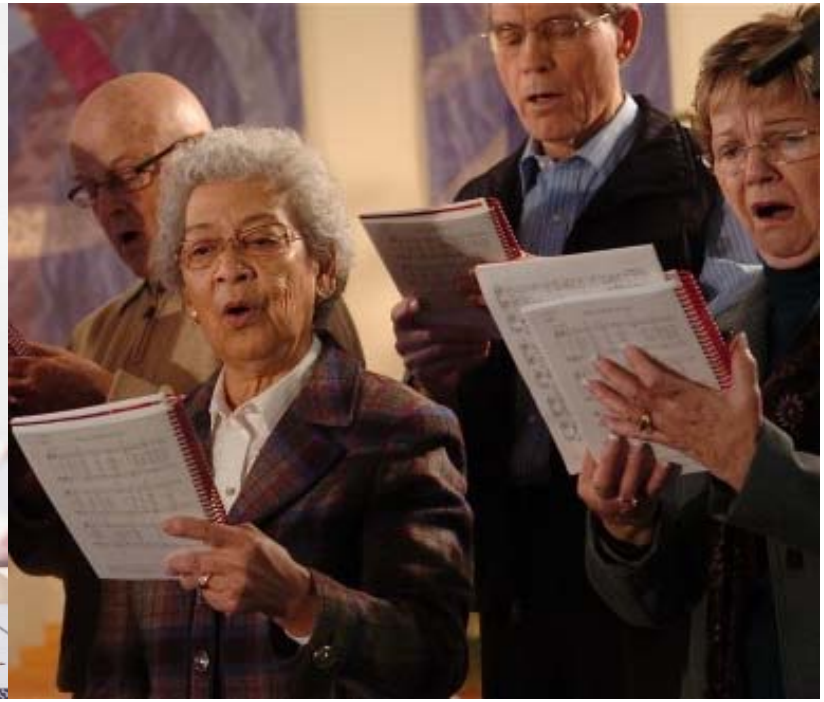
KCE REPORT 256S

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

OROPHARYNGEAL, HYPOPHARYNGEAL AND LARYNGEAL CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

SUPPLEMENT



KCE REPORT 256S
GOOD CLINICAL PRACTICE

Federaal Kenniscentrum voor de Gezondheidszorg
Centre Fédéral d'Expertise des Soins de Santé
Belgian Health Care Knowledge Centre

OROPHARYNGEAL, HYPOPHARYNGEAL AND LARYNGEAL CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

SUPPLEMENT

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COLOPHON

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	Participation in scientific or experimental research as an initiator, principal investigator or researcher: Pierre Castadot (Clinical Investigator study GORTEC 2007-02), Sandra Nuyts (study EORTC, interfaculty teaching studies), Vincent Vander Poorten, Jean-François Daisne (PI study Lux-2 - Boehringer), Dirk Van Gestel (PI 2 dose-painting studies: 1 for NET recurrences and 1 for bone metastases), Paul Clement (various randomised studies in head and neck cancer), Elisabeth Van Eycken (participation RARECAREnet), Pol Specenier (clinical studies head and neck cancer), François-Xavier Hanin (study GETTEC PET rapid evaluation) A grant, fees or funds for a member of staff or another form of compensation for the execution of research: Sandra Nuyts (FWO, VCK, Stichting tegen Kanker) Consultancy or employment for a company, an association or an organisation that may gain or lose financially due to the results of this report: Jan Vermorken (Merck-Serono; Genetech) Payments to speak, training remuneration, subsidised travel or payment for participation at a conference: Pierre Castadot (fees from Merck Serono for 2 presentations), Jean-François Daisne (payment from Merck to take part at the ICHNO congress 2013), Jan Vermorken (Merck-Serono), Dirk Van Gestel (occasional payments for communications from Accuray), Paul Clement (Merck Serono: teaching grants, payment for communications), Elisabeth Van Eycken (subsidised travels for RARECAREnet) Presidency or accountable function within an institution, association, department or other entity on which the results of this report could have an impact: Vincent Vander Poorten (secretary Vlaamse Werkgroep Hoofd Hals tumoren), Marc Hamoir (director Centre du Cancer des Cliniques universitaires St Luc), Geert Vanhemelen (treasurer VBS-MKA ; Adjunct secretary Société scientifique belge de stomatologie et de chirurgie maxillo-faciale), Paul Graf (Antwerpse Vereniging voor Gelaryngectomeerden, Liga voor Gelaryngectomeerden), Carl Van Laer (VWHHT), Paul Clement (member of the Medical Council at UZ Leuven; Member of the Board of Executives at VWHHT), Joseph Schoenaers (member of the working group and program of oncology 'head and neck'), François-Xavier Hanin (member of Committee Therapy at European Association of Nuclear Medicine)
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APPENDIX REPORT

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1. COMPOSITION OF THE GUIDELINE DEVELOPMENT GROUP

1.1. Composition of the Guideline Development Group

Clinicians	Field of expertise, affiliations
Vincent Grégoire, President of the GDG	Radiation oncology, UCL
Johan Abeloos	Maxillofacial surgery, AZ Sint-Jan Brugge
Laurens Carp	Nuclear medicine, UZA
Jan Casselman	Radiology, AZ Sint-Jan Brugge
Paul Clement	Medical oncology, UZ Leuven
Philippe Deron	ENT surgery, UZ Gent
Marc Hamoir	ENT surgery, UCL
Olivier Lenssen	Maxillofacial surgery, ZNA
Sandra Nuyts	Radiation oncology, UZ Leuven
Carl Van Laer	ENT surgery, UZA
Jan Vermorken	Medical oncology, UZA

1.2. Composition of the KCE expert team

KCE member	Specific role
Kirstel De Gauquier	Program Director
Sabine Stordeur	Project Coordinator
Joan Vlayen	Principal Investigator
Roos Leroy	Scientific research and methodological support

1.3. External researchers involved in the guideline development

Subcontractor	Specific role
Rob Scholten	Senior clinical epidemiologist, Dutch Cochrane Centre
Lotty Hooft	Senior clinical epidemiologist, Dutch Cochrane Centre
Pauline Heus	Junior researcher, Dutch Cochrane Centre
Fleur T. van de Wetering	Junior researcher, Dutch Cochrane Centre
Johanna Damen	Junior researcher, Dutch Cochrane Centre
René Spijker	Medical information specialist, Dutch Cochrane Centre
Inge Wenger	PhD student, Department of Otorhinolaryngology - Head and Neck Surgery, UMC Utrecht, The Netherlands
Inge Stegeman	Epidemiologist, UMC Utrecht, The Netherlands

2. SEARCH STRATEGIES

2.1. Search strategy for guidelines

Table 1 – Search results - Guidelines on HNSCC

Date	02/04/2013	
Search engine	Search term	Number of hits
GIN database	"Head and neck cancer"	28
National Guideline Clearinghouse	"Head and neck cancer"	86
Medline	1 exp "Head and Neck Neoplasms"/ (226498) 2 Carcinoma, Squamous Cell/ (96686) 3 ((head or neck or oral or oropharyn* or hypopharyn* or laryn*) adj2 (neoplasm* or cancer* or carcin* or tumo* or malig*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (79701) 4 upper aerodigestive tract neoplasms.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2) 5 1 or 2 or 3 or 4 (280235) 6 Esophageal Neoplasms/ (35709) 7 Facial Neoplasms/ (6811) 8 ear neoplasms/ (4506) 9 nose neoplasms/ (8349) 10 parathyroid neoplasms/ (6533) 11 thyroid neoplasms/ (34812) 12 tracheal neoplasms/ (3107) 13 6 or 7 or 8 or 9 or 10 or 11 or 12 (97798) 14 5 not 13 (182437) 15 exp guideline/ (23377) 16 "guideline*".ti. (42165) 17 recommendation*.ti. (20588) 18 standard*.ti. (58642) 19 15 or 16 or 17 or 18 (129130) 20 14 and 19 (655) 21 exp animals/ not humans.sh. (3784285) 22 20 not 21 (653) 23 limit 22 to (yr="2008 -Current" and (dutch or english or french or german)) (245)	245

After removal of duplicate guidelines, 32 guidelines were selected based on title and abstract and retained for full-text evaluation. Of these, 14 guidelines were excluded for the following reasons:

- 2 guidelines were out of scope
- 3 documents could not be considered as guideline
- 5 documents did not contain any recommendation
- 1 guideline had been replaced by a more recent version
- 2 guidelines were archived
- 1 guideline was based on another guideline

Finally, 18 guidelines were retained for an evaluation of the methodological quality.

2.2. Search strategies for systematic reviews

2.2.1.1. Systematic reviews RQ1-6

Date	**08-08-2014**	
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Search Strategy	1	"Head and Neck Neoplasms"/
	2	Neoplasms/
	3	exp Carcinoma/
	4	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab.
	5	exp Larynx/
	6	exp Hypopharynx/
	7	exp Oropharynx/
	8	laryngopharyn*.ti,ab.
	9	larynx*.ti,ab.
	10	hypopharyn*.ti,ab.
	11	oropharyn*.ti,ab.
	12	or/1-3 [cancer]
	13	or/5-11 [anatomical location]
	14	12 and 13
	15	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or larynx* or hypopharyn* or oropharyn*)).ti,ab.
	16	14 or 15
	17	exp Laryngeal Neoplasms/
	18	exp Hypopharyngeal Neoplasms/

	19	exp Oropharyngeal Neoplasms/
	20	or/17-19 [specific cancer]
	21	16 or 20
	22	(MEDLINE or systematic review).tw. or meta-analysis.pt. or intervention$.ti.
	23	21 and 22
	24	limit 23 to ed=20080101-20150101

Date	**08-08-2014**	
Database	Embase Classic + Embase 1947 to current	
Search Strategy	1	*"head and neck cancer"/
	2	*neoplasm/
	3	*carcinoma/
	4	exp *larynx/
	5	exp *hypopharynx/
	6	exp *oropharynx/
	7	laryngopharyn*.ti,ab.
	8	larynx*.ti,ab.
	9	hypopharyn*.ti,ab.
	10	oropharyn*.ti,ab.
	11	or/1-3 [cancer]
	12	or/5-10 [anatomical location]
	13	11 and 12
	14	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or larynx* or hypopharyn* or oropharyn*)).ti,ab.
	15	13 or 14
	16	exp *larynx tumor/
	17	exp *hypopharynx tumor/
	18	exp *oropharynx tumor/
	19	or/16-18 [specific cancer]
	20	MEDLINE.tw. or exp systematic review/ or systematic review.tw. or meta-analysis/ or intervention$.ti.
	21	15 or 19
	22	20 and 21
	23	limit 22 to dd=20080101-20150101

Date	08-08-2014	
Database	The Cochrane Library	
Search Strategy	#1	[mh "Head and Neck Neoplasms"]
	#2	[mh neoplasms]
	#3	[mh ^Carcinoma]
	#4	[mh ^Larynx]
	#5	[mh ^Hypopharynx]
	#6	[mh ^Oropharynx]
	#7	laryngopharyn*:ti,ab
	#8	larynx*:ti,ab
	#9	hypopharyn*:ti,ab
	#10	oropharyn*:ti,ab
	#11	#1 or #2 or #3
	#12	#4 or #5 or #6 or #7 or #8 or #9 or #10
	#13	#11 and #12
	#14	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) near/5 (laryngopharyn* or larynx* or hypopharyn* or oropharyn*)):ti,ab
	#15	#13 or #14
	#16	[mh ^" Laryngeal Neoplasms"]
	#17	[mh ^"Hypopharyngeal Neoplasms"]
	#18	[mh ^"Hypopharyngeal Neoplasms"]
	#19	#16 or #17 or #18
	#20	#15 or #19 Publication Year from 2008 to 2014

2.2.1.2. Systematic reviews RQ7

Date	16-03-2015
Database	Medline
Search Strategy	1 exp Larynx/ (30930) 2 exp Oropharynx/ (11683) 3 exp Hypopharynx/ (1604) 4 exp Glottis/ (11189) 5 1 or 2 or 3 or 4 (43520) 6 exp Neoplasms/ (2650214) 7 5 and 6 (10070) 8 ((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. (22010) 9 exp Laryngeal Neoplasms/ (24178) 10 exp Hypopharyngeal Neoplasms/ (2437) 11 exp Oropharyngeal Neoplasms/ (6106) 12 7 or 8 or 9 or 10 or 11 (38805) 13 exp radiotherapy/ (142378) 14 (radia* or irradia* or radio*).ti,ab. (1070361) 15 rt.fs. (159975) 16 13 or 14 or 15 (1132783) 17 altered.ti,ab. (266944) 18 exp Dose fractionation/ (6564) 19 exp radiotherapy dosage/ (50057) 20 hyperfract*.ti,ab. (1673) 21 hypofract*.ti,ab. (1504) 22 17 or 18 or 19 or 20 or 21 (317526) 24 randomized controlled trial.pt. (386752) 25 controlled clinical trial.pt. (88805) 26 randomized.ab. (284659) 27 placebo.ab. (149432) 28 clinical trials as topic.sh. (171427) 29 randomly.ab. (201590) 30 trial.ti. (122947) 31 24 or 25 or 26 or 27 or 28 or 29 or 30 (884566) 32 exp animals/ not humans.sh. (4001382) 33 31 not 32 (811404)

	34	meta-analysis.mp,pt. or review.pt. or search:.tw. (2097410)
	35	33 or 34 (2783738)
	37	accelerated.ti,ab. (72608)
	38	22 or 37 (385893)
	39	12 and 16 and 38 (2051)
	40	35 and 39 (375)

Date	**16-03-2015**	
Database	PreMedline	
Search Strategy	8	((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. (1368)
	14	(radia* or irradia* or radio*).ti,ab. (101076)
	17	altered.ti,ab. (18884)
	20	hyperfract*.ti,ab. (60)
	21	hypofract*.ti,ab. (213)
	22	17 or 20 or 21 (19149)
	24	randomized controlled trial.pt. (596)
	25	controlled clinical trial.pt. (51)
	26	randomized.ab. (27133)
	27	placebo.ab. (9595)
	29	randomly.ab. (23988)
	30	trial.ti. (11331)
	31	24 or 25 or 26 or 27 or 29 or 30 (56916)
	34	meta-analysis.mp,pt. or review.pt. or search:.tw. (55662)
	35	31 or 34 (107353)
	37	accelerated.ti,ab. (7198)
	38	22 or 37 (26137)
	39	8 and 14 and 38 (15)
	40	35 and 39 (6)

Date	16-03-2015
Database	Embase
Search Strategy	'larynx cancer'/exp OR 'epiglottis cancer'/exp OR 'hypopharynx cancer'/exp OR 'oropharynx cancer'/exp OR ((laryn* OR hypopharyn* OR oropharyn* OR glotti* OR supraglotti* OR epiglotti* OR subglotti*) NEAR/5 (cancer* OR tumour* OR tumor* OR neoplas* OR malignan* OR carcinoma* OR metatasta*)):ab,ti AND ('radiotherapy'/exp OR radia*:ab,ti OR irradia*:ab,ti OR radio*:ab,ti) AND (altered:ab,ti OR hypofract*:ab,ti OR hyperfract*:ab,ti OR accelerated:ab,ti OR 'radiation dose fractionation'/exp OR 'radiation dose'/exp) AND ([cochrane review]/lim OR [systematic review]/lim OR [randomized controlled trial]/lim OR [meta analysis]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim)

Date	16-03-2015	
Database	Cochrane library	
Search Strategy	#1	MeSH descriptor: [Laryngeal Neoplasms] 1 tree(s) exploded
	#2	MeSH descriptor: [Hypopharyngeal Neoplasms] 1 tree(s) exploded
	#3	MeSH descriptor: [Oropharyngeal Neoplasms] 1 tree(s) exploded
	#4	((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) and (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)):ti,ab
	#5	#1 or #2 or #3 or #4
	#6	MeSH descriptor: [Radiotherapy] 1 tree(s) exploded
	#7	(radia* or irradia* or radio*):ti,ab
	#8	#6 or #7
	#9	altered:ti,ab
	#10	MeSH descriptor: [Dose Fractionation] 1 tree(s) exploded
	#11	MeSH descriptor: [Radiotherapy Dosage] 1 tree(s) exploded
	#12	(hypofract* or hyperfract*):ti,ab
	#13	#9 or #10 or #11 or #12
	#14	#5 and #8 and #13
	#15	accelerated:ti,ab
	#16	#13 or #15
	#17	#5 and #8 and #16

2.3. Search strategies for primary studies

2.3.1. RQ1: What is the effectiveness and/or diagnostic outcomes of locoregional staging (i.e. T- and N-staging) with MRI compared to CT in patients with head and neck squamous cell carcinoma

2.3.1.1. RCTs

Date	24-11-2014
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2004 to Present
Search Strategy	1. "Head and Neck Neoplasms"/ 2. (hnscc or scchn).ti,ab. 3. exp Neoplasms/ 4. "head and neck".ti,ab. 5. (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab. 6. exp Laryngeal Neoplasms/ 7. exp Hypopharyngeal Neoplasms/ 8. exp Oropharyngeal Neoplasms/ 9. exp Larynx/ 10. exp Oropharynx/ 11. exp Hypopharynx/ 12. exp Glottis/ 13. (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*).ti,ab. 14. 4 or 13 15. (("head and neck" or (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*)) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. 16. 9 or 10 or 11 or 12 17. 3 and 16 18. 1 or 2 or 6 or 7 or 8 or 15 or 17 19. exp Magnetic Resonance Imaging/ 20. MRI.ti,ab. 21. (magnet* adj4 imag*).ti,ab. 22. 19 or 20 or 21 23. exp Tomography, X-Ray Computed/ 24. (ct adj4 (scan* or imag*)).ti,ab. 25. (comp* adj3 tomogr*).ti,ab. 26. 23 or 24 or 25 27. 22 and 26 28. 18 and 27

	29. randomized controlled trials/ 30. "randomized controlled trial".pt. 31. controlled clinical trial.pt. 32. random allocation/ 33. exp Clinical Trial/ 34. clinical trial.pt. 35. random$.ti,ab. 36. or/35-41 37. 28 and 46 38. limit 37 to yr="2004 -Current"

Date	**24-11-2014**
Database	Embase Classic + Embase 2004 to current
Search Strategy	1. *"head and neck tumor"/ 2. (hnscc or scchn).ti,ab. 3. exp *neoplasm/ 4. "head and neck".ti,ab. 5. (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab. 6. exp *larynx cancer/ 7. exp *hypopharynx cancer/ 8. exp *oropharynx cancer/ 9. exp *larynx/ 10. exp *oropharynx/ 11. exp *glottis/ 12. exp *hypopharynx/ 13. (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*).ti,ab. 14. 4 or 13 15. (("head and neck" or (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*)) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. 16. or/9-12 17. 3 and 16 18. 1 or 2 or 6 or 7 or 8 or 15 or 17 19. exp *nuclear magnetic resonance imaging/ 20. MRI.ti,ab. 21. (magnet* adj4 imag*).ti,ab. 22. or/19-21

	23.	exp *computer assisted tomography/
	24.	(ct adj4 (scan* or imag*)).ti,ab.
	25.	(comp* adj3 tomogr*).ti,ab.
	26.	or/23-25
	27.	22 and 26
	28.	18 and 27
	29.	crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/
	30.	(crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).ti,ab,ot. or random$.ti,ab,ab. or trial$.ti.
	31.	29 or 30
	32.	28 and 31
	33.	limit 32 to yr="2004 -Current"

Date	**24-11-2014**	
Database	Cochrane central through http://crso.cochrane.org	
Search Strategy	#1	Head and Neck Neoplasms:MH
	#2	Neoplasms:MH
	#3	Carcinoma:MH
	#4	head and neck cancer:EH
	#5	neoplasm:EH
	#6	carcinoma:EH
	#7	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*):MH,EH,KY,KW,TI,AB
	#8	laryngopharyn*:MH,EH,KY,KW,TI,AB
	#9	larynx*:MH,EH,KY,KW,TI,AB
	#10	hypopharyn*:MH,EH,KY,KW,TI,AB
	#11	oropharyn*:MH,EH,KY,KW,TI,AB
	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#13	#8 OR #9
	#14	Laryngeal Neoplasms:MH OR larynx tumor:EH
	#15	Hypopharyngeal Neoplasms:MH OR hypopharynx tumor:EH
	#16	(#12 AND #13) OR #14
	#17	(#12 AND #10) OR #15
	#18	(#12 AND #11) OR #16
	#19	(glottis or supraglottis or epiglottis or subglottis):MH,EH,KY,KW,TI,AB
	#20	#12 AND #19
	#21	#16 OR #17 OR #18 OR #20
	#22	magnetic resonance imaging:EH,MH,kw,ti,ab

	#23	MRI:ti,ab
	#24	magnet*:ti,ab
	#25	#22 OR #23 OR #24
	#26	#21 AND #25
	#27	tomography:MH,EH
	#28	tomogr*:ti,ab
	#29	CT:ti,ab
	#30	#27 OR #28 OR #29
	#31	#26 AND #30

2.3.1.2. Observational studies

Date	**24-11-2014**
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Search Strategy	1. "Head and Neck Neoplasms"/ 2. (hnscc or scchn).ti,ab. 3. exp Neoplasms/ 4. "head and neck".ti,ab. 5. (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab. 6. exp Laryngeal Neoplasms/ 7. exp Hypopharyngeal Neoplasms/ 8. exp Oropharyngeal Neoplasms/ 9. exp Larynx/ 10. exp Oropharynx/ 11. exp Hypopharynx/ 12. exp Glottis/ 13. (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*).ti,ab. 14. 4 or 13 15. (("head and neck" or (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*)) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. 16. 9 or 10 or 11 or 12 17. 3 and 16 18. 1 or 2 or 6 or 7 or 8 or 15 or 17 19. exp Magnetic Resonance Imaging/ 20. MRI.ti,ab. 21. (magnet* adj4 imag*).ti,ab. 22. 19 or 20 or 21

	23. exp Tomography, X-Ray Computed/ 24. (ct adj4 (scan* or imag*)).ti,ab. 25. (comp* adj3 tomogr*).ti,ab. 26. 23 or 24 or 25 27. 22 and 26 28. 18 and 27 29. Epidemiologic studies/ 30. exp case control studies/ 31. exp cohort studies/ 32. Case control.tw. 33. (cohort adj (study or studies)).tw. 34. Cohort analy$.tw. 35. (Follow up adj (study or studies)).tw. 36. (observational adj (study or studies)).tw. 37. Longitudinal.tw. 38. Retrospective.tw. 39. Cross sectional.tw. 40. Cross-sectional studies/ 41. or/29-40 42. 28 and 41 43. exp "sensitivity and specificity"/ 44. exp "mass screening"/ 45. "reference values"/ 46. "false positive reactions"/ 47. "false negative reactions"/ 48. (specificit$ or screening or false positive$ or false negative$ or accuracy or predictive value$ or reference value$ or roc$ or likelihood ratio$).tw. 49. or/43-48 50. 28 and 49 51. 42 or 50

Date	**24-11-2014**
Database	Embase Classic + Embase 1947 to current
Search Strategy	1. *"head and neck tumor"/ 2. (hnscc or scchn).ti,ab. 3. exp *neoplasm/

4.	"head and neck".ti,ab.
5.	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab.
6.	exp *larynx cancer/
7.	exp *hypopharynx cancer/
8.	exp *oropharynx cancer/
9.	exp *larynx/
10.	exp *oropharynx/
11.	exp *glottis/
12.	exp *hypopharynx/
13.	(laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*).ti,ab.
14.	4 or 13
15.	(("head and neck" or (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*)) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab.
16.	or/9-12
17.	3 and 16
18.	1 or 2 or 6 or 7 or 8 or 15 or 17
19.	exp *nuclear magnetic resonance imaging/
20.	MRI.ti,ab.
21.	(magnet* adj4 imag*).ti,ab.
22.	or/19-21
23.	exp *computer assisted tomography/
24.	(ct adj4 (scan* or imag*)).ti,ab.
25.	(comp* adj3 tomogr*).ti,ab.
26.	or/23-25
27.	22 and 26
28.	18 and 27
29.	Clinical study/
30.	Case control study/
31.	Family study/
32.	Longitudinal study/
33.	Retrospective study/
34.	Prospective study/
35.	Randomized controlled trials/
36.	34 not 35
37.	Cohort analysis/
38.	(Cohort adj (study or studies)).mp.
39.	(Case control adj (study or studies)).tw.
40.	(follow up adj (study or studies)).tw.

	41.	(observational adj (study or studies)).tw.
	42.	(epidemiologic$ adj (study or studies)).tw.
	43.	(cross sectional adj (study or studies)).tw.
	44.	29 or 30 or 31 or 32 or 33 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
	45.	28 and 44

2.3.2. RQ2: What is the clinical effectiveness of surgery for patients with early oropharyngeal, hypopharyngeal and laryngealcancer?

a. Surgery versus non-surgery

b. Function-sparing surgery versus extensive surgery

2.3.2.1. RCTs

A combined search strategy for RCTs regarding RQ 2, 3 and 5 was developed.

Date	**24-09-2014**	
Database	Cochrane specialised registry of the ENT Disorders Cochrane review group	
Search Strategy	#1	Head and Neck Neoplasms:MH
	#2	Neoplasms:MH
	#3	Carcinoma:MH
	#4	head and neck cancer:EH
	#5	neoplasm:EH
	#6	carcinoma:EH
	#7	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*):MH,EH,KY,KW,TI,AB
	#8	laryngopharyn*:MH,EH,KY,KW,TI,AB
	#9	(larynx* or glottis or supraglottis or epiglottis or subglottis):MH,EH,KY,KW,TI,AB
	#10	hypopharyn*:MH,EH,KY,KW,TI,AB
	#11	oropharyn*:MH,EH,KY,KW,TI,AB
	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#13	#8 or #9
	#14	Laryngeal Neoplasms:MH OR larynx tumor:EH
	#15	Hypopharyngeal Neoplasms:MH OR hypopharynx tumor:EH
	#16	Oropharyngeal Neoplasms:MH OR oropharynx tumor:EH
	#17	(#12 AND #13) OR #14
	#18	(#12 AND #10) OR #15
	#19	(#12 AND #11) OR #16
	#20	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*):MH,EH,KY,KW,TI,AB

	#21	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)):MH,EH,KY,KW,TI,AB
	#22	#20 OR #21
	#23	#17 AND #22
	#24	#18 AND #22
	#25	#19 AND #22
	#26	radiother*:MH,EH,KY,KW,TI,AB
	#27	#25 not #26
	#28	(2004 or 2005 or 2006 or 2007 or 2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014):YR
	#29	#25 AND #28
	#30	(2011 or 2012 or 2013 or 2014):YR
	#31	#25 AND #30
	#32	#23 OR #24 OR #25
Note	Search for RCTs regarding research questions 2, 3 and 5	

Date	**24-09-2014**	
Database	Cochrane central register of trials online (CENTRAL)	
Search Strategy	#1	Head and Neck Neoplasms:MH
	#2	Neoplasms:MH
	#3	Carcinoma:MH
	#4	head and neck cancer:EH
	#5	neoplasm:EH
	#6	carcinoma:EH
	#7	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*):MH,EH,KY,KW,TI,AB
	#8	laryngopharyn*:MH,EH,KY,KW,TI,AB
	#9	(larynx* or glottis or supraglottis or epiglottis or subglottis):MH,EH,KY,KW,TI,AB
	#10	hypopharyn*:MH,EH,KY,KW,TI,AB
	#11	oropharyn*:MH,EH,KY,KW,TI,AB
	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#13	#8 or #9
	#14	Laryngeal Neoplasms:MH OR larynx tumor:EH
	#15	Hypopharyngeal Neoplasms:MH OR hypopharynx tumor:EH
	#16	Oropharyngeal Neoplasms:MH OR oropharynx tumor:EH
	#17	(#12 AND #13) OR #14
	#18	(#12 AND #10) OR #15
	#19	(#12 AND #11) OR #16

	#20	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*):MH,EH,KY,KW,TI,AB
	#21	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)):MH,EH,KY,KW,TI,AB
	#22	#20 OR #21
	#23	#17 AND #22
	#24	#18 AND #22
	#25	#19 AND #22
	#26	radiother*:MH,EH,KY,KW,TI,AB
	#27	#25 not #26
	#28	(2004 or 2005 or 2006 or 2007 or 2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014):YR
	#29	#25 AND #28
	#30	(2011 or 2012 or 2013 or 2014):YR
	#31	#25 AND #30
	#32	#23 OR #24 OR #25
Note	Search for RCTs regarding research questions 2, 3 and 5	

Date	**24-09-2014**	
Database	Cochrane central register of trials online (CENTRAL): Glottic add-on	
Search Strategy	#1	(glottis or supraglottis or epiglottis or subglottis):MH,EH,KY,KW,TI,AB
	#2	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*):MH,EH,KY,KW,TI,AB
	#3	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)):MH,EH,KY,KW,TI,AB
	#4	#2 OR #3
	#5	Head and Neck Neoplasms:MH
	#6	Neoplasms:MH
	#7	Carcinoma:MH
	#8	head and neck cancer:EH
	#9	carcinoma:EH
	#10	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*):MH,EH,KY,KW,TI,AB
	#11	#5 OR #6 OR #7 OR #8 OR #9 OR #10
	#12	#1 AND #11
	#13	#4 AND #12
	#14	(2004 or 2005 or 2006 or 2007 or 2008 or 2009 or 2010 or 2011 or 2012 or 2013 or 2014):YR
	#15	#13 AND #14
Note	Search for RCTs regarding research questions 2, 3 and 5	

2.3.2.2. Observational studies

Date	10-10-2014	
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Search Strategy	1	"Head and Neck Neoplasms"/
	2	Neoplasms/
	3	exp Carcinoma/
	4	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab.
	5	exp Larynx/
	6	exp Hypopharynx/
	7	exp Oropharynx/
	8	laryngopharyn*.ti,ab.
	9	(larynx* or glottis or supraglottis or epiglottis or subglottis).ti,ab.
	10	hypopharyn*.ti,ab.
	11	oropharyn*.ti,ab.
	12	or/1-4 [cancer]
	13	or/5-11 [anatomical location]
	14	12 and 13
	15	exp Laryngeal Neoplasms/
	16	exp Hypopharyngeal Neoplasms/
	17	exp Oropharyngeal Neoplasms/
	18	or/15-17 [specific cancer]
	19	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic)).ti,ab.
	20	early stage*.ti,ab.
	21	19 and 20
	22	(early adj5 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic))).ti,ab.
	23	(stage$ adj3 ("1" or "I" or "2" or "II" or T1 or T2)).ti,ab.
	24	14 or 18 or 19
	25	23 and 24 [stage 1/2 tumour]
	26	22 or 25
	27	21 or 26 [early or 1/2 stage tumour]
	28	(excision or excise or resect$).ti,ab.
	29	exp Surgical Procedures, Operative/
	30	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*).ti,ab.

	31	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)).ti,ab.
	32	or/28-31 [surgery]
	33	27 and 32
	34	(dissect$ adj2 neck$).ti,ab.
	35	(lymphadenectom$ or glossectom$).ti,ab.
	36	exp Lymph Node Excision/
	37	(lymph$ adj3 (excision or dissection)).ti,ab.
	38	34 or 35 or 36 or 37 [neck dissection]
	39	24 and 38
	40	Epidemiologic studies/
	41	exp case control studies/
	42	exp cohort studies/
	43	Case control.tw.
	44	(cohort adj (study or studies)).tw.
	45	Cohort analy$.tw.
	46	(Follow up adj (study or studies)).tw.
	47	(observational adj (study or studies)).tw.
	48	Longitudinal.tw.
	49	Retrospective.tw.
	50	Cross sectional.tw.
	51	Cross-sectional studies/
	52	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 [observational study filter]
	53	33 and 52
	54	limit 53 to yr="2004 -Current"

Date	10-10-2014	
Database	Embase Classic + Embase 1947 to current	
Search Strategy	1	*"head and neck cancer"/
	2	*neoplasm/
	3	*carcinoma/
	4	exp *larynx/
	5	exp *hypopharynx/
	6	exp *oropharynx/
	7	laryngopharyn*.ti,ab.
	8	(larynx* or glottis or supraglottis or epiglottis or subglottis).ti,ab.
	9	hypopharyn*.ti,ab.
	10	oropharyn*.ti,ab.
	11	or/1-3 [cancer]
	12	or/5-10 [anatomical location]
	13	11 and 12
	14	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic)).ti,ab.
	15	13 or 14
	16	exp *larynx tumor/
	17	exp *hypopharynx tumor/
	18	exp *oropharynx tumor/
	19	or/16-18 [specific cancer]
	20	early stage*.ti,ab.
	21	14 and 20
	22	(early adj5 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic))).ti,ab.
	23	(stage$ adj3 ("1" or "I" or "2" or "II" or T1 or T2)).ti,ab.
	24	15 or 19
	25	23 and 24
	26	21 or 25
	27	(excision or excise or resect$).ti,ab.
	28	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*).ti,ab.
	29	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)).ti,ab.
	30	exp *surgery/
	31	27 or 28 or 29 or 30
	32	26 and 31

	33	(dissect$ adj2 neck$).ti,ab.
	34	(lymphadenectom$ or glossectom$).ti,ab.
	35	exp *neck dissection/
	36	*lymph node dissection/
	37	33 or 34 or 35 or 36
	38	19 and 37
	39	Clinical study/
	40	Case control study/
	41	Family study/
	42	Longitudinal study/
	43	Retrospective study/
	44	Prospective study/
	45	Randomized controlled trials/
	46	44 not 45
	47	Cohort analysis/
	48	(Cohort adj (study or studies)).mp.
	49	(Case control adj (study or studies)).tw.
	50	(follow up adj (study or studies)).tw.
	51	(observational adj (study or studies)).tw.
	52	(epidemiologic$ adj (study or studies)).tw.
	53	(cross sectional adj (study or studies)).tw.
	54	39 or 40 or 41 or 42 or 43 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
	55	32 and 54
	56	38 and 54
	57	limit 55 to yr="2004 -Current"
Note	Search for observational studies regarding RQ2	

2.3.3. RQ3: Surgery versus organ / function preservation strategies

2.3.3.1. RCTs

See RQ2

2.3.3.2. Observational studies

Date	10-10-2014	
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Search Strategy	1	"Head and Neck Neoplasms"/
	2	Neoplasms/
	3	exp Carcinoma/
	4	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab.
	5	exp Oropharynx/
	6	oropharyn*.ti,ab.
	7	or/1-4 [cancer]
	8	or/5-6 [anatomical location]
	9	7 and 8
	10	exp Oropharyngeal Neoplasms/
	11	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 oropharyn*).ti,ab.
	12	(late stage* or advanced stage*).ti,ab.
	13	11 and 12
	14	((late or advance*) adj5 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 oropharyn*)).ti,ab.
	15	(stage$ adj3 ("3" or "III" or "4" or "IV" or T3 or T4 or M0)).ti,ab.
	16	9 or 10 or 11
	17	15 and 16 [stage 3/4 tumour]
	18	14 or 17
	19	13 or 18 [early or 3/4 stage tumour]
	20	(excision or excise or resect$).ti,ab.
	21	exp Surgical Procedures, Operative/
	22	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*).ti,ab.
	23	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)).ti,ab.
	24	20 or 21 or 22 or 23
	25	19 and 24
	26	Epidemiologic studies/
	27	exp case control studies/

	28	exp cohort studies/
	29	Case control.tw.
	30	(cohort adj (study or studies)).tw.
	31	Cohort analy$.tw.
	32	(Follow up adj (study or studies)).tw.
	33	(observational adj (study or studies)).tw.
	34	Longitudinal.tw.
	35	Retrospective.tw.
	36	Cross sectional.tw.
	37	Cross-sectional studies/
	38	or/26-37 [obs studies]
	39	25 and 38
	40	limit 39 to yr="2004 -Current"

Date	**10-10-2014**	
Database	Embase Classic + Embase 1947 to current	
Search Strategy	1	*"head and neck cancer"/
	2	*neoplasm/
	3	*carcinoma/
	4	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab.
	5	exp *oropharynx/
	6	oropharyn*.ti,ab.
	7	or/1-4
	8	or/5-6
	9	7 and 8
	10	exp *oropharynx tumor/
	11	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 oropharyn*).ti,ab.
	12	(late stage* or advanced stage*).ti,ab.
	13	11 and 12
	14	((late or advance*) adj5 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 oropharyn*)).ti,ab.
	15	(stage$ adj3 ("3" or "III" or "4" or "IV" or T3 or T4 or M0)).ti,ab.
	16	9 or 10 or 11
	17	15 and 16
	18	14 or 17
	19	13 or 18
	20	(excision or excise or resect$).ti,ab.

21	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*).ti,ab.
22	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)).ti,ab.
23	exp *surgery/
24	or/20-23
25	19 and 24
26	Clinical study/
27	Case control study/
28	Family study/
29	Longitudinal study/
30	Retrospective study/
31	Prospective study/
32	Randomized controlled trials/
33	31 not 32
34	Cohort analysis/
35	(Cohort adj (study or studies)).mp.
36	(Case control adj (study or studies)).tw.
37	(follow up adj (study or studies)).tw.
38	(observational adj (study or studies)).tw.
39	(epidemiologic$ adj (study or studies)).tw.
40	(cross sectional adj (study or studies)).tw.
41	or/26-30,33-40
42	25 and 41
43	limit 42 to yr="2004 -Current"

2.3.4. RQ4: Postoperative (chemo)radiotherapy

a. Postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy

b. Postoperative chemoradiotherapy versus postoperative radiotherapy

2.3.4.1. RCTs

Date	03-12-2014	
Database	Cochrane specialised registry of the ENT Disorders Cochrane review group	
Search Strategy	#1	Head and Neck Neoplasms:MH
	#2	Neoplasms:MH
	#3	Carcinoma:MH
	#4	head and neck cancer:EH
	#5	neoplasm:EH
	#6	carcinoma:EH
	#7	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*):MH,EH,KY,KW,TI,AB
	#8	laryngopharyn*:MH,EH,KY,KW,TI,AB
	#9	larynx*:MH,EH,KY,KW,TI,AB
	#10	hypopharyn*:MH,EH,KY,KW,TI,AB
	#11	oropharyn*:MH,EH,KY,KW,TI,AB
	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#13	#8 OR #9
	#14	Laryngeal Neoplasms:MH OR larynx tumor:EH
	#15	Hypopharyngeal Neoplasms:MH OR hypopharynx tumor:EH
	#16	#12 AND #13 OR 14
	#17	#12 AND #10 OR #15
	#18	#12 AND #11
	#19	(glottis or supraglottis or epiglottis or subglottis):MH,EH,KY,KW,TI,AB
	#20	#12 AND #19
	#21	#16 OR #17 OR #18 OR #20
	#22	radiotherapy:ti,ab,kw,MH,EH OR (radia* or irradia* or radio*):ti,ab,kw,mh,eh
	#23	(postoperat* or post-operat*):ti,ab,kw,mh,eh
	#24	#21 AND #22 AND #23
Note	Search for RCTs regarding RQ4	

Date	03-12-2014	
Database	Cochrane central through http://crso.cochrane.org	
Search Strategy	#1	Head and Neck Neoplasms:MH
	#2	Neoplasms:MH
	#3	Carcinoma:MH
	#4	head and neck cancer:EH
	#5	neoplasm:EH
	#6	carcinoma:EH
	#7	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*):MH,EH,KY,KW,TI,AB
	#8	laryngopharyn*:MH,EH,KY,KW,TI,AB
	#9	larynx*:MH,EH,KY,KW,TI,AB
	#10	hypopharyn*:MH,EH,KY,KW,TI,AB
	#11	oropharyn*:MH,EH,KY,KW,TI,AB
	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#13	#8 OR #9
	#14	Laryngeal Neoplasms:MH OR larynx tumor:EH
	#15	Hypopharyngeal Neoplasms:MH OR hypopharynx tumor:EH
	#16	#12 AND #13 OR 14
	#17	#12 AND #10 OR #15
	#18	#12 AND #11
	#19	(glottis or supraglottis or epiglottis or subglottis):MH,EH,KY,KW,TI,AB
	#20	#12 AND #19
	#21	#16 OR #17 OR #18 OR #20
	#22	radiotherapy:ti,ab,kw,MH,EH OR (radia* or irradia* or radio*):ti,ab,kw,mh,eh
	#23	(postoperat* or post-operat*):ti,ab,kw,mh,eh
	#24	#21 AND #22 AND #23
Note	Search for RCTs regarding RQ4	

2.3.4.2. Observational studies

Date	03-12-2014	
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Search Strategy	1	exp Neoplasms/
	2	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab.
	3	exp Laryngeal Neoplasms/
	4	exp Hypopharyngeal Neoplasms/
	5	exp Oropharyngeal Neoplasms/
	6	exp Larynx/
	7	exp Oropharynx/
	8	exp Hypopharynx/
	9	exp Glottis/
	10	(laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*).ti,ab.
	11	6 or 7 or 8 or 9
	12	1 and 11
	13	exp radiotherapy/
	14	(radia* or irradia* or radio*).ti,ab.
	15	rt.fs.
	16	13 or 14 or 15
	17	(postoperat* or post-operat*).ti,ab,kw,hw.
	18	randomized controlled trials/
	19	"randomized controlled trial".pt.
	20	controlled clinical trial.pt.
	21	random allocation/
	22	exp Clinical Trial/
	23	clinical trial.pt.
	24	random$.ti,ab.
	25	or/18-24
	26	Epidemiologic studies/
	27	exp case control studies/
	28	exp cohort studies/
	29	Case control.tw.
	30	(cohort adj (study or studies)).tw.
	31	Cohort analy$.tw.
	32	(Follow up adj (study or studies)).tw.
	33	(observational adj (study or studies)).tw.

	34	Longitudinal.tw.
	35	Retrospective.tw.
	36	Cross sectional.tw.
	37	Cross-sectional studies/
	38	or/26-37
	39	((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab.
	40	3 or 4 or 5 or 39 or 12
	41	16 and 17 and 40
	42	limit 41 to yr="2004 -Current"
	43	25 and 42
	44	38 and 42

Date	**03-12-2014**	
Database	Embase Classic + Embase 1947 to current	
Search Strategy	1	exp *neoplasm/
	2	exp *larynx cancer/
	3	exp *hypopharynx cancer/
	4	exp *oropharynx cancer/
	5	exp *larynx/
	6	exp *oropharynx/
	7	exp *glottis/
	8	exp *hypopharynx/
	9	((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab.
	10	5 or 6 or 7 or 8
	11	1 and 10
	12	2 or 3 or 4
	13	9 or 11 or 12
	14	exp *radiotherapy/
	15	(radia* or irradia* or radio*).ti,ab.
	16	rt.fs.
	17	14 or 15 or 16
	18	(postoperat* or post-operat*).ti,ab,kw,hw.
	19	13 and 17 and 18
	20	limit 19 to yr="2004 -Current"

	21	crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/
	22	(crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).ti,ab,ot. or random$.ti,ab,ab. or trial$.ti.
	23	21 or 22
	24	20 and 23
	25	Clinical study/
	26	Case control study/
	27	Family study/
	28	Longitudinal study/
	29	Retrospective study/
	30	Prospective study/
	31	Randomized controlled trials/
	32	30 not 31
	33	Cohort analysis/
	34	(Cohort adj (study or studies)).mp.
	35	(Case control adj (study or studies)).tw.
	36	(follow up adj (study or studies)).tw.
	37	(observational adj (study or studies)).tw.
	38	(epidemiologic$ adj (study or studies)).tw.
	39	(cross sectional adj (study or studies)).tw.
	40	25 or 26 or 27 or 28 or 29 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39
	41	20 and 40

2.3.5. RQ5: Management of the neck lymph nodes

a. Neck dissection versus no neck dissection

b. Neck dissection type X versus neck dissection type Y

2.3.5.1. RCTs

See RQ3.

2.3.5.2. Observational studies

Date	10-10-2014	
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present	
Search Strategy	1	"Head and Neck Neoplasms"/
	2	Neoplasms/
	3	exp Carcinoma/
	4	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab.
	5	exp Larynx/
	6	exp Hypopharynx/
	7	exp Oropharynx/
	8	laryngopharyn*.ti,ab.
	9	(larynx* or glottis or supraglottis or epiglottis or subglottis).ti,ab.
	10	hypopharyn*.ti,ab.
	11	oropharyn*.ti,ab.
	12	or/1-4 [cancer]
	13	or/5-11 [anatomical location]
	14	12 and 13
	15	exp Laryngeal Neoplasms/
	16	exp Hypopharyngeal Neoplasms/
	17	exp Oropharyngeal Neoplasms/
	18	or/15-17 [specific cancer]
	19	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic)).ti,ab.
	20	early stage*.ti,ab.
	21	19 and 20
	22	(early adj5 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic))).ti,ab.
	23	(stage$ adj3 ("1" or "I" or "2" or "II" or T1 or T2)).ti,ab.

	24	14 or 18 or 19
	25	23 and 24 [stage 1/2 tumour]
	26	22 or 25
	27	21 or 26 [early or 1/2 stage tumour]
	28	(excision or excise or resect$).ti,ab.
	29	exp Surgical Procedures, Operative/
	30	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*).ti,ab.
	31	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)).ti,ab.
	32	or/28-31 [surgery]
	33	27 and 32
	34	(dissect$ adj2 neck$).ti,ab.
	35	(lymphadenectom$ or glossectom$).ti,ab.
	36	exp Lymph Node Excision/
	37	(lymph$ adj3 (excision or dissection)).ti,ab.
	38	34 or 35 or 36 or 37 [neck dissection]
	39	24 and 38
	40	Epidemiologic studies/
	41	exp case control studies/
	42	exp cohort studies/
	43	Case control.tw.
	44	(cohort adj (study or studies)).tw.
	45	Cohort analy$.tw.
	46	(Follow up adj (study or studies)).tw.
	47	(observational adj (study or studies)).tw.
	48	Longitudinal.tw.
	49	Retrospective.tw.
	50	Cross sectional.tw.
	51	Cross-sectional studies/
	52	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 [observational study filter]
	53	33 and 52
	54	limit 53 to yr="2004 -Current"
	55	39 and 52
	56	limit 55 to yr="2004 -Current"

Date	10-10-2014	
Database	Embase Classic + Embase 1947 to current	
Search Strategy	1	*"head and neck cancer"/
	2	*neoplasm/
	3	*carcinoma/
	4	exp *larynx/
	5	exp *hypopharynx/
	6	exp *oropharynx/
	7	laryngopharyn*.ti,ab.
	8	(larynx* or glottis or supraglottis or epiglottis or subglottis).ti,ab.
	9	hypopharyn*.ti,ab.
	10	oropharyn*.ti,ab.
	11	or/1-3 [cancer]
	12	or/5-10 [anatomical location]
	13	11 and 12
	14	((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic)).ti,ab.
	15	13 or 14
	16	exp *larynx tumor/
	17	exp *hypopharynx tumor/
	18	exp *oropharynx tumor/
	19	or/16-18 [specific cancer]
	20	early stage*.ti,ab.
	21	14 and 20
	22	(early adj5 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic))).ti,ab.
	23	(stage$ adj3 ("1" or "I" or "2" or "II" or T1 or T2)).ti,ab.
	24	15 or 19
	25	23 and 24
	26	21 or 25
	27	(excision or excise or resect$).ti,ab.
	28	(surgical or surgery or operative or operation or dissection or microsurgery or excision or endoscop*).ti,ab.
	29	(laryngoscop* or laryngectom* or larynplast* or pharyngectom* or (laryn* and preserv*) or hemilaryngectom* or endolaryngectom* or endolaryngeal or transoral* or "trans oral" or (neck and incision) or cordectom* or (vocal and stripping)).ti,ab.
	30	exp *surgery/
	31	27 or 28 or 29 or 30
	32	26 and 31

33	(dissect$ adj2 neck$).ti,ab.
34	(lymphadenectom$ or glossectom$).ti,ab.
35	exp *neck dissection/
36	*lymph node dissection/
37	33 or 34 or 35 or 36
38	19 and 37
39	Clinical study/
40	Case control study/
41	Family study/
42	Longitudinal study/
43	Retrospective study/
44	Prospective study/
45	Randomized controlled trials/
46	44 not 45
47	Cohort analysis/
48	(Cohort adj (study or studies)).mp.
49	(Case control adj (study or studies)).tw.
50	(follow up adj (study or studies)).tw.
51	(observational adj (study or studies)).tw.
52	(epidemiologic$ adj (study or studies)).tw.
53	(cross sectional adj (study or studies)).tw.
54	39 or 40 or 41 or 42 or 43 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53
55	32 and 54
56	38 and 54
57	limit 56 to yr="2004 -Current"
58	limit 55 to yr="2004 -Current"

2.3.6. RQ6: Salvage treatment versus no/other treatment

Date	4-12-2014
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Search Strategy	1 exp Neoplasms/ 2 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*).ti,ab. 3 exp Laryngeal Neoplasms/ 4 exp Hypopharyngeal Neoplasms/ 5 exp Oropharyngeal Neoplasms/ 6 exp Larynx/ 7 exp Oropharynx/ 8 exp Hypopharynx/ 9 exp Glottis/ 10 (laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*).ti,ab. 11 6 or 7 or 8 or 9 12 1 and 11 13 ((laryn* or hypopharyn* or oropharyn* or glotti* or supraglotti* or epiglotti* or subglotti*) adj5 (cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*)).ti,ab. 14 3 or 4 or 5 or 12 or 13 15 exp Neoplasm Recurrence, Local/ 16 (second* adj3 primar*).ti,ab. 17 ((locoregional$ or local$) adj5 recurren$).ti,ab. 18 15 or 16 or 17 19 14 and 18 20 limit 19 to yr="2004 -Current" 21 salvage.ti,ab,kw,hw. 22 20 and 21 23 Epidemiologic studies/ or exp case control studies/ or exp cohort studies/ or Case control.tw. or (cohort adj (study or studies)).tw. or Cohort analy$.tw. or (Follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or Longitudinal.tw. or Retrospective.tw. or Cross sectional.tw. or Cross-sectional studies/ 24 (randomized controlled trial or controlled clinical trial).pt. or random*.ab. or placebo.ab. or trial.ab. or groups.ab. 25 22 and 24 26 22 and 23
Note	Search for RCTs (line 25) and observational studies (line 26) regarding RQ6

Date	4-12-2014
Database	Embase Classic + Embase 1947 to current
Search Strategy	1 *neoplasm/ 2 *carcinoma/ 3 exp *larynx/ 4 exp *hypopharynx/ 5 exp *oropharynx/ 6 3 or 4 or 5 7 1 or 2 8 6 and 7 9 exp *larynx tumor/ 10 exp *hypopharynx tumor/ 11 exp *oropharynx tumor/ 12 9 or 10 or 11 13 ((cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*) adj5 (laryngopharyn* or laryn* or hypopharyn* or oropharyn* or glottic or epiglottic or subglottic or supraglottic)).ti,ab. 14 8 or 12 or 13 15 exp *tumor recurrence/ 16 ((locoregional$ or local$) adj5 recurren$).ti,ab. 17 (second* adj3 primar*).ti,ab. 18 15 or 16 or 17 19 14 and 18 20 limit 19 to yr="2004 -Current" 21 salvage.ti,ab,kw,hw. 22 20 and 21 23 crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/ or crossover$.ti,ab,ot. or cross over$.ti,ab,ot. or placebo$.ti,ab,ot. or (doubl$ adj blind$).ti,ab,ot. or allocat$.ti,ab,ot. or random$.ti,ab,ab. or trial$.ti. 24 Clinical study/ or Case control study.mp. or Family study/ or Longitudinal study/ or Retrospective study/ or (Prospective study/ not Randomized controlled trials/) or Cohort analysis/ or (Cohort adj (study or studies)).mp. or (Case control adj (study or studies)).tw. or (follow up adj (study or studies)).tw. or (observational adj (study or studies)).tw. or (epidemiologic$ adj (study or studies)).tw. or (cross sectional adj (study or studies)).tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] 25 22 and 23 26 22 and 24
Note	Search for RCTs (line 25) and observational studies (line 26) regarding RQ6

Date	4-12-2014	
Database	CENTRAL	
Search Strategy	#1	Head and Neck Neoplasms:MH
	#2	Neoplasms:MH
	#3	Carcinoma:MH
	#4	head and neck cancer:EH
	#5	neoplasm:EH
	#6	carcinoma:EH
	#7	(cancer* or tumour* or tumor* or neoplas* or malignan* or carcinoma* or metatasta*):MH,EH,KY,KW,TI,AB
	#8	laryngopharyn*:MH,EH,KY,KW,TI,AB
	#9	larynx*:MH,EH,KY,KW,TI,AB
	#10	hypopharyn*:MH,EH,KY,KW,TI,AB
	#11	oropharyn*:MH,EH,KY,KW,TI,AB
	#12	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7
	#13	#8 OR #9
	#14	Laryngeal Neoplasms:MH OR larynx tumor:EH
	#15	Hypopharyngeal Neoplasms:MH OR hypopharynx tumor:EH
	#16	#12 AND #13 OR #14
	#17	#12 AND #10 OR #15
	#18	#12 AND #11 OR #16
	#19	(glottis or supraglottis or epiglottis or subglottis):MH,EH,KY,KW,TI,AB
	#20	#12 AND #19
	#21	#16 OR #17 OR #18 OR #20
	#22	Recurrence:mh,eh,ti,ab,kw
	#23	(second* adj3 primar*):ti,ab
	#24	((locoregional* or local*) adj5 recurren*):ti,ab
	#25	#22 OR #23 OR #24
	#26	#21 AND #25
	#27	salvage:eh,mh,ti,ab,kw
	#28	#26 AND #27
Note	Search for RCTs regarding RQ6	

2.3.7. RQ7: Altered fractionation radiotherapy versus standard radiotherapy

See chapter 0.

3. QUALITY APPRAISAL

3.1. Quality appraisal tools

3.1.1. Guidelines

The AGREE II evaluation score was used to critically appraise guidelines retrieved (Table 2).

Table 2 – AGREE II instrument

Critical appraisal of clinical practice guidelines - AGREE II
Domain 1. Scope and Purpose
1. The overall objective(s) of the guideline is (are) specifically described.
2. The health question(s) covered by the guideline is (are) specifically described.
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.
Domain 2. Stakeholder Involvement
4. The guideline development group includes individuals from all the relevant professional groups.
5. The views and preferences of the target population (patients, public, etc.) have been sought.
6. The target users of the guideline are clearly defined.
Domain 3. Rigour of Development
7. Systematic methods were used to search for evidence.
8. The criteria for selecting the evidence are clearly described.
9. The strengths and limitations of the body of evidence are clearly described.
10. The methods for formulating the recommendations are clearly described.
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.
12. There is an explicit link between the recommendations and the supporting evidence.
13. The guideline has been externally reviewed by experts prior to its publication.
14. A procedure for updating the guideline is provided.
Domain 4. Clarity of Presentation
15. The recommendations are specific and unambiguous.
16. The different options for management of the condition or health issue are clearly presented.
17. Key recommendations are easily identifiable.

Critical appraisal of clinical practice guidelines - AGREE II
Domain 5. Applicability
18. The guideline describes facilitators and barriers to its application.
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.
20. The potential resource implications of applying the recommendations have been considered.
21. The guideline presents monitoring and/ or auditing criteria.
Domain 6. Editorial Independence
22. The views of the funding body have not influenced the content of the guideline.
23. Competing interests of guideline development group members have been recorded and addressed.

3.1.2. Systematic reviews

AMSTAR criteria were used to assess systematic reviews (Table 3).

Table 3 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

3.1.3. Diagnostic accuracy studies

The quality assessment tool used for the quality assessment of diagnostic accuracy studies was QUADAS 2 Tool (Table 4).

Table 4 – The QUADAS tool

Domain 1: Patient selection	
A. Risk of bias	
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 2: Index test(s) ***(if more than 1 index test was used, please complete for each test)***	
A. Risk of bias	
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear

Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 3: Reference standard	
A. Risk of bias	
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR
B. Concerns regarding applicability	
Is there concern that the target condition as defined by the reference standard does not match the review question?	CONCERN: LOW/HIGH/UNCLEAR
Domain 4: Flow and timing	
A. Risk of bias	
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear
• **Did patients receive the same reference standard?**	Yes/No/Unclear
• **Were all patients included in the analysis?**	Yes/No/Unclear
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR

3.1.4. Primary studies for therapeutic interventions

To assess risk of bias of randomised controlled trials, we used Cochrane Collaboration's tool (Table 5). For the assessment of the quality of comparative observational studies the Cochrane Collaboration's tool for assessing risk of bias was used as well, but with the addition of two extra items that account for the potential bias due to the selection of the study cohorts or the lack of randomisation: 'Concurrency of the intervention and comparator group' and 'Comparability of the intervention and comparator group'. For the first item low risk of bias was assigned if the participants in the intervention and comparator group were enrolled and followed-up concurrently (i.e. in parallel). For the second item low risk of bias was assigned in case of a matched study design and/or appropriate adjustment for confounders in the analysis.

Table 5 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
Blinding of participants and personnel Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
Blinding of outcome assessment Assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		

Domain	Support for judgement	Review authors' judgement
Incomplete outcome data Assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

3.2. Guidelines selection and quality appraisal

The screening of the **guidelines** was performed on title and abstract by one researcher (RL). Eighteen potentially relevant guidelines were selected. These 18 guidelines were appraised with the AGREE II instrument by two researchers independently (RL and JV) (Table 6). Disagreement was solved through discussion.

Table 6 – AGREE scores of identified guidelines

Source	Title	Standardised Score						Final Appraisal
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence	
ACR 2010	Appropriateness Criteria® local-regional therapy for resectable oropharyngeal squamous cell carcinomas	36%	28%	27%	36%	0%	17%	Exclude
ACR 2011	Appropriateness Criteria® ipsilateral radiation for squamous cell carcinoma of the tonsil	36%	28%	27%	36%	0%	8%	Exclude
CCO 2009	The Management of Head and Neck Cancer in Ontario	56%	42%	45%	78%	4%	100%	Exclude
CCO 2011	Epidermal Growth Factor Receptor (EGFR) Targeted Therapy in Stage III and IV Head and Neck Cancer	67%	22%	68%	78%	13%	88%	Include
CCO 2011	The role of IMRT in head & neck cancer	78%	44%	63%	81%	17%	100%	Include
CCO 2012	PET Imaging in Head and Neck Cancer	94%	22%	68%	56%	0%	50%	Include
CCO 2012	The Role of Endolaryngeal Surgery (With or Without Laser) versus Radiotherapy in the Management of Early (T1) Glottic Cancer	89%	44%	58%	83%	13%	100%	Include
DKG 2012	Diagnosis and treatment of oral cavity cancer	83%	78%	65%	92%	25%	96%	Include
EHNS-ESMO-ESTRO 2010	Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up	25%	8%	10%	17%	0%	25%	Exclude
ESMO 2009	Squamous cell carcinoma of the head and neck	25%	0%	10%	8%	0%	25%	Exclude
GEC-ESTRO 2009	GEC-ESTRO recommendations for brachytherapy for head and neck squamous cell carcinomas	28%	11%	10%	6%	0%	0%	Exclude
IKNL 2010	Hypofarynxcarcinoom	72%	78%	65%	72%	27%	21%	Include

Source	Title	Standardised Score						Final Appraisal
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence	
IKNL 2010	Larynxcarcinoom	25%	47%	19%	61%	21%	0%	Exclude
INCA 2009	Cancer des voies aérodigestives supérieures	44%	47%	11%	33%	4%	0%	Exclude
NCCN 2011	Head and neck cancers	53%	25%	18%	78%	25%	50%	Exclude
Bardet et al. 2009	Locally advanced head and neck cancers: recommendations of an expert panel and perspectives for the use of TPF regimen (docetaxel, cisplatin and fluoro-uracil) as induction therapy	31%	28%	5%	6%	0%	0%	Exclude
ACR 2010	Appropriateness Criteria® retreatment of recurrent head and neck cancer after prior definitive radiation	31%	28%	26%	33%	0%	8%	Exclude
SEOM 2011	SEOM clinical guidelines for the treatment of head and neck cancer	19%	0%	3%	53%	15%	50%	Exclude

3.3. Study selection and quality appraisal

3.3.1. RQ1-6: Systematic reviews

On August 8, 2014 a search was performed to identify SRs regarding imaging modalities and interventions for treatment of laryngeal, oropharyngeal and hypopharyngeal cancer (all RQs). MEDLINE, Embase and the Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database) were searched from January 2008 onwards. In addition, the review lists of the Cochrane Oral Health Group (COHG) and the Cochrane Ear Nose Throat Group (ENT) were browsed for relevant reviews. Members of the KCE GDG put forward relevant systematic reviews.

In total, 407 potentially relevant references were identified from databases and three from other sources (Figure 1). After deduplication 256 references remained. Based on title and abstract 185 references were excluded. Of the 71 remaining references 60 were excluded with reason. Eleven reviews were included (Abdurehim 2012;Almeida 2014;Bessell 2011;Dey 2002;Francis 2014;Furness 2011;Goudakos 2009;Liao 2012;Loon 2012;McLeod 2009;Wu 2012) (Table 7) and 62 were excluded with reason (Table 8). One of the included systematic reviews, the review of Bessell 2011 was included for RQ2, RQ3 and RQ5.

Figure 1 – Study flow of selection of SRs regarding RQ1-6

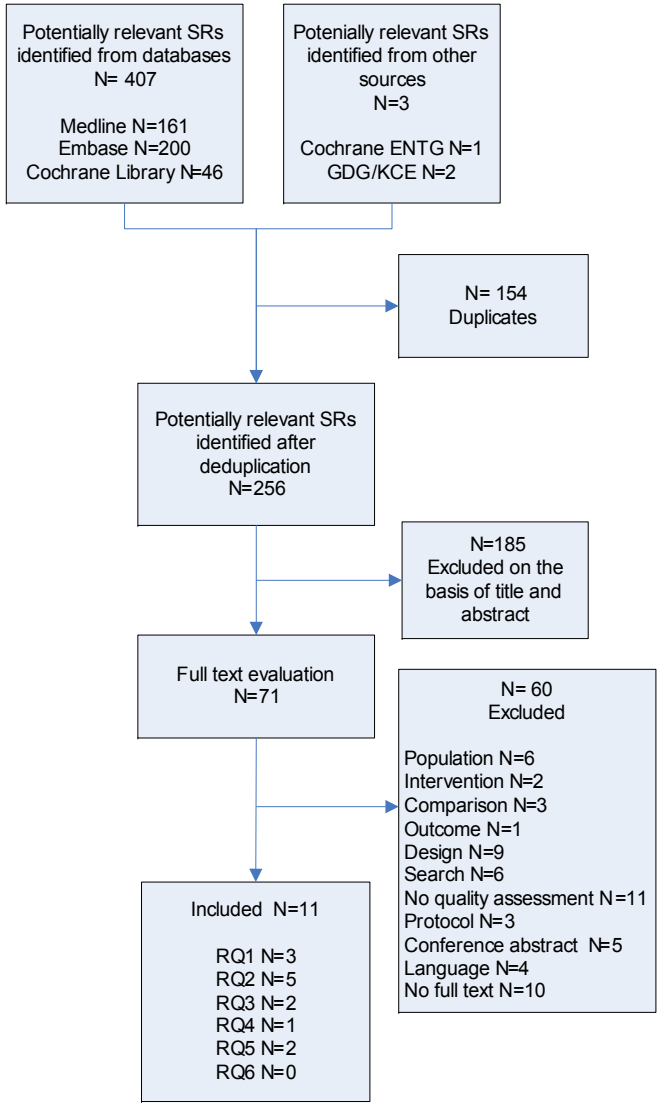


Table 7 – Included SRs regarding RQ1-6 (n=11)

Reference	Interventions	RQ
Abdurehim 2012	Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of T1a glottic cancer	2
Almeida 2014	Transoral robotic surgery versus intensity modulated radiotherapy for early oropharynx cancer	2
Bessell 2011	Surgical treatment for the treatment of oral and oropharyngeal cancers	2,3,5
Dey 2002	Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer	2
Francis 2014	Interventions for the treatment of T4a laryngeal cancer	3
Furness 2011	Chemotherapy for the treatment of oral cavity and oropharyngeal cancer	4
Goudakos 2009	Neck dissection versus another therapeutic treatment (radiotherapy, combined therapy, 'wait and see' policy) patients with supraglottic laryngeal carcinoma (SGLC) and clinically negative neck (cN0)	5
Liao 2012	Different imaging modalities, including CT, MRI, PET and US, in clinically N0 head and neck cancer patients	1
Van Loon 2011	Radiotherapy or laser surgery in early glottic carcinoma	2
McLeod 2007	Role of chest ct in staging of oropharyngeal cancer	1
Wu 2012	Magnetic resonance imaging (MRI) in detecting lymph node metastases in patients with head and neck squamous cell carcinoma	1

Table 8 – Excluded SRs regarding RQ1-6 (n=61, of which n=1 (Dey 2002) is excluded for RQ3, but included for RQ2)

Reference	Reason for exclusion	RQ
Aarts 2011	No relevant intervention and comparison	6
Al-Saleh 2012	No full text available	No specific RQ
Arora 2011	No quality assessment	2
Baujat 2010	Population: postoperative radiotherapy excluded	4
Blanchard 2011	No quality assessment	4
Bogaardt 2013	Conference abstract	4
Bonilla-Velez 2013	Non-systematic review	No specific RQ
Brouwer 2008	Population: prior radiotherapy	1
Brown 2012	Population: oral cavity cancer; No quality assessment of included studies	4
Chan 2013	Protocol	4
Clayburgh 2013	Non-systematic review (no search described)	2,3,5
Cote 2007	No full text available	No specific RQ
Cripps 2010	Guideline, no quality assessment	4,6
Denaro 2014	Searched one database	3
Dey 2002	Population	3
Diaz de Cerio 2013	No systematic review	2
Dowthwaite 2012	Searched one database ("pubmed and medline"), no quality assessment	2
Feng 2010	Language	No specific RQ
Feng 2011	No reproducible quality assessment	2
Folz 2008	Historical overview, no relevant comparison	No specific RQ
Glenny 2010	Intervention (postoperative radiotherapy excluded)	4
Guha 2012	No full text available	No specific RQ
Guigay 2011	No full text available	No specific RQ
Herranz 2007	Language	No specific RQ
Higgins 2009	No full text available	No specific RQ
Higgins 2011	Cost utility analysis based on included SR of Dey 2002	2
Hotte 2008	No full text available	No specific RQ
Howard 2014	Protocol	2
Huang 2011	No full text available	No specific RQ
Hutcheson 2011	Searched one database; no methodological quality assessment; non-comparative studies included; population not defined	2
Kelly 2014	No reproducible quality assessment	2
Kreeft 2009	Population >T2	2

Reference	Reason for exclusion	RQ
Lagha 2013	No quality assessment	3
LeBon 2009	Population not relevant	6
Marur 2008	No full text available	No specific RQ
Mifsud 2014	No relevant population (melanoma instead of head and neck cancer)	No specific RQ
Moergel 2011	One database searched	4
Moore 2012	No systematic review	No specific RQ
Nakayama 2012	Non-systematic review	3
Nijdam 2008	No systematic review (primary study)	2,3
O'hara 2013	No reproducible quality assessment	2
Oliver 2007	Protocol of (excluded) systematic review of Glenny 2010	4
Paleri 2008	No quality assessment, only non-comparative studies identified	5
Paleri 2011	Comparison	6
Pavitt 2007	No full text available	No specific RQ
Qu 2012	Language	2
Ramaekers 2010	Conference abstract of review for which one database was searched and without quality assessment	4
Ramakrishnan 2014	Comparison	6
Rigby 2011	No full text available	No specific RQ
Rudolph 2011	One database searched; no quality assessment	No specific RQ
Sayles 2014	No outcomes of interest.	2,4,6
Skladowski 2014	Conference abstract	4
Spielmann 2010	No quality assessment	2
Thankappan 2012	One database searched, no quality assessment	No specific RQ
Thomas 2012	No comparison, searched for case series only	2
Tulunay-Ugur 2013	Conference abstract (of chart review; no systematic review)	No specific RQ
Turner 2013	No quality assessment	No specific RQ
van de Water 2011	No quality assessment	4
van der Walde 2013	Conference abstract	4
Wang 2012	Language	2
Yoo 2013	No reproducible quality assessment	2

Quality appraisal

Table 9 shows the results of the quality assessment for the included systematic reviews (SRs) for RQ2, 3 and 5. Only one of the SRs scored positively on all AMSTAR items, except for one item that was not applicable (Bessell 2011). Looking at the three key domains ('Was a comprehensive literature search performed'?, 'Was the scientific quality of the included studies assessed and documented'? and 'Were the methods used to combine the findings of studies appropriate'?), seven SRs scored positively on all three key domains (Abdurehim 2012;Almeida 2014;Bessell 2011;Furness 2011;Liao 2012;Loon 2012;Wu 2012). One SR scored positively on two of the three key items and N/A on the third item (Dey 2002). The remaining SRs are considered as of low quality.

Table 9 – Methodological quality of the included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion criterion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Abdurehim 2012	?	-	+	-	+	+	+	+	+	-	-
Almeida	?	+	+	+	-	-	+	+	+	-	-
Bessell 2011	+	+	+	+	+	+	+	+	+	NA*	+
Dey 2002	+	-	+	+	+	+	+	+	NA	NA*	-
Francis 2014	+	+	+	-	-	+	-	-	+	-	-
Furness 2011	+	+	+	+	+	+	+	+	+	+	+
Goudakos 2009	?	+	+	-	-	+	-	+	NA	NA*	+
Liao 2012	?	+	+	-	-	-	+	-	+	-	-
Van Loon 2011	?	+	+	-	-	-	+	+	+	-	-
McLeod 2007	?	?	+	+	-	-	-	-	+	+	-
Wu 2012	?	+	+	-	+	+	+	+	+	+	-

NA=not applicable
**less than 10 included studies*

3.3.2. RQ1: What is the effectiveness and/or diagnostic outcomes of locoregional staging (i.e. T- and N-staging) with MRI compared to CT in patients with head and neck squamous cell carcinoma

Selection of primary studies

On November 24th, 2014 a search was performed to identify RCTs comparing the effectiveness of locoregional staging (i.e. T- and N-staging) with MRI versus CT (RQ1) for patients with oropharyngeal, hypopharyngeal and laryngealcancer. MEDLINE, Embase and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from 2004 onwards.

In total, 70 potentially relevant references were identified from databases (Figure 2). After deduplication 62 references remained. Based on title and abstract 55 references were excluded. The remaining seven references were excluded with reason (Table 10). No RCTs were included for this research question (Figure 2).

Figure 2 – Study flow of selection of primary studies regarding RQ1

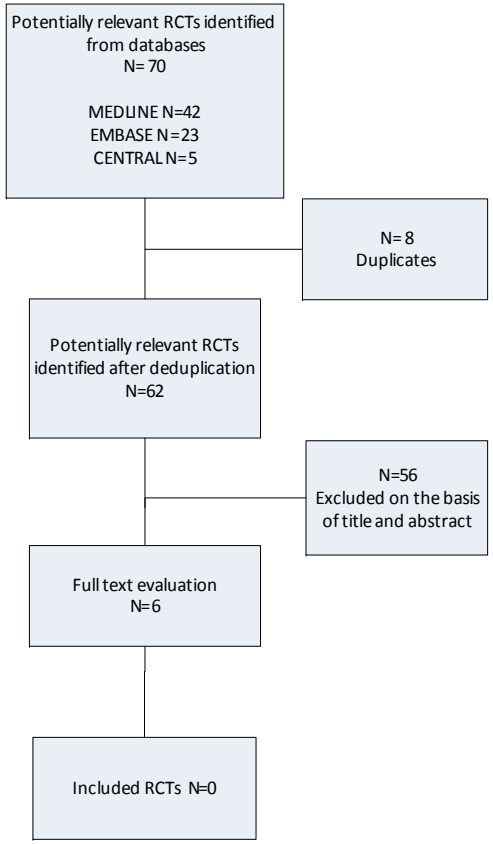


Table 10 – Excluded RCTs regarding RQ 1 (n=6), based on full-text evaluation

Reference	Reason for exclusion
Chikamatsu 2004	Population
Connell 2007	Type of diagnostic modalities: FDG-PET/CT versus conventional modalities (CT or MRI)
Eiber 2011	Population (combination of head and neck cancer, breast cancer, ovarian cancer, thyroid cancer, non-Hodgkin's lymphoma, melanoma, etc) and outcome.
Geets 2005	Outcome: not tumour staging, but pretherapeutic tumour volume delineation
Herborn 2005	Population and type of diagnostic modalities
Yoshimoto 2005	Excluded on comparator test (CT)

Selection of observational studies

On November 24th, 2014 a search was performed to identify observational studies comparing the clinical effectiveness of locoregional staging (i.e. T- and N-staging) with MRI versus CT for patients with oropharyngeal, hypopharyngeal and laryngealcancer. MEDLINE and Embase were searched from 2004 onwards. For the diagnostic outcomes MEDLINE and Embase were searched from January 2011 (to update the systematic review of Wu 2012) onwards.

In total, 897 potentially relevant references were identified from databases (Figure 3). After deduplication 820 references remained. Based on title and abstract 758 references were excluded. Of the remaining 62 references, 4 were included (Table 12) and 58 were excluded with reason (Figure 3 and Table 11).

Figure 3 – Study flow of selection of observational studies regarding RQ1

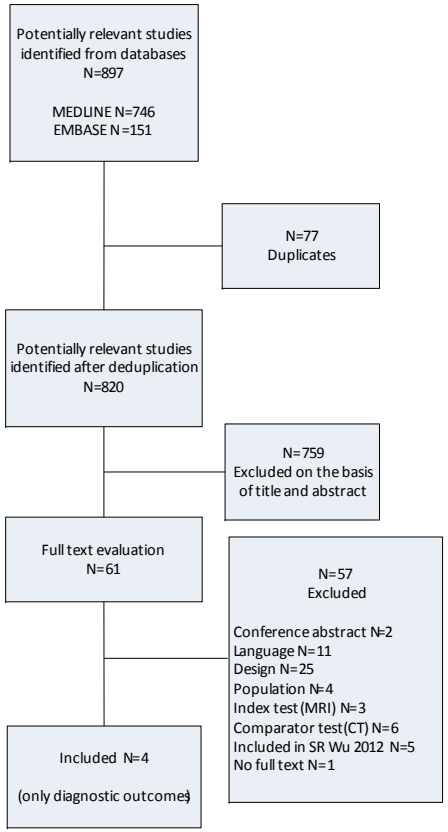


Table 11 – Excluded observational studies regarding research question 4 (n=57)

Reference	Reason
Ahmad 2008	Excluded on design
Akoglu 2005	Included in SR Wu 2012 (included for RQ1)
Ala Eddine 2008	Excluded on language
Allen 2012	Excluded on design
Anand 2007	Excluded on index test (MRI)
Babin 2004	Excluded on language
Becker 2009	Excluded on language
Bertrand 2010	Excluded on language
Blitz 2008	Excluded on design
Brouwer 2004	Included in SR Wu 2012 (included for RQ1)
Bundschuh 2012	Conference abstract
Curtin 2004	Excluded on design
Curtin 2005	Excluded on design
Dammann 2005	Excluded on design
Dammann 2014	Excluded on design
de Bondt 2007	Excluded on design (SR)
de Souza Figueiredo 2012	Excluded on population
Dirix 2010	Included in SR Wu 2012 (included for RQ1)
Fahimi 2013	Excluded on design
Guimaraes 2013	Excluded on design
Hafidh 2006	Included in SR Wu 2012 (included for RQ1)
Hermans 2005	Excluded on design
Holzapfel 2009	Excluded on comparator test (CT)
Hudgins 2013	Excluded on design
Joshi 2012	Excluded on design
Kim 2008	Excluded on index test (MRI)
Kolk 2011	Conference abstract
Kolk 2014	Excluded on population
Krabbe 2008	Excluded on index test (MRI)
Krestan 2006	Excluded on design
Kubiessa 2014	Excluded on population
Kuhn 2014	Excluded on comparator test (CT)
Kuno 2014	Excluded on design

Reference	Reason
Kurooka 2009	Excluded on comparator test (CT)
Lewis-Jones 2005	No full-text available
Lim 2011	Excluded on comparator test (CT)
Lodder 2013	Excluded on comparator test (CT)
Marcy 2011	Excluded on design
McCabe 2005	Excluded on design
Moulding 2004	Excluded on design
Peters 2012	Excluded on comparator test (CT)
Petrou 2008	Excluded on design
Prazenica 2006	Excluded on language
Prestwich 2010	Excluded on design
Reimann 2013	Excluded on language
Reimann 2013	Excluded on language
Romann 2011	Excluded on language
Schwartz 2008	Excluded on design
Vergez 2013	Excluded on design
Vikulova 2012	Excluded on language
Vogl 2007	Excluded on design
Wasniewski 2007	Excluded on language
Wu 2012	Excluded on design (SR)
Wycliffe 2007	Excluded on design
Xue 2009	Excluded on language
Yoon 2009	Included in SR Wu 2012 (included for RQ1)
Zbaren 2007	Excluded on population

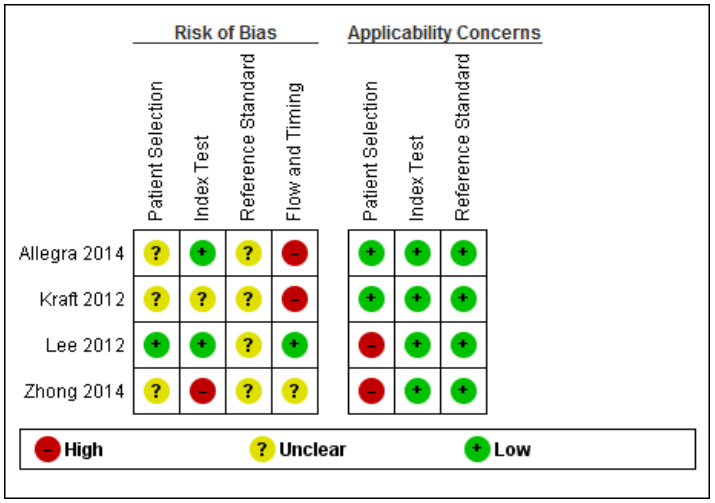
Table 12 – Included diagnostic accuracy studies regarding RQ1 (n=4)

Reference	Diagnostic modalities
Allegra 2014	Early glottic cancer: role of MRI in the preoperative staging compared with CT
Kraft 2013	Clinical value of endosonography in the assessment of laryngeal cancer where MRI and CT are compared
Lee 2012	Type of diagnostic modalities (besides PET/CT also regular CT)
Zhong 2014	The diagnostic value of cervical lymph node metastasis in head and neck squamous carcinoma by using diffusion-weighted magnetic resonance imaging and computed tomography perfusion

Quality appraisal of selected observational studies

The results of the risk of bias assessment and concerns about applicability of the results (using the QUADAS-2 checklist) for the four included studies about diagnostic outcomes for RQ1 are presented in Figure 4. Most studies scored an unclear / high risk of bias, except for Lee 2012 that scored a low risk of bias. There was uncertainty for most studies about the patient selection (random sampling or consecutive enrolment) and whether the reference standard (pathology) results were interpreted without knowledge of the results of the imaging tests (blinding). Risk of bias due to flow and timing was also scored high or unclear in three studies (Allegra 2014; Kraft 2012; Zhong 2014). In these studies, it was unclear why patients were excluded from the analysis or whether the interval between index tests and reference test was appropriate. Concerns about the applicability of the results was scored as low for two studies (Allegra 2014; Kraft 2014). In the other two studies, there were concerns about the applicability because of the mixed HNSCC patient population (Zhong 2014; Lee 2012).

Figure 4 – Results of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS) checklist of the included studies regarding RQ1



3.3.3. RQ2: What is the clinical effectiveness of surgery for patients with early oropharyngeal, hypopharyngeal and laryngealcancer?

a. Surgery versus non-surgery

b. Function-sparing surgery versus extensive surgery

Selection of RCTs

On September 24th, 2014 a search was performed to identify RCTs regarding surgical interventions for treatment of laryngeal, oropharyngeal and hypopharyngeal cancer (RQ 2, 3 and 5). The specialised register of trials of the Cochrane Ear, Nose and Throat (ENT) disorders group was searched from 2004 onwards. In this Cochrane ENT database RCTs relevant for ear, nose and throat disorders from MEDLINE and Embase, as well as relevant RCTs identified by handsearching, are registered. Further RCT's were searched in the Cochrane Central Register of Controlled Trials (CENTRAL). An additional search for glottis laryngeal cancer was carried out to identify those specific searches that might have been missed with the initial studies

In total, 580 potentially relevant references were identified from databases (Figure 5). After deduplication 538 references remained. Based on title and abstract 441 references were excluded. Of the remaining 97 RCTs, seven were included (Beauvillain 1997;Bhalavat 2003;Department of Veterans Affairs Laryngeal Cancer 1991;Lefebvre 1996;Lefebvre 2012;Terrell 1998;Brazilian Head and Neck Cancer Study Group 1999) and 90 were excluded with reason (Table 13).

For research question 2 no RCTs were included.

