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

ORAL CAVITY CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

APPENDIX

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APPENDIX

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Layout: Ine Verhulst

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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
Laurens Carp	Nuclear medicine, UZA
Paul Clement	Medical oncology, UZ Leuven
Philippe Deron	ENT surgery, UZ Gent
Karolien Goffin	Nuclear medicine, UZ Leuven
Marc Hamoir	ENT surgery, UCL
Esther Hauben	Pathology, UZ Leuven
Kristof Hendrickx	Maxillofacial surgery, AZ Nikolaas
Robert Hermans	Radiology, UZ Leuven
Sidney Kunz	Maxillofacial surgery, AZ Groeninge – Ziekenhuis Oost-Limburg
Olivier Lenssen	Maxillofacial surgery, ZNA
Sandra Nuyts	Radiation oncology, UZ Leuven
Carl Van Laer	ENT surgery, UZA
Jan Vermorken	Medical oncology, UZA
Eline Appermont	Speech therapist, UZ Leuven
Véronique Brogniez	Dentist, UCL
Annelies De Prins	Oncology nurse, UZ Gent
Valentine Deslangles	Speech therapist, UCL
Dominique Gihousse	Nutritional therapist, UCL

Clinicians	Field of expertise, affiliations
Eline Hebbelinck	Nutritional therapist, UZ Gent
Geert Hommez	Dentist, UZ Gent
Lieke Hoppenbrouwers	Speech therapist, AZ St. Augustinus Wilrijk
Caroline Vandenbruane	Speech therapist, AZ St. Jan Brugge
Eveline Vanhalewyck	Nutritional therapist, UZ Leuven

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
Leen Verleye	Scientific research and methodological support

1.3. External researchers involved in the guideline development

Subcontractor	Specific role
Rob Scholten	Senior clinical epidemiologist
Lotty Hooft	Senior clinical epidemiologist
Miranda Langendam	Senior clinical epidemiologist
W. Annefloor van Enst	Junior researcher
Pauline Heus	Junior researcher
Fleur T. van de Wetering	Junior researcher
Paul R. Brocklehurst	NIHR Clinician Scientist and Honorary Specialist Registrar in Dental Public Health, School of Dentistry, The University of Manchester, Manchester, UK
Charlotte L. Zuur	Oncologist and head and neck surgeon, Netherlands Cancer Institute (Antoni van Leeuwenhoek Ziekenhuis), Amsterdam, 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)	245

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)

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 other publications (systematic reviews, meta-analyses, individual studies)

2.2.1. RQ1: PET/CT in the staging of oral cavity cancer

2.2.1.1. Systematic reviews

Date	24-07-2013
Database	Medline
Search Strategy	1 deoxyglucose/ or deoxyglucose.tw. or desoxyglucose.tw. or deoxy-glucose.tw. or desoxy-glucose.tw. or deoxy-d-glucose.tw. or desoxy-d-glucose.tw. or 2deoxyglucose.tw. or 2deoxy-d-glucose.tw. or fluorodeoxyglucose.tw. or fluorodesoxyglucose.tw. or fludeoxyglucose.tw. or fluordeoxyglucose.tw. or fluordesoxyglucose.tw. or 18fluorodeoxyglucose.tw. or 18fluorodesoxyglucose.tw. or 18fluordeoxyglucose.tw. or fdg*.tw. or 18fdg*.tw. or 18f-dg*.tw. (33394) 2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (31303) 3 glucose.tw. (311106) 4 2 and 3 (5721) 5 Fluorodeoxyglucose F18/ (17971) 6 1 or 4 or 5 (36279) 7 (pet or petscan*).tw. or tomography, emission-computed/ (60832) 8 emission.tw. (89388) 9 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (225514) 10 8 and 9 (45318) 11 Positron-Emission Tomography/ (28029) 12 "Positron-Emission Tomography and Computed Tomography"/ (2530) 13 7 or 10 or 11 or 12 (84663) 14 6 and 13 (21939) 15 animals/ not humans/ (3909032) 16 14 not 15 (20807) 17 "Head and Neck Neoplasms"/ (40349) 18 exp Mouth Neoplasms/ (54216) 19 pharyngeal neoplasms/ or hypopharyngeal neoplasms/ or exp oropharyngeal neoplasms/ (13833) 20 Laryngeal Neoplasms/ (23567) 21 hnscc.mp. (3684) 22 scchn.mp. (1282)

23   (cancer* or tumo?r* or carcinoma* or neoplasm* or metastas?s or malign* or squamous cell carcinoma).tw. (2100605)
24   squamous cell carcinoma/ (102276)
25   neoplasms, squamous cell/ (1349)
26   23 or 24 or 25 (2110509)
27   (palate or palatal).tw. (29268)
28   palate/ (8781)
29   tongue*.tw. (27568)
30   tongue/ (14655)
31   ((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw. (699)
32   mouth mucosa/ (22213)
33   (mouth adj3 (bottom or floor)).tw. (2728)
34   mouth floor/ (2336)
35   uvula.tw. (1014)
36   uvula/ (1462)
37   (gingival or gum$).tw. (31167)
38   gingiva/ (14074)
39   (lip or lips).tw. (28040)
40   lip/ (8253)
41   larynx/ (13193)
42   oropharynx/ (3267)
43   hypopharynx/ (1431)
44   laryn*.tw. (62251)
45   oropharyn*.tw. (13603)
46   hypopharyn*.tw. (5591)
47   or/27-46 (214451)
48   26 and 47 (47473)
49   17 or 18 or 19 or 20 or 21 or 22 or 48 (132247)
50   16 and 49 (1119)
51   meta-analysis.mp,pt. or review.pt. or search:.tw. (2041367)
52   50 and 51 (165)
53   limit 52 to yr="2008 - 2013" (75)

Date	24-07-2013
Database	PreMedline
Search Strategy	1 deoxyglucose.tw. or desoxyglucose.tw. or deoxy-glucose.tw. or desoxy-glucose.tw. or deoxy-d-glucose.tw. or desoxy-d-glucose.tw. or 2deoxyglucose.tw. or 2deoxy-d-glucose.tw. or fluorodeoxyglucose.tw. or fluorodesoxyglucose.tw. or fludeoxyglucose.tw. or fluordeoxyglucose.tw. or fluordesoxyglucose.tw. or 18fluorodeoxyglucose.tw. or 18fluorodesoxyglucose.tw. or 18fluordeoxyglucose.tw. or fdg*.tw. or 18fdg*.tw. or 18f-dg*.tw. (1881) 2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (4138) 3 glucose.tw. (17652) 4 2 and 3 (312) 6 1 or 4 (1907) 7 (pet or petscan*).tw. (4222) 8 emission.tw. (22237) 9 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (17839) 10 8 and 9 (3083) 13 7 or 10 (5600) 14 6 and 13 (1623) 21 hnscc.mp. (263) 22 scchn.mp. (65) 23 (cancer* or tumo?r* or carcinoma* or neoplasm* or metastas?s or malign* or squamous cell carcinoma).tw. (112098) 27 (palate or palatal).tw. (2023) 29 tongue*.tw. (1866) 31 ((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw. (31) 33 (mouth adj3 (bottom or floor)).tw. (165) 35 uvula.tw. (83) 37 (gingival or gum$).tw. (2477) 39 (lip or lips).tw. (2005) 44 laryn*.tw. (3667) 45 oropharyn*.tw. (786) 46 hypopharyn*.tw. (246) 47 or/27-46 (11594) 48 23 and 47 (2439)

49   21 or 22 or 48 (2715)
50   14 and 49 (38)
51   meta-analysis.mp,pt. or review.pt. or search:.tw. (25129)
52   50 and 51 (1)
53   limit 52 to yr="2008 - 2013" (1)

Date	24-07-2013
Database	Embase
Search Strategy	#1. 'whole body pet'/exp OR 'positron emission tomography'/exp (76853)
	#2. 'head and neck cancer'/de OR 'head and neck squamous cell carcinoma'/exp OR 'lip cancer'/de OR 'mouth cancer'/de OR 'neck cancer'/de OR 'pharynx cancer'/de OR 'hypopharynx cancer'/de OR 'oropharynx cancer'/de OR 'tongue cancer'/de OR 'larynx cancer'/de OR 'larynx squamous cell carcinoma'/exp OR hnscc:ab,ti OR scchn:ab,ti (54497)
	#3. #1 AND #2 (1494)
	#4. #3. AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [2008-2014]/py (23)

Date	24-07-2013
Database	Cochrane Library (CDSR, DARE, HTA)
Search Strategy	#1 deoxyglucose or desoxyglucose or deoxy-glucose or desoxy-glucose or deoxy-d-glucose or desoxy-d-glucose or 2deoxyglucose or 2deoxy-d-glucose or fluorodeoxyglucose or fluorodesoxyglucose or fludeoxyglucose or fluordeoxyglucose or fluordesoxyglucose or 18fluorodeoxyglucose or 18fluorodesoxyglucose or 18fluordeoxyglucose or fdg* or 18fdg* or 18f-dg*
	#2 MeSH descriptor: [Deoxyglucose] 1 tree(s) exploded
	#3 fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*
	#4 glucose
	#5 #3 and #4
	#6 MeSH descriptor: [Fluorodeoxyglucose F18] explode all trees
	#7 #1 or #2 or #5 or #6
	#8 emission
	#9 tomograph or tomographs or tomographic* or tomography or tomographies
	#10 #8 and #9

#11   pet or petscan*

#12   MeSH descriptor: [Tomography, Emission-Computed] explode all trees

#13   MeSH descriptor: [Positron-Emission Tomography] explode all trees

#14   #10 or #11 or #12 or #13

#15   #7 and #14

#16   MeSH descriptor: [Head and Neck Neoplasms] this term only

#17   MeSH descriptor: [Mouth Neoplasms] explode all trees

#18   MeSH descriptor: [Pharyngeal Neoplasms] this term only

#19   MeSH descriptor: [Hypopharyngeal Neoplasms] this term only

#20   MeSH descriptor: [Oropharyngeal Neoplasms] explode all trees

#21   MeSH descriptor: [Laryngeal Neoplasms] this term only

#22   hnscc or scchn

#23   #16 or #17 or #18 or #19 or #20 or #21 or #22

#24   #15 and #23

2.2.1.2. Primary studies

Date	31-07-2013
Database	Medline
Search Strategy	1 deoxyglucose/ or deoxyglucose.tw. or desoxyglucose.tw. or deoxy-glucose.tw. or desoxy-glucose.tw. or deoxy-d-glucose.tw. or desoxy-d-glucose.tw. or 2deoxyglucose.tw. or 2deoxy-d-glucose.tw. or fluorodeoxyglucose.tw. or fluorodesoxyglucose.tw. or fludeoxyglucose.tw. or fluordeoxyglucose.tw. or fluordesoxyglucose.tw. or 18fluorodeoxyglucose.tw. or 18fluorodesoxyglucose.tw. or 18fluordeoxyglucose.tw. or fdg*.tw. or 18fdg*.tw. or 18f-dg*.tw. (33422)
	2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (31318)
	3 glucose.tw. (311314)
	4 2 and 3 (5726)
	5 Fluorodeoxyglucose F18/ (17989)
	6 1 or 4 or 5 (36308)
	7 (pet or petscan*).tw. or tomography, emission-computed/ (60876)
	8 emission.tw. (89473)
	9 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (225715)
	10 8 and 9 (45356)

11 Positron-Emission Tomography/ (28054)

12 "Positron-Emission Tomography and Computed Tomography"/ (2540)

13 7 or 10 or 11 or 12 (84737)

14 6 and 13 (21962)

15 animals/ not humans/ (3910647)

16 14 not 15 (20828)

17 "Head and Neck Neoplasms"/ (40378)

18 exp Mouth Neoplasms/ (54249)

19 pharyngeal neoplasms/ or hypopharyngeal neoplasms/ or exp oropharyngeal neoplasms/ (13839)

20 Laryngeal Neoplasms/ (23573)

21 hnscc.mp. (3692)

22 scchn.mp. (1282)

23 (cancer* or tumo?r* or carcinoma* or neoplasm* or metastas?s or malign* or squamous cell carcinoma).tw. (2102271)

24 squamous cell carcinoma/ (102337)

25 neoplasms, squamous cell/ (1352)

26 23 or 24 or 25 (2112178)

27 (palate or palatal).tw. (29295)

28 palate/ (8786)

29 tongue*.tw. (27583)

30 tongue/ (14660)

31 ((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw. (699)

32 mouth mucosa/ (22224)

33 (mouth adj3 (bottom or floor)).tw. (2728)

34 mouth floor/ (2336)

35 uvula.tw. (1016)

36 uvula/ (1462)

37 (gingival or gum$).tw. (31187)

38 gingiva/ (14084)

39 (lip or lips).tw. (28052)

40 lip/ (8257)

41 larynx/ (13198)

42 oropharynx/ (3271)

43   hypopharynx/ (1431)
44   laryn*.tw. (62284)
45   oropharyn*.tw. (13619)
46   hypopharyn*.tw. (5591)
47   or/27-46 (214582)
48   26 and 47 (47505)
49   17 or 18 or 19 or 20 or 21 or 22 or 48 (132330)
50   16 and 49 (1119)
54   limit 50 to yr="2009 - 2013" (467)

Date	31-07-2013
Database	PreMedline
Search Strategy	1 deoxyglucose.tw. or desoxyglucose.tw. or deoxy-glucose.tw. or desoxy-glucose.tw. or deoxy-d-glucose.tw. or desoxy-d-glucose.tw. or 2deoxyglucose.tw. or 2deoxy-d-glucose.tw. or fluorodeoxyglucose.tw. or fluorodesoxyglucose.tw. or fludeoxyglucose.tw. or fluordeoxyglucose.tw. or fluordesoxyglucose.tw. or 18fluorodeoxyglucose.tw. or 18fluorodesoxyglucose.tw. or 18fluordeoxyglucose.tw. or fdg*.tw. or 18fdg*.tw. or 18f-dg*.tw. (1897) 2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (4161) 3 glucose.tw. (17798) 4 2 and 3 (315) 6 1 or 4 (1924) 7 (pet or petscan*).tw. (4257) 8 emission.tw. (22321) 9 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (17992) 10 8 and 9 (3114) 13 7 or 10 (5650) 14 6 and 13 (1647) 21 hnscc.mp. (268) 22 scchn.mp. (65) 23 (cancer* or tumo?r* or carcinoma* or neoplasm* or metastas?s or malign* or squamous cell carcinoma).tw. (112380) 27 (palate or palatal).tw. (2021) 29 tongue*.tw. (1874)

31   ((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw. (30)
33   (mouth adj3 (bottom or floor)).tw. (164)
35   uvula.tw. (83)
37   (gingival or gum$).tw. (2482)
39   (lip or lips).tw. (2018)
44   laryn*.tw. (3648)
45   oropharyn*.tw. (787)
46   hypopharyn*.tw. (251)
47   or/27-46 (11613)
48   23 and 47 (2458)
49   21 or 22 or 48 (2737)
50   14 and 49 (39)
54   limit 50 to yr="2009 - 2013" (38)

Date	31-07-2013
Database	Embase
Search Strategy	#1. 'whole body pet'/exp OR 'positron emission tomography'/exp AND ('head and neck cancer'/de OR 'head and neck squamous cell carcinoma'/exp OR 'lip cancer'/de OR 'mouth cancer'/de OR 'neck cancer'/de OR 'pharynx cancer'/de OR 'hypopharynx cancer'/de OR 'oropharynx cancer'/de OR 'tongue cancer'/de OR 'larynx cancer'/de OR 'larynx squamous cell carcinoma'/exp OR hnscc:ab,ti OR scchn:ab,ti) (1495) #2. #1 AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND [2009-2014]/py (558)

Date	31-07-2013
Database	CENTRAL
Search Strategy	#1 deoxyglucose or desoxyglucose or deoxy-glucose or desoxy-glucose or deoxy-d-glucose or desoxy-d-glucose or 2deoxyglucose or 2deoxy-d-glucose or fluorodeoxyglucose or fluorodesoxyglucose or fludeoxyglucose or fluordeoxyglucose or fluordesoxyglucose or 18fluorodeoxyglucose or 18fluorodesoxyglucose or 18fluordeoxyglucose or fdg* or 18fdg* or 18f-dg* #2 MeSH descriptor: [Deoxyglucose] 1 tree(s) exploded #3 fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu* #4 glucose

#5	#3 and #4
#6	MeSH descriptor: [Fluorodeoxyglucose F18] explode all trees
#7	#1 or #2 or #5 or #6
#8	emission
#9	tomograph or tomographs or tomographic* or tomography or tomographies
#10	#8 and #9
#11	pet or petscan*
#12	MeSH descriptor: [Tomography, Emission-Computed] explode all trees
#13	MeSH descriptor: [Positron-Emission Tomography] explode all trees
#14	#10 or #11 or #12 or #13
#15	#7 and #14
#16	MeSH descriptor: [Head and Neck Neoplasms] this term only
#17	MeSH descriptor: [Mouth Neoplasms] explode all trees
#18	MeSH descriptor: [Pharyngeal Neoplasms] this term only
#19	MeSH descriptor: [Hypopharyngeal Neoplasms] this term only
#20	MeSH descriptor: [Oropharyngeal Neoplasms] explode all trees
#21	MeSH descriptor: [Laryngeal Neoplasms] this term only
#22	hnscc or scchn
#23	#16 or #17 or #18 or #19 or #20 or #21 or #22
#24	#15 and #23

2.2.2. RQ2: HPV testing in patients with oral cavity cancer

Date	07-01-2014
Database	Medline
Search Strategy	1 exp "Head and Neck Neoplasms"/ (240938)
	2 exp Carcinoma, Squamous Cell/ (104981)
	3 HNSCC.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] (3877)
	4 cancer?.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] (1068557)
	5 carcinoma?.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] (617716)
	6 neoplasm?.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] (2157655)
	7 tumo?r?.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] (1444050)
	8 malignan$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (394512)
	9 4 or 5 or 6 or 7 or 8 (2848588)
	10 (oropharyngeal adj2 (cancer? or carcinoma? or neoplasm? or tumo?r? or malignan$)).mp. (4291)
	11 (pharyngeal adj2 (cancer? or carcinoma? or neoplasm? or tumo?r? or malignan$)).mp. (7570)
	12 (laryngeal adj2 (cancer? or carcinoma? or neoplasm? or tumo?r? or malignan$)).mp. (24936)
	13 (hypopharyngeal adj2 (cancer? or carcinoma? or neoplasm? or tumo?r? or malignan$)).mp. (2788)
	14 (oral cavity adj2 (cancer? or carcinoma? or neoplasm? or tumo?r? or malignan$)).mp. (1303)
	15 10 or 11 or 12 or 13 or 14 (35503)
	16 1 and 2 (53675)
	17 exp Oropharynx/ (11475)
	18 exp Larynx/ (30443)
	19 exp Hypopharynx/ (1549)
	20 exp Mouth/ (235094)

21	17 or 18 or 19 or 20 (275531)
22	16 and 21 (6442)
23	3 or 15 or 22 (42714)
24	HPV.tw. (24709)
25	human papillomavirus.tw. (21546)
26	papillomavirus.tw. (23848)
27	24 or 25 or 26 (31898)
28	immunohistochemistry.mp,tw. (320899)
29	p16.mp,tw. (13012)
30	PCR.mp,tw. (331342)
31	polymerase chain reaction.mp,tw. (460083)
32	(polymerase adj2 chain adj2 reaction).mp,tw. (460108)
33	exp In Situ Hybridization/ (87733)
34	(in adj2 situ adj2 hybridization).mp,tw. (119461)
35	$ISH.mp,tw. (3785)
36	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (936648)
37	23 and 27 and 36 (785)
38	37 (785)
39	limit 37 to yr="2013 - 2014" (57)

Date	08-01-2014
Database	Embase
Search Strategy	hnscc OR oropharyngeal NEAR/2 (cancer* OR carcinoma* OR neoplasm* OR tumo*r OR malignan*) OR laryngeal NEAR/2 (cancer* OR carcinoma* OR neoplasm* OR tumo*r OR malignan*) OR pharyngeal NEAR/2 (cancer* OR carcinoma* OR neoplasm* OR tumo*r OR malignan*) OR hypopharyngeal NEAR/2 (cancer* OR carcinoma* OR neoplasm* OR tumo*r OR malignan*) OR ('larynx'/exp OR 'hypopharynx'/exp OR 'oropharynx'/exp OR 'mouth cavity'/exp AND 'head and neck cancer'/exp AND 'squamous cell carcinoma'/exp) AND ('p16' OR immunohistochemistry OR 'polymerase chain reaction' OR pcr OR 'polymerase chain reaction'/exp OR 'in situ hybridization'/exp OR 'in situ hybridization' OR fish) AND (hpv OR papillomavirus OR 'alphapapillomavirus'/exp OR 'wart virus'/exp) AND (2013:py OR 2014:py)

2.2.3. RQ3: elective lymph node dissection for patients with cN0 oral cavity cancer

2.2.3.1. Systematic reviews

Date	31-07-2013
Database	Medline
Search Strategy (attention, for PubMed, check « Details »)	1. ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	2. (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	3. (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	4. scchn.ti,ab.
	5. hnscc.ti,ab.
	6. exp "Head and Neck Neoplasms"/
	7. 1 or 2 or 3 or 4 or 5 or 6
	8. (lymph adj3 (excision or extirpation or resection or dissection)).ti,ab.
	9. lymph?adectomy.ti,ab.
	10. (neck adj2 dissection).ti,ab.
	11. exp Lymph Node Excision/
	12. 8 or 9 or 10 or 11
	13. 7 and 12
	14. MEDLINE.tw.
	15. systematic review.tw.
	16. exp Meta-Analysis/
	17. (search* adj12 (literature or database?)).ti,ab.
	18. intervention$.ti.
	19. 14 or 15 or 16 or 17 or 18
	20. 13 and 19
	21. limit 20 to ed=20080101-20130801
Note	Also applied for question 4

Date	31-07-2013
Database	Embase
Search Strategy	1. exp "head and neck tumor"/
	2. hnscc.ti,ab.
	3. scchn.ti,ab.
	4. (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	5. (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	6. ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	7. or/1-6
	8. lymph node dissection/
	9. (lymph adj3 (excision or extirpation or resection or dissection)).ti,ab.
	10. lymph?adectomy.ti,ab.
	11. neck dissection/
	12. (neck adj2 dissection).ti,ab.
	13. or/8-12
	14. MEDLINE.tw.
	15. exp systematic review/ or systematic review.tw.
	16. meta-analysis/
	17. (search* adj12 (literature or database?)).ti,ab.
	18. or/14-17
	19. 7 and 13 and 18
	limit 19 to dd=20080101-20130801
Note	Also applied for question 4

Date	31-07-2013
Database	Cochrane Library: Cochrane database of Systematic Reviews
Search Strategy	#1 MeSH descriptor: [Otorhinolaryngologic Neoplasms] explode all trees
	#2 hnscc:ti,ab
	#3 scchn:ti,ab
	#4 (((upper near/1 aerodigestive near/1 tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab
	#5 (ent near/4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab
	#6 MeSH descriptor: [Head and Neck Neoplasms] explode all trees
	#7 ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab
	#8 #1 or #2 or #3 or #4 or #5 or #6 or #7
	#9 (lymph next/3 (excision or extirpation or resection or dissection)):ti,ab
	#10 MeSH descriptor: [Lymph Node Excision] explode all trees
	#11 (neck next/2 dissection):ti,ab
	#12 #9 or #10 or #11
	#13 #8 and #12
Note	Also applied for question 4

2.2.3.2. RCTs and observational studies

Date	07-08-2013
Database	Medline
Search Strategy (attention, for PubMed, check « Details »)	1. "Head and Neck Neoplasms"/ 2. "Mouth Neoplasms"/ 3. "Gingival Neoplasms"/ 4. "Palatal Neoplasms"/ 5. "Tongue Neoplasms"/ 6. ((cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or metatasta$) adj5 (oral$ or intra-oral$ or intraoral$ or "intra oral$" or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek$ or gum$ or palatal$ or palate$ or "head and neck")).mp. 7. or/1-6 8. exp Surgical Procedures, Operative/ 9. (dissect$ adj2 neck$).ti,ab. 10. (excision or excise or resect$).ti,ab. 11. Lymph Node Excision/ 12. (lymphadenectom$ or glossectom$).ti,ab. 13. randomized controlled trial.pt. 14. controlled clinical trial.pt. 15. randomized.ab. 16. placebo.ab. 17. drug therapy.fs. 18. randomly.ab. 19. trial.ab. 20. groups.ab. 21. or/13-20 22. exp animals/ not humans.sh. 23. 21 not 22

24.	Epidemiologic studies/
25.	exp case control studies/
26.	exp cohort studies/
27.	Case control.tw.
28.	(cohort adj (study or studies)).tw.
29.	Cohort analy$.tw.
30.	(Follow up adj (study or studies)).tw.
31.	(observational adj (study or studies)).tw.
32.	Longitudinal.tw.
33.	Retrospective.tw.
34.	Cross sectional.tw.
35.	Cross-sectional studies/
36.	or/24-35
37.	8 or 9 or 10 or 11 or 12
38.	7 and 37
39.	23 and 38
40.	limit 39 to ed=20110101-20130901
41.	36 and 38
42.	41 not 22
43.	limit 42 to ed=20110101-20130901
44.	40 or 43
Note	Search strategy from Bessel et al 2011
	Also applied for question 4

Date	07-08-2013
Database	Embase
Search Strategy	1 "head and neck cancer"/
	2 "Mouth Cancer"/
	3 "gingiva tumor"/
	4 "jaw tumor"/
	5 "Tongue tumor"/
	6 ((cancer$ or tumour$ or tumor$ or neoplas$ or malignan$ or carcinoma$ or metatasta$) adj5 (oral$ or intra-oral$ or intraoral$ or "intra oral$" or gingiva$ or oropharyn$ or mouth$ or tongue$ or cheek$ or gum$ or palatal$ or palate$ or "head and neck")).mp.
	7 or/1-6
	8 exp Surgical technique/
	9 (dissect$ adj2 neck$).ti,ab.
	10 (excision or excise or resect$).ti,ab.
	11 Lymph Node dissection/
	12 (lymphadenectom$ or glossectom$).ti,ab.
	13 crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/
	14 crossover$.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.
	15 Clinical study/
	16 Case control study
	17 Family study/
	18 Longitudinal study/
	19 Retrospective study/
	20 Prospective study/
	21 Randomized controlled trials/
	22 20 not 21
	23 Cohort analysis/
	24 (Cohort adj (study or studies)).mp.

	25	(Case control adj (study or studies)).tw.
	26	(follow up adj (study or studies)).tw.
	27	(observational adj (study or studies)).tw.
	28	(epidemiologic$ adj (study or studies)).tw.
	29	(cross sectional adj (study or studies)).tw.
	30	0r/13-19,22-29
	31	exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
	32	human/ or normal human/ or human cell/
	33	31 and 32
	34	31 not 33
	35	or/8-12
	36	7 and 30 and 35
	37	36 not 34
	38	limit 37 to dd=20110101-20130901
Note		Search strategy from Bessel et al 2011
		Also applied for question 4

Date	**07-08-2013**	
Database	Cochrane Library: Trials	
Search Strategy	1	MeSH descriptor Head and Neck Neoplasms this term only
	2	MeSH descriptor Mouth neoplasms this term only
	3	MeSH descriptor Gingival Neoplasms this term only
	4	MeSH descriptor Palatal neoplasms this term only
	5	MeSH descriptor Tongue neoplasms this term only
	6	((cancer* near/5 oral*) or (cancer* near/5 intra-oral*) or (cancer* near/5 intraoral*) or (cancer* near/5 "intra) and oral"*) or (cancer* near/5 gingiva*) or (cancer* near/5 oropharyn*) or (cancer* near/5 mouth*) or (cancer* near/5 tongue*) or (cancer* near/5 cheek*) or (cancer* near/5 gum*) or (cancer* near/5 palatal*) or (cancer* near/5 palate*) or (cancer* near/5 "head and neck"))
	7	((tumour* near/5 oral*) or (tumour* near/5 intra-oral*) or (tumour* near/5 intraoral*) or (tumour* near/5 "intra) and oral"*) or

(tumour* near/5 gingiva*) or (tumour* near/5 oropharyn*) or (tumour* near/5 mouth*) or (tumour* near/5 tongue*) or (tumour* near/5 cheek*) or (tumour* near/5 gum*) or (tumour* near/5 palatal*) or (tumour* near/5 palate*) or (tumour* near/5 "head and neck"))

8   ((tumor* near/5 oral*) or (tumor* near/5 intra-oral*) or (tumor* near/5 intraoral*) or (tumor* near/5 "intra) and oral"*) or (tumor* near/5 gingiva*) or (tumor* near/5 oropharyn*) or (tumor* near/5 mouth*) or (tumor* near/5 tongue*) or (tumor* near/5 cheek*) or (tumor* near/5 gum*) or (tumor* near/5 palatal*) or (tumor* near/5 palate*) or (tumor* near/5 "head and neck"))

9   ((neoplas* near/5 oral*) or (neoplas* near/5 intra-oral*) or (neoplas* near/5 intraoral*) or (neoplas* near/5 "intra) and oral"*) or (neoplas* near/5 gingiva*) or (neoplas* near/5 oropharyn*) or (neoplas* near/5 mouth*) or (neoplas* near/5 tongue*) or (neoplas* near/5 cheek*) or (neoplas* near/5 gum*) or (neoplas* near/5 palatal*) or (neoplas* near/5 palate*) or (neoplas* near/5 "head and neck"))

10   ((malignan* near/5 oral*) or (malignan* near/5 intra-oral*) or (malignan* near/5 intraoral*) or (malignan* near/5 "intra) and oral"*) or (malignan* near/5 gingiva*) or (malignan* near/5 oropharyn*) or (malignan* near/5 mouth*) or (malignan* near/5 tongue*) or (malignan* near/5 cheek*) or (malignan* near/5 gum*) or (malignan* near/5 palatal*) or (malignan* near/5 palate*) or (malignan* near/5 "head and neck"))

11   ((carcinoma* near/5 oral*) or (carcinoma* near/5 intra-oral*) or (carcinoma* near/5 intraoral*) or (carcinoma* near/5 "intra) and oral"*) or (carcinoma* near/5 gingiva*) or (carcinoma* near/5 oropharyn*) or (carcinoma* near/5 mouth*) or (carcinoma* near/5 tongue*) or (carcinoma* near/5 cheek*) or (carcinoma* near/5 gum*) or (carcinoma* near/5 palatal*) or (carcinoma* near/5 palate*) or (carcinoma* near/5 "head and neck"))

12   ((metatasta* near/5 oral*) or (metatasta* near/5 intra-oral*) or (metatasta* near/5 intraoral*) or (metatasta* near/5 "intra) and oral"*) or (metatasta* near/5 gingiva*) or (metatasta* near/5 oropharyn*) or (metatasta* near/5 mouth*) or (metatasta* near/5 tongue*) or (metatasta* near/5 cheek*) or (metatasta* near/5 gum*) or (metatasta* near/5 palatal*) or (metatasta* near/5 palate*) or (metatasta* near/5 "head and neck"))

13   (1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12)

14   MeSH descriptor Surgical Procedures, Operative explode all trees

15   (dissect* near/2 neck*)

16   (excision or excise* or resect*)

17   MeSH descriptor Lymph node excision this term only

18   (lymphadenectom* or glossectom*)

19   (14 or 15 or 16 or 17 or 18)

20   (13 and 19)

Note	Limit to 2011-2013
	Search strategy from Bessel et al 2011
	Also applied for question 4

2.2.4. RQ4: elective lymph node dissection for patients with cN+ oral cavity cancer

2.2.4.1. Systematic reviews

Same search strategies were applied as for question 3.

2.2.4.2. Primary studies

Same search strategies were applied as for question 3.

2.2.5. RQ5: elective lymph node dissection of contralateral neck

Date	Systematic reviews: 24/08/2013 Primary studies: 12/08/2013
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Search Strategy	1 "Head and Neck Neoplasms"/ (40349) 2 exp mouth neoplasms/ (54216) 3 scchn.tw. (1282) 4 hnscc.tw. (3684) 5 ocscc.tw. (32) 6 1 or 2 or 3 or 4 or 5 (91985) 7 (cancer* or tumo?r* or malign* or carcinoma* or neoplasm* or metastas?s or squamous cell carcinoma).tw. (2100605) 8 squamous cell carcinoma/ (102276) 9 neoplasms, squamous cell/ (1349) 10 7 or 8 or 9 (2110509) 11 (palatal or palate).tw. (29268) 12 palate/ (8781) 13 tongue/ (14655) 14 tongue*.tw. (27568) 15 ((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw. (699) 16 mouth mucosa/ (22213) 17 (mouth adj3 (bottom or floor)).tw. (2728) 18 mouth floor/ (2336) 19 uvula.tw. (1014) 20 uvula/ (1462)

21 (gingiva$ or gum$).tw. (39762)
22 gingiva/ (14074)
23 (lip or lips).tw. (28040)
24 lip/ (8253)
25 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (145505)
26 10 and 25 (21897)
27 6 or 26 (99380)
28 lymph node dissection/ (24170)
29 (lymph adj3 (excision or extirpation or resection or dissection)).tw. (12040)
30 lymph?adectomy.tw. (40)
31 neck dissection/ (5227)
32 (neck adj2 dissection).tw. (5476)
33 28 or 29 or 30 or 31 or 32 (36909)
34 27 and 33 (4704)
35 meta-analysis.mp,pt. or review.pt. or search:.tw. (2041367)
36 34 and 35 (495)
37 limit 36 to yr="2008 -Current" (162)

Note

For primary studies, lines 33-37 were replaced by:
34 contralat*.tw. (64717)
35 ipsilat*.tw. (45584)
36 bilat*.tw. (186142)
37 symmetr*.tw. (58536)
38 34 or 35 or 36 or 37 (314611)
39 33 and 38 (3649)
40 27 and 39 (565)
41 40 (565)
42 limit 41 to yr="2003 -Current" (295)

Date	**Systematic reviews: 24/08/2013**
	Primary studies: 12/08/2013
Database	Embase OVID
Search Strategy	'head and neck cancer'/de OR 'head and neck squamous cell carcinoma'/de OR 'lip cancer'/de OR 'mouth cancer'/de OR 'tongue cancer'/de OR 'jaw cancer'/de OR hnscc:ab,ti OR scchn:ab,ti AND ('lymph node dissection'/de OR (lymph NEAR/3 (excision OR extirpation OR resection OR dissection)):ab,ti OR lymphadectomy:ab,ti OR 'neck dissection'/de OR (neck NEAR/2 dissection):ab,ti) AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [2008-2014]/py
Note	For primary studies, the last 3 lines were replaced by: (contralat*:ab,ti OR ipsilat*:ab,ti OR bilat*:ab,ti OR symmetr*:ab,ti)

Date	**Systematic reviews: 24/08/2013**
	Primary studies: 12/08/2013
Database	CENTRAL
Search Strategy	1 MeSH descriptor: [Head and Neck Neoplasms] this term only 2 MeSH descriptor: [Mouth Neoplasms] explode all trees 3 hnscc 4 scchn 5 #1 or #2 or #3 or #4 6 MeSH descriptor: [Lymph Node Excision] this term only 7 MeSH descriptor: [Neck Dissection] this term only 8 lymph adj3 (excision or extirpation or resection or dissection) 9 lymphadectomy 10 neck adj2 dissection 11 #6 or #7 or #8 or #9 or #10 12 #5 and #11 from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols) and Other Reviews

2.2.6. RQ6: value of PET / MRI in the decision of neck dissection after CRT

Date	Systematic reviews: 26/11/2013
	Primary studies: 03/01/2014
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to November Week 2 2013
Search Strategy	1 "Head and Neck Neoplasms"/ (41178)
	2 exp mouth neoplasms/ (54992)
	3 pharyngeal neoplasms/ or hypopharyngeal neoplasms/ or exp oropharyngeal neoplasms/ (14064)
	4 laryngeal neoplasms/ (23789)
	5 hnscc.tw. (3862)
	6 scchn.tw. (1323)
	7 ocscc.tw. (36)
	8 1 or 2 or 3 or 4 or 5 or 6 or 7 (121735)
	9 (cancer* or tumo?r* or carcinoma* or malign* or neoplasm* or metastas?s or squamous cell carcinoma).tw. (2148910)
	10 squamous cell carcinoma/ (104107)
	11 neoplasms, squamous cell/ (1389)
	12 9 or 10 or 11 (2158919)
	13 (palatal or palate).tw. (29775)
	14 palate/ (8878)
	15 tongue/ (14908)
	16 tongue*.tw. (28117)
	17 ((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw. (710)
	18 mouth mucosa/ (22540)
	19 (mouth adj3 (bottom or floor)).tw. (2762)
	20 mouth floor/ (2370)
	21 uvula.tw. (1036)
	22 uvula/ (1484)
	23 (gingiva$ or gum$).tw. (40536)
	24 gingiva/ (14260)
	25 (lip or lips).tw. (28610)
	26 lip/ (8391)

27	larynx/ (13410)
28	oropharynx/ (3342)
29	hypopharynx/ (1460)
30	laryn$.tw. (63478)
31	oropharyn$.tw. (14017)
32	hypopharyn$.tw. (5695)
33	13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (224498)
34	12 and 33 (48914)
35	8 or 34 (134727)
36	lymph node dissection/ (24627)
37	(lymph adj3 (excision or extirpation or resection or dissection)).tw. (12372)
38	lnd.tw. (457)
39	lymph?adectomy.tw. (40)
40	neck dissection/ (5353)
41	(neck adj2 dissection).tw. (5597)
42	neoplasm metastasis/ and (lymph$ or nodal or node$).mp. (16538)
43	lymphatic metastasis/ (69875)
44	neoplasms, residual/ (7115)
45	response assessment.mp. (1247)
46	viable disease.mp. (29)
47	residual.mp. (132200)
48	post-treatment.mp. (20420)
49	or/36-48 (253606)
50	35 and 49 (15173)
51	exp Magnetic Resonance Imaging/ (317399)
52	magnetic resonance imag$.mp. (332822)
53	chemical shift imaging.mp. (762)
54	mr tomograph$.mp. (488)
55	magnetization transfer contrast imaging.mp. (20)
56	proton spin tomograph$.mp. (38)
57	zeugmatograph$.mp. (37)
58	exp Magnetic Resonance Spectroscopy/ (183393)

59 exp MR Spectroscopy/ (183393)

60 exp NMR Tomography/ (317399)

61 exp NMR Imaging/ (317399)

62 MRS.mp. (11330)

63 MRI.mp. (131934)

64 NMR.mp. (102711)

65 KST.mp. (81)

66 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 (570124)

67 deoxyglucose/ or deoxyglucose.tw. or desoxyglucose.tw. or deoxy-glucose.tw. or desoxy-glucose.tw. or deoxy-d-glucose.tw. or desoxy-d-glucose.tw. or 2deoxyglucose.tw. or 2deoxy-d-glucose.tw. or fluorodeoxyglucose.tw. or fluorodesoxyglucose.tw. or fludeoxyglucose.tw. or fluordeoxyglucose.tw. or fluordesoxyglucose.tw. or 18fluorodeoxyglucose.tw. or 18fluorodesoxyglucose.tw. or 18fluordeoxyglucose.tw. or fdg*.tw. or 18fdg*.tw. or 18f-dg*.tw. (34466)

68 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (32169)

69 glucose.tw. (319128)

70 68 and 69 (5886)

71 67 or 70 (34969)

72 (pet or petscan*).tw. or tomography, emission-computed/ (62823)

73 emission.tw. (92114)

74 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (232500)

75 73 and 74 (46734)

76 72 or 75 (81241)

77 71 and 76 (20335)

78 "Positron-Emission Tomography and Computed Tomography"/ (3146)

79 "Positron-Emission Tomography"/ (29262)

80 Fluorodeoxyglucose F18/ (18735)

81 77 or 78 or 79 or 80 (42326)

82 66 or 81 (602283)

83 50 and 82 (1165)

84 meta-analysis.mp,pt. or review.pt. or search:.tw. (2093078)

85 83 and 84 (230)

86 limit 85 to yr="2008-current" (92)

| Note | *For primary studies on MRI:* |

lines 67-81 were deleted

lines 82-86 were replaced by:

67   50 and 66

For primary studies on PET:

lines 51-66 were deleted

lines 82-86 were replaced by:

66   50 and 65

67   limit 66 to yr="2010-current"

Date	Systematic reviews: 26/11/2013
	Primary studies: 03/01/2014
Database	Embase
Search Strategy	'head and neck cancer'/de OR 'head and neck squamous cell carcinoma'/de OR 'lip cancer'/de OR 'mouth cancer'/de OR 'tongue cancer'/de OR 'jaw cancer'/de OR hnscc:ab,ti OR scchn:ab,ti OR ocscc:ab,ti AND ('lymph node dissection'/de OR (lymph NEAR/3 (excision OR extirpation OR resection OR dissection)):ab,ti OR lymphadectomy:ab,ti OR 'neck dissection'/de OR (neck NEAR/2 dissection):ab,ti) OR ('neoplasm metastasis'/de AND (lymph$:ab,ti OR nodal:ab,ti OR node$:ab,ti)) OR 'lymph node metastasis'/de OR 'minimal residual disease'/de OR (response NEAR/2 assessment):ab,ti OR (viable NEAR/2 disease):ab,ti OR residual:ab,ti OR 'post treatment':ab,ti) AND ('nuclear magnetic resonance imaging'/exp OR 'cardiovascular magnetic resonance'/exp OR 'diffusion weighted imaging'/exp OR 'magnetic resonance angiography'/exp OR 'perfusion weighted imaging'/exp OR mrs:ab,ti OR mri:ab,ti OR nmr:ab,ti OR kst:ab,ti OR 'whole body pet'/exp OR 'positron emission tomography'/exp) AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [2008-2014]/py
Note	*For primary studies on MRI:*
	the last 7 lines were deleted:
	For primary studies on PET:
	lines "('nuclear magnetic resonance imaging'/exp OR 'cardiovascular magnetic resonance'/exp OR 'diffusion weighted imaging'/exp OR 'magnetic resonance angiography'/exp OR 'perfusion weighted imaging'/exp OR mrs:ab,ti OR mri:ab,ti OR nmr:ab,ti OR kst:ab,ti OR" were deleted
	the last 3 lines were replaced by:
	[2010-2014]/py

Date	06/01/2014
Database	CENTRAL
Search Strategy	1 MeSH descriptor: [Head and Neck Neoplasms] this term only 2 MeSH descriptor: [Mouth Neoplasms] explode all trees 3 hnscc 4 scchn 5 ocscc 6 #1 or #2 or #3 or #4 or #5 7 MeSH descriptor: [Lymph Node Excision] this term only 8 MeSH descriptor: [Neck Dissection] this term only 9 lymph adj3 (excision or extirpation or resection or dissection) 10 lymphadectomy 11 MeSH descriptor: [Neoplasm Metastasis] this term only 12 (lymph$ or nodal or node$) 13 #11 and #12 14 MeSH descriptor: [Lymphatic Metastasis] this term only 15 MeSH descriptor: [Neoplasm, Residual] this term only 16 response assessment 17 viable disease 18 residual 19 post-treatment 20 #7 or #8 or #9 or #10 or #13 or #14 or #15 or #16 or #17 or #18 or #19 21 #6 and #20 22 MeSH descriptor: [Magnetic Resonance Spectroscopy] explode all trees 23 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees 24 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees 25 (MRS or MRI or NMR or KST):ti,ab 26 #22 or #23 or #24 or #25 27 MeSH descriptor: [Positron-Emission Tomography] this term only 28 MeSH descriptor: [Positron-Emission Tomography and Computed Tomography] this term only 29 MeSH descriptor: [Fluorodeoxyglucose F18] this term only

	30	#27 or #28 or #29
	31	#26 or #30
	32	#21 and #31

2.2.7. *RQ7: neck dissection after chemoradiotherapy in patients with oral cavity cancer*

Date	**Systematic reviews: 23/09/2013**
	Primary studies: 25/09/2013
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Search Strategy	1 "Head and Neck Neoplasms"/ (40840)
	2 exp mouth neoplasms/ (54635)
	3 pharyngeal neoplasms/ or hypopharyngeal neoplasms/ or exp oropharyngeal neoplasms/ (13960)
	4 laryngeal neoplasms/ (23703)
	5 hnscc.tw. (3802)
	6 scchn.tw. (1309)
	7 ocscc.tw. (35)
	8 1 or 2 or 3 or 4 or 5 or 6 (120923)
	9 (cancer* or tumo?r* or carcinoma* or malign* or neoplasm* or metastas?s or squamous cell carcinoma).tw. (2128938)
	10 squamous cell carcinoma/ (103327)
	11 neoplasms, squamous cell/ (1373)
	12 9 or 10 or 11 (2138890)
	13 (palatal or palate).tw. (29578)
	14 palate/ (8823)
	15 tongue/ (14746)
	16 tongue*.tw. (27843)
	17 ((oral or buccal or mouth or cheek$) adj (mucous or (mucosa adj membrane$))).tw. (704)
	18 mouth mucosa/ (22373)
	19 (mouth adj3 (bottom or floor)).tw. (2747)
	20 mouth floor/ (2350)
	21 uvula.tw. (1024)
	22 uvula/ (1473)
	23 (gingiva$ or gum$).tw. (40201)

24 gingiva/ (14183)
25 (lip or lips).tw. (28385)
26 lip/ (8314)
27 larynx/ (13254)
28 oropharynx/ (3297)
29 hypopharynx/ (1440)
30 laryn$.tw. (62795)
31 oropharyn$.tw. (13824)
32 hypopharyn$.tw. (5636)
33 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (222473)
34 12 and 33 (48534)
35 8 or 34 (133788)
36 Antineoplastic Combined Chemotherapy Protocols/ (114763)
37 chemothera$.mp. (328255)
38 Drug Therapy/ (34187)
39 antineoplastic agents combined/ (114763)
40 drug therapy combination/ (145270)
41 36 or 37 or 38 or 39 or 40 (493684)
42 radiothera$.tw. (109766)
43 Radiotherapy/ (35198)
44 42 or 43 (131524)
45 41 and 44 (42415)
46 chemoradi$.mp. (14392)
47 combined modality therapy/ or exp chemoradiotherapy/ (146984)
48 crt.mp. (7451)
49 45 or 46 or 47 or 48 (183034)
50 35 and 49 (11103)
51 lymph node dissection/ (24419)
52 (lymph adj3 (excision or extirpation or resection or dissection)).tw. (12250)
53 lnd.tw. (445)
54 lymph?adectomy.tw. (40)

	55 neck dissection/ (5304)
	56 (neck adj2 dissection).tw. (5548)
	57 51 or 52 or 53 or 54 or 55 or 56 (37603)
	58 50 and 57 (1346)
	59 meta-analysis.mp,pt. or review.pt. or search:.tw. (2073678)
	60 58 and 59 (190)
	61 limit 60 to yr="2008-current" (69)
Note	For primary studies, lines 59-61 were replaced by:
	59 limit 58 to yr="2003 -Current" (703)

Date	**Systematic reviews: 23/09/2013**
	Primary studies: 25/09/2013
Database	Embase
Search Strategy	'head and neck cancer'/de OR 'head and neck squamous cell carcinoma'/de OR 'lip cancer'/de OR 'mouth cancer'/de OR 'tongue cancer'/de OR 'jaw cancer'/de OR hnscc:ab,ti OR scchn:ab,ti AND ('chemoradiotherapy'/exp OR chemoradi*:ab,ti OR crt:ab,ti
	OR ('antineoplastic agent'/exp OR 'cancer chemotherapy'/exp OR 'cancer combination chemotherapy'/exp OR 'combination chemotherapy'/exp AND 'radiotherapy'/exp) OR 'radiotherapy'/exp AND ('lymph node dissection'/de OR (lymph NEAR/3 (excision OR extirpation OR resection OR dissection)):ab,ti OR lymphadectomy:ab,ti OR 'neck dissection'/de OR (neck NEAR/2 dissection):ab,ti) AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [2008-2014]/py
Note	For primary studies, the last 3 lines were replaced by:
	[2003-2014]/py

Date	**25/09/2013**
Database	CENTRAL
Search Strategy	1 MeSH descriptor: [Head and Neck Neoplasms] this term only
	2 MeSH descriptor: [Mouth Neoplasms] explode all trees
	3 hnscc
	4 scchn
	5 #1 or #2 or #3 or #4

6	MeSH descriptor: [Antineoplastic Combined Chemotherapy Protocols] this term only
7	MeSH descriptor: [Drug Therapy] explode all trees
8	chemothera*
9	#6 or #7 or #8
10	MeSH descriptor: [Radiotherapy] explode all trees
11	radiothera*
12	#10 or #11
13	#9 and #12
14	MeSH descriptor: [Combined Modality Therapy] explode all trees
15	MeSH descriptor: [Chemoradiotherapy] explode all trees
16	chemoradi*
17	crt
18	#14 or #15 or #16 or #17
19	#5 and #18
20	MeSH descriptor: [Lymph Node Excision] this term only
21	MeSH descriptor: [Neck Dissection] this term only
22	lymph adj3 (excision or extirpation or resection or dissection)
23	lymphadectomy
24	neck adj3 dissection
25	#20 or #21 or #22 or #23 or #24
26	#19 and #25

2.2.8. RQ8: IMRT for patients with locally advanced HNSCC

2.2.8.1. Systematic Reviews

Date	12-08-2013
Database	Medline
Search Strategy	1 exp "Head and Neck Neoplasms"/ 2 hnscc.ti,ab. 3 scchn.ti,ab. 4 (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab. 5 (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab. 6 ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab. 7 or/1-6 8 (intensity adj modulated).ti,ab. 9 IMRT.ti,ab. 10 exp Radiotherapy, Intensity-Modulated/ 11 (volum* adj1 modulated).ti,ab. 12 (intensity adj1 modulated).ti,ab. 13 (helical adj1 tomotherap*).ti,ab. 14 or/8-13 15 7 and 14 16 MEDLINE.tw. 17 systematic review.tw. 18 meta-analysis.pt. 19 (search* adj12 (literature or database?)).ti,ab. 20 or/16-19 21 animals/ not humans/ 22 20 not 21

	23	15 and 22
	24	limit 23 to ed=20080101-20130901
Note	/	

Date	**12-08-2013**	
Database	Embase	
Search Strategy	1	exp "head and neck tumor"/
	2	(((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	3	(ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	4	((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	5	hnscc.ti,ab.
	6	scchn.ti,ab.
	7	or/1-6
	8	(intensity adj modulated).ti,ab.
	9	IMRT.ti,ab.
	10	exp intensity modulated radiation therapy/
	11	(volum* adj1 modulated).ti,ab.
	12	(intensity adj1 modulated).ti,ab.
	13	(helical adj1 tomotherap*).ti,ab.
	14	or/8-13
	15	MEDLINE.tw.
	16	exp systematic review/ or systematic review.tw.
	17	meta-analysis/
	18	(search* adj12 (literature or database?)).ti,ab.
	19	or/15-18
	20	7 and 14 and 19
	21	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)

22	20 not 21
23	limit 22 to dd=20080101-20130901
Note	/

Date	04-11-2013
Database	Cochrane
Search Strategy	1. Radiotherapy AND (head neck OR oropharyngeal OR oropharynx)
	2. limit #1 >=2008
Note	/

2.2.8.2. Primary studies

Date	15-08-2013
Database	Medline
Search Strategy	exp "Head and Neck Neoplasms"/
	2 imrt.mp. or exp Radiotherapy, Intensity-Modulated/
	3 brachytherapy.mp. or exp Brachytherapy/
	4 exp Protons/ or proton therapy.mp.
	5 biological marker.mp. or exp Biological Markers/
	6 gene therapy.mp. or exp Gene Therapy/
	7 children.mp. or exp Child/
	8 pediatric cancer.mp.
	9 childhood cancer.mp.
	10 exp Quality Assurance, Health Care/ or quality assurance.mp.
	11 treatment plan comparison.mp.
	12 aperture optimization.mp.
	13 independent dose calculation.mp.
	14 EPID dosimetry.mp.
	15 set up errors.mp.

	16	planning.mp.
	17	3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16
	18	1 and 2
	19	1 and 17
	20	18 not 19
	21	limit 20 to (english language and humans)
	22	limit 21 to ed=20090201-20130901
Note	Search strategy from o' Sullivan et al., 2012	

Date	**15-08-2013**	
Database	Embase	
Search Strategy	1	head cancer.mp. or exp Head Cancer/
	2	neck cancer.mp. or exp Neck Cancer/
	3	1 or 2
	4	imrt.mp. or exp Intensity Modulated Radiation Therapy/
	5	brachytherapy.mp. or exp Brachytherapy/
	6	proton therapy.mp. or exp Proton Therapy/
	7	biological marker.mp. or exp Biological Marker/
	8	gene therapy.mp. or exp Gene Therapy/
	9	child/ or child.mp. or children.mp.
	10	childhood cancer.mp. or exp Childhood Cancer/
	11	quality assurance.mp. or exp Quality Control/
	12	treatment plan comparison.mp.
	13	aperture optimization.mp.
	14	independent dose calculation.mp.
	15	EPID dosimetry.mp.
	16	set up errors.mp.
	17	exp Planning/ or planning.mp.

18	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17
19	3 and 4
20	3 and 18
21	19 not 20
22	limit 21 to (human and english language)
23	limit 22 to dd=20090201-20130901

Note	Search strategy from o' Sullivan et al., 2012 was updated, hence no search in CENTRAL

2.2.9. RQ9: induction chemotherapy in patients with HNSCC

2.2.9.1. Systematic Reviews

Date	12-08-2013
Database	Medline
Search Strategy	1 exp "Head and Neck Neoplasms"/
	2 hnscc.ti,ab.
	3 scchn.ti,ab.
	4 (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	5 (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	6 ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	7 or/1-6
	8 exp Antineoplastic Agents/
	9 exp Drug Therapy/
	10 cetuximab.ti,ab.
	11 carboplatin$.ti,ab.
	12 hydroxyurea.ti,ab.
	13 docetaxel$.ti,ab.
	14 methotrexa$.ti,ab.
	15 doxorubicin$.ti,ab.

16	adriamycin$.ti,ab.	
17	5fu.ti,ab.	
18	bleomycin$.ti,ab.	
19	vinblastine$.ti,ab.	
20	paclitaxel$.ti,ab.	
21	cisplatin$.ti,ab.	
22	5-fluorouracil$.ti,ab.	
23	fluorouracil$.ti,ab.	
24	(onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).ti,ab.	
25	antineoplas$.ti,ab.	
26	neoadjuvant.ti,ab.	
27	(adjuvant or neo-adjuvant).ti,ab.	
28	chemotherap$.ti,ab.	
29	chemoradiotherap$.ti,ab.	
30	or/8-29	
31	7 and 30	
32	MEDLINE.tw.	
33	systematic review.tw.	
34	meta-analysis.pt.	
35	(search* adj12 (literature or database?)).ti,ab.	
36	or/32-35	
37	animals/ not humans/	
38	36 not 37	
39	31 and 38	
40	limit 39 to ed=20080101-20130901	

Note

Date	12-08-2013
Database	Embase
Search Strategy	1 exp "head and neck tumor"/

1   exp "head and neck tumor"/

2   (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.

3   (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.

4   ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.

5   hnscc.ti,ab.

6   scchn.ti,ab.

7   or/1-6

8   exp *Antineoplastic Agent/

9   exp *cancer chemotherapy/ or *antibody directed enzyme prodrug therapy/ or *cancer adjuvant therapy/ or *cancer combination chemotherapy/ or *cancer hormone therapy/ or *chemoembolization/ or *electrochemotherapy/

10   *multimodality cancer therapy/

11   cetuximab.ti,ab.

12   carboplatin$.ti,ab.

13   hydroxyurea.ti,ab.

14   docetaxel$.ti,ab.

15   methotrexa$.ti,ab.

16   doxorubicin$.ti,ab.

17   adriamycin$.ti,ab.

18   5fu.ti,ab.

19   bleomycin$.ti,ab.

20   vinblastine$.ti,ab.

21   paclitaxel$.ti,ab.

22   cisplatin$.ti,ab.

23   5-fluorouracil$.ti,ab.

24   fluorouracil$.ti,ab.

	25	(onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).ti,ab.
	26	antineoplas$.ti,ab.
	27	neoadjuvant.ti,ab.
	28	(adjuvant or neo-adjuvant).ti,ab.
	29	chemotherap$.ti,ab.
	30	chemoradiotherap$.ti,ab.
	31	or/8-30
	32	MEDLINE.tw.
	33	exp systematic review/ or systematic review.tw.
	34	meta-analysis/
	35	(search* adj12 (literature or database?)).ti,ab.
	36	or/32-35
	37	7 and 31 and 36
	38	limit 37 to dd=20080101-20130901
Note		

Date	04-11-2013
Database	Cochrane
Search Strategy	1. Induction chemotherapy
	2. limit #1 >=2008
Note	/

2.2.9.2. Primary studies

Date	22-08-2013
Database	Medline
Search Strategy	1 (induction chemotherapy or induc$ chemotherapy or neoadjuvant chemotherapy or preoperative chemotherapy or sequential chemotherapy or adjuvant chemotherapy or primary chemotherapy or initial chemotherapy).tw.
	2 ("head and neck" or oral or pharyngeal or oropharyngeal or hypopharyngeal or maxillofacial or laryngeal or paranasal

sinus).tw.

3	1 and 2
4	randomized controlled trials/
5	"randomized controlled trial".pt.
6	controlled clinical trial.pt.
7	random allocation/
8	exp Clinical Trial/
9	clinical trial.pt.
10	random$.ti,ab.
11	or/4-10
12	3 and 11
13	limit 12 to ed=20120101-20130901

Note	Search strategy from Ma et al., 2012

Date	22-08-2013
Database	Embase
Search Strategy	1 (induction chemotherapy or induc$ chemotherapy or neoadjuvant chemotherapy or preoperative chemotherapy or sequential chemotherapy or adjuvant chemotherapy or primary chemotherapy or initial chemotherapy).tw.
	2 ("head and neck" or oral or pharyngeal or oropharyngeal or hypopharyngeal or maxillofacial or laryngeal or paranasal sinus).tw.
	3 1 and 2
	4 crossover procedure/ or double-blind procedure/ or single-blind procedure/ or randomized controlled trial/
	5 (crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).ti,ab,ot. or random$.ti,ab,ab. or trial$.ti.
	6 4 or 5
	7 3 and 6
	8 limit 7 to dd=20120101-20130901
Note	Search strategy from Ma et al., 2012

Date	22-08-2013
Database	Cochrane
Search Strategy	#1 induction chemotherapy:ti,ab,kw or induc* chemotherapy:ti,ab,kw or neoadjuvant chemotherapy:ti,ab,kw or preoperative chemotherapy:ti,ab,kw or sequential chemotherapy:ti,ab,kw or adjuvant chemotherapy:ti,ab,kw or primary chemotherapy:ti,ab,kw or initial chemotherapy:ti,ab,kw #2 head and neck:ti,ab,kw or oral:ti,ab,kw or pharyngeal:ti,ab,kw or oropharyngeal:ti,ab,kw or hypopharyngeal:ti,ab,kw or maxillofacial:ti,ab,kw or laryngeal:ti,ab,kw or paranasal sinus:ti,ab,kw #3 #1 and #2 from 2012 to 2013
Note	Search strategy from Ma et al., 2012

2.2.10. RQ10: primary CRT for patients with non-resectable M0 HNSCC

2.2.10.1. Systematic Reviews

Date	07-11-2013
Database	Medline
Search Strategy	1 exp "Head and Neck Neoplasms"/ 2 hnscc.ti,ab. 3 scchn.ti,ab. 4 (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab. 5 (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab. 6 ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab. 7 or/1-6 8 exp Antineoplastic Agents/ 9 exp Drug Therapy/ 10 cetuximab.ti,ab. 11 carboplatin$.ti,ab. 12 hydroxyurea.ti,ab. 13 docetaxel$.ti,ab.

14	methotrexa$.ti,ab.
15	doxorubicin$.ti,ab.
16	adriamycin$.ti,ab.
17	5fu.ti,ab.
18	bleomycin$.ti,ab.
19	vinblastine$.ti,ab.
20	paclitaxel$.ti,ab.
21	cisplatin$.ti,ab.
22	5-fluorouracil$.ti,ab.
23	fluorouracil$.ti,ab.
24	(onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).ti,ab.
25	antineoplas$.ti,ab.
26	neoadjuvant.ti,ab.
27	(adjuvant or neo-adjuvant).ti,ab.
28	chemotherap$.ti,ab.
29	chemoradiotherap$.ti,ab.
30	or/8-29
31	7 and 30
32	MEDLINE.tw.
33	systematic review.tw.
34	meta-analysis.pt.
35	(search* adj12 (literature or database?)).ti,ab.
36	or/32-35
37	animals/ not humans/
38	36 not 37
39	31 and 38
40	limit 39 to ed=20080101-20130901
41	Cetuximab.mp.
42	Panitumumab.mp.

	43	Gefitinib.mp.
	44	Erlotinib.mp.
	45	Lapatinib.mp.
	46	Afatinib.mp.
	47	Vandetanib.mp.
	48	exp Antibodies/
	49	antibod$.ti,ab.
	50	or/41-49
	51	7 and 38 and 50
	52	limit 51 to ed=20080101-20130901
	53	52 not 40
Note		This is an additional search strategy on top of the strategy used in Q9 for systematic reviews

Date	**07-11-2013**	
Database	Embase	
Search Strategy	1	Cetuximab.mp.
	2	Panitumumab.mp.
	3	Gefitinib.mp.
	4	Erlotinib.mp.
	5	Lapatinib.mp.
	6	Afatinib.mp.
	7	Vandetanib.mp.
	8	exp antibody/
	9	antibod$.ti,ab.
	10	or/1-9
	11	exp "head and neck tumor"/
	12	(((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.

13   (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.

14   ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.

15   hnscc.ti,ab.

16   scchn.ti,ab.

17   or/11-16

18   exp *Antineoplastic Agent/

19   exp *cancer chemotherapy/ or *antibody directed enzyme prodrug therapy/ or *cancer adjuvant therapy/ or *cancer combination chemotherapy/ or *cancer hormone therapy/ or *chemoembolization/ or *electrochemotherapy/

20   *multimodality cancer therapy/

21   cetuximab.ti,ab.

22   carboplatin$.ti,ab.

23   hydroxyurea.ti,ab.

24   docetaxel$.ti,ab.

25   methotrexa$.ti,ab.

26   doxorubicin$.ti,ab.

27   adriamycin$.ti,ab.

28   5fu.ti,ab.

29   bleomycin$.ti,ab.

30   vinblastine$.ti,ab.

31   paclitaxel$.ti,ab.

32   cisplatin$.ti,ab.

33   5-fluorouracil$.ti,ab.

34   fluorouracil$.ti,ab.

35   (onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).ti,ab.

36   antineoplas$.ti,ab.

37   neoadjuvant.ti,ab.

38   (adjuvant or neo-adjuvant).ti,ab.

39   chemotherap$.ti,ab.

40   chemoradiotherap$.ti,ab.

41	or/18-40
42	MEDLINE.tw.
43	exp systematic review/ or systematic review.tw.
44	meta-analysis/
45	(search* adj12 (literature or database?)).ti,ab.
46	or/42-45
47	17 and 41 and 46
48	10 and 17 and 46
49	48 not 47
50	limit 49 to dd=20080101-20130901

Note	This is an additional search strategy on top of the strategy used in Q9 for systematic reviews

Date	**23-12-2013**	
Database	Cochrane	
Search Strategy	#1	MeSH descriptor: [Head and Neck Neoplasms] explode all trees
Note	#2	hnscc:ti,ab or scchn:ti,ab or oral:ti,ab or oropharyn*:ti,ab or laryn*:ti,ab or pharyn*:ti,ab
	#3	(chemotherap*:ti,ab and radiotherapy:ti,ab) or chemoradiotherap*:ti,ab
	#4	cetuximab:ti,ab or panitumumab:ti,ab or gefitinib:ti,ab or erlotinib:ti,ab or lapatinib:ti,ab or vandetanib:ti,ab
	#5	#1 or #2
	#6	#3 or #4
	#7	#5 and #6 from 2008

2.2.10.2. Primary studies

Date	06-12-2013
Database	Medline
Search Strategy	1. ((advanced or recurrent or inoperable or unresectable or (stage$ adj3 (ivb or 4b))) adj5 (hnscc or scchn or (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)) or (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)) or ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)))).ti,ab.
	2. exp "Head and Neck Neoplasms"/
	3. hnscc.ti,ab.
	4. scchn.ti,ab.
	5. (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	6. (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	7. ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	8. or/2-7
	9. Neoplasm Recurrence, Local/
	10. 8 and 9
	11. 1 or 10 [population: M0 stage head and neck neoplasms]
	12. exp Antineoplastic Agents/
	13. exp Drug Therapy/
	14. (cetuximab or carboplatin$ or hydroxyurea or docetaxel$ or methotrexa$ or doxorubicin$ or adriamycin$ or 5fu or bleomycin$ or vinblastine$ or paclitaxel$ or cisplatin$ or 5-fluorouracil$ or fluorouracil$ or (onyx-015 or amifostine$ or misonidazole$ or erythropoietin$) or antineoplas$).ti,ab.
	15. neoadjuvant.ti,ab.
	16. (adjuvant or neo-adjuvant).ti,ab.
	17. chemotherap$.ti,ab.
	18. chemoradiotherap$.ti,ab.
	19. exp Chemoradiotherapy, Adjuvant/ or exp Chemoradiotherapy/
	20. Cetuximab.mp.

21. Panitumumab.mp.

22. Gefitinib.mp.

23. Erlotinib.mp.

24. Lapatinib.mp.

25. Afatinib.mp.

26. Vandetanib.mp.

27. exp Antibodies/

28. antibod$.ti,ab.

29. or/12-28 [internevtion: chemotherapy including EGFR]

30. radiat$.ti,ab.

31. radiotherap$.ti,ab.

32. irradiat$.ti,ab.

33. exp Radiotherapy/

34. or/30-33 [comparator: radiotherapy]

35. random$.af. [randomised controlled trials]

36. (phase iii trial$ or phase iii study).af.

37. or/35-36 [study type]

38. 11 and 29 and 34 and 37

39. limit 38 to ed=20031201-20140101

| **Note** | For identification of randomised trials we followed guidance from Royle, P. *BMC Medical Research Methodology* 2005, **5**:23 |

Date	06-12-2013
Database	Embase
Search Strategy	1. ((advanced or recurrent or inoperable or unresectable or (stage$ adj3 (ivb or 4b))) adj5 (hnscc or scchn or (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)) or (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)) or ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)))).ti,ab.
	2. exp "head and neck tumor"/
	3. (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	4. (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	5. ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	6. hnscc.ti,ab.
	7. scchn.ti,ab.
	8. or/2-7
	9. *tumor recurrence/
	10. 8 and 9
	11. 1 or 10 [population: M0 stage head and neck neoplasms]
	12. exp *Antineoplastic Agent/
	13. exp *cancer chemotherapy/ or *antibody directed enzyme prodrug therapy/ or *cancer adjuvant therapy/ or *cancer combination chemotherapy/ or *cancer hormone therapy/ or *chemoembolization/ or *electrochemotherapy/
	14. *multimodality cancer therapy/
	15. cetuximab.ti,ab.
	16. carboplatin$.ti,ab.
	17. hydroxyurea.ti,ab.
	18. docetaxel$.ti,ab.
	19. methotrexa$.ti,ab.
	20. doxorubicin$.ti,ab.
	21. adriamycin$.ti,ab.

22. 5fu.ti,ab.
23. bleomycin$.ti,ab.
24. vinblastine$.ti,ab.
25. paclitaxel$.ti,ab.
26. cisplatin$.ti,ab.
27. 5-fluorouracil$.ti,ab.
28. fluorouracil$.ti,ab.
29. (onyx-015 or amifostine$ or misonidazole$ or erythropoietin$).ti,ab.
30. antineoplas$.ti,ab.
31. neoadjuvant.ti,ab.
32. (adjuvant or neo-adjuvant).ti,ab.
33. chemotherap$.ti,ab.
34. chemoradiotherap$.ti,ab.
35. Cetuximab.mp.
36. Panitumumab.mp.
37. Gefitinib.mp.
38. Erlotinib.mp.
39. Lapatinib.mp.
40. Afatinib.mp.
41. Vandetanib.mp.
42. exp *antibody/
43. antibod$.ti,ab.
44. or/12-43 [internevtion: chemotherapy including EGFR]
45. radiat$.ti,ab.
46. radiotherap$.ti,ab.
47. irradiat$.ti,ab.
48. exp *radiotherapy/
49. or/45-48 [comparator: radiotherapy]
50. random$.af.

51. (phase iii trial$ or phase iii study).af.

52. or/50-51 [study type]

53. 11 and 44 and 49 and 52

54. limit 53 to dd=20031201-20140101

Note	For identification of randomised trials we followed guidance from Royle, P. *BMC Medical Research Methodology* 2005, **5**:23

Date	**06-12-2013**
Database	Cochrane Library- Central Registry of Studies Randomised Controlled trials
Search Strategy	#1. ((advanced or recurrent or inoperable or unresectable or (stage* next/3 (ivb or 4b))) next/5 (hnscc or scchn or (((upper next/1 aerodigestive next/1 tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)) or (ent next/4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)) or ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)))):ti,ab
	#2. MeSH descriptor: [Head and Neck Neoplasms] explode all trees
	#3. scchn:ti,ab (Word variations have been searched)
	#4. hnscc:ti,ab
	#5. (((upper next/1 aerodigestive next/1 tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab (Word variations have been searched)
	#6. (ent next/4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab (Word variations have been searched)
	#7. ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab (Word variations have been searched)
	#8. #2 or #3 or #4 or #5 or #6 or #7
	#9. MeSH descriptor: [Neoplasm Recurrence, Local] explode all trees
	#10. #9 and #8
	#11. #1 or #10
	#12. MeSH descriptor: [Drug Therapy] explode all trees
	#13. (cetuximab or carboplatin* or hydroxyurea or docetaxel* or methotrexa* or doxorubicin* or adriamycin* or 5fu or bleomycin*

or vinblastine* or paclitaxel* or cisplatin* or 5-fluorouracil* or fluorouracil* or (onyx-015 or amifostine* or misonidazole* or erythropoietin*) or antineoplas*):ti,ab (Word variations have been searched)

#14. neoadjuvant:ti,ab (Word variations have been searched)

#15. (adjuvant or neo-adjuvant):ti,ab (Word variations have been searched)

#16. chemotherap*:ti,ab (Word variations have been searched)

#17. chemoradiotherap*:ti,ab (Word variations have been searched)

#18. MeSH descriptor: [Chemoradiotherapy] explode all trees

#19. MeSH descriptor: [Chemoradiotherapy, Adjuvant] explode all trees

#20. Cetuximab:ti,ab or Panitumumab:ti,ab or Gefitinib:ti,ab or Erlotinib:ti,ab or Lapatinib:ti,ab or Afatinib:ti,ab or Vandetanib:ti,ab (Word variations have been searched)

#21. MeSH descriptor: [Antibodies] explode all trees

#22. antibod*:ti,ab

#23. MeSH descriptor: [Antineoplastic Agents] explode all trees

#24. #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23

#25. #24 and #11 from 2003 to 2013

| **Note** | / |

2.2.11. RQ11: interventions for M+ disease or recurrent disease not suitable for curative treatment

Systematic reviews and primary studies

Date	29-11-2013
Database	Medline
Search Strategy	1 exp "Head and Neck Neoplasms"/

	2 hnscc.ti,ab.
	3 scchn.ti,ab.
	4 (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	5 (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	6 ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.
	7 or/1-6
	8 exp Palliative Care/
	9 exp Terminal Care/
	10 exp Terminally Ill/
	11 (terminal* adj6 (care* or caring or ill)).ti,ab.
	12 (terminal* ill and symptom management).ti,ab.
	13 chemo*.ti,ab.
	14 ((induced or related) adj6 (vomiting or sickness)).ti,ab.
	15 13 and 14
	16 (induced adj6 (hypersalivation or hyposalivation or xerostomi* or cachexi*)).ti,ab.
	17 ((anorexi* adj6 cancer*) or (anorexi* adj6 carcinoma*)).ti,ab.
	18 (anorexi* adj6 radiotherap*).ti,ab.
	19 (anorexi* adj6 radio-chemotherap*).ti,ab.
	20 ((cancer* adj6 weight-gain*) or (cancer* adj6 "weight gain*") or (carcinoma* adj6 weight-gain*) or (carcinoma* adj6 "weight gain*")).ti,ab.
	21 ((cancer adj6 "appetite stimulat*") or (carcinoma adj6 "appetite stimulat*")).ti,ab.
	22 ((cancer* and "hot flush") or (cancer* and "hot flash")).ti,ab.

