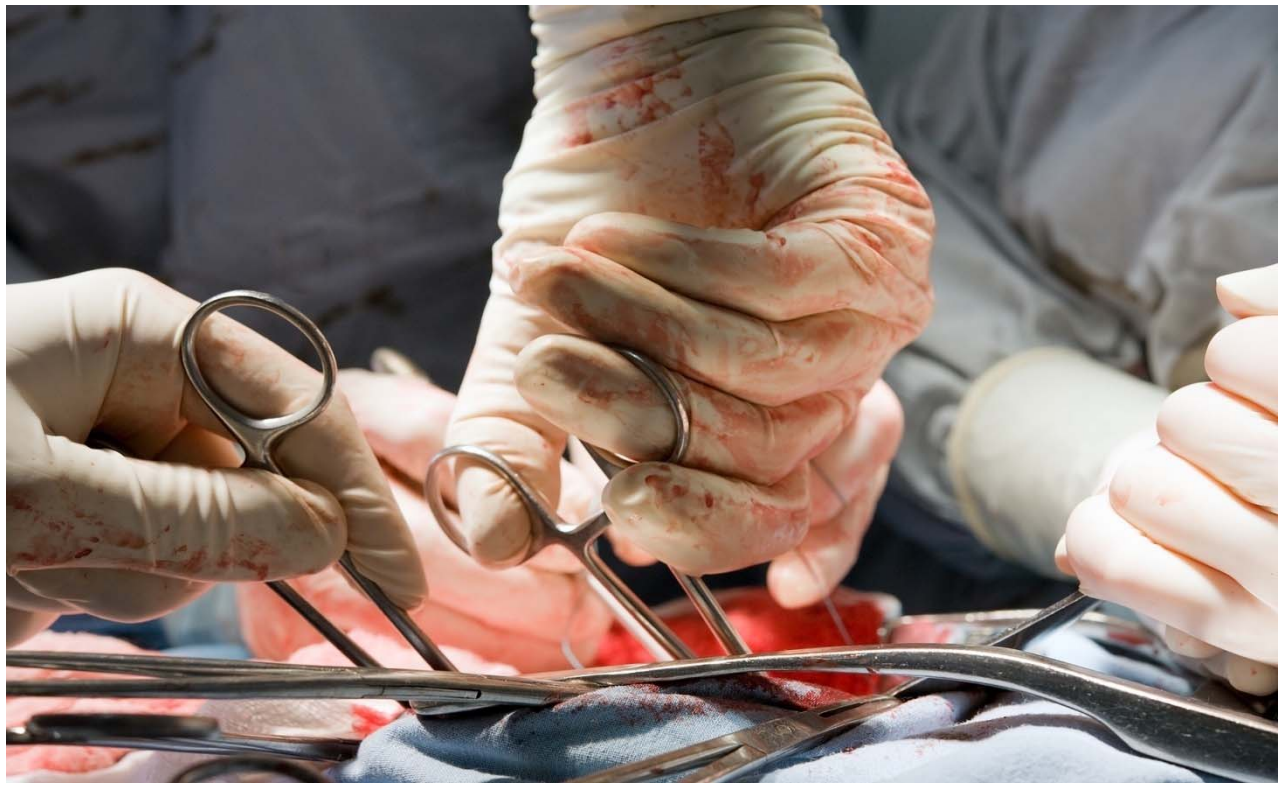
KCE REPORT 179S

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

UPDATE OF THE NATIONAL GUIDELINE ON UPPER GASTROINTESTINAL CANCER

APPENDIX



2012 www.kce.fgov.be

KCE REPORT 179S
GOOD CLINICAL PRACTICE

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

UPDATE OF THE NATIONAL GUIDELINE ON UPPER GASTROINTESTINAL CANCER

APPENDIX

TONI LERUT, SABINE STORDEUR, LEEN VERLEYE, JOAN VLAYEN, TOM BOTERBERG, GERT DE HERTOGH, JOHAN DE MEY, PIERRE DEPREZ, PATRICK FLAMEN, PIET PATTYN, JEAN-LUC VAN LAETHEM, MARC PEETERS

COLOPHON

Title:	Update of the national guideline on upper gastrointestinal cancer - Appendix
Authors:	Toni Lerut (UZ Leuven), Sabine Stordeur (KCE), Leen Verleye (KCE), Joan Vlayen (KCE), Tom Boterberg (UZ Gent), Gert De Hertogh (UZ Leuven), Johan De Mey (UZ Brussel), Pierre Deprez (Cliniques St.-Luc), Patrick Flamen (Institut Jules Bordet), Piet Pattyn (UZ Gent), Jean-Luc Van Laethem (ULB), Marc Peeters (UA)
External Experts:	Michel Buset (Belgian Society of Gastrointestinal Endoscopy)[1,2], Wim Ceelen (Belgian Society of Surgical Oncology)[2], Donald Claeys (Upper GI section of the Royal Belgian Society of Surgery)[1,2], Claude Cuvelier (Belgian Society of Pathology)[1], Pieter Demetter (Belgian Digestive Pathology Club)[1,2], Karin Haustermans (Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-Oncologie)[1,2], Ghislain Houbiers (Belgian Group of Digestive Oncology)[1,2], Anne Jouret-Mourin (Belgian Society of Pathology, Belgian Digestive Pathology Club)[1], Philippe Martinive (Belgische Vereniging voor Radiotherapie-Oncologie - Association Belge de Radiothérapie-Oncologie)[2], Hans Prenen (Belgian Society of Medical Oncology)[1,2], Eric Van Cutsem (Belgian Group of Digestive Oncology)[2], Daniel Van Daele (Société Royale Belge de Gastro-Entérologie)[1,2], Joseph Weerts (Belgian Society of Surgical Oncology, Upper GI section of the Royal Belgian Society of Surgery)[2] [1] Present at the expert meeting; [2] Provided written comments and/or scores
External Validators:	P.D. Siersema (UMC Utrecht, the Netherlands), Jean-Marie Collard (St.-Luc Hospital, Brussels), Marc De Man (OLV Ziekenhuis, Aalst)
Conflict of interest:	Ghislain Houbiers has received a remuneration for a scientific lecture.
Layout:	Ine Verhulst

Publication date:	05 June 2012
Domain:	Good Clinical Practice (GCP)
MeSH:	Esophageal Neoplasms ; Stomach Neoplasms; Practice guidelines
NLM Classification:	WI 149
Language:	English
Format:	Adobe® PDF™ (A4)
Legal depot:	D/2012/10.273/35

How to refer to this document?

Lerut T, Stordeur s, Verleye L, Vlayen J, Boterberg T, De Hertogh G, De Mey J, Deprez P, Flamen P, Pattyn P, Van Laethem J-L, Peeters M. Update of the national guideline on upper gastrointestinal cancer - Appendix. Good Clinical Practice (GCP). Brussels: Belgian Health Care Knowlegde Centre (KCE). 2012. KCE Report 179S. D/2012/10.273/35.

This document is available on the website of the Belgian Health Care Knowledge Centre.

APPENDIX REPORT

TABLE OF CONTENTS

1. SEARCH STRATEGIES 5
1.1. UPDATE SYSTEMATIC REVIEWS 5
1.1.1. OVID Medline 5
1.1.2. OVID PreMedline 5
1.1.3. EMBASE 6
1.1.4. Cochrane Library 6
1.2. UPDATE RANDOMIZED CONTROLLED TRIALS 7
1.2.1. OVID Medline 7
1.2.2. OVID PreMedline 7
1.2.3. EMBASE 9
1.2.4. CENTRAL 9
1.3. UPDATE DIAGNOSTIC STUDIES 9
1.3.1. OVID Medline 9
1.3.2. OVID PreMedline 12
1.3.3. EMBASE 15
2. EXTERNAL EXPERT REVIEW 16
3. TNM-7 CLASSIFICATION [1] 21
3.1. OESOPHAGUS INCLUDING OESOPHAGOGASTRIC JUNCTION (ICD-O C15 AND C16.0) 21
3.1.1. TNM clinical classification 21
3.1.2. pTNM pathological classification 21
3.1.3. Stage grouping 21
3.1.4. Prognostic grouping 22
3.2. STOMACH (ICD-O C16) 22
3.2.1. Anatomical subsites 22
3.2.2. TNM clinical classification 22

3.2.3. pTNM pathological classification 23
3.2.4. Stage grouping 23
4. EVIDENCE TABLES: OESOPHAGEAL CANCER 24
4.1. INITIAL STAGING 24
4.1.1. Imaging techniques (EUS, CT, PET, PET/CT) and minimally invasive surgical procedures 24
4.2. NEOADJUVANT TREATMENT 43
4.2.1. Radiotherapy 43
4.2.2. Neoadjuvant Chemotherapy vs. surgery alone 44
4.2.3. Neoadjuvant chemotherapy vs. Adjuvant Chemotherapy 47
4.2.4. Neoadjuvant Chemoradiotherapy vs. surgery alone 48
4.2.5. Neoadjuvant chemotherapy vs neoadjuvant chemoradiotherapy 54
4.2.6. Definitive chemoradiotherapy (dCRT) versus neoadjuvant treatment followed by surgery or surgery alone 55
4.3. RESTAGING AFTER NEOADJUVANT TREATMENT 56
4.3.1. Systematic reviews 56
4.3.2. Primary studies 61
4.4. TREATMENT OF MUCOSAL CANCER 64
4.4.1. Systematic reviews 64
4.5. SURGERY FOR CANCER BEYOND MUCOSA 66
4.5.1. Esophageal transthoracic technique vs. oesophageal transhiatal technique 66
4.5.2. Open oesophagectomy vs. minimally invasive surgery 70
4.5.3. Anastomotic techniques 73
4.5.4. Volume-outcomes relationship 76
4.6. ADJUVANT TREATMENT 78
4.6.1. Chemotherapy 78
4.6.2. Radiotherapy 78
4.6.3. Chemoradiotherapy 78
4.7. NON-SURGICAL TREATMENT WITH CURATIVE INTENT 78
4.7.1. Definitive chemoradiotherapy vs. Radiotherapy alone 78

4.7.2. Definitive chemoradiotherapy ... 80
4.8. TREATMENT OF METASTATIC DISEASE ... 81
4.8.1. Chemotherapy ... 81
4.8.2. Radiotherapy ... 83
4.8.3. Other interventions (laser, thermotherapy, brachytherapy ... 84
4.8.4. Stenting ... 86
4.8.5. Radiotherapy ... 89
4.9. FOLLOW-UP ... 91
4.9.1. Primary studies: RCTs ... 91
4.9.2. Primary studies: diagnostic accuracy studies ... 92
5. EVIDENCE TABLES: GASTRIC CANCER ... 93
5.1. STAGING ... 93
5.1.1. Endoscopic Ultrasound (EUS) ... 93
5.1.2. Conventional imaging ... 98
5.1.3. Laparoscopic staging ... 115
5.1.4. Sentinel node biopsy ... 117
5.2. TREATMENT EARLY GASTRIC CANCER ... 120
5.2.1. Endoscopic submucosal resection versus endoscopic mucosal dissection ... 120
5.2.2. Endoscopic mucosal resection versus gastrectomy ... 121
5.3. TREATMENT GASTRIC CANCER BEYOND MUCOSA: RESECTABLE GASTRIC CANCER ... 122
5.3.1. Neoadjuvant treatment ... 122
5.3.2. Surgery ... 124
5.3.3. Adjuvant treatment ... 140
5.4. TREATMENT GASTRIC CANCER BEYOND MUCOSA: ADVANCED (UN)RESECTABLE GASTRIC CANCER ... 152
5.4.1. Surgery: gastrectomy +/- Multivisceral resection (MVR) ... 152
5.4.2. IP chemotherapy ... 154
5.4.3. Chemotherapy ... 156
5.4.4. Surgery for gastric perforation ... 166

5.4.5. Surgery or stenting for malignant gastric outlet obstruction 167
5.5. TREATMENT OF RECURRENT DISEASE 170
6. REFERENCES 171

1. SEARCH STRATEGIES

1.1. Update systematic reviews

1.1.1. OVID Medline

Search date: 21 November 2011

N hits: 2280

1 exp esophageal neoplasms/ (34833)
2 (esophag$ adj5 neoplas$).tw. (1095)
3 (oesophag$ adj5 neoplas$).tw. (181)
4 (esophag$ adj5 cancer$).tw. (14095)
5 (oesophag$ adj5 cancer$).tw. (2773)
6 (esophag$ adj5 carcin$).tw. (10867)
7 (oesophag$ adj5 carcin$).tw. (2218)
8 (esophag$ adj5 tumo$).tw. (3823)
9 (oesophag$ adj5 tumo$).tw. (714)
10 (esophag$ adj5 metasta$).tw. (1369)
11 (oesophag$ adj5 metasta$).tw. (193)
12 (esophag$ adj5 malig$).tw. (1992)
13 (oesophag$ adj5 malig$).tw. (496)
14 exp stomach neoplasms/ (68456)
15 (stomach adj5 neoplas$).tw. (705)
16 (stomach adj5 cancer$).tw. (9593)
17 (stomach adj5 carcin$).tw. (4036)
18 (stomach adj5 tumo$).tw. (3182)
19 (stomach adj5 metasta$).tw. (884)
20 (stomach adj5 malig$).tw. (1045)
21 (gastric adj5 neoplas$).tw. (1435)
22 (gastric adj5 cancer$).tw. (32176)
23 (gastric adj5 carcin$).tw. (14657)
24 (gastric adj5 tumo$).tw. (6394)
25 (gastric adj5 metasta$).tw. (4001)
26 (gastric adj5 malig$).tw. (2496)
27 exp Esophagogastric Junction/ (6231)
28 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (1925790)
29 exp Cardia/ (3583)
30 or/1-26 (114253)
31 (egj or ogj).mp. (202)
32 (gej or goj).mp. (190)
33 27 or 29 or 31 or 32 (9516)
34 28 and 33 (3105)
35 30 or 34 (114372)
36 meta-analysis.mp,pt. or review.pt. or search:.tw. (1837533)
37 35 and 36 (12560)
38 limit 37 to (yr="2007 - 2011" and (dutch or english or french)) (**2280**)

1.1.2. OVID PreMedline

Search date: 21 November 2011

N hits: 67

1 (esophag$ adj5 neoplas$).tw. (39)
2 (oesophag$ adj5 neoplas$).tw. (15)
3 (esophag$ adj5 cancer$).tw. (472)
4 (oesophag$ adj5 cancer$).tw. (117)
5 (esophag$ adj5 carcin$).tw. (329)
6 (oesophag$ adj5 carcin$).tw. (133)
7 (esophag$ adj5 tumo$).tw. (110)
8 (oesophag$ adj5 tumo$).tw. (27)
9 (esophag$ adj5 metasta$).tw. (39)
10 (oesophag$ adj5 metasta$).tw. (11)
11 (esophag$ adj5 malig$).tw. (56)

12 (oesophag$ adj5 malig$).tw. (47)
13 (stomach adj5 neoplas$).tw. (14)
14 (stomach adj5 cancer$).tw. (204)
15 (stomach adj5 carcin$).tw. (121)
16 (stomach adj5 tumo$).tw. (88)
17 (stomach adj5 metasta$).tw. (26)
18 (stomach adj5 malig$).tw. (19)
19 (gastric adj5 neoplas$).tw. (68)
20 (gastric adj5 cancer$).tw. (1334)
21 (gastric adj5 carcin$).tw. (460)
22 (gastric adj5 tumo$).tw. (238)
23 (gastric adj5 metasta$).tw. (157)
24 (gastric adj5 malig$).tw. (83)
25 or/1-24 (2962)
26 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (75618)
27 (egj or ogj).mp. (9)
28 (gej or goj).mp. (15)
29 27 or 28 (24)
30 26 and 29 (17)
31 25 or 30 (2966)
32 meta-analysis.mp,pt. or review.pt. or search:.tw. (15499)
33 31 and 32 (86)
34 limit 33 to (yr="2007 - 2011" and (dutch or english or french)) (**67**)

1.1.3. EMBASE

Search date: 14 November 2011

N hits: 412

'esophagus cancer'/exp OR 'lower esophagus sphincter'/exp OR 'cardia carcinoma'/exp OR (esophag* NEAR/5 neoplas*):ab,ti OR (oesophag* NEAR/5 neoplas*):ab,ti OR (esophag* NEAR/5 cancer*):ab,ti OR (oesophag* NEAR/5 cancer*):ab,ti OR (esophag* NEAR/5 carcin*):ab,ti OR (oesophag* NEAR/5 carcin*):ab,ti OR (esophag* NEAR/5 tumo*):ab,ti OR (oesophag* NEAR/5 tumo*):ab,ti OR (esophag* NEAR/5 metasta*):ab,ti OR (oesophag* NEAR/5 metasta*):ab,ti OR (esophag* NEAR/5 malig*):ab,ti OR (oesophag* NEAR/5 malig*):ab,ti OR 'stomach cancer'/exp OR (stomach NEAR/5 neoplas*):ab,ti OR (gastric NEAR/5 neoplas*):ab,ti OR (stomach NEAR/5 cancer*):ab,ti OR (gastric NEAR/5 cancer*):ab,ti OR (stomach NEAR/5 carcin*):ab,ti OR (gastric NEAR/5 carcin*):ab,ti OR (stomach NEAR/5 tumo*):ab,ti OR (gastric NEAR/5 tumo*):ab,ti OR (stomach NEAR/5 metasta*):ab,ti OR (gastric NEAR/5 metasta*):ab,ti OR (stomach NEAR/5 malig*):ab,ti OR (gastric NEAR/5 malig*):ab,ti AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim AND [2007-2011]/py

1.1.4. Cochrane Library

Search date: 14 November 2011

N hits:

- CDSR: 13

- DARE: 107

- HTA: 51

#1 MeSH descriptor Stomach Neoplasms explode tree 1
#2 MeSH descriptor Esophageal Neoplasms explode tree 1
#3 MeSH descriptor Esophagogastric Junction explode tree 1
#4 MeSH descriptor Cardia explode all trees
#5 #1 OR #2 OR #3 OR #4

1.2. Update randomized controlled trials

1.2.1. OVID Medline

Search date: 21 November 2011

N hits: 976

1 exp esophageal neoplasms/ (34833)
2 (esophag$ adj5 neoplas$).tw. (1095)
3 (oesophag$ adj5 neoplas$).tw. (181)
4 (esophag$ adj5 cancer$).tw. (14095)
5 (oesophag$ adj5 cancer$).tw. (2773)
6 (esophag$ adj5 carcin$).tw. (10867)
7 (oesophag$ adj5 carcin$).tw. (2218)
8 (esophag$ adj5 tumo$).tw. (3823)
9 (oesophag$ adj5 tumo$).tw. (714)
10 (esophag$ adj5 metasta$).tw. (1369)
11 (oesophag$ adj5 metasta$).tw. (193)
12 (esophag$ adj5 malig$).tw. (1992)
13 (oesophag$ adj5 malig$).tw. (496)
14 exp stomach neoplasms/ (68456)
15 (stomach adj5 neoplas$).tw. (705)
16 (stomach adj5 cancer$).tw. (9593)
17 (stomach adj5 carcin$).tw. (4036)
18 (stomach adj5 tumo$).tw. (3182)
19 (stomach adj5 metasta$).tw. (884)
20 (stomach adj5 malig$).tw. (1045)
21 (gastric adj5 neoplas$).tw. (1435)
22 (gastric adj5 cancer$).tw. (32176)
23 (gastric adj5 carcin$).tw. (14657)
24 (gastric adj5 tumo$).tw. (6394)
25 (gastric adj5 metasta$).tw. (4001)
26 (gastric adj5 malig$).tw. (2496)
27 exp Esophagogastric Junction/ (6231)
28 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (1925790)
29 exp Cardia/ (3583)
30 or/1-26 (114253)
31 (egj or ogj).mp. (202)
32 (gej or goj).mp. (190)
33 27 or 29 or 31 or 32 (9516)
34 28 and 33 (3105)
35 30 or 34 (114372)
36 randomized controlled trial.pt. (321917)
37 controlled clinical trial.pt. (83985)
38 randomized.ab. (226812)
39 placebo.ab. (130106)
40 clinical trials as topic.sh. (159410)
41 randomly.ab. (163219)
42 trial.ti. (97578)
43 36 or 37 or 38 or 39 or 40 or 41 or 42 (747822)
44 exp animals/ not humans.sh. (3715340)
45 43 not 44 (690009)
46 35 and 45 (4593)
47 limit 46 to (yr="2007 - 2011" and (dutch or english or french)) (**976**)

1.2.2. OVID PreMedline

Search date: 21 November 2011

N hits: 98

1 (esophag$ adj5 neoplas$).tw. (39)
2 (oesophag$ adj5 neoplas$).tw. (15)
3 (esophag$ adj5 cancer$).tw. (472)
4 (oesophag$ adj5 cancer$).tw. (117)
5 (esophag$ adj5 carcin$).tw. (329)
6 (oesophag$ adj5 carcin$).tw. (133)
7 (esophag$ adj5 tumo$).tw. (110)
8 (oesophag$ adj5 tumo$).tw. (27)
9 (esophag$ adj5 metasta$).tw. (39)
10 (oesophag$ adj5 metasta$).tw. (11)
11 (esophag$ adj5 malig$).tw. (56)
12 (oesophag$ adj5 malig$).tw. (47)
13 (stomach adj5 neoplas$).tw. (14)
14 (stomach adj5 cancer$).tw. (204)
15 (stomach adj5 carcin$).tw. (121)
16 (stomach adj5 tumo$).tw. (88)
17 (stomach adj5 metasta$).tw. (26)
18 (stomach adj5 malig$).tw. (19)
19 (gastric adj5 neoplas$).tw. (68)
20 (gastric adj5 cancer$).tw. (1334)
21 (gastric adj5 carcin$).tw. (460)
22 (gastric adj5 tumo$).tw. (238)
23 (gastric adj5 metasta$).tw. (157)
24 (gastric adj5 malig$).tw. (83)
25 or/1-24 (2962)
26 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (75618)
27 (egj or ogj).mp. (9)
28 (gej or goj).mp. (15)
29 27 or 28 (24)
30 26 and 29 (17)
31 25 or 30 (2966)
32 randomized controlled trial.pt. (465)
33 controlled clinical trial.pt. (31)
34 randomized.ab. (10583)
35 placebo.ab. (4264)
36 randomly.ab. (10708)
37 trial.ti. (4339)
38 or/32-37 (24574)
39 31 and 38 (153)
40 limit 39 to (yr="2007 - 2011" and (dutch or english or french)) (**98**)

1.2.3. EMBASE

Search date: 14 November 2011

N hits: 461

'esophagus cancer'/exp OR 'lower esophagus sphincter'/exp OR 'cardia carcinoma'/exp OR (esophag* NEAR/5 neoplas*):ab,ti OR (oesophag* NEAR/5 neoplas*):ab,ti OR (esophag* NEAR/5 cancer*):ab,ti OR (oesophag* NEAR/5 cancer*):ab,ti OR (esophag* NEAR/5 carcin*):ab,ti OR (oesophag* NEAR/5 carcin*):ab,ti OR (esophag* NEAR/5 tumo*):ab,ti OR (oesophag* NEAR/5 tumo*):ab,ti OR (esophag* NEAR/5 metasta*):ab,ti OR (oesophag* NEAR/5 metasta*):ab,ti OR (esophag* NEAR/5 malig*):ab,ti OR (oesophag* NEAR/5 malig*):ab,ti OR 'stomach cancer'/exp OR (stomach NEAR/5 neoplas*):ab,ti OR (gastric NEAR/5 neoplas*):ab,ti OR (stomach NEAR/5 cancer*):ab,ti OR (gastric NEAR/5 cancer*):ab,ti OR (stomach NEAR/5 carcin*):ab,ti OR (gastric NEAR/5 carcin*):ab,ti OR (stomach NEAR/5 tumo*):ab,ti OR (gastric NEAR/5 tumo*):ab,ti OR (stomach NEAR/5 metasta*):ab,ti OR (gastric NEAR/5 metasta*):ab,ti OR (stomach NEAR/5 malig*):ab,ti OR (gastric NEAR/5 malig*):ab,ti AND [randomized controlled trial]/lim AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim AND [2007-2011]/py

1.2.4. CENTRAL

Search date: 14 November 2011

N hits: 1938

#1 MeSH descriptor Stomach Neoplasms explode tree 1

#2 MeSH descriptor Esophageal Neoplasms explode tree 1

#3 MeSH descriptor Esophagogastric Junction explode tree 1

#4 MeSH descriptor Cardia explode all trees

#5 #1 OR #2 OR #3 OR #4

1.3. Update diagnostic studies

For the update of the search for diagnostic studies the following systematic reviews were chosen as starting point for oesophageal cancer:

- CT, MRI, PET, EUS, thoracoscopy, laparoscopy: AETMIS 2009 (search date: 7/2008)

- Restaging with PET: Chen 2011 (search date: 1/2010)

- Restaging with EUS: Ngamruengphong 2010 (search date: 2/2008)

For gastric cancer the following systematic reviews were chosen as starting point:

- EUS: Mocellin 2011 (search date: 7/2010)

- CT, MRI, PET, US: Seevaratnam 2011 (search date: 12/2009)

- SLNB: Wang 2011 (search date: 4/2011)

- Laparoscopy: Leake 2011 (search date: 12/2009)

1.3.1. OVID Medline

1.3.1.1. Oesophageal cancer

Search date: 17 January 2012

N hits: 945

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. (28582)

2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (26502)

3 glucose.tw. (270101)

4 3 and 2 (4874)

5 1 or 4 (28972)

6 (pet or petscan*).tw. or tomography, emission-computed/ (51187)

7 emission.tw. (74731)

8 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (191304)

9 8 and 7 (37988)

10 6 or 9 (66077)

11 5 and 10 (15677)

12 animals/ not humans/ (3550250)

13 deoxyglucose/ (10067)

14 Fluorodeoxyglucose F18/ (14596)

15 14 or 5 (30827)

16 Positron-Emission Tomography/ (21046)

17 10 or 16 (70163)

18 17 and 15 (17569)

19 18 not 12 (16718)

20 exp Magnetic Resonance Imaging/ (254188)

21 magnetic resonance imag$.mp. (266990)

22 chemical shift imag$.mp. (694)

23 mr tomograph$.mp. (479)

24 magnetization transfer contrast imag$.mp. (23)

25 proton spin tomograph$.mp. (38)

26 zeugmatograph$.mp. (34)

27 exp Magnetic Resonance Spectroscopy/ (160209)

28 exp NMR Imaging/ (254188)

29 MRS.mp. (8906)

30 MRI.mp. (102795)

31 NMR.mp. (85841)

32 KST.mp. (80)

33 or/20-32 (468098)

34 exp Tomography, X-Ray Computed/ (255174)

35 Tomography Scanners, X-Ray Computed/ (1546)

36 34 or 35 (256194)

37 ((CT or CTs or CAT) adj3 (scan* or x-ray* or cine or helical or spiral or volume* or cone beam*)).ti,ab. (64443)

38 (compute* adj3 tomograph*).ti,ab. (146784)

39 (tomodensitometr* or electron beam tomograph* or tomograph* scan* or EBCT or MDCT).ti,ab. (23481)

40 (x ray* adj3 (microtomograph* or microcomput*)).ti,ab. (307)

41 or/36-40 (330107)

42 Endosonography/ (7296)

60 exp esophageal neoplasms/ (33579)

61 (esophag$ adj5 neoplas$).tw. (1035)

62 (oesophag$ adj5 neoplas$).tw. (183)

63 (esophag$ adj5 cancer$).tw. (13424)

64 (oesophag$ adj5 cancer$).tw. (2744)

65 (esophag$ adj5 carcin$).tw. (10472)

66 (oesophag$ adj5 carcin$).tw. (2214)

67 (esophag$ adj5 tumo$).tw. (3715)

68 (oesophag$ adj5 tumo$).tw. (718)

69 (esophag$ adj5 metasta$).tw. (1306)

70 (oesophag$ adj5 metasta$).tw. (190)

71 (esophag$ adj5 malig$).tw. (1943)

72 (oesophag$ adj5 malig$).tw. (493)

86 exp Esophagogastric Junction/ (6110)

87 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (1874814)

88 exp Cardia/ (3495)

90 (egj or ogj).mp. (201)

91 (gej or goj).mp. (188)

92 86 or 88 or 90 or 91 (9315)

93 87 and 92 (3059)

116 eus.mp. (3822)

118 exp laparoscopy/ or mediastinoscopy/ or exp thoracoscopy/ (66980)

125 19 or 33 or 41 or 42 or 116 or 118 (802408)

126 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 93 (40115)

127 125 and 126 (3748)

128 limit 127 to yr="2008 - 2012" (**945**)

1.3.1.2. Gastric cancer

Search date: 17 January 2012

N hits: 806

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. (28582)

2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (26502)

3 glucose.tw. (270101)

4 3 and 2 (4874)

5 1 or 4 (28972)

6 (pet or petscan*).tw. or tomography, emission-computed/ (51187)

7 emission.tw. (74731)

8 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (191304)

9 8 and 7 (37988)

10 6 or 9 (66077)

11 5 and 10 (15677)

12 animals/ not humans/ (3550250)

13 deoxyglucose/ (10067)

14 Fluorodeoxyglucose F18/ (14596)

15 14 or 5 (30827)

16 Positron-Emission Tomography/ (21046)

17 10 or 16 (70163)

18 17 and 15 (17569)

19 18 not 12 (16718)

20 exp Magnetic Resonance Imaging/ (254188)

21 magnetic resonance imag$.mp. (266990)

22 chemical shift imag$.mp. (694)

23 mr tomograph$.mp. (479)

24 magnetization transfer contrast imag$.mp. (23)

25 proton spin tomograph$.mp. (38)

26 zeugmatograph$.mp. (34)

27 exp Magnetic Resonance Spectroscopy/ (160209)

28 exp NMR Imaging/ (254188)

29 MRS.mp. (8906)

30 MRI.mp. (102795)

31 NMR.mp. (85841)

32 KST.mp. (80)

33 or/20-32 (468098)

34 exp Tomography, X-Ray Computed/ (255174)

35 Tomography Scanners, X-Ray Computed/ (1546)

36 34 or 35 (256194)

37 ((CT or CTs or CAT) adj3 (scan* or x-ray* or cine or helical or spiral or volume* or cone beam*)).ti,ab. (64443)

38 (compute* adj3 tomograph*).ti,ab. (146784)

39 (tomodensitometr* or electron beam tomograph* or tomograph* scan* or EBCT or MDCT).ti,ab. (23481)

40 (x ray* adj3 (microtomograph* or microcomput*)).ti,ab. (307)

41 or/36-40 (330107)
42 Endosonography/ (7296)
43 Laparoscopy/ (50054)
44 Ultrasonography/ (59510)
46 exp Lymph Nodes/ and (sentinel or SLN).mp. (3655)
47 exp Sentinel Lymph Node Biopsy/ (6512)
73 exp stomach neoplasms/ (66025)
74 (stomach adj5 neoplas$).tw. (668)
75 (stomach adj5 cancer$).tw. (9228)
76 (stomach adj5 carcin$).tw. (3928)
77 (stomach adj5 tumo$).tw. (3105)
78 (stomach adj5 metasta$).tw. (843)
79 (stomach adj5 malig$).tw. (1013)
80 (gastric adj5 neoplas$).tw. (1402)
81 (gastric adj5 cancer$).tw. (30860)
82 (gastric adj5 carcin$).tw. (14264)
83 (gastric adj5 tumo$).tw. (6242)
84 (gastric adj5 metasta$).tw. (3883)
85 (gastric adj5 malig$).tw. (2441)
86 exp Esophagogastric Junction/ (6110)
87 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (1874814)
88 exp Cardia/ (3495)
90 (egj or ogj).mp. (201)
91 (gej or goj).mp. (188)
92 86 or 88 or 90 or 91 (9315)
93 87 and 92 (3059)
116 eus.mp. (3822)
129 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 93 (79184)
130 19 or 33 or 41 or 43 or 44 (830155)
131 129 and 130 (4781)
132 limit 131 to (yr="2009 - 2012" and (dutch or english or french)) (749)
133 46 or 47 (7517)
134 129 and 133 (229)
135 limit 134 to (yr="2011 - 2012" and (dutch or english or french)) (10)
136 42 or 116 (8519)
137 129 and 136 (777)
138 limit 137 to (yr="2010 - 2012" and (dutch or english or french)) (66)
139 132 or 135 or 138 (**806**)