Figure 5 – Study flow of selection of RCTs regarding RQ 2, 3 and 5

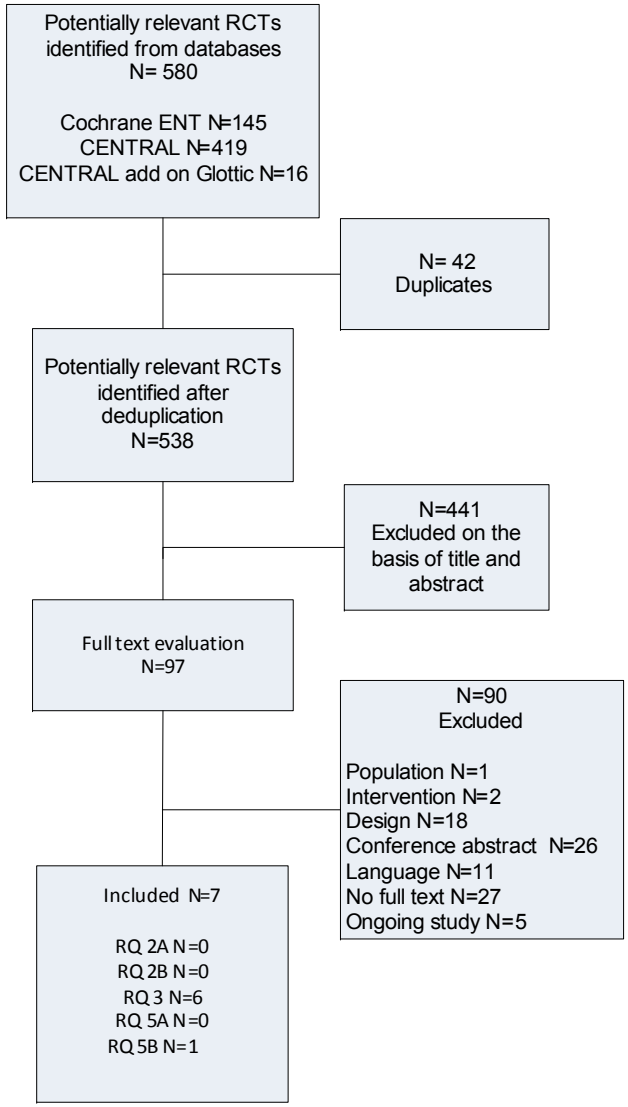


Table 13 – Excluded RCTs regarding RQ 2, 3 and 5 (n=90)

Reference	Reason for exclusion
Abo-Faries 2010	No PDF
ACTRN12612000443897 2012	Ongoing study
Airoldi 2010	Conference abstract
Appold 1999	No PDF
Boscolo-Rizzo 2009	Excluded on design
Bosl 1991	No PDF
Ceylan 2003	Excluded on language
Dunn 2012	Conference abstract
Düring 1987	No PDF
Eckel 1995	No PDF
El Samaa 2003	Conference abstract
Finizia 2000	Conference abstract
Garza 2004	Conference abstract
Garzaro 2011	Conference abstract
Gryczynski 1995	Excluded on language
Gultekin 2011	Excluded on design
Hagen 1999	No PDF
Hamid 2004	Conference abstract
Hamid 2005	Conference abstract
Hanna 2000	Conference abstract
Hillman 1998a	No PDF
Hillman 1998b	No PDF
Hinerman 2002	Excluded on design
Hintz 1979	No PDF
Hong 1987	Conference abstract
Huang 2010	Excluded on design
ISRCTN13735240 2007	Ongoing study
Jacobs 1990	Excluded on intervention
Jia 2004	Excluded on language
Jones 2004	Excluded on design
Kim 2010	Excluded on design
Kramer 1987	No PDF
Krengli 2004	Excluded on design

Reference	Reason for exclusion
Lefebvre 1994	Conference abstract
Lefebvre 2004a	Conference abstract
Lefebvre 2004b	Conference abstract
Lefebvre 2011	Conference abstract
Levitt 1971	Excluded on design
Li 2000 {Li, 2000 #130}	Excluded on language
Lippert 1999	No PDF
Lord 1973	No PDF
Mahe 1995	Conference abstract
Mantovani 1996	Conference abstract
Mantovani 1996	No PDF
Maor 2002	Conference abstract
Mazeron 1992	No PDF
McCaul 2012a	Excluded on design
McCaul 2012b	Excluded on design
McCaul 2013	Conference abstract
McMahon 2010	Excluded on design
More 2013a	Excluded on design
More 2013b	Excluded on design
More 2013c	Excluded on design
Namyslowski 1997	Excluded on language
NCT00128817 2005	Ongoing study
NCT01590355 2012	Ongoing study
NCT01687413 2013	Ongoing study
Nguyen 1996	Excluded on design
Nichols 2013	Excluded on design
Ogol'tsova 1990a	Excluded on language
Ogol'tsova 1990b	Excluded on language
Ogol'tsova 1990c	Excluded on language
Olthoff 2006	Excluded on design
Pandjatcharam 2011	Conference abstract
Pearlman 1985	Excluded on intervention
Pen Yuan 2000	Conference abstract
Pericot 2000	No PDF

Reference	Reason for exclusion
Profant 2004	Conference abstract
Racadot 2004	No PDF
Richard 1998	No PDF
Robertson 1998	Excluded on population
Rogowska 1996	Excluded on language
Salami 2008	No PDF
Schuller 1989	No PDF
Shik Kim 2012	Conference abstract
Sjogren 2008	No PDF
Skladowski 2000	Excluded on language
Song 2013	Excluded on language
Soo 2004	Conference abstract
Soo 2005	No PDF
Spaulding 1994	No PDF
Su 2000	Conference abstract
Su 2002	No PDF
Veyseller 2010	No PDF
Vignoud 1991	Conference abstract
von Ilberg 1974	No PDF
Wolf 1991	No PDF
Wolf 1992	No PDF
Wolf 1993	Conference abstract
Yiotakis 2003	Excluded on design

Selection of observational studies

On October 10th, 2014 a search was performed to identify observational studies comparing surgery and non-surgical interventions (RQ2A) or observational studies comparing function-sparing surgery and extensive surgery (RQ2B) in patients with early stage orhopharyngeal, hypopharyngeal or laryngeal cancer. MEDLINE and Embase were searched from 2004 onwards.

In total, 630 potential relevant references were identified (420 In MEDLINE and 210 in Embase) (Figure 6). After de-duplication 474 references remained. Based on title and abstract 446 papers were excluded. Of the remaining 28 studies, 10 studies were included (nine for RQ2A [Aydil 2013;Dinapoli 2010;Jotic 2012;Luo 2012;Milovanovic 2013;O'Hara 2011;Remmelts 2013;Swisher-Mcclure 2014;Gogh 2012], Table 14, and one for RQ2B [Karatzanis 2010], Table 15) and 18 were excluded (Table 16).

Figure 6 – Study flow of selection of observational studies regarding RQ 2

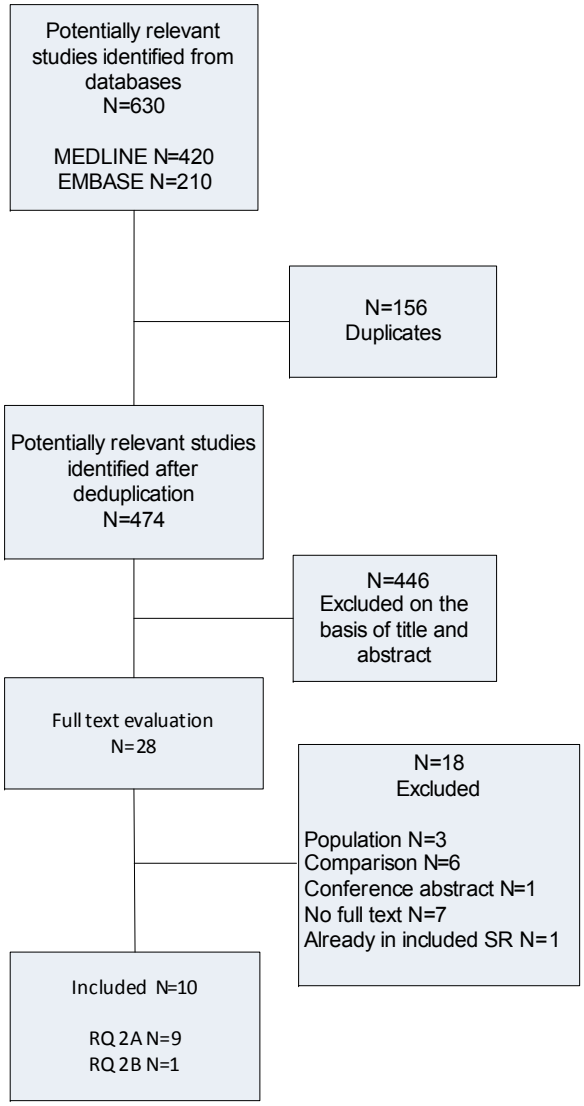


Table 14 – Included observational studies regarding RQ 2a (n=9)

Reference	Interventions
Aydil 2013	Surgery (endolaryngeal laser surgery or open partial laryngectomy) versus radiotherapy
Dinapoli 2010	CO2 laser surgery versus radiotherapy
Jotic 2012	CO2 laser versus cordectomy through laryngofissure versus radiotherapy
Luo 2012	Transoral laser microsurgery versus radiation therapy
Milovanovic 2013	Transoral laser microsurgery versus cordectomy through laryngofissure versus radiotherapy
O'Hara 2011	Surgical treatments (included both transoral resections with primary closure, secondary intention healing, local flaps, or transcervical resections) versus non-surgical treatment (RT, chemotherapy or both)
Remmelts 2013	Laser surgery versus radiotherapy
Swisher 2014	Surgery versus external beam radiation therapy
Van Gogh 2012	Endoscopic laser surgery (Sharplan CO2-laser) versus radiotherapy

Table 15 – Included observational study regarding research question 2b (n=1)

Reference	Interventions
Karatzanis 2010	Transoral CO2 laser microsurgery versus horizontal laryngectomy versus total laryngectomy

Table 16 – Excluded observational studies regarding research question 2 (n=18)

Reference	Reason for exclusion
Chun 2010	Excluded on population
de Visscher 2013	Excluded on comparison
Ebisumoto 2011	No PDF available
Iizuka 2011	Excluded on comparison
Kerr 2012	No PDF available
Kitamura 2010	No PDF available
Kujath 2011	No PDF available
Kuo 2012	Excluded on population
Kuo 2013	Excluded on comparison
Milovanovic 2014	Excluded on comparison
Osborn 2011	No PDF available
Petrakos 2012	No PDF available
Roosli 2009	Excluded on population
Sachse 2009	Excluded on comparison
Schrijvers 2009	Excluded already included in used SR
Smith 2012	No PDF available

Reference	Reason for exclusion
Swisher-McClure 2012	Conference abstract
Tomifuji 2013	Excluded on comparison

Quality appraisal of selected observational studies

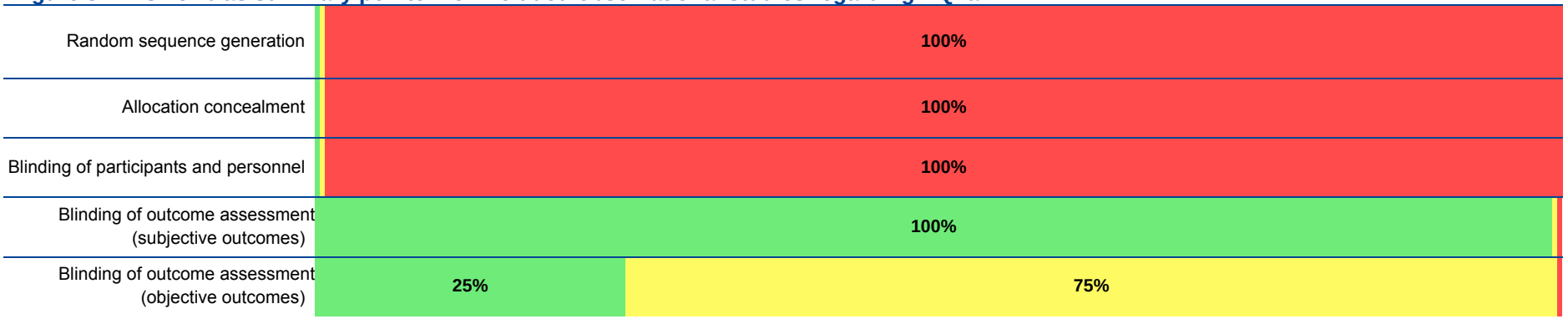
The results of the risk of bias assessment for the nine comparative observational studies for RQ2A are presented Figure 7 and Figure 8, and for the one study for RQ2B in Figure 9. All studies relevant for RQ2A scored a high risk of selection bias and performance bias. Detection bias was judged to be at high risk for subjective outcomes for all studies. For objective outcomes all studies scored a low risk of detection bias. There was uncertainty about attrition bias for most studies, except for the studies of Aydil and Remmelts that scored a low risk (Aydil 2013;Remmelts 2013). Not applicable was scored in case there were no subjective or objective outcomes (Jotic 2012;Luo 2012;O'Hara 2011). Risk of reporting bias was judged to be unclear as there were no study protocols available (not common for observational studies). However, all outcomes mentioned in methods section were reported in the results section. Risk of bias due to nonconcurrency for the intervention and comparator group was scored as low for three studies (Jotic 2012;Luo 2012;O'Hara 2011), high for one study (Dinapoli 2010) and unclear for the remaining five studies. The item 'Comparability of the intervention and comparative group' was scored as unclear or 'high risk' of confounding by indication for six of the nine studies (Aydil 2013;Dinapoli 2010;Jotic 2012;Milovanovic 2013;O'Hara 2011;Remmelts 2013), mostly because details about patient characteristics lacked or tumor stages differed between study groups.

The observational study included for RQ2B was at high risk of selection bias, performance bias and detection bias for subjective outcomes (Karatzanis 2010) There was also concern about the comparability of the study groups. Unclear risk of bias was scored for the items on attrition bias, reporting bias and 'concurrency of the intervention and comparator groups'. Detection bias was judged to be at low risk for objective outcomes and there was no indication of other bias.

Figure 7 – Risk of bias assessment of included observational studies regarding RQ2a

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Aydil (2013)	-	-	-	-	+	+	+	?	?	?	+
Dinapoli (2010)	-	-	-	-	+	?	?	?	-	?	+
Jotic (2012)	-	-	-	-	N/A	?	N/A	?	+	?	+
Luo (2012)	-	-	-	-	N/A	?	N/A	?	+	+	+
Milovanovic (2013)	-	-	-	-	+	?	?	?	?	-	+
O'Hara (2011)	-	-	-	N/A	+	N/A	?	?	+	-	+
Remmelts (2013)	-	-	-	-	+	+	+	?	?	-	+
Swisher-Mcclure (2014)	-	-	-	-	+	?	?	?	?	+	+
van Gogh (2012)	-	-	-	-	+	?	?	?	?	+	+

Figure 8 – Risk of bias summary per item of included observational studies regarding RQ2a



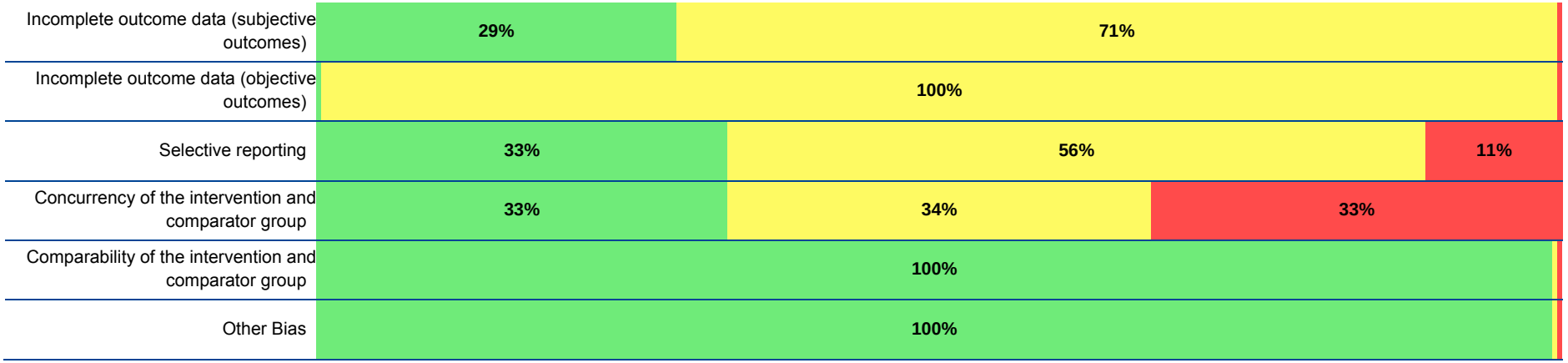


Figure 9 – Risk of bias assessment of included observational study regarding RQ2b

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnell	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Karatzanis (2010)	-	-	-	-	+	?	?	?	?	-	+

3.3.4. RQ3: Surgery versus organ / function preservation strategies

Selection of RCTs

On September 24th, 2014 a search was performed to identify RCTs regarding surgical interventions for treatment of laryngeal, oropharyngeal and hypopharyngeal cancer (RQ 2, 3 and 5). The specialised register of trials of the Cochrane Ear, Nose and Throat (ENT) disorders group was searched from 2004 onwards. In this Cochrane ENT database RCTs relevant for ear, nose and throat disorders from MEDLINE and Embase, as well as relevant RCTs identified by handsearching, are registered. Further RCT's were searched in the Cochrane Central Register of Controlled Trials (CENTRAL). An additional search for glottis laryngeal cancer was carried out to identify those specific searches that might have been missed with the initial studies

In total, 580 potentially relevant references were identified from databases (Figure 5). After deduplication 538 references remained. Based on title and abstract 441 references were excluded. Of the remaining 97 RCTs, seven were included (Beauvillain 1997;Bhalavat 2003;Department of Veterans Affairs Laryngeal Cancer 1991;Lefebvre 1996;Lefebvre 2012;Terrell 1998;Brazilian Head and Neck Cancer Study Group 1999) and 90 were excluded with reason (Table 13).

For RQ 3 six publications were included, concerning four RCTs (Table 17).

Table 17 – Included RCTs regarding RQ 3

Reference	Interventions
Beauvillain 1997	Total laryngopharyngectomy plus unilateral or bilateral radical or conservative lymph node dissection plus postoperative radiotherapy vs radiotherapy with or without salvage surgery
Bhalavat 2003	Radical surgery (total laryngectomy, near-total laryngectomy or laryngo-pharyngectomy with/without modified nodal dissection) followed by postoperative radiation therapy vs radical radiation therapy followed by salvage surgery
Department of Veterans Affairs Laryngeal Cancer Study 1991	Surgery and radiation therapy vs three cycles of chemotherapy (cisplatin and fluorouracil) and radiation therapy
Lefebvre 1996	Total laryngectomy with partial pharyngectomy, radical neck dissection and postoperative irradiation vs larynx-preserving treatment (induction chemotherapy plus definitive, radiation therapy in patients who showed a complete response or surgery in those who did not respond)

Risk of bias assessment of selected RCTs

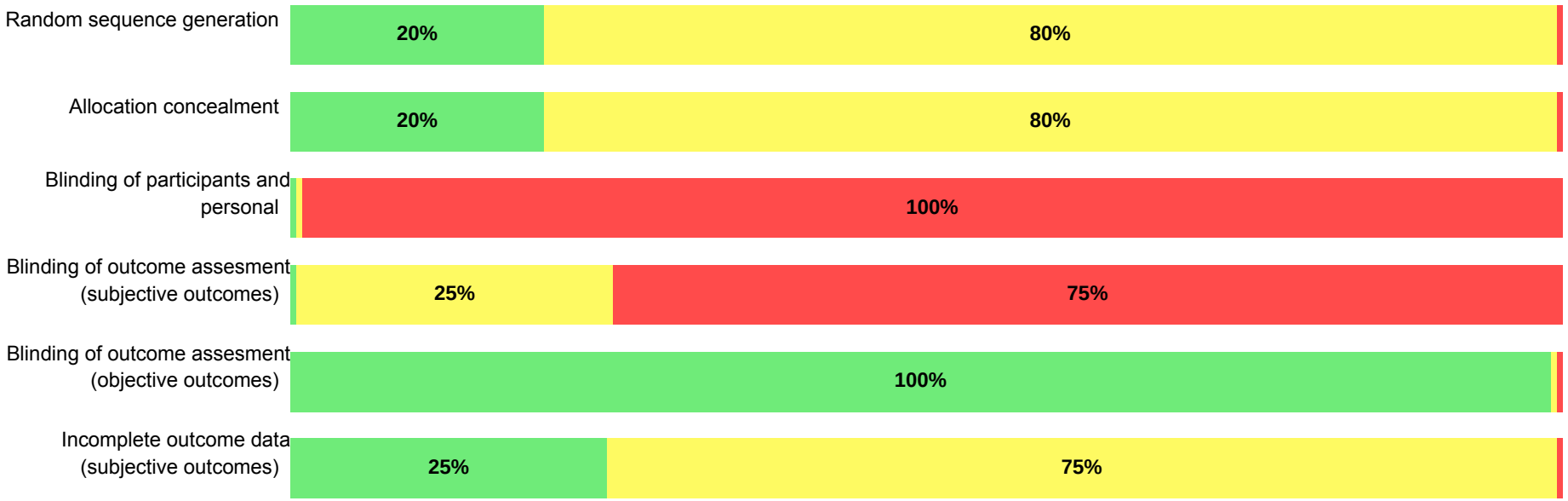
Figure 10 and Figure 11 show the results of the assessment of methodological quality of the RCTs included for RQ3. As the publications of Department of Veterans Affairs and Terell are addressing the same RCT, methodological quality was assessed for both publications together (Department of Veterans Affairs Laryngeal Cancer 1991;Terrell 1998). The same applies to the two publications of Lefebvre (Lefebvre 1996;Lefebvre 2012).

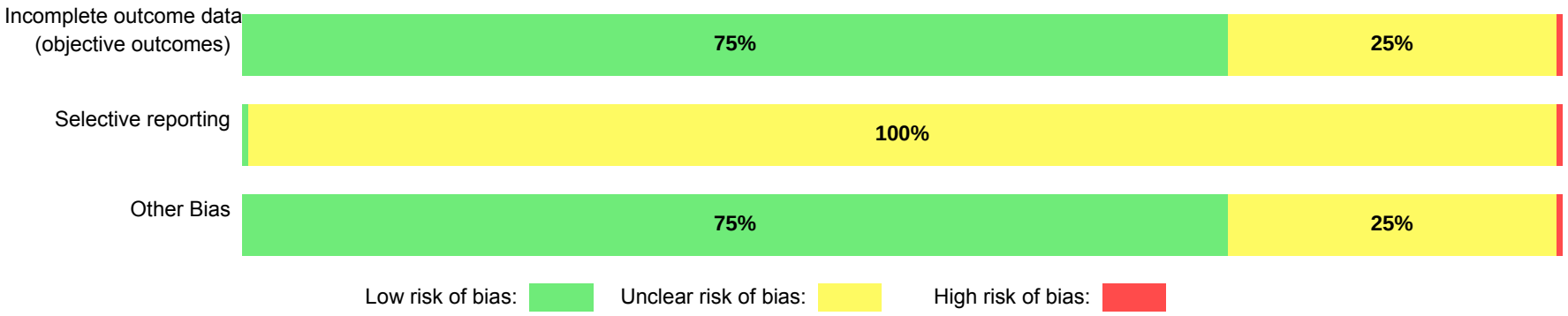
Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), none of the studies were assessed as 'low risk' of bias for all items. Due to insufficient information on randomization and allocation concealment an unclear risk of selection bias was scored for all but one RCT, which scored a low risk (Lefebvre 1996;Lefebvre 2012). Risk of performance bias was high and the risk of reporting bias unclear for all studies. For subjective outcomes there was a high risk of detection bias for all but one study, which scored unclear (Lefebvre 1996;Lefebvre 2012), as well as an unclear risk of attrition bias for all studies, except for the study of Beauvillain which scored low risk (Beauvillain 1997). For objective outcomes there was a low risk of detection bias for all studies and a low risk of attrition bias for all but one study, which was judged to have an unclear risk (Bhalavat 2003).

Figure 10 – Risk of bias assessment of included RCTs regarding RQ3

Short Title	Random sequence generation	Allocation concealment	Blinding of participants and personal	Blinding of outcome assesment (subjective outcomes)	Blinding of outcome assesment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Other Bias
Beauvillain (1997)	?	?	-	-	+	+	+	?	+
Bhalavat (2003)	?	?	-	-	+	?	?	?	?
Department of Veterans (1991) + Terrell 1998	?	?	-	-	+	?	+	?	+
Induction chemotherapy... (1991)	?	?	-	N/A	N/A	N/A	N/A	N/A	N/A
Lefebvre (1996)	+	+	-	?	+	?	+	?	+
Lefebvre (2012)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Terrell (1998)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Figure 11 – Risk of bias summary per item of included RCTs regarding RQ3





Selection of observational studies

On October 10th, 2014 a search was performed to identify observational studies comparing surgery and organ / function preservation strategies in patients with resectable locally-advanced (M0, stage III-IV) orhopharyngeal, hypopharyngeal or laryngeal cancer (RQ3). MEDLINE and Embase were searched from 2004 onwards

In total, 370 potential relevant references were identified (216 In MEDLINE and 154 in Embase) (Figure 12). After de-duplication 263 references remained. Based on title and abstract 255 papers were excluded. Of the remaining eight studies, five studies were included (Boscolo-Rizzo 2009;Boscolo-Rizzo 2011;Kuo 2013;Mowry 2006;O'Connell 2013) (Table 18) and three were excluded (Table 19).

Figure 12 – Study flow of observational studies regarding research question 3

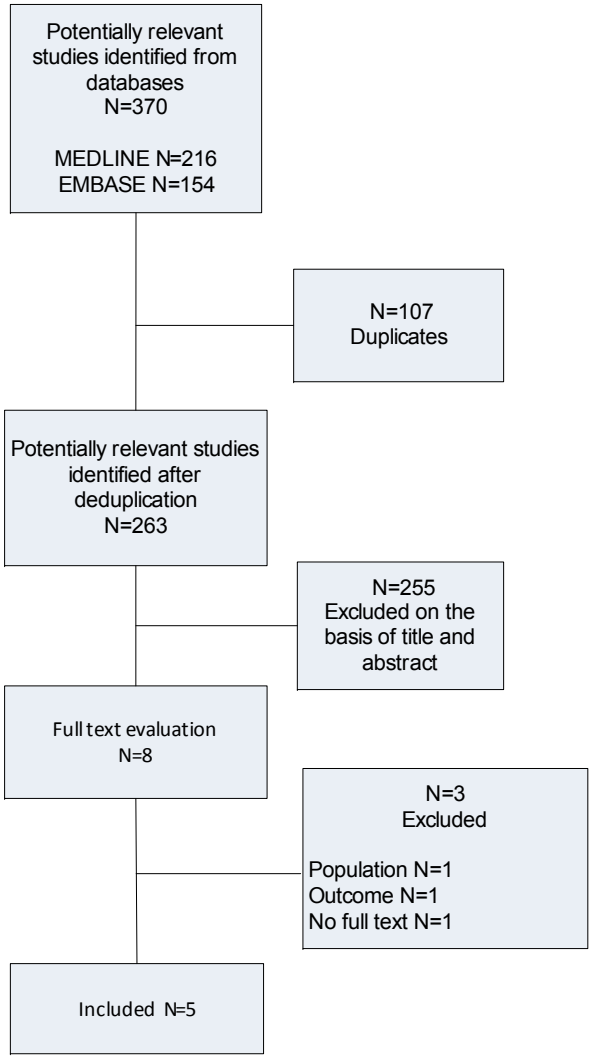


Table 18 – Included observational studies regarding RQ 3 (n=5)

Reference	Interventions
Boscolo-Rizzo 2009	Surgery and postoperative radiotherapy versus concurrent platinum-based chemoradiotherapy
Boscolo-Rizzo 2011	Surgery and postoperative radiotherapy versus platinum-based induction-concurrent chemoradiotherapy group
Kuo 2013	Primary surgery with or without adjuvant therapy versus radiotherapy/chemoradiotherapy
Mowry 2006	Surgery followed by radiation versus primary CRT
O'Connell 2013	Surgery with adjuvant chemotherapy and radiation versus surgery with adjuvant radiotherapy

Table 19 – Excluded observational studies regarding RQ 3 (n=3)

Reference	Reason for exclusion
Diaz-Molina 2012	Excluded on population
Ebisumoto 2011	No PDF available
More 2013	Excluded on outcome

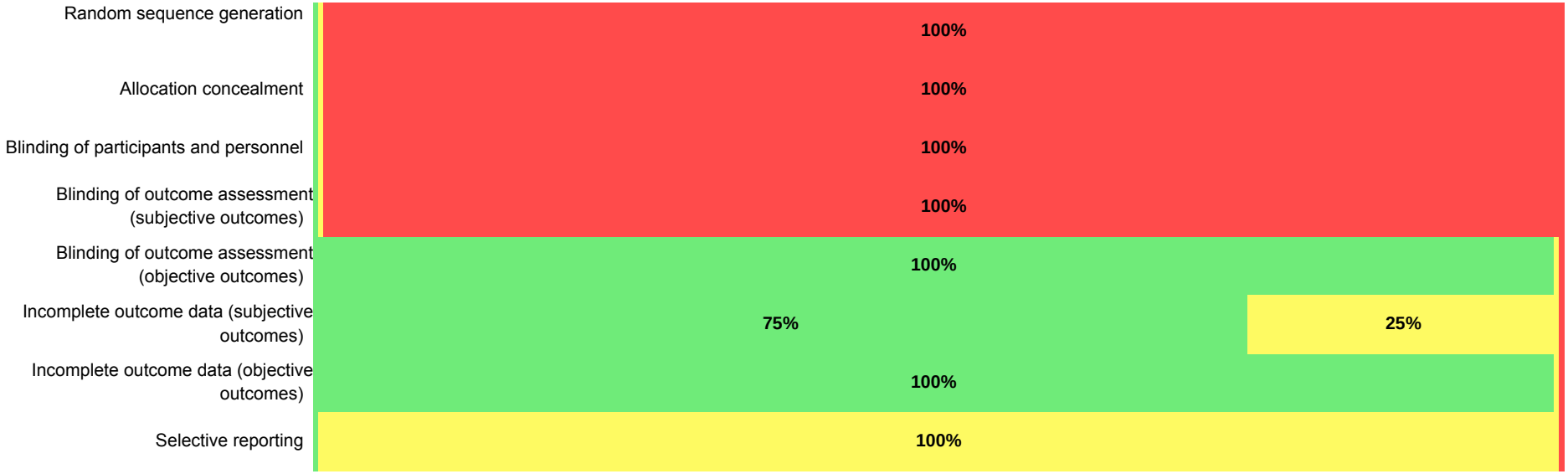
Quality appraisal of selected observational studies

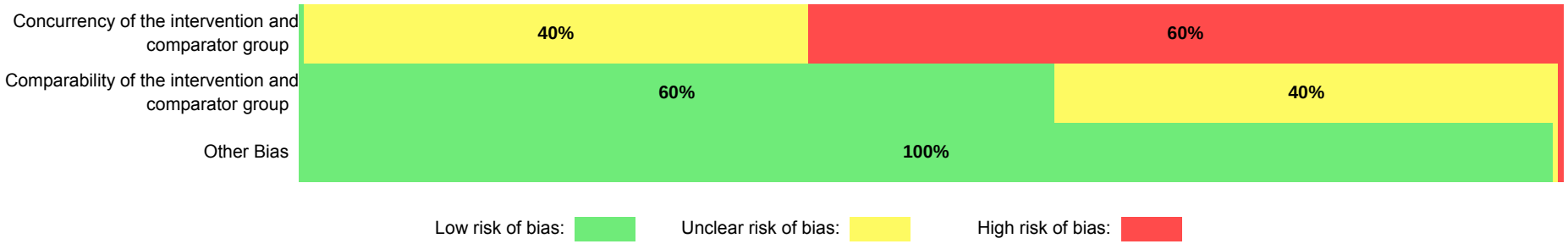
The results of the risk of bias assessment for the five comparative observational studies for RQ3 are presented Figure 13 and Figure 14. All studies scored a high risk of selection bias and performance bias. Detection bias was judged to be at high risk for subjective outcomes for all studies that addressed subjective outcomes. All studies that addressed objective outcomes scored a low risk of detection bias for objective outcomes. There was a low risk of attrition bias for most studies, for subjective as well as objective outcomes. Only one study was judged to be at unclear risk of attrition bias for subjective outcomes (Mowry 2006). Risk of reporting bias was judged to be unclear as there were no study protocols available (not common for observational studies). However, all outcomes mentioned in methods section were reported in the results section. Risk of bias due to nonconcurrency for the intervention and comparator group was judged to be high for three studies (Boscolo-Rizzo 2009;Boscolo-Rizzo 2011;Kuo 2013) and unclear for the remaining two. Study groups were judged to be comparable in three studies (Boscolo-Rizzo 2011;Boscolo-Rizzo 2009;O'Connell 2013) and for the remaining two this was unclear. There was no indication of other bias in any of the selected observational studies.

Figure 13 – Risk of bias assessment of included observational studies regarding RQ3

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Boscolo-Rizzo (2009)	-	-	-	-	+	+	+	?	-	+	+
Boscolo-Rizzo (2011)	-	-	-	-	+	+	+	?	-	+	+
Kuo (2013)	-	-	-	-	+	+	+	?	-	?	+
Mowry (2006)	-	-	-	-	N/A	?	N/A	?	?	?	+
O'Connell (2013)	-	-	-	N/A	+	N/A	+	?	?	+	+

Figure 14 – Risk of bias summary per item of included observational studies regarding RQ3





3.3.5. RQ4: Postoperative (chemo)radiotherapy

a. Postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy

b. Postoperative chemoradiotherapy versus postoperative radiotherapy

Selection of RCTs

On December 3th, 2014 a search was performed to identify RCTs comparing postoperative (chemo)radiotherapy with no postoperative (chemo)radiotherapy (RQ4A) or RCTs comparing postoperative chemoradiotherapy with postoperative radiotherapy (RQ4B) in patients with oropharyngeal, hypopharyngeal or laryngeal cancer. The specialised register of trials of the Cochrane Ear, Nose and Throat (ENT) disorders group was searched. In this Cochrane ENT database RCTs relevant for ear, nose and throat disorders from MEDLINE and Embase, as well as relevant RCTs identified by handsearching, are registered. Further RCT's were searched in the Cochrane Central Register of Controlled Trials (CENTRAL).

In total, 170 potentially relevant references were identified from databases (Figure 15). After deduplication 119 references remained of which 52 with a publication date since 2004. Based on title and abstract 44 references were excluded, leaving eight references for full text evaluation. From the included systematic review of Furness seven more potentially relevant RCTs were identified. As the systematic review of Furness addresses only oral cavity and oropharyngeal cancers, these RCTs were excluded for the systematic review because of a study population with less than 50% oral cavity and oropharyngeal cancers. However, for research question 4 these RCTs are relevant. Of the 15 references that were evaluated in full text, six RCTs were included of which one addresses research question 4A (Table 20) and five address research question 4B (Table 21). Nine references were excluded with reason (Table 10).

Figure 15 – Study flow of selection of RCTs regarding RQ 4

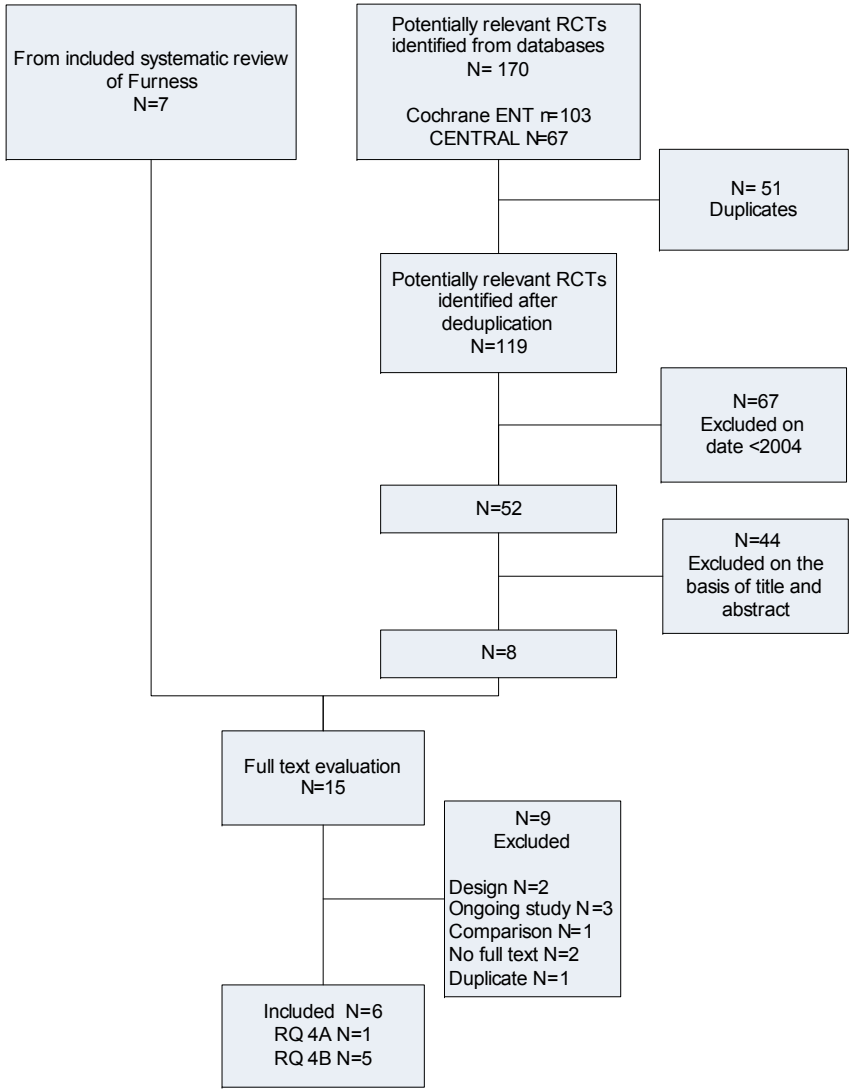


Table 20 – Included RCT regarding RQ 4a (n=1)

Reference	Interventions
Rodrigo 2004	Postoperative radiotherapy versus no postoperative radiotherapy

Table 21 – Included RCTs regarding RQ 4b (n=5)

Reference	Interventions
Bachaud 1996	Radiotherapy and concurrent cisplatin versus radiotherapy alone
Haffty 1993	Radiotherapy and mitomycin C versus radiotherapy alone; radiotherapy and mitomycin C plus dicoumarol versus radiotherapy alone
Racadot 2008	Radiotherapy and concomitant carboplatin versus radiotherapy alone
Smid 2003	Radiotherapy and mitomycin C plus bleomycin versus radiotherapy alone
Weissberg 1989	Radiotherapy and mitomycin C versus radiotherapy alone

Table 22 – Excluded RCTs regarding RQ 4 (n=9)

Reference	Reason for exclusion
Abo-Faries 2010	No full text available
Haffty 1997	No full text available
Harari 2014	Excluded on comparison
Isrctn; Suwinski 2011	Ongoing study
Moergel 2009	Protocol of ongoing study
Nct 2014 (NCT02215265)	Ongoing study
Olthoff 2006	Excluded on design
Patel 2014	Excluded on design
Racadot 2008	Duplicate

Risk of bias assessment of selected RCTs

The results of the risk of bias assessment for the included RCT for research question 4A is presented in Figure 16. Risk of detection bias and risk of attrition bias were judged to be high. Due to insufficient information on randomization and allocation concealment an unclear risk of selection bias was scored. There was also an unclear risk of reporting bias. Because of baseline imbalances between study groups for T-stage distribution a high risk of other bias was scored. Overall, focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), risk of bias for the study was judged to be high.

The results of the risk of bias assessment for the included RCTs for research question 4B are presented in Figure 17 and Figure 18. As the RCT in the publication of Weissberg is also described by Haffty, methodological quality was assessed for both publications together. Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), none of the studies were assessed as 'low risk' of bias for all items. The risk of selection bias was judged to be unclear as information about randomization was incomplete for all studies, except for the studies of Haffty/Weissberg and Racadot in which information about either random sequence (Haffty/Weissberg) or allocation concealment (Racadot) was provided. Considering the type of interventions, blinding was impossible, leading to a high risk of performance bias and detection bias for subjective outcomes in all studies. For objective outcomes, however, the risk of detection bias in all studies was judged to be low. Risk of attrition bias was also low for all studies, except for the study of Racadot, for which an unclear risk of attrition bias for subjective outcomes was scored. There was an unclear risk of reporting bias and a low risk of other bias in all but one studies; the study of Bachaud was judged to be at high risk of both reporting bias and other bias.

Figure 16 – Risk of bias assessment of included RCT regarding RQ4a

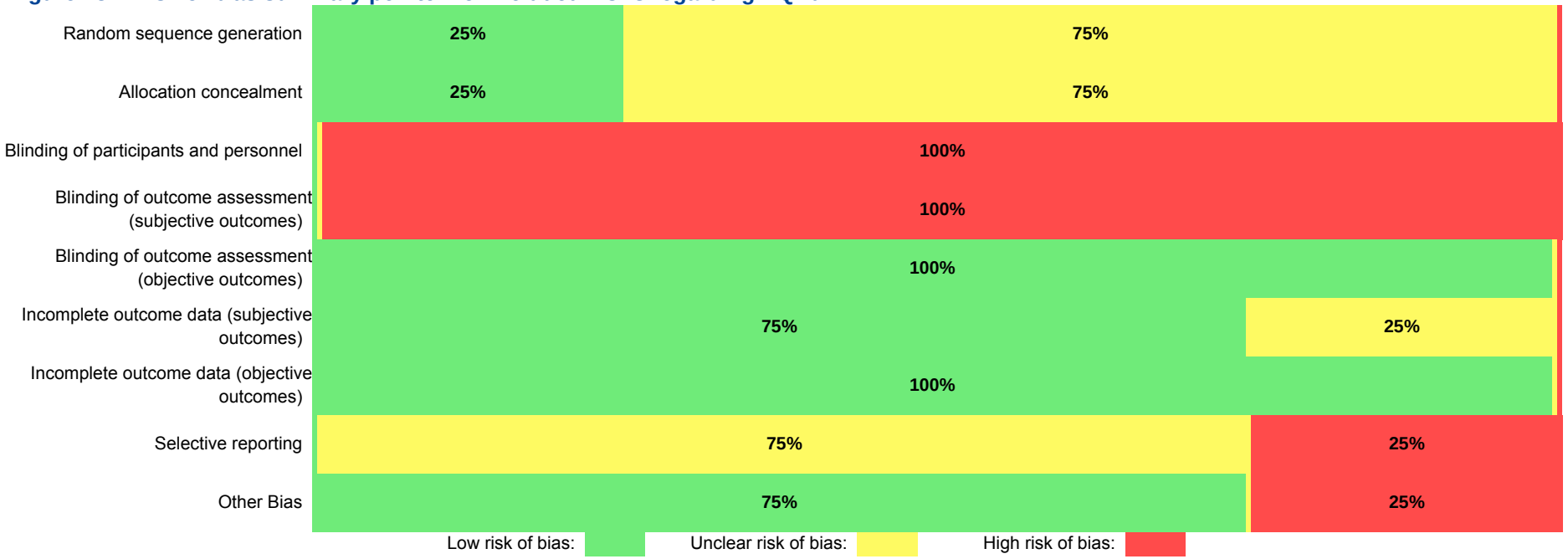
Short Title	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Other Bias
Rodrigo (2004)	?	?	-	-	N/A	-	N/A	?	-

Figure 17 – Risk of bias assessment of included RCT regarding RQ4b

Short Title	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Other Bias
Bachaud (1996)	?	?	-	-	+	+	+	-	-
Haffty (1993), Weissberg (1989)	+	?	-	-	+	+	+	?	+

Racadot (2008)	?	+	-	-	+	?	+	?	+
Smid (2003)	?	?	-	-	+	+	+	?	+

Figure 18 – Risk of bias summary per item of included RCTs regarding RQ4b



Selection of observational studies

On December 3th, 2014 a search was performed to identify observational studies comparing postoperative radiotherapy with no postoperative radiotherapy (RQ4A) or RCTs comparing postoperative chemoradiotherapy with postoperative radiotherapy (RQ4B) in patients with oropharyngeal, hypopharyngeal or laryngeal cancer. MEDLINE and Embase were searched from 2004 onwards.

In total, 914 potentially relevant references were identified from databases (Figure 15). After deduplication 641 references remained. Based on title and abstract 569 references were excluded. Of the remaining 72 references, 19 were included (Table 12 – Included diagnostic accuracy studies regarding RQ1 (n=4) and Table 24) and 53 were excluded with reason (Table 25). Two studies were included for both RQ4A and RQ4B (Yokota 2014;Roosli 2010).

Figure 19 – Study flow of selection of observational studies regarding RQ 4

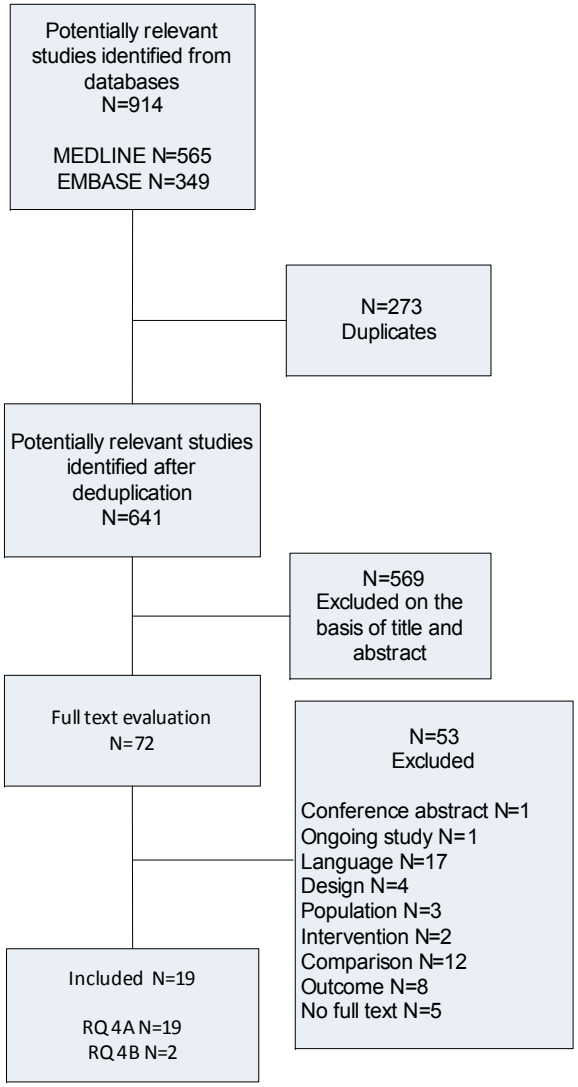


Table 23 – Included observational studies regarding RQ 4a (n=19)

Reference	Interventions
Ampil 2007	Surgery with or without postoperative radiotherapy
Bastos de Souza 2014	Surgical tumor resection and neck dissection with or without postoperative radiotherapy
Bindewald 2007	Surgery with or without postoperative radiotherapy
Broglie 2013	Surgery with or without postoperative radiotherapy
Cho 2010	Supracricoid laryngectomy with or without postoperative (chemo)radiotherapy
Chu 2008	Surgery with or without postoperative radiotherapy
Davis 2004	Endoscopic vertical partial laryngectomy with or without postoperative irradiation
Dechaphunkul 2011	Surgery with or without postoperative radiotherapy
Gourin 2014	Surgery with or without postoperative radiotherapy
Joo 2012	Surgery with or without postoperative radiotherapy
Lim 2008	Surgery with or without postoperative radiotherapy
Olthoff 2006	Surgery with or without postoperative radiotherapy
Patel 2014	Transoral laser microsurgery with or without neck dissection with or without postoperative radiotherapy
Roosli 2010	Surgery with or without postoperative (chemo)radiotherapy
Schmitz 2009	Surgical tumor resection with unilateral or bilateral selective neck dissection with or without postoperative radiotherapy
Shin 2009	Surgery with or without postoperative radiotherapy
Wang 2006	Phayngolaryngo-esophagectomy and reconstruction with or without adjuvant radiotherapy
Yilmaz 2005	Surgery with or without postoperative radiotherapy
Yokota 2014	Surgery versus surgery and radiotherapy versus surgery and chemoradiotherapy

Table 24 – Included observational study regarding RQ 4b (n=2)

Reference	Interventions
Röösli 2010	Surgery followed by (chemo)radiotherapy versus surgery alone
Yokota 2014	Surgery versus surgery and radiotherapy versus surgery and chemoradiotherapy

Table 25 – Excluded observational studies regarding RQ 4 (n=53)

Reference	Interventions
Alicandri-Ciufelli 2013	Excluded on outcome
Al-Khatib 2009	No full-text available
Arce 2012	Excluded on population
Baskota 2004	Excluded on intervention
Becker 2005	Excluded on design
Bernier 2005	Excluded on design

Reference	Interventions
Burnip 2013	Excluded on outcome
Canis 2014	Excluded on comparison
Chin 2014	Conference abstract
Chone 2011	No full-text available
Chu 2010	Excluded on comparison
Crespo 2006	Excluded on comparison
Fujimoto 2007	Excluded on outcome
Gourin 2014	Excluded on comparison
Gultekin 2011	Excluded on outcome
Guo 2011	Excluded on language
Huang 2006	Excluded on intervention
Iseh 2011	Excluded on comparison
Iseh 2011	No full-text available
Jaimanti 2004	Excluded on comparison
Kalavrezos 2014	Excluded on outcome
Kovacs 2004	Excluded on population
Kubrak 2010	Excluded on language
Laccourreye 2013	Excluded on comparison
Lai 2008	Excluded on language
Lee 2013	Excluded on outcome
Liu 2004	Excluded on language
Liu 2009	Excluded on language
Moergel 2009	Ongoing study
Moergel 2011	Excluded on design
Moon 2011	Excluded on comparison
Ortega 2012	Excluded on language
Patel 2014	Excluded on comparison
Petrovic 2004	Excluded on population
Rewari 2006{	Excluded on design
Rogers 2005	Excluded on comparison
Sakamoto 2005	Excluded on language
Schache 2009	Excluded on outcome
Steffen 2009	Excluded on outcome
Tian 2006	Excluded on language

Reference	Interventions
Tian 2007	Excluded on language
Turgut 2008	No full-text available
Vilaseca 2013	Excluded on comparison
Vinogradov 2010	Excluded on language
Wang 2006	Excluded on language
Wang 2009	Excluded on language
Windfuhr 2008	No full-text available
Xu 2004	Excluded on language
Xu 2014	Excluded on language
Yom 2006	Excluded on comparison
Yu 2006	Excluded on language
Zhang 2005	Excluded on language
Zhou 2004	Excluded on language

Quality appraisal of selected observational studies

Figure 20 and Figure 21 show the results of the assessment of the methodological quality of the 19 observational studies included for research question 4A. Due to the observational design all studies were at high risk of selection bias. As interventions could not be blinded there was a high risk of performance bias and detection bias of subjective outcomes (if applicable) as well. For all studies addressing objective outcomes the risk of detection bias for objective outcomes was judged to be low. Attrition bias was suspected for subjective outcomes in two studies (Ampil 2007;Bindewald 2007), and for objective outcomes in one study (Dechaphunkul 2011), in four studies the risk of attrition bias was judged to be low (Bastos de Souza 2014;Joo 2012;Roosli 2010;Wang 2006) and for the remaining studies there was an unclear risk of attrition bias. Risk of reporting bias was unclear for all studies. Regarding concurrency of the intervention and comparator group two studies scored a low risk of bias (Gourin 2014;Olthoff 2006) and three a high risk of bias (Bindewald 2007;Joo 2012;Roosli 2010). Study groups were judged to be comparable in two studies (Gourin 2014;Yilmaz 2005) and eight studies scored a high risk of bias for this item (Ampil 2007;Bastos de Souza 2014;Bindewald 2007;Broglie 2013;Davis 2004;Patel 2014;Roosli 2010;Yokota 2014). None of the studies had a risk of other bias.

Two of the studies included for research question 4A were also included for research question 4B. Assessment of the methodological quality of these two studies are presented in Figure 22 and Figure 23. There was a high risk of selection bias, performance bias and detection bias for subjective outcomes in both studies. Risk of detection bias for objective outcomes was judged to be low. There was a low risk of attrition bias in one study and an unclear risk in the other study. There was concern about the comparability of study groups in both included studies and for concurrency of the intervention and comparator group in one study. Risk of reporting bias was unclear in both studies and there was a low risk of other bias.

Figure 20 – Risk of bias assessment of included observational studies regarding RQ4a

Short Title	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Ampil (2007)	-	-	-	-	+	-	?	?	?	-	+
Bastos de Souza (2014)	-	-	-	-	+	+	+	?	?	-	+
Bindewald (2007)	-	-	-	-	N/A	-	N/A	?	-	-	+
Broglie (2013)	-	-	-	-	N/A	?	N/A	?	?	-	+
Cho (2010)	-	-	-	N/A	+	N/A	?	?	?	?	+
Chu (2008)	-	-	-	-	N/A	?	N/A	?	?	?	+
Davis (2004)	-	-	-	-	+	?	?	?	?	-	+
Dechaphunkul (2011)	-	-	-	N/A	+	N/A	-	?	?	?	+
Gourin (2014)	-	-	-	N/A	+	N/A	?	?	+	+	+
Joo (2012)	-	-	-	-	N/A	+	N/A	?	-	?	+
Lim (2008)	-	-	-	-	N/A	?	N/A	?	?	?	+
Olthoff (2006)	-	-	-	-	N/A	?	N/A	?	+	?	+
Patel (2014)	-	-	-	-	+	?	?	?	?	-	+
Roosli (2010)	-	-	-	-	+	+	+	?	-	-	+
Schmitz (2009)	-	-	-	-	N/A	?	N/A	?	?	?	+

Shin (2009)	-	-	-	N/A	+	N/A	?	?	?	?	+
Wang (2006)	-	-	-	N/A	+	N/A	+	?	?	?	+
Yilmaz (2005)	-	-	-	-	N/A	?	N/A	?	?	+	+
Yokota (2014)	-	-	-	-	+	?	?	?	?	-	+

Figure 21 – Risk of bias summary per item of included observational studies regarding RQ4a

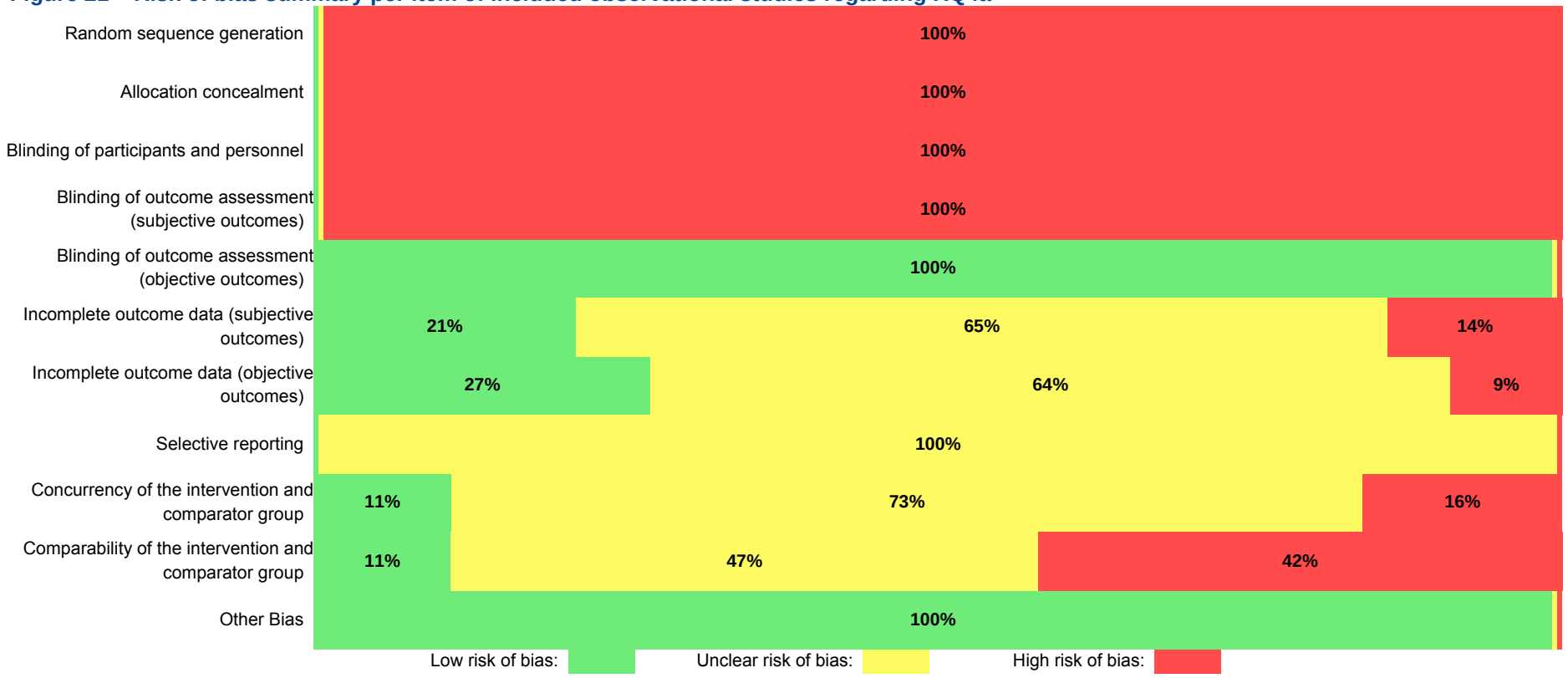
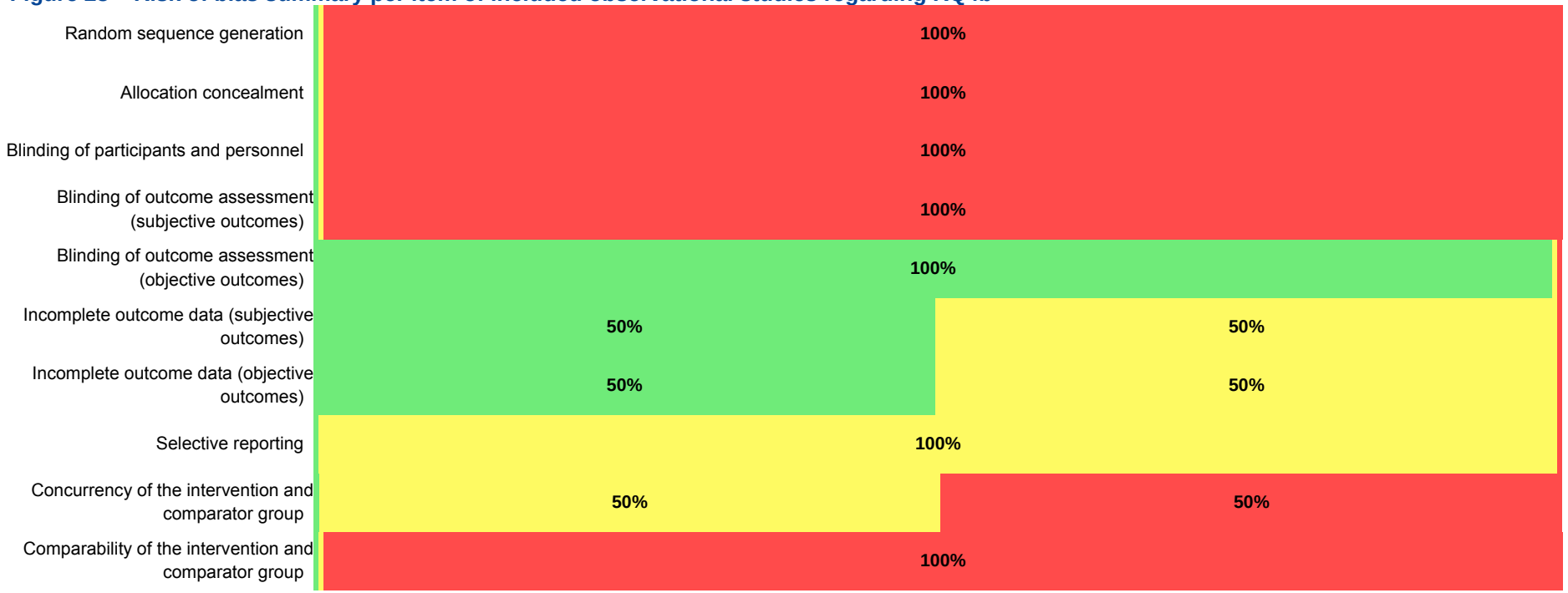
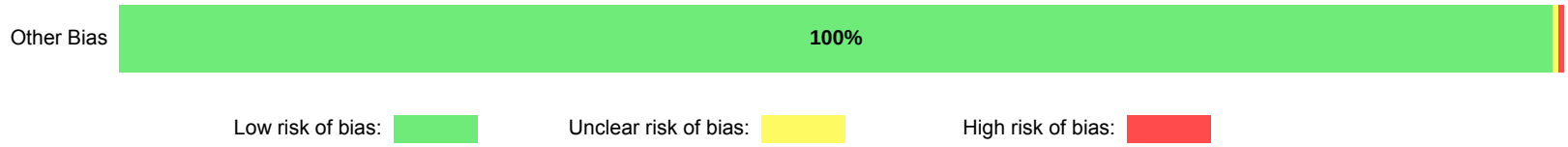


Figure 22 – Risk of bias assessment of included observational studies regarding RQ4b

Short Title	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Roosli (2010)	-	-	-	-	+	+	+	?	-	-	+
Yokota (2014)	-	-	-	-	+	?	?	?	?	-	+

Figure 23 – Risk of bias summary per item of included observational studies regarding RQ4b





3.3.6. RQ5: Management of the neck lymph nodes

a. Neck dissection versus no neck dissection

b. Neck dissection type X versus neck dissection type Y

Selection of RCTs

On September 24th, 2014 a search was performed to identify RCTs regarding surgical interventions for treatment of laryngeal, oropharyngeal and hypopharyngeal cancer (RQ 2, 3 and 5). The specialised register of trials of the Cochrane Ear, Nose and Throat (ENT) disorders group was searched from 2004 onwards. In this Cochrane ENT database RCTs relevant for ear, nose and throat disorders from MEDLINE and Embase, as well as relevant RCTs identified by handsearching, are registered. Further RCT's were searched in the Cochrane Central Register of Controlled Trials (CENTRAL). An additional search for glottis laryngeal cancer was carried out to identify those specific searches that might have been missed with the initial studies.

In total, 580 potentially relevant references were identified from databases (Figure 5). After deduplication 538 references remained. Based on title and abstract 441 references were excluded. Of the remaining 97 RCTs, seven were included (Beauvillain 1997;Bhalavat 2003;Department of Veterans Affairs Laryngeal Cancer 1991;Lefebvre 1996;Lefebvre 2012;Terrell 1998;Brazilian Head and Neck Cancer Study Group 1999) and 90 were excluded with reason (Table 13).

For RQ 5 one RCT was included (Table 26) (Brazilian Head and Neck Cancer Study Group 1999).

Table 26 – Included RCT regarding RQ 5

Reference	Interventions
Brazilian Head and Neck Cancer Study Group 1999	Type III modified radical neck dissection versus lateral neck dissection

Risk of bias assessment of selected RCT

Figure 24 shows the assessment of the risk of bias for the included RCT for RQ5B. For this RCT the risk of performance bias was judged to be high. Risk of selection bias, detection bias (subjective outcomes) and reporting bias was judged to be unclear. This RCT had a low risk of attrition bias and detection bias (objective outcomes). There was no indication of other bias. Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), risk of bias for this RCT was assessed as 'unclear'.

Figure 24 – Risk of bias assessment of included RCT regarding RQ5B

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Other Bias
End results of a prospective... (1999)	?	?	-	?	+	+	+	?	+

Selection of observational studies

On October 10th, 2014 a search was performed to identify observational studies comparing neck dissection and no neck dissection (RQ5A) and studies comparing different types of neck dissection (RQ5B) in patients with oropharyngeal, hypopharyngeal or laryngeal cancer. MEDLINE and Embase were searched from 2004 onwards

In total, 904 potential relevant references were identified (669 In MEDLINE and 235 in Embase) (Figure 25). After de-duplication 673 references remained. Based on title and abstract 638 papers were excluded. Of the remaining 35 studies, 15 studies were included (Al-Mamgani 2013;Bohannon 2010;Boscke 2014;Donatelli-Lassig 2008;Gallo 2006;Jin 2012;Lanzer 2012;Liu 2012;Pantel 2011; Psychogios 2013;Sakashita 2014;Suzuki 2013;Dias 2009;Hillel 2009;Rodrigo 2006) (Table 27 and Table 28) and 20 were excluded (Table 29). Two of the 15 included studies were relevant for both RQ5A and RQ5B (Donatelli-Lassig 2008;Gallo 2006).

Figure 25 – Study flow of observational studies regarding RQ 5

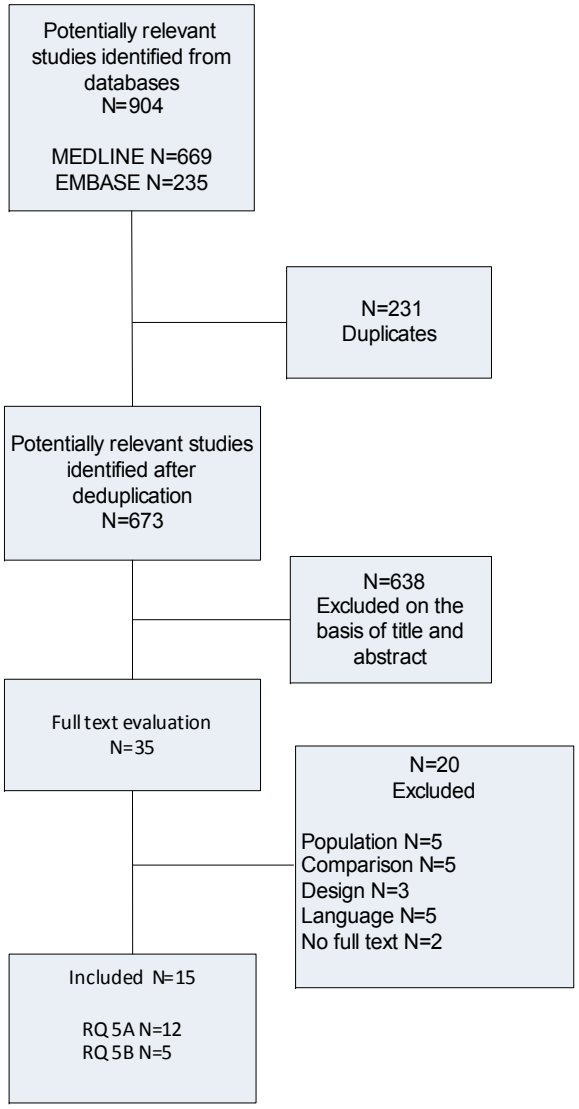


Table 27 – Included observational studies regarding RQ 5a (n=12)

Reference	Interventions
Al-Mamgani 2013	Up-front neck dissection versus no up-front neck dissection
Bohannon 2010	Neck dissection versus no neck dissection
Böscke 2014	Elective neck dissection versus observation
Donatelli 2008	Chemoradiation and neck dissection versus chemoradiation
Gallo 2006	Elective neck dissection versus wait-and-see protocol
Jin 2012	Surgery versus radiotherapy versus wait-and-see
Lanzer 2012	Elective contralateral neck dissection versus observation
Liu 2012	Pretreatment neck dissection (following organ preservation chemoradiation) versus no pretreatment neck dissection (in a chemoradiation protocol)
Pantel 2011	Elective neck dissection versus no neck dissection
Psychogios 2013	Elective neck dissection versus observation
Sakashita 2014	Initial neck dissection versus wait-and-see policy
Suzuki 2013	Neck dissection versus no neck dissection

Table 28 – Included observational studies regarding RQ 5b (n=5)

Reference	Interventions
Dias 2009	Selective neck dissection with or without adjuvant radiotherapy versus modified radical neck dissection with adjuvant radiotherapy
Donatelli 2008	Selective neck dissection versus modified radical neck dissection
Gallo 2006	Radical neck dissection versus functional neck dissection versus selective jugular node dissection
Hillel 2009	Comprehensive neck dissection versus selective neck dissection
Rodrigo 2006	Ipsilateral functional neck dissection versus bilateral functional neck dissections

Table 29 – Excluded observational studies regarding RQ 5 (n=20)

Reference	Reason for exclusion
Allegra 2014	Excluded on comparison
Canis 2013	Excluded on comparison
Cappiello 2005	Excluded on population
Cong 2012	Excluded on language
Dagan 2010	Excluded on population
Jia 2004	Excluded on language
Jia 2010	Excluded on language
Kohler 2010	Excluded on population

Reference	Reason for exclusion
Layland 2005	Excluded on comparison
Li 2013	Excluded on language
Lim 2009	Excluded on design
Osmolski 2005	Excluded on language
Oz 2009	Excluded on comparison
Sarno 2004	Excluded on design
Selcuk 2008	No PDF available
Spector 2004	Excluded on design
Thariat 2012	Excluded on population
van der Putten 2011	Excluded on population
Veyseller 2010	No PDF available
Villaret 2007	Excluded on comparison

Quality appraisal of selected observational studies

The results of the risk of bias assessment for the twelve comparative observational studies for RQ5A are presented Figure 26 and Figure 27. All studies scored a high risk of selection bias and performance bias. Detection bias was judged to be at high risk for subjective outcomes for all studies. For objective outcomes all studies scored a low risk of detection bias, except for the study of Donatelli that did not address objective outcomes. For most studies there was uncertainty about the risk of attrition bias for subjective as well as objective outcomes. Four studies scored a low risk of attrition bias for both subjective and objective outcomes (Gallo 2006;Jin 2012;Pantel 2011), or just for objective outcomes (Al-Mamgani 2013). Risk of reporting bias was judged to be unclear as there were no study protocols available (not common for observational studies). However, all outcomes mentioned in methods section were reported in the results section. Risk of bias due to nonconcurrency for the intervention and comparator group was judged to be high or unclear for the majority of the studies. Study groups were judged to be comparable in three studies (Bohannon 2010;Lanzer 2012;Pantel 2011), non-comparable in two studies (Al-Mamgani 2013;Boscke 2014) and for the remaining seven this was unclear. There was no indication of other bias in any of the selected observational studies.

The results of the risk of bias assessment for the five comparative observational studies selected for RQ5B are presented Figure 28 and Figure 29. There was a high risk of selection bias, performance bias and detection bias for subjective outcomes for all studies. The four studies that addressed objective outcomes were all at low risk for detection bias for objective outcomes. The risk of attrition bias for both subjective and objective outcomes was low in one study (Gallo 2006) and unclear in the remaining studies. Selective reporting was suspected in one study (Dias 2009) and was uncertain in the other four, due to the fact that no study protocols were available. However, all outcomes mentioned in methods section were reported in the results section. The item 'Concurrency of the intervention and comparator group' was scored high risk in two (Gallo 2006;Rodrigo 2006) and unclear in three studies. Study groups were judged to be comparable in one study (Rodrigo 2006), non-comparable in another study (Hillel 2009) and unclear in the remaining three studies. There was no indication of other bias in any of the studies.

Figure 26 – Risk of bias assessment of included observational studies regarding RQ5a

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Al-Mamgani (2013)	-	-	-	-	+	?	+	?	-	-	+
Bohannon (2010)	-	-	-	-	+	?	?	?	+	+	+
Boscke (2014)	-	-	-	-	+	?	?	?	-	-	+
Donatelli-Lassig (2008)	-	-	-	-	N/A	?	N/A	?	?	?	+
Gallo (2006)	-	-	-	-	+	+	+	?	-	?	+
Jin (2012)	-	-	-	-	+	+	+	?	-	?	+
Lanzer (2012)	-	-	-	-	+	?	?	?	-	+	+
Liu (2012)	-	-	-	-	+	?	?	?	-	?	+
Pantel (2011)	-	-	-	-	+	+	+	?	?	+	+
Psychogios (2013)	-	-	-	-	+	?	?	?	-	?	+
Sakashita (2014)	-	-	-	-	+	?	?	?	+	?	+
Suzuki (2013)	-	-	-	-	+	?	?	?	?	?	+

Figure 27 – Risk of bias summary per item of included observational studies regarding RQ5a

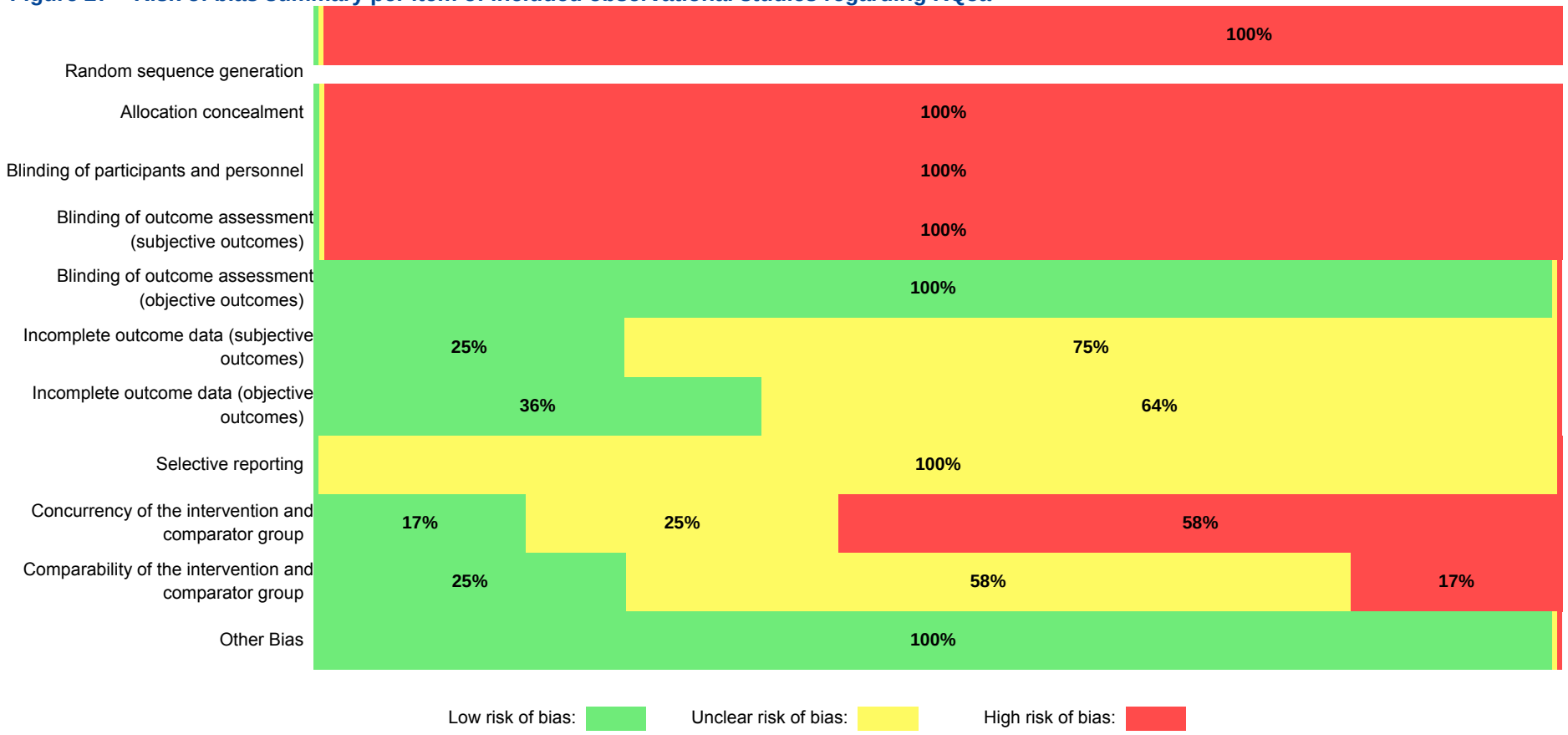
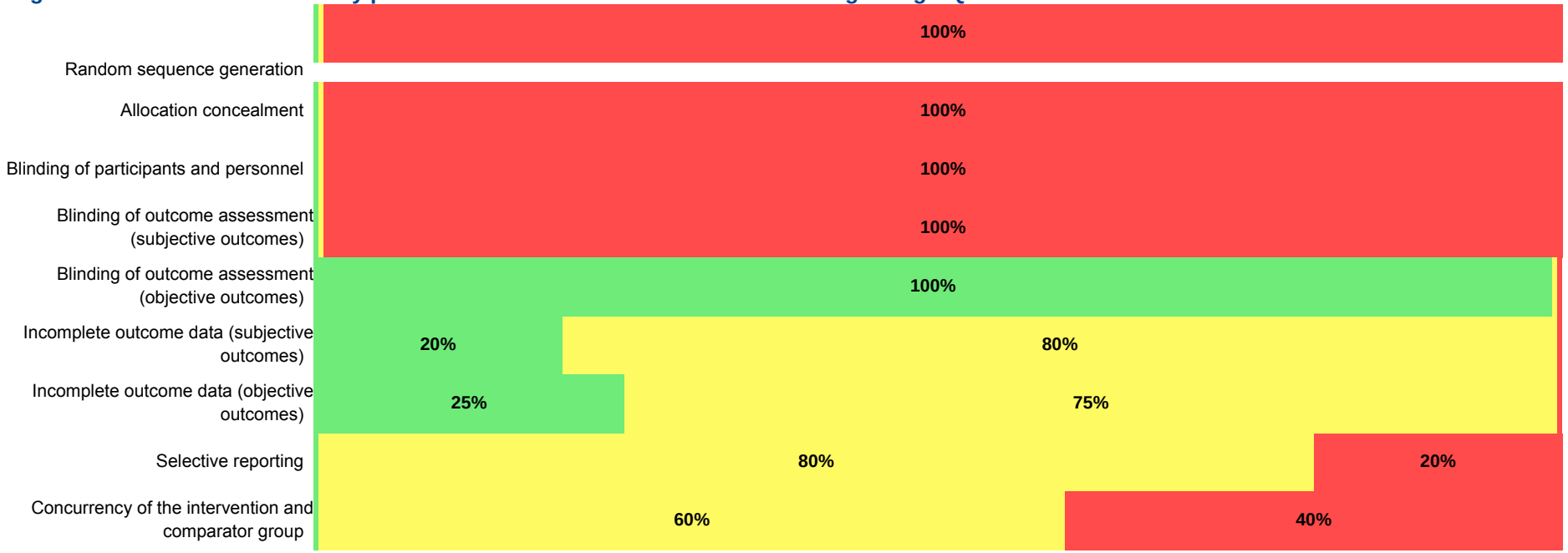
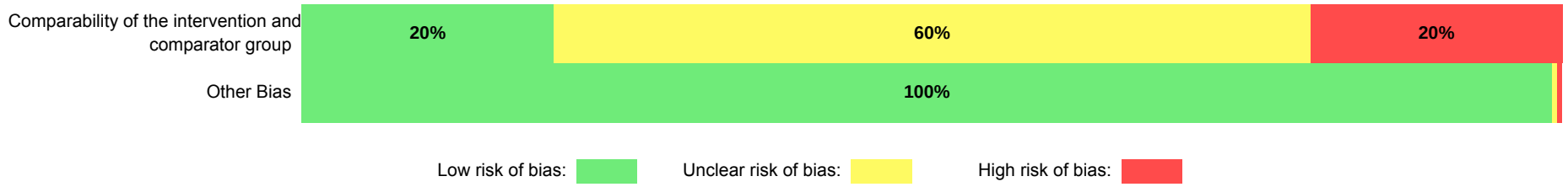


Figure 28 – Risk of bias assessment of included observational studies regarding RQ5b

Reference	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment (subjective outcomes)	Blinding of outcome assessment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Dias (2009)	-	-	-	-	+	?	?	-	?	?	+
Donatelli-Lassig (2008)	-	-	-	-	N/A	?	N/A	?	?	?	+
Gallo (2006)	-	-	-	-	+	+	+	?	-	?	+
Hillel (2009)	-	-	-	-	+	?	?	?	?	-	+
Rodrigo (2006)	-	-	-	-	+	?	?	?	-	+	+

Figure 29 – Risk of bias summary per item of included observational studies regarding RQ5b





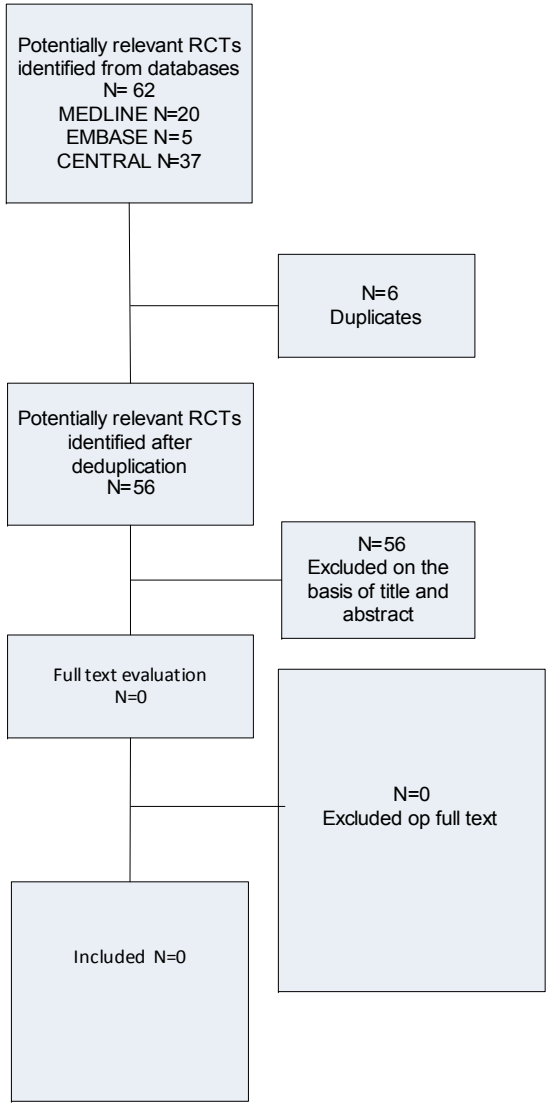
3.3.7. RQ6: Salvage treatment versus no/other treatment

Selection of RCTs

On December 4, 2014 a search was performed to identify RCTs regarding salvage treatment in patients with second primaries or locoregional recurrence after curative treatment for oropharyngeal, hypopharyngeal and laryngealcancer. MEDLINE, Embase and CENTRAL were searched from 2004 onwards.