23	(related adj cachexi*).ti,ab.
24	((induced adj6 constipat*) or (induced adj6 emesis)).ti,ab.
25	"morphine induced".ti,ab.
26	"methodone induced".ti,ab.
27	((cancer* or carcinoma*) and "music therap*").ti,ab.
28	((cancer* or carcinoma*) and (aromatherap* or "aroma therap*" or aroma-therap*)).ti,ab.
29	((dysphag* adj6 cancer*) or (dysphag* adj6 carcinoma*)).ti,ab.
30	((symptom adj control*) and (cancer* or carcinoma*)).ti,ab.
31	((chemotherap* or radiotherap*) adj6 induced).ti,ab.
32	("radiotherap* related" or "chemotherap* related").ti,ab.
33	("cancer related" or "carcinoma* related").ti,ab.
34	palliative.ti,ab.
35	8 or 9 or 10 or 11 or 12 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	7 and 35
37	MEDLINE.tw.
38	systematic review.tw.
39	meta-analysis.pt.
40	(search* adj12 (literature or database?)).ti,ab.
41	37 or 38 or 39 or 40
42	36 and 41
43	limit 42 to ed=20080101-20130901

Note	/

Date	29-11-2013
Database	Embase
Search Strategy	1 exp "head and neck tumor"/

<table>
<tr><td></td><td>2   (((upper adj aerodigestive adj tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.</td></tr>
<tr><td></td><td>3   (ent adj4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.</td></tr>
<tr><td></td><td>4   ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)).ti,ab.</td></tr>
<tr><td></td><td>5   hnscc.ti,ab.</td></tr>
<tr><td></td><td>6   scchn.ti,ab.</td></tr>
<tr><td></td><td>7   or/1-6</td></tr>
<tr><td></td><td>8   exp palliative therapy/</td></tr>
<tr><td></td><td>9   exp terminal care/</td></tr>
<tr><td></td><td>10   terminally ill patient/</td></tr>
<tr><td></td><td>11   (terminal* adj6 (care* or caring or ill)).ti,ab.</td></tr>
<tr><td></td><td>12   (terminal* ill and symptom management).ti,ab.</td></tr>
<tr><td></td><td>13   chemo*.ti,ab.</td></tr>
<tr><td></td><td>14   ((induced or related) adj6 (vomiting or sickness)).ti,ab.</td></tr>
<tr><td></td><td>15   13 and 14</td></tr>
<tr><td></td><td>16   (induced adj6 (hypersalivation or hyposalivation or xerostomi* or cachexi*)).ti,ab.</td></tr>
<tr><td></td><td>17   ((anorexi* adj6 cancer*) or (anorexi* adj6 carcinoma*)).ti,ab.</td></tr>
<tr><td></td><td>18   (anorexi* adj6 radiotherap*).ti,ab.</td></tr>
<tr><td></td><td>19   (anorexi* adj6 radio-chemotherap*).ti,ab.</td></tr>
<tr><td></td><td>20   ((cancer* adj6 weight-gain*) or (cancer* adj6 "weight gain*") or (carcinoma* adj6 weight-gain*) or (carcinoma* adj6 "weight gain*")).ti,ab.</td></tr>
<tr><td></td><td>21   ((cancer adj6 "appetite stimulat*") or (carcinoma adj6 "appetite stimulat*")).ti,ab.</td></tr>
<tr><td></td><td>22   ((cancer* and "hot flush") or (cancer* and "hot flash")).ti,ab.</td></tr>
<tr><td></td><td>23   (related adj cachexi*).ti,ab.</td></tr>
<tr><td></td><td>24   ((induced adj6 constipat*) or (induced adj6 emesis)).ti,ab.</td></tr>
</table>

25	"morphine induced".ti,ab.
26	"methodone induced".ti,ab.
27	((cancer* or carcinoma*) and "music therap*").ti,ab.
28	((cancer* or carcinoma*) and (aromatherap* or "aroma therap*" or aroma-therap*)).ti,ab.
29	((dysphag* adj6 cancer*) or (dysphag* adj6 carcinoma*)).ti,ab.
30	((symptom adj control*) and (cancer* or carcinoma*)).ti,ab.
31	((chemotherap* or radiotherap*) adj6 induced).ti,ab.
32	("radiotherap* related" or "chemotherap* related").ti,ab.
33	("cancer related" or "carcinoma* related").ti,ab.
34	palliative.ti,ab.
35	8 or 9 or 10 or 11 or 12 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34
36	7 and 35
37	MEDLINE.tw.
38	exp systematic review/ or systematic review.tw.
39	meta-analysis/
40	(search* adj12 (literature or database?)).ti,ab.
41	37 or 38 or 39 or 40
42	36 and 41

Note	/

Date	29-11-2013
Database	Cochrane
Search Strategy	1. MeSH descriptor: [Otorhinolaryngologic Neoplasms] explode all trees
	2. hnscc:ti,ab
	3. scchn:ti,ab
	4. (((upper near/1 aerodigestive near/1 tract) or uadt) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab
	5. (ent near/4 (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab
	6. MeSH descriptor: [Head and Neck Neoplasms] explode all trees
	7. ((head or neck or tongue or lip or tonsil or nasal or oropharyn* or pharyn* or laryn* or throat or EAR or glotti* or nasopharyn* or hypopharyn*) and (cancer* or carcinom* or tumor* or tumour* or neoplas* or malignan* or metasta*)):ti,ab
	8. #1 or #2 or #3 or #4 or #5 or #6 or #7
	9. MeSH descriptor: [Hospice Care] explode all trees
	10. MeSH descriptor: [Hospices] explode all trees
	11. MeSH descriptor: [Quality of Life] explode all trees
	12. ((support* or supplement or substitute) near/3 (oncology or care or therapy or treatment)):ti,ab
	13. (qol or quality of life):ti,ab
	14. comfort*:ti,ab
	15. #9 or #10 or #11 or #12 or #13 or #14
	16. #15 and #8
Note	

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.

Critical appraisal of clinical practice guidelines - AGREE II

17. Key recommendations are easily identifiable.

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?	Yes
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.	No
	Can't answer
	Not applicable
5. Was a list of studies (included and excluded) provided?	Yes
A list of included and excluded studies should be provided.	No
	Can't answer
	Not applicable
6. Were the characteristics of the included studies provided?	Yes
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.	No
	Can't answer
	Not applicable
7. Was the scientific quality of the included studies assessed and documented?	Yes
'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.	No
	Can't answer
	Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Yes
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.	No
	Can't answer
	Not applicable
9. Were the methods used to combine the findings of studies appropriate?	Yes
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?).	No
	Can't answer
	Not applicable

10. Was the likelihood of publication bias assessed?	Yes
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).	No
	Can't answer
	Not applicable
11. Was the conflict of interest stated?	Yes
Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	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		
Incomplete outcome data	Describe the completeness of outcome data for each main	Attrition bias due to amount, nature or handling of

Domain	Support for judgement	Review authors' judgement
Assessments should be made for each main outcome (or class of outcomes)	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	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-	Squamous cell carcinoma of the head and neck: EHNS-ESMO-ESTRO	25%	8%	10%	17%	0%	25%	Exclude

Source	Title	Standardised Score						Final Appraisal
		Scope	Stakeholder involvement	Rigour of development	Clarity	Applicability	Editorial Independence	
ESTRO 2010	Clinical Practice Guidelines for diagnosis, treatment and follow-up							
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
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: PET/CT in the staging of oral cavity cancer

On July 24, 2013 a search was performed to identify SRs evaluating the staging accuracy of PET or PET/CT in patients with HNSCC, published since 2008. MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DARE) were searched.

In MEDLINE, PreMedline and Embase 75, 1 and 23 potential relevant references were identified, respectively. The searches in the Cochrane databases resulted in 14 relevant systematic reviews. After de-duplication 92 references remained. Based on title and abstract 83 reviews were excluded. Nine reviews were included for full-text evaluation.

Based on the full-text evaluation, 3 reviews were excluded (Table 7).

Table 7 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Kyzas P et al. 18F-fluorodeoxyglucose positron emission tomography to evaluate cervical node metastases in patients with head and neck squamous cell carcinoma: a meta-analysis. J. Natl. Cancer Inst. 2008; 100(10): 712-720	Searches only in Medline
Yoo J et al. Evidence-based guideline recommendations on the use of positron emission tomography imaging in head and neck cancer. Clin. Oncol. 2013; 25(4): e33-e66	Article on the CCO guideline that was excluded during the scoping phase
Zaim R et al. Cost-effectiveness of positron emission tomography in head and neck squamous cell carcinoma: A systematic review. Value Health 2012; 15(7): A355-A356	Abstract on review of cost-effectiveness studies

Quality appraisal of selected systematic reviews

Table 8 shows the results of the risk of bias assessment for the 6 included systematic reviews, using AMSTAR criteria.

Table 8 – Methodological quality of the included systematic review (AMSTAR)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	List of in- and exclude d studies	Charac-teristics of included studies provided	Study quality assessed and docu-mented	Quality assess-ment used in conclus-ions	Approp-riate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated	Global evalua-tion
Fletcher JW 2008[1]	N	N	Y	N	N	N	N	Y	NA	N	N	High
Liao LJ 2012[2]	N	N	Y	N	N	Y	N	N	Y	N	N	High
Xu G 2012[3]	N	N	Y	N	N	Y	Y	N	Y	N	N	Moderate
Xu GZ, Head Neck 2011[4]	N	Y	Y	N	Y	Y	Y	N	Y	N	N	Moderate
Xu GZ, Oral Oncol 2011[5]	N	Y	Y	N	Y	Y	Y	N	Y	N	N	Moderate
Yongkui L 2013[6]	N	Y	Y	N	N	Y	Y	N	Y	N	N	Moderate

Since Fletcher et al. provided a review of reviews,[1] their review was not considered further for our research question. The other 5 reviews[2-6] served as a source for primary studies. Where available, data on quality appraisal and diagnostic accuracy were used as such. In case this information was unavailable, the full-text of the primary studies was ordered.

Selection of primary studies

On July 31, 2013 a search was performed to identify RCTs and observational studies evaluating the staging accuracy of PET or PET/CT in patients with HNSCC. MEDLINE (including PreMedline), Embase and CENTRAL were searched, limited from 2009 onwards (search date of Xu 2011 [4]). In MEDLINE, PreMedline and Embase 467, 38 and 558 potential relevant references were identified, respectively. The search in CENTRAL identified 1 additonal reference. After de-duplication, 876 references remained. Based on title and abstract 838 studies were excluded. Of the remaining 38 studies, 16 studies were included after full-text evaluation and 22 studies were excluded with reason (Table 9). Of the 16 included studies, 9 were not yet included in one of the selected systematic reviews and were subjected to quality appraisal with the QUADAS 2 instrument.

In addition, 20 relevant studies (including 7 studies identified through the update) were identified in the selected systematic reviews.

Table 9 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Chan SC et al. Utility of 18F-fluoride PET/CT and 18F-FDG PET/CT in the detection of bony metastases in heightened-risk head and neck cancer patients. J Nucl Med 2012; 53(11): 1730-5	Not only patients with primary disease; also patients with known metastases
Chan SC et al. 18F-FDG PET for retropharyngeal lymph node metastasis in oropharyngeal and hypopharyngeal cancers: impact on diagnosis and prediction analysis. Nucl Med Commun 2010; 31(3): 260-5	No diagnostic study: no reference standard used
Chu HR et al. Additional diagnostic value of (18)F-FDG PET-CT in detecting retropharyngeal nodal metastases. Otolaryngol Head Neck Surg 2009; 141(5): 633-8	Also patients with recurrence; no separate results for primary disease
El-Khodary M et al. The role of PET/CT in the management of head and neck squamous cell carcinoma. Egypt. J. Radiol. Nucl. Med. 2011; 42(2): 157-167	No full-text available
Fogh SE et al. Value of fluoro-2-deoxy-D-glucose-positron emission tomography for detecting metastatic lesions in head and neck cancer. Am J Clin Oncol 2012; 35(4): 311-5	Also patients with recurrence; no separate results for primary disease
Iyer NG et al. Role of pretreatment 18FDG-PET/CT in surgical decision-making for head and neck cancers. Head Neck 2010; 32(9): 1202-8	Also thyroid cancer and skin cancer; 20% non-SCC tumours
Kastrinidis N et al. 18F-FDG-PET/CT for the assessment of the contralateral neck in patients with head and neck squamous cell carcinoma. Laryngoscope 2013 123(5):1210-5	All patients had bilateral FDG uptake
Kim JY et al. Diagnostic value of neck node status using 18F-FDG PET for salivary duct carcinoma of the major salivary glands. J Nucl Med 2012; 53(6): 881-6	Salivary glands
Lee SH et al. Diagnostic value of only 18F-fluorodeocyglucose positron emission tomography/computed tomography-positive lymph nodes in head and neck squamous cell carcinoma. Otolaryngol Head Neck Surg 2012 147(4):692-8	2x2 tables not reconstructable
Lonneux M et al. Positron emission tomography with [18F]fluorodeoxyglucose improves staging and patient management in patients with head and neck squamous cell carcinoma: a multicenter prospective study. J Clin Oncol 2010; 28(7): 1190-5	Reference standard not used for all patients
Nakamura S et al. Dual-time-point fluorodeoxyglucose positron emission tomography for diagnosis of cervical lymph node metastases in patients with head and neck squamous cell carcinoma. J Comput Assist Tomogr 2011; 35(2): 303-7	Also patients who already underwent treatment; no separate results
O'Neill JP et al. Prospective, blinded trial of whole-body magnetic resonance imaging versus computed tomography positron emission tomography in staging primary and recurrent cancer of the head and neck. J Laryngol Otol 2010; 124(12): 1274-7	Also patients with recurrence; no separate results for primary disease
Prestwich RJ et al. The Impact of (18)F-FDG PET CT Prior to Chemoradiotherapy for Stage III/IV Head and Neck Squamous Cell Carcinoma. Isrn Oncology Print 2012: 636379	Reference standard not used for all patients
Sadick M et al. Effect of reconstruction parameters in high-definition PET/CT on assessment of lymph node metastases in head and neck squamous cell carcinoma. J. Nucl. Med. Technol. 2013; 41(1): 19-25	Technical article
Seitz O et al. 18F-Fluorodeoxyglucose-PET/CT to evaluate tumor, nodal disease, and gross tumor volume of	Also patients with recurrence; no

Reference	Reason(s) for exclusion
oropharyngeal and oral cavity cancer: comparison with MR imaging and validation with surgical specimen. Neuroradiology 2009 51(10):677-86	separate results for primary disease
Spector ME et al. Diagnostic modalities for distant metastasis in head and neck squamous cell carcinoma: Are we changing life expectancy? Laryngoscope 2012; 122(7): 1507-1511	No diagnostic study
Stoeckli SJ et al. Initial staging of the neck in head and neck squamous cell carcinoma: a comparison of CT, PET/CT, and ultrasound-guided fine-needle aspiration cytology. Head Neck 2012 34(4):469-76	2x2 tables not reconstructable
Sugawara C et al. Preoperative evaluation of patients with squamous cell carcinoma of the oral cavity: fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography and ultrasonography versus histopathology. Oral Surg Oral Med Oral Pathol Oral Radiol 2012 114(4):516-25	Discordant results presented; impossible to reconstruct 2x2 tables with patient- and lesion-based data
Takei T et al. A novel PET scanner with semiconductor detectors may improve diagnostic accuracy in the metastatic survey of head and neck cancer patients. Ann. Nucl. Med. 2013; 27(1): 17-24	Also patients with recurrence; no separate results for primary disease
Tauzin M et al. PET-CT staging of the neck in cancers of the oropharynx: patterns of regional and retropharyngeal nodal metastasis. World Journal of Surgical Oncology 2010: 8(70)	No diagnostic study
Wallowy P et al. 18F-FDG PET for detecting metastases and synchronous primary malignancies in patients with oral and oropharyngeal cancer. Nucl Med (Stuttg) 2009; 48(5): 192-9	Only PET-positive patients
Xiang ZL et al. Diagnostic values of PET/CT fusion in head and neck cancer. Chin. J. Cancer Prev. Treat. 2009; 16(6): 457-459	Chinese

Quality appraisal of selected primary studies for diagnosis

Table 10 – Methodological quality of the included primary studies for N-staging with PET-scan

	Haerle 2011a[7]	Hoshikawa 2012[8]	Krabbe 2010[9]	Liao 2011[10]	Matsubara 2012[11]	Ozer 2012[12]
Domain 1: Patient selection						
A. Risk of bias						
• **Was a consecutive or random sample of patients enrolled?** Yes/No/Unclear	No	Yes	No	No	Unclear	Unclear
• **Was a case-control design** Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes

		Haerle 2011a[7]	Hoshikawa 2012[8]	Krabbe 2010[9]	Liao 2011[10]	Matsubara 2012[11]	Ozer 2012[12]
avoided?							
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear	No: only patients undergoing PET/CT and neck dissection were included	Unclear: patients referred for surgery or CRT	No: patients not undergoing PET were not included	No: only patients undergoing surgery and without metastases on imaging	No: only patients undergoing PET/CT and neck dissection were included	No: only patients undergoing neck dissection were included
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**High**	**Unclear**	**High**	**High**	**High**	**High**
B. **Concerns regarding applicability**							
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR	**High**	**Unclear**	**High**	**High**	**High**	**High**
Domain 2: Index test(s))							
A. **Risk of bias**							
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**Low**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
B. **Concerns regarding**							

		Haerle 2011a[7]	Hoshikawa 2012[8]	Krabbe 2010[9]	Liao 2011[10]	Matsubara 2012[11]	Ozer 2012[12]
applicability							
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR	**Low**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**Unclear**
Domain 3: Reference standard							
A. Risk of bias							
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear	Yes	Yes	Unclear for follow-up	Yes	Yes	Yes
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear	Yes	Unclear	Unclear	Unclear	Unclear	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**Low**	**Unclear**	**Unclear**	**Unclear**	**Unclear**	**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	**Low**	**Low**	**High**	**Low**	**Low**	**Low**
Domain 4: Flow and timing							
A. Risk of bias							
• **Was there an appropriate interval between index**	Yes/No/Unclear	Yes: within 4 weeks	Unclear	Unclear	Unclear	Unclear	Unclear

		Haerle 2011a[7]	Hoshikawa 2012[8]	Krabbe 2010[9]	Liao 2011[10]	Matsubara 2012[11]	Ozer 2012[12]
test(s) and reference standard?							
• **Did all patients receive a reference standard?**	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
• **Did patients receive the same reference standard?**	Yes/No/Unclear	Yes	Yes	No	Yes	Yes	Yes
• **Were all patients included in the analysis?**	Yes/No/Unclear	Yes, but 2 patients were counted twice (2 neck dissections)	Yes	Yes	Yes	Yes	Yes
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**Low**	**Low**	**High**	**Low**	**Low**	**Low**

Table 11 – Methodological quality of the included primary studies for M-staging with PET-scan

	Abd El-Hafez 2011[13]	Chan 2011[14]	Haerle 2011b[15]
Domain 1: Patient selection			
A. Risk of bias			
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear	Unclear	Yes	No
• **Was a case-control design avoided?**	Yes/No/Unclear	Yes	Yes	Yes
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear	No: patients not undergoing surgery or PET/CT or MRI	Yes	No: patients not undergoing PET/CT were

		Abd El-Hafez 2011[13]	Chan 2011[14]	Haerle 2011b[15]
		were excluded		excluded
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**High**	**Low**	**High**
B. Concerns regarding applicability				
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR	**High**	**Low**	**High**
Domain 2: Index test(s)				
A. Risk of bias				
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear	Unclear	Unclear	Unclear
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear	Unclear	Unclear	Unclear
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**Unclear**	**Unclear**	**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	**Low**	**Low**	**Low**
Domain 3: Reference standard				
A. Risk of bias				
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear	Yes	Yes for histology, unclear for imaging follow-up	Yes for histology, unclear for imaging follow-up
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear	No	Unclear	Unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**High**	**Unclear**	**Unclear**

		Abd El-Hafez 2011[13]	Chan 2011[14]	Haerle 2011b[15]
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	**Low**	**Low**	**Low**
Domain 4: Flow and timing				
A. Risk of bias				
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear	Yes: median of 2 days	Yes for histology (within 14 days), unclear for imaging follow-up	Unclear
• **Did all patients receive a reference standard?**	Yes/No/Unclear	Yes	Yes	Yes
• **Did patients receive the same reference standard?**	Yes/No/Unclear	Yes	No	No
• **Were all patients included in the analysis?**	Yes/No/Unclear	No: exclusion of 2 patients for MRI (uninterpretable images)	No: exclusion of 6 patients that were lost to follow-up	Yes
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**Low**	**High**	**High**

3.3.2. RQ2: HPV testing in patients with oral cavity cancer

The research question on HPV is based on an evidence-based guideline of Cancer care Ontario that included a systematic review on the research question.

Table 12 – Methodological quality of the included systematic review

Systematic review	A priori study design	Duplicate study selection and data extraction	Comprehensive literature search	Publication status not used as inclusion	List of in- and excluded studies	Characteristics of included studies provided	Study quality assessed and documented	Quality assessment used in conclusions	Appropriate methods to combine findings	Likelihood of publication bias assessed	Conflict of interest stated
Lacchetti, 2013[16]	yes	yes	yes	yes	no	no	yes	yes	yes	no	no

The search for randomized controlled trials (RCTs) that evaluated tumour HPV status was updated from the search date of the SR onwards (see 0).

In MEDLINE, PreMedline and Embase 57, 60 and 199 potential relevant references were identified, respectively. After deduplication, 234 artikels were screened based on paper and abstract of which five were retrieved for full text evaluation. Finally, no RCT that evaluated results by HPV status could be identified.

3.3.3. RQ3 & RQ4: elective lymph node dissection for patients with oral cavity cancer

3.3.3.1. Selection of studies

Selection of systematic reviews

On July 31, 2013 a search was performed to identify SRs comparing the effect of elective lymph node dissection versus watchful waiting in adult patients (≥18 years of age) diagnosed with oral cavity cancer cTanyN0M0 (research question 3) and SRs comparing the effect of selective lymph node dissection versus modified radical lymph node dissection in adult patients (≥18 years of age) diagnosed with oral cavity cancer cTanyN+M0 (research question 4). 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. In total, 109 potentially relevant references were identified after deduplication (Figure 1). Based on title and abstract 102 references were excluded. Two reviews were included (Bessell *et al.*, 2011); (Fasunla *et al.*, 2011) (Table 13) and five were excluded with reason (Table 14). One review addressed both research questions 3 and 4 (Bessell *et al.*, 2011). Because the most recent and complete review of Bessell includes all RCTs that were included in Fasunla (2011), only the results of the review of Bessell (2011) will be discussed.

Figure 1 – Study flow of selection of SRs regarding research question 3 and 4

```
┌─────────────────────────┐
│ Potentially relevant SRs│
│    identified after     │
│      deduplication      │
│         N=109           │
│                         │
│      Medline N=27       │          ┌──────────────────┐
│      Embase N=79        │─────────▶│     N= 102       │
│   CLIB/COHG/ENT N=3     │          │ Excluded on the  │
└───────────┬─────────────┘          │ basis of title and│
            │                        │     abstract     │
            ▼                        └──────────────────┘
┌─────────────────────────┐
│  Full text evaluation   │
│          N=7            │
└───────────┬─────────────┘
            │                        ┌──────────────────┐
            │                        │   Excluded N=5   │
            │                        │                  │
            │                        │  No oral cavity  │
            │─────────────────────▶ │   cancer N= 4    │
            │                        │ Lymph node level │
            │                        │  treatment  N=1  │
            │                        └──────────────────┘
            ▼
┌─────────────────────────┐
│     Included  N=2       │
│                         │
│       RQ3 N= 2          │
│       RQ4 N= 1          │
└─────────────────────────┘
```
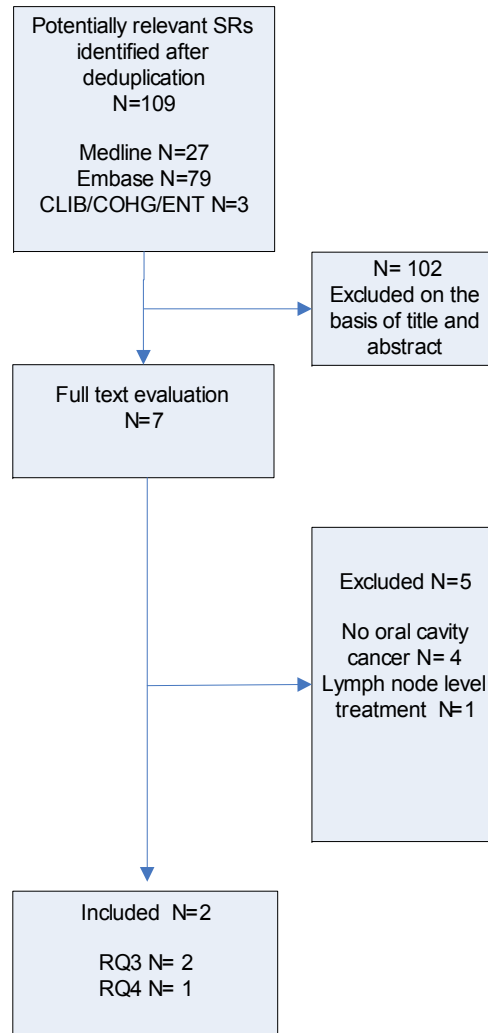
Table 13 – Included SRs regarding research question 3 and 4

Reference	Interventions
(Bessell *et al.*, 2011)[17]	Surgical treatment of the primary tumour and removal of lymph nodes in the neck (RQ3 and 4)
(Fasunla *et al.*, 2011)[18]	Elective neck dissection versus therapeutic neck dissection (RQ3)

Table 14 – Excluded SRs regarding research question 3 and 4

Reference	Reason for exclusion
(De Rosa *et al.*, 2011)	No oral cavity cancer
(Goudakos *et al.*, 2009)	No oral cavity cancer
(Servato *et al.*, 2013)	No oral cavity cancer
(Tandon *et al.*, 2011)	Lymph node level treatment
(Tanis *et al.*, 2008)	No oral cavity cancer

Selection of primary studies

On August 7, 2013 a search was performed to identify RCTs comparing the effect of elective lymph node dissection versus watchful waiting in adult patients (≥18 years of age) diagnosed with oral cavity cancer cTanyN0M0 (research question 3) and selective lymph node dissection versus modified radical lymph node dissection in adult patients (≥18 years of age) diagnosed with oral cavity cancer cTanyN+M0 (research question 4). MEDLINE, Embase and CENTRAL were searched from February 2011 onwards to identify primary studies published after the search date of the included review (Bessell *et al.*, 2011).[17] In addition, on August 12, 2013 a search was performed to identify observational studies for the same research questions. MEDLINE and Embase were searched, limited from January 2011 onwards to identify primary studies published after the search date of the Clinical Practice Guideline of the German Cancer Society (Wolff *et al.*, 2012).[19] From this guideline, six potentially relevant primary studies (RQ3: (D'Cruz *et al.*, 2009);[20] (Huang *et al.*, 2008)[21] (RQ4: (Huang *et al.*, 2008)[21]; (Patel *et al.*, 2008)[22]; (Rapoport *et al.*, 2007)[23]; (Shepard *et al.*, 2010)[24] were identified.

Two thousand two hundred and ninety-six potentially relevant references were identified (Figure 2). After deduplication, 2278 references remained. Based on title and abstract 2239 studies were excluded. Of the remaining 39 studies, 7 studies were included (Table 15) and 32 studies were excluded with reason (Table 16). In total, including the previous six studies retrieved from the CPG of the German Cancer Society, 13 studies were included, seven for research question 3 and 8 for research question 4 ((An *et al.*, 2008)[25]; (D'Cruz *et al.*, 2009)[20]; (Ebrahimi *et al.*, 2012)[26]; (Flach *et al.*, 2013)[27]; (Huang *et al.*, 2008)[21]; (Lin *et al.*, 2011)[28]; (Masuda *et al.*, 2012)[29]; (Park *et al.*, 2013)[30]; (Patel *et al.*, 2008)[22]; (Rapoport *et al.*, 2007)[23]; (Shepard *et al.*, 2010)[24]; (Yanai *et al.*, 2012)[31]; (Yildirim *et al.*, 2011)[32]).

Figure 2 – Study flow of selection of primary studies regarding research question 3 and 4
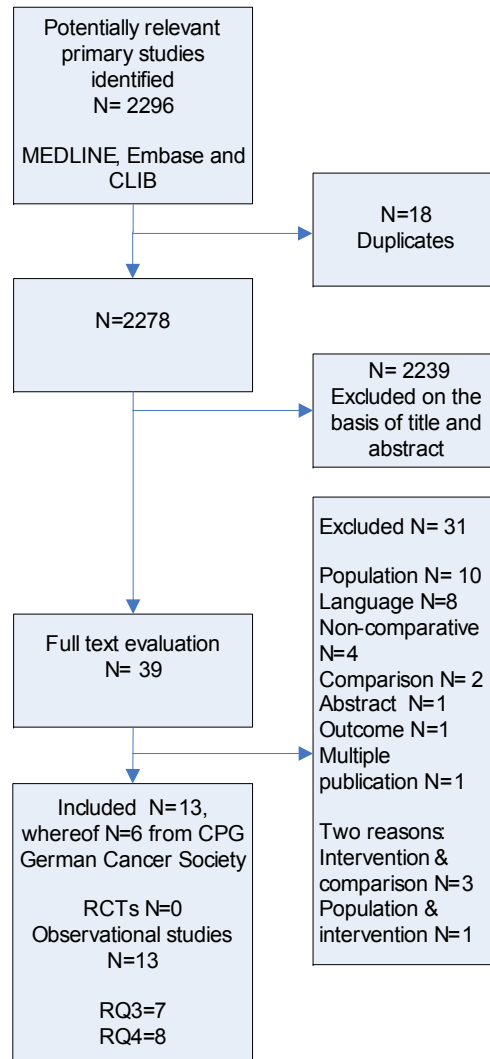
Table 15 – Included primary studies regarding research question 3 and 4

Reference	Interventions	RQ
(An *et al.*, 2008)[25]	Elective unilateral neck dissection **vs** Observation	3
(D'Cruz *et al.*, 2009)[20]	Elective neck (supra-omohyoid neck dissection and modified radical neck dissection) **vs** Wait and watch	3
(Ebrahimi *et al.*, 2012)[26]	Elective neck dissection (including bilateral procedures) **vs** Observation	3
(Flach *et al.*, 2013)[27]	Direct elective neck dissection **vs** Wait and scan policy	3
(Huang *et al.*, 2008)[21]	Elective neck dissection (supraomohyoid neck dissection and modified radical neck dissection **vs** Observation	3 & 4
(Lin *et al.*, 2011)[28]	Elective neck dissection (ipsilateral selective neck dissection (I-III)) **vs** Observation	3
(Masuda *et al.*, 2012)[29]	Elective selective neck dissection **vs** Elective comprehensive neck dissection (modified radical neck dissection)	4
(Park *et al.*, 2013)[30]	Selective neck dissection **vs** Conversion from SND to modified radical neck dissection	4
(Patel *et al.*, 2008)[22]	Selective neck dissection **vs** Comprehensive (radical or modified radical) neck dissection	4
(Rapoport *et al.*, 2007)[23]	Selective neck dissection **vs** Radical neck dissection	4
(Shepard *et al.*, 2010)[24]	Selective neck dissection **vs** Comprehensive neck dissection	4
(Yanai *et al.*, 2012)[31]	Elective neck dissection (selective submandibular neck dissection and modified radical neck dissection) **vs** Observation	3 & 4
(Yildirim *et al.*, 2011)[32]	Selective neck dissection **vs** Comprehensive neck dissection	4

Table 16 – Excluded primary studies regarding research question 3 and 4

Reference	Reason for exclusion	RQ
(Broglie *et al.*, 2011)	Comparison not relevant	3
(Canis *et al.*, 2012)	Population	3
(Dequanter *et al.*, 2013)	Non comparative study	3
(Guo *et al.*, 2005)	Article in Chinese	3
(Hoch *et al.*, 2012)	Non comparative study	3
(Lanzer *et al.*, 2012)	Population not relevant	3
(Liu *et al.*, 2006)	Article in Chinese	3
(Liu *et al.*, 2011)	Population not relevant	3
(Montes *et al.*, 2011)	Outcomes not relevant	3
(Murer *et al.*, 2011)	Comparison not relevant	3
(Poeschl *et al.*, 2012)	Population not relevant	3
(Psychogios *et al.*, 2013)	Population not relevant	3
(Pugazhendi *et al.*, 2012)	Population not relevant	3
(Tai *et al.*, 2012)	Population not relevant	3
(Vergeer *et al.*, 2011)	Population not relevant	3
(Vijayakumar *et al.*, 2011)	Intervention & comparison not relevant	3
(Yamauchi *et al.*, 2012)	Population not relevant	3
(Yuasa-Nakagawa *et al.*, 2013)	Non comparative study	3
(Zhong *et al.*, 2010)	Article in Chinese	3
(Baserer and Damar, 2011)	Article in Turkish	4

(Cong *et al.*, 2012)	Article in Chinese	4
(Di *et al.*, 2005)	Article in Chinese	4
(Givi *et al.*, 2012)	Non comparative study	4
(Kohler *et al.*, 2010)	Intervention & comparison not relevant	4
(Tao *et al.*, 2008)	Article in Chinese	4
(Uppal *et al.*, 2012)	Conference abstract	4
(Walen *et al.*, 2011)	Intervention & comparison not relevant	4
(Wang *et al.*, 2005)	Population not relevant	4
(Wang *et al.*, 2013)	Article in Chinese	4

3.3.3.2. Quality appraisal

The methodological quality of included studies was assessed by pairs of two researchers independently (FW, PH and RS). Any disagreements were resolved by discussion or with consultation of a third researcher (ML or LH) in case of persisting disagreement. Content experts were involved to judge any other flaws that could have been overlooked by non-content experts.

Table 17 shows the results of the risk of bias assessment for the one included systematic review (Bessell *et al.*, 2011).[17] The review scored positively on all AMSTAR items. The item 'Appropriate methods to combine findings' (one of the key domains) was scored positive because the authors correctly decided to refrain from pooling because of differences in type of surgery and duration of follow-up made meta-analysis inappropriate. Overall, the SR is considered as having a 'low risk' of bias (Table 17).

Figure 3 and Figure 4 show the results of the risk of bias assessment for the RCTs that were included in the review for RQ3 (Vandenbrouck *et al.*, 1980)[33]; (Fakih *et al.*, 1989)[34]; (Kligerman *et al.*, 1994)[35]; (Yuen *et al.*, 2009)[36] and RQ4 (Bier, 1994)[37]; (BHNCSG, 1998)[38] combined. 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. Due to insufficient information on allocation concealment and blinding an unclear risk of selection bias, performance bias and detection bias was scored for all studies, except for Vandenbrouck (1980).[33] The items 'Blinding of participants and personnel (performance bias)', 'Blinding of outcome assessment (detection bias)' and 'Incomplete outcome data (attrition bias)' were not assessed separately for two groups of outcomes - objective outcomes and subjective outcomes - by the review authors (Bessell *et al.*, 2011).[17]

The results of the risk of bias assessment for the seven comparative observational studies for RQ 3 are presented in Figure 5 and Figure 6 and for the eight studies for RQ4 in Figure 7 and Figure 8. Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), none of the studies scored a 'low risk' of bias on all items. Only for the item 'Blinding of the outcome assessor', a 'low risk' of bias was scored for all studies for RQ3 and 4, except for Yildrim (2011)[32] for which this item was scored 'unclear'. The item 'Comparability of the intervention and comparative group' was scored as unclear or 'high risk' of confounding by indication for most studies. No adjustment for demonstrated baseline differences or no specification of baseline differences was made in these studies.

Table 17 – Methodological quality of the included systematic review (AMSTAR) Bessell 2011

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	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	Approp-riate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
(Bessell *et al.*, 2011)[17]	+	+	+	+	+	+	+	+	+	+	+

Figure 3 – Risk of bias summary of RCTs for RQ3 and RQ4 adapted from Bessell 2011

Figure 4 – Risk of bias summary per item of RCTs for RQ3 and 4 adapted from Bessell 2011

Figure 5 – Risk of bias summary of the comparative observational studies RQ3

Figure 6 – Risk of bias summary per item of the comparative observational studies RQ3

Figure 7 – Risk of bias summary of the comparative observational studies RQ4

Figure 8 – Risk of bias summary per item of the comparative observational studies RQ4
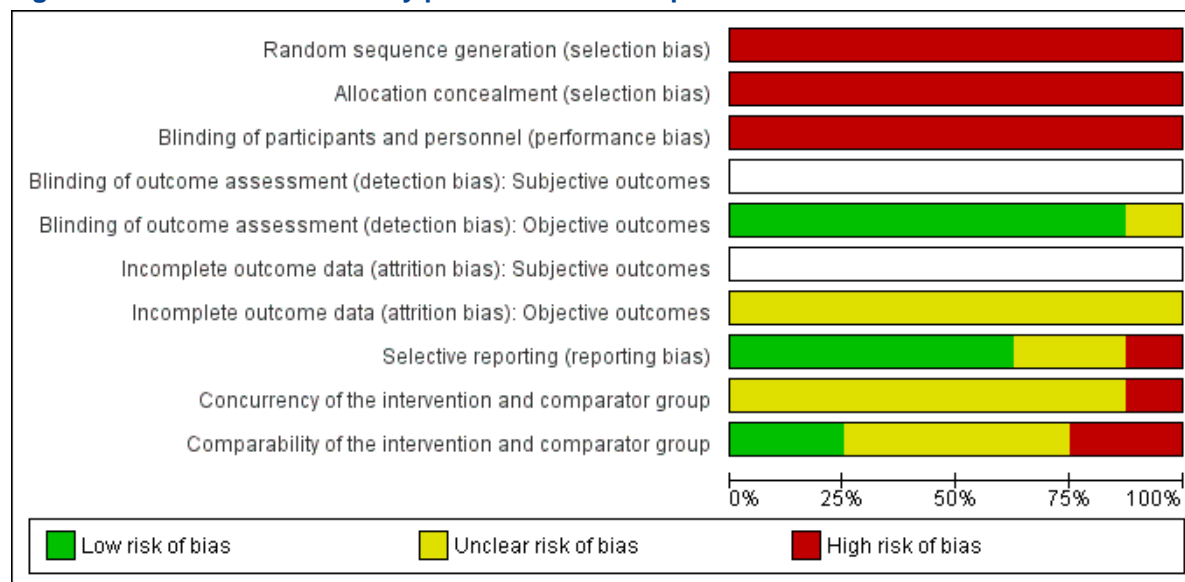
3.3.4. RQ5: elective lymph node dissection of contralateral neck

3.3.4.1. Selection of systematic reviews

The search for SRs evaluating the benefits and harms of elective neck dissection of the contralateral neck in patients with OCSCC, published since 2008, was performed on July 3, 2013. The following databases were searched: MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DARE).

In MEDLINE, PreMedline, Embase and the Cochrane databases 150, 2, 13 and 9 potentially relevant references were identified, respectively (Figure 9). After de-duplication 170 references remained. Based on title and abstract 3 reviews were selected for full-text evaluation and based on the full-text evaluation, all reviews were excluded (Table 18).

Figure 9 – Study flow of selection of SRs
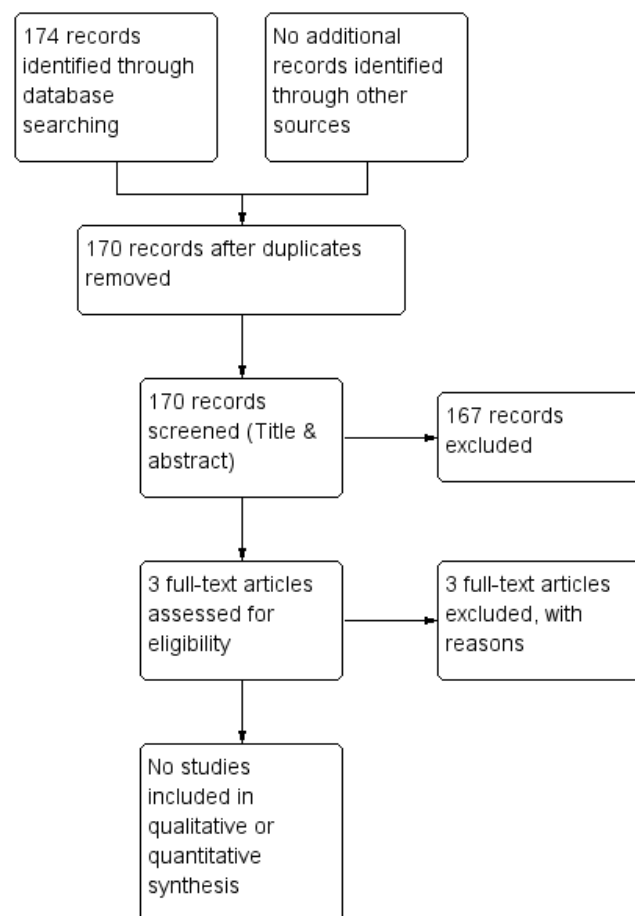
Table 18 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Bessell A et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database Syst Rev. 2011: CD006205.	Topic is not covered
Fan S et al. A review of clinical and histological parameters associated with contralateral neck metastases in oral squamous cell carcinoma. Int J Oral Sci 2011; 3(4): 180-91.	Narrative review
Fasunla A et al. A meta-analysis of the randomized controlled trials on elective neck dissection versus therapeutic neck dissection in oral cavity cancers with clinically node-negative neck. Oral Oncol 2011; 47(5): 320-4.	Topic is not covered

3.3.4.2. Selection of primary studies

On August 12, 2013 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify RCTs and observational studies evaluating the benefits and harms of elective neck dissection of the contralateral neck in patients with OCSCC, published from 2003 onwards. In MEDLINE, PreMedline and Embase 295, 8 and 161 potentially relevant references were identified, respectively (Figure 10); no references were found in CENTRAL. After de-duplication, 397 references remained. Based on title and abstract 391 articles were excluded. Of the remaining 6 studies, 3 studies were included after full-text evaluation; the rationale for exclusion of the other 3 articles is presented in Table 19.

Figure 10 – Study flow of selection of primary studies
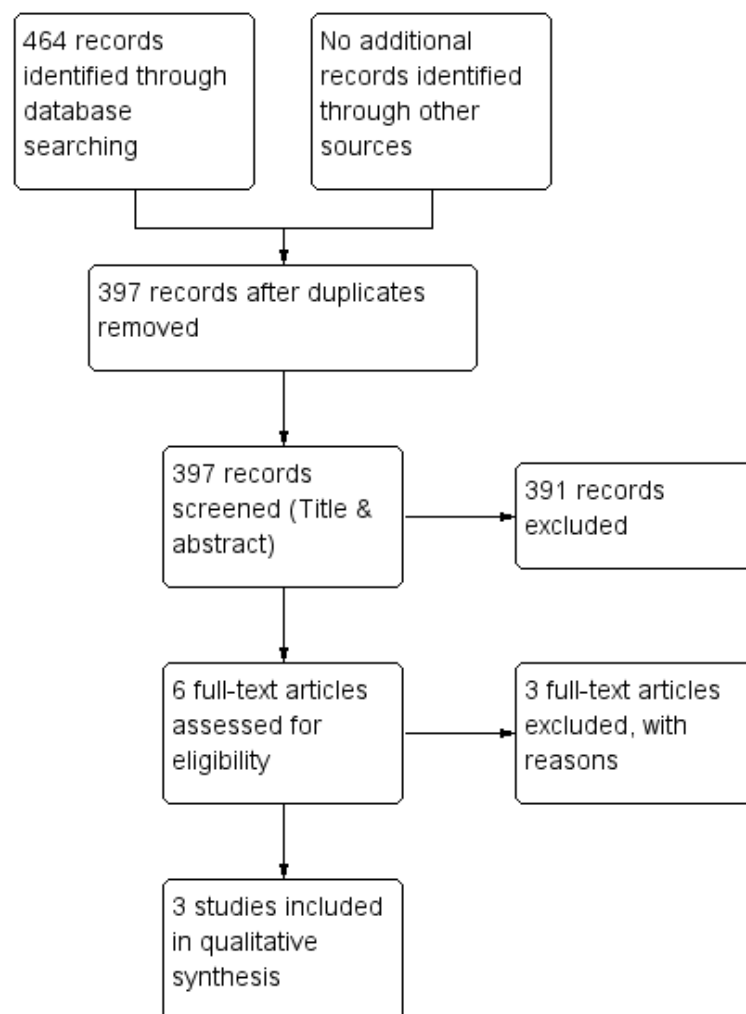
Table 19 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Capote-Moreno A et al. Prognostic factors influencing contralateral neck lymph node metastases in oral and oropharyngeal carcinoma. J Oral Maxillofac Surg 2010; 68(2): 268-75.	Data not separately presented for OCSCC and oropharyngeal cancer
Lim C and Choi EC. Unilateral, clinically T2N0, squamous cell carcinoma of the tongue: surgical outcome analysis. Int J Oral Maxillofac Surg 2007; 36(7): 610-4.	Data not separately presented for patients who had and who did not have elective neck dissection of the contralateral neck
Ellabban M A et al. Management of the clinically no neck in oral and oropharyngeal carcinoma in cotland. Eur J Plast Surg 2010; 33(6): 331-339.	Data not separately presented for patients who had oral cavity squamous cell carcinoma and oropharyngeal squamous cell carcinoma; elective neck treatment (ELNT) included prophylactic neck treatment in the form of surgical elective neck dissection (END), chemo-irradiation, or both.

3.3.4.3. Quality appraisal of selected primary studies

Figure 11 – Risk of bias summary of included primary studies

3.3.5. RQ6: value of PET / MRI in the decision of neck dissection after CRT

3.3.5.1. Selection of systematic reviews

The search for SRs evaluating the value of PET and MRI in the decision of neck dissection after (at least) chemoradiotherapy (CRT) in patients with head & neck squamous cell carcinoma (HNSCC), was performed on November 26, 2013. The following databases were searched: MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DARE).

In MEDLINE, Embase and the Cochrane databases 82 (after de-depulication), 13 and 10 potentially relevant references were identified, respectively (Figure 12); no additional systematic reviews were retrieved in pre-medline. After de-duplication 91 references remained. Based on title and abstract 4 reviews (all on the value of PET in the decision of neck dissection after CRT) were selected for full-text evaluation and based on the full-text evaluation, another 2 reviews were excluded (Table 20). No systematic reviews evaluated the diagnostic value of MRI in the decision of neck dissection after (at least) chemoradiotherapy in patients with head & neck squamous cell carcinoma.

Figure 12 – Study flow of SR selection
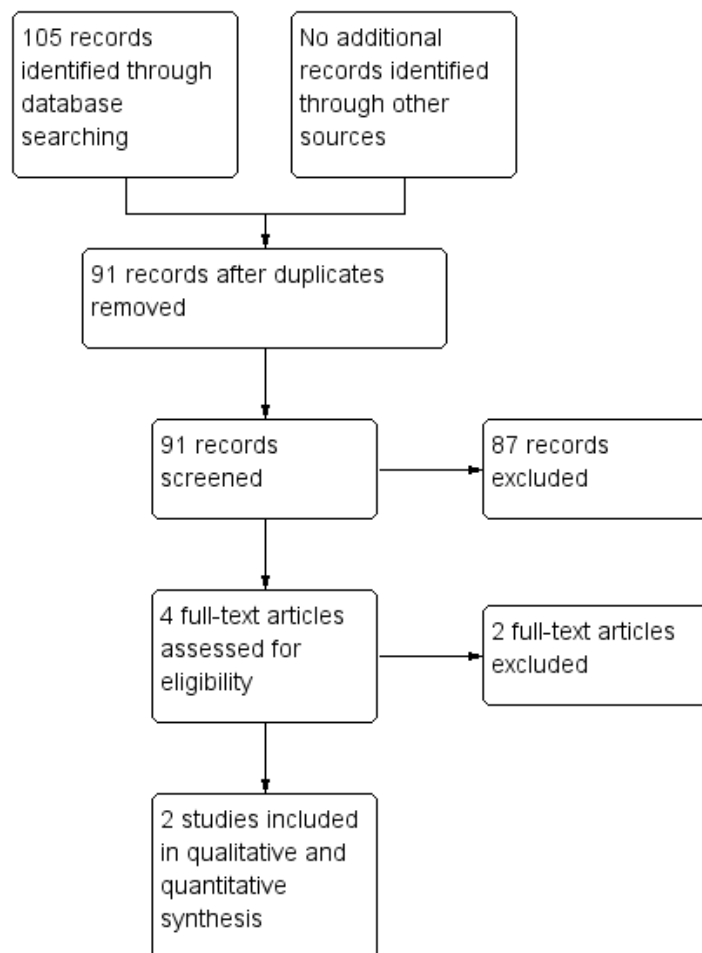
Table 20 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Bar-Ad V, Mishra M, Ohri N, Intenzo C. Positron emission tomography for neck evaluation following definitive treatment with chemoradiotherapy for locoregionally advanced head and neck squamous cell carcinoma. Rev Recent Clin Trials. 2012;7(1):36-41.	Narrative (clinical) review
Yoo J, Henderson S, Walker-Dilks C. Evidence-based guideline recommendations on the use of positron emission tomography imaging in head and neck cancer. Clin Oncol (R Coll Radiol). 2013;25(4):e33-66.	Topic is not covered

3.3.5.2. Quality appraisal of selected systematic reviews

Table 21 shows the results of the risk of bias assessment for the 2 included systematic reviews, using AMSTAR criteria.

Table 21 – 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	List of in- and exclude d studies	Charac-teristics of included studies provided	Study quality assessed and docu-mented	Quality assess-ment used in conclus-ions	Approp-riate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated	Global evalua-tion
Gupta 2011[39]	N	Y	Y	N	N	Y	Y	N	Y	N	N	Moderate
Isles 2008[40]	N	Y	Y	N	N	Y	Y	N	Y	N	N	Moderate

Both reviews critically appraised the primary studies with the Quadas 1 tool, but as not all included studies were applicable for our research question, both reviews only served as a source for primary studies. Where available, data on quality appraisal and diagnostic accuracy were used. Full texts were ordered to extract absolute numbers of true-positive, true-negative, false-positive and false-negative assessments for neck nodes. Isles et al.[40] reviewed 27 studies, Gupta et al.[41] 51; after de-duplication (i.e. 19 primary studies were included in both) 59 primary studies were searched for. Primary studies were excluded if 1) patients were N0 before CRT treatment, 2) if the majority of patients had nasopharyngeal cancer, 3) the treatment did not include CRT (at least ½ of the pts received CRT), 4) no separate data on residual neck disease (separately from the primary site) were available, 5) only recurrence was evaluated and 6) if the evaluation with PET(/CT) was not done within (a me(di)an of) 6 months after CRT. Based on these criteria 44 primary studies were excluded (see Table 22), leaving 15 studies for meta-analysis.

Table 22 – Excluded primary studies cited in Gupta 2011 and/or Isles 2008 and the reasons for exclusion

Reference	Reason(s) for exclusion
Abgral R, Querellou S, Potard G, Le Roux PY, Le Duc-Pennec A, Marianovski R, et al. Does 18F-FDG PET/CT improve the detection of posttreatment recurrence of head and neck squamous cell carcinoma in patients negative for disease on clinical follow-up? J Nucl Med. 2009;50(1):24-9.	MRI/PET not done within (a me(di)an of) 6 months after CRT
Andrade RS, Heron DE, Degirmenci B, Filho PA, Branstetter BF, Seethala RR, et al. Posttreatment assessment of response using FDG-PET/CT for patients treated with definitive radiation therapy for head and neck cancers. Int J Radiat Oncol Biol Phys. 2006;65(5):1315-22.	No separate evaluation of lymph nodes
Bongers V, Hobbelink MG, van Rijk PP, Hordijk GJ. Cost-effectiveness of dual-head 18F-fluorodeoxyglucose PET for the detection of recurrent laryngeal cancer. Cancer Biother Radiopharm. 2002;17(3):303-6.	Treatment did not include CRT
Chaiken L, Rege S, Hoh C, Choi Y, Jabour B, Juillard G, et al. Positron emission tomography with fluorodeoxyglucose to evaluate tumor response and control after radiation therapy. Int J Radiat Oncol Biol Phys. 1993;27(2):455-64.	Treatment did not include CRT
Cheon GJ, Chung JK, So Y, Choi JY, Kim BT, Jeong JM, et al. Diagnostic Accuracy of F-18 FDG-PET in the Assessment of Posttherapeutic Recurrence of Head and Neck Cancer. Clin Positron Imaging. 1999;2(4):197-204.	MRI/PET not done within (a me(di)an of) 6 months after CRT
Cho AH, Shah S, Ampil F, Bhartur S, Nathan CO. N2 disease in patients with head and neck squamous cell cancer treated with chemoradiotherapy: is there a role for posttreatment neck dissection? Arch Otolaryngol Head Neck Surg. 2009;135(11):1112-8.	Mix of residual and recurrent disease in the lymph nodes
Connell CA, Corry J, Milner AD, Hogg A, Hicks RJ, Rischin D, et al. Clinical impact of, and prognostic stratification by, F-18 FDG PET/CT in head and neck mucosal squamous cell carcinoma. Head Neck. 2007;29(11):986-95.	No absolute numbers of TP, TN, FP & FN
Enomoto K, Inohara H, Higuchi I, Hamada K, Tomiyama Y, Kubo T, et al. Prognostic Value of FDG-PET in patients with oropharyngeal carcinoma treated with concurrent chemoradiotherapy. Mol Imaging Biol. 2008;10(4):224-9.	No absolute numbers of TP & TN
Farber LA, Benard F, Machtay M, Smith RJ, Weber RS, Weinstein GS, et al. Detection of recurrent head and neck squamous cell carcinomas after radiation therapy with 2-18F-fluoro-2-deoxy-D-glucose positron emission tomography. Laryngoscope. 1999;109(6):970-5.	Only few patients received CRT
Fischbein NJ, OS AA, Caputo GR, Kaplan MJ, Singer MI, Price DC, et al. Clinical utility of positron emission tomography with 18F-fluorodeoxyglucose in detecting residual/recurrent squamous cell carcinoma of the head and neck. AJNR Am J Neuroradiol. 1998;19(7):1189-96.	Treatment did not include CRT
Gandhi D, Falen S, McCartney W, Shockley W, Weissler M, Wrenn S, et al. Value of 2-[18F]-fluoro-2-deoxy-D-glucose imaging with dual-head gamma camera in coincidence mode: comparison with computed tomography/magnetic resonance imaging in patients with suspected recurrent head and neck cancers. J Comput Assist Tomogr. 2005;29(4):513-9.	No PET
Goerres GW, Schmid DT, Bandhauer F, Huguenin PU, von Schulthess GK, Schmid S, et al. Positron emission tomography in the early follow-up of advanced head and neck cancer. Arch Otolaryngol Head Neck Surg. 2004;130(1):105-9; discussion 20-1.	No separate data on lymph nodes

Reference	Reason(s) for exclusion
Goguen LA, Posner MR, Tishler RB, Wirth LJ, Norris CM, Annino DJ, et al. Examining the need for neck dissection in the era of chemoradiation therapy for advanced head and neck cancer. Arch Otolaryngol Head Neck Surg. 2006;132(5):526-31.	No separate data on lymph nodes
Greven KM, Williams DW, 3rd, Keyes JW, Jr., McGuirt WF, Watson NE, Jr., Randall ME, et al. Positron emission tomography of patients with head and neck carcinoma before and after high dose irradiation. Cancer. 1994;74(4):1355-9.	Treatment did not include CRT
Greven KM, Williams DW, 3rd, McGuirt WF, Sr., Harkness BA, D'Agostino RB, Jr., Keyes JW, Jr., et al. Serial positron emission tomography scans following radiation therapy of patients with head and neck cancer. Head Neck. 2001;23(11):942-6.	Treatment did not include CRT
Horiuchi C, Taguchi T, Yoshida T, Nishimura G, Kawakami M, Tanigaki Y, et al. Early assessment of clinical response to concurrent chemoradiotherapy in head and neck carcinoma using fluoro-2-deoxy-d-glucose positron emission tomography. Auris Nasus Larynx. 2008;35(1):103-8.	No data on lymph nodes
Hoshikawa H, Mitani T, Nishiyama Y, Yamamoto Y, Ohkawa M, Mori N. Evaluation of the therapeutic effects and recurrence for head and neck cancer after chemoradiotherapy by FDG-PET. Auris Nasus Larynx. 2009;36(2):192-8.	Qualitative (visual inspection) and semi-quantitative evaluation (standardized uptake value) of PET
Ito K, Yokoyama J, Kubota K, Morooka M, Shiibashi M, Matsuda H. 18F-FDG versus 11C-choline PET/CT for the imaging of advanced head and neck cancer after combined intra-arterial chemotherapy and radiotherapy: the time period during which PET/CT can reliably detect non-recurrence. Eur J Nucl Med Mol Imaging. 2010;37(7):1318-27.	Only recurrence evaluated
Kao J, Vu HL, Genden EM, Mocherla B, Park EE, Packer S, et al. The diagnostic and prognostic utility of positron emission tomography/computed tomography-based follow-up after radiotherapy for head and neck cancer. Cancer. 2009;115(19):4586-94.	No absolute numbers of TP, TN, FP & FN
Kim HJ, Boyd J, Dunphy F, Lowe V. F-18 FDG PET scan after radiotherapy for early-stage larynx cancer. Clin Nucl Med. 1998;23(11):750-2.	Treatment did not include CRT
Kim SY, Lee SW, Nam SY, Im KC, Kim JS, Oh SJ, et al. The Feasibility of 18F-FDG PET scans 1 month after completing radiotherapy of squamous cell carcinoma of the head and neck. J Nucl Med. 2007;48(3):373-8.	Only 50% of the patients received CRT
Krabbe CA, Pruim J, Dijkstra PU, Balink H, van der Laan BF, de Visscher JG, et al. 18F-FDG PET as a routine posttreatment surveillance tool in oral and oropharyngeal squamous cell carcinoma: a prospective study. J Nucl Med. 2009;50(12):1940-7.	Only 5/48 patients received CRT
Kubota K, Yokoyama J, Yamaguchi K, Ono S, Qureshy A, Itoh M, et al. FDG-PET delayed imaging for the detection of head and neck cancer recurrence after radio-chemotherapy: comparison with MRI/CT. Eur J Nucl Med Mol Imaging. 2004;31(4):590-5.	No separate data on lymph nodes
Lee JC, Kim JS, Lee JH, Nam SY, Choi SH, Lee SW, et al. F-18 FDG-PET as a routine surveillance tool for the detection of recurrent head and neck squamous cell carcinoma. Oral Oncol. 2007;43(7):686-92.	Only recurrence evaluated
Li P, Zhuang H, Mozley PD, Denittis A, Yeh D, Machtay M, et al. Evaluation of recurrent squamous cell carcinoma	MRI/PET not done within (a me(di)an

Reference	Reason(s) for exclusion
of the head and neck with FDG positron emission tomography. Clin Nucl Med. 2001;26(2):131-5.	of) 6 months after CRT
Lowe VJ, Boyd JH, Dunphy FR, Kim H, Dunleavy T, Collins BT, et al. Surveillance for recurrent head and neck cancer using positron emission tomography. J Clin Oncol. 2000;18(3):651-8.	No separate data on lymph nodes
Malone JP, Gerberi MA, Vasireddy S, Hughes LF, Rao K, Shevlin B, et al. Early prediction of response to chemoradiotherapy for head and neck cancer: reliability of restaging with combined positron emission tomography and computed tomography. Arch Otolaryngol Head Neck Surg. 2009;135(11):1119-25.	No absolute numbers of TP, TN, FP & FN
Martin RC, Fulham M, Shannon KF, Hughes C, Gao K, Milross C, et al. Accuracy of positron emission tomography in the evaluation of patients treated with chemoradiotherapy for mucosal head and neck cancer. Head Neck. 2009;31(2):244-50.	No separate evaluation of lymph nodes
Nam SY, Lee SW, Im KC, Kim JS, Kim SY, Choi SH, et al. Early evaluation of the response to radiotherapy of patients with squamous cell carcinoma of the head and neck using 18FDG-PET. Oral Oncol. 2005;41(4):390-5.	Patients received RT
Nayak JV, Walvekar RR, Andrade RS, Daamen N, Lai SY, Argiris A, et al. Deferring planned neck dissection following chemoradiation for stage IV head and neck cancer: the utility of PET-CT. Laryngoscope. 2007;117(12):2129-34.	Mix of residual and recurrent disease in the lymph nodes
Oe A, Kawabe J, Torii K, Kawamura E, Kotani J, Hayashi T, et al. Detection of local residual tumor after laryngeal cancer treatment using FDG-PET. Ann Nucl Med. 2007;21(1):9-13.	Only evaluation of local residual disease
Passero VA, Branstetter BF, Shuai Y, Heron DE, Gibson MK, Lai SY, et al. Response assessment by combined PET-CT scan versus CT scan alone using RECIST in patients with locally advanced head and neck cancer treated with chemoradiotherapy. Ann Oncol. 2010;21(11):2278-83.	No absolute numbers of TP, TN, FP & FN
Porceddu SV, Jarmolowski E, Hicks RJ, Ware R, Weih L, Rischin D, et al. Utility of positron emission tomography for the detection of disease in residual neck nodes after (chemo)radiotherapy in head and neck cancer. Head Neck. 2005;27(3):175-81.	Not all patients received CRT
Rege S, Maass A, Chaiken L, Hoh CK, Choi Y, Lufkin R, et al. Use of positron emission tomography with fluorodeoxyglucose in patients with extracranial head and neck cancers. Cancer. 1994;73(12):3047-58.	No evaluation of residual disease in lymph nodes
Rogers JW, Greven KM, McGuirt WF, Keyes JW, Jr., Williams DW, 3rd, Watson NE, et al. Can post-RT neck dissection be omitted for patients with head-and-neck cancer who have a negative PET scan after definitive radiation therapy? Int J Radiat Oncol Biol Phys. 2004;58(3):694-7.	Treatment did not include CRT
Ryan WR, Fee WE, Jr., Le QT, Pinto HA. Positron-emission tomography for surveillance of head and neck cancer. Laryngoscope. 2005;115(4):645-50.	Not all patients received CRT
Salaun PY, Abgral R, Querellou S, Couturier O, Valette G, Bizais Y, et al. Does 18fluoro-fluorodeoxyglucose positron emission tomography improve recurrence detection in patients treated for head and neck squamous cell carcinoma with negative clinical follow-up? Head Neck. 2007;29(12):1115-20.	PET not done within (a me(di)an of) 6 months after CRT
Stokkel MP, Terhaard CH, Hordijk GJ, van Rijk PP. The detection of local recurrent head and neck cancer with fluorine-18 fluorodeoxyglucose dual-head positron emission tomography. Eur J Nucl Med. 1999;26(7):767-73.	Treatment did not include CRT

Reference	Reason(s) for exclusion
Stokkel MP, Terhaard CH, Mertens IJ, Hordijk GJ, van Rijk PP. Fluorine-18-FDG detection of laryngeal cancer postradiotherapy using dual-head coincidence imaging. J Nucl Med. 1998;39(8):1385-7.	Treatment did not include CRT
Tan A, Adelstein DJ, Rybicki LA, Saxton JP, Esclamado RM, Wood BG, et al. Ability of positron emission tomography to detect residual neck node disease in patients with head and neck squamous cell carcinoma after definitive chemoradiotherapy. Arch Otolaryngol Head Neck Surg. 2007;133(5):435-40.	Mix of residual and recurrent disease in the lymph nodes
Terhaard CH, Bongers V, van Rijk PP, Hordijk GJ. F-18-fluoro-deoxy-glucose positron-emission tomography scanning in detection of local recurrence after radiotherapy for laryngeal/ pharyngeal cancer. Head Neck. 2001;23(11):933-41.	Treatment did not include CRT
Ware RE, Matthews JP, Hicks RJ, Porceddu S, Hogg A, Rischin D, et al. Usefulness of fluorine-18 fluorodeoxyglucose positron emission tomography in patients with a residual structural abnormality after definitive treatment for squamous cell carcinoma of the head and neck. Head Neck. 2004;26(12):1008-17.	Not all patients received CRT
Yao M, Smith RB, Hoffman HT, Funk GF, Lu M, Menda Y, et al. Clinical significance of postradiotherapy [18F]-fluorodeoxyglucose positron emission tomography imaging in management of head-and-neck cancer-a long-term outcome report. Int J Radiat Oncol Biol Phys. 2009;74(1):9-14.	Not all patients received CRT
Yen TC, Lin CY, Wang HM, Huang SF, Liao CT, Kang CJ, et al. 18F-FDG-PET for evaluation of the response to concurrent chemoradiation therapy with intensity-modulated radiation technique for Stage T4 nasopharyngeal carcinoma. Int J Radiat Oncol Biol Phys. 2006;65(5):1307-14.	Only nasopharyngeal cancer

3.3.5.3. Selection of primary studies evaluating the value of PET(/CT)

On January 3 & 6, 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify RCTs and observational studies evaluating the value of PET in the decision of neck dissection after (at least) chemoradiotherapy (CRT) in patients with head & neck squamous cell carcinoma (HNSCC), published from 2010 (i.e. search date review by Gupta et al.) onwards. In MEDLINE, PreMedline, Embase and CENTRAL 210, 7, 193 and 1 potentially relevant references were identified, respectively (Figure 13). After de-duplication, 350 references remained. Based on title and abstract 27 articles were excluded. Of these 27 studies, 7 were excluded as they were confined to congress abstracts and 2 as they had been included in the Gupta et al. review. After full-text evaluation 6 studies were included; the rationale for exclusion of the other 12 articles is presented in Table 23.

Figure 13 – Study flow of selection of primary studies evaluating the value of PET
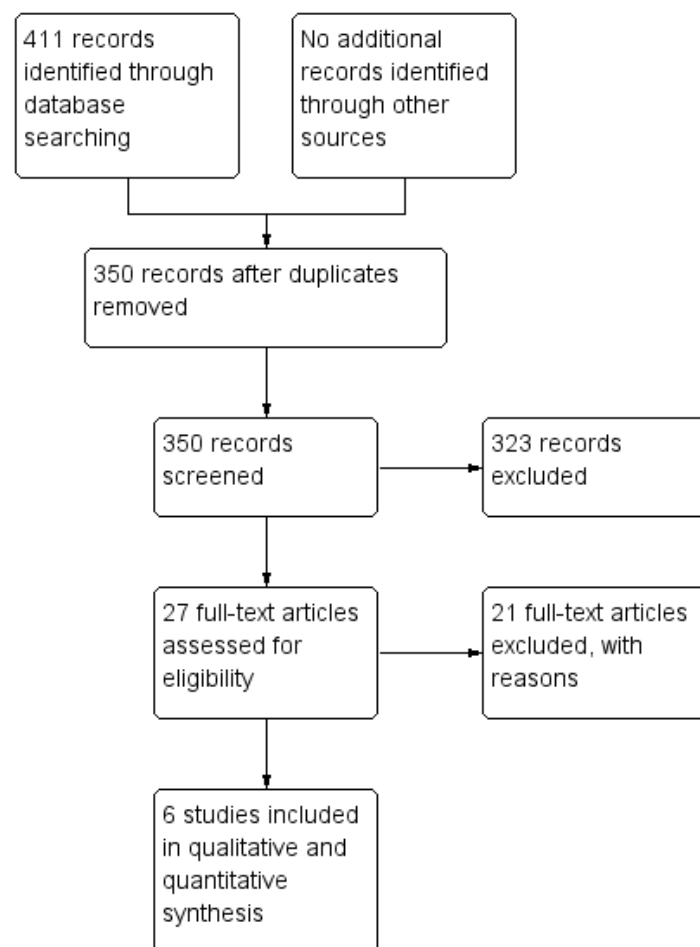
Table 23 – Excluded primary PET(/CT) studies based on full-text evaluation

Reference	Reason(s) for exclusion
Ghanooni R, Delpierre I, Magremanne M, Vervaet C, Dumarey N, Remmelink M, et al. 18F-FDG PET/CT and MRI in the follow-up of head and neck squamous cell carcinoma. Contrast Media Mol Imaging. 2011;6(4):260-6.	Only 13/32 patients received CRT
Gilbert MR, Branstetter BFt, Kim S. Utility of positron-emission tomography/computed tomography imaging in the management of the neck in recurrent laryngeal cancer. Laryngoscope. 2012;122(4):821-5.	Unclear what the primary treatment was
Hoshikawa H, Kishino T, Nishiyama Y, Yamamoto Y, Yonezaki M, Mori N. Early prediction of local control in head and neck cancer after chemoradiotherapy by FDG-PET. Nucl Med Commun. 2011;32(8):684-9.	No separate LN evaluation; no absolute TP, FP, TN, FN data
Hoshikawa H, Mori T, Kishino T, Yamamoto Y, Inamoto R, Akiyama K, et al. Changes in (18)F-fluorothymidine and (18)F-fluorodeoxyglucose positron emission tomography imaging in patients with head and neck cancer treated with chemoradiotherapy. Ann Nucl Med. 2013;27(4):363-70.	No absolute TP, FP, TN, FN data
Inokuchi H, Kodaira T, Tachibana H, Nakamura T, Tomita N, Nakahara R, et al. Clinical usefulness of [18F] fluoro-2-deoxy-D-glucose uptake in 178 head-and-neck cancer patients with nodal metastasis treated with definitive chemoradiotherapy: consideration of its prognostic value and ability to provide guidance for optimal selection of patients for planned neck dissection. Int J Radiat Oncol Biol Phys. 2011;79(3):747-55.	Evaluation of pre-treatment PET
Kim SY, Kim JS, Yi JS, Lee JH, Choi SH, Nam SY, et al. Evaluation of 18F-FDG PET/CT and CT/MRI with histopathologic correlation in patients undergoing salvage surgery for head and neck squamous cell carcinoma. Ann Surg Oncol. 2011;18(9):2579-84.	Only 13/39 patients received CRT
Kishino T, Hoshikawa H, Nishiyama Y, Yamamoto Y, Mori N. Usefulness of 3'-deoxy-3'-18F-fluorothymidine PET for predicting early response to chemoradiotherapy in head and neck cancer. J Nucl Med. 2012;53(10):1521-7.	No absolute TP, FP, TN, FN data
Nakamura S, Toriihara A, Okochi K, Watanabe H, Shibuya H, Kurabayashi T. Optimal timing of post-treatment [18F]fluorodeoxyglucose-PET/CT for patients with head and neck malignancy. Nucl Med Commun. 2013;34(2):162-7.	Only 38/319 patients received CRT
Ng SH, Chan SC, Yen TC, Liao CT, Lin CY, Tung-Chieh Chang J, et al. PET/CT and 3-T whole-body MRI in the detection of malignancy in treated oropharyngeal and hypopharyngeal carcinoma. Eur J Nucl Med Mol Imaging. 2011;38(6):996-1008.	PET not done within (a me(di)an of) 6 months after CRT
Nishimura G, Matsuda H, Taguchi T, Takahashi M, Komatsu M, Sano D, et al. Treatment evaluation of metastatic lymph nodes after concurrent chemoradiotherapy in patients with head and neck squamous cell carcinoma. Anticancer Res. 2012;32(2):595-600.	No separate LN evaluation; no absolute TP, FP, TN, FN data
Sher DJ, Tishler RB, Annino D, Punglia RS. Cost-effectiveness of CT and PET-CT for determining the need for adjuvant neck dissection in locally advanced head and neck cancer. Ann Oncol. 2010;21(5):1072-7.	Cost-effectiveness study
Sherriff J, McConkey C, Ogunremi T, Colley S, Sanghera P, Hartley A. The role of PET-CT imaging in head and neck cancer patients after radical chemoradiotherapy. Radiother. Oncol. 2011;99:S337.	No separate LN evaluation

3.3.5.4. Selection of primary studies evaluating the value of MRI

On January 3 & 6, 2014 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify RCTs and observational studies evaluating the value of MRI in the decision of neck dissection after (at least) chemoradiotherapy (CRT) in patients with head & neck squamous cell carcinoma (HNSCC). In MEDLINE, PreMedline, Embase and CENTRAL 782, 12, 491 and 5 potentially relevant references were identified, respectively. After de-duplication, 1130 references remained. Based on title and abstract evaluation, it was decided to exclude all articles written before 2004; based on title and abstract evaluation 17 articles were excluded. Of these 17 studies, 5 were excluded as they were confined to congress abstracts. After full-text evaluation 1 study was included; the rationale for exclusion of the other 11 articles is presented in Table 24.