1.3.2. OVID PreMedline

1.3.2.1. Oesophageal cancer

Search date: 17 January 2012

N hits: 84

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. (1168)
2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (3003)
3 glucose.tw. (12912)
4 3 and 2 (222)
5 1 or 4 (1190)
6 (pet or petscan*).tw. or tomography, emission-computed/ (2738)
7 emission.tw. (17509)
8 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (11489)

9 8 and 7 (2023)
10 6 or 9 (3666)
11 5 and 10 (974)
21 magnetic resonance imag$.mp. (6306)
22 chemical shift imag$.mp. (28)
23 mr tomograph$.mp. (5)
24 magnetization transfer contrast imag$.mp. (0)
25 proton spin tomograph$.mp. (0)
26 zeugmatograph$.mp. (2)
29 MRS.mp. (551)
30 MRI.mp. (6303)
31 NMR.mp. (14125)
32 KST.mp. (1)
33 or/20-32 (24436)
37 ((CT or CTs or CAT) adj3 (scan* or x-ray* or cine or helical or spiral or volume* or cone beam*)).ti,ab. (3095)
38 (compute* adj3 tomograph*).ti,ab. (7580)
39 (tomodensitometr* or electron beam tomograph* or tomograph* scan* or EBCT or MDCT).ti,ab. (1414)
40 (x ray* adj3 (microtomograph* or microcomput*)).ti,ab. (58)
41 or/37-40 (9697)
61 (esophag$ adj5 neoplas$).tw. (41)
62 (oesophag$ adj5 neoplas$).tw. (12)
63 (esophag$ adj5 cancer$).tw. (528)
64 (oesophag$ adj5 cancer$).tw. (117)
65 (esophag$ adj5 carcin$).tw. (371)
66 (oesophag$ adj5 carcin$).tw. (131)
67 (esophag$ adj5 tumo$).tw. (130)
68 (oesophag$ adj5 tumo$).tw. (26)
69 (esophag$ adj5 metasta$).tw. (48)
70 (oesophag$ adj5 metasta$).tw. (11)
71 (esophag$ adj5 malig$).tw. (67)
72 (oesophag$ adj5 malig$).tw. (49)
87 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (81045)
90 (egj or ogj).mp. (10)
91 (gej or goj).mp. (14)
92 90 or 91 (24)
93 87 and 92 (17)
116 eus.mp. (269)
125 11 or 33 or 41 or 116 (33293)
126 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 93 (1162)
127 125 and 126 (96)
128 limit 127 to yr="2008 - 2012" (**84**)

1.3.2.2. Gastric cancer

Search date: 17 January 2012

N hits: 79

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. (1168)
2 (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (3003)
3 glucose.tw. (12912)
4 3 and 2 (222)
5 1 or 4 (1190)
6 (pet or petscan*).tw. or tomography, emission-computed/ (2738)

7 emission.tw. (17509)

8 (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (11489)

9 8 and 7 (2023)

10 6 or 9 (3666)

11 5 and 10 (974)

21 magnetic resonance imag$.mp. (6306)

22 chemical shift imag$.mp. (28)

23 mr tomograph$.mp. (5)

24 magnetization transfer contrast imag$.mp. (0)

25 proton spin tomograph$.mp. (0)

26 zeugmatograph$.mp. (2)

29 MRS.mp. (551)

30 MRI.mp. (6303)

31 NMR.mp. (14125)

32 KST.mp. (1)

33 or/20-32 (24436)

37 ((CT or CTs or CAT) adj3 (scan* or x-ray* or cine or helical or spiral or volume* or cone beam*)).ti,ab. (3095)

38 (compute* adj3 tomograph*).ti,ab. (7580)

39 (tomodensitometr* or electron beam tomograph* or tomograph* scan* or EBCT or MDCT).ti,ab. (1414)

40 (x ray* adj3 (microtomograph* or microcomput*)).ti,ab. (58)

41 or/37-40 (9697)

74 (stomach adj5 neoplas$).tw. (15)

75 (stomach adj5 cancer$).tw. (232)

76 (stomach adj5 carcin$).tw. (131)

77 (stomach adj5 tumo$).tw. (86)

78 (stomach adj5 metasta$).tw. (25)

79 (stomach adj5 malig$).tw. (19)

80 (gastric adj5 neoplas$).tw. (82)

81 (gastric adj5 cancer$).tw. (1499)

82 (gastric adj5 carcin$).tw. (478)

83 (gastric adj5 tumo$).tw. (265)

84 (gastric adj5 metasta$).tw. (178)

85 (gastric adj5 malig$).tw. (81)

87 (neoplas$ or cancer$ or carcin$ or tumo$ or metasta$ or malig$).tw. (81045)

90 (egj or ogj).mp. (10)

91 (gej or goj).mp. (14)

92 90 or 91 (24)

93 87 and 92 (17)

116 eus.mp. (269)

129 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 93 (2247)

130 11 or 33 or 41 (33086)

131 129 and 130 (103)

132 limit 131 to (yr="2009 - 2012" and (dutch or english or french)) (69)

137 129 and 116 (13)

138 limit 137 to (yr="2010 - 2012" and (dutch or english or french)) (10)

139 132 or 135 or 138 (**79**)

1.3.3. EMBASE

1.3.3.1. Oesophageal cancer

Search date: 18 January 2012

N hits: 1345

'esophagus cancer'/exp OR 'lower esophagus sphincter'/exp OR 'cardia carcinoma'/exp OR (esophag* NEAR/5 neoplas*):ab,ti OR (oesophag* NEAR/5 neoplas*):ab,ti OR (esophag* NEAR/5 cancer*):ab,ti OR (oesophag* NEAR/5 cancer*):ab,ti OR (esophag* NEAR/5 carcin*):ab,ti OR (oesophag* NEAR/5 carcin*):ab,ti OR (esophag* NEAR/5 tumo*):ab,ti OR (oesophag* NEAR/5 tumo*):ab,ti OR (esophag* NEAR/5 metasta*):ab,ti OR (oesophag* NEAR/5 metasta*):ab,ti OR (esophag* NEAR/5 malig*):ab,ti OR (oesophag* NEAR/5 malig*):ab,ti AND ('computer assisted tomography'/exp OR 'computed tomography scanner'/exp OR 'nuclear magnetic resonance imaging'/exp OR 'whole body pet'/exp OR 'endoscopic echography'/exp OR 'thoracoscopy'/exp OR 'laparoscopy'/exp OR 'mediastinoscopy'/exp) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim AND [2008-2012]/py

1.3.3.2. Gastric cancer

Search date: 18 January 2012

N hits: 1443

'lower esophagus sphincter'/exp OR 'cardia carcinoma'/exp OR (stomach NEAR/5 neoplas*):ab,ti OR (gastric NEAR/5 neoplas*):ab,ti OR (stomach NEAR/5 cancer*):ab,ti OR (gastric NEAR/5 cancer*):ab,ti OR (stomach NEAR/5 carcin*):ab,ti OR (gastric NEAR/5 carcin*):ab,ti OR (stomach NEAR/5 tumo*):ab,ti OR (gastric NEAR/5 tumo*):ab,ti OR (stomach NEAR/5 metasta*):ab,ti OR (gastric NEAR/5 metasta*):ab,ti OR (stomach NEAR/5 malig*):ab,ti OR (gastric NEAR/5 malig*):ab,ti OR 'stomach cancer'/exp AND ('computer assisted tomography'/exp OR 'computed tomography scanner'/exp OR 'nuclear magnetic resonance imaging'/exp OR 'whole body pet'/exp OR 'laparoscopy'/exp OR 'echography'/de) AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim AND [2009-2012]/py OR ('lower esophagus sphincter'/exp OR 'cardia carcinoma'/exp OR (stomach NEAR/5 neoplas*):ab,ti OR (gastric NEAR/5 neoplas*):ab,ti OR (stomach NEAR/5 cancer*):ab,ti OR (gastric NEAR/5 cancer*):ab,ti OR (stomach NEAR/5 carcin*):ab,ti OR (gastric NEAR/5 carcin*):ab,ti OR (stomach NEAR/5 tumo*):ab,ti OR (gastric NEAR/5 tumo*):ab,ti OR (stomach NEAR/5 metasta*):ab,ti OR (gastric NEAR/5 metasta*):ab,ti OR (stomach NEAR/5 malig*):ab,ti OR (gastric NEAR/5 malig*):ab,ti OR 'stomach cancer'/exp AND 'sentinel lymph node biopsy'/exp AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim AND [2011-2012]/py) OR ('lower esophagus sphincter'/exp OR 'cardia carcinoma'/exp OR (stomach NEAR/5 neoplas*):ab,ti OR (gastric NEAR/5 neoplas*):ab,ti OR (stomach NEAR/5 cancer*):ab,ti OR (gastric NEAR/5 cancer*):ab,ti OR (stomach NEAR/5 carcin*):ab,ti OR (gastric NEAR/5 carcin*):ab,ti OR (stomach NEAR/5 tumo*):ab,ti OR (gastric NEAR/5 tumo*):ab,ti OR (stomach NEAR/5 metasta*):ab,ti OR (gastric NEAR/5 metasta*):ab,ti OR (stomach NEAR/5 malig*):ab,ti OR (gastric NEAR/5 malig*):ab,ti OR 'stomach cancer'/exp AND 'endoscopic echography'/exp AND ([article]/lim OR [article in press]/lim OR [review]/lim) AND ([dutch]/lim OR [english]/lim OR [french]/lim) AND [embase]/lim AND [2010-2012]/py)

2. EXTERNAL EXPERT REVIEW

Item	Recommendation(s)	GOR	LoE	EE1	EE2	EE3	EE4	EE5	EE6	EE7	EE8	EE9	Comments	Min	Max	Mean	Median	% 4 or 5	Decision
Oesophageal cancer																			
Staging	All patients diagnosed with oesophageal cancer should be discussed at a multidisciplinary meeting	Strong	Low	5	5	5	5	5	5	5	5	5		5	5	5	5	100%	
	In patients with newly diagnosed oesophageal cancer, CT scan of the neck (including lower neck region), thorax and abdomen should be performed routinely	Strong	Low	4	5	5	4	5	4	5	5	5	EE4: is CT sensitive enough for neck region?	4	5	5	5	100%	No change, is discussed in the text
	Endoscopic ultrasonography (EUS), combined with fine needle aspiration cytology (FNAC) if technically feasible, should be considered to evaluate locoregional invasion (T and N stage) and celiac lymph nodes in patients with oesophageal cancer	Strong	Low	5	5	5	4	5	4	5	4	5	EE4: why celiac LN only, cervical also EE6: FNAC most important in case of coeliac lymphnodus	4	5	5	5	100%	No change, is discussed in the text
	PET/CT should be considered for M staging if a patient with T2-4 N+ oesophageal cancer is a candidate for a curative treatment after CT and EUS	Strong	Low	4	5	4	4	4	5	4	4	5	EE5: Also if N0 in case of surgery planified	4	5	4	4	100%	Little benefit to be expected in N0, no evidence
	The following examinations can be considered for specific indications: MRI, bronchoscopy +/- bronchial ultrasonography (BUS) +/- biopsy, thoracoscopy, or laparoscopy	Weak	Low	5	5	4	4	4	4	4	4	4	EE5: Bronchoscopy should be performed routinely in squamous cell carcinoma EE9: precise which specific indications? (staging)	4	5	4	4	100%	Small discussion added to text
Treatment of mucosal cancer	When T1a oesophageal cancer is suspected, diagnostic staging endoscopic mucosal resection (EMR) should be performed whenever possible. If the diagnosis is pathologically confirmed, this procedure can be considered therapeutic, taking into account well-defined criteria relating to stage, size, length of Barrett, histological type, differentiation grade, lymphovascular invasion and completeness of resection	Strong	Low	4	4	4	5	5	3	5	4	5	EE4: what about depth of submucosal invasion forLN risk?	3	5	4	4	89%	In that case it is T1b; the recommendation is about T1a Formulation changed to: **Endoscopic mucosal resection (EMR) should be performed whenever possible for a T1a oesophageal cancer aiming at staging and curative resection. If the staging and R0 resection is pathologically confirmed, this procedure can be considered therapeutic, taking into account other well-defined criteria relating to size, length of Barrett, histological type, differentiation grade and lymphovascular invasion**
	Mucosal ablative techniques, such as argon plasma coagulation (APC), photodynamic therapy (PDT), radiofrequency ablation (RFA) or laser, are investigational and should be limited to units with appropriate expertise	Strong	Low	5	NA	5	5	5	5	5	4	5		4	5	5	5	100%	Formulation changed to: **(Destructive) mucosal ablative techniques cannot be recommended as a curative option for patients with T1a oesophageal cancer and should be limited to centers with appropriate expertise**
Neoadjuvant treatment	If after multidisciplinary discussion neoadjuvant treatment is considered for a locally-advanced oesophageal tumour (T2-4 N+ M0), neoadjuvant chemoradiotherapy is recommended	Strong	Low	5	1	5		4	5	5	5	5	EE2: Neoadjuvant CRT must be considered as a standard, with several metaanalysis that demonstrate the benefit of neoadjuvant CRT (see point 4.4.1.3). It should be a strong recommandation with a high level of evidence because metaanalysis are the highest level of evidences. It is probably the highest evidences we have in the treatment of oesophageal cancer (T2-4 any N or any T and N+) . EE4: need a more clear definition of wich stage benefit of neoadjuvant therapy	1	5	4	5	88%	The quality of the RCTs was poor; down-graded to low level of evidence. Since the effect is for both SCC and adeno; no distinction made in recommendations. Formulation changed to: **If after multidisciplinary discussion neoadjuvant treatment is considered for a locally-advanced oesophageal or junction tumour, neoadjuvant chemoradiotherapy is recommended**
Response assessment & restaging	The use of PET and EUS (with or without FNA) for the assessment of treatment response early in the course or after neoadjuvant treatment remains strictly investigational and requires a central prospective registration of all cases	Weak	Low	5	3	4	4	5	4	4	4	4		3	5	4	4	89%	
Surgery	Surgical resection is considered standard treatment for patients with resectable oesophageal cancer	Strong	High	5	1	5	2	5	5	5	5	5	EE2: The sentence should be wirten in :" Surgical resection should be considered for patients...." On the points 4.4.3.1 and 4.4.5.1 you write: " OS is equivalent between surgery and CRT" and "Treatment related mortality is significantly higher in the surgery group (12.8%vs 3.5%)". Your ref. 124 confirms these results. How can we considered a treatment as standard when the mortality is 4 folds higher and the efficacy the same !!!! The only small benefit of surgery is in term of locally PFS. Surgery must be combined with neoadjuvant radiotherapy or may be used as a salvage therapy after CRT. Therefore Surgery alone or CRT alone are on the same level of evidence. There are very few studies that compared surgery alone with CRT (only 1 direcly see your ref 124) most of the other compared with a neoadjuvant treatment. Therefore there are no evidences of the superiority of surgery on another curative treatment intent. EE4: depending on location and histology	1	5	4	5	78%	Formulation changed to: **For patients with resectable oesophageal cancer beyond the mucosa, surgery (+/- neoadjuvant chemoradiotherapy) is considered standard**

Item	Recommendation(s)	GOR	LoE	EE1	EE2	EE3	EE4	EE5	EE6	EE7	EE8	EE9	Comments	Min	Max	Mean	Median	% 4 or 5	Decision
	Surgery for oesophageal cancer should be aimed at achieving an R0 resection, and should be considered preferentially through a transthoracic en bloc resection	Strong	High	5	4	5	4	5	5	5	NA	4	EE2: the RO is score 5; the surgery technique should be the object of a new items. EE4: need a clear definition of predictive factors for R0 resection	4	5	5	5	100%	No change
	Minimally invasive esophagectomy is under development and is not recommended in routine practice	Weak	Low	4	NA	4	4	5	5	5	NA	4		4	5	4	4	100%	
	Extensive two field lymphadenectomy should be standard during oesophagectomy to improve staging, local disease control and potentially cure rate. The recommended minimum number of lymph nodes removed and examined is 10 for T1, 15 for T2 and 20 for T3/T4	Strong	Low	5	5	5	4	5	4	4	NA	5		4	5	5	5	100%	Second part removed from recommendation (discussed in text)
	Three-field lymphadenectomy during oesophagectomy is strictly investigational	Weak	Low	3	4	5	5	5	5	5	NA	NA		3	5	5	5	86%	
	Oesophageal cancer surgery should be carried out in high-volume specialist units with experience and/or specialist training in oesophageal and gastro-oesophageal junction cancer	Strong	Low	5	5	3	4	5	3	3	NA	5	EE3: what is high volume? EE7: profession driven audit of surgical outcome may be more efficient than strict volume criteria	3	5	4	4,5	63%	centres' instead of 'units'
Adjuvant treatment	Adjuvant treatment is not recommended for patients with oesophageal cancer	Strong	Low	2	5	5	3	5	5	5	4	5	EE1: although there are no randomized trials available adjuvant therapy could be considered for those without neo-adj therapy with positive lymphnodes and/or T3,T4 disease, especially in adenocarcinoma. (cfr subgroup analysis in MAGIC study and RTOG8911 trial) EE4: separate ADK of GOJ and SCC	2	5	4	5	78%	Extra data added on differences between SCC and aceno, but no need to make separate recommendations Formulation changed to: **Adjuvant treatment is not routinely recommended for patients with oesophageal cancer**
Non-surgical treatment with curative intent	Definitive concomitant chemoradiotherapy should be considered in patients with oesophageal cancer who have locally advanced disease that is considered unresectable, in patients who are unfit for surgery, or in patients who decline surgery	Strong	Moderate	5	1	5	2	5	4	5	4	5	EE2: The sentence must be written: " Definitive concomitant chemoradiotherapy is a standard of treatment in patients with oesophageal cancer who have locally advanced disease that is considered unresectable in R0 (e.g. any N+ or T2-4), in patients who are unfit for surgery, or in patients who decline surgery,..." EE4: there is a place for definitive RDCHtherapy for resectable SCC and rescue surgery. Becerne and Stahl data in JCO	1	5	4	5	79%	Formulation changed to: **Definitive concomitant chemoradiotherapy should be considered:** **o In patients with squamous cell carcinoma of the oesophagus who have locally advanced disease;** **o In patients with locally advanced oesophageal cancer of any histological type:** **- Who are unfit for surgery;** **- Who decline surgery.**
	Definitive concomitant chemoradiotherapy can be considered for patients with cervical oesophageal cancer in order to preserve the larynx	Weak	Low	5	4	4	5	5	3	5	4	4		3	5	4	4	89%	
Metastatic disease	Control of obstruction caused by oesophageal cancer should be obtained with stent placement or laser/ argon plasma coagulation (APC) therapy, depending on the local availability and expertise	Strong	High	5	1	5	5	5	5	5	NA	5	EE2: This recommendation must include Radiotherapy as a way to control obstruction cfr your ref 52.170, 171,172	1	5	5	5	88%	Is already recommended below
	Partially covered self-expanding metal stents or plastic expandable stents are the best options for palliation of dysphagia caused by oesophageal cancer	Strong	Moderate	5	1	5	5	5	4	5	NA	5	EE2: The recommandation should be write: "Partially covered self-expanding metal stents or plastic expandable stents are the most rapid way to relieve dysphagia, in a palliation treatment..."	1	5	4	5	88%	No change
	Laser therapy, argon plasma coagulation (APC) therapy or restenting should be considered for control of tumour ingrowth or overgrowth in stented patients	Strong	Low	4	1	5	5	5	4	5	NA	5	EE2: why not Radiotherapy?	1	5	4	5	88%	Is already recommended below Formulation changed to: **Ablative therapies or restenting should be considered for control of tumour ingrowth or overgrowth in stented patients**
	The use of oesophageal dilatation alone should be avoided	Weak	Low	4	NA	4	5	5	5	4	NA	5		4	5	5	5	100%	
	Oesophagectomy (transthoracic or transhiatal) should not be performed with palliative intent in patients with oesophageal cancer	Strong	Low	5	5	5	5	5	4	4	NA	5		4	5	5	5	100%	
	Substernal bypass for oesophageal cancer should not be performed with palliative intent	Strong	Low	5	5	5	5	5	4	4	NA	5		4	5	5	5	100%	
	In patients with locally advanced or metastatic cancer of the oesophagus, chemotherapy or chemoradiotherapy are treatment options that should be discussed in the multidisciplinary team	Weak	High	4	5	5	5	5	5	5	4	5		4	5	5	5	100%	
	Palliative external-beam radiotherapy or endoluminal brachytherapy should be considered in patients with dysphagia from oesophageal cancer and with the perspective of a more prolonged survival	Strong	Low	2	5	4	5	5	5	4	5	4	EE1: I agree that it should be considered, but there is no proof that this prolonges survival	2	5	4	5	89%	No change, misunderstood
	Patients with oesophageal cancer should have access to a specialist palliative care team, in particular in relation to comfort and symptom control, nutrition and quality of life	Strong	Low	3	5	5	5	5	5	5	4	5		3	5	5	5	89%	
Follow-up	It is recommended that the follow-up of patients treated for oesophageal cancer includes a physical examination and blood analysis every three months, and a CT scan every six months in the first year and afterwards annually until the fifth year	Weak	Very low	2	3	5	2	3	5	4	4	5	EE1: I think that interval of 1 y already after 1y is too long EE4: Data? Physical examination and lab insensitive. Can PetCTscan be considered	2	5	4	4	56%	Formulation changed to: **It is recommended that the follow-up of patients treated for oesophageal cancer includes a physical examination and blood analysis every three months, with targeted imaging if needed. A routine CT scan is recommended every six months in the first year and afterwards annually until the fifth year**
	Patients treated with endoscopic mucosal resection (EMR) should have a follow-up endoscopy after three months, then every six months in the first two years, and then annually	Weak	Very low	4	3	5	4		5	5	4	5		3	5	4	4	75%	
Treatment of recurrent disease	In patients with recurrent oesophageal cancer, treatment options should be discussed in the multidisciplinary team	Strong	Very low	4	5	5	5	5	5	5	5	5		4	5	5	5	100%	
	In patients with a local recurrence or new tumour after endoscopic mucosal resection (EMR), treatment options, including local treatment, should be discussed in the multidisciplinary team	Strong	Very low	4	5	5	5	5	5	5	5	5		4	5	5	5	100%	Removed

Item	Recommendation(s)	GOR	LoE	EE1	EE2	EE3	EE4	EE5	EE6	EE7	EE8	EE9	Comments	Min	Max	Mean	Median	% 4 or 5	Decision
Gastric cancer																			
Staging	Treatment options for patients with gastric cancer should be discussed at the multidisciplinary team meeting	Strong	Low	5	5	5	5	5	5	5	5	5		5	5	5	5	100%	
	In patients with newly diagnosed gastric cancer, CT scan of the chest and abdomen should be performed routinely	Strong	Low	5	5	5	5	5	4	5	5	5		4	5	5	5	100%	
	Endoscopic ultrasonography can be considered in patients to be treated with curative intent based on clinical presentation and/or CT. Fine-needle aspiration cytology of suspicious lymph nodes can be considered if technically feasible	Weak	Low	5	5	5	5	5	4	5	4	5		4	5	5	5	100%	or metastases' added
	The following examinations can be considered for specific indications: PET scan, Magnetic Resonance Imaging, laparoscopy	Weak	Low	4	5	4	5	5	4	5	4	4		4	5	4	4	100%	
Treatment of mucosal cancer	When T1a gastric cancer is suspected, diagnostic staging endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) should be performed whenever possible. If the diagnosis is pathologically confirmed, the procedure can be considered therapeutic, taking into account well-defined criteria relating to stage, size, histological type, lymphovascular invasion, differentiation grade and completeness of resection	Weak	Low	4	NA	5	5	5	5	5	4	5		4	5	5	5	100%	Formulation changed to: **Endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) should be performed whenever possible for a T1a gastric cancer aiming at staging and curative resection. If the staging and R0 resection is pathologically confirmed, the procedure can be considered therapeutic, taking into account other well-defined criteria relating to size, histological type, lymphovascular invasion and differentiation grade**
	Mucosal ablative techniques, such as photodynamic therapy (PDT), laser or argon plasma coagulation (APC), cannot be recommended as a curative option for patients with T1a gastric cancer	Weak	Very low	4	NA	5	5	5	5	5	4	5		4	5	5	5	100%	Formulation changed to: **(Destructive) mucosal ablative techniques cannot be recommended as a curative option for patients with T1a gastric cancer and should be limited to centers with appropriate expertise**
Neoadjuvant treatment	If after multidisciplinary discussion neoadjuvant treatment is considered for a locally-advanced gastric tumour (T2-4 N+ M0), neoadjuvant chemotherapy is recommended	Strong	Moderate	5	5	5	5	4	5	5	4	5	EE5: Also considered if T3T4 N0 or T1N2	4	5	5	5	100%	T4N0 and T1N2 are very rare; for T3N0 primary surgery is indicated Formulation changed to: **If after multidisciplinary discussion neoadjuvant treatment is considered for a locally-advanced gastric tumour, neoadjuvant chemotherapy is recommended**
Surgery	Surgical resection should be considered standard treatment for patients with resectable gastric cancer	Strong	Low	5	5	5	5	5	5	5	5	5		5	5	5	5	100%	
	Surgery for gastric cancer should aim at achieving an R0 resection	Strong	Low	5	5	5	5	5	5	5	5	5		5	5	5	5	100%	
	D2 lymphadenectomy (with a minimum of 15 lymph nodes removed and examined) performed in high-volume, specialized units with experience and/or specialist training should be standard during gastrectomy	Weak	Low	4	5	5	5	5	5	5	5	4		4	5	5	5	100%	Formulation changed to: **D2 lymphadenectomy performed in high-volume, specialized centers with experience and/or specialist training should be standard during gastrectomy**
	Splenectomy and pancreatectomy should not be considered standard practice during gastrectomy if no disease infiltration in the spleen or pancreas is present	Weak	Low	5	5	5	5	5	5	5	NA	4		4	5	5	5	100%	
	Laparoscopic surgery is strictly investigational	Weak	Low	3	NA	5	4	5	5	4	NA	3		3	5	4	4	71%	No change
Adjuvant treatment	Patients with gastric cancer who received neoadjuvant chemotherapy can be considered for postoperative chemotherapy	Weak	Low	5	5	5	5	5	3	5	5	4	EE1: There is evidence from MAGIC trial, and French FFCD trial	3	5	5	5	89%	No change
	Postoperative chemotherapy and chemoradiotherapy are optional treatments for patients with gastric cancer who did not receive neoadjuvant chemotherapy, and are not routinely recommended	Weak	Low	1	5	5	5	5	4	5		4	EE1: see comment above and also US intergroup trial. Also Meta-analysis statistic significant difference in OS with adj chemo (paoletti et al JAMA 2010). EE8: Sentence? Mc Donald INT Trial?	1	5	4	5	88%	Last part of sentence removed
	Postoperative adjuvant radiotherapy is not recommended for patients with gastric cancer	Weak	Low	4	5	5	5	5	4	5	4	4	EE4: add alone?	4	5	5	5	100%	Agree, 'alone' added
Metastatic disease	Palliative gastric surgery is limited to symptomatic stenoses, bleeding tumours and perforation	Weak	Low	4	5	4	5	5	4	5	4	4		4	5	4	4	100%	
	For patients with malignant gastric outlet obstruction, treatment options include endoscopic stenting or surgical gastroenterostomy	Weak	Low	4	5	4	5	5	4	5	4	3	EE9: Endocopic stenting should always be prefered whenever available and possible.	3	5	4	4	89%	Equal options: no change
	In patients with locally advanced or metastatic cancer of the stomach with good performance status combination chemotherapy is recommended	Strong	High	5	5	5	5	5	4	5	4	5		4	5	5	5	100%	
	Patients with gastric cancer should have access to a specialist palliative care team, in particular in relation to comfort and symptom control, and quality of life	Strong	Low	4	5	5	5	5	4	5	4	5		4	5	5	5	100%	
Follow-up	It is recommended that the follow-up of patients treated for gastric cancer includes a physical examination and blood analysis every three months, and a CT scan every six months in the first year and afterwards annually until the fifth year	Weak	Very low	2	4	5		3	5	5	4	4	EE1: same comment as in esophageal cancer EE4: Why not every 3 months for imaging?	2	5	4	4	75%	Formulation changed to: **It is recommended that the follow-up of patients treated for gastric cancer includes a physical examination and blood analysis every three months, with targeted imaging if needed. A routine CT scan is recommended every six months in the first year and afterwards annually until the fifth year**
	Patients treated with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) should have a follow-up endoscopy after three months, then every six months in the first two years, and then annually	Weak	Very low	3	4	5	5	5	3	5	4	5		3	5	4	5	78%	
Treatment of recurrent disease	In patients with recurrent gastric cancer, treatment options should be discussed in the multidisciplinary team	Strong	Very low	4	5	5	5	5	5	5	5	5	EE9: More precisions on indications of chemotherapy?	4	5	5	5	100%	
	In patients with a local recurrence or new tumour after endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD), treatment options, including local treatment, should be discussed in the multidisciplinary team	Strong	Very low	4	5	5	5	5	5	5	5	5		4	5	5	5	100%	Removed

After the validation meeting of April 18th the following changes were made to the recommendations:

- Oesopahgeal cancer, staging, 2nd recommendation: “always” instead of “routinely”
- Oesophageal cancer, staging 3rd recommendation: addition of “presence of positive”
- All recommendations with “remains strictly investigational”: replaced by “should be restricted to clinical studies”
- Oesophageal cancer, surgical treatment, 3rd recommendation: removal of “and should be considered”
- Oesophageal cancer, non-surgical treatment with curative intent, 1st recommendation: reformulation of 3 options
- Oesophageal cancer, treatment of metastatic disease, 8th recommendation: “a longer life expectancy” instead of “the perspective of a more prolonged survival”
- Oesophageal cancer, treatment of metastatic disease, 9th recommendation: addition of “advanced”
- Oesophageal cancer, follow-up, 1st recommendation: “then” instead of “afterwards”
- Gastric cancer, staging, 2nd recommendation: “always” instead of “routinely”
- Gastric cancer, staging, 3rd recommendation: reformulation of first sentence
- Gastric cancer, surgical treatment, 3rd recommendation: last part moved forward
- Gastric cancer, adjuvant treatment, 2nd recommendation: “can be considered” instead of “are optional treatments”
- Gastric cancer, treatment of metastatic disease, 9th recommendation: addition of “advanced”
- Gastric cancer, follow-up, 1st recommendation: “then” instead of “afterwards”

3. TNM-7 CLASSIFICATION [1]

3.1. Oesophagus including oesophagogastric junction (ICD-O C15 and C16.0)

3.1.1. TNM clinical classification

T – Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

Tis Carcinoma in situ/high-grade dysplasia

T1 Tumour invades lamina propria, muscularis mucosae, or submucosa

- T1a Tumour invades lamina propria or muscularis mucosae
- T1b Tumour invades submucosa

T2 Tumour invades muscularis propria

T3 Tumour invades adventitia

T4 Tumour invades adjacent structures

- T4a Tumour invades pleura, pericardium, or diaphragm
- T4b Tumour invades other adjacent structures such as aorta, vertebral body, or trachea

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1-2 regional lymph nodes

N2 Metastasis in 3-6 regional lymph nodes

N3 Metastasis in 7 or more regional lymph nodes

M – Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

3.1.2. pTNM pathological classification

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

pN0 Histological examination of a regional lymphadenectomy specimen will ordinarily include 6 or more lymph nodes.