In total, 61 potentially relevant references were identified from databases (Figure 1). After deduplication 56 references remained. Based on title and abstract all 56 references were excluded.

Figure 30 – Study flow of selection of RCTs regarding RQ 6



Selection of observational studies

On date a search was performed to identify observational studies comparing salvage treatment with no or other treatment in patients with second primaries or locoregional recurrence after curative treatment for oropharyngeal, hypopharyngeal and laryngealcancer. MEDLINE and Embase were searched from 2004 onwards In total, 179 potential relevant references were identified (164 in MEDLINE and 65 in Embase) (Figure 31). After de-duplication 159 references remained. Based on title and abstract 149 papers were excluded. Of the remaining ten studies, four studies were included (Table 30) (Kano 2013;Lim 2010;Yasumatsu 2013;Zafereo 2009) and six were excluded (Table 31) (Jin 2013;Kadota 2010;Mercante 2005;Ritoe 2006;Relic 2009;Roedel 2010).

Figure 31 – Study flow of selection of observational studies regarding RQ 6

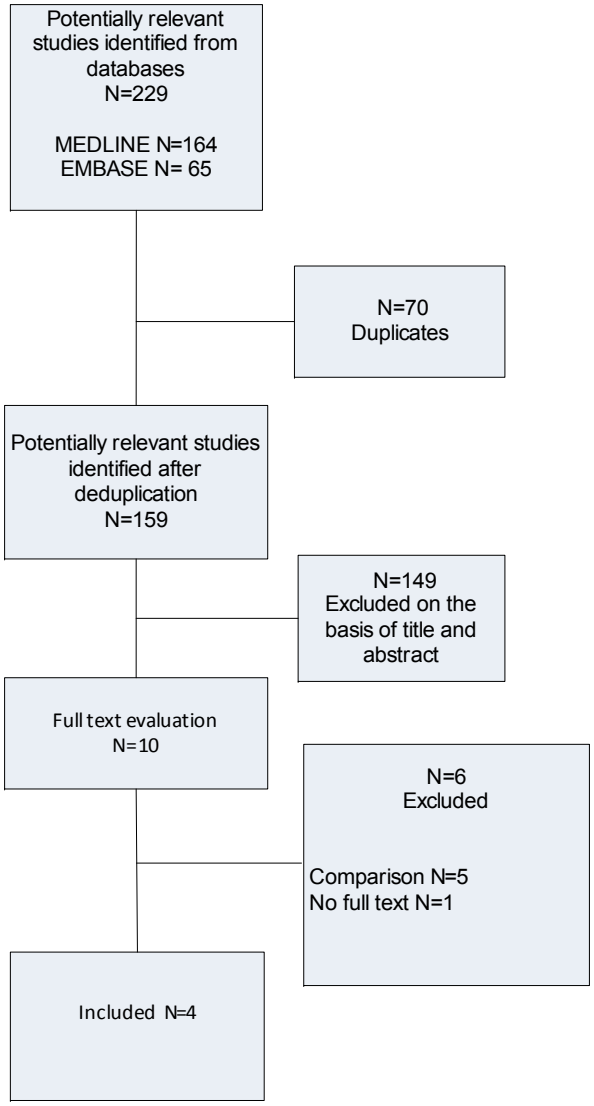


Table 30 – Included observational studies regarding RQ 6 (n=4)

Reference	Interventions
Kano 2013	Salvage surgery vs. nonsurgical treatment
Lim 2010	Salvage treatment vs. supportive care
Yasumatsu 2013	Salvage surgery +/- CRT vs. CRT
Zafereo 2009	Salvage surgery vs. nonsurgical treatment (nonsurgical treatment or supportive care)

Table 31 – Excluded observational studies regarding RQ 6 (n=6)

Reference	Interventions
Jin 2013	Comparison not of interest
Kadota 2010	Comparison not of interest
Mercante 2005	No PDF
Ritoe 2006	Non-comparative study
Relic 2009	No comparison of interest
Roedel 2010	Non-comparative study

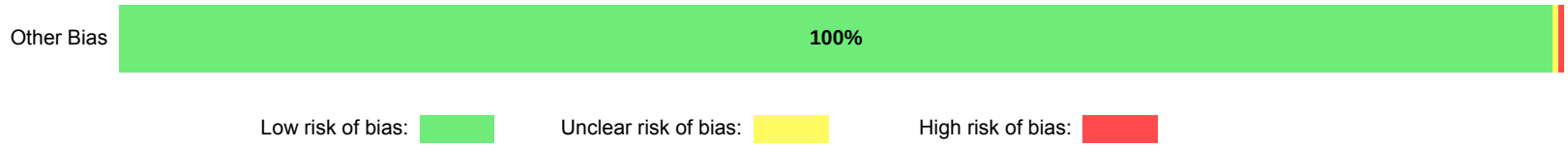
Quality appraisal of selected observational studies

The results of the risk of bias assessment for the four comparative observational studies included for RQ6 are presented in Figure 32 and Figure 33 (Kano 2013;Lim 2010;Yasumatsu 2013;Zafereo 2009). All studies scored a high risk of selection bias and performance bias. A high risk of detection bias for subjective outcomes was scored for one study, the remaining studies did not assess objective outcomes. All studies scored a low risk of detection bias for objective outcomes. There was uncertainty about attrition bias for three studies, except for the studies of Zafereo 2009, which scored a high risk of attrition bias. Risk of reporting bias was judged to be unclear for all studies as no study protocols were available (not common for observational studies). However, in all studies the outcomes mentioned in methods section were all reported in the results section. Risk of bias due to nonconcurrency of the intervention and comparator group was scored low for one study (Kano 2013) and unclear for the remaining studies. The item 'Comparability of the intervention and comparative group' was scored as high risk of confounding by indication for all studies as indications for treatment were different (thus as a consequence patient characteristics between groups should be different) and details about patient characteristics were lacking.

Figure 32 – Risk of bias assessment of included observational studies regarding RQ6

Short Title	Random sequence generation	Allocation concealment	Blinding of participants and personal	Blinding of outcome assesment (subjective outcomes)	Blinding of outcome assesment (objective outcomes)	Incomplete outcome data (subjective outcomes)	Incomplete outcome data (objective outcomes)	Selective reporting	Concurrency of the intervention and comparator group	Comparability of the intervention and comparator group	Other Bias
Kano (2013)	-	-	-	N/A	+	N/A	?	?	+	-	+
Lim (2010)	-	-	-	N/A	+	N/A	?	?	?	-	+
Yasumatsu (2013)	-	-	-	N/A	+	N/A	?	?	?	-	+
Zafereo (2009)	-	-	-	-	+	-	-	?	?	-	+

Figure 33 – Risk of bias summary per item of included observational studies regarding RQ6



3.3.8. RQ7: Altered fractionation radiotherapy versus standard radiotherapy

Selection of SR and RCTs

On March 16, 2015 a search was performed to identify SR and RCTs regarding altered fractionation radiotherapy versus standard radiotherapy in patients with oropharyngeal, hypopharyngeal and laryngeal cancer. MEDLINE, Embase and the Cochrane Library were searched without time restriction.

In total, 751 potentially relevant references were identified from databases. After deduplication (N=239) and removal of references in a wrong language (N=44), 468 references remained. Based on title and abstract 437 references were excluded.

Of the remaining 31 studies, 27 studies were included and 4 were excluded (Table 32).

Of the 27 included studies, 4 were SR (Baujat 2010, Bourhis 2006, Budach 2006, Glenny 2010). Of the 23 RCTs, 6 were not already included in at least one of the 4 SR (Moon 2014, Overgaard 2010, Zackrisson 2011, Miszczyk 2014, Trotti 2014, Yamazaki 2006). Two additional RCTs were an update of a previously published study (Beitler 2014, Fallai 2006).

Table 32 – Excluded studies regarding RQ 5 (N=4)

Reference	Reason for exclusion
Hansen O 1997	Not on altered fractionation
Nakamura K 2008	Protocol
Skladowski K 2013	Not versus standard radiotherapy
ISRCTN01483375	Ongoing trial

Quality appraisal of systematic reviews

Table 33 shows the results of the quality assessment for the included systematic reviews (SRs) for RQ7. The two Cochrane reviews (Baujat 2010, Glenny 2010) scored positive on most items, the two other SR were considered to be of low quality.

Table 33 – Methodological quality of the included systematic reviews (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion criterion	List of in- and excluded studies	Charac-teristics of included studies provided	Study quality assess-ed and docu-mented	Quality assess-ment used in conclus-ions	Appro-priate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Baujat 2010	Y	?	Y	Y	Y	Y	Y	Y	Y	N	N
Bourhis 2006	Y	?	?	Y	Y	Y	?	N	Y	N	N
Budach 2006	?	?	?	?	Y	Y	?	N	Y	N	N
Glenny 2010	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N

Quality appraisal of RCTs

	Moon 2014	Overgaard 2010	Zackrisson 2011	Miszczyk 2014	Trotti 2014	Yamazaki 2006
Random sequence generation (selection bias)	Low risk	Low risk	Unclear risk	Low risk	Low risk	Unclear risk
Allocation concealment (selection bias)	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk	Unclear risk
Blinding of participants and personnel (performance bias): OBJECTIVE OUTCOMES	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of participants and personnel (performance bias): SUBJECTIVE OUTCOMES	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Blinding of outcome assessment (detection bias): OBJECTIVE OUTCOMES	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of outcome assessment (detection bias): SUBJECTIVE OUTCOMES	Unclear risk	High risk	Unclear risk	Unclear risk	Unclear risk	Unclear risk
Incomplete outcome data (attrition bias)	Low risk	Low risk	Low risk	High risk	Unclear risk	High risk
Selective reporting (reporting bias)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	High risk	Low risk	Low risk	Low risk	Low risk	Low risk

4. EVIDENCE TABLES BY CLINICAL QUESTION

4.1. RQ1: What is the effectiveness and/or diagnostic outcomes of locoregional staging (i.e. T- and N-staging) with MRI compared to CT in patients with head and neck squamous cell carcinoma

4.1.1. Evidence tables of systematic reviews RQ1

Wu 2012 Value of magnetic resonance imaging for nodal staging in patients with head and neck squamous cell carcinoma: a meta-analysis	
Methods	
• **Design**	Systematic review and meta-analysis
• **Source of funding and competing interest**	Shanghai Leading Academic Discipline Project and Shanghai Jiaotong University School of Medicine Leading Academic Discipline Project
• **Search date**	January 2011
• **Searched databases**	MEDLINE, EMBASE, Cancerlit and the Cochrane Library.
• **Included study designs**	Retrospective and prospective observational studies
• **Number of included studies**	n=16 (n=10 studies with direct comparisons MRI vs. CT)
• **Statistical analysis**	Pooled sensitivity and specificity. A value of 0.5 was added to all cells of studies that contained a count of zero to avoid potential problems in odds calculations for studies with sensitivities or specificities of 100%. Derived estimates of sensitivity, specificity and respective variances were used to construct a summary receiver operating characteristic (ROC) curve. Chi-square test for heterogeneity, random effects model for meta-analysis if heterogeneous, Deeks' funnel plot asymmetry tests for publication bias.
Study characteristics	
• **Eligibility criteria**	MRI used to evaluate cervical lymph node metastasis in patients with head and neck squamous cell carcinoma (HNSCC); for per-lesion level statistics, sufficient data were presented to calculate the true positive (TP), false-negative (FN), false-positive (FP), and true negative (TN) values; five or more patients were included, reference standard was histopathological analysis (obtained by surgery or biopsy) and/or close clinical follow-up. Only articles in English language and with a positive score on at least nine of the QUADAS items were included.
• **Exclusion criteria**	No pre-specified exclusion criteria reported
• **Patient & disease characteristics**	N=878 patients with head and neck squamous cell carcinoma included (N=16 studies). Age range: 24 to 87 years, sex distribution (N=11 studies) (M/F): 523/143, median number of participants per study: 55 (range, 7 to 213), median prevalence of lymph node metastases: 43% (all studies).
Diagnostic modalities	
• **Index test**	**Group 1.** MRI

• **Comparator test**	**Group 2.** CT
• **Other comparator tests**	PET and US (not relevant for research question 1)
Results	
• **Overall survival**	Not assessed
• **Disease-free survival**	Not assessed
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
• **Diagnostic accuracy (sensitivity, specificity, PPV, NPV)**	**Group 1** (MRI) vs. **Group 2** (CT) (n=10 studies; n=688 participants) Sensitivity: 0.67 (0.65–0.70) vs. 0.64 (0.61–0.68) Specificity: 0.79 (0.77–0.80) vs. 0.75 (0.63–0.80)
Limitations and other comments	
• **Limitations**	"Reference standard used in this meta-analysis was histopathological analysis (obtained by surgery or biopsy) and/or close clinical follow-up, some included studies simply did not dissect out all cervical lymph node. The surgical procedure followed by these studies is to remove only those lymph nodes detected by preoperative MRI; hence, those lymph nodes left behind in the neck, which may or may not be positive for metastases, are ignored. This makes the sensitivity provided by these studies may not very accurate." "The major problem is the absence of interval time between the performance of histopathologic confirmation and index tests. The information of interval time is really crucial because the lymph node metastasis could progress fast. The disease may deteriorate if the interval time was not short enough." Potential publication bias (search limited to English language studies)

4.1.2. Evidence tables of observational studies RQ1

Allegra 2014 Early Glottic Cancer: Role of MRI in the Preoperative Staging	
Methods	
• **Design**	Prospective patient cohort study (from August 2011 to November 2013)
• **Source of funding and competing interest**	Competing interests: none declared Sponsorships: not reported Funding sources: not reported
• **Setting**	Single centre: Department of Otolaryngology, University of Catanzaro, Italy
• **Sample size**	Number of patients = 26 No sample size calculation reported
• **Time interval between tests**	Not reported
• **Statistical analysis**	The images of MRI and CT were analysed to define the expansion of glottic lesion to anterior commissure, laryngeal cartilages, subglottic and/or supraglottic site, and paraglottic space. The results of MRI and CT were compared with each other and with the definitive pathological examination, each of the two methods for calculating the sensitivity, and the specificity and positive predictive value.
Patient characteristics	
• **Eligibility criteria**	Adults suspected of laryngeal cancer of glottis region based on indirect laryngoscopy and eligible for supracricoid laryngectomy or cordectomy by CO2 laser. Patients treated with radiotherapy were excluded (n=6).
• **Patient characteristics**	Analyzed number: n=20 - Median age 63.6 years (range 52-79); - M/F: 20/0; - Localization (larynx): 20; - Classification (T1a/T1b/T3): 10/4/6.
• **Prevalence of disease**	Paraglottic space involvement: 6/20 Thyroid cartilage invasion: 4/10 Arytenoid cartilage invasion: 2/20 Cricoid cartilage invasion: 0/20 Anterior commissure involvement: 8/20
Interventions	

• **Index and comparator test**	**Group 1:** MRI scan. MR images were obtained with a Philips Achieva 1.5 TMR system. MR examinations were performed with an anterior surface neck coil and T1-weighted spin echo and T2 turbo spin echo images in axial and coronal projection, without contrast, diffusion weighted imaging (DWI) and T1w spin echo sequences with fat saturation after paramagnetic contrast infusion of gadolinium chelate were obtained. The number of the sections was 20 for all sequences. The sections were 3-4mm of interspace thickness with a 1-mm intersection gap. The evaluation of cartilage invasion followed the new criteria proposed by Becker et al. Specifically, T2-weighted or T1-weighted post-Mdc cartilage signal intensity greater than that of the adjacent tumor was considered to indicate inflammation, and signal intensity similar to that of the adjacent tumor was considered to indicate neoplastic invasion. **Group 2:** CT scan. CT images were obtained with a Toshiba Aquilion CX 64 Multislice CT system. The axial cuts of neck and chest were performed with 2-3mm of thickness and with 1mm of intersection gap, before and after intravenous administration of contrast medium. CT criteria used for determining neoplastic invasion of the thyroid cartilage include sclerosis, erosion, lysis, and transmural extralaryngeal tumor spread. Radiologists were unaware of surgical findings.
• **Other comparator tests**	None (not relevant for research question 1).
• **Reference standard**	Pathological staging, not otherwise specified.
Results	
• **Overall survival**	Not assessed.
• **Disease-free survival**	Not assessed.
• **Quality of life**	Not assessed.
• **Adverse events**	Not assessed.
• **Diagnostic accuracy (sensitivity, specificity, PPV, NPV)**	**Group 1** (MRI) vs. **Group 2** (CT). *Paraglottic space involvement:* Sensitivity: 1.00 (0.55-1.00) vs. 0.33 (0.10-0.70). Specificity: 1.00 (0.74-1.00) vs. 1.00 (0.74-1.00). PPV: 1.00 (0.55-1.00) vs. 1.00 (0.29-1.00). NPV: 1.00 (0.74-1.00) vs. 0.78 (0.54-0.91). *Thyroid cartilage invasion:* Sensitivity: 1.00 (0.45-1.00) vs. 0.50 (0.12-0.77). Specificity: 1.00 (0.77-1.00) vs. 1.00 (0.77-1.00). PPV: 1.00 (0.45-1.00) vs. 1.00 (0.29-1.00).

	NPV: 1.00 (0.77-1.00) vs. 0.89 (0.66-0.98). *Arytenoid cartilage invasion:* Sensitivity: 1.00 (0.29-1.00) vs. 1.00 (0.29-1.00). Specificity: 1.00 (0.79-1.00) vs. 1.00 (0.79-1.00). PPV: 1.00 (0.29-1.00) vs. 1.00 (0.29-1.00). NPV: 1.00 (0.79-1.00) vs. 1.00 (0.79-1.00). *Cricoid cartilage invasion:* Sensitivity: cannot be calculated since no patients had cricoid cartilage invasion. Specificity: 1.00 (0.81-1.00) vs. 1.00 (0.81-1.00). PPV: cannot be calculated since no patients had cricoid cartilage invasion. NPV: 1.00 (0.81-1.00) vs. 1.00 (0.81-1.00). *Anterior commissure involvement:* Sensitivity: 1.00 (0.62-1.00) vs. 0.25 (0.07-0.60). Specificity: 0.83 (0.54-0.96) vs. 1.00 (0.71-1.00). PPV: 0.80 (0.48-0.95) vs. 1.00 (0.29-1.00). NPV: 1.00 (0.67-1.00) vs. 0.67 (0.44-0.84).
Limitations and other comments	
• **Limitations**	Unclear whether consecutive or random sample of patients was enrolled; unclear whether any patients were excluded for inappropriate reasons; unclear whether the pathology was interpreted without knowledge of the results of imaging; unclear whether there was an appropriate interval between imaging and pathology; and not all patients were included in the analysis.

Kraft 2013 Clinical value of endosonography in the assessment of laryngeal cancer	
Methods	
• **Design**	Prospective patient cohort study (inclusion period not stated).
• **Source of funding and competing interest**	Competing interests: not reported Sponsorships: not reported Funding sources: not reported
• **Setting**	Not reported (affiliation authors: Kantonsspital AG, Aarau, Switzerland, and University Hospital of Magdeburg, Magdeburg, Germany, and Klinikum Kassel GmbH, Kassel, Germany).
• **Sample size**	Number of patients = 84 No sample size calculation reported
• **Time interval between tests**	Not reported
• **Statistical analysis**	Sensitivity, specificity, accuracy, and positive and negative predictive values in the assessment of laryngeal cancer were calculated for each imaging method. Fisher's exact test was used for statistical analysis. A value of $p < .05$ was considered statistically significant, whereas values of $p < .01$ were defined as highly significant.
Patient characteristics	
• **Eligibility criteria**	Patients undergoing microlaryngoscopy for laryngeal cancer. Patients receiving curative radiotherapy instead of surgery were excluded.
• **Patient characteristics**	Analyzed number: 76 (with complete surgical excision of their tumors) - Mean age: 63 years (range 41-90); - M/F: 71/5; - Localization (glottis/supraglottic/glotto-supraglottic/glotto-subglottic): 27/15/13/10; - Classification (T1/T2/T3/T4): 11/26/21/18; - Histology (squamous cell carcinoma/rare tumor entities): 73/3.
• **Prevalence of disease**	Not reported.
Interventions	
• **Index and comparator test**	**Group 1:** MRI scan, not otherwise specified. **Group 2:** CT scan, not otherwise specified. Ten criteria were used for staging: infiltration of the vocal fold, ventricular fold, arytenoid, epiglottis, pre-epiglottic space, paraglottic space, inner perichondrium of thyroid, thyroid cartilage, midline crossing, and maximum tumor diameter. Radiologists were blinded.
• **Other comparator tests**	Endosonography (not relevant for research question 1).
• **Reference standard**	Histopathologic examination, not otherwise specified.
Results	
• **Overall survival**	Not assessed
• **Disease-free survival**	Not assessed

• **Quality of life**	Not assessed.
• **Adverse events**	Not assessed
• **Diagnostic accuracy (sensitivity, specificity, PPV, NPV)**	**Group 1** (MRI) vs. **Group 2** (CT) **All criteria combined:** Sensitivity: 0.63 (0.51-0.73) vs. 0.68 (0.62-0.74) Specificity: 0.89 (0.80-0.94) vs. 0.84 (0.80-0.88) PPV: 0.83 (0.71-0.91) vs. 0.78 (0.72-0.83) NPV: 0.73 (0.64-0.81) vs. 0.77 (0.72-0.81) **Infiltrated structure (single criterion):** *Vocal fold* Sensitivity: 0.91 (0.60-1,00) vs. 0.92 (0.78-0.98) Specificity: 1.00 (0.45-1.00) vs. 0.43 (0.22-0.67) PPV: 1.00 (0.67-1.00) vs. 0.81 (0.66-0.90) NPV: 0,80 (0.36-0.98) vs. 0.67 (0.35-0.88) *Ventricular fold* Sensitivity: 0.50 (0.24-0.76) vs. 0.63 (0.45-0.78) Specificity: 1.00 (0.51-1.00) vs. 0.71 (0.50-0.86) PPV: 1.00 (0.51-1.00) vs. 0.76 (0.56-0.89) NPV: 0.50 (0.24-0.76) vs. 0.58 (0.39-0.74) *Arytenoid cartilage invasion* Sensitivity: 0.60 (0.23-0.88) vs. 0.42 (0.19-0.68) Specificity: 1.00 (0.67-1.00) vs. 0.79 (0.64-0.89) PPV: 1.00 (0.38-1.00) vs. 0.38 (0.18-0.65) NPV: 0.83 (0.54-0.96) vs. 0.82 (0.66-0.91) *Epiglottis* Sensitivity: 0.86 (0.46-0.99) vs 0.90 (0.80-1.00) Specificity: 0.88 (0.51-1.00) vs. 1.00 (0.86-1.00) PPV: 0.86 (0.46-0.99) vs. 1.00 (0.80-1.00) NPV: 0.88 (0.51-1.00) vs. 0.94 (0.79-0.99) *Preepiglottic space* Sensitivity: 0.60 (0.23-0.88) vs. 0.67 (0.39-0.86) Specificity: 1.00 (0.67-1.00) vs. 0.95 (0.82-0.99) PPV: 1.00 (0.38-1.00) vs. 0.80 (0.48-0.95) NPV: 0.83 (0.54-0.96) vs. 0.90 (0.77-0.97) *Paraglottic space involvement*

	Sensitivity: 0.00 (0.00-0.62) vs. 0.50 (0.29-0.71) Specificity: 0.92 (0.62-1.00) vs. 0.91 (0.76-0.98) PPV: 0.00 (0.00-0.83) vs. 0.75 (0.46-0.92) NPV: 0.79 (0.52-0.93) vs. 0.77 (0.61-0.88) *Inner perichondrium* Sensitivity: 0.25 (0.04-0.71) vs. 0.47 (0.26-0.69) Specificity: 0.91 (0.60-1.00) vs. 0.94 (0.80-0.99) PPV: 0.50 (0.10-0.90) vs. 0.80 (0.48-0.95) NPV: 0.77 (0.49-0.92) vs. 0.78 (0.63-0.88) *Thyroid cartilage invasion* Sensitivity: 0.33 (0.06-0.80) vs. 0.57 (0.33-0.79) Specificity: 0.83 (0.54-0.96) vs. 0.95 (0.81-0.99) PPV: 0.33 (0.06-0.80) vs. 0.80 (0.48-0.95) NPV: 0.83 (0.54-0.96) vs. 0.85 (0.71-0.93) *Midline crossing (anterior commissure involvement)* Sensitivity: 0.73 (0.43-0.91) vs. 0.80 (0.66-0.90). Specificity: 0.75 (0.29-0.96) vs. 0.90 (0.57-1.00). PPV: 0.89 (0.54-1.00) vs. 0.97 (0.84-1.00). NPV: 0.50 (0.19-0.81) vs. 0.53 (0.31-0.74). *Tumor diameter* Sensitivity: 0.64 (0.35-0.85) vs. 0.50 (0.34-0.66) Specificity: 0.25 (0.04-0.71) vs. 0.37 (0.19-0.59) PPV: 0.70 (0.39-0.89) vs. 0.57 (0.39-0.73) NPV: 0.20 (0.03-0.64) vs. 0.30 (0.16-0.51)
Limitations and other comments	
• **Limitations**	Unclear whether consecutive or random sample of patients was enrolled; unclear whether any patients were excluded for inappropriate reasons; unclear whether the pathology was interpreted without knowledge of the results of imaging; unclear whether there was an appropriate interval between imaging and pathology; not all patients were included in the analysis.

Zhong 2014 The Diagnostic Value of Cervical Lymph Node Metastasis in Head and Neck Squamous Carcinoma by Using Diffusion-Weighted Magnetic Resonance Imaging and Computed Tomography Perfusion	
Methods	
• **Design**	Patient cohort study, prospective or retrospective nature not cited by the authors (from May 2010 – April 2012).
• **Source of funding and competing interest**	Competing interests: none declared Sponsorships: not reported Funding sources: not reported
• **Setting**	Not reported (affiliation authors: Tianjin Union Medicine Centre, China).
• **Sample size**	Number of patients = 30 Number of lymph nodes = 65 No sample size calculation reported.
• **Time interval between tests**	Not reported
• **Statistical analysis**	ADC values and blood flow, blood volume, and mean transit time of the LNs were compared using Student's t-test. The two imaging techniques were compared using receiver operating characteristic curves (ROC curves). $P < 0.05$ was considered statistically significant.
Patient characteristics	
• **Eligibility criteria**	Previously untreated patients with head and neck squamous cell carcinoma.
• **Patient characteristics**	Analyzed number: 30 - Mean age: 53.6 years (range 38-70); - M/F: 21/9; - Localization (larynx/tongue/nasopharynx/floor of mouth/nasal cavity/oropharynx/gingiva): 9/3/6/3/4/4/1.
• **Prevalence of disease**	48/65 histologically proven metastatic lymph nodes.
Interventions	
• **Index and comparator test**	**Group 1:** DW-MRI scan. All MRI examinations were performed using a 1.5 T MRI unit (Philips Intera Achieva, Philips Medical Systems, Best, The Netherlands) with a head and neck coil. Thirty patients underwent conventional MRI and DWI to include nodes fromthe base of the skull to the suprasternal notch. Before scanning, all patients were trained to avoid swallowing during the MRI examination. In all patients the following protocol was performed: (i) fast spin-echo (FSE) T2-weighted images (TR, 4600 ms; TE, 80 ms; slice thickness, 3mm) in the axial plane; (ii) fast spin-echo (FSE) T2-weighted images (TR, 3850 ms; TE, 75ms; slice thickness, 3 mm), in the coronal plane; (iii) fast spin-echo (FSE) T1-weighted images, with fat suppression (TR, 480ms; TE, 15ms; slice thickness, 3 mm) in the axial plane; (iv) diffusion-weighted imaging with background body signal suppression (DWIBS) images (TR, 17131ms; TE, 60ms; TI, 165ms; Matrix 132 °— 98; SENSE factor 2; NSA, 6; b, 600s/mm2) in the axial and coronal planes. Image of black and white reverse image was constructed.

	The ADC values were automatically measured by standard software (Philips Extended MR Workspace, PhilipsMedical Systems, Best, The Netherlands). The ADC values were obtained by drawing ROIs around the solid portions of nodes, avoiding necroticappearing areas. Two experienced radiologists analyzed the results independently. Cut-off value ADC threshold for distinguishing benign from metastatic nodes on DW-MRI: 0.960 x 10−3 mm2/s. Disagreements (controversy about positive nodes) regarding image findings were resolved with mutual accord. **Group 2:** CT scan. Preoperative routine CT and perfusion CT scans using a multidetector 16-slice CT scanner (Philips MX 8000, Philips Medical Systems, Andover MA, USA). Selection of the nodal targets was based on a plain CT scan; nonionic iodinated contrast agent (Ultravist 370, Bayer, Germany) (45 mL, 350mg I/mL) was injected at a flow rate of 5mL/s via the antecubital vein with an injector (Liebel-Flarsheim, Cincinnati, OH, USA) for dynamic perfusion CT scanning. The perfusion CT parameters were as follows: 120 kVp, 150mAs, 16 °— 1.5 detector collimation, 3-mm slice thickness, and a scanning speed of 1 s/rotation. Thus, flow perfusion was evaluated in eight slices, including 24 mm from top to bottom. Choosing the common carotid or internal carotid artery as the input artery and internal jugular vein as the output vein, time density curves were obtained and blood flow, blood volume, and mean transit time were calculated of the regions of interest (ROIs) with perfusion software (deconvolution arithmetic) from the workstation (Extended Brilliance, Philips Medical Systems, Best,The Netherlands). ROIs again were placed in solid areas. Cut-off value blood flow for distinguishing benign from metastatic nodes on CT perfusion: 100.36 mL/100 g/min. No diagnostic values reported for blood volume or mean transit time.
• **Other comparator tests**	None (not relevant for research question 1).
• **Reference standard**	Pathologic evaluation, not otherwise specified.
Results	
• **Overall survival**	Not assessed.
• **Disease-free survival**	Not assessed.
• **Quality of life**	Not assessed.
• **Adverse events**	Not assessed.
• **Diagnostic accuracy (sensitivity, specificity, PPV, NPV)**	**Group 1** (DW-MRI) vs. **Group 2** (CT). Sensitivity: 0.90 (0.77-0.96) vs. 0.69 (0.55-0.80). Specificity: 0.77 (0.52-0.91) vs. 0.53 (0.31-0.74). PPV: 0.92 (0.79-0.97) vs. 0.81 (0.66-0.90). NPV: 0.72 (0.49-0.88) vs. 0.38 (0.21-0.57).
Limitations and other comments	
• **Limitations**	Unclear whether a consecutive or random sample of patients was enrolled; unclear whether radiologists were blinded for pathologic results and unclear whether pathologists were blinded for the results of the index tests; the thresholds that were used were not pre-specified, but based on the results of this study; and unclear whether the interval between index tests and reference test was appropriate.

Lee 2012 Diagnostic value of only 18F-fluorodeocyglucose Positron Emission Tomography/Computed Tomography–positive lymph nodes in head and neck squamous cell carcinoma	
Methods	
• **Design**	Retrospective patient cohort study.
• **Source of funding and competing interest**	Competing interests: none declared Sponsorships: none declared Funding sources: none declared
• **Setting**	Not reported (affiliation authors: Kangbuk Samsung Hospital, Seoul, Korea and Hallym University Medical Center, Seoul, Korea).
• **Sample size**	Number of patients = 114 Number of neck sides = 167 Number of nodal levels = 702 No sample size calculation reported
• **Time interval between tests**	All tests within 3 weeks prior to surgery with neck dissection.
• **Statistical analysis**	The sensitivity, specificity, accuracy, negative predictive value (NPV), and positive predictive value (PPV) were calculated for each imaging modality regarding N-classification.
Patient characteristics	
• **Eligibility criteria**	Previously untreated patients that underwent CT, MRI, US and PET/CT within three weeks prior to surgery with neck dissection. Diagnosis of squamous cell carcinoma through histopathological examination.
• **Patient characteristics**	Analyzed number: 114. - Mean age: 59.8 year (range 21-89); - M/F: 90/24; - Localisation (oral cavity/oropharynx/larynx/hypopharynx/other): 41/25/25/16/7; - Classification (T1/T2/T3/T4): 31/52/25/6.
• **Prevalence of disease**	Not reported
Interventions	
• **Index and comparator test**	**Group 1:** MRI scan. All patients underwent axial, sagittal, and coronal spinecho T1-weighted MRI imaging (Gyroscan Intera; Philips Medical Systems; repetition time [TR, ms]/echo time [TE, ms], 600/10; field of view, 200-300 nm; slice thickness, 6 mm; interslice gap, 1.2-1.8 mm; flap angle, 90 degrees; matrix, 256 æ 256; number of excitations) and 2 axial turbo spin-echo T2-weighted images (with the same parameters, except for a TR of 4000 milliseconds and TE of 100 milliseconds). Furthermore, all patients underwent T1-weighted fat suppressed imaging after intravenous administration of gadodiamide (Omniscan; GE Healthcare) at a dose of 0.1 mmol/kg body weight. **Group 2:** CT scan. Conventional 16-detector-row CT scanner (MX8000 Infinite Detector Technology; Philips Medical Systems, Best, The Netherlands) with the following parameters: 3-mm section thickness, pitch of 1.5, 4- 3 1.5-mm collimation, 120 kV, and 200 mAs. Contrast material enhancement was achieved by intravenous administration of 100 mL of nonionic contrast medium (Omnipaque 300; GE Healthcare, Princeton, New Jersey) with an injector rate of 2 mL/s.

	The diagnostic criteria for malignant LNs on CT and MRI were as follows: (1) maximum axial diameter >15 mm on level I and II and >10 mm on the other levels, (2) central necrosis or cystic degeneration, (3) spherical in shape, (4) and abnormal grouping of 3 or more borderline size LNs. All imaging tests were interpreted on an imaging-based nodal classification and were compared with histopathological findings, which served as the reference standard. The neck was divided into 10 levels (5 bilaterally, I-V), and the analysis was made on a level-by-level basis. For example, if at least a single LN met the diagnostic criteria, this was considered positive. All CT and MR images were interpreted independently by 2 radiologists. To minimize learning bias, CT and MR images were reviewed in 3 different random orders, and the reviewing procedure was performed during 3 separate sessions at 2-week intervals. Readers were blinded to the results of other imaging modalities, of each other's interpretation, and of the histopathological examination.
• **Other comparator tests**	PET/CT and US (not relevant for research question 1).
• **Reference standard**	Definitive surgery and the neck dissection were performed according to standard surgical procedures. The type of neck dissection was determined by the surgeon through clinical and 3 conventional (CT, MRI, and US) imaging findings. Negative findings on the 3 conventional imaging modalities were defined as a clinical N0 neck. A modified radical neck dissection was performed for N1 necks and selective neck dissection was performed for N0 necks, according to the primary cancer site. Specimens were labeled carefully in the operating room by the surgeon to allow correlation of histopathological findings with preoperative imaging findings. All specimens were examined by experienced pathologists, and the total number of LNs including metastatic LNs at each level were counted and reported.
Results	
• **Overall survival**	Not assessed
• **Disease-free survival**	Not assessed
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
• **Diagnostic accuracy (sensitivity, specificity, PPV, NPV)**	**Group 1** (MRI) vs. **Group 2** (CT). Sensitivity: 0.66 (0.58-0.74) vs. 0.63 (0.55-0.71). Specificity: 0.95 (0.93-0.97) vs. 0.94 (0.92-0.96). PPV: 0.79 (0.71-0.86) vs. 0.74 (0.65-0.81). NPV: 0.92 (0.89-0.94) vs. 0.91 (0.88-0.93).
Limitations and other comments	
• **Limitations**	Unclear whether the reference standard results were interpreted without knowledge of the results of the index tests.

4.2. RQ2: What is the clinical effectiveness of surgery for patients with early oropharyngeal, hypopharyngeal and laryngealcancer?

a. Surgery versus non-surgery

b. Function-sparing surgery versus extensive surgery

4.2.1. Evidence tables of systematic reviews RQ2a & RQ2b

4.2.1.1. Oropharynx

A systematic review of transoral robotic surgery and radiotherapy for early oropharynx cancer: a systematic review; Almeida 2014	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	None reported
• **Search date**	September 2012
• **Searched databases**	MEDLINE, EMBASE, CENTRAL, PsychInfo, CINAHL, and bibliographies of relevant studies
• **Included study designs**	Observational studies
• **Number of included studies**	N=20
• **Statistical analysis**	"Because of the heterogeneity of existing studies and the lack of comparator arms, meta-analysis could not be performed. However, pooled analysis was performed for certain outcomes where possible."
Patient characteristics	
• **Eligibility criteria**	Patients diagnosed with predominantly early T-stage (T1 and T2, or at least 75% of patients with T1 and T2 or subgroup data) oropharyngeal squamous cell carcinoma treated with either transoral robotic surgery (TORS) or intensity modulated radiotherapy (IMRT).
• **Exclusion criteria**	Studies were excluded if they involved nonoropharyngeal head and neck cancers.
• **Patient & disease characteristics**	Eight studies with 1,337 patients (1,010 patients with T1 or T2 tumours) investigated the role of IMRT. Twelve studies including 772 patients (502 patients with T1 or T2 tumours; 185 patients did not have stage indicated) investigated TORS.
Interventions	
• **Intervention group**	Transoral robotic surgery (TORS)
• **Control group**	Intensity modulated radiotherapy (IMRT)
Results	
• **Disease-free survival**	No results as no (randomized) comparative studies were identified.
• **Recurrence rate**	No results as no (randomized) comparative studies were identified.
• **(Loco)regional control**	No results as no (randomized) comparative studies were identified.
• **Overall survival**	No results as no (randomized) comparative studies were identified.
• **Quality of life**	No results as no (randomized) comparative studies were identified.
• **Adverse events**	No results as no (randomized) comparative studies were identified.

Limitations and other comments	
• **Limitations**	Only non-comparative studies included.

Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment; Bessell 2011	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	None known
• **Search date**	February 2011
• **Searched databases**	The Cochrane Oral Health Group Trials Register, CENTRAL, MEDLINE and EMBASE
• **Included study designs**	Randomised controlled trials
• **Number of included studies**	N=7, of which one applied to oropharyngeal cancer patients (amongst others) (N=1, yet this RCT only included two participants with cancer of the 'Tonsil/lateral pharyngeal wall')
• **Statistical analysis**	N/A (only one included study)
Patient characteristics	
• **Eligibility criteria**	Randomised controlled trials where more than 50% of participants had primary tumours of the oral cavity or oropharynx, and which compared two or more surgical treatment modalities or surgery versus other treatment modalities. Patients with oral cancer as defined by the International Classification of Diseases for Oncology (ICD-O) codes as C01-C02, C03, C04, C05-C06 (oral cavity) and cancer of the oropharynx (ICDO:C09, C10) were included.
• **Exclusion criteria**	Patients with cancer of the hypopharynx (ICD-O: C13), nasopharynx (ICD-O: C11), larynx (ICD-O: C32) or lip (ICD-O: C00) were excluded.
• **Patient & disease characteristics**	A total of 669 patients were randomly allocated; 570 were included in the analyses. Of those, only 2 patients had oropharyngeal tumours; all other patients suffered from oral cavity cancer.
Interventions	
• **Intervention group**	Surgical treatment modalities: traditional 'scalpel based' surgery, laser cutting or ablation, or harmonic scalpel.
• **Control group**	Other surgical interventions, or different treatment modalities such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery; any combinations were considered providing they were compared to surgery in at least one arm of the study.
Results	
• **Disease-free survival**	No results regarding our target population.
• **Recurrence rate**	No results regarding our target population.
• **(Loco)regional control**	No results regarding our target population.
• **Overall survival**	No results regarding our target population.
• **Quality of life**	No results regarding our target population.
• **Adverse events**	No results regarding our target population.
• **Limitations**	N/A

4.2.1.2. Hypopharynx

No systematic reviews identified.

4.2.1.3. Larynx

Transoral laser surgery versus radiotherapy: systematic review and meta-analysis for treatment options of t1a glottic cancer; Abdurehim 2012	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	None reported.
• **Search date**	February 2010
• **Searched databases**	MEDLINE, EMBASE, Cochrane Library for English-language literature and CBM disc, CNKI and VIP for Chinese-language literature
• **Included study designs**	Randomized controlled trials or head-to-head comparative studies were searched for. However, all studies identified and evaluated were nonrandomized, comparative observational studies.
• **Number of included studies**	N=19
• **Statistical analysis**	Odds ratios (ORs) and 95% CIs for dichotomous outcomes, weighted mean difference and 95% CIs for continuous outcomes, Chi-square statistic for heterogeneity evaluation, (significance set at p< .1), I^2 test for inconsistency among results. Fixed effect model in case of homogeneity, random effects model if there was significant heterogeneity among the studies. Z statistic for overall pooled effect (significance set at p< 0.05).
Patient characteristics	
• **Eligibility criteria**	Patients with T1a squamous cell carcinoma (SCC) of the glottic larynx diagnosed by laryngoscopy and biopsy.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	The total number of patients 1729 (858 vs. 871). All but 21 patients in the surgery group had stage T1a cancer; in the RT group there were 94 patients with stage T1b.
Interventions	
• **Intervention group**	Transoral laser surgery (TLS)
• **Control group**	Radiotherapy (RT)
Results	
• **Disease-free survival**	No data available.
• **Recurrence rate**	Not assessed.
• **(Loco)regional control**	Local control • 6-MV >65 Gy (7 studies, TLS n=508 vs. RT n=465) OR=0.63 (95%CI 0.42 to 0.96) • 6-MV ≤60 Gy (3 studies, TLS n=257 vs. RT n=215) OR=2.66 (95%CI 1.35 to 5.42) Overall OR=0.94 (95%CI 0.57 to 1.57), however significant heterogeneity
• **Overall survival**	TLS vs. RT (7 studies, n=520 vs. n=547)

	OR=1.22 (95%CI 0.89 to 1.66; p=0.21).
• **Quality of life**	Larynx preservation: OR= 3.11 (95%CI 1.16 to 8.34) Voice Handicap Index (VHI)[a]: MD= 1.76 (-12.81 to 16.33] Fundamental frequency (F0): MD= 13.89 (95%CI 9.64 to 18.13) Air flow rate (AFR): MD= 21.46 (95%CI -78.79 to 121.72) Jitter: MD= 0.30 (95%CI -0.29 to 0.90) Shimmer: MD= 0.19 (95%CI -0.62 to 1.01)
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	All studies identified and evaluated were nonrandomized, comparative observational studies and only 1 was prospective in design.

Radiotherapy versus open surgery versus endolaryngeal surgery (with or without laser) for early laryngeal squamous cell cancer; Dey 2002	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	Freeman Hospital Trustees, Newcastle upon Tyne, UK
• **Search date**	October 2009
• **Searched databases**	Cochrane Ear, Nose and Throat Disorders Group Trials Register; the Cochrane Central Register of Controlled Trials (CENTRAL); PubMed; EMBASE; CINAHL; Web of Science; BIOSIS Previews; Cambridge Scientific Abstracts; ISCTRN and additional sources for published and unpublished trials.
• **Included study designs**	RCT
• **Number of included studies**	N=1
• **Statistical analysis**	NA (only one included study)
Patient characteristics	
• **Eligibility criteria**	Patients diagnosed with early squamous cell carcinoma of the glottic larynx following laryngoscopy and biopsy. Early stage tumours were defined as carcinoma in situ (Tis) or invasive cancers confined to the vocal cords or with supraglottic or subglottic extension without cord fixation or nodal metastases (T1-T2, N0).
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	One multicenter RCT, undertaken in Eastern Europe, was included that evaluated 269 patients of whom 234 had glottic laryngeal cancer.
Interventions	
• **Intervention group**	Open surgery
• **Control group**	Radiotherapy and chemotherapy.

[a] Range from 0 (no impairment) to 120 (maximal impairment)

Results	
• **Disease-free survival**	**5-year disease-free survival rate (surgery vs radiotherapy; 1 RCT: n=76+129 analysed):** T1 tumours: 100% vs 71.1% ('not significant'; p-value not reported) T2 tumours: 78.8% vs 60.1% (one-sided p = 0.036)
• **Recurrence rate**	No data available
• **(Loco)regional control**	No data available
• **Overall survival**	**5-year overall survival rate** (**surgery vs radiotherapy; 1 RCT: n=76+129 analysed):** T1 tumours: 100% vs 91.7% (NS) T2 tumours: 97.4% vs 88.8% (NS)
• **Quality of life**	No data available
• **Adverse events**	No data available
Limitations and other comments	
• **Limitations**	No duplicate data extraction for the review. The authors had a number of concerns about the methodology of the included trial, such as lack of allocation concealment, no indication of how many patients were allocated to the treatment arms, unbalanced allocation, no data on diagnostic and staging procedures, no blinded outcome assessment.

Functional outcomes after radiotherapy or laser surgery in early glottic carcinoma: a systematic review; van Loon 2012	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	ZOLEON, Stichting Oncologie Holland West, Leiden, The Netherlands.
• **Search date**	August 2009
• **Searched databases**	PubMed, EMBASE, Web of Science, Cochrane Library, PsycINFO, Academic Search Premier and CINAHL.
• **Included study designs**	Observational studies
• **Number of included studies**	N=19, of which 5 compared laser with RT
• **Statistical analysis**	"Heterogeneity of outcome measures prevented data pooling."
Patient characteristics	
• **Eligibility criteria**	Patients with T1–T2 glottic or early glottic carcinoma (or tumour), treated with laser surgery, or radiotherapy or both (but only 1 modality per patient).
• **Exclusion criteria**	Studies assessing laryngeal cancer in general without specifying the location of the tumour.
• **Patient & disease characteristics**	"Thirteen papers investigated laser surgery, 5 papers compared laser surgery with radiotherapy, and 1 paper investigated radiotherapy. Nine studies reported on Tis data, and all studies reported on T1 and 7 studies on T2 tumours."
Interventions	
• **Intervention group**	Laser surgery
• **Control group**	Radiotherapy
•	

Results	
• **Disease-free survival**	Not assessed.
• **Recurrence rate**	Not assessed.
• **(Loco)regional control**	Not assessed.
• **Overall survival (5 year)**	Not assessed.
• **Quality of life**	"No statistical differences were found between laser surgery and radiotherapy using the COOP/Wonca questionnaire [one study]. However, more invasive tumours were irradiated." Voice performance: "Only 1 study evaluated voice handicap. The mean VHI score of 18 for a group of 40 irradiated patients was significantly higher than the mean VHI of 12 for 52 laser-treated patients. However, deeper invading tumours were treated with radiotherapy."
• **Adverse events**	Not assessed.
Limitations and other comments	
• **Limitations**	Study only addressed several voice quality and QoL outcomes

4.2.2. Evidence tables of observational studies RQ2a

4.2.2.1. Oropharynx

Surgical versus non-surgical management of early stage oropharyngeal squamous cell carcinoma; O'Hara 2011	
Methods	
• **Design**	Observational study (government-sponsored prospectively collated database of all new head and neck cancer patients – The Scottish Head and Neck Cancer Audit (SHNCA))
• **Source of funding and competing interest**	None reported
• **Setting**	Multi institutional database, Scotland
• **Sample size**	N=72
• **Duration**	Patient enrollment: September 1999 to August 2001
• **Follow-up**	5 years (5-year outcome data were calculated)
• **Statistical analysis**	Chi-squared test; Kaplan–Meier for survival
Patient characteristics	
• **Eligibility criteria**	Patients with stage 1 and 2 oropharyngeal squamous cell carcinoma undergoing surgical or non-surgical treatments.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=42 ; Group 2: n=30 - Mean age (range): 59 y.o. (35–89 y.o.) vs 62 (46–78 y.o.) - Sex (M/F): 27/15 vs 16/14 - Clinical T stage: T1: 20 vs 9, T2: 22 vs 21 (p = 0.54)

Interventions	
• **Intervention group (1)**	**Group 1**: Surgical treatments (included both transoral resections with primary closure, secondary intention healing, local flaps, or transcervical resections)
• **Control group (2)**	**Group 2:** Non-surgical treatment (RT, chemotherapy or both)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Local recurrences: 4/42 vs. 4/30 Regional recurrences: 3/42 vs. 2/30 (all patients with regional recurrence died of their disease)
• **(loco)regional control**	Not assessed
• **Overall survival**	Five-year OS: 60% vs 50%
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias (objective outcomes) and selective reporting; baseline imbalances; variable treatment schemes in the non-surgery group; no clear exclusion criteria

4.2.2.2. Hypopharynx

No observational studies were identified.

4.2.2.3. Larynx

An individualised treatment algorithm for tumour stage 1 glottic squamous cell carcinoma; Aydil 2013	
Methods	
• **Design**	Retrospective chart review / outcome analysis study
• **Source of funding and competing interest**	None declared
• **Setting**	University hospital (tertiary referral centre)
• **Sample size**	N=102
• **Duration**	Patient enrolment: between 2001 and 2011
• **Follow-up**	Median follow-up: 48 months (range 12 to 136 months).
• **Statistical analysis**	Chi-square test; t-test; Kaplan–Meier.
Patient characteristics	
• **Eligibility criteria**	Patients managed for T1 glottic SCC between 2001 and 2011 and with at least 12 months follow up (using the TNM staging system).
• **Exclusion criteria**	Patients with in situ carcinoma, a previous history of head and neck cancer, or previous treatment for laryngeal cancer.
• **Patient & disease characteristics**	Group 1: n=26 ; Group 2: n=69 - Mean age, years (range): 60.5 y.o. (33 to 86) (not specified per treatment group) - Sex (M/F): 92/3 (not specified per treatment group) - Clinical T stage: T1a: 86; T1b: 9 (not specified per treatment group)

Interventions	
• **Intervention group (1)**	**Group 1**: Surgery (endolaryngeal laser surgery or open partial laryngectomy). NB: Only patients with selected T1a tumours were treated with endolaryngeal laser surgery.
• **Control group (2)**	**Group 2:** Radiotherapy
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Local recurrence 3- and 5-year: 10% vs 19.3% (p=0.220) Regional recurrence 3- and 5-year: 5.6% vs 0% (p=?)
• **(loco)regional control**	Not assessed
• **Overall survival**	Overall survival 3- and 5-year: 92.3% vs 92.2% (p=?)
• **Quality of life**	Laryngeal preservation 3- and 5-year: 95.7% vs 86.7% (p=0.220)
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear concurrency of intervention and comparator group, selective reporting and unclear baseline comparability.

Multidisciplinary approach in the treatment of T1 glottic cancer; Dinapoli 2010	
Methods	
• **Design**	Retrospective analysis
• **Source of funding and competing interest**	None reported
• **Setting**	Non-academic hospital in Rome, Italy
• **Sample size**	N=143
• **Duration**	Patients treated with surgery since 1994 and with radiotherapy since 2001
• **Follow-up**	5-years
• **Statistical analysis**	Log rank test and Kaplan–Meier for survival
Patient characteristics	
• **Eligibility criteria**	Patients with T1 glottic carcinoma treated since 1994 for surgery and 2001 for radiotherapy
• **Exclusion criteria**	Not specified

• **Patient & disease characteristics**	Group 1: n=73 ; Group 2: n=70 - Median age, years (range): 63 y.o. vs 64.5 y.o. - Sex (M/F): 70/3 vs 64/6 - Clinical T stage: T1a: 61 vs 48 ; T1b: 8 vs 9 - Staging not available: 4 vs 13
Interventions	
• **Intervention group (1)**	**Group 1**: CO_2 laser surgery
• **Control group (2)**	**Group 2:** Radiotherapy (RT)
Results	
• **Disease-free survival**	5-year DFS HR=0.93 (95% CI 0.30 to 2.88) (log rank test: p=0.8979) T1a: 86.5% vs 97.8%; HR=0.25 (95% CI 0.08 to 1.50) T1b: 100% vs 53.3% (p=0.07, HR not calculable)
• **Recurrence rate**	Not assessed
• **(loco)regional control**	Not assessed
• **Overall survival**	5-year OS HR=1.11 (95% CI 0.40 to 3.30) (log rank test: p=0.7983)
• **Quality of life**	Voice Handicap Index (VHI; lower scores indicating better results) Median score 18 vs 4 (p<0.0001) RT patients scored better for all VHI domains (physical: p=0.0023, functional: p<.0001, environmental: p<0.0001)
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; high risk for concurrency of intervention and comparator group; unclear risk of selective reporting, attrition bias and unclear baseline comparability.

Voice quality after treatment of early glottic carcinoma; Jotic 2012	
Methods	
• **Design**	Prospective controlled study
• **Source of funding and competing interest**	None reported
• **Setting**	Institute of Otorhinolaryngology and Maxillofacial Surgery of the Clinical Centre of Serbia, Belgrade
• **Sample size**	N=69
• **Duration**	Patient enrolment: between November 1, 2006, and October 31, 2007
• **Follow-up**	12 months
• **Statistical analysis**	Student t tests / Wilcoxon signed rank test and the Mann-Whitney test; Post hoc Bonferroni multiple comparison correction
Patient characteristics	
• **Eligibility criteria**	Patients treated for TisN0 and T1N0 glottic carcinoma between November 2006 and October 2007 in the Institute of Otorhinolaryngology and Maxillofacial Surgery of the Clinical Centre of Serbia in Belgrade (staged using the TNM clinical classification)

• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=19 ; Group 2: n=35 ; Group 3: n=15 - Median age (range): baseline characteristics not specified - Clinical T stage: baseline characteristics not specified - N stage: baseline characteristics not specified
Interventions	
• **Intervention group (1)**	**Group 1**: CO2 laser (types III–IV cordectomy according to recommended European Laryngological Society classification of endoscopic cordectomies) (LC)
• **Control group (2)**	**Group 2**: Cordectomy through laryngofissure (CC)
• **Control group (3)**	**Group 3**: Radiotherapy (60 Gy midline doses split up in fractions of 2 Gy, five fractions each week)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(loco)regional control**	Not assessed
• **Overall survival**	Not assessed
• **Quality of life**	Voice quality "There was a significant difference in fundamental frequency (F0) values between the LC group and RT group ($p < 0.01$); jitter values also differed between the RT group and the other two groups ($z=-2.65$, $p < 0.05$ for CC group and $z=-2.06$, $p < 0.01$ for LC group). Normalized noise energy (NNE) values differed between the group treated with radiotherapy and the other two groups ($p < 0.01$), one month after treatment. Six and 12 months after the treatment, there were few differences among the groups." The authors concluded: "In the long run, patients treated with radiotherapy show better voice quality in comparison with other two groups."
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of selective reporting, attrition bias (subjective outcomes) and unclear baseline comparability. In addition, the presentation of the various results lacked clarity.

Transoral laser microsurgery elevates fundamental frequency in early glottic cancer; Luo 2012	
Methods	
• **Design**	Case series with chart review
• **Source of funding and competing interest**	Chang Gung Memorial Hospital
• **Setting**	Tertiary care medical center, Taiwan
• **Sample size**	N=42
• **Duration**	Duration of patient enrolment: 12 months (not specified when)
• **Follow-up**	Every 1 to 3 months regular follow up in the first year, every 3 to 6 months subsequently
• **Statistical analysis**	Wilcoxon signed ranked test
Patient characteristics	
• **Eligibility criteria**	Patients who received definitive treatment for early glottic cancer (Tis-2, N0, M0) over 12 months
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=18 ; Group 2: n=24 - Mean age (range): 68.6 y.o. (46–89) vs 67.6 y.o. (39–82) - Sex (M/F): 17/1 vs 23/1 - Clinical T stage: T1a: 9 vs 11 ; T1b: 3 vs 9 ; T2: 6 vs 4 - Pathology: well differentiated SCC: 5 vs 6; moderately differentiated: 8 vs 13; grade not identified: 5 vs 5
5 vs 5	
• **Intervention group (1)**	**Group 1:** Transoral laser microsurgery (TLM) (suspension laryngoscopy with adjustments for optimum exposure of the lesion under direct visualization)
• **Control group (2)**	**Group 2:** Radiation therapy (total dose of around 65–70 Gy in the larynx (33–35 fractions))
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	None of the patients had tumour recurrences
• **(loco)regional control**	Not assessed
• **Overall survival**	Not assessed
• **Quality of life**	Voice handicap index (VHI-10; lower scores indicating better results): 4.5 vs 5.6 (p=0.950) Functional Assessment of Cancer Therapy (FACT-H&N): • Physical well-being: 25.87 vs 25.48 (p=0.419) • Social/Family Well Being: 23.25 vs 25.38 (p=0.028) • Emotional well-being: 22.47 vs 21.82 (p=0.421) • Functional well-being: 22.67 vs 23.68 (p=0.575) • Head and neck cancer-specific concerns: 31.53 vs 28.61 (p=0.041) Voice Laboratory Measurements (lower scores indicating better results):

	• Maximal phonation time (s) (range): 9.43 ± 4.7 (3–18) vs 11.23 ± 6.17 (2–23) (p=0.136) • Fundamental frequency (F0): o male (Hz) (range, SD): 171.4 ± 44.6 (131–268) vs 126.8 ± 39.6 (85–189) (p=0.005*) o female (Hz): 231.5 vs 239.8 (based on 1 patient in each group) • Jitter (%):1.167 vs 1.010 (p=0.74) • Shimmer (dB): 1.779 vs 1.259 (p=0.40) • Harmonic-to-noise ratio (dB): 9.846 vs 7.927 (p=0.158)
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias (subjective outcomes) and selective reporting

Clinical outcome of early glottic carcinoma in Serbia; Milovanovic 2013	
Methods	
• **Design**	Prospective observational study
• **Source of funding and competing interest**	None reported
• **Setting**	Clinic for Otorhinolaryngology and Maxillofacial surgery of Clinical Centre of Serbia in Belgrade.
• **Sample size**	N=221
• **Duration**	Patient enrolment: from January 1 1998 to December 31 2003
• **Follow-up**	38 to 107 months
• **Statistical analysis**	Chi-squared test; Kaplan Meier; the Log-rank test; Cox proportional hazards models; Student's t test and Bonferroni multiple comparisons.
Patient characteristics	
• **Eligibility criteria**	"Patients treated with Tis and T1a glottic carcinoma in the Clinic for Otorhinolaryngology and Maxillofacial surgery of Clinical Centre of Serbia in Belgrade. Patients had no previous surgical or radiation treatment for cancer with curative intent."
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=72 ; Group 2: n=75 ; Group 3: n=74 - Mean age (range): 59.5 y.o. vs 60.9 y.o. vs 62.9 y.o. - Sex (M/F): 65/7 vs 67/8 vs 67/7 - Clinical T stage: T0: 28 vs 2 vs 0; T1a: 44/73/74 - Smokers: 69 vs 72 vs 72 - Recurrent carcinoma: 3 vs 4 vs 5
Interventions	
• **Intervention group (1)**	**Group 1**: Transoral laser microsurgery (TLM)
• **Control group (2)**	**Group 2**: Cordectomy through laryngofissure
• **Control group (3)**	**Group 3:** Radiotherapy (RT)

Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	4.2% vs 5.3% vs 6.7%
• **(loco)regional control**	Not assessed
• **Overall survival**	5-year OS: 97.2 vs 97.3 vs 95.9 6-year OS: 94.4 vs 96.0 vs 93.2 8-year OS: 91.7 vs 96.0 vs 91.9 No significant differences between the groups
• **Quality of life**	Acoustic parameters after treatment: (mean (SD)) • F0 (Hz): 162.4 (14.68) vs 151.2 (13.61) vs 159.7 (14.15) • Maximal Phonation Time (s): 15.3 (2.12) vs 14.3 (1.82) vs 17.6 (2.10) • Jitter (%):1.08 (0.11) vs 0.89 (0.11) vs 0.91 (0.14) • Shimmer (%): 3.75 (0.34) vs 2.34 (0.39) vs 2.76 (0.60) • Harmonic to Noice Ratio (dB):14.9 (1.87) vs 12.8 (1.41) vs 13.7 (0.88) "There is a highly significant difference in values of F0, shimmer and HNR between all groups ($p < 0.01$) before and six months after the treatment. There was little difference in mean values of MPT among TLM and RT group before and after the treatment, and in mean values of jitter between TLM and RT group six months after the treatment ($p > 0.05$)."
• **Adverse events**	Postoperative complications, N (%) • Local infection: 0/72 (0.0%) vs 3/75 (4.0%) vs 0/74 (0.0%) • Tracheotomy: 0/72 (0.0%) vs 0/75 (0.0%) vs 1/74 (1.4%) • Emphysema: 0/72 (0.0%) vs 3/75 (4.0%) vs 0/74 (0.0%)
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear attrition bias (subjective outcomes), selective reporting; baseline imbalances.

Evaluation of laser surgery and radiotherapy as treatment modalities in early stage laryngeal carcinoma: tumour outcome and quality of voice; Remmelts 2013	
Methods	
• **Design**	Retrospectively collected database
• **Source of funding and competing interest**	None reported
• **Setting**	The Netherlands Cancer Institute
• **Sample size**	N=248
• **Duration**	Patient enrolment: between January 2000 and July 2008
• **Follow-up**	"Minimal duration of follow-up 12 months from diagnosis, with the exception of patients who were lost to follow-up or died during this period. Regular follow-up ended 60 months after start of initial treatment." Mean follow-up in months, (range): 44 (3 to 89) vs 48 (2 to 108)
• **Statistical analysis**	Fisher's exact test, Chi-square test and Kruskal–Wallis test for patient characteristics; Kaplan–Meier with the log-rank test for assessing equality of distributions, Student's test to compare averages and Chi squared test for proportions.

Patient characteristics	
• **Eligibility criteria**	Patients with early stage (≤T2) glottic laryngeal carcinoma treated at The Netherlands Cancer Institute between January 2000 and July 2008 (classification performed according to the 2002 UICC TNM staging system).
• **Exclusion criteria**	Previous/synchronous malignancy of the head and neck (n=8), laryngeal cancer of unusual (neuro-endocrine) histology (n=2) or regional involvement at presentation (n=2)
• **Patient & disease characteristics**	Group 1: n=89 ; Group 2: n=159 - Mean age (range): 67 y.o. (41 to 87) vs 64 y.o. (39 to 89) - Sex ratio (M/F): 88/12% vs 87/13% - Clinical T stage: Tis: 23 vs 3; T1a: 49 vs 54; T1b: 15 vs 27; T2: 2 vs 75 "There were no statistically significant differences in sex or duration of follow-up. However, primary and regional tumour stages were not distributed equally between the two groups. Tumour stage was higher in the radiotherapy group, which contained the vast majority of patients with stage T2 carcinomas as well as the majority of T1b carcinomas."
Interventions	
• **Intervention group (1)**	**Group 1**: Laser surgery (direct microlaryngoscopy with complete resection of the lesion with CO2 laser)
• **Control group (2)**	**Group 2:** Radiotherapy (4-MV or 6-MV photon linear accelerator)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Local recurrence: 17/89 vs 18/159 (p=0.091) • Glottic Tis: 6/24 vs 0/3 (p=0.277) • Glottic T1a: 7/50 vs 3/54 (p=0.307) • Glottic T1b and T2: 4/17 vs 14/102 (p=0.288) Regional recurrence: 2/89 vs 2/159 (p=0.620) Distant metastases: 0/89 vs 1/159 (p=0.641)
• **(loco)regional control**	Local control (with initial treatment modality): 77/89 vs 142/159 5-year local control: 75% vs 86% (p=0.070) Glottic Tis Local control (with initial treatment modality): 20/24 vs 3/3 5-year local control: 86% vs 100% (p=0.566) Glottic T1a Local control (with initial treatment modality): 45/50 vs 51/54 5-year local control: 81% vs 93% (p=0.382) Glottic T1b and T2 Local control (with initial treatment modality):14/17 vs 89/102 5-year local control: 78% vs 80% (p=0.310)
• **Overall survival**	Overall survival: 80/89 vs 125/159

	5-year overall survival 90% vs 72% (p=0.106) Glottic Tis Overall survival: 21/24 vs 3/3 5-year overall survival: 96% vs 66% (p=0.084) Glottic T1a Overall survival: 45/50 vs 44/54 5-year overall survival: 86 % vs 89% (p=0.561) Glottic T1b and T2 Overall survival: 14/17 vs 77/102 5-year overall survival: 85% vs 81% (p=0.885)
• **Quality of life**	Larynx preservation 87/89 vs 142/159 5-year larynx preservation 93% vs 83% (p=0.049) Glottic Tis Larynx preservation: 23/24 vs 3/3 5-year larynx preservation: 95% vs 100% (p=0.808) Glottic T1a Larynx preservation: 50/50 vs 52/54 5-year larynx preservation: 100% vs 93% (p=0.267) Glottic T1b and T2 Larynx preservation: 15/17 vs 88/102 5-year larynx preservation: 67% vs 75 % (p=0.097) Quality of voice after treatment (analysed by means of the ‘‘physical subscale’’ of the voice handicap index (VHI; lower scores indicating better results) and percentage of voice deficiency (based on a five-item questionnaire designed by van Gogh et al.) Tis: (n=13) vs (n=0) VHI, mean ± SD (range): 10.6 ± 6.1 (0–20) vs - five-item: 31% vs - T1a: (n =36) vs (n=31) VHI, mean ± SD (range): 12.0 ± 9.9 (0–28) vs 7.9 ± 7.5 (0–24) (p=0.06) five-item: 33% vs 23% (p=0.330) T1b: (n=8) vs (n=14) VHI, mean ± SD (range): 16.7 ± 9.0 (0–26) vs 4.9 ± 6.6 (0–21) (p=0.003) five-item: 75% vs 7% (p=0.001)

	T2: (n=2) vs (n=38) VHI, mean ± SD (range): 10.0 ± 4.2 (7–13) vs 9.9 ± 8.0 (0–30) five-item: 0% vs 29% Total: (n=59) vs (n=83) VHI, mean ± SD (range) 12.4 ± 8.9 (0–28) vs 8.3 ± 7.7 (0–30) (p=0.005) five-item: 37% vs 23% (p=0.062)
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of selective reporting and concurrency of the intervention and comparator group; high risk of bias due to baseline imbalances.

Risk of fatal cerebrovascular accidents after external beam radiation therapy for early stage glottic larynx cancer; Swisher-McClure 2014	
Methods	
• **Design**	Retrospective observational cohort study (using registry data from the Surveillance, Epidemiology, and End Results (SEER) Database)
• **Source of funding and competing interest**	Paul Celebresi National Cancer Institute Career Development Award (K12-CA076931)
• **Setting**	Unclear
• **Sample size**	N=8721
• **Duration**	Patient enrolment: between January 1, 1983 and December 31, 2008
• **Follow-up**	Median follow-up time: 5.3 years (interquartile range 2.4–9.4 years)
• **Statistical analysis**	Chi-square statistics for categorical variables and t-tests for continuous variables; competing risks data analysis for survival and cumulative incidence of fatal CVA by treatment; cumulative incidence functions using k-sample test statistics, multivariable competing risks regression models to adjust for potential confounders and sensitivity analysis.
Patient characteristics	
• **Eligibility criteria**	Patients diagnosed with pathologically confirmed squamous cell carcinoma of the glottic larynx (stage I disease) diagnosed between January 1, 1983 and December 31, 2008.
• **Exclusion criteria**	Patients receiving both surgery and EBRT were excluded.
• **Patient & disease characteristics**	Group 1: n=1484 ; Group 2: n=7237 - Mean age (SD): 64.5 y.o. (12.3) vs 65.3 y.o. (11.3) - Clinical T stage: not specified “The two treatment groups were similar with respect to patient and demographic characteristics. There was a statistically significant difference between the treatment groups in mean age (EBRT: 65.3 yrs, Surgery: 64.5 yrs; p=0.01) and race.”
Interventions	
• **Intervention group (1)**	**Group 1**: Surgery
• **Control group (2)**	**Group 2**: External beam radiation therapy (EBRT)

Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(loco)regional control**	Not assessed
• **Overall survival**	Overall Survival (EBRT vs. Surgery): HR=1.03, 95% CI 0.91–1.13 "There was no significant difference in overall survival between the treatment groups in either unadjusted analyses (data not shown) or in multivariable Cox proportional hazards models."
• **Quality of life**	Not assessed
• **Adverse events**	Death from CVA (Cumulative incidence): 5 year % (95% CI): 0.6 (0.2–1.0) vs 1.0 (0.8–1.3) 10 year % (95% CI): 1.4 (0.7–2.1) vs 2.0 (1.6–2.4) 15 year % (95% CI): 1.5 (0.8–2.3) vs 2.8 (2.3–3.4) 20 year % (95% CI): 1.5 (0.8–2.3) vs 3.7 (2.9–4.5) 25 year % (95% CI): 1.5 (0.8–2.3) vs 4.0 (3.0–4.9) Death from Heart Disease (Cumulative incidence): 5 year % (95% CI): 5.7 (4.4–7.0) vs 5.2 (4.6–5.7) 10 year % (95% CI): 11.2 (9.2–13.2) vs 10.2 (9.3–11.0) 15 year % (95% CI): 14.8 (12.4–17.3) vs 14.3 (13.2–15.5) 20 year % (95% CI): 19.0 (15.8–22.1) vs 17.7 (16.2–19.2) 25 year % (95% CI): 21.6 (17.8–25.4) vs 20.2 (18.0–22.3) Risk of Fatal CVA (EBRT vs. Surgery) Multivariable Competing Risks Regression Model: HR=1.75, 95% CI 1.04–2.96 Univariate Unadjusted Competing Risks Regression Model: HR=1.72, 95% CI 1.02–2.89 Risk of Fatal Heart Disease (EBRT vs. Surgery) Multivariable Competing Risks Regression Model: HR=0.912, 95% CI 0.77–1.09
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias, selective reporting and concurrency of the intervention and comparator group

Prospective evaluation of voice outcome during the first two years in male patients treated by radiotherapy or laser surgery for T1a glottic carcinoma; van Gogh 2012	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	Not reported
• **Setting**	Not reported
• **Sample size**	N=106
• **Duration**	9 years
• **Follow-up**	24 months
• **Statistical analysis**	Independent t tests and paired t tests
Patient characteristics	
• **Eligibility criteria**	Male patients treated for T1aN0M0 (T1a: tumour limited to one vocal fold with normal mobility; N0: no regional lymph node metastasis; M0: no distant metastasis, UICC staging system) glottic cancer.
• **Exclusion criteria**	Patients who were treated for recurrence or suspicion of recurrence of the tumour during the follow-up period.
• **Patient & disease characteristics**	Group 1: n=67 ; Group 2: n=39 - Mean age, years (range): 66 (34 to 87) vs 65 (44 to 85) - Clinical T stage: all T1aN0M0 - All males
Interventions	
• **Intervention group (1)**	**Group 1**: Endoscopic laser surgery (Sharplan CO2-laser)
• **Control group (2)**	**Group 2**: Radiotherapy (total radiation was 57.5–60.0 Gy (2.5 Gy per fraction, five times a week)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	2/39 vs 2/67 (RR=1.72; 95% CI 0.25 to 11.72)
• **(loco)regional control**	Not assessed
• **Overall survival**	Not assessed
• **Quality of life**	Larynx preservation at 2 years 37/39 (94.9%) vs 67/67 (100%) (RR=0.95; 95% CI 0.88 to 1.02) Voice outcomes (lower scores indicating better results), mean (SD) • At 3 months o Jitter: 0.31 (.22) vs 0.64 (0.55) o Shimmer: 4.55 (1.98) vs 6.78 (3.26) o NNE: -8.38 (3.90) vs -6.94 (3.79) o F0: 153 (40) vs 121 (29) • At 6 months o Jitter: 0.36 (0.30) vs 0.51 (0.54)

	o Shimmer: 4.89 (2.75) vs 5.70 (2.54) o NNE: -9.46 (4.43) vs -8.57 (3.92) o F0: 147 (28) vs 132 (37) • At 12 months o Jitter: 0.47 (0.75) vs 0.48 (0.41) o Shimmer: 5.06 (4.46) vs 5.39 (2.66) o NNE: -9.64 (5.09) vs -8.11 (4.45) o F0: 144 (31) vs 129 (32) • At 24 months o Jitter: 0.46 (0.49) vs 0.62 (0.62) o Shimmer: 5.28 (3.19) vs 5.81 (3.75) o NNE: -8.39 (4.23) vs -7.17 (4.00) o F0: 141 (33) vs 124 (29)
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias, selective reporting and concurrency of the intervention and comparator group

4.2.3. Evidence tables of observational studies RQ2b

4.2.3.1. Oropharynx

No observational studies were identified.

4.2.3.2. Hypopharynx

No observational studies were identified.

4.2.3.3. Larynx

Evaluation of available surgical management options for early supraglottic cancer; Karatzanis 2009	
Methods	
• **Design**	Retrospective study
• **Source of funding and competing interest**	Not reported
• **Setting**	Department of Otorhinolaryngology, Head and Neck Surgery, University of Erlangen–Nuremberg Medical School, Erlangen, Germany
• **Sample size**	N=101
• **Duration**	Patient enrolment between 1970 and 2004
• **Follow-up**	Mean follow up 67 months
• **Statistical analysis**	Kaplan–Meier method and chi-square test.

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Patient characteristics	
• **Eligibility criteria**	Patients who underwent primary surgical treatment for pT1 or pT2/pN0 or cN0/M0 supraglottic carcinomas between 1970 and 2004 (AJCC and UICC classification). NB: “It was noted that all patients who underwent a neck dissection were pN0 while the rest were cN0” NB: ”Only cases that had been observed for at least 60 months were evaluated.”
• **Exclusion criteria**	Patients with insufficient data, systemic disease at the time of diagnosis, histology other than squamous cell carcinoma, patients with second primary tumors at the time of diagnosis, and those who received postoperative radiotherapy and/or chemotherapy.
• **Patient & disease characteristics**	Group 1: n= 49; Group 2: n= 29; Group 3: n= 23 (only T2) - Mean age, years (range): 60 (36 to 83) - Sex (M/F): 90/11 (results not specified per treatment group) - Clinical T stage: T1: 19 (TLM) vs 10 (HL) vs 0 (TL) ; T2: 30 (TLM) vs 19 (HL) vs 23 (TL) “No significant differences were noted regarding age and sex distribution among groups of patients undergoing different surgical procedures.”
Interventions	
• **Intervention group (1)**	**Group 1**: Transoral CO2 laser microsurgery (TLM)
• **Control group (2)**	**Group 2**: Horizontal laryngectomy (HL)
• **Control group (3)**	**Group 3**: Total laryngectomy (TL)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(loco)regional control**	Local control T1 cases (TLM vs HL) “No statistically significant differences were noted between the different types of procedures (p=0.924).” Local control T2 cases (TLM vs HL vs TL) “No statistically significant differences were noted among the different types of procedures (p=0.143).”
• **Overall survival**	Not assessed (disease-specific survival only)
• **Quality of life**	Not assessed
• **Adverse events**	Complications: 5/49 (10.2%) vs 7/29 (24.1%) vs 4/23 (17.4%) “Major complications in this series included postoperative bleeding, aspiration, fistula or granulation tissue formation, and dyspnea. A lower incidence was noted for TLM compared with open techniques, although statistical significance was not reached (TLM vs HL p=.09 and TLM vs TL p=.20).” “A significantly lower incidence of related tracheotomies was found regarding TLM compared to transcervical techniques (TLM vs HL and TLM vs TL, p<0 .001).”
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias and concurrency of intervention and comparator group; baseline imbalances.

4.3. RQ3: Surgery versus organ / function preservation strategies

4.3.1. Evidence tables of systematic reviews RQ3

4.3.1.1. Oropharynx

Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment; Bessell 2011	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	None known
• **Search date**	February 2011
• **Searched databases**	The Cochrane Oral Health Group Trials Register, CENTRAL, MEDLINE and EMBASE
• **Included study designs**	Randomised controlled trials
• **Number of included studies**	N=7, of which one applied to oropharyngeal cancer patients (amongst others) (N=1, yet this RCT only included two participants with 'Tonsil/lateral pharyngeal wall'
• **Statistical analysis**	N/A (only one included study)
Patient characteristics	
• **Eligibility criteria**	Randomised controlled trials where more than 50% of participants had primary tumours of the oral cavity or oropharynx, and which compared two or more surgical treatment modalities or surgery versus other treatment modalities. Patients with oral cancer as defined by the International Classification of Diseases for Oncology (ICD-O) codes as C01-C02, C03, C04, C05-C06 (oral cavity) and cancer of the oropharynx (ICDO:C09, C10) were included.
• **Exclusion criteria**	Patients with cancer of the hypopharynx (ICD-O: C13), nasopharynx (ICD-O: C11), larynx (ICD-O: C32) or lip (ICD-O: C00) were excluded.
• **Patient & disease characteristics**	A total of 669 patients were randomly allocated; 570 were included in the analyses. Of those, only 2 patients had oropharyngeal tumours; all other patients suffered from oral cavity cancer.
Interventions	
• **Intervention group**	Surgical treatment modalities: traditional 'scalpel based' surgery, laser cutting or ablation, or harmonic scalpel.
• **Control group**	Other surgical interventions, or different treatment modalities such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery; any combinations were considered providing they were compared to surgery in at least one arm of the study.
Results	
• **Disease-free survival**	No results regarding our target population.
• **Recurrence rate**	No results regarding our target population.
• **(Loco)regional control**	No results regarding our target population.
• **Overall survival**	No results regarding our target population.
• **Quality of life**	No results regarding our target population.
• **Adverse events**	No results regarding our target population.
• **Limitations**	N/A

4.3.1.2. Hypopharynx

No systematic reviews were identified

4.3.1.3. Larynx

T4a Laryngeal Cancer Survival: Retrospective Institutional Analysis and Systematic Review; Francis 2014	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	None
• **Search date**	April 2013
• **Searched databases**	MEDLINE (via PubMed) and Embase
• **Included study designs**	All types of studies
• **Number of included studies**	N=24 retrospective studies (both comparative studies and case series), N=7 relevant for RQ 3 No RCT was identified.
• **Statistical analysis**	Meta-analysis could not be performed
Patient characteristics	
• **Eligibility criteria**	Studies reporting overall survival outcomes in T4a laryngeal cancer. Only studies published in English or French were included.
• **Exclusion criteria**	No separation of OS by treatment modality, other types of survival outcomes, and no isolation of T4 cases of laryngeal cancer (other stages/other sites of tumor).
• **Patient & disease characteristics**	No baseline patient characteristics reported.
Interventions	
• **Intervention group**	Any treatment modality for laryngeal cancer For this RQ, only surgical procedures were relevant and are therefore reported (neck dissection; supracricoid laryngectomy; salvage surgery; primary laryngectomy; transoral laser microsurgery)
• **Control group**	Organ/function preservation strategies.
Results	
• **Disease-free survival**	Not addressed
• **Recurrence rate**	Not addressed
• **(Loco)regional control**	Not addressed
• **Overall survival**	Primary laryngectomy (+ radiotherapy/chemotherapy if needed) vs chemoradiation therapy (3 studies) Bussu 2012: 2 years: 100% vs 60% Patel 2011: 2 years: 90% vs <30% Gourin 2009: 5 years: 55% vs 25% Primary laryngectomy (+ radiotherapy/chemotherapy if needed) vs radiotherapy (4 studies) Dziegielewski 2012: 2 years: 60% vs 12%; 5 years: (2 years), 49% vs. 5% Jancic 2012: 1 year: 60% vs. 54.6%; 2 years: 30% vs. 21.2%; 5 years: 10% vs 9.1% Santos 1998: 5 years: 41% vs 11%

	Finizia 1996: 5 years: 58% vs 32%
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
Limitations and other comments	
• **Limitations**	Only retrospective studies identified; limited numbers of patients in single institutions; heterogeneity (no meta-analysis possible).