Table 24 – Excluded primary MRI studies based on full-text evaluation

Reference	Reason(s) for exclusion
Ghanooni R, Delpierre I, Magremanne M, Vervaet C, Dumarey N, Remmelink M, et al. 18F-FDG PET/CT and MRI in the follow-up of head and neck squamous cell carcinoma. Contrast Media Mol Imaging. 2011;6(4):260-6.	Only 13/32 patients received CRT
Kim SY, Kim JS, Yi JS, Lee JH, Choi SH, Nam SY, et al. Evaluation of 18F-FDG PET/CT and CT/MRI with histopathologic correlation in patients undergoing salvage surgery for head and neck squamous cell carcinoma. Ann Surg Oncol. 2011;18(9):2579-84.	Only 13/39 patients received CRT
King AD, Mo FKF, Yu KH, Yeung DKW, Zhou H, Bhatia KS, et al. Squamous cell carcinoma of the head and neck: Diffusion-weighted MR imaging for prediction and monitoring of treatment response. Eur. Radiol. 2010;20(9):2213-20.	Post-treatment MRI was performed in 20 patients with a residual mass only.
King AD, Keung CK, Yu KH, Mo FKF, Bhatia KS, Yeung DKW, et al. T2-weighted MR imaging early after chemoradiotherapy to evaluate treatment response in head and neck squamous cell carcinoma. Am. J. Neuroradiol. 2013;34(6):1237-41.	Analysis for primary tumour only
Nakamoto Y, Tamai K, Saga T, Higashi T, Hara T, Suga T, et al. Clinical value of image fusion from MR and PET in patients with head and neck cancer. Mol Imaging Biol. 2009;11(1):46-53.	Imaging not performed after chemoradiation (48 patients freshly diagnosed, 15 patients during FU after surgery, 2 LN of unknown origin) Many N0 patients
Ng SH, Chan SC, Yen TC, Liao CT, Lin CY, Tung-Chieh Chang J, et al. PET/CT and 3-T whole-body MRI in the detection of malignancy in treated oropharyngeal and hypopharyngeal carcinoma. Eur J Nucl Med Mol Imaging. 2011;38(6):996-1008.	PET not done within (a me(di)an of) 6 months after CRT
Nishimura G, Matsuda H, Taguchi T, Takahashi M, Komatsu M, Sano D, et al. Treatment evaluation of metastatic lymph nodes after concurrent chemoradiotherapy in patients with head and neck squamous cell carcinoma. Anticancer Res. 2012;32(2):595-600.	No separate LN evaluation; no absolute TP, FP, TN, FN data

Reference	Reason(s) for exclusion
Tshering Vogel DW, Zbaeren P, Geretschlaeger A, Vermathen P, De Keyzer F, Thoeny HC. Diffusion-weighted MR imaging including bi-exponential fitting for the detection of recurrent or residual tumour after (chemo)radiotherapy for laryngeal and hypopharyngeal cancers. Eur Radiol. 2013;23(2):562-9.	Majority of patients N0
Van den Broek GB, Rasch CR, Pameijer FA, Peter E, van den Brekel MW, Balm AJ. Response measurement after intraarterial chemoradiation in advanced head and neck carcinoma: magnetic resonance imaging and evaluation under general anesthesia? Cancer. 2006;106(8):1722-9.	Lack of qualifying pretreatment (n=4) or posttreatment (n=10) MRI reason for exclusion 29 out of 82 patients N0 Reference standard is local failure/control three years after treatment AT PRIMARY SITE
Vandecaveye V, De Keyzer F, Nuyts S, Deraedt K, Dirix P, Hamaekers P, et al. Detection of head and neck squamous cell carcinoma with diffusion weighted MRI after (chemo)radiotherapy: Correlation between radiologic and histopathologic findings. Int. J. Radiat. Oncol. Biol. Phys. 2007;67(4):960-71.	Only patients with suspected recurrence included, median time after end of treatment 8 months (inter-quartile range 6-21 months).
Vandecaveye V, Dirix P, De Keyzer F, Op de Beeck K, Vander Poorten V, Hauben E, et al. Diffusion-weighted magnetic resonance imaging early after chemoradiotherapy to monitor treatment response in head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2012;82(3):1098-107.	MRI performed three weeks after completion of treatment. Reference standard clinical

3.3.5.5. *Methodological quality of selected primary studies*

Table 25 – Methodological quality of selected primary PET(/CT) studies

		Kishino, 2012[42]	Loo, 2011[43]	Mori, 2011[44]	Porceddu, 2011[45]	Prestwich, 2012[46]	Zundel, 2011[47]
Domain 1: Patient selection							
C. Risk of bias							
• **Was a consecutive or random sample of patients enrolled?**	Yes/No/Unclear	Unclear	Yes	Yes	Yes	Yes	Unclear
• **Was a case-control design avoided?**	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
• **Did the study avoid inappropriate exclusions?**	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
D. Concerns regarding applicability							
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Domain 2: Index test(s) *(if more than 1 index test was used, please complete for each test)*							
C. Risk of bias							
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear	NA	NA	NA	NA	NA	Yes

		Kishino, 2012[42]	Loo, 2011[43]	Mori, 2011[44]	Porceddu, 2011[45]	Prestwich, 2012[46]	Zundel, 2011[47]
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
D. Concerns regarding applicability							
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Domain 3: Reference standard							
C. Risk of bias							
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear	No	No	No	No	No	No
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear	No	No	No	No	No	No
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**High**	**High**	**High**	**High**	**High**	**High**
D. 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	**Low**	**Low**	**Low**	**Low**	**Low**	**Low**
Domain 4: Flow and timing							
B. Risk of bias							
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

		Kishino, 2012[42]	Loo, 2011[43]	Mori, 2011[44]	Porceddu, 2011[45]	Prestwich, 2012[46]	Zundel, 2011[47]
• Did all patients receive a reference standard?	Yes/No/Unclear	Yes	Yes	Yes	Yes	Yes	Yes
• Did patients receive the same reference standard?	Yes/No/Unclear	No	No	No	No	No	No
• Were all patients included in the analysis?	Yes/No/Unclear	No, 2 patients (3 nodes) had no post-CRT PET	Yes	Yes	Yes	Yes	Yes
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR	High, due to differential verification	High, due to differential verification	High, due to differential verification	High, due to differential verification	High, due to differential verification	High, due to differential verification

Table 26 – Methodological quality of selected primary MRI studies

Lin 2007[48]		
Domain 1: Patient selection		
E. Risk of bias		
• Was a consecutive or random sample of patients enrolled?	Yes/No/Unclear	unclear
• Was a case-control design avoided?	Yes/No/Unclear	yes
• Did the study avoid inappropriate exclusions?	Yes/No/Unclear	yes
Could the selection of patients have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**unclear**

Lin 2007[48]		
F. Concerns regarding applicability		
Is there concern that the included patients do not match the review question?	CONCERN: LOW/HIGH/UNCLEAR	**low**
Domain 2: Index test(s) *(if more than 1 index test was used, please complete for each test)*		
E. Risk of bias		
• **Were the index test results interpreted without knowledge of the results of the reference standard?**	Yes/No/Unclear	yes
• **If a threshold was used, was it pre-specified?**	Yes/No/Unclear	yes
Could the conduct or interpretation of the index test have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**low**
F. Concerns regarding applicability		
Is there concern that the index test, its conduct, or interpretation differ from the review question?	CONCERN: LOW/HIGH/UNCLEAR	**low**
Domain 3: Reference standard		
E. Risk of bias		
• **Is the reference standard likely to correctly classify the target condition?**	Yes/No/Unclear	no
• **Were the reference standard results interpreted without knowledge of the results of the index test?**	Yes/No/Unclear	unclear
Could the reference standard, its conduct, or its interpretation have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**unclear**
F. 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	**low**

Lin 2007[48]		
Domain 4: Flow and timing		
C. **Risk of bias**		
• **Was there an appropriate interval between index test(s) and reference standard?**	Yes/No/Unclear	no
• **Did all patients receive a reference standard?**	Yes/No/Unclear	yes
• **Did patients receive the same reference standard?**	Yes/No/Unclear	no
• **Were all patients included in the analysis?**	Yes/No/Unclear	yes
Could the patient flow have introduced bias?	RISK: LOW/HIGH/UNCLEAR	**low**

3.3.6. RQ7: neck dissection after chemoradiotherapy in patients with oral cavity cancer

3.3.6.1. Selection of studies

Selection of systematic reviews

The search for SRs evaluating the benefits and harms of elective neck dissection after chemoradiotherapy in patients with HNSCC, published since 2008, was performed on September 24, 2013. The following databases were searched: MEDLINE (including PreMedline), Embase and the Cochrane Database of Systematic Reviews (CDSR), the Health Technology Assessment Database (CLIB HTA), and the Database of Abstracts of Reviews of Effects (DARE).

In MEDLINE, Embase and the Cochrane databases 62, 6 and 2 potentially relevant references were identified, respectively (Figure 14); no additional systematic reviews were retrieved in pre-medline. After de-duplication 72 references remained. Based on title and abstract 8 reviews were selected for full-text evaluation and based on the full-text evaluation, all reviews were excluded (Table 27).

Figure 14 – Study flow of SR selection
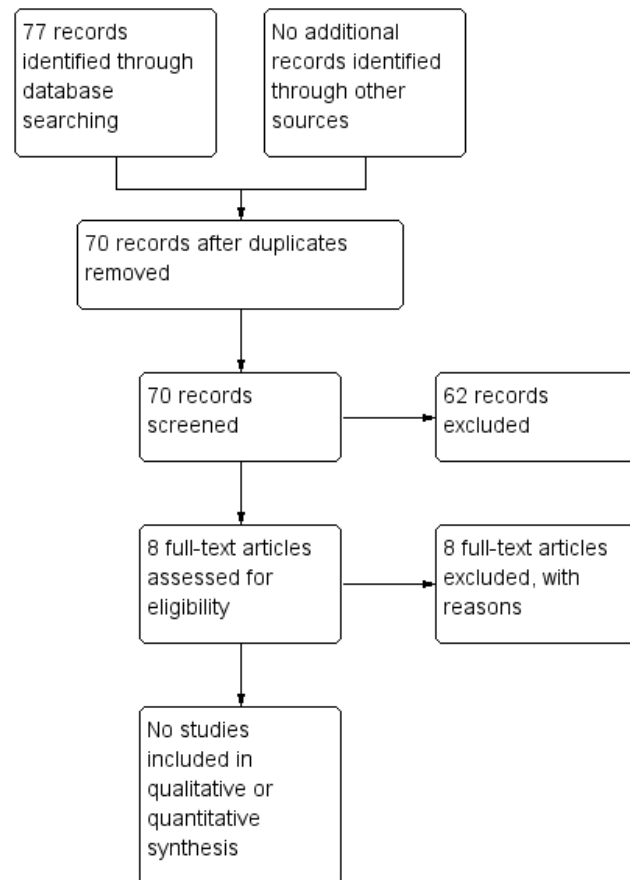
Table 27 – Reviews excluded based on full-text evaluation

Reference	Reason(s) for exclusion
Hermann RM et al. Lymph node positive head and neck carcinoma after curative radiochemotherapy: A long lasting debate on elective post-therapeutic neck dissections comes to a conclusion. Cancer Radiother. 2013;17(4):323-31.	Narrative review
Denaro N et al.The role of neck dissection after radical chemoradiation for locally advanced head and neck cancer: should we move back? Oncology. 2013;84(3):174-85.	Narrative review
Hamoir M et al. The role of neck dissection in the setting of chemoradiation therapy for head and neck squamous cell carcinoma with advanced neck disease. Oral Oncol. 2012;48(3):203-10.	Narrative review
Bessell A et al. Interventions for the treatment of oral and oropharyngeal cancers: surgical treatment. Cochrane Database Syst Rev. 2011: CD006205.	Topic is not covered
Javidnia H, Corsten MJ. Number needed to treat analysis for planned neck dissection after chemoradiotherapy for advanced neck disease. J Otolaryngol Head Neck Surg. 2010;39(6):664-8.	No characteristics of included studies provided; no scientific quality of included studies assessed
Ferlito A et al. Planned neck dissection for patients with complete response to chemoradiotherapy: a concept approaching obsolescence. Head Neck. 2010;32(2):253-61.	Narrative review
Thariat J, Hamoir M, Janot F, De Mones E, Marcy PY, Carrier P, et al. Place du curage ganglionnaire apres chimioradiotherapie dans les carcinomes epidermoides des voies aerodigestives superieures avec atteinte ganglionnaire initiale (nasopharynx exclu). Cancer Radiother. 2009;13(8):758-70.	Narrative review
Brown KM, Lango M, Ridge JA. The role of neck dissection in the combined modality therapy setting. Semin Oncol. 2008;35(3):229-35.	Narrative review

Selection of primary studies

On September 25, 2013 a search was performed in MEDLINE (including PreMedline), Embase and CENTRAL to identify RCTs and observational studies evaluating the benefits and harms of elective neck dissection of the contralateral neck in patients with OCSCC, published from 2003 onwards. In MEDLINE, PreMedline, Embase and CENTRAL 703, 17, 493 and 15 potentially relevant references were identified, respectively (Figure 15). After de-duplication, 1040 references remained. Based on title and abstract 1009 articles were excluded. Of the remaining 31 studies, 9 studies were included after full-text evaluation; the rationale for exclusion of the other 22 articles is presented in Table 28.

Figure 15 – Study flow of selection of primary studies
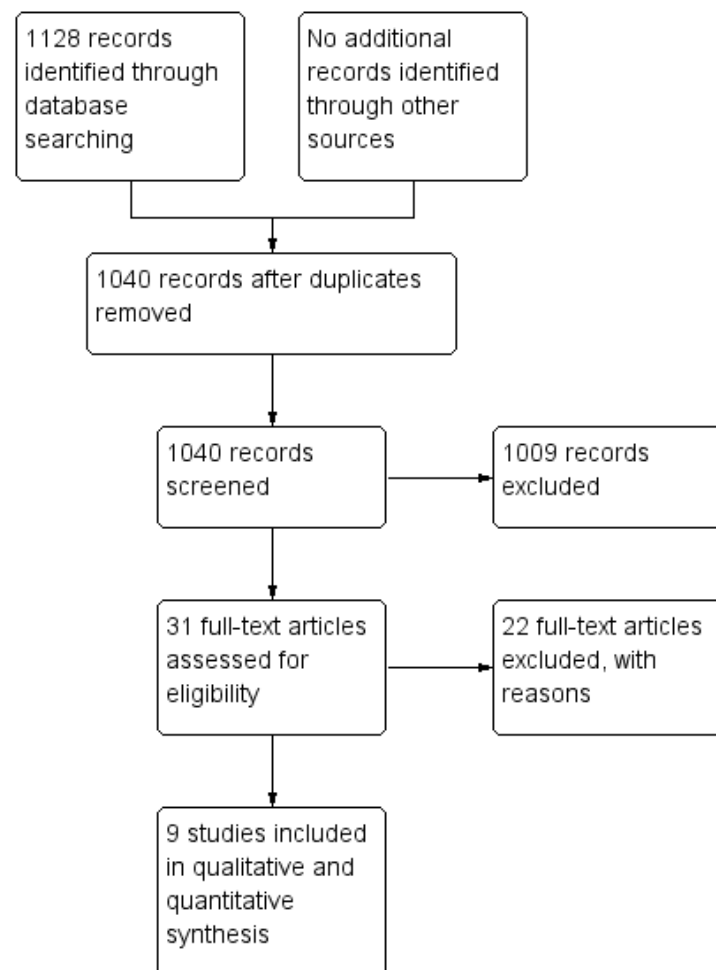
Table 28 – Excluded primary studies based on full-text evaluation

Reference	Reason(s) for exclusion
Suzuki M et al. The contribution of neck dissection for residual neck disease after chemoradiotherapy in advanced oropharyngeal and hypopharyngeal squamous cell carcinoma patients. Int J Clin Oncol. 2013;18(4):578-84.	None of the CR patients received ND
Sakashita T et al. Regional control after concomitant chemoradiotherapy without planned neck dissection in node-positive head and neck squamous cell carcinomas. Auris Nasus Larynx. 2013;40(2):211-5.	None of the CR patients received ND
Sanders JG et al. Persistent neck disease after chemoradiation for head and neck squamous cell carcinoma. J Laryngol Otol. 2012;126(11):1121-6.	None of the CR patients received ND
Loo SW et al. Neck dissection can be avoided after sequential chemoradiotherapy and negative post-treatment positron emission tomography-computed tomography in N2 head and neck squamous cell carcinoma. Clin Oncol (R Coll Radiol). 2011;23(8):512-7.	Study on diagnostic accuracy of PET-CT after CRT
Dooley LM et al. Treatment outcome in the residually positive neck after definitive chemotherapy and irradiation. Laryngoscope. 2011;121(8):1656-61.	None of the CR patients received ND
Igidbashian L et al. Outcome with neck dissection after chemoradiation for N3 head-and-neck squamous cell carcinoma. Int J Radiat Oncol Biol Phys. 2010;77(2):414-20.	None of the CR patients received ND
van der Putten L et al. Effectiveness of salvage selective and modified radical neck dissection for regional pathologic lymphadenopathy after chemoradiation. Head Neck. 2009;31(5):593-603.	None of the CR patients received ND
Sabatini PR & Ducic Y. Planned neck dissection following primary chemoradiation for advanced-stage head and neck cancer. Otolaryngol Head Neck Surg. 2009;141(4):474-7.	All patienst received ND
Hillel AT et al. Selective versus comprehensive neck dissection after chemoradiation for advanced oropharyngeal squamous cell carcinoma. Otolaryngol Head Neck Surg. 2009;141(6):737-42.	Unclear if also CR patients received ND
Vedrine PO et al. Need for neck dissection after radiochemotherapy? A study of the French GETTEC group. Laryngoscope. 2008;118(10):1775-80.	None of the CR patients received ND
Reza Nouraei SA et al. Role of planned postchemoradiotherapy selective neck dissection in the multimodality management of head and neck cancer. Laryngoscope. 2008;118(5):797-803.	After CRT all patients had ND
Lau H et al. Absence of planned neck dissection for the N2-N3 neck after chemoradiation for locally advanced squamous cell carcinoma of the head and neck. Arch Otolaryngol Head Neck Surg. 2008;134(3):257-61.	None of the CR patients received ND
Greven KM et al. Radiographic complete response on post treatment CT imaging eliminates the need for adjuvant neck dissection after treatment for node positive head and neck cancer. Am. J. Clin. Oncol. Cancer Clin. Trials. 2008;31(2):169-72.	Not all patients received CRT
Christopoulos A et al. Neck dissection following concurrent chemoradiation for advanced head and neck carcinoma: pathologic findings and complications. J Otolaryngol Head Neck Surg. 2008;37(4):452-6.	ND only in N3 group and PR group
Schwentner I et al. Modified radical neck dissection and minimal invasive tumor surgery in the middle of split course of concomitant chemoradiotherapy of advanced HNSCC. Auris Nasus Larynx. 2007;34(1):85-9.	ND was performed between the 2 cycles of radiation and chemotherapy
Robbins KT et al. Superselective neck dissection after chemoradiation: feasibility based on clinical and pathologic	Only data available for PR patients

Reference	Reason(s) for exclusion
comparisons. Arch Otolaryngol Head Neck Surg. 2007;133(5):486-9.	
Hitchcock YJ et al. Planned neck dissection after definitive radiotherapy or chemoradiation for base of tongue cancers. Otolaryngol Head Neck Surg. 2007;137(3):422-7.	Not all patients received CRT
Stenson KM et al. Planned post-chemoradiation neck dissection: significance of radiation dose. Laryngoscope. 2006;116(1):33-6.	All CR patients had ND after CRT
Homma A et al. "Watch-and-see" policy for the clinically positive neck in head and neck cancer treated with chemoradiotherapy. Int J Clin Oncol. 2006;11(6):441-8.	All CR patients had ND
Robbins KT et al. Effectiveness of superselective and selective neck dissection for advanced nodal metastases after chemoradiation. Arch Otolaryngol Head Neck Surg. 2005;131(11):965-9.	First part of the study: ND in all N2-3 patients and PR; in second part of the study: none of the CR patients received ND
Vongtama R et al. Early nodal response as a predictor for necessity of functional neck dissection after chemoradiation. Cancer J. 2004;10(6):339-42.	None of the CR patients received ND
Argiris A et al. Neck dissection in the combined-modality therapy of patients with locoregionally advanced head and neck cancer. Head Neck. 2004;26(5):447-55.	Part of ND group reveived ND prior to CRT

ND: neck dissection; CRT: chemoradiation therapy; CR: complete response (after CRT); PR: patial response (after CRT)

3.3.6.2. Quality appraisal

Figure 16 – Risk of bias summary of included primary studies

3.3.7. RQ8: IMRT for patients with locally advanced HNSCC

3.3.7.1. Selection of studies

Selection of systematic reviews

On August 12, 2013 a search was performed to identify SRs assessing the clinical effectiveness of IMRT for adult patients (≥18 years of age) with locally advanced HNSCC (stage 3 and 4); the search in Cochrane was done on November 4, 2013. MEDLINE and Embase were searched from January 2008 onwards. In total, 52 potential relevant references were identified after deduplication (Figure 17). Based on title and abstract 42 references were excluded. Three reviews were included ([49;49 50; 51]) (Table 29) and seven were excluded with reason (Table 30). As the review of [49] was most recent and complete, only the results of this review are discussed. An additional search in the Cochrane Library did not result in the inclusion of any further systematic reviews (Figure 18).

Figure 17 – Study flow of selection of SRs regarding research question 8

Potentially relevant SRs
identified after
deduplication
N=52

Medline N=2
Embase N=50

N= 42
Excluded on the
basis of title and
abstract

Full text evaluation
N=10

Excluded N=7

No RoB
assesment N=4
Search insufficient
N=2
Intervention N=1
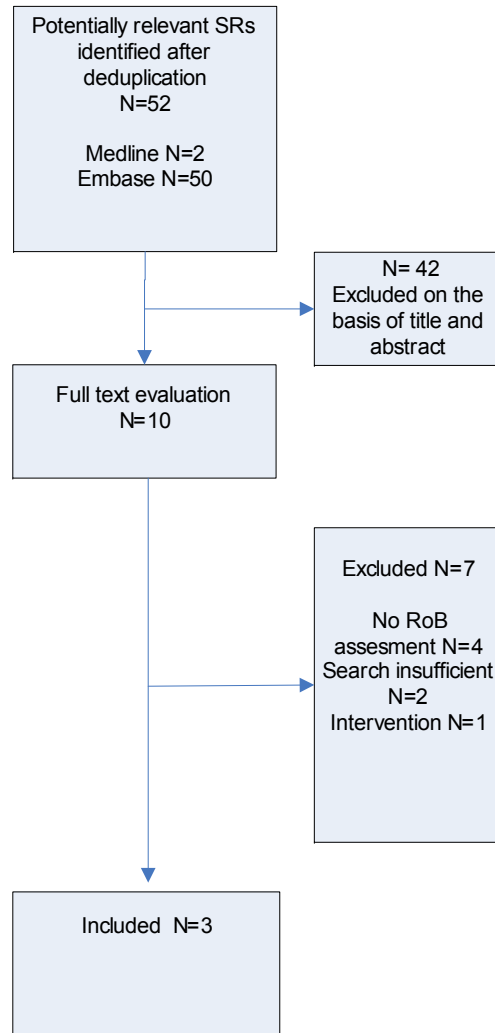
Included N=3

Figure 18 – Study flow of selection of SRs regarding research question 8 from The Cochrane Library
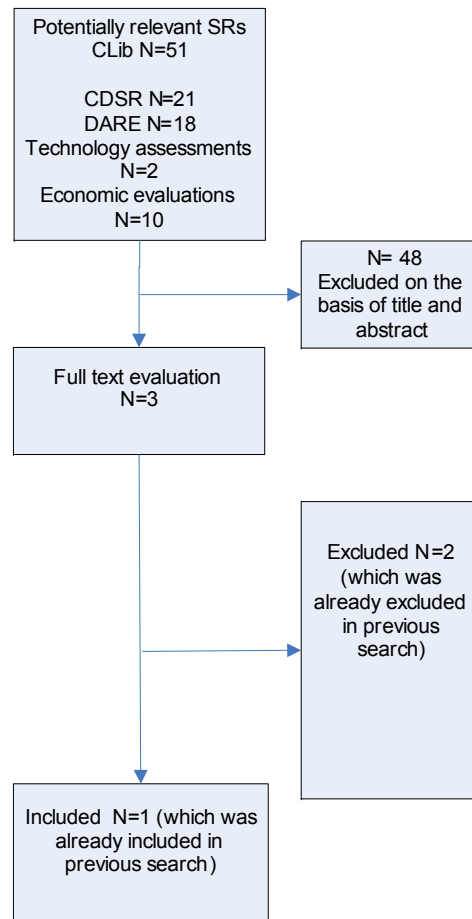
Table 29 – Included SRs regarding research question 8

Reference	Interventions
[49]	Intensity modulated radiation therapy versus 2-D EBRT
[51]	Carbon-ion therapy versus conventional photon therapy
[50]	Intensity modulated radiation therapy versus conventional techniques

Table 30 – Excluded SRs regarding research question 8

Reference	Reason for exclusion
[52]	No RoB assessment, no patient information
[53]	No RoB assesment, no patient information
[54]	No RoB assesment, no patient information, only Medline was searched,
[55]	No details on search
[56]	Only Medline was searched
[57]	Intervention not relevant (radiotherapy with protons)
[58]	No risk of bias (RoB) assesment, no patient information

Selection of primary studies

On August 15, 2013 a search was performed to identify studies (RCTs and observational studies) assessing the clinical effectiveness of IMRT for adult patients (≥18 years of age) with locally advanced HNSCC (stage 3 and 4). MEDLINE and Embase were searched from February 1st, 2009 onwards to identify primary studies published after the search date of the included review ((O'sullivan, Rumble et al. 2012),[49] search date March 2009).

Nine hundred nine potential relevant references were identified (Figure 22). After deduplication, 689 references remained. Based on title and abstract 644 studies were excluded. Of the remaining 45 studies, eight observational studies ((Chen, Hwang et al. 2009)[59]; (Chen, Li et al. 2011)[60]; (Chen, Farwell et al. 2012)[61]; (Clavel, Nguyen et al. 2012)[62]; (Dirix and Nuyts 2010)[63]; (Jilani, Singh et al. 2012)[64]; (Lambrecht, Nevens et al. 2013)[65] and (Tai, Hsieh et al. 2009)[66] and two RCTs were included (Gupta et al., 2012)[41] (Nutting et al., 2011).[67] The two RCTs also involved patients with TNM stage I and II, which is not in line with the PICO of RQ8. However, in consultation with the guideline group these two RCTs were included (Table 30). Thirty-five studies were excluded with reason (Table 31).

Figure 19 – Study flow of selection of primary studies regarding research question 8
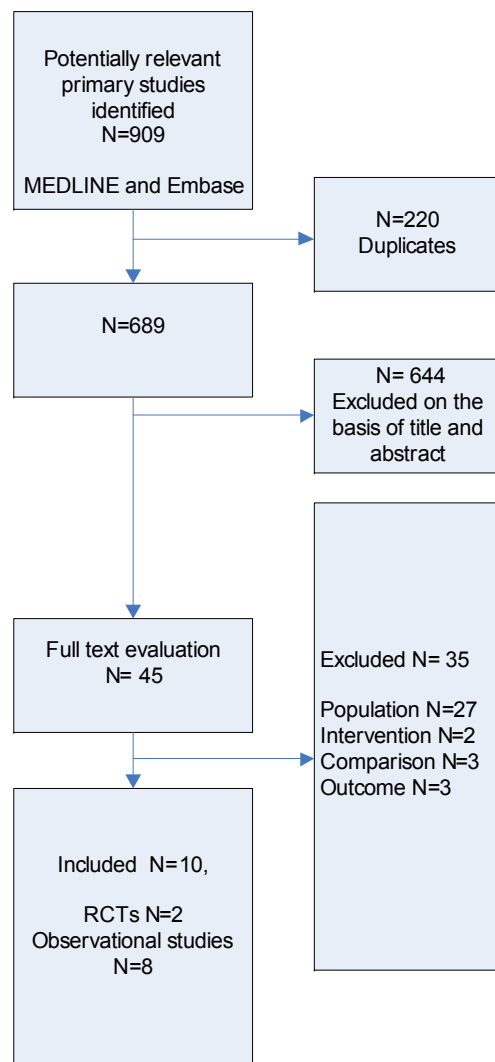
Table 31 – Included primary studies regarding research question 8

Reference	Interventions
Observational studies	
[61]	Intensity modulated radiation therapy versus three-dimensional conformal radiotherapy
[62]	Intensity modulated radiation therapy versus conventional radiotherapy (2D/3D technique)
[59]	Intensity modulated radiation therapy versus conventional radiotherapy
[60]	Intensity modulated radiation therapy versus conventional radiotherapy
[63]	Intensity modulated radiation therapy versus. three-dimensional radiotherapy
[64]	Intensity modulated radiation therapy versus three-dimensional conformal radiotherapy
[65]	Intensity modulated radiation therapy versus three-dimensional conformal radiotherapy
[66]	Intensity modulated radiation therapy versus 2DRT adjuvant conventional radiotherapy (2DRT) with intensity modulated radiation therapy
RCTs	
(Gupta *et al.*, 2012)[41]	Intensity modulated radiation therapy versus three-dimensional conformal radiotherapy
(Nutting *et al.*, 2011)[67]	Intensity modulated radiation therapy versus conventional radiotherapy

Table 32 – Excluded primary studies regarding research question 8

Reference	Reason for exclusion
[68]	Population not relevant (50% other carcinoma than SCC)
[69]	Population not relevant (24% N0 and type of tumour not mentioned)
[70]	Population not relevant (type of tumour not mentioned)
[71]	Population unclear (type of tumour not mentioned; mixture of stages)
[72]	Population: stage not reported; type of tumour not reported; includes nasopharyngeal cancer; selected patients O: tooth loss (not quantified; p-values)
[73]	Intervention (RT vs chemoRT) and population (mix of a little stage I and II and a lot of stage III en IV patients)
[74]	Population unclear (stage not mentioned and 14% N0)
[75]	Population (17% N0 and type of tumour not mentioned) and comparison not relevant

76	Population not relevant (stage I and II also included)
77	Population not relevant (nasopharyngeal carcinoma)
78	Population not relevant
79	Population not relevant (nasopharyngeal and stage I en II)
80	Intervention and comparison (treatment failure factors)
81	Population (18/117 UICC stage I and II) and outcome (parotid gland)
82	Population not relevant (also includes 13% stage II)
83	Protocol for RCT (ongoing study) / Comparison not relevant
84	Protocol for RCT (ongoing study) / Population (not only SCC) and comparison not relevant
85	Comparison not relevant
86	Population (not only SCC and stage not mentioned) and comparison not relevant
87	Outcome not relevant
88	Population not relevant (not only SCC and 21% stage I and II)
89	Population not relevant (nasopharyngeal carcinoma)
90	Population (50% stage 1-2 and type of cancer not reported) and intervention (combination of IMRT + 3D-CRT vs 2D-RT) not relevant
91	Population not relevant (nasopharyngeal carcinoma and a lot of stage I and II also included)
92	Population not relevant (a lot of stage I and II also included)
93	Population not relevant (20% stage I and II) (see also Gupta 2012)
94	Outcomes not relevant (TNM stage patients unclear)
95	Comparison not relevant
96	Population not relevant (20% stage I and II)
97	Population not relevant (UICC stage 2 NPC (T1N1, T2N0, T2N1 disease) and type of tumour not reported)
98	Population not relevant (type of cancer unclear; includes nasopharyngeal cancers)
99	Population not relevant (circa 30% stage UICC 1-2)
100	Population (33% stage I and II; type of cancer not reported) and comparison not relevant
101	Outcomes not relevant (cost effectiveness study)

| 102 | Population not relevant (stage or type of cancer not reported) |

3.3.7.2. Quality appraisal

Table 33 shows the results of the risk of bias assessment for the one included systematic review [49].[49] The review scored positive on all AMSTAR items, except item 'Quality assessment used in conclusions'. Overall, the SR is considered as having a 'low risk' of bias (Table 33).

Figure 20 and Figure 21 show the results of the risk of bias assessment for the observational studies that were included for RQ8 ([59; 60; 75; 62;63; 64; 65] and [66]). All studies scored a high (or unclear) risk of selection bias and performance bias. 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. Only for the item 'Attrition bias' and 'Reporting bias', a 'low risk' of bias was scored for all studies, except for [64] for which the latter item was scored 'unclear'. The item 'Comparability of the intervention and comparative group' was scored as unclear or 'high risk' of confounding by indication for most studies. No adjustment for demonstrated baseline differences or no specification of baseline differences was made in these studies.

Figure 22 and Figure 23 show the results of the risk of bias assessment for the RCTs that were included for RQ8 (Gupta *et al.*, 2012; Nutting *et al.*, 2011).[41, 67] The study of Gupta 2012 scored an unclear risk of selection bias due to insufficient information. Both studies scored a high risk of performance and detection bias (subjective outcomes), as the studies were non-blinded. The study of Nutting 2012[67] scored an unclear risk of attrition bias. For the remaining items, an unclear risk of bias was scored for both studies. Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), none of the RCTs were assessed as 'low risk' of bias.

Table 33 – Methodological quality of the included systematic review (AMSTAR) [49]

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusion	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	Approp-riate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
49	+	+	+*	+	+	+	+/-**	-	N.A.	+	+***

+ Yes; - No; ? Can't answer; N.A. Not applicable;
* searches in databases supplemented by checking conference proceedings, reference checking is not mentioned
** only randomization and blinding; completeness of f-u not assessed
*** in full guideline: conflicts of interest: none declared

Figure 20 – Risk of bias summary of comparative observational studies for RQ8

Figure 21 – Risk of bias summary per item of comparative observational studies for RQ8

Figure 22 – Risk of bias summary of RCTs for RQ8

Figure 23 – Risk of bias summary per item of RCTs for RQ8
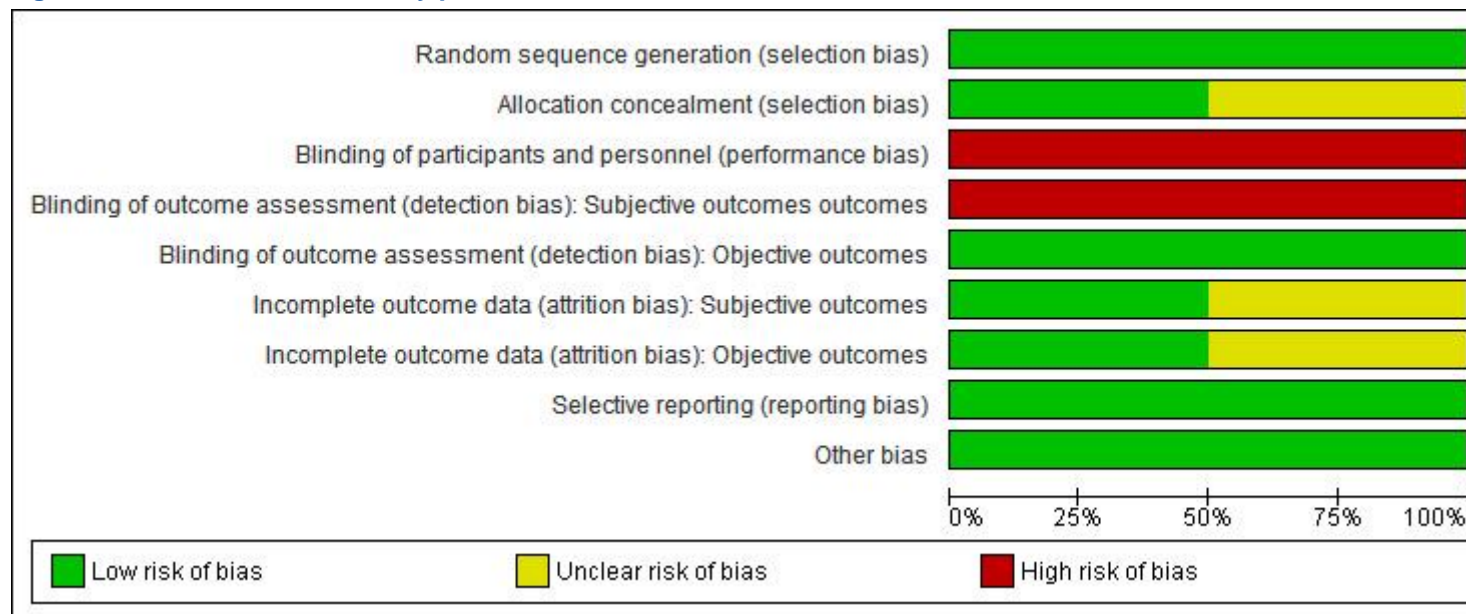
3.3.8. RQ9: induction chemotherapy in patients with HNSCC

3.3.8.1. Selection of studies

Selection of systematic reviews

On August 12, 2013 a search was performed to identify SRs comparing the effect of induction chemotherapy before locoregional therapy (i.e. RT, CRT or surgery) versus no induction chemotherapy (but identical locoregional therapy) in adult patients (≥18 years of age) diagnosed with stage 3 and 4 HNSCC (research question 9). MEDLINE and Embase were searched from January 2008 onwards. The Cochrane Library (Cochrane Database of Systematic Reviews, DARE and HTA database) was searched on November 4, 2013. 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. In total, 529 potentially relevant references were identified after deduplication (Figure 24). Based on title and abstract 525 references were excluded. Two reviews were included (Furness et al., 2011)[103]; (Ma et al., 2012) (Table 34) and two were excluded with reason (Table 35). The reviews of Chen (Chen et al., 2011)[104]) and Ma (Ma et al., 2012)[105] include the population as indicated by KCE. Because the most recent and complete review of Ma (Ma et al., 2012)[105] includes all RCTs that were included in Chen (Chen et al., 2011), only the results of the review of (Ma et al., 2012)[105] will be discussed. One review had smaller inclusion criteria regarding the study population (only oral cavity and oropharyngeal cancer) than indicated by KCE (Furness et al., 2011),[103] but the results will be discussed as well, because only their searches attempted to identify all relevant trials irrespective of language.

Figure 24 – Study flow of selection of SRs regarding research question 9
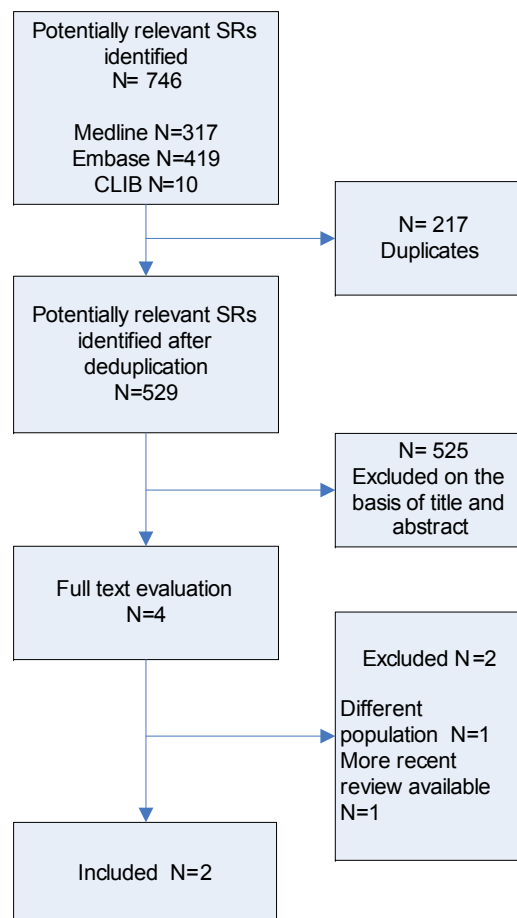
Table 34 – Included SRs regarding research question 9 (n=2)

Reference	Interventions
(Furness et al., 2011)[103]	Induction chemotherapy plus locoregional treatment vs Locoregional treatment alone in patients with oral cavity or oropharyngeal cancer
(Ma et al., 2012)[105]	Induction chemotherapy followed by locoregional treatment vs Locoregional treatment alone; and
	Induction chemotherapy followed by concomitant chemotherapy and radiotherapy vs Concomitant chemotherapy and radiotherapy alone in patients with locally advanced HNSCC

Table 35 – Excluded SRs regarding research question 9 (n=2)

Reference	Reason for exclusion
(Baujat et al., 2009)	Population different than indicated by KCE (nasopharyngeal carcinoma)
(Chen et al., 2011)	More recent review available covering all included studies

Selection of primary studies

On August 22, 2013 a search was performed to identify RCTs comparing the effect of induction chemotherapy before locoregional therapy (i.e. RT, CRT or surgery) versus no induction chemotherapy (but identical locoregional therapy) in adult patients (≥18 years of age) diagnosed with stage 3 and 4 HNSCC (research question 9). MEDLINE, Embase and CENTRAL were searched from January 2011 onwards to identify primary studies published after the search date of the included reviews ((Furness *et al.*, 2011)[103]; (Ma *et al.*, 2012)[105]).

After deduplication 235 potentially relevant references were identified (Figure 25). Based on title and abstract 215 studies were excluded. Of the remaining 20 studies, 5 RCTs were included ((Forastiere *et al.*, 2013)[106]; (Haddad *et al.*, 2013)[107]; (Lefebvre *et al.*, 2012)[108]; (Mitra *et al.*, 2006)[109]; (Zhong *et al.*, 2013)[110]) (Table 36) and 15 studies were excluded with reason (Table 37). The identification of the RCT of Mitra *et al.,*[109] (published in 2006) could be explained by the fact that this record was added to PubMed on November 30th, 2011.

Figure 25 – Study flow of selection of primary studies regarding research question 9
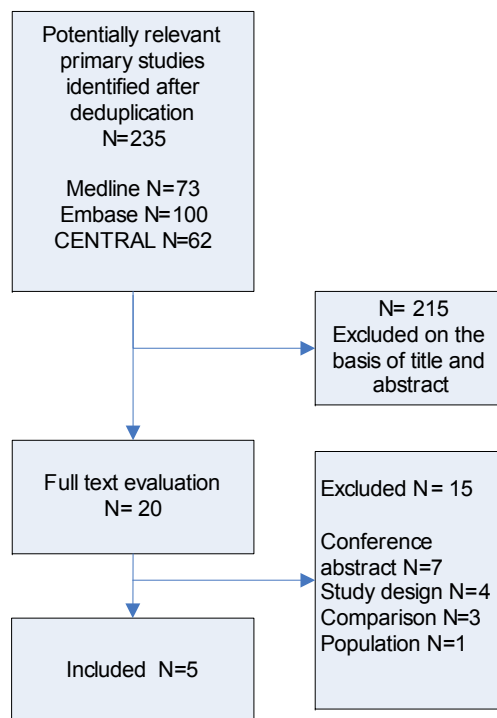
Table 36 – Included primary studies regarding research question 9 (n=5)

Reference	Interventions
(Forastiere *et al.*, 2013)[106]	Radiotherapy followed by Induction chemotherapy **vs** Radiotherapy followed by concomitant chemotherapy **vs** Radiotherapy alone
(Haddad *et al.*, 2013)[107]	Induction chemotherapy followed by concurrent chemoradiotherapy **vs** Concurrent chemoradiotherapy
(Lefebvre *et al.*, 2012)[108]	Induction chemotherapy followed by surgery + radiotherapy or radiotherapy alone **vs** Immediate surgery + radiotherapy
(Mitra *et al.*, 2006)[109]	Chemotherapy followed by radiotherapy **vs** Radiotherapy
(Zhong *et al.*, 2013)[110]	TPF (docetaxel, cisplatin, and fluorouracil) induction chemotherapy followed by surgery and postoperative radiotherapy **vs** Surgery followed by postoperative radiotherapy

Table 37 – Excluded primary studies regarding research question 9 (n=15)

Reference	Reason for exclusion
(Abgral *et al.*, 2012)	Study design (no RCT)
(Caudell *et al.*, 2011)	Conference abstract
(Cohen *et al.*, 2012)	Conference abstract
(Ghi *et al.*, 2013)	Conference abstract
(Haddad *et al.*, 2012)	Conference abstract
(Haigentz, Jr. *et al.*, 2012)	Study design (no RCT)
(Klautke, 2013)	Study design (no RCT; comment on Zhong 2013)
(Koh *et al.*, 2013)	Conference abstract
(Lefebvre *et al.*, 2012)	Comparison not relevant
(Liberato *et al.*, 2012)	Comparison not relevant
(Loewenthal *et al.*, 2012)	Study design (no RCT)
(Lorch and -R-I-Haddad, 2012)	Conference abstract

(Lu *et al.*, 2010)	Population (nasopharyngeal carcinoma)
(Majumder *et al.*, 2012)	Conference abstract
(Sher *et al.*, 2011)	Comparison not relevant

3.3.8.2. Quality appraisal

Table 38 shows the results of the risk of bias assessment for the two included systematic reviews (Furness *et al.*, 2011) and (Ma *et al.*, 2012). The review of Furness scored positively on all AMSTAR items. The review of (Ma *et al.*, 2012) scored positively on all AMSTAR items which we defined as key domains for systematic reviews ('Was a comprehensive literature search performed?', 'Was the scientific quality of the included studies used appropriately in formulating conclusions?', 'Were the methods used to combine the findings of studies appropriate?', and 'Was the likelihood of publication bias assessed?'). Overall, both SRs were considered as having a 'low risk' of bias (Table 38).

Figure 26 and Figure 27 show the results of the risk of bias assessment for the five newly identified RCTs for RQ 9 ((Forastiere *et al.*, 2013), (Haddad *et al.*, 2013), (Lefebvre *et al.*, 2012), (Mitra *et al.*, 2006), (Zhong *et al.*, 2013)). Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), only one study scored a 'low risk' of bias on all items (Lefebvre *et al.*, 2012). A high or unclear risk of selection bias was scored in two RCTs ((Forastiere *et al.*, 2013), (Mitra *et al.*, 2006)). Because of the difficulties of blinding participants, an unclear or high risk of performance bias and detection bias was scored for all studies. Only for the item 'Blinding of the outcome assessor' for the objective outcomes, a 'low risk' of bias was scored for all studies.

Table 38 – Methodological quality of the included systematic reviews (AMSTAR) (n=2)

Systematic review	A priori study design	Duplicate study selection and data extraction	Compre-hensive literature search	Publica-tion status not used as inclusionc riterion	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	Approp-riate methods to combine findings	Likelihood of publica-tion bias assessed	Conflict of interest stated
(Furness *et al.*, 2011)[103]	+	+	+	+	+	+	+	+	+	+	+
(Ma *et al.*, 2012)[105]	+	+	+	-	-	-	+	+	+	+	+

+ Yes; - No; ? Can't answer; N.A. Not applicable

Figure 26 – Risk of bias summary of newly identified RCTs for RQ9

Figure 27 – Risk of bias summary per item of newly identified RCTs for RQ9
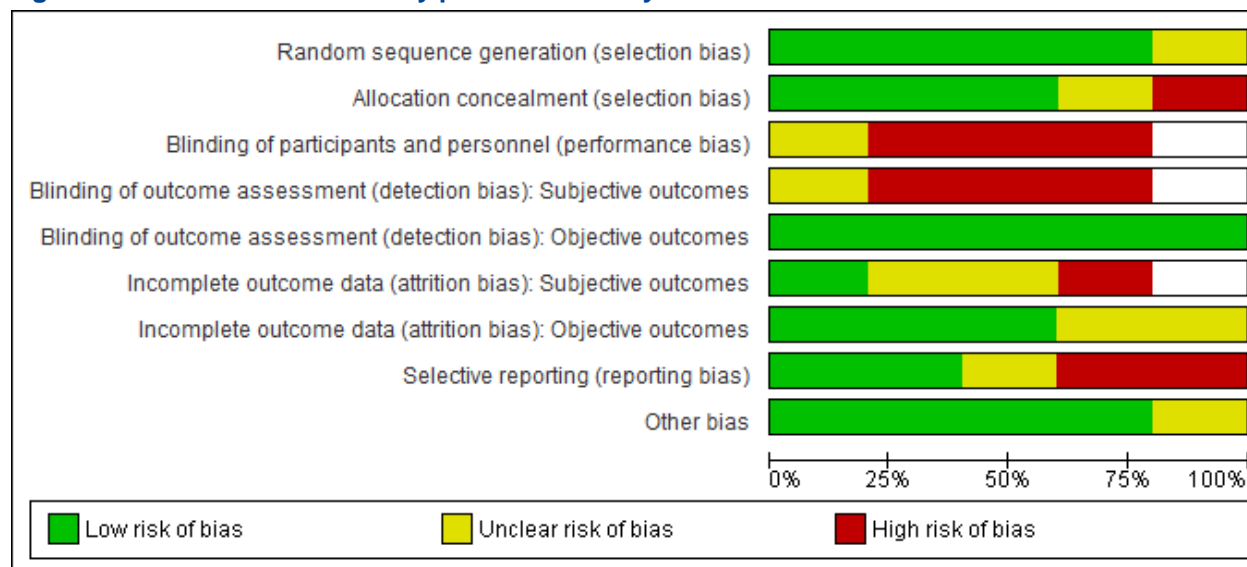
3.3.9. RQ10: primary CRT for patients with non-resectable M0 HNSCC

3.3.9.1. Selection of studies

Selection of systematic reviews

On November 7, 2013 a search was performed to identify SRs assessing the clinical effectiveness of primary CRT for adult patients (≥18 years of age) with non-resectable (T4b) M0 HNSCC; the search in Cochrane was done on December 23, 2013. MEDLINE, Embase and the Cochrane Library were searched from January 2008 onwards. In total, 651 potential relevant references were identified after deduplication (Figure 28). Based on title and abstract, 633 references were excluded. Full reports of the remaining 18 reviews were retrieved. After detailed assessment, all were excluded with reason (Table 39).

Figure 28 – Study flow of selection of SRs regarding research question 10
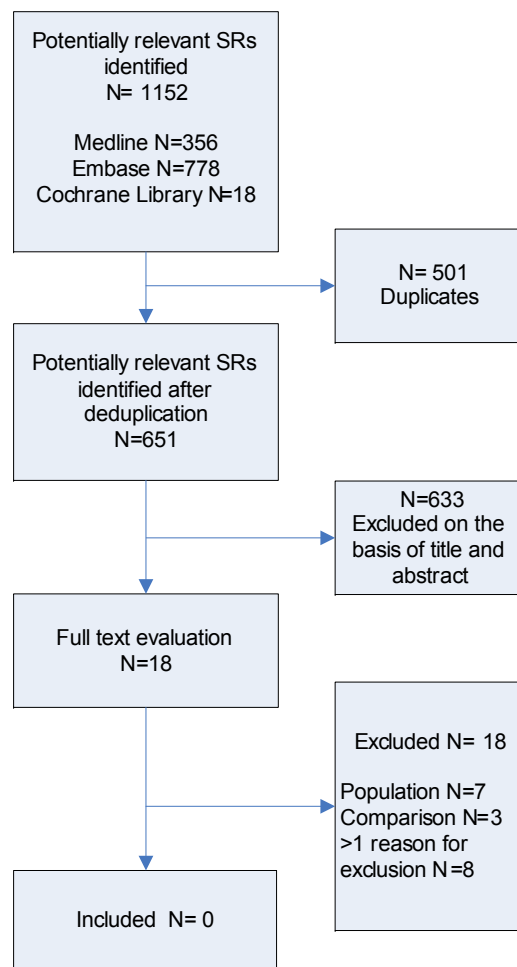
Table 39 – Excluded SRs regarding research question (n=18)

Reference	Reason for exclusion
(Argiris *et al.*, 2013)	Mixed population and comparison different than indicated by KCE
(Blanchard *et al.*, 2011a)	Comparison different than indicated by KCE
(Blanchard *et al.*, 2011b)	Population different than indicated by KCE (locally advanced MTMA)
(Budach *et al.*, 2006)	Mixed population
(Furness *et al.*, 2011)	Mixed population
(Jacobi *et al.*, 2010)	Comparison and outcomes different than indicated by KCE
(Jensen *et al.*, 2010)	Population and comparison different than indicated by KCE (salivary gland)
(Klug *et al.*, 2008)	Population and comparison different than indicated by KCE (preoperative)
(Levy *et al.*, 2011)	Mixed population
(Liu *et al.*, 2010)	Only one relevant RCT included, (Bonner *et al.*, 2006), of which the population was not of interest.
(Petrelli and Barni, 2012)	Mixed population
(Pignon *et al.*, 2009)	Population and comparison different than indicated by KCE
(Reeves *et al.*, 2011)	Mixed population
(Sharafinski *et al.*, 2010)	Comparison different than indicated by KCE
(Singer *et al.*, 2013)	Population and comparisons to broad (focus on quality of life)
(Sundvall *et al.*, 2010)	Comparison different than indicated by KCE
(Van Der Molen *et al.*, 2009)	Comparison and outcomes different than indicated by KCE
(Zhang *et al.*, 2012)	Mixed population and comparison different than indicated by KCE

Selection of primary studies

On December 6, 2013 a search was performed to identify RCTs assessing the clinical effectiveness of primary CRT for adult patients (≥18 years of age) with non-resectable (T4b) M0 HNSCC. As no systematic review was included, MEDLINE, Embase and CENTRAL were searched from 2003 onwards. One thousand six hundred and eighty-one potential relevant references were identified (Figure 29). After deduplication, 764 references remained. Based on title and abstract 711 studies were excluded. Of the remaining 53 studies, two studies were included that fully fulfilled the PICO for RQ10 [Bensadoun et al., 2006;Ruo Redda et al., 2010].[111, 112] In consultation with KCE, another five studies which involved mixed populations (not solely stage T4b) were included [Budach et al., 2005;Chauhan et al., 2008;Rodriguez et al., 2010;Semrau et al., 2006;Quon et al., 2011][113-117] (Table 40). Forty-six studies were excluded with reason (Table 41).

Figure 29 – Study flow of selection of primary studies regarding research question 10

```
┌─────────────────────────┐
│ Potentially relevant    │
│ primary studies         │
│ identified              │
│ N=1681                  │
│                         │          ┌─────────────────┐
│ Medline N=553           │─────────▶│ N=917           │
│ Embase N=692            │          │ Duplicates      │
│ CENTRAL N=436           │          └─────────────────┘
└─────────────────────────┘
            │
            ▼
┌─────────────────────────┐
│                         │          ┌─────────────────┐
│      N=764              │─────────▶│ N= 711          │
│                         │          │ Excluded on the │
│                         │          │ basis of title  │
│                         │          │ and abstract    │
└─────────────────────────┘          └─────────────────┘
            │
            ▼
┌─────────────────────────┐          ┌─────────────────────┐
│                         │          │ Excluded N= 46      │
│ Full text evaluation    │          │                     │
│ N= 53                   │─────────▶│ Population N=24      │
│                         │          │ Study design        │
│                         │          │ N=11                │
└─────────────────────────┘          │ Intervention/       │
            │                        │ Comparison N=7      │
            ▼                        │ Study protocol      │
┌─────────────────────────┐          │ N=2                 │
│                         │          │ Conference          │
│ Included  N=7           │          │ abstract N=1        │
│                         │          │ No full text N=1    │
└─────────────────────────┘          └─────────────────────┘
```
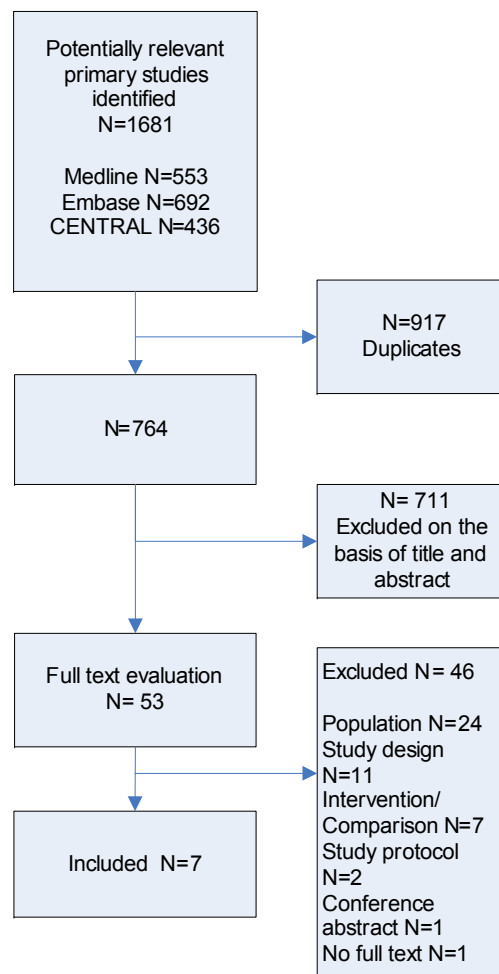
Table 40 – Included primary studies regarding research question 10 (n=7)

Reference	Interventions
(Bensadoun *et al.*, 2006)[59, 11859, 118]	Combination of chemotherapy CP and 5FU with concomitant twice-daily radiotherapy vs twice-daily radiotherapy alone.
(Ruo Redda *et al.*, 2010)[112]	Radiotherapy alone vs with concomitant daily low-dose carboplatin. NB: also Stage III patients were included but results were presented according to TNM stage.
Mixed population	
(Budach *et al.*, 2005)[119]	Chemotherapy and hyperfractionated accelerated radiation therapy vs hyperfractionated accelerated radiation therapy alone. (94% stage IV with majority T4, but not sufficient information to determine whether T4a or T4b or stage IVa or IVb. Does not appear to provide outcomes based on staging.)
(Chauhan *et al.*, 2008)[114]	Gemcitabine concurrent with radiotherapy vs radiotherapy alone. (50% stage IV)
(Quon *et al.*, 2011)[117]	Radiotherapy plus concomitant cisplatin vs radiotherapy. (>70% stage IV; but T4 N3 25-26%)
(Rodriguez *et al.*, 2010)[115]	Nimotuzumab in combination with radiotherapy vs placebo and radiotherapy. (60% stage IV)
(Semrau *et al.*, 2006)[116]	Concurrent hyperfractionated and accelerated radiochemotherapy vs hyperfractionated and accelerated radiotherapy. (96% stage IV with majority T4, but not sufficient information to determine whether T4a or T4b or stage IVa or IVb. Doesn't appear to provide outcomes based on staging.)

Table 41 – Excluded primary studies regarding research question 10 (n=46)

Reference	Reason for exclusion
[Asif et al., 2003]	Population not of interest (48% stage IV)
[Bensadoun et al., 2004]	Conference abstract
(Bernier *et al.*, 2004)	Intervention not of interest
(Bonner *et al.*, 2006)	Population not of interest
(Bonner *et al.*, 2010)	Population not of interest
(Bourhis *et al.*, 2012)	Population not of interest (does not state 'unresectable'; majority of patients with stage IV disease, majority T4, but not sufficient information to determine whether T4a or T4b or stage IVa or IVb. Doesn't appear to provide outcomes based on staging.)

(Brown *et al.*, 2008)	No RCT (economic evaluation)
(Bucci *et al.*, 2004)	No RCT
(Budihna *et al.*, 2005)	No RCT
[Chitapanarux et al., 2013]	Population not of interest (54-65% Stage IV)
(Curran *et al.*, 2007)	Population not of interest (stage III and IV patients included, however distribution grade III/IV patients not reported)
(Denis *et al.*, 2003) [68]	Population not of interest (stage III and IV patients included, however, distribution grade III/IV patients not reported and results were not separated according to TNM stage)
(Denis *et al.*, 2004)	Population not of interest (67-69% stage IV)
(Ezzat *et al.*, 2005)	Population not of interest (60% stage IV)
(Fallai *et al.*, 2006)	Population not of interest (stage III and IV, with minority T4 and N3, so few stage IVB patients)
(Forastiere *et al.*, 2003)	Population not of interest (33-36% stage IV)
(Forastiere *et al.*, 2013)	Population not of interest (33-36% stage IV)
(Fountzilas *et al.*, 2004)	Population not of interest (78% stage IV)
(Ghadjar *et al.*, 2012a)	Population not of interest (66-70% stage IV)
(Ghadjar *et al.*, 2012b)	Population not of interest (66-70% stage IV); intervention/comparison of this secondary analysis (of (Ghadjar *et al.*, 2012a)) not of interest
(Grau *et al.*, 2003)	Population not of interest (32% stage IV)
(Hehr *et al.*, 2004)	Population not of interest (does not state 'unresectable'; 98% stage IV with majority T4, but not sufficient information to determine whether T4a or T4b or stage IVa or IVb. Doesn't appear to provide outcomes based on staging.)
(Heukelom *et al.*, 2013)	Comparison not of interest
[Hoebers et al., 2007]	No RCT
(Huguenin *et al.*, 2004)	Population not of interest (68% stage IV)
(Jeremic *et al.*, 2004)	No RCT
[Kader HA et al., 2011]	No RCT
(Katori *et al.*, 2007)	Intervention/comparison not of interest
(Manocha *et al.*, 2006)	No RCT, population not of interest (28% stage IV)
(Masud *et al.*, 2006)	No full-text available
(Mitra *et al.*, 2006)	Intervention (and population) not of interest

(Mori M *et al.*, 2011)	Intervention/comparison not of interest
[Okamoto Y, 2012]	Protocol / Intervention not relevant
(Olmi *et al.*, 2003)	Population not of interest (73% Stage IV)
(Plataniotis *et al.*, 2004)	Population not of interest (71-88% stage IV)
(Racadot and Mazeron, 2004)	No RCT (commentary)
(Rishi *et al.*, 2013)	Population not of interest (Stage IVA)
(Saarilahti *et al.*, 2010)	No RCT, no full-text available
(Semrau *et al.*, 2011)	No RCT
(Sharma *et al.*, 2010)	Population not of interest (55% stage IV)
(Singh *et al.*, 2013)	Population not of interest (73% stage IV)
(Tobias *et al.*, 2010)	Population not of interest (38-45% stage IV)
[Wong SJ, 2010]	Protocol
(Yom, 2013)	No RCT (commentary)
[Yoon et al., 2008]	Intervention/comparison not of interest
(Zeng *et al.*, 2010)	Intervention not of interest

3.3.9.2. Quality appraisal

Figure 30 and Figure 31 show the results of the risk of bias assessment of the seven RCTs that were included for RQ10 [Bensadoun et al., 2006;Budach et al., 2005;Chauhan et al., 2008;Rodriguez et al., 2010;Ruo Redda et al., 2010;Semrau et al., 2006;Quon et al., 2011].[112, 114-119] Three RCTs [Chauhan et al., 2008;Ruo Redda et al., 2010;Semrau et al., 2006] scored an unclear risk of selection bias as there was insufficient information reported on the method of sequence generation. In five RCTs [Budach et al., 2005;Chauhan et al., 2008;Rodriguez et al., 2010;Ruo Redda et al., 2010;Semrau et al., 2006] it was unclear whether the allocation was concealed. All but one RCT [Rodriguez et al., 2010] scored a high risk of performance bias and detection bias (subjective outcomes) as the studies were non-blinded. 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. The study of Bensadoun [Bensadoun et al., 2006] did score a low risk on selection bias, detection bias (objective outcomes) and attrition bias.

Figure 30 – Risk of bias summary of comparative observational studies regarding RQ10

Figure 31 – Risk of bias summary per item of comparative observational studies regarding RQ10
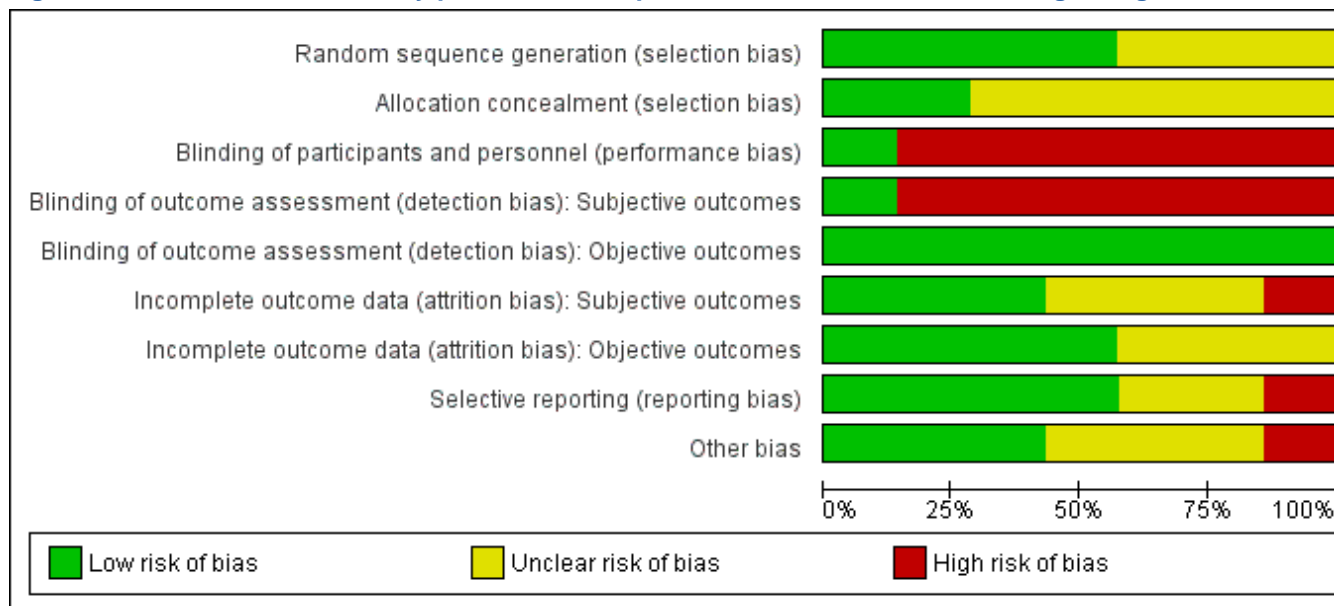
3.3.10. RQ11: interventions for M+ disease or recurrent disease not suitable for curative treatment

3.3.10.1. Selection of studies

Because of the diversity of the various comparisons of RQ11 it was expected that no SRs could be identified that addressed all those different treatment options for this particular patient population. Therefore, it was decided, in consultation with KCE, to perform one single search for both SRs and primary studies (randomized controlled trials and observational studies). This search was performed on November 29, 2013 to identify SRs and primary studies assessing the clinical effectiveness of treatment interventions for adult patients (≥18 years of age) with M+ or recurrent disease not suitable for curative treatment. MEDLINE, Embase and the Cochrane Library were searched from December 2003 onwards. In total, 1211 potential relevant references were identified after deduplication (Figure 32). Based on title and abstract, 1188 references were excluded. One review (Reeves 2011)[120] was not identified by our search but brought forward by the GDG and was also evaluated in full text. Thus 25 references were evaluated in full text, of which three references (Leon et al., 2005;Zafereo et al., 2009(Machiels et al., 2011))[121-123] were included (Table 42) and 22 excluded with reason (Table 43).

Figure 32 – Study flow of selection of studies regarding research question 11

Potentially relevant
studies identified
N= 1839

MEDLINE N=937
Embase N=636
CLIB N=266

N=628
Duplicates

N=1211

N=1188
Excluded on the
basis of title and
abstract

Full text evaluation
N=24
Identified by GDG
N=1

Excluded N=22

Intervention N=2
Comparison N=3
No SR N=9
Language N=1
Design N=7

Included N=3

SRs N=0
RCTs N=1
Observational studies
N=2
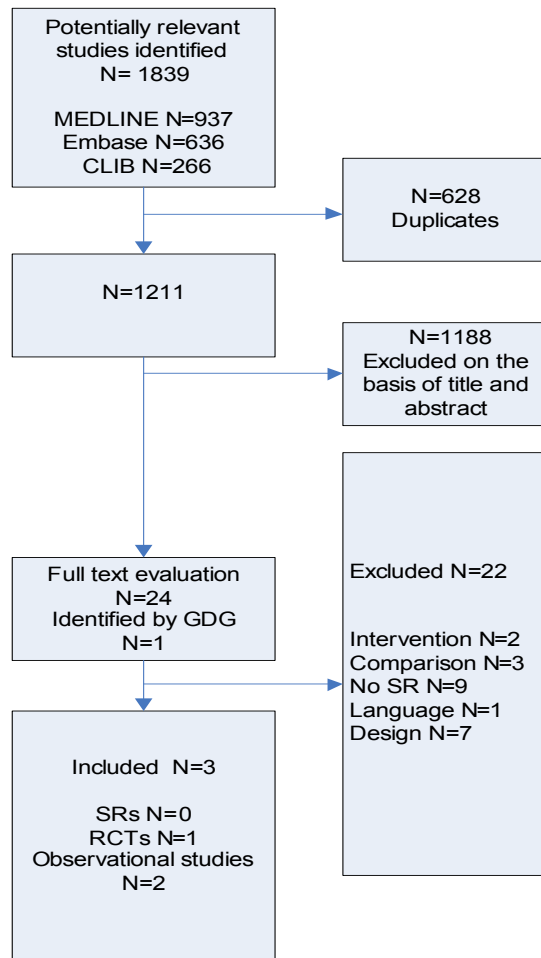
Table 42 – Included studies regarding research question 11

Reference	Interventions
[59]Leon 2005 (Leon *et al.*, 2005)[121]	Second-line therapies (best supportive care alone vs second-line chemotherapy, radiotherapy and chemoradiotherapy)
Machiels 2011 (Machiels *et al.*, 2011)[122]	Zalutumumab plus best supportive care vs best supportive care with optional methotrexate
Zafereo 2009 (Zafereo *et al.*, 2009)[123]	Supportive care vs salvage surgery, re-irradiation or brachytherapy (with or without chemotherapy) and palliative chemotherapy

Table 43 – Excluded studies regarding research question 11

Reference	Reason for exclusion
Excluded primary studies (observational studies and RCTs)	
Al-mamgani 2009 (Al-mamgani *et al.*, 2009)	Non-comparative study
Bisht 2010 (Bisht *et al.*, 2010)	Non-comparative study
Bisht 2011 (Bisht *et al.*, 2011)	Non-comparative study
Brook 2008 (Brook *et al.*, 2008)	Non-comparative study
[68]Castro 2003 (Castro *et al.*, 2003)	Comparison not relevant
Guntinas-Lichius 2009 (Guntinas-Lichius *et al.*, 2009)	Non-comparative study
Owen 2011 (Owen *et al.*, 2011)	Non-comparative study

Schick 2012 (Schick *et al.*, 2012)	Non-comparative study
Semple 2009 (Semple *et al.*, 2009)	Intervention not relevant
Vermorken 2008 (Vermorken *et al.*, 2008)	Intervention not relevant
Excluded reviews	
Arnold 2004 (Arnold *et al.*, 2004)	Not a systematic review
Colevas 2006 (Colevas, 2006)	Not a systematic review
De Andrade 2012 (de Andrade and Machiels, 2012)	Not a systematic review
Escobar Alvarez 2010 (Escobar Alvarez *et al.*, 2010)	Language (Spanish)
Machiels 2011 (Machiels and Schmitz, 2011)	Not a systematic review
Molin 2011 (Molin and Fayette, 2011)	Not a systematic review
Mouttet-Audouard 2011 (Mouttet-Audouard *et al.*, 2011)	Not a systematic review
Mouttet-Audouard 2012 (Mouttet-Audouard *et al.*, 2012)	Not a systematic review
Moyer 2004 (Moyer *et al.*, 2004)	Not a systematic review

Petrelli 2012 (Petrelli and Barni, 2012)	Comparison not of interest
Vermorken 2010 (Vermorken and Specenier, 2010)	Not a systematic review/comparator not of interest
Excluded review identified by the GDG	
Reeves 2011	Comparison not of interest

3.3.10.2. Quality appraisal

Figure 33 and Figure 34 show the results of the risk of bias assessment for the two observational studies that were included for RQ11 (Leon *et al.*, 2005;Zafereo *et al.*, 2009).[121, 123] 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. The study of Leon (2005)[121] did not address subjective outcomes, but did score a low risk of detection bias for objective outcomes and a low risk of reporting bias. The study of Zafereo (2009)[123] did not score low risk of bias on any of the items.

Figure 35 and Figure 36 show the results of the risk of bias assessment of the one included RCT (Machiels *et al.*, 2011).[122] The study scored a high risk of performance bias and detection bias for subjective outcomes as both participants and investigators were not blinded. The study was also judged as having a high risk of reporting and attrition bias (for subjective outcomes) as data for quality of life outcomes was not shown and the number of drop outs was substantial (no intention to treat analysis was performed for subjective outcomes). An unclear risk of other bias was scored as the sponsor of the study did the data management, statistical analyses, and interpreted the data. Focusing on the three key items (allocation concealment; blinding of outcome assessment and completeness of follow-up), the study was assessed as 'high risk' of bias.