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

pM1 Distant metastasis microscopically confirmed

3.1.3. Stage grouping

Stage	T-category	N-category	M-category
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T1, T2	N1	M0
Stage IIIA	T4a	N0	M0
	T3	N1	M0
	T1, T2	N2	M0
Stage IIIB	T3	N2	M0
Stage IIIC	T4a	N1, N2	M0
	T4b	Any N	M0
	Any T	N3	M0
Stage IV	Any T	Any N	M1

3.1.4. Prognostic grouping

3.1.4.1. Squamous cell carcinoma

Group	T-category	N-category	M-category	Grade	Location *
Group 0	Tis	N0	M0	1	Any
Group IA	T1	N0	M0	1, X	Any
Group IB	T1	N0	M0	2, 3	Any
	T2, T3	N0	M0	1, X	Lower, X
Group IIA	T2, T3	N0	M0	1, X	Upper, middle
	T2, T3	N0	M0	2, 3	Lower, X
Group IIB	T2, T3	N0	M0	2, 3	Upper, middle
	T1, T2	N1	M0	Any	Any
Group IIIA	T1, T2	N2	M0	Any	Any
	T3	N1	M0	Any	Any
	T4a	N0	M0	Any	Any
Group IIIB	T3	N2	M0	Any	Any
Group IIIC	T4a	N1, N2	M0	Any	Any
	T4b	Any N	M0	Any	Any
	Any T	N3	M0	Any	Any
Group IV	Any T	Any N	M1	Any	Any

* *Lower, middle and upper correspond to the intrathoracic thirds of the oesophagus.*

3.1.4.2. Adenocarcinoma

Group	T-category	N-category	M-category	Grade
Group 0	Tis	N0	M0	1
Group IA	T1	N0	M0	1, 2, X
Group IB	T1	N0	M0	3
	T2	N0	M0	1, 2, X
Group IIA	T2	N0	M0	3
Group IIB	T3	N0	M0	Any
	T1, T2	N1	M0	Any
Group IIIA	T1, T2	N2	M0	Any
	T3	N1	M0	Any
	T4a	N0	M0	Any
Group IIIB	T3	N2	M0	Any
Group IIIC	T4a	N1, N2	M0	Any
	T4b	Any N	M0	Any
	Any T	N3	M0	Any
Group IV	Any T	Any N	M1	Any

3.2. Stomach (ICD-O C16)

3.2.1. Anatomical subsites

Fundus: C16.1
Corpus: C16.2
Antrum: C16.3
Pylorus: C16.4

3.2.2. TNM clinical classification

T – Primary tumour

TX Primary tumour cannot be assessed
T0 No evidence of primary tumour

Tis Carcinoma in situ: intraepithelial tumour without invasion of the lamina propria, high-grade dysplasia

T1 Tumour invades lamina propria, muscularis mucosae, or submucosa

- T1a Tumour invades lamina propria or muscularis mucosae
- T1b Tumour invades submucosa

T2 Tumour invades muscularis propria

T3 Tumour invades subserosa

T4 Tumour perforates serosa or invades adjacent structures

- T4a Tumour perforates serosa
- T4b Tumour invades adjacent structures

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Metastasis in 1-2 regional lymph nodes

N2 Metastasis in 3-6 regional lymph nodes

N3 Metastasis in 7 or more regional lymph nodes

- N3a Metastasis in 7-15 regional lymph nodes
- N3b Metastasis in 16 or more regional lymph nodes

M – Distant metastasis

M0 No distant metastasis

M1 Distant metastasis

3.2.3. pTNM pathological classification

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

pN0 Histological examination of a regional lymphadenectomy specimen will ordinarily include 16 or more lymph nodes.

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

pM1 Distant metastasis microscopically confirmed

3.2.4. Stage grouping

Stage	T-category	N-category	M-category
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0, N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4a	N3	M0
	T4b	N2, N3	M0
Stage IV	Any T	Any N	M1

4. EVIDENCE TABLES: OESOPHAGEAL CANCER

4.1. Initial staging

4.1.1. Imaging techniques (EUS, CT, PET, PET/CT) and minimally invasive surgical procedures

4.1.1.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Thosani 2012[2]	• Design: SR and MA • Sources of funding: authors disclosed no financial relationships relevant to this publication • Search date: June 2010 • Searched databases: MEDLINE (PubMed and Ovid from 1980 to June 2010), SCOPUS (Consisting of MEDLINE and Embase databases), Cochrane Database of Systemic Reviews, Google scholar, and CINAHL Plus databases • Included study designs: retrospective or prospective studies (case reports and case series were excluded) • Number of included studies: 19 o Murata 1998	• Patients with oesophageal lesions suspicious for oesophageal cancer or confirmed oesophageal cancer based on endoscopic biopsy and imaging studies like EUS, CT scan, and MRI	• Index test: EUS • Standard reference: histopathological diagnosis by EMR or surgical resection	***T1a staging*** Pooled Se: 85% (95%CI 82-88%) Pooled Sp: 87% (95% CI 84-90%) Positive Likelihood Ratio: 6.62 (95%CI 3.61-12.12) Negative Likelihood Ratio: 0.20 (95%CI 0.14-0.30) DOR: 40.64 (95%CI 18.55-89.04) Adjusted DOR*: 13.49 (95%CI 5.85-31.09) ***T1b staging*** Pooled Se: 86% (95%CI 82%-89%) Pooled Sp: 86% (95%CI 83%-89%) Positive Likelihood Ratio: 5.13 (95%CI 3.36-7.82), Negative Likelihood Ratio: 0.17 (95% CI 0.09-0.30). DOR: 39.62 (95%CI 18.38-85.42) Adjusted DOR*: 13.46 (95%CI 5.93-30.58) The P value for χ^2 heterogeneity for all	• Quality appraisal: studies were selected based on the predefined inclusion and exclusion criteria and completeness of data reporting in the studies (ability to draw 2x2 table) • Test of heterogeneity between studies • Subgroup analysis to determine the source of heterogeneity • Test of robustness of the meta-analysis to the publication bias (Egger and Fail-safe N tests

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o Kouzu 1992 o Toh 1993 o Yoshikane 1994 o Simizu 1995 o Murata 1996 o Yanai 1996 o Shinkai 2000 o Kukuda 2000 o Scotiniotis 2001 o Kawano 2003 o Yanai 2003 o Buskens 2004 o Arima 2004 o May 2004 o Larghi 2005 o Pech 2006 o Rampado 2008 o Chemaly 2008			pooled estimates was <.05. *Publication bias → adjustment of DORs The area under the curve was at least 0.93 for both mucosal and submucosal lesions	and the trimand-fill method)
Tranchemontagne (AETMIS) 2009[3]	• Design: SR • Sources of funding: Governmental Agency • Search date: July 2008 • Searched databases: Medline and The Cochrane Library + Copernic, Google Scholar, AlltheWeb and Scirus + Websites • Included study designs: HTA, SR, primary studies • Number of included studies: – *SR* o Harris 1998	• Eligibility criteria: a) initial staging; b) oesophageal cancer (AC or SCC) • Exclusion criteria a) staging after neoadjuvant trt; b) ≤ 10 patients; c) Barrett's oesophagus; d) other publication languages than FR and EN ; e) data on lesions, exams or LN	• Index test: o CT o EUS o ^{18}FDG PET-CT o MRI o Minimally invasive surgical procedures (thoracoscopy and laparoscopy) • Reference : o Stage T: histopathology o Stage N: LN dissection o Stage M:	**Performance of CT** *Stage N* Se: median=41.7% Sp: median=82.4% *Stage M* Se: median=49.2% Sp: median=87.2% N.B. some studies do not separately evaluate metastases or included earlier stages cancer **Performance of PET** *Stage T* Detection rate: 95-100% *Stage N*	• Included studies: low quality level and small sample size; a lot of studies are retrospective; reference standard (histopathology) is not always mentioned; heterogeneous results; indirect comparison of all technologies; lack of use of international

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o MSAC 2001 o BCBS 2002 o Van Weestrenen 2004 o MSAC 2006 o Facey 2007 – *Primary studies : CT and EUS* o Barbour 2007 o Bowrey 1999 o Catalano 1999 o Choi 2000 o Czekajska-Chehab 2002 o Eloubeidi 2001 o Flamen 2000; Lerut 2000 o Giovannini 1999 o Heeren 2004 o Heidemann 2000 o Kato 2005 o Kienle 2002 o Kutup 2007 o Lowe 2005 o Meltzer 2000 o Menzel 1999 o Pedrazzani 2005 o Rice 2003 o Richards 2000 o Salminen 1999 o Schlick 1999 o Shimoyama 2004 o Sihvo 2004; Rasanen 2003 o Van Vliet 2007		histopathology on biopsy or clinical FU	Se: 57% (95%CI 43-70%) Sp: 85% (95%CI 76-95%) *Stage M* Se: 71% (95%CI 62-79%) Sp: 93% (95%CI 89-97%) **Performance of PET-CT (2 studies)** *Stages N and M1a* Se: 83.3 – 93.9% Sp: 92.1% **Performance of EUS** *Stage T* Se: median=97.1% Sp: median= 75% *Stage N* Se: median= 76.2% Sp: median= 66.7% *Stage M1a (celiac LN metastases)* Se: median= 75% Sp: median= 93.7% **Performance of EUS-FNA** *Stage N* Se= 83.3 – 93.3% Sp=92.9% *Stage M* Se=92.9 – 97.8% Sp=100% **Performance of thoracoscopy** *Stage N*	TNM classification • Stratified analysis by tumour TNM stage, histological type and position • Diagnostic performance is expressed as a weighted mean or a median

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o Vazquez-Sequeiros 2001 o Vazquez-Sequeiros 2003 o Wren 2002 o Yoon 2003 o Zhang 2005 – *Primary studies: PET-CT* o Bar-Shalom 2005 o Fiore 2006 o Yuan 2006 – *Primary studies: minimally invasive surgery techniques* o Kaushik 2007 o Krasna 2001, 2002 o Luketich 2000 – *Primary studies: MRI* o Ozawa 2000 o Wu 2003 – *Primary studies on stenosing tumours* o Bowrey 1999 o Jacobson 2007 o Jethwa 2005 o Mallery 1999 o Mortensen 2005 o Parmar 2002 o Pfau 2000 o Vu 2007 o Wallace 2000			Se= 45.5% Sp=100% **Performance of laparoscopy** *Stage N* Se= 90.9% Sp=100% **Comparison of technologies (correctly staged tumours)** *Stage T* EUS: median= 79.5% Spiral CT: median= 61.8% *Stage N* EUS : Se=80% (95%CI 75-84%); Sp=70% (95%CI 65-75%) CT : Se=50% (95%CI 41-60%) ; Sp=83% (95%CI 77-89%) PET : Se=57% (95%CI 43-70%) ; Sp= 85% (95%CI 76-95%) *Stage M* EUS-FNA : Se= 92.9% EUS : Se=75% Sp not reported due to a lack of patients with stage M0	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Van Vliet 2008[4]	• Design: SR and MA • Sources of funding: Erasmus MC – University Medical centre Rotterdam - NL • Search date: January 2006 • Searched databases: Medline • Included studies: – *Primary studies : EUS* o Barbour 2007 o Binmoeller 1995 o Botet 1991 o Bowrey 1999 o Catalano 1999 o Choi 2000 o DeWitt 2005 o Dittler 1993 o Eloubeidi 2001 o Greenberger 1994 o Grimm 1993 o Hasegawa 1996 o Heeren 2004 o Heidemann 2000 o Hunerbein 1996 o Kato 2005 o Lowe 2005 o Natsugoe 1996 o Nesje 2000 o Nishimaki 1999 o Parmar 2002 o Pedrazzani 2005	• Eligibility criteria: a) initial staging; b) oesophageal cancer (AC or SCC) • Exclusion criteria a) staging after neoadjuvant trt; b) ≤ 10 patients; c) Barrett's oesophagus; d) other publication languages than FR and EN ; e) data on lesions, exams or LN	• Index test: o CT o EUS o ^{18}FDG PET-CT • Reference : • Resection, result of FNA, FU with Rx and/or clinical FU	**Regional lymph nodes metastases** *EUS (31 studies, n=1841 patients)* Pooled Se: 0.80 (95% CI 0.75-0.84) Pooled Sp: 0.70 (95%CI 0.65-0.75) *CT (17 studies; n= 943 patients)* Pooled Se: 0.50 (95%CI 0.41-0.60) Pooled Sp: 0.83 (95%CI 0.77-0.89) *FDG-PET (10 studies; n=424 patients)* Pooled Se: 0.57 (95% 0.43-0.70) Pooled Sp: 0.85 (95%CI 0.76-0.95) *CT vs. EUS* DOR: 0.76 (95%CI 0.48-1.21); p=0.25 *FDG-PET vs. EUS* DOR : 0.95 (95%CI 0.54-1.67) ; p=0.86 **Celiac lymph nodes metastases** *EUS (5 studies ; n=339 patients)* Pooled Se: 0.85 (95% CI 0.72-0.99) Pooled Sp: 0.96 (95%CI 0.92-1.00) **Abdominal lymph nodes metastases** *CT (5 studies ; n=254 patients)* Pooled Se: 0.42 (95% CI 0.29-0.54) Pooled Sp: 0.93 (95%CI 0.86-1.00) **Distant metastases** *CT (7 studies ; n=437 patients)* Pooled Se: 0.52 (95% CI 0.33-0.71) Pooled Sp: 0.91 (95%CI 0.86-0.96) *FDG-PET (9 studies; n=475 patients)* Pooled Se: 0.71 (95% 0.62-0.79)	• No quality appraisal of the included studies • Visual inspection of funnel plots for publication bias • Meta-analysis using random effects model

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o Pham 1998 o Rice 1991 o Richards 2000 o Salminen 1999 o Shinkai 2000 o Sihvo 2004; Rasanen 2003 o Tio 1990 o Vazquez-Sequeiros 2001 o Vazquez-Sequeiros 2003 o Vickers 1998 o Wu 2003 o Yoshikane 1994 o Ziegler 1991 – *Primary studies: CT* o Becker 1986 o Botet 1991 o Choi 2000 o Flamen 2000 o Flanagan 1997 o Greenberg 1994 o Heeren 2004 o Lowe 2005 o Nishikami 1999 o Parmar 2002 o Rasanen 2003 o Sihvo 2004 o Sondenaa 1992 o Quint 1985 o Van Overhagen 1993 o Vazquez-Sequeiros 2003			Pooled Sp: 0.93 (95%CI 0.89-0.97) *FDG-PET vs. CT* DOR=2.26 (95%CI 1.09-4.71) p<0.03	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o Watt 1989 o Wren 2002 o Wu 2003 o Yoon 2003 o Yoshikane 1994 o Ziegler 1991 – *Primary studies: FDG-PET* o Choi 2000 o Flamen 2000 o Flanagan 1997 o Heeren 2004 o Lerut 2000 o Lowe 2005 o Luketisch 1997 o Rasanen 2003 o Sihvo 2004 o Wren 2002 o Yoon 2003				
Puli 2008[5]	• Design: SR and MA • Sources of funding: not reported • Search date: not reported • Searched databases: Medline, PubMed, Ovid journals, CINAHL, ACP Journal Club, DARE, International Pharmaceutical Abstracts, Old Medline, Medline Non indexed Citations, OVID Healthstar, and	• Eligibility criteria: oesophageal cancer, EUS, completeness of data, inclusion criteria (TNM staging, 2x2 table)	• Index test: EUS • Reference standard: surgery	**T staging (43 studies) - EUS** *T1* Pooled Se : 81.6% (95% CI: 77.8-84.9) Pooled Sp: 99.4% (95% CI: 99.0-99.7) *T2* Pooled Se : 81.4% (95% CI: 77.5-84.8) Pooled Sp: 96.3% (95% CI: 95.4-97.1) *T3* Pooled Se : 91.4% (95% CI: 89.5-93.0) Pooled Sp: 94.44% (95% CI: 93.1-95.5) *T4* Pooled Se: 92.4% (95% CI: 89.2-95.0)	• Use of QUOROM method for reporting • Use of Standards for Reporting of Diagnostic Accuracy (STARD) • Sensitivity analyses for periods of time (1986-1994, 1995-1999,

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	Cochrane Controlled Trials Registry • Studies included (n=2558): o Takemoto 1986 o Tio 1986 o Murata 1988 o Tio 1989 o Vilgrain 1990 o Botet 1991 o Tio 1989 o Heintz 1991 o Rice 1991 o Ziegler 1991 o Tio 1990 o Fok 1992 o Rosch 1992 o Dittler 1993 o Grimm 1993 o Hordijik 1993 o Yoshikane 1993 o Catalano 1994 o Greenberg 1994 o Peters 1994 o Binmoeller 1995 o Kallimanis 1995 o McLoughlin 1995 o Francois 1996 o Hasegawa 1996 o Holden 1996 o Hunerbein 1996 o Massari 1996 o Natsugoe 1996 o Vikers 1997 o Shimizu 1997 o Pham 1998			Pooled Sp : 97.4% (95% CI: 96.6-98.0) Heterogeneity (χ^2 test) for all pooled estimates : p>0.1 **N staging (44 studies with EUS; 4 studies with EUS-FNA)** *EUS* Pooled Se: 84.7% (95% CI: 82.9-86.4) Pooled Sp: 84.6% (95% CI: 83.2-85.9) *EUS-FNA* Pooled Se: 96.7% (95% CI: 92.4-98.9) Pooled Sp: 95.5% (95% CI: 91.0-98.2) Heterogeneity (χ^2 test) for all pooled estimates : p>0.1	2000-2006) and duplicates (e.g. Tio) • Evaluation of publication bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o Vikers 1998 o Browney 1999 o Catalano 1999 o Nishimaki 1999 o Salminen 1999 o Giovannini 1999 o Krasna 1999 o Heidemann 2000 o Nesje 2000 o Vazquez-Sequeiros 2001 o Wiersema 2001 o Kienle 2002 o Wakelin 2002 o Schwartz 2002 o Wu 2003 o Shimoyama 2004 o DeWitt 2005				

4.1.1.2. Primary studies

Study ID	Population	Index test	Outcome	Results	Comments
Yen 2012[6]	118 consecutive patients with oesophageal squamous cell carcinoma who underwent oesophagectomy with (group 2; n= 90) or without (group 1; n=28 patients) neoadjuvant chemoradiotherapy (CRT) over a near 3-year period between January 2005 and November 2008 at a tertiary hospital in Taiwan	• EUS • FDG PET/CT • Standard reference: surgical pathology	Performance of FDG PET/CT and EUS for T staging and N staging (before surgery)	***T staging*** *EUS (Group 1; n=27)* T1 (n=14): Se 85.7% ; Sp 84.6% T2 (n=7): Se 71.4% ; Sp 90% T3 (n=6): Se 100% ; Sp 100% *EUS (Group 2; n=83)* T0 (n=2) : Se 5.9% ; Sp 100% T1 (n=3): Se 0% ; Sp 96.2% T2 (n=10): Se 15.8% ; Sp 89.1% T3 (n=65): Se 92.3% ; Sp 40.4% *FDG PET/CT(Group 1; n=27): Difference between tumour free and viable tumour* Se: 100% Sp: NA Overall accuracy: 100% *FDG PET/CT(Group 2; n=83): Difference between tumour free and viable tumour* Se: 68.4% Sp: 70.5% Overall accuracy: 69.4% ***N staging*** *EUS (Group 1 ; n=27; 10 N0, 17 N1)* Se: 100% Sp: 45.4% Overall accuracy: 55.6% *EUS (Group 2; n=83; 22 N0, 61 N1)* Se: 82.4%	• Retrospective study • Small sample size • This study also investigated the respective role of EUS and PET/CT in assessing treatment response (NACRT)

Study ID	Population	Index test	Outcome	Results	Comments
				Sp: 28.8% Overall accuracy: 39.8% *FDG PET/CT(Group 1; n=27)* Se: 0% Sp: 75% Overall accuracy: 54.5% *FDG PET/CT(Group 2; n=83)* Se: 42.9% Sp: 96.6% Overall accuracy: 86.1%	
Ba-Ssalamah 2011[7]	• 131 patients with oesophageal cancer who will undergo surgery with or without NACRT	• Hydro-MCT • Standard reference: post surgical histopathological results	Performance of multidetector computed tomography with water filling (Hydro-MDCT) in the T-staging of patients with oesophageal cancer	***T staging (reader 1)*** Se: 96% Sp: 50% PPV: 97% NPV: 44% Accuracy: 76% ***T staging (reader 2)*** Se: 95% Sp: 40% PPV: 97% NPV: 40% Accuracy: 68%	• Prospective study • Potential bias in image interpretation, since both readers know the presence of the oesophageal cancer
Eloubeidi 2011[8]	• 196 patients who will undergo Ivor Lewis oesophagogastrectomy	• EUS/FNA • Standard reference: histopathology	True negative rate of EUS-FNA in patients predicted to be N0 (NPV)	***N Staging*** Se 44% Sp 96% PPV 57% NPV 94%	• Interpretation of results from histopathology without knowledge of index tests

Study ID	Population	Index test	Outcome	Results	Comments
					results?
Shum 2011[9]	• 26 patients with histologically proved oesophageal squamous cell carcinoma who underwent dual-time FDG PET/CT before radical surgery	• FDG PET/CT • Standard reference: histopathology	Performance of FDG PET/CT for N and M staging according to 4 diagnostic criteria	***N staging*** *Early SUVmax ≥2.5* Se 30% Sp 93.8% PPV 75% NPV 68% *Retention index (RI) ≥10%* Se 60% Sp 56.3% PPV 46% NPV 69% *Early SUVmax ≥2.5 and RI ≥10%* Se 20% Sp 93.8% PPV 67% NPV 65% *Early SUVmax ≥2.5 or RI ≥10%* Se 70% Sp 56.3% PPV 50% NPV 75% ***M staging*** *Early SUVmax ≥2.5* Se 17% Sp 100% PPV 100% NPV 80% *Retention index (RI) ≥10%*	• Small number of cases • Short interval of follow up → higher risk of false negative results

Study ID	Population	Index test	Outcome	Results	Comments
				Se 50% Sp 85% PPV 50% NPV 85% *Early SUVmax ≥2.5 and RI ≥10%* Se 17% Sp 100% PPV 100% NPV 80% *Early SUVmax ≥2.5 or RI ≥10%* Se 50% Sp 85% PPV 50% NPV 85%	
Smith 2010[10]	• 71 patients with a diagnosis of biopsy-proven oesophageal cancer who were staged with EUS	• EUS • Standard reference: histopathology of the surgical specimen	Performance of EUS for T staging and N staging	***T staging*** 51 patients were staged correctly; overall accuracy: 72% *T0* Se: 57% Sp: 98% PPV: 80% NPV: 95% Accuracy: 94% *T1* Se: 63% Sp: 92% PPV: 75% NPV: 87% Accuracy: 80%	• Interpretation of results from histopathology without knowledge of index tests results?

Study ID	Population	Index test	Outcome	Results	Comments
				T2 Se: 54% Sp: 81% PPV: 88% NPV: 90% Accuracy: 76% *T3* Se: 88% Sp: 90% PPV: 88% NPV: 90% Accuracy: 88.4% ***N Staging*** Se: 84% Sp: 67% PPV: 74% NPV: 79% Accuracy: 76%	
Choi 2010[11]	• 109 patients with a diagnosis of biopsy-proven oesophageal cancer who will undergo surgical resection	• EUS, FDG PET/CT and chest CT • Standard reference: histopathology of the surgical specimen	Performance of EUS, FDG PET/CT and chest CT	***T staging*** *EUS - T1:* Se 80%, Sp 100%, PPV 100%, NPV 86% Accuracy 91% *EUS – T2* Se 53%, Sp 82%, PPV 32%, NPV 91% Accuracy 78% *EUS – T3* Se 78%, Sp 80%, PPV 71%, NPV 86% Accuracy 80% ***N staging***	• Only surgically resectable patients were enrolled, leading to a possible underestimation of both sensitivity and accuracy in the detection of metastasis to lymph nodes

Study ID	Population	Index test	Outcome	Results	Comments
				EUS Se 42%, Sp 91%, PPV 82%, NPV 60% Accuracy 66% *PET/CT* Se 49%, Sp 87%, PPV 79%, NPV 63% Accuracy 68% *Chest CT* Se 35%, Sp 93%, PPV 83%, NPV 58% Accuracy 63% *Combined 3 methods* Se 65%, Sp 80%, PPV 77%, NPV 69% Accuracy 72% ***M staging*** *PET/CT* Se 40%, Sp 99%, PPV 66%, NPV 97% Accuracy 96% *Chest CT* Se 20%, Sp 99%, PPV 50%, NPV 96% Accuracy 95% *Combined 2 methods* Se 40%, Sp 98%, PPV 50%, NPV 97% Accuracy 95%	
Hsu 2009[12]	• 45 patients having a squamous cell carcinoma who underwent a curative oesophagectomy or threefield (cervical, thoracic, and abdominal) lymph	• FDG PET/CT • Standard reference: cervical, thoracic, and abdominal lymphadenectomy followed by a	Performance of FDG-PET CT to identify regional and non regional LN involvement	***Regional nodal involvement*** Se: 57.1% Sp: 83.3% Accuracy: 71.1% PPV: 75% NPV: 69%	• Retrospective analysis of a selected sample of patients having a SCC • Possibility of

Study ID	Population	Index test	Outcome	Results	Comments
	node assessment	pathology examination		***Nonregional nodal involvement*** Se: 36.4% Sp: 84% Accuracy: 71.1% PPV: 40% NPV: 80%	interpretation bias: blind comparison?
Noble 2009[13]	• 191 patients with histologically confirmed oesophageal cancer either confined to the oesophagus or involving the oesophagogastric junction (2006-2007)	• FDG PET/CT performed after staging done by CT and EUS • Standard reference: surgery+ histopathology OR FNA, MRI, biopsy, colonoscopy, laparoscopy for non operated patients	Performance of FDG-PET CT to identify metastases and LN involvement	***Diagnostic performance*** Se: 91% Sp: 94% PPV: 68% NPV: 99% FP: 10/191 (5.2%) FN: 2/191 (1.0%) ***Whole population or selective sample*** PET/CT was performed routinely in 167 (87%) and selectively in 24 cases (13%) to assist with preoperative staging. True positive rate : 9/167 (5%) vs. 9/24 (38%) for metastatic disease ***Restaging procedure and management*** PET/CT was found to be helpful in planning management in 174 cases (91%), changed staging in 65 cases (34%), and management in 50 cases (26%).	• Multicentre prospective cohort study • Results of the standard test interpreted with knowledge of the results of the index test • Small selection bias towards greater identification of undetected distant metastases in more advanced stage disease by conventional imaging.
Kato 2008[14]	• 167 consecutive patients with thoracic oesophageal squamous cell carcinoma (1999-2007)	• FDG-PET : 117 patients • FDG-PET/CT: 50 patients • Standard reference:	Performance of FDG-PET/CT compared with PET alone for the evaluation of initial lymph node staging	***Staging accuracy (N0/N1)*** *FDG-PET/CT (50 patients)* Se: 75.9% Sp: 81% Accuracy: 78%	• Study conducted in Japan

Study ID	Population	Index test	Outcome	Results	Comments
		oesophagectomy + histopathology		PPV: 84.6% NPV: 70.8% *F-FDG PET (117 patients)* Se: 55% Sp: 86% Accuracy: 70.1% PPV: 80.5% NPV: 64.5% *CT (117 patients)* Se: 48.3% Sp: 73.7% Accuracy: 60.7% PPV: 65.9% NPV: 57.5% ***Lymph node group accuracy*** LN based analysis	
Mennigen 2008[15]	• 97 patients who were histologically diagnosed oesophageal cancer or cancer of the gastroesophageal junction (squamous cell cancer and adenocarcinoma), having a preoperative EUS, and complete tumor resection with two-field	• EUS using a conventional probe in nonstenotic tumors and a miniprobe in stenotic tumors • Standard reference: histopathology of the surgical specimen	Staging accuracy of conventional EUS probe and miniprobe (T and N staging)	***T stage*** Accuracy: 73.2% for T stage *T1* Se: 68% Sp: 96% PPV: 81% NPV: 93% *T2* Se: 73% Sp: 76%	• The examiner was not blinded to other available clinical information (CT scan, endoscopy, etc.). • No T4 tumors were included in this study; exclusion of patients with induction therapy

Study ID	Population	Index test	Outcome	Results	Comments
	lymphadenectomy			PPV: 47% NPV: 90% *T3* Se: 78% Sp: 88% PPV: 89% NPV: 76% ***N stage*** Accuracy: 74.2% (95%CI 64.3–82.6%) Se: 83.1% (71.0–91.6%) Sp: 60.5% (43.4–76.0%) PPV: 76.6% (64.3–86.2%) NPV: 69.7% (51.3–84.4%). Accuracy was similar for the miniprobe used in stenotic tumors vs the conventional probe used in nonstenotic tumors: - T staging accuracy: 75.4% and 70.0% (p=0.64) - N staging accuracy: 68.4% vs. 80% (p=0.25) A learning curve was observed, as the second set of patients (nos. 50–97) had a significantly better T staging accuracy than the first set of patients (nos. 1–49; 83.3% vs. 63.3%, p=0.038).	
Schreurs 2008[16]	• 125 patients with cancer of the oesophagus and gastroesophageal junction (GEJ).	• Index tests: EUS, multidetector computed tomography (md-CT), 18F- FDG-PET and external US.	Accuracy of the staging procedures → to evaluate the value of external ultrasonography (US) of the neck in current dedicated	***Diagnostic performance of all modalities*** *External US* Se: 86% Sp: 100% PPV: 89%	• Risk of interpretation bias • Risk of partial verification bias

Study ID	Population	Index test	Outcome	Results	Comments
		• Standard reference: histopathologic conclusions and/or clinical evidence of disease during the first 6 month of follow-up.	preoperative staging to detect cervical metastases	NPV: 76% Accuracy : 99% *md-CT* Se: 71% Sp: 100% PPV: 100% NPV: 98% Accuracy : 98% *FDG PET* Se: 100% Sp: 98% PPV: 80% NPV: 100% Accuracy : 98% Md CT + FDG PET Se: 100% Sp: 99% PPV: 89% NPV: 100% Accuracy : 99%	

4.2. Neoadjuvant treatment

4.2.1. Radiotherapy

4.2.1.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Arnott 2010[17]	• Design: SR and MA • Sources of funding: Medical Research Council, UK • Search date: September 2008 (update) • Searched databases: Medline, Embase, Cancer LIT and The Cochrane Library + handsearching • Included study designs: RCTs • Number of included studies: 5 RCTs (n=1147 patients) o Nygaard 1992 (1983-1988); o Arnott 1992 (1979-1983); o Wang 1989 (1977-1988); o Gignoux 1988 (1976-1982); o Launois 1981 (1973-1976);	• Eligibility criteria: patients with potentially resectable carcinoma of the oesophagus (of any histological type) • Patients characteristics: o men (78%), o < 65 years (80%) o SCC (86%) o middle or lower third (74%) of the thoracic oesophagus • Median FU: 9 years	• Intervention: Neoadjuvant RT (± CT) + surgery o 20-40 Gy o 10-20 fractions o over a period of 1 to 4 weeks • Comparator: (± CT) + surgery *N.B. CT was only given in Nygaard*	***Survival (overall; n= 1147)*** HR=0.89 (95%CI 0.78-1.01) ***Survival (RT only; n=1038)*** HR=0.91 (95%CI 0.80-1.04) ***2 years-survival*** 30% → 34% (+4%; 95%CI 0-9%) ***5 years-survival*** 15% → 18% (+3%; 95%CI 0-8%) No differences by sex, age or tumour location	• Individual patient data • Analyses carried out on an ITT basis • Nygaard 1992: factorial design to examine the role of preoperative RT whilst controlling for the effect of CT • MA: only 75% power to detect an effect (min. 2000 patients to detect an overall benefit of 5%; 90% power, 5% significance) • Outdated staging techniques and RT schemes