4.3.2. Evidence tables of RCTs RQ3

Final results of a randomized trial comparing chemotherapy plus surgery plus radiotherapy in locally advanced resectable hypopharyngeal carcinomas; Beauvillain 1997	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center (France)
• **Sample size**	N=92
• **Duration**	Patient enrolment between 1985 and 1989
• **Follow-up**	Regular follow-up at 3-month intervals for the first and second year, 6-month intervals for the third to the fifth year, and 12-month intervals thereafter. Mean follow-up: 92 months (range 64-115 months).
• **Statistical analysis**	Kaplan-Meier and log-rank test for local control and survival. Intention-to-treat analysis.
Patient characteristics	
• **Eligibility criteria**	Patients less than 70 years of age with T3 or T4, N0-N3 resectable squamous cell hypopharyngeal carcinoma and a performance status of 2 or less.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=47 ; Group 2: n=45 - Median age (range): 56 (35 to 69) vs 54.5 (38 to 68) - Clinical T stage: T3: 45 vs 41, T4: 1 vs 3 - N stage: N0: 13 vs 14, N1: 8 vs 4, N2: 19 vs 20, N3: 6 vs 6 'No differences were noted in sex, age and performance status. The distribution of T and N stages (1987 TNM classification) was similar between the two arms. The tumour was located in the pyriform sinus in all cases.'
Interventions	
• **Intervention group (1)**	**Group 1**: total laryngopharyngectomy plus unilateral or bilateral radical or conservative lymph node dissection plus postoperative radiotherapy All patients received three courses of neoadjuvant chemotherapy prior to locoregional treatment
• **Control group (2)**	**Group 2** : radiotherapy with or without salvage surgery All patients received three courses of neoadjuvant chemotherapy prior to locoregional treatment
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed

• **(loco)regional control**	5-year local control: 63% vs 39% (p<0.01)
• **Overall survival**	5-year overall survival: 37% vs 19% (p=0.04) Died (any cause; mean follow-up 92 months): 33/46 vs 38/44 (RR=0.83; 95% CI 0.67 to 1.03)
• **Quality of life**	Not assessed
• **Adverse events**	Toxicity of chemotherapy: 24/46 vs 23/44 (RR=1.00; 95% CI 0.67 to 1.48) Grade III-IV Hematologic: 4 vs 4 Infectious 1 vs 1 Venous 1 vs 2 Neurologic 1 vs 0
Limitations and other comments	
• **Limitations**	High risk of bias for blinding of participants and personnel and blinding outcome assessment (subjective outcomes)

Radical radiation vs surgery plus post-operative radiation in advanced (resectable) supraglottic larynx and pyriform sinus cancers: a prospective randomized study; Bhalavat 2003	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Not reported
• **Setting**	Single centre (India)
• **Sample size**	N=72
• **Duration**	Patient enrolment between August 1991 and December 1995
• **Follow-up**	Mean follow-up 24 months
• **Statistical analysis**	Kaplan-Meier and log-rank test for local control and survival. Intention-to-treat analysis
Patient characteristics	
• **Eligibility criteria**	Patients with T3/T4 squamous carcinoma of supraglottic larynx and ipsilateral early nodal disease (N0-2b) with good general condition
• **Exclusion criteria**	Age >70years, bilateral nodal disease at presentation or in stridor
• **Patient & disease characteristics**	Group 1: n=39 ; group 2: n=33 - Median age (range): 54 y (42–66) vs 53 y (42–65) - Sex (male/female): 31/4 vs 28/1 - Clinical T stage: T3: 28 vs 27, T4: 7 vs 2 - Clinical N stage: N0: 16 vs 15, N1: 12 vs 10, N2a: 4 vs –, N2b: 3 vs 4 'Clinical T and N distributions were almost equal in both arms.'
Interventions	
• **Intervention group (1)**	**Group 1**: radical surgery (total laryngectomy, near-total laryngectomy or laryngo-pharyngectomy with/without modified nodal dissection) followed by postoperative radiation therapy
• **Control group (2)**	**Group 2**: radical radiation therapy followed by salvage surgery

Results	
• **Disease-free survival**	5-years disease free survival: 70% vs 50% (p=0.04)
• **Recurrence rate**	6/35 vs 13/29 (RR=0.38; 95% CI 0.17 to 0.88)
• **(loco)regional control**	23/35 vs 19/29 (RR=1.0; 95% CI 0.70 to 1.43)
• **Overall survival**	5-year overall survival: 73% vs 77% (p=0.79)
• **Quality of life**	Not assessed
• **Adverse events**	Immediate post-operative complications: 8/35 'Seven patients had complications in the form of necrosis, anastomotic leak, fistulae, or delayed wound healing while one resulted in a post-operative death. Three out of seven patients died later of post-operative complications while remaining four patients were lost to follow-up.'
Limitations and other comments	
• **Limitations**	High risk of bias for blinding of participants and personnel and blinding outcome assessment (subjective outcomes)

Larynx preservation in pyriform sinus cancer: preliminary results of a European Organisation for Research and Treatment of Cancer phase III trial; Lefebvre 1996 Laryngeal preservation with induction chemotherapy for hypopharyngeal squamous cell carcinoma: 10-year results of EORTC trial 24891; Lefebvre 2012	
Methods	
• **Design**	RCT + 10-year follow-up of the same RCT
• **Source of funding and competing interest**	National Cancer Institute, EORTC
• **Setting**	Multicenter (France)
• **Sample size**	N=202 (10-year follow-up: N=194)
• **Duration**	December 1993 - ?
• **Follow-up**	Lefebvre 1996: median 51 months (range 3-106 months) Lefebvre 2012: median 10.5 years
• **Statistical analysis**	Kaplan-Meier and one-sided logrank test for equivalence. Both 95% confidence intervals and corrected 95% confidence intervals (based on an O'Brien-Fleming procedure with an alpha spending function, which corresponds to the 99.65% confidence interval) were presented.
Patient characteristics	
• **Eligibility criteria**	Histologically proven squamous cell carcinoma of the pyriform sinus or of the hypopharyngeal aspect of the aryepiglottic fold classified (American Joint Committee on Cancer/International Union Against Cancer joint classification 1987) as T2 (excluding exophytic T2 lesions of the membranous portion of the pyriform sinus or of the aryepiglottic fold), T3, or T4 with N0, N1, N2a, or N2b stages of neck involvement, had not received any previous treatment and were free of other cancers (except in situ carcinoma of the cervix and adequately treated basal or squamous cell carcinoma of the skin) as well as distant metastases, were between 18 and 75 years of age and had to have a medical condition that could be treated with surgery under general anesthesia or with chemotherapy.
• **Exclusion criteria**	Patients with a possibility of either surgery for preserving functional larynx or extended surgery requiring a plastic procedure for pharyngeal closure were not eligible.

• **Patient & disease characteristics**	Group 1: n=99 ; Group 2: n=103 - Median age (range): 54.5 (35.8–70.3) vs 56.3 (37.9–70.4) - Stage: II: 6 vs 7, III: 51 vs 59, IV: 37 vs 34 - Tumour site: Pyriform sinus: 74 vs 78, Aryepiglottic fold: 20 vs 22 - Clinical N stage: N0: 6 vs 7, N1: 4 vs 8, N2a: 0 vs 3, N2b: 5 vs 2, N3: 1 vs 2 - Clinical T stage: T2: 16 vs 22, T3: 69 vs 74, T4: 7 vs 4 'There was no significant difference between the distribution of patients in the two arms with respect to sex, age, World Health Organization performance status, presence of associated diseases, primary site and histology, T classification, N classification, or stage grouping'
Interventions	
• **Intervention group (1)**	**Group 1**: total laryngectomy with partial pharyngectomy, radical neck dissection and postoperative irradiation.
• **Control group (2)**	**Group 2** : larynx-preserving treatment (induction chemotherapy plus definitive, radiation therapy in patients who showed a complete response or surgery in those who did not respond).
Results	
• **Disease-free survival**	Median DFS: 20 vs 25 months 3-year : 32% (95% corrected CI 17% to 47%) vs 43% (95% corrected CI 28% to 58%) 5-year: 27% (eight patients at risk) vs 25% (11 patients at risk) Lefebvre 2012: Progression-free survival Median in years (95% CI): 1.6 (1.2 to 2.4) to 2.1 (1.4 to 3.6) 5-year event-free rate (95% CI) 26.4% (17.5 to 35.4) vs 31.7% (22.5 to 40.9) 10-year event-free rate (95% CI) 8.5% (2.0 to 15.0) vs 10.8% (3.8 to 17.9)
• **Recurrence rate**	Not assessed
• **(loco)regional control**	Not assessed
• **Overall survival**	Median OS: 25 vs 44 mo 3 years 43% (95% corrected CI 27% to 59%) vs 57% (95% corrected CI 42% to 72%) "Observed dead HR" of CRT vs surgery: RR=0.86 (corrected 95%-CI 0.50 to 1.48) 5-year survival rate (95% CI): 32.6% (23.0 to 42.1) vs 38.0% (28.4 to 47.6) 10-year survival rate (95% CI): 13.8% (6.1 to 21.6) vs 13.1% (5.6 to 20.6)
• **Quality of life**	Not assessed
• **Adverse events**	'No drug-related serious adverse events were noted.'
Limitations and other comments	
• **Limitations**	High risk of bias for blinding of participants and personnel

Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer; Veterans 1991 Long-term quality of life after treatment of laryngeal cancer. The Veterans Affairs Laryngeal Cancer Study Group; Terrell 1998	
Methods	
• **Design**	RCT + long-term follow-up survey of quality of life
• **Source of funding and competing interest**	Department of Veterans Affairs Cooperative Studies Program
• **Setting**	Multicenter (USA)
• **Sample size**	N=332
• **Duration**	Patient enrolment: unclear
• **Follow-up**	Veterans 1991: Median follow-up 33 months (range 11 to 62 months) Terrell 1998: mean 10.4 years (range 8.5-12.7 years).
• **Statistical analysis**	Kaplan-Meier and log-rank test. Chi-square test and Student's t-test for analysis of categorical and continuous variables. All randomized patients were included in the analysis.
Patient characteristics	
• **Eligibility criteria**	Biopsy-proven, previously untreated Stage III or IV squamous carcinoma of the larynx, according to the 1985 classification system of the American Joint Committee on Cancer. The laboratory criteria required before treatment included a score for performance status above 50 points on the Karnofsky scale, a creatinine clearance ≥ ml per second, a white cell count ≥4000 per cubic millimetre, a platelet count ≥ 100.000 per cub millimeter, and a adequate auditory, nutritional, pulmonary and cardiac status.
• **Exclusion criteria**	Patients with T1N1 carcinomas, unresectable cancers, distant metastases, previous radiation therapy to the head or neck or previous cancers.
• **Patient & disease characteristics**	Group 1: n=166 ; Group 2: n=166 - Median age (range): 62 years (24 to 79) (median age not specified per group) - Stage: III: 95 vs 93, IV: 71 vs 73 - Tumour class: T1,2 : 15 vs 16, T3 : 109 vs 107, T4 : 42 vs 43 - Node class : N0 : 94 vs 86, N1 : 26 vs 34, N2 : 21 vs 16, N3 : 25 vs 30 - Site: glottic: 63 vs 61, supraglottic: 103 vs 105, cartilage invasion: 13 vs 17, fixed vocal cords: 98 vs 90. 'There were no significant differences between the treatment groups with respect to age, sex, or known prognostic factors, including performance status, T class, tumour stage, tumour site, tumour grade, cartilage involvement or vocal-cord fixation.' QoL follow-up study in 46 of 65 survivors: 'Baseline demographic and clinical characteristics among survey responders were similar, except that those in the CT + RT group were significantly older compared to those in the surgery and RT group (mean 61.2 years vs mean 55.7 years, p<.05)'
Interventions	
• **Intervention group (1)**	**Group 1**: surgery and radiation therapy
• **Control group (2)**	**Group 2:** three cycles of chemotherapy (cisplatin and fluorouracil) and radiation therapy

Results	
• **Disease-free survival**	'Disease free survival tended to be shorter in the chemotherapy group than in the surgery group, but the difference was not statistically significant (p=0.1195).'
• **Recurrence rate**	42/166 vs 52/166 (RR=0.81; 95% CI 0.57 to 1.14) Primary (recurrences with either positive or negative nodes): 4/166 vs 20/166 (RR=0.20; 95% CI 0.07 to 0.57) Regional: 9/166 vs 14/166 (RR=0.64; 95% CI 0.29 to 1.44) Distant: 29/166 vs 18/166 (RR=1.61; 95% CI 0.93 to 2.79)
• **(loco)regional control**	Not assessed
• **Overall survival**	2-year survival: 68% (95% CI 60 to 75%) vs 68% (95% CI 60 to 76%) (P=0.9846) Died: 58/166 vs 65/166 (RR=0.89; 95% CI 0.67 to 1.18)
• **Quality of life**	Long-term quality of life survey assessed by University of Michigan Head and Neck Quality of Life (HNQOL) instrument, SF-36, and the Beck Depression Inventory in 46 of 65 survivors. 'Patients randomized to the CT + RT group had significantly better (P<.05) quality-of-life scores on the SF-36 mental health domain (76.0) than the surgery and RT group (63.0), and also had better HNQOL pain scores (81.3 vs 64.3). Compared with patients who underwent laryngectomy, patients with intact larynges (CT + RT with larynx) had significantly less bodily pain (88.5 vs 56.5), better scores on the SF-36 mental health (79.8 vs 64.7), and better HNQOL emotion (89.7 vs 79.4) scores. More patients in the surgery and RT group (28%) were depressed than in the CT + RT group (15%).'
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	High risk of bias for blinding of participants and personnel and blinding outcome assessment (subjective outcomes)

4.3.3. Evidence tables of observational studies RQ3

Long-term quality of life after treatment for locally advanced oropharyngeal carcinoma: Surgery and postoperative radiotherapy versus concurrent chemoradiation; Boscolo-Rizzo 2009	
Methods	
• **Design**	Cross-sectional study
• **Source of funding and competing interest**	None declared
• **Setting**	Single center: University of Padua, Treviso Regional Hospital, Italy
• **Sample size**	N=57 (n=60 eligible of which n=3 refused to participate)
• **Duration**	Cross-sectional evaluation in May 2008 of patients treated between January 1998 and April 2006

• **Follow-up**	Median follow-up for surviving patients was 56 months (range, 11–124)
• **Statistical analysis**	Survival was calculated from the date of the end of treatment and was analyzed using the standard Kaplan–Meier method. Hazard ratios were calculated with the use of the Cox proportional-hazards model. Chi-square test, Fisher's exact test, Student t test were used to assess group differences. The scores of the quality of life were calculated according to the EORTC QLQ scoring manual. Nonparametric Wilcoxon rank sum analysis was used.
Patient characteristics	
• **Eligibility criteria**	Patients with previously untreated T3–T4 oropharyngeal carcinoma, who have complete remission after surgery plus postoperative radiotherapy (PORT) or chemoradiotherapy (CRT), and treatment was completed at least 24 months prior to inclusion in the study.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1 (Surgery + PORT): n=26 vs. Group 2 (CRT): n=31 - Mean age (range) at time of evaluation 57 (45-77) yrs vs. 62 (42–73) yrs; - Gender M/F: 22/4 vs. 26/5; - Stage III/IV: 14/12 vs. 15/16; - Neck dissection yes/no: 20/6 vs. 6/25; - Mean time (range) from the end of treatment 72 (34–123) months vs. 56 (25–124) months Median age (range) at diagnosis: 61 (42–77) yrs, male (84.2%) "The two groups did not differ significantly with respect to age, sex, tumor stage, comorbidities, and average time of QoL assessment."
Interventions	
• **Intervention group (1)**	**Group 1:** Surgery and postoperative radiotherapy (PORT) (n=26) Resection of the primary tumor via transoral, transcervical, or combined approach with an elective neck dissection in the N0 neck (selective neck dissection or type III radical modified neck dissection) or a therapeutic neck dissection in the N+ neck (radical or radical modified neck dissection depending on N-stage). PORT was performed in patients with more than one positive lymph node, extracapsular extension, perineural tumor invasion, lymphovascular invasion, positive tumor margins, and in patients with T4 tumors. A volume encompassing the primary site and all draining lymph nodes at risk was prescribed to receive a dose of 60 Gy in 30 fractions over a period of 6 weeks. Both sides of the neck were prescribed to receive a boost of electrons with a dose of 4 Gy in N0 and 14 Gy in N+ cases.
• **Control group (2)**	**Group 2:** Concurrent platinum-based chemoradiotherapy (CRT) (n=31) Radiotherapy: a volume encompassing the primary site and all draining lymph nodes at risk was prescribed to receive 70 Gy in 35 fractions over a period of 7 weeks. Both sides of the neck were prescribed to receive a boost of electrons with a dose of 4 Gy in N0 and 14 Gy in N+ cases. Concurrently with radiation therapy, patients were administered at least two cycles of chemotherapy using cis-platinum 100 mg/m2 on day 1, 5-fluorouracil 1000 mg/m2 as a continuous infusion on days 1–5.

	A neck dissection was planned for patients with node metastasis larger than 3 cm regardless of the response to therapy and for patients who had suspected persistent neck disease 8–12 weeks after completing treatment.
Results	
• **Disease-free survival (at 4 yrs)**	Group 1 (Surgery + PORT) vs. Group 2 (CRT): 55.2% (95% CI, 36.1–74.3%) vs. 54.2% (95% CI, 37.0–71.5%) (p=0.406, logrank test)
• **Recurrence rate**	Not addressed
• **(Loco)regional control**	Not addressed
• **Overall survival (at 4 yrs)**	Group 1 (Surgery + PORT) vs. Group 2 (CRT): 61.4% (95% CI, 43.7–79.1%) vs. 58.5% (95% CI, 42.2–74.8%) (p=0.280, logrank test)
• **Quality of life**	Group 1 (Surgery + PORT) vs. Group 2 (CRT): *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)* A high score for a functional or global QoL scale represents a relatively high/healthy level of functioning or global QoL, whereas a high score for a symptom scale indicates a higher level of symptoms or problems. 1. *Functional scales [0-100]* - Physical functioning: 79.2 (95% CI 70.9 to 87.5) vs. 87.7 (95% CI 80.7 to 94.8), p=0.043 - Role functioning: 85.2 (95% CI 74.9 to 95.6) vs. 91.0 (95% CI 83.8 to 98.1), p=0.357 - Social functioning: 84.6 (95% CI 74.2 to 95.0) vs. 93.5 (95% CI 86.4 to100.0), p=0.036 - Emotional functioning: 76.2 (95% CI 66.0 to 86.3) vs. 84.7 (95% CI 78.0 to 91.4), p=0.210 - Cognitive functioning: 85.9 (95% CI 77.2 to 94.6) vs. 90.3 (95% CI 84.2 to 96.4), p=0.392 2. *Symptomatic scales [0-100]* - Fatigue: 22.9 (95% CI 13.9 to 31.9) vs. 12.9 (95% CI 5.9 to 19.8), p=0.047 - Nausea and vomiting: 6.4 (95% CI 0.7 to 13.5) vs. 2.1 (95% CI 1.3 to 5.6), p=0.152 - Pain: 21.8 (95% CI 12.3 to 31.3) vs. 8.6 (95% CI 3.6 to 13.6), p=0.027 3. *Global QoL [0-100]*: 68.6 (95% CI 60.11 to 77.0) vs. 79.8 (95% CI 72.9 to 86.9), p=0.027 4. *Six single items [0-100]* - Dyspnea: 10.3 (95% CI 1.9 to 18.6) vs. 14.0 (95% CI 6.4 to 21.6), p=0.368 - Sleep disturbance: 9.0 (95% CI 2.9 to 15.1) vs. 10.7 (95% CI 1.6 to19.9), p=0.661 - Appetite loss 12.8 (95% CI 3.4 to 22.2) vs. 11.8 (95% CI 5.1 to 18.6), p=0.842 - Diarrhea: 5.1 (95% CI 1.1 to 11.4) vs. 2.1 (95% CI 0.9 to 5.2), p=0.482 - Constipation: 16.7 (95% CI 5.7 to 27.6) vs. 14.0 (95% CI 4.6 to 23.3), p=0.660 - Financial impact: 15.4 (95% CI 5.1 to 25.6) vs. 14.0 (95% CI 4.1 to 23.8), p=0.598 *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck 35 (EORTC QLQ-H&N35)*. A high score for a symptom scale indicates a higher level of symptoms or problems. - Pain: 9.0 (95% CI 3.2 to 14.7) vs. 10.7 (95% CI 4.8 to 16.7), p=0.810

	- Swallowing: 36.2 (95% CI 24.1 to 48.3) vs. 19.3 (95% CI 11.3 to 27.4), p=0.042 - Senses: 25.6 (95% CI 14.7 to 36.6) vs. 22.0 (95% CI 13.5 to 30.6), p=0.715 - Speech: 30.3 (95% CI 18.6 to 42.0) vs. 16.8 (95% CI 10.8 to 22.7), p=0.056 - Social eating: 26.6 (95% CI 16.1 to 37.1) vs. 14.0 (95% CI 7.2 to 20.7), p=0.038 - Social contact: 14.9 (95% CI 5.4 to 24.3) vs. 4.7 (95% CI 0.89 to 10.3), p=0.002 - Sexuality: 23.7 (95% CI 9.7 to 37.7) vs. 15.6 (95% CI 5.5 to 25.7), p=0.462 - Teeth: 20.5 (95% CI 8.4 to 32.6) vs. 39.8 (95% CI 27.4 to 52.2), p=0.049 - Open mouth: 14.1 (95% CI 5.4 to 22.8) vs. 32.2 (95% CI 19.8 to 44.7), p=0.036 - Dry mouth: 38.5 (95% CI 24.9 to 52.0) vs. 58.1 (95% CI 47.6 to 68.5), p=0.022 - Sticky saliva: 35.9 (95% CI 21.7 to 50.1) vs. 52.7 (95% CI 41.4 to 64.0), p=0.044 - Coughing: 15.4 (95% CI 3.8 to 26.9) vs. 24.7 (95% CI 13.8 to 35.6), p=0.123 - Felt ill: 6.4 (95% CI 2.9 to 15.7) vs. 0.0 (95% CI 0.0 to 0.0), p=0.119 - Painkillers: 38.5 (95% CI 18.4 to 58.5) vs. 19.3 (95% CI 4.6 to 34.1), p=0.113 - Nutritional supplements: 23.1 (95% CI 5.7 to 40.4) vs. 22.6 (95% CI 7.0 to 38.2), p=0.965 - Feeding tube: 3.8 (95% CI 0.1 to 11.8) vs. 6.4 (95% CI 2.7 to15.6), p=0.664 - Weight loss: 23.1 (95% CI 5.7 to 40.4) vs. 16.1 (95% CI 2.4 to 29.8), p=0.512 - Weight gain: 11.5 (95% CI 1.6 to 24.7) vs. 25.8 (95% CI 9.5 to 42.1), p=0.178
• **Adverse events**	Not addressed
Limitations and other comments	
• **Limitations**	There is a possibility that patients may be influenced by the way in which treatment alternatives were presented during informed consent. There was a high risk of detection bias for quality of life outcomes as well.

Matched survival analysis in patients with locoregionally advanced resectable oropharyngeal carcinoma: latinum-based induction and concurrent chemoradiotherapy versus primary surgical resection ; Boscolo-Rizzo 2011	
Methods	
• **Design**	Matched-pair comparison between a prospective case series and a historical cohort treated in the same institution
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center: University of Padua, Treviso Regional Hospital, Italy
• **Sample size**	N=94
• **Duration and follow-up**	Prospective case series: January 2000 until June 2006, median follow-up of survivors (range): 45 (26-108) months; Historical cohort of matched pairs: from 1985, median follow-up of survivors (range): 63 (24-166) months
• **Statistical analysis**	“Local and regional control (persistent disease or locoregional recurrence considered as an event), distant failure (metastasis to any site beyond the primary tumor and regional lymph nodes considered as an event), overall survival ([OS], death from any cause was considered as an event), and progression-free survival ([PFS], recurrence or progression, and death considered as an event) were measured from the end of treatment. […] The actuarial curves for OS and PFS were analyzed using the standard

	Kaplan-Meier method. […] The matched analysis of survival was completed using Cox proportional hazard models. Matching was accounted for in the Cox proportional hazard models by incorporating a matching variable that accounted for the matching according to age, gender, nodal status, and overall stage."
Patient characteristics	
• **Eligibility criteria**	Patients with: previously untreated, histologically proven, resectable locoregionally advanced oropharyngeal squamous cell carcinoma (Stage III or IV), with tumor considered technically resectable with planned surgical excision if no fixation/invasion to the base of the skull or cervical vertebrae, no involvement of the nasopharynx, no fixed lymph nodes, no carotid encasement, and no invasion of the mediastinum was present; age ≤80 years; Karnofsky performance status ≥60%; no history of head-and-neck cancer; absence of synchronous primary lesions; absence of distant metastases; and acceptable medical and laboratory status to tolerate chemotherapy.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1 (surgery+postoperative radiotherapy): n= 47 vs. Group 2 (platinum-based induction-concurrent chemoradiotherapy group): n= 47 - Median age (range) 62 (41-77) yrs vs. 61 (42-76) yrs; - Gender M/F: 38/9 vs. 38/9; - nodal status negative/positive: 13/34 vs. 13/34; - Stage III/IV: 22/25 vs. 22/25; - Tumor stage T2/T3/T4a: 6/27/14vs. 5/24/18; - Nodal stage N0/N1/N2/N3: 13/12/20/2 vs. 13/15/17/2; - Neck dissection yes/no: 40/7 vs. 7/40. Groups were matched for disease stage, nodal status, gender, and age (±5 years) "The two groups did not differ significantly with respect to T stage (p=0.207), N stage (p=0.472), or comorbidities (p=0.384)."
Interventions	
• **Intervention group (1)**	**Group 1:** Surgery + postoperative radiotherapy (PORT) Surgery involved resection of the primary tumor using a transoral, transcervical, or combined approach with elective neck dissection of the N0 neck (selective neck dissection or Type III radical modified neck dissection) or therapeutic neck dissection of the N+ neck (radical or radical modified neck dissection depending on N stage). Regional myocutaneous or microvascular free flaps were used for reconstruction. Postoperative RT (PORT) was performed in patients with multiple positive lymph nodes, extracapsular extension, perineural tumor invasion, lymphovascular invasion, positive tumor margins, and those with Stage T4a tumors. Radiotherapy was performed using 4–6-MV photons from a linear accelerator administrated in 2-Gy daily fractions, five times weekly. A volume encompassing the primary site and all draining lymph nodes at risk was prescribed to receive a dose of 60 Gy in 30 fractions within a 6-week period. The dose to the clinically uninvolved nodal region was 50 Gy. The spinal cord was limited to a maximal dose of 46 Gy. Radiotherapy was started within 6 weeks after surgery.
• **Control group (2)**	**Group 2:** Platinum-based induction-concurrent chemoradiotherapy group (IC/CCRT) Induction cisplatinum (100 mg/m2) was administered on Day 1; 5-fluorouracil (1,000 mg/m2/d) was administered as a 24-hour continuous infusion for 5 days.

	Definitive RT started 3 weeks after induction chemotherapy, regardless of the response to induction chemotherapy. Concurrently with the RT, the patients received two cycles of chemotherapy using cisplatinum (100 mg/m2) on Day 1 and 5-fluorouracil (1,000 mg/m2/d) as a continuous infusion for 5 days during the first and fourth week of the RT course. Neck dissection was planned for patients with nodal metastasis >3 cm, regardless of the response to therapy and for patients who had suspected persistent neck disease at 8–12 weeks after completing treatment.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (Surgery + PORT) vs. Group 2 (IC/CCRT) *Recurrence or progression* 10/47 vs. 13/47 (RR= 0.77; 95% CI 0.38 to 1.58)
• **(Loco)regional control**	Group 1 (Surgery + PORT) vs. Group 2 (IC/CCRT) *Local control, 3-year actuarial rate* 79.5% (95% CI 66.7 to 92.3) vs. 79.3% (95% CI 64.6 to 94.0), p=0.813 *Regional control, 3-year actuarial rate* 87.3% (95% CI 76.7 to 97.9) vs. 80.1% (95% CI 68.2 to 92.0) without planned neck dissection 87.3% (95% CI 76.7 to 97.9) vs. 86.3% (95% CI 73.3 to 98.6) with planned neck dissection p=0.549
• **Overall survival (3 year)**	Group 1 (Surgery + PORT) vs. Group 2 (IC/CCRT) 73.6% (95% CI 56.3 to 90.9) vs. 73.5% (95% CI 57.7 to 89.3), p=0.599 HR 0.74 (95% CI 0.36 to 1.54)
• **Quality of life**	Not assessed
• **Adverse events**	IC/CCRT: Grade 2 toxicity: 25/47 Grade 3 toxicity (mucositis): 16/47 Grade 4 toxicity (mucositis): 4/47
Limitations and other comments	
• **Limitations**	This study is a matched-pair comparison between a prospective case series and a historical cohort. Patients in both study groups were recruited from different periods. Enrollment and follow-up was not concurrently for study groups. Furthermore detection bias for subjective outcomes is to be expected.

Treatment selection for tonsillar squamous cell carcinoma; Kuo 2013	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	National Science Council of Taiwan (Grant No. NSC 98-2314-B-010-013-MY3) and Taipei Veterans General Hospital (grant nos. V100C-090 and V101C-057)
• **Setting**	Single center: Department of Otolaryngology, Taipei Veterans General Hospital, Taiwan
• **Sample size**	N=105
• **Duration**	From January 1996 to December 2005
• **Follow-up**	Median follow-up (range) primary surgery vs. organ preservation: 82.7 (6-170) months vs. 108.2 (8-146) months
• **Statistical analysis**	Local and regional controls were defined as no evidence of disease at the primary site and the neck. The rates of disease-specific survival (DSS) and overall survival (OS) were calculated using the Kaplan Meier product limit method and compared by the logrank test. DSS was defined as the time to death from cancer or treatment-related events. Functional results were evaluated by long-term dependency on feeding tubes for nutrition and tracheostomy for breathing. Major complications were defined as treatment-related events that necessitated a second operation, prolonged hospitalization, or were life-threatening.
Patient characteristics	
• **Eligibility criteria**	Patients with histologically confirmed tonsillar squamous cell carcinoma who were curatively treated
• **Exclusion criteria**	Previous history of cancer
• **Patient & disease characteristics**	Group 1 (primary surgery): n= 43 vs. Group 2 (organ preservation): n= 62 “None of the patients had radiologic evidence of distant metastasis at presentation.” - Mean age (range): 53.7 (34-81) yrs vs. 54.8 (30-83) yrs; - Gender M/F: 37/6 vs. 52/10; - T classification T1-2/T3-4: 26/17 vs. 39/23; - N classification N0-1/N2-3: 25/18 vs. 28/34; - Stage I-II/III-IV: 17/26 vs. 17/45 “There were no differences between the two groups in terms of age, gender, T and N classifications, TNM stage, and histological differentiation.”
Interventions	
• **Intervention group (1)**	**Group 1:** Primary surgery with or without adjuvant therapy (primary surgery group) Postoperative radiotherapy (PORT) was delivered at 2 Gy per fraction, 5 days per week, at a total dose of 60e66 Gy to the primary site and/or positive neck levels and 50 Gy to the N0 neck levels. In postoperative concurrent chemoradiotherapy (POCCRT) treatment, the chemotherapy regimen consisted of weekly cisplatin (30 mg/m2) and daily oral tegafureuracil (250 mg/m2) concurrently with PORT
• **Control group (2)**	**Group 2:** Radiotherapy/chemoradiotherapy (RT/CRT, organ preservation group) RT delivered at 2 Gy per fraction, 5 days per week with a total dose of 70 Gy to the primary site and gross lymphadenopathy (≥1 cm), and 50 Gy to the N0 neck.

	Cisplatin-based induction chemotherapy was given mainly to those patients with bulky T3e4 primary tumors and/or neck diseases. In primary concurrent chemoradiotherapy (CCRT) treatment, weekly cisplatin (20 mg/m2) and 5-fluorouracil (400 mg/m2) were delivered concurrently with the RT.
Results for patients with T3-T4 tumors	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Group 1 (primary surgery) vs. Group 2 (organ preservation) *Local control* 88.2% vs. 69.6%, p=0.256 *Regional control* 88.2% vs. 82.6%, p=0.978
• **Overall survival (5 year)**	Group 1 (primary surgery) vs. Group 2 (organ preservation) *5-year overall survival* 46.3% vs. 51.5%, p=0.921 *5-year disease-specific survival* 46.3% vs. 62.8%, p=0.638
• **Quality of life**	Not assessed
• **Adverse events**	Group 1 (primary surgery) vs. Group 2 (organ preservation) *Major complications* 35.3% vs. 17.4%, p=0.274 *Feeding tube dependent* 35.3% vs. 21.7%, p=0.477 *Tracheostomy dependent* 5.9% vs.18.2%, p=0.363
Limitations and other comments	
• **Limitations**	Retrospective chart review with subgroup analysis of patients with T3-T4 tumors. Patient characteristics of this subgroup were not presented, nor were the analyses adjusted for patient or disease characteristics. Authors state that the treatment paradigm significantly changed during the period in which the study population was treated.

Quality of Life in Advanced Oropharyngeal Carcinoma After Chemoradiation Versus Surgery and Radiation; Mowry 2006	
Methods	
• **Design**	Cross-sectional study
• **Source of funding and competing interest**	None reported
• **Setting**	Multicenter; University of California Los Angeles Medical Center and the West Los Angeles Veterans Affairs Medical Center
• **Sample size**	N=71 eligible, n=35 responded to questionnaire
• **Duration**	Period not specified. Cross-sectional evaluation of quality of life of patients treated earlier.
• **Follow-up**	Mean time from end of treatment to evaluation was for surgery and radiation group vs. chemoradiation (CRT) group 26.1 months vs. 24.7 months (range, 3–73 months)
• **Statistical analysis**	The UW-QOL v.4 instrument is scored on a scale of zero to 100 for the first and third segments (higher score means better quality of life). Statistical analysis of the responses was conducted using the Wilcoxon's rank sum test and the $\chi 2$ test.
Patient characteristics	
• **Eligibility criteria**	Patients had biopsy-proven squamous cell carcinoma of the oropharynx (including tonsil, base of tongue, or pharynx), clinically staged as stage II through IV based on criteria described by the American Joint Committee on Cancer (AJCC).
• **Exclusion criteria**	Patients were excluded if they required surgical salvage after CRT or had metastatic disease at the time of diagnosis.
• **Patient & disease characteristics**	Group 1 (surgery followed by radiation): n=18 vs. Group 2 (primary chemoradiotherapy, CRT): n=17 - Gender M/F: 16/2 vs. 17/0; - Mean/median time from end of treatment to evaluation (range): 26.1/19.6 (4-73) vs. 24.7/15.5 (3-53); - Stage II/III/IV: 1/2/14 vs. 1/4/14 (as presented by authors, numbers are not in agreement with sample sizes of study groups) Overall: mean age at the time of questionnaire: 62.5 years; Gender M/F: 33/2.
Interventions	
• **Intervention group (1)**	**Group 1:** Surgery followed by radiation
• **Control group (2)**	**Group 2:** Primary CRT All patients who underwent surgery had composite resection, neck dissection, and microvascular flap reconstruction.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival (5 year)**	Not assessed
• **Quality of life**	Surgery followed by radiation vs. primary CRT *University of Washington Quality of Life Questionnaire, version four (UW-QOL v.4)* - Swallowing o 0 (food chokes me): 2/18 vs. 2/17 o 33 (can only swallow liquid): 2/18 vs. 5/17

	o 66 (cannot swallow certain food): 12/18 vs. 9/17 o 100 (can swallow as well as ever): 2/18 vs. 1/17 - Saliva o 0 (no saliva): 4/17 vs. 6/17 o 33 (too little saliva): 11/17 vs. 8/17 o 66 (less than normal, but adequate): 1/17 vs. 3/17 o 100 (normal): 1/17 vs. 0/17 - Taste o 0 (cannot taste any food): 3/18 vs. 2/17 o 33 (can taste some food): 3/18 vs. 11/17 o 66 (taste most food normally): 10/17 vs. 3/17 o 100 (taste all food normally): 2/17 vs.1/17 - Overall quality of life in the last 7 days o 0 (very poor): 2/18 vs. 0/17 o 20 (poor): 1/18 vs. 1/17 o 40 (fair): 5/18 vs. 9/17 o 60 (good): 1/18 vs. 3/17 o 80 (very good): 7/18 vs. 3/17 o 100 (outstanding): 2/18 vs. 1/17
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	As little details about initial study groups and the treatment they received are presented, it is not possible to judge whether groups were comparable and treated concurrently. Risk of attrition bias is unclear as well.

Primary surgery versus chemoradiotherapy for advanced oropharyngeal cancers: a longitudinal population study; O'Connell 2013	
Methods	
• **Design**	Retrospective analysis of a prospectively collected population based database (Alberta Cancer Registry)
• **Source of funding and competing interest**	No source of funding described. The authors declare that they have no competing interests.
• **Setting**	Two tertiary care facilities, northern Alberta, Canada
• **Sample size**	N=344
• **Duration**	January 1, 1998 until December 31, 2009
• **Follow-up**	Not reported
• **Statistical analysis**	Overall Survival (OS) was defined as death from any and all causes. The Kruskall-Wallis test, the Wilcoxon and log rank statistic, and the Cox regression multivariate analysis were used.

Patient characteristics	
• **Eligibility criteria**	All patients diagnosed with advanced oropharyngeal squamous cell carcinoma (OPSCC) and treated with their definitive therapy in Edmonton, Alberta between January 1st, 1998 and December 31st, 2009, were included in the analysis. Advanced OPSCC was defined as those with stage III and IV disease.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1 (Surgery with adjuvant chemotherapy and radiation, S-CRT): n=94 vs. Group 2 (Surgery with adjuvant radiotherapy, S-RT): n=131 vs. Group 3 (Concomitant chemotherapy and radiotherapy, CRT): n=56 vs. Group 4 (radiotherapy (RT): n=63 - Mean age (SD): 54.69 (8.48) yrs vs. 56.77 (10.30) yrs vs. 58.5 (10.43) yrs vs. 69.11 (10.41); - Gender M/F: 80/14 vs. 29/102 vs. 12/44 vs. 20/43; "The Kruskal-Wallis test showed no statistical differences between the S-CRT, S-RT and CRT groups in regards to gender. The age distribution was found to be significantly different ((H)2 = 65.15, p < 0.001).
Interventions	
• **Intervention group (1)**	**Group 1:** Surgery with adjuvant chemotherapy and radiation (S-CRT, n=94). Surgery involved both primary site ablation with locoregional or free tissue transfer reconstruction and unilateral or bilateral neck dissections. Neck dissection alone was not included in the surgical group. Patients undergoing radiotherapy as part of their OPSCC treatment had varying protocols of fractionated, hyperfractionated, and IMRT type external beam radiation. Patients undergoing chemotherapy as a component of treatment had varying combinations of platinum based chemotherapy agents, 5-fluorouracil, doxorubicin, and/or taxanes. Information where available revealed the majority of patients were treated with cisplatin or carboplatin based protocols.
• **Intervention group (2)**	**Group 2:** Surgery with adjuvant radiotherapy (S-RT, n=131) Surgery involved both primary site ablation with locoregional or free tissue transfer reconstruction and unilateral or bilateral neck dissections. Neck dissection alone was not included in the surgical group. Patients undergoing radiotherapy as part of their OPSCC treatment had varying protocols of fractionated, hyperfractionated, and IMRT type external beam radiation.
• **Intervention group (3)**	**Group 3:** Concomitant chemotherapy and radiotherapy (CRT, n=56) Patients undergoing radiotherapy as part of their OPSCC treatment had varying protocols of fractionated, hyperfractionated, and IMRT type external beam radiation. Patients undergoing chemotherapy as a component of treatment had varying combinations of platinum based chemotherapy agents, 5-fluorouracil, doxorubicin, and/or taxanes. Information where available revealed the majority of patients were treated with cisplatin or carboplatin based protocols.
• **Intervention group (4)**	**Group 4:** Radiotherapy (RT, n=63) RT group was excluded from survival analysis as a significant number were treated with palliative intent.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (S-CRT) vs. Group 2 (S-RT) vs. Group 3 (CRT) *Overall survival*

	2-year: 87.7% vs. 69.7% vs. 51.7% *5-year:* 63.1% vs. 47.4% vs. 39.8% *Disease-specific survival* *2-year:* 90.1% vs. 73.7% vs. 57.4% *5-year:* 71.1% vs. 53.9% vs. 48.6% Cox regression analysis was used to compare survival with the three treatment strategies, however it is unclear whether overall survival or disease-specific survival is concerned Group 1 vs. Group 2 HR 1.974 (95% CI 1.170 to 3.330) Group 1 vs. Group 3 HR 2.785 (95% CI 1.525 to 5.086)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Patients from an 11-year period (January 1, 1998 until December 31, 2009) were included and it is unclear whether interventions were concurrent. Unclear whether results for Cox regression analysis were for overall survival or disease-specific survival.

4.4. RQ4: Postoperative (chemo)radiotherapy

a. Postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy

4.4.1. Evidence tables of systematic reviews RQ4a

No systematic reviews were identified

4.4.2. Evidence tables of RCTs RQ4a

Efficacy of postoperative radiation therapy for squamous cell carcinoma of the head and neck: results of a prospective randomised clinical trial Rodrigo 2004	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: not reported
• **Setting**	Not reported. Country: Spain
• **Sample size**	N=51 randomized , n=42 analysed (21 per group)
• **Duration**	Patient enrollment between September 1994 and December 1995
• **Follow-up**	At least 36 months until aproximately 105 months (read from figure)

• **Statistical analysis**	The statistical analysis of the data was carried out using the Chi-square test and Fisher Exact Test. Survival curves were obtained using the Kaplan-Meier method. The differences between the curves of survival were analyzed with the log-rank method.
Patient characteristics	
• **Eligibility criteria**	Patients with squamous cell carcinoma of the head and neck, classified in stages III and IV, that presented negative margins of the tumor without extracapsular extension from the affected cervical lymphatic nodes (independent of the number affected).
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Average age 59.5 years (range 32-86), 41 males and 1 female. Group 1 (postoperative radiotherapy): n=21; Group 2 (no postoperative radiotherapy): n=21 - Localization: oral cavity: 1 vs. 0; oropharynx: 9 vs. 9; suppraglottis: 4 vs. 7; hypopharynx: 7 vs. 5 - Classification pT: T1: 0 vs. 3; T2: 4 vs. 6; T3: 15 vs. 4; T4 2 vs. 8 - Classification pN: N0: 2 vs. 2; N1: 7 vs. 6; N2: 12 vs. 13 - Stage: III: 8 vs. 5; IV: 13 vs. 16 - Grade of differentiation: well-differentiated: 8 vs. 11; Moderately differentiated: 10 vs. 9; Poorly differentiated: 3 vs. 1 "These two groups of patients were comparable in so far as the localization of the tumor, cervical metastasis, stage and grade of differentiation (Table1). The differences observed in the distribution according to the T classification disappeared after grouping the cases in T1 - T2 vs. T3 - T4 (P = 0.18)."
Interventions	
• **Intervention group (1)**	Group 1: Surgery + radiotherapy The administration of RT started in the 8 weeks after surgery; fractions of 1.8 to 2 Gy, one fraction a day, five days in a continuous course weekly; total dose varied from 50 to 60 Gy, depending on the probability of residual illness (size of primary tumor and number of lymphatic nodes affected).
• **Control group (2)**	Group 2: Surgery
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *Recurrences* Stage III: 50% vs. 80% - Local:25% vs. 80% - Cervical: 0% vs. 0% - Local and cervical: 25% vs. 0% Stage IV: 84% vs. 68% - Local: 31% vs. 62% - Cervical: 46% vs. 0% - Local and cervical: 8% vs. 6%

• **(Loco)regional control**	"for stage III patients the loco-regional control of the illness was better in the irradiated group, while for the patients in stage IV, the loco-regional control was better in the non-irradiated group of patients, offsetting the overall loco-regional control for the irradiated and non-irradiated patients."
• **Overall survival**	*Overall survival* not assessed. *Disease specific survival (5 years)* Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) 35% vs. 35% (p=0.39)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Small sample size No details provided about method of randomization and blinding, leading to unclear risk of selection bias and detection bias for subjective outcomes. Unclear risk of reporting bias, as no study protocol was available. High risk of performance bias and attrition bias. Baseline imbalances in T stage (relatively more T3 tumors in RT group and more T4 tumors in no RT group).

4.4.3. Evidence tables of observational studies RQ4a

4.4.3.1. Mixed population

Results of selective neck dissection in the primary management of head and neck squamous cell carcinoma; Schmitz 2009	
Methods	
• **Design**	Retrospective analysis of medical records
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Single center, Department of Head and Neck Surgery at St Luc University Hospital and Cancer Center, Brussels, Belgium
• **Sample size**	N=163 included; for analysis of locoregional control n=146 available
• **Duration**	January 1990 - December 2002
• **Follow-up**	Mean follow-up: 58 months (range 1–180 months), median follow-up: 37 months.
• **Statistical analysis**	The comparisons of proportion were tested by the Chi-square test. The Kaplan–Meier method was used for survival and regional control analysis. The correlation of survival and different clinical (T and N staging, postoperative radiotherapy) and histological factors (extracapsular spread, histologic differentiation, presence of perineural and vascular invasion) was evaluated.
Patient characteristics	
• **Eligibility criteria**	Previously untreated patients with squamous cell carcinoma (SCC) of the larynx, hypopharynx, oropharynx and oral cavity.
• **Exclusion criteria**	Not specified

• **Patient & disease characteristics**	- Age and sex not reported - N-stage: (N0 /N1 /N2b / more advanced): 119/20/6/18 - Location (larynx / hypopharynx / oropharynx / oral cavity): 99/27/19/18
Interventions	
• **Intervention group (1)**	Group 1: surgery and postoperative radiotherapy Surgery: all patients had uni- or bilateral SND, in combination with surgical resection of the primary tumour. Radiotherapy: SND was followed by adjuvant PORT in selected indications: pN2b stage, ECS and pT4 stage; depending on the risk factors, doses ranged from 60 to 64–66 Gy, in 2 Gy fraction over 6–6.5 weeks.
• **Intervention group (2)**	Group 2: surgery alone All patients had uni- or bilateral SND, in combination with surgical resection of the primary tumour.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (surgery + postoperative radiotherapy): n=48 vs. group 2 (surgery alone): n=98 Neck recurrence pN0 (n=194 necks): 0 vs. 3/194 pN1 (n=39 necks): 2/21 vs. 1/18 pN2b (n=16 necks) 1/16 vs. 0
• **(Loco)regional control**	Not assessed
• **Overall survival**	Not reported for comparison of interest
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective analysis with high risk of selection bias, incomparable groups. No blinding and unclear risk of attrition bias. Patients who died before end of treatment and those without adequate follow-up were excluded of the regional control analysis.

4.4.3.2. Oropharynx

Long-term results of surgical treatment for advanced oropharyngeal squamous cell carcinoma Bastos de Souza 2014	
Methods	
• **Design**	Retrospective review of medical charts of consecutive patients
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: not reported
• **Setting**	Two centers: Heliopolis Hospital and A C Camargo Hospital, São Paulo, Brazil
• **Sample size**	N=256 included
• **Duration**	Inclusion between 1990 and 2004
• **Follow-up**	Mean follow-up time 52.8 months (range 1–213 months)
• **Statistical analysis**	Overall survival (OS) and disease free survival (DFS) were estimated using the Kaplan–Meier method, and the log-rank test was performed to verify the differences among survival curves. The multivariate risk of death and respective 95% confidence intervals were estimated by Cox regression model.
Patient characteristics	
• **Eligibility criteria**	Patients with histologically confirmed diagnosis of clinical stage III or IV oropharyngeal squamous cell carcinoma
• **Exclusion criteria**	Previously treated, other previous primary tumors.
• **Patient & disease characteristics**	Group1 (postoperative radiotherapy): n=201; Group 2 (no postoperative radiotherapy): n=55 Gender (M/F): 232/24 Median age: 55 years (range 30–83 years) Stage: III: 59; IV: 161 Classification pT: T1: 14; T2: 88; T3: 89; T4: 65 Classification pN: N0: 58; N1: 38; N2: 144; N3: 16 Classification pN1ECS: N1ECS-: 51; N1ECS1: 141 Grade: Well differentiated: 58; Moderate: 148; Poorly differentiated: 46 Location: Tonsillar fossa: 171; Soft palate: 20; Base of the tongue: 62; Posterior pharyngeal wall: 3
Interventions	
• **Intervention group (1)**	**Group 1:** surgery and postoperative radiotherapy Radiotherapy: Indicated in cases of pT4, close or involved margins, vascular embolization, perineural infiltration, or lymph node metastasis. The primary site was treated to a median of 61 Gy (range, 14–75 Gy).
• **Control group (2)**	**Group 2:** surgery
Results	
• **Disease-free survival**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *Disease-free survival (5 years)* 57.4% vs. 43.3%, p=0.010 (log rank test)

• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *Overall survival (5 years)* 45.8% vs. 32.8%, p=0.010 (log rank test)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study, which might lead to selection bias. Unclear risk of attrition bias. Baseline characteristics not presented separately for treatment groups, but radiotherapy was indicated for high risk patients which might have led to baseline imbalances.

Quality of Life of Oropharyngeal Cancer Patients With Respect to Treatment Strategy and p16-Positivity Broglie 2012	
Methods	
• **Design**	Retrospective chart analysis and cross-sectional evaluation of quality of life
• **Source of funding and competing interest**	"The authors have no funding, financial relationships, or conflicts of interest to disclose."
• **Setting**	Single center, University Hospital of Zurich, Switzerland
• **Sample size**	N=227 were treated between 2002 and 2007; in 2010 n=139 survivors identified, of which n=120 invited to respond to questionnaire, n=98 responded
• **Duration**	Patients treated between 2002 and 2007 were included
• **Follow-up**	Median follow-up: 72 months (range 30–101 months); survey by the questionnaires was performed after a median of 67 months after treatment (range 26–99 months).
• **Statistical analysis**	Mann-Whitney test was used to compare scores for the different treatment groups
Patient characteristics	
• **Eligibility criteria**	Patients treated for a newly diagnosed oropharyngeal squamous cell carcinoma
• **Exclusion criteria**	Patients treated in a palliative intent or with an uneventful follow-up of less than 2 years.
• **Patient & disease characteristics**	Group 2 (postoperative radiotherapy): N=30 vs. Group 3 (no postoperative radiotherapy): N=13 - Mean age: 59 (43–73) vs. 61 (50–74) - Male gender: 25 vs. 7 - Tumor localization: tonsil: 23 vs. 13; Base of tongue: 6 vs. 0; posterior pharyngeal wall: 1 vs. 0 - Tumor stage: T1/T2: 28 vs. 12; T3/T4: 2 vs. 1 - Nodal stage: N0/N1/N2a: 5 vs. 12; N2b/N2c/N3: 25 vs. 1 - Stage: I/II: 1 vs. 6; III/IV: 29 vs. 7

Interventions	
• **Intervention group (1)**	**Group 1:** primary intensity modulated radiotherapy (IMRT) with or without concomitant chemotherapy (CCT) (n=55; n=37 treated with CCT) *Chemotherapy*: cisplatin (40mg/m^2/weekly); indications: stages III/IV
• **Intervention group (2)**	**Group 2:** Surgery with IMRT, with or without CCT (n=30; n=22 treated with CCT) *Surgery*: radical resection with simultaneous ipsilateral or bilateral neck dissection, according to the tumor stage. *Radiotherapy*: Indications for postoperative irradiation included T3/4, ≥pN2a, extracapsular tumor spread (ECS), lymphangiosis, and perineural tumor invasion. *Chemotherapy*: indications: positive margins and/or ECS
• **Control group (3)**	**Group 3:** Surgery (n=13) Radical resection with simultaneous ipsilateral or bilateral neck dissection, according to the tumor stage.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Not assessed
• **Quality of life**	Group 2 (postoperative radiotherapy) vs. group 3 (no postoperative radiotherapy) *General quality of life (Median EORTC-QLQ-C30 scores)* Functional scales - Physical: 100.00 vs. 93.33 (NS) - Role: 100.00 vs. 100.00 (NS) - Emotional: 83.33 vs. 91.66 (NS) - Cognitive: 91.67 vs. 100.00 (NS) - Social: 100.00 vs. 100.00 (NS) - Global health: 83.33 vs. 83.33 (NS) Symptom scales - Fatigue: 11.11 vs. 0.00 (NS) - Nausea and vomiting: 0.00 vs. 0.00 (NS) - Pain: 0.00 vs. 0.00 (NS) - Dyspea: 0.00 vs. 0.00 (NS) - Insomnia: 33.33 vs. 33.33 (NS) - Appetite loss: 0.00 vs. 0.00 (NS) - Constipation: 0.00 vs. 0.00 (NS) - Diarrhea: 0.00 vs. 0.00 (NS) - Financial difficulties: 0.00 vs. 0.00 (NS) *Head- and neck-specific quality of life (Median EORTC-QLQ-H&N35 scores)*

	- Pain: 8.33 vs. 0.00 (NS) - Swallowing: 8.33 vs. 16.67 (NS) - Senses problems: 8.33 vs. 0.00 (NS) - Speech problems: 0.00 vs. 0.00 (NS) - Social eating: 0.00 vs. 0.00 (NS) - Social contact: 0.00 vs. 0.00 (NS) - Less sexuality: 0.00 vs. 0.00 (NS) - Teeth: 0.00 vs. 0.00 (p=0.08) - Mouth opening: 0.00 vs. 0.00 (NS) - Dry mouth: 33.33 vs. 0.00 (NS) - Sticky saliva: 33.33 vs. 33.33 (NS) - Coughing: 0.00 vs. 0.00 (NS) - Felt ill: 0.00 vs. 0.00 (NS) - Pain killers: 0.00 vs. 0.00 (NS) - Nutritional supplements: 0.00 vs. 0.00 (NS) - Feeding tube: 0.00 vs. 0.00 (NS) - Weight loss: 0.00 vs. 0.00 (NS) - Weight gain: 0.00 vs. 0.00 (NS)
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study which might lead to selection bias; small sample size. Patients treated with postoperative radiotherapy had a higher nodal and tumor stage, but only univariate analyses were performed. No details about treatment presented.

Combined surgery and postoperative radiotherapy for oropharyngeal squamous cell carcinoma in Korea: analysis of 110 cases; Lim 2008	
Methods	
• **Design**	Retrospective analysis
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Single center, Department of Otorhinolaryngology at Yonsei University, Seoul, Korea
• **Sample size**	N=110
• **Duration**	Between May 1992 and December 2004
• **Follow-up**	Mean follow-up (range): 41 (2 to 138) months. Patients were followed-up for a minimum 2 years or until death.
• **Statistical analysis**	Survival rates were calculated according to the Kaplan–Meier method. The differences in survival rates between curves were determined using the log-rank test. The relationship between tumour recurrence and clinical factors such as age, sex, stage of primary lesion and the presence of postoperative radiotherapy were analyzed using Fisher's exact test or the X2 test.

Patient characteristics	
• **Eligibility criteria**	Patients with histologically confirmed oropharyngeal squamous cell carcinoma; patients not previously treated; and patients who had curative surgery on the primary tumour and the neck in the same session as their initial treatment.
• **Exclusion criteria**	Treatment with preoperative radiotherapy or neoadjuvant chemotherapy to the primary lesion; patients in whom the primary tumour recurred; or patients with distant metastasis at the time of initial presentation. 110 patients met these criteria and were included in the study.
• **Patient & disease characteristics**	- Median age (range): 57 yrs (32-78 yrs) - Sex (M/F): 96/14 - T-stage (T1/T2/T3/T4): 24 (22%) / 50 (45%) / 19 (17%) / 17 (16%) - N-stage (N0/N1/N2a/N2b/N2c/N3): 35 (32%) / 20 (18%) / 18 (16%) / 24 (22%) / 5 (5%) / 8 (7%) - Stage (I/II/III/IV): 5 (4%) / 21 (19%) / 20 (19%) / 64 (58%) - Site: o Tonsillar region: n=73 (66%) o Base of the tongue: n=21 (19%) o Soft palate: n=14 (13%) o Posterior pharyngeal wall: n=2 (2%)
Interventions	
• **Intervention group (1)**	**Group 1:** Surgery and postoperative radiotherapy (n=84) Patients with pathologic lymph node metastases or positive/close resection margins at the primary site were selected additionally to undergo postoperative adjuvant radiotherapy. The radiation dose ranged from 5040 to 6780 cGy; the mean was 6002 cGy.
• **Control group (2)**	**Group 2:** Surgery alone (n=26)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (postoperative radiotherapy) vs. Group 2 (no postoperative radiotherapy) *Local recurrence* 6/84 (7%) vs. 3/26 (12%), p=ns *Regional recurrence* 17/84 (20%) vs. 2/26 (8%), p=ns
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. Group 2 (no postoperative radiotherapy) *5-year disease specific survival* 56% vs. 83%, p<0.05
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	No details on group characteristics for study groups of interest, no adjustments in analyses.

Relapse patterns after transoral laser microsurgery and postoperative irradiation for squamous cell carcinomas of the tonsil and tongue base; Patel 2014	
Methods	
• **Design**	Retrospective analysis of database
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Two centers: Mayo Clinic in Florida and Mayo Clinic in Arizona, USA
• **Sample size**	N=79
• **Duration**	From December 1, 1996, until December 31, 2005
• **Follow-up**	Median follow-up for living patients is 42.5 or 47 months (range 10 to 107 months), different values reported in abstract and results section of the publication. For all patients the median follow-up period was 42 months (range, 1 to 107 months)
• **Statistical analysis**	Because of the relatively small sample size, most of the statistical analysis was descriptive in nature and focused on summarizing crude outcome rates in different patient groups. The probabilities of treatment failure were estimated with the Kaplan-Meier method and compared between the respective intermediate/high-risk subgroups for the TLM-alone and adjuvant-RT groups with log-rank tests. The log-rank test was also used to examine the difference in time to relapse between the TLM-alone and adjuvant-RT groups. Logistic regression analysis was used to compare the overall risk of relapse between the TLM-alone and adjuvant-RT groups
Patient characteristics	
• **Eligibility criteria**	Patients with biopsy-proven, previously untreated primary squamous cell carcinoma of the tonsil or tongue base, who underwent TLM with or without neck dissection with curative intent and who had either at least 24 months of follow-up or a documented relapse or death after definitive treatment.
• **Exclusion criteria**	Twenty-two patients were excluded because they were lost to follow-up.
• **Patient & disease characteristics**	Group 1 (TLM and adjuvant radiotherapy) vs. Group 2 (TLM alone) - Mean age (range): o Tongue base carcinoma: 62 (45-86) yrs vs. 65 (42-81) yrs; o Tonsil carcinoma: 50 (45-70) yrs vs. 60 (42-76) yrs; - Sex (M/F): o Tongue base carcinoma: 22/1 vs. 21/3; o Tonsil carcinoma: 13/2 vs. 14/3; - Stage (I/II/III/IV): o Tongue base carcinoma: 0/0/5/18 vs. 4/4/5/11; o Tonsil carcinoma: 0/2/0/13 vs. 2/3/4/8; - T-Stage (Tx/T1/T2/T3/T4): o Tongue base carcinoma: 0/9/7/3/4 vs. 0/7/12/3/2; o Tonsil carcinoma: 1/3/5/4/2 vs. 0/6/10/1/0; - N-Stage (Nx/N0/N1/N2a/N2b/N2c/N3): o Tongue base carcinoma: 0/2/4/4/8/5/0 vs. 4/5/6/3/4/0/2; o Tonsil carcinoma: 1/1/0/4/7/1/1 vs. 0/5/4/1/7/0/0;

	- Adjuvant radiotherapy indications o Tongue base carcinoma: 23 vs.14; o Tonsil carcinoma: 15 vs. 10.
Interventions	
• **Intervention group (1)**	**Group 1**: Transoral laser microsurgery with adjuvant radiotherapy (n=38) Radiotherapy: median total dose was 62 Gy (range, 59.4 to 72 Gy); the majority had standard fractionation sizes of 1.8 to 2.0 Gy per fraction. Concurrent chemotherapy was administered in only 1 patient.
• **Control group (2)**	**Group 2**: Transoral laser microsurgery alone (n=41)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (TLM+RT) vs. Group 2 (TLM) *Treatment failures* 7/38 (18%) vs. 10/41 (24%), p = 0.41 - Local: 0 vs. 4 - Regional: 2 vs. 6 - Distant: 6 vs. 4 Subgroup of tongue base cancers: 6/23 vs. 6/24 - Local: 0 vs. 3 - Regional: 1 vs. 3 - Distant: 5 vs. 2 Subgroup of tonsil cancers: 1/15 vs. 4/17 - Local: 0 vs. 1 - Regional: 1 vs. 3 - Distant: 1 vs. 2 *3-year failure rates for intermediate or high-risk patients** *Local*: 0% vs. 21%, p=0.004 *Regional*: 6% vs. 21.4%, p=0.08 *Locoregional*: 6% vs. 32%, p=0.008 *Distant*: 18.1% vs. 5.9%, p=0.33 * All patients were categorized as being at low, intermediate, or high risk for disease recurrence as defined by Ang et al (Ang KK, Trotti A, Brown BW, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int J Radiat Oncol Biol Phys 2001;51:571-8.)

• **(Loco)regional control**	See above at 'recurrence rate'
• **Overall survival**	Group 1 (TLM+RT) vs. Group 2 (TLM) *Number of deaths* 6/38 (16%) vs. 3/41 (7%) *3-year overall survival for intermediate or high-risk patients* 93.8% vs. 94.1%, p=0.63
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study design, in which a high risk of selection bias, no blinding and possible attrition bias. Treatment groups were not completely comparable and only univariate analyses.

Salvage treatment for recurrent oropharyngeal squamous cell carcinoma; Röösli 2010 (For some details authors refer to previously published report of this study: Roosli 2009)	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Single center, University Hospital of Zurich, Switzerland
• **Sample size**	N=427
• **Duration**	From January 1, 1990 through June 30, 2006
• **Follow-up**	Mean follow-up: 64 months (range, 1–195 months) - Primary radiation therapy group: mean follow-up of 72 months (range 3–192 months) - Surgery + radio(chemo)therapy group: mean follow-up of 49 months (range 1–195 months) - Surgery group: mean follow-up of 76 months (range 2–184 months)
• **Statistical analysis**	Calculations of OS and DSS were made with Kaplan–Meier estimates and compared by the means of the log-rank (Mantel–Cox) test.
Patient characteristics	
• **Eligibility criteria**	Patients with previously untreated, biopsy-proven squamous cell carcinoma of the oropharynx, treated with curative intent from January 1, 1990 through June 30, 2006.
• **Exclusion criteria**	Patients with signs of synchronous second primary, distant metastasis, previous head and neck cancer of any other site, patients with an uneventful follow-up of less than two years, and patients treated in a palliative regimen were excluded.
• **Patient & disease characteristics**	Group 1 (primary radio(chemo)therapy): n=166; Group 2+3 (surgery + radio(chemo)therapy): n=159; Group 4 (surgery): n=102 - Mean age (range): 58 (33–84) yrs; - Sex (M/F): 319/108;

	- Location: lateral wall: 347; base of tongue: 75; soft palate: 5; - T-stage (T1/T2/T3/T4): 86/152/115/74 - N-stage (N0/N1/N2a/N2b/N2c/N3): 99/72/25/168/48/15 - Stage (I/II/III/IV): 31/32/80/284 Group 2+3 (surgery + radio(chemo)therapy): n=159 vs. Group 4 (surgery): n=102 - Mean age (range): 56 (33–84) yrs vs. 59 (41–88) yrs - Sex (M/F): 120/39 vs. 72/30 - Stage: I: 5 vs. 25; II: 5 vs. 22; III: 32 vs. 25; IV: 124 vs. 30
Interventions	
• **Intervention group (1)**	**Group 1**: Primary radio(chemo)therapy (n=166) Primary 3D-CRT was either hyperfractionated with twice-daily 1.2 Gy to a total dose of 74.4 Gy (72–76.8 Gy) or accelerated with 6 sessions/week of 2 Gy to 68 to 70 Gy or 7 sessions of 1.8 Gy to 70.2 Gy. Primary IMRT was delivered with 30 x 2.2 Gy, 33 x2.11 Gy, or 35 x 2.0 Gy, 5 times/week, respectively. Simultaneous cisplatin chemotherapy (40 mg/m2/week) was used in most patients.
• **Intervention group (2)**	**Group 2**: Surgery followed by radiotherapy (n=133) Surgery: radical resection of the primary tumour followed by an ipsilateral or bilateral neck dissection. Radiotherapy: indications: close or positive resection margins, large primary tumours (T3/4), the involvement of 2 or more neck nodes (pN2b), involvement of a large single node (pN2a/pN3), or histologic evidence for extracapsular spread of tumour. The volume was individualized according to the areas of risk.
• **Intervention group 3**	**Group 3:** Surgery followed by radiochemotherapy (n=26)
• **Control group (4)**	**Group 4**: Surgery alone (n=102) Surgery: radical resection of the primary tumour followed by an ipsilateral or bilateral neck dissection.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 2+3 (surgery + radio(chemo)therapy) vs. Group 4 (surgery alone) Patients with recurrence: 39 (24.5%) vs. 33 (32%) - Local: 16 vs. 10 - Locoregional: 15 vs. 9 - Regional: 4 vs. 12 - Distant metastasis: 4 vs. 2
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 2+3 (surgery + radio(chemo)therapy) vs. Group 4 (surgery alone) *5-year overall survival* 66.6% vs. 70.3%

	5-year disease specific survival 78.9% vs. 76.5%
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study design leading to selection bias; no blinding. Study groups not comparable for stage of disease and intervention and comparator group were possibly not concurrent.

Role of primary surgery for early-stage (T1–2N0) squamous cell carcinoma of the oropharynx; Shin 2009	
Method	
• **Design**	Retrospective analysis
• **Source of funding and competing interest**	Source of funding: no information Conflict of interest: none declared
• **Setting**	Single center, Department of Otorhinolaryngology at Yonsei University, Seoul, Korea
• **Sample size**	N=46
• **Duration**	May 1992 to December 2006
• **Follow-up**	Mean follow-up: 57 months (range 19–156 months)
• **Statistical analysis**	Statistical analysis was performed using SPSS v.12 (Chicago, IL) program. Survival rates were calculated according to the Kaplan–Meier method and the log-rank test was used to assess differences in survival rates between curves. The relationships between categorical variables were analyzed by the Fisher's exact or chi-square tests.
Patient characteristics	
• **Eligibility criteria**	Patients who had not previously been treated for oropharyngeal squamous cell carcinoma, with biopsy-proven squamous cell carcinoma and an early primary oropharyngeal lesion (<4 cm), without clinically suspicious metastatic neck nodes.
• **Exclusion criteria**	Patients satisfying at least one of the following criteria were excluded: (1) patients undergoing chemoradiation for primary treatment due to refusal of surgery; (2) patients in whom the primary tumour had recurred; or (3) patients with distant metastasis at the time of initial presentation.
• **Patient & disease characteristics**	- Median age (range): 58 (40-78) yrs; - Sex (M/F): 37/9; - T stage: T1: n=12, T2: n=34; - N stage: N0: n=29, N1: n=8, N2b: n=4 - Primary subsite (tonsil /soft palate / base of the tongue / posterior wall): 25/9/7/5.
Interventions	
• **Intervention group (1)**	**Group 1**: Surgery and postoperative radiotherapy (n=17) The indications for adjuvant radiotherapy were as follows: a positive/close resection margin, multiple pathologic lymph node metastases, or extra capsular spread of a neck lymph node. The radiation dose ranged from 5040 cGy to 6780 cGy, with a median of 6132 cGy.

• **Control group (2)**	**Group 2**: Surgery alone (n=29)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not reported for comparison of interest
• **(Loco)regional control**	Not reported for comparison of interest
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. Group 2 (no postoperative radiotherapy) *5-year disease-specific survival rate* 82% vs. 86%, p=0.704
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Characteristics of patients not specified for the studygroups of interest (radiotherapy vs. no radiotherapy) and only univariate analysis was done without adjustment for possible confounders. Small sample size as well.

Is postoperative adjuvant chemoradiotherapy necessary for high-risk oropharyngeal squamous cell carcinoma?; Yokota 2014	
Methods	
• **Design**	Retrospective analysis of medical records
• **Source of funding and competing interest**	Source of funding: none reported Authors report no conflicts of interest
• **Setting**	Single center: Shizuoka Cancer Center (Shizuoka, Japan)
• **Sample size**	N=45
• **Duration**	2003-2011
• **Follow-up**	Median follow-up period in patients surviving without recurrence was 41.0 months (range, 5.6 to110.7 months).
• **Statistical analysis**	Fisher's exact test, Kaplan–Meier method for survival (compared using the log-rank test). Univariate comparison of factors that could potentially affect the survival time using the log-rank test, multivariate analysis using the Cox proportional hazards model to investigate significant prognostic factors.
Patient characteristics	
• **Eligibility criteria**	Oropharyngeal squamous cell carcinoma patients who underwent primary resection and/or neck dissection and meeting at least 1 of the following pathological features were selected: (1) microscopically involved mucosal resection margins (positive margin), (2) positive extracapsular spread of the disease (ECS), and (3) involvement of C2 regional lymph nodes.
• **Exclusion criteria**	No exclusion criteria reported
• **Patient & disease characteristics**	Group 1 (primary tumour resection and/or neck dissection and radiotherapy): n=17 vs. Group 2 (primary tumour resection and/or neck dissection and chemoradiotherapy): n=9 vs. Group 3 (primary tumour resection and/or neck dissection): n=19 - Age ≥65: 7 vs. 2 vs. 10; age <65: 10 vs. 7 vs. 9; - Sex (M/F): 12/5 vs. 8/1 vs. 16/3;

	- Performance status of 0 or 1: all patients; - T-stage: T1/T2: 11 vs. 5 vs. 12; T3/T4: 6 vs. 4 vs. 7; - N-stage: N1: 4 vs. 1 vs. 7; N2/N3: 13 vs. 8 vs. 12; - Level of lymph node positivity (single/multiple): 10/6 (n=1 not evaluated) vs. 3/6 vs. 11/5 (n=3 not evaluated); - Surgical margins (negative/positive): 6/11 vs. 3/6 vs. 9/9 (n=1 not evaluated); - Number of lymph nodes 0 or 1: 7 vs. 2 vs. 5; ≥2: 9 vs. 7 vs. 11 (not evaluated: 1 vs. 0 vs. 3); - Extra capsular spread (negative/positive): 7/9 (n=1 not evaluated) vs. 1/8 vs. 10/6 (n=3 not evaluated).
Interventions	
• **Intervention group (1)**	**Group 1:** Primary tumour resection and/or neck dissection and radiotherapy The decision to choose the adjuvant therapy was made during a multidisciplinary tumour board discussion. Median dose of radiotherapy to primary site (min-max): 60 (0–70) Gy, to neck (min-max): 60 (0–60) Gy
• **Intervention group (2)**	**Group 2:** Primary tumour resection and/or neck dissection and chemoradiotherapy The decision to choose the adjuvant therapy was made during a multidisciplinary tumour board discussion. Median dose of radiotherapy to primary site (min-max): 60 (0–60) Gy, to neck (min-max): 60 (39.6–60) Gy. Chemotherapy: Cisplatin monotherapy (8 patients; 6 patients received cisplatin at 80 mg/m2/day, one patient at 100 mg/m2/day, and one patient at 20 mg/m2/day for 4 days, given every 3 weeks. 4 patients completed 3 cycles, 2 completed 2 cycles, and 2 tolerated only 1 cycle), Cisplatin + 5-fluorouracil (1 patient; intravenous cisplatin (20 mg/m2) and a continuous infusion of 5-FP (400 mg/m2/day) for 5 days, given every 4 weeks for two cycles.)
• **Control group (3)**	**Group 3:** Primary tumour resection and/or neck dissection
Results	
• **Disease-free survival**	Group 1 (primary tumour resection and/or neck dissection and radiotherapy) vs. Group 3 (primary tumour resection and/or neck dissection) "…the RT group had a trend toward longer DFS than the no adjuvant therapy group": HR 0.31, 95% CI 0.08 to 1.19, p=0.087 Group 2 (primary tumour resection and/or neck dissection and chemoradiotherapy) vs. Group 3 (primary tumour resection and/or neck dissection) "DFS for the CRT group was not different from that for the no adjuvant therapy group": HR 0.71, 95% CI 0.19 to 2.66, p=0.606 Group 1 + 2 (primary tumour resection and/or neck dissection and (chemo)radiotherapy) vs. Group 3 (primary tumour resection and/or neck dissection) HR 3.02, 95% CI 0.80 to 11.3, p=0.101
• **Recurrence rate**	Not assessed for comparison of interest
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (primary tumour resection and/or neck dissection and radiotherapy): vs. Group 3 (primary tumour resection and/or neck dissection)

	HR 0.32, 95% CI 0.06 to 1.67, p = 0.176 Group 2 (primary tumour resection and/or neck dissection and chemoradiotherapy) vs. Group 3 (primary tumour resection and/or neck dissection) HR 0.79, 95 % CI 0.15 to 4.08, p = 0.779
• **Quality of life**	Not assessed
• **Adverse events**	Group 1 (primary tumour resection and/or neck dissection and radiotherapy) vs. Group 2 (primary tumour resection and/or neck dissection and chemoradiotherapy) vs. Group 3 (primary tumour resection and/or neck dissection) *≥3 hematological toxicity* Neutrophils: 0 vs. 1 (11%) vs. 0 Hemoglobin: 0 vs. 1 (11%) vs. 4 (21%) Platelets: 0 vs. 0 vs. 0 *≥3 non-hematological toxicity* Nausea/vomiting: 0 vs. 1 (11%) vs. 0 Dysphagia: 1 (6%) vs. 2 (22%) vs. 3 (16%) Mucositis: 4 (24%) vs. 4 (44%) vs. 0 Anorexia: 3 (18%) vs. 2 (22%) vs. 0 Dysgeusia (grade 2): 6 (35%) vs. 5 (56%) vs. 0 Creatinine: 0 vs. 0 vs. 0 Infection: 1 (6%) vs. 1 (11%) vs. 0
Limitations and other comments	
• **Limitations**	High risk of selection bias due to retrospective study design. No blinding. Unclear risk of attrition and reporting bias. Incomparable study groups, although multivariate analyses were done. the small sample size may have impaired statistical significance of the results.

4.4.3.3. Hypopharynx

Clinical and Pathologic Predictors of Survival in Patients With Squamous Cell Carcinoma of the Hypopharynx After Surgical Treatment Chu 2008	
Methods	
• **Design**	Retrospective review of consecutive patients
• **Source of funding and competing interest**	Source of funding: grant from the Taipei Veterans General Hospital, Taiwan (VGH92-205) Declaration of interest: not reported
• **Setting**	Single center, Department of Otolaryngology, Taipei Veterans General Hospital, Taiwan
• **Sample size**	N=104 patients identified, N=94 patients included in analyses
• **Duration**	Inclusion between January 1986 and December 1995
• **Follow-up**	Median follow-up 50 months (range, 1 to 176 months)
• **Statistical analysis**	Kaplan-Meier method, univariate comparison by the log-rank test. All significant factors were entered into multivariate analysis by the Cox proportional hazards model. Parametric and nonparametric comparisons were performed by the Pearson X^2 test and the Fisher exact test.
Patient characteristics	
• **Eligibility criteria**	Patients with hypopharyngeal squamous cell carcinoma who underwent primary surgery for curative intent with or without postoperative radiotherapy
• **Exclusion criteria**	Poor quality or inadequate surgical specimens
• **Patient & disease characteristics**	Group 1 (postoperative radiotherapy): n=30; Group 2 (no postoperative radiotherapy): n=64* Age range: 36 to 80 years (median, 60 years) Age: <60 yrs: 45; ≥60 yrs: 49 Gender (M/F):97/3 Primary site: pyriform sinus: 82; posterior pharyngeal wall: 6; postcricoid: 6 T stage: T2: 10; T3: 39; T4: 45 N stage: N0:39; N1: 20; N2:35 TNM stage: II: 7; III: 28; IV: 59 *disagreement between numbers mentioned in table 1 and text (text: n=64 radiotherapy, table n=64 no radiotherapy)
Interventions	
• **Intervention group (1)**	Surgery and postoperative radiotherapy Radiotherapy: The median dose was 6,000 cGy (range, 4,000 to 7,400) to the primary site and 6,000 cGy (range, 3,000 to 7,400) to the neck. Indications: positive surgical margins, perineural invasion, lymphovascular invasion, multiple lymph node metastases, and ECS of lymph node metastases
• **Control group (2)**	Surgery

Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *Disease-specific survival (5 years)* 41% vs. 70% (p=0.007)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Baseline characteristics not presented separate for treatment groups. Participants and outcome assessors were not blinded. Uncertainty about numbers of participants in study groups.

Role of larynx-preserving partial hypopharyngectomy with and without postoperative radiotherapy for squamous cell carcinoma of the hypopharynx; Joo 2012	
Methods	
• **Design**	Retrospective analysis
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Single center, Department of Otolaryngology-Head and Neck Surgery, College of Medicine, The Catholic University of Korea, Seoul, Korea,
• **Sample size**	N=43
• **Duration**	Between September 1998 and September 2009
• **Follow-up**	Mean follow-up (range): 39 (11-149) months; patients were followed-up for a minimum of 1 year or until death.
• **Statistical analysis**	Overall as well as disease-specific survival was determined using the Kaplan–Meier method. The relationships between categorical variables were analyzed by the Fisher's exact or chi-square tests.
Patient characteristics	
• **Eligibility criteria**	Patients had not previously been treated for hypopharyngeal squamous cell carcinomas; they possessed biopsy-proven squamous cell carcinoma; or they underwent free fasciocutaneous flap reconstruction for hypopharyngeal defects.
• **Exclusion criteria**	Patients received chemoradiotherapy for primary treatment due to refusal of surgery; patients in whom the primary tumour had recurred; patients with distant metastasis at the time of initial presentation; or patients underwent transoral laser hypopharyngectomy or total laryngopharyngectomy.
• **Patient & disease characteristics**	- Median age (range): 61.5 yrs (43–73 yrs) - Sex (M/F): 42/1 - Site: pyriform sinus n=35 (81%), posterior pharyngeal wall n=8 (19%) - T-stage (T2/T3/T4): 25 (58%) / 13 (30%) / 5 (12%) - N-stage (N0/N1/N2/N3): 10 (23%) / 10 (23%) / 22 (51%) / 1 (3%)

Interventions	
• **Intervention group (1)**	**Group 1:** Surgery and postoperative (chemo)radiotherapy (n=30) Additional radio (chemo) therapy was performed in patients with multiple lymph node metastases. Indications and modalities for adjuvant treatments varied over time. Patients with a positive or a close margin, an advanced T stage, lymphovascular invasion, perineural invasion, multiple nodal metastases, or extracapsular spread received additional treatment. The radiation dose ranged from 4320 cGy to 6660 cGy, with a median of 6190 cGy.
• **Control group (2)**	**Group 2:** Surgery alone (n=13)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. Group 2 (postoperative radiotherapy) *Disease specific survival (5 years)* 64% vs. 75%, p=0.606
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Small sample size, no details on group characteristics for study groups of interest, no adjustments in analyses.

A reappraisal of surgical management for squamous cell carcinoma in the pharyngoesophageal junction; Wang 2006	
Methods	
• **Design**	Retrospective analyses of medical records
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Single center, Taiwan
• **Sample size**	N=41
• **Duration**	January 1984 – December 2002
• **Follow-up**	Mean follow-up: 42.6 months (range, 0.2–201.2months)
• **Statistical analysis**	Survival analyses were performed using the Kaplan–Meier method. Comparisons of survival between groups were assessed by log-rank test. Differences in clinicopathologic variables among various groups were calculated using Chi-squared test, Fisher exact test, and Student t-test when appropriate. Multivariate analysis with a stepwise Cox regression model was conducted to evaluate the independent prognostic factors. A P-value of less than 0.05 was considered statistically significant. All the analyses were performed with SPSS software version 11.0 (SPSS, Inc., Chicago, IL).

Patient characteristics	
• **Eligibility criteria**	Patients with primary squamous cell carcinomas at the pharyngoesophageal junction with simultaneous involvement of both the hypopharynx and cervical esophagus treated (with curative intent) with total pharyngolaryngoesophagectomy and visceral interposition between January 1984 and December 2002.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	- Mean age (range): 59.7 (34-76) yrs - Sex (M/F): 36/5 - Localization and tumour characteristics o hypopharyngeal cancer with esophageal extension: n=26 (63.4%) ▪ T status: all T4 ▪ N status (N0/N1/N2a/N2b/N2c/N3): 8/1/2/11/4/0 ▪ Cervical lymph node metastasis n=18 (69,2%) ▪ M status: all M0 o cervical esophageal cancer with hypopharyngeal invasion: n=15 (36.6%) ▪ T status (T1/T2/T3/T4): 0/3/5/7 ▪ N status (N0/N1/N2a/N2b/N2c/N3): 7/8/0/0/0/0 ▪ Cervical lymph node metastasis n=8 (53,3%) ▪ M status: all M0
Interventions	
• **Intervention group (1)**	**Group 1:** Surgery and adjuvant radiotherapy (n=27, of which n=6 received preoperative radiotherapy and n=21 received postoperative radiotherapy) Mean dose of preoperative irradiation was 47.3 Gy (range, 40–60 Gy). Postoperative radiotherapy was generally administered 3–4 weeks after surgery, with the mean dose of 47.5 Gy (range, 26–60 Gy)
• **Intervention group (2)**	**Group 2:** Surgery alone (n=14)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not reported for comparison of interest
• **(Loco)regional control**	Not reported for comparison of interest
• **Overall survival**	Group 1 (surgery and postoperative radiotherapy) vs. Group 2 (surgery alone) *Median survival*: 37.2 vs. 6.4 months *1-year survival rate*: 81.5% vs. 42.9% *5-year survival rate*: 48.2% vs. 0% p<0.001 (univariate analyses) “This survival advantage remained statistically significant when the cases of hospital mortality were excluded from the analysis (p=0.003).” Overall survival adjusted for age, gender, tumour localization, tumour size and local invasion (multivariate Cox regression analysis) HR 0.27, 95%CI 0.13 to 0.60 (p=0.001)

• **Quality of life**	Not assessed
• **Adverse events**	Not reported for comparison of interest
Limitations and other comments	
• **Limitations**	Retrospective study design with high risk of selection bias and no blinding. Characteristics of patients not specified for the study groups of interest (radiotherapy vs. no radiotherapy). Adjuvant radiotherapy group consists of patients with either preoperative (n=6) or postoperative radiotherapy (n=21). Small sample size.