Figure 33 – Risk of bias summary of comparative observational studies regarding RQ11

Figure 34 – Risk of bias summary per item of comparative observational studies regarding RQ11
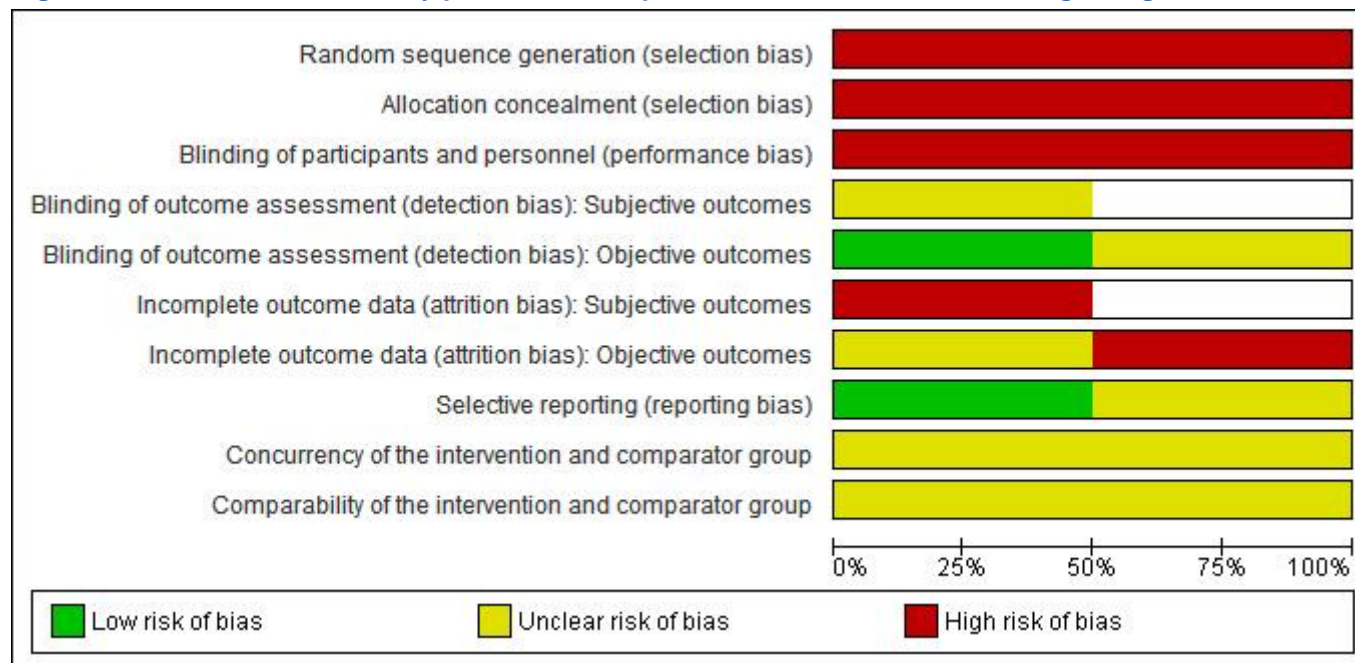
Figure 35 – Risk of bias summary of the RCT regarding RQ11

Figure 36 – Risk of bias summary per item of the RCT regarding RQ11

4. EVIDENCE TABLES BY CLINICAL QUESTION

4.1. RQ1: PET/CT for staging of HNSCC

4.1.1. Nodal staging

Table 44 – N-staging of HNSCC with PET or PET/CT: systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of review quality

Liao LJ, 2012[124]	• Design: SR + MA
	• Sources of funding: supported by the National Science Council of the Republic of China (Grant NSC-100-2314-B418-005) and grants from the Far Eastern Memorial Hospital (FEMH - 100-2314-B418-005); no CoI declared
	• Search date: May 2011
	• Searched databases: Medline, CENTRAL, screening of references
	• Included study designs: diagnostic accuracy studies
	• Included studies: PET: N=11 (CT: N=7; MRI: N=6; US: N=8)
		• Eligibility criteria: studies including patients with HNSCC, individual patient data available for cN0 patients, sufficient data to construct 2x2 tables
		• Patients characteristics: HNSCC, cN0
		• Prevalence of disease: not reported
			• Index test(s): PET (and, CT, MRI, US)
			• Reference standard: histology of neck specimen or sufficient follow-up
				Pooled estimate for detection of N+
				• PET:
				  o Se: 66% (47-80%)
				  o Sp: 87% (77-93%)
				  o LR+: 5.2 (2.6-10.4)
				  o LR-: 0.39 (0.24-0.65)
				• CT:
				  o Se: 52% (39-65%)
				  o Sp: 93% (87-97%)
				  o LR+: 7.9 (3.6-17.4)
				  o LR-: 0.51 (0.38-0.68)
				• MRI:
				  o Se: 65% (34-87%)
				  o Sp: 81% (64-91%)
				  o LR+: 3.4 (1.8-6.2)
				  o LR-: 0.44 (0.21-0.98)
				• US:
				  o Se: 66% (54-77%)
				  o Sp: 78% (71-83%)
				  o LR+: 3.0 (2.1-4.2)
				  o LR-: 0.44 (0.3-0.64)
					• Results critical appraisal:
					  o Duplicate study selection and quality appraisal
					  o Language restriction (English only)
					  o No detailed quality appraisal results per individual study
					  o Overall AMSTAR score: 3/11

Yongkui L, 2013[6]	• Design: SR + MA
	• Sources of funding: no external fund, no CoI declared
	• Search date: July 2012
	• Searched databases: Medline, Embase, EBM Review Databases, reference lists
	• Included study designs: diagnostic accuracy
		• Eligibility criteria: patients with primary HNSCC that underwent FDG-PET/CT before treatment; no chemotherapy or radiotherapy before neck dissection; sufficient data to construct 2x2 tables; results presented on a per-nodal- or per-side-level; at least 10 patients
		• Patients characteristics:
		• Prevalence of disease: per-neck-side analysis 31.3%, per-nodal-level analysis 20.8%
			• Index test(s): FDG-PET/CT
			• Reference standard: histology of neck specimen
				Neck-side based analysis: 5 studies, 575 neck sides
				• FDG-PET/CT:
				  o Se: 84% (77-89%)
				  o Sp: 84% (78-89%)
				  o DOR: 27.4 (15.5-18.9)
				  o LR+: 5.3 (3.7-7.6)
				  o LR-: 0.19 (0.14-0.27)
				
				Node-based analysis: 12 studies, 3619
					• Results critical appraisal:
					  o Duplicate study selection and quality appraisal
					  o Language restriction (English only)
					  o Overall AMSTAR score: 5/11

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of review quality

	studies
	• Included studies: N=14
				nodes
				• FDG-PET/CT:
				  ○ Se: 84% (78-88%)
				  ○ Sp: 96% (94-98%)
				  ○ DOR: 134.7 (65.8-276.1)
				  ○ LR+: 22.8 (14.1-36.7)
				  ○ LR-: 0.17 (0.12-0.24)	

Table 45 – N-staging of HNSCC with PET or PET/CT: primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

Haerle SK, Head Neck 2011[7]	• Design: diagnostic study, retrospective
	• Sources of funding: not reported
	• Setting: university hospital, Switzerland
	• Sample size: N=34
	• Duration: inclusion 1/2002 – 12/2007
		• Eligibility criteria: patients with previously untreated tonsillar SCC who underwent pretreatment contrast-enhanced FDG-PET/CT followed by neck dissection as part of initial treatment
		• Patients characteristics: mean age 58y; 82.4% males; 100% tonsillar SCC; pT1 32%, pT2 59%, pT3 6%, pT4 3%
		• Prevalence of disease: 85.3% cervical lymph node involvement
			• Index test(s): FDG-PET, non-enhanced FDG-PET/CT, contrast-enhanced FDG-PET/CT, contrast-enhanced CT
			• Reference standard: histology of neck specimen
				Neck-side based analysis
				• FDG-PET:
				  ○ Se: 93% (77-99%)
				  ○ Sp: 71% (29-96%)
				  ○ PPV: 93%
				  ○ NPV: 71%
				  ○ LR+: 3.26
				  ○ LR-: 0.097
				• Non-enhanced FDG-PET/CT:
				  ○ Se: 93% (77-99%)
				  ○ Sp: 71% (29-96%)
				  ○ PPV: 93%
				  ○ NPV: 71%
				  ○ LR+: 3.26
				  ○ LR-: 0.097
				• Contrast-enhanced FDG-PET/CT:
				  ○ Se: 97% (82-100%)
				  ○ Sp: 71% (29-96%)
				  ○ PPV: 93%
				  ○ NPV: 83%
				  ○ LR+: 3.38
				  ○ LR-: 0.048
				• Contrast-enhanced CT:
				  ○ Se: 97% (82-100%)
				  ○ Sp: 71% (29-96%)
				  ○ PPV: 93%
				  ○ NPV: 83%
				  ○ LR+: 3.38
				  ○ LR-: 0.048
					• Dropouts: none reported
					• Results critical appraisal:
					  ○ No consecutive cohort
					  ○ Selection by indication
					  ○ Blinded imaging and histology review
					  ○ Neck-side based analysis: 2 patients underwent bilateral neck dissection and were counted twice in the analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

Hoshikawa H, 2012[8]	• Design: diagnostic study, prospective
	• Sources of funding: not reported; no CoI
	• Setting: university hospital, Japan
	• Sample size: N=23
	• Duration: inclusion 4/2006 – 11/2011
		• <u>Eligibility criteria</u>: patients with histopathologically proven HNSCC referred for surgery or CRT
		• <u>Patients characteristics</u>: mean age 62y; 82.6% males; 100% SCC; 22% OCC, 39% OPC, 17% HPC, 22% LC; pT1 13%, pT2 43%, pT3 17%, pT4 26%; Sx alone 48%, Sx + CRT 9%, CRT + Sx 43%
		• <u>Prevalence of disease</u>: 12.7% positive lymph nodes, 75% positive neck dissections
			• <u>Index test(s)</u>: non-enhanced FDG-PET/CT, contrast-enhanced CT
			• <u>Reference standard</u>: histology of neck specimen
				<u>Node-based analysis</u>
				• FDG-PET/CT:
				  ○ Se: 64% (51-76%)
				  ○ Sp: 99% (98-100%)
				  ○ PPV: 93%
				  ○ NPV: 95%
				  ○ LR+: 86.95
				  ○ LR-: 0.36
				• Contrast-enhanced CT:
				  ○ Se: 73% (60-84%)
				  ○ Sp: 100% (98-100%)
				  ○ PPV: 96%
				  ○ NPV: 96%
				  ○ LR+: 147.58
				  ○ LR-: 0.27
					• Dropouts: none reported
					• Results critical appraisal:
					  ○ Consecutive cohort, but potential selection by indication
					  ○ Blinding unclear
					  ○ Node-based analysis: 464 lymph nodes from 32 neck dissections

Krabbe CA, 2010[9]	• Design: diagnostic study, retrospective
	• Sources of funding: not reported
	• Setting: university hospital, the Netherlands
	• Sample size: N=80
	• Duration: inclusion 1999 – 2004
		• <u>Eligibility criteria</u>: patients with newly diagnosed SCC of the oral cavity and/or oropharynx who had undergone FDG-PET
		• <u>Patients characteristics</u>: mean age 61.3y; 61.3% males; 100% SCC; 78% OCC, 22% OPC; pT1 21%, pT2 24%, pT3 13%, pT4 43%; Sx alone 23%, Sx + RT 48%, primary (C)RT 24%, palliation 6%
		• <u>Prevalence of disease</u>: 48.8% cervical lymph node involvement
			• <u>Index test(s)</u>: FDG-PET
			• <u>Reference standard</u>: histology (N=50), cytology (N=10) or follow-up (CT, MRI and/or US + follow-up for at least 1.5y; N=20)
				<u>Neck-side based analysis</u>
				• FDG-PET:
				  ○ Se: 61% (46-74%)
				  ○ Sp: 97% (92-99%)
				  ○ PPV: 91%
				  ○ NPV: 84%
				  ○ LR+: 22.09
				  ○ LR-: 0.40
					• Dropouts: none reported
					• Results critical appraisal:
					  ○ No consecutive cohort
					  ○ Selection by indication
					  ○ Blinding unclear
					  ○ Differential verification
					  ○ Neck-side based analysis
					• Only results of NPMI reported here

Liao CT, 2011[10]	• Design: diagnostic study, retrospective
	• Sources of funding: supported by grants NMRPG160031 and CMRPG370061 from the Chang Gung Memorial Hospital at Linko; CoI not reported
	• Setting: university hospital, Taiwan
	• Sample size: N=473
	• Duration: inclusion 8/2001 – 5/2008
		• <u>Eligibility criteria</u>: patients with a histologic diagnosis of oral SCC, previously untreated, scheduled for radical surgery, no suspected distant metastases detected by imaging (including CT/MRI and FDG-PET/CT)
		• <u>Patients characteristics</u>: 81% >40y; 94.1% males; 100% oral SCC; pT1-2 58%, pT3-4 42%; Sx alone 45%, Sx + RT 23%, Sx + CRT 31%
		• <u>Prevalence of disease</u>: 44.6% cervical lymph node involvement
			• <u>Index test(s)</u>: FDG-PET or FDG-PET/CT (non-enhanced)
			• <u>Reference standard</u>: histology of neck specimen
				<u>Patient-based analysis</u>
				• FDG-PET:
				  ○ Se: 78% (72-83%)
				  ○ Sp: 58% (52-64%)
				  ○ PPV: 60%
				  ○ NPV: 76%
				  ○ LR+: 1.85
				  ○ LR-: 0.38
					• Dropouts: none reported
					• Results critical appraisal:
					  ○ No consecutive cohort
					  ○ Selection bias (only patients without metastases on imaging)
					  ○ Blinding unclear
					  ○ Patient-based analysis

Matsubara R,	• Design: diagnostic	• <u>Eligibility criteria</u>: patients with primary oral	• <u>Index test(s)</u>: non-	<u>Node-based analysis</u>	• Dropouts: none reported

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

2012[11]	study, retrospective
	• Sources of funding: not reported
	• Setting: university hospital, Japan
	• Sample size: N=38
	• Duration: inclusion 1/2004 – 9/2008
		cavity SCC undergoing neck dissection and preoperative FDG-PET/CT
		• Patients characteristics: mean age 63.5y; 73.7% males; 100% oral SCC; cStage I 3%, II 37%, III 13%, IV 47%
		• Prevalence of disease: 9.6% positive lymph nodes, 54% positive neck dissections
			enhanced FDG-PET/CT, CT/US
			• Reference standard: histology of neck specimen
				• FDG-PET/CT:
				  o Se: 77% (63-88%)
				  o Sp: 97% (95-99%)
				  o PPV: 76%
				  o NPV: 98%
				  o LR+: 28.91
				  o LR-: 0.24
				• CT/US:
				  o Se: 73% (58-85%)
				  o Sp: 99% (97-100%)
				  o PPV: 88%
				  o NPV: 97%
				  o LR+: 65.63
				  o LR-: 0.27
					• Results critical appraisal:
					  o Probably consecutive cohort, but selection by indication
					  o Blinding unclear
					  o Node-based analysis: 498 lymph nodes from 48 neck dissections

Ozer E, 2012[12]	• Design: diagnostic study, retrospective
	• Sources of funding: no CoI
	• Setting: single centre, USA
	• Sample size: N=243
	• Duration: inclusion 1/2005 – 12/2007
		• Eligibility criteria: patients with upper aerodigestive tract SCC undergoing therapy that included diagnostic or therapeutic neck dissections
		• Patients characteristics: 100% SCC; 37% OCC, 34% OPC, 19% LC, 4% HPC, 7% other
		• Prevalence of disease: 56% cervical lymph node involvement
			• Index test(s): non-enhanced FDG-PET/CT
			• Reference standard: histology of neck specimen
				Neck-side based analysis
				• FDG-PET/CT:
				  o Se: 85% (79-89%)
				  o Sp: 80% (71-87%)
				  o PPV: 87%
				  o NPV: 76%
				  o LR+: 4.16
				  o LR-: 0.19
					• Dropouts: none reported
					• Results critical appraisal:
					  o Selection by indication
					  o Blinding unclear
					  o Neck-side based analysis

4.1.2. M-staging

Table 46 – M-staging of HNSCC with PET or PET/CT: systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of review quality

Xu G, 2012[3]	• Design: SR + MA
	• Sources of funding: no funding or CoI to disclose
	• Search date: Jan 2012
	• Searched databases: Medline, Embase, screening of references
	• Included study designs: diagnostic accuracy studies
		• Eligibility criteria: patients with HNSCC of all ages at any disease stage; per-patient analysis; at least 10 patients included; sufficient data to construct 2x2 tables
		• Prevalence of disease: not reported
			• Index test(s): PET or PET/CT, conventional anatomic imaging
			• Reference standard: histology of surgical specimen and/or clinical and imaging follow-up
				Detection of distant malignancies, non-nasopharyngeal cancer: 4 studies, 377 patients
				• PET or PET/CT:
				  o Se: 85% (73-93%)
				  o Sp: 95% (91-97%)
				  o LR+: 16.0 (9.8-26.1)
				  o LR-: 0.15 (0.08-0.30)
				• Conventional anatomic imaging:
				  o Se: 62% (43-78%)
				  o Sp: 93% (69-99%)
					• Results critical appraisal:
					  o Duplicate study selection and quality appraisal not mentioned
					  o No language restriction
					  o Overall AMSTAR score: 4/11

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of review quality
	• Included studies: N=8			○ LR+: 8.8 (2.0-40.1) ○ LR-: 0.41 (0.27-0.62)	

Xu GZ, Head Neck 2011[4]	• Design: SR + MA
	• Sources of funding: not reported
	• Search date: Sept 2009
	• Searched databases: Medline, Embase, Cochrane Database of Systematic Reviews, reference lists
	• Included study designs: diagnostic accuracy studies
	• Included studies: N=12
		• <u>Eligibility criteria</u>: patients with head-and-neck cancer; per-patient analysis; at least 10 patients included; sufficient data to construct 2x2 tables
		• <u>Prevalence of disease</u>: 14.4% distant M+ or 2nd primary cancer
			• <u>Index test(s)</u>: PET or PET/CT
			• <u>Reference standard</u>: histology of surgical specimen and/or clinical and imaging follow-up
				Detection of distant metastasis or 2nd primary tumour:
				• PET: 8 studies, 795 patients
				  ○ Se: 85% (78-91%)
				  ○ Sp: 95% (93-97%)
				  ○ DOR: 107.23 (59.26-194.04)
				  ○ LR+: 17.40 (12.16-24.9)
				  ○ LR-: 0.17 (0.12-0.25)
				• PET/CT: 7 studies, 797 patients
				  ○ Se: 88% (79-94%)
				  ○ Sp: 95% (93-96%)
				  ○ DOR: 174.24 (77.11-393.72)
				  ○ LR+: 16.65 (11.996-23.12)
				  ○ LR-: 0.14 (0.083-0.24)
					• Results critical appraisal:
					  ○ Duplicate study selection and quality appraisal
					  ○ Language restriction (English only)
					  ○ Overall AMSTAR score: 6/11

Xu GZ, Oral Oncol 2011[5]	• Design: SR + MA
	• Sources of funding: no funding or CoI to disclose
	• Search date: Mar 2011
	• Searched databases: Medline, Embase, EBM Review Databases, reference lists
	• Included study designs: diagnostic accuracy studies
	• Included studies: N=12
		• <u>Eligibility criteria</u>: patients with head-and-neck cancer; per-patient analysis; at least 10 patients included; sufficient data to construct 2x2 tables
		• <u>Prevalence of disease</u>: not reported
			• <u>Index test(s)</u>: PET/CT
			• <u>Reference standard</u>: histology of surgical specimen and/or clinical and imaging follow-up
				Detection of distant metastasis or 2nd primary tumour (initial staging only): 8 studies, 824 patients
				• PET/CT:
				  ○ Se: 88% (80-94%)
				  ○ Sp: 95% (93-97%)
				  ○ DOR: 174.54 (79.29-384.19)
					• Results critical appraisal:
					  ○ Duplicate study selection and quality appraisal
					  ○ Language restriction (English only)
					  ○ Overall AMSTAR score: 6/11

Table 47 – M-staging of HNSCC with PET or PET/CT: primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
Abd El-Hafez YG, 2011[13]	• Design: diagnostic study, retrospective • Sources of funding: supported in part by a Grant-in-Aid for FDG PET Research in Oral Cancer from Chang Gung Memorial Hospital-Linkou (CMRPG370062); no CoI declared • Setting: university hospital, Taiwan • Sample size: N=114 • Duration: inclusion 6/2006 – 12/2009	• Eligibility criteria: patients with a diagnosis of SCC originating from the alveolar ridge (upper or lower) or other oral cavity subsites but involving the alveolar ridge; preoperative PET/CT and MRI staging studies and surgical management (marginal or segmental mandibulectomy, either with or without inferior maxillectomy) • Patients characteristics: median age 50y; 1.8% males; 100% SCC of the oral cavity; pT1 2.6%, pT2 33.3%, pT3 12.3%, pT4 51.8% • Prevalence of disease: 32.5% pathological bone marrow invasion	• Index test(s): non-enhanced FDG-PET/CT, MRI (1.5 or 3.0T) • Reference standard: histology of surgical specimen	Bone marrow invasion: • FDG-PET/CT: 　○ Se: 78% (62-90%) 　○ Sp: 83% (73-91%) 　○ PPV: 69% 　○ NPV: 89% 　○ LR+: 4.64 　○ LR-: 0.26 • MRI: 　○ Se: 97% (86-100%) 　○ Sp: 61% (49-72%) 　○ PPV: 55% 　○ NPV: 98% 　○ LR+: 2.52 　○ LR-: 0.044	• Dropouts: exclusion of 2 patients for MRI analysis because of uninterpretable images • Results critical appraisal: 　○ Selection by indication; unclear if consecutive cohort 　○ Blinding not reported for index test 　○ Pathologist was aware of clinical staging
Chan SC, 2011[14]	• Design: diagnostic study, prospective • Sources of funding: grants from the National Science Council-Taiwan (NSC97-2314-B-182A-100-MY2 and NSC99-2314-B-182-039-MY3) and from the Chang Gung Memorial Hospital (CMRPG360083); no CoI declared • Setting: university hospital, Taiwan • Sample size: N=103 included in analysis • Duration: inclusion 4/2006 – 9/2008	• Eligibility criteria: patients with a histological diagnosis of primary oropharyngeal or hypopharyngeal SCC • Patients characteristics: mean age 53.6y; 94.2% males; 100% SCC; 52.4% OPC, 47.6% HPC; T1 14.6%, T2 23.3%, T3 10.7%, T4 51.4%; N0 18.4%, N1 4.9%, N2 63.1%, N3 13.6% • Prevalence of disease: 17.3% M+ or 2nd primaries; 1.9% bone M+, 3.9% lung M+, 1.0% liver M+, 3.9% head and neck M+, 3.9% distant LNM+, 5.8% other M+ of aerodigestive tract	• Index test(s): non-enhanced FDG-PET/CT, 3.0T MRI • Reference standard: histology of surgical specimen and imaging follow-up (at least 12 months)	Detection of M+ or 2nd primaries: • FDG-PET/CT: 　○ Se: 83% (59-96%) 　○ Sp: 94% (87-98%) 　○ PPV: 75% 　○ NPV: 96% 　○ LR+: 14.33 　○ LR-: 0.177 • MRI: 　○ Se: 67% (41-87%) 　○ Sp: 96% (90-99%) 　○ PPV: 80% 　○ NPV: 93% 　○ LR+: 18.89 　○ LR-: 0.35 Bone M+: • FDG-PET/CT: 　○ Se: 100% (16-100%) 　○ Sp: 100% (96-100%) 　○ PPV: 100% 　○ NPV: 100% 　○ LR+: -	• Dropouts: 6 patients lost to follow-up and excluded from the analysis • Results critical appraisal: 　○ Consecutive cohort (N=116: 7 met exclusion criteria, 6 lost) 　○ Blinding not reported 　○ Differential verification

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

o LR-: 0.00
- MRI:
  o Se: 100% (16-100%)
  o Sp: 99% (95-100%)
  o PPV: 67%
  o NPV: 100%
  o LR+: 101.00
  o LR-: 0.00

Lung M+:
- FDG-PET/CT:
  o Se: 50% (7-93%)
  o Sp: 99% (95-100%)
  o PPV: 67%
  o NPV: 98%
  o LR+: 49.5
  o LR-: 0.51
- MRI:
  o Se: 50% (7-93%)
  o Sp: 99% (95-100%)
  o PPV: 67%
  o NPV: 98%
  o LR+: 49.5
  o LR-: 0.51

Liver M+:
- FDG-PET/CT:
  o Se: 100% (3-100%)
  o Sp: 100% (96-100%)
  o PPV: 100%
  o NPV: 100%
  o LR+: -
  o LR-: 0.00
- MRI:
  o Se: 0% (0-97%)
  o Sp: 100% (96-100%)
  o PPV: -
  o NPV: 99%
  o LR+: -
  o LR-: 1.0

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

Head and neck M+:
- FDG-PET/CT:
  - Se: 100% (40-100%)
  - Sp: 100% (96-100%)
  - PPV: 100%
  - NPV: 100%
  - LR+: -
  - LR-: 0.00
- MRI:
  - Se: 100% (40-100%)
  - Sp: 100% (96-100%)
  - PPV: 100%
  - NPV: 100%
  - LR+: -
  - LR-: 0.00

Distant LN M+:
- FDG-PET/CT:
  - Se: 50% (7-93%)
  - Sp: 98% (93-100%)
  - PPV: 50%
  - NPV: 98%
  - LR+: 24.75
  - LR-: 0.51
- MRI:
  - Se: 0% (0-60%)
  - Sp: 99% (95-100%)
  - PPV: 0%
  - NPV: 96%
  - LR+: 0.00
  - LR-: 1.01

Other M+ of aerodigestive tract:
- FDG-PET/CT:
  - Se: 100% (54-100%)
 - Sp: 99% (94-100%)
  - PPV: 86%
  - NPV: 100%
  - LR+: 97.0

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

				o LR-: 0.00
				• MRI:
				  o Se: 83% (36-100%)
				  o Sp: 98% (93-100%)
				  o PPV: 71%
				  o NPV: 99%
				  o LR+: 40.42
				  o LR-: 0.17	

Haerle SK, Oral Oncol 2011[15]	• Design: diagnostic study, retrospective
	• Sources of funding: nothing to disclose
	• Setting: university hospital, Switzerland
	• Sample size: N=299
	• Duration: inclusion 1/2002 – 12/2007
		• Eligibility criteria: patients presenting for initial treatment of a newly diagnosed HNSCC, undergoing FDG-PET/CT for initial staging
		• Patients characteristics: mean age 60y; 78.6% males; 100% SCC; 10.4% OC, 56.4% OPC, 19.1% HPC, 12.1% LC, 2.3% NPC; 100% stage III and IV
		• Prevalence of disease: 10% M+ or 2nd primaries
			• Index test(s): non-enhanced FDG-PET/CT
			• Reference standard: histology of surgical specimen and imaging follow-up (with repeated PET/CT or CT)
				Detection of M+ or 2nd primaries:
				• FDG-PET/CT:
				  o Se: 97% (83-100%)
				  o Sp: 95% (91-97%)
				  o PPV: 67%
				  o NPV: 99.6%
				  o LR+: 18.57
				  o LR-: 0.035
					• Dropouts: none reported
					• Results critical appraisal:
					  o Selection by indication; no consecutive cohort
					  o Blinding not reported
					  o Incorporation bias
					  o Differential verification

4.2. RQ3: elective lymph node dissection for patients with cN0 oral cavity cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
(An *et al.*, 2008)[25]	• Design: retrospective chart review • Source of funding: none reported • Setting: Department of Otorhino-laryngology Head and Neck Surgery in Seoul National University Hospital, Korea • Sample size: n=63 • Duration: medical records between 1987 and 2006 were reviewed; median follow-up 59 months (range 12 - 191)	• Eligibility criteria: stage I/II (T1-2N0M0) squamous cell carcinoma of the oral tongue, no neoadjuvant chemotherapy or treatment by radiotherapy alone. • *A priori* patient characteristics: mean age 56 yr (range 26-88); MF: 35/28; cT1N0M0 n=49, cT2N0M0 n=14 • Group comparability: unclear as	Elective unilateral neck dissection (stage I n=13, stage II n=7) vs Observation (stage I n=36 stage II n=7)	**5 year disease free survival** Stage I 100% vs 68.7% (P=0.045) Stage II Not reported **5 year overall survival** Stage I 100% vs 96% (P=0.527) Stage II Not reported. **Regional recurrence** Not reported per treatment group **Quality of life** Not assessed.	• Dropouts: not reported. • Results critical appraisal: low risk of detection (objective outcomes) and reporting bias; high risk of selection and performance bias; unclear risk of bias for the remaining items

		characteristics were not specified per study group		**Adverse events** Not assessed.	
(D'Cruz *et al.*, 2009)[20]	• Design: retrospective chart review • Source of funding: none reported • Setting: tertiary cancer care center • Sample size: n=359 • Duration: charts of patients between January 1997 and December 2001 were included; follow up not reported	• Eligibility criteria: patients with T1/T2 N0 cancer of the oral anterior tongue who underwent a per-oral wide local resection of the primary lesion with or without neck dissection • *A priori* patient characteristics: <u>All participants</u>: median age 49 yrs (range 20-83); men-to-women ratio = 2:1. <u>Elective neck dissection vs wait and watch</u>: T1/T2: 69/90 vs 118/82 • Group comparability: there were more patients with T1 tumours and tumours with thickness < 9 mm in the wait-and-watch group compared with the elective neck dissection group.	Elective neck dissection (n=159) - n=79 supra-omohyoid neck dissection - n=80 modified radical neck dissection vs Wait and watch (n=200) Indications for adjuvant radiotherapy were: positive cut margins, poor differentiation, perineural invasion, increasing T size, positive nodes. Adjuvant radiotherapy (RT) was given to 55 (34.59%) patients in the elective neck dissection group and 21 (10.5%) patients in the wait-and-watch group.	**Disease-free survival** **3 years** 76% vs 71% **5 years** 74% vs 68% (P=0.53) Disease-free status at last follow up: 117/159 (73.6%) vs 131/200 (65.5%) Alive with disease at last follow up: 25/159 (15.7%) vs 38/200 (19%) **Overall survival** **3 years** 69% vs 62% **5 years** 60% vs 60% P=0.24 **Recurrence** Patterns of recurrences - Primary 18/159 (11.3%) vs 9/200 (4.5%) - Neck 9/159 (5.7%) vs 94/200 (47%) - Primary + Neck 2/159 (1.3%) vs 3/200 (1.5%) - Second primary 2/159 (1.3%) vs 1/200 (0.5%) **Quality of life** Not assessed. **Adverse events** Not assessed.	• Dropouts: lost to follow up: 11/159 (6.9%) vs 17/200 (8.5%) • Results critical appraisal: low risk of detection bias (objective outcomes); reporting bias and concurrency of the intervention and comparator group; high risk of selection bias; performance bias and comparability of the intervention and comparator group; unclear risk of bias for the remaining items
(Ebrahimi *et al.*, 2012)[26]	• Design: retrospective analysis of hospital database • Source of funding: none reported • Setting: The Sydney Head and Neck Cancer Institute at Royal	• Eligibility criteria: patients with clinically N0 neck and pathologically confirmed T1 or T2 oral SCC ≥4 mm thick undergoing primary surgical resection with	Elective neck dissection (n=114, of which n=23 bilateral procedures) vs Observation (n=39)	**Overall survival** <u>multivariate analysis:</u> (T classification, tumor thickness, margin status, perineural invasion, and provision of adjuvant radiotherapy and age were included in the multivariable analysis) HR = 0.3 (95% CI 0.1 to 0.6)	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias (objective outcomes) and reporting bias; high risk of selection

Prince Alfred Hospital, Australia
- Sample size: n=153
- Duration: 1987 and 2009, mean FU 3.5 years

curative intent between 1987 and 2009

- *A priori* patient characteristics
Sex (M/F): 71/43 vs 22/17; median age, years (range): 64 (30-92) - <65 42.1% vs. 59.0%; tumour site (oral tongue - floor of mouth/alveolus/retromolar trigone/ buccal: 97/7/6/4 vs 32/3/2/2; pathological T classification T1/T2: 36/78 vs 28/11; radiotherapy (no/yes): 70/44 vs 38/1

- Group comparability: Patients undergoing elective neck dissection were significantly more likely to have pT2 tumours compared to those under observation (68.4% vs 28.2%, respectively; p < .001), were more likely to have involved margins (11.4% vs 0.0%; p = .040) and more likely to receive adjuvant radiotherapy (38.6% vs 2.6%; p < .001). The elective neck dissection group also demonstrated non-significant higher rates of perineural invasion (19.3% vs 7.7%; p = .091) and younger age (57.9% vs 41%

Adjuvant radiotherapy was administered to 45 patients.

Regional recurrence
HR = 0.1 (95% CI 0.0 to 0.3)

Recurrence rate
Not assessed

Quality of life
Not assessed

Adverse events
Not assessed

bias; performance bias and comparability of the intervention and comparator group; unclear risk of bias for the remaining items

- Note: confounding by indication (see baseline comparison)

			younger than 65 years; p = .068).	
(Flach *et al.*, 2013)[27]	• Design: retrospective cohort based on consecutive medical records • Source of funding: none • Setting: Department of Otolaryngology/Head and Neck Surgery, VU University Medical Center, Amsterdam • Sample size: n=285 • Duration: 15 year period (1990–2004); FU: not specified	• Eligibility criteria: consecutive series of previously untreated patients who were treated by transoral excision for a T1–T2 carcinoma of the mobile tongue or floor of mouth during a 15 year period (1990–2004). All patients were classified clinically N0 by ultrasound guided fine needle aspiration cytology. Exclusion criteria were prior or simultaneous second primary tumour and adjuvant radiotherapy. • *A priori* patient characteristics: sex (M/F): 31/20 vs 139/95; median age, years (range): 56 (29 - 82.3) vs 60.8 (29.7 -87.6); pT-classification (T1/T2): 2/49 vs 160/74; tumour site (lateral tongue/floor of mouth): 19/32 vs 134/100 • Group comparability: patients in the END group were younger, had more pT2 tumours, more tumours of the floor of the mouth and less differentiated tumours (significant differences)	Direct elective neck dissection (n=51) vs Wait and scan policy (n=234) "The patients who underwent elective neck dissection were treated prior to adaptation of the current wait and scan policy, or needed this because of technical reasons or were deemed unavailable for strict adherence to surveillance protocol."	**5-year overall survival** 69.5% vs 81.6% (P= 0.082) "After correction for pT-classification, tumour differentiation and age the difference in survival remained not significant (P= 0.500)." **Recurrence rate** Only presented for subgroups of patients with metastases **Quality of life** Not assessed **Adverse events** Not assessed	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias (objective outcomes) and reporting bias; high risk of selection bias; performance bias and comparability of the intervention and comparator group; unclear risk of bias for the remaining items
(Huang *et al.*,	• Design: retrospective	• Eligibility criteria:	Elective neck	**5-year disease-free survival**	• Dropouts: not reported.

| 2008)[21] | review
• Source of funding: National Science Council of Taiwan, grant numbers NSC-96-2628B -182A -098-MY3
• Setting: Chang Gung University, Taoyuan, Taiwan
• Sample size: n=380
• Duration: patients were included between January 1995 and August 2002; median follow-up period: 37.8 months. | patients with early-stage SCC of the oral tongue undergoing primary radical surgery; preoperatively staged as lymph node negative by CT or MRI scans

• *A priori* patient characteristics: age ≤ / >40 yr: 89/235 vs 9/47; M/F 279/45 vs 46/10; Alcohol 210 vs 29; Smoking 257 vs 39; T1/T2: 153/171 vs 42/14

• Group comparability: statistically significant difference between the groups for clinical tumour status: relatively more T1 status in observation group compared to elective neck dissection group. | dissection (n=324)
- supraomohyoid neck dissection (n=278; T1 n=148, T2 n=139)
- modified radical neck dissection (n=37; T1 n=5, T2 n=32)

vs

Observation (n=56)

Postoperative radiotherapy (RT) was performed on patients with 1 positive lymph nodes or close margins (≤4 mm). | Supraomohyoid neck dissection (SOND) vs modified radical neck dissection (MRND) vs observation (OBS): 78.5% vs 83.3% vs 55.6%

Difference between END (SOND + MRND) vs OBS: P = 0.0001; difference between SOND and MRND: P=0.645.

Multivariate analysis (with T-stage in model)
- SOND vs OBS HR=0.32 (95%CI 0.19 to 0.52)
- MRND vs OBS HR=0.21 (95%CI 0.08 to 0.55)

5-year overall survival
SOND vs MRND vs OBS: 87.2% vs 79.6% vs 75.1%
END (SOND + MRND) vs OBS: P=0.029

Multivariate analysis (with T-stage in model)
- SOND vs OBS HR=0.36 (95%CI 0.18 to 0.73)
- MRND vs OBS HR=0.49 (95%CI 0.18 to 1.33)

Regional control rate
Patterns of neck recurrence
40/324 vs 16/56

5-year neck control rate
86.1% vs 69.3%, P<0.001

Multivariate analysis (with T-stage in model)
- SOND vs OBS HR=0.36 (95%CI 0.19 to 0.65)
- MRND vs OBS HR=0.19 (95%CI 0.05 to 0.69)

Quality of life
Not assessed.

Adverse events
Not assessed. | • Results critical appraisal: low risk of detection bias (objective outcomes), reporting bias and concurrency of the intervention and comparator group; high risk of selection bias; performance bias and comparability of the intervention and comparator group; unclear risk of bias for the remaining items |
| (Lin *et al.*, 2011)[28] | • Design: retrospective study | • Eligibility criteria: biopsy-confirmed | Elective neck dissection (n=184) | *NB: study results were presented in a very confusing way which makes interpretation* | • Dropouts: for some analyses participants |

- Source of funding: none reported
- Setting: China Medical University Hospital, Taiwan
- Sample size: n=265 (n=97 buccal squamous cell carcinoma, n=168 tongue squamous cell carcinoma)
- Duration: from January 1997 to December 2006; duration of follow-up at least 60 months or until death.

diagnosis of squamous cell carcinoma of oral tongue and buccal mucosa, curative surgery as first treatment, stage T1/T2 N0, no neo-adjuvant or adjuvant treatment.

- *A priori* patient characteristics: average age 50 years; tongue cancer T1/T2: 56/112, buccal cancer T1/T2: 29/68

- Group comparability: unclear as characteristics were not specified per study group.

(ipsilateral selective neck dissection (I-III))

vs

Observation (n=81; of which: n=34 T1 tongue cancer, n=16 T2 tongue cancer, n=21 T1 buccal cancer, n=10 T2 buccal cancer)

difficult!

Disease-free survival rate
5 year
Univariate HR= 0.55 (95% CI 0.31 to 0.97)
Multivariate analysis (apparently with T-stage in the model) HR = 0.37 (95% CI 0.19 to 0.71)

DFS rates based on Kaplan-Meier:
93.7% vs 78.2% (P=0.001)
- T1 buccal cancer: 71.4% vs 71.3% (P=0.337)
- T2 buccal cancer: 91.7% vs 55.6% (P=0.034)
- T1 tongue cancer: 77.8% vs 91.8% (P=0.483)
- T2 tongue cancer: 90.2% vs 71.4% (P=0.063)

10 year
- T2 buccal cancer: 46.3% vs 18.5% (P not reported)

Overall survival rate
5 year
Univariate HR: not presented
Multivariate analysis (apparently with T-stage, age, gender, alcohol use, primary site and tumour differentiation in the model) HR = 0.34 (95% CI 0.17 to 0.68)

OS rates based on Kaplan-Meier:
94.7% vs 78.7, P=0.036
- T1 buccal cancer: 100% vs 95% (P=0.584)
- T2 buccal cancer: 90.1% vs 77.8% (P=0.494)
- T1 tongue cancer: 92.9% vs 79.3% (P=0.075)
- T2 tongue cancer: 94.8% vs 65.0%, (P=0.002)

10 year
- T2 buccal cancer: 74.1% vs 77.8% (P not reported)

were missing, but reasons not reported.

- Results critical appraisal: low risk of bias for blinding of outcome assessment (objective outcomes), high risk of selection bias and performance bias, unclear risk of bias for other items.

Recurrence (local, locoregional or regional)
- T1 buccal cancer:
  2/8 (25.0%) vs 7/21 (33.3%)
  RR= 0.75 (95% CI 0.20 to 2.88)
- T2 buccal cancer:
  11/58 (19.0%) vs 5/10 (50.0%)
  RR= 0.38 (95% CI 0.17 to 0.86)
- T1 tongue cancer:
  4/22 (18.2%) vs 4/34 (11.8%)
  RR= 1.55 (95% CI 0.43 to 5.55)
- T2 tongue cancer:
  14/96 (14.6%) vs 6/16 (37.5%)
  RR= 0.39 (95% CI 0.18 to 0.86)

Quality of life
Not assessed.

Adverse events
Not assessed.

(Yanai *et al.*, 2012)[31]	• Design: retrospective cohort study • Source of funding: none reported • Setting: Department of Oral and Maxillofacial Surgery, Kyushu University Hospital, Fukuoka, Japan • Sample size: n=297, of which n=229 contribute to the comparison of interest (N0 neck, elective neck dissection vs observation) • Duration: records of patients between 1989 and 2009 were reviewed; median follow-up 72 months (range 12-210)(of n=297)	• Eligibility criteria: definitive surgery for untreated oral squamous cell carcinoma, no distant metastasis at initial visit, no positive surgical margins at primary tumour site, minimum of 5 years follow up. • *A priori* patient characteristics: <u>all participants (n=297)</u>: mean age 64.3 years (range 24-87); M/F: 172/125 <u>Elective neck dissection vs Observation (n=229)</u>: Clinically N0 neck; primary site tumour: tongue/lower gum/upper gum/buccal mucosa/oral floor/other:	Elective neck dissection (n=110) - n=77 selective submandibular neck dissection - n=33 modified radical neck dissection vs Observation (n=119) Most patients who had advanced disease (stage III or IV) received neoadjuvant chemoradiotherapy	**5 year disease-specific survival** 88.0% vs 85.5%, P=0.78 **Regional control** - Regional recurrence: 16/110 (14.5%) vs 21/119 (17.6%) RR=0.82 (95%CI 0.45 to 1.50) - 5 year regional control rate: 85.2% vs 82.9%, P=0.68 **Overall survival** Not assessed. **Quality of life** Not assessed. **Adverse events** Not assessed.	• Dropouts: not reported • Results critical appraisal: low risk of detection bias (objective outcomes), reporting bias and comparability of the intervention and comparator group; high risk of selection and performance bias; unclear risk of bias for the remaining items

41/44/10/9/3/3 vs
43/38/13/14/8/3; cT1/2
/ cT3/4: 78/32 vs 86/33

- Group comparability:
  groups seem
  comparable on tumor
  characteristics

4.3. RQ4: elective lymph node dissection for patients with cN+ oral cavity cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
(Huang *et al.*, 2008)[21]	• Design: retrospective review • Source of funding: National Science Council of Taiwan, grant numbers NSC-96-2628B -182A -098-MY3 • Setting: Chang Gung University, Taoyuan, Taiwan • Sample size: n=380 of which n=324 contribute to the comparison of interest (selective neck dissection vs modified radical neck dissection) • Duration: patients between January 1995 and August 2002 were included; median follow-up period was 37.8 months (n=380).	• Eligibility criteria: patients with early-stage SCC of the oral tongue undergoing primary radical surgery; preoperatively staged as lymph node negative (N0) by CT or MRI scans • *A priori* patient characteristics: All neck dissection patients (n=324): age ≤ / >40 yr: 89/235; M/F 279/45 ; Alcohol n=210 ; Smoking n=257; T1/T2: 153/171 Selective neck dissection vs modified radical neck dissection: T1/T2: 148/139 vs 5/32. • Group comparability: not reported for comparison of interest.	Supraomohyoid neck dissection (n=287; T1 n=148, T2 n=139) vs Modified radical neck dissection (n=37; T1 n=5, T2 n=32) Postoperative radiotherapy (RT) was performed on patients with 1 positive lymph node or close margins (≤4 mm).	**Disease-free survival** 78.5% vs 83.3%, P= 0.645 **"Neck control rate"** No significant difference between the groups (P= 0.810) **Overall survival** 87.2% vs 79.6%, P= 0.174 **Quality of life** Not assessed. **Adverse events** Not assessed.	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias and reporting bias; high risk of selection bias and performance bias; unclear risk of bias for other items.
(Masuda *et al.*, 2012)[29]	• Design: retrospective chart review • Source of funding: Grants-in-Aid for Scientific Research	• Eligibility criteria: primary head and neck squamous cell carcinoma patients who underwent neck	N0: Elective neck dissection (n=15): Elective selective neck dissection (n=12)	Therapeutic selective neck dissection vs comprehensive neck dissection: **Disease-free survival** Not assessed	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias; high

	(C): 21592195 • Setting: Department of Otolaryngology, and Head and Neck Surgery, Kyushu Koseinenkin Hospital, Fukuoka, Japan • Sample size: n=66 patients (n=21 oral cavity); n=78 neck dissections • Duration: patients between June 2004 and June 2010 were included; median follow-up period was 34.1 months (range 7 - 85 months)	dissection during primary treatment; follow-up at least 12 months. • *A priori* patient characteristics: mean age 62.1 (range 34-80); M/F: 55/11; Primary tumour site: nasopharynx / mesopharynx / hypopharynx / larynx / oral cavity / unknown: 3/16/14/11/21/1; T1a/T1/T2b/T2/T3/T4a/T4b: 1/5/1/21/20/14/3; N0/N1/N2/N2a/N2b/N2c/N3: 14/10/2/5/26/6/2; clinical stage I/II/III/IVa/IVb: 0/4/15/32/4 • Group comparability: unclear as patient characteristics were not specified per group.	vs Elective comprehensive neck dissection (modified radical neck dissection) (n=3) <u>N+: Therapeutic neck dissection (n=63)</u> Therapeutic selective neck dissection (n=36) vs Therapeutic comprehensive neck dissection (n=27) - modified radical neck dissection (n=20) - radical neck dissection (n=7) Concurrent chemoradiotherapy when necessary, except for cN0 T1/early T2.	**Recurrence rate** Recurrence rate Patients with N+ 3/35 (8.3%) vs 3/27 (11.1%) RR= 0.77 (95% CI 0.17 to 3.53) **(Loco)regional control** Regional control rates Patients with N+ 92.0% vs 87.8%, P=0.57 (logrank) All patients (N0 and N+): 94.7% vs 89.9%, P= 0.53 (logrank) **Overall survival** All patients (N0 and N+): 64.0% vs 46.8%, P=0.065 (logrank) **Quality of life** Not assessed. **Adverse events** Not assessed.	risk of selection bias and performance bias; unclear risk of bias for other items.
(Park *et al.*, 2013)[30]	• Design: cohort study • Source of funding: none • Setting: Ilsong Memorial Institute of Head and Neck Cancer, Hallym University Medical Center, Seoul, Korea • Sample size: n=44 • Duration: from 2000 to 2006; mean follow-up 55 (6-118) months	• Eligibility criteria: head and neck squamous cell carcinoma, primary surgical treatment, preoperatively node negative by clinical evaluation (CT, PET/CT and ultrasound) but node positive by pathologic results after neck dissection. • *A priori* patient	Selective neck dissection (SND) (n=29) vs Conversion from selective neck dissection to modified radical neck dissection (based on suspicious metastatic nodes in operative field and	**Disease-free survival** Not assessed. **(Loco) regional control** Logrank test: P=0.2719 **Recurrence rate** Nodal recurrence 1/29 vs 2/15 RR= 0.26 (95% 0.03 to 2.63) **Overall survival** Logrank test: P=0.7596 **Quality of life**	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias and reporting bias; high risk of selection bias and performance bias; unclear risk of bias for other items.

		characteristics mean age: not reported; M/F: not reported; primary site (oral cavity/ oropharynx/laryn-go-hypopharynx): 16/3/10 vs 6/2/7; pT1/pT2/pT3/pT4a/pT4 b/: 2/18/3/6/0 vs 2/8/4//1/0; pN1/pN2a/pN2b/pN2c/ pN3: 16/0/12/1/0 vs 7/0/6/2/0; extra capsular spread: 8 vs 6 • Group comparability: authors state "There was no statistically significant difference for the primary site or the T and N distribution between the SND and MRND groups." However, other patient characteristics were not specified per group.	positive frozen biopsy) (MRND) (n=15) Postoperative radiation therapy or concurrent chemo-radiation therapy was done for n=20 in the SND group and n=11 in the MRND group	Not assessed. **Adverse events** Not assessed.	

(Patel *et al.*, 2008)[22]	• Design: retrospective study/cohort; prospective data collection
	• Source of funding: none reported
	• Setting: Sydney Head and Neck Cancer Institute, Royal Prince Alfred Hospital, Sydney, Australia
	• Sample size: n=205 patients (oral cavity n=67), n=232 neck dissections
	• Duration: data from 1987 until December
		• Eligibility criteria: therapeutic neck dissection as part of primary treatment for mucosal head and neck squamous cell carcinoma,; minimum follow-up of 2 years.
		
		• *A priori* patient characteristics: median age (range) 60 (28-99) vs 59 (23-89) yrs; M/F: 45/9 vs 123/27; primary site: oral cavity / oropharynx / hypopharynx / larynx:
			Selective neck dissection (n=72)
			- n=47 unilateral
			- n=7 bilateral
			- n=11 combined with comprehensive neck dissection
			
			vs
			
			Comprehensive (radical or modified radical) neck dissection (n=160)
			- n=131 unilateral
			- n=9 bilateral
				Disease free survival
				Not assessed
				
				5-year regional control
				selective neck dissection vs modified radical neck dissection
				
				Control
				96% vs 86%, P=0.06
				
				Ipsilateral neck recurrence
				- cN1-3:
				    2/54 vs 8/71
				    RR=0.33 (95%CI 0.07 to 1.49)
				
				5-year actuarial overall survival
				selective neck dissection versus comprehensive
					• Dropouts: not reported.
					
					• Results critical appraisal: low risk of detection bias and reporting bias; high risk of selection bias, performance bias and bias due to lack of comparability of study groups; unclear risk of bias for other items.

		2003; median follow-up 54 months (range 24-177)	24/12/9/9 vs 43/59/37/12; pT1/2 / pT 3/4: 27/27 vs 66/85; pN0/1 / pN2/3: 21/33 vs 24/127. • Group comparability: primary tumour site differed between groups and patients having selective neck dissection had fewer adverse prognostic factors compared with patients having comprehensive dissection	- n=11 combined with selective neck dissection Adjuvant postoperative irradiation was prescribed if pathological assessment revealed multiple nodal involvement or extracapsular spread (ECS). Additional indications for adjuvant radiotherapy included advanced primary disease or positive resection margins.	*neck dissection* 43% vs 33%, P= 0.25 **Quality of life** Not assessed. **Adverse events** Not assessed.	
(Rapoport *et al.*, 2007)[23]	• Design: retrospective analysis • Source of funding: none reported • Setting: Head & Neck and ORL Department of the Heliopolis Hospital Sao Paolo, Brazil • Sample size: n=460 patients; n=573 neck dissections • Duration: patient files between 1978 and 2002 were included; median follow-up not reported.	• Eligibility criteria: previously untreated squamous cell carcinoma in lower region of the mouth (tongue, floor of the mouth, retromolar region and the lower gingiva), radical or selective (supraomohyoid) neck dissection, minimum follow-up period of 12 months or until death. • *A priori* patient characteristics: median age: 53 yrs (Q25-75%: 47 - 62); M/F:406/54; tumour site floor of mouth/tongue/ retromolar region/ lower gingival: 180/136/74/70; T1/T2/T3/T4/Tx: 14/157/146/138/5; cN0/N1/N2a/N2b/N2c/	Selective neck dissection (n=128) vs Radical neck dissection (n=445) Some patients (number of patients not reported) received postoperative radiation therapy. NB: the analysis addressed neck dissections instead of patients	**Disease-free survival** Not assessed. **(Loco) regional control** Not assessed. **Recurrence** 6/117 (5.1%) vs 16/410 (3.9%) RR 1.31 (95% CI 0.53 to 3.28) Recurrence according to pN stage: pN0: 4/97 (4.1%) vs 5/157 (3.2%) RR 1.29 (95% CI 0.36 to 4.70) pN+: 2/20 (10.0%) vs 11/253 (4.3%) RR= 2.30 (95% CI 0.55 to 9.67) **Overall survival** Not assessed. **Quality of life** Not assessed. **Adverse events** Not assessed.	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias; high risk of selection bias, performance bias and reporting bias; unclear risk of bias for other items.

		N3/Nx): 227/119/18/58/23/14/1; pN0/pN1/pN2a/pN2b/pN2c/pN3/pNx: 214/246/62/7/138/23/5/11 • Group comparability: unclear as patient characteristics were not specified per study group.			
(Shepard et al., 2010)[24]	• Design: historical cohort study • Source of funding: none • Setting: the University of Wisconsin Hospital and Clinics comprehensive head and neck cancer database • Sample size: n=156 • Duration: between 1994 and 2006; average follow up: 3.1 years (selective neck dissection: range 9 months to 11 years; comprehensive neck dissection: range 3 months to 12 years)	• Eligibility criteria: mucosal squamous cell carcinoma and clinically positive regional nodal disease, primary surgical management, without prior head and neck cancer or radiotherapy. • *A priori* patient characteristics: median age: 61 vs 61 years; (M/F): 42/27 vs 64/23; primary tumour site oral cavity/oropharynx/larynx/nasopharynx/paranasal sinuses/unknown: 33/5/5/25/0/0/1 vs 37/22/6/14/1/1/6; Tx/T1/T2/T3/T4: 1/2/11/24/31 vs 6/6/16/26/33; cN1/cN2/cN3: 22/47/0 vs 11/72/4; pN0/pN1/pN2/pN3) 15/13/41/0 vs 7/8/69/3; extracapsular spread: 12 vs 38; year of surgery (1994-1999 / 2000-2007) 13/56 vs 18/42	Selective neck dissection (n=69) vs Comprehensive neck dissection (n=87) Postoperative radiotherapy was given to subjects who had extracapsular spread or nodal staging of N2 or greater based on pathology.	**Disease-free survival** Not assessed. **Free of 3-year ipsilateral regional recurrence** 96% vs 86% (P=0.053) **3-year regional recurrence (defined as regional recurrence without local recurrence)** HR= 1/4.0 = 0.25 (P=0.07) Multivariate analysis: (differences in nodal and primary tumour stage, primary tumour site, year of surgery, extracapsular spread, postoperative radiotherapy radiotherapy rates, and neck dissection type were considered) HR= 1/4.77 = 0.21 (P=0.055) **5-year overall survival** 46% vs 33% (P=0.14) HR for survival = 1/0.71 = 1.41 (P=0.14) Multivariate analysis: (differences in nodal and primary tumour stage, primary tumour site, year of surgery, extracapsular spread, postoperative radiotherapy, radiotherapy rates, and neck dissection type were considered) HR for survival = 1/0.79 = 1.27 (P=0.41) **Quality of life** Not assessed. **Adverse events** Not assessed.	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias, high risk of selection bias, performance bias and high risk of bias due to lack of comparability and concurrence of study groups; unclear risk of bias for other items.

			N0		
		• Group comparability: significant differences between groups included primary tumour site, clinical and pathological nodal stage, extracapsular spread, and year of surgery.			
(Yanai *et al.*, 2012)[31]	• Design: retrospective cohort study • Source of funding: none reported • Setting: Department of Oral and Maxillofacial Surgery, Kyushu University Hospital, Fukuoka, Japan • Sample size: n=297, of which n=110 contribute to the comparison 'selective submandibular neck dissection vs modified radical neck dissection' and n=68 to the comparison selective submandibular neck dissection vs radical neck dissection • Duration: records of patients between 1989 and 2009 were reviewed; median follow-up 72 months (range 12-210)	• Eligibility criteria: definitive surgery for untreated oral squamous cell carcinoma, no distant metastasis at initial visit, no positive surgical margins at primary tumour site. • *A priori* patient characteristics: <u>All participants (n=297):</u> mean age 64.3 years (range 24-87); M/F: 172/125 <u>Selective submandibular neck dissection vs modified radical neck dissection (n=110)</u> Clinically N0 neck; primary site tumour: tongue/lower gum/upper gum/buccal mucosa/oral floor/other: 28/31/7/6/2/3 vs 13/13/3/3/1/0; cT1/2 / cT3/4: 55/22 vs 23/10 <u>Selective submandibular neck dissection vs radical neck dissection (n=68)</u>	N0 Selective submandibular neck dissection (n=77) vs Modified radical neck dissection (n=33) AND N+ Selective submandibular neck dissection (n=32) vs Radical neck dissection (n=36) Most patients who had advanced disease (stage III or IV) received neoadjuvant chemoradiotherapy.	**Disease-free survival** Not assessed **Regional control** *Selective neck dissection vs modified radical neck dissection (N0)* - Regional recurrence: 11/77 (14.3%) vs 5/33 (15.2%) HR=0.94 (95%CI 0.34 to 2.62) - 5 year regional control rate: 85.2% vs 83.3%, P=0.89 *Selective neck dissection vs radical neck dissection (N+)* - Regional recurrence: 6/32 vs 6/36 HR=1.12 (95%CI 0.41 to 3.46) - 5 year regional control rate: 81.3% vs 83.0%, P=0.72 **Overall survival** Not assessed. **Quality of life** Not assessed. **Adverse events** Not assessed.	• Dropouts: not reported. • Results critical appraisal: low risk of detection bias and reporting bias, and bias due to non-comparability of study groups; high risk of selection bias and performance bias; unclear risk of bias for other items.

		Clinically N1 neck, metastasis to level I; primary site tumour: tongue/lower gum/upper gum/buccal mucosa/oral floor/other: 14/11/3/1/3/0 vs 13/14/4/3/2/0; cT1/2 / cT3/4: 10/22 vs 9/27. • Group comparability: groups seem comparable in tumour characteristics			
(Yildirim *et al.*, 2011)[32]	• Design: retrospective study • Source of funding: none reported • Setting: Uludağ University School of Medicine Department of Otorhinolaryngology, Bursa, Turkey • Sample size: n=61 • Duration: patients between January 1996 and December 2005 were evaluated; mean follow-up period was 35.4 months (SE 24.8).	• Eligibility criteria: squamous cell carcinoma localized to the oral cavity, larynx, oropharynx, or hypopharynx, single metastatic lymph node< 3 cm in pathological examination, follow-up at least for two years or until death or until development of neck recurrence, no previous treatments. • A priori patient characteristics: mean age (SD) 56.0 (12.2) vs 54.0 (10) yrs; M/F 31/3 vs 25/2; location larynx/oral cavity/oro-hypohparynx: 24/5/5 vs 18/7/2; T1/T2/T3/T4: 1/7/13/13 vs 1/7/15/4; N0/N1/N2/N3: 16/9/9/0 vs 5/17/4/1; extracapsular spread 14.7% vs 18.5% • Group comparability: no significant	Selective neck dissection (SND) (n=34) vs Comprehensive neck dissection (CND) (n=27) Adjuvant radiotherapy SND: n=13 CND: n=12 Adjuvant cemoradiotherapy SND: n=10 CND: 0=5 indications for postoperative adjuvant radiotherapy and/or chemotherapy were: - perineural invasion - vascular invasion - T4 tumour - subglottic extension - poor prognosis - positive surgical margins	**Disease-free survival** Not assessed. **Recurrence rate** 2/34 (5.9%) vs 1/27 (3.7%) RR 1.59 (95% CI 0.15 to 16.60) **(Loco)regional control** Not assessed. **Overall survival rate** **2 years** 67.6% vs 81.5%, P>0.05 **5 years** 58.0% vs 66.0%, P>0.05 **Quality of life** Not assessed. **Adverse events** Not assessed.	• Dropouts: not reported. • Results critical appraisal: low risk of selection bias and bias due to lack of comparability of study groups, high risk of selection bias and performance bias, unclear risk of bias for other items.

	differences for age and gender, no statsically significant difference among oncologic parameters, except for the side of the neck dissection.	- metastasis in >2 lymph nodes or extracapsular spread.	

4.4. RQ5: elective lymph node dissection of contralateral neck

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

Gonzalez-Garcia, 2008[125a][125]	• <u>Design</u>: prospective cohort
	• <u>Sources of funding</u>: none reported
	• <u>Setting</u>: University hospital, Madrid
	• <u>Sample size</u>: N=315
	• <u>Duration</u>: June 1979 – December 1999
	• <u>Follow-up</u>: 210 months[b]
	• <u>Statistical analysis</u>: Kaplan-Meier survival analysis
		• <u>Eligibility criteria</u>:
		  o Histologic confirmation of SCC of the oral cavity
		  o No prior chemo- or radiotherapy
		• <u>Exclusion criteria</u>:
		  o Primary tumour on the midline
		  o Recurrent primary tumour
		  o Multiple primary tumours
		  o Contra-indication for surgery
		  o Distant metastasis
		• <u>Characteristics and group comparability of patients (entire cohort)</u>:
		  o Female: 30%
		  o Mean age: 60; range: 18-90 y.o.
		  o T1:23%; T2: 39%; T3: 12%; T4: 24%
			• Gr 1: Ipsilateral modif type III RND (T2-4N0 or with nodes without extracapsular extension <3cm; n=137)
			• Gr 2: Bilateral modif type III RND (N0-1 pts with midline invasion; n=55)
			• Gr 3: Ipsilateral classical RND (nodes ≥3 cm, fixed nodes or n. Spinalis affected; n=13)
			• Gr 4: Ipsilateral classical RND + contralateral modif type III RND (ipsilateral N2-3 and contralat N0 AND affection of midline; n=5)
			• Gr 5: Ipsilateral modif type III RND + contralateral classical RND (N2 at
				o Contralateral neck relapse rate after primary unilateral vs. bilateral neck dissection: 7.3% vs. 3.1% (NS)
				o Contralateral neck relapse rate in pN0 neck:
				  ▪ Gr 1: 8/98
				  ▪ Gr 2: 0/29
				  ▪ Gr 3: 0/0
				  ▪ Gr 4: 0/2
				  ▪ Gr 5: 1/1
				o Contralateral neck relapse rate in pN+ neck:
				  ▪ Gr 1: 2/39
				  ▪ Gr 2: 1/26
				  ▪ Gr 1/8
				  ▪ Gr 4: 0/3
				  ▪ Gr 5: 0/3
					• Dropouts: none reported
					• Results critical appraisal:
					  o High risk of selection bias (different types of cervical dissections according to TNM staging); high risk that intervention and control group were not comparable
					  o High risk of performance bias
					  o High risk of detection bias
					  o High risk of reporting bias
					  o Unclear risk of attrition bias
					  o Concurrent inclusion and treatment of intervention and control group
					  o Careless reporting of data
					  o Small subgroups
					  o 106 pts received additional radiotherapy

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[a]   The 203 patients with squamous cell carcinoma of the lateral side of the tongue described in Gonzalez-Garcia et al., 2007[126] were most probably also included in the 2008 publication and hence not separately reported in the evidence table. Contralateral relapse rate for primary tumour in the tongue after primary unilateral vs. bilateral neck dissection: 7.1% vs. 1.7% (NS).

[b]   Estimated based on survival analysis – fig 1

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
			contralat neck; n=4) • 101 pts: no dissection		– correlation with contralateral lymph neck node metastasis not reported ○ No survival data per intervention group reported
Lim, 2006[127]	• Design: retrospective review of database • Sources of funding: none reported • Setting: University hospital, Seoul, South Korea • Sample size: 54 • Duration: 1992-2003 • Follow-up: mean: 56.3 months; range: 3 – 110 months • Statistical analysis: Kaplan-Meier survival analysis	• Eligibility criteria: ○ Stage I or II SCC of the tongue ○ Histopathologic confirmation of SCC ○ No prior treatment for H&N tumours ○ Primary tumour unilaterally located ○ Ipsilateral elective neck dissection ○ Clinically N0 neck (diagnosed by physical examination and/or CT or MRI • Exclusion criteria: ○ Simultaneous distant metastasis ○ Elective radiotherapy to the contralateral neck ○ Peroral excision without ipsilateral elective neck dissection • Characteristics and group comparability of patients (entire cohort): ○ Female: 37% ○ Mean age: 53; range: 22-79 y.o. ○ Gr 1: 21 T1 & 8 T2 vs Gr 2: 4 T1 & 21 T2	Partial glossectomy and ipsilateral elective neck dissection and: • Gr 1: Observation (n=29) +/- radiotherapy (n=7) • Gr 2: Contralateral elective (supraomohyoid) neck dissection (n=25) +/- radiotherapy (n=13)	○ 5-year disease-free survival (DFS) after primary unilateral vs. bilateral neck dissection: 82% vs. 68% (NS) ○ Contralateral neck recurrence rate after primary unilateral vs. bilateral neck dissection: 0% vs. 0% (NS) ○ Ipsilateral neck recurrence rate after primary unilateral vs. bilateral neck dissection: 14% vs. 16% (NS)	• Dropouts: none reported • Results critical appraisal: ○ Different treatment protocols over time: prior to 1998: only unilateral elective neck dissection performed; after 1998: primary tumour > 1cm: bilateral elective neck dissection - primary tumour < 1cm: no (ipsilateral nor contralateral) neck dissection ○ High risk of selection bias (assignment to subgroups not explained); ○ High risk that intervention and control group were not comparable ○ High risk of performance bias ○ High risk of detection bias ○ Unclear risk of reporting bias ○ Low risk of attrition bias ○ No concurrent inclusion and treatment of intervention and control group ○ Small subgroups

4.5. RQ6: value of PET / MRI in the decision of neck dissection after CRT

Table 48 – Value of PET(/CT) in the decision of neck dissection after CRT: systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of review quality
Gupta, 2011[39]	• Design: SR + MA • Sources of funding: none declared • Search date: September 2011 • Searched databases: Pubmed/Medline, CENTRAL, screening of references • Included study designs: prospective & retrospective • Included studies: 51 (of which 30 reported on the neck nodes and 24 on the primary site)	• <u>Eligibility criteria</u>: studies including patients with HNSCC; data on sensitivity, specificity, PPV, NPV and total number of patients • <u>Patients characteristics</u>: various HNSCC • <u>Prevalence of disease</u>: not reported	• <u>Index test(s)</u>: FDG PET or FDG PET/CT • <u>Reference standard</u>: histopathological confirmation if applicable and/or close clinicoradiological FU of at least 6 months	Weighted mean pooled estimate of DFG PET(CT) for neck nodes: • Se: 72.7% (66.6-78.2%) • Sp: 87.6% (85.7-89.3%) • PPV: 52.1% (46.6%-57.6%) • NPV: 94.5% (93.1-95.7%)	• Results critical appraisal: ○ Duplicate study selection and quality appraisal ○ Language restriction (English only) ○ Detailed quality appraisal results per individual study in appendix ○ Overall AMSTAR score: 5/11
Isles, 2008[40]	• Design: SR + MA • Sources of funding: none supported • Search date: October 2007 • Searched databases: Medline (and Pubmed), Cochrane, screening of references • Included study designs: prospective & retrospective • Included studies: 27	• <u>Eligibility criteria</u>: Prospective and retrospective studies (excluding reviews), studies including patients with HNSCC, FDG-PET in posttreatment phase following primary treatment by RT or CRT, minimum dataset of sensitivity/specificity or false positive/negative rates for either primary site or neck disease • <u>Patients characteristics</u>: various HNSCC • <u>Prevalence of disease</u>: not reported	• <u>Index test(s)</u>: PET (and, CT, MRI, US) • <u>Reference standard</u>: histology of neck specimen or sufficient follow-up	Pooled estimate for recurrent/residual nodal disease: • PET: ○ Se: 74% (50-89%) ○ Sp: 88% (74-95%) ○ PPV: 49% (29%-70%) ○ NPV: 96% (84-99%)	• Results critical appraisal: ○ Duplicate study selection and quality appraisal ○ Language restriction (English only) ○ Detailed quality appraisal results per individual study in appendix ○ Overall AMSTAR score: 5/11

Table 49 – Value of PET(/CT) in the decision of neck dissection after CRT: primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

Kishino, 2012[42]	• Design: Prospective
	• Sources of funding: not reported
	• Setting: Kagawa University, Japan
	• Sample size: N= 28
	• Duration: inclusion 5/2006 – 9/2010
		• <u>Eligibility criteria</u>: newly diagnosed patients with HNSCC treated with CRT
		• <u>Patients characteristics</u>: age range: 50-83 y.o.; female: 11%; SCC: 100%; OPC: 32%, HPC: 32%, LC: 29%, NPC: 4%, OCC: 4%; stage II: 21%, stage III: 32%, stage IV: 46%;
		• <u>Prevalence of residual disease (after CRT)</u>: primary: 14%; LN: 18%
			• <u>Index test(s)</u>: ^{18}F-FLT PET; ^{18}F-FDG PET
			• <u>Reference standard</u>: endoscopy, radiography, pathology
			• <u>Treatment</u>: cCRT
				<u>Node based analysis</u>
				• ^{18}F-FLT-PET:
				  ○ Se: 100%
				  ○ Sp: 68%
				  ○ PPV: 38%
				  ○ NPV: 100%
				• ^{18}F-FDG-PET:
				  ○ Se: 100%
				  ○ Sp: 64%
				  ○ PPV: 38%
				  ○ NPV: 100%
					• Dropouts: 2 patients (because of the condition of the patient)
					• Results critical appraisal:
					  ○ Unclear if sample was consecutively recruited
					  ○ Small sample
					  ○ 4/28 patients had T>0 after CRT
					  ○ 4% had nasopharyngeal cancer
					  ○ Qualitative evaluation of PET
					  ○ Low risk of selection bias
					  ○ High risk that interpretation of ref standards introduced bias
					  ○ Differential verification

Loo, 2011[43]	• Design: Retrospective
	• Sources of funding: not reported
	• Setting: NHS hospital, UK
	• Sample size: N= 34
	• Duration: inclusion 4/2005 – 9/2007
		• <u>Eligibility criteria</u>: patients with N2 HNSCC
		• <u>Patients characteristics</u>: median age: 54 y.o.; female: 24%; HNSCC: 100%; OPC: 82%, HPC: 6%, NPC: 3%, unknown primary: 9%; stage IV: 100%
		• <u>Prevalence of residual disease (after CRT)</u>: primary: 6%; LN: 0%
			• <u>Index test(s)</u>: FDG PET
			• <u>Reference standard</u>: pathology & FU
			• <u>Treatment</u>: sCRT
				<u>Patient based analysis</u>
				• FDG-PET:
				  ○ Se: /
				  ○ Sp: 97%
				  ○ PPV: 0%
				  ○ NPV: 100%
					• Dropouts: none
					• Results critical appraisal:
					  ○ Small sample
					  ○ Retrospective study
					  ○ Consecutive sample
					  ○ 3% had nasopharyngeal cancer, 9% had unknown primary
					  ○ Low risk of selection bias
					  ○ High risk that interpretation of reference standards introduced bias
					  ○ Differential verification

Mori, 2011[44]	• Design: Prospective
	• Sources of funding: not reported
	• Setting: Yokohama
		• <u>Eligibility criteria</u>: previously untreated HNSCC
		• <u>Patients characteristics</u>: mean age: 64 (range: 36-85) y.o.; female: 13%; HNSCC: 100%; OCC: 7%, OPC: 22%, HPC: 36%,
			• <u>Index test(s)</u>: FDG-PET
			• <u>Reference standard</u>: pathology & FU (after FNA)
				<u>Patient based analysis</u>
				• FDG-PET (residual disease only)
				  ○ Se: 50%
				  ○ Sp: 70
					• Dropouts: none reported
					• Results critical appraisal:
					  ○ Consecutive sample
					  ○ 15% had

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
	University, Japan • Sample size: N= 65 • Duration: inclusion 11/2002 – 4/2007	LC: 20%, NPC: 15%; stage I: 5%, stage II: 6%, stage III: 23%, stage IV: 66% • Prevalence of residual disease (after CRT): primary: 11%; LN: 4%	• Treatment: cCRT	○ PPV: 7 ○ NPV: 97 • FDG-PET (residual +recurrent disease) ○ Se: 33% ○ Sp: 70% ○ PPV: 20% ○ NPV: 82%	nasopharyngeal cancer ○ 7/64 patients had T>0 after CRT ○ Low risk of selection bias ○ High risk that interpretation of reference standards introduced bias ○ Differential verification
Porceddu, 2011[45]	• Design: Prospective • Sources of funding: not reported • Setting: Princess Alexandra hospital Brisbane, Australia • Sample size: N= 112 • Duration: inclusion 1/20025 – 4/2009	• Eligibility criteria: patients with N+HNSCC suitable for organ preservation after (C)RT, biopsy proven SCC, no evidence of distant metastases, CR at primary after (C)RT • Patients characteristics: median age: 55 (range: 25-88) y.o.; female: 19%; HNSCC: 100%; OPC: 74%, HPC: 6%, NPC: 9%, LC: 6%, unknown primary: 4%; stage III: 11%, stage IV: 89% • Prevalence of residual disease (after CRT): primary: 0%; LN: 2%	• Index test(s): PET • Reference standard: pathology & FU • Treatment: CRT: 102 (91%), RT: 10 (9%)	Patient based analysis • FDG-PET: ○ Se: 100% ○ Sp: 94% ○ PPV: 22% ○ NPV: 100%	• Dropouts: none reported • Results critical appraisal: ○ Retrospective study ○ Consecutive sample ○ 9% had nasopharyngeal cancer, 4% had unknown primary ○ All patients had T=0 after CRT ○ Risk of selection bias (5 pts had no post-treatment PET and were excluded) ○ High risk that interpretation of reference standards introduced bias ○ Differential verification
Prestwich, 2012[46]	• Design: Retrospective • Sources of funding: not reported • Setting: NHS hospital Leeds, UK • Sample size: N= 44 • Duration: inclusion 8/2008 – 4/2011	• Eligibility criteria: histologically confirmed HNSCC, reviewed in MDT meeting, Stage III or IV, (C)RT (no surgery), PET at BL and after therapy • Patients characteristics: median age: 55 (range: 29-75) y.o.; female: 30%; HNSCC: 100%; OPC: 68%, HPC: 14%, NPC: 2%, LC: 7%, unknown primary: 9%; stage III: 2%, stage IV: 98% • Prevalence of residual disease (after CRT): primary: 8%; LN: 13%	• Index test(s): FDG-PET/CT • Reference standard: pathology & FU • Treatment: RT: 7 (16%), cCRT: 24 (54%), ICT + cCRT: 12 (27%), CT: 1 (2%)	Patient based analysis • FDG-PET: ○ Se: 100% ○ Sp: 92% ○ PPV: 63 ○ NPV: 100%	• Dropouts: none reported • Results critical appraisal: ○ Small sample ○ Retrospective study ○ Consecutive sample ○ 2% had nasopharyngeal cancer, 9% had unknown primary ○ 8% had T>0 after CRT ○ Low risk of selection bias ○ High risk that

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
					interpretation of reference standards introduced bias o Differential verification
Zundel, 2011[47]	• Design: Retrospective • Sources of funding: not reported • Setting: Medical college Wisconsin, USA • Sample size: N= 52 • Duration: inclusion 7/2002 – 3/2006	• Eligibility criteria: patients with carcinoma of the head & neck, (C)RT, no prior treatment for HNSCC • Patients characteristics: mean age: 56 (range: 24-81) y.o.; female: 31%; HNSCC: 100%; OCC: 6%, OPC: 56%, HPC: 10%, NPC: 4%, LC: 25%; stage I: 4%, stage II: 12%, stage III: 31%, stage IV: 54% • Prevalence of residual disease (after CRT): primary: 8%; LN: 0%	• Index test(s): FDG PET/CT • Reference standard: FU (for primary sites also pathology) • Treatment: RT: 14 (27%), cCRT: 38 (73%)	Patient based analysis • FDG-PET: o Se: / o Sp: 100% o PPV: / o NPV: 100%	• Dropouts: none reported • Results critical appraisal: o Retrospective study o All patients had carcinoma (unclear if it was SCC for all) o Unclear if sample was consecutively recruited o 4% had nasopharyngeal cancer o 8% had T>0 after CRT o Low risk of selection bias o High risk that interpretation of reference standards introduced bias o Differential verification

Table 50 – Value of MRI in the decision of neck dissection after CRT: primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results secondary and other outcome(s)	Critical appraisal of review quality
Lin, 2007[48]	• Design: retrospective • Sources of funding: none stated • Setting: single centre, USA • Sample size: 38 patients • Duration: January 2000 - July 2005	• Eligibility criteria: biopsy-proven HNSCC with N2 or N3 neck disease who underwent primary chemoradiation • Patients characteristics: age range 34-84 y.o., 33/38 men, 32/38 oropharyngeal tumours, 2 laryngeal, 1 hypopharyngeal and 3 unknown. 34/38 N2, 4/38 N3. • Prevalence of residual disease after CRT: 13% residual neck disease, residual disease in primary tumour unclear	• Index test(s): MRI 6-8 weeks posttreatment • Reference standard: neck dissection + follow-up • Treatment: CRT	Patient based analysis: • Se: 60% • Sp: 62% • PPV: 19% • NPV: 91% Residual disease only: Sp: 67% NPV: 100%	• Dropouts: none • Results critical appraisal: nodal disease > 6 months after treatment considered "disease positive"

4.6. RQ7: neck dissection after chemoradiotherapy in patients with oral cavity cancer

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

Da Mosto, 2013[128]	• <u>Design</u>: retrospective cohort study
	• <u>Sources of funding</u>: None reported
	• <u>Setting</u>: Treviso Regional Hospital, Italy
	• <u>Sample size</u>: 75
	• <u>Duration</u>: enrolment bw Jan 2000 – July 2007
	• <u>Follow-up</u>: median: 77 months (range: 26-120 months)
	• <u>Statistical analysis</u>: survival analysis
		• <u>Eligibility criteria</u>:
		o Previously untreated, histologically proven nonmetastatic **stage III or IV** squamous cell carcinoma of the oral cavity, oropharynx, larynx, or hypopharynx
		o Age ≤ 80 y.o.
		o Karnofsky performance status ≥ 60%
		o No history of head and neck cancer
		o Acceptable medical and laboratory status in order to tolerate chemotherapy
		o Informed consent
		o cCR[c], assessed with fiber-optic endoscopy and contrast-enhanced CT or MRI, after **IC/CCRT**[d]
		• <u>Exclusion criteria</u>: Patients with extensive invasion of bone and/or cartilage with organ destruction
		• <u>Characteristics and group comparability of patients (entire cohort)</u>:
		o Female: 10%
		o Median age: 61; range: 39-77 y.o.
		o T2: 32%; T3: 25%; T4: 43%
		o Primary site: oropharynx: 46; Larynx: 12; Hypopharynx: 12; Oral cavity: 5
			• Gr 1: modified radical type III ND (high-volume node metastasis (>3cm) – only first part of the study; n=8)
			• Gr 2: watchful waiting (n=43)
			• Gr 3: PR after CRT (n=18; results not presented)
			• Gr 4: progression of disease after CRT (n=6; results not presented)
				o 5-year regional control: p=0.962
				  ▪ Gr 1: not reported
				  ▪ Gr 2: 82% (95% CI 61-100%)
				o 5-year progression free survival: p=0.952
				  ▪ Gr 1: not reported
				  ▪ Gr 2: 59% (95% CI 36-83%)
				o 5-year overall survival: p=0.800
				  ▪ Gr 1: not reported
				  ▪ Gr 2: 64% (95% CI 45-84%)
				o Regional recurrence:
				  ▪ Gr 1: not reported
				  ▪ Gr 2: 5/43
					• Dropouts: none reported
					• Results critical appraisal:
					o High risk of selection bias (ND in first part of study only performed in patients with high-volume node metastasis; during the second part no ND performed); high risk that intervention and control group were not comparable
					o Unclear risk of performance bias
					o High risk of detection bias
					o Unlcear risk of reporting bias (unclear why OS, PFS and Recurrence FS were not reported for gr 1)
					o Unclear risk of attrition bias
					o No concurrent inclusion and treatment of intervention and control group
					o Small subgroups

Soltys, 2012[129]	• <u>Design</u>: retrospective cohort study
	• <u>Sources of funding</u>:
	• <u>Setting</u>: Stanford University Medical
		• <u>Eligibility criteria</u>:
		o Head and neck squamous cell carcinoma with N2-3 neck disease
		o cCR[e], assessed using physical examination, direct fiberoptic evaluation and CT or MRI, after **sequential**
			• Gr 1: planned ND (n=8)
			• Gr 2: watchful waiting (n=48)
			• Gr 3: PR after CRT
				o 5-year disease free survival:
				  ▪ Gr 1 & 2: 53% (95% CI, 66-39%)
				o 5-year overall survival:
				  ▪ Gr 1 & 2: 68% (95% CI, 81-55%)
					• Dropouts: none reported
					• Results critical appraisal:
					o High risk of selection bias; unclear whether intervention and

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[c]   cCR: assessed as disappearance of all measurable and evaluable disease

[d]   IC/CCRT: induction-concurrent chemoradiotherapy

[e]   Neck cCR: assessed as no palpable lymph nodes on physical examination and no lymph nodes with maximum cross-sectional diameter of > 1.0 cm on CT or MRI.