4.2.2. Neoadjuvant Chemotherapy vs. surgery alone

4.2.2.1. Systematic reviews

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

Boughrassa 2009 (AETMIS)[18]	• Design: SR
	• Sources of funding: Governmental Agency
	• Search date: End 2008
	• Searched databases: Medline, Embase and The Cochrane Library
	• Included study designs: MA, SR of RCTs, RCTs
	• Number of included studies: 10 RCTs (n=2258)
	  • Roth 1988
	  • Nygaard 1992
	  • Schlag 1992
	  • Maipang 1994
	  • Law 1997
	  • Ancona 2001
	  • Kelsen 1998, 2007
	  • MRC 2002
	  • Baba 2000
		• Eligibility criteria: histologically confirmed, previously untreated oesophageal cancer, suitable for radical surgery
		• Patients characteristics:
		  o SCC, adenocarcino-ma, undifferentiated carcinoma
		  o T0–3, N0–1 disease
		• Median FU: 7.5-106 months
			• Intervention: Neoadjuvant CT plus surgery
			• Comparator: Surgery alone
			• NB. Different CT schemes (products, dosages, number of cycles)
				Survival
				Narrative review of results reported by primary RCTs and meta-analyses of these RCTs.
				Ccl:
				- majority of the studies: no benefit from neoadjuvant chemotherapy for patients with resectable oesophageal cancer (mainly squamous cell carcinoma).
				- one large trial (MRC 2002, fair quality), including a large number of adenocarcinomas, showed a significant improvement in the 5‑year survival rate in patients treated with two cycles of cisplatin and 5-fluorouracil, especially in those who presented with resectable oesophageal adenocarcinomas, and also revealed an improvement in disease-free survival.
				- Pooling the results of that study and of those that obtained negative results showed similar overall survival rates in the two treatment groups.
				Tumour recurrence
				- locoregional and distant tumour recurrence: similar risk. The neoadjuvant chemotherapy protocols used did not permit effective locoregional tumour control.
					• Methodological weaknesses of included studies (small sample sizes, ITT analyses not done in all RCTs, no description of randomization process in some RCTs, low JADAD score for many studies)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Sjoquist 2011[19]	• Design: SR and MA • Sources of funding: Cancer Australia and Cancer Institute (NSW) to the National Health and Medical Research Council Clinical Trials Centre and AGITG (no impact on the publication itself) • Search date: November 2010 • Searched databases: Medline, Embase, and Central (Cochrane clinical trials database) + manual search for abstracts • Included study designs: RCTs based on ITT analysis • Number of included studies: 9 RCTs (n=2062 patients) • Roth 1988 • Nygaard 1992 • Schlag 1992 • Maipang 1994 • Law 1997 • Ancona 2001 • Kelsen 2007 • Allum 2009 (update of MRC 2002) • Ychou 2011 • Boonstra 2011	• Eligibility criteria: histologically confirmed, previously untreated oesophageal cancer, suitable for radical surgery • Patients characteristics: o SCC, adenocarcino-ma, undifferentiated carcinoma o T0–3, N0–1 disease • Median FU: 7.5-106 months	• Intervention: Neoadjuvant CT plus surgery (n=1046 ; 54% had a SCC) • Comparator: Surgery alone (n=1016; 53% had a SCC) NB. Different CT schemes (products, dosages, number of cycles)	***Survival*** *All groups* HR=0.87 (95%CI 0.79–0.96; p=0.005) Absolute survival benefit at 2 years: 5.1%, NNT=19. Heterogeneity: χ^2=15.77, df=9 (p=0.07); I^2=43% *SCC* IG: n=554 CG: n=530 HR=0.92 (95%CI 0.81–1.04; p=0.18) Heterogeneity: χ^2=14.70, df=8 (p=0.07); I^2=46% *Adenocarcinomas* IG: n=470 CG: n=476 HR=0.83 (95%CI 0.71–0.95; p=0.01). *Oesophageal and oesophagogastric junction tumours* IG: n=85 CG:n=84 HR=0.63 (95% CI 0.45–0.89)	• Methodological weaknesses of included studies (small sample sizes, ITT analyses not done in all RCTs, no description of randomization process in some RCTs, low JADAD score for many studies) • Test for potential publication bias: zero potentially unpublished studies

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

Kranzfelder 2011[20]	• Design: SR and MA
	• Sources of funding: NR
	• Search date: March 2010
	• Searched databases: Cochrane Library database CENTRAL, MEDLINE, Premedline, Journals Ovid, Embase, Biosis and the Science Citation Index Database
	• Included study designs: RCTs based on ITT analysis, SR, MA
	• Number of included studies: 9 RCTs (n=2062 patients)
	  • Roth 1988
	  • Nygaard 1992
	  • Schlag 1992
	  • Maipang 1994
	  • Law 1997
	  • Ancona 2001
	  • Kelsen 2007
	  • MRC 2002
	  • Allum 2009
	  • Cao 2009
	  • Baba 2000
		• Eligibility criteria: pathological diagnosis of invasive oesophageal cancer
		• Patients characteristics:
		  o SCC, adenocarcino-ma
		  o T1–3, N0–1, M0
		• Median FU: 17-75 months
			• Intervention: Neoadjuvant CT plus surgery
			• Comparator: Surgery alone
			NN. Different CT schemes (products, dosages, number of cycles)
				R0 resection rate
				IG: n=850
				CG: n=888
				HR=1.16 (95%CI 1.05, -1.30)
				Heterogeneity: ζ^2=0.01, χ^2=9.54, df=5, P=0.089, I^2=48%
				Postoperative morbidity
				IG: n=797
				CG: n=893
				HR=1.03 (95%CI 0.90- 1.19)
				Heterogeneity: ζ^2=0.00, χ^2=6.32, df=6, P=0.388, I^2=5%
				30-day mortality
				IG: n=849
				CG: n=939
				HR=1.04 (95%CI 0.76- 1.43)
				Heterogeneity: ζ^2=0.00, χ^2=3.59, df=7, P=0.826, I^2=0%
					• Methodological weaknesses of included studies (small sample sizes, ITT analyses not done in all RCTs, no description of randomization process in some RCTs, low JADAD score for many studies)

4.2.3. Neoadjuvant chemotherapy vs. Adjuvant Chemotherapy

4.2.3.1. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Ando 2011[21] (primary outcomes) **Hirao 2001**[22] (secondary outcomes)	• Design: RCT 2 arms • Research funding: Grant-in-Aid for Cancer Research from the Ministry of Health, Labor and Welfare of Japan • Setting: 24 Japanese hospitals • Sample size: 330 patients • Period: 2000-2006 • Median FU: 62 months (range: 10.7–106.8)	• Eligibility criteria: patients with locally advanced oesophageal SCC, stage II or III excluding T4 disease • Clinical staging: Upper GI endoscopy, oesophagography, CT or MRI, EUS	• Intervention: Neoadjuvant CT (two courses of cisplatin plus 5-fluorouracil) followed by surgery within 5 weeks; n=164 • Control: Adjuvant CT (two courses of cisplatin plus 5-fluorouracil) after 2 to 10 weeks; n=166; pN0 patients do not receive CT (23%) Surgery: total or subtotal thoracic oesophagectomy and regional lymphadenectomy (mediastinal and perigastric) with curative intent	***5-year progression-free survival*** IG: 44% (95%CI 36.4–51.8) CG: 39% (95%CI 31.3–46.3) P=0.22 ***5-year overall survival*** IG: 55% (95%CI 46.7–62.5) CG: 43% (95%CI 34.6–50.5) P=0.04 *Sub group analysis*: 54.5/49.4% (IG/CG) in cN0 patients 55.3/39.5% (IG/CG) in cN1 patients.	***Intraoperative complications*** *Pulmonary problems* IG: 15.7% CG:13% *Anastomotic leakage* IG: 12.4% CG: 14.9% *Recurrent nerve palsy* IG: 22.9% CG: 15.5% p>0.05 ***In-hospital death*** IG: 0.7% CG: 1.2% P=1.000	• Randomisation method: not specified • Double blinding? • Difference between the completion rate of CT in each group • The postoperative chemotherapy is not given to pN0 patients

4.2.4. Neoadjuvant Chemoradiotherapy vs. surgery alone

4.2.4.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality

Boughrassa 2009 (AETMIS)[18]	• Design: SR
	• Sources of funding: Governmental Agency
	• Search date: End 2008
	• Searched databases: Medline, Embase and The Cochrane Library
	• Included study designs: MA, SR of RCTs, RCTs
	• Number of included studies: 9 RCTs (n=1099)
	  • Nygaard 1992
	  • Apinop 1994
	  • Le Prise 1994
	  • Urba 2001
	  • Bosset 1997
	  • Burmeister 2005
	  • Tepper 2008
	  • Lee 2004
	  • Natsugoe 2006
		• Eligibility criteria: histologically confirmed, previously untreated oesophageal cancer, suitable for radical surgery
		• Patients characteristics:
		  o SCC, adenocarcino-ma, undifferentiated carcinoma
		  o T0–3, N0–1 disease
		• Median FU: 12-98 months
			• Intervention: Neoadjuvant CRT + surgery
			• Comparator: surgery alone
			• NB. RT and CT were either sequential or concurrent
				Survival
				Narrative review of results reported by primary RCTs and meta-analyses of these RCTs.
				Ccl:
				- no evidence for efficacy of neoadjuvant CRT (2 RCTs reported improvement in disease-free survival in patients with squamous cell carcinoma).
				Tumour recurrence
				- similar risk of locoregional or distant tumour recurrence with both neoadjuvant CRT and surgery alone.
						• Methodological weaknesses of included studies (small sample sizes, ITT analyses not done in all RCTs, no description of randomization process in some RCTs, low JADAD score for many studies)

Sjoquist 2011[19]	• Design: SR and MA • Sources of funding: Cancer Australia and Cancer Institute (NSW) to the National Health and Medical Research Council Clinical Trials	• Eligibility criteria: histologically confirmed, previously untreated oesophageal cancer, suitable for radical surgery	• Intervention: Neoadjuvant CRT + surgery (n=980) • Comparator: surgery alone	***Survival*** *All groups* HR=0.78 (95%CI 0.70–0.88; p<0·0001) Absolute survival benefit at 2 years: 8.7%; NNT=11		• Methodological weaknesses of included studies (ITT analyses not done in all RCTs, no description of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality

	Centre and AGITG (no impact on the publication itself)
	• Search date: November 2010
	• Searched databases: Medline, Embase, and Central (Cochrane clinical trials database) + manual search for abstracts
	• Included study designs: RCTs based on ITT analysis
	• Number of included studies: 12 RCTs (n=1932 patients)
	  • Nygaard 1992
	  • Apinop 1994
	  • Le Prise 1994
	  • Urba 2001
	  • Bosset 1997
	  • Walsh 1995-96
	  • Burmeister 2005
	  • Tepper 2008
	  • Lv 2010
	  • Lee 2004
	  • Mariette 2010
	  • van der Gaast 2010
		• Patients characteristics:
		  o SCC, adenocarcinoma, undifferentiated carcinoma
		  o T0–3, N0–1 disease
		• Median FU: 12-98 months
			(n=952)
			NB. RT and CT were either sequential or concurrent
				SCC
				IG: n=498
				CG: n=467
				HR=0.80 (95%CI 0.68–0.93; p=0.004)
				Heterogeneity: χ^2=5.31, df=8 (p=0.72); I^2=0%
				Adenocarcinomas
				IG: n=175
				CG: n=170
				HR=0.75 (95%CI 0.59–0.95; p=0.02)
				Heterogeneity: χ^2=3.11, df=2 (p=0.21); I^2=36%
						randomization process in some RCTs, low JADAD score for some studies)
						• Test for potential publication bias: the meta-analysis is robust to publication bias
						• Sensitivity analyses with subgroup analyses py type of tumour (AC vs. SCC) but not by cancer stages
						• 3 more recent studies included:
						▪ Lv 2010 (see below)
						▪ Marriette 2010 (unpublished, abstract only)
						▪ Van der Gaast 2010 (unpublished, abstract only)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality

Kranzfelder 2011[20]	• Design: SR and MA
	• Sources of funding: NR
	• Search date: March 2010
	• Searched databases: Cochrane Library database CENTRAL, MEDLINE, Premedline, Journals Ovid, Embase, Biosis and the Science Citation Index Database
	• Included study designs: RCTs based on ITT analysis, SR, MA
	• Number of included studies: 9 RCTs (n=1099 patients)
	  • Nygaard 1992
	  • Apinop 1994
	  • Le Prise 1994
	  • Urba 2001
	  • Bosset 1997
	  • Walsh 1995-96
	  • Burmeister 2005
	  • Tepper 2008
	  • Lee 2004
	  • Cao 2009
	  • Natsugoe 2006
		• Eligibility criteria: pathological diagnosis of locally advanced resectable oesophageal cancer
		• Patients characteristics:
		  o SCC, adenocarcino-ma
		  o T1–4, N0–1, M0
		• Median FU: 10-98 months
			• Intervention: Neoadjuvant CRT + surgery
			• Comparator: surgery alone
			NB. RT and CT were either sequential or concurrent; variations in RT doses (20-50 Gy) and CT sequences
				R0 resection rate
				IG: n=551
				CG: n=564
				HR=1.15 (95%CI 1.00, -1.32)
				Heterogeneity: ζ^2=0.03, χ^2=37.76, df=6, P<0.001, I^2=84%
				Postoperative morbidity
				IG: n=534
				CG: n=549
				HR=0.94 (95%CI 0.82-1.07)
				Heterogeneity: ζ^2=0.00, χ^2=4.76, df=6, P=0.573, I^2=0%
				30-day mortality
				IG: n=509
				CG: n=510
				HR=1.46 (95%CI 0.91-2.33)
				Heterogeneity: ζ^2=0.00, χ^2=4.74, df=7, P=0.692, I^2=0%
						• Methodological weaknesses of included studies (ITT analyses not done in all RCTs, no description of randomization process in some RCTs, low JADAD score for some studies)

Jin 2009[23]	• Design: SR and MA • Sources of funding: NR	• Eligibility criteria: pathological diagnosis of locally	• Intervention: Neoadjuvant	***Survival*** Updated in Sjoquist 2011	***Loco-regional cancer***	• Methodological weaknesses of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality

	• Search date: 2008
	• Searched databases: MEDLINE, Embase
	• Included study designs: RCTs based on ITT analysis, SR, MA
	• Number of included studies: 7 RCTs (n=741 patients)
	  • Le Prise 1994
	  • Urba 2001
	  • An 2003
	  • Burmeister 2005
	  • Tepper 2008
	  • Lee 2004
	  o Natsugoe 2006
		advanced resectable oesophageal cancer
		• Patients characteristics:
		  o SCC, adenocarcino-ma
		  o T1–4, N0–1, M0
		• Median FU: 5 years
			CRT + surgery (n=370)
			• Comparator: surgery alone (n=371)
			NB. RT and CT were either sequential or concurrent; variations in RT doses (20-50 Gy) and CT sequences
				Postoperative mortality
				Updated in Kranzfelder 2011
					recurrence
					OR=0.64 (95%CI 0.41-0.99)
					Test for heterogeneity: χ^2=6.02, df=6 (p=0.42), I^2=0.4%
					
					Distant cancer recurrence
					OR=0.94 (95%CI 0.68-1.31)
					Test for heterogeneity: χ^2=9.42, df=6 (p=0.15), I^2=36.3%
						included studies (ITT analyses not done in all RCTs, no description of randomization process in some RCTs, low JADAD score for some studies)

4.2.4.2. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of quality
Lv 2010[24]	• Design: RCT 2 arms • Research funding: not reported • Setting: one hospital in China • Sample size: 238patients • Period: 1997 - 2004 • Complete FU: 5 to 124 months (median 45 months)	• Eligibility criteria: Patients with thoracic SCC (stage II – III) using preoperative CT staging . • Exclusion criteria : not reported • Patients characteristics:	• Intervention: group I=preoperative CRT (n=80); group II=postoperative CRT (n=78) • Control: surgery alone (n=80) Surgery= radical resection by oesophagectomy (thoracotomy+ 2-field lymphadenectomy) or palliative resection or oesophageal bypass RT = 40 Gy (20 fractions at 2 Gy per fraction) CT = 2 cycles paclitaxel + cisplatin	***Progression-free survival (Group I, Group II, Group III)*** 1 year 89.3% - 89.1% - 84.5% (χ^2=0.64, p=0.41) 3 years 61.3% - 61.1% - 49.3% (χ^2=4.16, p=0.03) 5 years 37.5% - 37.2% - 25.9% (χ^2=4.14, p=0.03) 10 years 18.1% - 17.8% - 6.2% (χ^2=5.38, p=0.02) No difference between Group I and Group II: χ^2=0.14, p=0.71 ***Overall survival (Group I, Group II, Group III)*** 1 year 91.3% - 91% - 87.5% (χ^2=0.72, p=0.39) 3 years 63.5% - 62.8% - 51.3% (χ^2=3.98, p=0.04)	• Inadequate reporting of randomization procedure • Analysis : no ITT • Comparable groups: no (more stage III cancers in groups II and III) and no sub-group analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of quality
				5 years 43.5% - 42.3% - 33.8% (χ^2=4.76, p=0.04) 10 years 24.5% - 24.4% - 12.5% (χ^2=4.27, p=0.04) No difference between Group I and Group II: χ^2=0.46, p=0.49	

4.2.5. Neoadjuvant chemotherapy vs neoadjuvant chemoradiotherapy

4.2.5.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Sjoquist 2011[19]	• Design: SR and MA • Sources of funding: Cancer Australia and Cancer Institute (NSW) to the National Health and Medical Research Council Clinical Trials Centre and AGITG (no impact on the publication itself) • Search date: November 2010 • Searched databases: Medline, Embase, and Central (Cochrane clinical trials database) + manual search for abstracts • Included study designs: RCTs based on ITT analysis • Number of included studies : 2 RCTs (n=194 patients) o Stahl 2009 o Burmeister 2005	• Eligibility criteria: histologically confirmed, previously untreated oesophageal cancer, suitable for radical surgery • Patients characteristics: o adenocarcinoma o T0–3, N0–1 disease • Median FU: 46-70 months	• Intervention: Neoadjuvant CRT + surgery (n=99) • Comparator: Neoadjuvant CT + surgery (n=95) NB. CT and RT: Induction and concurrent	***Survival*** 2 RCTs: HR=0.77 (95%CI 0.53–1.12) Pooled trials with other studies (9CT / 12CRT/ 2CT-CRT): HR=0.90 (95%CI 0.77–1.04; p=0.15).	***30 days PO or in-hospital mortality*** Little association between risk of PO mortality (in-hospital or 30-day PO death) and the neo-adjuvant interventions	•Both trials closed prematurely and were consequently underpowered to detect a significant survival advantage

4.2.6. Definitive chemoradiotherapy (dCRT) versus neoadjuvant treatment followed by surgery or surgery alone

4.2.6.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality

Kranzfelder 2011[20]	• Design: SR and MA
	• Sources of funding: NR
	• Search date: March 2010
	• Searched databases: Cochrane Library database CENTRAL, MEDLINE, Premedline, Journals Ovid, Embase, Biosis and the Science Citation Index Database
	• Included study designs: RCTs based on ITT analysis
	• Number of included studies: 3 RCTs (n=512 patients)
	  • Bedenne 2007
	  • Stahl 1992
	  • Chiu 2005
		• Eligibility criteria: pathological diagnosis of locally advanced resectable oesophageal cancer
		• Patients characteristics:
		  o SCC
		  o T1–4, N0–1, M0
		• Median FU: 15-24 months
			• Intervention: (Neoadjuvant C(R)T) + surgery (n=260)
			• Comparator: dCRT (n=252)
				Morbidity
				IG: n=130
				CG: n=122
				HR=0.78 (95%CI 0.47-1.30)
				Heterogeneity: ζ^2=0.11, χ^2=4.67, df=1, P=0.031, I^2=79%
				Overall survival
				IG: n=259
				CG: n=252
				HR=7.60 (95%CI 1.76-32.88)
				Heterogeneity: ζ^2=0.00, χ^2=0.31, df=2, P=0.856, I^2=0%
						• Bedenne included only responders to neoadjuvant therapy

4.3. Restaging after neoadjuvant treatment

4.3.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Chen 2011[25]	• Design: SR and MA • Sources of funding: research training foundation of Shanghai Renji Hospital • Search date: January 2010 • Searched databases: Medline and Embase • Included study designs: not reported • Number of included studies: 13 studies 1. Klaeser 2009 2. Roedl 2009 3. Roedl 2008 4. Higuchi 2008 5. McLoughlin 2008 6. Wieder 2007 7. Port 2007 8. Kim 2007 9. Mamede 2007 10. Bruzzi 2007 11. Ott 2006 12. Westerterp 2006 13. Cerfolio 2005	• Eligibility criteria: a) ^{18}F-FDG PET used to assess neo-adjuvant therapy response in patients with oesophageal cancer; b) postsurgery pathological outcome used as the gold standard; c)^{18}F-FDG used as the tracer; d) scanner PET or PET-CT; e) adequate sample size to calculate sensitivity and specificity, ≥ 10 participants • Exclusion criteria: a) clinical follow-up and imaging examination as gold standard; b) scanner dual head coincidence imaging SPECT or a clinical PET;	• Intervention: ^{18}F-FDG PET or PET-CT after neoadjuvant CT (4 studies) or CRT (9 studies) • Reference standard: post-surgical histopathology	***Assessment of neoadjuvant therapy response*** Pooled sensitivity = 0.70 (95% CI: 0.64 − 0.76) χ^2 =37.04; df=12 (P=0.0002) Inconsistency (I^2) = 67.6% Pooled specificity = 0.70 (95%CI: 0.65 − 0.75) χ^2=85.60; df=12 (P=0.0000) Inconsistency (I^2)=86.0% The pooled DOR was 9.389 (95% CI: 3.482–25.319; χ^2=61.35, P=0.000). The area under the symmetric SROC curve was 0.8244, and the Q* value was 0.7575	• Use of QUADAS quality assessment tool: the 13 studies fulfilled the 14 inclusion questions (spectrum composition, selection criteria, reference standard, disease progression bias, partial / differential verification, incorporation bias, index test / reference standard execution, test / reference standard review bias, clinical review bias, uninterpretable test results, withdrawals) • No description of the sample size of each study,

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
		c) other radiotracers; d) small sample size.			the study design. • The pooled Se and Sp are based on the random-effects model due to heterogeneity
Kwee 2010[26]	• Design: SR and MA • Sources of funding: not reported • Search date: June 2009 • Searched databases: Medline and Embase • Included study designs: not reported • Number of included studies: 20 studies (n= 11-104 patients; total sample size=849 patients) 1. Schmidt 2009 2. Smith 2009 3. Smithers 2008 4. Lordick 2007 5. Gillham 2006 6. Levine 2006 7. Song 2005 8. Brink 2004 9. Kroep 2003 10. Arslan 2002 11. Brücher 2001 12. Roedl 2008 13. McLoughlin 2008 14. Wieder 2004 15. Port 2007 16. Mamede 2007	• Eligibility criteria: a) ^{18}F-FDG PET used to assess neo-adjuvant therapy response in patients with oesophageal cancer; b) postsurgery pathological outcome used as the gold standard; c)^{18}F-FDG used as the tracer; d) adequate sample size to calculate sensitivity and specificity, > 10 participants • Exclusion criteria: a) clinical follow-up and imaging examination as gold standard; b) no or insufficient data with which	• Intervention: ^{18}F-FDG PET or PET-CT after neoadjuvant CT (4 studies) or CRT (16 studies) • Reference standard: post-surgical histopathology	***Assessment of neoadjuvant therapy response*** Pooled sensitivity = 0.67 (95% CI: 0.62 − 0.72) Heterogeneity (p>0.0001) Pooled specificity = 0.68 (95%CI: 0.64 − 0.73) Heterogeneity (p>0.0001) Area under sROC= 0.7815	• Use of (adapted) QUADAS quality assessment tool: maximum score ranged from 47% to 87% (median 67%) • The pooled Se and Sp are based on the random-effects model due to heterogeneity

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	17. Bruzzi 2007 18. Ott 2006 19. Westerterp 2006 20. Cerfolio 2009	to construct a 2x2 contingency table; c) sample size; d) review articles, MA, abstracts, editorials, case reports, guidelines, studies in animals, ex vivo studies.			
Ngamruengphong 2010[27]	• Design: SR and MA • Sources of funding: no financial support • Search date: February 2008 • Searched databases: Medline, Embase and Cochrane databases • Included study designs: not reported • Number of included studies: 19 studies (total sample size= 966 patients) o 7 studies: EUS (n=13 –103) 1. Hirata 1997 2. Giovannini 1997 3. Willis 2002 4. Kroep 2003 5. Swisher 2004 6. Cerfolio 2005 7. Ota 2005	• Eligibility criteria: a) ^{18}F-FDG PET and EUS used to assess neo-adjuvant therapy response (before and after therapy) in patients with oesophageal cancer; b) histopathologic confirmation of cancer documented; c) pathological findings used as the gold standard; d) ≥ 10 patients included; e) articles in English • Exclusion	• Intervention : EUS / FDG-PET • Reference standard: histopathology	***Sensitivity*** EUS: 20-100% FDG-PET: 42-100% ***Specificity*** EUS: 36-100% FDG-PET: 27-100% ***Diagnostic accuracy*** *Area under the SROC curve (AUC)* EUS: 0.86 (95% CI 0.77-0.96) FDG-PET: 0.80 (95%CI 0.72-0.89) P=0.37 *Maximum joint Se and Sp (Q* index)* EUS: 0.79 (95%CI 0.70-0.88) FDG-PET : 0.74 (95%CI 0.66-0.81) P=0.38 ***Subgroups analysis*** *EUS : Tumour size*	• Use of QUADAS quality assessment tool: positive score on at least 10 items on 14 • Analysis of heterogeneity between individual studies by an inverse variance weighted metaregression analysis • Subgroup analysis: - EUS: restaging vs. tumour size measurement - PET: early FDG-PET vs. after

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o 15 studies: FDG-PET 1. Brusher 2001 2. Flamen 2002 3. Kroep 2003 4. Wieder 2004 5. Swisher 2004 6. Cerfolio 2005 7. Song 2005 8. Bruzzi 2006 9. Gillham 2006 10. Levine 2006 11. Ott 2006 12. Westertep 2006 13. Lordick 2007 14. Mamede 2007 15. Port 2007 o 3 papers: both modalities	criteria: a) insufficient data to construct a 2x2 contingency table; b) data analysis not done on a per patient protocol; c) duplicate studies on the same patients • Patients: AC-SCC; stages II-IV		AUC: 0.83 (95%CI 0.57-1.00) Q* index : 0.76 (95%CI 0.52-1.00) *EUS : Restaging* AUC : 0.98 (95%CI 0.92-1.00) Q* index : 0.94 (95%CI 0.82-1.00) *FDG-PET: During neoadj. Trt* AUC : 0.78 (95%CI 0.62-0.93) Q* index : 0.72 (95%CI 0.58-0.86) *FDG-PET: After neoadj. Trt* AUC : 0.80 (95%CI 0.71-0.89) Q* index : 0.73 (95%CI 0.65-0.81) *Type of PET machine: PET only* AUC : 0.84 (95%CI 0.78-0.90) Q* index : 0.77 (95%CI 0.72-0.83 *Type of PET machine: PET/CT* AUC : 0.77 (95%CI 0.39-1.00) Q* index : 0.71 (95%CI 0.39-1.00 *EUS vs. FDG-PET* AUC : p=0.37 Q* index : p=0.38 *Tumour stage vs. restaging* AUC : p=0.27 Q* index : p=0.19 *Early PET vs. late PET* AUC : p=0.83 Q* index : p=0.84 *PET (16 studies) vs. PET/CT (3 studies)*	neoadj. Trt - PET vs. PET/CT

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
				AUC : p=0.71 Q* index : p=0.70 *PET after CT (4 studies) vs. PET after CRT (11 studies)* AUC: p=0.24 Q* index: p=0.26	

Note: DOR: diagnostic odds ratio; AC: adenocarcinoma; SCC: squamous cell cancer

4.3.2. Primary studies

Study ID	Population	Index test	Outcome	Results	Comments
Yen 2012[6]	118 consecutive patients with oesophageal squamous cell carcinoma who underwent oesophagectomy with (group 2; n= 90) or without (group 1; n=28 patients) neoadjuvant chemoradiotherapy (CRT) over a near 3-year period between January 2005 and November 2008 at a tertiary hospital in Taiwan	• EUS • FDG PET/CT • Standard reference: surgical pathology	Performance of FDG PET/CT and EUS in assessing treatment response and restaging after NACRT	***Assessment of treatment response after NACRT: distinction in complete response rate*** *EUS* Se: 5% Sp: 38% *FDG PET/CT* Se: 32% Sp: 90%	• Retrospective study • Small sample size
Misra 2011[28]	110 patients with histologically proven squamous cell carcinoma or adenocarcinoma of the oesophagus who underwent EUS before and after NACT.	• Index test: EUS • Standard reference: postsurgical pathology	Performance of EUS in assessing treatment response and restaging after NACT	***N Staging accuracy of EUS after NACT (n=110)*** Se: 63% Sp: 54% PPV: 58% NPV: 58%	
Van Heijl 2011[29]	145 patients with histologically proven squamous cell carcinoma or adenocarcinoma of the oesophagus or gastroesophageal junction who underwent oesophagectomy after neoadjuvant concurrent	• Index test: FDG PET (n= 100) • Reference standard: histopathology	Performance of FDG PET in assessing treatment response and restaging after NACRT	***FDG-PET response versus histopathologic response using a 0% decrease (any change) as SUV Cutoff*** Se 91% Sp 50% PPV 76% NPV 75% ***FDG-PET response versus histopathologic response using a 10%***	• Part of phase III RCT • 45 of 145 patients (31%) were unable to complete the study protocol. The applicability of FDG-PET as early response

Study ID	Population	Index test	Outcome	Results	Comments
	CRT (90.3% were T3)			***decrease as SUV Cutoff*** Se 81% Sp 56% PPV 76% NPV 63% ***FDG-PET response versus histopathologic response using a 20% decrease as SUV Cutoff*** Se 70% Sp 64% PPV 78% NPV 55% ***FDG-PET response versus histopathologic response using a 30% decrease as SUV Cutoff*** Se 55% Sp 67% PPV 75% NPV 45%	assessment modality might be further hampered by this relatively high number of dropouts
Van Heijl 2011[30]	39 patients with histologically proven squamous cell carcinoma or adenocarcinoma of the oesophagus or gastroesophageal junction who underwent oesophagectomy after neoadjuvant concurrent CRT	• Index Test: 3D-CT • Standard reference: histopathology	Performance of 3D-CT in assessing treatment response and restaging after NACRT	***3D-CT response versus histopathologic response using a 0% Cutoff (ROC analysis)*** Se 35% Sp 77% PPV 75% NPV 37% ***3D-CT response versus histopathologic response using a 10% Cutoff (ROC analysis)*** Se 19%	• Part of phase III RCT

Study ID	Population	Index test	Outcome	Results	Comments
				Sp 92% PPV 83% NPV 36% ***3D-CT response versus histopathologic response using a 20% Cutoff (ROC analysis)*** Se 8% Sp 100% PPV 100% NPV 35%	
Eloubeidi 2011[8]	112 patients who will undergo Ivor Lewis oesophagogastrectomy after neoadjuvant therapy	• EUS/FNA • Standard reference: histopathology	True negative rate of EUS-FNA in patients predicted to be N0 (NPV)	***N Staging accuracy of EUS-FNA after NACRT (n=107)*** Se 26% Sp 88% PPV 41% NPV 78%	• Interpretation of results from histopathology without knowledge of index tests results?