4.4.3.4. Larynx

Total laryngectomy and T3-T4 laryngeal cancer without other adverse histopathology Ampil 2007	
Methods	
• **Design**	Retrospective study
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: not reported
• **Setting**	Two university-affiliated hospitals: Louisiana State University Health Sciences Center and Feist-Weiller Cancer Center, Shreveport, LA, USA
• **Sample size**	N=30 patients included
• **Duration**	Inclusion between 1983 and 2001
• **Follow-up**	Median follow-up 44 months (range 6-122 months).
• **Statistical analysis**	The Kaplan-Meier method and the log-rank sum test were used to estimate and compare survival rates of the studied patient groups.
Patient characteristics	
• **Eligibility criteria**	Patients were included if they had clinicopathological T3-4 laryngeal cancers managed by total laryngectomy, histologically negative cervical nodes, and no additional detrimental histopathology
• **Exclusion criteria**	Patients were excluded if they had early stage I or II carcinoma of the larynx; received treatment of stage III or IV neoplasms by radiation alone or chemoradiation; underwent total laryngectomy as salvage therapy of recurrent neoplasm after prior definitive radiotherapy; and had histologically documented metastatic involvement of cervical lymph nodes, extracapsular lymph node disease extension, or tumor-positive resection margins and/or perineural invasion.
• **Patient & disease characteristics**	Mean age at diagnosis: 57 years (range 38-76 years) Sex (M/F): 27/3 Group 1 (postoperative radiotherapy): n=18; Group 2 (no postoperative radiotherapy): n=12 Mean age at diagnosis: 55.2 vs. 59.7 years Elderly (≥65 years): 3 vs. 4 Other illness present: 1 vs. 2

	Mean number of nodes: 30.8 vs. 32.9 Tumor stage: T3: 8 vs. 9; T4: 10 vs. 3 Transglottic tumor: 17 vs. 10 "Statistically significant differences were not found between the compared patient groups with regard to age, the occurrence of coexisting illnesses, number of recovered cervical nodes, T stage, or the presence of transglottic tumors."
Interventions	
• **Intervention group (1)**	**Group 1:** surgery and postoperative radiotherapy (n=18) *Surgery*: total laryngectomy was performed most often.. Selective neck dissection (unilateral in 15 patients or bilateral in 15 patients) was conducted as indicated by the clinical presence of cervical adenopathy and primary tumor location. *Radiotherapy*: dose information was available for 17 patients: mean total dose to the primary site including the upper neck: 58 ± (SD) 4 Gy (range, 50-65 Gy), to the lower neck 50 ± 2 Gy (range, 45-60 Gy).
• **Control group (2)**	**Group 2**: surgery alone (n=12)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *Relapse in the neck* 0/16 vs. 3/12 (p=0.07) *Distant metastasis* 1/16 vs. 1/12
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *Survival rate (5 years)* 61% vs. 50% (p=0.63)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study, which might lead to selection bias. No blinding, high risk of attrition bias and small sample size.

Quality of Life Correlates After Surgery for Laryngeal Carcinoma Bindewald 2007	
Methods	
• **Design**	Reanalysis of data of two multi-institutional cross-sectional studies
• **Source of funding and competing interest**	Source of funding: grants from the German Federal Ministry of Education and Research (# 7DZAIQTX) and the Federal State of Saxony (NBL3-promotion, # formel.1-57). Declaration of interest: not reported
• **Setting**	Multicenter: University Hospital Leipzig, University Hospital Halle-Wittenberg, Community Hospital St. Georg Leipzig, Community Hospital Dresden-Friedrichstadt, Community Hospital Chemnitz, and Community Hospital Halle-Doelau, Germany
• **Sample size**	N=371 participated, n=205 participants with complete data were analyzed
• **Duration**	Patients operated between 1986 and 2004 were invited for an interview.
• **Follow-up**	Crossectional analysis; mean time since operation for laryngectomy: 5.7 (range 0.11–16.58) years, for partial laryngectomy: 4.5 (range 0.19–15.14) years
• **Statistical analysis**	Two multifactorial multivariate models were calculated, one each for the correlated scales of EORTC QLQ-C30 and EORTC QLQ-H&N35. Operation mode (laryngectomy [LE] vs. partial laryngectomy [PL]), radiotherapy (irradiated vs. non-irradiated patients), and disease stage (UICC-stage I/II vs. III/IV) were regarded as independent variables. All multivariate analyses were adjusted to the patient's age and the time elapsed since the operation. Multifactorial univariate analyses were applied to every scale and item for differentiation of the results of multivariate testing.
Patient characteristics	
• **Eligibility criteria**	Patients in the vicinity of Leipzig, Germany, who had been diagnosed with a laryngeal carcinoma and who had undergone an operation of the larynx between 1986 and 2004.
• **Exclusion criteria**	No exclusion criteria specified.
• **Patient & disease characteristics**	Mean age: - Laryngectomy: 61.8 (range 32–79) years - Partial laryngectomy: 66.5 (range 46–84) years Group 1 (postoperative radiotherapy): n=108 vs. group 2 (no postoperative radiotherapy): n=97 Stage: I/II: 28 vs. 82; III/IV: 80 vs. 15 Operation: laryngectomy: 72 vs. 20; partial laryngectomy: 26 vs. 77
Interventions	
• **Intervention group (1)**	**Group 1:** (Partial) laryngectomy and postoperative radiotherapy (n=108)
• **Control group (2)**	**Group 2:** (Partial) laryngectomy (n=97)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed

• **Overall survival**	Not assessed
• **Quality of life**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *General quality of life (EORTC-QLQ-C30 scores)* Marginal means of multifactorial univariate analyses Functioning scales - Physical functioning: 67.9 vs. 79.5 (p=0.059) - Role functioning: 61.7 vs. 80.7 (p=0.042) - Emotional functioning: 70.1 vs. 83.1 (p=0.077) - Cognitive functioning: 80.4 vs. 91.0 (p=0.096) - Social functioning:65.8 vs. 84.9 (p=0.027) - Global health status/ Quality of life: 57.7 vs. 68.6 (p=0.142) Symptom scales - Fatigue: 40.0 vs. 19.4 (p=0.012) - Nausea/vomiting: 6.8 vs. 3.2 (p=0.448) - Pain: 26.2 vs. 10.5 (p=0.061) - Dyspnea: 41.3 vs. 18.8 (p=0.036) - Insomnia: 32.0 vs. 11.6 (p=0.055) - Appetite loss: 16.7 vs. 5.0 (p=0.151) - Financial difficulties: 32.8 vs. 23.7 (p=0.340) Multivariate model including operation mode, postoperative radiotherapy, disease stage groups, age, and time since operation: “On the EORTC QLQ-C30 in total, only age had a significant influence in our sample (F= 5.64, p≤.001, η^2=0.286).” *Head- and neck-specific quality of life (EORTC-QLQ-H&N35 scores)* Marginal means of multifactorial univariate analyses - Pain in the mouth: 17.5 vs. 4.8 (p=0.006) - Swallowing problems: 20.2 vs. 6.5 (p=0.016) - Problems with smell: 51.5 vs. 37.1 (p=0.129) - Problems with taste: 35.4 vs. 6.4 (p=0.001) - Speech problems: 33.2 vs. 31.5 (p=0.833) - Social eating problems: 19.1 vs. 11.8 (p=0.219) - Social contact problems: 13.0 vs. 6.7 (p=0.147) - Sexuality problems: 36.1 vs. 26.4 (p=0.359) - Problems with teeth: 27.1 vs. 10.4 (p=0.082) - Problems opening mouth: 20.2 vs. 3.1 (p=0.017) - Dry mouth: 42.7 vs. 16.2 (p=0.001) - Sticky saliva: 42.6 vs. 19.2 (p=0.010) - Coughing: 51.9 vs. 48.1 (p=0.694)

	- Feeling ill: 30.6 vs. 14.6 (p=0.100) Multivariate model including operation mode, postoperative radiotherapy, disease stage groups, age, and time since operation: "…both operation mode and postoperative radiotherapy were decisive (F=4.41, p≤ 0.001, η^2=0.253 and F=1.90, p≤.0.05, η^2=0.127, respectively). The influence of disease stage, age, and time since operation did not reach level of significance."
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Cross-sectional study, more than half of the participants was excluded due to incomplete data. Baseline characteristics were not comparable for treatment groups. No details about treatment presented.

Supracricoid laryngectomy: oncologic validity and functional safety Cho 2010	
Methods	
• **Design**	Retrospective review of medical records
• **Source of funding and competing interest**	Source of funding: not reported No competing interest
• **Setting**	Single center: Seoul St. Mary's Hospital, Seoul, Korea
• **Sample size**	N=114 included
• **Duration**	Patients treated between August 1994 and December 2008 were retrospectively included.
• **Follow-up**	Mean: 49 months (range 2 to 132 months)
• **Statistical analysis**	Survival curves were plotted using the Kaplan–Meier method. Comparison of survival was performed using the log-rank test.
Patient characteristics	
• **Eligibility criteria**	Patients with endolaryngeal cancer that underwent supracricoid laryngectomy
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1 (supracricoid laryngectomy and postoperative (chemo)radiotherapy): n=16; Group 2 (supracricoid laryngectomy): n=98 Mean age: 60.84 (range 40–75 years) Gender (M/F): 107/7 Cancer types: squamous cell carcinoma: 112; sarcoma: 1; carcinosarcoma: 1; malignant fibrous histiocytoma: 1 Location: glottis: 84; supraglottis: 15; transglottis 15 Tumor stage (of n=104 previously untreated cases)*: T1b: 23; T2: 46; T3: 30; T4a: 5 Nodal stage (of n=104 previously untreated cases)*: N0: 90; N1: 5; N2a: 2; N2b: 2; N2c: 4; N3: 1 * n=10 salvage procedure
Interventions	
• **Intervention group (1)**	Supracricoid laryngectomy and postoperative (chemo)radiotherapy (n=16)
• **Control group (2)**	Supracricoid laryngectomy (n=96)

Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) *Disease-specific survival (5 years)* Approximately 50% vs. 90% (p=0.000) (read from figure) *Overall survival (5 years)* Approximately 36% vs. 78% (p=0.000) (read from figure) "However, the survival rate of the patients that received radiation or concurrent chemoradiation after SCL was significantly lower than that of the patients without adjuvant treatment after SCL"
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study which might lead to selection bias. Small sample size for one treatment group (postoperative radiotherapy). Baseline characteristics not reported for separate treatment groups and only univariate analyses performed. No details about treatment presented.

Endoscopic Vertical Partial Laryngectomy Davis 2004	
Methods	
• **Design**	Retrospective review
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: not reported
• **Setting**	Single center, University of Utah Health Science Center, USA
• **Sample size**	N=26 included
• **Duration**	Patients included between 1987 and 2000.
• **Follow-up**	Mean: 6 years and 7 months (range 1 year and 3 months to 15 years and 4 months)
• **Statistical analysis**	Kaplan Meier survival curves.
Patient characteristics	
• **Eligibility criteria**	Patients aged 32 to 76 with T1b or T2 squamous cell carcinomas of the glottic larynx who underwent endoscopic vertical partial laryngectomy with or without postoperative radiotherapy

• **Exclusion criteria**	Patients unable to be fully exposed endoscopically
• **Patient & disease characteristics**	Group 1 (postoperative radiotherapy): n=13 vs. group 2 (no postoperative radiotherapy): n=13 Gender (M/F): 11/2 vs. 9/4 Age range: 32-74 vs. 37-76 T stage: T1B: 0 vs. 2; T2: 1 vs. 6; T2B: 9 vs. 1; T2L: 0 vs. 1; T2N2B: 0 vs. 1; T3: 2 vs. 0; T4: 1 vs. 2 Months with disease (range): 26-151 vs. 15-184
Interventions	
• **Intervention group (1)**	Endoscopic vertical partial laryngectomy and postoperative radiotherapy (n=13) Radiotherapy: indications: clinically staged T2i carcinomas, cancer extension to the inferior aspect of the thyroid cartilage or to the cricothyroid membrane or upper trachea Patients received 66 Gy in 33 daily fractions of 200 cGy.
• **Control group (2)**	Endoscopic vertical partial laryngectomy (n=13)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Local control 84.5% vs. 100%
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. group 2 (no postoperative radiotherapy) 84.5% vs. 92.3%
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective review, leading to high risk for selection bias. Participants and outcome assessors were not blinded. Small sample size, only univariate analyses. Patients with clinically staged T2i carcinomas, as well as patients with cancer extension to the inferior aspect of the thyroid cartilage or to the cricothyroid membrane or upper trachea, received planned postoperative irradiation, so patients receiving postoperative radiotherapy might differ from patients receiving only surgery.

Epidemiology, Risk Factors, and Overall Survival Rate of Laryngeal Cancer in Songklanagarind Hospital Dechaphunkul 2011	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	Source of funding: not reported No competing interest
• **Setting**	Single center, Songklanagarind Hospital, Thailand
• **Sample size**	N=625 patients identified, N=289 patients with complete data analysed.
• **Duration**	From January 1, 1999 until December 29, 2008
• **Follow-up**	Not reported.
• **Statistical analysis**	The mean and standard deviation were used to describe parametric and non-parametric continuous data, and number and percentages to describe categorical data. The following data was assessed using the Fisher's exact test and estimate survival probability was assessed with Kaplan-Meier methods.
Patient characteristics	
• **Eligibility criteria**	Patients diagnosed with laryngeal cancer
• **Exclusion criteria**	Incomplete data
• **Patient & disease characteristics**	Median age: 64 years (range 29 to 90 years) Male gender: 92.3% Supraglottic cancer patients (n=106) Group 3 (postoperative radiotherapy): n=29; group 4 (no postoperative radiotherapy): n=3 Stage: I or II: 2 vs. 2; III, Iva, IVb: 27 vs. 1 Glottic cancer patients (n=180) Group 3 (postoperative radiotherapy): n=52; group 4 (no postoperative radiotherapy): n=12 Stage: I, II: 33 vs. 7; III, Iva, IVb: 19 vs. 5
Interventions	
• **Intervention group (1)**	**Group 1:** Primary radiation (n=182)
• **Intervention group (2)**	**Group 2:** Concurrent chemoradiation (n=8)
• **Intervention group (3)**	**Group 3:** Surgery + postoperative radiation (n=81)
• **Control group (4)**	**Group 4:** Surgery (n=15)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed

• **Overall survival**	Overall survival rate (5 years) Group 3 (postoperative radiotherapy) vs. group 4 (no postoperative radiotherapy) Supraglottic cancer patients 52.2% vs. – (too small number of patients to be analysed) Glottic cancer patients 61.4% vs. 87.5%
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study resulting in a high risk of selection bias. More than half of the patients was excluded due to missing data, resulting in a small sample size, especially in the group treated with surgery only.

Treatment, Survival, and Costs of Laryngeal Cancer Care in the Elderly Gourin 2014	
Methods	
• **Design**	Retrospective cross-sectional study of Surveillance, Epidemiology, and End Results (SEER) – Medicare data
• **Source of funding and competing interest**	Source of funding: American Academy of Otolaryngology–Head and Neck Surgery Percy Memorial Research Award No competing interest
• **Setting**	Population-based registries, USA.
• **Sample size**	N=2370 included in analyses, N=1288 for comparison of interest
• **Duration**	Patients diagnosed between 2004 and 2007 were included.
• **Follow-up**	Follow-up through December 2009 until the end of data (ineligibility or end of claims) or death
• **Statistical analysis**	Associations between variables were analyzed using cross-tabulations and multivariate regression modeling. Initial treatment and subsequent additional cancer-directed treatment were examined as dependent variables using multinomial and multiple logistic regression analysis. Independent variables included age, sex, race, comorbidity, marital status, median income quintile, primary site, stage, urban/rural location, SEER region, hospital volume, and initial treatment. Overall survival, defined as time from diagnosis to either last claim date or death, was analyzed using the Kaplan-Meier method and multivariate Cox proportional hazard analysis.
Patient characteristics	
• **Eligibility criteria**	Patients with larynx (SEER site code 38) squamous cell cancer without a previous diagnosis of head and neck cancer (01-10, 37, 38, and 41) or lymphoma (68-69, 71-72), aged 66 years and older
• **Exclusion criteria**	Patients with in situ disease, distant metastatic disease, diagnosis by autopsy or death certificate, and less than 1 year of continuous claims.
• **Patient & disease characteristics**	Group 1 (postoperative radiotherapy): n=1017 vs. group 2 (no postoperative radiotherapy): n=271 Location: Glottic: 774 vs. 185; supraglottic: 175 vs. 64; other larynx: 68 vs. 22

	Age 66-74 years: 556 vs. 148; 75-79 years: 223 vs. 53; ≥80 years: 238 vs. 70 Sex (M/F): 836/181 vs. 206/65 TNM stage: I: 603 vs. * ; II: 177 vs. 36; III: 88 vs. 40; IV: * vs. * ; unknown; * vs. * T stage: T1: 613 vs. 165; T2: 207 vs. 42; T3: 87 vs. 36; T4 * vs. * ; missing: * vs. * N stage: N0/N1: 838 vs. 232; N2/N3: 54 vs. *; Missing: 125 vs. * *The exact number of patients was suppressed because of the presence of cells with <11 observations to comply with the SEER–Medicare data use agreement.
Interventions	
• **Intervention group (1)**	Surgery with postoperative radiation (including postoperative chemoradiation) (n=1017)
• **Control group (2)**	Surgery (n=271)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative radiotherapy) vs. Group 2 (no postoperative radiotherapy): HR 0.66 (95% CI 0.52-0.84) “Patients whose initial treatment was surgery with postoperative radiation had improved survival, which remained significant after controlling for subsequent additional cancer-directed treatment.”
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study, so a high risk of selection bias. No blinding of participants.

Quality of life after treatment for laryngeal carcinomas; Olthoff 2006	
Methods	
• **Design**	Prospective study
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Multicenter study, five university hospitals in Germany
• **Sample size**	N=146
• **Duration**	Not reported
• **Follow-up**	The observation period was 60 weeks.

• **Statistical analysis**	QL data were obtained by using the EORTC QLQ-C30 questionnaire (developed by the European Organization for Research and Treatment of Cancer) before (week 0), during (week 8, week 28) and after (week 60) treatment. The QLQ-C30 (with a total of 30 items) includes 5 functional scales, 3 symptom scales, a global QL scale with 2 items and 6 single items. All subscales and item scores were linearly converted to a 0–100 scale. For functional and global QL scales, higher scores indicate a higher level, whereas for symptom scales and single items, higher scores represent a lower level of functioning and QL. An extension of the Wilcoxon-Mann-Whitney test for factorial designs with longitudinal data was applied to analyze the time profiles and group effects of the scores of the different groups. All interactions were included using a three-factorial design with time-dependent replications. In case of a significant higher-level interaction, a stratified analysis was added. Statistical significance was defined as $p<0.05$.
Patient characteristics	
• **Eligibility criteria**	Patients with laryngeal cancers who underwent a primary surgical treatment with curative intention.
• **Exclusion criteria**	All patients who developed recurrences at local, regional or distant sites or second primary cancers during the study period were excluded. In addition, the data of patients who died during this period were not considered, irrespective of the cause of death.
• **Patient & disease characteristics**	- Mean age (range): 56 (29–70) yrs - Sex (M/F): 133/13 - Stage (I/II/III/IV): 54/37/20/35 - Procedure: o Total laryngectomy: n=32 o Laser microsurgical partial laryngectomy: n=81 o Open partial laryngectomy: n=33 - Radiotherapy: n=44
Interventions	
• **Intervention group (1)**	**Group 1**: surgery with postoperative radiotherapy (n=44) Surgery: either total laryngectomy, laser microsurgical partial laryngectomy or open partial laryngectomy Radiotherapy: 2 Gy per day, 5 days per week, median total dose of 60 Gy
• **Control group (2)**	**Group 2**: surgery alone (n=102) Surgery: either total laryngectomy, laser microsurgical partial laryngectomy or open partial laryngectomy
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	Not assessed
• **Quality of life**	Group 1 (postoperative radiotherapy) vs. Group 2 (no postoperative radiotherapy): *EORTC QLQ-C30 questionnaire* Functional scales - Cognitive functioning: not significant - Emotional functioning: not significant - Physical functioning: not significant

	- Role functioning: not significant - Social functioning: not significant Symptom scales - Fatigue: p=0.006 - Pain: p=0.035 - Nausea and vomiting: p=0.002 Single items - Appetite loss: significant higher-level interaction - Constipation: significant higher-level interaction - Diarrhea: not significant - Dyspnea: significant higher-level interaction - Financial difficulties: significant higher-level interaction - Sleep disturbance: not significant Global quality of life: not significant
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	No details on group characteristics for study groups of interest, no adjustments in analyses. Patients who developed local recurrences or distant metastasis, were excluded from the study, as were patients who died during follow up.

Post-operative radiotherapy in advanced laryngeal cancer: effect on local and regional recurrence, distant metastases and second primaries; Yilmaz 2005	
Methods	
• **Design**	Retrospective analysis of medical records
• **Source of funding and competing interest**	No source of funding reported; competing interests: none declared
• **Setting**	Single center, Departments of Otolaryngology-Head & Neck Surgery and Radiation Oncology, Faculty of Medicine, Hacettepe University, Ankara, Turkey
• **Sample size**	N=530
• **Duration**	Patients treated between 1964 and 1997 were included
• **Follow-up**	A minimum follow-up period of three years was required for inclusion.
• **Statistical analysis**	Multivariate statistical analysis using Cox proportional hazards regression was performed. The significance values (p values) are Wald's tests to compare each category with the baseline value.
Patient characteristics	
• **Eligibility criteria**	Laryngeal cancer patients who were or were not given postoperative radiotherapy, treated between 1964 and 1997 and with a minimum follow-up period of three years.
• **Exclusion criteria**	Not specified.
• **Patient & disease characteristics**	Group 1 (surgery and postoperative radiotherapy): n=236 vs. Group 2 (surgery alone): n=294

	- Mean age (range): 53 (24-86) yrs vs. 52 (23-79) yrs; - Sex (M/F): 231/5 vs. 284/10; - Tumour stage (T1/T2/T3/T4): 37/95/56/48 vs. 47/157/90/0; - Nodal stage (N0/N1/N2/N3): 132/54/43/7 vs. 193/61/40/0; - Laryngectomy (total / partial): 166/70 vs. 204/90.
Interventions	
• **Intervention group (1)**	**Group 1:** Surgery and postoperative radiotherapy Surgery: all patients were treated with neck dissection en bloc, together with total or partial laryngectomy depending on the apparent extent of disease as determined at direct laryngoscopy. For N0 necks a selective (level I-IV) neck dissection or modified radical type-III neck dissection was performed. For node-positive (N+) cases a radical neck dissection was the procedure of choice. Radiotherapy: indications were primary tumour at T3–4 stage; neck staged as containing N2–3 disease; or positive surgical margins or extracapsular invasion; pN+ disease treated by selective neck dissection; cartilage, perineural or lymphovascular invasion; or metastases in more than one lymph node region. Radiotherapy was given after surgery and as soon as wound healing was complete. Daily fractions of 1.8–2.0 Gy were used to total doses of between 5000 and 6300 cGy.
• **Intervention group (2)**	**Group 2**: Surgery alone All patients were treated with neck dissection en bloc, together with total or partial laryngectomy depending on the apparent extent of disease as determined at direct laryngoscopy. For N0 necks a selective (level I-IV) neck dissection or modified radical type-III neck dissection was performed. For node-positive (N+) cases a radical neck dissection was the procedure of choice.
Results	
• **Disease-free survival**	Not reported for comparison of interest
• **Recurrence rate**	Group 1 (surgery + radiotherapy) vs. Group 2 (surgery alone) *Recurrences (number of patients)* Local: 10/236 (4%) vs. 9/294 (3%) Regional: 44/236 (19%) vs. 15/294 (5%) Locoregional: 9/236 (4%) vs. 8/294 (3%) Locoregional and distant metastasis*:* 2/236 (0.8%) vs. 0/294 (0%) Regional and distant metastasis: 4/236 (1.7%) vs. 0/294 (0%) *Locoregional recurrence* HR 1.574, 95%CI 0.941 to 2.633
• **(Loco)regional control**	Not assessed
• **Overall survival**	Not assessed
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed

Limitations and other comments	
• **Limitations**	Retrospective study design leading to high risk of selection bias and there was no blinding. Unclear risk of attrition bias and reporting bias.

b. Postoperative chemoradiotherapy versus postoperative radiotherapy

4.4.4. Evidence tables of systematic reviews RQ4b

Interventions for the treatment of oral cavity a Interventions for the treatment of oral cavity and oropharyngeal cancer: chemotherapy and oropharyngeal cancer: chemotherapy Furness 2011	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	National Institute of Health, National Institute of Dental & Craniofacial Research, USA; Central Manchester & Manchester Children's University Hospitals NHS Trust, UK.
• **Search date**	December 2010
• **Searched databases**	MEDLINE via OVID, The Cochrane Oral Health Group's Trials Register, CENTRAL, EMBASE via OVID, Allied and Complementary Medicin Database (AMED), Current Controlled trials, reference lists checked and specialists in the field contacted.
• **Included study designs**	RCTs
• **Number of included studies**	n=89 RCTs (n=16767 patients) of which n=11 RCTs (n= patients) for comparison of interest.
• **Statistical analysis**	Primary outcome is total mortality expressed as hazard ratio of death. If hazard ratios were not quoted in studies, log hazard ratio and the standard error (SE) was calculated from the available summary statistics (Parmar et al 1998), or data were requested from authors. Risk ratios were combined for dichotomous data, and hazard ratios for survival data, using fixed-effect models, unless there were more than four trials to be combined, when random-effects were used; Cochran's test for heterogeneity and the I2 statistic were used, any heterogeneity was investigated. A sensitivity analysis was planned
Patient characteristics	
• **Eligibility criteria**	Patients with primary squamous cell oral cancer ICD-O codes as C01-C06 (oral cavity including mouth, tongue, gum, or palate), tonsil (ICD-O: C09) or oropharynx, (ICD-O: C10).
• **Exclusion criteria**	RCTS regarding patients with cancer of hypopharynx (ICD-O: C13), nasopharynx, (ICD-O: C11), larynx (ICD-O: C32) or lip (ICDO:C00), epithelial malignancies of the salivary glands, odontogenic tumours, all sarcomas and lymphomas, and trials where participants present with recurrent or metastatic disease.
• **Patient & disease characteristics**	Comparison 2 of this SR included 11 RCTs. Of those, five RCTs (Argiris 2008, Bernier 2004, Cooper 2004, Laramore 1992, UKHAN 2010) with 1621 participants, are of relevance for this research question 4. All of the patients included in the trials had surgical resection with curative intent. Following surgery, patients were randomized to either post-operative (adjuvant) chemotherapy ± radiotherapy or surgery ± radiotherapy alone. Most of the patients had advanced staged disease and/or were deemed 'high risk'.

Interventions	
• **Intervention group**	Surgery ± radiotherapy + chemotherapy
• **Control group**	Surgery ± radiotherapy alone
Results	
• **Disease-free survival**	Post-surgery concomitant chemoradiotherapy versus post-surgery radiotherapy alone (3 studies) HR 0.87 (95%CI 0.73 to 1.04)
• **Recurrence rate**	Post-surgery concomitant chemoradiotherapy (cisplatin) versus post-surgery radiotherapy alone (1 study) Locoregional recurrence HR 0.61 (95% CI 0.41 to 0.91)
• **(Loco)regional control**	Not assessed
• **Overall survival**	*Total mortality* Surgery + chemotherapy (cisplatin/ 5-FU) + radiotherapy vs. surgery + radiotherapy alone(1 study) HR 0.91 (95% CI 0.73 to 1.13) Post-surgery concomitant chemoradiotherapy versus post-surgery radiotherapy alone (4 studies) HR 0.84 (95% CI 0.72 to 0.98)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	High quality systematic review; all AMSTAR items adhered

4.4.5. Evidence tables of RCTs RQ4b

Combine postoperative radiotherapy and weekly cisplatin infusion for locally advanced head and neck carcinoma: final report of a randomized trial; Bachaud 1996 (for some details authors refer to a preliminary report of this RCT)	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: not reported
• **Setting**	Not reported. Country: France
• **Sample size**	N=88 randomized, n=83 analyzed Calculated sample size was n=200 patients. However, mainly because of the growing use of neoadjuvant chemotherapy in the treatment of locally advanced carcinomas of the upper aerodigestive tract, the rate of inclusions dramatically decreased and accrual was terminated in 1988.

• **Duration**	Patient enrollment between April 1984 and March 1988.
• **Follow-up**	Follow-up was obtained until death or a minimum of 5 years in all but three cases. These three patients, all in the chemotherapy group, were lost to follow-up without disease 14, 21, and 52 months after completion of treatment, respectively.
• **Statistical analysis**	Differences in patient characteristics were evaluated by the chi-square test. Survival time was measured from the day of completion of radiotherapy. Analysis of survival and loco-regional relapse rates was done using the Kaplan-Meyer method. The log rank test was used to compare the survival and relapse curves. Cox's proportional hazard model was used to determine whether chemotherapy is an independent variable influencing the survival and the incidence of locoregional failures.
Patient characteristics	
• **Eligibility criteria**	Patients referred for postoperative irradiation of a stage III or IV squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, larynx, or carcinoma of unknown primary site with cervical metastatic nodes; and with histologic evidence of nodal extracapsular spread (ECS) of tumor in lymph node on the surgically obtained specimens.
• **Exclusion criteria**	Karnofsky performance status of <60, tumor treated previous to the surgical procedure, gross residual disease following surgery, distant metastasis at the time of radiotherapy, concurrent or previous second primary cancer (excluding non-melanoma skin cancer), serum creatinine >110 µ/l, leukocyte count <4000/mm^3 or platelet count <100000/mm^3.
• **Patient & disease characteristics**	Group 1 (postoperative chemoradiotherapy): n=39 vs. Group 2 (postoperative radiotherapy): n=44 - Mean age (±SD?): 59.8 ± 1.34 yrs vs. 59.3 ± 1.27 yrs - Primary site: o Oral cavity: 2 vs. 4 o Oropharynx: 7 vs. 5 o Hypopharynx: 10 vs. 16 o Larynx: 16 vs. 16 o Unknown primary: 4 vs. 3 - Clinical stage (III/IV): 6/33 vs. 15/29 "There is no statistical difference between the two groups with respect to the main prognostic factors."
Interventions	
• **Intervention group (1)**	Group 1: Surgery + chemoradiotherapy (n=39) Surgery: Primary site (if known) + cervical lymph node dissection Radiotherapy: 1 fraction/day, 5 days/week; all patients received 54 Gy on this volume following a 1.7 Gy daily dose schedule. Following the initial dose of 54 Gy, the primary site and/or cervical lymph nodes were boosted according to the clinical TN Stage and pathologic involvement. The final dose on the primary site was 65-70 Gy in case of close (<5 mm) or positive margins using a daily dose of 1.8 to 2 Gy. Chemotherapy: Cisplatin 50 mg on the first day of each week of the irradiation course; total number of planned chemotherapy cycles ranged from 7 to 9.
• **Control group (2)**	Group 2: Surgery + radiotherapy (n=44) Surgery: Primary site (if known) + cervical lymph node dissection Radiotherapy: 1 fraction/day, 5 days/week; all patients received 54 Gy on this volume following a 1.7 Gy daily dose schedule. Following the initial dose of 54 Gy, the primary site and/or cervical lymph nodes were boosted according to the clinical TN Stage and pathologic involvement. The final dose on the primary site was 65-70 Gy in case of close (<5 mm) or positive margins using a daily dose of 1.8 to 2 Gy.

Results	
• **Disease-free survival**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *2-year disease-free survival*: 68% vs. 44% *5-year disease-free survival*: 45% vs. 23% p<0.02 (log rank test)
• **Recurrence rate**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *Recurrences* Loco-regional recurrence: 9/39 (23%) vs. 18/44 (41%), RR 0.56 (95% CI 0.29 to 1.11), p=0.08 Isolated distant metastases: 10/39 (26%) vs. 13/44 (30%), RR 0.87 (95% CI 0.43 to 1.75) p>0.05 N.B. numbers mentioned in text and table differ; numbers from text extracted.
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *Median survival (months)*: 40 vs. 22 *2-year overall survival*: 72% vs. 46% *5-year overall survival*: 36% vs. 13% p<0.01 (log rank test)
• **Quality of life**	Not assessed
• **Adverse events**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *Acute severe toxicities (>grade 3, RTOG/EORTC scale)* 16/39 (41%) vs. 7/44 (16%), RR 2.58 (95% CI 1.19 to 5.61) - Weight loss (> 10% body weight) 8 (21%) vs. 3 (7%) - Mucositis (confluent mucositis + ulceration or dysphagia requiring feeding tube): 8 (21%) vs. 4 (9%) - Nausea and vomiting (>6/day despite medication) 9 (23%) vs. 0 - Neutrophils (< 1000/mm^3): 4 (10%) vs. 0 - Hemoglobin (transfusion required): 1 (3%) vs. 0 - Renal failure: 0 vs. 0 *Severe late toxicity (> Grade 2 on the RTOG/EORTC scale)* Fifty-six patients (26 in the RT group and 30 in the CM group) free of loco-regional disease were available for this analysis. 6/30 (20%) vs 4/26 (15%), RR 1.30 (95% CI 0.41 to 4.11) - Hypopharyngeal stenosis o permanent diet liquid: 1 vs. 3 (1 death) o gastrostomia : 1 vs. 0 - Severe cervical subcutaneous fibrosis 3 vs. 1 - Mandibular radionecrosis (requiting surgery): 1 vs. 0

Limitations and other comments	
• **Limitations**	Number of included participants much lower than prior calculated sample size. "The results should be considered with caution because small differences in the distribution of prognostic factors existed between the two therapeutic groups. For instance, there were more hypopharyngeal primary sites (16 vs. 10) and more positive margins (18 vs. 11) in the RT group (3). Although they were not statistically significant, such differences could have had a large influence on the final result of such a small series." No details provided about method of randomization and blinding, leading to unclear risk of selection bias and detection bias for subjective outcomes. High risk of reporting bias, as more outcomes were reported than prespecified in methods section. High risk of performance bias and low risk of attrition bias.

Mitomycin C as an adjunct to postoperative radiation therapy in squamous cell carcinoma of the head and neck: results from two randomized clinical trials; Haffty 1993 **Randomized clinical trial of mitomycin C as an adjunct to radiotherapy in head and neck cancer; Weissberg 1989**	
Methods	
• **Design**	Subgroup analysis of 2 RCTs Trial I was described before in the publication of Weissberg.
• **Source of funding and competing interest**	Source of funding: supported in part by ACS Grants #DHP-35 and #CH530 Competing interest: none reported
• **Setting**	Single center; Yale Comprehensive Cancer Center, Yale University School of Medicine, New Haven, USA
• **Sample size**	Enrolled in trial I: n=120, of which n=75 were treated in the postoperative setting Enrolled in trial II: n=62, of which n=38 were treated in the postoperative setting N=113 from both randomized trials treated in the postoperative setting are included in this analysis
• **Duration**	Trial I: 1980 - 1986 Trial II: 1986 - August 1992
• **Follow-up**	From October 1991 median follow-up of the 113 patients was 92.6 months (range: 6-135)
• **Statistical analysis**	Comparison between treatment groups were tested for significance with the contingency table chi-square test for all categorical factors and the student's T-test for continuous variables. Survivorship and recurrence-free survivorship at one year intervals were estimated using standard actuarial methods. Statistical comparisons between the two treatment groups were made using the Gehan-Wilcoxan test.
Patient characteristics	
• **Eligibility criteria**	All patients, aged 20-80 years, with previously untreated histologically proven epidermoid carcinoma of the head and neck (oral cavity, oropharynx, larynx, hypopharynx, paranasal sinus, nasopharynx, unknown primary), whose treatment normally would include radiation therapy; American Joint Commission Stage: I (T 1, NO-except T 1 vocal cord), II (T2, NO,MO), III (T3, NO; TI-T3, NI. MO), IV (T4, NO-NI, MO; any T, N2-N3, MO); no distant metastases; no history of other malignancies active in past 5 years (other than basal or squamous cell cancer outside the treatment area or in-situ carcinoma of the cervix); no prior radiation at proposed treatment site; no chemotherapy within 3 years; no history of peptic ulcer-esophageal varices or known bleeding

	disorder; no other serious or life-threatening illness; not currently taking anti-coagulants or barbiturates; tests within specified/acceptable limits: hematocrit > 30, WBC > 3,000, platelets > 100000/mm3, PT < 13 set and < 1 set over control, PTT 25-40 set, total bilirubin < 1.5 mg/dl, BUN < 20 mg/dl, creatinine < 2.0 mg/dl, calcium 9.1-10.6 mg/dl, phosphate 3. I-4.5 mg/dl, SGOT 0-35 µ/l, SGPT 0-35 µ/l, chest x-ray WNL.
• **Exclusion criteria**	Patients with T1 lesions of the true vocal cords were excluded.
• **Patient & disease characteristics**	Group 1+2 (postoperative radiotherapy + mitomycin C ± dicoumarol): n=55 vs. Group 3 (postoperative radiotherapy): n=58 - Median age (range): 57.1 (31-78) vs. 57.7 (35-71); - Sex (M/F): 48/7 vs. 48/10; - TNM group 1. T1N0-2 or T2N0: 28 vs. 26; 2. T1N3 or T2N1-2 or T3N0:18 vs. 21; 3. T2N3 or T3N≥1 or T4 anyN: 9 vs. 11; - Site o Oral cavity: 16 vs. 20; o Oropharynx: 10 vs. 9; o Hypopharynx: 13 vs. 12; o Larynx: 14 vs. 13; o Unknown primary: 2 vs. 3; o Paranasal sinus: 0 vs. 1; - Therapeutic intent (prophylactic / residual disease): 35/20 vs. 37/21 "There were no significant differences between the radiation arm and the radiation plus mitomycin/dicoumarol arms with respect to median radiation dose, treatment time, follow-up, age or sex. Because patients were stratified by TNM group, treatment intent and site, there were no significant differences between the two groups with respect to these parameters." Group 1 (postoperative radiotherapy + mitomycin C): n=37 vs. Group 3 (postoperative radiotherapy): n=41 (Trial I) - Therapeutic intent (prophylactic / residual disease): 22/15 vs. 26/15
Interventions	
• **Intervention group (1)**	**Group 1:** postoperative radiotherapy + mitomycin C (Trial I) Radiotherapy: 180-200 cGy daily, 5 days a week; total dose was left to the discretion of the treating radiation oncologist. Median dose (range): 5954 cGy (4580-7000); treatment time (range): 45 days (30-73). Mitomycin: intravenously, dose of 15 mg/M^2 ,following radiation treatment on the 5th day of the radiotherapy course. Patients with residual disease, who were scheduled for more than six weeks of radiation therapy, also received a second dose of mitomycin C, 15 mg/M^2 six weeks following the first dose of mitomycin.
• **Intervention group (2)**	**Group 2:** postoperative radiotherapy + mitomycin C + dicoumarol (Trial II) Radiotherapy: 180-200 cGy daily, 5 days a week; total dose was left to the discretion of the treating radiation oncologist. Median dose (range): 5954 cGy (4580-7000); treatment time (range): 45 days (30-73). Mitomycin: intravenously, dose of 15 mg/M^2 ,following radiation treatment on the 5th day of the radiotherapy course. Patients with residual disease, who were scheduled for more than six weeks of radiation therapy, also received a second dose of mitomycin C, 15 mg/M^2 six weeks following the first dose of mitomycin.

	Dicoumarol: patients receiving mitomycin also received a total of 500 mg of dicoumarol administered orally, with 300 mg given the day before mitomycin C and 200 mg given on the day of mitomycin C. Patients scheduled to receive a second dose of mitomycin also received a second course of dicoumarol.
• **Control group (3)**	**Group 3:** postoperative radiotherapy Radiotherapy: 180-200 cGy daily, 5 days a week; total dose was left to the discretion of the treating radiation oncologist. Median dose (range): 5891 cGy (3850-7200); treatment time (range): 47 days (28-87).
Results	
• **Disease-free survival**	Group 1+2 (postoperative radiotherapy + mitomycin C ± dicoumarol) vs. group 3 (postoperative radiotherapy) *5-year actuarial disease-free survival ± SE* 67 ± 6% vs. 47 ± 6%, p<0.03
• **Recurrence rate**	Group 1+2 (postoperative radiotherapy + mitomycin C ± dicoumarol) vs. group 3 (postoperative radiotherapy) *Local recurrence* 0/55 vs. 12/58, RR 0.04 (95% CI 0.00 to 0.70) *Regional recurrence* 5/55 vs. 8/58, RR 0.66 (95% CI 0.23 to 1.89) *Distant recurrence* 7/55 vs. 9/58, RR 0.82 (95% CI 0.33 to 2.05)
• **(Loco)regional control**	Group 1+2 (postoperative radiotherapy + mitomycin C ± dicoumarol) vs. group 3 (postoperative radiotherapy) *5-year actuarial local regional control rate ± SE* 87 ± 5% vs. 67 ± 7%, p<0.02 *5-year actuarial local control rate ± SE* 100 ± 0% vs. 75 ± 7%, p<0.01 Group 1 (postoperative radiotherapy + mitomycin C) vs. group 3 (postoperative radiotherapy) (Trial I) *5-year actuarial local regional control rate ± SE* - Prophylactic treatment: 93 ± 6% vs. 75 ± 9%, p<0.07 - Treatment of residual disease: 83 ± 11% vs. 60 ± 13%, p<0.07 *5-year actuarial local control rate ± SE* - Prophylactic treatment intent: 100% vs. 83 ± 8%, p<0.07 - Treatment of residual disease: 100% vs. 65 ± 13%, p<0.02
• **Overall survival**	Group 1+2 (postoperative radiotherapy + mitomycin C ± dicoumarol) vs. group 3 (postoperative radiotherapy) *5-year actuarial overall survival ± SE* 56 ± 7% vs. 41 ±7 %, p=NS

• **Quality of life**	Not assessed
• **Adverse events**	Group 1+2 (postoperative radiotherapy + mitomycin C ± dicoumarol) vs. group 3 (postoperative radiotherapy) <u>Hematologic toxicity (nadir values)</u> *Hemoglobin* - Mild (9.5-11): 8/55 vs. 6/58 - Moderate (8-9.5): 3/55 vs. 3/58 - Severe (<8): 0/55 vs. 0/58 *Leukopenia* - Mild (3000-4000): 18/55 vs. 7/58 - Moderate (2000-3000): 14/55 vs. 1/58 - Severe (1000-2000): 4/55 vs. 0/58 Moderate to severe: 18/55 vs. 1/58, RR 18.98 (95% CI 2.62 to 137.42) *Thrombocytopenia* - Mild (75000-100000): 7/55 vs. 0/58 - Moderate (50000-75000): 7/55 vs. 0/58 - Severe (25000-50000): 3/55 vs. 0/58 - Life-threatening (<25000): 2/55 vs. 0/58 Moderate, severe or life-threatening: 12/55 vs. 0/58, RR 26.34 (95% CI 1.60, 434.42) <u>Non-hematologic toxicity</u> *Mucositis** - 0-1: 26/55 vs. 21/58 - 2: 21/55 vs. 26/58 - 3: 6/55 vs. 6/58 - Not recorded: 2/55 vs. 5/58 *Epidermitis*** - 0-1: 27/55 vs. 30/58 - 2: 13/55 vs. 12/58 - 3: 4/55 vs. 5/58 - Not recorded: 11/55 vs. 11/58 *Nausea/vomiting* - Mild: 3/55 vs. 0/58 - Moderate: 2/55 vs. 1/58 - Severe: 0/55 vs. 0/58 - Not recorded: 30/55 vs. 20/58 *Extravasation / skin ulceration* 2/55 vs. not applicable

	"No significant difference in mucositis or epidermitis occurred between the control arm and treatment arm in either study." "Chronic radiation fibroses are not reported here, as follow-up from the second trial is limited. In the first mitomycin C trial, however, there was no significant difference in the level of chronic subcutaneous fibrosis between the groups receiving radiation alone or radiation plus mitomycin C. […]O ne additional toxicity which should be noted is the potential for delayed adverse tissue reactions near the injection site, secondary to extravasation of mitomycin. Although several reports of minor irritation at or near the site of drug administration occurred, there were two cases of skin ulceration secondary to extravasation that ultimately required surgical intervention." *Mucositis was graded from 0-4 as follows: 0-none; 1 -erythema; 2-patchy mucositis; 3-confluent mucositis; 4-ulceration or necrosis. **Epidermitis was graded 0-4 as follows: O-none; 1 -erythema; 2-dry desquamation; 3-moist desquamation; 4-ulceration or necrosis.
Limitations and other comments	
• **Limitations**	High risk of performance bias and detection bias for subjective outcomes due to the lack of blinding. Unclear whether allocation was concealed. Unclear risk of reporting bias.

Randomized clinical trial of post-operative radiotherapy versus concomitant carboplatin and radiotherapy for head and neck cancers with lymph node involvement Racadot 2008	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Source of funding: not reported Declaration of interest: not reported
• **Setting**	Multicenter, n=13 institutions in France
• **Sample size**	N=144 (72 per group). Calculated sample size was n=189 (56 events), however, enrollment stopped earlier because of publication of the preliminary results of the EORTC study,
• **Duration**	Inclusion between February 1994 and June 2002
• **Follow-up**	Median follow up of surviving eligible patients: 106 months (95% CI 92 to119). Maximal follow up 156 months (read from figure).
• **Statistical analysis**	Intention-to treat analyses; t-test for continuous variables and Fisher's exact test for categorical variables; rates of loco-regional control, or of loco-regional and metastasis control, and overall survival were estimated according to the Kaplan– Meier method. Data were compared using the log-rank test and a Cox regression model (including stratification and confounding factors).
Patient characteristics	
• **Eligibility criteria**	Untreated histologically proven squamous cell carcinoma arising from the oropharynx, hypopharynx, or larynx (clinically T1 to T4 and N0 to N3), macroscopically complete resection of disease (tumour and lymph nodes), histological evidence of invasion of one or more regional lymph nodes with or without extracapsular extension, age less than 75 years, Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, adequate hematological, renal and hepatic functions

• **Exclusion criteria**	Patients were excluded if they had lost more than 20% of their body weight during the previous 4 months, if they had any other cancer except basal-cell carcinoma of the skin or in situ carcinoma of the cervix, or if they had distant metastases
• **Patient & disease characteristics**	Group 1 (postoperative chemoradiotherapy): n=72; Group 2 (postoperative radiotherapy): n=72 - Sex (M/F): 67/5 vs. 68/4 - Mean age ± 2SD (years): 55 ± 8.8 vs. 56 ± 8.5 - ECOG (performance status): 0: 37 vs. 30; 1: 25 vs. 28; 2: 2 vs. 3; unknown: 8 vs. 11 - Location of tumor: oropharynx: 36 vs. 34; hypopharynx: 17 vs. 25; larynx: 19 vs. 13 - Tumor stage: T1: 5 vs. 6; T2: 29 vs. 29; T3: 25 vs. 30; T4: 13 vs. 7 - Nodal stage: N0: 26 vs. 16; N1: 17 vs. 19; N2: 22 vs. 28; N3: 6 vs. 9 - Histologic differentiation: high: 37 vs. 43; moderate: 21 vs. 26; poor: 14 vs. 3 - Chemotherapy before surgery (yes): 25 vs. 18 - Resection margin status: positive (R1): 12 vs. 19; negative (R0): 53 vs. 50; unknown: 7 vs. 3 - Lymph node involvement: 1 positive node: 19 vs. 26; ≥2 positive nodes: 53 vs. 46; Median (min–max): 3 (1–24) vs. 3 (1–34) - Extracapsular spread (yes): 21 vs. 24 - Number of extracapsular spread nodes (ESN): 0: 23 vs. 25; 1: 20 vs. 24; ≥2: 29 vs. 23 "There were no significant differences between the two groups except for histologic differentiation."
Interventions	
• **Intervention group (1)**	Group 1: Surgery + chemoradiotherapy (n=72) *Surgery*: Procedures included oropharyngectomy with or without partial glossectomy, total pharyngolaryngectomy, total laryngectomy, partial pharyngolaryngectomy, partial laryngectomy, depending on the extent and location of the tumor. Neck dissection was either radical, modified radical or partial. *Radiotherapy*: between 4 and 6 weeks and no later than 9 weeks after surgery; conventional daily doses of 1.8 Gy given in five sessions per week; 75th percentiles of total dose (range): 65 (3.6-72) vs. 63 (3.6-74) Gy *Chemotherapy*: (concomitant carboplatin, at a dose of 50 mg per square metre of body surface, given twice weekly during radiotherapy for a total of 6 weeks in patients with negative resection margins and 8 weeks in patients with positive margins. Median dose (range): 1030 (140-1800) mg
• **Control group (2)**	Group 2: Surgery + radiotherapy (n=72) *Surgery*: Procedures included oropharyngectomy with or without partial glossectomy, total pharyngolaryngectomy, total laryngectomy, partial pharyngolaryngectomy, partial laryngectomy, depending on the extent and location of the tumor. Neck dissection was either radical, modified radical or partial. *Radiotherapy*: between 4 and 6 weeks and no later than 9 weeks after surgery; conventional daily doses of 1.8 Gy given in five sessions per week; 75th percentiles of total dose (range): 65 (3.6-72) vs. 63 (3.6-74) Gy
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *Number of local and/or regional treatment failures*: 19/72 vs. 26/72, RR 0.73 (95% CI 0.45 to 1.20) *Number of local, regional or metastatic failures*: 36/72 vs. 30/72, RR 1.20 (95% CI 0.84 to 1.72)

• **(Loco)regional control**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *2-year rate of locoregional control*: 73% (95% C: 0.61 to 0.84) vs. 68% (95% CI 0.57 to 0.80), p=0.26 (log rank test) HR 0.77, 95% CI 0.40 to 1.48, p=0.44 (multivariate analysis, adjusted to histological evidence of invasion of two or more regional lymph nodes, extracapsular spread, positive margin, tumor site, histologic differentiation and neoadjuvant chemotherapy) "Two-year loco-regional control was lower for oropharyngeal tumors than for laryngeal tumors (RR = 2.8, 95% CI 1.1 to 7.4; p = 0.029), whereas there was no significant difference between hypopharyngeal and laryngeal tumors (RR = 1.21, 95% CI 0.42 to 3.48; p = 0.72)." *2-year rate of loco-regional and metastasis control*: 54% (95% CI 0.42 to 0.65) vs. 64% (95% CI 0.51 to 0.74), p=0.40 (log rank test) "Multivariate analysis of control data adjusted to histological evidence of invasion of two or more regional lymph nodes, extracapsular spread, positive margin, tumour site, histologic differentiation and neoadjuvant chemotherapy revealed no differences between groups (p = 0.40)"
• **Overall survival**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) Number of deaths: 53 vs. 56 Median survival time (months): 28 (95% CI 20 to 55) vs. 34 (95% CI 23 to 55), p=0.80 2-year overall survival: 55% (95% CI 0.43 to 0.66) vs. 58% (95% CI 0.46 to 0.69) HR 1.05, 95% CI 0.69 to 1.60 (multivariate analysis of overall survival adjusted to histological evidence of invasion of two or more regional lymph nodes, extracapsular spread, positive margin, tumor site, histologic differentiation and neoadjuvant chemotherapy
• **Quality of life**	Not assessed
• **Adverse events**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *Acute treatment-related adverse events (<90 days after start of radiotherapy)* *(grading according to RTOG and EORTC criteria)* - Hematologic o Anemia: grade 2: 3/52 vs. 2/51; grade 3: 0/52 vs. 0/51; p not reported o Leucopenia: grade 2: 9/52 vs. 0/51; grade 3: 2/52 vs. 0/51; p not reported o Thrombopenia: grade 2: 3/52 vs. 0/51: grade 3: 1/52 vs. 0/51; p not reported - Skin toxicity: grade 2: 25/52 vs. 22/51; grade 3: 24/52 vs. 6/51; p=0.10 - Mucositis: grade 2: 26/52 vs. 24/51; grade 3: 10/52 vs. 12/5; p=0.26 - Nausea and vomiting: grade 2: 0/52 vs. 1/51: grade 3: 0/52 vs. 0/51; p=0.07 *Late treatment-related adverse events (continuing or occurring >90 days)* *(grading according to RTOG and EORTC criteria)* - Xerostomia: grade 2: 21/52 vs. 25/51; grade 3: 3/52 vs. 2/51; p=0.57 - Agueusia: grade 2: 1/52 vs. 2/51; grade 3: 1/52 vs. 0/51; p=0.22 - Mucous membrane necrosis: grade 2: 2/52 vs. 2/51; grade 3: ? vs. 0/51; p=0.85

	- Mandible necrosis: grade 2: 0/52 vs. 1/51; grade 3: 0/52 vs. 2/51; p=0.25 - Pharynx pain: grade 2: 0/52 vs. 0/51; grade 3: 0/52 vs. 0/51; p=0.30 - Trismus: grade 2: 1/52 vs. 0/51; grade 3: 0/52 vs. 1/51; p=0.39 - Cutaneous fibrosis: grade 2: 6/52 vs. 6/51; grade 3: 2/52 vs. 2/51; p=0.86 - Telangiectasia: grade 2: 3/52 vs. 3/51; grade 3: ? vs. 1/51; p=0.50 - Subcutaneous fibrosis: grade 2: 6/52 vs. 6/51; grade 3: 2/52 vs. 4/51; p=0.56 - Oedema: grade 2: 7/52 vs. 3/51; grade 3: 1/52 vs. 2/51; p=0.37 - Deafness: grade 2: 2/52 vs. 1/51; grade 3: 0/52 vs. 0/51; p=0.51 - Pneumonia: grade 2: 0/52 vs. 0/51; grade 3: 0/52 vs. 0/51; p=0 "The incidence of late adverse effects did not differ significantly between the groups. No grade 4 or 5 toxicity was reported."
Limitations and other comments	
• **Limitations**	Low risk of selection bias. No details provided about blinding, however blinding was impossible considering the characteristics of the interventions, leading to a high risk of performance bias and detection bias for subjective outcomes. Unclear risk of reporting bias and attrition bias.

Postoperative concomitant irradiation and chemotherapy with mitomycin C and bleomycin for advanced head-and-neck carcinoma; Smid 2003	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Source of funding: Ministry of Science and Technology, Slovenia Declaration of interest: not reported
• **Setting**	Not reported
• **Sample size**	N=192 calculated sample size N=114 randomized
• **Duration**	Inclusion between March 1997 and December 2001
• **Follow-up**	Follow-up 2–57 months (median 32.2)
• **Statistical analysis**	The intention-to-treat analysis was calculated for loco-regional recurrence, disease-free survival, and overall survival from the beginning of treatment using the Kaplan-Meier method, and a log–rank test was used to test the differences between groups. The Cox regression model was used to define independent prognostic factors. The differences in the degree of toxicity were tested with Fischer's exact test
Patient characteristics	
• **Eligibility criteria**	Patients with squamous cell carcinoma of the head and neck with a performance status <3 (World Health Organization), haemoglobin > 100 g/L, leukocytes >3.5 x 10^9/L, platelets >100 x 10^9/L, and normal renal and hepatic tests and prothrombin time.
• **Exclusion criteria**	Patients were excluded if they had distant metastases, previous or simultaneous malignancy other than cured skin carcinoma, medical contraindications for chemotherapy (cardiopulmonary, renal, or hepatic disorders, diseases of the hematopoietic system, peptic ulcer), and psychosis or senility.
• **Patient & disease characteristics**	Group 1 (postoperative chemoradiotherapy): n=59; Group 2 (postoperative radiotherapy): n=55

	- Gender (M/F): 53/6 vs. 49/6 - Median age (range): 53 (41–73) yrs vs. 53 (37–72) yrs - Site: nose and paranasal sinuses: 0 vs. 2; oral cavity: 10 vs. 11; oropharynx: 18 vs. 16; hypopharynx: 17 vs. 14; larynx: 14 vs. 12 - Stage: III: 14 vs. 10; IV: 45 vs. 45
Interventions	
• **Intervention group (1)**	Group 1: surgery + chemoradiotherapy *Surgery*: Primary surgical treatment was performed with curative intent in all patients.. Selective neck dissections were performed as elective procedures in patients with Stage N0 in the neck and as curative in those with Stage N1 or N2 in the neck. Classic radical neck dissection was performed in the case of Stage N3 in the neck and when preoperatively or intraoperatively evident infiltration of metastases into surrounding structures was found. *Radiotherapy*: daily dose was 2 Gy applied in one fraction, 5 times weekly; total dose was aimed to be 56–70 Gy and thiswas reached in all patients except for one. *Chemotherapy*: Mitomycin C was applied at the dose of 15 mg/m2 after 10 Gy of RT. During RT, 5 mg of bleomycin was given intramuscularly twice weekly. Patients also received nicotinamide (225 mg daily) and chlorpromazine (75 mg) with bleomycin. Dicumarol (300 mg) was given on the evening before the day of mitomycin C application, as well as on the following morning, immediately before the application of mitomycin C.
• **Control group (2)**	Group 2: surgery + radiotherapy *Surgery*: Primary surgical treatment was performed with curative intent in all patients.. Selective neck dissections were performed as elective procedures in patients with Stage N0 in the neck and as curative in those with Stage N1 or N2 in the neck. Classic radical neck dissection was performed in the case of Stage N3 in the neck and when preoperatively or intraoperatively evident infiltration of metastases into surrounding structures was found. *Radiotherapy*: daily dose was 2 Gy applied in one fraction, 5 times weekly; total dose was aimed to be 56–70 Gy and this was reached in all patients.
Results	
• **Disease-free survival**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) 76% vs. 60% (p=0.099)
• **Recurrence rate**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *Local and/or regional recurrences with or without distant metastases*: 7/59 (12%) vs. 15/55 (27%), RR 0.44 (95% CI 0.19 to 0.99) *Distant metastases with or without loco-regional recurrence*: 6/59 (10%) vs. 8/55 (15%), RR 0.70 (95% CI 0.26 to 1.89) *Distant metastases*: 5/59 (8%) vs. 4/55 (7%), RR 1.17 (95% CI 0.33 to 4.12)
• **(Loco)regional control**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *2-year loco-regional control*: 86% vs. 69% (p=0.037) HR 2.82, 95% CI 1.12 to 7.09, p=0.027 (multivariate analysis)
• **Overall survival**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *2-year overall survival* 74% vs. 62% (p=0.036)

	HR 0.503, 95% CI 0.256 to 0.990, p=0.047 (multivariate analysis)
• **Quality of life**	Not assessed
• **Adverse events**	Group 1 (postoperative chemoradiotherapy) vs. Group 2 (postoperative radiotherapy) *Acute toxic effects (grading according to National Cancer Institute Common Toxicity Criteria)* - Mucositis o Grade 0: 0/58 vs. 0/54 o Grade 1: 0/58 vs. 5/54 o Grade 2: 7/58 vs. 19/54 o Grade 3: 34/58 vs. 29/54 o Grade 4: 17/58 vs. 1/54 "The difference in degree of mucositis (Grade 4 vs. others) between both groups was statistically significant (p<0.0001)." - Dermatitis o Grade 0: 0/58 vs. 0/54 o Grade 1: 8/58 vs. 6/54 o Grade 2: 29/58 vs. 28/54 o Grade 3: 17/58 vs. 20/54 o Grade 4: 4/58 vs. 0/54 - Infection o Grade 0: 9/58 vs. 32/54 o Grade 1: 37/58 vs. 18/54 o Grade 2: 6/58 vs. 3/54 o Grade 3: 6/58 vs. 1/54 o Grade 4: - vs. – "No statistically significant difference was found between the groups in the incidence of dermatitis and infection." - Leukocytes o Grade 0: 12/59 vs. 40/55 o Grade 1: 21/59 vs. 14/55 o Grade 2: 22/59 vs. 1/55 o Grade 3: 3/59 vs. 0/55 o Grade 4: 1/59 vs. 0/55 - Thrombocytes o Grade 0: 40/59 vs. 54/55 o Grade 1: 13/59 vs. 1/55 o Grade 2: 2/59 vs. 0/55 o Grade 3: 4/59 vs. 0/55 o Grade 4: 0/59 vs. 0/55

	- Hemoglobin o Grade 0: 29/59 vs. 45/55 o Grade 1: 28/59 vs. 10/55 o Grade 2: 2/59 vs. 0 o Grade 3: 0/59 vs. 0 o Grade 4: 0/59 vs. 0 "The difference in the degree of severe leukopenia, thrombopenia, and hemoglobin levels between both groups was not statistically significant." - Mean weight loss 7.5% vs. 3.3.%, p=0.001 *Late toxic effects (grading according to National Cancer Institute Common Toxicity Criteria)* - Necrosis of the mandible after tooth extraction: 3/59 vs. 0/55 - Lhermitte sign without further progression: 1/59 vs. 0/55 - Necrosis of the thyroid cartilage: 0/59 vs. 1/55 - Edema and/or fibrosis: 45/59 vs. 40/55 - Elevated thyroid-stimulating hormone: 22/59 vs. 13/55
Limitations and other comments	
• **Limitations**	No details provided about method of randomization and blinding, leading to unclear risk of selection bias and detection bias for subjective outcomes. Unclear risk of reporting bias, as no study protocol was available. Low risk of performance bias and attrition bias.

4.4.6. Evidence tables of observational studies RQ4b

Salvage treatment for recurrent oropharyngeal squamous cell carcinoma; Röösli 2010 (For some details authors refer to a previously published report of this study)	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	No information on source of funding and competing interest
• **Setting**	Single center, University Hospital of Zurich, Switzerland
• **Sample size**	N=427
• **Duration**	From January 1, 1990 through June 30, 2006
• **Follow-up**	Mean follow-up: 64 months (range, 1–195 months) - Primary radiation therapy group: mean follow-up of 72 months (range 3–192 months) - Surgery + radio(chemo)therapy group: mean follow-up of 49 months (range 1–195 months) - Surgery group: mean follow-up of 76 months (range 2–184 months)
• **Statistical analysis**	Calculations of OS and DSS were made with Kaplan–Meier estimates and compared by the means of the log-rank (Mantel–Cox) test.
Patient characteristics	
• **Eligibility criteria**	Patients with previously untreated, biopsy-proven squamous cell carcinoma of the oropharynx, treated with curative intent from January 1, 1990 through June 30, 2006.
• **Exclusion criteria**	Patients with signs of synchronous second primary, distant metastasis, previous head and neck cancer of any other site, patients with an uneventful follow-up of less than two years, and patients treated in a palliative regimen were excluded.
• **Patient & disease characteristics**	Group 1 (primary radio(chemo)therapy): n=166; Group 2+3 (surgery + radio(chemo)therapy): n=159; Group 4 (surgery): n=102 - Mean age (range): 58 (33–84) yrs; - Sex (M/F): 319/108; - Location: lateral wall: 347; base of tongue: 75; soft palate: 5; - T-stage (T1/T2/T3/T4): 86/152/115/74 - N-stage (N0/N1/N2a/N2b/N2c/N3): 99/72/25/168/48/15 - Stage (I/II/III/IV): 31/32/80/284 Group 2+3 (surgery + radio(chemo)therapy): n=159 vs. Group 4 (surgery): n=102 - Mean age (range): 56 (33–84) yrs vs. 59 (41–88) yrs - Sex (M/F): 120/39 vs. 72/30 - Stage: I: 5 vs. 25; II: 5 vs. 22; III: 32 vs. 25; IV: 124 vs. 30
Interventions	
• **Intervention group (1)**	**Group 1**: Primary radio(chemo)therapy (n=166)

	Primary 3D-CRT was either hyperfractionated with twice-daily 1.2 Gy to a total dose of 74.4 Gy (72–76.8 Gy) or accelerated with 6 sessions/week of 2 Gy to 68 to 70 Gy or 7 sessions of 1.8 Gy to 70.2 Gy. Primary IMRT was delivered with 30 x 2.2 Gy, 33 x2.11 Gy, or 35 x 2.0 Gy, 5 times/week, respectively. Simultaneous cisplatin (40 mg/m2/week) was used in most patients.
• **Intervention group (2)**	**Group 2**: Surgery followed by radiotherapy (n=133) Surgery: radical resection of the primary tumour followed by an ipsilateral or bilateral neck dissection. Radiotherapy: indications: close or positive resection margins, large primary tumours (T3/4), the involvement of 2 or more neck nodes (pN2b), involvement of a large single node (pN2a/pN3), or histologic evidence for extracapsular spread of tumour. The volume was individualized according to the areas of risk.
• **Intervention group (3)**	**Group 3:** Surgery followed by radiochemotherapy (n=26)
• **Control group (4)**	**Group 4**: Surgery alone (n=102) Surgery: radical resection of the primary tumour followed by an ipsilateral or bilateral neck dissection.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed for comparison of interest
• **(Loco)regional control**	Not assessed
• **Overall survival**	Group 3 (postoperative radiochemotherapy) vs. Group 2 (postoperative radiotherapy) *5-year overall survival* and *5-year disease-specific survival*: 45.7% vs. 38%, p=0.493
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study design leading to selection bias; no blinding. Study groups not comparable for stage of disease and intervention and comparator group were possibly not concurrent.

Is postoperative adjuvant chemoradiotherapy necessary for high-risk oropharyngeal squamous cell carcinoma?; Yokota 2014	
Methods	
• **Design**	Retrospective analysis of medical records
• **Source of funding and competing interest**	Source of funding: none reported Authors report no conflicts of interest
• **Setting**	Single center: Shizuoka Cancer Center (Shizuoka, Japan)
• **Sample size**	N=45
• **Duration**	2003-2011
• **Follow-up**	Median follow-up period in patients surviving without recurrence was 41.0 months (range, 5.6 to110.7 months).
• **Statistical analysis**	Fisher's exact test, Kaplan–Meier method for survival (compared using the log-rank test). Univariate comparison of factors that could potentially affect the survival time using the log-rank test, multivariate analysis using the Cox proportional hazards model to investigate significant prognostic factors.

Patient characteristics	
• **Eligibility criteria**	Oropharyngeal squamous cell carcinoma patients who underwent primary resection and/or neck dissection and meeting at least 1 of the following pathological features were selected: (1) microscopically involved mucosal resection margins (positive margin), (2) positive extracapsular spread of the disease (ECS), and (3) involvement of C2 regional lymph nodes.
• **Exclusion criteria**	No exclusion criteria reported
• **Patient & disease characteristics**	Group 2 (primary tumour resection and/or neck dissection and chemoradiotherapy): n= 9 vs. Group 1 (primary tumour resection and/or neck dissection and radiotherapy): n=17. - Age ≥65: 2 vs. 7; age <65: 7 vs. 10; - Sex (M/F): 8/1 vs. 12/5 - Performance status of 0 or 1: all patients; - T-stage: T1/T2: 5 vs. 11; T3/T4: 4 vs. 6; - N-stage: N1: 1 vs. 4; N2/N3: 8 vs. 13; - Level of lymph node positivity (single/multiple): 3/6 vs. 10/6 (n=1 not evaluated); - Surgical margins (negative/positive): 3/6 vs. 6/11; - Number of lymph nodes 0 or 1: 2 vs. 7; ≥2: 7 vs. 9 (not evaluated: 0 vs. 1); - Extra capsular spread (negative/positive): 1/8 vs. 7/9 (n=1 not evaluated).
Interventions	
• **Intervention group (1)**	**Group 1:** Primary tumour resection and/or neck dissection and radiotherapy The decision to choose the adjuvant therapy was made during a multidisciplinary tumour board discussion. Median dose of radiotherapy to primary site (min-max): 60 (0–70) Gy, to neck (min-max): 60 (0–60) Gy
• **Intervention group (2)**	**Group 2:** Primary tumour resection and/or neck dissection and chemoradiotherapy The decision to choose the adjuvant therapy was made during a multidisciplinary tumour board discussion. Median dose of radiotherapy to primary site (min-max): 60 (0–60) Gy, to neck (min-max): 60 (39.6–60) Gy. Chemotherapy: Cisplatin monotherapy (8 patients; 6 patients received cisplatin at 80 mg/m2/day, one patient at 100 mg/m2/day, and one patient at 20 mg/m2/day for 4 days, given every 3 weeks. 4 patients completed 3 cycles, 2 completed 2 cycles, and 2 tolerated only 1 cycle), Cisplatin + 5-fluorouracil (1 patient; intravenous cisplatin (20 mg/m2) and a continuous infusion of 5-FP (400 mg/m2/day) for 5 days, given every 4 weeks for two cycles.)
• **Control group (3)**	**Group 3:** Primary tumour resection and/or neck dissection
Results	
• **Disease-free survival**	No assessed for comparison of interest
• **Recurrence rate**	Group 2 (primary tumour resection and/or neck dissection and chemoradiotherapy) vs. Group 1 (primary tumour resection and/or neck dissection and radiotherapy) “The relative risk of recurrence for patients treated with RT alone was 0.95 compared with patients treated with CRT (p=0.971; multivariate analysis using the 26 patients who received adjuvant therapy).”
• **(Loco)regional control**	Not assessed
• **Overall survival**	No assessed for comparison of interest
• **Quality of life**	Not assessed

• **Adverse events**	Group 2 (primary tumour resection and/or neck dissection and chemoradiotherapy vs. Group 1 (primary tumour resection and/or neck dissection and radiotherapy) *≥3 hematological toxicity* Neutrophils: 1 (11%) vs. 0 Hemoglobin: 1 (11%) vs. 0 Platelets: 0 vs. 0 *≥3 non-hematological toxicity* Nausea/vomiting: 1 (11%) vs. 0 Dysphagia: 2 (22%) vs. 1 (6%) Mucositis: 4 (44%) vs. 4 (24%) Anorexia: 2 (22%) vs. 3 (18%) Dysgeusia (grade 2): 5 (56%) vs. 6 (35%) Creatinine: 0 vs. 0 Infection: 1 (11%) vs. 1 (6%)
Limitations and other comments	
• **Limitations**	High risk of selection bias due to retrospective study design. No blinding. Unclear risk of attrition and reporting bias. Incomparable study groups, although multivariate analyses were done. the small sample size may have impaired statistical significance of the results.

4.5. RQ5: Management of the neck lymph nodes

a. Neck dissection versus no neck dissection

4.5.1. Evidence tables of systematic reviews RQ5a

Goudakos 2009	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	None
• **Search date**	December 2006
• **Searched databases**	MEDLINE, EMBASE, The Cochrane Library (Issue 3, 2006) and the Cochrane Central Register of Controlled Trials (CENTRAL). Extensive hand searching of the references of all relevant studies.
• **Included study designs**	Any comparative study design.
• **Number of included studies**	N=6 (retrospective studies only)
• **Statistical analysis**	No meta-analysis was performed due to clinical heterogeneity between studies.
Patient characteristics	
• **Eligibility criteria**	Patients treated for clinically negative neck supraglottic laryngeal carcinoma (SGLC) of the squamous epithelium, without regard to size, site and histological grade of the primary carcinoma; (b) reported the management of the initial supraglottic cancer; (c) included a comparison of neck dissection with one of the other therapeutic procedures for the cN0 of SGLC (neck dissection versus neck radiotherapy; (ii) neck dissection versus neck dissection plus preoperative and/or postoperative neck radiotherapy; and (iii) neck dissection versus 'wait and see' policy (conservative approach); (d) the follow-up protocol should have included assessments of patients' clinical status, at least once a year, and for a period of 3 years; (e) the results should have been presented according to a time-to-event analysis.
• **Exclusion criteria**	Not specified.
• **Patient & disease characteristics**	A total of 792 patients were reviewed (neck dissection = 259, radiotherapy = 272, combined therapy = 142 and 'wait and see' = 119). The majority of the tumours in studies analysed were early stage (T1/T2) (75% of the total cases). Three studies provided data regarding the location of the primary carcinoma. Most frequent sites: epiglottis (67%), ventricular bands (30%), arytenoidepiglottis folds (10%) and ventricule (5%). Data concerning the grade degree was provided by two studies, in which tumours of grade 2 were the most frequent.
Interventions	
• **Intervention group**	Neck dissection
• **Control group**	Other therapeutic treatments (radiotherapy, combined therapy (dissection plus radiotherapy), 'wait and see' policy)
Results	
• **Disease-free survival**	Neck dissection versus neck radiotherapy **5-year neck disease-free survival rate (four studies: N=648)**

	"The neck disease-free survival rate did not differ significantly between patients that received neck dissection and those that had neck radiotherapy in any of the five [?] studies." Neck dissection versus 'wait and see' policy **5-year neck disease-free survival rate (three studies: N=unclear)** "The neck disease-free survival rate did not differ significantly between patients that received neck dissection and those that had a conservative approach in any of the three studies."
• **Recurrence rate**	Not addressed.
• **(Loco)regional control**	Not addressed.
• **Overall survival**	Neck dissection versus neck radiotherapy **5-year overall survival rate (one study: N=115)** 55% (95% CI 31 to 79) vs 71% (95% CI 61 to 81) (logrank = 0.4) Neck dissection versus 'wait and see' policy **5-year overall survival rate (two studies: N=95)** Study one: 64% vs 50% ($p < 0.05$) Study two: 46.4% (95% CI 29.5 to 64.2) vs 50% (95% CI 23.7 to 76.3) (RD = -3.6%, 95% CI -34.9 to +28.2)
• **Quality of life**	Not addressed.
• **Adverse events**	Not addressed.
Limitations and other comments	
• **Limitations**	Only retrospective studies with small sample sizes were identified. Quality assessment not documented for the individual studies, no search for grey literature, no publication bias assessed.

4.5.2. Evidence tables of observational studies RQ5a

Node-positive hypopharyngeal cancer treated by (chemo)radiotherapy: Impact of upfront neck dissection on outcome, toxicity, and quality of life Al-Mamgani 2013	
Methods	
Design	Retrospective analysis of institutional data
Source of funding and competing interest	Not reported
Setting	Single center: Erasmus MC–Daniel den Hoed Cancer Center, Rotterdam, The Netherlands
Sample size	N=135
Duration	Patients treated From January 1996 to November 2010 were included.
Follow-up	Median follow-up(range): 34 months (5–158) Median follow-up for quality of life analysis: 30 months
Statistical analysis	The incidences of toxicities were compared by use of logistic regression. The Mann-Whitney sign test was used for nonparametric significance tests. Univariate and multivariate analyses were performed to identify variables predicting outcome. Regression models were used to evaluate the impact of up-front neck dissection and definitive (chemo)radiation on QOL scores.
Patient characteristics	
Eligibility criteria	135 consecutive, previously untreated patients with node-positive hypopharyngeal cancer (HPC) treated with curative intent at our institution from January 1996 to November 2010.
Exclusion criteria	Not specified
Patient & disease characteristics	Group 1 (Up-front neck dissection (ND)): n=32 vs. Group 2 (No up-front ND): n=103 Median age (range): 60 (38-87) vs. 61 (43-85), p value NS M/F: 26/6 vs. 85/18, p value NS Nodal classification N1/N2+3: 6/26 vs. 26/77, p value NS Tumor classification T1-2/T3-4: 19/13 vs. 33/70, p value NS Locally advanced disease (T3 and T4): 41% vs. 68%, p=0.007 Chemoradiation: 28% vs 77%, p < .0001 Quality of life (QoL) was assessed prospectively in all patients treated from January 2006 onward (N=55, of which n=48 were included in the analysis; group 1: n=21, group 2: n=27). Median age: 60 years M/F: 38/10
Interventions	
Intervention group (1)	**Group 1:** Up-front ND (n=32) Radiotherapy was delivered to the neck according to the pathologic findings of the neck dissection. In 6 patients with N1 disease without extracapsular extension (ECE), only 46 Gy of radiotherapy was given. Patients with ECE (n = 14) received 70 Gy of radiotherapy, and in 8 of them chemotherapy was also added because they had T3, T4, or N3 disease. In all other patients, 66 Gy of radiotherapy was delivered.

Control group (2)	**Group 2:** No up-front ND (n=103) In patients treated in group 2 with definitive (chemo)radiation, a mean dose of 70 Gy was delivered to the involved neck and 46 Gy to the uninvolved neck.
Results	
Disease-free survival	Group 1 (Up-front ND) vs. Group 2 (No up-front ND) 64% vs. 45%, p=0.06
Recurrence rate	Not addressed
(Loco)regional control	Group 1 (Up-front ND) vs. Group 2 (No up-front ND) *Local control* 84% vs. 72%, p=0.15 *Regional control* 92% vs. 87%, p=0.37
Overall survival (3 year)	Group 1 (Up-front ND) vs. Group 2 (No up-front ND) 66% vs. 42%, p=0.04 Cancer-related mortality rate was significantly higher in group 2 (44% vs. 22%, p=0.03), whereas non–cancer-related mortality rates were similar in both groups (14%). On multivariate analysis high T classification was the only significant predictor for poor OS (OR 3.0, 95% CI 1.16 to 7.56, p=0.02)
Quality of life	Group 1 (Up-front ND) vs. Group 2 (No up-front ND) *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)* A high score for a functional or global QoL scale represents a relatively high/healthy level of functioning or global QoL, whereas a high score for a symptom scale indicates a higher level of symptoms or problems. *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Head and Neck 35 (EORTC QLQ-H&N35)*. A high score for a symptom scale indicates a higher level of symptoms or problems. “The patient population functioned reasonably within the tested domains at baseline but with relatively impaired scores on Global health, swallowing or dry mouth scales. QOL-scores on all scales and in both treatment groups deteriorated during treatment, reaching the worst scores around the end of treatment. The scores on all scales started to improve within 2 to 4 weeks and returned to baseline levels at 3 to 6 months after treatment. After 2-year follow-up, the scores on all scales of the EORTC QLQ-C30 and the EORTC QLQ-H&N35 had returned to or were even better than baseline levels; with the exception of EORTC QLQ-H&N35 dry mouth, dysphagia, and sticky saliva scales. The scores on these scales remained slightly worse than baseline levels. Slight differences were observed between both groups on some scales (Figure 5). However, the differences between both treatment groups were statistically not significant (p>0.05).”

Adverse events	Group 1 (Up-front ND) vs. Group 2 (No up-front ND) *Acute toxicity* *Incidence of grade ≥2 acute toxicity* 88% vs. 94%, p =0.6 Skin: 81% vs. 93%, p=0.06 Mucosal: 81% vs. 93%, p=0.06 Dysphagia: 78% vs. 90%, p=0.07 Sticky saliva: 59% vs. 62%, p=0.93 Pain: 63% vs. 71%, p=0.37 *Incidence of grade 3 acute toxicity* 50% vs. 72%, p=0.02 *Incidence of feeding tube dependency (grade 3 dysphagia)* 22% vs. 46%, p=0.02 Significantly more patients in group 2 received chemoradiotherapy (28% vs. 77%, respectively; p < 0.0001); significantly more patients in group 2 had T3 or T4 tumors (41% vs 68%, respectively; p =0.007) necessitating larger radiation fields and thus increasing the chances for development of serious acute toxicity. *Late toxicity* *3-year incidence of grade ≥2 late toxicity* 30% vs. 33%, p=0.8 Skin: 10% vs. 14%, p=0.57 Mucosal: 13% vs. 9%, p=0.09 Xerostomia: 16% vs. 20%, p=0.16 Dysphagia: 18% vs. 23%, p=0.09 Trismus: 3% vs. 6%, p=0.12 Fibrosis: 7% vs. 4%, p=0.06 Pain: 0% vs. 1%, p=0.16 *3-year incidence of grade 3 late toxicity* 12% vs. 13%, p=0.8
Limitations	The retrospective nature of the study introduces limitations, including selection bias. Groups differed significantly for T-stage and the number of patients treated with chemoradiation. As late toxicity was retrospectively scored using chart review only it is likely that some, especially mild, late toxicities were not captured.