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
	Centre, Canada • <u>Sample size</u>: 90 • <u>Duration</u>: enrolment bw 1991 and 2001 • <u>Follow-up</u>: median: 5.4 years (range: 0.6 – 16.3 years) • <u>Statistical analysis</u>: Kaplan Meier	**chemoradiotherapy** • <u>Exclusion criteria</u>: Patients with nasopharynx and paranasal sinus primaries • <u>Characteristics and group comparability of patients (entire cohort)</u>: o Female: 16% o Median age: 58; range: 39-80 y.o. o T0: 2%; T1: 11%; T2: 31%; T3: 15%; T4: 41% o Primary site: oropharynx: 60; Larynx: 8; Hypopharynx: 18; Oral cavity: 3; Unknown: 2	(n=30; results not presented) • Gr 4: progression of disease after CRT (n=4; results not presented)	o Relapse with lymph node involvement: ▪ Gr 1: 0/8 ▪ Gr 2: 5/48 (10%; neck & primary: 2/48; neck, primary and distant: 1/48; neck only 1/48; neck & distant: 1/48)	control groups were comparable o Unclear risk of performance bias o High risk of detection bias o High risk of reporting bias (OS en DFS not separately presented for Gr1 and Gr2) o Unclear risk of attrition bias o Concurrent inclusion and treatment of intervention and control group o Small subgroups
Cannady, 2010[130]	• <u>Design</u>: retrospective chart review • <u>Sources of funding</u>: None reported • <u>Setting</u>: Cleveland Clinic, USA • <u>Sample size</u>: 329 positive necks at diagnosis in 241 patients • <u>Duration</u>: enrolment bw 1989 and 2007 • <u>Follow-up</u>: at least 1 yr • <u>Statistical analysis</u>: Kaplan-Meier survival	• <u>Eligibility criteria</u>: o Head and neck squamous cell carcinoma stage IV (N2-3 neck disease) o CR[f] at the primary site after **concurrent CRT** • <u>Exclusion criteria</u>: Patients with nasopharyngeal or sinonasal primaries • <u>Characteristics and group comparability of patients (entire cohort)</u>: o Female: 19% o Median age: 56; range: 24-77 y.o. o Tx: 4; T0: 2; T1: 36; T2: 64; T3: 64; T4: 71 o Primary site: oropharynx: 165; Larynx: 26; Hypopharynx: 29; Oral cavity: 13; Unknown: 5; multiple: 3	• Gr 1: cCR in the neck - ND (n=65 necks) • Gr 2: cCR in the neck - watchful waiting (n=145 necks) • Gr 3: PR in the neck - ND (n=96 necks; results not presented) • Gr 4: PR in the neck - watchful waiting (n=23 necks; results not presented)	At patient level: o 3-year overall survival: p>0.05 ▪ Gr 1: 86% ▪ Gr 2: 85.2% o 5-year overall survival: p>0.05 ▪ Gr 1: 78.6% ▪ Gr 2: 77.7% o 3-year freedom from recurrence: p>0.05 ▪ Gr 1: 80% ▪ Gr 2: 81.6% o 5-year freedom from recurrence: p>0.05 ▪ Gr 1: 72.6% ▪ Gr 2: 78.1% At neck level: o Regional control: ▪ Gr 1 & 2: 203/210 necks	• Dropouts: none reported • Results critical appraisal: o Careless reporting of data (confusing mix up of data at patient and at neck level) o High risk of selection bias; unclear whether intervention and control groups were comparable o Unclear risk of performance bias o High risk of detection bias o Low risk of reporting bias o Unclear risk of attrition bias o Concurrent inclusion and treatment of

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[f]   cCR was considered to have occurred if all assessment modalities - including physical exam, CT and PET, in varying combinations for each patient – were negative for signs of residual disease.

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
					intervention and control group o Unclear follow-up period o cCR assessment was not identical in all patients

Donatelli-Lassig, 2008[131]	• <u>Design</u>: prospective cohort study
	• <u>Sources of funding</u>: NIH through the UofM Head and Neck Cancer SPORE
	• <u>Setting</u>: 2 tertiary otolaryngology clinics and a veterans administration hospital
	• <u>Sample size</u>: 103
	• <u>Duration</u>: enrolment bw 2003-2008
	• <u>Follow-up</u>: 1 yr
	• <u>Statistical analysis</u>:
		• <u>Eligibility criteria</u>:
		o Newly diagnosed oral cavity & oropharynx cancer stage IV
		o Treatment with CRT
		o ≥ 18 y.o.
		• <u>Exclusion criteria</u>:
		o Pts who did not speak English
		o Pregnancy
		o Psychological instability
		o Previous major H&N surgery
		o Previous chemo or radiation therapy in the H&N region (other than lymphoma)
		o Distant metastases
		o No informed consent
		o Survival of < 1 yr
			• Gr 1: selective (n= 22) or modified radical ND (n= 16)(total n=38)
			• Gr 2: watchful waiting (n=65)
				• Evolution from baseline to 1 yr FU:
				  ▪ Body pain[g]: Gr 1: -2.2[h] vs. Gr 2: +8.0; p=0.041
				  ▪ Physical functioning[i]: Gr 1: -8.2[j] vs. Gr 2: -8.3[k]; p=0.993
				  ▪ Mental health[l]: Gr 1: 7.8[m] vs. Gr 2: 6.2[n]; p=0.700
				  ▪ Eating[o]: Gr 1: -24.8[p] vs. Gr 2: -20.9[q]; p=0.511
				  ▪ Communication[r]: Gr 1: -6.6 vs. Gr 2: -5.2; p=0.834
				  ▪ Emotional distress[s]: Gr 1: 11.1[t] vs. Gr 2: 11.0[u]; p=0.977
					• Dropouts: excluded from analysis; number not reported
					• Results critical appraisal:
					o High risk of selection bias and high risk that intervention and control group were not comparable (higher proportion of ND pts were N3)
					o Indications for ND changed over time and varied among surgeons, hence

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[g]	Measured with the SF-36
h	Within group statistically significant evolution
i	Measured with the SF-36
j	Within group statistically significant evolution
k	Within group statistically significant evolution
l	Measured with the SF-36
m	Within group statistically significant evolution
n	Within group statistically significant evolution
o	Measured with the HNQoL (Head and Neck Quality of Life Instrument)
p	Within group statistically significant evolution
q	Within group statistically significant evolution
r	Measured with the HNQoL (Head and Neck Quality of Life Instrument)

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality

	descriptive and inferential statistics	o Surgical resection at the primary site
		o Bilateral neck dissections
		o Radical neck dissection with resection of the cranial nerve XI
		• <u>Characteristics and group comparability of patients (entire cohort)</u>:
		o Female: Gr 1: 5% - Gr 2: 14%
		o Mean age: Gr 1: 58.8 (SD: 9.9) – Gr 2: 55.4 (SD: 8.4)
		o Primary site: base of the tongue: 29; tonsil: 32; oropharynx: 73
		o Educational level:
		  ▪ High school or less: Gr 1: 32% - Gr 2: 37%
		  ▪ Some college or more: Gr 1: 68% - Gr 2: 63%
					heterogenous ND group
					o ND performed by 7 MDs
					o High risk of performance bias
					o High risk of detection bias
					o Low risk of reporting bias
					o High risk of attrition bias (loss to FU and pts without consent for study, excluded from analysis)
					o Unclear whether concurrent inclusion and treatment of intervention and control group as protocol and indication for ND changed over time
					o Small subgroups
					o Not reported how missing data were handled
					o Not clear if baseline data were collected before or after CRT

Goguen, 2006[132]	• <u>Design</u>: retrospective review
	• <u>Sources of funding</u>:
		• <u>Eligibility criteria</u>:
		o Head and neck squamous cell carcinoma advanced stage III or IV (N2-3 neck
			• Gr 1: cCR in the neck - ND (n=7)
			• Gr 2: cCR in the
				o Median progression free survival:
				  ▪ Gr 1[w]: 43.2 months or longer
				  ▪ Gr 2[x]: 37.9 months or longer
					• Dropouts: none reported
					• Results critical appraisal:
					o High risk of selection

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s   Measured with the HNQoL (Head and Neck Quality of Life Instrument)

t   Within group statistically significant evolution

u   Within group statistically significant evolution

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
	none reported • <u>Setting</u>: Brigham and Women's Hospital and the Dana Farber Cancer Institute, Boston, USA • <u>Sample size</u>: 52 • <u>Duration</u>: Enrolment bw June 1999 – December 2002 • <u>Follow-up</u>: 3.5 years • <u>Statistical analysis</u>: descriptive and inferential statistics	disease) without distant metastases o cCR[v] after **induction chemotherapy** followed by **concurrent CRT** • <u>Exclusion criteria</u>: o Unknown primary cancer o Primary cancer in the sinonasal cavity, nasopahrynx and salivary glands • <u>Characteristics and group comparability of patients (entire cohort)</u>: o Female: 21% o Median age: 54; range: 38-75 y.o. o T1: 9; T2: 16; T3: 15; T4: 12 o Primary site: Oropharynx: 39; Larynx: 7; Hypopharynx: 3; Oral cavity: 3	neck - watchful waiting (n=13) • Gr 3: PR in the neck (n=32; results not presented)	o Median overall survival: ▪ Gr 1[y]: 43.2 months or longer ▪ Gr 2[z]: 37.9 months or longer o Regional recurrence: ▪ Gr 1: 0/7 ▪ Gr 2: 1/13	bias; unclear whether intervention and control group were comparable o Unclear risk of performance bias o High risk of detection bias o Low risk of reporting bias o Unclear risk of attrition bias o Unclear whether there was concurrent inclusion and treatment of intervention and control group o Small subgroups
Forest, 2006[133]	• <u>Design</u>: prospective cohort study • <u>Sources of funding</u>: none reported • <u>Setting</u>: Notre-Dame Hospital Montreal, Canada • <u>Sample size</u>: 184 • <u>Duration</u>: Enrolment bw July 1998 – April 2004 • <u>Follow-up</u>: median: 36 months • <u>Statistical analysis</u>: descriptive and	• <u>Eligibility criteria</u>: o Head and neck squamous cell carcinoma advanced stage III or IV with nodal metastases o cCR[aa] after **concurrent CRT** • <u>Exclusion criteria</u>: o FU < 6 months o Primary cancer in the sinonasal cavity, nasopahrynx, the orbit or salivary glands o Local or regional surgery before treatment o Persistent or recurrent disease at the primary site o Presence of distant metastasis before treatment	• Gr 1: cCR in the neck - ND (n=3) • Gr 2: cCR in the neck - watchful waiting (n=123) • Gr 3: PR in the neck (n=58; results not presented)	o Regional recurrence: ▪ Gr 1: 0/3 ▪ Gr 2: 6/123	• Dropouts: none reported • Results critical appraisal: o High risk of selection bias; unclear whether intervention and control group were comparable o Unclear risk of performance bias o High risk of detection bias o Unclear risk of reporting bias o Unclear risk of attrition bias

w	Mean FU: 46.4 months
x	Mean FU: 40.6 months
v	cCR assessed by means of physical examination and CT or MRI and PET (n=14), physical examination and CT or MRI (n=4) or physical examination only (n=2)
y	Mean FU: 46.4 months
z	Mean FU: 40.6 months
aa	cCR assessed by means of physical examination and CT

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
	inferential statistics and Kaplan-Meier method	• <u>Characteristics and group comparability of patients (entire cohort)</u>: ○ Female: 24% ○ Median age: 57; range: 31-78 y.o. ○ T1: 26; T2: 43; T3: 54; T4: 50; Tx: 11 ○ Primary site: Oropharynx: 134; Larynx: 24; Hypopharynx: 11; Oral cavity: 4; Unknown: 11			○ Unclear whether there is concurrent inclusion and treatment of intervention and control group ○ Small subgroups

Brizel, 2004[134]	• <u>Design</u>: prospective cohort study
	• <u>Sources of funding</u>: none reported
	• <u>Setting</u>: Duke University Medical Centre
	• <u>Sample size</u>: 108
	• <u>Duration</u>: Enrolment bw 1990 - 2000
	• <u>Follow-up</u>: median: 48 months (range: 4-127 months)
	• <u>Statistical analysis</u>: Kaplan-Meier method
		• <u>Eligibility criteria</u>:
		○ Advanced head and neck squamous cell carcinoma
		○ cCR[bb] after **concurrent CRT**
		• <u>Exclusion criteria</u>:
		○ Persistent disease at the primary site
		○ Distant metastasis before treatment
		• <u>Characteristics and group comparability of patients (entire cohort)</u>:
		○ Female: not reported
		○ Median age: not reported
		○ T1: ?; T2: ?; T3: ?; T4: ?
		○ Primary site: Oropharynx: 64%; Larynx: 16%; Hypopharynx: 13%; Oral cavity: 7%
			• Gr 1: cCR in the neck – Modified ND (n=27)
			• Gr 2: cCR in the neck - watchful waiting (n=16)
			• Gr 3: PR in the neck (n=25; results not presented)
			• Gr 4: N2-3 patients with locally persistent or systemically progressive disease (n=10; results not presented)
			• Gr 5: N1 (n=30; results not presented)
				○ 4-year disease free survival rate: p=0.08
				   ▪ Gr 1: 75%
				   ▪ Gr 2: 53%
				○ 4-year overall survival rate: p=0.04
				   ▪ Gr 1: 77%
				   ▪ Gr 2: 50%
				○ Regional recurrence:
				   ▪ Gr 1: ?
				   ▪ Gr 2: 3/16
				• Post-MND complication rate:
				   ▪ Gr 1: 4/27 (8%)
					• Dropouts: none reported
					• Results critical appraisal:
					○ High risk of selection; unclear whether intervention and control group were comparable
					○ Unlcear risk of performance bias
					○ High risk of detection bias
					○ Low risk of reporting bias
					○ Unclear risk of attrition bias
					○ Unclear whether there was concurrent inclusion and treatment of intervention and control group
					○ Small subgroups

McHam, 2003[135]	• <u>Design</u>: retrospective review of records
	• <u>Sources of funding</u>: none reported
	• <u>Setting</u>: University Hospitals Cleveland
	• <u>Sample size</u>: 109
	• <u>Duration</u>: enrolment bw
		• <u>Eligibility criteria</u>:
		○ Histologically confirmed HNSCC
		○ N2-N3M0 disease
		○ cCR[cc] after **concurrent CRT**
		• <u>Exclusion criteria</u>:
		○ Primary cancer in the nasopahrynx, the paranasal sinuses or salivary glands
		• <u>Characteristics and group comparability of</u>
			• Gr 1: cCR in the neck – ND (n=32)
			• Gr 2: cCR in the neck - watchful waiting (n=33)
			• Gr 3: cPR in the neck (n=44; results not presented)
				○ Regional recurrence:
				   ▪ Gr 1: 1/32
				   ▪ Gr 2: 4/33
					• Dropouts: none reported
					• Results critical appraisal:
					○ High risk of selection bias; unclear whether intervention and control group were comparable
					○ Unclear risk of

[bb]   Assessment of cCR not clearly defined.

[cc]   cCR defined after clinical examination and CT.

Study ID	Method	Patient characteristics	Intervention(s)	Results (95%CI)	Critical appraisal of quality
	1989 - 2001 • Follow-up: not reported • Statistical analysis: logistic regression analyses	patients (entire cohort): ○ Female: not reported ○ Median age: not reported ○ T1: 10; T2: 25; T3: 29; T4: 40; other: 5 ○ Primary site: Oropharynx: 60; Larynx: 19; Hypopharynx: 18; Oral cavity: 7; other: 5			performance bias ○ High risk of detection bias ○ Unclear risk of reporting bias ○ Unclear risk of attrition bias ○ Unclear whether there is concurrent inclusion and treatment of intervention and control group ○ Small subgroups

Grabenbauer, 2003[136]	• Design: retrospective
	• Sources of funding: Partial funding from the ELAN fund and the Interdisciplinary Centre for Clinical Research of the mediacl faculty of the University of Erlangen
	• Setting: University Medical Centre Erlangen, Germany
	• Sample size: 97
	• Duration: Enrolment bw 1987 - 1997
	• Follow-up: 37 months (range: 22-124 months)
	• Statistical analysis: Kaplan Meier
		• Eligibility criteria:
		○ Biopsy proven squamous cell carcinoma of the oral cavity, oropharynx and hypopharynx
		○ Stage III-IV not amenable to resection with acceptable functional and cosmetic outcome
		○ ECOG performance status 0-2
		○ Normal renal and bone marrow function
		○ Absence of distant metastases
		○ cCR[dd] after primary platin based (**concurrent**) CRT
		• Exclusion criteria: none reported
		• Characteristics and group comparability of patients (entire cohort):
		○ Female: Gr 1: 20% - Gr 2: 7%
		○ Median age: Gr 1: 52 – Gr 2: 51
		○ T2: Gr 1: 10% - Gr 2: 16%; T3: Gr 1: 27% - Gr 2: 36%; T4: Gr 1: 63% - Gr 2: 48%
		○ Primary site: Oropharynx: Gr 1: 39% - Gr 2: 43%; Hypopharynx: Gr 1: 46% - Gr 2: 50%; Oral cavity: Gr 1: 15% - Gr 2: 7%
			• Gr 1: cCR in the neck – ND (n=56)
			• Gr 2: cCR in the neck - watchful waiting (n=41)
				○ 5-year overall survival rate: p=0.9
				  ▪ Gr 1: 44%
				  ▪ Gr 2: 42%
				○ 10-year overall survival rate: p=0.9
				  ▪ Gr 1: 35%
				  ▪ Gr 2: 20%
				○ 5-year disease specific survival rate: p=0.7
				  ▪ Gr 1: 55%
				  ▪ Gr 2: 47%
				○ 10-year disease specific survival rate: p=0.7
				  ▪ Gr 1: 50%
				  ▪ Gr 2: 42%
				○ 5-year regional tumour control rate: p=0.47
				  ▪ Gr 1: 80%
				  ▪ Gr 2: 85%
				○ Regional recurrence rate: NS
				  ▪ Gr 1: 9/56 (16%)
				  ▪ Gr 2: 4/41 (10%)
				○ Complication rate:
				  ▪ Gr 1: 14/56
				  ▪ Gr 2: 4/41 (10%)
					• Dropouts: none reported
					• Results critical appraisal:
					○ High risk of selection bias
					○ Significantly more pts with advanced nodal disease in Gr 1 (18/56, 32%) compared to Gr 2 (7/41, 17%)
					○ Unclear risk of performance bias
					○ High risk of detection bias
					○ Low risk of reporting bias
					○ Unclear risk of attrition bias
					○ Small subgroups
					○ Not clearly mentioned whether it was a prospective study

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[dd]   Assessment of cCR not clearly defined.

4.7. RQ8: IMRT for patients with locally advanced HNSCC

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Gupta 2012[41]	• Design: RCT • Source of funding: Siemens Oncology Care Systems, USA • Setting: Tata Memorial Centre, Navi Mumbai, India • Sample size: n=62 • Duration: enrolment: 2005 until 2008; median follow-up: 40 months (inter-quartile range 26–50)	• Eligibility criteria: previously untreated squamous cell carcinoma of the oropharynx, larynx, or hypopharynx with AJCC stage T1-T3, N0-2b, M0 (excepting T1 glottic larynx). • A priori patient characteristics: median age (range): 51 (31 – 65) vs 55 (33 – 65) yrs; sex (M/F): 29/3 vs 25/3; T1-T2 / T3: 14/18 vs 12/16; N0-N1 /N2a-b: 21/11 vs 19/9; overall stage grouping (I/II/IV): 7/16/9 vs 5/14/9; primary site (oropharynx / hypopharynx / larynx): 17/9/6 vs 15/8/5. • Group comparability: well balanced. "There were no significant differences in the baseline patient, disease, and treatment characteristics which were well matched in the two arms."	IMRT (n=32) vs 3D-CRT (n=28) "Concurrent weekly cisplatin (30 mg/m2) with adequate hydration, antiemetic prophylaxis, and forced diuresis was offered to all patients with bulky T2, T3, or node positive disease in either arm."	**Disease-free survival** Not assessed. **Overall survival** 3-year Kaplan–Meier estimates: 68% (95% CI 51.2 to 84.8%) vs 80.5% (95% CI 66.1 to 94.9%) **(loco) regional control** 3-year Kaplan–Meier estimates: 70.6% (95% CI 53 to 88.2%) vs 88.2% (95% CI 75.4 to 100%) **Recurrence rate** Not assessed. **Secondary tumours** Not assessed. Quote: "…our study was not adequately powered to demonstrate equivalence or non-inferiority of IMRT in terms of loco-regional control or survival, which would need over 1000 patients to be randomized." **Quality of life** Not assessed. **Adverse events** <u>Acute toxicity</u> <u>RTOG Grade 2 or worse acute salivary gland toxicity:</u> 19/32 vs 25/28 RR=0.67 (95% CI 0.49 to 0.91) <u>Grade 2-3 acute dermatitis</u> 30/32 vs 27/28 RR=0.97 (95% CI 0.87 to 1.09) <u>Grade 2-3 acute mucositis</u> 25/32 vs 26/28 RR=0.84 (95% CI 0.68 to 1.04)	• Dropouts: n=2 (1 in each arm) refused treatment after randomization and were considered inevaluable for the primary endpoint, leaving 60 patients eligible for analysis (modified intention-to-treat analysis). • Results critical appraisal: high risk of performance bias and detection bias; unclear risk of selection bias; low risk of bias for the remaining items.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				Grade 2-3 acute dysphagia 19/32 vs 20/28 RR=0.83 (95% CI 0.57 to 1.20) ≥10% weight loss 5/32 vs 10/28 RR=0.44 (95% CI 0.17 to 1.13) Late morbidity Late xerostomia and subcutaneous fibrosis assessed at 6, 12, 18, 24, 30, and 36 months using the RTOG late morbidity criteria: "At each time point, significantly lesser proportion of IMRT patients had physician-rated Grade 2 or worse xerostomia compared with 3D-CRT." "Late xerostomia and subcutaneous fibrosis were also significantly lesser with IMRT at most time points." "There was significant recovery of salivary function over time in patients treated with IMRT (p-value for trend=0.0036)."	
Nutting 2011[67]	• Design: multicentre RCT • Source of funding: Cancer Research UK; Royal Marsden NHS Foundation Trust • Setting: six UK radiotherapy centres • Sample size: n=94 • Duration: recruitment: Jan 2003 and Dec 2007; median follow-up was 44.0 months (IQR 30.0 to 59.7).	• Eligibility criteria: Histologically confirmed HNSCC arising from the oropharynx or hypopharynx and to be treated by radiotherapy either primarily or postoperatively without concomitant chemotherapy; WHO performance status 0 or 1 and any stage of disease except M1. Exclusion criteria included previous head or neck radiotherapy; previous malignancy except non-melanoma skin cancer; pre-existing salivary gland disease; tumour involvement of the parotid glands; or previous or concurrent illness that would compromise completion of treatment or follow-up. No prophylactic amifostine or	IMRT (n=47) vs Conventional radiotherapy (n=47)	**Disease-free survival** Not assessed. **Overall survival (12 months?)** 14/47 vs 18/47; HR=0.68 (95% CI 0.34 to 1.37) Estimated 2-year overall survival 78% (63 to 88) vs 76% (95% CI 60 to 86) (absolute difference 2%, 95% CI –20 to 16). "Our trial was not powered to reliably assess small differences in locoregional PFS or overall survival, although these are reported for completeness." **(loco) regional control**	• Dropouts: Six patients from each group died before 12 months and seven patients from the conventional radiotherapy and two from the IMRT group were not assessed at 12 months. • Results critical appraisal: high risk of performance bias and detection bias (subjective outcomes); unclear

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
		pilocarpine. • *A priori* patient characteristics: *Mean age* in years (SD): 59.5 (9·2) vs 57.3 (10.2); Number of women: 14 (30%) vs 12 (26%); WHO performance status, 0: 41 (87%) vs 42 (89%); 1: 6 (13%) vs 5 (11%); *Tumour s*ite, Oropharynx: 40 (85%) vs 40 (85%); Hypopharynx: 7 (15%) vs 7 (15%); Tumour stage: T1: 6 (13%) vs 6 (13%); T2: 22 (47%) vs 27 (57%); T3: 16 (34%) vs 11 (23%); T4: 3 (6%) vs 3 (6%); Nodal stage *N0: 23 (*49%) vs 16 (34%); N1: 15 (32%) vs 9 (19%); N2a: 2 (4%) vs 7 (15%); N2b: 6 (13%) vs 10 (21%); N2c: 0 vs1 (2%); N2 (unknown): 1 (2%) vs 1 (2%); N3: 0 vs 3 (6%); *AJCC* sta*ge, 1 and 2: 15 (32%) vs 8 (17%); 3 and 4: 32 (68%) vs 39 (83%); Neoadjuvant chemotherapy*:* 20 (43%) vs 19 (40%); *Type of* radiotherapy, Primary: 39 *(83%) vs* 32 (68%); Postoperative: 8 (17%) vs 15 (32%) • Group comparability: groups were balanced except for nodal stage and AJCC stage. The mean dose to the whole contralateral parotid was significantly less in the IMRT group		2-year locoregional PFS was 78% (95% CI 62 to 87) in the IMRT group and 80% (95% CI 65 to 90) in the conventional radiotherapy group (absolute difference 3% (95% CI –15 to 20); HR 1.53 (95% CI 0.63 to 3.70) **Recurrence rate** locoregional recurrences 12/47 vs 7/47: RR=1.71 (95% CI 0.74 to 3.97) **Secondary tumours** Not assessed. **Quality of life** Mean changes in global health status from baseline to 12 months (95% CI): 3.0 (–11.9 to 17.9) vs 1.1 (–9.9 to 12.1); MD= 1.90 (95% CI -16.13 to 19.93) At 24 months: 8.3 (–6.6 to 23.2) vs –2.8 (–17.1 to 11.6) MD=11.10 (95% CI -9.01 to 31.21) **Adverse events** Acute Xerostomia (Grade 2 to 4) 33/47 vs 40/44 (RR=0.77; 95% CI 0.63 to 0.95) Mucositis/stomatitis (clinical) (Grade 2 to 4) 43/46 vs 43/44 (RR=0.96; 95% 0.88 to 1.05) Mucositis/stomatitis (functional/symptomatic) (Grade 2 to 4) 35/40 vs 38/39 (RR=0.90; 95% CI 0.79 to 1.02) Dysphagia (Grade 2 to 4) 40/47 vs 43/44 (RR=0.87; 95% CI 0.77 to 0.99) Weight loss (Grade 2 to 4) 21/44 vs 15/40 (RR=1.27; 95% CI 0.77 to 2.11)	risk of attrition bias; low risk of bias for the remaining items.

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
				RTOG late Salivary gland (Grade 2 to 4) 34/46 vs 38/42 (RR=0.82; 95% CI 0.67 to 1.00) Mucous membranes (Grade 2 to 4) 13/46 vs 18/42 (RR=0.66; 95% CI 0.37 to 1.18) Oesophagus (Grade 2 to 4) 10/46 vs 9/42 (RR=1.01; 95% 0.46 tot 2.25) *LENT-SOMA late* Xerostomia (Grade 2 to 4) 38/46 vs 38/41 (RR=0.89; 95% CI 0.76 to 1.04) Salivary gland (Grade 2 to 4) 38/46 vs 38/41 (RR=0.89; 95% CI 0.76 to 1.04) Mucosa (Grade 2 to 4) 26/46 vs 31/41 (RR=0.75; 95% CI 0.55 to 1.02) Oesophagus (Grade 2 to 4) 10/46 vs 11/41 (RR=0.81; 95% CI 0.38 to 1.71) For the remaining adverse events, only significant differences were found for rash (RR=0.84, 95% CI 0.71 to 1.00) and fatigue (RR=1.82; 95% CI 1.23 to 2.70)	

4.8. RQ9: induction chemotherapy in patients with HNSCC

Table 51 – Induction chemotherapy: systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality

Furness 2011[103]	• Design: SR
	• Funding: 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
	• 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.
	• Number and design of included studies: n=89 RCTs (n=16767 patients) of which n=26 RCTs (n=4393 patients) for comparison of interest.
		Included were RCTs (minimum follow-up of 6 months) comparing chemotherapy treatment with
		
		• either chemotherapy combined with locoregional treatment (radiotherapy or surgery),
		• a different chemotherapy regimen
		• or chemotherapy given at different times relative to locoregional treatment (either induction, concomitant or adjuvant chemotherapy)
		
		as primary treatment in 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).
		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, were excluded.
		
		Description of stage of cancer of patients eligible for inclusion in 50 trials
		• Stage 2-4 in 6 trials
			Induction chemotherapy plus locoregional treatment
			
			vs
			
			Locoregional treatment alone
				Induction chemotherapy plus locoregional treatment *versus* locoregional treatment alone (26 studies)
				
				Total mortality (25 studies)
				HR=0.92 (95%CI 0.84 to 1.00)
				- sensitivity analysis: low risk of bias studies (4 studies)
				HR=0.80 (95%CI 0.67 to 0.97)
				- subgroup analysis:
				  ○ cisplatin or carboplatin plus 5FU (7 studies): HR=0.94, (95%CI 0.86 to 1.04)
				  ○ methotrexate alone (4 studies): HR=0.90 (95%CI 0.72 to 1.14)
				  ○ bleomycine plus vincristine (2 studies): HR=0.67 (95%CI 0.50 to 0.91)
				
				Disease free survival (8 studies)
				HR=0.78 (95%CI 0.67 to 0.90)
					• SR: low risk of bias; all AMSTAR items were adequately addressed.
					• Included studies: four studies had low risk of bias with regard to total mortality, no blinding but adequate with regard to the other five domains of the assessment; ten studies had high risk of bias with regard to all outcomes reported (no blinding, unclear sequence generation and allocation concealment and a problem in at least one of the other domains assessed); twelve had unclear risk of bias with regard to total mortality (no blinding and insufficient information provided on sequence generation and allocation concealment) and moderate to high risk of bias for the outcomes of disease free survival, progression free survival, locoregional control and disease recurrence

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality

		• Stage 3-4 in 44 trials
		
		TNM system for description of cancer stage used in 22 trials
		• specified in inclusion criteria:
		  ○ T2-T4 tumours in 3 trials
		  ○ T1-T4 tumours in 3 trials
		• not specified in inclusion criteria: n=16			

Ma 2012[105]	• Design: SR
	• Funding: grants 30973344 and 30700953 from National Natural Science Foundation of China; grant 2007BAI18B03 from National Key Technology R&D Program of China; grants 1052nm04700, 10140902200 and 10dz1951300 from Science and Technology Commission of Shanghai Municipality.
	• Search date: 2011
	• Databases: MEDLINE, EMBASE, reference lists and conference proceedings.
	• Number and design of included studies: n=40 RCTs
		RCTs with recruitment between January 1 1965 and December 31, 2011 and published in English, studying induction chemotherapy in patients with head and neck squamous cell carcinoma without distant metastasis were included. All randomized patients had a potentially curable primary lesion with locoregional treatment and no additional cancer treatment. Tumour sites included oral cavity, oropharynx, hypopharynx, and larynx, but the nasopharynx was excluded.	Induction chemotherapy followed by locoregional treatment
			
			vs
			
			Locoregional treatment alone
			
			Induction chemotherapy followed by concomitant chemotherapy and radiotherapy
			
			vs
			
			Concomitant chemotherapy and radiotherapy alone
			
			Other comparisons in review, but excluded for this KCE report
			
			Induction chemotherapy followed by radiotherapy
				Induction chemotherapy followed by locoregional treatment *versus* locoregional treatment alone (28 studies, n=4189 patients)
				Overall survival
				HR=0.94 (95%CI 0.87 to 1.01)
				Subgroups:
				- patients with resectable tumours: HR=0.96 (95%CI 0.82 to1.13)
				- patients with unresectable tumours: HR=0.97 (95%CI 0.82 to 1.15)
				- IC protocol cisplatin and 5-fluorouracil (10 trials, n=2088 patients): HR=0.87 (95%CI 0.78 to 0.97)
				
				Difference of combined 2-year and 5-year locoregional recurrence rate (2 studies, n=432 patients):
				2-year: RD=- 2% (95%CI -11% to 8%)
				5-year: RD -1% (95%CI -14% to 13%)
				
				Induction chemotherapy followed by concomitant chemotherapy and radiotherapy *versus* concomitant chemotherapy and radiotherapy alone (2 studies, n=331 patients)
				Overall survival
				HR=0.96 (95%CI 0.71 to 1.30)
					• SR: all but 3 AMSTAR items adequately addressed:
					  ○ publication not used as an inclusion criterion
					  ○ list of in- and excluded studies
					  ○ characteristics of included studies provided
					• Included studies: random sequence generation was adequate in approximately one third of included studies, in the remaining studies the method of randomization was unclear; concealment of allocation was adequate in approximately forty percent of included studies, for the remaining studies it was unclear.
					All other items were at low risk of bias, except for 'selective reporting', for which a high risk of bias was scored in

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of review quality
			vs Concomitant chemotherapy and radiotherapy *or* Alternating chemotherapy and radiotherapy IC followed by RT vs surgery followed by RT IC followed by RT vs CCRT		approximately 15%. Authors state: "Although randomization was adequate in all trials, only two articles explicitly stated that the data analysis adhered to the intention-to-treat principle, which could lead to overestimation of treatment effect in most of the trials."

Table 52 – Induction chemotherapy: RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
Forastiere 2013[106]	• Design: RCT • Source of funding: Radiation Therapy Oncology Group Grant No. U10 CA21661, Community Clinical Oncology Program Grant No. U10 CA37422, and Eastern Cooperative Oncology Group Grants No. CA16116 and CA21115 from the National Cancer Institute. • Setting: multicenter,	• Eligibility criteria: stage III or IV squamous cell cancer of the supraglottic or glottic larynx curable with laryngectomy and RT; no T1 primaries and high-volume T4 primaries (invasion >1 cm into the base of tongue or penetration through cartilage). • *A priori* patient characteristics: stage III: 64%; primary site	Radiotherapy + Induction chemotherapy (cisplatin and fluorouracil, up to three cycles) (n=182 randomised; n=174 analysed) vs Radiotherapy + concomitant chemotherapy (n=182 randomised, n=174 analysed)	**Radiotherapy + induction chemotherapy vs radiotherapy** **Overall survival** 5 years: 58.1% vs 53.8% 10 years: 38.8% vs 31.5% HR=0.87 (95%CI 0.68 to 1.12) **Quality of life** Impaired speech or voice ("moderate difficulty saying some words, and cannot use the phone; only family and/or friends can understand me; or cannot be understood") during years 2 to 5 (% of patients): 3% to 9% vs 5% to 8.5%	• Dropouts: RT + induction CT: n=6 (ineligible per protocol criteria) RT + concomitant CT: n=7 (n=1 withdrew consent, n=6 ineligible per protocol criteria) RT: n=13 (ineligible per protocol criteria) • Results critical appraisal:

USA • Sample size: n=547 randomised, n=520 analysed. • Duration: enrolment between August 1992 and May 2000; median follow-up for surviving patients: 10.8 years (range 0.07 to 17 years).	supraglottic: 69%; T2/T3/T4: 11/79/10%; N0/N1/N2/N3: 50/21/28/2% Radiotherapy + induction chemotherapy vs radiotherapy alone (data from 2003 publication on same study) median age (range): 59 (36-78) vs 59 (31-79) yrs; sex (M/F): 131/42 vs 133/40; Karnofsky performance score (100/90/80/70/60): 35/88/38/10/2 vs 26/93/41/10/3; site (supraglottis / glottis): 118/55 vs 124/49; American Joint Commision on Cancer stage (III/IV): 111/62 vs 111/62; T stage (T2/T3 with fixed cord involvement/T3 without fixed cord fixation/T4): 19/82/54/18 vs 20/76/61/16; N stage (N0/N1/N2A/N2B/N2C/N3): 87/38/2/17/26/3 vs 87/32/3/13/23/4 • Group comparability: patient characteristics are comparable between study groups	vs Radiotherapy alone (n=185 randomised, n=172 analysed)	Swallowing dysfunction ("can only swallow soft foods" or worse reported) during years 2 to 5 (% of patients): 13% to 14% vs 10% to 17% "The ability to swallow only liquids was reported in less than 4% of patients in all groups, and inability to swallow was reported in less than 3% of patients in all groups at any time point." **Disease-free survival** 5 years: 37.7% vs 28.0% 10 years: 20.4% vs 14.8% HR=0.79 (95%CI 0.63 to 1.00) **Local control** 5 years: 58.2% vs 53.6% 10 years: 53.7% vs 50.1% HR=0.85 (95%CI 0.63 to 1.15) **Recurrence rate** Not assessed. **Adverse events - grade 3-5 late toxicity** (Radiation Therapy Oncology Group criteria) - Hematologic 0/154 vs 1/158 RR=0.34 (95%CI 0.01 to 8.41) - Skin 7/154 vs 3/158 RR=2.39 (95%CI 0.63 to 9.09) - Mucous membrane/stomatitis 5/154 vs 4/158 RR=1.28 (95%CI 0.35 to 4.69) - Subcutaneous tissue 12/154 vs 11/158 RR=1.12 (95%CI 0.51 to 2.46) - Salivary gland	low risk of bias for items on sequence generation and blinding of outcome assessment in objective outcomes; high risk of selection bias, performance and detection bias in subjective outcomes; unclear risk of bias for all other items.

9/154 vs 6/158
RR=1.54 (95%CI 0.56 to 4.22)

- Pharynx/esophagus
20/154 vs 24/158
RR=0.85 (95%CI 0.49 to 1.48)

- Larynx
17/154 vs 29/158
RR=0.60 (95%CI 0.34 to 1.05)

- Upper GI
2/154 vs 0/158
RR=5.13 (95%CI 0.25 to 105.98)

- Genitourinary / renal
0/154 vs 0/158
RR not estimable

- Spinal cord
0/154 vs 0/158
RR not estimable

- Neurologic
0/154 vs 2/158
RR=0.21 (0.01 to 4.24)

- Bone
2/154 vs 0/158
RR=5.13 (0.25 to 105.98)

- Joint
2/154 vs 1/158
RR=2.05 (95%CI 0.19 to 22.40)

- Other
4/154 vs 14/158
RR=0.29 (95%CI 0.10 to 0.87)

"Subcutaneous, salivary gland, pharynx/esophagus, and larynx toxicities were the most frequent serious events. These complications led to fatal events in all groups (four deaths, three deaths, and one death in induction, concomitant, and RT alone arms, respectively).
The 10-year cumulative rates of grade 3 to 5 late

toxicity were 30.6%, 33.3%, and 38% in induction, concomitant, and RT alone arms, respectively. We did not detect any significant differences in cumulative incidence between treatment groups."

Post treatment mortality

Total deaths
120/174 vs 124/172
RR=0.96 (95%CI 0.83 to 1.10)

Cause of death:
- Cancer under study: 45/174 vs 60/172, RR=0.74 (95%CI 0.54 to 1.03)
- Second malignancy: 15/174 vs 15/172, RR=0.99 (95%CI 0.50 to 1.96)
- Complications of protocol treatment: 9/174 vs 5/172, RR=1.78 (95%CI 0.61 to 5.20)
- Complications of other treatment: 3/174 vs 3/172, 0.99 (95%CI 0.20 to 4.83)
- Unrelated to cancer or treatment: 25/174 vs 21/172, RR=1.18 (95%CI 0.69 to 2.02)
- Unknown/not reported: 23/174 vs 20/172, RR=1.14 (95%CI 0.65 to 1.99)

Haddad 2013[107]	• Design: RCT • Source of funding: Sanofi-Aventis; RH received research grants and is a consultant to Alder Biopharmaceuticals, Boehringer Ingelheim, Astra Zeneca, and Exilixis. MP is a consultant to Eisai, Cel-Sci, and Oncolytics, and is a stock holder of Promedior. NS was employed by Sanofi - Aventis at the time of the study and owns stock for Sanofi - Aventis. • Setting:14 hospitals	• Eligibility criteria: measurable, previously untreated, non-metastatic, histologically proven stage III or IV squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx (unresectable tumour or of low surgical curability, or if the patient was a candidate for organ preservation); age ≥ 18 years, WHO performance status of 0 or 1 and adequate bone marrow, liver, and renal function; no	Induction chemotherapy (docetaxel, cisplatin and fluorouracil, for three cycles) + concurrent chemoradiotherapy (n=70) - n=27 docetaxel - n=37 carboplatin - n=6 other vs Concurrent chemoradiotherapy (n=75)	**Overall survival, 3-year rates (95%CI)** 73% (60-82) vs 78% (66-86) HR=1.09 (95%CI 0.59 to 2.03) Within the induction chemotherapy group: docetaxel vs carboplatin: 52% (95%CI 31 to 69) vs 92% (95%CI 76 to 97) **Quality of life** Not assessed. **Disease-free survival** Not assessed. **Local control** local or regional failure only: 9/70 vs 6/75, RR=1.61 (95%CI 0.60 to 4.28) both local or regional and distant failures: 2/70 vs	• Dropouts: induction chermotherapy + concurrent chemoradiotherapyn= 14 - n=1 did not start treatment; - n=13 did not complete treatment protocol (n=1 died during induction, n=5 toxic effects, n=3 voluntary withdrawal, n=2 non-compliant n=2 other) concurrent

(13 in the USA and one in Europe), 16 sites
- Sample size: n=145
- Duration: from Augustus 24, 2004, to December 29, 2008; median follow-up was 49 months (IQR 39–63).

previous chemotherapy or radiotherapy, no cancer diagnosis within the previous 5 years, no severe weight loss (>25% of bodyweight) in the preceding 2 months, no symptomatic altered hearing or peripheral neuropathy greater than grade 1 by National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, and no other serious illnesses or medical disorders such as chronic obstructive pulmonary disease or unstable cardiac disease.

- *A priori* patient characteristics: median age (IQR) 55 (50-61) vs 54 (48-60) yrs; sex (M/F): 64/6 vs 63/12; ethnic origin (white/other): 64/6 vs 63/12; T stage (T1/T2/T3/T4): 4/28/22/16 vs 6/21/29/19; N stage (N0/N1/N2/N3): 7/6/50/7 vs 10/4/55/6; stage III/IV: 10/60 vs 11/64; primary disease site (hypopharynx / larynx / oral cavity / oropharynx): 8/10/13/39 vs 7/14/13/41; WHO performance state 0/1:

5/75, RR=0.43 (95%CI 0.09 to 2.14)
total local or regional failure
11/70 vs 11/75, RR=1.07 (95%CI 0.50 to 2.31)
"We noted no clinically significant differences between the two groups with respect to number or site of recurrence."

Recurrence rate
Not assessed.

Adverse events – grade 3-4 (National Cancer Institute CTCAE (version 3.0))

- Mucositis
  33/70 vs 12/75
  RR=2.95 (95%CI 1.66 to 5.24)

- Febrile neutropenia:
  16/70 vs 1/75
  RR=17.14 (95%CI 2.33 to 125.90)

- Pain
  2/70 vs 9/75
  RR=0.24 (95%CI 0.05 to 1.06)

- Xerostomia
  5/70 vs 5/75
  RR=1.07 (95%CI 0.32 to 3.54)

- Neuropathy
  0/70 vs 2/75
  RR=0.21 (95%CI 0.01 to 4.38)

PEG tube placed
55/70 vs 64/75
RR=0.92 (95%CI 0.79 to 1.07)

Post treatment mortality
Total number of deaths:
20/70 vs 21/75
RR=1.02 (95%CI 0.61 to 1.71)

Cause of death

chemoradiotherapy
n=9
- n=3 did not start treatment;
- n=6 did not complete treatment protocol (n=3 toxic effects, n=2 voluntary withdrawal, n=1 protocol violation)

- Results critical appraisal: low risk of selection bias, detection bias for objective outcomes and other bias; high risk of performance bias, detection bias for subjective outcomes and reporting bias; unclear risk of attrition bias.

		47/23 vs 50/25.		disease progression 14/70 vs 17/75, RR=0.88 (95%CI 0.47 to 1.65) other cause 6/70 vs 4/75, RR=1.61 (95%CI 0.47 to 5.46) "No treatment-related deaths occurred on this study."	
	• Group comparability: patient characteristics were well balanced between groups.				

Lefebvre 2012[108]	• Design: RCT
	• Source of funding: grants number (5U10-CA11488-18S2) through (5U10-CA11488-38) from the National Cancer Institute (Bethesda, MD); Ligue Française Contre le Cancer; EORTC.
	• Setting: multicenter study in France, Belgium, Italy, the Netherlands and Switzerland.
	• Sample size: n=202
	• Duration: 1986 to 1993; 10.5 years median follow-up
		• Eligibility criteria: age 18-75 years; histologically proven SCC of the piriform sinus or hypopharyngeal aspect of the aryepiglottic fold; stages T2–T4 N0-2b necks (AJCC/UICC 1987); Hypopharynx tumours had to be operable at the first attempt and suitable for only classical total laryngectomy with partial pharyngectomy; disease had to be measurable or evaluable and to be documented by endoscopy and if possible, by computed tomography scan; no previous treatment in the head and neck, no distant metastases or another cancer, no medical condition incompatible with surgery under general anesthesia or with cisplatin/5-FU.
		
		• *A priori* patient characteristics: chemotherapy vs surgery
		median age (range):
			Induction chemotherapy (cisplatin, fluorouracil, up to three cycles) (n=103; n=100 eligible*) followed by
			- Surgery + radiotherapy (n=34)
			- Radiotherapy (n=60)
			- No further treatment (n=3)
			N=3/100 did not receive induction chemo, but immediately started with RT(+S)
			
			vs
			
			Immediate surgery (n=99; n=94 eligible*) followed by radiotherapy (n=92)
			N=2/94 pts didn't undergo surgery or any other treatment
				Surgery arm vs. induction chemotherapy arm *(results for induction chemotherapy + surgery + radiotherapy versus immediate surgery + radiotherapy were not reported separately)*
				
				Overall survival
				Induction chemotherapy arm vs surgery arm
				
				Median years (95%CI):
				3.67 (2.3 to 4.7) vs 2.1 (1.8 to 4.2)
				
				5-year survival rate (95%CI):
				38.0% (28.4 to 47.6) vs 32.6 (23.0 to 42.1)
				
				10-year survival rate
				13.1% (5.6 to 20.6) vs 13.8% (6.1 to 21.6)
				
				HR=0.88 (95%CI 0.65 to 1.19)
				
				Quality of life
				Not assessed.
				
				Disease-free survival
				Not assessed.
				
				Local control
				Induction chemotherapy arm vs surgery arm
				Number of patients with:
				- local failure: 8/100 vs 8/94
				  RR=0.94 (95%CI 0.37 to 2.40)
				- locoregional failure: 12/100 vs 5/94
				  RR=2.26 (95%CI 0.83 to 6.16)
				
				Number of failures:
				- Local: 20 vs 13
					• Dropouts:
					Induction chemotherapy group:
					n=6 did not receive chemotherapy (n=3 ineligible (n=1 no data); n=1 refusal; n=1 angina pectoris; n=1 dyspnoea)
					
					n=3 had no further treatment after chemotherapy (n=2 refusal; n=1 died of toxicity)
					
					of the 34 patients that underwent surgery after chemotherapy n=1 did not receive radiotherapy (died after surgery)
					
					included in final analysis n=100 (= patients eligible for chemotherapy)
					
					Immediate surgery group:
					n=7 did not have surgery (n=5 ineligible (n=1 no data); n= 1 severe lung infection; n=1 N+ during operation)

					n=3 did not have radiotherapy after surgery (n=1 refusal; n=2 complications)
		• Group comparability: baseline characteristics were well balanced between the two arms.		**Recurrence rate** Not assessed.	included in final analysis n=94
				Adverse events Not assessed.	• Results critical appraisal: low risk of bias for all items.
				Post treatment mortality Induction chemotherapy arm vs surgery arm 83/100 vs. 81/94 RR=0.96 (95%CI 0.85 to 1.09)	
				Causes of death: Index primary tumour evolution: 41/100 vs 41/94 Second primary cancer: 15/100 vs 21/94 Another disease without any cancer evolution: 17/100 vs 11/94 ICT-related toxicity: 1/100 vs - Postoperatively (salvage surgery for local recurrence): 1/100 vs - Unknown: 10/100 vs 8/94	
Mitra 2006[109]	• Design: RCT • Source of funding: none reported • Setting: tertiary academic referral center, Calcutta, India. • Sample size: n=180 • Duration: between 1-8-1998 and 31-07-1999; median duration of follow up: 60 months.	• Eligibility criteria: age 18-70 years; histology proved squamous cell carcinoma of head and neck; locally advanced disease (stage III and IV); Karnofsky Performance Status (KPS) >70; Lab values: Hb >10gm%, absolute polymorphic nuclear cell count >1800 cells/cmm, platelets >100000/cmm, serum creatinine <1.5mg/dl, bilirubin < 2mg/dl; no presence of metastatic disease, no prior anti-cancer therapy, no second primary tumour, no pregnancy.	Chemotherapy (cisplatin and fluorouracil, three cycles) followed by radiotherapy (n=90) vs Radiotherapy (n=90)	**Overall survival** (5 year, Kaplan Meier) 21% vs 16% **Quality of life** Not assessed. **Disease-free survival** Results not reported. **Local control** Results not reported. **Recurrence rate** Not assessed. **Adverse events** (Radiation Therapy Oncology Group criteria)	• Dropouts: "All patients who could be assessed were included in the intent to treat analysis" No numbers of dropouts reported, however in chemotherapy + radiotherapy group n=14 did not complete chemotherapy protocol and n=2 did not turn up for radiotherapy • Results critical appraisal: low risk of detection bias for objective outcomes,

- *A priori* patient characteristics: median age (range) 55 (28-73) vs 57 (26-72) yrs; sex (M/F): 84/6 vs 86/4; KPS (90-100/70-80): 33/57 vs 29/61; site (larynx / oropharynx / hypopharynx): 39/20/31 vs 41/17/32; stage (III/IV): 35/55/39/51

- Group comparability: "The two arms were found to be statistically comparable in respect of site, stage of disease, age and sex of patients."

Chemotherapy
Gastro-intestinal toxicity
- Nausea
  - o Grade I&II: 83/90
  - o Grade III: 7/90
- Vomiting
  - o Grade I&II: 52/90
  - o Grade III: 8/90
- Diarrhoea
  - o Grade I&II: 9/90
  - o Grade III: 0/90
Haematological toxicity
- Hb
  - o Grade I&II: 16/90
  - o Grade III: 0/90
- W B C
  - o Grade !&II: 22/90
  - o Grade III: 0/90
- Platelet
  - o Grade I&II: 4/90
  - o Grade III: 0/90
Others
- Mucositis
  - o Grade I&II: 7/90
  - o Grade III: 0/90
- Renal
  - o Grade I&II: 2/90
  - o Grade III: 0/90
Grade III acute toxicity of radiotherapy
- Skin
  3/88 vs 4/90
  RR=0.77 (95%CI 0.18 to 3.33)
- Mucous membrane
  5/88 vs 1/90
  RR=5.11 (95%CI 0.61 to 42.90)
- Larynx
  14/88 vs 13/90
  RR=1.10 (95%CI 0.55 to 2.21)
- Upper G.I.
  0/88 vs 0/90
  RR not estimable
- Leucopenia
  0/88 vs 0/90
  RR not estimable
Grade III&IV late toxicity of radiotherapy
- Skin
  0/88 vs 0/90

attrition bias for objective outcomes and other bias; high risk of attrition bias for subjective outcomes and reporting bias; unclear risk of selection bias, performance bias and detection bias for subjective outcomes.

RR not estimable
- Mucous membrane
  0/88 vs 0/90
  RR not estimable
- Subcutaneous tissue
  3/88 vs 2/90
  RR=1.53 (95%CI 0.26 to 8.96)
- Larynx
  3/88 vs 1/90
  RR=3.07 (95%CI 0.33 to 28.94)

Post treatment mortality
Number of deaths was not reported.

Zhong 2013[110]					

	• Design: RCT
	• Source of funding: Research Grants No. 2007BAI18B03 from the National Key Technology Research and Development Program of China, No. 81272979, 30973344, and 30700953 from the National Natural Science Foundation of China, and No. 10dz1951300 from the Science and Technology Commission of Shanghai Municipality.
	• Setting: Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China.
	• Sample size: n=256
	• Duration: from March 2008 to December 2010; median follow-up time was 30 months.
		• Eligibility criteria: age 18 to 75 years; histologically confirmed oral squamous cell carcinoma (originating in oral cavity); resectable lesion; clinical stage III or IVA disease (T1-2N1-2M0 or T3-4N0-2M0); Karnofsky performance status >60%; no distant metastasis or other cancers; no surgery involving primary tumour or lymph nodes (except diagnostic biopsy); no prior radiotherapy or chemotherapy; no other malignancies within 5 years; had creatinine clearance >30 mL/min.
		
		• *A priori* patient characteristics: median age (range) 55 (29-74) vs 56 (26-75) yrs; sex (M/F): 91/37 vs 88/40; site (tongue / bucca / gingiva / floor of mouth / palate / tetromolar trigone):
			Induction chemotherapy (docetaxel, cisplatin, and fluorouracil for two cycles) followed by surgery and postoperative radiotherapy (n=128)
			
			vs
			
			Surgery followed by postoperative radiotherapy (n=128)
			
			Surgery was performed at least 2 weeks after completion of induction chemotherapy. Radiotherapy was initiated 4 to 6 weeks after surgery.
				Overall survival
				2 year overall survival: 68.8% vs 68.2%
				HR=0.977 (95%CI 0.634 to 1.507)
				
				Quality of life
				Not assessed.
				
				Disease-free survival
				62.2% vs 63.6%
				HR=0.974 (95%CI 0.654 to 1.45)
				
				Local control
				Not presented.
				
				Recurrence rate
				Locoregional recurrence
				31.3% vs 30.5%
				HR=1.019 (95%CI 0.618 to 1.524)
				
				Adverse events (Common Terminology Criteria for Adverse Events (version 3.0)
				
				Induction chemotherapy
				- Hematologic toxicity
				  ○ Grade 1: 18/122
				  ○ Grade 2: 9/122
				  ○ Grade 3: 8/122
				- Diarrhoea
				  ○ Grade 1: 11/122
					• Dropouts: no patients lost to follow-up, all patients analyzed.
					
					patients who not completed whole treatment
					
					induction chemotherapy group:
					n=19 (n=4 not received allocated intervention; n=12 discontinued intervention, n=3 died of non-cancer related and non-treatment-related causes)
					
					control group:
					n=15 (n=1 not received allocated intervention, discontinued intervention n=14)
					
					• Results critical appraisal: low risk of bias for all items, except performance bias and detection bias for subjective outcomes, for which there was a high risk of bias.

53/25/21/12/12/5 vs
60/20/19/18/6/5; T
stage (T1/T2/T3/T4):
3/30/70/25 vs
6/27/79/16; N stage
(N0/N1/N2): 49/52/27
vs 61/42/25; stage
(III/IVA): 84/44 vs
93/35; smoking status
(current or former /
never): 69/59 vs 57/71;
alcohol use >1 drink
per day for 1 year:
52/46.

- Group comparability:
baseline patient
demographic and
clinical characteristics
are comparable
between study groups.

-      o   Grade 2: 6/122
-      o   Grade 3: 1/122
- Alopecia
  - o   Grade 1: 83/122
  - o   Grade 2: 3/122
  - o   Grade 3: 0/122
- Nausea and/or vomiting
  - o   Grade 1: 66/122
  - o   Grade 2: 2/122
  - o   Grade 3: 0/122
- Altered liver function tests
  - o   Grade 1: 19/122
  - o   Grade 2: 5/122
  - o   Grade 3: 0/122
- Febrile neutropenia
  - o   Grade 1: -
  - o   Grade 2: -
  - o   Grade 3: 2/122

No grade 4 toxicities occurred.

Postoperative radiotherapy – grade 3
- Oral mucositis
  7/111 vs 7/113
  RR=1.02 (95%CI 0.37 to 2.81)
- Trismus
  6/111 vs 6/113
  RR=1.02 (95%CI 0.34 to 3.06)
- Dermatitis
  5/111 vs 4/113
  RR=1.27 (95%CI 0.35 to 4.62)
- Dyhsphagia and odynophagia
  6/111 vs 6/113
  RR=1.02 (95%CI 0.34 to 3.06)

Post treatment mortality
number of deaths:
40/128 vs 42/128
RR=0.95 (95%CI 0.67 to 1.36)

4.9. RQ10: primary CRT for patients with non-resectable M0 HNSCC

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
[Bensadoun et al., 2006][118]	• Design: RCT • Source of funding: none reported • Setting: multicenter: eight centres, France • Sample size: n=171 enrolled, 163 analyzed • Duration: between November 1997 and March 2002; median (95% CI) follow-up: 50 vs. 40 months.	• Eligibility criteria: age 18-75 years; strictly unresectable Stage IV (T4 or large pan-pharyngeal T3, TNM, International Union Against Cancer, 1988), not previously treated, squamous cell carcinoma of the oropharynx or hypopharynx (histologic confirmation), regardless of lymph node status (N0 to N3), and with no evidence of distant metastases; a Karnofsky performance status score of at least 60 and adequate hematologic, renal, and liver functions. • *A priori* patient characteristics: median age (range) 53 (41-76) vs 54.6 (38-73) years; sex (M/F): 72/9 vs 72/10; performance status (0/1/2/-): 29/47/4/1 vs 21/56/4/1; primary tumour site (oropharynx/hypopharynx): 61/20 vs 62/20; T-classification (T3/T4): 28/53 vs 26/56; N-classification (N0/N1/N2b/N2c/N3)	Chemotherapy (CP-5FU, three courses) and concurrent twice-daily radiotherapy (n=81) vs Radiotherapy alone, (two daily fractions of 1.2 Gy with a minimal 6-h interval between fractions).twice-daily (n=82) Patients were considered during the overall treatment time for enteral nutritional support and mucositis prevention (low-energy helium-neon laser in Nice).	**Overall survival (Kaplan Meier estimation)** At 24 months 37.8% vs 20.1% (p=0.038) Subgroup: - Oropharynx patients 41% vs 22% (p=0.038) - Hypopharynx patients 21.5% vs 21.7% (NS) Median overall survival (months) (95% CI) 16 (12-22) vs 10 (8-14) Subgroup: - Oropharynx patients 17 (13-36) vs 10 (8-17) - Hypopharynx patients 12 (6-50) vs 9 (7-24) Total deaths: 33/81 vs 61/82 (RR=0.55; 95% CI 0.41 to 0.73) Cause of death - Primary cancer 13/81 vs 47/82 (RR=0.28; 95% CI 0.16 to 0.48) - Secondary cancer 3/81 vs 2/82 (RR=1.52; 95% CI 0.26 to 8.85) - Early (<2 months after end of treatment) deaths: 11/81 vs 6/82 (RR=1.86; 95% CI 0.72 to 4.78) - Other causes 6/81 vs 6/82 (RR=1.01; 95% CI 0.34 to 3.01) **Disease-free survival (Kaplan Meier estimation)** At 24 months 48.2% vs. 25.2% (p=0.002) Subgroup: - Oropharynx patients 51% vs 27% (p=0.001) - Hypopharynx patients 38% vs 22% (NS) **Quality of life** Not assessed.	• Dropouts: 171 patients were enrolled, eight patients were excluded from analysis (n=4 died between inclusion and start of treatment), n=2 resectable tumours, n=2 refused treatment). 163 patients were analyzed according to the intention-to-treat principle. • Results critical appraisal: high risk of performance bias and detection bias for subjective outcomes; low risk of bias for remaining items.

7/10/16/31/17 vs
16/6/18/29/13.

- Group comparability:
  "Patients were evenly
  distributed between the
  two arms, as were
  patients within each
  investigating center."
  Yet small (non-
  significant) differences
  between groups for
  performance status
  were found.

Local and regional control (at 2 years)
Local control: 63.34% vs 34.48%
Subgroup:
- Oropharynx patients:
  66.88% vs 34.4%
- Hypopharynx patients:
  50.7% vs 33.8%
Regional control: 70.6% vs 53.02%
- Oropharynx patients:
  69.18% vs 55.32%
- Hypopharynx patients:
  71.4% vs 45.7%

Rate of locoregional control (extrapolated by
Kaplan-Meier method)
58.87% vs 27.5% (p=0.0003)
Subgroup:
- Oropharynx patients:
  61.2% vs 28.23% (p=<0.0004)
- Hypopharynx patients:
  50.7% vs 24.3% (NS)

Adverse events

Grade 3-4 acute toxicity (World Health Organization
criteria)
- Mucositis
  67/81 vs 57/82
  (RR= 1.19; 95% CI 1.00 to 1.42)
- Dermatitis
  31/81 vs 22/82
  (RR=1.43; 95% CI 0.91 to 2.24)
- Nausea and diarrhoea
  5/81 vs 0/82
  (RR=11.13; 95% CI 0.6 to 198.13)
- Neutropenia
  27/81 vs 2/82
  (RR=13.67; 95% CI 3.36 to 55.59)

Early deaths (<2 months after end of treatment):
11/81 vs 6/82 (RR=1.99; 95% CI 0.70 to 5.67)

Prevalence of gastrostomy tube
Before treatment: 54/81 vs 38/82 (RR=1.44; 95% CI
1.09 to 1.90)
6 months: 10/49 vs 2/41 (RR=4.18; 95% CI 0.97 to
18.02)

12 months: 3/39 vs 1/26 (RR=2.00; 95% CI 0.22 to 18.20)
24 months: 1/28 vs 0/15 (RR=1.66; 95% CI 0.07 to 38.31)

Grade 3 late toxicity
(Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer criteria)

Prevalence at 12 months after end of treatment
- Xerostomia: 3/39 vs 0/26 (RR=4.72; 95% CI 0.25 to 87.84)
- Chronic mucositis 0/39 vs 1/26 (RR=0.23; 95% CI 0.01 to 5.32)
- Mucosal necrosis: 1/39 vs 0/26 (RR=2.02; 95% CI 0.09 to 47.88)
- Mandibular necrosis: 0/39 vs 0/26 (RR not estimable)
- Dysphagia: 3/39 vs 1/26 (RR=2.00; 95% CI 0.22 to 18.20)
- Trismus: 2/39 vs 1/26, (RR=1.33; 95% CI 0.13 to 13.96)
- Subcutaeous sclerosis: 0/39 vs 1/26, (RR=0.23; 95% CI 0.01 to 5.32)
- Chronic dermatitis: 0/39 vs 0/26 (RR not estimable
- Laryngeal edema: 0/39 vs 0/26 (RR not estimable)
- Hypoacousia: 1/39 vs 0/26 (RR=2.02; 95% CI 0.09 to 47.88)

Prevalence at 24 months after end of treatment
- Xerostomia; 1/28 vs 1/15 (RR=0.54; 95% CI 0.04 to 7.79)
- Chronic mucositis: 1/28 vs 0/15 (RR=1.66; 95% CI 0.07 to 38.31)
- Mucosal necrosis: 0/28 vs 0/15 (RR not estimable)
- Mandibular necrosis: 0/28 vs 0/15 (RR not estimable)
- Dysphagia: 0/28 vs 0/15 (RR not estimable)
- Trismus: 0/28 vs 0/15 (RR not estimable)
- Subcutaeous sclerosis: 0/28 vs 0/15 (RR not estimable)
- Chronic dermatitis: 0/28 vs 0/15 (RR not

estimable)
- Laryngeal edema: 0/28 vs 0/15 (RR not estimable)
- Hypoacousia: 0/28 vs 0/15 (RR not estimable)

Recurrence rate
Local regional and distant tumour failure, or uncontrolled disease
55/81 vs 69/82 (RR=0.81; 95% CI 0.68 to 0.96)

Recurrence
- Site of primary tumour: 17/81 vs 33/82
- Lymph nodes: 13/81 vs 17/82
- Distant metastases: 18/81 vs 28/82
- Locoregional and metastatic spread: 35/81 vs 54/82

| [Budach et al., 2005][119] | • Design: RCT
• Source of funding: Deutsche Krebshilfe
• Setting: multicenter: 10 institutions, Germany
• Sample size: n=384
• Duration: between March 1995 and June 1999; follow up: 5 years | • Eligibility criteria: age between 18 and 70 years; previously untreated and, according to surgeon assessment, inoperable stage III and IV (International Union Against Cancer 1987 criteria) head and neck carcinomas of the oropharynx and hypopharynx and oral cavity with no evidence of distant metastases; Karnofsky performance score >70; and squamous cell or undifferentiated histologies; no earlier or synchronic cancer other than skin, lymphoepithelial carcinoma of the nasopharynx; no surgery exceeding biopsy; no previous chemotherapy or radiation therapy; no | Chemotherapy and hyperfractionated accelerated radiation therapy (30 Gy (2 Gy every day) followed by 1.4 Gy bid to a total of 70.6 Gy concurrently with FU (600 mg/m2, 120 hours continuous infusion) days 1 through 5 and MMC (10 mg/m2) on days 5 and 36) (n=190)

vs

Hyperfractionated accelerated radiation therapy alone (14 Gy (2 Gy every day) followed by 1.4 Gy bid to a total dose of 77.6 Gy) (n=194) | **Overall survival (Kaplan-Meier method)**
2-year rate, % (95% CI):
48.0 (41.3 to 55.9) vs 38.2 (31.9 to 45.8)
3-year rate, % (95% CI):
37.5 (31.1 to 45.4) vs 28.6 (22.8 to 36.0)
5-year rate, % (95% CI):
28.6 (22.5 to 36.3) vs 23.6 (18.2 to 30.9) (p=0.023)

Median overall survival time (months):
23 vs 16
(HR= 0.71; 95% CI, 0.52 to 0.96)

"The multivariate proportional hazards Cox regression analyses revealed the treatment as independent prognostic factor for OS.[…] Nodal status and grading were significant parameters for OS"

Disease-free survival
Not assessed.