4.4. Treatment of mucosal cancer

4.4.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
McCann 2011[31]	• Design: SR • Sources of funding: not reported • Search date: January 2009 • Searched databases: Medline, Pubmed, Embase, CINAHL, The Cochrane Library, CRD databases, Web of Science and EconLit + Grey literature (ASCO, Digestive Disease Week meetings abstracts, websites of cancer organizations, CPG and clinical trials) • Included study designs: RCTs, non-randomized controlled studies; retrospective, prospective or concurrent cohort studies; case or clinical series • Number of included studies: 75 studies (n=3124 patients)	• Inclusion criteria: o Patients: Early oesophageal cancer (SCC/AC, stages 0–IIA; no spread to the lymph nodes) o Interventions: Photodynamic therapy, oesophagectomy, RT, CRT, CT, Endomucosal resection, other ablative treatments (including argon plasma coagulation, cryoablation, and radiofrequency ablation) o Comparators: Same as interventions above o Outcomes: tumour	• *Endoscopic techniques* o Ablative techniques: photodynamic therapy, radiofrequency ablation, argon plasma coagulation, and cryotherapy o Endoscopic mucosal resection (EMR) o Endoscopic submucosal dissection (ESD) • *Non-endoscopic techniques* o Open surgery o CT, RT, CRT	***Safety*** *Endoscopic techniques (16 /26 studies)* • PDT: Photosensitizing agent used: - Porfimer sodium : stricture (pooled incidence: 13%) - aminolevulinic acid : chest pain and nausea/vomiting (half of the patients) • EMR studies (8/12 studies) - bleeding (10%) - stenosis (6%) - stricture (0.5%) *Non-endoscopic techniques (2 /20 studies): oesophagectomy vs. EMR + PDT* - stricture (16% vs 8%) - infection and anastomotic leaks (8% vs 0%) - respiratory complication (9% vs 0%) - cardiac complication (8% vs 0%) - treatment related death (2% vs 0%) ***Efficacy : tumour response*** *Endoscopic ablative techniques* - Pooled mean complete response: 54% in ACC and 71% in SCC *Endoscopic non-ablative techniques* - Pooled mean complete response: 98% in ACC and 88% in SCC *Non-endoscopic ablative treatments* - RT: Pooled mean complete response:	• 20% of studies were comparative • 50% of studies: n<20 patients • Majority of studies on ablative therapies included patients ineligible for surgery • Treatment protocols, outcomes measured and lengths of FU periods varied across studies; some patients received additional interventions after trt failure • Qualitative analysis: 5-years OS, 5-years disease specific survival, tumour response, disease progression • Quantitative analysis (ITT)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
		response, recurrence, Cause-specific/disease-specific survival, overall survival		NR in ACC and 81% in SCC - CRT: Pooled mean complete response: NR in ACC and 86% in SCC ***Efficacy : 5-years overall survival*** *Endoscopic ablative techniques (PDT)* - 28% in ACC and NR in SCC *Non-endoscopic ablative treatments* - Esophagectomy: 96% in ACC and 39% in SCC ***Efficacy : 5-years cause-specific survival*** *Endoscopic ablative techniques (PDT)* - Both ACC and SCC: 92% *Endoscopic non-ablative techniques (EMR)* - 100% in ACC and 95% in SCC	• Results on efficacy: few studies reported results and pooled values across disease stages (I-IV) • No MA

4.5. Surgery for cancer beyond mucosa

4.5.1. Esophageal transthoracic technique vs. oesophageal transhiatal technique

4.5.1.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Boughrassa (AETMIS) 2011[32]	• Design: SR • Sources of funding: Governmental Agency • Search date: December 2009 + updates • Searched databases: Medline, The Cochrane Library and Embase • Included study designs: HTA reports, SR w/without MA, RCTs, non-randomized controlled studies • Number of included studies: o 3 SR 1. Lagarde 2010 2. Hulscher 2001 3. Rindani 1999 o 3 RCTs 1. Hulscher 2002 (same patients : Omloo 2007, De Boer 2004) 2. Chu 1997 3. Jacobi 1997 o 8 comparative studies	• Eligibility criteria: HTA reports, SR, MA, RCTs, non-randomised controlled studies, surgically curative oesophagus cancer (AC or SCC) , publication language (EN, FR, SP)	• Invasive oesophageal transthoracic (OTT) vs oesophageal transhiatal (OTH) surgical techniques	***Post-operative mortality (2 RCTs and 5 comparative studies) : OTT (%) vs OTH (%), p*** - 0/19 (0) vs. 3/20 (15) ns* - 5/114 (4) vs. 2/106 (2) 0.45 - 5/37 (13) vs. 8/49 (16) ns* - 3/24 (13) vs. 8/63 (13) ns* - 13/152 (9) vs. 7/141 (5) ns* - 2/28 (7) vs. 5/29 (17) ns* - 27/159 (17) vs. 8/70 (11) 0.27 ***30 days mortality (2 RCTs and 3 comparative studies), OTT (%) vs OTH (%), p*** - 0/19 (0) vs 0/20 (0) ns* - 1/16 (6) vs 1/16 (6) ns* - 2/33 (6) vs 3/65 (5) ns* - 3/41 (7) vs 4/43 (9) 0.74 - 12/159 (8) vs 3/70 (4) 0.35 ***5-year overall survival : OTT (%) vs OTH (%), p*** *Omloo 2007: patients with adenocarcinoma of the distal oesophagus (type I) or gastric cardia involving the distal oesophagus (type II) : OTT (n=110) vs OTH (n=95)*	• Studies of poor and average methodological quality • No meta-analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	1. Homesh 2006 2. Junginger 2006 3. Johansson 2004 4. Gluch 1999 5. Torres 1999 6. Tilanus 1993 7. Jauch 1992 8. Moon 1992			- 36% vs 34% (p= 0.71, per protocol analysis) - No survival benefit for either surgical approach in patients with type II tumour (p=0.81) or type I tumour (p=0.33) - Patients (n = 104) with 1 to 8 positive lymph nodes in the resection specimen: 39% vs 19%, p=0.05 - No difference for N0 or N1>8 LN+ *Torres 1999: OTT (+ LN dissection) vs OTH without LN dissection* - 36% vs 9%, p<0.05 - N0: 44% vs 17%, ns* - N1: 19% vs 6%, ns* *Junginger 2006: 229 patients with a SCC pN0* - 33% vs 12%, p=0.023 ***5-year disease-free survival : OTT (%) vs OTH (%), p*** *Omloo 2007*: - N0: 89% vs 86%, p=0.64 - N1 with 1 to 8 LN+: 64% vs 23%, p=0.02 - N1, >8 LN+, p=0.24 ***Adverse events: OTT (%) vs OTH (%), p*** *Chylothorax* - Hulscher 2002: 10% vs 2%, p=0.02 - Tilanus 1993: 5% vs 2%, p not reported *Recurrent laryngeal nerve lesions* - Chu 1997: 5% vs 5% - Tilanus 1993: 6% vs 16%, p<0.01 - Homesch 2006: 0% vs 19%, p=0.004	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
				- Gluch 1999, Jauch 1992, Moon 1992: no difference *Cardiac complications* - Hulscher 2002: 26% vs 16%, p=0.10 - Chu 1997: 16% vs 15%, p not reported *Anastomotic leakages* No differences between groups *Infectious events* No differences between groups	

Note. MIE : minimally invasive oesophagectomy; VATS: video-assisted thoracoscopy; ACC: adenocarcinoma; SCC: squamous cell carcinoma

4.5.1.2. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of quality
Chou 2009[33]	• Design: RCT 2 arms • Research funding: not reported • Setting: one hospital in Taiwan • Sample size: 87 patients • Period: 2003 • Complete FU: 1 year	• Eligibility criteria: Asian patients with stage II or stage III resectable oesophageal cancer • Exclusion criteria : upper third and T4 cancer • Patients characteristics: mean age between 54 and 59 years, more males; 78% had stage III	• Intervention: transthoracic oesophagectomy (TTE); n=47 patients • Control: transhiatal oesophagectomy (THE); n=40 patients Reconstruction with the stomach interposition through the retrosternal route; cervical oesophagogastrostomy by hand-sewn anastomosis	***Mean operative stay*** TTE: 33.7±25.4 days THE: 21.6±13.7 days P<0.05 ***Postoperative complications*** Pneumonia: 12.8% vs. 10% (NS) GI Bleeding: 6.4% vs. 5% (NS) Anastomotic leakage: 21.3% vs. 5% (p<0.05) ***Two-year survival rate*** Not significantly different (p=0.286; log-rank test) ***Quality of life*** *3 months* 20.45±2.32 vs. 25.58± *6 months* 28.23±1.64 vs. 32.68± *12 months* 30.26±1.62 vs. 34.38±1.13 T test, p<0.001	• Block for randomization 1:1 • Procedure not blinded • No ITT analysis

4.5.2. Open oesophagectomy vs. minimally invasive surgery

4.5.2.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Boughrassa 2011[32] **AETMIS**	• Design: SR • Sources of funding: Governmental Agency • Search date: December 2009 + updates • Searched databases: Medline, The Cochrane Library and Embase • Included study designs: HTA reports, SR w/without MA, RCTs, non-randomized controlled studies • Number of included studies: o 3 SR 1. Lagarde 2010 2. Verhage 2009 3. Gemmill 2007 o 3 MA 1. Nagpal 2010 2. Sgourakis 2010 3. Biere 2009	• Eligibility criteria: HTA reports, SR, MA, RCTs, non-randomised controlled studies, surgically curative oesophagus cancer (AC or SCC) , publication language (EN, FR, SP)	• Total minimally invasive oesophagectomy (MIE) versus open oesophagectomy (thoracotomy/laparotomy)	***Morbidity and mortality and overall 5-year survival*** *Narrative discussion of results:* SR: MIE leads to lower postoperative morbidity and mortality and shorter hospital stays. 2 retrospective studies: invasive and minimally invasive oesophagectomy are equivalent in terms of postoperative morbidity and mortality and overall five-year survival. The procedure is longer with MIE. *Description of one included MA (Sgourakis 2010) is presented below (Nagpal 2010 and Biere 2009 were excluded by quality appraisal)*	• Exclusion of one SR due to its methodological weaknesses (Gemmil 2007)
Sgourakis 2010[34]	• Design: SR and MA • Sources of funding: not reported • Search date: 2009 • Searched databases:	• Inclusion criteria: (a) at least one treatment arm to have undergone minimally invasive	• Total minimally invasive oesophagectomy (VATS/laparoscopy) versus open esophagectomy	***3-year survival (2 studies, 244 patients)*** RR = 0.73 (95%CI 0.49–1.08); Heterogeneity: P = 0.60; I^2 = not applicable	• Use of QUOROM statement for meta-analysis + quantification of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	Medline, Pubmed, The Cochrane Library and Embase • Included study designs: RCTs, non-randomized controlled studies • Number of included studies: 8 comparative studies (n=1008 patients) 1. Smithers 2007 2. Braghetto 2006 3. Nguyen 2000 4. Law 1997 5. Kunisaki 2004 6. Tagushi 2003 7. Morris 2007 8. Zingg 2009	oesophagectomy; (b) the intent to treat; (c) all participants to have had oesophageal cancer or Barrett's oesophagus with high-grade dysplasia or upper aerodigestive tract primary tumors (only for morbidity outcomes); (d) procedures: OTT or OTH • Exclusion criteria: (a) type Siewert I cancer, (b) emergency oesophagectomy and (c) subtotal gastrectomy and primary colonic interposition • Patient characteristics: SCC, AC and others; Stages 0-IV; FU: 0-114 months	(thoracotomy/laparotomy)	Test for overall effect: $\chi 2 = 2.49$; P = 0.114 ***30 days mortality (5 studies; 344 patients)*** RR = 1.45 (95%CI 0.53–3.97); Heterogeneity: P = 0.83; I^2 = 0% Test for overall effect: $\chi 2 = 0.51$; P = 0.474 ***Stricture (2 studies, 244 patients)*** OR = 0.11 (95%CI 0.04–0.31) Heterogeneity: P = 0.80; I^2 = not applicable Test for overall effect: $\chi 2 = 17.02$; P<0.001 (favours open surgery) ***Total complications(3 studies, 255 patients)*** OR = 1.93 (95%CI 1.08–3.43) Heterogeneity: P = 0.16; I^2 = 43.8% Test for overall effect: $\chi 2 = 4.3$; P<0.05 (favours MIE) ***Anastomotic leaks, cardiovascular events, chylothorax, fistulas, gastric conduit ischemia, pleural effusion, pneumonia, recurrent laryngeal nerve palsy, lymph nodes removed*** No differences found	the level of agreement between reviewers (Maxwell and McNemar tests) • No significant publication bias • Inclusion of patients with Barrett's oesophagus and HGD • Retrospective comparative studies, small sample sizes, no description over similarity of non trial treatment • No heterogeneity among studies (the test for inconsistency only applied in 9 out of 12 comparisons)
			• Hybrid MIE (VATS oesophagectomy/ laparotomy) vs open oesophagectomy	***5-years survival (3 studies, 607 patients)*** RR = 1.12 (95%CI 0.58–1.56) Heterogeneity: P = 0.26; I^2 = 25.7%	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
			(thoracotomy/laparotomy)	Test for overall effect: $\chi 2$= 0.41; P=0.522 (no differences for 1, 2, 3 years survival) ***Anastomic leaks(3 studies, 658 patients)*** OR = 0.99 (95%CI 0.54–1.8) Heterogeneity: P = 0.16; I^2 = 44% Test for overall effect: $\chi 2$= 0.02; P=0.896 ***Pleural effusion (3 studies, 658 patients)*** OR = 1.17 (95%CI 0.62–2.19) Heterogeneity: P = 0.707; I^2 = 0% Test for overall effect: $\chi 2$= 0.11; P=0.740	

Note. MIE : minimally invasive oesophagectomy; VATS: video-assisted thoracoscopy; ACC: adenocarcinoma; SCC: squamous cell carcinoma

4.5.3. Anastomotic techniques

4.5.3.1. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes		Critical appraisal of quality
Nederlof 2011[35]	• Design: RCT 2 arms • Research funding: not reported • Setting: one hospital in The Netherlands • Sample size: 128 patients • Period: 2005 - 2007 • Complete FU: 1 year or until death	• Eligibility criteria: age above 18 years and biopsy proven T1–3,N0–2,M0–1a cancer of the oesophagus or oesophago-gastric junction. • Exclusion criteria : previous gastric surgery, benign disease, other reconstruction than gastric tube reconstruction and unwillingness to participate in the trial. • Patients characteristics: SCC/ACC with Barrett's oesophagus, stages 0-IVB, different (neo)adjuvant treatments	• Intervention: single-layered hand-sewn cervical end-to-end (ETE) anastomosis • Control: single-layered hand-sewn cervical end-to-side (ETS) anastomosis	***Benign stenosis of the anastomosis requiring a dilatation*** ETE (40%) vs. ETS (18%), P < 0.01 after 1 year of follow-up. ***One-year actuarial stricture-free survival*** ETE (58%) vs. ETS (83%), P = 0.005 ***Mild stenosis*** ETE (3%) vs. ETS (2%) ***Severe stenosis*** ETE (37%) Vs. ETS (16%), P = 0.01 ***Anastomotic leak rate*** ETE (22%) vs. ETS (41%), P = 0.04 ***Pneumonia*** ETE (17%) vs. ETS 44%, P = 0.002 ***In-hospital stay*** ETE (15 days) vs. ETS (22 days), P = 0.02. ***Operative (30-day) mortality*** ETE (0%) vs. ETS (6%), P = 0.13.	***One-year survival*** ETE (63%; (median survival 315 days, 95% CI 306–400 days) ETS (72%; median 366 days, 95% CI 334–465 days) P = 0.63	• Adequate randomization procedure • Analysis : no ITT • Comparable groups: more females and SCC in IG, more ACC with Barrett's in CG

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of quality
				Overall in-hospital mortality ETE (3%) vs. ETS (11%) , P = 0.16	
Dai 2011[36]	• Design: RCT 2 arms • Research funding: not reported • Setting: one hospital in China • Sample size: 255 patients • Period: 2004 - 2008 • Median FU for surviving patients: 22 months (range, 3-52).	• Eligibility criteria: patients with previously untreated oesophagus cancer • Exclusion criteria: other previous or concomitant malignant diseases, previous gastric or oesophageal surgery, neoadjuvant CT or RT, T4 disease, M1 disease, or a poor pulmonary reserve • Patients characteristics: mean age= 63.5 years, sex ratio (M/F: 4/1), stages I-III	• Intervention: oesophagogastrectomy with reinforcement of the anastomosis with pedicle omental flap • Control: oesophagogastrectomy without using the pedicle omental flap around the anastomosis Different surgical approaches (transthoracic or transhiatal) were used in both groups	***Anastomotic strictures*** IG: 8 patients (6%) CG: 20 patients (16%) P < 0.05 ***Anastomotic leakages*** IG: 1 patient (1%) CG: 7 patients (6%) P =0.032	• Randomisation with permuted blocks of 4 or 6 patients with variations in length of the permuted blocks • No ITT analysis • No analysis taking into account confounding factors (e.g. surgical approaches)
Aly 2010[37]	• Design: RCT 2 arms • Research funding:	• Eligibility criteria: Patients	• Intervention: fundoplication anastomosis (Wrap)	***Reflux at 12 months*** 40% vs. 70% (p = 0.04)	• Randomisation: process unclear • Analysis on a

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of quality
	not reported • Setting: multicenter setting (3 sites in • Australia and 1 site in UK) • Sample size: 56 patients • Period: 2004 - 2007 • Median FU for surviving patients: 12 months	planned to undergo radical oesophagectomy with intrathoracic anastomosis • Exclusion criteria: patients for which oesophagectomy with cervical anastomosis was planned or if the stomach was not the planned conduit • Patients characteristics: majority of males, stages I-III, comparable groups	• Control: standard end-side oesophago-gastric anastomosis (no wrap)	***Severe reflux symptoms at 12 months*** 8% vs. 30% ***Insomnia score at 6 months*** 10±7 vs. 42±12 (p=0.04) ***Sleep disturbance due to reflux*** 25% vs. 82% (p<0.005) ***Dysphagia severity score at 12 months*** 0.4±0.8 vs. 1.6±3.1 (p=0.19)	ITT basis • Blinding of assessors

Note: ACC: adenocarcinoma, SCC: squamous cell carcinoma; IG: intervention group; CG: control group

4.5.4. Volume-outcomes relationship

4.5.4.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Wouters 2011[38]	• Design: SR and MA • Sources of funding: no specific funding was disclosed • Search date: July 2010 • Searched database: PubMed • Included study designs: multicenter studies • Number of included studies: 43 studies	• Eligibility criteria: studies using primary data, scope: surgical treatment of oesophageal cancer, more than one hospital or surgeon described, language: EN • Exclusion criteria: lack of comparisons between providers (hospitals or surgeons); no definition for procedural volume as a distinct number or cutoff value; no postoperative morbidity, mortality, survival, or quality of life among outcome parameters.	• Esophagectomy	***Postoperative mortality*** *Hospital volume(low vs. high volume)* Allareddy 2007, 12 vs. 13 Birkmeyer 2002, 1 vs. 20 Dimick & Cataneo 2001, 3 vs. 16 Dimick & Cowan 2003, 2 vs. 17 Dimick & Pronovost 2003, 8 vs. 9 Finlayson 2003, 3 vs. 10 Gasper 2009, 1 vs. 6 Kuo 2001, 5 vs. 6 Leigh 2009, 19 vs. 86 Lin 2006, 19 vs. 86 McCulloch 2003, 10 vs. 21 Ra 2008, 1 vs. 2 Simunovic 2006, 7 vs. 44 Swisher 2000, 4 vs. 5 Urbach 2003, 2 vs. 19 Wouters 2008, 6 vs. 7 OR 2.30; 95% CI 1.89-2.80 Heterogeneity between studies: I^2 =60 Sensitivity analyses: - In USA: OR 2.56; p<0.001 - In studies based on clinical data: OR 2.29; p<0.001 - Adjustment for urgent	• Most studies are retrospective and based on administrative databases • Search of papers: only in PubMed • The data-extraction form was based on the STROBE criteria (Strengthening the Reporting of Observational studies in Epidemiology) • A statistical adjustment was done for the case mix factors • Studies without a multivariate analysis and/or with no reporting of OR, HR, or risk rates were excluded from the meta-analysis. • Reference

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
				intervention: OR 2.84; p<0.001 - Adjustment for tumour characteristics: OR 2.2; p<0.001 *Surgeon volume (low vs. high volume)* Bachmann 2002, ? vs. ? Birkmeyer 2003, 1 vs. 6 Rodgers 2007, 1 vs. 7 OR 1.55; 95% CI 0.88-2.75 Heterogeneity between studies: I^2 =75 ***Survival*** *Hospital volume(low vs. high volume)* Rouvelas 2007, 1 vs. 7 Sundelöf 2008, 9 vs. 10 Simunovic 2006, 7 vs. 44 Birckmeyer 2007, 3 vs. 14 HR 1.17; 95% CI 1.05-1.31 Heterogeneity between studies: I^2 =0.0 *Surgeon volume (low vs. high volume)* Bachmann 2002, ? vs. ? Sundelöf 2008, 9 vs. 10 HR 1.16; 95% CI 0.94-1.45 Heterogeneity between studies: I^2 =48	category: the highest volume group. The OR of mortality or the HR of survival reflected the odds of mortality in the lowest volume group compared with the odds of mortality in the highest volume group. • Use of the random effect model for meta-analyses +sensitivity analyses + search for publication bias

4.6. Adjuvant treatment

4.6.1. Chemotherapy

No additional studies found

4.6.2. Radiotherapy

No additional studies found

4.6.3. Chemoradiotherapy

No additional studies found

4.7. Non-surgical treatment with curative intent

4.7.1. Definitive chemoradiotherapy vs. Radiotherapy alone

4.7.1.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Liu 2010[39]	• Design: SR and MA • Sources of funding: not reported • Search date: January 2009 • Searched database: PubMed database, China National Knowledge Infrastructure (CNKI), Chinese Biomedical Database (CBM), and Wanfang database • Included study designs: RCTs • Number of included studies: 21 studies (n=2030 patients; 99.6% had SCC) o Yang et al 2008	• Inclusion criteria: RCT; patients with pathologically confirmed oesophageal cancer; LCAHFR + FP vs. LCAHFR alone; literature quality with a Jadad score ≥3; outcomes: survival rate, local control rate, radiation oesophagitis, bronchitis, hematological and gastrointestinal toxicity • Exclusion criteria: combined with other treatment;	• Intervention: late course accelerated hyperfractionated radiotherapy (LCAHFR) combined with FP chemotherapy (n=1024) • Control LCAHFR alone (n=1006) NB. radiation dose varied from 49 to 70 Gy, with the accelerated fraction dose from 1.3 to 1.5 Gy. Doses and chemotherapy cycles were quite different (and not always described)	***Survival rates*** 1 year : OR 1.92 (95%CI 1.56-2.37, p< 0.001); χ^2 19.15 (p=0.45) 2 years : OR 2.01 (95% CI 1.61-2.49, p< 0.001); χ^2 6.6 (p=0.91) 3 years : OR 1.90 (95% CI 1.57-2.29, p< 0.001); χ^2 7.54 (p=0.98) 5 years: OR 1.85 (95% CI 1.06-3.24, p= 0.03); χ^2 0.03 (p=0.87) ***Local control rates*** 1 year : OR 1.69 (95% CI 1.27-2.26, p< 0.001), χ^2 2.75 (p=0.99) 2 years : OR 1.84 (95% CI 1.39-2.42, p< 0.001), χ^2 2.42 (p=0.97) 3 years: OR 1.87 (95% CI 1.44-2.44,	• No description about all characteristics of included studies (randomization process, blinding, ITT analysis, groups comparison before and after treatment) • Test of publication bias • Applicability: Clinical trials in Europe and America used 50.4 Gy as radiation dose.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
	o Wang et al 2008 o Li et al 2003 o Wu et al 2003 o Duan et al 2003 o Zhou et al 2003 o Dai et al 2004 o Lu et al 2005 o Liu et al 2005 o Hou et al 2005 o Chen et al 2005 o Zhao et al 2006 o Zhang et al 2006 o Zhu et al 2006 o Zhang et al 2006 o Ye et al 2006 o Duan et al 2007 o Chen et al 2007 o Li et al 2008 o Ren et al 2004	non FP CT; duplicate reports, and literatures with less information and unknown data		p< 0.001), χ^2 5.36 (p=0.72) ***Acute radiation toxicity*** *Grade 1-2 radiation bronchitis* OR 2.02 (95%CI 1.57-2.60, p<0.001), χ^2 17.62 (p=0.09) *Grade 3-4 radiation bronchitis* OR 3.01 (95%CI 1.33-7.24, p=0.009), χ^2 1.43 (p=0.96) *Grade 1-2 radiation oesophagitis* OR 1.82 (95%CI 1.17-2.84, p=0.008), χ^2 4.49 (p<0.001) *Grade 3-4 radiation oesophagitis* OR 2.60 (95%CI 1.69-4.0, p<0.001), χ^2 9.29 (p=0.51) *Myelosuppression with leukopenia* OR 3.57 (95%CI 2.67-4.78, p<0.001), χ^2 11.29 (p=0.19) *Gastrointestinal toxicities (nausea, vomiting, diarrhea)* OR 5.34 (95%CI 3.72-7.66, p<0.001), χ^2 5.74 (p=0.33)	In China, high dose of 65-70 Gy is commonly used

4.7.2. Definitive chemoradiotherapy

4.7.2.1. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of quality
Crehange 2007[40]	• Design: RCT 2 arms • Research funding: Ligue Nationale contre le Cancer, Fonds de Recherche de la Société Nationale française de gastro-entérologie, Programme Hospitalier pour la Recherche Clinique, Association pour la Recherche contre le Cancer • Setting: Multicenter study in France • Sample size: 446 included patients • Period: 1993 - 2000 • Median FU: 47.4 months	• Eligibility criteria: Patients with operable T3N0-1M0 thoracic oesophageal cancer, and with response to chemoradiation (two cycles of FU/cisplatin and either conventional (46 Gy in 4.5 weeks) or split course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy) and no contraindication to either treatment (n = 444, of which 259 were randomly assigned). • Exclusion criteria : tumors less than 18 cm from the dental ridge or infiltrating the gastric cardia, tracheobronchial involvement, visceral metastases or supraclavicular lymph nodes, weight loss of more than 15%, symptomatic coronary heart disease, cirrhosis of Child-Pugh class B or C, and respiratory insufficiency	Arm A: Continuation of chemoradiation (three cycles of FU/cisplatin and conventional RT [46 Gy over 4.5 weeks then 20 Gy over 2 weeks] (n= 161) Vs. Arm 2: Continuation of chemoradiation (three cycles of FU/cisplatin and split course RT [two courses of 15 Gy over 1 week with a break of 2 weeks then 15 Gy over 1 week] (n = 285)	***Response rate to induction CRT*** 67% vs. 68% p=0.09 ***2-year local relapse-free survival rate*** 76.7% vs. 56.8% p=0.002 Multivariate Cox analysis: HR=0.51 (95%CI 0.33-0.79; p=0.002 ***2-year overall survival rate*** 37.1% vs. 30.5% p=0.25 HR=0.83 (95%CI 0.63-1.08; p=0.17)	• Analysis : ITT • 259 patients were randomly assigned • Sub-analysis of Bedenne 2007 between the two different CRT schemes

4.8. Treatment of metastatic disease

4.8.1. Chemotherapy

4.8.1.1. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
Cunningham 2008[41]	• Design: RCT 4 arms • Research funding: Hoffmann–La Roche and Sanofi-Aventis together with the Gastrointestinal Unit Clinical Research Fund of the Royal Marsden Hospital • Setting: 59 centers in the United Kingdom and 2 in Australia • Sample size: 1002 patients • Median follow-up : 17.5 months (ECF), 17.6 months (ECX), 19.3 months (EOF), and 18.9 months (EOX).	Inclusion criteria: adult patients with a histologically proven adenocarcinoma, SCC, or undifferentiated carcinoma of the oesophagus, GEJ, or stomach that was locally advanced (inoperable) or metastatic.	Intervention: Oxaliplatin-based chemotherapy : triplet therapy with epirubicin and oxaliplatin plus either fluorouracil (EOF) or capecitabine (EOX) Comparator: cisplatin-based chemotherapy : triplet therapy with epirubicin and cisplatin plus either fluorouracil (ECF) or capecitabine (ECX)	***Death*** *Capecitabine–fluorouracil comparison* HR in the capecitabine group: 0.86 (95% CI, 0.80 to 0.99) In the ITT analysis, overall survival in the capecitabine groups did not differ significantly from that in the fluorouracil groups (HR, 0.88; 95% CI, 0.77 to 1.00; P = 0.06) *Oxaliplatin–cisplatin comparison* HR for the oxaliplatin group: 0.92 (95% CI, 0.80 to 1.10) In the ITT analysis, overall survival in the oxaliplatin groups differ significantly from	***Safety*** *Grade 3 and 4 adverse events* oxaliplatin was associated with significantly less neutropenia and alopecia but more diarrhea and peripheral neuropathy.	• Randomisation process OK, and allocation concealment • Blinding: Both investigators and patients were aware of study-group assignments • Inclusion of patients with gastric cancer • Calculation of sample size (power) • ITT based analyses • Funding source for this research: Hoffmann–La Roche and Sanofi-Aventis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
				that in the cisplatin groups (HR 0.91; 95% CI, 0.79 to 1.04; P = 0.16). ***Median survival times*** ECF, 9.9 months ECX, 9.9 months EOF, 9.3 months EOX , 11.2 months, ***Survival rates at 1 year*** ECF, 37.7% ECX, 40.8% EOF, 40.4% EOX, 46.8%		

4.8.2. Radiotherapy

4.8.2.1. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of quality
Rosenblatt 2010[42]	• Design: RCT 3 arms • Research funding: the International Atomic Energy Agency (IAEA) • Setting: multi-centre randomized clinical trial (Brazil, China, Croatia, India, South Africa and Sudan) • Sample size: 219 patients • Period: 2003 - 2006 • Follow-up: median=197 days	• Inclusion criteria: SCC of the oesophagus; successful completion of one HDRBT insertion; and signed informed consent. • Exclusion criteria: fistulae at baseline; perforation during the first HDRBT; prior therapy (e.g. CT, laser, surgery, stent) except one prior dilatation; disease beyond the mediastinum, or being eligible and agreeing to potentially curative therapies.	• Intervention: combination of high dose-rate brachytherapy (HDRBT) and External Beam Radiation Therapy (EBRT) • Control group: HDRBT alone HDBRT: 8 Gy at 1 cm from source centre. EBRT: 30 Gy in 10 fractions	***Dysphagia-relief*** The difference in absolute, estimated per cent chance of not having experienced a dysphagia-event, and in favor of the addition of EBRT to HDRBT, was of 16%, 17.8% and 19% at 100, 200 and 300 days respectively P<0.02 Scores for dysphagia (p = 0.00005), odynophagia (p = 0.006), regurgitation (p = 0.00005), chest pain (p = 0.0038) and performance status (p = 0.0015) were all significantly improved in IG. Weight, toxicities and overall survival were not different between study arms.	• 1 to 1 allocation • Calculation of the sample size • Non-blinding • Analyses based on ITT