Management of the N0 Neck in Recurrent Laryngeal Squamous Cell Carcinoma Bohannon 2010	
Methods	
• **Design**	Retrospective cohort study
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center: University of Alabama at Birmingham, Birmingham, Alabama, U.S.A
• **Sample size**	N=71
• **Duration**	Retrospective review of patients with N0 necks who underwent salvage laryngectomy between January 2001 and December 2007
• **Follow-up**	Median follow up (range) in Group 1 (neck dissection) vs. Group 2 (no neck dissection): 18.0 (1-63) vs. 10.0 (0-72) months
• **Statistical analysis**	Descriptive statistics were compared by the t test for continuous variables and the v2 test or Fisher exact test for categorical variables. Survival analysis was performed by the Kaplan-Meier method. Follow-up time was calculated from the time of salvage procedure to date of death or last follow-up date.
Patient characteristics	
• **Eligibility criteria**	Patients with N0 necks who underwent salvage laryngectomy between January 2001 and December 2007. A neck was considered clinically N0 if there was no pathologic adenopathy on physical exam or imaging studies.
• **Exclusion criteria**	Patients with laryngectomy for chronic aspiration, stricture, nonsquamous cell carcinoma, hypopharyngeal carcinoma, or primary cancer outside of the laryngeal sites were excluded. Those patients with clinical evidence of nodal disease at the time of initial presentation or recurrence were also excluded.
• **Patient & disease characteristics**	Group 1 (neck dissection): n=38 (n=71 dissections) vs. Group 2 (no neck dissection): n=33 - Median age: 62 yrs vs. 64 yrs - M/F: 35/3 vs. 28/5, p=0.33 - Site: supraglottic/glottic: 34/4 vs. 25/8, p=0.12 - T stage: T1/T2/T3/T4/unknown: 9/9/7/4/9 vs. 10/6/9/0/8 - Treatment modality: radiation / radiation+chemotherapy / radiation+surgery / radiation+chemotherapy+surgery: 22/11/5/0 vs. 19/7/6/1 "There was no significant difference in subject gender, primary site, flap procedures, age, or length of follow-up for patients with neck dissections compared to the no neck dissection group. The T stage of patients at initial presentation and at recurrence was similar in both groups."
Interventions	
• **Intervention group (1)**	**Group 1:** Neck dissection (n=38 patients, n=71 dissections) Neck dissections were performed at the time of the salvage laryngectomy based on the surgeon. Extent of the neck dissection ranged from selective (levels II–III) to radical, and was tailored to each clinical situation. Free flap reconstruction was performed as needed on a case-by-case basis.
• **Control group (2)**	**Group 2**: No neck dissection (n=33)

Results	
• **Disease-free survival**	Not addressed
• **Recurrence rate**	Group 1(neck dissection) vs. Group 2 (no neck dissection) *Local recurrence* 10.5% vs.15% *Regional recurrence* 7.9% vs. 15%, p=0.5
• **(Loco)regional control**	Not addressed
• **Overall survival**	Group 1(neck dissection) vs. Group 2 (no neck dissection) *Survival rate at 2 years* 52% vs. 48%, p=0.48 "There was no survival advantage for patients who underwent neck dissection compared to no neck dissection, p=0.48". "There were no overall differences in survival when stratified by complications (p=0.46). Cohort analysis of laryngeal subsites did not demonstrate a survival advantage with or without neck dissection (p=0.63)."
• **Quality of life**	Not addressed
• **Adverse events**	Group 1(neck dissection) vs. Group 2 (no neck dissection) *Complications* 16/38 (42.2 %) vs. 7/33 (21.3%), p=0.04 - Death: 0 (0.0%) vs.1 (6.2%) - Surgical complications: 25 (65.8%) vs. 14 (42.4%) o Salivary fistula or leak: 9 (32.0%) vs. 3 (18%) o Wound infection: 1 (3.6%) vs. 2 (12.5%) o Wound dehiscence: 0 (0.0%) vs. 1 (6.3%) o Chyle leak: 1 (3.6%) vs. 0 (0.0%) o Hematoma/bleeding: 4 (14.3%) vs. 2 (12.5%) o Flap failure: 1 (3.6%) vs. 0 (0.0%) o Revision procedure 9 (32.1%) vs. 6 (37.5%) - Medical complications 3 (7.9%) vs. 1 (3.0%) o Cardiovascular: 2 (7.1%) vs. 1 (6.2%) o DVT/PTE: 1 (3.6%) vs. 0 (0.0%)
• **Limitations**	The retrospective nature of the study introduces limitations. Although study groups seem quite comparable, there are relatively small numbers of participants in the groups.

Outcome after elective neck dissection and observation for the treatment of the clinically node-negative neck (cN0) in squamous cell carcinoma of the oropharynx Böscke 2014	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	Not reported
• **Setting**	Single center: University Medical Center Schleswig–Holstein, Germany
• **Sample size**	N=49
• **Duration**	Between 1986 and 2004
• **Follow-up**	Mean follow up for elective neck dissection group vs. observation group: 60 months vs. 65 months.
• **Statistical analysis**	The efficacy variables overall survival (OS), disease-free survival (DFS) and disease-specific survival (DSS) were calculated to compare the two neck management groups (END and OBS). Hazard ratios were calculated as primary endpoint. The Kaplan–Meier method was used to plot survival curves and calculates survival rates. Survival curves were compared by log-rank or generalized- Wilcoxon test depending on plausible proportionality of hazards. Cox proportional-hazards models were used to estimate hazard ratios. SPSS© 18.0 (IBM,Somers, USA) was used for statistical analysis.
Patient characteristics	
• **Eligibility criteria**	Patients with previously untreated histologically proven oropharyngeal squamous cell carcinoma (OPSCC) and clinically negative neck lymph node involvement (cN0), undergoing surgical treatment of the primary lesion with or without elective neck dissection (END) between 1986 and 2004. A cN0 neck was defined as a neck staged N0 by palpation, CT-scan and ultrasound.
• **Exclusion criteria**	Patients who presented with synchronous secondary lesions and patients who received post-operative radiotherapy of the untreated neck were excluded from the study.
• **Patient & disease characteristics**	Group 1: elective neck dissection (END): n=32 vs. Group 2: observation (OBS): n=17 - Mean age: 57 yrs vs. 58 yrs (range total population 42–77 years) - M/F: 23/9 vs. 15/2 - T stage T1/T2/T3/T4: 9/17/6/0 vs. 11/1/5/0 - Primary surgery: transoral laser microsurgery / conventional surgery: 24/8 vs. 15/2 - Postoperative radiotherapy (n/%): 18 (56%) vs. 0
Interventions	
• **Intervention group (1)**	**Group 1:** elective neck dissection (END, n=32)
• **Control group (2)**	**Group 2:** observation (OBS, n=17)
Results	
• **Disease-free survival**	Group 1 (END) vs. Group 2 (OBS) *3 years:* 87 % vs. 76 % *5 years:* 78 % vs. 67 % HR 1.79 (95% CI 0.57 to 5.56)
• **Recurrence rate**	Group 1 (END) vs. Group 2 (OBS)

	Patients with local and/or regional recurrence, n(%) 3/32 (10%) vs. 4/17 (24%)
• **(Loco)regional control**	Not addressed
• **Overall survival**	Group 1 (END) vs. Group 2 (OBS) *Overall survival* *3 years:* 93% vs. 82% *5 years:* 82% vs. 76% HR 1.01 (95% CI 0.44 to 2.27) *Disease-specific survival* *3 years:* 97% vs. 88% *5 years:* 97% vs. 81% HR 2.22 (95% CI 0.49 to 10)
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
• **Limitations**	The retrospective nature of the study introduces limitations. A source for potential bias is the fact that the decision-making for or against a therapeutic procedure did not follow a standardized protocol. Furthermore, the retrospective structure of the study did not allow for the incorporation of known confounders. Although study groups seem quite comparable, there are relatively small numbers of participants in the groups, which may have impaired the statistical significance of the results.

The effect of neck dissection on quality of life after chemoradiation Donatelli 2008	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	Funding: a grant made available by the U.S. National Institutes of Health through the University of Michigan's Head and Neck Cancer SPORE (P50 CA97248) Competing interest: none reported
• **Setting**	Multicenter: the University of Michigan Health System and Henry Ford Hospital (two tertiary otolaryngology clinics) and the Ann Arbor Veterans Affairs (VA) Hospital, USA
• **Sample size**	N=103
• **Duration**	From 2003 to present (*note from review team:* present was end 2007/early 2008)
• **Follow-up**	One-year follow-up

• **Statistical analysis**	Data points were recorded at baseline and one year. For continuous variables analysis was conducted on the change in score from baseline to one year. Descriptive statistics (means or frequency distributions) were computed for all variables. Bivariate analyses using *t* tests, χ2, and Fisher's exact tests compared the two treatment groups on age, gender, race, marital status, education level, comorbidities, hospital site, and specific tumor site within the oropharynx. Paired *t* tests and the sign test were used to detect changes within groups from baseline to one year. *t* tests were used to compare the change in scores for differences between treatment groups. Because this is a pilot study, no multiple test corrections were used. The data were analyzed with SAS (SAS Institute, Inc, Cary, NC).
Patient characteristics	
• **Eligibility criteria**	Patients with newly diagnosed, stage IV oropharynx cancer treated with chemoradiation.
• **Exclusion criteria**	Subjects were excluded if they did not speak English, were pregnant, were under 18, were psychologically unstable, had previous major head and neck surgery, had previous chemotherapy or radiation therapy to the head and neck (other than for lymphoma), had evidence of distant metastatic disease, did not agree to participate, or did not survive to one year. Patients who were treated with surgical resection at the primary site (11 patients), had bilateral neck dissections (two patients), or had a radical neck dissection with resection of cranial nerve (CN) XI (four patients) were also excluded.
• **Patient & disease characteristics**	Group 1 (Chemoradiation and neck dissection): n=38 vs. Group 2 (Chemoradiation): n=65 - Mean age (SD): 55.4 (8.4) yrs vs. 58.8 (9.9) yrs; - M/F: 36/2 vs. 56/9; - Race (white / non-white): 37/1 vs. 62/3; - Cancer site (base of tongue / tonsil / other): 18/18/2 vs. 29/32/4; - T and N stages: o N3: 12/38 (32%) vs. 8/65 (12%), p=0.03 o "Other T and N designations were equally represented in both groups." - Comorbidity (non-mild / moderate-severe): 29/9 vs. 46/19. "There were no statistically significant differences in the baseline characteristics of the treatment groups other than N3 status."
Interventions	
• **Intervention group (1)**	**Group 1:** Chemoradiation and neck dissection (n=38) Selective neck dissection was the procedure of choice and was extended by surgeons to modified radical neck dissection if necessary for complete resection. All selective neck dissections included at least levels II and III, but not level V. Although the surgeons who took part in the study all maintain a similar approach to neck dissection, there remains inherent heterogeneity within the surgical group. Modified radical neck dissections were performed in the standard fashion, and selective neck dissections included nodal groups described by Medina. This included Sparing CN XI only; Sparing CN XI and IJ vein; and Sparing CN XI, SCM, IJ vein.
• **Control group (2)**	**Group 2:** Chemoradiation (n=65) All patients in the study were treated with chemoradiation therapy under several protocols for cure. At the treating institutions, the indications for postchemoradiation neck dissection continue to evolve.
Results	
• **Disease-free survival**	Not addressed
• **Recurrence rate**	Not addressed
• **(Loco)regional control**	Not addressed

• **Overall survival**	Not addressed
• **Quality of life**	Group 1 (Chemoradiation and neck dissection) vs. Group 2 (Chemoradiation) *SF-36, change scores between baseline and one year* Physical functioning: –8.2 vs. –8.3, p=0.993 Role physical: –8.6 vs. –10.9, p=0.829 Body pain: –2.2 vs. 8.0, p=0.041 General health perceptions: 1.6 vs. –0.4, p=0.661 Vitality: 1.2 vs. 1.8, p=0.901 Social functioning: 8.2 vs. 2.5, p=0.338 Role emotional: 7.9 vs. 6.3, p=0.877 Mental health: 7.8 vs. 6.2, p=0.700 *Head and Neck Quality of Life Instrument (HNQoL)* Eating: –24.8 vs. –20.9, p=0.511 Communication: –6.6 vs. –5.2, p=0.834 Emotional distress: 11.1 vs. 11.0, p=0.977 Pain: 3.3 vs. 4.7, p=0.801 "Mean baseline QOL scores were very similar between the testing groups with all mean domain scores on the SF-36 and the HNQOL falling within 0.2 to 6.9 points of each other." *[RQ5b: Table 4B compares changes in QOL from baseline to one year within the neck dissection group (selective neck dissection versus modified radical neck dissection)].*
• **Adverse events**	Not addressed
• **Limitations**	The authors state: "At our treating institutions, the indications for postchemoradiation neck dissection continue to evolve. During the study period, surgeons performed post-treatment neck dissections for evidence of nodal disease on clinical examination and post-treatment computed tomography (CT), as well as for new regional disease during follow-up. In addition, during the first two years of the study, surgeons performed post-treatment neck dissection for patients with evidence of 3 cm or larger pretreatment nodes. During the last year of the study, some surgeons used PET/CT at 3 or 4 months post-treatment in the setting of "complete response" to detect residual neck disease and determine if neck dissection was indicated, whereas others continued to dissect for pretreatment nodes 3 cm or larger. Although the surgeons who took part in the study all maintain a similar approach to neck dissection, there remains inherent heterogeneity within the surgical group."

Evolution of elective neck dissection in N0 laryngeal cancer Gallo 2006	
Methods	
• **Design**	Retrospective chart review / Medical record review
• **Source of funding and competing interest**	Funding source and declaration of interest not stated
• **Setting**	Single center; Department of Oto-Neuro-Ophthalmological Sciences of the University of Florence, ENT Clinic, Florence, Italy
• **Sample size**	N=2207; N=759 elective neck dissection
• **Duration**	A retrospective review of the medical records of patients treated from January 1978 to December 2003.
• **Follow-up**	Follow-up was for a minimum of 5 years or until death in the group treated in the 80ies and the 90ies (mean 69 ± 19 months, minimum 38, maximum 110), a minimum of 3 years for the patients in the more recent group (1998-2003).
• **Statistical analysis**	A comparison was made between the radical neck dissection (RND), functional neck dissection (FND) and jugular node dissection (JND)/selective neck dissection (SND) groups, in terms of treatment failures and actuarial survival according to the Kaplan Meier method by log rank test. To test the differences in our electively dissected patients (ED population), Fisher test was used. Considering the day of the initial surgery as the starting day of the observation, the disease-free curve was calculated according to the Kaplan Meier method. Statistical analysis was performed by Stata (Stata Corporation, College Station, TX, USA) and StatXact (Cambridge, MA, USA) programmes.
Patient characteristics	
• **Eligibility criteria**	Consecutive cN0 laryngeal cancer patients who underwent surgical treatment between January 1978 and December 2003.
• **Exclusion criteria**	No patients who had previously received chemotherapy or radiotherapy for head and neck cancers were included in this study.
• **Patient & disease characteristics**	Group 1+2+3 Elective neck dissection (ED): n= 759 vs. Group 4 (wait-and-see protocol): n=1448 *[Group 1 (RND): n= 128; Group 2 (FND): n= 403; Group 3 (JND/SND)]* - Gender: 1950 males / 257 females; - Median age (range): 63 (38-82) years; - Tumor location ED: supraglottic 52%, glottic 40.3% , subglottic 7.7%; - Tumor location WAS: supraglottic 50.4%, glottic 48.4% , subglottic 1.2%
Interventions	
• **Intervention group (1)**	**Group 1:** Radical Neck Dissection The criteria for selecting N0 laryngeal cancer patients for elective neck surgery were mostly subjective; however, elective treatment was reserved for patients with: advanced lesions (T3-4), supraglottic lesions, well-lateralized lesions involving “marginal” laryngeal structures (usually at higher risk of occult node metastases), poorly differentiated lesions (G3), short fat neck with clearly difficult clinical examination.
• **Intervention group (2)**	**Group 2:** Functional Neck Dissection
• **Intervention group (3)**	**Group 3:** Selective Jugular Node Dissection Removing Levels II, III and IV.

• **Control group (4)**	**Group 4:** Wait-and-see protocol A wait-and-see policy was often adopted in patients with early stage lesions, mainly glottic, in elderly patients or when the general conditions were poor, implicating high-risk surgical procedures].
Results	
• **Disease-free survival**	Not addressed
• **Recurrence rate**	Group 1+2+3 (elective neck dissection, ED) vs. Group 4 (wait-and-see protocol) *The 5-year neck recurrence rate* 65/795 (8.5%) vs. 225/1448 15.5%)
• **Local/regional control**	Group 1+2+3 (elective neck dissection, ED) vs. Group 4 (wait-and-see protocol) Not addressed
• **Overall survival**	Group 1+2+3 (elective neck dissection, ED) vs. Group 4 (wait-and-see protocol) Not addressed
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
Limitations and other comments	
• **Limitations**	Retrospective chart review with analysis unadjusted for patient or disease characteristics, which might differ between the treatments groups.

Management of the clinically negative neck (N0) of T2N0M0 supraglottic laryngeal carcinoma: a retrospective study Jin 2012	
Methods	
• **Design**	Retrospective analysis of consecutive cases
• **Source of funding and competing interest**	Source of funding: none reported Competing interest: none declared
• **Setting**	Double center: Sun Yat-sen University Cancer Center and Zhejiang Cancer Hospital, China
• **Sample size**	N=101
• **Duration**	Between 1993 and 2009
• **Follow-up**	Median follow-up time: 62 months (range 6–176 months)
• **Statistical analysis**	Overall survival, local disease-free survival, neck disease-free survival, loco-regional control probabilities were estimated by the Kaplan–Meier method and the significance of differences was assessed by the logrank test.
Patient characteristics	
• **Eligibility criteria**	Patients with biopsy proven squamous cell carcinoma (SCC) of the supraglottic larynx, previously untreated, with a clinically negative neck; enrolment criteria: (a) each patient's complete clinical and pathological data including age, gender, blood style, stage, smoking index, alcohol consumption, histological differentiation, and treatment status; (b) patients were restaged according to the guidelines of

	the 2002 Union for International Cancer Control by the cancer staging system; (c) the primary tumours were restaged as cT2 and (d) no patient had distant metastasis at the time of initial staging.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1 (surgery): n=37 vs. Group 2 (radiotherapy): n=18 vs. Group 3 (wait and see): n=46 Patient characteristics were not specified for these three study groups. All participants - Median age ≤ 63 yrs n=55, median age >63 yrs n=46; - M/F: 95/6; - Smoking index (number of cigarettes used per day × total smoking time (years) ≤600: n=60, smoking index>600: n=41; - Alcohol consumption yes/no: 41/60; - Grade (well differentiated / moderately differentiated / poorly differentiated): 40/36/25.
Interventions	
• **Intervention group (1)**	**Group 1**: Surgery No details given.
• **Intevention group (2)**	**Group 2**: Radiotherapy No details given.
• **Control group (3)**	**Group 3**: Wait and see No details given.
Results	
• **Disease-free survival**	Group 1 (surgery) vs. Group 2 (radiotherapy) vs. Group 3 (wait and see) *5-year neck disease-free survival rate* 78.5% vs. 83.3% vs. 87.3%, $\chi 2$=1.576, p=0.455
• **Recurrence rate**	Not addressed
• **(Loco)regional control**	Group 1 (surgery) vs. Group 2 (radiotherapy) vs. Group 3 (wait and see) *5-year local-regional control rates* 74.3% vs. 65.7% vs. 74.0%, $\chi 2$=0.003, p=0.998
• **Overall survival**	Group 1 (surgery) vs. Group 2 (radiotherapy) vs. Group 3 (wait and see) *5-year overall survival rate* 65.8% vs. 83.3% vs. 72.4%, $\chi 2$=2.422, p=0.298
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
• **Limitations**	Patients included from period 1993-2009. No details presented for study groups of interest. No details given about the treatments.

Do patients with oral and oropharyngeal squamous cell carcinoma benefit from elective contralateral neck dissection? A long-term analysis Lanzer 2012	
Methods	
• **Design**	Retrospective patient cohort study
• **Source of funding and competing interest**	Source of funding: none reported Competing interest: none declared
• **Setting**	Single center: Department of Otorhinolaryngology and Head and Neck (ORL) at the Medical University Hospital, Graz, Austria
• **Sample size**	N=496
• **Duration**	Between 1 January, 1999 and 31 December, 2009
• **Follow-up**	Mean follow-up period: 58 months. Since follow-up started in 1999, some patients were followed-up for >10 years
• **Statistical analysis**	Descriptive statistics (mean, frequency and range) were computed for each study variable. Bivariate analyses (χ^2, t test) were computed to measure the association between any two variables of interest. A log-rank test as well as the Kaplan–Meier method was used for survival analysis.
Patient characteristics	
• **Eligibility criteria**	Patients with squamous cell carcinoma of the oral cavity or oropharynx with contralateral clinically negative neck, who had undergone operative resection of primary with or without adjacent adjuvant radiotherapy.
• **Exclusion criteria**	Subjects were excluded from the study in case they had squamous cell carcinoma at a location other than the oral cavity or oropharyngeal region, histological findings other than SCC, distant metastasis before ND, and patients not treated initially at the ORL at the Medical University Hospital, Graz. Patients undergoing a contralateral ND for contralateral clinically positive neck were also excluded.
• **Patient & disease characteristics**	Group 1 (elective contralateral neck dissection): n=24 vs. Group 2 (observation group): n=128 - Mean age: 60 vs. 64 yrs; - M/F: 19/5 vs. 100/28; - Localisation (oral cavity / oropharynx): 12/12 vs. 56/72; - Classification (T1/T2/T3/T4): 6/9/6/3 vs. 42/48/21/17; - Differentiation (well/moderate/poor): 1/13/10 vs. 8/46/74; - Lymph node status (N0/N1/N2/N3): 14/0/10/0 vs. 49/19/56/4. "There was no significant difference in the χ^2 test results between the two groups for all analysed variables. […] There was no statistical difference in the χ^2 test results between the two groups with regard to resection margin, adjuvant therapy or type of neck dissection."
Interventions	
• **Intervention group (1)**	**Group 1:** Elective contralateral neck dissection
• **Control group (2)**	**Group 2:** Observation group
Results	
• **Disease-free survival**	Not addressed

• **Recurrence rate**	Group 1 (elective contralateral neck dissection) vs. Group 2 (observation group) *5-year, recurrence-free survival rate* 59% vs. 66%
• **(Loco)regional control**	Group 1 (elective contralateral neck dissection) vs. Group 2 (observation group) *5-year locoregional (lymph node) recurrence-free survival rate* 90% vs. 89%, p=0.452 *Local recurrence* 5/24 (20.8%) vs. 14/128 (10.9%) *Lymph node recurrence* 1/24 (4.2%) vs. 11/128 (8.6%) “Eighty-seven of 124 (70.2%) patients in the observation group and 14 of 24 (58.3%) in the elective ND group did not experience any recurrence”
• **Overall survival**	Group 1 (elective contralateral neck dissection) vs. Group 2 (observation group) *5-year overall survival rate* 72.5% vs. 70%, p=0.971
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
• **Limitations**	Limitations were introduced by the retrospective nature of the study, including selection bias. Patients who were treated between 1999 and 2009 were included and the intervention and comparator group might be nonconcurrent. As it is not stated whether enrollment was consecutively and whether patients were left out of the analyses, risk of attrition bias is unclear.

Liu 2012 **Planned neck dissection before combined chemoradiation in organ preservation protocol for n2-n3 of supraglottic or hypopharyngeal carcinoma**	
Methods	
• **Design**	Retrospective study
• **Source of funding and competing interest**	South China State Key Laboratory for Cancer Research, Cancer Center, Sun Yat-sen University, Guangzhou, Guangdong, China, and funds from Scientific and Technique Program of Guangdong Province.
• **Setting**	Single center: Sun Yat-Sen University Cancer Center
• **Sample size**	N=85
• **Duration**	January 1, 1999 to December 31, 2005
• **Follow-up**	Median follow-up 4.1 years (range 1.2 to 10)
• **Statistical analysis**	Kaplan-Meier
Patient characteristics	
• **Eligibility criteria**	Previously untreated patients with N2/3 nodal diseases from SCC of the supraglottis or hypopharynx.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=46 vs. Group 2: n=39 - Mean age (range): 56 (39 to 76) vs. 54 (36 to 70) - Sex (M/F): 44/2 vs. 38/1 - Primary site : supraglottic larynx 28 vs. 26 ; hypopharynx 18 vs. 13 - Clinical T stage: T1 : 5 vs. 2 ;T2: 11 vs. 7; T3: 18 vs. 20 ;T4: 12 vs. 10 - N stage: N2a: 12 vs. 10; N2b: 17 vs. 1; N2c: 5 vs. 5; N3: 12 vs. 8 - M classification: M0: 46 vs. 39; M1: 0 vs. 0
Interventions	
• **Intervention group (1)**	**Group1:** Pretreatment neck dissection (following organ preservation chemoradiation) “Neck dissections were performed according to the N status: modified radical neck dissection (MRND) was performed in N2 patients without invasion of nonlymphatic structures. Radical neck dissection (RND) was performed in N2 patients with invasion of nonlymphatic structures and in N3 patients. Bilateral neck dissection (BND) was performed in 5 patients for bilateral neck disease.”
• **Control group (2)**	**Group 2:** No pretreatment neck dissection (in a chemoradiation protocol) “Salvage surgeries were used for local or cervical node residual tumor or recurrence after chemoradiotherapy.”
Results	
• **Disease-free survival**	Not addressed
• **Recurrence**	Group 1 vs. Group 2 16/46 (34.8%) vs. 15/39 (38.5%)
• **(Loco)regional control**	Group 1 vs. Group 2 *5-year control rate of neck nodes* 86.3% vs. 65.9%, p=0.02

• **Overall survival**	Group 1 vs. Group 2 *5-year overall survival rate* 46.4% vs. 35.1%
• **Quality of life**	Not addressed
• **Adverse events**	Group 1 vs. Group 2 Major postoperative local / wound complications: 0 vs. 7/15 (46.7%) Surgery related mortalities: 0 vs. n/a Suture line dehiscence secondary to underlying seroma: 2 (4.3%) vs. n/a Woundhealing problem: 0 vs. 1 (3%) Light chylous fistula 1 (2.2%) vs. n/a Pharyngocutaneous fistulas: 0 vs. 2 (5%)
• **Limitations**	Lack of blinding; unclear risk of attrition bias and selective reporting; high risk for nonconcurrency, unclear risk of baseline comparability.

Pantel 2011 **Diversity of treatment of T2N0 glottic cancer of the larynx: lessons to learn from epidemiological cancer registry data**	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	None declared
• **Setting**	Multicenter: Data from the five Thuringian cancer databases in the Thuringian towns (Nordhausen, Gera, Suhl, Jena, and Erfurt), Germany.
• **Sample size**	N=73
• **Duration**	From 1996 to 2005
• **Follow-up**	Median follow up: 38.1 months (range 0.2 to 114)
• **Statistical analysis**	Kaplan–Meier; univariate (log-rank test) and multivariate analysis (Cox proportional hazard model).
Patient characteristics	
• **Eligibility criteria**	All patients identified as having newly diagnosed glottic squamous cell carcinomas with TNM stage pT2cN0M0, (AJCC Cancer Staging Classification) who were primarily treated by surgical means.
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=35 vs. Group 2: n=38, patient characteristics not specified per treatment group - Median age (range): 62.1 years - Sex (M/F): 69/4 - Side, left/right/both sides/unknown: 26/26/11/10 - Type of surgery, endoscopic laser/open: 63/10

Interventions	
• **Intervention group (1)**	**Group 1:** Elective neck dissection "Ipsilateral elective selective neck dissection in at least level IIa and III and partly of level IV was performed in 35 (47.9%) patients as part of the therapy of the primary tumor [……..] Adjuvant radiotherapy was performed in 35 (47.9%) cases."
• **Control group (2)**	**Group 2:** No neck dissection "[……] Also, 38 (52.1%) patients did not receive neck dissection as part of the treatment of the primary and underwent routine follow-up visits within the respective center. Adjuvant radiotherapy was performed in 35 (47.9%) cases."
Results	
• **Disease-free survival**	Not addressed
• **Recurrence rate**	Not addressed Group 1 vs. Group 2 *Recurrence-free survival rates at 5 years* 42.6% vs 76.9%, p=0.072
• **(Loco)regional control**	Not addressed
• **Overall survival**	Group 1 vs. Group 2 *5-year overall survival* 48.0% vs 64.5%
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
Limitations and other comments	
• **Limitations**	Lack of blinding; low risk of attrition bias, unclear risk of selective reporting and concurrency, low risk of baseline comparability.

Psychogios 2013 **Elective neck dissection vs. observation in transorally treated early head and neck carcinomas with cN0 neck**	
Methods	
• **Design**	Retrospective study
• **Source of funding and competing interest**	None declared
• **Setting**	Academic tertiary care center
• **Sample size**	N=224 patients
• **Duration**	1980-2010
• **Follow-up**	Mean follow up (range): 61.8 months (3 to 216)
• **Statistical analysis**	Kaplan–Meier and log-rank test.

Patient characteristics	
• **Eligibility criteria**	Previously untreated head and neck squamous cell carcinoma (HNSCC) with definitive surgical treatment as a monotherapy between 1980 and 2010. "Selected patients all had preoperative cN0 cervical status and had undergone a primary transoral removal of the primary tumor with or without elective ND as part of the primary surgical treatment. Those finally selected were all patients who proved to have a pT1-2- primary tumor. Because patients with early glottis carcinomas never received an elective ND in cases with cN0 status, the finally included patients had pT1-2 carcinoma of the oral, oropharyngeal, hypopharyngeal or supraglottic region."
• **Exclusion criteria**	"Patients previously treated for head and neck carcinomas or with histology other than squamous cell carcinoma (SCC) were excluded from the study. Also excluded were patients who received adjuvant radiotherapy or chemoradiation after the surgical treatment."
• **Patient & disease characteristics**	Group 1 (Elective neck dissection): n=101 ; Group 2 (Observation): n=123 - Mean age, years (range): 59.1 (37 to 85) - Sex (M/F): 177/47 - N stage, pN0/PN1/pN2b/pN2c: 91/3/5/2 - T stage, pT1/pT2: 146/78 - Surgical technique, TLM/Electrocautery: 94/130
Interventions	
• **Intervention group**	Elective neck dissection
• **Control group**	Observation
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Group 1 (elective neck dissection) vs. Group 2 (observation) *5-year regional control*: 96.0% vs 90.3% (p=0.07)
• **Overall survival**	Group 1 (elective neck dissection) vs. Group 2 (observation) *5-year overall survival*: 72.4% vs. 67.4% (p=0.197) Cases with pN0 classification had a better overall survival (74.6% vs 46.9%, p= 0.07)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias and selective reporting; high risk for concurrency, unclear risk of baseline comparability.

Sakashita 2014 The role of initial neck dissection for patients with node-positive oropharyngeal squamous cell carcinomas	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	None declared
• **Setting**	Multi center: 12 institutions belonging to the Head and Neck Cancer Study Group in the Japan Clinical Oncology Group (JCOG).
• **Sample size**	N= 202
• **Duration**	Patient enrollment between April 2005 and March 2007
• **Follow-up**	Median follow-up of survivors, years (range): 4.5 (2.3–5.7) vs. 4.6 (0.9–5.7)
• **Statistical analysis**	Chi-square test for associations, Kaplan–Meier method for survival and control rates.
Patient characteristics	
• **Eligibility criteria**	Patients with previously untreated node-positive oropharyngeal squamous cell carcinomas between April 2005 and March 2007
• **Exclusion criteria**	Patients with N0, patients treated with induction chemotherapy and patients not treated with curative intent. Patients who were observed for less than 24 months without regional recurrence were also excluded.
• **Patient & disease characteristics**	Group 1 (Initial neck dissection): n=93; Group 2 (Wait-and-see): n=109 - Age (range): <62 yrs: 49 vs. 54; >63: 44 vs. 55 ; - Sex (M/F): 77/16 vs. 93/16 ; - Clinical T stage: T1-2: 54 vs. 71; T3-4: 39 vs. 38 ; - N stage: 1: 17 vs. 16; 2a: 13 vs. 16 ; 2b: 38 vs. 43; 2c: 19 vs. 25; 3: 6 vs 9. - Smoking behaviour (present/absent) : 69/24 vs. 84/25 ‘’There were no significant differences in any factor between the wait-and-see group and the initial ND group.’’
Interventions	
• **Intervention group**	Initial neck dissection (ND)
• **Control group**	“Wait-and-see” policy (CRT or RT, if residual neck disease was observed after initial therapy, salvage ND was indicated)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (ND) vs. Group 2 (Wait-and-see) 17/93 (18.3%) vs. 40/109 (36.7%)
• **(Loco)regional control**	Group 1 (ND) vs. Group 2 (Wait-and-see) *4-year regional control rate* 84.9% vs. 77.6% (p=0.2382) *4-year regional control rates according to N classification* N1: 94.1% vs 93.8% (p=0.95)

	N2a: 100% vs 62.5% (p=0.02) N2b: 86.6% vs 86.1% (p=0.87) N2c: 76% vs 68.4% (p=0.68) N3: 66.7% vs 37.0% (p=0.32)
• **Overall survival**	Group 1 (ND) vs. Group 2 (Wait-and-see) *4-year overall survival rate* 78.7% vs. 74.0% (p=0.34) *4-year overall survival rates according to N classification* N1: 82.4% vs 68.2% (p=0.22) N2a: 100% vs 74.6% (p=0.06) N2b: 76.8% vs 82.8% (p=0.53) N3: 100% vs 50.8% (p=0.05)
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias and selective reporting; unclear risk of baseline comparability.

Suzuki 2013 **The contribution of neck dissection for residual neck disease after chemoradiotherapy in advanced oropharyngeal and hypopharyngeal squamous cell carcinoma patients**	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	Ministry of Health, Labor and Welfare of Japan
• **Setting**	Single center: Aichi Cancer Center Hospital, Japan
• **Sample size**	N=84
• **Duration**	Patient enrollment between 1995 and 2006
• **Follow-up**	Median follow-up time (range): 5.8 years (0.6 to 16.7)
• **Statistical analysis**	Kaplan–Meier; uni- and multivariate Cox proportional hazard models; chi-squared test or Fisher's exact test.
Patient characteristics	
• **Eligibility criteria**	Oro- and hypopharyngeal squamous cell carcinoma patients with N2–3 disease treated with chemoradiotherapy
• **Exclusion criteria**	Not specified

• **Patient & disease characteristics**	Group 1 (Neck dissection): n=36 ; Group 2 (Observation): n=48 - Median age, years (range): 59 (36 to 80) - Sex (M/F): 75/9 - Primary site (oropharynx / hypopharynx): 59/25 o Oropharynx (neck dissection / observation) : 27/32 o Hypopharynx (neck dissection / observation) : 9/16 - Clinical T stage, (T1/T2/T3/T4): 10/39/22/13 - N stage, (N2a/N2b/N2c/N3): 15/35/22/12 - UICC stage, (4a/4b): 72/12
Interventions	
• **Intervention group**	Neck dissection (ND)
• **Control group**	No neck dissection (OBS)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group1 (ND) vs. Group 2 (OBS) *Relapse* 14/36 (38.9%) vs. 20/48 (41.7%) - Local recurrence 7 vs. 6 - Regional metastases 1 vs. 6
• **(Loco)regional control**	Group1 (ND) vs. Group 2 (OBS) *5-year regional control* 91.6% (95% CI 76.1 to 97.2) vs 81.1% (95% CI 65.4 to 90.2) (p=0.252) HR 0.48 (95% CI 0.11 to 2.15), p=0.335 (adjusted by age and sex) *5-year regional control stratified by primary tumor site* Oropharynx: 96.3% (95% CI 76.5 to 99.5) vs 78.6% (95% CI 58.0 to 89.9) (p=0.072), HR 0.17 (95% CI 0.02 to1.86), p=0.146, p for heterogeneity=0.094 (adjusted by age, sex, tumor and nodal classification) Hypopharynx: 77.8% (95S% CI 36.5 to 93.9) vs 85.9% (95% CI 54.0 to 96.3) (p=0.541) HR 0.32 (95% CI 0.02 to 5.93), p=0.445 (adjusted by age, sex, tumor and nodal classification)
• **Overall survival (5 year)**	Group1 (ND) vs. Group 2 (OBS) 76.7% (95% CI 58.8 to 87.6) vs 73.9% (95% CI 58.6 to 84.3) (p=0.883) HR 1.55 (95% CI 0.63 to 3.82), p=0.345 (adjusted by age and sex) Oropharynx: HR 0.73 (95% CI 0.23 to 2.31), p=0.587, p for heterogeneity=0.005 (adjusted by age, sex, tumor and nodal classification) Hypopharynx: HR 7.76 (95% CI 0.58 to 103.83), p=0.121 (adjusted by age, sex, tumor and nodal classification)
• **Quality of life**	Not assessed

• **Adverse events**	Complications "Nine patients (25.0%) experienced postoperative complications from ND; 3 for laryngeal edema, 3 for lymph fluid leaks, 2 for dysphagia, and 1 for lingual nerve paralysis. Two patients with laryngeal edema underwent tracheostomy. No patients died as a result of ND."
Limitations and other comments	
• **Limitations**	Lack of blinding; unclear risk of attrition bias, selective reporting, concurrency and risk of baseline comparability.

b. Neck dissection type X versus neck dissection type Y

4.5.3. Evidence tables of systematic reviews RQ5b

Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment; Bessell 2011	
Methods	
• **Design**	Systematic review
• **Source of funding and competing interest**	None known
• **Search date**	February 2011
• **Searched databases**	The Cochrane Oral Health Group Trials Register, CENTRAL, MEDLINE and EMBASE
• **Included study designs**	Randomised controlled trials
• **Number of included studies**	N=7, of which one applied to oropharyngeal cancer patients (amongst others) (N=1, yet this RCT only included two participants with 'Tonsil/lateral pharyngeal wall'
• **Statistical analysis**	N/A (only one included study)
Patient characteristics	
• **Eligibility criteria**	Randomised controlled trials where more than 50% of participants had primary tumours of the oral cavity or oropharynx, and which compared two or more surgical treatment modalities or surgery versus other treatment modalities. Patients with oral cancer as defined by the International Classification of Diseases for Oncology (ICD-O) codes as C01-C02, C03, C04, C05-C06 (oral cavity) and cancer of the oropharynx (ICDO:C09, C10) were included.
• **Exclusion criteria**	Patients with cancer of the hypopharynx (ICD-O: C13), nasopharynx (ICD-O: C11), larynx (ICD-O: C32) or lip (ICD-O: C00) were excluded.
• **Patient & disease characteristics**	A total of 669 patients were randomly allocated; 570 were included in the analyses. Of those, only 2 patients had oropharyngeal tumours; all other patients suffered from oral cavity cancer.
Interventions	
• **Intervention group**	Surgical treatment modalities: traditional 'scalpel based' surgery, laser cutting or ablation, or harmonic scalpel.
• **Control group**	Other surgical interventions, or different treatment modalities such as radiotherapy, chemotherapy, immunotherapy/biotherapy with or without surgery; any combinations were considered providing they were compared to surgery in at least one arm of the study.

Results	
• **Disease-free survival**	No results regarding our target population.
• **Recurrence rate**	No results regarding our target population.
• **(Loco)regional control**	No results regarding our target population.
• **Overall survival**	No results regarding our target population.
• **Quality of life**	No results regarding our target population.
• **Adverse events**	No results regarding our target population.
• **Limitations**	N/A

4.5.4. Evidence tables of RCTs RQ5b

End results of a prospective trial on elective lateral neck dissection vs type III modified radical neck dissection in the management of supraglottic and transglottic carcinomas. **Brazilian Head and Neck Cancer Study Group 1999**	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	Ludwig Institute for Cancer Research, Sao Paulo branch
• **Setting**	Multicenter, 7 Head and Neck Surgery Departments in São Paulo, Brazil
• **Sample size**	N=132
• **Duration**	Patient enrolment: March 1990 to December 1993
• **Follow-up**	Mean follow-up: 42.9 months
• **Statistical analysis**	Distribution of clinical and pathologic characteristics and certain treatment variables and complications in the two groups studied were compared by means of the chi-square or Fisher's test. The differences between the mean values of the period of hospitalization were compared by t test. Product-limit estimates of the survivorship function were used for the computation of the cumulative survival rates. The log-rank test was used to assess the significance of differences among actuarial survival curves.
Patient characteristics	
• **Eligibility criteria**	Resectable supraglottic or transglottic T2–T4 tumors, clinically negative neck (N0) findings, no prior treatment, histologic diagnosis of squamous cell carcinoma, and a Karnofski's score of 60 or greater. Each case was staged according to the 1987 UICC classification.
• **Exclusion criteria**	Patients with significant cardiac or pulmonary diseases, distant metastases, or multiple primary cancers.

• **Patient & disease characteristics**	Group 1 (type III modified radical neck dissection, MRND): n=71 (13 bilateral) vs. Group 2 (lateral neck dissection, LND): n=61 (18 bilateral) - Age group: <40 yrs: 1 vs. 3, 41-65 yrs: 47 vs. 45, >65 yrs: 23 vs. 13 - Sex (M/F): 63/8 vs. 54/7 - Clinical T stage: T2: 12 vs. 12, T3: 47 vs. 42, T4: 12 vs. 7 - Site of primary tumour: supraglottic: 12 vs. 9, transglottic: 59 vs. 52 'No significant differences were present in pretreatment variables for patients allocated in each trial group.'
Interventions	
• **Intervention group (1)**	**Group 1**: Type III modified radical neck dissection (with preservation of the internal jugular vein, accessory nerve, and sternomastoid muscle) Postoperative irradiation was indicated in cases with positive margins or positive lymph nodes in the specimen.
• **Control group (2)**	**Group 2**: Lateral neck dissection (levels II, III, and IV) Whenever a positive node was confirmed during the procedure, the operation was converted to a MRND with accessory nerve preservation. The indications and technique of postoperative irradiation were similar to the MRND group.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Group 1 (MRND) vs. Group 2 (LND) *Number of patients with recurrence* 15/71 vs. 15/61 (RR 0.86, 95% CI 0.46 to 1.61) - Local: 4 vs. 5 - Ipsilateral neck: 1 vs. 2 - Contralateral neck (undissected): 0 vs. 2 - Contralateral neck (dissected): 0 vs. 1 - Stomal: 2 vs. 1 - Distant metastasis: 5 vs. 3 - Local + ipsilateral neck: 1 vs. 0 - Local + distant: 0 vs. 1 - Ipsilateral and contralateral neck (undissected): 1 vs. 0 - Local + ipsilateral and contralateral neck (dissected) + stomal: 1 vs. 0
• **(loco)regional control**	Not assessed
• **Overall survival**	Group 1 (MRND) vs. Group 2 (LND) *Five-year actuarial overall survival rates* 72.3% vs. 62.4%, p=0.312

	"The 5-year OS differences were not significant in unilateral (72.3 % vs. 59.9%, p=0.190) and bilateral dissections (72.7% vs. 68.7%, p=0.715). The 5-year overall survival analysis made on the basis of the 34 patients with metastasis diagnosed from the pathologic examination of the specimen showed no significant differences (74.7% vs. 62.7%, p=0.596))." *5-year cancer-specific survival rates* 81.3% vs.81.0%, p=0.778 "Twelve cancer-related deaths occurred in the MRND group (17%) and 9 in the LND group (15%) (p 4 .737). Fifteen patients (11.4%) died of causes unrelated to cancer."
• **Quality of life**	Not assessed
• **Adverse events**	Group 1 (MRND) vs. Group 2 (LND) "Significant complications": 35/71 vs. 28/61 (RR 1.07, 95% CI 0.75 to 1.54) - Flap necrosis: 10 vs. 4, p=0.161 - Wound infection: 18 vs. 10, p=0.209 - Fistula: 18 vs. 14, p=0.748 - Hematoma/seroma: 3 vs. 4, p=0.703 - Chyle fistula: 4 vs. 4, p=0.999 - Postoperative death: 3 vs. 1, p=0.387
Limitations and other comments	
• **Limitations**	No details provided about method of randomization and blinding, leading to unclear risk of selection bias and detection bias for subjective outcomes. Unclear risk of reporting bias, as no study protocol was available. High risk of performance bias due to the fact that blinding of the interventions was probably impossible.

4.5.5. Evidence tables of observational studies RQ5b

Management of the N0 neck in moderately advanced squamous carcinoma of the larynx Dias 2009	
Methods	
• **Design**	Retrospective chart review / Medical record review
• **Source of funding and competing interest**	Competing interests: None. Sponsorships: None.
• **Setting**	Single center; Department of Head and Neck Surgery, Brazilian National Cancer Institute.
• **Sample size**	n=327 patients (n=654 heminecks (HNs))
• **Duration**	A retrospective review of the clinical charts from January 1981 to August 2000

• **Follow-up**	The median follow-up interval was 45 months (range 24-187 months).
• **Statistical analysis**	Overall survival was calculated according to the Kaplan-Meier method. Univariate analysis of the impact of the factors on regional recurrence (RR) was performed with the log-rank test. Each side of the neck was analyzed separately.
Patient characteristics	
• **Eligibility criteria**	Patients with moderately advanced/advanced (T3-4 N0) squamous cell carcinoma (SCC) of the larynx, who underwent primary surgical treatment at the Brazilian National Cancer Institute.
• **Exclusion criteria**	Not reported.
• **Patient & disease characteristics**	Group 1 + 2: n=603 (unit=dissection); Group 3: n= 51 (unit =dissection). - Gender: Male (88.4%); - Mean age (range): 57 years (37 to 77); - Tumor type: 183 (56%) transglottic tumors, 74 (22.6%) supraglottic tumors and 70 (21.4%) glottic tumors; - Type of surgery: 221 (67.6%) total laryngectomy, 57 (17.4%) supracricoid laryngectomy with cricohyoidoepiglottopexy, and 49 (15%) Pearson's "near-total" laryngectomy The characteristics were not presented separately for the 3 study groups.
Interventions	
• **Intervention group (1)**	**Group 1**: Selective neck dissection (SND) SND consisted of removal of LN levels II to IV.
• **Intervention group (2)**	**Group 2**: Selective neck dissection (SND) + adjuvant radiotherapy (RT) SND consisted of removal of LN levels II to IV. Adjuvant radiotherapy (RT) was indicated in cases of extracapsular extension (ECE), multiple pathological nodes (>1), microvascular or perineural invasion, and T4 tumors. External beam radiotherapy was delivered in a dose ranging from 45 to 70 Gy.
• **Control group (3)**	**Group 3:** Modified radical neck dissection (MRND) + adjuvant radiotherapy (RT) MRND type III consisted of removal of LN levels I to V, sparing the sternocleidomastoid muscle, the internal jugular vein, and the spinal accessory nerve. Adjuvant radiotherapy (RT) was indicated in cases of extracapsular extension (ECE), multiple pathological nodes (>1), microvascular or perineural invasion, and T4 tumors. External beam radiotherapy was delivered in a dose ranging from 45 to 70 Gy.
Results	
• **Disease-free survival**	Not addressed
• **Recurrence rate**	*Regional recurrence (RR)* Group 1 + 2 (SND): 3% vs. Group 3 (MRND): 11.7%, p=0.005 for pN0 patients: Group 1 + 2: 3.2% vs. Group 3: 17.2%, p=0.0003 for pN+ patients: Group 1 + 2: 2.6% vs. Group 3: 4.7%, p=0.50
• **Local/regional control**	*5-year regional control* for pN0 patients: Group 1 + 2 (SND): 96.8% vs. Group 3 (MRND): 82.2%, p=0.0003 for pN+ patients: Group 1 + 2 (SND): 97.4% vs. Group 3 (MRND): 95.3%, p=0.50
• **Overall survival**	Not reported

	5-year disease-specific survival (DSS) Group 1: 81% vs. Group 2: 77% vs. Group 3: 56.5% *10-year disease-specific survival (DSS)* Group 1: 29% vs. Group 2: 74% vs. Group 3: 0%, p=0.04, unadjusted
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
Limitations and other comments	
• **Limitations**	The retrospective nature of the study introduces limitations, including selection bias. It's not clear whether the primary analyses were performed on patient level or dissection level. Overall survival is not reported. Analyses were unadjusted for patient or disease characteristics, which might differ between the 3 treatments groups.

The effect of neck dissection on quality of life after chemoradiation Donatelli-Lassig 2008	
Methods	
• **Design**	Prospective cohort study
• **Source of funding and competing interest**	Funding: a grant made available by the U.S. National Institutes of Health through the University of Michigan's Head and Neck Cancer SPORE (P50 CA97248) Competing interest: none reported
• **Setting**	Multicenter: the University of Michigan Health System and Henry Ford Hospital (two tertiary otolaryngology clinics) and the Ann Arbor Veterans Affairs (VA) Hospital, USA
• **Sample size**	N=103, of whom 38 undergoing neck dissection
• **Duration**	From 2003 to present (*note from review team:* present was end 2007/early 2008)
• **Follow-up**	One-year follow-up
• **Statistical analysis**	Data points were recorded at baseline and one year. For continuous variables analysis was conducted on the change in score from baseline to one year. Descriptive statistics (means or frequency distributions) were computed for all variables. Bivariate analyses using *t* tests, $\chi 2$, and Fisher's exact tests compared the two treatment groups on age, gender, race, marital status, education level, comorbidities, hospital site, and specific tumor site within the oropharynx. Paired *t* tests and the sign test were used to detect changes within groups from baseline to one year. *t* tests were used to compare the change in scores for differences between treatment groups. Because this is a pilot study, no multiple test corrections were used. The data were analyzed with SAS (SAS Institute, Inc, Cary, NC).
Patient characteristics	
• **Eligibility criteria**	Patients with newly diagnosed, stage IV oropharynx cancer treated with chemoradiation.
• **Exclusion criteria**	Subjects were excluded if they did not speak English, were pregnant, were under 18, were psychologically unstable, had previous major head and neck surgery, had previous chemotherapy or radiation therapy to the head and neck (other than for lymphoma), had evidence of distant metastatic disease, did not agree to participate, or did not survive to one year.

	Patients who were treated with surgical resection at the primary site (11 patients), had bilateral neck dissections (two patients), or had a radical neck dissection with resection of cranial nerve (CN) XI (four patients) were also excluded.
• **Patient & disease characteristics**	Group 1 (Selective neck dissection): n=22 and Group 2 (Modified radical neck dissection): n=16 - Mean age (SD): 55.4 (8.4) yrs; - M/F: 36/2; - Race (white / non-white): 37/1; - Cancer site (base of tongue / tonsil / other): 18/18/2; - T and N stages: o N3: 12/38 (32%) - Comorbidity (non-mild / moderate-severe): 29/9.
Interventions	
• **Intervention group (1)**	**Group 1:** Selective neck dissection At the treating institutions, the indications for postchemoradiation neck dissection continue to evolve. Selective neck dissection was the procedure of choice and was extended by surgeons to modified radical neck dissection if necessary for complete resection. All selective neck dissections included at least levels II and III, but not level V. Although the surgeons who took part in the study all maintain a similar approach to neck dissection, there remains inherent heterogeneity within the surgical group.
• **Control group (2)**	**Group 2:** Modified radical neck dissection At the treating institutions, the indications for postchemoradiation neck dissection continue to evolve. Modified radical neck dissections were performed in the standard fashion, and selective neck dissections included nodal groups described by Medina. This included Sparing CN XI only; Sparing CN XI and IJ vein; and Sparing CN XI, SCM, IJ vein. Modified radical neck dissections were performed in the standard fashion, and selective neck dissections included nodal groups described by Medina. This included Sparing CN XI only; Sparing CN XI and IJ vein; and Sparing CN XI, SCM, IJ vein. Although the surgeons who took part in the study all maintain a similar approach to neck dissection, there remains inherent heterogeneity within the surgical group.
Results	
• **Disease-free survival**	Not addressed
• **Recurrence rate**	Not addressed
• **(Loco)regional control**	Not addressed
• **Overall survival**	Not addressed
• **Quality of life**	Group 1 (Selective neck dissection) vs. Group 2 (Modified radical neck dissection) *SF-36, change scores between baseline and one year* Physical functioning: -5.5 vs. -12.0, p=0.440 Role physical: -12.5 vs. -3.1, p=0.620 Body pain: -2.4 vs. -1.9, p=0.955 General health perceptions: 4.0 vs. -1.8, p=0.461 Vitality: 1.4 vs. 0.9, p=0.952

	Social functioning: 6.3 vs. 10.9, p=0.632 Role emotional: 15.1 vs. -2.1, p=0.322 Mental health: 13.6 vs. -0.3, p=0.029 *Head and Neck Quality of Life Instrument (HNQoL)* Eating: -24.6 vs. -25.0, p=0.967 Communication: -5.1 vs. -8.6, p=0.778 Emotional distress: 12.7 vs. 8.9, p=0.575 Pain: 2.8 vs. 3.9, p=0.903
• **Adverse events**	Not addressed
• **Limitations**	The authors state: "At our treating institutions, the indications for postchemoradiation neck dissection continue to evolve. During the study period, surgeons performed post-treatment neck dissections for evidence of nodal disease on clinical examination and post-treatment computed tomography (CT), as well as for new regional disease during follow-up. In addition, during the first two years of the study, surgeons performed post-treatment neck dissection for patients with evidence of 3 cm or larger pretreatment nodes. During the last year of the study, some surgeons used PET/CT at 3 or 4 months post-treatment in the setting of "complete response" to detect residual neck disease and determine if neck dissection was indicated, whereas others continued to dissect for pretreatment nodes 3 cm or larger. Although the surgeons who took part in the study all maintain a similar approach to neck dissection, there remains inherent heterogeneity within the surgical group."

Evolution of elective neck dissection in N0 laryngeal cancer Gallo 2006	
Methods	
• **Design**	Retrospective chart review / Medical record review
• **Source of funding and competing interest**	Funding source and declaration of interest not stated
• **Setting**	Single center; Department of Oto-Neuro-Ophthalmological Sciences of the University of Florence, ENT Clinic, Florence, Italy
• **Sample size**	N=2207; N=759 elective neck dissection
• **Duration**	A retrospective review of the medical records of patients treated from January 1978 to December 2003.
• **Follow-up**	Follow-up was for a minimum of 5 years or until death in the group treated in the 80ies and the 90ies (mean 69 ± 19 months, minimum 38, maximum 110), a minimum of 3 years for the patients in the more recent group (1998-2003).
• **Statistical analysis**	A comparison was made between the radical neck dissection (RND), functional neck dissection (FND) and jugular node dissection (JND)/selective neck dissection (SND) groups, in terms of treatment failures and actuarial survival according to the Kaplan Meier method by log rank test. To test the differences in our electively dissected patients (ED population), Fisher test was used. Considering the day of the initial surgery as the starting day of the observation, the disease-free curve was calculated according to the Kaplan Meier method.

	Statistical analysis was performed by Stata (Stata Corporation, College Station, TX, USA) and StatXact (Cambridge, MA, USA) programmes.
Patient characteristics	
• **Eligibility criteria**	Consecutive cN0 laryngeal cancer patients who underwent surgical treatment between January 1978 and December 2003.
• **Exclusion criteria**	No patients who had previously received chemotherapy or radiotherapy for head and neck cancers were included in this study.
• **Patient & disease characteristics**	Group 1 (RND): n= 128; Group 2 (FND): n= 403; Group 3 (JND/SND): n=228 *[Group 1+2+3 Elective neck dissection (ED): n= 759 vs. Group 4 (wait-and-see protocol): n=1448; comparison RQ5a]* - Gender: 1950 males / 257 females; - Median age (range): 63 (38-82) years; - Tumor location ED: supraglottic 52%, glottic 40.3% , subglottic 7.7%; - *[Tumor location WAS: supraglottic 50.4%, glottic 48.4% , subglottic 1.2%; RQ5a]*
Interventions	
• **Intervention group (1)**	**Group 1:** Radical Neck Dissection The criteria for selecting N0 laryngeal cancer patients for elective neck surgery were mostly subjective; however, elective treatment was reserved for patients with: advanced lesions (T3-4), supraglottic lesions, well-lateralized lesions involving “marginal” laryngeal structures (usually at higher risk of occult node metastases), poorly differentiated lesions (G3), short fat neck with clearly difficult clinical examination.
• **Intervention group (2)**	**Group 2:** Functional Neck Dissection
• **Intervention group (3)**	**Group 3:** Selective Jugular Node Dissection Removing Levels II, III and IV.
• ***[Control group (4)***	**Group 4:** *Wait-and-see protocol → RQ 5a* *A wait-and-see policy was often adopted in patients with early stage lesions, mainly glottic, in elderly patients or when the general conditions were poor, implicating high-risk surgical procedures].*
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	*The 5-year neck recurrence rate* No significant difference in the rate of 5-year neck recurrence was detected between RND, FND and JND groups, p=0.178 During follow-up, overall 65 neck recurrences were documented in the ED group (8.5%) (ranging from 6 to 21 months). A higher risk of neck failure was documented in the JND group when compared with those who received a more extended lymph-adenectomy, although the differences were not statistically significant, p=0.233 *[RQ5a: In the wait-and-see group (Group 4), 225 cN0 laryngeal cancer patients experienced neck relapse in the undissected neck(s) (15.5%), while 84.5% of the remainder were disease-free in the neck].*

	For all ED patients: 7.7% (estimated by the Kaplan Meier method).
• **Local/regional control**	JND (Group 3), compared to more extensive neck dissections (Group 1+2), did not show statistically significant differences in terms of neck control (p=0.233), in terms of impact on survival, p=0.122 *Total N0+ recurrences: No. (%)* Group 1 (RND): 2/128 (1.5) vs. Group 2 (FND): 4/403 (1.7) vs. Group 3 (JND): 4/228 (0.9), p=0.434 *Total N0- recurrences: No. (%)* Group 1 (RND): 7/128 (5.4) vs. Group 2 (FND): 21/403 (5.2) vs. Group 3 (JND): 27/228 (11.8), p = 0.178 *Occult lymph node metastases* Group 1 (RND): 22.6% vs. Group 2 (FND): 19.4% vs. Group 3 (JND/SND): 18.4%
• **Overall survival**	In the survival curves, no differences, in terms of actuarial survival by Kaplan Meier analysis, were observed, as far as concerns type of elective neck dissection performed, p = 0.222
• **Quality of life**	Not addressed
• **Adverse events**	Not addressed
Limitations and other comments	
• **Limitations**	Retrospective chart review with analysis unadjusted for patient or disease characteristics, which might differ between the 3 treatments groups.

Selective versus comprehensive neck dissection after chemoradiation for advanced oropharyngeal squamous cell carcinoma Hillel 2009	
Methods	
• **Design**	Case series with Retrospective chart review / Medical record review
• **Source of funding and competing interest**	Competing interests: Eva S. Zinreich, IZI Corporation, part owner. Sponsorships: None.
• **Setting**	Single center (community teaching hospital); Greater Baltimore Medical Center (GBMC), USA
• **Sample size**	N=76 standard CRT, and N=41 patients with neck dissection (n=48 with unit neck dissections)
• **Duration**	Between 2001 and 2007
• **Follow-up**	The mean clinical follow-up was 39.4 months with a range of 6 to 83 months. Follow-up time began at the completion of planned neck dissection(s) for each patient.
• **Statistical analysis**	Patient survival rates and disease-free survival rates were estimated by the Kaplan-Meier method and compared between groups by means of a log-rank test. Univariate regression analysis was performed for tobacco exposure, alcohol use, complications, and positive pathological status. P values were determined with Fisher exact tests with less than 0.05 considered significant. All analyses were performed with MedCalc 3000 (Foundation Internet Services, LLC, Pittsburgh, PA).

Patient characteristics	
• **Eligibility criteria**	Medical records of patients treated with planned post–primary chemoradiation treatment (CRT) for histologically confirmed locoregionally advanced oropharyngeal squamous cell carcinoma (OPSCC) at Greater Baltimore Medical Center (GBMC) between 2001 and 2007 were reviewed.
• **Exclusion criteria**	Evidence of positive pathology at the primary site following CRT was a criterion for exclusion from this study because resection of the primary tumor and neck would be necessary.
• **Patient & disease characteristics**	Group 1 (comprehensive): n=23 ; Group 2 (selective): n= 25 (unit is dissections; N=41 patients) - Median age (range): 56.6 vs. 57.0 yrs (total 56.7 (42-77 years)); - Gender (M/F): 86%/14% vs. 77%/23% (total 83%/17%); - Neck stage (residual disease): N2a 4 (0) vs. 5 (1); N2b 8 (3) vs. 9 (1); N2c 6 (1) vs. 3 (3) ; N3 4 (2) vs. 5 (1) The characteristics were well balanced between the 2 groups. All had stage IVa disease.
Interventions	
• **Intervention group (1)**	**Group 1**: Comprehensive neck dissection Including levels I through V.
• **Control group (2)**	**Group 2**: Selective neck dissection Defined as anything less than levels I through V.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **Local/regional control**	*The three-year regional disease control rate* Group 2: 100% vs. Group 1: 94% Overall there was no association between type of neck dissection performed and regional failure.
• **Overall survival**	*Three-year overall survival* Group 2 + CRT: 95% vs. Group 1 +CRT 89% There was no significant difference in the overall survival between the CND and SND groups. *Three-year disease-specific survival* Group 2: 72% vs. Group 1: 81% There was no significant difference in the disease-specific survival between the CND and SND groups.
• **Quality of life**	Not addressed
• **Adverse events**	Group 2 8% (n=2) vs. Group 1 26% (n=6) - CND: Shoulder weakness greater than six months (n=4); chyle leaks (n=2); - SND Shoulder weakness greater than six months In total eight postoperative complications among the 48 heminecks. No cases of postoperative hematoma or wound breakdown. There was no significant difference between postoperative complications and type of neck dissection (p=0.15).

	Although complication rates were not significantly different between Group 1 and 2, the trend in this study indicates that SND results in less morbidity.
Limitations and other comments	
• **Limitations**	The retrospective nature of this study introduces some limitations. Although survival and regional recurrence rates are similar between the two cohorts in this study, there may be an initial selection bias in patients receiving CND. Although patients with multilevel regional disease were more often treated with CND, overall the patients in the two groups had comparable regional disease burden in this study. Another limitation of this study is the small number of patients in both the SND and CND groups, which results in an inability to perform multivariate analysis. Therefore these data should be interpreted with some caution.

Efficacy of routine bilateral neck dissection in the management of the N0 neck in T1-T2 unilateral supraglottic cancer Rodrigo 2006	
Methods	
• **Design**	Retrospective chart review / Medical record review
• **Source of funding and competing interest**	Source of funding and declaration of interest not stated
• **Setting**	Single center; Servicio de Otorrinolaringologia, Hospital Universitario Central de Asturias, Oviedo, Spain
• **Sample size**	N=108
• **Duration**	Between January 1975 and December 1998
• **Follow-up**	Patients were observed for at least 60 months. Mean length of follow-up (months): Total population 51 vs. Ipsilateral functional neck dissection (IFND) 54 vs. (Bilateral functional neck dissections) BFND 48
• **Statistical analysis**	Statistical analysis was performed using chisquare, with Yates' correction where appropriate, and the Fisher exact test. Means were compared using the t test. Survival curves were calculated using the Kaplan–Meier product limit estimate. Deaths from causes other than the index tumor or its metastases were not considered treatment failures, and these patients were censored in all analysis involving the length of survival. Differences between survival times were analyzed by the logrank method.
Patient characteristics	
• **Eligibility criteria**	Primary previously untreated squamous cell carcinoma of the supraglottic larynx, pathologic T classification T1 or T2, lateral localization of the tumor, surgery on the primary tumor and the neck in the same session, clear surgical margins, and no administration of postoperative radiotherapy (which excluded all the patients with pathologic N2 status)
• **Exclusion criteria**	Clinically positive necks. "Out of 192 patients with clinically early-stage (T1 – T2 N0) supraglottic carcinoma, 62 (32%) of these patients were demonstrated to have nodal metastases. We did not include patients with clinically positive necks to avoid confounding factors, because these patients received therapeutic instead of elective neck dissections, which included radical neck dissections, and most of these patients also received bilateral neck dissections because of the high risk of bilateral metastasis."
• **Patient & disease characteristics**	Group 1 (IFND): n=48 vs. Group 2 (BFND): n= 60 - Median age (range): 56 years (45–70) vs. 59 years (42–74), p=0.04

	- Gender: only men; 100% vs. 100% - pT classification: o T1/T2: 19/29 vs. 15/45, p=0.14 - pN classification: total (%): o N0: 42 (87) vs. 50 (83) o N1: 6 (13) vs. 10 (17), p=0.59 - Tobacco consumption: total (%) o None 1 (2) vs. 1 (2), p=0.89 o Mild 3 (6) vs. 5 (8) o Moderate 20 (42) vs. 28 (47) o Severe 24 (50) vs. 26 (43) - Alcohol consumption: total (%) o None 5 (10) vs. 10 (17), p=0.45 o Mild 5 (10) vs. 5 (8) o Moderate 20 (42) vs. 30 (50) o Severe 18 (38) vs. 15 (25) Patient and disease characteristics were balanced, except for age, between the 2 groups.
Interventions	
• **Intervention group (1)**	**Group 1:** Ipsilateral functional neck dissection (IFND) Treated before 1992; Functional neck dissections included levels II–V; None of the patients received a radical neck dissection; None of these patients received adjuvant radiotherapy.
• **Control group (2)**	**Group 2:** Bilateral functional neck dissections (BFND) Treated from 1992 to 1998; Functional neck dissections included levels II–V; None of the patients received a radical neck dissection; None of these patients received adjuvant radiotherapy.
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Recurrent disease developed in 21 (20%) patients. Five patients (5%) had local recurrence and 16 patients (15%) had cervical recurrence Group 1 (IFND) vs. Group 2 (BFND) *Regional recurrence* 17% (8/48) vs. 13% (8/60) (p =0.78)
• **Local/regional control**	5/21 local recurrences; 16/21 neck recurrences; specified by T classification and not by treatment.
• **Overall survival**	Group 1 (IFND) vs. Group 2 (BFND) *The 5-year disease-specific survival*

	81% vs. 73% p=0.51 The 5-year disease-specific survival according to the Kaplan–Meier method for all 108 patients was 77%.
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
• **Limitations**	The retrospective nature of the study introduces limitations, including selection bias. Although study groups seem quite comparable, except for age, there are relatively small numbers of events (recurrences) in the groups.

4.6. RQ6: Salvage treatment versus no/other treatment

4.6.1. Evidence tables of systematic reviews RQ6

No systematic reviews were identified

4.6.2. Evidence tables of RCTs RQ6

No RCTs were identified

4.6.3. Evidence tables of observational studies RQ6

Salvage surgery for recurrent oropharyngeal cancer after chemoradiotherapy; Kano 2013	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	None declared
• **Setting**	Multicenter; 12 institutions belonging to the Head and Neck Cancer Study Group in Japan Clinical Oncology Group (JCOG).
• **Sample size**	N=523 of which n=35 relevant for this RQ (failure cases of oropharyngeal cancer undergoing initial chemoradiotherapy)
• **Duration**	Patient enrolment between April 2005 to March 2007
• **Follow-up**	Median follow-up period was 4.4 years (range 0.3 to 5.9 years)
• **Statistical analysis**	Unpaired Student's t test or chi-square test for associations between patient characteristics; Kaplan–Meier and log-rank test for overall survival.
Patient characteristics	
• **Eligibility criteria**	Failure cases of oropharyngeal cancer undergoing initial chemoradiotherapy.
• **Exclusion criteria**	Patients who received palliative therapy were excluded
• **Patient & disease characteristics**	Group 1: n=11; Group 2: n=24

	- Median age, years (range): 54 (42–75) vs 64.5 (46–78) - Sex (M/F): 11/0 vs 20/4 - T classification 1/2-3/4: 6/5 vs 5/19 - N classification 0/1-3: 6/5 vs 6/18 - Stage I/II-III/IV: 3/8 vs 2/22 - Disease status, recurrent/residual: 8/3 vs 14/10 - Regional recurrence, no/yes: 10/1 vs 11/13 - Distant metastasis, no/yes: 11/0 vs 18/6
Interventions	
• **Intervention group (1)**	**Group 1:** Salvage surgery (open surgery, requiring microvascular free flap reconstruction or transoral surgery)
• **Control group (2)**	**Group 2:** Nonsurgical treatment (including reirradiation, chemotherapy and best supportive care)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	*3-year OS:* 61.8% vs 24.4% *5-year OS:* 49.1% vs 16.3% "The overall survival rate for patients treated with salvage surgery was significantly higher than that for patients treated without salvage surgery (p=0.04)."
• **Quality of life**	Not assessed
• **Adverse events**	*Swallowing function and larynx preservation in patients with local recurrence or residual disease after salvage surgery (n=11) (preoperative vs postoperative):* Oral feeding: preoperative 9/11; postoperative 6/11 Oral and tube feeding: preoperative 2/11; postoperative 3/11 Tube feeding: preoperative 0/11; postoperative 2/11 Larynx preservation: postoperative 8/11
Limitations and other comments	
• **Limitations**	Retrospective study. Unclear risk of attrition bias as it involves a retrospective chart review of subgroup of patients. Comparability of the intervention and comparator group was low due to significant differences between groups in patient age and the presence of a simultaneous regional recurrence. Patients who had more aggressive initial disease and developed distant metastasis tended to belong to the nonsurgical treatment group, however, the difference was not significant.

Factors predictive of successful outcome following salvage treatment of isolated neck recurrences; Lim 2010	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	Inha University research grant
• **Setting**	Tertiary clinic, single center (Yonsei Head and Neck Cancer Clinic, Seoul, Korea)
• **Sample size**	N=924 patients included of which N=236 patients with recurrence after primary curative surgery. N=61 relevant for this review question (patients with isolated neck recurrence receiving salvage treatment or supportive care)
• **Duration**	Patient enrolment between 1991 and 2006
• **Follow-up**	Median follow up: 10 months (range 1 to 144 months)
• **Statistical analysis**	Kaplan-Meier, log-rank test, Cox proportional hazard model
Patient characteristics	
• **Eligibility criteria**	Patients who underwent primary curative surgery with or without adjuvant radiotherapy for SCC of the oral cavity, oropharynx, larynx, and hypopharynx
• **Exclusion criteria**	Not specified
• **Patient & disease characteristics**	Group 1: n=49; Group 2: n=12 - Median age (range): 57 years (28 to 74 years) - Sex (M/F), total group: 52/9 - N stage (pathologic), N-/N+: 23/38
Interventions	
• **Intervention group (1)**	**Group 1:** Salvage treatment (n=35 surgical salvage; n=14 nonsurgical salvage)
• **Control group (2)**	**Group 2:** Supportive care (n=12)
Results	
• **Disease-free survival**	Not assessed
• **Recurrence rate**	Not assessed
• **(Loco)regional control**	Not assessed
• **Overall survival**	*3-year OS* Surgical salvage: 36% Nonsurgical salvage: 12% Supportive care: 0%
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed

Limitations and other comments	
• **Limitations**	Retrospective study. Unclear risk of attrition bias as it involves a retrospective chart review of subgroup of patients. Patients who were treated between 1991 and 2006 were included and the intervention and comparator group might be nonconcurrent. A high risk was scored for comparability of the intervention and comparator group as indications for treatment are different and patient characteristics were not reported per treatment group.

Salvage of recurrent hypopharyngeal carcinoma after primary curative treatment; Yasumatsu 2013	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	None declared; the authors report no conflicts of interest
• **Setting**	Kyushu University Hospital, Japan
• **Sample size**	N=49
• **Duration**	Patient enrolment between January 2002 and December 2010
• **Follow-up**	Mean follow-up period: 19 months (range 2 to 61 months)
• **Statistical analysis**	Not reported; the authors apparently applied Kaplan-Meier analysis
Patient characteristics	
• **Eligibility criteria**	Japanese patients with recurrent hypopharyngeal squamous cell carcinoma, who underwent an initial curative treatment between 2002 and 2010 at the Department of Otolaryngology in Kyushu University Hospital,
• **Exclusion criteria**	Not reported
• **Patient & disease characteristics**	Group 1: n=23; Group 2: n=26 Patient characteristics for whole group: - Median age: 65.0 years - Sex (M/F): 46/3 - Site of recurrent tumour, local/locoregional/regional/distant: 13 (27%)/4 (8%)/6 (12%)/26 (53%) - N1/N2/N3: 12 (32%)/24 (63%)/2 (5%) - Stage of recurrent tumour, stage I - II/stage III - IV: 7 (14%)/42 (86%)
Interventions	
• **Intervention group (1)**	**Group 1:** Salvage surgery followed by chemotherapy and/ or radiotherapy
• **Control group (2)**	**Group 2:** Chemotherapy and/or radiotherapy
Results	
• **Disease-free survival (at 4 yrs)**	Not assessed
• **Recurrence rate**	Not assessed

• **(Loco)regional control**	Not assessed
• **Overall survival (at 4 yrs)**	*Cure rate* 18/23 (78%) vs 0/26 (0%) *1-year tumour-free actuarial survival rate* Salvage surgery followed by chemotherapy and/or radiotherapy: 96% *3-year tumour-free actuarial survival rate* Salvage surgery followed by chemotherapy and/or radiotherapy: 79% "There was no 3-year survivor among the patients who received only chemotherapy and/or radiotherapy." "The mean survival of patients without surgical salvage was 9 months (range 1 to 33 months)." *Salvage survival time* "Patients who underwent salvage surgery followed by chemotherapy and/ or radiotherapy had significantly improved salvage time compared with patients who received chemotherapy and/or radiotherapy for their recurrence ($p < 0.05$). On the other hand, salvage time was not significantly influenced by the initial stage of the primary tumours. However, the early stage of the recurrent tumours trended towards a significantly long salvage time."
• **Quality of life**	Not assessed
• **Adverse events**	Not assessed
Limitations and other comments	
• **Limitations**	Retrospective study. Unclear risk of attrition bias as it involves a retrospective chart review of subgroup of patients. Patients who were treated between 2002 and 2010 were included and the intervention and comparator group might be nonconcurrent. A high risk was scored for comparability of the intervention and comparator group as indications for treatment are different and patient characteristics were not reported per treatment group.

The Role of Salvage Surgery in Patients With Recurrent Squamous Cell Carcinoma of the Oropharynx; Zafereo 2009	
Methods	
• **Design**	Retrospective chart review
• **Source of funding and competing interest**	None declared
• **Setting**	Single center (The University of Texas M. D. Anderson Cancer Center)
• **Sample size**	N=168
• **Duration**	Patient enrolment between 1998 and 2005
• **Follow-up**	Median follow-up after a diagnosis of recurrent or residual SCCOP: 9.8 months (range 0.5 to 87.7 months)

• **Statistical analysis**	Pearson chi-square test, Fisher's exact test, t test / Wilcoxon rank sum test, Kaplan-Meier and log-rank for survival
Patient characteristics	
• **Eligibility criteria**	Patients with locally recurrent or residual squamous cell carcinoma of the oropharynx who completed definitive therapy for primary SCCOP
• **Exclusion criteria**	Patients with distant metastases or regional recurrence only
• **Patient & disease characteristics**	Group 1: n=41 ; Group 2: n=127 - Mean age, years: 57.4 vs 59.3 - Sex (M/F): 33/8 vs 100/27 - Tumour classification: T1 or T2/T3 or T4: 19/22 vs 21/106 - Neck disease, no/yes: 31/10 vs 81/46 - Overall disease stage, I or II/III or IV: 15/26 vs 12/115 - Disease status, residual/recurrent: 14/27 vs 66/61
Interventions	
• **Intervention group (1)**	**Group 1:** Salvage surgery (segmental mandibulectomy in 18 patients and total laryngectomy in 7 patients)
• **Control group (2)**	**Group 2:** Nonsurgical treatment (nonsurgical treatment or supportive care) (n=18 reirradiation or brachytherapy; n=70 palliative chemotherapy; n=39 supportive care)
Results	
• **Disease-free survival**	*3-year DFS* Salvage surgery: 26% *5-year DFS* Salvage surgery: 22%
• **Recurrence rate**	*Second recurrence after salvage surgery* 26/39 (66.7%; n=2 recurrence data not available) "Local failure was most common, occurring in 20 patients, followed by regional failure in 10 patients, and distant failure in 8 patients. T1 or T2 initial tumour classification, use of chemotherapy during initial treatment, absence of a disease-free interval, recurrent neck disease, and positive surgical margins were associated significantly with higher second recurrence rates." "Patients with recurrent neck disease (p=.01) and positive surgical margins (p=.04) had higher rates of recurrence after salvage surgery."
• **(Loco)regional control**	Not assessed
• **Overall survival**	*3-year OS*

	Salvage surgery: 48.7% (NB: in the text 42% is mentioned) Reirradiation: 31.6% Palliative chemotherapy: 3.7% Supportive care: 5.1% *5-year OS* Salvage surgery: 28% Reirradiation: 32% Palliative chemotherapy: 0% Supportive care: 0% *P-values*: • Salvage surgery versus reirradiation: p=0.59 • Salvage surgery versus palliative chemotherapy or supportive care: p<0.001 • Reirradiation versus palliative chemotherapy or supportive care: p<0.001 • Palliative chemotherapy versus supportive care: p=0.10 "For patients who underwent salvage surgery, older age (p=.03), the absence of a disease-free interval (p<.01), and advanced recurrent tumour stage (p=.07) were associated with lower overall survival." "Stratifying the salvage surgery group and the nonsurgical groups (excluding the patients who received supportive care) according to disease-free interval revealed that patients who underwent salvage surgery had a significantly higher 3-year overall survival rate (56%) than patients who underwent salvage surgery for residual disease (18%; p< .01 for the difference between curves)." "Stratifying the salvage surgery group and the nonsurgical groups (excluding the patients who received supportive care) according to recurrent tumour classification revealed that salvage surgery patients who had recurrent T1 or T2 tumours had a higher 3-year overall survival rate (63%) than salvage surgery patients who had recurrent T3 or T4 tumours (25%), although this difference was not significant (p=.28 for the difference between curves)." "Among patients who had both a disease-free interval and a recurrent T1 or T2 tumour, the 3-year overall survival rates for patients who underwent salvage surgery and patients who received nonsurgical treatment (excluding patients who received supportive care) were 74% and 11%, respectively (p=.02 for the difference between curves)."
• **Quality of life**	*Quality of life variables for patients treated with salvage surgery* Nutrition • Nonoral: 13/41 • Partial oral: 13/41

	• Liquid only: 2/41 • Soft/regular: 13/41 Speech production • Oral speech: 32/41 • TEP (tracheoesophageal puncture): 2/41 • Electrolarynx: 4/41 • Writing: 3/41 Speech intelligibility • <50%: 7/41 • 50%-80%: 5/41 • >80%: 29/41 Decannulation • Yes: 26/41 • No: 4/41
• **Adverse events**	*Postoperative complications*: 19 patients • surgical wound infection: 7 • fistula: 6 • donor site complications: 5 • pneumonia: 4 There were no perioperative deaths
Limitations and other comments	
• **Limitations**	Retrospective study. High risk of attrition bias as n=31 patients who received nonsurgical treatment or supportive care were lost to follow up and excluded from the study. Patients who were treated between 1998 and 2005 were included and the intervention and comparator group might be nonconcurrent. The comparability of the intervention and comparator group was low due to significant differences between groups on comorbidity (diabetes), tumour classification, treatment (surgery to primary site and chemotherapy), disease status (residual/recurrent) and overall disease stage.