Quality of life
Not assessed.

Local control (Kaplan-Meier method)
Locoregional control rate, % (95% CI):
2 years: 57.7 (50.6 to 65.9) vs 42.4 (35.3 to 50.8)
3 years: 51.8 (44.4 to 60.4) vs 39.2 (32.2 to 47.8)
5 years: 49.9 (42.3 to 58.7) vs 37.4 (30.4 to 46.0) | • Dropouts:
Radiotherapy with chemotherapy arm:
n=7 before start of therapy (n=2 not eligible; n=3 presence of metastases; n=2 second primary tumour);
n=32 after start of therapy (n=1 died during therapy; n=5 noncompliance; n=6 chemo refused; n=6 radiotherapy incorrect; n=14 no 2nd cycle MMC)

Radiotherapy arm:
n=4 before start of therapy (n=3 presence of metastases; n=1 died)
n=15 after start of therapy (n=5 died during therapy; n=4 noncompliance; n=6 radiotherapy incorrect) |

severe vascular risk factors; no insulin-dependent diabetes; no symptomatic liver cirrhosis, HIV, pregnancy, or a serum creatinine of more than 1.5 mg/dL or clearance of less than 80 mL

- *A priori* patient characteristics: mean age (SD): 54.0 (8.0) vs 55.0 (8.1) years; sex (M/F): 157/33 vs 165/29; stage (III/IV): 12/178 vs 11/183; tumour stage (T1/T2/T3/T4/missing): 2/14/42/131/1 vs 4/15/30/144/1; node stages (N0/N1/N2/N3): 9/19/135/27 vs 11/16/137/30; site (oropharynx/hypopharynx/oral cavity): 109/62/19 vs 119/62/13; 82% of the patients received gastric feeding tubes

- Group comparability: no statistically significant differences in patient baseline characteristics between both treatment groups.

(p=0.001)

Median locoregional control surviving time (months): 48 vs 15
(HR= 0.48; 95% CI, 0.33 to 0.71)

"The multivariate proportional hazards Cox regression analyses revealed the treatment as independent prognostic factor for LRC. [...] N0 versus N3 status was significant."

Adverse events

Acute toxicity
Grade 3-4 (European Organisation for Research and Treatment of Cancer acute morbidity scales)
- Erythema
  53/169 vs 81/177
  (RR=0.69; 95% CI 0.52 to 0.90)
- Moist desquamation
  50/169 vs 82/177
  (RR=0.65; 95% CI 0.49 to 0.86)
- Pigmentation
  16/169 vs 24/177
  (RR=0.70; 95% CI 0.38 to 1.27)
- Mucositis
  111/169 vs 134/177
  (RR=0.87; 95% CI 0.76 to 1.00)
- Dysphagia
  121/169 vs 127/177
  (RR=1.00; 95% CI 0.87 to 1.14)
- Xerostomia
  17/169 vs 19/177
  (RR=0.94; 95% CI 0.50 to 1.74)
- Dysgeusia
  16/169 vs 24/177
  (RR=0.70; 95% CI 0.38 to 1.27)
- Leukopenia
  9/106 vs -
- Thrombocytopenia
  2/106 vs -
- Anemia
  3/106 vs -

- Results critical appraisal: high risk of selection bias and detection bias; unclear risk of selection bias, attrition bias (subjective outcomes) and other bias; low risk of bias on remaining items.

Late toxicity
Grade 3-4 (Radiation Therapy Oncology
Group/European Organisation for Research and
Treatment of Cancer late morbidity scales)
- Xerostomia
  47/165 vs 43/163
  (RR=1.08; 95% CI 0.76 to 1.54)
- Dysgeusia
  70/166 vs 74/162
  (RR=0.92; 95% CI 0.72 to 1.18)
- Dysphagia
  83/165 vs 85/163
  (RR=0.96; 95% CI 0.78 to 1.19)
- Telangiectasia
  4/165 vs 3/159
  (RR=1.28; 95% CI 0.29 to 5.65)
- Skin fibrosis
  30/165 vs 23/160
  (RR=1.26; 95% CI 0.77 to 2.08)
- Trismus
  6/166 vs 9/160
  (RR=0.64; 95% CI 0.23 to 1.76)
- Transient plexopathia
  5/166 vs 6/158
  (RR=0.79; 95% CI 0.25 to 2.55)
- Osteoradionecrosis
  10/164 vs 8/158
  (RR=1.20; 95% CI 0.49 to 2.97)
- Pigmentation
  13/165 vs 23/160
  (RR=0.55; 95% CI 0.29 to 1.04)
- Lymphedema
  6/166 vs 13/159
  (RR=0.44; 95% CI 0.17 to 1.13)
- Mucosal necrosis
  10/166 vs 12/147
  (RR=0.74; 95% CI 0.33 to 1.66)
- Transient L'Hermitte's syndrome
  6/166 vs 6/156
  (RR=0.94; 95% CI 0.31 to 2.85)

Recurrence rate
 "A 5.2% (n=20) overall rate of secondary neoplasms
was observed at 5 years, which was not significantly
different for both treatment arms by using cumulative
incidences (log-rank test, p=0.114)."

| [Chauhan et al., 2008][114] | • Design: RCT
• Source of funding: none described
• Setting: Department of Radiotherapy, Pt. B.D. Sharma Post Graduate Institute of Medical Sciences, Rohtak, India
• Sample size: n=80
• Duration: from November 2000 to March 2003; median follow-up: 9 months (range 6–52) in the RT group vs 11 months (range 5-51) in the CT/RT group | • Eligibility criteria: locally advanced (T3, T4, any N, M0) previously untreated histopathologically proven squamous cell carcinoma of head and neck; unresectable disease or refusal of surgery; Karnofsky performance status score ≤70%, adequate liver function tests, bone marrow reserve and renal function.

• *A priori* patient characteristics: median age (range): 51.5 (30-69) vs 50 (28-72) years; sex (M/F): 38/2 vs 37/3; primary site (oral cavity / oropharynx/hypopharynx/larynx): 4/30/5/1 vs 3/30/6/1; stage (III/IV): 20/20 vs 18/22; tumour size (T3/T4): 37/3 vs 36/4; nodal status (N0/N1/N2/N3): 7/16/14/3 vs 6/16/19/0

• Group comparability: "There was good balance in the prognostic factors, including performance status, tumour and nodal stages, and histology, between the two groups" | Gemcitabine (intravenously over 30 minutes once weekly, 1–2 h before radiation, for 6 consecutive weeks at a dose of 100 mg/m2) concurrent with radiotherapy (once daily, 5 days a week as a single 2 Gy fraction to a total dose of 64 Gy) (n=40)

vs

Radiotherapy alone (once daily, 5 days a week as a single 2 Gy fraction to a total dose of 64 Gy) (n=40) | **Overall survival**
Not assessed.

Disease-free survival
At 3 years follow-up: 63.3% vs 20%

Quality of life
Not assessed.

Local control
"Local control was good, none of the 19 patients with complete response developed relapse in the CT/RT group. Seven of the 13 patients with complete response in the radiation only group relapsed (3 at primary site, 3 at nodal and 1 distant):"
Relapses:
Primary: 0/30 vs 3/30 (RR=0.14; 95% CI 0.01 to 2.65)
Nodal: 0/30 vs 3/30 (RR=0.14; 95% CI 0.01 to 2.65)
Distant: 0/30 vs 1/30 (RR=0.33; 95% CI 0.01 to 7.87)

Adverse events
Acute reactions (WHO criteria)
% of patients
• Haematological
Haemoglobin level:
Grade I toxicity: 80% vs 47.5%
Grade II toxicity: 20% vs 7.5%
(p<0.05)
"The leukocyte and platelet counts remained within normal limits during the treatment schedule in both the groups."
• Skin reactions
Level 5: 50% vs 7.5%
Level 6: 7.5% vs 2.5%
(p<0.05)
• Oral mucosal reactions
Level 5: 67.5% vs 17.5 (p<0.05)
Level 6: "During the 5th week in the CT/RT group two patients developed level-6 mucosal reactions due to which treatment had to be interrupted"
• Nausea and vomiting: "In both the RT and | • Dropouts: none: "All 80 patients were assessable for toxicity and response."

• Results critical appraisal: high risk of performance bias and detection bias (subjective outcomes); unclear risk of selection, reporting and other bias; low risk of bias on remaining items. |

				CT/RT groups only mild nausea and transient vomiting, which did not require medication were observed. • Weight loss Grade I: 47.5% vs 85.7% Grade II: 52.5% vs 14.3% "Thus, there was significant loss of weight in the CT/RT group (p<0.05) as compared to the RT group during the later half of treatment which seems to be due to poor intake because of the debilitating oral mucosal reactions." **Recurrence rate** Not assessed.	
[Quon et al., 2011][117]	• Design: RCT • Source of funding: Public Health Service, National Cancer Institute, National Institutes of Health and the Department of Health and Human Services • Setting: multicenter, USA • Sample size: n=371 randomized, n=308 analyzed • Duration: from November 1982 to June 1987; median follow-up period: 62 months	• Eligibility criteria: patients with biopsy-proven head-and neck squamous cell or undifferentiated carcinoma, technically unresectable American Joint Committee on Cancer 1980 clinical Stage III or IV with no distant metastasis; all anatomic sites of the head and neck were included including nasopharyngeal carcinomas restricted to T3/4 or N2/3 disease; Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–3; adequate hematologic, hepatic, and renal function; no existing cardiac conditions, pregnancy or lactation, prior treatment with RT or chemotherapy, and no prior or synchronous	RT Radiotherapy plus concomitant cisplatin dosed at 20 mg/m² per week (n=149) vs Radiotherapy (n=159) Radiotherapy was given once daily, 5 days a week, prescribed dose to the primary lesion and involved nodal disease 68–76 Gy, daily fraction 1.8–2 Gy (radiation arm) or 1.8 (radiation+cisplatin arm)	**Overall survival** Median survival in months: 11.8 vs 13.3 (p =0.81) " Also not significantly different with an intent-to-treat analysis (data not shown)." "Univariate analysis demonstrated that a poorer OS was associated with several factors: white race (p=0.04), greater smoking exposure (p=0.002), greater alcohol consumption (p<0.001), ECOG PS 2–4 (p<0.003), better cell differentiation (p=0.034), higher stage (p=0.021), and nonnasopharynx primary site (p=0.001). " "Multivariate analysis demonstrated no significant treatment effect (p=0.60)" **Disease-free survival** Not assessed. **Quality of life** Not assessed. **Local control** Not assessed. **Adverse events** <u>Acute adverse effects</u> "The addition of weekly cisplatin significantly increased the frequency and severity of nausea/vomiting (p <0.001) and of neurologic (p=0.002), renal (p < 0.001), and hematologic	• Dropouts: Of the 371 patients randomized, 63 were excluded from the primary analyses *Radiotherapy + cisplatin:* n=37 (n=27 ineligible; n=4 patient refusal; n=3 died before treatment; n=1 elected non-protocol treatment; n=1 decreased serum creatinine and creatinine clearance; n=1 unknown) *Radiotherapy:* n=26 (n=18 ineligible; n=5 patient refusal, n=1 died before treatment; n=1 received non-protocol treatment, n=1 could not be positioned for radiation therapy) • Results critical appraisal: high risk of

malignancy.
NB: "At the initiation of the trial, from November 1982 to August 1983, patients with an incomplete resection and gross residual tumor were permitted to enroll in the absence of documented distant disease. After August 1983, these patients were excluded."

- *A priori* patient characteristics: median age (range): 61y (20-81) vs 60y (19-85); sex (M/F): 117/32 vs 133/26; race (white/non-white): 115/34 vs 122/37; performance status (0/1/2/3): 33/87/23/6 vs 42/81/29/7;T-stage (0/1/2/3/4): 0/3/12/45/89 vs 2/5/14/49/89; N-stage (0/1/2/3): 32/24/27/66 vs 39/17/32/71; Stage (III / IV excluding T4 N3 / T4 N3): 21/89/39 vs 23/97/39; prior surgery (yes/no): 41/108 vs 38/121; primary site (nasopharynx/oral cavity/oropharynx/larynx/hypopharynx/other): 16/51/37/14/27/4 vs 25/43/48/7/30/6

- Group comparability: "There were some imbalances with

toxicities (p < 0.001)."

"Respiratory acute toxicities were increased in the RT + cisplatin group. The increased frequency of toxicities was primarily mild to moderate in severity. Toxicities within the radiation fields did not seem to be increased. Additional evaluation for laryngeal edema and nutritional toxicity was also evaluated with different grading schemas. The addition of weekly cisplatin also did not significantly increase the spectrum and the severity of any of these toxicities"

"When each patient was classified by the worst grade of any type of toxicity, the treatment groups were comparable (p=0.21)."

Head and Neck Radiation Therapy Form.
- Grade 3+ laryngeal edema: 5% vs 3%
- Grade 3+ nutritional toxicity: 35% vs 31%

Late toxicities (recorded on the Radiotherapy Long Term Follow-up Form)
- Skin: 15% vs 21% (p=0.18)
- Mucous membrane: 22% vs 28%, (p=0.29)
- Subcutaneous tissue: 13% vs 11%, (p=0.60)
- Esophagus: 9% vs 3% (p=0.03)
- Larynx: 11% vs 4% (p=0.05)
- Other: 16% vs 13% (p=0.52)

Recurrence rate
Not assessed.

performance bias, detection bias (subjective outcomes) and other bias; unclear risk of attrition bias; low risk on remaining items.

			the RT + cisplatin group: a higher number of patients with age >65, weight loss ≥10% in the previous 6 months, >40 pack-years exposure to smoking, well or moderate cell differentiation, and nonnasopharyngeal primary tumors. These imbalances contributed to a bias against the RT + cisplatin treatment group with the as-treated analysis."		
[Rodriguez et al., 2010][115]	• Design: RCT • Source of funding: none reported • Setting: multi-center, most patients collected by the National Institute of Oncology and Radiobiology, Cuba • Sample size: n=106 • Duration: from July 2002 to February 2007; median follow-up period: 45.2 months	• Eligibility criteria: histologically documented advanced (stages III and IV) locoregional (unresectable) squamous-cell carcinoma of the head and neck; suitable for radiation therapy; measurable lesions; age ≥18y, ;ECOG performance status ≤2; life expectancy greater than 6 months; normal functioning of the organs and of te bone marrow; no prior radiotherapy or chemotherapy, concurrent active cancer, any uncontrolled illness and pregnancy or lactation. • *A priori* patient characteristics:	Nimotuzumab in combination with radiotherapy (n=54) vs Placebo and radiotherapy (n=51) The mean monoclonal antibody (mAb) cumulative dose was 1,057 mg. The mean cumulative radiotherapy dose for the group receiving nimotuzumab was 6,030 cGy, whereas patients of the control group were treated with 5,931 cGy, as average.	**Overall survival** 9/54 vs 5/51 (RR=1.70; 95% CI 0.61 to 4.73) Intent to treat analysis (Kaplan-Meier) Mean survival (in months): 22.71 vs 17.71 Median survival (in months): 12.50 vs 9.47 Mean survival intent to treat analysis (in months) Kaplan-Meier method: 22.71 vs 17.71 Median survival intent to treat analysis (in months) Kaplan-Meier method: 12.50 vs 9.47 Death rate within 90 days post-randomization 4/54 vs 3/52 **Disease-free survival** Not assessed. **Quality of life** European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30 (version 3.0) and the QLQ-H&N35 (head & neck cancer module) validated questionnaires. "Quality of life was evaluated in 42 patients, 21	• Dropouts: n=86 received at least four doses of the investigational product (n=44 nimotuzumab, n=42 placebo), and n=77 completed six doses (n=39, nimotuzumab, n=37, placebo). The most frequent causes of treatment interruption were voluntary withdrawal, lost of follow up, severe adverse events (not attributed to nimotuzumab) and tumour progression. Exact numbers and reasons for lost to follow up were not reported per group. • Results critical appraisal: unclear risk of selection bias and

median age: 59 vs 65 y; sex (M/F): 44/10 vs 37/14;; median weight (kg): 60 vs 57; stage (III/IV): 21/32 vs 21/30; ECOG performance status (Grade 0/1/2): 21/31/- vs 14/35/1; primary tumour site (tonsil/base of tongue/alveolar ridge/tetromolar trigone/hypopharynx/larynx/anterior tongue/oral mucosa/soft palate/hard/palate/pharyngeal wall/maxillary sinus/floor of mouth): 17/10/1/5/1/1/4/3/6/1/2/1/2 vs 24/10/-/5/-/-/2/-/5/3/-/1/2

- Group comparability: "No significant differ-ences were detected between the two arms regarding demography or tumor characteristics." "Even though, no statistically significant unbalance was found between both treatment groups, 46.2% of tumors in the placebo arm were located at the tonsil while only 31.5% of patients in the nimotuzumab group had tonsil tumors." Significant differences were found in relation with the global health status/QoL questionnaire The

treated with nimotuzumab and radiotherapy and 21 treated with a placebo and radiotherapy."

"Differences between the two groups were only found in relation with the general pain evaluation at month six. Patients treated with placebo referred less pain than patients treated with nimotuzumab. These differences were not found in the following evaluations (months 9 and 12). Notably, no differences were found either regarding pain or pain killer consumption between the two groups at any evaluation when applying the head and neck specific survey. Given that these differences were subtle and the results were not supported at other time points or the second scale, it is likely that this result occurred by chance."

"The remaining parameters of the global questionnaire did not show significant differences between the treatment groups at the 3, 6, 9 and 12 months. With regards to the specific head and neck questionnaire, no discernible differences were found between the monoclonal antibody and placebo groups for the 18 head and neck quality of life aspects at baseline and at 3, 6, 9 and 12 months" In summary, a quality of life increase and a reduction of the general and specific symptoms of the disease for both groups during the trial were detected. No negative impact of the use of nimotuzumab as compared to placebo was detected regarding quality of life."

Local control
Not assessed.

Adverse events
Common Toxicity Criteria of the US National Cancer Institute, Version 2, April 30, 1999 (NCI-CTC, Version 2)

Overall adverse events: 38/54 vs 30/52 (RR=1.22; 95% CI 0.91 to 1.63)

Adverse events definitively, probably or possibly

reporting bias; low risk of bias on remaining items.

		monoclonal antibody treated group showed the highest health score. For the rest of the five functional scales as well as for the individual symptoms of the general health scale, there were no differences at baseline between both groups.		related to the investigational drug Grade I or II adverse events: 17/54; mainly: • Asthenia: 14.6% • Fever: 9.8% • Headache: 9.8% • Chills: 7.8% • Anorexia: 7.8% • Skin rash: no skin rash Most frequent reactions due to radiotherapy • Mucositis: 20.1% vs 16.8% • Dry mouth: 17% vs 23% • Dry radio-dermitis: 10.3% vs 12.1% • Odynophagia: 8% vs 11.3 "There was no exacerbation of the adverse reactions related to irradiation after the administration of the monoclonal antibody." **Recurrence rate** Not assessed.	
[Ruo Redda et al., 2010][112]	• Design: RCT • Source of funding: none reported • Setting: multicenter: six centres, Italy • Sample size: randomized n=164, n=157 started treatment • Duration: November 1992 through December 1995; median follow-up period: 26.2 months (range, 6.2-169.5) with a median observation period for surviving patients of 154.3 months	• Eligibility criteria: age >18 and ≤70 years; biopsy-proven diagnosis of locally advanced and unresectable stage III or IV non-metastatic HNSCC, using the criteria of the International Union Against Cancer by use of the 4th edition of the TNM classification of malignant tumours; no prior chemotherapy or radiotherapy for any kind of cancer (except for non-melanoma skin cancer or *in situ* cervical cancer); Eastern Cooperative Oncology Group (ECOG) performance	Radiotherapy with concurrent daily low-dose carboplatin (n=80) vs Radiotherapy alone (n=77)	**Overall survival (Kaplan Meier method)** 3 year rate: 28.9% vs 11.1% 5 year rate: 9.0% vs 6.9% 10 year rate: 5.5% vs 6.9% (p=0.02) **Disease-free survival (Kaplan Meier method)** 3 year rate: 16% vs 9.0% 5 year rate: 6.8% vs 5.5% 10 year rate: 6.8% vs 5.5% (p=0.09) **Quality of life** Not assessed. **Local control (Kaplan Meier method)** 3 year rate: 21.7% vs 15.0% 5 year rate: 15.1% vs 10.7% 10 year rate: 15.1% vs 10.7% (p=0.11)	• Dropouts: *Radiotherapy with chemotherapy* arm: n=7 died during treatment (n=3 fatal bleeding; n=3 pneumonia; n=1 bowel perforation) *Radiotherapy* arm: n=5 died during treatment (n=3 fatal bleeding; n=2 bowel perforation) • Results critical appraisal: Unclear risk of selection bias, performance bias and detection bias for subjective outcomes;

status of ≤2, without any serious concomitant diseases; adequate bone marrow reserve, renal function and liver function; adequate nutritional and liquid intake.

- *A priori* patient characteristics: median age (range) in years: 58 (39-70) vs 61 (40-71); sex (M/F): 66/7 vs 63/9; performance status (0/1/2/): 47/18/8 vs 30/33/9; site (oral cavity/oroparynx/larynx/hypopharynx): 14/42/9/8 vs 14/39/12/7; stage (III/IV): 18/55 vs 15/57

- Group comparability: "There were no differences between the two treatment arms as regard age, sex, primary tumour site and staging."

Exploratory subgroup analysis

"No significant difference in outcome when considering age, site of primary disease or nodal status."

Considering only stage IV patients:

3 year rate: 21.5% vs 12.8%
5 year rate: 15.9% vs 7.7%
10 year rate: 15.9% vs 7.7%
(p=0.04)
"However, the difference was not confirmed in multivariate analysis, possibly suggesting a possible imbalance in other prognostic factors in this subset of patients."

"Furthermore, multivariate analysis did not find any prognostic factor that was statistically significant."

Adverse events
Acute toxicity
Grade 3-4 (World Health Organization criteria)
- Hemoglobin:
  3/80 vs 0/77 (RR=6.74; 95% CI 0.35 to 128.38)
- Leukocytes:
  7/80 vs 0/77 (RR= 14.44; 95% CI 0.84 to 248.66)
- Thrombocytes:
  1/80 vs 0/77 (RR=3.00; 95% CI 0.12 to 72.56)
- Mucositis:
  10/80 vs 9/77 (RR=1.07; 95% CI 0.46 to 2.49)

Feeding tube required for nutritional support
n=110

Late toxicity
"The incidence of late toxicity in the combined arm was no higher than that observed in patients treated with radiotherapy alone, except for the observation of more severe neck fibrosis in patients who received both chemotherapy and radiotherapy":
7/80 vs 3/77 (RR=2.25; 95% CI 0.60 to 8.37)

"No radiation myelitis or toxic-related death was

low risk of bias for all other items.

observed in either treatment arm."

Recurrence rate
Not assessed.

| [Semrau et al., 2006][116] | • Design: RCT
• Source of funding: none reported
• Setting: five participating German centers (universities of Heidelberg, Wuerzburg, and Cologne, community hospitals of Kassel and Oldenburg)
• Sample size: n=263 randomized, n=240 started treatment
• Duration: between July 1995 and April 1999; median follow-up period (range): 57.3 (10.7-84.4) months | • Eligibility criteria: histologically proven locoregionally advanced unresectable cancers of the head and neck, located in oropharynx or hypopharynx, International Union Against Cancer Stage III or IV; free of distant metastasis, no history of prior malignant neoplasm, no prior chemotherapy or radiation therapy; baseline routine laboratory tests had to be fulfilled; performance status between 0 and 2 (WHO scale).

• *A priori* patient characteristics: median age (range) 57y (38–73) vs 56y (28–73); sex (M/F): 96/17 vs 108/19; tumour site (oropharynx/hypopharynx):: 87/26 vs 91/36;; T-stage (T1/T2/T3/T4): 0/1/19/91 vs 2/3/20/102 ;N-stage (N0/N1/N2/N3): 12/8/85/8 vs 11/7/92/17 ; Stage UICC III/IV: 4/109 vs 5/122 | Concurrent hyperfractionated and accelerated radiochemotherapy (RCT) with two cycles 5-fluorouracil (600 mg/m2/day) and carboplatin (70 mg/m2/day) on Days 1–5 and 29–33 (n=113)

vs

Hyperfractionated and accelerated Radiotherapy (RT) (n=127)

Total RT dose in both arms was 69.9 Gy in 38 days in concomitant boost technique.

The majority of patients (138 of 240; 57.5%; no statistical difference between RCT and RT) received a gastric feeding tube, facilitating enteral nutrition during radiotherapy. | **Overall survival**
"Patients treated with RCT have a statistically significant improved overall survival compared with patients treated with RT alone."

5-year survival
25.6% (95% CI 15.8 to 35.4%) vs 15.8% (95% CI 9.1 to 22.4%) (p=0.016)
Subgroup:
• Oropharyngeal:26.1% (95%CI 14.3 to 37.8) vs 13.0% (95%CI 5.3 to 20.6) (p=0.008)
• Hypopharyngeal: percentages not reported (p=0.72)

Disease-free survival
5-year rates of survival reported under 'local control'

Quality of life
Not reported

Local control
5-year rates of survival with local control (Kaplan-Meier estimate)
22.7% (95% CI, 13.3–32.0%) vs 12.6% (95% CI, 6.6 –18.6%) (p=0.01)

Subgroup:
- Oropharyngeal: 22.9%, (95% CI 11.5 to 34.3%) vs 10.0% (95% CI, 3.2 to 16.4%) (p=0.002)
• Hypopharyngeal: 19.2% vs 19.4%, (p=0.885)

Adverse events

Acute adverse effects, Grade 3–4 (according to CTC/RTOG-criteria) (reported in Staar 2001)
Mucositis: 68% vs 52% (p=0.01)
Dermatitis: 30% vs 28%
WBC: 18% vs -
Platelets: 5% vs -
Anemia: - vs 1% | • Dropouts: n=23 did not start treatment (n=1 died because of cardiac failure; n=7 missing qualification; n=7 refusals; n=3 infection of feeding tubes; n=2 alcohol excess; n=2 distant metastases; n=2 unknown reason). Drop outs were not specified per intervention group.

• Results critical appraisal: high risk of performance bias, detection bias (subjective outcomes) and reporting bias; unclear risk of selection bias; low risk of bias on remaining items. |

- Group comparability: "The two treatment arms were well balanced for tumor site, TN stage, grading, and pre therapeutical hemoglobin levels (intention-to-treat population)."

Vomiting under therapy: 8.2% vs 1.6% (p=0.02)
Pain: "In both treatment arms, 17% of patients reported Grade 3 + 4 pain (p=0.8)

"Hematologic toxicity for patients with chemotherapy was low. No patient developed Grade 3 + 4 neurotoxicity, ototoxicity, or nephrotoxicity." No further details reported.

Late adverse effects (any Grade) Xerostomia: 99/113 vs 115/127 (RR=

0.97; 95% CI 0.88 to 1.06)

Sense of taste: 89/113 vs 104/127 (RR=0.96; 95% CI 0.85 to 1.09)
Lymph edema: 82/113 vs 101/127 (RR=0.91; 95% CI 0.79 to 1.05)
Skin induration: 71/113 vs 87/127 (RR=0.92; 95% CI 0.76 to 1.10)
Skin pigmentation: 69/113 vs 84/127 (RR=0.92; 95% CI 0.76 to 1.12)
Skin fibrosis: 35/113 vs 32/127 (RR=1.23; 95% CI 0.82 to 1.85)
Hearing problems: 13/113 vs 15/127 (RR=0.97; 95% CI 0.48 to 1.96)
Skin ulcers: 8/113 vs 10/127 (RR=0.90; 95% CI 0.37 to 2.20)
Osteoradionecrosis: 10/113 vs 7/127 (RR=1.61; 95% CI 0.63 to 4.08)

Recurrence rate
Not assessed.

4.10. RQ11: interventions for M+ disease or recurrent disease not suitable for curative treatment

Study ID	Method	Patient characteristics	Intervention(s)	Results	Critical appraisal of study quality
[59]Machiels 2011[122]	- Design: RCT - Source of funding: Genmab - Setting: medical centres in Europe, Brazil, and Canada - Sample size: n=286 - Duration: between Nov 21, 2006, and June 29, 2009, median follow-up (range): 6 months (0 to 32)	Eligibility criteria: pathologically or cytologically proven squamous-cell carcinoma of the oral cavity, oropharynx, hypopharynx, or larynx. Patients were required to be regarded as incurable by standard therapy and have measurable disease and progressive disease according to RECIST confirmed by an independent review committee (before inclusion) during or within 6 months after failure of, or intolerance to, platinum-based chemotherapy. *A priori* patient characteristics: median age years (range) 57 (29–81) vs 58 (28–78); sex (M/F): 169/22 vs 83/12; primary tumour location (hypopharynx/ larynx/oral cavity/ oropharynx/other): 35/36/64/53/3 vs 19/24/24/26/2; WHO performance status (0 to 1 / 2): 157/34 vs 79/16; previous therapy as a part of multimodality curative treatment (radiotherapy alone/ surgery/ curative chemoradiation/adjuvant chemotherapy/concurrent chemotherapy/induction chemotherapy): 80/104/3/72/30 vs 37/53/1/38/16; number of previous chemotherapy regimens (one/two/three/four): 98/77/12/4 vs 45/43/7/0; progressive disease (within 6	Zalutumumab plus best supportive care (n=191) vs Best supportive care (defined as the best palliative care available and included nutritional support, hydration, transfusion, antibiotics, antimicrobials, pain medication, and treatment for nausea) with optional methotrexate (n=95) NB: Patients in the control group could receive methotrexate up to a maximum dose of 50 mg/m² per week when it was defined as best supportive care at the site. Methotrexate was not used in combination with zalutumumab. After disease progression, patients could receive any available treatment to be chosen at the treating doctor's discretion.	**Quality of life (QLQ 30 and H&N 35)** "The quality of life assessment indicated that adding zalutumumab to best supportive care did not adversely affect quality of life (data not shown)." **Adverse events** Grade 3–4 adverse events: Rash 39/189 vs 0/94 (RR=39.40; 95% CI 2.45 to 634.01) Anaemia 11/189 vs 5/94 (RR=1.09; 95% CI 0.39 to 3.06) Pyrexia 0/189 vs 0/94 (RR not estimable Headache 5/189 vs 1/94 (RR= 2.49; 95% CI 0.29 to 20.98) Weight decrease 4/189 vs 2/94 (RR=0.99; 95% CI 0.19 to 5.33) Diarrhoea 0/189 vs 1/94 (RR=0.17; 95% CI 0.01 to 4.04) Hypomagnesaemia 7/189 vs 0/94 (RR=7.48; 95% CI 0.43 to 129.59) Pneumonia 9/189 vs 2/94 (RR=2.24; 95% CI 0.49 to 10.15) Bronchitis 3/189 vs 1/94 (RR=1.49; 95% CI 0.16 to 14.15) Stomatitis 0/189 vs 1/94 (RR=0.17; 95% CI 0.01 to 4.04) Neutropenia 1/189 vs 5/94 (RR=0.10; 95% CI 0.01 to 0.84) Mucosal inflammation 1/189 vs 0/94 (RR=1.50; 95% CI 0.06 to 36.38) Disease progression 1/189 vs 0/94 (RR=1.50; 95% CI 0.06 to 36.38) Grade 3/4 infections 28/189 vs 8/94 (RR=1.74; 95% CI 0.83 to 3.67) The most common serious adverse events: Tumour haemorrhage 28/191 vs 13/94 (RR=1.07; 95% CI 0.58 to 1.97) Pneumonia: 13/191 vs 3/94 (RR=2.16; 95% CI 0.63 to 7.38) Dysphagia: 11/191 vs 2/94 (RR=2.74; 95% CI 0.62 to 12.09)	[59] Dropouts: n=157 (153 deaths, 4 refused to continue) vs n=84 (78 deaths, 6 refused to continue). Intention-to-treat population for survival outcomes. - Results critical appraisal: high risk of performance bias, detection bias (subjective outcomes) and reporting bias. Unclear risk of other bias. Low risk of bias on remaining items.

		months of first line-palliative platform chemotherapy/within 6 months of concomitant platinum-based chemoradiation): 159/32 vs 79/16; platinum intolerance: 21/10; location of relapse at inclusion (presence of distant metastases with or without local/regional relapse/local or regional relapse only: 124/67 vs 63/32; EGFR expression (immunochemistry) (1+/2+/3+): 22/51/74 vs 15/16/24 • Group comparability: "Baseline characteristics of the patients were much the same between groups'		**Median overall survival (months)** 6.7 (95% CI 5.8 to 7.0) vs 5.2 (4.1 to 6.4) (p=0.065) HR for death, stratified by WHO performance status: 0.77 (97.06% CI 0.57 to 1.05)	

(Leon *et al.*, 2005)[121]	• Design: multi-institutional retrospective analysis of registers
	• Source of funding: Merck KGaA, Darmstadt, Germany.
	• Setting: multicenter, Europe (Spain, Italy, Germany, France, Switzerland)
	• Sample size: n=151
	• Duration: records of patients treated between 1990 and 2000; duration of follow-up: not reported (max 750 days)
		• Eligibility criteria: age ≥18 yrs; histologically confirmed diagnosis of stage III/IV recurrent and metastatic HNSCC (AJCC Classification) not suitable for local therapy, and 2-4 courses of a first-line platinum-based therapy (cisplatin ≥60 mg/m^2/course or carboplatin ≥250 mg/m^2/course) between 1990–2000; documented, measurable tumour progression during or within 30 days of completing chemotherapy (computed tomography or magnetic resonance imaging, or clinically by callipers in two dimensions); no nasopharyngeal cancer; no treatment with any experimental drug not commercially available on 1 January 2001.
		
		• *A priori* patient characteristics: mean (±SD) age: 57.8 (10.45) yrs; sex (M/F): 139/12;
			Second-line therapies
			- best supportive care alone n=68
			- second-line chemotherapy n=43
			- radiotherapy (>30Gy) n=25
			- chemoradiotherapy n=15
				Quality of life
				Not assessed.
				
				Adverse events
				Not assessed.
				
				Overall survival (survival frequencies from the start of second-line treatment)
				
				Chemoradiotherapy vs best supportive care Kaplan Meier estimates (95%CI)
				- 3 months:
				  80.0% (60.0–100.0) vs 27.9% (17.3–38.6)
				- 6 months:
				  53.3% (28.1–78.6) vs 8.8% (2.1–15.6)
				- 9 months:
				  33.3% (9.5–57.2) vs 1.5% (0.0–4.3)
				- 12 months:
				  6.7% (0.0–19.3) vs 0%
				p=0.0001 (Log rank test)
				
				Median days of survival (95%CI):
				212 (154–274) vs 56.5 (46–67)
					• Dropouts: not reported
					
					• Results critical appraisal: low risk of detection bias (objective outcomes), high risk of selection and performance bias, unclear risk of bias for remaining items. No adjustment for baseline characteristics.

| | | Caucasian race: n=151, tumour location (pharynx/larynx/other): 88/36/27; disease stage III/IV: 31/120; tumour type(local recurrence/ metastatic): 100/51; prior therapies on initial diagnosis: n=97 (radiotherapy: n=87, surgery: n=84, induction chemotherapy with platinum-based regimen: n=42, chemoradiotherapy: n=8)

• Group comparability: unclear as baseline characteristics are not specified per group | | *Chemotherapy vs best supportive care*
Kaplan Meier estimates (95%CI)
- 3 months:
  60.5% (45.9–75.1) vs 27.9% (17.3–38.6)
- 6 months:
  23.3% (10.6–35.9) vs 8.8% (2.1–15.6)
- 9 months:
  9.3% (0.6–18.0) vs 1.5% (0.0–4.3)
- 12 months:
  2.3% (0.0–6.8) vs 0%
p=0.0011 (Log rank test)

Median days of survival (95%CI):
107 (83–135) vs 56.5 (46–67)

Radiotherapy vs best supportive care
Kaplan Meier estimates (95%CI)
- 3 months:
  96.0% (88.3–100.0) vs 27.9% (17.3–38.6)
- 6 months:
  56.0% (36.5–75.5) vs 8.8% (2.1–15.6)
- 9 months:
  32.0% (13.7–50.3) vs 1.5% (0.0–4.3)
- 12 months:
  12% (0.0–24.7) vs 0%
p=0.0001 (Log rank test)

Median days of survival (95%CI):
188 (139–280) vs 56.5 (46–67) | |
| **(Zafereo et al., 2009)**[123] | • Design: retrospective review of medical records
• Source of funding: none
• Setting: University of Texas M. D. Anderson Cancer Center
• Sample size: n=168
• Duration: patients | • Eligibility criteria: locally recurrent or residual squamous cell carcinoma of the oropharynx (SCCOP); no distant metastases; no second primary SCCOP.

• *A priori* patient characteristics: not reported for comparisons of interest (palliative chemotherapy versus supportive care), <u>only for surgical salvage vs nonsurgical treatment</u> | Salvage surgery (n=41)

Re-irradiation or brachytherapy with or without chemotherapy (n=18)

Palliative chemotherapy (n=70)

Supportive care (n=39) | **Quality of life**
Only presented for salvage surgery group.

Adverse events
Only presented for salvage surgery group.

Overall survival
<u>*Salvage surgery vs supportive care*</u>
3-year overall survival: 42% vs 5%
5-year overall survival: 28% vs 0%

<u>*Re-irradiation or brachytherapy (with or without chemotherapy) vs supportive care*</u>
3-year overall survival: 32% vs 5% | • Dropouts: 31 patients lost to follow up and not analyzed, all in non-surgical group. Reasons not specified.

• Results critical appraisal: high risk of selection bias, performance bias and attrition |

treated between 1998 and 2005; median

follow-up after diagnosis 9.8 months (range, 0.5-87.7 months).

mean age at presentation (yrs): 57.4 vs 59.3; sex (M/F): 33/8 vs 100/27; tumour site initial disease (tonsil/base of tongue/soft palate): 14/25/2 vs 45/67/15; tumour classification recurrent or residual disease (T1-2/T3-4): 19/22 vs 21/106, overall disease stage (I-II/III-IV): 15/26 vs 12/115

- Group comparability: unclear as patient characteristics were not presented for all intervention groups separately.

5-year overall survival: 32% vs 0%

Palliative chemotherapy vs supportive care
1-year overall survival: 32% vs 13% (p=0.04).
3-year overall survival: 4% vs 5%
5-year overall survival: 0% vs 0%

bias, unclear risk of bias for remaining items. No adjustment for baseline characteristics.

5. SUMMARY OF FINDINGS TABLES AND GRADE PROFILES

5.1. RQ1: PET/CT in the staging of oral cavity cancer

Table 53 – Evidence profile for diagnosis: PET for nodal staging

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with N+) and False negatives (patients incorrectly classified as N0)							
Patient-based analysis							
4 (513 patients)	Cross-sectional studies	Serious limitations[1]	None	None	None	None	**Moderate**
Neck-side-based analysis							
5 (269 neck sides)	Cross-sectional studies	Serious limitations[2]	None	Serious inconsistency[3]	Serious imprecision[4]	None	**Very low**
Node-based analysis							
2 (441 nodes)	Cross-sectional studies	Very serious limitations[5]	None	None	None	None	**Low**
True negatives (patients with N0) and False positives (patients incorrectly classified as N+)							
Patient-based analysis							
4 (513 patients)	Cross-sectional studies	Serious limitations[1]	None	Serious inconsistency[6]	Serious imprecision[4]	None	**Very low**
Neck-side-based analysis							
5 (269 neck sides)	Cross-sectional studies	Serious limitations[2]	None	Serious inconsistency[3]	Serious imprecision[4]	None	**Very low**
Node-based analysis							
2 (441 nodes)	Cross-sectional studies	Very serious limitations[5]	None	None	None	None	**Low**

[1] *Unclear blinding and selection bias in 3 out of 4 studies.*
[2] *Unclear or no blinding and selection bias in 3 out of 5 studies.*
[3] *Non-overlapping CI.*

[4] *Large CI around point estimate.*
[5] *Selection bias and no blinding in 1 out of 2 studies; biased basis of analysis.*
[6] *Clearly different result in largest study, almost non-overlapping CI.*

Table 54 – Evidence profile for diagnosis: non-enhanced PET/CT for nodal staging

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with N+) and False negatives (patients incorrectly classified as N0)							
Patient-based analysis							
1 (63 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[2]	None	**Low**
Neck-side-based analysis							
4 (613 neck sides)	Cross-sectional studies	Serious limitations[3]	None	None	None	None	**Moderate**
Node-based analysis							
10 (3609 nodes)	Cross-sectional studies	Very serious limitations[4]	None	None[5]	None	None	**Low**
True negatives (patients with N0) and False positives (patients incorrectly classified as N+)							
Patient-based analysis							
1 (63 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[2]	None	**Low**
Neck-side-based analysis							
4 (613 neck sides)	Cross-sectional studies	Serious limitations[3]	None	None	None	None	**Moderate**
Node-based analysis							
10 (3609 nodes)	Cross-sectional studies	Very serious limitations[4]	None	None	None	None	**Low**

[1] *Selection bias and unclear blinding.*

[2] *Large CI around point estimate; small sample size.*

[3] *Selection bias in 3 out of 4 studies.*

[4] *Biased basis of analysis.*

[5] *Smallest study is clear outlier. No important heterogeneity apart from that.*

Table 55 – Evidence profile for diagnosis: contrast-enhanced PET/CT for nodal staging

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with N+) and False negatives (patients incorrectly classified as N0)							
Patient-based analysis							
No evidence							
Neck-side-based analysis							
3 (208 neck sides)	Cross-sectional studies	Serious limitations[1]	None	None	Serious imprecision[2]	None	**Low**
Node-based analysis							
2 (498 nodes)	Cross-sectional studies	Very serious limitations[3]	None	None	None	None	**Low**
True negatives (patients with N0) and False positives (patients incorrectly classified as N+)							
Patient-based analysis							
No evidence							
Neck-side-based analysis							
3 (208 neck sides)	Cross-sectional studies	Serious limitations[1]	None	None	Serious imprecision[4]	None	**Low**
Node-based analysis							
2 (498 nodes)	Cross-sectional studies	Very serious limitations[3]	None	None	None	None	**Low**

[1] *Selection bias in all 3 studies.*
[2] *Small number of observations (84 positive neck sides).*
[3] *Biased basis of analysis.*
[4] *Large CIs, small number of observations (124 negative neck sides).*

Table 56 – SoF table for diagnosis: PET or PET/CT versus conventional imaging for nodal staging – neck-side-based analysis [*]

Test result	Illustrative comparative numbers per 1000 patients tested (95%CI) Prevalence 60% [$]		No. of studies	Quality of evidence
	PET or PET/CT	Conventional imaging		
True positives (TP)	576 (462 to 594)	492 (390 to 546)	4 (314 neck sides)	**Very low** [1]
TP absolute difference	84 more			
False negatives (FN)	24 (6 to 138)	108 (54 to 210)		
FN absolute difference	84 less			
True negatives (TN)	332 (272 to 364)	336 (288 to 368)	4 (314 neck sides)	**Very low** [1]
TN absolute difference	4 less			
False positives (FP)	68 (36 to 128)	64 (32 to 112)		
FP absolute difference	4 more			

[*] *Pooled sensitivity PET or PET/CT: 96% (95%CI 77-99%); pooled specificity PET or PET/CT: 83% (68-91%); pooled sensitivity conventional imaging: 82% (65-91%); pooled specificity conventional imaging: 84% (72-92%).*
[$] *Prevalence of 60% was estimated based on the mean prevalence of lymph node involvement in the included studies.*
[1] *Selection bias in 3 out of 4 studies; serious inconsistency (almost non-overlapping CI); serious imprecision (large CI; node-based analysis)*

Table 57 – SoF table for diagnosis: PET or PET/CT versus conventional imaging for nodal staging – node-based analysis *

Test result	Illustrative comparative numbers per 1000 patients tested (95%CI) Prevalence 20% $		No. of studies	Quality of evidence
	PET or PET/CT	**Conventional imaging**		
True positives (TP)	**166** (148 to 178)	**136** (114 to 156)		
TP absolute difference	**30 more**		9 (3203 nodes)	**Very low** ¹
False negatives (FN)	**34** (22 to 52)	**64** (44 to 86)		
FN absolute difference	**30 less**			
True negatives (TN)	**776** (752 to 784)	**784** (760 to 792)		
TN absolute difference	**8 less**		9 (3203 nodes)	**Low** ²
False positives (FP)	**24** (16 to 48)	**16** (8 to 40)		
FP absolute difference	**8 more**			

* *Pooled sensitivity PET or PET/CT: 83% (95%CI 74-89%); pooled specificity PET or PET/CT: 96% (93-98%); pooled sensitivity conventional imaging: 68% (57-78%); pooled specificity conventional imaging: 98% (95-99%).*
$ *Prevalence of 20% was estimated based on the mean prevalence of lymph node involvement in the included studies.*
¹ *Selection bias in 6/9 studies, differential verification in 2 other studies, unclear blinding in 5/9 studies; serious inconsistency (non-overlapping CI); serious imprecision (large CI; node-based analysis).*
² *Selection bias in 6/9 studies, differential verification in 2 other studies, unclear blinding in 5/9 studies; node-based analysis.*

Table 58 – SoF table for diagnosis: PET/CT versus CT for nodal staging – node-based analysis [*]

Test result	Illustrative comparative numbers per 1000 patients tested (95%CI) Prevalence 20% [$]		No. of studies	Quality of evidence
	PET/CT	**CT**		
True positives (TP)	170 (140 to 188)	161 (142 to 175)		
TP absolute difference	**9 more**		4 (1204 nodes)	**Very low** [1]
False negatives (FN)	30 (12 to 60)	39 (25 to 58)		
FN absolute difference	**9 less**			
True negatives (TN)	790 (781 to 794)	790 (768 to 797)		
TN absolute difference	**0 more**		4 (1204 nodes)	**Low** [2]
False positives (FP)	10 (6 to 19)	10 (3 to 32)		
FP absolute difference	**0 less**			

[*] *Pooled sensitivity PET/CT: 85% (95%CI 70-94%); pooled specificity PET/CT: 99% (98-99%); pooled sensitivity CT: 80% (71-87%); pooled specificity CT: 99% (96-99.6%).*

[$] *Prevalence of 20% was estimated based on the mean prevalence of lymph node involvement in the included studies.*

[1] *Selection bias in 3/4 studies, differential verification in 1 other study; serious inconsistency (non-overlapping CI); serious imprecision (large CI; node-based analysis).*

[2] *Selection bias in 3/4 studies, differential verification in 1 other study; node-based analysis.*

Table 59 – Evidence profile for diagnosis: PET or PET/CT for detection of distant metastases or second primary tumours

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with distant M+ or 2nd primary) and False negatives (patients incorrectly classified as having no distant M+ or 2nd primary)							
7 (859 patients)	Cross-sectional studies	Serious limitations[1]	None	None	None	None	**Moderate**
True negatives (patients without distant M+ or 2nd primary) and False positives (patients incorrectly classified as having distant M+ or 2nd primary)							
7 (859 patients)	Cross-sectional studies	Serious limitations[1]	None	None	None	None	**Moderate**

[1] *Unclear blinding and differential verification in most studies; selection bias in some studies.*

Table 60 – Evidence profile for diagnosis: PET or PET/CT for detection of bone metastases

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with bone M+) and False negatives (patients incorrectly classified as having no bone M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
True negatives (patients without bone M+) and False positives (patients incorrectly classified as having bone M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[1] *Unclear blinding and differential verification.*
[2] *Very large CI, small sample size with only 2 positives.*
[3] *Small sample size.*

Table 61 – Evidence profile for diagnosis: PET or PET/CT for detection of bone marrow invasion

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with bone marrow invasion) and False negatives (patients incorrectly classified as having no bone marrow invasion)							
1 (114 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[2]	None	**Low**
True negatives (patients without bone marrow invasion) and False positives (patients incorrectly classified as having bone marrow invasion)							
1 (114 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[1] Unclear blinding for index test, no blinding for reference standard; and selection bias.
[2] Large CI, small sample size.

Table 62 – Evidence profile for diagnosis: PET or PET/CT for detection of lung metastases

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with lung M+) and False negatives (patients incorrectly classified as having no lung M+)							
2 (130 patients)	Cross-sectional studies	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
True negatives (patients without lung M+) and False positives (patients incorrectly classified as having lung M+)							
2 (130 patients)	Cross-sectional studies	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[1] Unclear blinding and differential verification.
[2] Very large CIs, small sample size with only 7 positives in total.
[3] Small sample size.

Table 63 – Evidence profile for diagnosis: PET or PET/CT for detection of liver metastases

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with liver M+) and False negatives (patients incorrectly classified as having no liver M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
True negatives (patients without liver M+) and False positives (patients incorrectly classified as having liver M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[1] Unclear blinding and differential verification.
[2] Very large CI, small sample size with only 2 positives.
[3] Small sample size.

Table 64 – Evidence profile for diagnosis: PET or PET/CT for detection of head and neck metastases

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with head and neck M+) and False negatives (patients incorrectly classified as having no head and neck M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
True negatives (patients without head and neck M+) and False positives (patients incorrectly classified as having head and neck M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[1] Unclear blinding and differential verification.
[2] Very large CI, small sample size with only 4 positives.
[3] Small sample size.

Table 65 – Evidence profile for diagnosis: PET or PET/CT for detection of distant lymph node metastases

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with distant lymph node M+) and False negatives (patients incorrectly classified as having no distant lymph node M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
True negatives (patients without distant lymph node M+) and False positives (patients incorrectly classified as having distant lymph node M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[1] Unclear blinding and differential verification.
[2] Very large CI, small sample size with only 4 positives.
[3] Small sample size.

Table 66 – Evidence profile for diagnosis: PET or PET/CT for detection of other metastases of aerodigestive tract

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with other aerodigestive M+) and False negatives (patients incorrectly classified as having no other aerodigestive M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
True negatives (patients without other aerodigestive M+) and False positives (patients incorrectly classified as having other aerodigestive M+)							
1 (103 patients)	Cross-sectional study	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[1] Unclear blinding and differential verification.
[2] Very large CI, small sample size with only 6 positives.
[3] Small sample size.

5.2. RQ3: elective lymph node dissection for patients with cN0 oral cavity cancer

5.2.1. *Elective lymph node dissection versus watchful waiting for patients with cTanyN0M0 oral cavity cancer*

Included studies: RCTs: a) (Kligerman *et al.*, 1994)[35], b) (Vandenbrouck *et al.*, 1980)[33]; Observational studies: c) (Ebrahimi *et al.*, 2012)[26], d) (Flach *et al.*, 2013)[27], e) (Lin *et al.*, 2011)[28], f) (Yanai *et al.*, 2012)[31]

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Elective	Watchful waiting	Effect	Quality	Importance
			Quality assessment				No of patients		Effect	Quality	Importance
Disease-free survival (3 to 3.5 years)											
2	randomised trials (a,b)	no serious risk of bias[1]	serious[2]	no serious indirectness[3]	very serious[4]	none[5]	34 18/39 (46%)	33 21/36 (58%)	HR 0.32 (0.12-0.84) RR 0.79 (0.51-1.23)*	⊕◯◯◯ VERY LOW	CRITICAL
Disease-free survival (5 years)											
1	observational study (e)	no serious risk of bias	not applicable	no serious indirectness	serious[4]	none	184	81	adj HR 0.37 (0.19-0.71)	⊕◯◯◯ VERY LOW	CRITICAL
Overall mortality (3 to 3.5 years)											
2	randomised trials (a,b)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[3]	very serious[4]	none[5]	7/34 (21%) 39	17/33 (52%) 36	RR 0.40 (0.19-0.84) HR 1.35 (0.59-3.07)*	⊕⊕◯◯ LOW	IMPORTANT
Overall survival (5 years)											
3	observational studies (c-e)	no serious risk of bias	serious[2]	no serious indirectness	no serious imprecision	none	114 51 184	39 234 81	adj HR 0.3 (0.1-0.6) adj 70% vs 82% p = 0.500 adj HR 0.34 (0.17-0.68)	⊕◯◯◯ VERY LOW	IMPORTANT
Locoregional recurrence (3 to 3.5 years)[6]											
2	randomised trials (a,b)	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[3]	very serious[4]	none[5]	8/34 (24%) 6/39 (15%)	14/33 (42%) 8/36 (22%)	0.55 (0.27-1.14) 0.69 (0.27-1.80)*	⊕⊕◯◯ LOW	IMPORTANT

No of studies	Design	Quality assessment					No of patients		Effect	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Elective	Watchful waiting			
Regional recurrence (during follow up[8])											
2	observational studies (c,f)	serious[87]	serious[2]	no serious indirectness	serious[4]	none	114 16/110 (15%)	39 21/119 (18%)	HR 0.1 (0.0-0.3) RR 0.82 (0.45-1.50)*	⊕◯◯◯ VERY LOW	IMPORTANT
Regional control rate (5 years)											
1	observational study (f)	serious[6]	not applicable	no serious indirectness	serious[4]	none	110	119	85% vs 83% p = 0.68*	⊕◯◯◯ VERY LOW	IMPORTANT
Quality of life											
0											IMPORTANT
Adverse events											
0											IMPORTANT

* Studies with stages >T2
1 Unclear risk of bias (as assessed by (Bessell et al., 2011)), no reason for downgrading
2 Different direction of effects
3 Trials performed in 1994 and 1980, unclear whether results are recently applicable; no downgrading
4 Confidence interval includes both benefit and harm
5 Large time gap between published RCTs; no downgrading
6 As presented by (Bessell et al., 2011)
7 Bias by indication: no adjustment for demonstrated baseline differences or no specification of baseline differences
8 Length of follow up not reported for each study arm.

5.2.2. Elective lymph node dissection versus watchful waiting for patients with cT1-2N0M0 cancer of the tongue

Included studies: RCTs: a) (Fakih *et al.*, 1989)[34], b) (Yuen *et al.*, 2009)[36].; Observational studies: c) (An *et al.*, 2008)[25], d) (D'Cruz *et al.*, 2009)[20], e) (Huang *et al.*, 2008)[21], f) (Lin *et al.*, 2011)[28]

No of studies	Quality assessment						No of patients		Effect	Quality	Importance
	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Elective	Watchful waiting			
Disease-free survival (1 year)											
1	randomised trial (a)	serious[1]	not applicable	no serious indirectness[2]	very serious[3]	none[4]	T1/2: 19/28 (68%)	T1/2: 21/37 (57%)	T1/2: RR 1.20 (0.82-1.75)	⊕◯◯◯ VERY LOW	CRITICAL
Disease-free survival (5 years)											
4	observational studies (c-f)	serious[5]	no serious inconsistency	no serious indirectness	very serious imprecision[3]	none	T1: 22 13	T1: 34 36	T1: 78% vs 92% p = 0.483 100% vs 67% p = 0.045	⊕◯◯◯ VERY LOW	CRITICAL
					very serious imprecision[3]		T2: 90	T2: 16	T2: 90% vs 71% p = 0.063		
					no serious imprecision		T1/2: 159	T1/2: 200	T1/2: 74% vs 68% p = 0.53		
							adj T-stage 278 37	adj T-stage 56 56	adj T-stage HR 0.32 (0.19-0.52)(SO) HR 0.21 (0.08-0.55)(MR)		
							Total N=599 range 13-278 % DFS	Total N=342 range 16-200 % DFS	Total Except one study, all studies: difference in		

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	No of patients		Effect	Quality	Importance
							Elective	Watchful waiting			
							range 74-100%	range 68-92%	favor of elective ND; 2 studies with p<0.05		
Overall mortality (1 year)											
1	randomised trial (a)	serious[1]	not applicable	no serious indirectness[2]	very serious[3]	none[4]	T1/2: 9/28 (32%)	T1/2: 16/37 (43%)	T1/2: RR 0.74 (0.39-1.43)	⊕◯◯◯ VERY LOW	IMPORTANT
Overall survival (5 years)											
4	observational studies (c-f)	serious[5]	no serious inconsistency	no serious indirectness	very serious[3]	none	T1: 22 13	T1: 34 36	T1: 93% vs 79% p = 0.075 100% vs 96% p = 0.527	⊕◯◯◯ VERY LOW	IMPORTANT
					very serious[3]		T2: 90	T2: 16	T2: 95% vs 65% p = 0.002		
					no serious imprecision		T1/2: 159	T1/2: 200	T1/2: 60% vs 60% p = 0.24		
							adj T-stage: 278 37	adj T-stage: 56 56	adj T-stage: HR 0.36 (0.18-0.73)(SO) HR 0.49 (0.18-1.33)(MR)		
							Total N=599 range N 13-278	Total N=342 range N 16-200	Total Except 1 study all studies difference in favor of elective ND;		

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Elective	Watchful waiting	Effect	Quality	Importance
				Quality assessment				**No of patients**	**Effect**	**Quality**	**Importance**
							% surv 60-100	% surv 60-96	2 with p<0.05		
Locoregional recurrence[6]											
2	randomised trials (a,b)	serious[1]	no serious inconsistency	no serious indirectness	very serious[3]	none[4]	T1/2: 11/28 (39%) 6/36 (17%)	T1/2: 23/37 (62%) 14/35 (40%)	T1/2: RR 0.63 (0.37-1.07) RR 0.42 (0.18-0.96)	⊕OOO VERY LOW	IMPORTANT
Regional neck recurrence (during follow up[7])											
3	observational studies (d-f)	serious[4]	serious[8]	no serious indirectness	very serious[3]	none	T1: 4/22 (18%)	T1: 34 (12%)	T1: RR 1.55 (0.43-5.55)	⊕OOO VERY LOW	IMPORTANT
					very serious[3]		T2: 14/96 (15%)	T2: 6/16 (38%)	T2: RR 0.39 (0.18-0.86)		
					serious[3]		T1/2: 9/159 (6%)	T1/2: 94/200 (47%)	T1/2: RR 0.07 (0.03-0.14)		
							adj T-stage: 278 37	adj T-stage: 56 56	adj T-stage: HR 0.36 (0.19-0.65)(SO) HR 0.21 (0.19-0.69)(MR)		
							Total N=592 range N 22-278 % recurr 6-18	Total N=306 range N 16-200 % recurr 12-47	Total All but 1 study difference in favor of elective ND ; 2 studies p<0.05		

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Elective	Watchful waiting	Effect	Quality	Importance
header: Quality assessment							No of patients		Effect	Quality	Importance
Neck control rate (5 years)											
1	observational study (e)	serious[4]	not applicable	no serious indirectness	serious[3]	none	159	200	86% vs 69% p<0.001	⊕◯◯◯ VERY LOW	IMPORTANT
Quality of life											
0											IMPORTANT
Adverse events											
0											IMPORTANT

adj= adjusted; SO=supraomohyoid neck dissection; MR=modified radical neck dissection
1 High risk of bias because of incomplete outcome data (outcome DFS, overall mortality and locoregional recurrence) and selective outcome reporting (outcome locoregional recurrence)(as assessed by (Bessell et al., 2011))
2 Trial performed in 1989; no downgrading for indirectness because consistent results for outcome locoregional recurrence which includes a recent study
3 Confidence interval includes both benefit and harm
4 Large time gap between published RCTs, no downgrading
5 Confounding by indication: no adjustment for demonstrated baseline differences or no specification of baseline differences
6 As presented in (Bessell et al., 2011)
7 Length of follow up not reported for each study arm.
8 Relatively large difference in percentage recurrence; definition of recurrence not provided

5.2.3. Elective lymph node dissection versus watchful waiting for patients with cT1-2N0M0 buccal cancer

Included studies: Observational studies: (Lin *et al.*, 2011)

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Elective	Watchful waiting	Effect	Quality	Importance
Quality assessment							**No of patients**		**Effect**	**Quality**	**Importance**
Disease-free survival (5 years)											
1	observational study	serious[1]	not applicable	no serious indirectness	very serious[2]	none	T1: 8 T2: 58	T1: 21 T2: 10	T1: 71% vs 71% p = 0.337 T2: 92% vs 56% p = 0.034	⊕ΟΟΟ VERY LOW	CRITICAL
Overall survival (5 years)											
1	observational study	serious[1]	not applicable	no serious indirectness	very serious[2]	none	T1: 8 T2: 58	T1: 21 T2: 10	T1: 100% vs 95% p = 0.584 T2: 90% vs 78% p = 0.494	⊕ΟΟΟ VERY LOW	IMPORTANT
Recurrence											
1	observational study	serious[1]	not applicable	no serious indirectness	very serious[2]	none	T1: 2/8 T2: 11/58	T1: 7/21 T2: 5/10	T1: 25% vs 33% RR 0.75 (0.20-2.88) T2: 19% vs 50% RR 0.38 (0.17-0.86)	⊕ΟΟΟ VERY LOW	IMPORTANT
Quality of life											
0											IMPORTANT
Adverse events											
0											IMPORTANT

1 Confounding by indication: no adjustment for demonstrated baseline differences or no specification of baseline differences

2 Very small sample size

5.3. RQ4: elective lymph node dissection for patients with cN+ oral cavity cancer

5.3.1. Selective lymph node dissection versus modified radical lymph node dissection for patients with cTanyN+M0 oral cavity cancer

Included studies: RCTs: a) BHNCSG 1998;[38] b) Bier 1994;[37] Observational studies: c) (Huang *et al.*, 2008);[21] d) (Masuda *et al.*, 2012);[29] e) (Park *et al.*, 2013);[30] f) (Patel *et al.*, 2008);[22] g) (Rapoport *et al.*, 2007);[23] h) (Shepard *et al.*, 2010);[24] i) (Yanai *et al.*, 2012);[31] j) (Yildirim *et al.*, 2011);[32]

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Selective ND	Modified radical ND	Effect	Quality	Importance
Disease-free survival (4 years)											
1	RCT (b)	serious[1]	not applicable	serious[2]	very serious[3]	none	56	48	HR 1.75 (0.90-3.45)*/**	⊕◯◯◯ VERY LOW	CRITICAL
Disease-free survival (during follow up[4])											
1	observational study (c)	serious[5]	not applicable	serious[2]	serious[3]	none	278	37	79% vs. 83% p = 0.645*	⊕◯◯◯ VERY LOW	CRITICAL
Disease recurrence (5 years)											
1	RCT (a)	none	not applicable	serious[2]	very serious[3]	none	13/71 (18%)	16/72 (22%)	RR 0.83 (0.43-1.59)*	⊕◯◯◯ VERY LOW	CRITICAL
Regional neck recurrence (3 or 5 years or during follow up[4])											
7	observational studies (d-j)	serious[5]	none[6]	very serious[2]	serious[3]	none	3/35 (8%) 1/29 (3%) 2/54 (4%) 6/117 (5%) 69 77 2/34 (6%)	3/27 (11%) 2/15 (13%) 8/71 (11%) 16/410 (4%) 87 33 1/27 (4%)	RR 0.77 (0.17- 3.53)** RR 0.26 (0.03- 2.63)* RR 0.33 (0.07-1.49) RR 1.31 (0.53-3.28)** HR adj 0.21 p = 0.055** HR 0.94 (0.34- 2.62)* RR 1.59(0.15-16.60)*/**	⊕◯◯◯ VERY LOW	CRITICAL

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Selective ND	Modified radical ND	Effect	Quality	Importance
							N=318 range N 20-77 % recurr 4-10	N=513 range N 15-253 % recurr 4-13	range RR/HR 0.21-2.30 All studies no sign difference		
Neck control rate (during follow up[4])											
5	observational studies (c-f,i)	serious[5]	no serious inconsistency	very serious[2]	serious[3]	none	287 38 (92%) 29 72 (96%) 77	37 25 (88%) 15 160 (86%) 33	p = 0.810* logrank p = 0.57** logrank p = 0.2719* p = 0.06*/** 85% vs 83% p = 0.89*	⊕◯◯◯ VERY LOW	IMPORTANT
							N=503 range N 29-287 contr 92-96	N=270 range N 15-160 contr 86-88	All studies no sign difference		
Overall mortality (4 and 5 years)											
2	RCTs (a,b)	serious[1]	no serious inconsistency	very serious[2]	serious[3]	none	71 56	72 48	HR 0.88 (0.54-1.43)* HR 1.15 (0.55-2.44)*/**	⊕◯◯◯ VERY LOW	IMPORTANT
Overall survival (5 years or during follow up[4])											
6	observational studies (c-f, h,j)	serious[5]	no serious inconsistency[6]	very serious[2]	serious[3]	none	278 (87%) 41 (64%) 29 72 (43%) 69 34 (58%)	37 (80%) 25 (47%) 15 160 (33%) 87 27 (66%)	p = 0.174* p = 0.065*/** logrank p = 0.7596* p = 0.25*/** HR adj 1.27 p = 0.41** p>0.05*/**	⊕◯◯◯ VERY LOW	IMPORTANT

	Quality assessment						No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Selective ND	Modified radical ND			
							N=523 range N 29-278 % surv 43-87	N=351 range N 15-160 % surv 33-80	All studies no sign difference		

| **Quality of life** | | | | | | | | | | | |
| 0 | | | | | | | | | | | IMPORTANT |

| **Adverse events** | | | | | | | | | | | |
| 0 | | | | | | | | | | | IMPORTANT |

* N0 or N0 and N1 patients
** radical ND or comprehensive ND
1 High risk of bias because of incomplete outcome data (as assessed by (Bessell et al., 2011)).
2 Indirectness because of patient group, and/or intervention and duration of follow up (see * and **)
3 Confidence interval includes both benefit and harm
4 Length of follow up not reported for each study arm
5 Confounding by indication: no adjustment for demonstrated baseline differences or no specification of baseline differences
6 Inconsistency probably because of indirectness; no downgrading

5.4. RQ5: elective lymph node dissection of contralateral neck

Table 67 – Clinical evidence profile: Contralateral elective neck dissection vs. watchfull waiting in patients with oral cavity squamous cell carcinoma (OCSCC)

	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 *Time frame is* 3-110 months	
							Contralateral elective neck dissection	watchfull waiting		Risk with intervention	Risk difference with comparator only (95% CI)
(Loco)regional control (CRITICAL OUTCOME)											
No evidence											
Recurrence rate in contralateral neck (CRITICAL OUTCOME)											
369 (2 studies) 3-110 months[ee]	Very serious[ff]	No serious inconsistency	Serious[gg]	No serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to risk of bias and indirectness	See text				NA
Overall survival (IMPORTANT OUTCOME)											
No evidence											
5-year disease-free survival (IMPORTANT OUTCOME)											
54 (1 study)	Very serious [hh]	No serious inconsistency	Serious[ii]	No serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to risk of	68%	82%		Not reported	

[ee] Only reported in the Lim 2006 study

[ff] No randalization, no blinding, more T2 pts in contralateral elective dissection subgroup, no concurrency of intervention and control group

[gg] Only patients with squamous cell carcinoma of the tongue included in the Lim 2006 study

[hh] No randomization, no blinding, more T2 pts in contralateral elective dissection subgroup, no concurrency of intervention and control group

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 *Time frame is* 3-110 months	
								Contralateral elective neck dissection	watchfull waiting		Risk with intervention	Risk difference with comparator only (95% CI)
3-110 months						bias and indirectness						
Quality of life (IMPORTANT OUTCOME)												
No evidence												
Adverse events (IMPORTANT OUTCOME)												
No evidence												

5.5. RQ6: value of PET / MRI in the decision of neck dissection after CRT

Table 68 – Evidence profile for evaluating the need for neck dissection after (at least) chemoradiotherapy: FDG-PET/CT

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with N+) and False negatives (patients incorrectly classified as N0)							
Patient-based analysis							
7 (339 patients)	Prospective and retrospective studies	Serious limitations[1]	None	None	Serious imprecision[2]	None	**Low**
Hemi-neck-based analysis							
2 (119 hemi-	Retrospective	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

[ii] Only patients with SCC of the tongue included, no other primary OCSCC considered

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
necks)	studies						

Node-based analysis

| No studies retrieved | | | | | | | |

True negatives (patients with N0) and False positives (patients incorrectly classified as N+)

Patient-based analysis

| 7 (339 patients) | Prospective and retrospective studies | Serious limitations[1] | None | Serious inconsistency[4] | Very serious imprecision[2] | None | **Very low** |

Hemi-neck-based analysis

| 2 (119 hemi-necks) | Retrospective studies | Serious limitations[1] | None | Serious inconsistency[4] | Serious imprecision[5] | None | **Very low** |

Node-based analysis

| No studies retrieved | | | | | | | |

[1] All studies had some form of methodological limitations (e.g. selection bias, unclear if diagnostic review bias was avoided, unclear if test review bias was avoided, high risk that the reference standard had introduced bias, differential verification).

[2] Large CI around point estimate.

[3] Low sample size and low number of positives.

[4] Non-overlapping CI's.

[3] Low sample size and low number of negatives.

Table 69 – Evidence profile for evaluating the need for neck dissection after (at least) chemoradiotherapy: FDG-PET

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with N+) and False negatives (patients incorrectly classified as N0)							
Patient-based analysis							
7 (308 patients)	Prospective and retrospective studies	Serious limitations[1]	None	None	Serious imprecision [3]	None	**Low**
Hemi-neck-based analysis							
4 (170 hemi-necks)	Retrospective studies	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
Node-based analysis							
1 (27 nodes)	Prospective study	Serious limitations[1]	None	NA	Very serious imprecision	None	**Very low**
True negatives (patients with N0) and False positives (patients incorrectly classified as N+)							
Patient-based analysis							
7 (308 patients)	Prospective and retrospective studies	Serious limitations[1]	None	Serious inconsistency	Serious imprecision	None	**Very low**
Hemi-neck-based analysis							
4 (170 hemi-necks)	Retrospective studies	Serious limitations[1]	None	Serious inconsistency	Very serious imprecision	None	**Very low**
Node-based analysis							
1 (27 nodes)	Prospective study	Serious limitations[1]	None	NA	Very serious imprecision	None	**Very low**

[1] All studies had some form of methodological limitations (e.g. selection bias, unclear if diagnostic review bias was avoided, unclear if test review bias was avoided, high risk that the reference standard had introduced bias, differential verification).

[2] Large CI around point estimate.

[3] Low sample size and low number of positives.

[4] Non-overlapping CI's.

[3] Low sample size and low number of negatives.

Table 70 – Evidence profile for evaluating the need for neck dissection after (at least) chemoradiotherapy: MRI

No. of studies	Design	Risk of bias	Indirectness of patients, intervention and comparator	Inconsistency	Imprecision	Other considerations	Quality of evidence
True positives (patients with N+) and False negatives (patients incorrectly classified as N0)							
Patient-based analysis							
1 (38 patients)	retrospective study	Serious limitations[1]	None	None	Very serious imprecision[2]	None	**Very low**
True negatives (patients with N0) and False positives (patients incorrectly classified as N+)							
Patient-based analysis							
1 (38 patients)	retrospective study	Serious limitations[1]	None	None	Serious imprecision[3]	None	**Low**

1 unclear if consecutive or random patient sample, differential verification
2 CI includes good (>90%), moderate (80-90%) and poor (< 80%) sensitivity. Small sample size.
3 Small sample size.