4.8.3. Other interventions (laser, thermotherapy, brachytherapy

4.8.3.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Critical appraisal of review quality
Sgourakis 2010[43]	• Design: SR and MA • Sources of funding: Search date: 2008 • Searched databases: Medline, Embase, PubMed and the Cochrane Library • Included study designs: RCTs • Number of included studies: 16 studies (n= 1027 patients) o Laasch 2002 o Homs 2004 o Shim 2005 o Shim 2005 o Wenger 2006 o Power 2007 o Sabharwal 2003 o Conio 2007 o Sabharwal 2003 o Siersema 2001 o Siersema 2001 o Verschuur 2008 o Verschuur 2008 o Adam 1997 o Dallal 2001 o Bergquist 2005 o Homs 2004 o Königsrainer 2000 o Shenfine 2005	• Inclusion criteria: patients with histologically verified cancer of the oesophagus or gastroesophageal junction and/or with metastatic disease (M1), T4 tumors or those who were unsuitable for surgery or curative CRT (TxNxM1, T4NxMx or TxNxMx), irrespective or poor medical condition, at least one treatment arm included a stent placement as its sole treatment modality, analysis by intention to treat, • Exclusion criteria: use of conventional prosthetic tubes (Celestin or Mackler tube)	• Intervention: laser therapy, thermotherapy ablation (TTA) or brachytherapy • Control: Stent	***Number of patients requiring re-interventions (5 studies, n=509)*** Random Effects, OR: 6.31 (95%CI 1.47-27.0) I^2 = 82%; p < 0.001 Overall effect: Chi^2 = 6.14; p < 0.013 ***One-year survival (4 studies, n=497)*** Risk difference: 0.06 (95% CI -0.01-0.11) I^2=0%, p=0.74 Overall effect: Chi^2 = 4.86; p = 0.0274	• Quality of included RCTs assessed with Jadad scores (mean score 2.7) but one study obtained only 1 point • Analysis of heterogeneity and publication bias • Sensitivity analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes		Critical appraisal of review quality
Rupinski 2011[44]	• Design: RCT 3 arms • Research funding: State Committee for Scientific Research • Setting: 1 hospital in Warsaw, Poland • Sample size: 93 patients • Period: 1997 - 2001 • Follow-up: until death	• Inclusion criteria: patients with histologically proven, inoperable cancer of the oesophagus or GEJ, and a dysphagia score of 2-4 (Mellow scale 0-4) • Exclusion criteria: patients with poor medical condition, previous CT, RT or PDT, or re-canalization during the previous 30 days, presenting an oesophageal fistula or with infiltration on the trachea or main bronchi (CT or EUS)	• Intervention groups: • 1. Argon plasma coagulation (APC) + high dose rate (HDR) brachyterapy • 2. APC + photodynamic therapy (PDT) • Control group: APC alone	***Dysphagia-free period*** HDR group= 88 days PDT group=59 days Control group=35 days Overall test: p=0.006 HDR vs. control: log-rank p=0.002 PDT vs. control: log-rank p=0.036 HDR vs. PDT: log-rank p=0.36 NB. Mean number of procedures required to achieve re-canalization=5.5	***Median survival*** HDR:6.2 months (95%CI: 4.4-9.9) PDT: 5.2 months (95%CI 2.9-7.1) CG: 6.0 months (95%CI 2.0-9.2) P=0.27 ***QoL (Spitzer Quality of Life Index)*** Improved in all groups after successful re-canalization (p<0.001) Declined at the 30-days follow-up. Higher in the HDR group. ***Treatment-associated complications*** No deaths, perforations, hemorrhages, fistula formations. Major complication: fever (PDT group)	• Block randomization computer generated • Calculation of the sample size • Blinding unclear • Per protocol analysis

4.8.4. Stenting

4.8.4.1. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
Blomberg 2010[45]	• Design: RCT 2 arms • Research funding: Swedish Cancer Society, Wilson-Cook Medical, the Swedish Cancer and Traffic Injury Fund • Setting: Multicenter trial in 11 hospitals in Sweden • Sample size: 72 patients • Period: 2003-2008 • Follow-up: 3 months (median survival 2 months)	• Inclusion criteria: patients with an inoperable cancer of the distal oesophagus or cardia, having a dysphagia of at least grade 2, and a clinical need for a stent • Exclusion criteria: inability to follow the study protocol, concomitant malignant disease and expected survival < 1 month	• Intervention: self-expanded covered easophageal Z-stent with a dual anti-reflux valve (ARS) • Control: conventional stent (stainless-steel Z stent without anti-reflux sleeve, Ultraflex single-strand nitinol wire stent, or a Wall stent)	***Health related quality-of-life (n=34)*** No statistical differences between the 2 groups at 1 month		•Randomisation process correct •Blinding of patients and clinicians •Power calculation based on 210 included patients during a 3-year period → only 72 patients included (65 participated) and followed-up 6 months •More oesophageal cancers in the control group •ITT based analysis
Shenfine 2009[46] **(same study published as HTA report in 2005 and**	• Design: RCT 4 arms • Research funding: NHS HTA Programme, UK • Setting: multicenter trial, 7 centers in	• Inclusion criteria: adult patients with previously untreated primary carcinoma of	• 3 Intervention groups (n=108): self-expanding metal stents (SEMSs) with 2 different diameters, 18 and 24 mm; rigid plastic	***Dysphagia (6 weeks following treatment)*** Significant difference in mean dysphagia grade between treatment arms (P=0.046), with worse swallowing reported by rigid		•Computer-generated block randomization •Blinding of patients and caregivers to

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
included in Sgourakis 2010)	UK • Sample size: 215 patients • Period: 1997-2001 • Follow-up: 6 weeks	the oesophagus with ≥50% of the tumour causing dysphagia with sufficient luminal obstruction to hold a stent and unsuitable for curative resection • Exclusion criteria: dysphagia due to external compression or from a recurrence of a previously resected oesophageal cancer, poor medical condition, or presence of a aerodigestive fistula	stents • Control group (n=107): other palliative therapies	stent-treated patients (mean dysphagia score difference=-0.49; 95% CI -0.10 to -0.89, P=0.014). ***Quality of life (QoL) 6 weeks following treatment*** Global QL scores were lower for patients treated by SEMSs (mean difference QL index week 6=-1.01; 95% CI -0.30 to -1.72, P=0.006). ***Complications*** Late complications (stent migration) were more frequent after rigid stenting (risk ratio=2.47; 95% CI 1.88-3.04). ***Survival*** There was a survival advantage for non-stent-treated patients (log-rank statistic=4.21, P=0.04).		the received stent (but not for other treatments) •Sample size powered •Intention-to-treat analysis
Guo 2008[47]	• Design: RCT 2 arms • Research funding: No financial relationship • Setting: 1 hospital	• Inclusion criteria: Patients who had unresectable tumors due to extensive lesions,	• Intervention group: a self expandable oesophageal stent loaded with ^{125}I seeds for intraluminal brachytherapy	***Dysphagia relief*** *1st month* IG: mean grade = 1.22 ± 0.42; CG: mean grade = 1.17 ± 0.38 (P=0.732, Kruskal-		•Good randomization process •Adequate blinding of patients, care

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
	in China • Sample size: 53 patients • Period: 2004-2006 • Follow-up: maximum 15 months (IG) vs 6.7 months (CG)	metastatic disease, or poor medical condition (unfit to undergo surgery) • Exclusion criteria: tumor growth within 3.0 cm of the upper oesophageal sphincter, deep ulceration, trachea-esophageal fistula, and previous radiation therapy or stent placement	(irradiation stent group) • Control group: conventional covered stent	Wallis test). ***Survival time from stent insertion to death*** *Intervention group* Median: 7 months (95% CI: 5.0, 10.0) Mean: 8.3 months (95% CI: 6.36, 10.21) *Control group* Median: 4 months (95% CI: 2.0, 4.0) Mean: 3.5 months (95% CI: 2.72, 4.16). (P < .001, log-rank test) ***Complications*** No severe procedure-related complications in any case.		givers and assessors •Analysis not based on ITT

4.8.5. Radiotherapy

4.8.5.1. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
Rosenblatt 2010[42]	• Design: RCT 3 arms • Research funding: the International Atomic Energy Agency (IAEA) • Setting: multi-centre randomized clinical trial (Brazil, China, Croatia, India, South Africa and Sudan) • Sample size: 219 patients • Period: 2003 - 2006 • Follow-up: median=197 days	• Inclusion criteria: SCC of the oesophagus; successful completion of one HDRBT insertion; and signed informed consent. • Exclusion criteria: fistulae at baseline; perforation during the first HDRBT; prior therapy (e.g. CT, laser, surgery, stent) except one prior dilatation; disease beyond the mediastinum, or being eligible and agreeing to potentially curative therapies.	• Intervention: combination of high dose-rate brachytherapy (HDRBT) and External Beam Radiation Therapy (EBRT) • Control group: HDRBT alone HDBRT: 8 Gy at 1 cm from source centre. EBRT: 30 Gy in 10 fractions	***Dysphagia-relief*** The difference in absolute, estimated per cent chance of not having experienced a dysphagia-event, and in favor of the addition of EBRT to HDRBT, was of 16%, 17.8% and 19% at 100, 200 and 300 days respectively P<0.02 Scores for dysphagia (p = 0.00005), odynophagia (p = 0.006), regurgitation (p = 0.00005), chest pain (p = 0.0038) and performance status (p = 0.0015) were all significantly improved in IG. Weight, toxicities and overall survival were not different between study arms.		• 1 to 1 allocation • Calculation of the sample size • Non-blinding • Analyses based on ITT
Javed 2010[48]	• Design: RCT 2 arms	• Inclusion criteria: patients with locally	• Intervention group: stenting combined with palliative EBRT	***Dysphagia relief*** more sustained in IG than		• Randomisation process correct

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
	• Research funding: All India Institute of Medical Sciences, New Delhi, India • Setting: 1 hospital in New Delhi, India • Sample size: 84 patients • Period: 2007-2009 • Follow-up: 1 year (visit or telephone)	advanced unresectable cancer of the oesophagus, metastatic disease, poor performance status and comorbid conditions precluding major surgical procedure with grades 3 and 4 dysphagia • Exclusion criteria: patients with carcinoma of the cervical oesophagus, who had received prior radiotherapy, chemotherapy, or any other modality of treatment	(30 Gy in 10 fractions over 2 weeks) administered 4-6 weeks after stent placement • Control group: stenting alone	in CG (7 vs. 3months, p=0.002). ***Mean dysphagia-free survival*** 118.6±55.8 vs. 96.8± 43.0 days, p=0.054. ***Overall median survival*** higher in IG than in CG (180 vs. 120 days, p=0.009).		• No ITT analysis • No power calculation

4.9. Follow-up

4.9.1. Primary studies: RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary outcomes	Critical appraisal of quality
Verschuur 2009[49]	• Design: RCT 2 arms • Research funding: Health Care Research Program Erasmus MC Rotterdam and the Dutch Digestive Disease Foundation (SWO 02-04) • Setting: 2 hospitals in The Netherlands • Sample size: 109 included patients • Period: 2004 - 2006 • FU: 12 months	• Inclusion criteria: Patients surgically treated for oesophageal or gastric cardia cancer • Exclusion criteria: patients with irresectable cancer, admitted to a nursing home after hospital discharge or if they had insufficient knowledge of the Dutch language	• Intervention: regular home visits of a specialist nurse with more than 10 years experience in oncological care (nurse-led follow-up; n=54). • Control: follow-up of surgeons at the outpatient clinic (standard follow-up; n=55) NB. Scheduled follow-up visits for both groups were 6 weeks, and 3, 6, 9 and 12 months after randomisation.	***Generic quality of life*** Improvement in both groups for EQ-5D index (p<0.001) and the EQ-VAS for overall self-rated health (p<0.001) 4 and 7 months FU: EQ-VAS scores (IG vs. CG): 74 vs. 69, p=0.13 and p=0.12 ***Disease-specific quality of life*** Mean scores were similar between groups over time. Dysphagia scale favoured CG (p=0.11). Deglutition scale favoured IG (p=0.14)	***Patient satisfaction*** 8.3±1.2 vs. 7.9±1.2 at 7 months (P=0.14). ***Spouses satisfaction*** 8.1 vs. 7.4; p=0.03 ***Costs*** *FU visits* €234 vs. €503 P<0.001 *Intramural care during FU* €1477 vs. €2277; P=0.19 *Diagnostic procedures* €588 vs. €689, p=0.34 *Additional treatments* €182 vs. €255, p=0.29 *Extramural care* €111 vs. €74, p=0.97 *Total costs* €2592 vs. €3789, p=0.11	• Central randomization using computer-generated lists • No blinding (difficult except for assessors) • No ITT analysis

4.9.2. Primary studies: diagnostic accuracy studies

Study ID	Population	Index test	Outcome	Results	Comments
Roedl 2008[50]	• 47 patients who underwent PET/CT in the follow-up period after surgery; median follow-up : 25 months (range 10 – 39 months)	• PET/CT • Standard reference: biopsy for recurrence or progression, EUS for disease-free patients	• Detection of recurrence (locoregional, lymph nodes and distant metastases)	27 of the 47 patients were found to have recurrent disease, whereas 20 patients were recurrence free. ***Accuracy*** Se 89% Sp 75% PPV 83% NPV 83%	• High risk of incorporation bias • High risk of interpretation bias

5. EVIDENCE TABLES: GASTRIC CANCER

5.1. Staging

5.1.1. Endoscopic Ultrasound (EUS)

5.1.1.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Mocellin 2011[51]	• Design: SR and MA • Sources of funding: none • Search date: July 2010 • Searched databases: Medline, Cochrane, Cancerlit, Embase • Included study designs: all • Number of included studies: 54 (5601 pts in 16 countries)	• Inclusion criteria: minimal 10 pts with histologically proven primary carcinoma of the stomach, EUS compared with histopathology, ability to construct 2X2 tables; English language only • Exclusion criteria: overlap with other studies	• Intervention: EUS • Reference standard: histopathology	<u>T1-2 vs. T3-4</u> • Pooled Se: 86% (81-90%) • Pooled Sp: 91% (89-93%) • LR+: 9.8 (7.5-12.8) • LR-: 0.15 (0.11-0.21) • DOR: 65 (41-105) <u>Lymph node + vs. –</u> • Se: 69% (63-74%) • Sp: 84% (81-88%) • LR+: 4.4 (3.6-5.4) • LR-: 0.37 (0.32-0.44) • DOR: 12 (9-16)	<u>T1 vs. non- T1</u> • Se: 83% (77-88%) • Sp: 96% (93-97)% • LR+: 19.8 (12.7-31.1) • LR-: 0.18 (0.13-0.24) • DOR: 112 (70-179) <u>T1m vs. T1sm</u> • Se: 83% (76-89%) • Sp: 79% (65-88%) • LR+: 3.9 (2.4-6.3) • LR-: 0.21 (0.16-0.28) • DOR: 19 (13-27) <u>T4 vs. non-T4</u> • Se: 66% (52-77%) • Sp: 98% (97-98%)	• Substantial between-study heterogeneity • No information on / comparison with other imaging such as CT, MRI, PET • Although search strategy seems complete, 1 study found by Puli et al. and 5 found by Kwee et al. not included • <u>T1-2 vs. T3-4:</u> Subgroup analysis shows on average higher sensitivity and specificity in studies performed before 2000 • No significant publication bias • <u>LN + vs. LN –:</u> 37% heterogeneity likely caused by threshold effect

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
					• LR+: 28.1 (18.5-42.5) • LR-: 0.35 (0.24-0.51) • DOR: 80 (41-153)	• Higher sensitivity and lower specificity with higher disease prevalence • Lower sensitivity and higher specificity with higher high-frequency US
Kwee 2008[52]	• Design: SR • Sources of funding: • Search date: 16 January 2008 • Searched databases: Medline, Embase • Included study designs: original RCT, observational studies with more than 10 patients • Number of included studies: 18	• Inclusion criteria: histologically proven carcinoma of the stomach; publications in English, German, French, Spanish, Italian, Dutch; histology as reference standard • Exclusion criteria: studies investigating gastric cancer confined to a specific part of the stomach only; staging after radio- or chemotherapy; insufficient data; duplicate data	• Intervention: EUS • Reference standard: histopathology	<u>T1m vs. non-Tm</u> • Se: 18.2-100% (median 87.8%) • Sp: 34.7-100% (median 80.2%) • AUC: 0.8924	Subgroup analysis: • If only patients with endoscopic suspicion of early gastric cancer included, homogeneous Se of 91% (85-94%) • If only studies with transducer frequency ≥ 15 MHz included, homogeneous Se of 87% (78-93%)	• Substantial between-study heterogeneity • Low quality of included studies • No information on / comparison with other imaging such as CT, MRI, PET

Comment: As only 2/22 papers of Puli et al. (2008) are not included in the review by Mocellin et al. (2011), Puli et al. is not reported in the evidence table.

5.1.1.2. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Choi J 2010[53]	• Design: retrospective analysis of prospective database • Sources of funding: not reported; no conflicts of interest • Setting: single university centre, South-Korea • Sample size: N=388 • Duration: inclusion 8/2005-12/2009, duration of follow-up not reported	• Eligibility criteria: o Patients with pathologically confirmed gastric adenocarcinoma, which was suspected to be early gastric cancer by conventional endoscopy o Exclusion if: complete pathological evaluation of tumor depth not performed; patient had undergone preoperative radiation and/or chemotherapy; miniprobe found that the patient had obvious advanced gastric cancer; evidence of distant metastasis or extensive adjacent organ invasion on abdominal CT scan • Patient characteristics: o Male: 72.9% o Mean age: 63.5y o Upper 1/3: 7.5%; middle 1/3: 14.7%; lower 1/3: 77.8% • Prevalence of disease: o T1m: N=305 o T1sm: N=76 o T2: N=7	• Index test: EUS (miniprobe) • Reference standard: histopathology of specimen at surgery (N=63) or endoscopic resection (N=325)	<u>T1m vs. higher</u>: • Se: 99% • Sp: 11% • PPV: 80% • NPV: 69%		• No dropouts • Consecutive patient inclusion • Inclusion based on receiving of reference standard • Exclusion of 'obvious advanced' disease based on index test (EUS) • Results of endoscopy were not taken into account when interpreting the results
Hye 2009[54]	• Design: unclear • Sources of funding:	• Eligibility criteria: o Patients preoperatively	• Index test: CT (N=434), EUS	<u>Early (T1) vs. advanced gastric</u>		• No dropouts • Selection bias:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	not reported • Setting: single university centre, South-Korea • Sample size: N=434 • Duration: inclusion 1/2005-12/2005	diagnosed as early gastric cancer using endoscopy or CT and undergoing curative gastrectomy o Patients who received endoscopic submucosal dissection before the surgery or underwent gastrectomy without lymph node dissection were excluded • Patient characteristics: o Male: 64.1% o Mean age: 55.9y o Upper 1/3: 9%; middle 1/3: 18.7%; lower 1/3: 71.7%; entire: 0.7% • Prevalence of disease: o Early gastric cancer: N=382 o Advanced gastric cancer: N=52	(N=71) • Reference standard: histopathology of resected specimen	<u>cancer (T2-4)</u>: • CT: o Se: 92% o Sp: 42% o PPV: 92% o NPV: 43% • EUS: o Se: 96% o Sp: 0% o PPV: 94% o NPV: 0% <u>N-stage (N+ vs. N0)</u>: • CT: o Se: 17% o Sp: 92% o PPV: 20% o NPV: 90% • EUS: o Se: 17% o Sp: 97% o PPV: 33% o NPV: 93%		inclusion of patients also determined by index test • Unclear if consecutive inclusion
Zheng 2011[55]	• Design: retrospective analysis of prospective database • Sources of funding: not reported • Setting: single centre, China	• Eligibility criteria: o Patients treated surgically for gastric cancer o Patients who received neoadjuvant therapy were excluded • Patient characteristics: o Male: 78.4% o Mean age: 58.3	• Index test: EUS • Reference standard: histopathology	<u>T-stage</u>: • pT1: Se 79%, Sp 95%, PPV 85%, NPV 93% • pT2: Se 82%, Sp 88%, PPV 74%, NPV 92% • pT3: Se 68%, Sp 90%, PPV 78%,		• No dropouts • Unclear if consecutive inclusion • Inclusion based on receiving of reference standard

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Sample size: N=162 • Duration: inclusion 9/2007-3/2009, duration of follow-up not reported	○ Fundus/cardia: 32.1%; body: 13%; body/antrum: 6.2%; antrum/pylorus: 45.7%; diffuse: 3.1% • Prevalence of disease: ○ pT1: N=42 ○ pT2: N=49 ○ pT3: N=56 ○ pT4: N=15 ○ pN+: N=97		NPV 84% • pT4: Se 67%, Sp 95%, PPV 59%, NPV 97% <u>N-stage</u>: • Se: 49% • Sp: 69% • PPV: 71% • NPV: 48%		

5.1.2. Conventional imaging

5.1.2.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Seevaratnam 2011[56]	• Design: SR and MA • Sources of funding: Canadian Cancer Society, Ontario Ministry of health and long term care, Hanna Family chair in surgical oncology • Search date: Dec 2009 • Searched databases: Medline, Embase, Central • Included study designs: RCT, observational studies with more than 30 patients included • Number of included studies: 40 (29 prospective + 11 retrospective studies) AUS: 3 studies CT: 32 studies MRI: 3 studies PET: 9 studies	• Inclusion criteria: newly diagnosed patients with histologically confirmed gastric adenocarcinoma, staging confirmed by surgery, > 30 patients, English • Exclusion criteria: animal and ex vivo studies, mixed cancer population without separate results for gastric cancer, other design	• Intervention: abdominal ultrasound, CT, MRI, PET • Reference standard: Surgical staging	<u>T staging</u> • AUS: AUC 67.8% ± 10.8 • CT: AUC 71.5% ± 2.7 • MRI: AUC 82.9% ± 3.7 <u>N staging</u> AUS • AUC: 68.1% ± 5.8 • Pooled Se: 63.0% ±16.5 • Pooled Sp: 78.8% ±13.9 CT • AUC: 66.1% ± 2.1 • Se: 77.2% ± 2.6 • Sp: 78.3% ±2.5 MRI • AUC: 53.4% ± 5.9 • Se: 85.3% ±4.7 • Sp: 75.0%±9.3 PET • AUC: 60.0% ± 10.8 • Se: 40.3%± 10.9 • Sp: 97.7%±1.3 <u>M staging</u> • AUS: AUC 64.7% ± 21.0 • CT: AUC 81.2% ± 3.4 • PET: AUC 88.2% ± 5.8	Accuracy of <u>T staging using CT</u> dependant on number of detectors and use of MPR images: < 4 detectors • <4 detectors: AUC 62.8% ± 3.6 • ≥4 detectors: AUC 80.4% ± 2.7 • Axial images: AUC 65.2% ± 3.3 • MPR images: AUC 81.9% ± 3.1	•No critical appraisal of primary studies •No good reference standard for inoperable disease •Very few studies for AUS and MRI
Wang 2011[57]	• Design: SR and MA	• Inclusion	• Intervention:	<u>Liver M+</u>		• 25/33 studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	• Sources of funding: National Natural Science Foundation of China • Search date: February 2011 • Searched databases: Pubmed, Embase, Cochrane library, china biological medicine database • Included study designs: all if > 10 patients • Number of included studies: 33 AUS: 8 studies EUS: 5 studies CT: 22 studies MRI: 2 studies PET: 5 studies	criteria: standard reference surgery or histopathology, sufficient data for per-patient calculations, PET performed with 18F-FDG • Exclusion criteria: non-adenocarcinoma, studies confined to a specific part of the stomach, staging after chemotherapy or radiotherapy; animal or ex vivo studies, sample size > 10, not original research	US, EUS, CT, MRI, PET for detection of liver and peritoneal M+ • Reference standard: surgical staging	US • Pooled Se: 54% (34-73%) • Pooled Sp: 98% (90-99%) • DOR: 50.25 (13.48-187.32) CT • Se: 74% (59-85%) • Sp: 99% (97-100%) • DOR: 251.14 (83.53-755.07 PET • Se: 70% (36-90%) • Sp: 96% (81-99%) • DOR: 56.46 (8.47-376.23 <u>Peritoneal M+</u> US • Se: 9% (3-21%) • Sp: 99% (96-100%) • DOR: 10.63 (1.54-73.36) EUS • Se: 34% (10-69%) • Sp: 96% (87-99%) • DOR: 13.07 (6.42-26.62) CT • Se: 33% (16-56%) • Sp: 99% (98-100%) • DOR: 66.18 (27.28-160.53) PET • Se: 28% (17-44%) • Sp: 97% (83-100%) • DOR: 12.49 (2.22-70.10)		considered good quality (score ≥ 17) • Verification bias and no reporting of intermediate results and patients in some studies not representative • Significant heterogeneity between included studies • Low risk of publication bias (only tested for CT) • No direct comparison with other imaging techniques, no info on added values • Only few studies for US, MRI, PET

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Kwee 2009[58]	• Design: SR • Sources of funding: not stated • Search date: July 7, 2008 • Searched databases: Pubmed, Embase • Included study designs: all original research ≥ 10 patients • Number of included studies: 54 AUS: 6 studies EUS: 30 studies MDCT: 10 studies MRI: 3 studies PET: 4 studies PET-CT: 1 study	• Inclusion criteria: pts with newly diagnosed , histologically proven adenocarcinoma of the stomach, sample size ≥ 10, publication in English • Exclusion criteria: animal and ex vivo studies, staging after chemotherapy or radiotherapy, studies confined to a certain part of the stomach only, insufficient data, duplicate data	• Intervention: AUS, EUS, MDCT, MRI, PET, PET-CT to determine lymph node status in gastric cancer • Reference standard: surgery + histopathology	AUS • Se: 12.2-80% (median 39.9%) • Sp: 56.3-100% (median 81.8%) EUS • Se: 16.7-96.8% (median 70.8%) • Sp: 48.4-100% (median 84.6%) MDCT • Se: 62.5-91.9% (median 80.0%) • Sp: 50.0-87.9% (median 77.8%) MRI • Se: 54.6-85.3% (median 68.8%) • Sp: 50.0-100% (median 75%) PET • Se: 33.3-64.6% (median 34.3%) • Sp: 85.7-97.0% (median 93.2%) PET-CT • Se: 54.7% • Sp: 92.2%		• No significant difference between results from studies with high and low methodological quality • Only few studies for AUS, MRI, PET and PET-CT • Only MDCT included • No direct comparison between imaging techniques, no info on added values

5.1.2.2. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Anzidei 2009[59]	• Design: prospective study • Sources of funding: not reported; no conflicts of interest • Setting: single university centre, Italy • Sample size: N=40 • Duration: inclusion 1/2008-10/2008	• Eligibility criteria: o Patients with an endoscopic diagnosis of gastric carcinoma o Patients with extranodal metastases (liver, lungs, brain) were excluded • Patient characteristics: o Male: 65% o Mean age: 53.6y • Prevalence of disease: o pT1: N=8 o pT2: N=13 o pT3: N=15 o pT4: N=4	• Index test: 64-MDCT, 1.5-T MRI • Reference standard: histopathology or laparoscopy	<u>T-stage</u>: • 64-MDCT: o pT1: Se 38%, Sp 100%, PPV 100%, NPV 86% o pT2 : Se 100%, Sp 93%, PPV 87%, NPV 100% o pT3 : Se 87%, Sp 100%, PPV 100%, NPV 93% o pT4 : Se and Sp 100% • 1.5-T MRI: o pT1: Se 50%, Sp 94%, PPV 67%, NPV 88% o pT2 : Se 85%, Sp 93%, PPV 85%, NPV 93% o pT3 : Se 87%, Sp 100%, PPV 100%, NPV 93% o pT4 : Se and Sp 100%		• No dropouts • Unclear if consecutive inclusion • 7 patients received neoadjuvant chemotherapy before surgery; all other patients underwent resection within 1 week from staging • Unclear how extranodal metastases were diagnosed • Unclear how many patients had histopathology available • Blinding not reported, but probable for the index test considering the order of investigations
Bilici 2011[60]	• Design: retrospective study • Sources of funding: • Setting: single	• Eligibility criteria: o Patients who had undergone curative gastrectomy for gastric	• Index test: FDG-PET/CT • Reference standard:	<u>Diagnosis of recurrence</u>: (using SUVmax cut-off of 2.3)		• No dropouts • Unclear if consecutive inclusion

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	centre, Turkey • Sample size: N=34 • Duration: inclusion 2/2003-9/2009	cancer o Suspected gastric cancer recurrence and FDG-PET/CT for recurrence diagnosis o Exclusion criteria were contraindications to FDG-PET/CT scanning, including a blood glucose level higher than 200 mg/dl and intolerance of FDG PET/CT owing to claustrophobia • Patient characteristics: o Male: 79.4% o Median age: 58.5y o Upper 1/3: 26.5%; middle 1/3: 38.2%; lower 1/3: 32.4%; diffuse: 2.9% • Prevalence of disease: o Recurrence: N=24	Histopatho-logical examination after surgery, laparotomy or biopsy, or clinical follow-up of at least 6 months	• Se 96% • Sp 100% • PPV 100% • NPV 91%		• Inclusion based on receiving of reference standard • Differential verification • No blinded evaluation • Clinical follow-up is not clearly described, although diagnosis of recurrence required CT (clinical recurrence was defined as the detection of recurrent disease by contrast-enhanced diagnostic CT within 6 months of the FDG PET/CT scan)
Chung 2010[61]	• Design: unclear • Sources of funding: supported in part by Konkuk University in 2008; no conflicts of interest • Setting: single university centre, South-Korea	• Eligibility criteria: o Patients with gastric adenocarcinoma o Distant M+ validated by histologic confirmation or by contrast-enhanced CT and serial follow-up o No palliative gastrectomy	• Index test: FDG-PET/CT • Reference standard: histologic confirmation or conventional imaging methods	<u>Detection of solid organ M+</u>: • Se 95% • Sp 100% • PPV 100% • NPV 93%		• No dropouts • Important selection bias: inclusion of patients with distant M+ validated by histologic confirmation or by contrast-enhanced

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Sample size: N=35 • Duration: inclusion 4/2006-12/2008	o FDG-PET/CT should be performed prior to first-line palliative chemotherapy, within 1 month • Patient characteristics: o Male: 68.6% o Mean age: 57y • Prevalence of disease: o Solid organ M+: N=21				CT and serial follow-up • Consecutive patients • Differential verification • No blinded evaluation
Cidon 2009[61]	• Design: retrospective study • Sources of funding: not reported; no conflicts of interest • Setting: single university centre, Spain • Sample size: N=72 • Duration: inclusion 1/2004-3/2008	• Eligibility criteria: o Patients diagnosed with gastric cancer who underwent potentially curative surgery and preoperative staging CT of quality o At least D1 lymphadenectomy • Patient characteristics: o Male: 76.4% o Median age: 67y • Prevalence of disease: o T1/2: N=10 o N+: N=55	• Index test: 64-MDCT • Reference standard: histopathology	<u>T1/2 vs. T3/4</u>: • Se 70% • Sp 61% • PPV 23% • NPV 93% <u>N+ vs. N0</u>: • Se 49% • Sp 53% • PPV 77% • NPV 24%		• No dropouts • Unclear if consecutive inclusion • Inclusion based on receiving of reference standard • Blinding not reported
Graziosi 2011[62]	• Design: retrospective study • Sources of funding: not reported; no conflicts of interest • Setting: single	• Eligibility criteria: o Patients undergoing surgery for gastric adenocarcinoma • Patient characteristics: o Mean age: 68.4y	• Index test: FDG-PET/CT • Reference standard: histopathology or imaging,	<u>Detection of recurrence</u>: • Se 90% • Sp 86% • PPV 90%		• No dropouts • Selection criteria not clearly reported • Unclear if consecutive