4.7. RQ7: Altered fractionation radiotherapy versus standard radiotherapy

4.7.1. Evidence tables of systematic reviews RQ7

Baujat 2010	
Methods	
• **Design**	SR + MA
• **Source of funding and competing interest**	No conflicts of interest Sources of funding: • Institut Gustave-Roussy, France • Association pour la Recherche sur le Cancer n°5137, France • Programme Hospitalier de Recherche Clinique n°IDF98083, France • Ligue Nationale Contre le Cancer, France • Sanofi Aventis unrestricted grant, France • US National Cancer Institute 2U10CA11488-36, USA
• **Search date**	Aug 2010
• **Searched databases**	The Cochrane Ear, Nose and Throat Disorders Group Trials Register; CENTRAL; PubMed; EMBASE; CINAHL; LILACS; KoreaMed; IndMed; PakMediNet; CAB Abstracts; Web of Science; BIOSIS Previews; CNKI; ISRCTN; ClinicalTrials.gov; ICTRP and Google Reference lists Conference abstracts (Cochrane Ear, Nose and Throat Disorders Group Trials Register and the websites for ASCO, ESMO, ASTRO, ECCO, ESTRO and PDQ)
• **Included study designs**	RCTs
• **Number of included studies**	N=15: BCCA 9113 1997; CAIR 2000; CHART 1997; DAHANCA 2003; EORTC 22791 1992; EORTC 22851 1997; GORTEC 9402 2006; KBN PO 79 2002; Oro 9301 2003; PMHToronto 2007; RIO1991; RTOG7913 1987; RTOG 9003HF 2000; RTOG9003B 2000; RTOG9003S 2000; TROG 9101 2001; Vienna 2000
• **Statistical analysis**	Individual hazard ratios (HR) and overall HR based on log-rank observed minus expected numbers of deaths (O-E) and their variances
Patient characteristics	
• **Eligibility criteria**	Previously untreated patients (those who had not received prior radiotherapy or prior chemotherapy), with non-metastatic head and neck squamous cell carcinomas of the oral cavity, oropharynx, hypopharynx or larynx
• **Exclusion criteria**	Trials including mainly or exclusively nasopharyngeal carcinomas
Interventions	
• **Intervention group**	Accelerated or hyperfractionated radiotherapy
• **Control group**	Conventional radiotherapy
Results	
• **See updated meta-analyses**	

Limitations and other comments	
• **Comments**	• High-quality Cochrane review • Unclear if duplicate selection and data extraction • No assessment of publication bias

Glenny 2010	
Methods	
• **Design**	SR + MA
• **Source of funding and competing interest**	No conflicts of interest Sources of funding: • School of Dentistry, The University of Manchester, UK • Cochrane Oral Health Group, UK • The University of Dundee, UK • The University of Glasgow, UK • Manchester Academic Health Sciences Centre (MAHSC) and NIHR Manchester Biomedical Research Centre, UK • National Institute of Health, National Institute of Dental & Craniofacial Research, USA • Central Manchester & Manchester Children's University Hospitals NHS Trust, UK
• **Search date**	Jul 2010
• **Searched databases**	Cochrane Oral Health Group's Trials Register; CENTRAL; MEDLINE via OVID; EMBASE via OVID; Current Controlled Trials Reference lists
• **Included study designs**	RCTs
• **Number of included studies**	N=16 on right comparison; Fu 2000; Horiot 1992; Pinto 1991; Bourhis 2006; Dobrowsky 2000; Marcial 1987; Poulsen 2001; Bartelink 2002; Horiot 1997; Olmi 2003; Skladowski 2006; Weissberg 1983; Ang 2001; Ghoshal 2008; Sanguineti 2005; Marcial 1993
• **Statistical analysis**	Risk ratios were combined for dichotomous data, and hazard ratios for survival data, using a fixed-effect model, unless there were more than four trials to be combined, when a random-effects model was used. Hazard ratio data were entered into the meta-analysis using the inverse variance method
Patient characteristics	
• **Eligibility criteria**	Patients with oral cancer as defined by the International Classification of Diseases for Oncology (ICD-O) codes as C01-C02, C03, C04, C05-C06 (oral cavity) and cancer of the oropharynx (ICDO: C09, C10) Studies of head and neck cancer with cases of oral cancer as long as at least 50% of participants who have oral cavity or oropharyngeal cancer are included, or data for these cancers alone are available separately
Interventions	
• **Intervention group**	Accelerated or hyperfractionated radiotherapy
• **Control group**	Conventional radiotherapy

Results	
• **See updated meta-analyses**	
Limitations and other comments	
• **Comments**	• High-quality Cochrane review • No assessment of publication bias

4.7.2. Evidence tables of RCTs RQ7

Moon 2014 (KROG-0201)	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	• Supported by NCC Grant No. 1310070 from National Cancer Center • No competing interests
• **Setting**	Multicentre trial (N=13), Korea
• **Sample size**	N=156
• **Duration and follow-up**	• Recruitment period: Nov 2002 – Oct 2010 • Median follow-up: 67 months
• **Statistical analysis**	• Survival curves were generated using the Kaplan–Meier method • Log-rank test was used to compare Kaplan–Meier events on univariate analysis • For multivariate analysis, the Cox proportional hazards model was used. It was assumed that the observed differences were statistically significant if the p value was <0.05
Patient characteristics	
• **Eligibility criteria**	• Histologically confirmed glottic squamous cell carcinoma, 18 years of age or older, Karnofsky Performance Score of 60 or higher, 1997 American Joint Committee on Cancer stage I or II (T1–2N0M0), no prior RT or chemotherapy for laryngeal cancer, and no history of malignancies for 5 years except basal cell or squamous cell carcinoma of the skin
• **Patient & disease characteristics**	

	Conventional	Accelerated	p
Age <65y	51%	45%	0.41
Male	96%	97%	0.74
T1a	59%	61%	0.85
T1b	32%	27%	
T2a	8%	9%	
T2b	1%	3%	

Interventions	
• **Intervention group**	Accelerated radiotherapy (N=74): 63-67.5 Gy, daily fractions of 2.25 Gy

• **Control group**	Conventional radiotherapy (N=82): 66-70 Gy, daily fractions of 2 Gy
Results	
• **Local progression-free survival**	• 5y: 88.5% vs. 77.8%; HR 1.55, p=0.213
• **Overall survival**	• 5y: 86.6% vs. 82.5%, p=0.359
• **Acute toxicity**	• No severe complication of RTOG/EORTC grade 3 or higher • No significant difference in the incidence of acute toxicities for skin, mucous membrane, or larynx
• **Late toxicity**	• No severe complication of RTOG/EORTC grade 3 or higher • No significant difference in the incidence of late toxicities for skin, mucous membrane, or larynx
Limitations and other comments	
• **Limitations**	• Early closure because of poor accrual • Unclear allocation concealment • Unclear blinding

Overgaard 2010 (IAEA-ACC)	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	• Supported by the International Atomic Energy Agency, Coordinated Research Project (IAEA-CRP E.3.30.18), the Danish Cancer Society, the Danish Strategic Research Council, and the Lundbeck Centre for Interventional Research in Radiation Oncology (CIRRO) • No competing interests
• **Setting**	Multicentre trial (N=9), international
• **Sample size**	N=908 (8 not eligible)
• **Duration and follow-up**	• Recruitment period: Jan 1999 – Mar 2004 • Median follow-up: 99 months
• **Statistical analysis**	• Actuarial values of the endpoints were assessed by the Kaplan-Meier product-limit method • The Mantel-Cox test was used for comparison, and a test for trend with equal weighing was done when more than two groups were compared
Patient characteristics	
• **Eligibility criteria**	• Stage 1–4 invasive squamous-cell carcinoma of the larynx, pharynx, and oral cavity (except nasopharynx and stage 1 glottic carcinoma), and no evidence of distant metastases; age over 18 years, performance status of 0–2 • Candidates for primary curative radiotherapy alone (without previous or planned surgical excision of the primary tumour or lymph nodes)
• **Patient & disease characteristics**	

	Conventional	Accelerated	p
Age >65y	23%	19%	NS

	Male	82%	78%	NS
	T1-2	43%	42%	NS
	N+	42%	44%	NS
Interventions				
• **Intervention group**	Accelerated radiotherapy (N=452): 66-70 Gy, 6 daily fractions of 2 Gy per week			
• **Control group**	Conventional radiotherapy (N=448): 66-70 Gy, 5 daily fractions of 2 Gy per week			
Results				
• **Locoregional control**	• 5y: 42% vs. 30%; HR 0.63, 95%CI 0.49-0.83, p=0.004 • Not significant for oral cavity (HR 0.89) and stage 4 (HR 0.78)			
• **Disease-free survival**	• 5y: 50% vs. 40%; HR 0.70, 95%CI 0.54-0.91, p=0.03			
• **Overall survival**	• 5y: 35% vs. 28%; HR 0.78, 95%CI 0.59-1.03, p=0.07			
• **Acute toxicity**	• Severe skin reaction: 20% vs. 11%, HR 1.91 (1.31-2.79) • Confluent mucositis: 10% vs. 5%, HR 2.15 (1.27-3.35) • Tube feeding: 52% vs. 45%, HR 1.34 (1.03-1.75)			
• **Late toxicity**	• Moderate fibrosis: 35% vs. 29%, HR 1.31 (0.96-1.79) • Severe fibrosis: 1% vs. 2%, HR 0.58 (0.17-1.99) • Moderate-severe laryngeal oedema: 15% vs. 17%, HR 0.84 (0.56-1.25) • Moderate-severe xerostomia: 44% vs. 48%, HR 0.94 (0.71-1.26)			
Limitations and other comments				
• **Limitations**	• Randomization was done by a fax to the IAEA-ACC data centre, where the eligibility criteria were checked and patients allocated to treatment • Open label • Stratification according to tumour site (larynx, pharynx or oral cavity), tumour classification (T1–2 vs. T3–4), histopathological differentiation (poor, moderate or well, unknown), and institution • Early closure due to slow intake and lack of funding			

<table>
<tr><th colspan="2">Zackrisson 2011 (ARTSCAN)</th></tr>
<tr><td colspan="2">Methods</td></tr>
<tr><td>• Design</td><td>RCT</td></tr>
<tr><td>• Source of funding and competing interest</td><td>• Swedish Cancer Society, Laryngfonden (Sweden), Lions Cancer Research Foundation at Umeå University, the Cancer Research Foundation of Northern Sweden
• Conflicts of interest not reported</td></tr>
<tr><td>• Setting</td><td>Multicentre trial (N=12), Sweden</td></tr>
<tr><td>• Sample size</td><td>N=750 (17 not eligible)</td></tr>
<tr><td>• Duration and follow-up</td><td>• Recruitment period: Nov 1998 – Jun 2006
• Median follow-up: 5.1 years</td></tr>
<tr><td>• Statistical analysis</td><td>• Statistical inference on the duration of locoregional control and survival was performed by the log rank test
• Prognostic factors and the association with loco-regional control and survival were assessed by comparing the Kaplan–Meier estimators at two years follow-up
• Hazard ratios and their confidence intervals at two years were calculated with the Cox proportional hazard model</td></tr>
<tr><td colspan="2">Patient characteristics</td></tr>
<tr><td>• Eligibility criteria</td><td>• Patients over the age of 18 years with a histologically proven, previously untreated, squamous cell carcinoma of all grades and stages in the oral cavity, oropharynx, hypopharynx or larynx (except T1–2, N0 glottic carcinoma) without distant metastases</td></tr>
<tr><td>• Patient & disease characteristics</td><td>
<table>
<tr><th></th><th>Conventional</th><th>Accelerated</th><th>p</th></tr>
<tr><td>Age >65y</td><td>37%</td><td>34%</td><td>0.56</td></tr>
<tr><td>Male</td><td>75%</td><td>74%</td><td>0.69</td></tr>
<tr><td>T1-2</td><td>47%</td><td>50%</td><td>0.39</td></tr>
<tr><td>N0</td><td>39%</td><td>39%</td><td>0.90</td></tr>
</table>
</td></tr>
<tr><td colspan="2">Interventions</td></tr>
<tr><td>• Intervention group</td><td>Accelerated radiotherapy (N=366): 68 Gy, 23 daily fractions of 2 Gy, 4.5-5 weeks, concomitant boost of 20 daily fractions of 1.1 Gy</td></tr>
<tr><td>• Control group</td><td>Conventional radiotherapy (N=367): 68 Gy, daily fractions of 2 Gy, 7 weeks</td></tr>
<tr><td colspan="2">Results</td></tr>
<tr><td>• Local recurrence rate</td><td>• 2y: 61.7% vs. 57.8%, p=0.27</td></tr>
<tr><td>• Overall survival</td><td>• 2y: 67.5% vs. 67.3%, p=0.93</td></tr>
<tr><td>• Acute toxicity</td><td>• Acute normal tissue reactions were significantly stronger during and after AF compared to CF</td></tr>
<tr><td>• Late toxicity</td><td>• No significant differences
• No cases of severe fibrosis or severe skin reactions</td></tr>
<tr><td>• Quality of life</td><td>• Global health status was assessed by QoL questionnaires and was rated significantly lower ($p < 0.05$) three months after radiotherapy for AF patients</td></tr>
</table>

	• This difference was no longer detectable six months or later after treatment
Limitations and other comments	
• **Limitations**	• Central randomization • Unclear randomization method • Unclear blinding

Miszczyk L 2014	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	• Maria Sklodowska-Curie memorial Cancer Center and Institute of Oncology, Gliwice Branch, Gliwice, Poland • Conflicts of interest not reported
• **Setting**	Single centre trial, Poland
• **Sample size**	N=101 (76 completers)
• **Duration and follow-up**	• Recruitment period: Mar 2003 – Sept 2009 • Median follow-up: 12.5 months
• **Statistical analysis**	• To test whether the QOL scores were different between the two radiotherapies, a mixed effects' model with random intercepts and fixed effects of the interaction between the time of observation and treatment methods was applied • Student's t-test, Wilcoxon's test • Kaplan Meier
Patient characteristics	
• **Eligibility criteria**	• Patients with advanced HNSCC (T2N3, T3N0-3, T4N0-3), excluding nasopharyngeal cancers
• **Patient & disease characteristics**	**Whole group** **Mean age** 57y **Male** 77% **T1-2** 2% **N0** 3%
Interventions	
• **Intervention group**	Accelerated radiotherapy (N=39): 64 Gy/40 fractions/3 weeks, split-course
• **Control group**	Conventional radiotherapy (N=37): 72-74 Gy/36-37 fractions/7.5 weeks
Results	
• **Overall survival**	• No significant difference (p=0.02) (+/- 10% at 5y in both groups)
• **Quality of life**	• More deteriorated quality of life (measured with the EORTC QLQ-C30 and the QLQ-H&N35) with accelerated fractionation: o Social functioning: interaction 2.35, p=0.023 o Pain: interaction -2.9, p=0.046

	o Appetite loss: interaction -4.8, p=0.006 o Financial difficulties: interaction -3.14, p=0.03 o Pain killers: interaction 5.42, p=0.03
• **Adverse events**	• Acute mucosal reaction (Dische scores): significantly worse in accelerated group first 4 weeks • Late effects (LENT-SOMA scale): no significant differences
Limitations and other comments	
• **Limitations**	• Unclear allocation concealment • Unclear blinding

Trotti A 2014

Methods

• **Design**	RCT
• **Source of funding and competing interest**	• National Cancer Institute grant U10CA021661 • Conflicts of interest: none
• **Setting**	Multicentre study, US (N=87)
• **Sample size**	N=250 (239 analyzable)
• **Duration and follow-up**	• Recruitment period: Apr 1996 – Jul 2003 • Median follow-up: 7.9y
• **Statistical analysis**	• Local control rates were estimated using the cumulative incidence method to account for the competing risk of death without local failure • Patients were censored for locoregional control after 5 years • Disease-free and overall survival rates were estimated with the Kaplan-Meier method • The Cox proportional hazards model with T-subcategory as a covariate was used to estimate and test the HR
Patient characteristics	
• **Eligibility criteria**	• Patients with previously untreated biopsy-proven T2N0 glottic cancer • Karnofsky performance status (KPS) at least 60, no surgery except biopsy • Patients undergoing prior debulking or complete laser excision of the primary were ineligible
• **Patient & disease characteristics**	

	Conventional	Hyperfractionation	p
Median age	64.5y	65y	?
Male	95%	92.4%	?
T2a	61.7%	62.2%	?
N0	100%	100%	

Interventions	
• **Intervention group**	Hyperfractionation (N=120): 79.2 Gy/66 fractions/6.5 weeks

• **Control group**	Conventional fractionation (N=119): 70 Gy/35 fractions/7 weeks
Results	
• **Overall survival**	• HR 0.82, p=0.29 • At 5 years: 72% vs. 63%
• **Disease-free survival**	• HR 0.79, p=0.13 • At 5 years: 49% vs. 40%
• **Local control**	• HR 0.70, p=0.14 • At 5 years: 78% vs. 70%
• **Acute toxicity, grade 3-4**	• Skin: 13/120 vs. 6/120 • Mucositis/stomatitis: 10/120 vs. 5/119 • Salivary gland: 1/120 vs. 0/119 • Pharynx/oesophagus: 4/120 vs. 4/119 • Larynx: 21/120 vs. 15/119 • Upper gastrointestinal: 1/120 vs. 0/119
• **Late toxicity, grade 3-4**	• Skin: 2/119 vs. 1/118 • Mucositis/stomatitis: 3/119 vs. 2/118 • Salivary gland: 1/119 vs. 0/118 • Pharynx/oesophagus: 3/119 vs. 3/118 • Larynx: 6/119 vs. 9/118 • Upper gastrointestinal: 0/119 vs. 1/118
Limitations and other comments	
• **Limitations**	• Randomization according to Zelen's principle, stratified by substage T2a versus T2B • Unclear allocation concealment • Unclear blinding • Unclear if ITT analysis

Yamazaki H 2006	
Methods	
• **Design**	RCT
• **Source of funding and competing interest**	• Supported by a grant from the Ministry of Health and Welfare of Japan • Conflicts of interest: not reported
• **Setting**	Single centre study, Japan; university hospital
• **Sample size**	N=189 (9 patients excluded)
• **Duration and follow-up**	• Recruitment period: Dec 1993 – Dec 2001

	• Median follow-up: 64 months
• **Statistical analysis**	• Local control and survival probability were calculated using the Kaplan-Meier method and compared using the log–rank test • Multivariate analysis was performed using Cox's proportional hazard model • Statistical significance was tested by Student's t test, log–rank test, or chi-square test
Patient characteristics	
• **Eligibility criteria**	• Patients with invasive, previously untreated, T1 squamous cell carcinoma of the true vocal cords
• **Patient & disease characteristics**	

	Conventional	Accelerated	p
Mean age	64y	65y	NS
Male	97%	92%	NS
T1a	81%	79%	NS

Interventions	
• **Intervention group**	Accelerated fractionation: 56.25-63 Gy/30-33 fractions/6-6.6 weeks (N=92)
• **Control group**	Conventional fractionation: 60-66 Gy/25-28 fractions/5-5.6 weeks (N=88)
Results	
• **Overall survival**	• At 5y: 88% vs. 87% (NS)
• **Cause-specific survival**	• At 5y: 100% vs. 98% (NS)
• **Local control**	• At 5y: 92% vs. 77%, p=0.004
• **Acute toxicity**	• Skin: no moist desquamation or confluent moist desquamation with pain • Mucosa: diffuse coating 7/92 vs. 8/88, edema 2/92 vs. 2/88
• **Late toxicity, grade 3-4**	• None
Limitations and other comments	
• **Limitations**	• Unclear randomization method and allocation concealment • Unclear blinding • No ITT analysis

5. SUMMARY OF FINDINGS TABLES AND GRADE PROFILES

5.1. RQ1: What is the effectiveness and/or diagnostic outcomes of locoregional staging (i.e. T- and N-staging) with MRI compared to CT in patients with head and neck squamous cell carcinoma

Outcome	No. of studies	Study design	Factors that may decrease quality of evidence					**Quality of evidence**
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias	
True positives (patients with laryngeal cancer) **False negatives** (patients incorrectly classified as not having laryngeal cancer)	2	Prospective cohort study (2)	Serious[1]	None[2]	Serious[3]	Imprecise[4]	Unlikely	⊕OOO Very low
True negatives (patients without laryngeal cancer) **False positives** (patients incorrectly classified as having laryngeal cancer)	2	Prospective cohort study (2)	Serious[1]	None[2]	Serious[3]	Imprecise[4]	Unlikely	⊕OOO Very low

Sources: Allegra 2014; Kraft 2013

[1] Low to unclear risk of bias studies due to patient selection, time between tests unclear; unclear if the gold standard test results were made with knowledge of the test under investigation or other clinical data; not all patients were included in the analysis.

[2] Patients with laryngeal cancer.

[3] Inconsistencies due to the use of multiple criteria/abnormalities upon imaging or single criteria/abnormality.

[4] Allegra 2014 used MRI and CT to define the expansion of glottic lesion to anterior commissure, laryngeal cartilages, subglottic and/or supraglottic site, and paraglottic space.paraglottic space involvement. Diagnostic outcomes were calculated for these five lesions with very broad 95%CI (see Table). Kraft 2012 presented diagnostic outcomes for 10 separate criteria

vocal fold; ventricular fold; arytenoid cartilage invasion; epiglottis; preepiglottic; paraglottic space involvement; inner perichondrium; thyroid cartilage invasion; midline crossing (anterior commissure involvement); tumor diameter. Overall, the diagnostic outcomes for MRI and CT for all separate criteria were estimated imprecise (95%CI ≥10%; see Table).

Bibliography: Wu 2012, Zhong 2014; Lee 2012.

Outcome	No. of studies	Study design	Factors that may decrease quality of evidence					Quality of evidence	Effect per 1000 patients[5]					
									pre-test probability of 47%[6]		pre-test probability of 40%		pre-test probability of 54%	
			Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		MRI	CT	MRI	CT	MRI	CT
True positives (patients with HNSCC)	3	Systematic review (10 studies) Cohort study (2)	Serious[1]	Serious[2]	Serious[3]	Precise[4]	Unlikely	⊕OOO Very low	315 (306 to 329)	301 (287 to 320)	268 (260 to 280)	256 (244 to 272)	362 (351 to 378)	346 (329 to 367)
									TP absolute difference: 14 fewer		**TP absolute difference**: 12 fewer		**TP absolute difference**: 16 fewer	
False negatives (patients incorrectly classified as not having HNSCC)									155 (164 to 141)	169 (183 to 150)	132 (140 to 120)	144 (156 to 128)	178 (189 to 162)	194 (211 to 173)
									FN absolute difference: 14 more		**FN absolute difference**: 12 more		**FN absolute difference**: 16 more	
True negatives (patients without HNSCC)	3	Systematic review (10 studies) Cohort study (2)	Serious[1]	Serious[2]	Serious[3]	Imprecise[4]	Unlikely	⊕OOO Very low	419 (408 to 424)	398 (334 to 424)	474 (462 to 480)	450 (378 to 480)	363 (354 to 368)	345 (290 to 368)
									TN absolute difference: 21 fewer		**TN absolute difference**: 24 fewer		**TN absolute difference**: 18 fewer	
False positives (patients incorrectly classified as having HNSCC)									111 (122 to 106)	132 (196 to 106)	126 (138 to 120)	150 (222 to 120)	97 (106 to 92)	115 (170 to 92)
									FP absolute difference: 21 more		**FP absolute difference**: 24 more		**FP absolute difference**: 18 more	

[1] Unclear or high risk of bias in primary studies due to differential verification; time between tests unclear; unclear whether the persons interpreting the tests under investigation had knowledge of the gold standard test result; unclear if the gold standard test results were made with knowledge of the test under investigation or other clinical data.
[2] Not solely laryngeal, hypopharyngeal and/or oropharyngeal patients included.
[3] Inconsistencies due to use of different type of MRI (DW-MRI vs. regular contrast-enhanced MRI).

[4] Unfortunately, not all diagnostic outcome results of the included primary studies were reported in the review of Wu 2012; therefore, updating of the meta-analysis with results of Zhong 2014 and Lee 2012 was not possible. The pooled Se 67% (95% CI: 65%–70%) and Sp 79% (95% CI: 77%–80%) of MRI, and the pooled Se 64% (95% CI: 61%–68%) of CT were estimated precise (95%CI interval < 10%). However, the pooled Sp 75% (95% CI: 63%–80%) of CT was estimated imprecise (95%CI interval ≥ 10%).
[5] Based on the pooled results of the review Wu 2012.
[6] Median prevalence (range 9-89%) of lymph nodes metastases of the 10 included studies in review Wu 2012 that made a direct comparison between MRI and CT.

5.2. RQ2: What is the clinical effectiveness of surgery for patients with early oropharyngeal, hypopharyngeal and laryngeal cancer?

a. Surgery versus non-surgery

5.2.1. Oropharynx

Question: Should surgery vs nonsurgical interventions be used for patients with T1-2 oropharyngeal cancer?
Bibliography: O'Hara 2011

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Nonsurgical interventions	With Surgery		Risk with Nonsurgical interventions	Risk difference with Surgery (95% CI)
Disease-free survival - not measured											
-	-	-	-	-	-	-	-	-	-	--	-
Recurrence rate: local (CRITICAL OUTCOME)											
72 (1 study) 5 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	4/30 (13.3%)	4/42 (9.5%)	-	**133 per 1000**	-[3]
Recurrence rate: regional (CRITICAL OUTCOME)											
72 (1 study) 5 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	2/30 (6.7%)	3/42 (7.1%)	-	**67 per 1000**	-[3]
(Loco)regional control - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival (CRITICAL OUTCOME)											

72 (1 study) 5 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	60%	50%	-	-	-[3]
Quality of life - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Adverse effects - not measured											
-	-	-	-	-	-	-	-	-	-	-	-

[1] Baseline imbalances
[2] Small samples, optimal information size (OIS) not reached.
[3] Unadjusted numbers; no RR calculated.

5.2.2. Hypopharynx

No evidence

5.2.3. Larynx

Question: Should surgery vs nonsurgical interventions be used for patients with T1-2 laryngeal cancer?

Bibliography: 1 SR with 1 RCT; 2 SRs with 7 and 5 obs studies; 8 primary obs studies

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Surgery vs Nonsurgical interventions	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with Nonsurgical interventions	Risk difference with Surgery (95% CI)
Disease-free survival (RCT) (CRITICAL OUTCOME)										
205 (1 study) 5 years	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	T1: 100% vs 71.1% (NS) T2: 78.8% vs 60.1% (one-sided p= 0.036)	-	-	-[3]
Disease-free survival (CRITICAL OUTCOME)										
143 (1 study) 5 years	serious[4]	no serious inconsistency	no serious indirectness	very serious[5]	undetected	⨁⊖⊖⊖ **VERY LOW**[4,5] due to risk of bias, imprecision	HR=0.93 (95% CI 0.30 to 2.88) T1a: HR=0.25 (95% CI 0.08 to 1.50)		-	-[3]

							T1b: (p=0.07, HR not calculable)			
Recurrence rate (CRITICAL OUTCOME)										
712 (5 studies) 12-107 months	serious[6]	serious[7]	no serious indirectness	serious[8]	undetected	⊕⊖⊖⊖ **VERY LOW**[6,7,8] due to risk of bias, inconsistency, imprecision	0% vs 0% 4.2% / 5.3% vs 6.7% Loc: 17/89 (19.1%) vs 18/159 (11.3%) Reg: 2/89 (2.2%) vs 2/159 (1.3%) Loc: 10% vs 19.3% Reg: 5.6% vs 0% 2/39 (5.1%) vs 2/67 (3.0%) All NS	**not pooled**	-	-
(Loco)regional control (CRITICAL OUTCOME)										
>248[9] (8 studies) 5-139 (SR) and 44-48 months	serious[6]	serious[7]	no serious indirectness	very serious[5,8]	undetected	⊕⊖⊖⊖ **VERY LOW**[5,6,7,8] due to risk of bias, inconsistency, imprecision	OR=0.94 (95%CI 0.57 to 1.57) 5-yr: 75% vs 86% (p=0.070)		-	-
Overall survival (RCT) (CRITICAL OUTCOME)										
205 (1 study) 5 years	very serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	T1: 100% vs 91.7% (NS) T2: 97.4% vs 88.8% (NS)	-	-	-[3]
Overall survival (CRITICAL OUTCOME)										
>9428[9] (12 studies) 5 mo - 5.3 y	serious[6]	serious[7]	no serious indirectness	serious[3,8]	undetected	⊕⊖⊖⊖ **VERY LOW**[3,6,7,8] due to risk of bias, inconsistency, imprecision	SR: OR=1.22 (95%CI 0.89 to 1.66) Primary studies (5 year): 97.2% / 97.3% vs 95.9% 90% vs 72% 92.3% vs 92.2% HR=1.11 (95% CI 0.40 to 3.30)	**not pooled**	-	-

							RT vs surgery: HR=1.03 (95% CI 0.91 to 1.13) All NS			
Quality of life: Voice Handicap Index (CRITICAL OUTCOME)										
>111[9] (4 studies) 5-139 months	serious[6]	serious[7]	no serious indirectness	serious[8]	undetected	⊕⊖⊖⊖ **VERY LOW**[6,7,8] due to risk of bias, inconsistency, imprecision	SRs MD= 1.76 (-12.81 to 16.33] Mean score 12 vs 18 Primary studies: 4.5 vs 5.6 (p=0.950) 12.4 vs 8.3 (p=0.005) Median 18 vs 4 (p<0.0001)	**not pooled**	-	-
Quality of life: larynx preservation (CRITICAL OUTCOME)										
>396[9] (10 studies) 5-139 months	serious[6]	serious[7]	no serious indirectness	serious[8]	undetected	⊕⊖⊖⊖ **VERY LOW**[6,7,8] due to risk of bias, inconsistency, imprecision	SR OR= 3.11 (95%CI 1.16 to 8.34) Primary studies: 93% vs 83% (p=0.049) 95.7% vs 86.7% (p=0.220) RR=0.95 (95% CI 0.88 to 1.02)	**not pooled**	-	-
Quality of life: COOP/Wonca (CRITICAL OUTCOME)										
? (4 studies) ? months	serious[6]	serious[7]	no serious indirectness	serious[8]	undetected	⊕⊖⊖⊖ **VERY LOW**[6,7,8] due to risk of bias, inconsistency, imprecision	NS	**not pooled**	-	-

Adverse events (CRITICAL OUTCOME)										
>8942[9] (2 studies) 38 mo - 5.3 y	serious[6]	serious[7]	no serious indirectness	serious[5]	undetected	⊕⊖⊖⊖ **VERY LOW**[6,7] due to risk of bias, inconsistency	RT vs surgery: Fatal CVA HR=1.75 (95% CI 1.04 to 2.96) Fatal Heart Disease HR=0.91 (95% CI 0.77 to 1.09) Postoperative complications: NS	**not pooled**	-	-

[1] High risk of bias of the only included study according to the authors of the systematic review. No data presented by group.
[2] No original numbers / numbers per group reported. Total sample size = 234. No significant differences.
[3] No quantification of effects
[4] No concurrent cohorts
[5] Notable benefit or harm can't be excluded
[6] High risk of bias in (almost) all studies
[7] Various types of interventions
[8] No quantification due to unadjusted figures
[9] Review doesn't mention totals per outcome

b. Function-sparing surgery versus extensive surgery

5.2.4. Oropharynx

No evidence

5.2.5. Hypopharynx

No evidence

5.2.6. Larynx

Question: Should function-sparing surgery vs extensive surgery be used for patients with T1-2 laryngeal cancer?
Bibliography: Karatzanis 2010

Quality assessment							Summary of Findings				
Participants (studies) Follow up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Extensive surgery	With Function-sparing surgery		Risk with Extensive surgery	Risk difference with Function-sparing surgery (95% CI)
Disease-free survival (CRITICAL OUTCOME)											
0 (0)						-	-	-	-	-	-
(Loco)regional control (CRITICAL OUTCOME)											
101 (1 study) 67 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	"No statistically significant differences between the 3 intervention groups"		-	-	-[3]
Recurrence rate (CRITICAL OUTCOME)											
0 (0)						-	-	-	-	-	-
Overall survival (CRITICAL OUTCOME)											
0 (0)						-	-	-	-	-	-
Quality of life (CRITICAL OUTCOME)											
0 (0)						-	-	-	-	-	-
Adverse events (CRITICAL OUTCOME)											
101 (1 study) 67 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	Complications: 5/49 and 7/29 vs 4/23 "No statistically significant differences between the 3 intervention groups"		-	-	-[3]

[1] Baseline imbalances
[2] Small samples; OIS not reached
[3] Unadjusted numbers; no RR calculated

5.3. RQ3: Surgery versus organ / function preservation strategies

5.3.1. Oropharynx

Question: Should surgery vs organ / function sparing strategies be used for patients with locally advanced oropharyngeal cancer?
Bibliography: five observational studies

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
									Risk with Organ / function sparing strategies	Risk difference with Surgery(95% CI)
Disease-free survival (CRITICAL OUTCOME)										
57 (1 study) 4 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	55.2% vs. 54.2% (p=0.406)	-	-	-
Recurrence or progression (CRITICAL OUTCOME)										
94 (1 study) median 45 and 63 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	10/47 vs. 13/47 (RR= 0.77; 95% CI 0.38 to 1.58)	-	-	-
Local control (CRITICAL OUTCOME)										
199 (2 studies) median 45 to 108 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	3-year 79.5% vs. 79.3% (p=0.813) Median 7 to 9 year: 88.2% vs. 69.6% (p=0.256)	**not pooled**	-	-
Regional control (CRITICAL OUTCOME)										
199 (2 studies) median 45 to 108 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	3-year 87.3% vs. 80.1% without planned neck dissection (p= ?) 3-year 87.3% vs. 86.3% with planned neck dissection (p=0.549) Median 7 to 9 year: 88.2% vs. 82.6% (p=0.978)	**not pooled**	-	-

Overall survival (CRITICAL OUTCOME)										
537 (4 studies) median 45 to 108 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	4 y: 61.4% vs. 58.5% (p=0.280) 3 y: 73.6% vs. 73.5% (p=0.599) / HR 0.74 (95% CI 0.36 to 1.54) 5-y: 46.3% vs. 51.5% (p=0.921) 2-year: 87.7% (S-CRT) / 69.7% (S-RT) vs. 51.7% (CRT) 5-year: 63.1% (S-CRT) / 47.4% (S-RT) vs. 39.8% (CRT S-CRT vs CRT: HR 2.79 (95% CI 1.53 to 5.09) (NB: OS or DSS?)	**not pooled**	-	-
Quality of life (CRITICAL OUTCOME)										
92 (2 studies) median 24.7 and 56 months	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1] due to risk of bias	Global QoL [0-100]: 68.6 vs. 79.8 (p=0.027) and many functional and symptom dimensions significantly in favour of RT UW-QOL v.4: NS	**not pooled**	-	-
Adverse effects (CRITICAL OUTCOME)										
199 (2 studies) median 45 to 108 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	Only grade 2-4 toxicity in RT group reported (mucositis) in study 1 Major complications 35.3% vs. 17.4% Feeding tube dependent 35.3% vs. 21.7% Tracheostomy dependent 5.9% vs.18.2% All NS	**not pooled**	-	-

1 Lack of blinded outcome assessment; no concurrent cohorts

2 (Very) small samples. OIS not reached.

5.3.2. Hypopharynx

Question: Should surgery vs organ / function sparing strategies be used for patients with locally advanced hypopharyngeal cancer?
Bibliography: two RCTs

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Surgery vs CRT	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with Organ / function sparing strategies	Risk difference with Surgery(95% CI)
Disease-free survival (CRITICAL OUTCOME)										
202 (1 study) 3, 5 and 10 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2,3]	undetected	⨁⨁⨀⨀ **LOW**[1,2,3] due to risk of bias, imprecision	Median DFS: 20 vs 25 mo 3-year: 32% (17% to 47%) vs 43% (28% to 58%) 5-year: 27% vs 25%	**-**	-	-
Recurrence - not measured										
-	-	-	-	-	-	-	- -	**-**	-	-
Local control (CRITICAL OUTCOME)										
92 (1 study) 5 year	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⨁⨀⨀ **LOW**[1,3] due to risk of bias, imprecision	63% vs 39% (p<0.01)	**not pooled**	-	-
Overall survival (CRITICAL OUTCOME)										
294 (2 studies) 92 and 51/126 months	serious[1]	serious[4]	no serious indirectness	serious[3]	undetected	⨁⨀⨀ **VERY LOW**[1,3,4] due to risk of bias, inconsistency, imprecision	5-year OS: 37% vs 19% (p=0.04) Died (any cause; mean follow-up 92 months): 33/46 vs 38/44 (RR=0.83; 95% CI 0.67 to 1.03) Median OS: 25 vs 44 mo 3 year: 43% (95% corrected CI 27% to 59%) vs 57% (95% corrected CI 42% to 72%); 5-year: 32.6% (23.0 to 42.1) vs 38.0% (28.4 to 47.6) 10-year: 13.8% (6.1 to 21.6) vs 13.1% (5.6 to 20.6) "Observed dead hazard ratio" CRT vs S RR=0.86 (corrected 95%-CI 0.50 to 1.48)	**not pooled**	-	-

Quality of life - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Adverse effects (CRITICAL OUTCOME)										
294 (2 studies) 51 and 92 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[3,5]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,3,5] due to risk of bias, imprecision	Toxicity of chemotherapy: 24/46 vs 23/44 (RR=1.00; 95% CI 0.67 to 1.48) 'No drug-related serious adverse events were noted.'	**not pooled**	-	-

[1] Lack of blinding and/or unclear RoB
[2] No quantification
[3] OIS not reached
[4] Conflicting results
[5] CI includes considerable benefit and harm

5.3.3. Larynx

Question: Should surgery vs organ / function sparing strategies be used for patients with locally advanced laryngeal cancer?
Bibliography: two RCTs

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Surgery vs organ / function sparing strategies		Risk with Organ / function sparing strategies	Risk difference with Surgery (95% CI)
Disease-free survival (CRITICAL OUTCOME)										
404 (2 studies) 24-33 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⊖⊖ **LOW**[12] due to risk of bias, imprecision	5-years disease free survival: 70% vs 50% (p=0.04) 'Disease free survival tended to be shorter in the chemotherapy group than in the surgery group, but the difference was not statistically significant (p=0.1195).'	**not pooled**	-	-
Recurrence (CRITICAL OUTCOME)										
404 (2 studies) 24-33 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⊖⊖ **LOW**[12] due to risk of bias, imprecision	Pooled: RR= 0.72 (95% CI 0.53 to 0.996)		-	-

Local control (CRITICAL OUTCOME)										
72 (1 study) 24 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	undetected	⊕⊕⊕⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	23/35 vs 19/29 (RR=1.0; 95% CI 0.70 to 1.43)		-	-
Overall survival (CRITICAL OUTCOME)										
404 (2 studies) 2-5 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2,4]	undetected	⊕⊕⊖⊖ **LOW**[1,2,4] due to risk of bias, imprecision	5-year overall survival: 73% vs 77% (p=0.79) 2-year survival: 68% (95% CI 60 to 75%) vs 68% (95% CI 60 to 76%) (P=0.9846) Died: 58/166 vs 65/166 (RR=0.89; 95% CI 0.67 to 1.18)	**not pooled**	-	-
Quality of life (CRITICAL OUTCOME)										
332 (1 study) 10.4 years	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊖⊖ **LOW**[1,4] due to risk of bias, imprecision	'Patients randomized to the CT + RT group had significantly better (P<.05) quality-of-life scores on the SF-36 mental health domain (76.0) than the surgery and RT group (63.0), and also had better HNQOL pain scores (81.3 vs 64.3). Compared with patients who underwent laryngectomy, patients with intact larynges (CT + RT with larynx) had significantly less bodily pain (88.5 vs 56.5), better scores on the SF-36 mental health (79.8 vs 64.7), and better HNQOL emotion (89.7 vs 79.4) scores. More patients in the surgery and RT group (28%) were depressed than in the CT + RT group (15%).'		-	-
Adverse effects - not measured										
-	-	-	-	-	-	-			-	-

[1] Lack of blinding and/or unclear RoB
[2] OIS not reached
[3] CI includes both appreciable benefit and harm
[4] No quantification

Question: Should surgery vs organ / function sparing strategies be used for patients with T4a laryngeal cancer?

Bibliography: one systematic review with seven relevant observational studies

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Organ / function sparing strategies	With Surgery		Risk with Organ / function sparing strategies	Risk difference with Surgery (95% CI)
Disease-free survival - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Recurrence - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
(Loco)regional control - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival of surgery vs CRT (CRITICAL OUTCOME)											
(3 studies)	no serious risk of bias[1]	serious[2]	no serious indirectness	serious[3]	undetected	⨁⨁⊖⊖ **LOW**[1,2,3] due to inconsistency, imprecision	2 y: 100% vs 60% 2 y: 90% vs <30% 5 y: 55% vs 25%		**not pooled**	-	-
Overall survival of surgery vs RT (CRITICAL OUTCOME)											
(4 studies)	no serious risk of bias[1]	serious[2]	no serious indirectness	serious[3]	undetected	⨁⨁⊖⊖ **LOW**[1,2,3] due to inconsistency, imprecision	2 y: 60% vs 12%; 5 y: 49% vs. 5% 1 y: 60% vs. 54.6%; 2 y: 30% vs. 21.2%; 5 y: 10% vs 9.1% 5 y: 41% vs 11% 5 y: 58% vs 32%		**not pooled**	-	-
Quality of life - not reported											
-	-	-	-	-	-	-	-	-	-	-	-
Adverse effects - not reported											
-	-	-	-	-	-	-	-	-	-	-	-

[1] Note: the SR did not present RoB results for individual studies
[2] According to review authors: vast clinical heterogeneity
[3] No quantification

5.4. RQ4: Postoperative (chemo)radiotherapy

a. Postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy

5.4.1. Mixed population

Question: Should postoperative radiotherapy vs no postoperative radiotherapy be used in patients with head and neck cancer?
Bibliography: RCT: Rodrigo 2004; observational study: Schmitz 2009

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Postoperative radiotherapy versus no postoperative radiotherapy	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with No postoperative radiotherapy	Risk difference with Postoperative radiotherapy (95% CI)
Disease-free survival - not measured										
-	-	-	-	-	-	-	-	-	-	-
Recurrence (RCT) (CRITICAL OUTCOME)										
42 (1 study) 36-105 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	Stage III: 50% vs. 80% - Local:25% vs. 80% - Cervical: 0% vs. 0% - Local and cervical: 25% vs. 0% Stage IV: 84% vs. 68% - Local: 31% vs. 62% - Cervical: 46% vs. 0% - Local and cervical: 8% vs. 6%	-	-	-
Recurrence (Observational study) (CRITICAL OUTCOME)										
146 (1 study) 58 months	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	Neck recurrence pN0 (n=194 necks): 0 vs. 3/194 pN1 (n=39 necks): 2/21 vs. 1/18 pN2b (n=16 necks) 1/16 vs. 0	-	-	-

(Loco)regional control (CRITICAL OUTCOME)										
42 (1 study) 36-105 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	Stage III: better in radiated group; Stage IV: better in non-irradiated	**-**	-	**-**
Overall survival – not measured										
-	-	-	-	-	-	-	-	**-**	-	-
Quality of life - not measured										
-	-	-	-	-	-	-	-	**-**	-	-
Adverse events - not measured										
-	-	-	-	-	-	-	-	**-**	-	-

[1] High risk of bias due to no blinding, incomplete outcome data and baseline imbalances in T-stage distribution.
[2] No quantification; OIS not reached
[3] No blinding

5.4.2. Oropharynx

Question: Should postoperative (chemo)radiotherapy vs no postoperative (chemo)radiotherapy be used in patients with oropharyngeal cancer?

Bibliography: Bastos de Souza 2014, Broglie 2013, Lim 2008, Patel 2014, Röösli 2010, , Yokota 2014

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy		Risk with No postoperative (chemo) radiotherapy	Risk difference with Postoperative (chemo)radiotherapy
Disease-free survival (CRITICAL OUTCOME)										
301 (2 studies) 52.8 and 72 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	57.4% vs. 43.3%, p=0.010 (log rank test) HR 3.02, 95% CI 0.80 to 11.3, p=0.101 HR 0.31, 95% CI 0.08 to 1.19, p=0.087	**not pooled**	-	-
Recurrence (CRITICAL OUTCOME)										

450 (3 studies) 41. 42.5 and 64 months	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,3] due to risk of bias, imprecision	Local recurrence 6/84 (7%) vs. 3/26 (12%), p=ns Regional recurrence 17/84 (20%) vs. 2/26 (8%), p=ns Treatment failures: 7/38 (18%) vs. 10/41 (24%), p = 0.41 3-year failure rates for intermediate or high-risk patients Local: 0% vs. 21%, p=0.004 Regional: 6% vs. 21.4%, p=0.08 Locoregional: 6% vs. 32%, p=0.008 Distant: 18.1% vs. 5.9%, p=0.33 Patients with recurrence: 39 (24.5%) vs. 33 (32%)	**not pooled**	-	-
(Loco)regional control - not measured										
-	-	-	-	-	-	-	- -	**-**	-	-
Overall survival (CRITICAL OUTCOME)										
641 (4 studies) 41. 42.5. 52.8 and 64 months	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,4] due to risk of bias, imprecision	3-y (intermediate or high-risk patients): 93.8% vs. 94.1%, p=0.63 5y: 45.8% vs. 32.8%, p=0.010 (log rank test) 5y: 66.6% vs. 70.3% Postoperative radiotherapy vs. no postoperative radiotherapy: HR 0.32, 95% CI 0.06 to 1.67, p = 0.176 Postoperative chemoradiotherapy vs. no postoperative chemoradiotherapy: HR 0.79, 95 % CI 0.15 to 4.08, p = 0.779	**not pooled**	-	-
Quality of life (CRITICAL OUTCOME)										
43 (1 study) 72 months	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,3] due to risk of bias, imprecision	EORTC-QLQ-C30: Functional scales and symptom scales: no significant differences EORTC-QLQ-H&N35: no significant differences for all items	**-**	-	**-**
Adverse events (CRITICAL OUTCOME)										

45 (1 study) 41 months	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,3] due to risk of bias, imprecision	postoperative radiotherapy vs. postoperative chemotherapy vs. surgery alone ≥3 toxicity Neutrophils: 0 vs. 1 (11%) vs. 0 Hemoglobin: 0 vs. 1 (11%) vs. 4 (21%) Platelets: 0 vs. 0 vs. 0 Nausea/vomiting: 0 vs. 1 (11%) vs. 0 Dysphagia: 1 (6%) vs. 2 (22%) vs. 3 (16%) Mucositis: 4 (24%) vs. 4 (44%) vs. 0 Anorexia: 3 (18%) vs. 2 (22%) vs. 0 Dysgeusia (grade 2): 6 (35%) vs. 5 (56%) vs. 0 Creatinine: 0 vs. 0 vs. 0 Infection: 1 (6%) vs. 1 (11%) vs. 0	-	-	-

[1] No blinding, imbalanced prognostic factors at baseline.
[2] Wide confidence interval, OIS not reached.
[3] No quantification
[4] Quantification not for all studies
[5] No blinding
[6] 1 study with significant disease-specific survival benefit for postoperative radiotherapy, no significant differences in other two studies

5.4.3. Hypopharynx

Question: Should postoperative radiotherapy vs no postoperative radiotherapy be used in patients with hypopharyngeal cancer?
Bibliography: Wang 2006

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Postoperative radiotherapy versus no postoperative radiotherapy	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with No postoperative radiotherapy	Risk difference with Postoperative radiotherapy (95% CI)
Disease-free survival - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Recurrence - not measured										
-	-	-	-	-	-	-	- -	-	-	-
(Loco)regional control - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Overall survival (5 years) (CRITICAL OUTCOME)										

41 (1 study) 42.6 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	48.2% vs. 0%, p<0.001 (univariate analysis) HR 0.27, 95%CI 0.13 to 0.60, (p=0.001) (multivariate Cox regression analysis, adjusted for age, gender, tumour localization, tumour size and local invasion)	-	-	-
Quality of life - not measured										
-	-	-	-	-	-	-	-	-	-	-
Adverse events - not measured										
-	-	-	-	-	-	-	-	-	-	-

[1] No blinding, unclear whether study groups were comparable at baseline.
[2] OIS not reached

5.4.4. Larynx

Question: Should postoperative (chemo)radiotherapy vs no postoperative (chemo)radiotherapy be used in patients with laryngeal cancer?

Bibliography: Ampil 2007, Bindewald 2007, Cho 2010, Davis 2004, Dechaphunkul 2011, Gourin 2014, Olthoff 2006, Yilmaz 2005

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy		Risk with No postoperative (chemo) radiotherapy	Risk difference with Postoperative (chemo) radiotherapy
Disease-free survival - not measured										
-	-	-	-	-	-	-	-	-	-	-
Recurrence (CRITICAL OUTCOME)										
560 (2 studies) 44 months and >3 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	Relapse in the neck 0/16 vs. 3/12 (p=0.07) Distant metastasis 1/16 vs. 1/12 Local: 10/236 (4%) vs. 9/294 (3%) Regional: 44/236 (19%) vs. 15/294 (5%) Locoregional: 9/236 (4%) vs. 8/294 (3%); HR 1.574, 95%CI 0.941 to 2.633 Locoregional and distant metastasis: 2/236 (0.8%) vs. 0/294 (0%)	**not pooled**	-	-

							Regional and distant metastasis: 4/236 (1.7%) vs. 0/294 (0%)			
(Loco)regional control (CRITICAL OUTCOME)										
26 (1 study) 79 months	serious[3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[3,4] due to risk of bias, imprecision	Local control 84.5% vs. 100%	**-**	-	**-**
Overall survival (CRITICAL OUTCOME)										
1554 (5 studies) 44. 49 and 79 months[8]	serious[5]	serious[6]	no serious indirectness	serious[7]	undetected	⊕⊖⊖⊖ **VERY LOW**[5,6,7] due to risk of bias, inconsistency, imprecision	5y: 61% vs. 50% (p=0.63) 5y: 36% vs. 78% (p=0.000) (read from figure) 84.5% vs. 92.3% Supraglottic cancer patients 52.2% vs. – Glottic cancer patients: 61.4% vs. 87.5% HR 0.66 (95% CI 0.52-0.84) (in favour of RT)	**not pooled**	-	-
Quality of life (CRITICAL OUTCOME)										
351 (2 studies) 60 weeks and 4.5 to 5.7 years	serious[9]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[4,9] due to risk of bias, imprecision	EORTC-QLQ-C30: Functioning scales: NS except for role functioning and social functioning (worse for RT); Symptom scales: NS except for fatigue and dyspnea (more symptoms for RT); multivariate: NS Functioning scales: NS Symptom scales: significant more pain, fatigue, nausea/vomiting for RT Single items: appetite loss, constipation, dyspnea and financial difficulties: significant higher-level interactions EORTC-QLQ-H&N35: significant more pain, swallowing problems, problems with taste, problems opening mouth, dry mouth, sticky saliva for RT; multivariate: still significant difference RT vs no RT	**not pooled**	-	-
Adverse events - not measured										
-	-	-	-	-	-	-	-	**-**	-	-

[1] No blinding
[2] No quantification in one study
[3] No blinding, imbalances in baseline characteristics between study groups
[4] No quantification
[5] No blinding in all studies, imbalances in baseline characteristics in two studies
[6] Two of the studies report better survival for postoperative radiotherapy, while three report better survival for no postoperative radiotherapy.
[7] Quantification not for all studies
[8] Length of follow-up not reported in two studies.
[9] No blinding and imbalances in baseline characteristics in one study

b. *Postoperative chemoradiotherapy versus postoperative radiotherapy*

5.4.5. *Mixed population*

Question: Should postoperative chemoradiotherapy vs postoperative radiotherapy be used for head and neck cancer?

Bibliography: SR: Furness 2011; RCTs: Bachaud 1996, Haffty 1993 / Weissberg 1989, Racadot 2008, Smid 2003

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95%CI)	**Anticipated absolute effects**	
							With Postoperative chemoradiotherapy	With Postoperative radiotherapy		Risk with Postoperative radiotherapy	Risk difference with Postoperative chemotherapy (95%CI)
Disease-free survival (2 years) (CRITICAL OUTCOME)											
114 (1 study) 32.2 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⨁⨁⨀⨀ **LOW**[1,2] due to risk of bias, imprecision	76% vs. 60% (p=0.099)		-	-	-
Disease-free survival (5 years) (CRITICAL OUTCOME)											
784 (5 studies) 3.8-10 years	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⨁⨁⨁⨀ **MODERATE**[1] due to risk of bias	HR 0.87 (95%CI 0.73 to 1.04) (3 RCTs from SR) 45% vs. 23%, p<0.02 (log rank test) 67 ± SE 6% vs. 47 ± SE 6%, p<0.03		**pooled** **not pooled**	-	-

Recurrence (CRITICAL OUTCOME)										
454 (5 studies) 2.7 to 10 years	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias	Locoregional recurrence HR 0.61 (95%CI 0.41 to 0.91) 9/39 (23%) vs. 18/44 (41%), RR 0.56 (95%CI 0.29 to 1.11) p=0.08 Local and/or regional recurrence: 19/72 vs. 26/72, RR 0.73 (95%CI 0.45 to 1.20) Local and/or regional recurrences with or without distant metastases: 7/59 (12%) vs. 15/55 (27%), RR 0.44 (95%CI 0.19 to 0.99) Local recurrence: 0/55 vs. 12/58, RR 0.04 (95%CI 0.00 to 0.70) Regional recurrence: 5/55 vs. 8/58, RR 0.66 (95%CI 0.23 to 1.89) Distant recurrence: 7/55 vs. 9/58, RR 0.82 (95%CI 0.33 to 2.05)	**not pooled**	-	-
(Loco)regional control (2 years) (CRITICAL OUTCOME)										
258 (2 studies) 32.2 and 106 months	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊕⊖⊖ **LOW**[1,3] due to risk of bias, imprecision	HR 1.68 (95%CI 0.99 to 2.87)	**pooled**	-	**-**
(Loco)regional control (5 years) (CRITICAL OUTCOME)										
113 (1 study) 92.6 months	serious[1]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊕⊖⊖ **LOW**[1,4] due to risk of bias, imprecision	Local regional control rate (± SE): 87± 5% vs. 67±7%, p<0.02 Local control rate (± SE): 100 ± 0% vs. 75±7%, p<0.01	**not pooled**	-	-
Overall survival (2 years) (CRITICAL OUTCOME)										
258 (2 studies) 32.2 and 106 months	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	undetected	⊕⊕⊖⊖ **LOW**[1,5] due to risk of bias, imprecision	HR 0.86 (95%CI 0.60 to 1.22)	**pooled**	-	**-**

Overall survival (5 years) (CRITICAL OUTCOME)										
1314 (7 studies) 3.8 to 10 years	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊕⊕⊖ **MODERATE**[1] due to risk of bias	HR 0.84, (95%CI 0.72 to 0.98) (4 RCTs from SR) HR 0.91 (95%CI 0.73 to 1.13) (1 RCT from SR) 36% vs. 13%, p<0.01 (log rank test) 56 ± SE 7% vs. 41 ± SE 7 %, p=NS	**pooled** **not pooled**	-	-
Quality of life - not measured										
-	-	-	-	-	-	-	-	**-**	-	-
Adverse events										
454 (4 studies)	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	undetected	⊕⊕⊖⊖ **LOW**[1,6] due to risk of bias, imprecision	<u>acute toxicities</u> >grade 3: 16/39 vs. 7/44, RR 2.58 (95%CI 1.19 to 5.61) ≥grade 2: no significant differences, no grade 4 and 5 toxicities Mean weight loss 7.5% vs. 3.3.%, p=0.001 Mucositis (grade 4 vs. others): p<0.0001 worse in CRT group No statistically significant difference for incidence of dermatitis and infection, and for the degree of severe leukopenia, thrombopenia, and hemoglobin levels. (Timing of toxicity occurrence not clear) Moderate to severe leukopenia: 18/55 vs. 1/58, RR 18.98 (95%CI 2.62 to 137.42) Moderate, severe or life-threatening thrombocytopenia: 12/55 vs. 0, RR 26.34 (95%CI 1.60 to 434.42) No significant differences for non-hematological toxicities. <u>Late toxicities</u> >grade 2: 6/30 vs. 4/26, RR 1.30 (95%CI 0.41 to 4.11) ≥grade 2: no significant differences no grade 4 and 5 toxicities	**not pooled**	-	-

[1] No blinding
[2] Small sample size
[3] Small sample size, absence of benefit can't be excluded
[4] OIS not reached
[5] Small sample size, notable benefit or harm can't be excluded
[6] Quantification of results not for all studies

5.4.6. Oropharynx

Question: Should postoperative chemoradiotherapy vs postoperative radiotherapy be used for oropharyngeal cancer?

Bibliography: Roosli 2010, Yokota 2014

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** With Postoperative chemoradiotherapy	With Postoperative radiotherapy	**Relative effect** (95%CI)	**Anticipated absolute effects** Risk with Postoperative radiotherapy	Risk difference with Postoperative chemoradiotherapy (95%CI)
Disease-free survival - not measured											
-	-	-	-	-	-	-	-		-	-	-
Recurrence (CRITICAL OUTCOME)											
26 (1 study) 41 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	RR 1.06, p=0.971		-	-	-
(Loco)regional control - not measured											
-	-	-	-	-	-	See comment	-		-	-	-
Overall survival (CRITICAL OUTCOME)											
159 (1 study) 64 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	5 year: 45.7% vs. 38%, p=0.493		-	-	-
Quality of life - not measured											
-	-	-	-	-	-	See comment	-		-	-	-
Adverse events (CRITICAL OUTCOME)											
26 (1 study) 41 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	≥ grade 3 - oral mucositis: 44% vs. 24% - dysphagia: 22% vs. 6 % - dysgeusia: 56% vs. 35%		-	-	-

[1] Baseline imbalances
[2] (Very) small samples, OIS not reached

5.4.7. Hypopharynx

No evidence

5.4.8. Larynx

No evidence

5.5. RQ5: Management of the neck lymph nodes

a. Neck dissection versus no neck dissection

5.5.1. Oropharynx

Question: Should neck dissection vs no neck dissection be used for patients with oropharyngeal cancer (various stages) with varying degrees of node involvement?

Bibliography: Böscke 2014; Donatelli 2008; Lanzer 2012; Psychogios 2013; Sakashita 2014; Suzuki 2013

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Neck dissection versus no neck dissection		Risk with No neck dissection	Risk difference with Neck dissection(95% CI)
Disease-free survival (CRITICAL OUTCOME)										
49 (1 study) 60 and 65 months	serious[1,2,3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	3y: 87% vs. 76% 5y: 78% vs. 67% HR 1.79 (95%CI 0.57 to 5.56)	-	-	-
Recurrence (CRITICAL OUTCOME)										
487 (4 studies) 54-65 months	serious[1,2]	no serious inconsistency	serious[5]	no serious imprecision	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,5] due to risk of bias, indirectness	3/32 (10%) vs. 4/17 (24%) 17/93 (18.3%) vs. 40/109 (36.7%) 14/36 (38.9%) vs. 20/48 (41.7%) 5y recurrence-free survival: 59% vs. 66%	**not pooled**	-	-

(Loco)regional control (CRITICAL OUTCOME)										
662 (4 studies) 4.5 - 5.8 years	serious[1,2,7]	no serious inconsistency	serious[5]	serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,5,6,7] due to risk of bias, indirectness, imprecision	4y: 84.9% vs. 77.6% (p=0.2382) 5y: 96.3% (95% CI 76.5 to 99.5) vs 78.6% (95% CI 58.0 to 89.9) (p=0.072) HR 0.17 (95% CI 0.02 to1.86) (adjusted by age, sex, tumour and nodal classification) 5y: 90% vs. 89% (p=0.452); Local: 5/24 (20.8%) vs. 14/128 (10.9%); Lymph node: 1/24 (4.2%) vs. 11/128 (8.6%) 5y regional control: 96.0% vs 90.3% (p=0.07)	**not pooled**	-	-
Overall survival (CRITICAL OUTCOME)										
711 (5 studies) 4.5 - 5.8 years	serious[1,2,7]	no serious inconsistency	serious[5]	serious[6]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,5,6,7] due to risk of bias, indirectness, imprecision	3y: 93% vs. 82% 5y: 82% vs. 76% HR 1.01 (95% CI 0.44 to 2.27) 4y: 78.7% vs. 74.0% (p=0.34) HR 0.73 (95% CI 0.23 to 2.31) (adjusted by age, sex, tumour and nodal classification)	**not pooled**	-	-

							5y: 72.5% vs. 70% (p=0.971) 5y: 72.4% vs. 67.4% (p=0.197) Cases with pN0 classification had a better overall survival (74.6% vs 46.9%, p=0.07)			
Quality of life (CRITICAL OUTCOME)										
103 (1 study) 1 years	serious[1,8]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,4,8] due to risk of bias, imprecision	SF-36 and HNQoL: except for domain Body pain, no significant differences	**-**	-	-
Adverse effects (CRITICAL OUTCOME)										
84 (1 study) 5.8 years	serious[1,8]	no serious inconsistency	serious[5]	serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,5,6,8] due to risk of bias, indirectness, imprecision	Postoperative complications: 25 patients in ND group	**not pooled**	-	-

[1] *No blinding of participants or personnel*
[2] *No concurrent cohorts*
[3] *Baseline imbalances*
[4] *Small sample size(s); OIS not reached*
[5] *Mixed populations (various tumour locations)*
[6] *No significant differences; pooling not possible*
[7] *Unclear comparability at baseline*
[8] *Unclear concurrency and comparability at baseline*

5.5.2. Hypopharynx

Question: Should neck dissection vs no neck dissection be used for patients with node-positive hypopharyngeal cancer (all stages)?

Bibliography: Al-Mamgani 2013, Liu 2012, Psychogios 2013, Suzuki 2013

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Neck dissection Versus no neck dissection	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with No neck dissection	Risk difference with Neck dissection(95% CI)
Disease-free survival (CRITICAL OUTCOME)										
135 (1 study) 34 months	serious[1,2,3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	64% vs. 45% (p=0.06)	**-**	-	-
Recurrence (CRITICAL OUTCOME)										
169 (2 studies) 4.1 and 5.8 years	serious[1,2]	no serious inconsistency	serious[5]	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,4,5] due to risk of bias, indirectness, imprecision	14/36 (38.9%) vs. 20/48 (41.7%) Local recurrence 7 vs. 6 Regional metastases 1 vs. 6 16/46 (34.8%) vs. 7/39 (18%)	**not pooled**	-	-
(Loco)regional control (CRITICAL OUTCOME)										
528 (4 studies) 2.8 - 5.8 years	serious[1,2]	no serious inconsistency	serious[5]	serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,5,6] due to risk of bias, indirectness, imprecision	Local control 84% vs. 72% (p=0.15) Regional control: 92% vs. 87% (p=0.37) 5y regional control: 77.8% (95S% CI 36.5 to 93.9) vs 85.9% (95% CI 54.0 to 96.3) (p=0.541) HR 0.32 (95% CI 0.02 to 5.93) (adjusted by age, sex, tumour and nodal classification) Persistent nodular disease: 0 vs. 8 (21%)	**not pooled**	-	-

							5y regional control: 96.0% vs 90.3% (p=0.07)			
Overall survival (CRITICAL OUTCOME)										
528 (4 studies) 2.8 - 5.8 years	serious[1,2]	no serious inconsistency	serious[5]	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,5] due to risk of bias, indirectness	66% vs. 42% (p=0.04) HR 7.76 (95% CI 0.58 to 103.83) (adjusted by age, sex, tumour and nodal classification) 5y: 46.4% vs. 35.1% 5y: 72.4% vs. 67.4% (p=0.197) / pN0: 74.6% vs 46.9% (p= 0.07)	**not pooled**	-	-
Quality of life (CRITICAL OUTCOME)										
135 (1 study) 34 months	serious[1,2,3]	no serious inconsistency	no serious indirectness	serious[4]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, imprecision	EORTC QLQ-C30 and QLQ-H&N35: no statistically significant differences (p>0.05)	**-**	-	-
Adverse effects (CRITICAL OUTCOME)										
304 (3 studies) 2.8 to 5.8 years	serious[1,2]	no serious inconsistency	serious[5]	serious[6]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,5,6] due to risk of bias, indirectness, imprecision	Grade ≥2 acute toxicity 88% vs. 94% (p=0.6) Grade 3 acute toxicity 50% vs. 72% (p=0.02) Feeding tube dependency: 22% vs. 46% (p=0.02) 3y Grade ≥2 late toxicity: 30% vs. 33% (p=0.8) 3y Grade 3 late toxicity: 12% vs. 13% (p=0.8) Postoperative complications: 25% in ND group Major postoperative complications: 0 vs. 7 (18%)	**not pooled**	-	-

[1] *No blinding of participants or personnel*
[2] *No concurrent cohorts*
[3] *Baseline imbalances*
[4] *Small sample size(s); OIS not reached*
[5] *Mixed populations (various tumour locations)*
[6] *No significant differences; pooling not possible*

5.5.3. Larynx

Question: Should neck dissection vs no neck dissection be used for patients with laryngeal cancer with a clinically negative neck?

Bibliography: Goudakos 2009 (SR); Bohannon 2010; Gallo 2006; Jin 2012; Pantel 2011; Psychogios 2013

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Neck dissection versus No neck dissection	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with No neck dissection	Risk difference with Neck dissection(95% CI)
Disease-free survival (CRITICAL OUTCOME)										
>101 (8 studies) at least 3 to 5 years	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	SR: no significant differences with RT (5 studies) or with 'wait and see' policy (3 studies) 5y: ND 78.5% vs. RT 83.3% vs. Wait and see 87.3% (p=0.455)	**not pooled**	-	-
Recurrence (CRITICAL OUTCOME)										
2351 (3 studies) 10 mo to >5 years	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	Local 10.5% vs.15%; regional 7.9% vs. 15% (p=0.5) 5y local: 65/795 (8.5%) vs. 225/1448 (15.5%) (S) 5y recurrence-free survival 42.6% vs 76.9% (p=0.072)	**not pooled**	-	-
(Loco)regional control (CRITICAL OUTCOME)										
325 (2 studies) 62 months	serious[1,2]	no serious inconsistency	serious[4]	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, indirectness, imprecision	5y local-regional: Surgery 74.3% vs. RT 65.7% vs. Wait and see 74.0% (p=0.998) 5y regional: 96.0% vs 90.3% (p=0.07)	-	-	-
Overall survival (CRITICAL OUTCOME)										
>469 (5 studies) median 10 to 62 months	serious[1,2]	no serious inconsistency	serious[4]	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3,4] due to risk of bias, indirectness, imprecision	SR: ND vs RT (1 study) 5y: 55% (95% CI 31 to 79) vs 71% (95% CI 61% to 81%) (logrank = 0.4)	**not pooled**	-	-

							ND vs 'wait and see' (2 studies) 5y: 64% vs 50% (p < 0.05) and 46.4% (95% CI 29.5 to 64.2) vs 50% (95% CI 23.7 to 76.3) (RD = -3.6%, 95% CI -34.9 to +28.2) OBS 2y: 52% vs. 48% (p=0.48) "Cohort analysis of laryngeal subsites did not demonstrate a survival advantage with or without neck dissection (p=0.63)." 5y: Surgery 65.8% vs. RT 83.3% vs. Wait and see 72.4% (p=0.298) 5y: 48.0% vs 64.5% 5y: 72.4% vs. 67.4% (p=0.197); pN0 case: 74.6% vs 46.9% (p= 0.07)			
Quality of life - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Adverse effects (CRITICAL OUTCOME)										
71 (1 study) 18 and 10 months	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,5] due to risk of bias, imprecision	Complications 16/38 (42.2 %) vs. 7/33 (21.3%) (p=0.04); Death: 0 (0.0%) vs.1 (6.2%); Surgical complications: 25 (65.8%) vs. 14 (42.4%); Medical complications 3 (7.9%) vs. 1 (3.0%)	-	-	-

[1] *No blinding of participants or personnel*

[2] *No concurrent cohorts*

[3] *No significant differences; pooling not possible*

[4] *Mixed populations (various tumour locations) in one study*

[5] *Small sample size(s); OIS not reached*

b. *Neck dissection type X versus neck dissection type Y*

5.5.4. Oropharynx

Question: Should selective neck dissection vs modified radical / comprehensive neck dissection be used for patients with locally advanced (IV) oropharyngeal cancer?

Bibliography: Donatelli 2008, Hillel 2009

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Selective vs. Modified radical / Comprehensive neck dissection	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with Modified radical / comprehensive neck dissection	Risk difference with Selective neck dissection (95% CI)
Disease-free survival - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Recurrence - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Regional control (CRITICAL OUTCOME)										
48 (1 study) 39.4 months	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	3y: 100% vs. 94%	-	-	-
Overall survival (CRITICAL OUTCOME)										
48 (1 study) 39.4 months	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	3y: 95% vs. 89% (NS)	-	-	-
Quality of life (CRITICAL OUTCOME)										
38 (1 study) 1 years	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⨁⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	SF-36: no significant differences after one year, except for Mental health: 13.6 vs. -0.3 (p=0.029) HNQoL: no significant differences	-	-	-
Adverse effects (CRITICAL OUTCOME)										

48 (1 study) 39.4 months	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	2 shoulder weakness > 6 mo (8%) vs. 2 shoulder weakness > 6 mo + 2 chyle leaks (26%) Postoperative complications: p=0.15	-	-	-

[1] Baseline imbalances
[2] Lack of blinding
[3] Small samples. OIS not reached.

5.5.5. Hypopharynx

No evidence

5.5.6. Larynx

Question: Should type III modified radical neck dissection vs lateral neck dissection (levels II, III, and IV) be used for patients with resectable supraglottic or transglottic T2-T4 tumors cN0?

Bibliography: Brazilian Head and Neck Cancer Study Group 1999

Quality assessment							Summary of Findings				
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**		**Relative effect** (95% CI)	**Anticipated absolute effects**	
							With Lateral neck dissection (levels II, III, and IV)	With Type III modified radical neck dissection		Risk with Lateral neck dissection (levels II, III, and IV)	Risk difference with Type III modified radical neck dissection (95% CI)
Disease-free survival - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Recurrence rate (CRITICAL OUTCOME)											
132 (1 study) 42.9 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	15/61 (24.6%)	15/71 (21.1%)	**RR 0.86** (0.46 to 1.61)	**246 per 1000**	**34 fewer per 1000** (from 133 fewer to 150 more)
(Loco)regional control - not measured											
-	-	-	-	-	-	-	-	-	-	-	-

Overall survival (CRITICAL OUTCOME)										
132 (1 study) 42.9 months	serious[5]	no serious inconsistency	no serious indirectness	serious[2,4]	undetected	⊕⊕⊖⊖ **LOW**[2,4] due to imprecision	MRND vs LND 5y OS: 72.3% vs. 62.4% (p=0.312)		**not pooled**	-	-
Quality of life - not measured										
-	-	-	-	-	-	-	-	-	-	-	-
Adverse effects (CRITICAL OUTCOME)										
132 (1 study) 42.9 months	serious[1]	no serious inconsistency	no serious indirectness	very serious[2,3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	28/61 (45.9%)	35/71 (49.3%)	**RR 1.07** (0.75 to 1.54)	**459 per 1000**	**32 more per 1000** (from 115 fewer to 248 more)

[1] Lack of blinding
[2] OIS not reached
[3] CI includes both appreciable benefit and harm
[4] No quantification
[5] One study with poor description of methodology

Question: Should selective neck dissection with or without adjuvant RT vs modified radical neck dissection plus adjuvant RT be used for patients with moderately advanced/advanced (T3-4 N0) SCC of the larynx?

Bibliography: Dias 2009

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Selective neck dissection vs. modified radical neck dissection		Risk with Modified radical neck dissection plus adjuvant RT	Risk difference with Selective neck dissection +/-adjuvant RT (95% CI)
Disease-free survival - not measured										
-	-	-	-	-	-	-	-	-	-	-	-
Regional recurrence (CRITICAL OUTCOME)										
654 (1 study) 45 months	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3] due to risk of bias, imprecision	Regional recurrence: 3% vs. 11.7% (p=0.005) pN0 patients: 3.2% vs. 17.2% (p=0.0003) pN+ patients: 2.6% vs. 4.7% (p=0.50)	**not pooled**	-	-

(Loco)regional control (CRITICAL OUTCOME)										
654 (1 study) 45 months	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, Imprecision	5-year regional control pN0 patients 96.8% vs. 82.2% (p=0.0003) pN+ patients 97.4% vs. 95.3% (p=0.50)	**not pooled**	-	-
Overall survival - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Quality of life - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Adverse effects - not measured										
-	-	-	-	-	-	-	- -	-	-	-

[1] No blinding of participants or personnel; unclear incompleteness, concurrency and comparability
[2] Indications of selective reporting
[3] Rare event, especially for pN+; OIS not reached

Question: Should radical (1) or functional (2) neck dissection vs selective jugular node dissection (3) be used for patients with cN0 laryngeal cancer?

Bibliography: Gallo 2006

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Radical (1) or functional (2) neck dissection vs slective jugular node dissection (3)	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with Selective jugular node dissection (3)	Risk difference with Radical (1) or functional (2) neck dissection (95% CI)
Disease-free survival - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Regional recurrence (CRITICAL OUTCOME)										
759 (1 study) minimal 5 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	5y: no difference between the 3 groups (p=0.178)	**not pooled**	-	-

(Loco)regional control (CRITICAL OUTCOME)										
759 (1 study) minimal 5 years	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2] due to risk of bias, imprecision	JND (Group 3), compared to more extensive neck dissections (Group 1+2): p=0.233 Total N0+ recurrences: p=0.434 Total N0- recurrences: p=0.178 Occult lymph node metastases: 22.6% vs. 19.4% vs. 18.4%	**not pooled**	-	-
Overall survival (CRITICAL OUTCOME)										
759 (1 study) minimal 5 years	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[2,3] due to risk of bias, imprecision	Kaplan-Meier: NS (p=0.222)	**not pooled**	-	-
Quality of life - not measured										
-	-	-	-	-	-	-	- -	**-**	-	-
Adverse effects - not measured										
-	-	-	-	-	-	-	- -	**-**	-	-

[1] No blinding of participants or personnel; no concurrent cohorts; unclear baseline comparability

[2] No concurrent cohorts; unclear baseline comparability

[3] No quantification

Question: Should ipsilateral functional neck dissection (IFND) vs bilateral functional neck dissections (BFND) be used for patients with T1-T2 supraglottic squamous cell carcinoma?

Bibliography: Rodrigo 2006

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							IFND vs BFND		Risk with Bilateral functional neck dissections (BFND)	Risk difference with Ipsilateral functional neck dissection (IFND) (95% CI)
Disease-free survival - not measured										
-	-	-	-	-	-	-	- -	**-**	-	-
Regional recurrence (CRITICAL OUTCOME)										
108 (1 study) >60 months	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	undetected	⊕⊖⊖⊖ **VERY LOW**[1, 2] due to risk of bias, imprecision	17% (8/48) vs. 13% (8/60) (p =0.78)	**RR 1.25** (0.51 to 3.09)	-	-

(Loco)regional control - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Overall survival - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Quality of life - not measured											
-	-	-	-	-	-	-	-	-	-	-	-
Adverse effects - not measured											
-	-	-	-	-	-	-	-	-	-	-	-

[1] No blinding of participants, personnel or outcome assessor; no concurrent cohorts

[2] CI includes both appreciable benefit and harm; OIS not reached

5.6. RQ6: Salvage treatment versus no/other treatment

Question: Should salvage treatment vs no or other treatment be used for patients with second primaries or locoregional recurrence?

Bibliography: Kano 2013, Lim 2010, Yasumatsu 2013, Zafereo 2009

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Salvage treatment (including surgery or (chemo)radiotherapy) vs no or other treatment	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with salvage treatment (including surgery or (chemo)radiotherapy)	Risk difference with no or other treatment
Disease-free survival - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Recurrence rate - not measured										
-	-	-	-	-	-	-	- -	-	-	-
(Loco)regional control - not measured										
-	-	-	-	-	-	-	- -	-	-	-

Question: Should salvage treatment vs no or other treatment be used for patients with second primaries or locoregional recurrence?

Bibliography: Kano 2013, Lim 2010, Yasumatsu 2013, Zafereo 2009

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)** Salvage treatment (including surgery or (chemo)radiotherapy) vs no or other treatment	**Relative effect** (95% CI)	**Anticipated absolute effects** Risk with salvage treatment (including surgery or (chemo)radiotherapy)	Risk difference with no or other treatment
Overall survival (CRITICAL OUTCOME)										
313 (4 studies) 9.8 to 52 months	serious[1]	serious[2]	no serious indirectness	no serious imprecision[3]	undetected	⊕⊖⊖⊖ **VERY LOW**[1,2,3,] due to risk of bias, inconsistency	*3-year OS* Salvage surgery: 61.8% Nonsurgical treatment: 24.4% *5-year OS* Salvage surgery: 49.1% Nonsurgical treatment: 16.3% "The overall survival rate for patients treated with salvage surgery was significantly higher than that for patients treated without salvage surgery (p=0.04)." *3-year OS* Surgical salvage: 36% Nonsurgical salvage: 12% Supportive care: 0% *3-year tumour-free actuarial survival rate* Salvage surgery followed by chemotherapy and/or radiotherapy: 79% Only chemotherapy and/or radiotherapy: 0% *3-year OS*	**not pooled**	-	-

Question: Should salvage treatment vs no or other treatment be used for patients with second primaries or locoregional recurrence?

Bibliography: Kano 2013, Lim 2010, Yasumatsu 2013, Zafereo 2009

Quality assessment							Summary of Findings			
Participants (studies) Follow up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall quality of evidence**	**Study event rates (%)**	**Relative effect** (95% CI)	**Anticipated absolute effects**	
							Salvage treatment (including surgery or (chemo)radiotherapy) vs no or other treatment		Risk with salvage treatment (including surgery or (chemo)radiotherapy)	Risk difference with no or other treatment
							Salvage surgery: 48.7% (NB: in the text 42% is mentioned) Reirradiation: 31.6% Palliative chemotherapy: 3.7% Supportive care: 5.1% *5-year OS* Salvage surgery: 28% Reirradiation: 32% Palliative chemotherapy: 0% Supportive care: 0% P-values: salvage surg / reirradiation vs palliative chemotherapy or supportive care: both p<0.001			
Quality of life - not measured										
-	-	-	-	-	-	-	- -	-	-	-
Adverse events - not measured										
-	-	-	-	-	-	-	- -	-	-	-

[1] High risk of bias in all studies
[2] Different types of interventions studied
[3] No quantification of effects

5.7. RQ7: Altered fractionation radiotherapy versus standard radiotherapy

5.7.1. Hyperfractionation

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyperfractionated	Conventional	Relative (95% CI)	Absolute[7]		
Overall survival												
4	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	747	739	HR 0.78 (0.69 to 0.89)	-	⊕⊕⊕O MODERATE	CRITICAL
Locoregional control												
4	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	747	739	HR 0.77 (0.66 to 0.89)	-	⊕⊕⊕O MODERATE	CRITICAL
Disease-free survival												
2	randomised trials	serious[1,2]	no serious inconsistency	no serious indirectness	serious[3]	none	747	739	HR 0.86 (0.73 to 1.00)	-	⊕⊕OO LOW	CRITICAL
Adverse events: acute - skin, grade 3-4												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	60/589 (10.2%)	39/589 (6.6%)	RR 1.53 (1.05 to 2.24)	35 more per 1000 (from 3 more to 82 more)	⊕⊕OO LOW	CRITICAL
Adverse events: acute - mucositis, grade 3-4												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	349/751 (46.5%)	237/747 (31.7%)	RR 1.46 (1.29 to 1.65)	146 more per 1000 (from 92 more to 206 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: acute - larynx/oedema, grade 3-4												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	59/539 (10.9%)	45/541 (8.3%)	RR 1.31 (0.91 to 1.88)	26 more per 1000 (from 7 fewer to 73 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyperfractionated	Conventional	Relative (95% CI)	Absolute[7]		
Adverse events: acute - salivary glands, grade 3-4												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	1/383 (0.26%)	0/387 (0%)	RR 2.98 (0.12 to 72.31)	-	⊕OOO VERY LOW	CRITICAL
Adverse events: acute - pharynx/oesophagus, grade 3-4												
3	randomised trials	serious[2]	serious[5]	no serious indirectness	very serious[4]	none	97/539 (18%)	58/541 (10.7%)	RR 1.46 (0.76 to 2.82)	49 more per 1000 (from 26 fewer to 195 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: acute - upper GI, grade 3-4												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	4/383 (1%)	4/388 (1%)	RR 1.01 (0.28 to 3.73)	0 more per 1000 (from 7 fewer to 28 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, skin												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	13/541 (2.4%)	15/534 (2.8%)	RR 0.85 (0.41 to 1.78)	4 fewer per 1000 (from 17 fewer to 22 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, mucosa												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	35/676 (5.2%)	24/652 (3.7%)	RR 1.39 (0.84 to 2.31)	14 more per 1000 (from 6 fewer to 48 more)	⊕⊕OO LOW	CRITICAL
Adverse events: late, grade 3-4, larynx												
4	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	46/676 (6.8%)	36/652 (5.5%)	RR 1.2 (0.79 to 1.82)	11 more per 1000 (from 12 fewer to 45 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hyperfractionated	Conventional	Relative (95% CI)	Absolute[7]		
Adverse events: late, grade 3-4, pharynx/oesophagus												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	35/372 (9.4%)	29/372 (7.8%)	RR 1.21 (0.76 to 1.93)	16 more per 1000 (from 19 fewer to 72 more)	⊕⊕OO LOW	CRITICAL
Adverse events: late, grade 3-4, salivary												
3	randomised trials	serious[2]	serious[6]	no serious indirectness	very serious[4]	none	23/541 (4.3%)	25/534 (4.7%)	RR 0.85 (0.29 to 2.5)	7 fewer per 1000 (from 33 fewer to 70 more)	⊕OOO VERY LOW	CRITICAL

[1] Most studies had unclear allocation concealment.
[2] No blinding.
[3] MID included in CI in one direction.
[4] MID included in CI in both directions.
[5] I^2 70%, conflicting results.
[6] I^2 54%, conflicting results.
[7] For hazard ratios not all necessary information was available to allow a calculation of the absolute effect.