5.6. RQ7: neck dissection after chemoradiotherapy in patients with oral cavity cancer

Table 71 - Clinical evidence profile: Contralateral elective neck dissection vs. watchfull waiting in patients with oral cavity squamous cell carcinoma (OCSCC)

Participants[jj] (studies) Follow up	Quality assessment						Summary of Findings				
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall quality of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							Neck dissection	Watchfull waiting		Risk with intervention	Risk difference with comparator only (95% CI)
3-year recurrence-free survival (CRITICAL OUTCOME)											
210 (1 study) At least 1	Very seriou	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publicatio	⊕⊖⊖⊖ **VERY LOW** due to high risk of	80%	81.6%			

Quality assessment							Summary of Findings				
Participants[jj] (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	Watchfull waiting		Risk with intervention	Risk difference with comparator only (95% CI)
year	s[kk]				n bias detected	bias					
5-year recurrence-free survival (CRITICAL OUTCOME)											
210 (1 study[ll]) At least 1 year	Very serious[mm]	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias	72.6%	78.1%			
4-year disease-free survival (CRITICAL OUTCOME)											
43 (1 study) 4-127 months	Very serious[nn]	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias	75%	53%			
Progression-free survival (CRITICAL OUTCOME)											
20 (1 study[oo]) 42 months	Very serious[pp]	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias	Median: 43.2 months	Median: 37.9 months			

[kk]   No randomization, no allocation concealment, no blinding, unclear comparability of intervention and control group, careless reporting of data

[ll]   Data presented in Soltys, 2012 not considered since disease free survival calculated for Gr 1 and Gr 2 together.

[mm]   No randomization, no allocation concealment, no blinding, unclear comparability of intervention and control group, careless reporting of data

[nn]   No randomization, no allocation concealment, no blinding, unclear comparability and unclear concurrent inclusion of intervention and control group, small subgroups

[oo]   Data presented in Da Mosto, 2013 not considered since no progression free survival reported for Gr 1

[pp]   No randomization, no allocation concealment, no blinding, unclear comparability of intervention and control group, very small subgroups

Quality assessment							Summary of Findings				
Participants[jj] (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	Watchfull waiting		Risk with intervention	Risk difference with comparator only (95% CI)
3-year overall survival (CRITICAL OUTCOME)											
210 (1 study) At least 1 year	Very serious[qq]	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias	86%	85.2%			
4-year overall survival (CRITICAL OUTCOME)											
43 (1 study) 4-127 months	Very serious[rr]	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias	77%	50%			
5-year overall survival (CRITICAL OUTCOME)											
307 (2 studies[ss]) 12-124 months	Very serious[tt]	Serious inconsistency	No serious indirectness	Serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias	44-78.6%;	42-77.7%			
10-year overall survival (CRITICAL OUTCOME)											
97 (1 study) 22-124	Very serious[uu]	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publicatio	⊕⊖⊖⊖ **VERY LOW** due to high risk of	35%	20%			

[qq] No randomization, no allocation concealment, no blinding, unclear comparability of intervention and control group, careless reporting of data

[rr] No randomization, no allocation concealment, no blinding, unclear comparability and unclear concurrent inclusion of intervention and control group, small subgroups

[ss] Data presented in Da Mosto, 2013 not considered since no progression free survival reported for Gr 1; data presented in Soltys, 2012 not considered since progression free survival calculated for Gr 1 and Gr 2 together.

[tt] No randomization, no allocation concealment, no blinding, high risk that intervention and control group were not comparable (Grabenbauer, 2003), small subgroups (Grabenbauer, 2003)

[uu] No randomization, no allocation concealment, no blinding, high risk that intervention and control group were not comparable, small subgroups

	Quality assessment						Summary of Findings				
Participants[jj] (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	Watchfull waiting		Risk with intervention	Risk difference with comparator only (95% CI)
months					n bias detected	bias					
Regional recurrence rate (IMPORTANT OUTCOME)											
364 (5 studies[vv]) 7-196 months	Very serious[ww]	No serious inconsistency	No serious indirectness	Serious imprecision	No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias	After sequential CRT: 0%; after induction chemo and concurrent CRT: 0%; after concurrent CRT: 0-16%	After sequential CRT: 10%; after induction chemo and concurrent CRT: 8%; after concurrent CRT: 5-12%			
Regional control (IMPORTANT OUTCOME)											
97 (1 study[xx])	Very serious[yy]	No serious inconsistenc	No serious indirectnes	Serious imprecision	No serious publication bias	⊕⊖⊖⊖ **VERY LOW** due to				80%	85%

[vv]   Data presented in Da Mosto, 2013 and Brizel, 2004 not considered since no recurrence rate reported for Gr 1

[ww]   No randomization, no allocation concealment, no blinding, high risk that intervention and control group were not comparable (Grabenbauer, 2003), very small subgroups (Goguen, 2006)

[xx]   Data presented in Da Mosto, 2013 not considered since no recurrence rate reported for Gr 1; data presented in Cannady, 2002 not considered since regional control rate calculated for Gr 1 and Gr 2 together.

[yy]   No randomization, no allocation concealment, no blinding, high risk that intervention and control group were not comparable, small subgroups

Quality assessment							Summary of Findings				
Participants[jj] (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	Watchfull waiting		Risk with intervention	Risk difference with comparator only (95% CI)
22-124 months		y	s			detected		high risk of bias			
Complications (IMPORTANT OUTCOME)											
43 (1 study) 4-127 months	Very serious[zz]	No serious inconsistency	No serious indirectness	Serious imprecision		No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias			8%	Not reported
Quality of Life (IMPORTANT OUTCOME)											
103 (1 study) 12 months	Very serious[aaa]	No serious inconsistency	No serious indirectness	Serious imprecision		No serious publication bias detected	⊕⊖⊖⊖ **VERY LOW** due to high risk of bias			See text	See text

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[zz]   No randomization, no allocation concealment, no blinding, unclear comparability and unclear concurrent inclusion of intervention and control group, small subgroups

[aaa]   No randomization, no allocation concealment, no blinding, high risk that intervention and control group were not comparable, small subgroups, heterogenous ND group

5.7. RQ8: IMRT for patients with locally advanced HNSCC

Included studies: RCTs: a) (Gupta *et al.*, 2012),[41] b) (Nutting *et al.*, 2011),[67] c) [49] (ref 16); Observational studies: d) [49] (ref 7), e) [49] (ref 9), f) [49] (ref 11), g) [49] (ref 12); h) [59,59] i) [60,60] j) [75,75] k) [62,62] l) [63,63] m) [64,64] n) [65,65] o) [66]

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Otherconsiderations	IMRT	Conv/ConfRT	Effect	Quality	Importance
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	42 (48%) 5 (80%)	55 (60%) 8 (50%)	p=0.18 NS	⊕○○○ VERY LOW	CRITICAL
2	observational studies	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22 (64%) 110 (85%)	27 (66%) 149 (69%)	Multivariate analysis p=0.73 Multivariate analysis HR=2.11 (95%CI 1.06 to 4.17)	⊕○○○ VERY LOW	CRITICAL
2	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[6]	none	32 47	28 47	3-year Kaplan–Meier estimates: 68% (95% CI 51.2 to 84.8%) vs 80.5% (95% CI 66.1 to 94.9%) 14/47 vs 18/47; HR=0.68 (95% CI 0.34 to 1.37) Estimated 2-year overall survival 78% (63 to 88) vs 76% (95% CI 60 to 86) (absolute difference 2%, 95% CI 20 to 16)	⊕○○○ VERY LOW	CRITICAL
7	observational studies[7]	serious[1]	serious[4]	no serious indirectness	no serious imprecision[8]	none	41 (91%) 22 (67%) 27 (87%) 110(92	71 (81%) 27 (77%) 24 (86%) 149(75	p=0.10 p=0.70 p=0.43 p<0.001 p=0.29 p=0.5	⊕○○○ VERY LOW	CRITICAL

							G1	G2	Effect	Quality	Importance
							%)	%)	NS		
							42 (56%)	55 (73%)			
							110(64%)	135(61%)			
							5 (80%)	8 (50%)			
2	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[6]	none	32	28	3-year Kaplan–Meier estimates: 70.6% (95% CI 53 to 88.2%) vs 88.2% (95% CI 75.4 to 100%)	⊕◯◯◯ VERY LOW	CRITICAL
							47	47	2-year locoregional PFS was 80% (95% CI 65 to 90) in the conventional RT group and 78% (62 to 87) in the IMRT group (absolute difference 3%, 95% CI –15 to 20; HR 1.53, 95% CI 0.63 to 3.70)		
6	observational studies[7]	serious[1]	no serious inconsistency	serious[9]	no serious imprecision	none	41 (95%)	71 (85%)	p=0.17	⊕◯◯◯ VERY LOW	CRITICAL
							27 (92%)	24 (87%)	p=0.44		
							110 (95%)	149 (84%)	p=0.005		
							42 (81%)	55 (66%)	p=0.38		
							31 (94%)	42 (68%)	p=0.008		
							110 (70%)	135 (71%)	p=0.7		
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[3,6]	none	47	47	Locoregional recurrences 12/47 vs 7/47: RR= 1.71 (95% CI 0.74 to 3.97)	⊕◯◯◯ VERY LOW	IMPORTANT
1	observational studies[10]	serious[1]	no serious inconsistency	no serious indirectness	very serious[3,6]	none	8/22 (36%)	13/27 (48%)	RR=0.98 (95%CI 0.47 to 2.06)	⊕◯◯◯ VERY LOW	IMPORTANT

№	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	n1	n2	Effect	Quality	Importance
1	observational studies[10]	serious[1]	no serious inconsistency	no serious indirectness	very serious[3,6]	none	0/22 (0%)	1/27 (4%)	RR=0.41 (95%CI 0.02 to 9.5)	⊕OOO VERY LOW	IMPORTANT
1	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[3,11]	none	47	47	Mean changes in global health status from baseline to 12 months (95% CI): 3.0 (–11.9 to 17.9) vs 1.1 (–9.9 to 12.1); MD= 1.90 (95% CI -16.13 to 19.93) At 24 months: 8.3 (–6.6 to 23.2) vs –2.8 (–17.1 to 11.6) MD= 11.10 (95% CI -9.01 to 31.21)	⊕OOO VERY LOW	CRITICAL

Health-related Quality of Life (follow-up 1 to 2 years)

№	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	n1	n2	Effect	Quality	Importance
2	observational studies[10]	serious[1]	no serious inconsistency	serious[9]	serious[11]	none	26 / 84	27 / 71	Eating (p=0.007), Speech (p=0.059), Aesthetics (p=0.069), Social disruption (p =0.115) Mean HR QoL at 1 (p<0.001) and 2 years (p<0.001) Mean global quality of life at 1 (p=0.20) and 2 years (p<0.001) Domain-specific quality of life: only significant differences for the salivary domain All estimates in favour of IMRT	⊕OOO VERY LOW	CRITICAL
2	observational studies[10]	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	75 / 30	88 / 10	'Benefit in favour of IMRT' Adjusted median XQ score IMRT 20 points better (p=0.2)	⊕OOO VERY LOW	CRITICAL
1	observational studies[10]	serious[1]	no serious inconsistency	serious[9]	no serious imprecision	none	61/84 (73%)	35/71 (49%)	Adjusted score at 2 years (p<0.05) in favour IMRT	⊕OOO VERY LOW	CRITICAL
2	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[6]	none	32	28	Late xerostomia and subcutaneous fibrosis assessed at 6, 12, 18, 24, 30, and 36 months using the RTOG late	⊕OOO VERY LOW	CRITICAL

								morbidity criteria: "At each time point, significantly lesser proportion of IMRT patients had physician-rated Grade 2 or worse xerostomia compared with 3D-CRT."		
								"Late xerostomia and subcutaneous fibrosis were also significantly lesser with IMRT at most time points."		
						47	44	Acute Xerostomia (Grade 2 to 4) 33/47 vs 40/44 (RR=0.77; 95% CI 0.63 to 0.95)		
						46	41	LENT-SOMA late Xerostomia (Grade 2 to 4) 38/46 vs 38/41 (RR=0.89; 95% CI 0.76 to 1.04)		
7	observational studies	serious[1]	no serious inconsistency	serious[5]	serious[3,6]	none	47 (40%) 41 (12%) 22 (36%) 27 (11%) 100 42 (81%) 110 (23%)	47 (74%) 71 (67%) 27 (82%) 24 (58%) 149 55 (93%) 135 (68%)	p=0.005 p<0.002 p=0.01 p<0.001 p<0.001 p=0.08 p<0.001 All differences in favour of IMRT	⊕○○○ VERY LOW	CRITICAL
2	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[6]	none	78	72	Acute mucositis Grade 2+ Pooled RR=0.91 (95% CI 0.83 to 1.00)	⊕○○○ VERY LOW	CRITICAL
6	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	19/22	24/27	RR=0.97, 95%CI 0.79 to 1.20 p=0.01	⊕○○○ VERY LOW	CRITICAL

No	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other	n1	n2	Effect	Quality	Importance
							27 (28%)	24 (12%)	p=0.33		
							73/110	111/149	p=0.07		
							42 (55%)	55 (73%)	p=0.03		
							110 (32%)	135 (44%)	RR=0.23, 95%CI 0.04 to 1.35		
							1/5	7/8	All differences, except one, infavour of IMRT		
2	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[3]	none	77	72	Acute dysphagia Grade 2+ Pooled RR=0.86 (95% CI 0.74 to 0.99)	⊕OOO VERY LOW	CRITICAL
5	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	22 (21%)	27 (59%)	p=0.02	⊕OOO VERY LOW	CRITICAL
							27 (17%)	24 (42%)	p<0.001		
							46/110	75/149	p=0.50		
							110 (11%)	135 (21%)	p=0.08		
							2/5	3/8	p>0.05 All differences, except one, infavour of IMRT		
2	randomised trials	serious[1]	no serious inconsistency	serious[5]	serious[3]	none	47	44	Significant differences were found for: Rash: RR=0.84 (95% CI 0.71 to 1.00) Fatigue: RR=1.82 (95% CI 1.23 to 2.70)(NB: in favour of conventional RT) Not significant: Skin: RR=0.63 (95% 0.34 to 1.15) Larynx: RR=0.71 (95% CI 0.31 to 1.63) Mandible: RR=1.19 (95% CI 0.64 to 2.21] Ear: RR=0.53 (95% CI 0.21 to 1.34)	⊕OOO VERY LOW	CRITICAL

| 6 | observational studies | serious [1] | no serious inconsistency | no serious indirectness | no serious imprecision | none | 22 27 110 42 110 5 | 27 24 149 55 135 8 | Significant differences in at least one study in favour of IMRT for 'any' Grade 3+ late toxicity, acute Grade 3-4 dermatitis, acute Grade 2 or 3 nausea, acute Grade 2 or 3 pain, incidence of late subcutaneous tissue toxicity and salivary glands toxicity.

No significant differences in at least one study for other adverse events (toxicities to pharynx, esophagus (3 studies), skin (3 studies), larynx (2 studies); radiation fibrosis of neck, trismus related to radiation (2 studies); edema with hoarseness and otitis media; mild to moderate hearing loss/tinnitus; hospitalization, weight loss and death; radionecrosis, neurologicaldamage; acute erythema; speech ability. | ⊕◯◯◯ VERY LOW | CRITICAL |

[1] *High risk of bias*
[2] *Small sample size*
[3] *Confidence interval includes both benefit and harm (or non-significant difference)*
[4] *Effects in both directions*
[5] *Studie(s) include(s) also patients with TNM stage 1 and 2*
[6] *OIS not reached*
[7] *Both prospective and retrospective studies*
[8] *Sample sizes apparently sufficiently large*
[9] *Includes patients with nasopharyngeal cancer*
[10] *Retrospective study / studies*
[11] *Small sample size (<400)*

5.8. RQ9: induction chemotherapy in patients with HNSCC

5.8.1. Induction chemotherapy with cisplatin and 5-fluorouracil for patients with stage 3 and 4 HNSCC

Included studies: SRs**:** a) Furness 2011, b) Ma 2012; RCTs: c) Forastiere 2013, d) Lefebvre 2012, e) Mitra 2006

		Quality assessment					No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)			
Overall survival											
14	RCTs (11 included from SRs (a, b); RCTs (c-e))	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	serious[3]	none	1380 90	1375 90	HR=0.87 (95% CI 0.79 to 0.95) 21% vs 16%[4]	⊕⊕⊕O MODERATE	CRITICAL
Quality of life											
1	RCT (c)	serious[5]	not applicable	no serious indirectness	very serious[6]	none	174	172	Impaired speech or voice during years 2 to 5 (% of patients): 3% to 9% vs 5% to 8.5% Swallowing dysfunction during years 2 to 5 (% of patients): 13% to 14% vs 10% to 17% "The ability to swallow only liquids was reported in less than 4% of patients in all groups, and	⊕OOO VERY LOW	CRITICAL

	Quality assessment						No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)			
									inability to swallow was reported in less than 3% of patients in all groups at any time point"		
Disease free survival											
6	RCTs (5 included from SRs (a,b); RCT (c))	no serious risk of bias	no serious inconsistency	no serious indirectness[2]	no serious imprecision	none	507	501	HR=0.76 (95%CI 0.66 to 0.87)	⊕⊕⊕⊕ HIGH	IMPORTANT
Local control											
2	RCTs (c,d)	no serious risk of bias[7]	no serious inconsistency	serious[8]	serious[9]	unlikely	174	172	HR=0.85 (95%CI 0.63 to 1.15)	⊕⊕OO LOW	IMPORTANT
							8/100	8/94	local failure: RR=0.94 (95%CI 0.37 to 2.40)		
Recurrence rate											
0											IMPORTANT
Adverse events – Grade III Acute toxicity (skin, mucous membrane, larynx, upper G.I., leucopenia)											
1	RCTs (e)	serious[10]	not applicable	no serious indirectness	serious[9]	serious[11]	88	90	No significant differences were found for skin, mucous membrane, larynx, upper G.I. and leucopenia.	⊕OOO VERY LOW	IMPORTANT

		Quality assessment					No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)			
Adverse events– Grade III+ Late toxicity (hematologic, skin, mucous membrane/stomatitis, subcutaneous tissue, salivary gland, pharynx/esophagus, larynx, upper G.I., genitourinary/renal, spinal cord, neurologic, bone, joint, other)											
2	RCTs (c,e)	serious[12]	no serious inconsistency	no serious indirectness	very serious[13]	serious[11]	242	248	No significant differences for subcutaneous tissue, larynx (pooled results) and for hematologic, skin, mucous membrane, salivary gland, pharynx/esophagus, upper G.I., genitourinary/renal, spinal cord, neurologic, bone and joint (results of single studies) Significant difference for category 'other'.	⊕○○○ VERY LOW	IMPORTANT
Post treatment mortality[14]											
2	RCTs (c,d)	no serious risk of bias	no serious inconsistency	serious	very serious	unlikely	274	266	RR=2.11 (95%CI 0.75 to 5.92]	⊕○○○ VERY LOW	IMPORTANT

[1] *Unclear risk of selection bias for most studies; no downgrading*

[2] *Some studies included stage II patients as well; no downgrading*

[3] *Confidence interval close to 'no effect'*

[4] *One RCT (Mitra 2006) did not present a Hazard ratio; not in meta-analysis*

[5] *One RCT with randomisation by Zelen's design*

[6] *Effect not quantified*

[7] *One RCT Zelen's design, other studies overall low risk of bias; no downgrading*

[8] *One RCT solely presents results for the induction chemotherapy arm vs surgery arm (not separately for induction chemotherapy + surgery + radiotherapy versus immediate surgery + radiotherapy)*

[9] *Confidence interval includes both benefits and harms*

[10] *High risk of bias on subjective outcomes (adverse events)*

[11] *Only the results of newly identified RCTs were considered. The review authors (Furness 2011) found very little quantitative data in the reports of the randomised controlled trials concerning harms associated with treatment, and almost all data were in a form unsuitable for analysis. Therefore they have reported only the benefits associated with chemotherapy, in terms of survival and response to treatment*

[12] *One RCT randomisation by Zelen's design, other RCT high risk of bias for subjective outcomes*

[13] *Wide confidence intervals. Most confidence intervals include both benefits and harms*

[14] *Definitions used: Forastiere, complications of protocol treatment; Lefebvre, ICT-related toxicity en Postoperatively (salvage surgery for local recurrence)*

5.8.2. Induction chemotherapy with platin-containing combinations other than cisplatin and 5-fluorouracil in patients with stage 3 and 4 HNSCC

Included studies: SRs**:** a) Furness 2011,[103] b) Ma 2012;[105] RCTs: c) Haddad 2013,[107] d) Zhong 2013[110]

No of studies	Design	Quality assessment					No of patients		Effect	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)			
Overall survival											
13	RCTs (11 included from SRs (a, b); RCTs (c,d))	no serious risk of bias[1]	no serious inconsistency	no serious indirectness	serious[3]	none	626	603	HR=1.01 (95%CI 0.89 to 1.16)	⊕⊕⊕O MODERATE	CRITICAL
Quality of life											
0											CRITICAL
Disease free survival											
2	RCTs (1 included from SRs (a,b); RCT (d))	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[4]	none	176	180	HR=0.97 (95%CI 0.69 to 1.37)	⊕⊕OO LOW	IMPORTANT
Local control											
1	RCT (c)	serious risk of bias[5]	not applicable	no serious indirectness	very serious[4]	unlikely	70	75	Total local or regional failure: RR=1.07 (95%CI 0.50 to 2.31)	⊕OOO VERY LOW	IMPORTANT

No of studies	Design	Quality assessment					No of patients		Effect	Quality	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)			
Recurrence rate											
1	RCT (d)	no serious risk of bias	not applicable	no serious indirectness	very serious[4]	unlikely	128	128	HR=1.02 (95%CI 0.62 to 1.52)	⊕⊕OO LOW	IMPORTANT
Adverse events – Grade III+ Toxicity (mucositis, febrile neutropenia, pain, xerostomia, neuropathy, trismus, dermatitis, dysphagia and odynophagia)											
2	RCTs (c,d)	no serious risk of bias	no serious inconsistency	no serious indirectness	serious[6]	serious[7]	181	188	Significant differences for mucositis (pooled results) and febrile neutropenia (results of single study). No significant differences for pain, xerostomia, neuropathy, trismus, dermatitis, dysphagia and odynophagia (results of single studies).	⊕⊕OO LOW	IMPORTANT
Adverse events – PEG tube placed											
1	RCTs (c)	no serious risk of bias	not applicable	no serious indirectness	serious[6]	serious[7]	55/70	64/75	RR=0.92 (95%CI 0.79 to 1.07)	⊕⊕OO LOW	IMPORTANT
Post treatment mortality											
2	RCTs (c,d)	no serious risk of bias	no serious inconsistency	no serious indirectness	very serious[8]	unlikely	70	75	"No treatment-related deaths occurred on this study."	⊕⊕OO LOW	IMPORTANT

	Quality assessment						No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)			
							128	128	"No chemotherapy-, surgery-, or radiotherapy-related deaths occurred"		

[1] Unclear risk of selection bias for most studies; no downgrading
[2] Some studies included stage II patients as well; no downgrading
[3] Wide confidence intervals. Most confidence intervals include both benefits and harms
[4] Wide confidence interval. Confidence interval includes both benefits and harms
[5] One RCT at high risk of performance bias, detection bias for subjective outcomes and reporting bias; unclear risk of attrition bias
[6] Confidence interval(s) include(s) both benefits and harms
[7] Only the results of newly identified RCTs were considered. The review authors (Furness 2011) found very little quantitative data in the reports of the randomised controlled trials concerning harms associated with treatment, and almost all data were in a form unsuitable for analysis. Therefore they have reported only the benefits associated with chemotherapy, in terms of survival and response to treatment
[8] No deaths occurred

5.8.3. Multi-agent induction chemotherapy without platin in patients with stage 3 and 4 HNSCC

Included studies: SRs: a) Furness 2011,[103] b) Ma 2012[105]

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)	Effect	Quality	Importance
			Quality assessment				No of patients				
Overall survival											
8	RCTs (8 included from SRs (a, b))	no serious risk of bias[1]	no serious inconsistency	no serious indirectness[2]	very serious[3]	none	420	412	HR=0.95 (95%CI 0.73 to 1.24)	⊕⊕OO LOW	CRITICAL
Quality of life											
0											CRITICAL
Disease free survival											
1	RCT (included from SRs (a,b))	no serious risk of bias	not applicable	no serious indirectness	very serious[3]	none	43	40	HR=0.92 (95%CI 0.48 to 1.76)	⊕⊕OO LOW	IMPORTANT
Local control											
0											IMPORTANT
Recurrence rate											
0											IMPORTANT
Adverse events											

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)	Effect	Quality	Importance
			Quality assessment				No of patients				
0											IMPORTANT

Post treatment mortality

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemo	No induction	Effect	Quality	Importance
0											IMPORTANT

[1] *Unclear risk of selection bias for most studies; no downgrading*
[2] *Some studies included stage II patients as well; no downgrading*
[3] *Wide confidence interval. Confidence interval includes both benefits and harms*

Single agent induction chemotherapy (methotrexate) in patients with stage 3 and 4 HNSCC

Included studies: SRs**:** a) Furness 2011,[103] b) Ma 2012[105]

No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)	Effect	Quality	Importance
			Quality assessment				No of patients		Effect	Quality	Importance
Overall survival											
5	RCTs (included from SRs (a,b))	no serious risk of bias	no serious inconsistency	no serious indirectness[1]	Serious[2]	none	436	445	HR=0.93 (95%CI 0.77 to 1.14)	⊕⊕⊕O MODERATE	CRITICAL

	Quality assessment						No of patients		Effect	Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Induction chemotherapy before locoregional therapy	No induction chemotherapy (but identical locoregional therapy)			
Quality of life											
0											CRITICAL
Disease free survival											
0											IMPORTANT
Local control											
0											IMPORTANT
Recurrence rate											
0											IMPORTANT
Adverse events											
0											IMPORTANT
Post treatment mortality											
0											IMPORTANT

[1] *Some studies included stage II patients as well; no downgrading*
[2] *Confidence interval includes both benefits and harms*

5.9. RQ10: primary CRT for patients with non-resectable M0 HNSCC

5.9.1. Primary CRT for patients with non-resectable (T4b) M0 HNSCC

Included studies: RCTs: a) Bensadoun 2006,[118] b) Budach 2005,[119] c) Chauhan 2008,[114] d) Quon 2011,[117] e) RuoRedda 2010;[112] f) Semrau 2006[116]

No of studies	Design	Quality assessment					Summary of findings				Importance
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	No of patients		Effect	Quality	
							Primary chemoradiotherapy	Primary radiotherapy			
Overall survival (2 years)											
2	randomised trials (a,b)	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	81 190	82 194	37.8% vs 20.1% (p=0.038) 48.0 (95% CI 41.3 to 55.9) vs 38.2 (95% CI 31.9 to 45.8)	⊕⊕OO LOW	CRITICAL
Overall survival (3 years)											
2	randomised trials (b,e)	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	190 80	194 77	37.5 (95% CI 31.1 to 45.4) vs 28.6 (95% CI 22.8 to 36.0) 28.9% vs 11.1%	⊕OOO VERY LOW	CRITICAL
Overall survival (5 years)											
3	randomised trials (b,e,f)	serious[4]	no serious inconsistency	serious[1]	serious[2]	none	190 80 113	194 77 127	28.6 (22.5 to 36.3) vs 23.6 (18.2 to 30.9) HR= 0.71; 95% CI, 0.52 to 0.96 9.0% vs 6.9% 25.6% (95% CI 15.8 to 35.4%) vs 15.8% (95% CI 9.1 to 22.4%) (p=0.016)	⊕OOO VERY LOW	CRITICAL
Overall survival (10 years)											
1	randomised trials (e)	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	80	77	5.5% vs 6.9%	⊕⊕OO LOW	CRITICAL

	Quality assessment						Summary of findings				Importance
							No of patients		Effect	Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Primary chemoradiotherapy	Primary radiotherapy			
Median survival (months)											
3	randomised trials (a,b,d)	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	81	82	16 (95% CI 12-22) vs 10 (95% CI 8-14)	⊕⊕OO LOW	
							190	194	23 vs 16		
							149	159	11.8 vs 13.3 (p =0.81)		
Disease-free survival (2 years)											
1	randomised trials (a)	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	81	82	48.2% vs. 25.2% (p=0.002)	⊕⊕⊕O MODERATE	CRITICAL
Disease-free survival (3 years)											
1	randomised trials (e)	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	80	77	16% vs 9.0%	⊕⊕OO LOW	CRITICAL
Disease-free survival (5 years)											
1	randomised trials (e)	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	80	77	6.8% vs 5.5%	⊕⊕OO LOW	CRITICAL
Disease-free survival (10 years)											
1	randomised trials (e)	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	80	77	6.8% vs 5.5%	⊕⊕OO LOW	CRITICAL
Quality of life											
0	no evidence available										CRITICAL
Local control (2 years)											
2	randomised trials (a,b)	no serious limitations	no serious inconsistency	serious[1]	serious[2]	none	81	82	58.87% vs 27.5% (p=0.0003)	⊕⊕OO LOW	IMPORTANT
							190	194	57.7 (50.6 to 65.9) vs		

		Quality assessment					Summary of findings				Importance
							No of patients		Effect	Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Primary chemoradiotherapy	Primary radiotherapy			
									42.4 (35.3 to 50.8)		

Local control (3 years)

2	randomised trials (b,e)	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	190	194	51.8 (44.4 to 60.4) vs 39.2 (32.2 to 47.8)	⊕⊕OO VERY LOW	IMPORTANT
							80	77	21.7% vs 15.0%		

Local control (5 years)

3	randomised trials (b,e,f)	serious[4]	no serious inconsistency	serious[1]	serious[2]	none	190	194	49.9 (42.3 to 58.7) vs 37.4 (30.4 to 46.0) (p=0.001)	⊕OOO VERY LOW	IMPORTANT
							80	77	HR= 0.48 (95% CI, 0.33 to 0.71)		
							113	127	15.1% vs 10.7%		
									22.7% (95% CI, 13.3–32.0%) vs 12.6%(95% CI, 6.6 – 18.6%) (p=0.01)		

Local control (10 years)

1	randomised trials (e)	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	80	77	15.1% vs 10.7%	⊕⊕OO LOW	IMPORTANT

Median locoregional control surviving time (months)

1	randomised trials (b)	serious[3]	no serious inconsistency	serious[1]	serious[2]	none	190	194	48 vs 15	⊕OOO VERY LOW	IMPORTANT

Acute toxicity

2	randomised trials (c,d)	serious[6]	serious[7]	serious[1]	serious[2]	none	40	40	Significantly more toxicity for chemoradiotherapy vs radiotherapy for	⊕OOO VERY LOW	IMPORTANT

	Quality assessment						Summary of findings		Effect	Quality	Importance
							No of patients				
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Primary chemoradiotherapy	Primary radiotherapy			
							149	159	Grade I and II haemoglobin level, Level 5 and 6 skin reactions and Level 5 oral mucosal reactions. Significant weight loss for chemoradiotherapy during later half of treatment. Only mild nausea and vomiting.		
									"The addition of weekly cisplatin significantly increased the frequency and severity of nausea/vomiting (p <0.001) and of neurologic (p=0.002), renal (p < 0.001), and hematologic toxicities (p < 0.001)." Increased mild to moderate respiratory toxicities. No significant increase of laryngeal edema and nutritional toxicity.		
Acute toxicity - Grade 3-4											
5	randomised trials (a,b,d,e,f,)	serious[8]	no serious inconsistency	serious[1]	serious[2]	none	443 194	463 209	Pooled estimates Mucositis: RR = 1.05 (95% CI 0.95 to	⊕ΟΟΟ VERY LOW	IMPORTANT

	Quality assessment						Summary of findings			Importance
							No of patients		Effect	Quality
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Primary chemoradiotherapy	Primary radiotherapy		
									1.16)	
							193	204	Dermatitis: RR = 1.20 (95% CI 0.90 to 1.62)	
							193	204	Anemia: RR = 2.06 (95% CI 0.37 to 11.62)	
							193	204	Leukopenia: RR = 29.62 (95% CI 4.15 to 211.63) Thrombocytopenia: RR = 8.63 (95% CI 1.11 to 67.05)	

Single study evidence
Significant differences for erythema (RR = 0.69 (95% CI 0.52 to 0.90), moist desquamation (RR = 0.65 (95% CI 0.49 to 0.86) and vomiting under therapy (RR= 5.06 (95% CI 1.12 to 22.92).
No significant differences nausea and diarrhea, neutropenia, pigmentation, dysphagia, xerostomiadysgeusia, laryngeal edema and nutritional toxicity.

		Quality assessment					Summary of findings				Importance
							No of patients		Effect	Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Primary chemoradiotherapy	Primary radiotherapy			
Late toxicity											
3	randomised trials (d,e,f)	serious[9]	no serious inconsistency	serious[1]	serious[2,10]	none	149	159	No significant differences for toxicity of skin, mucous membrane, subcutaneous tissue. Significant more toxicity of esophagus and larynx.	⊕◯◯◯ VERY LOW	IMPORTANT
							80	77	No significant differences		
							113	127	No significant differences for xerostomia, sense of taste, lymph edema, skin induration, skin pigmentation, skin fibrosis, hearing problems, skin ulcers and osteoradionecrosis.		
Late toxicity - Grade 3 (at 12 months and at 24 months)											
1	randomised trials (a)	serious[11]	no serious inconsistency	no serious indirectness	very serious[10]	none	81	82	No significant differences for xerostomia, chronic mucositis, mucosal necrosis, mandibular necrosis, dysphagia, trismus, subcutaneous sclerosis, chronic dermatitis, laryngeal edema and hypoacousia.	⊕◯◯◯ VERY LOW	IMPORTANT

No of studies	Design	Quality assessment					Summary of findings				Importance
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	No of patients		Effect	Quality	
							Primary chemoradiotherapy	Primary radiotherapy			
Late toxicity - Grade 3-4											
1	randomised trials (b)	serious[12]	no serious inconsistency	serious[1]	serious[13,14]	none	190	194	No significant differences for xerostomia, dysgeusia, dysphagia, telangiectasia, skin fibrosis, trismus, transient plexopathia, osteoradionecrosis, pigmentation, lymphedema, mucosal necrosis, transient L'Hermite's syndrome.	⊕◯◯◯ VERY LOW	IMPORTANT
Recurrence rate											
2	randomised trials (a,c)	serious[14]	no serious inconsistency	serious[1]	serious[2]	none	81	82	Locoregional and distant tumour failure, or uncontrolled disease: RR=0.81; 95% CI 0.68 to 0.96	⊕◯◯◯ VERY LOW	IMPORTANT
							40	40	Relapses: Primary: 0/30 vs 3/30 (RR=0.14; 95% CI 0.01 to 2.65) Nodal: 0/30 vs 3/30 (RR=0.14; 95% CI 0.01 to 2.65) Distant: 0/30 vs 1/30 (RR=0.33; 95% CI 0.01 to 7.87)		

[1] Includes study/studies with mixed population, not solely T4b.

[2] Precision not quantified

[3] Unclear risk of selection bias

[4] High risk of reportingbias (one study), unclear risk of selection bias (three studies) and attrition bias (one study)

[5] Wide confidence interval.

[6] High risk of performance bias and detection bias in subjective outcomes for both studies and high risk of other bias for one of the studies; unclear risk of selection biasandreporting bias for one of the studies, unclear risk of attrition bias for the other study.

[7] Opposing statements of the two studies.

[8] High risk of performance bias and detection bias in subjective outcomes for all studies, high risk of attrition bias in subjective outcomes for one study and hig risk of reporting bias for one study; unclear risk of selection bias (three studies) and attrition bias in subjective outcomes (two studies).

[9] High risk of performance bias and detection bias in subjective outcomes (three studies), reporting bias (one study) and other bias (one study); unclear risk of selection bias (and attrition bias (two studies).

[10] Wide confidence intervals, including both benefit and harm.

[11] High risk of performance bias and detection bias in subjective outcomes

[12] High risk of performance bias, detection bias in subjective outcomes and attrition bias in subjective outcomes, unclear risk of selection bias (allocation concealment).

[13] Confidence intervals include both benefit and harm.

[14] High risk of performance bias and detection bias in subjective outcomes for both studies, unclear selection bias and reporting bias in one study.

5.9.2. Combination of EGFR-inhibitors and radiotherapy for patients with non-resectable (T4b) M0 HNSCC?

Included studies: RCTs: a) Rodriguez 2010[115]

No of studies	Design	Quality assessment					Summary of findings				Quality	Importance
		Limitations	Inconsistency	Indirectness	Imprecision	Otherconsiderations	No of patients		Effect			
							Primary treatment with EGFR-inhibitors combined with radiotherapy	Primaryradiotherapy	Relative (95% CI)	Absolute		
Overall survival (follow-up median 45.2 months)												
1	randomised trials (a)	serious[1]	no serious inconsistency	serious[2]	very serious[3]	none	9/54 (16.7%)	5/51 (9.8%)	RR 1.70 (0.61 to 4.73)	69 more per 1000 (from 38 fewer to 366 more)	⊕◯◯◯ VERY LOW	CRITICAL
Disease-free survival												
0	no evidence											CRITICAL

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Otherconsiderations	No of patients		Effect		Quality	Importance
							Primary treatment with EGFR-inhibitors combined with radiotherapy	Primaryradiotherapy	Relative (95% CI)	Absolute		
	available											
Quality of life												
1	randomised trials (a)	serious[1]	no serious inconsistency	serious[2]	serious[4]	none	54	51	"Differences between the two groups were only found in relation with the general pain evaluation at month six. Patients treated with placebo referred less pain than patients treated with nimotuzumab. In summary, a quality of life increase and a reduction of the general and specific symptoms of the disease for both groups during the trial were detected. No negative impact of the use of nimotuzumab as compared to placebo was detected regarding quality of life."		⊕OOO VERY LOW	CRITICAL
Local control												
0	no evidence available											IMPORTANT

	Quality assessment						Summary of findings				Quality	Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Otherconsiderations	Primary treatment with EGFR-inhibitors combined with radiotherapy	Primaryradiotherapy	Relative (95% CI)	Absolute		
Adverse events (Common Toxicity Criteria of the US National Cancer Institute, Version 2, April 30, 1999 (NCI-CTC, Version 2))												
1	randomised trials (a)	serious[1]	no serious inconsistency	serious[2]	serious[5]	none	38/54 (70.4%)	30/52 (57.7%)	RR 1.22 (0.91 to 1.63)	127 more per 1000 (from 52 fewer to 363 more)	⊕OOO VERY LOW	IMPORTANT
Recurrencerate												
0	no evidence available											IMPORTANT

[1] Unclear risk of selection, attrition and reporting bias
[2] Population consists of grade III/IV HNSCC; unclear how many T4b patients.
[3] Large confidence interval, includes both benefit and harm.
[4] No quantification of results
[5] Confidence interval includes both benefit and harm.

5.10. RQ11: interventions for M+ disease or recurrent disease not suitable for curative treatment

5.10.1. Chemoradiotherapy versus BSC for M+ HNSCC or recurrent HNSCC not suitable for curative treatment

Included studies: RCTs: a) Leon 2005[121]

No of studies	Design	Quality assessment					No of patients chemoradiotherapy	No of patients best supportive care	Effect	Quality	Importance
		Limitations	Inconsistency	Indirectness	Imprecision	Publication bias					
Quality of life											
0	no evidence available										CRITICAL
Adverse events											
0	no evidence available										CRITICAL
Overall survival (1 year)											
1	observational studies (a)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	15	68	6.7% (0.0–19.3) vs 0% p=0.0001 (Log rank test)	⊕OOO VERY LOW	IMPORTANT
Median days of survival (Better indicated by lower values)											
1	observational studies (a)	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	15	68	212 (95% CI 154–274) vs 56.5 (95% CI 46–67)	⊕OOO VERY LOW	IMPORTANT

[1] High risk of bias

[2] IOS not reached

[3] Insufficient information to evaluate the imprecision of results, however, IOS was also not reached

5.10.2. Chemotherapy versus BSC for M+ HNSCC or recurrent HNSCC not suitable for curative treatment

Included studies: RCTs: a) Leon 2005;[121] b) Zafereo 2009[123]

No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	No of patients chemotherapy	best supportive care	Effect	Quality	Importance
Quality of life											
0	no evidence available										CRITICAL
Adverse events											
0	no evidence available										CRITICAL
Overall survival (1 year)											
2	observational studies (a,b)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43 / 70	68 / 39	2.3% (0.0–6.8) vs 0% p=0.0011 (Log rank test) 32% vs 13% (p=0.04)	⊕OOO VERY LOW	IMPORTANT
Overall survival (3 years)											
1	observational studies (b)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70	39	4% vs 5%	⊕OOO VERY LOW	IMPORTANT
Overall survival (5 years)											
1	observational studies (b)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	70	39	0% vs 0%	⊕OOO VERY LOW	IMPORTANT
Median days of survival											
1	observational studies (a)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	43	68	107 (95%CI 83–135) vs 56.5 ((95% CI 46–67)	⊕OOO VERY LOW	IMPORTANT

[1] High risk of bias
[2] Insufficient information to evaluate the imprecision of results, however, IOS was also not reached

5.10.3. Radiotherapy versus BSC for M+ HNSCC or recurrent HNSCC not suitable for curative treatment

Included studies: RCTs: a) Leon 2005;[121] b) Zafereo 2009[123]

| No of studies | Quality assessment | | | | | | Summary of findings | | | | Importance |
| | Design | Limitations | Inconsistency | Indirectness | Imprecision | Publication bias | No of patients | | Effect | Quality | |
							radiotherapy	best supportive care	Relative (95% CI) Absolute		
Quality of life											
0	no evidence available										CRITICAL
Adverse events											
0	no evidence available										CRITICAL
Overall survival (1 year)											
1	observational studies (a)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	68	12% (0.0–24.7) vs 0% p=0.0001 (Log rank test)	⊕◯◯◯ VERY LOW	IMPORTANT
Overall survival (3 years)											
1	observational studies (b)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	39	32% vs 5%	⊕◯◯◯ VERY LOW	IMPORTANT
Overall survival (5 years)											
1	observational studies (b)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	18	39	32% vs 0%	⊕◯◯◯ VERY LOW	IMPORTANT
Median days of survival											
1	observational studies (a)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	25	68	188 (95% CI 139–280) vs 56.5 (95% CI 46–67)	⊕◯◯◯ VERY LOW	IMPORTANT

[1] High risk of bias
[2] Insufficient information to evaluate the imprecision of results, however, IOS was also not reached.

5.10.4. Salvage surgery versus BSC for M+ HNSCC or recurrent HNSCC not suitable for curative treatment

Included studies: RCTs: a) Zafereo 2009[123]

	Quality assessment						Summary of findings				Importance
							No of patients		Effect	Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	salvage surgery	supportive care			
Quality of life											
0	no evidence available										CRITICAL
Adverse events											
0	no evidence available										CRITICAL
Overall survival (3 years)											
1	observational studies (a)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41	39	42% vs 5%	⊕◯◯◯ VERY LOW	IMPORTANT
Overall survival (5 years)											
1	observational studies (a)	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	41	39	28% vs 0%	⊕◯◯◯ VERY LOW	IMPORTANT

[1] *High risk of bias*
[2] *Insufficient information to evaluate the imprecision of results, however, IOS was also not reached.*

5.10.5. Anti-EGFR plus BSC versus BSC alone for M+ HNSCC or recurrent HNSCC not suitable for curative treatment

Included studies: RCTs: a) Machiels 2011[122]

		Quality assessment					Summary of findings				Importance
							No of patients		Effect	Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Publication bias	EGFR-inhibitor plus best supportive care	best supportive care			
Quality of life											
1	randomised trials (a)	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	191	95	"The quality of life assessment indicated that adding zalutumumab to best supportive care did not adversely affect quality of life."	⊕⊕OO LOW	CRITICAL
Adverse events - Grade 3-4											
1	randomised trials (a)	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	191	95		⊕⊕OO LOW	CRITICAL
Median overall survival (months)											
1	randomised trials (a)	serious[2]	no serious inconsistency	no serious indirectness	serious[1]	none	191	95	6.7 (95% CI 5.8 to 7.0) vs 5.2 (4.1 to 6.4) (p=0.065)	⊕⊕OO LOW	IMPORTANT
Overall survival (18 months)											
1	randomised trials (a)	serious[2]	no serious inconsistency	no serious indirectness	serious[3]	none	191	95	HR: 0.77 (97.06% CI 0.57 to 1.05)	⊕⊕OO LOW	IMPORTANT

[1] Results not quantified / IOS not reached.
[2] High risk of bias.
[3] Wide confidence interval/ confidence interval includes both benefit and harm

6. FOREST PLOTS

6.1. RQ1: PET/CT in the staging of oral cavity cancer

6.1.1. Detection of cervical lymph nodes: PET (patient-based)

Figure 37 – Forest plot: detection of cervical lymph nodes with PET (patient-based analysis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brouwer 2004	2	1	1	11	0.67 [0.09, 0.99]	0.92 [0.62, 1.00]
Liao 2011	164	110	47	152	0.78 [0.72, 0.83]	0.58 [0.52, 0.64]
Myers 1998a	5	0	2	7	0.71 [0.29, 0.96]	1.00 [0.59, 1.00]
Myers 1998b	4	0	0	7	1.00 [0.40, 1.00]	1.00 [0.59, 1.00]
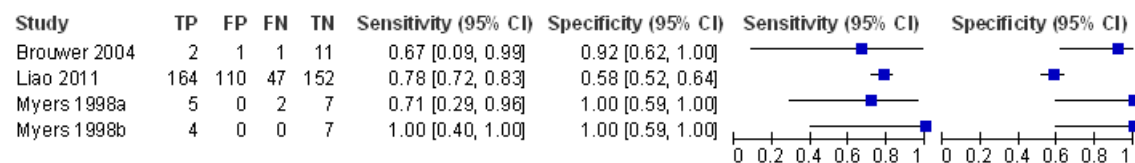
Figure 38 – SROC curve: detection of cervical lymph nodes with PET (patient-based analysis)
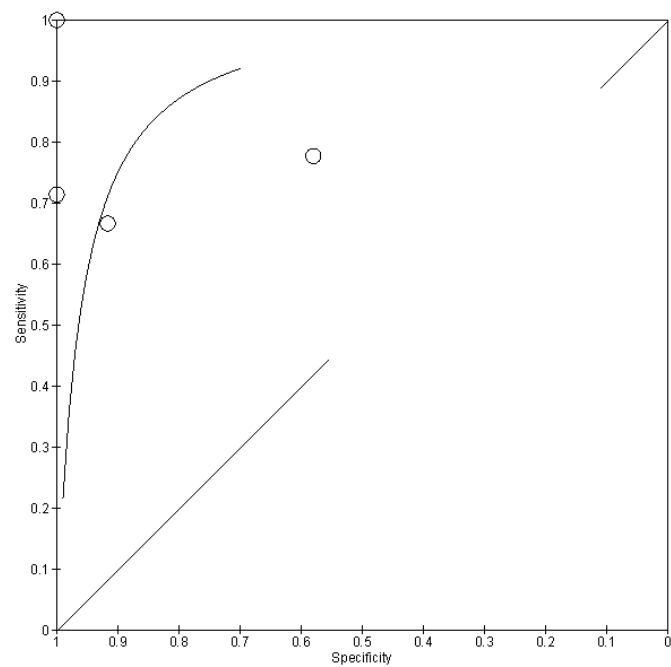
Figure 39 – Meta-analysis: detection of cervical lymph nodes with PET (patient-based analysis)

```
Log likelihood  = -15.147238                    Number of studies =       4

              |    Coef.    Std. Err.     z     P>|z|     [95% Conf. Interval]
--------------+------------------------------------------------------------------
Bivariate     |
  E(logitSe)  |  1.255796    .1884582                     .8864242    1.625167
  E(logitSp)  |  2.455466    1.268844                    -.0314218    4.942355
 Var(logitSe) |  .0000302    .0019606                     1.79e-60    5.10e+50
 Var(logitSp) |  2.583263    3.651267                     .1618278    41.23672
 Corr(logits) |  .4569302    .5503056                    -.7012569    .9523654
--------------+------------------------------------------------------------------
HSROC         |
       Lambda |  21.61671    344.1484                    -652.9018    696.1352
        Theta |  10.66475    174.4028                    -331.1584    352.4879
         beta |  5.678064    32.42711    0.18   0.861     -57.8779    69.23403
       s2alpha|  .0257446    .8365916                     5.63e-30    1.18e+26
       s2theta|  .0023991    .0777806                     6.07e-31    9.48e+24
--------------+------------------------------------------------------------------
Summary pt.   |
           Se |  .7783015    .0325181                     .7081517    .8355065
           Sp |  .9209603    .0923622                     .4921452    .9929128
          DOR |   40.9054    52.60583                     3.289307    508.6942
          LR+ |  9.846967     11.5213                     .9939547    97.5525
          LR- |  .2407254    .0431224                     .1694501    .341981
        1/LR- |  4.154111    .7441472                     2.924139    5.901443
--------------+------------------------------------------------------------------

Covariance between estimates of E(logitSe) & E(logitSp)    .0042042
```

6.1.2.   Detection of cervical lymph nodes: PET (neck-side-based)

Figure 40 – Forest plot: detection of cervical lymph nodes with PET (neck-side-based analysis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Haerle 2011b	27	2	2	5	0.93 [0.77, 0.99]	0.71 [0.29, 0.96]
Kim 2011	74	13	15	126	0.83 [0.74, 0.90]	0.91 [0.85, 0.95]
Ozer 2012	165	24	30	94	0.85 [0.79, 0.89]	0.80 [0.71, 0.87]
Schoder 2006	6	4	3	23	0.67 [0.30, 0.93]	0.85 [0.66, 0.96]
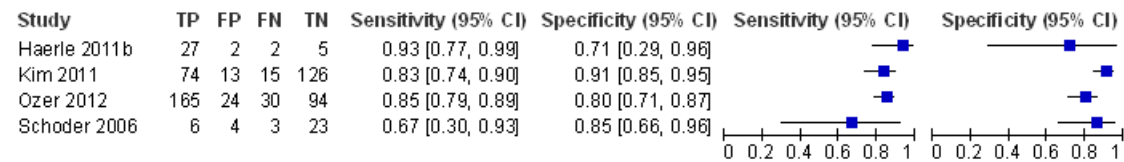
Figure 41 – HSROC curve: detection of cervical lymph nodes with PET (neck-side-based analysis)
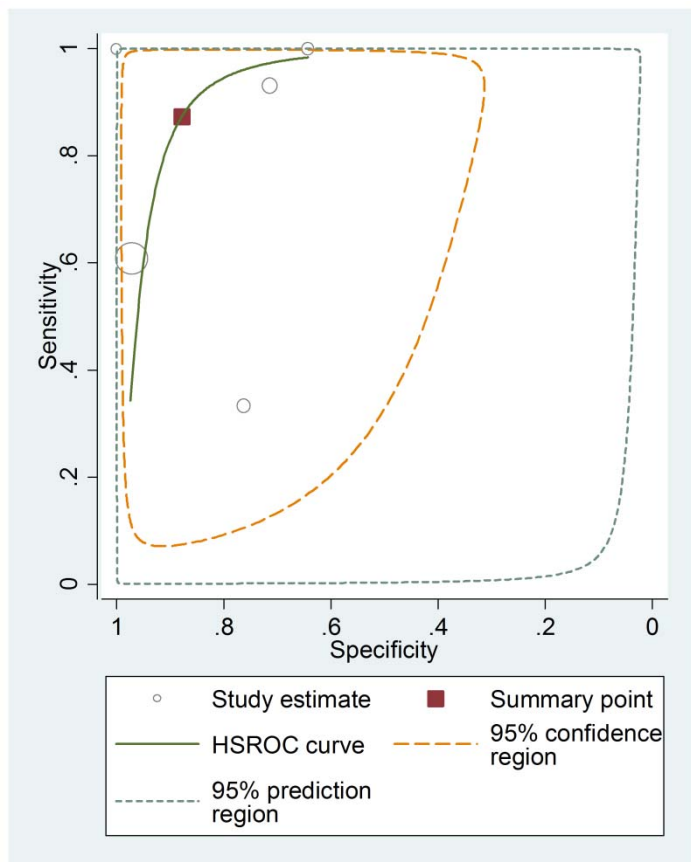
Figure 42 – Meta-analysis: detection of cervical lymph nodes with PET (neck-side-based analysis)

```
Log likelihood   = -23.607573                   Number of studies =        5

                   Coef.   Std. Err.      z     P>|z|     [95% Conf. Interval]

Bivariate
  E(logitSe)    1.973813   1.109855                      -.2014621    4.149088
  E(logitSp)     1.97625   .6396913                       .7224781    3.230022
Var(logitSe)    3.35983    3.594625                       .4126969     27.3529
Var(logitSp)   1.345346   1.244048                        .219646    8.240326
Corr(logits)   -.2237155    .59249                      -.8956937     .759434

HSROC
      Lambda   4.054478   1.214925                       1.673268    6.435688
       Theta  -.4571106   .7779313                      -1.981828    1.067607
        beta  -.4576197   .6977726    -0.66   0.512     -1.825229    .9099895
      s2alpha  3.300855   3.573038                        .395582    27.54333
      s2theta  1.300846   1.087635                        .252661    6.697518

Summary pt.
          Se   .8780201   .1188663                       .4498041    .9844663
          Sp   .8782808   .0683853                       .6731525    .9619485
         DOR   51.93864   62.06033                       4.993542    540.2222
         LR+   7.213491   4.023635                       2.417415    21.52483
         LR-   .1388849   .1341424                       .0209179    .9221276
       1/LR-   7.200209   6.954349                       1.084449    47.80587

Covariance between estimates of E(logitSe) & E(logitSp)  -.1066247
```

6.1.3. Detection of cervical lymph nodes: PET (node-based)

Figure 43 – Forest plot: detection of cervical lymph nodes with PET (node-based analysis)
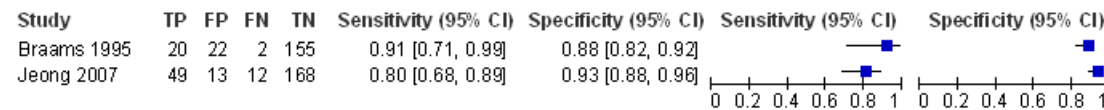
6.1.4. Detection of cervical lymph nodes: non-enhanced PET/CT (patient-based)

Figure 44 – Forest plot: detection of cervical lymph nodes with non-enhanced PET/CT (patient-based analysis)
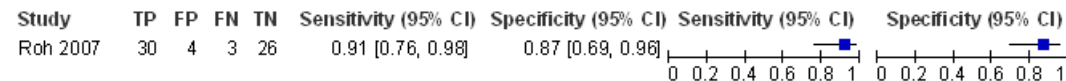
6.1.5. *Detection of cervical lymph nodes: non-enhanced PET/CT (neck-side-based)*

Figure 45 – Forest plot: detection of cervical lymph nodes with non-enhanced PET/CT (neck-side-based analysis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Haerle 2011b	27	2	2	5	0.93 [0.77, 0.99]	0.71 [0.29, 0.96]
Kim 2011	74	13	15	126	0.83 [0.74, 0.90]	0.91 [0.85, 0.95]
Ozer 2012	165	24	30	94	0.85 [0.79, 0.89]	0.80 [0.71, 0.87]
Schoder 2006	6	4	3	23	0.67 [0.30, 0.93]	0.85 [0.66, 0.96]
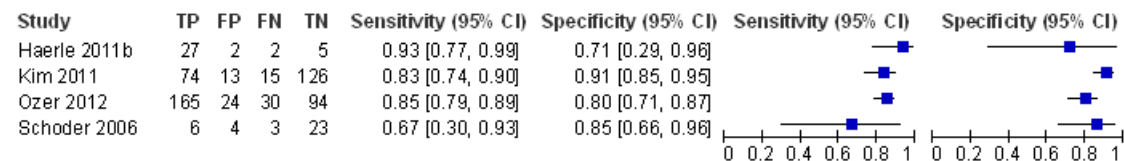
Figure 46 – HSROC curve: detection of cervical lymph nodes with non-enhanced PET/CT (neck-side-based analysis)
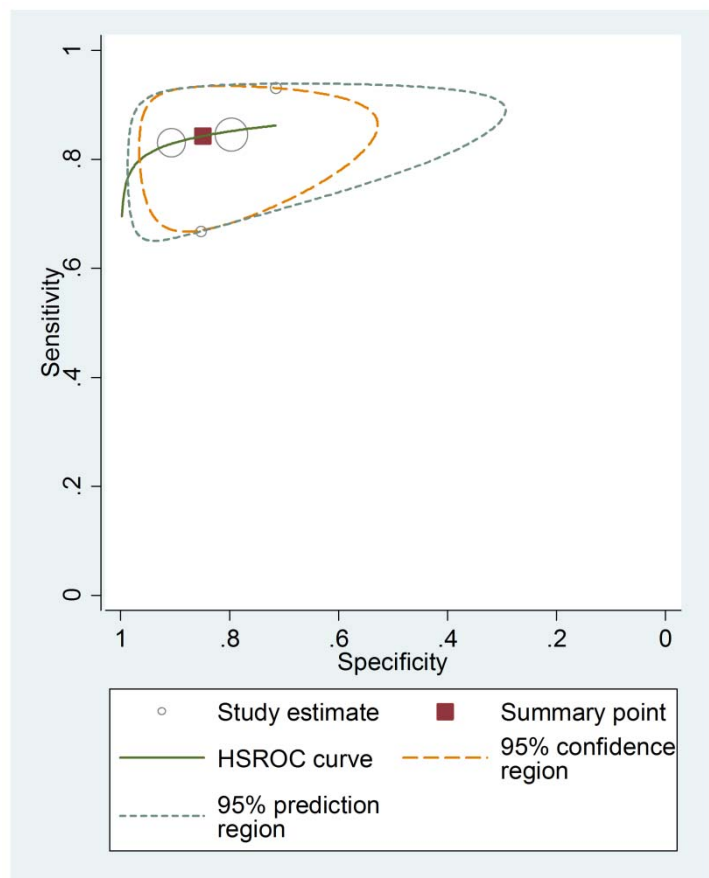
Figure 47 – Meta-analysis: detection of cervical lymph nodes with non-enhanced PET/CT (neck-side-based analysis)

```
Log likelihood   = -19.182689                    Number of studies =        4

                |    Coef.    Std. Err.     z     P>|z|     [95% Conf. Interval]
----------------+----------------------------------------------------------------
Bivariate       |
    E(logitSe)  |  1.683686    .1600172                     1.370058    1.997314
    E(logitSp)  |  1.727699    .2622681                     1.213663    2.241735
  Var(logitSe)  |  .0040563    .0231085                     5.74e-08    286.6642
  Var(logitSp)  |  .1105188    .1579259                      .006716    1.818699
  Corr(logits)  |       -1          .                             .           .
----------------+----------------------------------------------------------------
HSROC           |
      Lambda    |  4.602901    4.341231                    -3.905754    13.11156
       Theta    |  1.545242    3.200924                    -4.728454    7.818938
        beta    |  1.652457    2.761068    0.60    0.550    -3.759138    7.064052
      s2alpha   |  1.98e-08          .                             .           .
      s2theta   |   .021173    .0656877                      .0000484    9.259101
----------------+----------------------------------------------------------------
Summary pt.     |
          Se    |   .843392    .0211354                      .7973895    .8805148
          Sp    |  .8491179    .0336009                      .7709465    .9039352
         DOR    |  30.30719    8.604318                      17.37347    52.86945
         LR+    |  5.589741    1.229592                      3.632037    8.602666
         LR-    |  .1844362    .0247617                      .1417644    .2399524
       1/LR-    |  5.421931    .7279273                      4.167494    7.053959
----------------+----------------------------------------------------------------

Covariance between estimates of E(logitSe) & E(logitSp)  -.0068944
```

6.1.6. *Detection of cervical lymph nodes: non-enhanced PET/CT (node-based)*

Figure 48 – Forest plot: detection of cervical lymph nodes with non-enhanced PET/CT (node-based analysis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hoshikawa 2012	38	3	21	402	0.64 [0.51, 0.76]	0.99 [0.98, 1.00]
Jeong 2007	56	2	5	179	0.92 [0.82, 0.97]	0.99 [0.96, 1.00]
Kim 2011	129	36	34	700	0.79 [0.72, 0.85]	0.95 [0.93, 0.97]
Matsubara 2012	37	12	11	438	0.77 [0.63, 0.88]	0.97 [0.95, 0.99]
Murakami 2007	15	1	4	92	0.79 [0.54, 0.94]	0.99 [0.94, 1.00]
Pentenero 2008	0	5	3	71	0.00 [0.00, 0.71]	0.93 [0.85, 0.98]
Piao 2009	71	24	14	236	0.84 [0.74, 0.91]	0.91 [0.87, 0.94]
Richard 2010	87	24	18	375	0.83 [0.74, 0.90]	0.94 [0.91, 0.96]
Roh 2007	54	16	6	248	0.90 [0.79, 0.96]	0.94 [0.90, 0.96]
Schoder 2006	6	6	3	127	0.67 [0.30, 0.93]	0.95 [0.90, 0.98]

Figure 49 – HSROC curve: detection of cervical lymph nodes with non-enhanced PET/CT (node-based analysis)
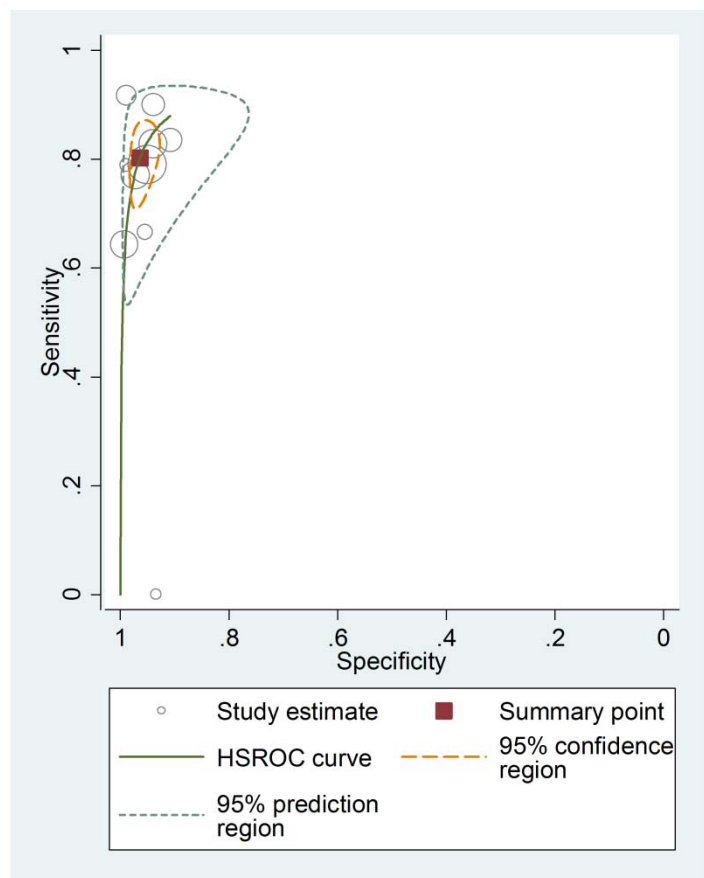
Figure 50 – Meta-analysis: detection of cervical lymph nodes with non-enhanced PET/CT (node-based analysis)

```
Log likelihood   = -62.901803                    Number of studies =       10

                │    Coef.    Std. Err.     z     P>|z|     [95% Conf. Interval]
────────────────┼──────────────────────────────────────────────────────────────
Bivariate       │
    E(logitSe)  │   1.403769   .1731753                    1.064352    1.743187
    E(logitSp)  │   3.286253   .2479272                    2.800325    3.772182
  Var(logitSe)  │   .1516319   .1519995                    .0212581    1.081573
  Var(logitSp)  │   .4403158   .2863248                    .1230983    1.574985
  Corr(logits)  │  -.5160773   .5316181                   -.9633992    .6906644
────────────────┼──────────────────────────────────────────────────────────────
HSROC           │
       Lambda   │   4.349911   .2896519                    3.782203    4.917618
        Theta   │  -.3424756   .6398974                   -1.596651    .9117003
         beta   │   .5330183   .5688884    0.94   0.349    -.5819826   1.648019
       s2alpha  │   .2500825   .3538293                    .0156229    4.003186
       s2theta  │   .1958703   .1213741                    .0581445    .6598253
────────────────┼──────────────────────────────────────────────────────────────
Summary pt.     │
           Se   │   .8027813   .0274177                    .7435213    .8510914
           Sp   │   .9639542   .0086146                    .9426934    .9775154
          DOR   │   108.8556   27.35334                    66.52122    178.1318
          LR+   │   22.27114   5.122355                    14.18948    34.95574
          LR−   │   .2045934   .0278935                    .1566181    .2672645
         1/LR−  │   4.887743   .6663769                    3.741612    6.384958
```

Covariance between estimates of E(logitSe) & E(logitSp) -.0141577

6.1.7. *Detection of cervical lymph nodes: contrast-enhanced PET/CT (neck-side-based)*

Figure 51 – Forest plot: detection of cervical lymph nodes with contrast-enhanced PET/CT (neck-side-based analysis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Haerle 2011b	28	2	1	5	0.97 [0.82, 1.00]	0.71 [0.29, 0.96]
Krabbe 2011	34	21	4	87	0.89 [0.75, 0.97]	0.81 [0.72, 0.88]
Schwartz 2005	17	0	0	9	1.00 [0.80, 1.00]	1.00 [0.66, 1.00]
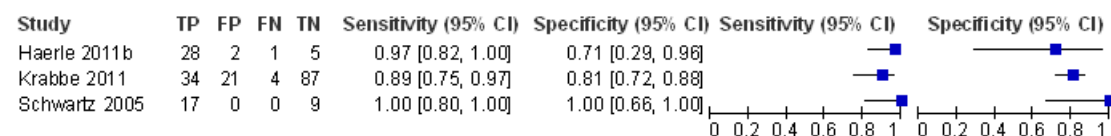
6.1.8. *Detection of cervical lymph nodes: contrast-enhanced PET/CT (node-based)*

Figure 52 – Forest plot: detection of cervical lymph nodes with contrast-enhanced PET/CT (node-based analysis)

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Schwartz 2005	26	1	1	68	0.96 [0.81, 1.00]	0.99 [0.92, 1.00]
Yoon 2009	60	6	14	322	0.81 [0.70, 0.89]	0.98 [0.96, 0.99]
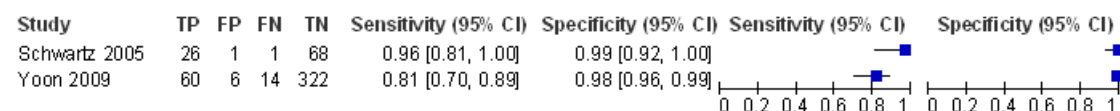
6.1.9. Detection of cervical lymph nodes: conventional imaging

Figure 53 – Forest plot: detection of cervical lymph nodes with conventional imaging (in studies comparing with PET or PET/CT)
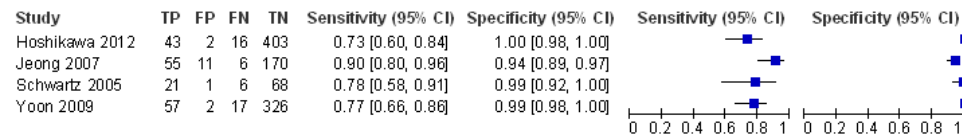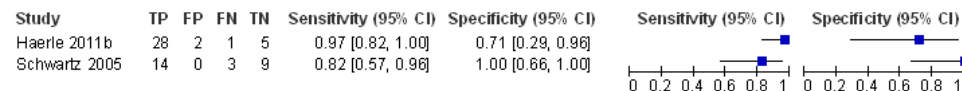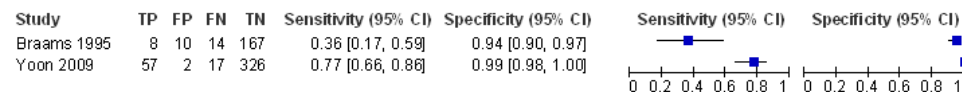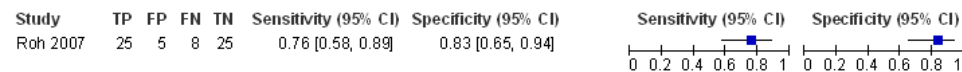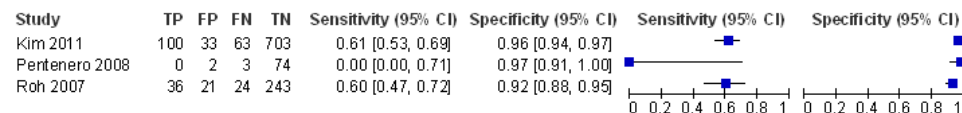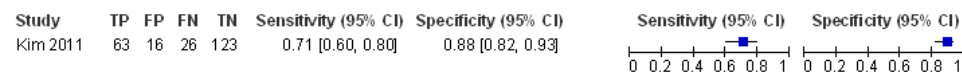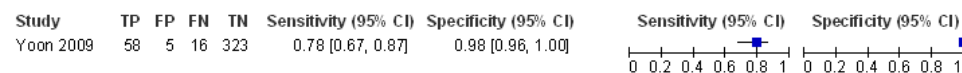
6.1.10. Detection of cervical lymph nodes: comparison between PET or PET/CT with conventional imaging

6.1.10.1. Analysis 1: neck-side-based – main analysis

Figure 54 – Meta-analysis: detection of cervical lymph nodes, neck-side-based analysis, PET or PET/CT in comparative studies [*]

```
Log likelihood  = -15.131761                    Number of studies =        4
_____

                |    Coef.    Std. Err.     z     P>|z|    [95% Conf. Interval]
_____|_____

Bivariate       |
  E(logitSe)    |  3.185532   1.021395                     1.183635   5.187429
  E(logitSp)    |  1.559614   .4096105                      .7567918   2.362436
 Var(logitSe)   |  1.321812   1.841785                      .0861239    20.2869
 Var(logitSp)   |  .2937157   .3513164                      .0281706   3.062374
 Corr(logits)   |        -1          .                            .          .
_____|_____

HSROC           |
       Lambda   |  4.458692   .7577367                     2.973555   5.943828
        Theta   | -.0422324   .8987611                    -1.803772   1.719307
         beta   | -.7520735   .7752389   -0.97   0.332    -2.271514    .7673669
       s2alpha  |  5.80e-11          .                            .          .
       s2theta  |  .6230866   .6490567                      .0808852   4.799851
_____|_____

Summary pt.     |
          Se    |  .9602862   .0389526                      .7656008   .9944447
          Sp    |  .8262979   .0587913                      .6806568   .9139176
         DOR    |  115.0246   108.9682                      17.96419   736.5015
         LR+    |  5.528351   1.799146                      2.921331    10.4619
         LR-    |  .0480624    .045969                      .0073736   .3132805
        1/LR-   |  20.80631   19.90011                      3.192028   135.6199
_____|_____

Covariance between estimates of E(logitSe) & E(logitSp)   -.156781
```

[*] *Haerle 2011b: results from contrast-enhanced PET/CT*

Figure 55 – Meta-analysis: detection of cervical lymph nodes, neck-side-based analysis, conventional imaging in comparative studies

```
Log likelihood   = -18.625405                        Number of studies =       4

                 |    Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]
-----------------+--------------------------------------------------------------------
Bivariate        |
   E(logitSe)    |  1.493781    .4418105                      .6278484    2.359714
   E(logitSp)    |  1.685565     .390009                       .921161    2.449968
 Var(logitSe)    |  .4345533    .5823691                      .0314268    6.008773
 Var(logitSp)    |  .1066694    .2751455                      .0006799    16.73587
 Corr(logits)    |       -1         .                              .           .
-----------------+--------------------------------------------------------------------
HSROC            |
      Lambda     |  3.446117    1.370686                       .759621    6.132612
       Theta     | -.6716143    1.409803                     -3.434777    2.091549
        beta     |  -.702292     1.40806   -0.50    0.618    -3.462038    2.057454
      s2alpha    |  6.38e-09         .                              .           .
      s2theta    |  .2152987    .3223797                      .0114416     4.05132
-----------------+--------------------------------------------------------------------
Summary pt.      |
          Se     |  .8166451    .0661549                      .6520014    .9137032
          Sp     |    .84364    .0514467                      .7152786    .9205591
         DOR     |  24.03102    11.09963                      9.718806    59.41985
         LR+     |  5.222851    1.602139                      2.862838    9.528366
         LR-     |  .2173379    .0742746                      .1112345    .4246501
        1/LR-    |  4.601131    1.572424                       2.35488    8.990016
-----------------+--------------------------------------------------------------------

Covariance between estimates of E(logitSe) & E(logitSp)   -.0669817
```