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	university centre, Italy • Sample size: N=50 • Duration: inclusion 2006-2009	• Prevalence of disease: recurrence in 29 patients	clinical evaluation and blood tests	• NPV 86%		patients • Blinding not reported
Ha 2011[63]	• Design: retrospective study • Sources of funding: not reported; no conflicts of interest • Setting: single university centre, South-Korea • Sample size: N=78 • Duration: inclusion 2/2007-10/2008	• Eligibility criteria: o Patients with gastric cancer who had undergone curative gastrectomy • Patient characteristics: o Male: 67.9% o Median age: 61y o Upper 1/3: 10.3%; middle 1/3: 38.5%; lower 1/3: 51.3% • Prevalence of disease: N+ in 33 patients	• Index test: FDG-PET/CT, MDCT • Reference standard: histopathology	<u>N+ vs. N0</u>: • MDCT: o Se 70% (vs. PET/CT: p=0.035) o Sp 69% o PPV 62% o NPV 76% • PET/CT: o Se 52% o Sp 87% (vs. MDCT: p=0.029) o PPV 74% o NPV 71%		• No dropouts reported • Unclear if consecutive patients • Inclusion based on receiving of reference standard • Blinding not reported
Hwang 2010[64]	• Design: unclear, probably retrospective • Sources of funding: not reported • Setting: single university centre, South-Korea • Sample size: N=277 • Duration: inclusion	• Eligibility criteria: o Patients that underwent EUS and MDCT, followed by gastrectomy with lymphadenectomy or endoscopic resection • Patient characteristics: o Male: 61.7% o Mean age: 53y • Prevalence of disease: o pT1: N=181	• Index test: MDCT • Reference standard: histopathology	<u>T-stage</u>: • pT1: Se 26%, Sp 91%, PPV 84%, NPV 39% • pT2: Se 31%, Sp 97%, PPV 76%, NPV 80% • pT3: Se 91%, Sp 87%, PPV 38%, NPV 99%		• Included in Mocellin 2011 for EUS • No dropouts • Only 247 patients included in N-stage analysis, unclear why: potential partial verification

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	7/2006-4/2008	o pT2: N=71 o pT3: N=22 o pT4: N=3		• pT4: Se 33%, Sp 99%, PPV 33%, NPV 99%		• Patients selected out of 425 consecutive patients • Blinding not reported
Kawaguchi 2011[65]	• Design: unclear probably retrospective • Sources of funding: not reported • Setting: single university centre, Japan • Sample size: N=92 • Duration: inclusion 1/2005-12/2007	• Eligibility criteria: o Patients with gastric cancer confirmed by endoscopic biopsy and who underwent preoperative MDCT o All patients received gastrectomy and lymphadenectomy • Patient characteristics: o Male: 69.6% o Mean age: 65.5y • Prevalence of disease: N+ in 45 patients	• Index test: MDCT • Reference standard: histopathology	N+ vs. N0: • Se 82% • Sp 81% • PPV 80% • NPV 83%		• No dropouts • Consecutive patients, but inclusion probably based on receiving of reference standard • Blinding not reported
Kim DW 2011[66]	• Design: retrospective study • Sources of funding: supported by a grant of the Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea (A100250)	• Eligibility criteria: o Interval of <3 yr between curative surgical resection and study inclusion o Both integrated PET/CT and CECT within 2 months for the surveillance of gastric cancer recurrence with or without suspicion of recurrence o For suspicious lesion of	• Index test: FDG-PET/CT, CECT • Reference standard: histopathologic examination for local recurrence or serial imaging study follow-up with at least 1 yr	• CECT: o Se 64% o Sp 86% o PPV 55% o NPV 91% • PET/CT: o Se 54% o Sp 85% o PPV 47% o NPV 88%	9 recurrences were missed by both interventions	• No dropouts • Consecutive patients • Blinding not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	• Setting: single university centre • Sample size: N=139 • Duration: inclusion 8/2007-7/2008	local or distant recurrence, histopathologic confirmation through endoscopic biopsy or serial imaging study follow-up for at least 1 yr interval • Patient characteristics: o Male: 63.3% o Age: 61.5y • Prevalence of disease: 28 patients with recurrence	interval	No significant differences		
Kim EY 2011[67]	• Design: retrospective study • Sources of funding: not reported • Setting: single university centre, South-Korea • Sample size: N=71 • Duration: inclusion 10/2003-10/2007	• Eligibility criteria: o Patients with surgically proven advanced gastric cancer • Patient characteristics: o Male: 67.9% o Mean age: 58y • Prevalence of disease: N+ in 59 patients	• Index test: FDG-PET/CT, CECT • Reference standard: histopathology	<u>N+ vs. N0</u>: • CECT: o Se 75% o Sp 92% o PPV 98% o NPV 42% • PET/CT: o Se 41% o Sp 100% o PPV 100% o NPV 26%		• No dropouts • Unclear if consecutive patients • Inclusion based on receiving of reference standard • Patients were selected out of 85 patients: exclusion of patients due to poor image quality (N=4), chronic renal insufficiency (N=1), previous gastric cancer treatment (N=2) and peritoneal

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
						seeding (N=7)
Kim JW 2011[68]	• Design: retrospective study • Sources of funding: supported by a grant (CRI11060-1) from the Chonnam National University Hospital Research Institute of Clinical Medicine in South Korea; conflicts of interest not reported • Setting: single university centre, South-Korea • Sample size: N=127 • Duration: inclusion 1/2010-5/2010	• Eligibility criteria: o Patients with gastric cancer and who had undergone both oesophago-gastro-duodenoscopy and 64-section CT • Patient characteristics: o Male: 67.7% o Mean age: 63y • Prevalence of disease: o pT1a: N=43 o pT1b: N=33 o pT2: N=16 o pT3: N=15 o pT4: N=20	• Index test: 64-MDCT • Reference standard: histopathology	<u>T-stage</u>: • pT1a: Se 93%, Sp 90%, PPV 83%, NPV 96% • pT1b: Se 70%, Sp 98%, PPV 92%, NPV 90% • pT2: Se 63%, Sp 94%, PPV 59%, NPV 95% • pT3: Se 67%, Sp 94%, PPV 59%, NPV 95% • pT4: Se 75%, Sp 95%, PPV 75%, NPV 95%		• No dropouts • Consecutive patients • Inclusion based on receiving of reference standard • Patients were selected out of 159 patients: 32 patients were excluded (14 were not pathologically confirmed, 3D images were not available in 6 patients, 5 patients underwent inadequate CT scanning, 5 patients had multiple foci of gastric cancer, 2 patients underwent endoscopic haemoclipping before CT) • Blinding not reported
Kim SJ 2009[69]	• Design: retrospective study • Sources of funding:	• Eligibility criteria: o Patients undergoing surgery for	• Index test: CT • Reference standard:	<u>Peritoneal M+ grade 2</u>: • Se 28%		• No dropouts • Patients selected out of 1285

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	Supported by the Korea Science and Engineering Foundation grant funded by the Ministry of Science and Technology; no conflicts of interest • Setting: single university centre, South-Korea • Sample size: N=498 • Duration: inclusion 1/2003-12/2007	histopathologically confirmed gastric cancer • Patient characteristics: o Male: 66.7% o Mean age: 59.6y • Prevalence of disease:	histopathology	• Sp 99% • PPV 75% • NPV 92% <u>Peritoneal M+ grade 1 or 2</u>: • Se 51% • Sp 96% • PPV 61% • NPV 94%		patients: exclusion if pT1 (N=660), CT in another hospital (N=83), no adenocarcinoma (N=25), previous gastric cancer treatment (N=11), history of malignancy (N=7), gastric perforation and peritonitis at presentation (N=1) • Blinding not reported
Kim YH 2009[70]	• Design: retrospective study • Sources of funding: supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare, Republic of Korea; no conflicts of interest • Setting: single university centre, South-Korea • Sample size: N=149 • Duration: inclusion	• Eligibility criteria: o Patients with gastric adenocarcinoma undergoing surgery and having T3 (N=110) or T4 lesions (N=39) (based on pathology and surgery) • Patient characteristics: o Male: 66.4% o Mean age: 61.1y • Prevalence of disease: adjacent organ invasion in 39 patients	• Index test: MDCT • Reference standard: histopathology	<u>Adjacent organ invasion</u>: • Se 85% • Sp 98% • PPV 94% • NPV 95%		• No dropouts • Selection based on pathologic and surgical findings, out of 163 patients: exclusion of 14 patients with unavailable thin-section CT data sets • Blinded evaluation of index test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	5/2003-9/2006					
Lee ES 2009[71]	• Design: retrospective study • Sources of funding: supported by a grant from the Seoul National University Hospital Research Fund; conflicts of interest not reported • Setting: single university centre, South-Korea • Sample size: N=46 • Duration: inclusion 2000-2007	• Eligibility criteria: o Patients with the confirmed or suspected diagnosis of polypoid gastric malignant lesions o Adequate CT images available • Patient characteristics: o Male: 69.6% o Mean age: 65.3y • Prevalence of disease: 27 patients had early gastric cancer, 19 had advanced gastric cancer	• Index test: CT • Reference standard: histopathology	Advanced (T2-3) vs. early gastric cancer (T1): • Se 74% • Sp 78% • PPV 70% • NPV 81%		• No dropouts • Inclusion based on receiving of reference standard • Blinded evaluation of index test
Lee SM 2009[72]	• Design: prospective study • Sources of funding: not reported • Setting: single university centre, South-Korea • Sample size: N=33 • Duration: inclusion 10/2004-4/2007	• Eligibility criteria: o Patients with biopsy-proven gastric adenocarcinoma and local lymph node M+ but without distant M+ o Who underwent CT and PET for the assessment of tumor response as part of a phase II study evaluating neoadjuvant chemotherapy o Patients were excluded if they had a previous or secondary malignancy within the last 5 years,	• Index test: CT • Reference standard: histopathology	T-stage: • pT1: Se 50%, Sp 97%, PPV 67%, NPV 93% • pT2: Se 25%, Sp 78%, PPV 75%, NPV 28% • pT3: Se 100%, Sp 37%, PPV 14%, NPV 100% N+ vs. N0: • Se 38% • Sp 95%		• No dropouts • Consecutive patients • Blinded evaluation of index test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		had previously undergone radiation therapy, chemotherapy, immunotherapy, were pregnant, had active bleeding from upper GIT, underwent allograft requiring immunosuppressive treatment, had uncontrolled and serious infection, or had a moderate or severe degree of nephropathy • Patient characteristics: o Male: 90.9% o Mean age: 53.8y • Prevalence of disease:		• PPV 83% • NPV 70% <u>Treatment response</u>: cut-off 35.6% volume reduction rate • Se 100% • Sp 59% • PPV 70% • NPV 100%		
Makino 2011[73]	• Design: retrospective study • Sources of funding: not reported • Setting: 2 centres, Japan • Sample size: N=616 • Duration: inclusion 1/2001-6/2009	• Eligibility criteria: o Histopathologically confirmed gastric adenocarcinoma based on endoscopic gastric biopsies o MDCT performed within 14 days before gastrectomy o Absence of any preoperative therapies o Appropriate scan conditions of MDCT	• Index test: MDCT • Reference standard: histopathology	<u>T-stage</u>: • pT1: Se 14%, Sp 100%, PPV 100%, NPV 39% • pT2/3: Se 75%, Sp 95%, PPV 78%, NPV 95% • pT4a: Se 92%, Sp 98%, PPV 89%, NPV 98% • pT4b: Se 75%, Sp 100%, PPV 75%,		• No dropouts • Inclusion based on receiving of reference standard • Blinded evaluation of index test

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		• Prevalence of disease: o pT1: N=396 o pT2/3: N=106 o pT4a: N=106 o pT4b: N=8		NPV 100%		
Marrelli 2011[74]	• Design: prospective study • Sources of funding: not reported • Setting: single university centre, Italy • Sample size: N=92 • Duration: 1/2003-4/2010	• Eligibility criteria: o Patients with primary gastric cancer undergoing potentially curative resection with extended lymphadenectomy plus PALN o Patients submitted to noncurative surgery or D1/D2 dissection without removal of para-aortic lymph nodes were excluded, as well as patients with gastric stump neoplasms, second primaries, linitis plastica, or those treated by neoadjuvant chemotherapy • Patient characteristics: o Male: 58.7% o Median age: 66y • Prevalence of disease: 13 patients had positive PALN	• Index test: 64-MDCT • Reference standard: histopathology	<u>PALN involvement</u>: • Se 85% • Sp 95% • PPV 73% • NPV 97%		• No dropouts • Consecutive inclusion, but based on receiving of reference standard • Blinded evaluation of index test
Moschetta 2010[75]	• Design: unclear • Sources of funding:	• Eligibility criteria: o Patients with an	• Index test: 16-row MDCT	<u>T-stage</u>: (VP) • pT1: Se 89%, Sp	<u>T-stage</u>: (axial) • pT1: Se	• No dropouts • Unclear if

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	not reported • Setting: single university centre, Italy • Sample size: N=33 • Duration: inclusion 1/2007-8/2008	endoscopic diagnosis and histologically proven gastric cancer • Patient characteristics: o Male: 73.6% o Mean age: 57.5y o Antrum: 45.3%; body: 20.8%; fundus/cardia: 34% • Prevalence of disease: o pT1: N=9 o pT2: N=18 o pT3: N=23 o pT4: N=3	• Reference standard: histopathology (50 patients underwent surgical resection, 3 patients underwent palliative gastrectomy)	98%, PPV 89%, NPV 98% • pT2: Se 94%, Sp 97%, PPV 94%, NPV 97% • pT3: Se 96%, Sp 100%, PPV 100%, NPV 97% • pT4: Se 100%, Sp 100%, PPV 100%, NPV 100%	44%, Sp 95%, PPV 67%, NPV 89% • pT2: Se 67%, Sp 77%, PPV 60%, NPV 82% • pT3: Se 74%, Sp 87%, PPV 81%, NPV 81% • pT4: Se 100%, Sp 96%, PPV 60%, NPV 100%	consecutive patients • Blinded evaluation of index test
Pan 2010[76]	• Design: prospective study • Sources of funding: not reported • Setting: single university centre, China • Sample size: N=350 • Duration: 2/2003-8/2007	• Eligibility criteria: o Patients with gastric cancer diagnosed by biopsy before surgery • Patient characteristics: o Male: 62.9% o Mean age: 52y • Prevalence of disease: o pT1: N=48 o pT2: N=62 o pT3: N=135 o pT4: N=105 o M+: N=35	• Index test: MDCT • Reference standard: histopathology	<u>T-stage</u>: • pT1: Se 63%, Sp 99%, PPV 94%, NPV 94% • pT2: Se 60%, Sp 90%, PPV 57%, NPV 91% • pT3: Se 85%, Sp 80%, PPV 73%, NPV 90% • pT4: Se 82%, Sp 96%, PPV 90%, NPV 93%	<u>M-stage</u>: • Se 14% • Sp 93% • PPV 19% • NPV 91%	• No dropouts • Unclear if consecutive patients • Only inclusion of patients undergoing surgery • Blinding not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Park 2009[77]	• Design: retrospective inclusion • Sources of funding: not reported • Setting: single university centre, South-Korea • Sample size: N=105 • Duration: inclusion 10/2003-5/2007	• Eligibility criteria: o Postoperative patients with gastric cancer who underwent PET/CT due to clinical or radiologic suspicion of recurrence during follow-up o At least 1 year of postoperative follow-up • Patient characteristics: o Male: 71.4% o Mean age: 58y • Prevalence of disease: 75 patients with recurrence	• Index test: FDG-PET/CT • Reference standard: histopathology or serial imaging	<u>Detection of recurrence</u>: • Se 75% • Sp 77% • PPV 89% • NPV 55%		• No dropouts • Unclear if consecutive patients • Blinding not reported • Differential verification
Sim 2009[78]	• Design: retrospective study • Sources of funding: supported by a grant (A080316) of the Korea Healthcare technology R&D Project, Ministry for Health, Welfare & Family Affairs, Republic of Korea; no conflicts of interest • Setting: single university centre, South-Korea • Sample size: N=52 • Duration: inclusion	• Eligibility criteria: o Patients with gastric cancer who received curative resection and had subsequently undergone contrast CT and PET/CT for the surveillance of recurrence • Patient characteristics: o Male: 82.6% o Median age: 62y • Prevalence of disease: 38 patients with recurrence	• Index test: FDG-PET/CT • Reference standard: histopathology or follow-up CT	<u>Detection of recurrence</u>: • Se 68% • Sp 71% • PPV 87% • NPV 45%		• No dropouts • Unclear if consecutive patients • Differential verification • Blinding not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	4/2004-12/2006					
Yan 2010[79]	• Design: retrospective study • Sources of funding: not reported; no conflicts of interest • Setting: single university centre, China • Sample size: N=305 • Duration: inclusion 1/2007-11/2008	• Eligibility criteria: o Patients with gastric cancer undergoing gastrectomy with D2 or greater lymphadenectomy • Patient characteristics: o Male: 60.7% o Mean age: 59y • Prevalence of disease: 162 patients with N+	• Index test: MDCT • Reference standard: histopathology	N+ vs. N0: cut-off 0.575 cm long axis diameter • Se 86% • Sp 59% • PPV 70% • NPV 79%		• No dropouts • Unclear if consecutive patients • All patients underwent surgery
Yan 2010[79]	• Design: prospective study • Sources of funding: not reported; no conflicts of interest • Setting: single university centre, China • Sample size: N=61 • Duration: inclusion 12/2008-4/2009	• Eligibility criteria: o Patients with gastric cancer undergoing gastrectomy with D2 or greater lymphadenectomy • Patient characteristics: o Male: 65.6% o Mean age: 59y • Prevalence of disease: 31 patients with N+	• Index test: MDCT • Reference standard: histopathology	N+ vs. N0: traditional MDCT method • Se 77% • Sp 73% • PPV 75% • NPV 76%		• No dropouts • Unclear if consecutive patients • All patients underwent surgery

5.1.3. Laparoscopic staging

5.1.3.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Leake 2011[80]	• Design: SR • Sources of funding: Canadian Cancer Society, Ontario Ministry of Health and Long-Term care, Hanna Family Chair in Surgical Oncology • Search date: January 1998 – December 2009 • Searched databases: medline, Embase, Cochrane central register of controlled trials • Included study designs: primary studies with ≥ 30 patients • Number of included studies: 21 (12 prospective + 9 retrospective)	• Inclusion criteria: studies investigating the role of laparoscopy in changing management and avoiding laparoscopy and correlation of laparoscopy with final pathology • Exclusion criteria: other designs than primary studies with ≥ 30 patients, no separate results for gastric adenocarcinoma, animal studies • Patients characteristics: T3-T4 in 4 studies, T1-T2 in 10 studies, not stated in 7 studies. Pre-operatie CT (+/- other imaging) in 18 studies	• Intervention: diagnostic laparoscopy for staging purposes • Reference standard: surgical staging	<u>T staging</u> • Se: 50-80.6% • Sp: 62-100% • Accuracy: 67-97.7% • Moderate to substantial agreement <u>N staging</u> • Se: 54.5-60.8% • Sp: 93.8-100% • Accuracy: 64.3-98.9% <u>M-staging</u> • Se: 64.3-100% • Sp: 80-100% • Accuracy: 85-100%	• Diagnostic laparoscopy altered management in 8.5-59.6% of cases • 8.5-43.8% of patients were able to avoid laparotomy based on diagnostic laparoscopy Change of management in 25-54% of patients with advanced gastric cancer, 3.8% in early gastric cancer	• No critical appraisal of primary studies • Peritoneal cytology used in 9 studies, laparoscopic US used in 7 studies • Only 3 studies report on the value of laparoscopy for N staging

5.1.3.2. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Mahadevan 2010[81]	• Design: prospective study • Sources of funding: no source of support or conflicts of interest • Setting: single centre, Malaysia • Sample size: N=40 • Duration: inclusion 2006-2008	• Eligibility criteria: o Patients with carcinoma of the stomach after a complete preoperative work-up o Patients with obvious unresectable disease, e.g., liver metastasis, ascites, on CT scan were excluded • Patient characteristics: o Male: 70% o Mean age: 60y • Prevalence of disease: 7 patients with peritoneal M+	• Index test: CT, laparoscopy • Reference standard: histopathology	Peritoneal M+: • Se and Sp 100% for laparoscopy		• No dropouts • Unclear if consecutive patients • CT was used for patient inclusion • Blinding not reported
Power 2009[82]	• Design: prospective study • Sources of funding: nothing to disclose • Setting: single university centre, US • Sample size: N=94 • Duration: inclusion 5/2003-5/2005	• Eligibility criteria: o Patients with pathologically confirmed adenocarcinoma of the stomach or gastroesophageal junction o Apparent localized gastric cancer with no acute surgical emergency, such as gastric outlet obstruction or bleeding, and who had no definite evidence of M1 disease on routine CT or MRI	• Index test: laparoscopy • Reference standard: cytohistology	M+ disease: • Se 95% • Sp 100% • PPV 100% • NPV 99%		• No dropouts • Unclear if patients with negative laparoscopy received verification • Blinding not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		• Patient characteristics: o Male: 55% o Median age: 61y o Junction: 13%; cardia: 20%; body: 32%; antrum: 34%; whole stomach: 1% • Prevalence of disease: 19 patients with M+				

5.1.4. Sentinel node biopsy

5.1.4.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Wang 2011[83]	• Design: SR and MA • Sources of funding: not stated • Search date: April 2011 • Searched databases: Pubmed, Embase, CENTRAL • Included study designs: all > 10 patients • Number of included studies: 38 (2128 patients)	• Eligibility criteria: value of sentinel in predicting LN status in gastric cancer. Reference standard = histopathology. TP, TN and FN can be calculated • Exclusion criteria: clinical > T3 or clinically diagnosed LN or distant M+, non-adenocarcinoma included, animal or in vitro studies. Sample size <11, duplicates	• Intervention: sentinel node biopsy for gastric cancer • Reference standard: histopathological examination +/- immunobiochemistry	Identification rate 0.937 (0.911-0.956) Sensitivity 0.769 (0.716-0.814) False negative rate 0.23 (0.186-0.284) NPV 0.903 (0.869-0.929) Accuracy 0.920 (0.899-0.937)	Sensitivity varies between 40.9 and 97.4%. False-negative rate varies between 2.6 and 59.1%.	• Heterogeneity between studies, cfr. scale of lymphadenectomy, T stage of included patients, techniques used, pathology techniques used etc.

5.1.4.2. Primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Cozzaglio 2011[84]	• Design: prospective study • Sources of funding: none declared, no conflicts of interest • Setting: single centre, Italy • Sample size: N=29 • Duration: inclusion 3/2004-11/2008	• Eligibility criteria: o Patients with clinical T1 and T2 N0 M0 gastric cancer less than 5 cm in diameter o Patients with preoperative evidence of metastatic disease, T3 and T4 tumours, metastatic LNs, or reported intolerance to Patent blue were excluded • Patient characteristics: o Male: 42.9% o Age: 62.5y o Upper 1/3: 10.7%; middle 1/3: 14.3%; lower 1/3: 75% • Prevalence of disease: 20 patients with N+	• Index test: SLNB • Reference standard: histopathology	N+ vs. N0: • Se 75% • Sp 75% • PPV 88% • NPV 55%		• No dropouts • Consecutive inclusion • Blinding not reported • In 1 patient no SLN detected (excluded from analysis)
Tajima 2010[85]	• Design: retrospective study • Sources of funding: supported by Grant-in-Aid for Scientific Research, Japan Society for the Promotion of Science • Setting: single	• Eligibility criteria: o Patients with cT1 or cT2 gastric cancer who had undergone open gastrectomy (N=39) or laparoscopic gastrectomy (N=38) o No preoperative radiotherapy and/or chemotherapy • Patient characteristics:	• Index test: SLNB • Reference standard: histopathology	N+ vs. N0: • Se 76% • Sp 100% • PPV 100% • NPV 93%		• No dropouts • Unclear if consecutive patients • Blinding not reported • In 4 patients no SLN detected (excluded from analysis)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	university centre, Japan • Sample size: N=77 • Duration: not reported	o Male: 50.6% o Mean age: 67.2y o Upper 1/3: 15.6%; middle 1/3: 50.6%; lower 1/3: 33.8% • Prevalence of disease: 17 patients with N+				
Toth 2011[86]	• Design: prospective study • Sources of funding: not reported • Setting: single centre, Hungary • Sample size: N=39 • Duration: inclusion 2/2008-10/2010; median follow-up 18 months	• Eligibility criteria: o Patients with gastric cancer undergoing open gastric resection with blue-dye mapping and modified D2 lymph node dissection o Exclusion criteria were distant metastases and involvement of the surrounding organs • Patient characteristics: o Male: 48.7% o Mean age: 64.3y o Upper 1/3: 20.5%; middle 1/3: 23.1%; lower 1/3: 56.4% o 19 patients with T3 • Prevalence of disease: 23 patients with N+	• Index test: SLNB • Reference standard: histopathology	N+ vs. N0: • Se 96% • Sp 100% • PPV 100% • NPV 94%		• No dropouts • Consecutive patients • Blinding not reported • In 1 patient no SLN detected (excluded from analysis)

5.2. Treatment early gastric cancer

5.2.1. Endoscopic submucosal resection versus endoscopic mucosal dissection

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Park 2011[87]	• Design: SR and MA • Sources of funding: not stated • Search date: January 1990 – 30 April 2010 • Searched databases: medline, Embase, Cochrane central, koreamed • Included study designs: RCT, controlled clinical trials, comparative observational studies • Number of included studies: 12 (3 non-concurrent prospective studies + 9 retrospective studies)	• Inclusion criteria: studies about (early) gastric adeno(carcino)ma, comparing ESD with EMD evaluating specified outcomes, in English or Korean • Exclusion criteria: animal or preclinical trials, duplicate publications, abstract-only publication, case reports, effectiveness not specific for ESD	• Intervention: ESD of early gastric cancer • Comparator: EMD for early gastric cancer	<u>Curative resection</u> ESD **79.5**% EMR 59.0% OR 3.28 (1.95-5.54) <u>Local recurrence</u> ESD **0.82**% EMR 5.03% RR 0.13 (0.04-0.41) <u>Mortality</u> ESD 0.86% EMR 0.93% RR 0.65 (0.08-5.38) <u>Perforation</u> ESD **5.54**% EMR 1.03% RR 3.58 (1.95-6.55)	<u>En bloc resection</u> ESD: 91.7% EMR : 52.1% OR : 8.43 (5.2-13.67) <u>Complete resection</u> ESD 91.9% EMR 43% OR 8.54 (4.44-16.45)	• Also resection for gastric adenoma included? • All included studies scored 2+ according to SIGN checklist for non-randomized studies • In most studies, patients not well balanced: larger tumours and tumours in difficult locations more frequent in ESD group • Data on bleeding appear not correctly reported • Several sensitivity analyses show no different results for subgroups

5.2.2. Endoscopic mucosal resection versus gastrectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Bennett 2011[88]	• Design: SR • Sources of funding: Chinese Cochrane center Chinese medical Board of New York • Search date: 27 March 2011 (not all databases) • Searched databases: CENTRAL, Medline, Embase, CINAHL, CBM • Included study designs: RCT • Number of included studies: 0	• Inclusion criteria: RCT comparing EMR with gastrectomy in early gastric cancer	• Intervention: EMR • Comparator: gastrectomy	No RCT's identified	Derived from non-randomized studies: - complete resection rate 71.9-97.7% for lesions < 2cm - local cure rate 98% for standard indications, overall disease specific 5 and 10 year survival 99% - no significant differences between survival after EMR vs. surgery - bleeding rate 1.2-20.5%, perforation 0.4-5.2%	• Adequate search • Adequate description of protocol; however, no included studies

5.3. Treatment gastric cancer beyond mucosa: resectable gastric cancer

5.3.1. Neoadjuvant treatment

5.3.1.1. Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Li 2010[89]	• Design: SR and MA • Sources of funding: not stated • Search date: April 2010 • Searched databases: Medline, Embase, ASCO proceedings • Included study designs: controlled trials Number of included studies: 14 (2271 patients) (9 Asian, 5 Western)	• Inclusion criteria: controlled trials comparing NAC versus no preoperative treatment for biopsy proven locally advanced gastric cancer eligible for potentially curative surgery. Oral, IV, intra-arterial or IP chemotherapy included • Exclusion criteria: non-controlled trials, immunotherapy, radiotherapy • Median FU: 54 months	• Intervention: neoadjuvant chemotherapy + potentially curative surgery for locally advanced gastric cancer +/- postoperative chemotherapy • Comparator: potentially curative surgery for locally advanced gastric cancer +/- postoperative chemotherapy	<u>Overall survival</u>: OR 1.27 (1.04-1.55) (p=0.02) <u>3y progression-free survival</u> OR 1.85 (1.39-2.46) (p<0.0001)	<u>R0 resection rate</u> OR 1.51 (1.19-1.91) (p=0.0006) <u>Subgroup analysis</u> NAC most beneficial for T3-T4, Western countries and with the use of IV and multi-chemotherapy regimens	• 6/14 studies considered high quality (Jadad score) • 4 studies also postoperative chemotherapy in control group • Included studies: Schumacher 2009 Boige 2007 Cunningham 2006 Hartgrink 2004 Nio 2004 Zhang 2004 Kobayashi 2000 Wang 2000 Takiguchi 2000 Lygidakis 1999 Kang 1996 Masuyama 1994 Yonemura 1993 Nishioka 1982

5.3.1.2. Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Biffi 2010[90]	• Design: RCT 2 arms • Research funding: Sanofi-Aventis • Setting: multicentre, Italy-Switzerland • Sample size: 70 • Period: November 1999-November 2005 • Median FU: not reported	• Eligibility criteria: o histologically proven gastric cancer, T3-4NanyM0 or TanyN1-3M0 o WHO PS ≤ 2 o age 18-75 o adequate blood tests o Siewert type I cardia location excluded • All patients underwent chest X-ray, EUS, spiral CT thorax-abdomen, bone scintigraphy, staging laparoscopy	• Intervention: pre-operative chemotherapy 4 cycles TCF before gastrectomy • Control: gastrectomy + 4 cycles TCF postoperatively	No significant difference in (peri-operative) morbidity: 28.5% vs. 25.7%		• Underpowered trial, early closure due to slow accrual • Randomization procedure, allocation concealment and blinding not reported • Not clear if collection of postoperative complication data was standardized in two arms

5.3.2. Surgery

5.3.2.1. Extent of lymphadenectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Memon 2011[91]	• Design: SR and MA • Sources of funding: none • Search date: January 1980 – December 2008 • Searched databases: Medline, Embase, Science Citation Index, Curent Contents, Pubmed • Included study designs: RCT's • Number of included studies: 6 (3 European, 2 Asian, 1 African), in total 1876 patients Studies included Dent 1988 Robertson 1994 Bonenkamp 1995 Cuschieri 1999 Degiuli 2004 Wu 2004	• Inclusion criteria: RCT published in English, reporting on at least one clinical outcome on D1 vs. D2 lymphadenectomy for curable gastric adenocarcinoma. Outcomes: length of hospital stay, overall complication rate, anastomotic leak rate, reoperation rate, 30-day mortality, 5y survival • Patient characteristics: adults with histologically proven gastric adenocarcinoma, preoperative staging (CT or US) negative for M+, 20-80y, ASA < 4, T0-2, no N2 involvement, R0	• Intervention: gastrectomy + D1 lymphadenectomy • Comparator: gastrectomy + D2 lymphadenectomy (Maruyama technique) including pancreatic and splenic resection (exept Italian trial, only resection if involved by cancer NB: training by Japanese surgeons before or during trial in 4 trials. No dedicated training in 2 trials	Hospital stay D1 6.37 days (10.66-2.08) reduction vs. D2 (p=0.0036) complications D1 OR for developing complications 0.42 (0.27-0.66) vs. D2 (p=0.0002) Anastomotic leak D1 OR 0.40 (0.25-0.63) vs. D2 (p=0.0001) Reoperation rate D1 OR 0.33 (0.15-0.72) vs. D2 (p=0.006) 30-day mortality rate D1 OR 0.59 (0.40-0.85) vs. D2 (p=0.0054) 5-year survival D1 OR 0.97 (0.78-1.20) vs. D2 (p=0.7662)	Minimal surgical complications in the two trials where surgeons had training by Japanese surgeons before entering the trial.	• Publication bias suggested for length of hospital stay and postoperative complications, no publication bias suggested for anastomotic leak, reoperation, mortality or 5y survival • Mean Jadad score 2/5, low quality as blinding not possible • Significant heterogeneity for hospital stay and complication rate, not for other outcomes • High proportion of protocol violations in Dutch trial • Pancreatic and splenic resection inconsistent throughout the