5.7.2. Accelerated fractionation without dose reduction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated (no dose reduction)	Conventional	Relative (95% CI)	Absolute[10]		
Overall survival												
10	randomised trials	no serious risk of bias	serious[1]	no serious indirectness	serious[2]	none	2706	2681	HR 0.93 (0.81 to 1.08)	-	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated (no dose reduction)	Conventional	Relative (95% CI)	Absolute[10]		
Locoregional control												
11	randomised trials	serious[3]	no serious inconsistency[4]	no serious indirectness	no serious imprecision	none	2849	2823	HR 0.76 (0.65 to 0.87)	-	⊕⊕⊕O MODERATE	CRITICAL
Disease-free survival												
5	randomised trials	serious[3]	no serious inconsistency[5]	no serious indirectness	no serious imprecision	none	1188	1175	HR 0.67 (0.51 to 0.89)	-	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: acute - confluent mucositis												
6	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	538/1751 (30.7%)	303/1739 (17.4%)	RR 1.84 (1.5 to 2.26)	146 more per 1000 (from 87 more to 220 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: acute - mucositis, grade 3-4												
6	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	316/903 (35%)	179/902 (19.8%)	RR 1.75 (1.47 to 2.09)	149 more per 1000 (from 93 more to 216 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: acute - skin, grade 3-4												
7	randomised trials	serious[3]	serious[6]	no serious indirectness	very serious[7]	none	156/1344 (11.6%)	113/1341 (8.4%)	RR 1.23 (0.77 to 1.95)	19 more per 1000 (from 19 fewer to 80 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: acute - larynx, grade 3-4												
4	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	31/668 (4.6%)	18/672 (2.7%)	RR 1.71 (0.97 to 3.01)	19 more per 1000 (from 1 fewer to 54 more)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated (no dose reduction)	Conventional	Relative (95% CI)	Absolute[10]		
Adverse events: acute - tube feeding												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[2]	none	231/441 (52.4%)	198/439 (45.1%)	RR 1.16 (1.01 to 1.33)	72 more per 1000 (from 5 more to 149 more)	⊕⊕OO LOW	CRITICAL
Adverse events: acute - salivary glands, grade 3-4												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[7]	none	1/52 (1.9%)	0/54 (0%)	RR 3.11 (0.13 to 74.74)	-	⊕OOO VERY LOW	CRITICAL
Adverse events: acute - pharynx/oesophagus, grade 3-4												
4	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	196/737 (26.6%)	90/732 (12.3%)	RR 2.16 (1.72 to 2.72)	143 more per 1000 (from 89 more to 211 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: acute - moderate/severe dysphagia												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[7]	none	3/195 (1.5%)	1/198 (0.51%)	RR 3.05 (0.32 to 29.03)	10 more per 1000 (from 3 fewer to 142 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, skin												
6	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[7]	none	17/1050 (1.6%)	18/1042 (1.7%)	RR 0.92 (0.48 to 1.76)	1 fewer per 1000 (from 9 fewer to 13 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, mucosa												
6	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	82/881 (9.3%)	35/856 (4.1%)	RR 2.24 (1.53 to 3.29)	51 more per 1000 (from 22 more to 94 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated (no dose reduction)	Conventional	Relative (95% CI)	Absolute[10]		
Adverse events: late, grade 3-4, xerostomia												
2	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	171/410 (41.7%)	178/414 (43%)	RR 0.98 (0.84 to 1.14)	9 fewer per 1000 (from 69 fewer to 60 more)	⊕⊕OO LOW	CRITICAL
Adverse events: late, moderate fibrosis												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	serious[7]	none	126/359 (35.1%)	107/366 (29.2%)	RR 1.2 (0.97 to 1.48)	58 more per 1000 (from 9 fewer to 140 more)	⊕⊕OO LOW	CRITICAL
Adverse events: late, grade 3-4, salivary glands												
1	randomised trials	serious[8]	no serious inconsistency	no serious indirectness	very serious[7]	none	4/37 (10.8%)	2/35 (5.7%)	RR 1.89 (0.37 to 9.69)	51 more per 1000 (from 36 fewer to 497 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, fibrosis												
3	randomised trials	serious[3]	very serious[9]	no serious indirectness	very serious[7]	none	33/922 (3.6%)	11/915 (1.2%)	RR 2.02 (0.18 to 22.62)	12 more per 1000 (from 10 fewer to 260 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, larynx												
6	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[7]	none	75/1039 (7.2%)	84/1033 (8.1%)	RR 0.89 (0.67 to 1.19)	9 fewer per 1000 (from 27 fewer to 15 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, spinal cord												
4	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	0/609 (0%)	0/592 (0%)	not pooled	not pooled	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: late, grade 3-4, mandibula												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[7]	none	2/51 (3.9%)	0/49 (0%)	RR 4.81 (0.24 to 97.68)	-	⊕OOO VERY LOW	CRITICAL

[1] I² 67%, conflicting results.
[2] MID included in CI in one direction.
[3] No blinding.
[4] I² 60%, mainly caused by one very positive study (CAIR). Most other studies also positive or at least trend.
[5] I² 80%, mainly caused by one very positive study (CAIR). Most other studies also positive or at least trend.
[6] I² 66%, conflicting results.
[7] MID included in CI in both directions.
[8] Unclear allocation concealment, no blinding.
[9] I² 89%, completely opposite results.
[10] For hazard ratios not all necessary information was available to allow a calculation of the absolute effect.

5.7.3. Accelerated fractionation with dose reduction

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated (dose reduction) versus conventional	Control	Relative (95% CI)	Absolute[5]		
Overall survival												
5	randomised trials	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[1]	none	1033	840	HR 0.94 (0.84 to 1.05)	-	⊕⊕⊕O MODERATE	CRITICAL
Locoregional control												
5	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	1033	840	HR 0.89 (0.77 to 1.02)	-	⊕⊕OO LOW	CRITICAL
Disease-free survival												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	757	568	HR 0.93 (0.81 to 1.07)	-	⊕⊕OO LOW	CRITICAL
Adverse events: acute - confluent mucositis												
3	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	631/827 (76.3%)	279/626 (44.6%)	RR 1.86 (1.28 to 2.72)	383 more per 1000 (from 125 more to 767 more)	⊕⊕⊕O MODERATE	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated (dose reduction) versus conventional	Control	Relative (95% CI)	Absolute[5]		
Adverse events: acute - mucositis, grade 3-4												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	142/231 (61.5%)	77/222 (34.7%)	RR 1.75 (1.45 to 2.11)	260 more per 1000 (from 156 more to 385 more)	⊕⊕⊕O MODERATE	CRITICAL
Adverse events: acute - skin, grade 3-4												
1	randomised trials	serious[3]	no serious inconsistency	no serious indirectness	very serious[4]	none	6/93 (6.5%)	7/94 (7.4%)	RR 0.87 (0.3 to 2.48)	10 fewer per 1000 (from 52 fewer to 110 more)	⊕OOO VERY LOW	CRITICAL
Adverse events: late, grade 3-4, fibrosis												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	23/109 (21.1%)	10/91 (11%)	RR 1.92 (0.96 to 3.82)	101 more per 1000 (from 4 fewer to 310 more)	⊕⊕OO LOW	CRITICAL
Adverse events: late, grade 3-4, skin												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	112/552 (20.3%)	97/366 (26.5%)	RR 0.77 (0.6 to 0.97)	61 fewer per 1000 (from 8 fewer to 106 fewer)	⊕⊕OO LOW	CRITICAL
Adverse events: late, grade 3-4, dysphagia												
1	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	140/552 (25.4%)	116/366 (31.7%)	RR 0.8 (0.65 to 0.98)	63 fewer per 1000 (from 6 fewer to 111 fewer)	⊕⊕OO LOW	CRITICAL
Adverse events: late, grade 3-4, larynx												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	214/661 (32.4%)	177/457 (38.7%)	RR 0.81 (0.69 to 0.94)	74 fewer per 1000 (from 23 fewer to 120 fewer)	⊕⊕OO LOW	CRITICAL

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Accelerated (dose reduction) versus conventional	Control	Relative (95% CI)	Absolute[5]		
Adverse events: late, grade 3-4, mucosa												
2	randomised trials	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	85/661 (12.9%)	48/457 (10.5%)	RR 1.27 (0.91 to 1.77)	28 more per 1000 (from 9 fewer to 81 more)	⊕⊕OO LOW	

[1] MID included in CI in one direction.
[2] No blinding.
[3] No blinding, unclear ITT analysis.
[4] MID included in CI in both directions.
[5] For hazard ratios not all necessary information was available to allow a calculation of the absolute effect.

6. FOREST PLOTS

6.1. RQ1: What is the effectiveness and/or diagnostic outcomes of locoregional staging (i.e. T- and N-staging) with MRI compared to CT in patients with head and neck squamous cell carcinoma

NA

6.2. RQ2: What is the clinical effectiveness of surgery for patients with early oropharyngeal, hypopharyngeal and laryngealcancer?

a. Surgery versus non-surgery

NA

b. Function-sparing surgery versus extensive surgery

NA

6.3. RQ3: Surgery versus organ / function preservation strategies

NA

6.4. RQ4: Postoperative (chemo)radiotherapy

a. Postoperative (chemo)radiotherapy versus no postoperative (chemo)radiotherapy

NA

b. Postoperative chemoradiotherapy versus postoperative radiotherapy

Figure 34 – Forest plot for 2-year overall survival for postoperative chemoradiotherapy versus postoperative radiotherapy

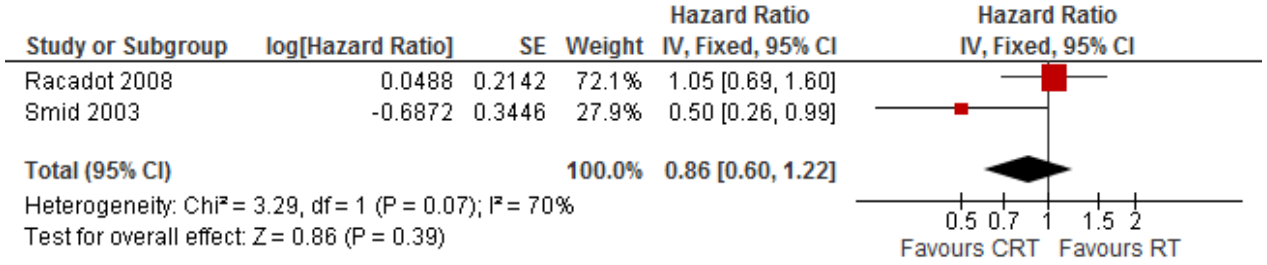
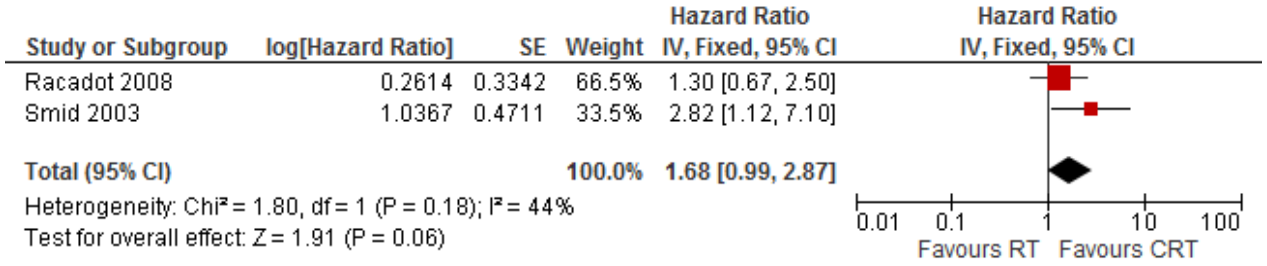


Figure 35 – Forest plot for 2-year locoregional control for postoperative chemoradiotherapy versus postoperative radiotherapy



6.5. RQ5: Management of the neck lymph nodes

a. Neck dissection versus no neck dissection

NA

b. Neck dissection type X versus neck dissection type Y

NA

6.6. RQ6: Salvage treatment versus no/other treatment

NA

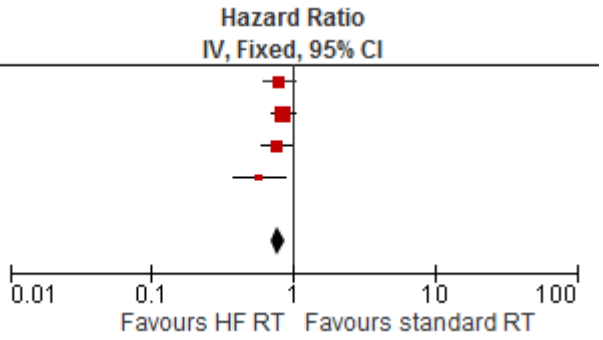
6.7. RQ7: Altered fractionation radiotherapy versus standard radiotherapy

6.7.1. Hyperfractionation

6.7.1.1. Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Cummings (PMHToronto)	-0.2357	0.1319	23.2%	0.79 [0.61, 1.02]
Fu 2000 (RTOG 9003)	-0.17	0.1	40.4%	0.84 [0.69, 1.03]
Horiot 1992 (EORTC 22791)	-0.27	0.12	28.0%	0.76 [0.60, 0.97]
Pinto 1991 (RIO)	-0.56	0.22	8.3%	0.57 [0.37, 0.88]
Total (95% CI)			**100.0%**	**0.78 [0.69, 0.89]**

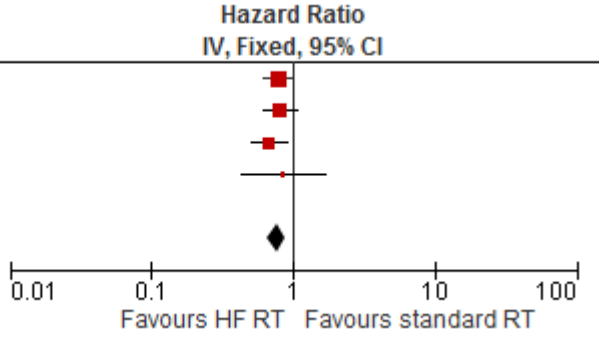
Heterogeneity: Chi² = 2.66, df = 3 (P = 0.45); I² = 0%
Test for overall effect: Z = 3.87 (P = 0.0001)



6.7.1.2. Locoregional control

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Beitler 2014 (RTOG 9003)	-0.2357	0.1236	39.5%	0.79 [0.62, 1.01]
Cummings (PMHToronto)	-0.2107	0.1447	28.8%	0.81 [0.61, 1.08]
Horiot 1992 (EORTC 22791)	-0.39	0.15	26.8%	0.68 [0.50, 0.91]
Pinto 1991 (RIO)	-0.17	0.35	4.9%	0.84 [0.42, 1.68]
Total (95% CI)			**100.0%**	**0.77 [0.66, 0.89]**

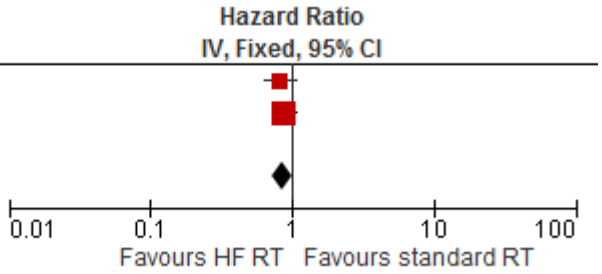
Heterogeneity: Chi² = 0.96, df = 3 (P = 0.81); I² = 0%
Test for overall effect: Z = 3.43 (P = 0.0006)



6.7.1.3. Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Cummings (PMHToronto)	-0.1985	0.1264	38.5%	0.82 [0.64, 1.05]
Fu 2000 (RTOG 9003)	-0.13	0.1	61.5%	0.88 [0.72, 1.07]
Total (95% CI)			**100.0%**	**0.86 [0.73, 1.00]**

Heterogeneity: Chi² = 0.18, df = 1 (P = 0.67); I² = 0%
Test for overall effect: Z = 1.99 (P = 0.05)

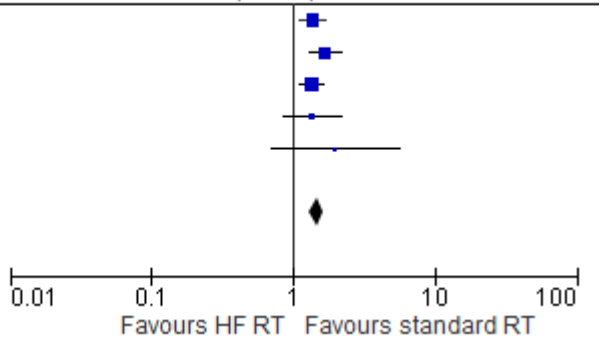


6.7.1.4. Acute toxicity

Mucositis, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cummings (PMHToronto)	97	156	70	154	29.6%	1.37 [1.11, 1.69]
Fu 2000 (RTOG 9003)	110	263	67	268	27.9%	1.67 [1.30, 2.15]
Horiot 1992 (EORTC 22791)	108	162	78	158	33.2%	1.35 [1.11, 1.64]
Pinto 1991 (RIO)	24	50	17	48	7.3%	1.36 [0.84, 2.19]
Trotti 2014 (RTOG 9512)	10	120	5	119	2.1%	1.98 [0.70, 5.63]
Total (95% CI)		**751**		**747**	**100.0%**	**1.46 [1.29, 1.65]**
Total events	349		237			

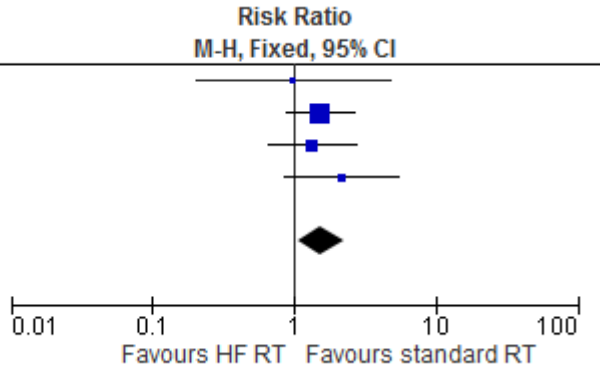
Heterogeneity: Chi² = 2.54, df = 4 (P = 0.64); I² = 0%
Test for overall effect: Z = 6.08 (P < 0.00001)



Skin, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cummings (PMHToronto)	3	156	3	154	7.7%	0.99 [0.20, 4.82]
Fu 2000 (RTOG 9003)	30	263	20	268	50.7%	1.53 [0.89, 2.62]
Pinto 1991 (RIO)	14	50	10	48	26.1%	1.34 [0.66, 2.73]
Trotti 2014 (RTOG 9512)	13	120	6	119	15.4%	2.15 [0.84, 5.46]
Total (95% CI)		**589**		**589**	**100.0%**	**1.53 [1.05, 2.24]**
Total events	60		39			

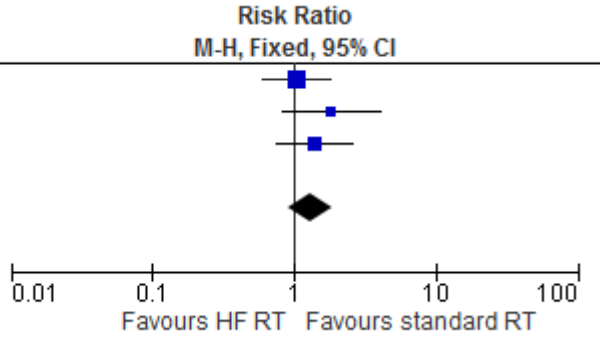
Heterogeneity: Chi² = 0.93, df = 3 (P = 0.82); I² = 0%
Test for overall effect: Z = 2.22 (P = 0.03)



Larynx / oedema, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cummings (PMHToronto)	22	156	21	154	46.8%	1.03 [0.59, 1.80]
Fu 2000 (RTOG 9003)	16	263	9	268	19.8%	1.81 [0.82, 4.03]
Trotti 2014 (RTOG 9512)	21	120	15	119	33.4%	1.39 [0.75, 2.56]
Total (95% CI)		**539**		**541**	**100.0%**	**1.31 [0.91, 1.88]**
Total events	59		45			

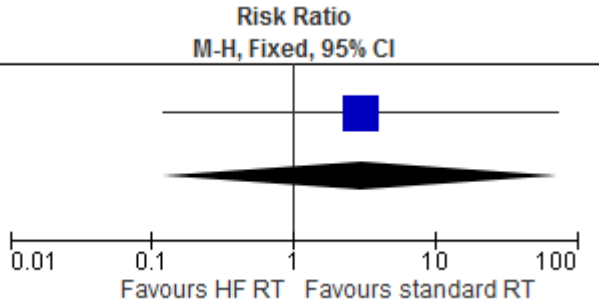
Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.44 (P = 0.15)



Salivary glands, grade 3-4

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fu 2000 (RTOG 9003)	0	263	0	268		Not estimable
Trotti 2014 (RTOG 9512)	1	120	0	119	100.0%	2.98 [0.12, 72.31]
Total (95% CI)		**383**		**387**	**100.0%**	**2.98 [0.12, 72.31]**
Total events	1		0			

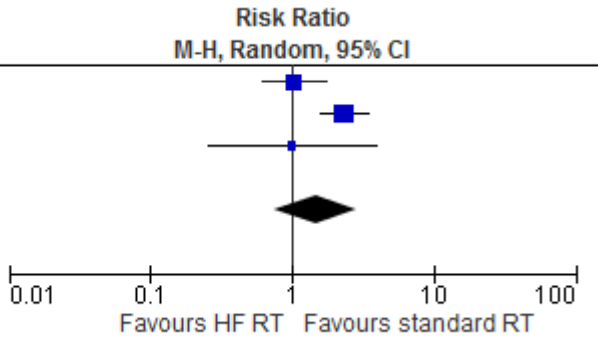
Heterogeneity: Not applicable
Test for overall effect: Z = 0.67 (P = 0.50)



Pharynx / oesophagus, grade 3-4

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Cummings (PMHToronto)	25	156	24	154	39.7%	1.03 [0.62, 1.72]
Fu 2000 (RTOG 9003)	68	263	30	268	44.1%	2.31 [1.56, 3.43]
Trotti 2014 (RTOG 9512)	4	120	4	119	16.1%	0.99 [0.25, 3.87]
Total (95% CI)		**539**		**541**	**100.0%**	**1.46 [0.76, 2.82]**
Total events	97		58			

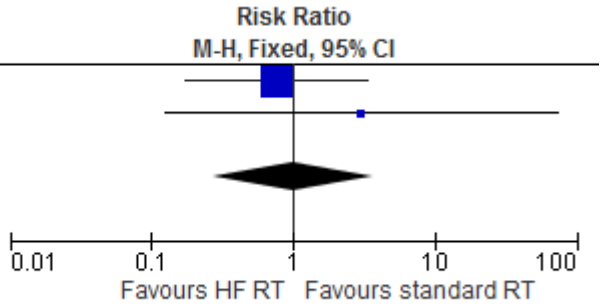
Heterogeneity: $Tau^2 = 0.21$; $Chi^2 = 6.58$, df = 2 (P = 0.04); $I^2 = 70\%$
Test for overall effect: Z = 1.13 (P = 0.26)



Upper gastrointestinal, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fu 2000 (RTOG 9003)	3	263	4	268	88.8%	0.76 [0.17, 3.38]
Trotti 2014 (RTOG 9512)	1	120	0	120	11.2%	3.00 [0.12, 72.91]
Total (95% CI)		**383**		**388**	**100.0%**	**1.01 [0.28, 3.73]**
Total events	4		4			

Heterogeneity: Chi² = 0.58, df = 1 (P = 0.45); I² = 0%
Test for overall effect: Z = 0.02 (P = 0.98)

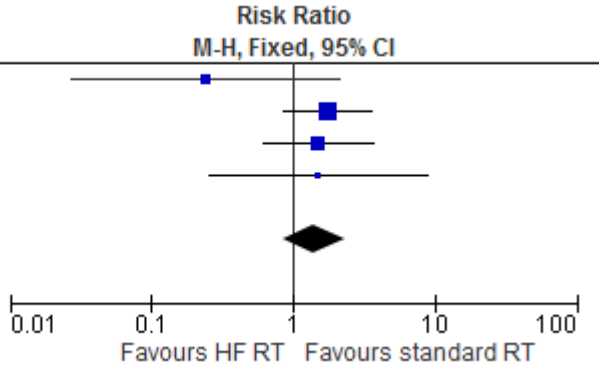


6.7.1.5. Late toxicity

Mucositis, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cummings (PMHToronto)	1	169	4	162	16.6%	0.24 [0.03, 2.12]
Fu 2000 (RTOG 9003)	19	253	11	254	44.7%	1.73 [0.84, 3.57]
Horiot 1992 (EORTC 22791)	12	135	7	118	30.4%	1.50 [0.61, 3.68]
Trotti 2014 (RTOG 9512)	3	119	2	118	8.2%	1.49 [0.25, 8.74]
Total (95% CI)		**676**		**652**	**100.0%**	**1.39 [0.84, 2.31]**
Total events	35		24			

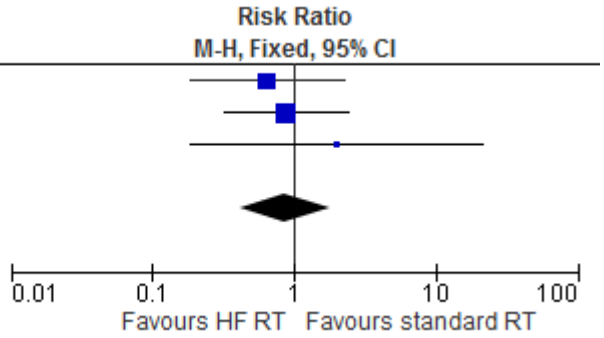
Heterogeneity: Chi² = 2.89, df = 3 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.29 (P = 0.20)



Skin, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cummings (PMHToronto)	4	169	6	162	40.5%	0.64 [0.18, 2.22]
Fu 2000 (RTOG 9003)	7	253	8	254	52.8%	0.88 [0.32, 2.39]
Trotti 2014 (RTOG 9512)	2	119	1	118	6.6%	1.98 [0.18, 21.58]
Total (95% CI)		**541**		**534**	**100.0%**	**0.85 [0.41, 1.78]**
Total events	13		15			

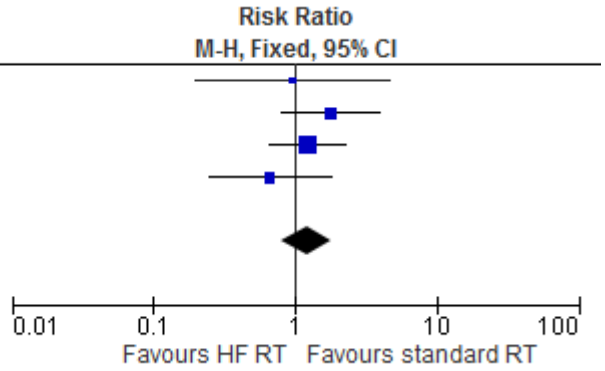
Heterogeneity: Chi² = 0.69, df = 2 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)



Larynx, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Cummings (PMHToronto)	3	169	3	162	8.3%	0.96 [0.20, 4.68]
Fu 2000 (RTOG 9003)	16	253	9	254	24.2%	1.78 [0.80, 3.96]
Horiot 1992 (EORTC 22791)	21	135	15	118	43.2%	1.22 [0.66, 2.26]
Trotti 2014 (RTOG 9512)	6	119	9	118	24.4%	0.66 [0.24, 1.80]
Total (95% CI)		**676**		**652**	**100.0%**	**1.20 [0.79, 1.82]**
Total events	46		36			

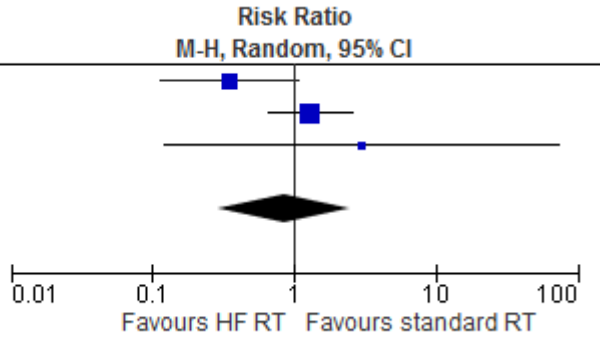
Heterogeneity: Chi² = 2.39, df = 3 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.86 (P = 0.39)



Salivary glands, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Cummings (PMHToronto)	4	169	11	162	38.3%	0.35 [0.11, 1.07]
Fu 2000 (RTOG 9003)	18	253	14	254	52.0%	1.29 [0.66, 2.54]
Trotti 2014 (RTOG 9512)	1	119	0	118	9.8%	2.98 [0.12, 72.30]
Total (95% CI)		**541**		**534**	**100.0%**	**0.85 [0.29, 2.50]**
Total events	23		25			

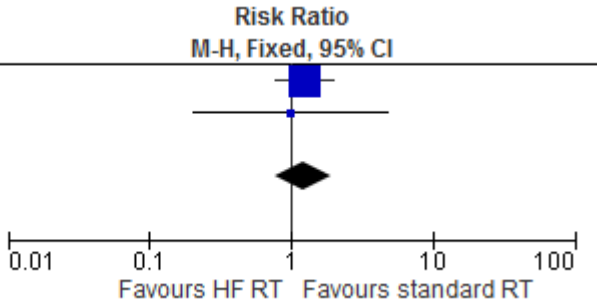
Heterogeneity: Tau² = 0.47; Chi² = 4.35, df = 2 (P = 0.11); I² = 54%
Test for overall effect: Z = 0.30 (P = 0.77)



Pharynx / oesophagus, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fu 2000 (RTOG 9003)	32	253	26	254	89.6%	1.24 [0.76, 2.01]
Trotti 2014 (RTOG 9512)	3	119	3	118	10.4%	0.99 [0.20, 4.81]
Total (95% CI)		**372**		**372**	**100.0%**	**1.21 [0.76, 1.93]**
Total events	35		29			

Heterogeneity: Chi² = 0.07, df = 1 (P = 0.79); I² = 0%
Test for overall effect: Z = 0.80 (P = 0.42)

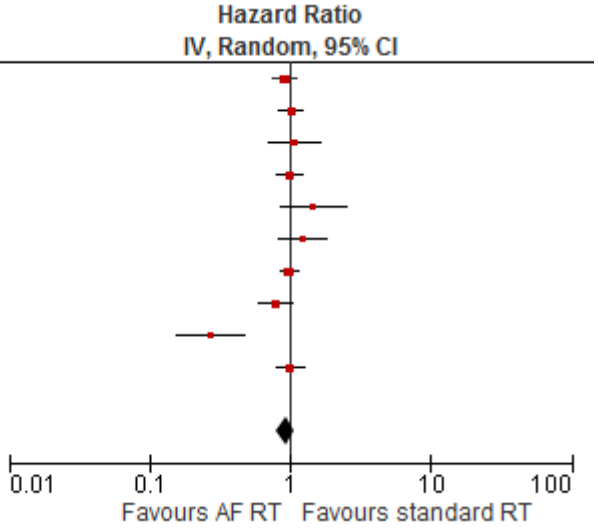


6.7.2. Accelerated fractionation without dose reduction

6.7.2.1. Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Fu 2000 (RTOG 9003)	-0.09	0.1	13.0%	0.91 [0.75, 1.11]
Fu 2000 (RTOG 9003)	0.01	0.1001	13.0%	1.01 [0.83, 1.23]
Hliniak 2002 (KBN PO 79)	0.0583	0.2191	6.8%	1.06 [0.69, 1.63]
Horiot 1997 (EORTC 22851)	-0.02	0.11	12.4%	0.98 [0.79, 1.22]
Jackson 1997 (BCCA 9113)	0.3646	0.275	5.1%	1.44 [0.84, 2.47]
Olmi 2003 (ORO 93-01)	0.2	0.2	7.6%	1.22 [0.83, 1.81]
Overgaard 2003 (DAHANCA)	-0.0202	0.0726	14.6%	0.98 [0.85, 1.13]
Overgaard 2010 (IAEA-ACC)	-0.2485	0.1424	10.4%	0.78 [0.59, 1.03]
Skladowski 2006 (CAIR)	-1.31	0.28	5.0%	0.27 [0.16, 0.47]
Zackrisson 2011 (ARTSCAN)	-0.0101	0.1144	12.1%	0.99 [0.79, 1.24]
Total (95% CI)			**100.0%**	**0.93 [0.81, 1.08]**

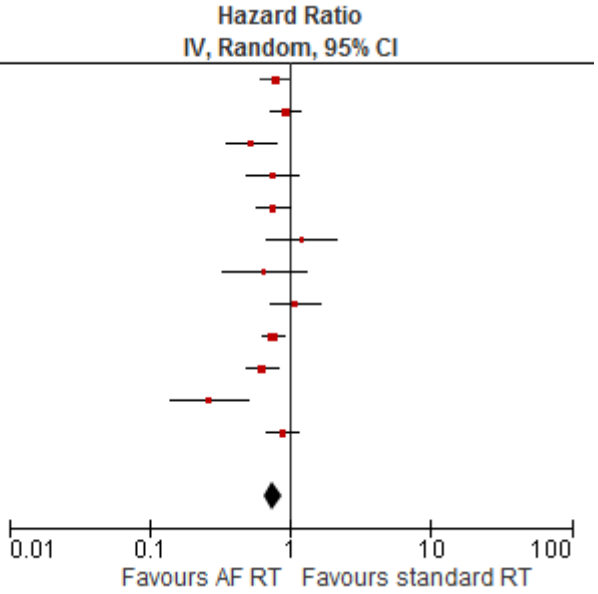
Heterogeneity: Tau² = 0.03; Chi² = 27.15, df = 9 (P = 0.001); I² = 67%
Test for overall effect: Z = 0.95 (P = 0.34)



6.7.2.2. Locoregional control

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Fu 2000 (RTOG 9003)	-0.2485	0.1171	11.6%	0.78 [0.62, 0.98]
Fu 2000 (RTOG 9003)	-0.0834	0.118	11.5%	0.92 [0.73, 1.16]
Ghoshal 2008	-0.6349	0.2117	6.8%	0.53 [0.35, 0.80]
Hliniak 2002 (KBN PO 79)	-0.2877	0.2172	6.6%	0.75 [0.49, 1.15]
Horiot 1997 (EORTC 22851)	-0.29	0.14	10.2%	0.75 [0.57, 0.98]
Jackson 1997 (BCCA 9113)	0.1906	0.294	4.4%	1.21 [0.68, 2.15]
Moon 2014 (KROG-0201)	-0.4385	0.3518	3.4%	0.65 [0.32, 1.29]
Olmi 2003 (ORO 93-01)	0.08	0.21	6.9%	1.08 [0.72, 1.63]
Overgaard 2003 (DAHANCA)	-0.2877	0.089	13.3%	0.75 [0.63, 0.89]
Overgaard 2010 (IAEA-ACC)	-0.462	0.1282	10.9%	0.63 [0.49, 0.81]
Skladowski 2006 (CAIR)	-1.33	0.32	3.9%	0.26 [0.14, 0.50]
Zackrisson 2011 (ARTSCAN)	-0.1278	0.1391	10.3%	0.88 [0.67, 1.16]
Total (95% CI)			**100.0%**	**0.75 [0.65, 0.87]**

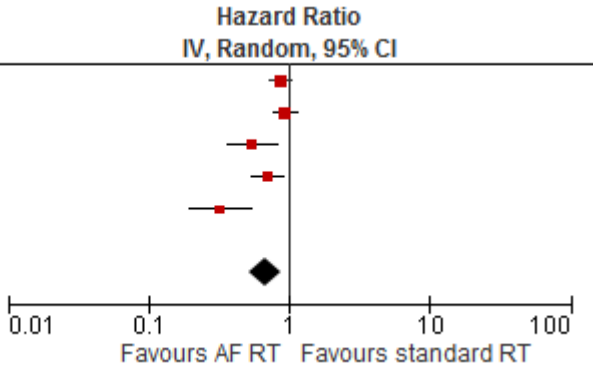
Heterogeneity: Tau² = 0.03; Chi² = 25.29, df = 11 (P = 0.008); I² = 57%
Test for overall effect: Z = 3.96 (P < 0.0001)



6.7.2.3. Disease-free survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Fu 2000 (RTOG 9003)	-0.1508	0.0978	23.8%	0.86 [0.71, 1.04]
Fu 2000 (RTOG 9003)	-0.07	0.1	23.7%	0.93 [0.77, 1.13]
Ghoshal 2008	-0.6162	0.2069	16.9%	0.54 [0.36, 0.81]
Overgaard 2010 (IAEA-ACC)	-0.3567	0.1324	21.7%	0.70 [0.54, 0.91]
Skladowski 2006 (CAIR)	-1.14	0.26	14.0%	0.32 [0.19, 0.53]
Total (95% CI)			**100.0%**	**0.67 [0.51, 0.89]**

Heterogeneity: Tau² = 0.07; Chi² = 19.77, df = 4 (P = 0.0006); I² = 80%
Test for overall effect: Z = 2.81 (P = 0.005)

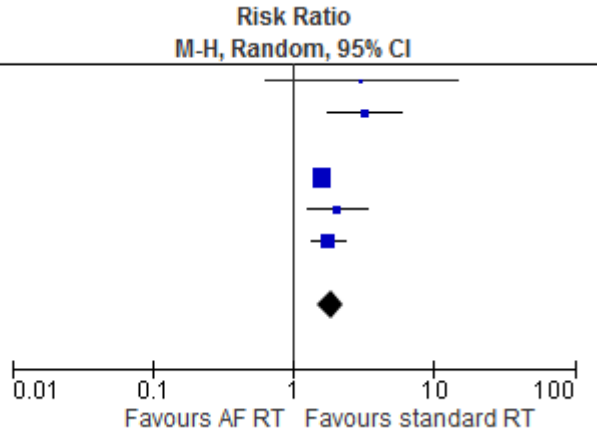


6.7.2.4. Acute toxicity

Confluent mucositis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Hliniak 2002 (KBN PO 79)	6	195	2	198	1.6%	3.05 [0.62, 14.91]
Horiot 1997 (EORTC 22851)	41	240	13	245	9.6%	3.22 [1.77, 5.85]
Moon 2014 (KROG-0201)	0	74	0	82		Not estimable
Overgaard 2003 (DAHANCA)	398	750	240	726	47.3%	1.61 [1.42, 1.82]
Overgaard 2010 (IAEA-ACC)	45	441	22	439	13.2%	2.04 [1.24, 3.33]
Skladowski 2006 (CAIR)	48	51	26	49	28.3%	1.77 [1.35, 2.33]
Total (95% CI)		**1751**		**1739**	**100.0%**	**1.84 [1.50, 2.26]**
Total events	538		303			

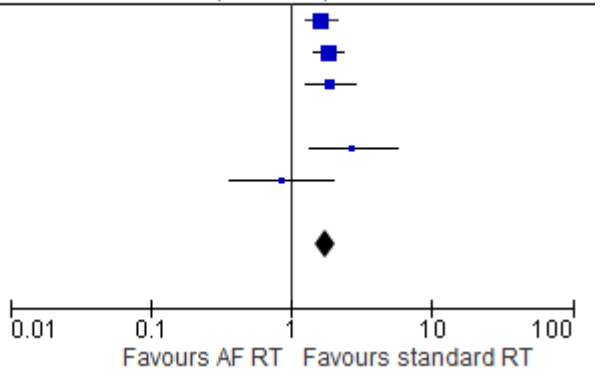
Heterogeneity: Tau² = 0.02; Chi² = 6.48, df = 4 (P = 0.17); I² = 38%
Test for overall effect: Z = 5.87 (P < 0.00001)



Mucositis, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Fu 2000 (RTOG 9003)	112	274	67	268	36.0%	1.64 [1.27, 2.10]
Fu 2000 (RTOG 9003)	123	268	67	268	37.4%	1.84 [1.44, 2.34]
Ghoshal 2008	51	143	27	142	16.7%	1.88 [1.25, 2.81]
Moon 2014 (KROG-0201)	0	74	0	82		Not estimable
Olmi 2003 (ORO 93-01)	21	52	8	54	5.8%	2.73 [1.33, 5.60]
Yamazaki 2006	9	92	10	88	4.2%	0.86 [0.37, 2.02]
Total (95% CI)		**903**		**902**	**100.0%**	**1.75 [1.47, 2.09]**
Total events	316		179			

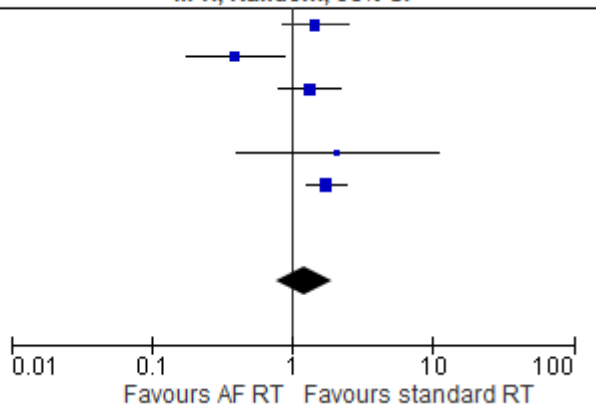
Heterogeneity: Tau² = 0.01; Chi² = 4.66, df = 4 (P = 0.32); I² = 14%
Test for overall effect: Z = 6.22 (P < 0.00001)



Skin, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Fu 2000 (RTOG 9003)	29	268	20	268	23.3%	1.45 [0.84, 2.50]
Fu 2000 (RTOG 9003)	8	274	20	268	16.9%	0.39 [0.18, 0.87]
Ghoshal 2008	28	143	21	142	24.0%	1.32 [0.79, 2.22]
Moon 2014 (KROG-0201)	0	74	0	82		Not estimable
Olmi 2003 (ORO 93-01)	4	52	2	54	6.4%	2.08 [0.40, 10.86]
Overgaard 2010 (IAEA-ACC)	87	441	50	439	29.4%	1.73 [1.26, 2.39]
Yamazaki 2006	0	92	0	88		Not estimable
Total (95% CI)		**1344**		**1341**	**100.0%**	**1.23 [0.77, 1.95]**
Total events	156		113			

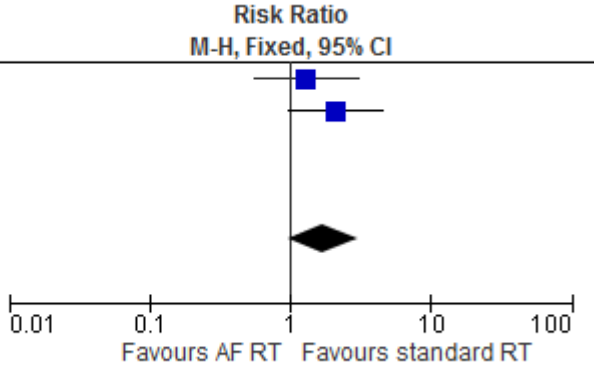
Heterogeneity: Tau² = 0.16; Chi² = 11.70, df = 4 (P = 0.02); I² = 66%
Test for overall effect: Z = 0.86 (P = 0.39)



Larynx, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fu 2000 (RTOG 9003)	12	274	9	268	50.3%	1.30 [0.56, 3.04]
Fu 2000 (RTOG 9003)	19	268	9	268	49.7%	2.11 [0.97, 4.58]
Moon 2014 (KROG-0201)	0	74	0	82		Not estimable
Olmi 2003 (ORO 93-01)	0	52	0	54		Not estimable
Total (95% CI)		**668**		**672**	**100.0%**	**1.71 [0.97, 3.01]**
Total events	31		18			

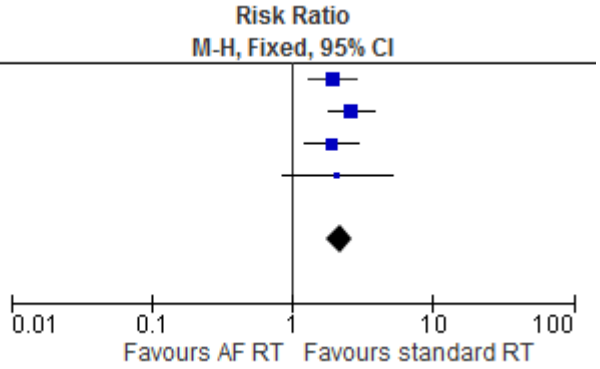
Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 1.84 (P = 0.07)



Pharynx / oesophagus, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fu 2000 (RTOG 9003)	59	274	30	268	33.6%	1.92 [1.28, 2.89]
Fu 2000 (RTOG 9003)	79	268	30	268	33.2%	2.63 [1.79, 3.87]
Ghoshal 2008	46	143	24	142	26.7%	1.90 [1.23, 2.94]
Olmi 2003 (ORO 93-01)	12	52	6	54	6.5%	2.08 [0.84, 5.12]
Total (95% CI)		**737**		**732**	**100.0%**	**2.16 [1.72, 2.72]**
Total events	196		90			

Heterogeneity: Chi² = 1.67, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 6.66 (P < 0.00001)

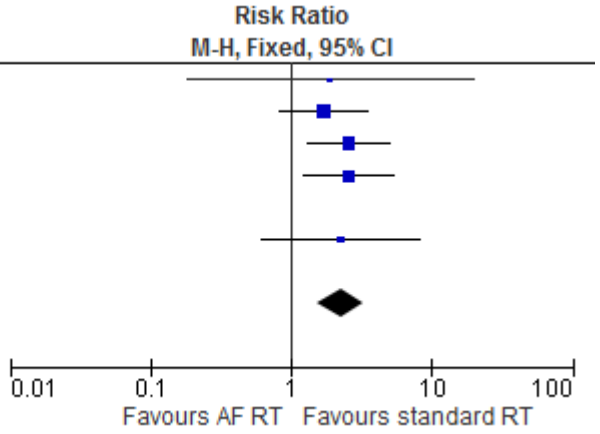


6.7.2.5. Late toxicity

Mucositis, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fallai 2006 (ORO 93-01)	2	37	1	35	2.9%	1.89 [0.18, 19.95]
Fu 2000 (RTOG 9003)	19	261	11	254	31.2%	1.68 [0.82, 3.46]
Fu 2000 (RTOG 9003)	29	261	11	254	31.2%	2.57 [1.31, 5.02]
Horiot 1997 (EORTC 22851)	25	197	9	182	26.2%	2.57 [1.23, 5.35]
Moon 2014 (KROG-0201)	0	74	0	82		Not estimable
Skladowski 2006 (CAIR)	7	51	3	49	8.6%	2.24 [0.61, 8.18]
Total (95% CI)		**881**		**856**	**100.0%**	**2.24 [1.53, 3.29]**
Total events	82		35			

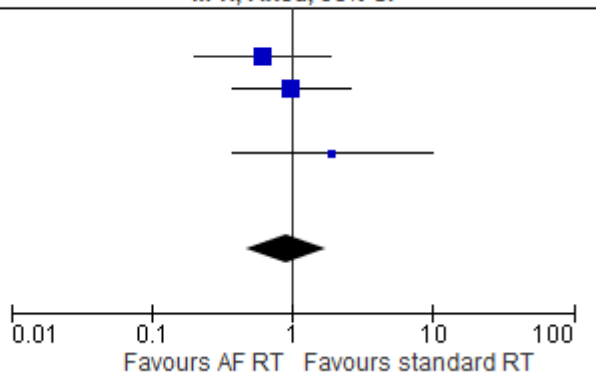
Heterogeneity: Chi² = 0.92, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 4.13 (P < 0.0001)



Skin, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fallai 2006 (ORO 93-01)	0	37	0	36		Not estimable
Fu 2000 (RTOG 9003)	5	261	8	254	44.4%	0.61 [0.20, 1.83]
Fu 2000 (RTOG 9003)	8	261	8	254	44.4%	0.97 [0.37, 2.55]
Moon 2014 (KROG-0201)	0	74	0	82		Not estimable
Skladowski 2006 (CAIR)	4	51	2	49	11.2%	1.92 [0.37, 10.02]
Zackrisson 2011 (ARTSCAN)	0	366	0	367		Not estimable
Total (95% CI)		**1050**		**1042**	**100.0%**	**0.92 [0.48, 1.76]**
Total events	17		18			

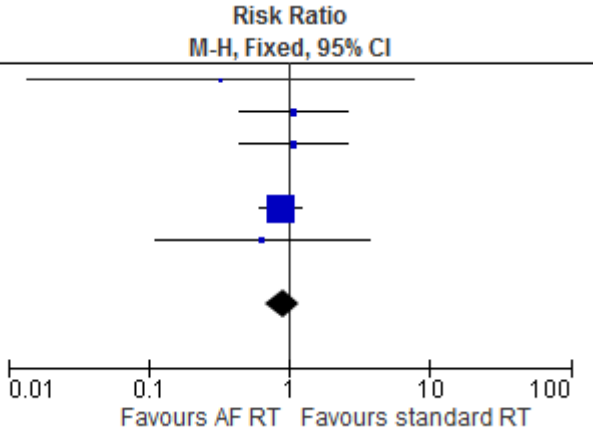
Heterogeneity: Chi² = 1.32, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 0.26 (P = 0.79)



Larynx, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Fallai 2006 (ORO 93-01)	0	36	1	35	1.8%	0.32 [0.01, 7.70]
Fu 2000 (RTOG 9003)	10	261	9	254	10.8%	1.08 [0.45, 2.62]
Fu 2000 (RTOG 9003)	10	261	9	254	10.8%	1.08 [0.45, 2.62]
Moon 2014 (KROG-0201)	0	74	0	82		Not estimable
Overgaard 2010 (IAEA-ACC)	53	356	62	359	73.0%	0.86 [0.62, 1.21]
Skladowski 2006 (CAIR)	2	51	3	49	3.6%	0.64 [0.11, 3.67]
Total (95% CI)		**1039**		**1033**	**100.0%**	**0.89 [0.67, 1.19]**
Total events	75		84			

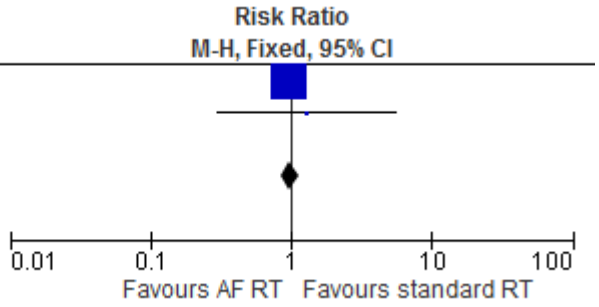
Heterogeneity: Chi² = 0.93, df = 4 (P = 0.92); I² = 0%
Test for overall effect: Z = 0.77 (P = 0.44)



Xerostomia, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Overgaard 2010 (IAEA-ACC)	167	359	175	365	98.3%	0.97 [0.83, 1.13]
Skladowski 2006 (CAIR)	4	51	3	49	1.7%	1.28 [0.30, 5.43]
Total (95% CI)		**410**		**414**	**100.0%**	**0.98 [0.84, 1.14]**
Total events	171		178			

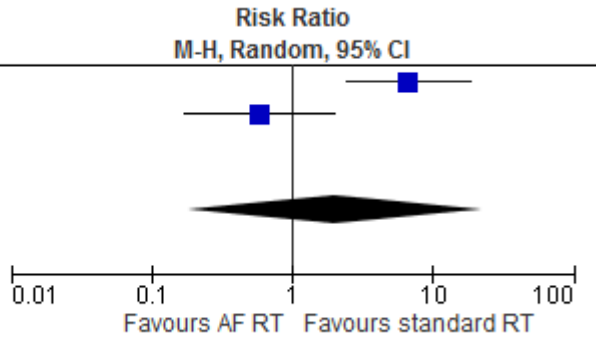
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%
Test for overall effect: Z = 0.31 (P = 0.75)



Fibrosis, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Horiot 1997 (EORTC 22851)	29	197	4	182	50.9%	6.70 [2.40, 18.68]
Overgaard 2010 (IAEA-ACC)	4	359	7	366	49.1%	0.58 [0.17, 1.97]
Zackrisson 2011 (ARTSCAN)	0	366	0	367		Not estimable
Total (95% CI)		**922**		**915**	**100.0%**	**2.02 [0.18, 22.62]**
Total events	33		11			

Heterogeneity: Tau² = 2.71; Chi² = 9.19, df = 1 (P = 0.002); I² = 89%
Test for overall effect: Z = 0.57 (P = 0.57)

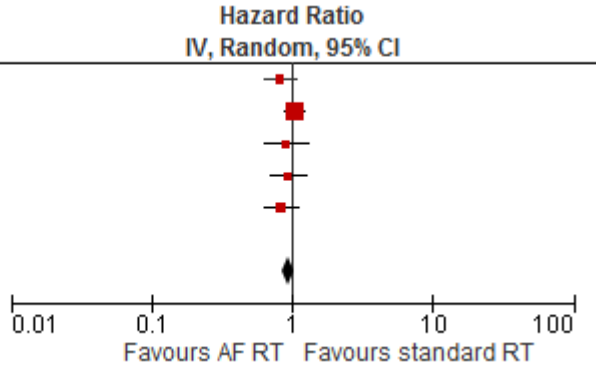


6.7.3. Accelerated fractionation with dose reduction

6.7.3.1. Overall survival

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Bourhis (GORTEC 9402)	-0.2	0.14	16.2%	0.82 [0.62, 1.08]
Dische 1997 (CHART)	0.0392	0.0852	43.7%	1.04 [0.88, 1.23]
Dobrowsky 2000 (Vienna)	-0.1	0.18	9.8%	0.90 [0.64, 1.29]
Marcial 1987 (RTOG 7913)	-0.07	0.15	14.1%	0.93 [0.69, 1.25]
Poulsen 2001 (TROG 9101)	-0.18	0.14	16.2%	0.84 [0.63, 1.10]
Total (95% CI)			**100.0%**	**0.94 [0.84, 1.05]**

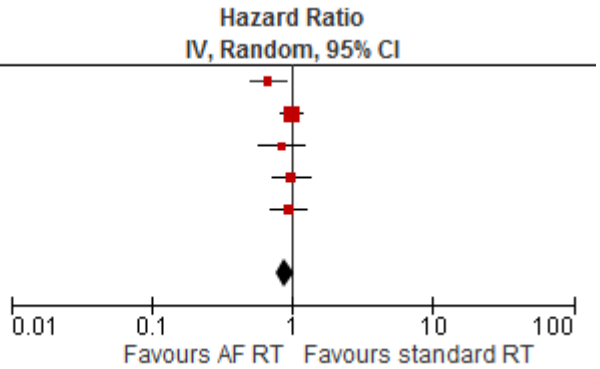
Heterogeneity: Tau² = 0.00; Chi² = 3.14, df = 4 (P = 0.53); I² = 0%
Test for overall effect: Z = 1.14 (P = 0.26)



6.7.3.2. Locoregional control

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Bourhis (GORTEC 9402)	-0.4	0.15	17.9%	0.67 [0.50, 0.90]
Dische 1997 (CHART)	-0.0202	0.0909	35.9%	0.98 [0.82, 1.17]
Dobrowsky 2000 (Vienna)	-0.17	0.19	12.1%	0.84 [0.58, 1.22]
Marcial 1987 (RTOG 7913)	-0.02	0.16	16.2%	0.98 [0.72, 1.34]
Poulsen 2001 (TROG 9101)	-0.07	0.15	17.9%	0.93 [0.69, 1.25]
Total (95% CI)			**100.0%**	**0.89 [0.77, 1.02]**

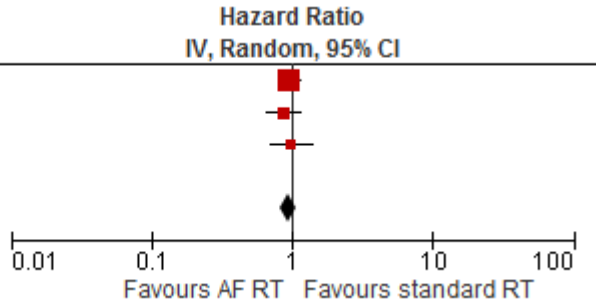
Heterogeneity: Tau² = 0.01; Chi² = 5.19, df = 4 (P = 0.27); I² = 23%
Test for overall effect: Z = 1.62 (P = 0.11)



6.7.3.3. *Disease-free survival*

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Dische 1997 (CHART)	-0.0513	0.0941	58.0%	0.95 [0.79, 1.14]
Poulsen 2001 (TROG 9101)	-0.14	0.14	26.2%	0.87 [0.66, 1.14]
Weissberg 1983	-0.02	0.18	15.8%	0.98 [0.69, 1.39]
Total (95% CI)			**100.0%**	**0.93 [0.81, 1.07]**

Heterogeneity: Tau² = 0.00; Chi² = 0.37, df = 2 (P = 0.83); I² = 0%
Test for overall effect: Z = 0.97 (P = 0.33)

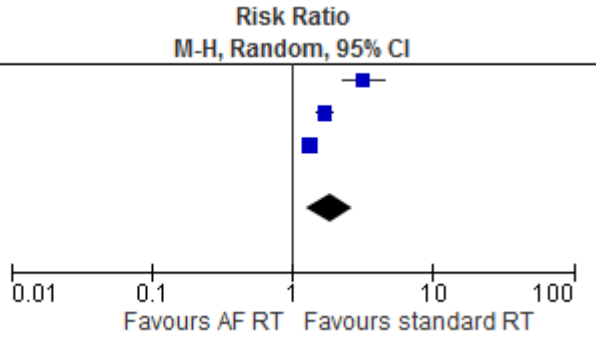


6.7.3.4. *Acute toxicity*

Confluent mucositis

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Bourhis (GORTEC 9402)	98	137	29	129	28.6%	3.18 [2.27, 4.46]
Dische 1997 (CHART)	403	552	157	366	35.6%	1.70 [1.50, 1.94]
Poulsen 2001 (TROG 9101)	130	138	93	131	35.8%	1.33 [1.18, 1.49]
Total (95% CI)		**827**		**626**	**100.0%**	**1.86 [1.28, 2.72]**
Total events	631		279			

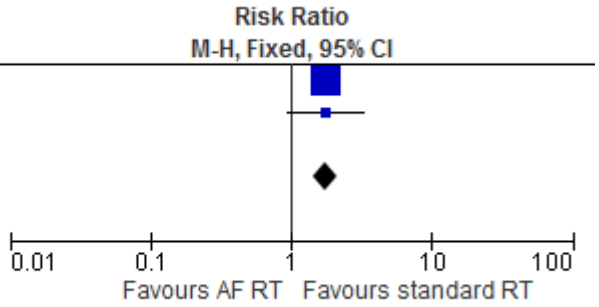
Heterogeneity: Tau² = 0.10; Chi² = 32.25, df = 2 (P < 0.00001); I² = 94%
Test for overall effect: Z = 3.22 (P = 0.001)



Mucositis, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bourhis (GORTEC 9402)	119	137	64	129	83.5%	1.75 [1.45, 2.11]
Marcial 1987 (RTOG 7913)	23	94	13	93	16.5%	1.75 [0.94, 3.24]
Total (95% CI)		**231**		**222**	**100.0%**	**1.75 [1.45, 2.11]**
Total events	142		77			

Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%
Test for overall effect: Z = 5.92 (P < 0.00001)

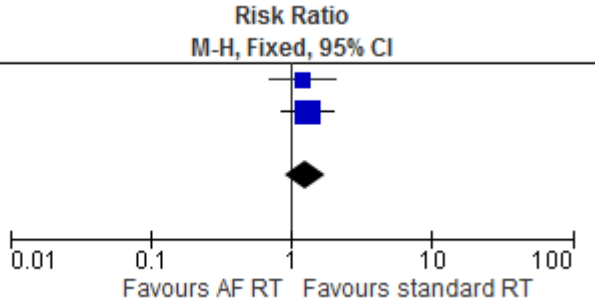


6.7.3.5. Late toxicity

Mucositis, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bourhis (GORTEC 9402)	26	109	18	91	35.2%	1.21 [0.71, 2.05]
Dische 1997 (CHART)	59	552	30	366	64.8%	1.30 [0.86, 1.98]
Total (95% CI)		**661**		**457**	**100.0%**	**1.27 [0.91, 1.77]**
Total events	85		48			

Heterogeneity: Chi² = 0.05, df = 1 (P = 0.82); I² = 0%
Test for overall effect: Z = 1.42 (P = 0.16)

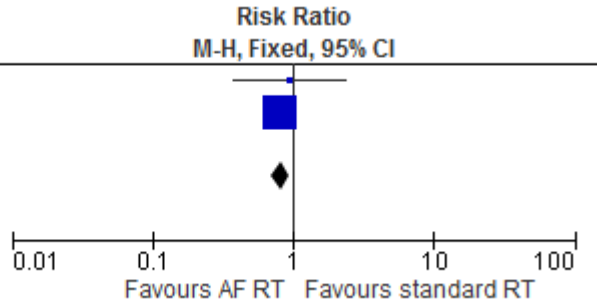


Larynx, grade 3-4

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Bourhis (GORTEC 9402)	9	109	8	91	4.1%	0.94 [0.38, 2.34]
Dische 1997 (CHART)	205	552	169	366	95.9%	0.80 [0.69, 0.94]
Total (95% CI)		**661**		**457**	**100.0%**	**0.81 [0.69, 0.94]**
Total events	214		177			

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%

Test for overall effect: Z = 2.69 (P = 0.007)



7. EXTERNAL REVIEW

7.1. Evaluation of the recommendations by the stakeholders

Item	Recommendation(s)	GDG	Comments	Comments	Min	Max	Med	Mean	N	% 4 or 5	Editorial comments	Decision (also taking into account proofreaders' comments)
Diagnosis and staging	Perform an MRI for primary T- and N-staging (i.e. before any treatment) in patients with newly diagnosed oropharyngeal cancer.	3	GDG3: MR is not needed for all oropharyngeal cancers	SH7: for N staging, please make quality/sequence recommendation to make difference with older recommendations/guidelines on the use of CT scan SH8: MRI from skull base to clavicle; if CT performed frequently no additional MR	4	5	5	4,6	5	100%	YES	In patients with newly diagnosed oropharyngeal cancer, perform an MRI for primary T- and N-staging (i.e. before any treatment). **Accepted, but quality criteria for MRI to be added to the text.**
	For patients with newly diagnosed hypopharyngeal and laryngeal cancer, MRI is the preferred technique, but its quality is more dependent on patient and radiologist factors.	3	GDG3: for many laryngeal and hypopharyngeal cancers, good quality CT gives more relevant information than	SH5: From the report, no direct evicence of superiority of MRI over CT. Should be reserved to answer to very specific questions if CT is dubious (e.g. pre-verterbral wall invasion in hypopharyngeal ca ?)	2	5	5	4,4	5	80%	YES	In patients with newly diagnosed hypopharyngeal and laryngeal cancer, MRI is the preferred technique for primary T- and N-staging, but in these locations its quality is more dependent on patient and radiologist factors. **Accepted, but quality criteria for MRI to be added to the text.**
	In case (a good) MRI is technically impossible (e.g. pacemaker, cochlear implant, claustrophobia, etc.), likely disturbed (e.g. anticipated motion artefacts, etc.) or not timely available, perform a contrast-enhanced CT for primary T- and N-staging in patients with oropharyngeal, hypopharyngeal and laryngeal cancer.	3	GDG3: if Mrscan is the preferred technique, many necks will be incompletely scanned, sinces many MR protocols do not scan from the base of skull to the thoracic inlet		5	5	5	5,0	5	100%	YES	In case (a good) MRI is technically impossible (e.g. pacemaker, cochlear implant, claustrophobia, etc.), likely to be distorted (e.g. anticipated motion artefacts, etc.), or not timely available, perform a contrast-enhanced CT for primary T- and N-staging in patients with oropharyngeal, hypopharyngeal and laryngeal cancer. **Accepted**
	In patients with stage III and IV oropharyngeal, hypopharyngeal and laryngeal cancer, and in patients with high-risk features irrespective of the locoregional staging (e.g. heavy smokers), perform a whole-body FDG-PET/CT for the evaluation of metastatic spread and/or the detection of second primary tumours.	4	GDG3: especially true for patients with important nodal involvement, lower neck nodes, Not so relevant for example for cT3N0 laryngeal cancer,which is also stage III	SH7: Is there evidence enough to state that FDG-PET/CT can replace all other examinations in the search for metastases and/or 2nd primaries? What about endoscopie for small 2nd primaries of esophagus and/or trachea? SH8: rather low treshold to use PET CT (T2N1 oropharynx? T1 heavy smoker?)	2	5	5	4,3	6	83%		**Rephrase as a 'negative' recommendation** In patients with stage I and II oropharyngeal, hypopharyngeal and laryngeal cancer and with low-risk features (e.g. no smoking), a whole-body FDG-PET/CT is not routinely recommended for the evaluation of metastatic spread and/or the detection of second primary tumours.
HPV testing	In patients with oropharyngeal cancer, p16 testing is recommended as it provides prognostic information. However, at present there is no evidence that it alters treatment decisions in these patients.	5			3	5	5	4,7	7	86%		**Accepted**
	Inclusion of p16-positive patients with oropharyngeal cancer in clinical trials should be encouraged.	5			3	5	5	4,6	7	86%		**Accepted**
	Due to insufficient evidence routine p16 testing is not recommended in patients with hypopharyngeal and laryngeal cancer.	5		SH4: If not done routinely, do we need to define when it should be done, i.e. In studies,... SH7: ... testing should be encouraged in order to objectify a possible benefit? SH8: high quality review indicates 25% prevalence	3	5	4	4,1	7	71%		**Accepted, but add to the text the justification that p16 is no prognostic factor.**

Item	Recommendation(s)	GDG	Comments	Comments	Min	Max	Med	Mean	N	% 4 or 5	Editorial comments	Decision (also taking into account proofreaders' comments)
Surgical treatment of primary non-metastatic HNSCC	The decision about treatment for early oropharyngeal, hypopharyngeal and laryngeal cancer should not only be based on efficacy, but also on the patient's general status, age, morbidity, and functionality and the tumour location.	5		SH8: leave out "surgical" from item row	5	5	5	5,0	5	100%	YES	The decision about treatment for early oropharyngeal, hypopharyngeal and laryngeal cancer should not only be based on efficacy, but also on the patient's general and functional status, age, morbidity and on the location of the tumour.
	In patients with early (stage I or II) oropharyngeal, hypopharyngeal and laryngeal cancer a single-modality function-sparing approach (e.g. surgery, external radiotherapy) should be preferred.	5		SH7: please specify that in this context a diagnostic tonsillectomie is not considered to be a surgical procedure Proof reader: what is difference between function-sparing and function preservation?	4	5	5	4,8	4	100%		**Accepted; comment not considered to be relevant**
	In patients with advanced oropharyngeal, hypopharyngeal and laryngeal cancer, organ and function preservation procedures are recommended. However, in patients with T4 laryngeal cancer, total laryngectomy should be considered.	5		SH7: However, in patients with T4a laryngeal cancer, total laryngectomy should be considered. For surgical preservation procedures patients should be referred to experienced centers/surgeons Proof reader: what is difference between function-sparing and function preservation?	3	5	5	4,6	5	80%	YES	In patients with advanced oropharyngeal, hypopharyngeal or laryngeal cancer, organ and function-sparing procedures are recommended. However, in patients with T4a laryngeal cancer, total laryngectomy should be considered. **Use 'function-sparing' everywhere.**
Radiotherapy for primary non-metastatic HNSCC	In medically fit patients with locally-advanced non-metastatic oropharyngeal, hypopharyngeal or laryngeal cancer, primary concomitant platinum-based chemoradiotherapy is recommended.	4	GDG3: difference with statement above	Proof reader: does this include stage II?	3	5	5	4,6	5	80%		**Consistently add stage in between brackets Make clear that T4a laryngeal cancer is an exception (see recommendation above)** In medically fit patients with locally-advanced **(stage III and IV)** non-metastatic oropharyngeal, hypopharyngeal or laryngeal cancer, primary concomitant platinum-based chemoradiotherapy is recommended **(except in patients with T4a laryngeal cancer)**.
	In view of the favourable benefit/risk balance, IMRT is recommended in patients with advanced oropharyngeal, hypopharyngeal or laryngeal cancer.	5			5	5	5	5,0	5	100%	YES	IMRT is recommended in patients with advanced oropharyngeal, hypopharyngeal or laryngeal cancer. **Removal of justification, as this is never given elsewhere.**
	In patients with stage II oropharyngeal, hypopharyngeal or laryngeal cancer primary radiotherapy with altered fractionation (hyperfractionation or accelerated fractionation without dose reduction) is an option.	5		SH7: … is recommended? Proof reader: change order of recommendations, e.g. keep all recommendations on locally-advanced together?	4	5	5	4,8	4	100%		**The evidence is quite strong, so it is recommended (and the strength of recommendation becomes strong).** In patients with stage II oropharyngeal, hypopharyngeal or laryngeal cancer, primary radiotherapy with altered fractionation (hyperfractionation or accelerated fractionation without dose reduction) **is recommended.**

Item	Recommendation(s)	DG	Comments	Comments	Min	Max	Med	Mean	N	% 4 or 5	Editorial comments	Decision (also taking into account proofreaders' comments)
	For patients with locally-advanced oropharyngeal, hypopharyngeal or laryngeal cancer for whom a non-surgical approach is chosen and for whom concomitant chemoradiotherapy is not an option, primary radiotherapy with hyperfractionation or accelerated fractionation without dose reduction can be considered.	5			5	5	5	5,0	4	100%	YES	In patients with locally-advanced (stage III and IV) oropharyngeal, hypopharyngeal or laryngeal cancer in whom a non-surgical approach is chosen and in whom concomitant chemoradiotherapy is not an option, primary radiotherapy with hyperfractionation or accelerated fractionation without dose reduction can be considered.
	Primary radiotherapy with accelerated fractionation with dose reduction is not recommended in patients with head and neck cancer.	5			4	5	5	4,8	5	100%		**Accepted**
	Postoperative (chemo)radiotherapy should be performed for advanced pT categories and lymph node involvement (> pN1). It should be considered for peri-neural extension or lymphatic vessels infiltration. For high-risk patients (e.g. close or positive resection margins, extracapsular spread) postoperative chemoradiotherapy is recommended.	5		SH7: (chemo)radiotherapy = can this more precise? when RT and when CRT? SH8: should be split up or first (chemo) left out Proof reader: same remark + what is definition of advanced pT?	4	5	5	4,6	5	100%	YES	**Remove '(chemo)' and replace e.g. by i.e.** Postoperative radiotherapy should be performed for advanced pT categories (T3 and T4) and lymph node involvement (> pN1). It should be considered for peri-neural extension or lymphatic vessels infiltration. In high-risk patients (i.e. close or positive resection margins, extracapsular spread) postoperative chemoradiotherapy is recommended.
	Postoperative radiotherapy should be fractionated conventionally (e.g. 60-66 Gy in 6 to 6.5 weeks, 2 Gy per day, 5 times a week).	5		SH7: Quid R2 resection? Is there a place for debulking surgery?	4	5	5	4,8	5	100%		**Accepted; comment is out of scope**
	Postoperative (chemo)radiotherapy should be commenced as early as possible, i.e. within 6 weeks after surgery, and should be completed within 12-13 weeks after surgery.	5		SH7: OTT should also be stated for radical (C)RT SH5: within 11 to 13 weeks (cfr randomized study by Ang in 2001 - I recognize limited value since it concerned RT only regimen. Though, shorter surgery + RT OTT should be the rule.	2	5	5	4,4	5	80%		**Agreement with 11-13 weeks** **As to OTT for radical (C)RT: in text it is mentioned that RT should be given without interruption. This is accepted as sufficient.** Postoperative (chemo)radiotherapy should be commenced as early as possible, i.e. within 6 weeks after surgery, and should be completed within 11-13 weeks after surgery.
	In concurrent postoperative chemoradiotherapy, radiotherapy should be fractionated conventionally (i.e. 2 Gy per fraction, 5 days per week, total dose 64-66 Gy) and chemotherapy should be platinum-based (100 mg/m² 3-weekly).	5		SH5: NB : one small study (N=50) showed the superiority of 3-we regimen over we in oral cavly (Tsan et al, Radiat Oncol 2013) - though directed to oral cavity only, should we state this ?	3	5	5	4,6	5	80%		**Accepted; comment is about oral cavity**
Induction chemotherapy	In patients with locally-advanced hypopharyngeal and laryngeal cancer, induction chemotherapy – followed by radiotherapy in responders and surgery in non-responders – is a valid option within the context of an organ-preserving treatment strategy. The preferred induction chemotherapy is TPF.	5		SH8: functional laryngeal outcome should probably be put in the balance: will be very low in the long run for advanced laryngeal cancer	4	5	4	4,3	3	100%		In patients with locally-advanced hypopharyngeal or laryngeal cancer, induction chemotherapy – followed by radiotherapy in responders and surgery in non-responders – is a valid option within the context of an function-sparing treatment strategy. The preferred induction chemotherapy is TPF (docetaxel, cisplatin and 5-fluoro-uracil). **Accepted**
	In patients with oropharyngeal cancer, the evidence is insufficient to recommend induction chemotherapy yet.	5			5	5	5	5,0	3	100%	YES	In patients with oropharyngeal cancer, the evidence is insufficient to recommend induction chemotherapy. **Accepted**

Item	Recommendation(s)	GDG	Comments	Comments	Min	Max	Med	Mean	N	% 4 or 5	Editorial comments	Decision (also taking into account proofreaders' comments)
	In strategies other than organ preservation, induction chemotherapy is not considered standard treatment.	5			5	5	5	5,0	4	100%	YES	In strategies other than function-sparing, induction chemotherapy is not recommended as a standard treatment. **Strong recommendation, so should be formulated as such.**
Management of the lymph nodes	Management of the neck lymph nodes should follow the same treatment principles as those applied for the primary tumour (e.g. if the primary tumour is surgically treated, a neck dissection should be performed).	5		SH7: and vice versa: Tu should follow LN (eg inoperable N)	4	5	5	4,7	6	100%		**Accepted**
	In patients with N0-1 oropharyngeal, hypopharyngeal and supraglottic cancer, bilateral selective neck treatment is recommended.	2	GDG3: well lateralized OP cancer does not need bilateral neck dissection	SH7: eg T1 tonsillar Tu, cfr unilateral RT for these tumors SH8: not true for tonsil unilateral or supraglottic aryepiglottic fold: not bilateral / unilateral suffices	2	5	4	3,6	5	60%		**Merge with recommendation on N2-3 cancer, and add exception for small lateralised tumours.** In patients with oropharyngeal, hypopharyngeal and laryngeal cancer, bilateral selective neck treatment is recommended. However, in small lateralised cancers, unilateral neck treatment can be considered.
	In patients with early (stage I or II) glottic cancer, neck treatment can be omitted.	4	GDG3: bulky T2 glottic tumor with important extension to the supraglottis might in rare cases need treatment of the neck	SH5: stage II strictly limited to vocal cords	2	5	5	4,4	5	80%		**Add exception of supraglottic extension.** In patients with early (stage I or II) glottic cancer, neck treatment can be omitted, with the exception of supraglottic extension.
	In patients with N2-3 oropharyngeal, hypopharyngeal and laryngeal cancer, bilateral neck treatment is recommended.	2	GDG3: well lateralized OP cancer stage N2a does not need bilateral neck treatment in all cases, some studies even suggest to omit contralat neck treatment in N2b and N3 disease	SH8: not true for tonsil unilateral or supraglottic aryepiglottic fold: not bilateral / unilateral suffices	3	5	5	4,4	5	80%	YES	**Merged**
	In node-positive patients, a diagnostic evaluation of the neck with PET/CT or MRI should be performed three months after completion of primary (chemo)radiotherapy.	2	GDG3: no proven benefit of MR over CT scan for nodal response evaluation	SH1: PET should be prefered as it shows higher NPV but not earlier than 3 month after completion	4	5	5	4,8	6	100%	YES	**DW-MRI is preferred over CT (see also below; comment on timing accepted** In node-positive patients treated with primary (chemo)radiotherapy, a diagnostic evaluation of the neck with PET/CT or DW-MRI should be performed not earlier than three months after completion of the primary therapy.
	In patients with oropharyngeal, hypopharyngeal and laryngeal cancer (N1-3) and complete response to chemoradiotherapy (assessed by FDG-PET/CT or MRI), there is no data to support an additional lymph node dissection.	4	GDG3: sugggest to add CT	SH1: PET should be prefered as it shows higher NPV. 3 month delay after completion of treatment required for high NPV	4	5	5	4,7	6	100%	YES	In patients with oropharyngeal, hypopharyngeal or laryngeal cancer (N1-3) and complete response to chemoradiotherapy (assessed by FDG-PET/CT or DW-MRI), there are no data to support an additional lymph node dissection. **Accepted**
Treatment of metastatic or recurrent disease not suitable for curative treatment	In patients with metastatic HNSCC or recurrent disease that is not eligible for curative treatment, palliative chemotherapy or targeted treatment can be considered after discussion with the patient.	5		SH7: cisplatin-5FU-Erbitux = considered standard?	4	5	5	4,8	5	100%	YES	In patients with metastatic HNSCC or recurrent disease that is not eligible for curative treatment, palliative chemotherapy or targeted therapies should be considered after discussion with the patient. **Accepted; comment is too specific**

Item	Recommendation(s)	DG	Comments	Comments	Min	Max	Med	Mean	N	% 4 or 5	Editorial comments	Decision (also taking into account proofreaders' comments)
Salvage treatment	Salvage surgery should be considered in any patient with a resectable locoregional recurrence after primary treatment with curative intent. The procedure should only be performed by an experienced surgical team.	5			4	5	5	4,8	6	100%	YES	**In patients** with a resectable locoregional recurrence after primary treatment with curative intent, **salvage surgery should be considered**. The procedure should only be performed by an experienced surgical team. *Accepted*
	Re-irradiation, possibly with curative intent, should be considered in any patient with a non-resectable locoregional recurrence after primary treatment with curative intent. Irradiation should only take place in facilities with adequate expertise.	5		SH7: with concommitant CT/BT in selected cases?	4	5	5	4,8	5	100%	YES	**In patients** with a non-resectable locoregional recurrence after primary treatment with curative intent, **re-irradiation, possibly with curative intent, should be considered**. Irradiation should only take place in facilities with adequate expertise. **Accepted; comment is too specific**

8. TNM CLASSIFICATION

8.1. cTNM Clinical classification

8.1.1. Oropharynx

Table 34 – TNM Classification of Tumours - International Union Against Cancer 7th edition

T – Primary Tumour	
T1	Tumour 2 cm or less in greatest dimension
T2	Tumour more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumour more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Tumour invades any of the following: larynx, deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), medial pterygoid, hard palate, or mandible
T4b	Tumour invades any of the following: lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, skull base; or encases carotid artery
N – Regional lymph nodes	
NX	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Mestastasis as described below: N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
M- Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

8.1.2. Hypopharynx

Table 35 – TNM Classification of Tumours - International Union Against Cancer 7th edition

T – Primary Tumour	
T1	Tumour limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumour invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension, without fixation of hemilarynx
T3	Tumour more than 4 cm in greatest dimension, or with fixation of hemilarynx or extension to oesophagus
T4a	Tumour invades any of the following: thyroid/cricoid cartilage, hyoid bone, thyroid gland, oesophagus, central compartiment soft tissue
T4b	Tumour invades prevertebral fascia, encases carotid artery, or invades mediastinal structures
N – Regional lymph nodes	
NX	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Mestastasis as described below: N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
M- Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

8.1.3. Larynx

8.1.3.1. Supraglottis

Table 36 – TNM Classification of Tumours - International Union Against Cancer 7th edition

T – Primary Tumour	
T1	Tumour limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumour invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecular, medial wall of piriform sinus) without fixation of the larynx
T3	Tumour limited to larynx with vocal cord fixation and/or invades any of the following: post-cricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Tumour invades through the thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus
T4b	Tumour invades prevertebral space, encases carotid artery, or mediastinal structures
N – Regional lymph nodes	
NX	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Mestastasis as described below: N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
M- Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

8.1.3.2. Glottis

Table 37 – TNM Classification of Tumours - International Union Against Cancer 7th edition

T – Primary Tumour	
T1	Tumour limited to vocal cord(s) (may involve anterior or posterior commissure) with normal mobility T1a: Tumour limited to one vocal cord T1b: Tumour involves both vocal cords
T2	Tumour extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumour limited to larynx with vocal cord fixation and/or invades paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Tumour invades through the outer cortex of the thyroid cartilage, and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus
T4b	Tumour invades prevertebral space, encases carotid artery, or mediastinal structures
N – Regional lymph nodes	
NX	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Mestastasis as described below: N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
M- Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

8.1.3.3. Subglottis

Table 38 – TNM Classification of Tumours - International Union Against Cancer 7th edition

T – Primary Tumour	
T1	Tumour limited to subglottis
T2	Tumour extends to vocal cord(s) with normal or impaired mobility
T3	Tumour limited to larynx with vocal cord fixation
T4a	Tumour invades crocoid or thyroid cartilage and/or invades tissues beyond the larynx, e.g., trachea, soft tissues of neck including deep/extrinsic muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), strap muscles, thyroid, oesophagus
T4b	Tumour invades prevertebral space, encases carotid artery, or mediastinal structures
N – Regional lymph nodes	
NX	Regional lymph nodes can not be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Mestastasis as described below: N2a Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension N2b Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension N2c Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension
M- Distant metastases	
M0	No distant metastasis
M1	Distant metastasis

8.2. pTNM Pathological Classification

The pT and pN categories correspond to the T and N categories.

pN0 Histological examination of a selective neck dissection specimen will ordinarily include 6 or more lymph nodes. Histological examination of a radical or modified radical neck dissection specimen will ordinarly include 10 or more lymph nodes.

If the lymph nodes are negative, but the number ordinarly examined is not met, classify as pN0.

When size is a criterion for pN classification, measurement is made of the metastasis, not of the entire lymph node.

pM1 Distant metastasis microscopically confirmed

8.3. Stage grouping

Table 39 – Staging oropharyngeal and hypopharyngeal cancer

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2, T3	N1	M0
	T3	N0	M0
Stage IVA	T4a	N0, N1, N2	M0
	T1, T2, T3	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Table 40 – Staging laryngeal cancer

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1, T2	N1	M0
	T3	N0, N1	M0
Stage IVA	T4a, T4b	N0, N1	M0
	T1, T2, T3	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1