6.1.10.2. Analysis 2: neck-side-based – sensitivity analysis

Figure 56 – Meta-analysis (sensitivity analysis): detection of cervical lymph nodes, neck-side-based analysis, PET or PET/CT in comparative studies [*]

```
Log likelihood  = -15.657314                    Number of studies =        4
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	2.723453	.7760098			1.202501	4.244404
E(logitSp)	1.595897	.4063371			.7994911	2.392303
Var(logitSe)	.6801654	1.061737			.0319073	14.49903
Var(logitSp)	.28365	.3507491			.0251318	3.201409
Corr(logits)	-1	.			.	.
HSROC						
Lambda	4.174502	.5766666			3.044257	5.304748
Theta	.101326	.8950909			-1.65302	1.855672
beta	-.4372975	.8738501	-0.50	0.617	-2.150012	1.275417
s2alpha	1.08e-07	.			.	.
s2theta	.4392367	.4850096			.0504421	3.824758
Summary pt.						
Se	.9383964	.04486			.7689694	.9858586
Sp	.8314442	.056946			.6898656	.9162385
DOR	75.13976	55.17136			17.81866	316.8578
LR+	5.567274	1.801754			2.952335	10.49832
LR-	.0740923	.0523325			.0185591	.2957943
1/LR-	13.49669	9.532921			3.380728	53.88206

```
Covariance between estimates of E(logitSe) & E(logitSp)  -.1140891
```

[*] *Haerle 2011b: results from non-enhanced PET/CT (or PET)*

6.1.10.3.Analysis 3: node-based – main analysis

Figure 57 – Meta-analysis: detection of cervical lymph nodes, node-based analysis, PET or PET/CT in comparative studies [*]

```
Log likelihood  = -57.52232                        Number of studies =        9

                 |     Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]
-----------------+--------------------------------------------------------------------
Bivariate        |
   E(logitSe)    |   1.588045    .279656                        1.03993    2.136161
   E(logitSp)    |   3.428584    .3128043                       2.815499    4.04167
  Var(logitSe)   |   .4675853    .4595168                       .0681314   3.209035
  Var(logitSp)   |    .662127    .402531                        .2011245   2.179805
  Corr(logits)   |  -.2353497    .5418542                      -.8773484   .7086382
-----------------+--------------------------------------------------------------------
HSROC            |
        Lambda   |   4.875342     .53537                        3.826036   5.924648
         Theta   |  -.7053316    .7150146                      -2.106735   .6960713
          beta   |   .1739378    .5639077    0.31   0.758       -.931301   1.279177
        s2alpha  |   .8509301    .8897331                       .1096168   6.605577
        s2theta  |   .3436853    .2153586                       .1006433   1.173646
-----------------+--------------------------------------------------------------------
Summary pt.      |
            Se   |   .8303409    .0393965                       .7388364   .8943685
            Sp   |    .968586    .0095177                       .9435077   .9827352
           DOR   |   150.9018    57.05209                       71.92456   316.6007
           LR+   |   26.43221    7.867974                        14.7489   47.37044
           LR-   |   .1751616    .0403839                       .1114789   .2752233
          1/LR-  |   5.709013    1.316224                       3.633414   8.970304
-----------------+--------------------------------------------------------------------
Covariance between estimates of E(logitSe) & E(logitSp)  -.0165569
```

[*] *Jeong 2007: results from non-enhanced PET/CT*

Figure 58 – Meta-analysis: detection of cervical lymph nodes, node-based analysis, conventional imaging in comparative studies

```
Log likelihood   = -58.233878                    Number of studies =        9

                |   Coef.    Std. Err.     z     P>|z|     [95% Conf. Interval]
----------------+------------------------------------------------------------
Bivariate       |
   E(logitSe)   |  .7739601   .2613836                     .2616576   1.286263
   E(logitSp)   |  3.697084   .3557063                     2.999912   4.394256
  Var(logitSe)  |  .4491978   .3355877                     .1038772   1.942474
  Var(logitSp)  |  .8559718   .5242116                     .2577325   2.842822
  Corr(logits)  |  .3246747   .3748916                    -.4498341    .820459
----------------+------------------------------------------------------------
HSROC           |
       Lambda   |  4.056025   .6551575                     2.771939    5.34011
        Theta   | -1.118677   .5099116                    -2.118085  -.1192687
         beta   |   .322387   .4708438    0.68   0.494    -.6004499   1.245224
       s2alpha  |  1.642812   .9750419                     .5133132   5.257667
       s2theta  |  .2093782   .1479886                     .0523965   .8366828
----------------+------------------------------------------------------------
Summary pt.     |
           Se   |  .6843769   .0564602                     .5650437   .7835139
           Sp   |  .9758042   .0083983                     .9525702   .9878025
          DOR   |  87.44798   42.91534                     33.42106   228.8123
          LR+   |  28.28498   10.63788                     13.53387   59.11391
          LR-   |  .3234492   .0586108                     .2267585   .4613691
         1/LR-  |  3.091676   .5602287                     2.167462   4.409977
----------------+------------------------------------------------------------
Covariance between estimates of E(logitSe) & E(logitSp)    .022995
```

6.1.10.4. Analysis 4: node-based – sensitivity analysis 1

Figure 59 – Meta-analysis (sensitivity analysis 1): detection of cervical lymph nodes, node-based analysis, PET or PET/CT in comparative studies [*]

```
Log likelihood  = -57.454343                    Number of studies =        9

              |    Coef.    Std. Err.     z    P>|z|    [95% Conf. Interval]
--------------+--------------------------------------------------------------
Bivariate     |
  E(logitSe)  |  1.457547   .1865723                    1.091872    1.823222
  E(logitSp)  |  3.189532   .2761574                    2.648273    3.73079
 Var(logitSe) |   .146234   .1541411                    .0185277    1.154186
 Var(logitSp) |  .5357184   .3239143                    .1637834    1.752278
 Corr(logits) | -.9079894   .3440609                   -.9999556    .9810681
--------------+--------------------------------------------------------------
HSROC         |
      Lambda  |  4.321929   .2539563                    3.824184    4.819675
       Theta  | -.1444809   .5710648                   -1.263747    .9747856
        beta  |  .6492004   .5391621   1.20   0.229    -.4075379    1.705939
      s2alpha |  .0515063   .2067727                    .0000197    134.5921
      s2theta |  .2670167   .1686329                    .0774402    .9206829
--------------+--------------------------------------------------------------
Summary pt.   |
         Se   |  .8111573   .0285794                    .7487341    .8609523
         Sp   |  .9604384    .010493                    .9339045    .9765874
         DOR  |    104.28    23.8725                    66.57909    163.3292
         LR+  |  20.50367    5.06193                    12.63827    33.26409
         LR-  |  .1966214   .0285882                     .147866    .2614528
        1/LR- |  5.085917   .7394791                    3.824782    6.762881
--------------+--------------------------------------------------------------

Covariance between estimates of E(logitSe) & E(logitSp)  -.0293323
```

[*] *Jeong 2007: results from PET*

6.1.10.5.Analysis 5: node-based – sensitivity analysis 2

Figure 60 – Meta-analysis (sensitivity analysis 2): detection of cervical lymph nodes, node-based analysis, PET or PET/CT in comparative studies [*]

```
Log likelihood   = -50.001185                   Number of studies =       8

                  Coef.    Std. Err.     z     P>|z|    [95% Conf. Interval]

Bivariate
  E(logitSe)    1.485883   .3303392                      .83843    2.133336
  E(logitSp)    3.624787   .2863296                     3.063592   4.185983
Var(logitSe)    .6419223   .6726054                     .0823369   5.004612
Var(logitSp)    .4259111   .3229857                     .0963425   1.882867
Corr(logits)    .1172908   .5674055                    -.7656685    .8470001

HSROC
      Lambda    5.357321   .8869329                     3.618964   7.095678
       Theta   -1.337614   .8472116                    -2.998119    .3228899
        beta   -.2051183   .6193525   -0.33   0.741    -1.419027    1.00879
     s2alpha    1.168414   1.177544                     .1620855   8.422667
     s2theta    .2307748   .1599096                     .059343    .8974432

Summary pt.
          Se    .8154595   .0497112                     .6981345    .8941013
          Sp    .9740373   .0072409                     .9553657    .9850206
         DOR    165.7815   75.14312                     68.18913    403.048
         LR+    31.40885   9.107318                     17.79252   55.44554
         LR-    .1894594   .0511623                     .1115975    .3216456
        1/LR-   5.278177   1.425338                     3.109012    8.960773

Covariance between estimates of E(logitSe) & E(logitSp)    .0071707
```

[*] *Braams 1995 excluded*

Figure 61 – Meta-analysis (sensitivity analysis 2): detection of cervical lymph nodes, node-based analysis, conventional imaging in comparative studies [*]

```
Log likelihood   = -50.768425                      Number of studies =        8

                        Coef.    Std. Err.      z     P>|z|      [95% Conf. Interval]

Bivariate
  E(logitSe)        .9450552    .2140672                        .5254912    1.364619
  E(logitSp)         3.83026    .3931849                        3.059632    4.600889
 Var(logitSe)       .2366947     .207345                        .0425142     1.31778
 Var(logitSp)       .9147834    .5797582                        .2641533    3.167966
 Corr(logits)       .1990037     .448752                       -.6132483    .8066979

HSROC
       Lambda      4.056853    .5474002                        2.983969    5.129738
        Theta     -.7033542    .5640344                       -1.808841    .4021328
         beta      .6759581    .5362898     1.26    0.208      -.3751505    1.727067
      s2alpha      1.115845     .730034                        .3095359    4.022506
      s2theta      .1863605    .1472356                        .0396146    .8767029

Summary pt.
           Se      .7201197    .0431447                        .6284309    .7965094
           Sp      .9787571     .008175                        .9551966     .990057
          DOR      118.5477    56.14843                        46.85262    299.9526
          LR+       33.8993    13.48476                        15.54506    73.92462
          LR-      .2859549    .0444832                        .2108067    .3878918
         1/LR-     3.497055     .544003                        2.578038    4.743683

Covariance between estimates of E(logitSe) & E(logitSp)     .0119558
```

[*] *Braams 1995 excluded*

6.1.10.6. Analysis 6: node-based – sensitivity analysis 3

Figure 62 – Meta-analysis (sensitivity analysis 3): detection of cervical lymph nodes, node-based analysis, PET/CT in comparative studies with CT

```
Log likelihood  = -18.704452                    Number of studies =        4

               │    Coef.    Std. Err.     z    P>|z|    [95% Conf. Interval]
───────────────┼────────────────────────────────────────────────────────────
Bivariate      │
  E(logitSe)   │  1.769009    .4745884                   .8388329    2.699185
  E(logitSp)   │  4.320351    .3202515                   3.692669    4.948032
 Var(logitSe)  │  .6518257     .646181                   .0933902    4.549481
 Var(logitSp)  │  .0400253    .1305849                   .0000669    23.95696
 Corr(logits)  │        -1          .                          .           .
───────────────┼────────────────────────────────────────────────────────────
HSROC          │
       Lambda  │  9.559578    6.619009                  -3.413441      22.5326
        Theta  │ -3.899185    4.013958                   -11.7664     3.968028
         beta  │ -1.395133    1.641327   -0.85   0.395   -4.612076     1.821809
      s2alpha  │         0          .                          .           .
      s2theta  │  .1615224    .2852861                   .0050677     5.148166
───────────────┼────────────────────────────────────────────────────────────
Summary pt.    │
           Se  │  .8543344    .0590612                   .6982194     .9369785
           Sp  │  .9868792    .0041468                   .9756998     .9929527
          DOR  │   441.139    218.2477                   167.2841     1163.312
          LR+  │  65.11311    19.82803                   35.84787     118.2697
          LR-  │  .1476023      .05968                   .0668232     .3260311
        1/LR-  │  6.774964    2.739319                   3.067192     14.96487

Covariance between estimates of E(logitSe) & E(logitSp)  -.0415154
```

Figure 63 – Meta-analysis (sensitivity analysis 3): detection of cervical lymph nodes, node-based analysis, CT in comparative studies with PET/CT

```
Log likelihood  = -18.86655                    Number of studies =       4
```

	Coef.	Std. Err.	z	P>|z|	[95% Conf.	Interval]
Bivariate						
E(logitSe)	1.415715	.267242			.89193	1.939499
E(logitSp)	4.370898	.6154717			3.164596	5.5772
Var(logitSe)	.1585309	.186804			.0157436	1.596329
Var(logitSp)	1.03315	.9147899			.1821704	5.859347
Corr(logits)	-1	.			.	.
HSROC						
Lambda	4.997612	.3728943			4.266753	5.728472
Theta	-.2368295	.7244517			-1.656729	1.18307
beta	.9372092	.548628	1.71	0.088	-.1380818	2.0125
s2alpha	0	.			.	.
s2theta	.4047051	.3586278			.0712607	2.29841
Summary pt.						
Se	.8046657	.0420048			.7092883	.8742971
Sp	.9875179	.0075865			.95948	.9962311
DOR	325.9072	159.9312			124.5624	852.7093
LR+	64.46551	37.13002			20.84795	199.3387
LR-	.1978033	.0415849			.1310034	.2986651
1/LR-	5.055528	1.062841			3.348232	7.633392

```
Covariance between estimates of E(logitSe) & E(logitSp)  -.1047056
```

6.1.11. Detection of distant metastases or second primaries

Figure 64 – Forest plot: detection of distant metastases or second primaries

Detection of M+ or 2nd primaries: PET

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chan 2011	15	5	3	81	0.83 [0.59, 0.96]	0.94 [0.87, 0.98]
Gourin 2008	5	1	0	21	1.00 [0.48, 1.00]	0.95 [0.77, 1.00]
Haerle 2011a	29	14	1	255	0.97 [0.83, 1.00]	0.95 [0.91, 0.97]
Krabbe 2009	24	8	2	115	0.92 [0.75, 0.99]	0.93 [0.88, 0.97]
Krabbe 2010	7	9	1	63	0.88 [0.47, 1.00]	0.88 [0.78, 0.94]
Ng 2008	20	8	6	126	0.77 [0.56, 0.91]	0.94 [0.89, 0.97]
Yoshida 2009	2	2	1	35	0.67 [0.09, 0.99]	0.95 [0.82, 0.99]

Detection of M+ or 2nd primaries: CT

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Krabbe 2009	17	22	6	37	0.74 [0.52, 0.90]	0.63 [0.49, 0.75]
Ng 2008	13	3	13	131	0.50 [0.30, 0.70]	0.98 [0.94, 1.00]

Detection of M+ or 2nd primaries: MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chan 2011	12	3	6	82	0.67 [0.41, 0.87]	0.96 [0.90, 0.99]

Figure 65 – SROC curve: detection of distant metastases or second primaries
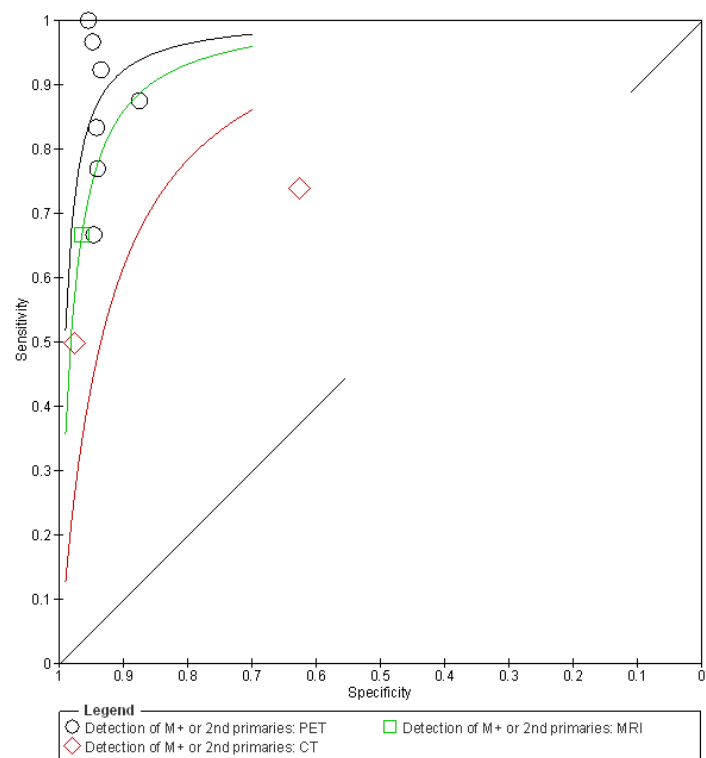
Figure 66 – Meta-analysis: detection of distant metastases or second primaries with PET or PET/CT

```
Log likelihood   = -25.368446                    Number of studies =        7

                │    Coef.    Std. Err.      z     P>|z|     [95% Conf. Interval]

Bivariate       │
    E(logitSe)  │   2.018335   .3515649                     1.329281    2.70739
    E(logitSp)  │   2.685357   .1561534                     2.379302   2.991412
   Var(logitSe) │   .1713736   .3529672                     .0030254   9.707532
   Var(logitSp) │   .0047835   .0269982                     7.51e-08   304.7315
   Corr(logits) │          1          .                            .          .

HSROC           │
       Lambda   │   7.39476    8.433835                    -9.135252   23.92477
       Theta    │  -2.872397   5.391112                    -13.43878   7.693989
        beta    │  -1.789332   2.904524    -0.62   0.538    -7.482094    3.90343
       s2alpha  │   .1145267   .3550711                      .000263   49.87874
       s2theta  │          0          .                            .          .

Summary pt.     │
         Se     │   .8827088   .0363989                     .7907216   .9374613
         Sp     │   .9361571   .0093328                     .9152353   .9521847
         DOR    │   110.3539   44.04466                     50.47247   241.2797
         LR+    │   13.82626   2.155865                     10.18546   18.76846
         LR-    │   .1252901   .0390297                     .0680385   .2307166
        1/LR-   │   7.981474   2.486348                     4.334322   14.69755
```

Covariance between estimates of E(logitSe) & E(logitSp)   .0056582

6.1.12. Detection of bone marrow invasion

Figure 67 – Forest plot: detection of bone marrow invasion

6.1.13. Detection of bone metastases

Figure 68 – Forest plot: detection of bone metastases

6.1.14. Detection of lung metastases

Figure 69 – Forest plot: detection of lung metastases

6.1.15. Detection of liver metastases

Figure 70 – Forest plot: detection of liver metastases
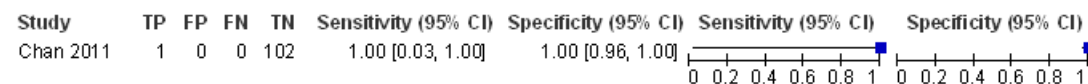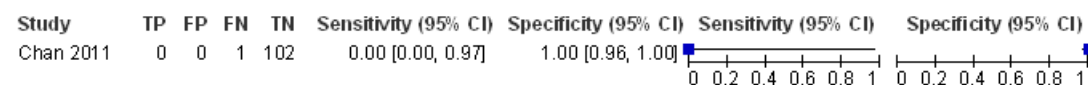
6.1.16. Detection of head and neck metastases

Figure 71 – Forest plot: detection of head and neck metastases

6.1.17. Detection of distant lymph node metastases

Figure 72 – Forest plot: detection of distant lymph node metastases

Distant LN: PET

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chan 2011	2	2	2	97	0.50 [0.07, 0.93]	0.98 [0.93, 1.00]		

Distant LN: MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chan 2011	0	1	4	98	0.00 [0.00, 0.60]	0.99 [0.95, 1.00]		

6.1.18. Detection of other metastases of aerodigestive tract

Figure 73 – Forest plot: detection of other metastases of aerodigestive tract

Other M+ aerodigestive tract: PET

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chan 2011	6	1	0	96	1.00 [0.54, 1.00]	0.99 [0.94, 1.00]		

Other M+ aerodigestive tract: MRI

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
Chan 2011	5	2	1	95	0.83 [0.36, 1.00]	0.98 [0.93, 1.00]		

6.2. RQ6: value of PET / MRI in the decision of neck dissection after CRT

Figure 74 – Forest plot: Detection of residual disease in cervical lymph nodes with PET/CT after (at least) CRT - Patient-based analysis

PET/CT, patient-based

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Chen 2006	4	7	0	19	1.00 [0.40, 1.00]	0.73 [0.52, 0.88]
Gourin 2009	6	14	4	8	0.60 [0.26, 0.88]	0.36 [0.17, 0.59]
Gupta 2010	5	1	3	48	0.63 [0.24, 0.91]	0.98 [0.89, 1.00]
Moeller 2009	6	16	2	51	0.75 [0.35, 0.97]	0.76 [0.64, 0.86]
Prestwich 2012	5	3	0	33	1.00 [0.48, 1.00]	0.92 [0.78, 0.98]
Rabalais 2009	4	6	0	42	1.00 [0.40, 1.00]	0.88 [0.75, 0.95]
Zundel 2011	0	0	0	52	Not estimable	1.00 [0.93, 1.00]
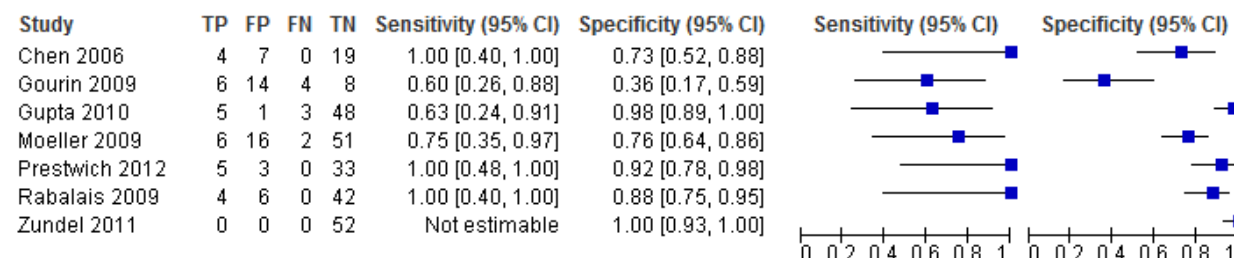
Figure 75 – Forest plot: Detection of residual disease in cervical lymph nodes with PET/CT after (at least) CRT – Hemi-neck-based analysis

PET/CT, neck-side-based

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Lyford-Pike 2009	8	6	6	17	0.57 [0.29, 0.82]	0.74 [0.52, 0.90]
Ong 2008	5	8	2	67	0.71 [0.29, 0.96]	0.89 [0.80, 0.95]
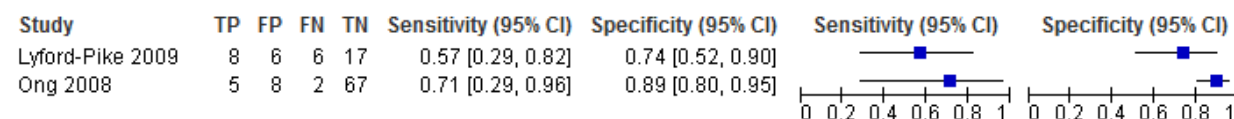
6.2.1.1. FDG-PET

Figure 76 – Forest plot: Detection of residual disease in cervical lymph nodes with PET after (at least) CRT – Patient-based analysis

PET, patient-based

| Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Hanasono 1999	6	4	1	11	0.86 [0.42, 1.00]	0.73 [0.45, 0.92]
Kitagawa 2003	0	6	0	17	Not estimable	0.74 [0.52, 0.90]
Loo 2011	0	1	0	33	Not estimable	0.97 [0.85, 1.00]
McCollum 2004	6	7	3	8	0.67 [0.30, 0.93]	0.53 [0.27, 0.79]
Mori 2011	1	14	1	33	0.50 [0.01, 0.99]	0.70 [0.55, 0.83]
Porceddu 2011	2	7	0	103	1.00 [0.16, 1.00]	0.94 [0.87, 0.97]
Wang 2009	10	1	0	33	1.00 [0.69, 1.00]	0.97 [0.85, 1.00]
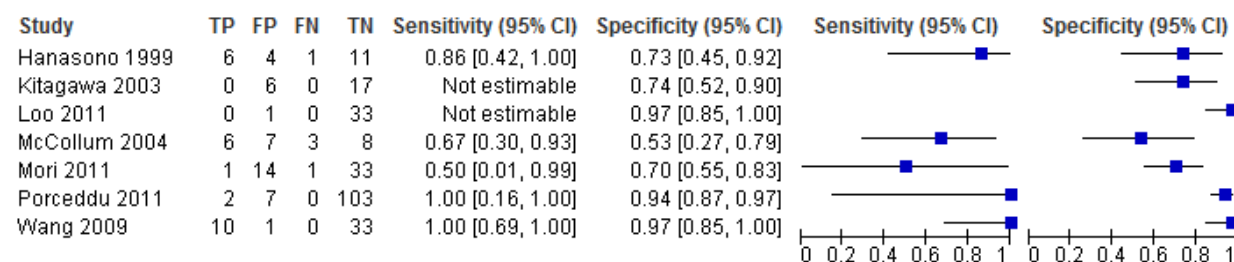
Figure 77 – Forest plot: Detection of residual disease in cervical lymph nodes with PET after (at least) CRT – Hemi-neck-based analysis


PET, neck-side-based

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Brkovich 2006	3	6	1	11	0.75 [0.19, 0.99]	0.65 [0.38, 0.86]
Inohara 2009	9	5	4	37	0.69 [0.39, 0.91]	0.88 [0.74, 0.96]
Yao 2005	3	4	0	63	1.00 [0.29, 1.00]	0.94 [0.85, 0.98]
Yao 2007	5	6	0	13	1.00 [0.48, 1.00]	0.68 [0.43, 0.87]
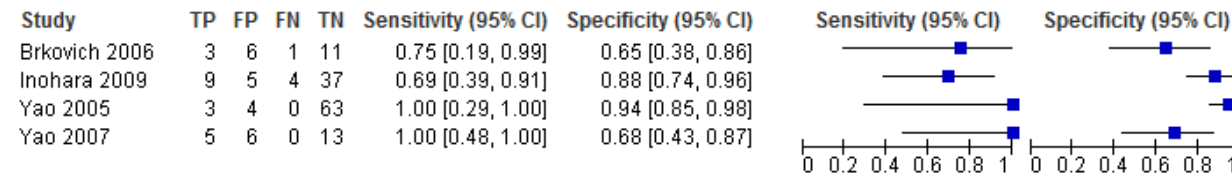
Figure 78 – Forest plot: Detection of residual disease in cervical lymph nodes with PET after (at least) CRT – Node-based analysis

PET, node-based

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Kishino 2012	5	8	0	14	1.00 [0.48, 1.00]	0.64 [0.41, 0.83]
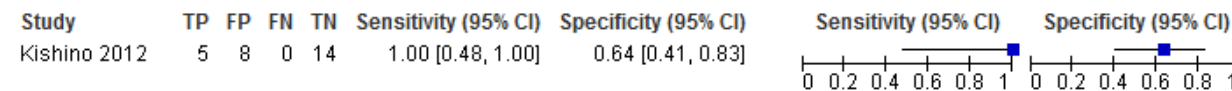
6.3. RQ8: IMRT

Figure 79 – Forest plot: Pooled result for mucositis grade 2 or more of IMRT vs conventional RT

Study or Subgroup	IMRT Events	Total	Conventional RT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gupta 2012	25	32	26	28	38.7%	0.84 [0.68, 1.04]
Nutting 2011	43	46	43	44	61.3%	0.96 [0.88, 1.05]
Total (95% CI)		78		72	100.0%	**0.91 [0.83, 1.00]**
Total events	68		69			

Heterogeneity: Chi² = 1.68, df = 1 (P = 0.20); I² = 40%
Test for overall effect: Z = 1.88 (P = 0.06)
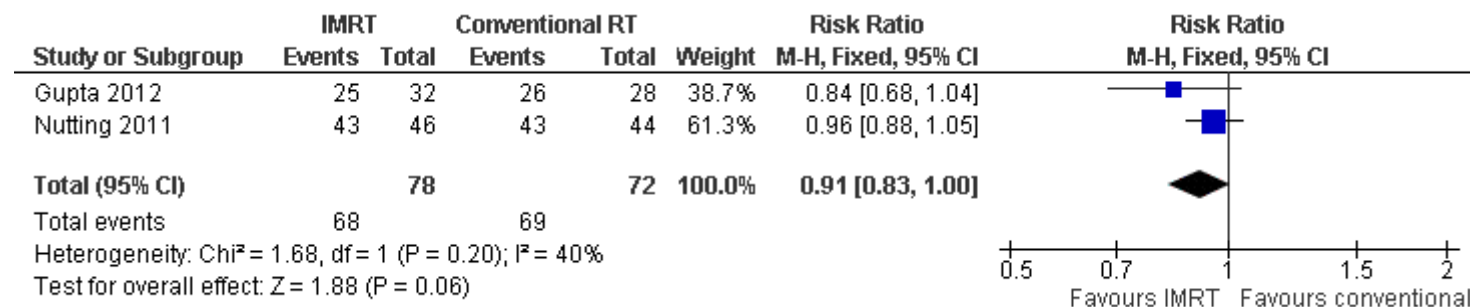
Figure 80 – Forest plot: Pooled results for dysphagia grade 2 or more of IMRT vs conventional RT

Study or Subgroup	IMRT Events	Total	Conventional RT Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gupta 2012	19	32	20	28	32.4%	0.83 [0.57, 1.20]
Nutting 2011	40	47	43	44	67.6%	0.87 [0.77, 0.99]
Total (95% CI)		79		72	100.0%	0.86 [0.74, 0.99]
Total events	59		63			

Heterogeneity: Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 2.05 (P = 0.04)
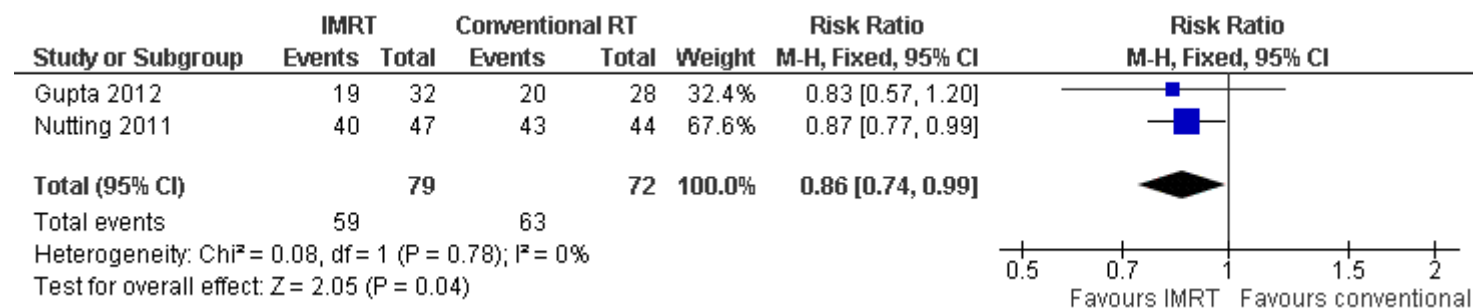
6.4. RQ9: induction chemotherapy in patients with HNSCC

Figure 81 – Meta-analysis for different types of induction chemotherapy (PF, other platin-containing combinations, multi-agent chemotherapy combination without platin, and single-agent chemotherapy (methotrexate)) followed by locoregional treatment versus locoregional treatment alone for outcome overall survival for patients with locally advanced HNSCC (stage 3 and 4)
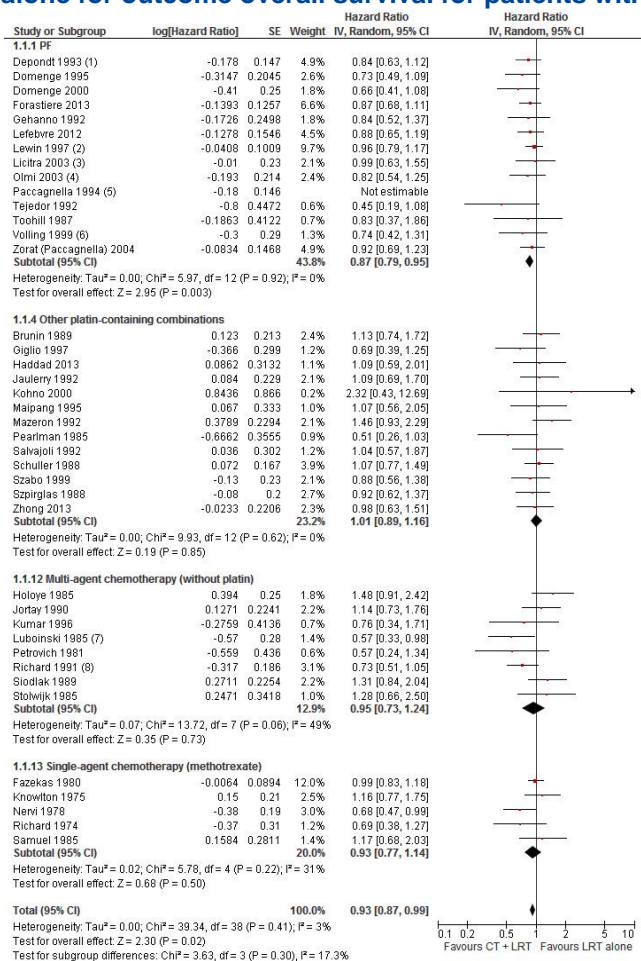
Figure 82 – Meta-analysis for different types of induction chemotherapy (PF, other platin-containing combinations, multi-agent chemotherapy combination without platin, and single-agent chemotherapy (methotrexate)) followed by locoregional treatment versus locoregional treatment alone for outcome disease-free survival for patients with locally advanced HNSCC (stage 3 and 4)
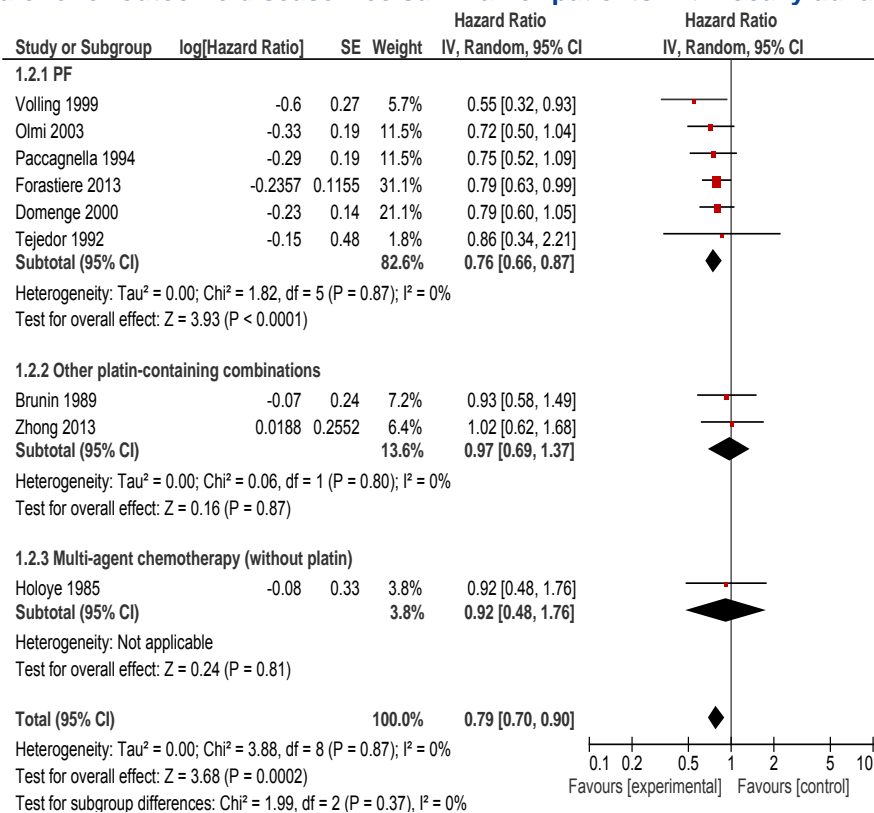
Figure 83 – Meta-analysis for PF induction chemotherapy followed by locoregional treatment versus locoregional treatment alone for outcome post-treatment mortality for patients with locally advanced HNSCC (stage 3 and 4)

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 PF						
Forastiere 2013	9	174	5	172	90.7%	1.78 [0.61, 5.20]
Lefebvre 2012	2	100	0	94	9.3%	4.70 [0.23, 96.70]
Subtotal (95% CI)		274		266	100.0%	2.05 [0.75, 5.58]
Total events	11		5			

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)

Total (95% CI)		274		266	100.0%	2.05 [0.75, 5.58]
Total events	11		5			

Heterogeneity: Chi² = 0.36, df = 1 (P = 0.55); I² = 0%
Test for overall effect: Z = 1.41 (P = 0.16)
Test for subgroup differences: Not applicable

6.5. RQ10: primary CRT for patients with non-resectable M0 HNSCC

Figure 84 – Pooled results for grade 3-4 mucositis of primary CRT with RT alone
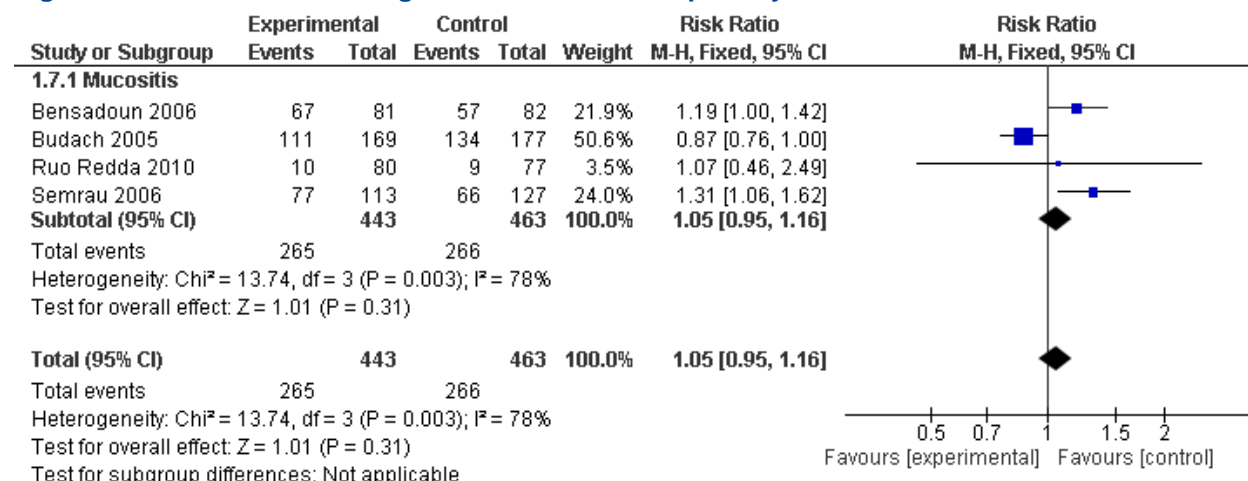
Figure 85 – Pooled results for grade 3-4 dermatitis of primary CRT with RT alone
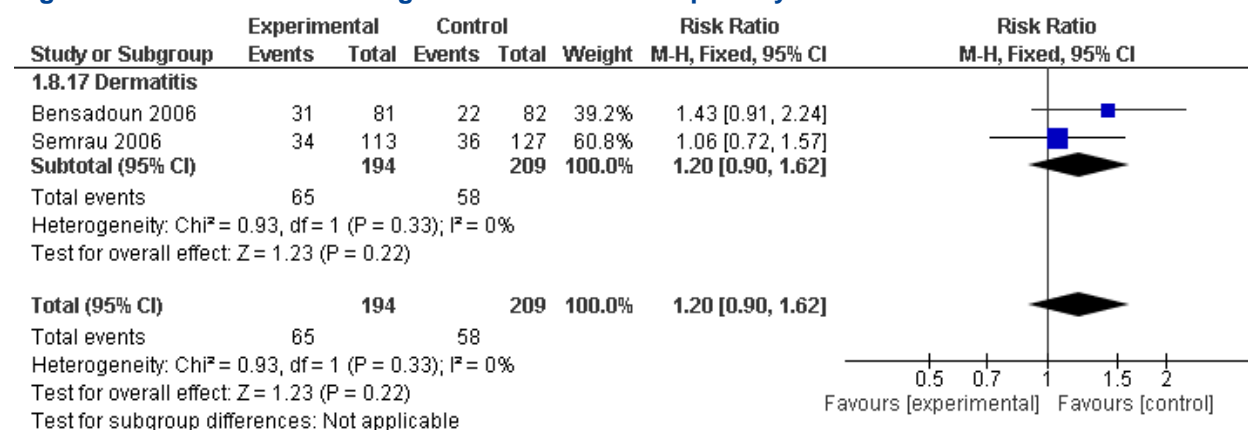
Figure 86 – Pooled results for grade 3-4 anemia of primary CRT with RT alone
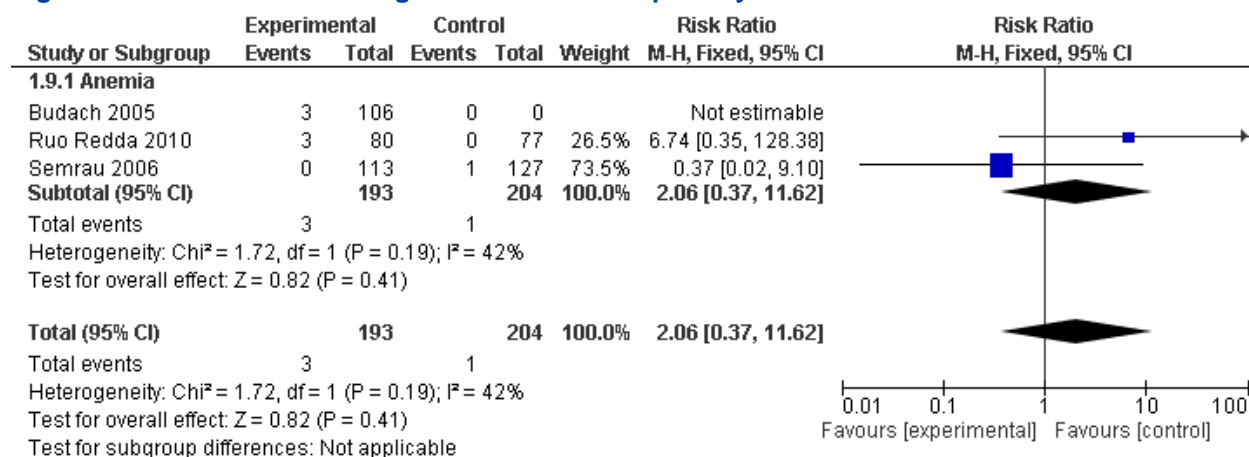
Figure 87 – Pooled results for grade 3-4 leukopenia of primary CRT with RT alone
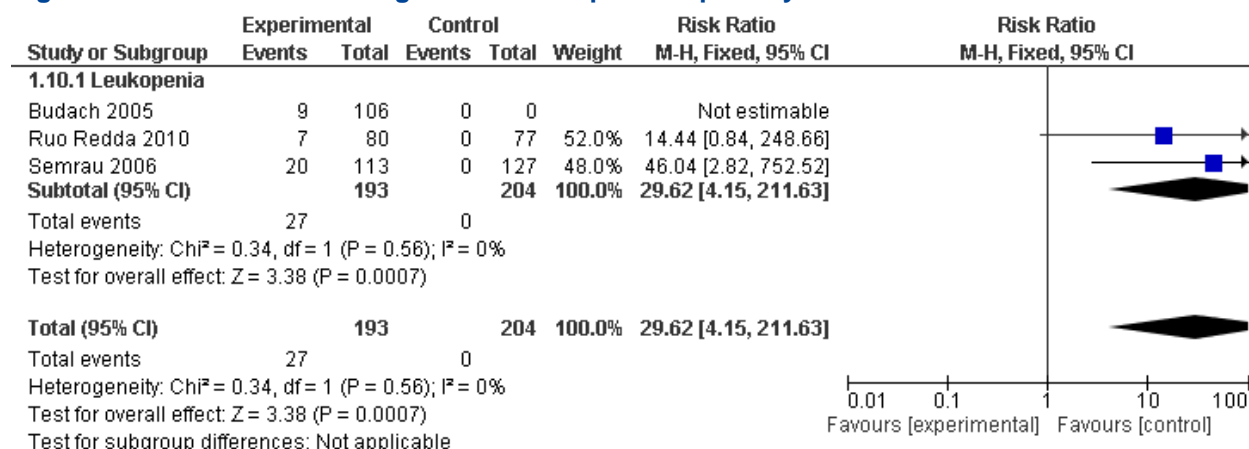
Figure 88 – Pooled results for grade 3-4 thrombocytopenia of primary CRT with RT alone

Study or Subgroup	Experimental Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.11.1 Thrombocytopenia						
Budach 2005	2	106	0	0		Not estimable
Ruo Redda 2010	1	80	0	80	51.5%	3.00 [0.12, 72.56]
Semrau 2006	6	113	0	127	48.5%	14.60 [0.83, 256.24]
Subtotal (95% CI)		193		207	100.0%	8.63 [1.11, 67.05]
Total events	7		0			

Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)

Total (95% CI)		193		207	100.0%	8.63 [1.11, 67.05]
Total events	7		0			

Heterogeneity: Chi² = 0.55, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 2.06 (P = 0.04)
Test for subgroup differences: Not applicable

Risk Ratio M-H, Fixed, 95% CI

0.01   0.1   1   10   100
Favours [experimental]   Favours [control]

7. EXTERNAL REVIEW

7.1. Evaluation of the recommendations by the stakeholders

		SoR	LoE	MIN	MAX	MED	%4-5	%5	Comment	Decision
	Diagnosis and staging									
	Patient information									
1	The patient must be kept fully informed about his condition, the treatment options and consequences. Information should be correct, complete and communicated in a clear and unambiguous way. Patient preferences should be taken into account when deciding on a treatment option.	Strong	Adapted	4	5	5	100%	75%	14: The term 'complete' should be omitted as it is impossible to explain all possible consequences/side effects.	Accepted: completeness is a clear demand from the patients. Can be part of a leaflet.
	Biopsy									
2	A biopsy should be taken from the most suspect part of the tumour. The pathologist should be provided with any clinically relevant information. If the result is inconclusive, or negative but the tumour is suspect, the biopsy should be repeated.	Strong	Adapted	4	5	5	100%	90%	14: please define 'most suspect'	Accepted
3	When a patient with a diagnosis of oral SCC is referred to another centre for work-up completion and treatment, and if no additional biopsies need to be performed in the reference centre, pathology specimens (slices and/or blocks) should be sent for revision to the reference laboratory for diagnosis confirmation upon request from the reference centre. Every uncommon tumour diagnosis beside classical SCC should be reviewed by an expert from a reference laboratory.	Strong	Adapted	2	5	5	90%	60%	2: upon request, not systematic 6: only if the biopsy report from the first center does not include tumour localization, tumour histology, tumour grade, depth of invasion (if assessable), lymphatic, vascular and perineural invasion	Accepted: 'upon request' covers the comments made.
4	The biopsy report should include: tumour localization, tumour histology, tumour grade, depth of invasion (if assessable), lymphatic, vascular and perineural invasion (if present). Some other prognostic factors, such as growing pattern (infiltrative vs. pushing border), can be considered.	Strong	Adapted	4	5	5	100%	80%	14: even if no lymphatic, vascular and perineural invasion is present, it should be mentioned so that one knows that there has been looked at	**The biopsy report should include: tumour localization, tumour histology, tumour grade, depth of invasion (if assessable), lymphatic, vascular and perineural invasion** ~~(if present)~~. **Some other prognostic factors, such as growing pattern (infiltrative vs. pushing border), can be considered.**
	Conventional imaging									
5	Perform an MRI for primary T- and N-staging (i.e. before any treatment) in patients with newly diagnosed oral cavity cancer.	Weak	Adapted	3	5	5	88%	63%	7: Access to MRI is sometimes tricky. Patients most of the time arrive in reference centre with a CT. If quality is judged good enough by the expert, no further MRI should be done (delaying the treatment). 14: please add the minimally required MRI sequences and that the MRI should be done from skull base to thoracic inlet (MRIs are often only focussing on the primary tumor); to be discussed: studies do not support superiority of one technique over the other but in clinical practice lymph nodes are generally harder to interpret on MRI, largely depending on its quality. Moreover, the criteria for a suspect lymphnode are better defined for CT.	Accepted; technical specifications are avoided in the recommendations. In text: first conventional imaging and than biopsy; well-performed CT is not necessarily inferior to MRI
6	In case MRI is technically impossible (e.g. pacemaker, cochlear implant, etc.) or likely disturbed (e.g. anticipated motion artefacts, etc.), perform a CT for primary T- and N-staging in patients with oral cavity cancer.	Weak	Adapted	4	5	5	100%	88%	14: a contrast-enhanced CT	**In case MRI is technically impossible (e.g. pacemaker, cochlear implant, etc.),** ~~or~~ **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 oral cavity cancer.**

#	Recommendation	Strength	GRADE				%	%	Comments	Revised recommendation
	PET scan									
7	When the risk for metastatic spread and/or second primary tumours is considered high (based on the patient profile and locoregional staging), perform a whole-body FDG-PET/CT in patients with oral cavity cancer.	Weak	Low	2	5	5	73%	64%	1: I can agree with the overall concept but the wording is not satisfactory : "patient profile" and "locoregional staging" characteristics that would justify a PET-CT should be clearly states (e.g. : any cT cN+ disease) 8: Details about the clinical cases where PET-CT is indicated should be provided (as example NCCN - SNM : >stage III; cTx cN1; high risk of disaminated disease)	**In patients with stage III and IV oral cavity 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.**
	Other staging interventions									
8	Because of its high specificity, consider doing an US-guided fine needle aspiration cytology of the neck lymph nodes in centres with an experienced physician.	Weak	Adapted	2	5	5	67%	56%		Omitted
9	To exclude synchronous secondary tumours in the head and neck area, all patients with oral cavity cancer should undergo clinical examination (including fiberoptic examination) of the upper aerodigestive tract. Endoscopy under general anaesthesia is mandatory for better local staging of large tumours.	Strong	Adapted	1	5	5	78%	67%	11: performing a PET-CT can make this obsolete 12: examination under general anaesthesia for large tumors: in my opinion 1. this rarely adds to the assessment by MRI/CT - now it seems that this is obligatory for "large tumors" … 2, on the other hand for large tumors general anaesthesia may be quite risky (difficult intubation) and result in more harm than benefit. Would use 'can be considered' instead of "mandatory" 14: place of Narrow band imaging?	To exclude synchronous secondary tumours in the head and neck area, all patients with oral cavity cancer should undergo clinical examination (including fiberoptic examination) of the upper aerodigestive tract. Endoscopy under general anaesthesia ~~is mandatory~~ **should be considered** for better local staging of large tumours.
10	Patients with carcinoma of the oral cavity should be examined by a dedicated dental practitioner prior to commencing oncological treatment. The dentist should give preventive advice and perform necessary restorative work.	Strong	Adapted	3	5	5	89%	89%		Accepted
	HPV testing									
11	Immunohistochemical testing for p16 can be considered in patients with oral cavity cancer.	Weak	No GRADE	2	5	4	60%	30%	2: what about HPV specific testing cfr Robinson M et al Head and Neck pathol 2012 7: p16 positivity is very rare in OC tumors. I would restrict this test to non drinkers, with no or low (<10 pack-year) tobacco consumption. 9: Why "can be" and not "should be"? In case of positivity a HPV typing should follow to confirm p16 positivity. False positive p16 have been described. 14: is this reimbursed?	**There is insufficient evidence to recommend routine p16 testing in patients with oral cavity cancer. In patients without common risk factors (e.g. smoking, alcohol abusus) for oral cavity cancer, testing for p16 can be considered.**

	Treatment of primary non-metastatic OCC									
	General recommendations									
12	Oral cavity carcinoma must be treated on an interdisciplinary basis after upfront discussion of the case in question by a tumour board, comprising the specialist disciplines of oral and maxillofacial surgery, ENT, radiation oncology, medical oncology, pathology, radiology and nuclear medicine. The general practitioner, dentist and paramedical disciplines (e.g. speech therapist, nutritional therapist, psychosocial worker) are recommended to be present.	Strong	Adapted	4	5	5	100%	75%		Oral cavity carcinoma must be treated on an interdisciplinary basis after upfront discussion of the case in question by a tumour board, comprising the specialist disciplines of oral and maxillofacial surgery, ENT, radiation oncology, medical oncology, pathology, radiology and nuclear medicine. The general practitioner, dentist and paramedical disciplines (e.g. speech therapist, nutritional therapist, psychosocial worker) are recommended to be present. Continuity of care should be guaranteed through a cooperation between the hospital and home care team.
	Surgery									
13	Provided the patient's general condition permits it and the oral cavity carcinoma can be curatively resected, surgical resection of the tumour should be performed and followed by immediate reconstruction, when required.	Strong	Adapted	4	5	5	100%	89%		Accepted
14	The treatment for oral cavity carcinoma must take the patient's individual situation into account. The decision to perform surgery must be made on the basis of the ability to achieve tumour-free resection margins and postoperative quality of life. For locally advanced tumors, the postoperative functional consequences need to be prospectively and carefully assessed. For instance, when a total glossectomy (+/- total laryngectomy) is the only oncologically suitable surgical option, non-surgical organ preservation protocols must be strongly considered.	Strong	Adapted	4	5	5	100%	80%		Accepted
15	In case of a microscopic residual tumour (R1 resection), targeted follow-up resection should ensue with the aim of improving the patient's prognosis, whenever possible.	Weak	Adapted	3	5	4	67%	33%	7: In case of upfront reconstruction with free flap, this is difficult to justify. Radio(chemo)therapy (or brachytherapy ?) are valid options. 14: What about the usefullness of clips to determine the operation bed/zone of difficult rection in order to guide reresection and/or postoperative radiotherapy?	Accepted, but add in text an explanation on 'whenever possible'
16	Continuity of the mandible should be preserved on tumour resection, provided no radiological or intraoperative evidence has been found of tumour invasion of the bone.	Strong	Adapted	2	5	5	75%	75%	12: My response depends on what is understood as "continuity" of the mandible. I would not want to exclude the possibility to access the tumor for resection by paramedian mandibulotomy with replating post resection. This can be advantageous for the primary goal i.e. complete resection , in selected patients, and is not associated with inferior functional outcomes (on the contrary: see Int J Oral Maxillofac Surg. 2001 Jun;30(3):199-204.) Of course, if the adequacy of the resection is possible without doing a mandibulotomy, this is to be preferred.	Continuity of the mandible should be preserved on tumour resection or restored post-resection, provided no radiological or intraoperative evidence has been found of tumour invasion of the bone.

Radiotherapy										
17	**Because of the increased caries risk induced by radiotherapy of the head and neck region, extra fluoride applications can be considered when starting radiotherapy.**	Weak	Adapted	3	5	4	75%	38%	14: difficult and painfull in case of oral mucositis	**Because of the increased caries risk induced by radiotherapy of the head and neck region, lifelong extra fluoride applications should be considered at least after completion of radiotherapy.**
18	**Patients with small but accessible tumours (T1/T2) in the oral cavity (e.g. lips) may be treated with interstitial brachytherapy in selected cases.**	Weak	Adapted	2	5	3	44%	44%	6: Surgery or brachytherapy according to center policy	Accepted: this recommendation considers interstitial brachytherapy as an option, and does not exclude other appropriate treatments.
19	**Patients with advanced and non-metastatic oral cavity carcinoma who are not suitable for curative surgery (T4b, N3, unacceptable functional consequences, excessive comorbidity) should preferably be administered primary radiochemotherapy rather than radiotherapy alone.**	Weak	Very low	3	5	4	89%	44%	12: I would clearly state what regimen is to be preferred. The evidence presented is not that convincing.	Accepted
20	**Postoperative radiotherapy should be performed for advanced T categories (T3/T4), close or positive resection margins, tumour thickness > 10 mm, lymph node involvement (> pN1) and extra capsular rupture/soft tissue infiltration. 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 radiochemotherapy can be considered.**	Strong	Adapted	3	5	5	78%	56%	7: Clear definition of "close" margin needed. 12: Close margins should be clearly defined. Specimen shrinkage (following 1.muscle contraction 2.formalin fixation) can turn a 1 cm peroperative margin into a 5 mm margin, 14: please define 'close' resection margin; In my opinion Tongue Tu thickness is also a determinant for LN iradiation	**Postoperative radiotherapy should be performed for advanced T categories (T3/T4), close (< 4 mm) or positive resection margins, tumour thickness > 10 mm, lymph node involvement (> pN1) and extra capsular rupture/soft tissue infiltration. 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 radiochemotherapy can be considered.**
21	**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).**	Weak	Adapted	2	5	4	57%	29%	7: Data by Ang (IJROBP 2001;51:571-578) show advantage to accelerated regimen. 14: you also have to say something about fractionation in the radical setting	Accepted: For high-risk patients, a trend toward higher LRC and survival rates was noted when PORT was delivered in 5 rather than 7 weeks.
22	**Postoperative radiotherapy should be commenced as early as possible, i.e. within 6-8 weeks after surgery.**	Strong	Adapted	2	5	5	88%	75%	7: Earlier is better (overall treatment time should be kept within 11 to 13 weeks - cfr Ang, same ref as above). 12: 4 to 6 weeks is ideal, efficacy drops after 6 weeks	**Postoperative radiotherapy should be commenced as early as possible, i.e. within 6-8 weeks after surgery, and should be completed within 12-13 weeks after surgery.**
23	**In concurrent (primary or postoperative) radiochemotherapy, chemotherapy should be platinum-based (100 mg/m² every three weeks in case of postoperative radiochemotherapy).**	Strong	Adapted	2	5	5	86%	71%		**In concurrent (primary or postoperative) radiochemotherapy, chemotherapy should be fractionated conventionally (i.e. 2 fractions per day, 5 days per week) and platinum-based (100 mg/m² every three weeks in case of postoperative radiochemotherapy).**
24	**In view of the favourable benefit/risk balance, IMRT is recommended in patients with advanced oral cavity cancer.**	Strong	Very low	3	5	5	75%	75%	7: Note : p.49, stated "no relevant RCTs were identified" - what about PARSPORT study ? (Nutting, Lancet Oncol 2011). 14: I aggree with the statement but the statement itself is way to narrow. It should be stated that IMRT has to be implemented carefully: image guidance and QA is of utmost importance (see Lester Petersen JCO 2010: 2Y survival difference of 20%!!); a review on guidelines for contouring of the gross tumor volume would be very interesting	Accepted; quality issue will be added to the text.

#	Recommendation								Comment	Acceptance
25	Interruption of radiotherapy is detrimental to tumour control and should be avoided.	Strong	Adapted	5	5	5	100%	100%		Accepted
26	Radiochemotherapy should only be performed at facilities in which radiotherapy- and chemotherapy-induced acute toxicities can be adequately managed.	Strong	Adapted	5	5	5	100%	100%		Accepted
27	There is insufficient evidence to recommend the combination of radiotherapy with EGFR inhibitors in patients with oral cavity cancer.	Strong	Very low	3	5	4,5	75%	50%		Accepted
	Induction chemotherapy									
28	In patients with oral cavity cancer, induction chemotherapy is not generally recommended.	Weak	Very low	3	5	5	86%	57%		Accepted
	Reconstructive surgery									
29	Reconstructive measures must basically form part of a surgical concept. When planning reconstruction, consideration must be given to the entire oncological scenario. The anticipated functional or cosmetic improvement must justify the efforts involved in reconstruction.	Strong	Adapted	5	5	5	100%	100%		Accepted
	Treatment of the neck									
30	Treatment of the neck 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).	Strong	Very low	3	5	5	89%	78%		Accepted
31	Perform a selective neck dissection of at least level I, II and III in all patients with a cN_0M_0 oral cavity SCC that is treated surgically.	Strong	Very low	3	5	5	89%	56%	12: evidence to suggest inclusion of level IV: Byers RM, Weber RS, Andrew s T, McGill D, Kare R, Wolf P. Frequency and therapeutic implications of "skip metastases" in the neck from squamous carcinoma of the oral tongue. Head Neck 1997;19(1):14-19.	Accepted, but an explanation of 'at least' will be added to the text.
32	A neck dissection can be ommitted exceptionally in some patients with a $cT1N_0M_0$ oral cavity SCC, depending on the localisation and thickness of the tumour (< 4 mm).	Weak	Very low	2	5	5	78%	56%	12: but I would mention that this requires good follow -up of the neck (ultrasound)	**A neck dissection can be ommitted exceptionally in some patients with a $cT1N_0M_0$ oral cavity SCC, depending on the localisation and thickness of the tumour (< 4 mm).** In text: explanation that <4 mm counts for oral tongue; good follow -up is needed
33	Perform a selective ipsilateral neck dissection of at least level I, II, III and IV with – if oncologically feasible – preservation of the sternocleidomastoid muscle, jugular vein and spinal accessory nerve in all patients with a $cN+M_0$ oral cavity SCC that is treated surgically.	Strong	Very low	2	5	5	78%	56%	6: Yes in most cases but level I, N1 lesion may be treated w ith a selective I-III neck dissection 12: the evidence as presented does not convince me of the higher value - or even equal value - of selective neck dissection as compared to Modified radical neck dissection for cN+ disease. All studies presented suffer from selection bias w ith prognostically better patients selected for selective neck dissection, yet most of the time - although not statistically significant - outcomes show a trend tow ards better results in MRND patients. I w ould caution against propagating selective neck dissection for more than N1 disease (for N1 disease selective neck dissection including level IV is acceptable)	Accepted, but an explanation of 'at least' will be added to the text.
34	Perform a contralateral neck dissection in patients with a non-metastatic oral cavity SCC that is at or crossing the midline or not clearly localized laterally.	Weak	Very low	3	5	5	89%	67%		Accepted

#	Recommendation	Strength	Level				%	%	Comments	Resolution
35	Only perform a sentinel node procedure for selected T$_{1-2}$N$_0$M$_0$ SCC of the oral cavity (with the exception of floor of mouth tumours) within the framework of clinical research.	Strong	Adapted	2	5	5	89%	89%	7: Evidence by comparative prospective studies shows SLNB is a viable option if performed by experienced teams. I am astonished that the current literature was not reviewed !? I agree with the exception of floor of mouth tumors where SLNB is less accurate.	Removed as a recommendation, and discussed in the text.
	Neck dissection after chemoradiotherapy									
36	Consider performing a diagnostic evaluation of the neck with conventional imaging techniques (CT or MRI) or PET/CT three months after completion of (chemo)radiotherapy.	Weak	Very low	2	5	4	78%	22%	7: PET is preferable because it also evaluates the metabolic response. 8: PET-CT should be performed 12 weeks after completion of radio-chemotherapy for detection of residual disease. Its very high negative predictive value allows to avoid neck dissection if negative.	Consider performing a diagnostic evaluation of the neck with conventional imaging techniques (CT or MRI) or PET/CT three months after completion of **primary** (chemo)radiotherapy. Evidence does not allow to make a choice between methods
37	For patients with oral cavity cancer (N1-3) and complete response to chemoradiotherapy, there is no data to support an additional lymph node dissection.	Weak	Very low	2	5	4	89%	33%	8: define complete response criteria 14: CR clinically, radiologically or evaluated by PET?	No consensus on correct definition of CR, which is also a rather technical issue.
	Histopathology									
38	To avoid a positive resection margin (which is associated with a poorer prognosis), frozen sections taken intraoperatively may be useful.	Weak	Adapted	3	5	5	78%	56%	14: please define where the frozen sections should be taken: near to critical structures, in zones of dysplasia, …..?	Accepted Technical issues are avoided in the recommendations.
39	A distance of at least 10 mm from the palpable tumour margin, whenever technically or anatomically possible, should be taken as a guide for resection to allow a minimal distance of 3-5 mm from the margin of the resected tissue to the primary tumour in the formalin-fixed specimen.	Weak	Adapted	2	5	5	89%	67%		Accepted
40	For discussion with the clinician, the histopathological findings must describe the exact localization of any existing R+ status. The anatomical topography must be clearly indicated when sending the tumour specimen to the pathologist. This may be done with suture markers or colour-coding. The histopathological result must include: tumour localization, macroscopic tumour size, histological tumour type, histological tumour grade, depth of invasion, lymphatic, vascular and perineural invasion, locally infiltrated structures, pT classification, details of affected areas and infiltrated structures, R status and p16.	Strong	Adapted	4	5	5	100%	80%	2: treatment effect in case of neoadjuvant therapy cfr CAP(College of American Pathologists (CAP).http://www.cap.org 7: See remark 19 about p16. 9: Why make p16 mandatory for the resection specimen and not for the diagnostic biopsy? Same remark, in case of positivity, HPV typing should be done 14: is P16 reimbursed?	**For discussion with the clinician, the histopathological findings must describe the exact localization of any existing R+ status. The anatomical topography must be clearly indicated when sending the tumour specimen to the pathologist. This may be done with suture markers or colour-coding. The histopathological result must include: tumour localization, macroscopic tumour size, histological tumour type, histological tumour grade, depth of invasion, lymphatic, vascular and perineural invasion, locally infiltrated structures, pT classification, details of affected areas and infiltrated structures, R status and p16 (if not done on biopsy).**
41	The histopathological findings from a neck dissection specimen must describe the anatomical topography, the side of the neck, type of neck dissection, eliminated levels, total number of lymph nodes plus number of lymph nodes affected, level of the affected lymph nodes, diameter of the largest tumour deposit, additionally removed structures and, if present, extracapsular spread.	Strong	Adapted	4	5	5	100%	80%	2: The anatomical topography mus also be clearly indicated when sending the tumour specimen to the pathologist. This may be done with suture markers or colour-coding 14: number of lymph nodes by level; distance of extracapsular spread?	**The histopathological findings from a neck dissection specimen must describe the anatomical topography, the side of the neck, type of neck dissection, eliminated levels, total number of lymph nodes plus number of lymph nodes affected, number of lymph nodes per level, level of the affected lymph nodes, diameter of the largest tumour deposit, additionally removed structures and, if present, extracapsular spread.**

Treatment of M+ or recurrent disease not suitable for curative treatment										
42	**In patients with metastatic oral cavity cancer or recurrent disease that is not suitable for curative treatment, palliative chemotherapy can be considered after discussion with the patient.**	Strong	Very low	4	5	5	100%	78%	7: Why was the EXTREME study not included ? It is stated that EGFR inhibitors are not reimbursed in Belgium in this setting, which is untrue since Cetuximab is being reimbursed together with cis and 5FU.	**In patients with metastatic oral cavity cancer or recurrent disease that is not suitable for curative treatment, palliative chemotherapy or targeted treatment can be considered after discussion with the patient.** Comment on reimbursement will be removed.
Locoregional recurrence										
43	**FDG-PET/CT may be performed in patients with suspected recurrence in the head and neck if this cannot be confirmed or ruled out by biopsy, CT and/or MRI.**	Weak	Adapted	4	5	5	100%	60%	8: PET should be performed BEFORE endoscopy and biopsies if there is a clinical or imaging suspicion of recurence.	**FDG-PET/CT may be performed in patients with suspected recurrence in the head and neck if this cannot be confirmed or ruled out by biopsy, CT and/or MRI.**
44	**Salvage surgery should be considered in any patient with a resectable locoregional recurrence having previously undergone radiotherapy or surgery. The procedure should only be performed by a surgical team with adequate experience of reconstructive techniques at a facility that offers suitable intensive care support.**	Weak	Adapted	3	5	5	90%	80%		Accepted
45	**Re-irradiation, possibly of a curative nature, should be considered in any patient with a non-resectable locoregional recurrence having already undergone irradiation. Re-irradiation should only take place at facilities with adequate expertise and ideally as part of a clinical therapeutic study.**	Weak	Adapted	3	5	4	90%	30%	10: score only pertains to second sentence. 12: no mention is made of mTHPC-mediated photodynamic therapy, which can be considered in selected patients with small oral cavity recurrences < 10 mm in depth - D'Cruz AK, Robinson MH, Biel MA. mTHPC-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: a multicenter study of 128 patients. Head Neck 2004;26(3):232-240. 2. Tan IB, Dolivet G, Ceruse P, Vander Poorten V, Roest G, Rauschning W. Temoporfin-mediated photodynamic therapy in patients with advanced, incurable head and neck cancer: A multicenter study. Head Neck 2010;32(12):1597-1604. On this basis it is a reimbursed treatment by RIZIV -INAMI 14: A recommendation on the CTV would be helpfull	Added to the text.

Follow-up											
46	The maximum follow-up intervals, even if the patient is free of symptoms, should be 3 months in the first and second year, 6 months in the third to fifth year, and annually afterwards. An individually structured follow-up schedule should be devised for each patient. The quality of life, side effects of treatment, nutritional status, speech, dental status, thyroid function, etc. should be surveyed periodically.	Weak	Adapted	2	5	4	70%	40%	14: evaluation of thyroid function also without clinical evidence of hypothyroidism? What about follow-up of smoking and drinking habits?	The maximum follow-up intervals, even if the patient is free of symptoms, should be 3 months in the first and second year, 6 months in the third to fifth year, and annually afterwards. An individually structured follow-up schedule should be devised for each patient. The quality of life, side effects of treatment, nutritional status, speech, dental status, thyroid function, **smoking and alcohol consumption** etc. should be surveyed periodically. **There is no evidence to support routine use of imaging techniques for the detection of locoregional or metastatic recurrence during follow-up.**
Supportive treatment and rehabilitation											
Dental care and rehabilitation											
47	In patients having undergone surgery and/or irradiation for carcinoma of the oral cavity, the masticatory function should be restored with the help of functional masticatory rehabilitation, using conventional prosthetics and/or implants. Surgical interventions (e.g. extractions) should be performed by professionals with experience in treating patients with head and neck cancer. The patients should undergo routine dental check-ups at a frequency depending on the individual patient case (usually every 4-6 months).	Strong	Adapted	5	5	5	100%	100%	14: please define conventional prosthetics and/or implants	Accepted
48	Infected osteoradionecrosis of the jaw is a serious treatment complication that should be managed in specialized centres.	Strong	Adapted	5	5	5	100%	100%	14: Can a treatment recommendation be proposed? AB, hyperbaric oxygen, ...?	Accepted
Speech and swallowing rehabilitation											
49	Patients with difficulties chewing, speaking and swallowing should be timely provided with appropriate functional therapy. The patients should be introduced to suitably qualified therapists prior to commencing treatment if the scheduled surgical or conservative procedures (e.g. radiotherapy) are likely to cause difficulties with chewing, swallowing and/or speech.	Strong	Adapted	4	5	5	100%	91%		Accepted
50	Patients with dysphagia should undergo appropriate diagnostic procedures, e.g. clinical exam by the speech therapist, videofluoroscopy or fiber-optic endoscopy.	Strong	Adapted	4	5	5	100%	91%		Accepted
51	Patients having difficulty eating and speaking due to carcinoma of the oral cavity and/or its management should have access to speech therapists and nutritional therapists with experience of such pathologies before, during and after treatment.	Strong	Adapted	3	5	5	91%	82%		Accepted
Nutritional therapy											
52	Patients should be regularly screened for malnutrition due to oral cavity cancer or its treatment. Patients at risk for malnutrition should receive timely and ongoing professional dietary counselling and nutritional therapy.	Strong	Adapted	3	5	5	91%	82%		Accepted
Psychosocial counselling and support											
53	Patients with oral cavity cancer (and their family, carers) should be offered psychosocial support on a continuous basis within the context of a multidisciplinary team.	Strong	Adapted	3	5	5	82%	73%	10: I agree, but the need for cooperation between the team in the hospital and the home care team is lacking in the recommendation	Accepted. The notion on continuity of care will be added to the recommendation on multidisciplinary team.

8. TNM CLASSIFICATION

8.1. cTNM Clinical classification

Table 72 – 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
T4a	(lip) Tumour invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin (chin or nose)
	(oral cavity) Tumor invades through cortical bone, into deep/extrinsic muscle of tongue (genioglossus, hypoglossus, palatoglossus, and styloglossus), maxillary sinus, or skin of face
T4b	(lip and oral cavity) Tumour invades masticator space, pterygoid plates, or skull base, or encases internal 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 ipsiletral 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 73 – Staging Lip and Oral Cavity 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	M0
	T1, T2, T3, T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

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