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
		resection				trials • Studies not published in English not included (cave Japanese studies)
Zheng 2011[92]	• Design: SR and MA • Sources of funding: not stated • Search date: September 2010 • Searched databases: CENTRAL, Pubmed, Embase, ISI databases, Chinese Biomedical Literature database • Included study designs: RCT's • Number of included studies: 3 (1067 patients) included studies: Sano 2004 Yonemura 2008 Kulig 2007	• Inclusion criteria: RCT comparing D2 with D4 lymphadenectomy for gastric cancer • Patients characteristics: histologically proven gastric adenocarcinoma without evidence of gross lymph node involvement or distant M+. < 75y. "suitable" for surgery". No neo-adjuvant therapy, radical excision of gastric cancer	• Intervention: radical gastrectomy + D4 lymphadenectomy • Comparator: radical gastrectomy + D2 lymphadenectomy (defined as D2 and para-aortic lymphadenectomy)	5-year survival OR 0.93 (0.69-1.25) (p=0.62) Overall morbidity OR 0.79 (0.47-1.31) (p=0.36) Hospital mortality OR 1.63 (0.59-4.54) (p=0.35)	Recurrence rate OR 1.12 (0.84-1.49) (p=0.45) Re-operation OR 1.01 (0.53-1.91) (p=0.97) Operation time One study reported a significant longer operation time for D4 resection	• Experience of surgeons, see above • Significant heterogeneity between studies • Influence of stage migration? • Splenectomy rate may influence results
Chen 2010[93]	• Design: SR and MA • Sources of funding: National Natural Science Foundation of China,	• Eligibility criteria: biopsy proven adenocarcinoma	• Intervention: gastrectomy + D2 lymphadenectomy • Comparator: gastrectomy + D2	5-year overall survival RR 1.03 (0.93-1.14) (p=0.80)	30-day mortality rate RR 1.03 (0.43-2.46) (p=0.95) Overall	• Good search strategy • Critical appraisal of included studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Multidisciplinary treatment project of Gastrointestinal tumours, Sichuan University • Search date: May 2009 • Searched databases: Pubmed, Embase, Cochrane library • Included study designs: RCT • Number of included studies: 3 (1067 patients) Included studies Kulig 2007 (PGCSG) Yonemura 2008 (EASOG) Sasako 2008 (FU Sano 2004) (JCOG-9501)		+ para-aortic (D4) lymphadenectomy		<u>morbidity rate</u> RR 1.19 (0.83-1.71) (p=0.35)	
Wang 2010[94]	• Design: SR and MA • Sources of funding: not stated • Search date: February 2009 • Searched databases: Pubmed, Embase, China Biological Medicine	• Inclusion criteria: biopsy proven gastric adenocarcinoma without distant metastases or secondary cancer • Exclusion criteria: pre- or postoperative	• Intervention: gastrectomy + D2 + para-aortic (D4) lymphadenectomy • Comparator: gastrectomy + D2 lymphadenectomy	<u>5-year overall survival</u> **RCT's** RR 1.04 (0.93-1.16) **Non-randomized studies** RR 0.96 (0.83-1.10) Analysis of RCT's	<u>Post-operative morbidity</u> No MA performed <u>Post-operative mortality</u> RCT's RR 0.99 (0.44-	• Good search strategy • Critical appraisal of included studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Database, CNKI, CENTRAL • Included study designs: comparative studies (historical comparisons excluded) • Number of included studies: 8 (4 RCT, 4 non-randomized) Included studies: Jiang 2000 Sasako 2008 Yonemura 2008 Kulig 2007 Maeta 1999 Bostanci 2004 Kunisaki 2006 Hu 2009	chemotherapy, serious co-morbidity		shows RR 1.14 (1.01-1.29) for the serosa negative subgroup. Analysis of non-randomized trials shows RR of 0.97 (0.74-1.27) for the serosa negative subgroup	2.24) Non-randomized studies RR 2.06 (0.69-6.15)	
Yang 2009[95]	• Design: SR and MA • Sources of funding: not stated • Search date: 1966-may 2007 • Searched databases: Medline, Embase, Cochrane controlled trial register databases, Chinese Biomedical Database • Included study	• Inclusion criteria: histologically proven gastric adenocarcinoma without clinical evidence of M+; Potential for radical resection of gastric tumour. No sever co-morbidity	• Intervention: gastrectomy + D1 lymphadenectomy • Comparator: gastrectomy + D2 lymphadenectomy	<u>3-year survival</u> OR 1.22 (0.98-1.51) (p=0.07) <u>5-year survival</u> OR 0.95 (0.79-1.14) (p=0.60)	<u>Postoperative morbidity</u> OR 0.40 (0.32-0.49) (p<0.0001) D1 vs. D2 <u>Operative mortality</u> OR 0.50 (0.32-0.76) (p=0.001)	• Good search strategy • Critical appraisal of included studies • Poor description of data extraction and characteristics of included studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	designs: RCT • Number of included studies: 12 Included studies Bonenkamp 1992,1995,1999 Cuschieri 1996,1999 Degiuli 2004 Liu 2001 Bunt 1995 Dent 1988 Wu 2004,2006 Robertson 1994					
Yang 2009[95]	• Design: SR and MA • Sources of funding: not stated • Search date: 1966-may 2007 • Searched databases: Medline, Embase, Cochrane controlled trial register databases, Chinese Biomedical Database • Included study designs: RCT • Number of included studies: 5 Sano 2004 Maeta 1999 Kulig 2007	• Inclusion criteria: histologically proven gastric adenocarcinoma without clinical evidence of M+; Potential for radical resection of gastric tumour. No sever co-morbidity	• Intervention: gastrectomy + D2 lymphadenectomy • Comparator: gastrectomy + D2 + para-aortic lymphadenectomy (D4)		<u>Postoperative morbidity</u> OR 0.78 (0.61-1.01) (p=0.06) <u>Operative mortality</u> OR 1.05 (0.49-2.27) (p=0.90)	• Good search strategy • Critical appraisal of included studies • Poor description of data extraction and characteristics of included studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Yonemura 2006 Jing 2000					
McCulloch 2009[96]	• Design: SR and MA • Sources of funding: not stated • Search date: April 2001 • Searched databases: Cochrane, Medline, Embase, LILACS, Cancerlit, Central Medical Journal Japanese Database • Included study designs: RCT + non-randomized comparative studies, cohort studies • Number of included studies: 19 (15) Included studies Cuschieri 1996,1999 Bonenkamp 1995, 1999 Arak 1994 Bozetti 1997,1999 Degiuli 1998 Ingberg 1975 Kodera 1997 Lee 1995 Lisborg 1994 Llanos 1999	• Inclusion criteria: studies comparing D1 with D2 lymphadenectomy in gastric cancer with clearly defined type of nodal resection and reporting on (crude) 30d mortality and 5y survival • Exclusion criteria: published before 1970, patients operated on before 1960. Other tumours than adenocarcinoma included. Neoadjuvant or adjuvant chemotherapy	• Intervention: gastrectomy + D2 lymphadenectomy • Comparator: gastrectomy + D1 lymphadenectomy	<u>5-year survival</u> **RCT** RR 1.06 (0.92-1.21) **Non-RCT** RR 0.92 (0.83-1.02) <u>Postoperative mortality</u> **RCT** RR 2.23 (1.45-3.45) **Non-RCT** RR 0.65 (0.45-0.93)	<u>Postoperative complications</u> RR 2.13 (1.66-2.74)	• Studies that did not comment on the use of chemotherapy were included • Single arm cohort studies not included in calculations, summarized as narrative only, limited added value • D1 cohort studies were performed in a non-specialized setting and showed a lower survival and higher 30d-mortality rate than D2 cohort studies, all performed in specialized settings • Definition and way of presenting complications made meta-analysis not

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	McCullogh 1994 Mendes de Almeida 1994 Pacelli 1993 Roukos 1998 Siewert 1993,1998					feasible???
Lustosa 2008[97]	• Design: SR and MA • Sources of funding: none • Search date: not stated • Searched databases: CENTRAL, Medline, Embase, LILACS, Science citation index, Ovid journals • Included study designs: RCT • Number of included studies: 3 Included studies Bonenkamp 1995,1999 Cuschieri 1996,1999 Degiuli 1998	• Inclusion criteria: not specified • Patients characteristics: not specified	• Intervention: gastrectomy + D2 lymphadenectomy • Comparator: gastrectomy + D1 lymphadenectomy	<u>5-year survival</u> RR 1.00 (0.87-1.16) (p<0.97) <u>Recurrence</u> RR 0.91 (0.82-1.01) (p=0.08)	<u>Overall morbidity</u> RR 1.83 (1.51-2.21) (p<0.00001) <u>In-hospital mortality</u> RR 2.12 (1.39-3.25) (p=0.0005) D2 vs. D1	• Poor description of selection process, data extraction and characteristics of included studies
Lustosa 2008[97]	• Design: SR and MA • Sources of funding: none • Search date: not stated • Searched	• Inclusion criteria: not specified • Patients characteristics: not specified	• Intervention: gastrectomy + D4 lymphadenectomy • Comparator: gastrectomy + D1 lymphadenectomy	<u>5-year survival</u> RR 1.24 (0.98-1.56) (p=0.08) <u>Recurrence</u> RR 0.76 (0.57-11.21)	<u>Overall morbidity</u> RR 4.07 (1.96-8.43) (p=0.0002) <u>In-hospital</u>	• Poor description of selection process, data extraction and characteristics of included studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	databases: CENTRAL, Medline, Embase, LILACS, Science citation index, Ovid journals • Included study designs: RCT • Number of included studies: 2 Included studies Robertson 1994 Wu 2004, 2006			(p=1.02)	<u>mortality</u> RR 2.22 (0.11-59.18) (p=0.57) D3 vs. D1	

5.3.2.2. Splenectomy and pancreatectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Brar 2011[98]	• Design: SR and MA • Sources of funding: Canadian Cancer Society, Ontario Ministry of health, Hanna Family chair in surgical oncology • Search date: 1 January 1998 – 31 December 2009 • Searched databases: Medline, Embase, CENTRAL • Included study designs: all > 30	• Inclusion criteria: newly diagnosed, biopsy proven gastric adenocarcinoma treated with surgery, complication or survival data reported. Published in English • Exclusion criteria: animal or ex vivo studies, mixed	• Intervention: D2 + spleen-/ pancreas preservation • Comparator: D2 + splenectomy +/- pancreatectomy	<u>Splenectomy/preservation</u> **Operative survival:** OR 1.59 (0.44-5.79) (p=0.48) calculated on 2 RCT's **Overall survival** OR 0.97 (0.56-1.68) (p=0.91) calculated on 3 RCT's <u>Pancreatectomy/preservation</u> **Overall survival** 1 RCT reports a non-significant difference	6 prospective, non-randomized studies show fewer complications after spleen-preservation or non-significant differences (or not reported). Retrospective studies show benefit after spleen- or pancreatic conservation or no difference. Prospective and retrospective, non-randomized studies show an improved OS after conservation of	• Potentially publication bias • RCT's appear underpowered • Patient selection not clear: pancreaticosplen-ectomy for direct organ invasion versus part of "prophylactic" D2 lymphadenectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	patients • Number of included studies: 40 (6354 patients) (4 RCT's, 6 prospective, 32 retrospective) Included RCT's: Csendes 2002 Furukawa 2000 Yu 2006 Okinaga 2006	cancer population without spate results for gastric cancer, insufficient data, reviews, MA, abstracts, editorials, letters, < 30 patients			spleen and pancreas or a non-significant difference (except 1 retrospective trial). Non-ramdomized studies show a decreased survival after pancreaticosplen-ectomy or no significant difference	
Roberts 2011[99]	• Design: SR • Sources of funding: Canadian Cancer Society, Ontario Ministry of health, Hanna Family chair in surgical oncology • Search date: 1 January 1985 – 31 December 2009 • Searched databases: Medline, Embase, CENTRAL • Included study designs: RCT, observational studies • Number of included studies: 8 retrospective case series (132 patients underwent	• Inclusion criteria: newly diagnosed, biopsy proven gastric adenocarcinoma complication or survival data reported. Published in English • Exclusion criteria: animal or ex vivo studies, mixed cancer population without spate results for gastric cancer, insufficient data, reviews, MA, abstracts, editorials, letters,	• Intervention: pancreaticoduode nectomy (PD) for gastric cancer infiltrating pancreas and/or duodenum or macroscopic nodal M+ • Comparator: no pancreaticoduo-denectomy, palliative stenting	<u>Overall survival</u> 3/5 studies show increased OS after PD, one study for T4 tumors only. Another study shows increased survival if no para-aortic LN involvement, no positive peritoneal cytology or peritoneal disease. One study shows no significant difference in OS	All studies: higher morbidity after PD	• 7 patients received neoadjuvant chemotherapy, 52 adjuvant chemotherapy • Information on other therapy missing for many patients

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	pancreaticoduo-denectomy					
Yang 2009[100]	• Design: SR and MA • Sources of funding: Multi-disciplinary treatment project of gastrointestinal tumours, Sichuan University, China • Search date: December 2008 • Searched databases: Pubmed, CENTRAL, J-STAGE Database, Chinese Biomedical database • Included study designs: RCT • Number of included studies: 3 Included studies: Toge 1985 Csendus 2002 Yu 2006	• Inclusion criteria: biopsy proven gastric cancer eligible for surgery without signs of distant M+ • Exclusion criteria: periopeative chemotherapy, immunotherapy, ..., other gastric tumours such as lymphoma, trials with marked inequality of characteristics at baseline	• Intervention: splenectomy • Comparator: no splenectomy	<u>Overall survival</u> RR 1.17 (0.97-1.41) (p=0.1)	<u>Postoperative morbidity</u> RR 1.76 (0.82-3.80) (p=0.15) <u>Postoperative morality</u> RR 1.58 (0.45-5.50) (p=0.47)	• No change of results after exclusion of trials with low quality

5.3.2.3. Bursectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Fujita 2011 (primary outcomes)[101] **Imamura 2011 (secondary outcomes)[102]**	• Design: RCT 2 arms • Research funding: not stated • Setting: 11 Japanese hospitals • Sample size: 210 • Period: July 2002-January 2007 • Median FU: 46 months	• Eligibility criteria: biopsy proven adenocarcinoma T2N0; T3N0, T2N1, T3N1. No Borrmann type 4, no prior chemotherapy or radiotherapy. Age20-80y, PS ECOG 0-2. No history of gastrectomy or other malignancy < 5y • Patient characteristics:	• Intervention: D2 gastrectomy with (prophylactic) bursectomy • Control: D2 gastrectomy without (prophylactic) bursectomy Clear surgical instructions in protocol, all operation supervised or performed by senior surgeons in high-volume hospitals. No adjuvant therapy	<u>3y overall survival</u> Bursectomy: 85.6% Non-bursectomy: 79.6% HR for death: 1.44 (0.79-2.61) in non-bursectomy group <u>3y recurrence-free survival</u> Bursectomy: 77.5% Non-bursectomy group: 75.6% HR for recurrence 1.18 (0.68-2.04) in the non-bursectomy group	No significant difference in overall complication rate or the following complications: pancreatic fistula, anastomotic leak, abdominal abscess, bowel obstruction, hemorrhage, pneumonia	• Early closure and unplanned interim analysis due to change of practice in adjuvant treatment, thus under-powered trial • Trial designed as non-inferiority

5.3.2.4. Laparoscopy (minimal invasive) versus laparotomy (open surgery)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Zorcolo 2011[103]	• Design: SR and MA • Sources of funding: not stated • Search date: 1994-July 2010 • Searched databases: Embase, medline, Cochrane, Pubmed • Included study designs: RCT • Number of included studies: 6 Included studies Kitano 2002 Lee 2005 Huscher 2005 Hayashi 2005 Kim 2008 Kim 2010	• Inclusion criteria: RCT comparing MIDG woth ODG for gastric cancer, written in English, no duplicate data • Exclusion criteria: outcomes of interest not reported, other cancer population, other operation than distal gastrectomy	• Intervention: minimal invasive distal gastrectomy (MIDG) • Comparator: open distal gastrectomy (ODG)	Mortality OR 0.4 (0.1-1.7) (p=0.3) Morbidity OR 0.30 (0.1-0.7) (p=0.01) Duration of hospital stay 2 (-4.7-0.6) dyas shorter for MIDG (p=0.1)	Similar rate of Billroth I technique and D1 lymphadenectomy in both groups. Conversion rate from MIDG to ODG 0.004. Number of resected LN OR -4.7 (-6.7- -2.7) (p<0.001) MIDG vs. ODG Operative time 81 (49-1113) min longer for MIDG (p=0.002) Blood loss 119 (67-171) ml less for MIDG (p<0.003)	• No critical appraisal of included studies • Number of removed LN adequate in both groups, but lower in MIDG
Martinez-Ramos 2011[104]	• Design: SR and MA • Sources of funding: • Search date: January 1991-October 2009 • Searched databases: Medline, Current Contents, Science citation index, Embase, Cochrane • Included study	• Inclusion criteria: articles comparing laparoscopic with open surgery for gastric cancer. • Exclusion criteria: articles referring only or predominantly to	• Intervention: laparoscopic surgery for advanced gastric cancer • Comparator: open surgery for advanced gastric cancer	Tumour-related mortality at 5y FU OR 0.53 (p=0.191) in favour of laparoscopy Postoperative stay WMD 6 days (p<0.001) shorter for laparoscopy	Operating time WMD 44 minutes (p<0.001) shorter for open surgery Blood loss WMD 122ml (p=0.005) less for laparoscopy Number of LN	• Limited description of selection criteria and critical appraisal • Definition of early and advanced gastric cancer not clarified • No publication

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	designs: RCT, prospective and retrospective non-randomized studies of high quality • Number of included studies: 7 (1 RCT, 1 prospective, 5 retrospective) Included studies: Huscher 2007 Dulucp 2005 Weber 2003 Ziqiang 2006 Valera 2006 Pugliese 2007 Strong 2009	early gastric cancer			removed WMD 1.57 LN (p=0.093) in favour of open surgery	bias statistically detected
Yakoub 2009[105]	• Design: SR and MA • Sources of funding: not stated • Search date: 2008 • Searched databases: Embase, Medline, Cochrane library, Google scholar database • Included study designs: RCT + observational studies • Number of included studies: 12 (3RCT + 9 retrospective studies) (951 patients)	• Inclusion criteria: studies comparing laparoscopic with open surgery for early distal gastric cancer only; Accurate description of surgical technique used • Exclusion criteria: duplicate, overlap of patients. Advanced gastric	• Intervention: laparoscopic gastrectomy for early (stage Ia or Ib) distal gastric cancer • Comparator: open gastrectomy for early (stage Ia or Ib) distal gastric cancer	Length of hospital stay WMD 5.72 (3.28-8.16) (p<0.001) shorter for LADG Postoperative complications OR 0.52 (0.34-0.80) (p=0.003) in favour of LADG) Recurrence One included study shows no recurrence in both groups after 42 months of FU	Operation time WMD 53.48 min (34.49-72.48) (p<0.001) longer for LADG N° LN removed WMD 4.61 (3.26-5.96) (<0.001) in favour of ODG Oral intake WMD 1.11 days (0.63-1.6) (p<0.001) less for LADG Analgesia use	• Significantly lower morbidity rate for LADG and higher number of LN removed for ODG confirmed in subgroup analysis with RCT only • Small sample size in most studies, significant heterogeneity between studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Included studies RCT: Kitano 2002 Lee 2005 Hayashi 2005 Retrospective: Adachi 2000 Mochiki 2005 Yano 2001 Shimizu 2000 Migoh 2003 Naka 2005 Tanimura 2001 Kim 2005 Lee 2006	cancer; More than one laparoscopic technique, conversion to open technique			WMD 2.05 days (1.8-2.31) (p<0.001) longer for ODG	
Chen 2009[106]	• Design: SR and MA • Sources of funding: Multidisciplinary treatment project of gastrointestinal tumours and clinical research foundation, Sichuan University, China • Search date: 1990-2008 • Searched databases: Pubmed, Embase, Cochrane, websites of professional societies • Included study designs: RCT • Number of included	• Inclusion criteria: biopsy proven gastric cancer, cT1 based on pre-operative staging reporting on relevant outcomes • Exclusion criteria: non-English language • FU: 1y-4y	• Intervention: laparoscopy-assisted distal gastrectomy (LADG) • Comparator: open distal gastrectomy (ODG) D1 or D2 allowed, depending on study	<u>Early morbidity</u> RR 0.61 (0.41-0.91) (p=0.02) in favour of LADG) <u>Early mortality</u> RD=0.01 (-0.01-0.03) (p=0.32) rare in both groups <u>Hospital stay</u> WMD -20.3 (-4.73-0.67) (p=0.14)	<u>Operation time</u> WMD 86.64 min (longer for LADG (p<00001) <u>Blood loss</u> WMD -108.33 ml (-174.94- -41.72) (p=0.001) less for LADG) <u>Number of LN</u> WMD -4.88 (-6.94- -2.82) (p<0.00001) less for LADG	• Potential publication bias • Sensitivity analysis did not change conclusions • Subgroup analysis shows decreased morbidity in the LADG group for D2 lymphadenectomy but not for D1 lymphadenectomy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	studies: 6 (629 patients) Included studies: Kitano 2002 Lee 2005 Hayashi 2005 Fujii 2003 Kim YW 2008 Kim H 2008					

5.3.2.5. Reconstruction after gastrectomy: pouch versus no pouch

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Gertler 2009[107]	• Design: SR and MA • Sources of funding: none • Search date: 31 October 2008 • Searched databases: Medline, Cochrane • Included study designs: RCT • Number of included studies: 13	• Inclusion criteria: RCT's addressing the formation of pouch reservoir after total gastrectomy. No language restriction	• Intervention: reconstruction after total gastrectomy with pouch • Comparator: reconstruction after total gastrectomy without pouch	**Roux-en-Y** Morbidity OR 1.09 (0.69-1.72) (p=0.71) Mortality OR 1.06 (0.33-3.35) (p=0.93) Quality of Life 6m WMD -2.16 (-9.35-5.22) '(p=0.57) 12m WMD (4.9 (-4.31-14.10) (p=0.30) 24m WMD 11.33 Quality of Life R0 patients 6m WMD 2.86 (-6.4-12.11) (p=0.55) 12m WMD 11.58 (1.31-21.85) (p=0.03) 24m WMD 14.4 (3.07-25.72) (p=0.01) **Jejunal interposition** Mortality OR 0.51 (0.10-2.51) (p=0.41)	**Roux-en-Y** Dumping syndrome 3m OR 0.36 (0.11-1.14) (p=0.08) 6m OR 0.25 (0.07-0.89) (p=0.03) 12m OR 0.24 (0.08-0.72) (p=0.01) Heartburn 12m OR 0.11 (0.02-0.81) (p=0.03) Food intake 3m OR 0.13 (0.00-3.92 (p=0.11) 6m OR 0.17 (0.02-1.45) (p=0.10) 12m OR 0.17 (0.05-0.54) Hospital stay WMD -0.9 (-8.2-6.41) (p=0.81) Operation time WMD 75 (-9.38-24.38) (p=0.38)	• Searched databases are limited • 4 trials assessed as unclear risk of bias, other trials assessed as low risk of bias • 9 trials used roux-en-Y with or without pouch, 4 trials used jejuna interposition with or without pouch • Two trials also included palliative resections, other simultaneous procedures differ from trial to trial

5.3.3. Adjuvant treatment

5.3.3.1. Chemotherapy

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
GASTRIC 2010[108]	• Design: SR and MA of individual patient data • Sources of funding: Japan Clinical Research Support Unit, ECRIN, Institut National du Cancer. Sanofi-Aventis funded 3 investigator meetings • Search date: 1970-2009 • Searched databases: Medline, Cochrane, clinicaltrials.gov, conference proceedings • Included study designs: RCT • Number of included studies: 17 (3838 patients)	• Inclusion criteria: randomized trials comparing adjuvant chemotherapy with surgery alone for resectable gastric cancer. Recruitment ended before 2004; Four groups included: monotherapy, 5FU+mitomycin C without anthracyclines, with anthracyclines, other polychemotherapy regimens. • Exclusion criteria: immunotherapy, neo-adjuvant therapy, IP chemotherapy, radiotherapy. • Median FU: 7y in	• Intervention: adjuvant chemotherapy for resectable gastric cancer • Comparator: surgery alone for resectable gastric cancer	<u>Overall survival</u> HR 0.82 (0.76-0.90) (p<0.001) Median OS 4.9y in surgery-only group, 7.8y in the adjuvant chemotherapy group. Absolute improvement of +/- 6% in OS after 5 years No significant heterogeneity between year of randomization or between continents No change in conclusions when summary statistics of other trials were included <u>Disease-free survival</u> HR 0.82 (0.75-0.90) (p<0.001)	<u>5y survival per treatment group</u> **Monotherapy** 53.9% surgery only 71.4% adjuvant chemo **Fluorouracil + mitomycin + others without anthracyclines** 76.6% surgery only 82.8% adjuvant chemotherapy **Fluorouracil + mitomycin + others with anthracyclines** 31.9% surgery only 39.3% adjuvant chemotherapy **Other polychemotherapy** No significant effect Overall 5y survival: 41.5%	• No critical appraisal of included studies • No search in Embase • 31 trials identified, 17 trials included as no individual patients data for other trials • No apparent heterogeneity between trials (p=0.52) • Fluorouracil + mitomycin + others without anthracyclines: only Japanese studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
		surgery group, 7.2 y in chemotherapy group				
Sun 2009[109]	• Design: SR and MA • Sources of funding: not stated • Search date: January 1998 – December 2007 • Searched databases: Pubmed, Embase, Ovid including Cochrane, ISI web of knowledge, Chinese Biomedical Literature Database • Included study designs: RCT • Number of included studies: 12 (3809 patients) (4 Japan, 8 European) Included studies: Cirera 1999 Neri 2001 Bajetta 2002 Bouche 2005 Nitti 2006 De Vita 2007 Sakuramoto 2007 Chipponi 2004 Popiela 2004 Nakajima 2007	• Inclusion criteria: Biopsy proven gastric cancer, subtotal or total gastrectomy with negative margins, D1 or more extensive lymphadenectomy. Chemotherapy started within 8 weeks after surgery. • Exclusion criteria: non-randomized trials, reviews, case-reports. IP dissemination or distant M+. T1 tumours only. IP chemotherapy, immunotherapy, chemoradiation, neo-adjuvant chemotherapy • Patient characteristics: T1-T4 depending on trial. % node-positive patients between 45-	• Intervention: adjuvant chemotherapy after complete resection of gastric carcinoma • Comparator: radical surgery only for gastric cancer NB: D1 in three trials, D2 in 8 trials, D1 or D2 in one trial	<u>Overall survival</u> HR 0.78 (0.71-0.85) (p<0.001)		• 5-FU used in all chemotherapy regimens

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Nakajima 1999 Nashimoto 2003	100%				
Liu 2008[110]	• Design: SR and MA • Sources of funding: none • Search date: November 2007 • Searched databases: Medline, Embase, CBM • Included study designs: RCT • Number of included studies: 23 (4919 patients)	• Inclusion criteria: patients should have undergone potentially curative surgery. Published as full paper in English • Exclusion criteria: non-randomized trials, reviews, IP chemotherapy, immunotherapy, duplicate reports. Distant M+ or residual disease after surgery	• Intervention: adjuvant chemotherapy after curative resection of gastric cancer • Comparator: observation after curative resection of gastric cancer	<u>Overall survival</u> RR 0.85 (0.80-0.90) (p=<0.00001) NNT 14 <u>Disease-free survival</u> RR 0.88 (0.77-0.99) (p=0.04) NNT 13	Results confirmed in sensitivity analysis with high quality studies only Subgroup analysis shows an survival benefit for adjuvant chemotherapy independent of % of LN positive patients, % of T3-T4 patients, Asia versus non-Asia, n° of chemotherapy cycles and monotherapy versus polychemotherapy	• 10 studies low risk of bias, 12 studies moderate risk of bias, 1 study high risk of bias • Intention-to-treat analysis in 9 studies • No obvious publication bias

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Di Costano 2008[111]	• Design: RCT 2 arms • Research funding: National council of research – clinical application of oncological research; Italian Association of Cancer Research • Setting: multicenter, Italy • Sample size: 258 • Period: January 1995-September 2000 • Median FU: 73 months	• Eligibility criteria: biopsy proven, radically resected gastric cancer. Surgery within 8 weeks before start of chemotherapy. Stages IB, II, IIIA-B or IV(T4N2M0), ECOG PS <2, age < 75y, no prior other cancer, no prior therapy	• Intervention: adjuvant chemotherapy (PELF) after radical resection of gastric cancer • Control: FU only after radical resection of gastric cancer	5y overall survival HR 0.90 (0.64-1.26) (p=0.542) Disease-free survival HR 0.90 (0.64-1.26) (p=0.592)	Grade 3-4 toxicity chemotherapy N&V 21% Diarrhea 12% Mucositis 8% Leucopenia 20% 1 toxic death	• Only 58% of patients in the chemo-therapy arm completed treatment, mainly due to toxicity or patient refusal • Trial designed to detect an absolute difference of 20% overall survival
Kulig 2010[112]	• Design: RCT 2 arms • Research funding: Polish State Committee for scientific research • Setting: multicentre Poland • Sample size: 309 • Period: January 1995-February 1999 • Median FU: 37 months (no patients lost of FU)	• Eligibility criteria: histologically confirmed nonmetastatic gastric cancer, R0 resection. Involvement of muscularis propria or nodal involvement. Karnofsky PS > 70, adequate blood tests. No prior chemo/radiothera	• Intervention: 3 courses EAP adjuvant chemotherapy • Control: FU only	Median survival Chemotherapy: 41.3 months Control: 35.9 months (p=0.398) Median disease-free survival Chemotherapy: 37 months Control: 35 months (p>0.05)	Per protocol analysis confirms results.	• No ITT analysis: only patients who received at least 1 cycle of chemo-therapy included

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		py or other cancer within last 5 years				
Zhang 2011[113]	• Design: RCT 2 arms • Research funding: Guangdong provincial Science and Technology Programs, China • Setting: single centre, China • Sample size: 80 patients • Period: 2005-2009 • Median FU: 36.2 months (10-42 months)	• Eligibility criteria: biopsy proven, resectable gastric cancer. No prior chemotherapy except adjuvant chemotherapy more than 6 months previously (?). ECOG PS 0-2. 18-75 years old. Adequate organ function	• Intervention: FOLFOX4 adjuvant chemotherapy • Control: 5-FU + leucovorin adjuvant chemotherapy	3-year progression-free survival significantly better in control group (p<0.05)	Grade 3-4 toxicities not significantly different in the two arms, except neurotoxicity more frequent in intervention group	• Quid patients with prior chemo-therapy allowed? • No power calculation (considered not feasible?) • Not clear if patients in control group received the same number of chemo-therapy cycles as intervention group (treatment continued until progression or patient's request to discontinue)

5.3.3.2. Radiotherapy

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Valentini 2009[114]	• Design: SR and MA • Sources of funding: • Search date: 15 May 2008 • Searched databases: pubmed, Cochrane Libary, Scopus, Embase • Included study designs: RCT • Number of included studies: 9 (2025 patients) Included studies MacDonald 2001 Skoropad 2002 Skoropad 2000 Moertel 1984 Takahashi 1986 Allum 1989 Zhang 1998 Shchepotin 1994 Dent 1979	• Inclusion criteria: comparison of surgery alone with surgery + radiotherapy in biopsy proven adenocarcinoma of the stomach or gastro-oesophageal junction. Neoadjuvant, adjuvant or intraoperative radiotherapy included. Additional chemotherapy included. • Exclusion criteria: non-RCT, radiotherapy in control arm, metastatic or unresectable disease	• Intervention: surgery + radiotherapy in biopsy proven adenocarcino-ma of the stomach or gastro-oesophageal junction • Comparator: surgery alone for biopsy proven adenocarcino-ma of the stomach or gastro-oesophageal junction	<u>3-year survival</u> RR 1.12 (0.99-1.27) (p=0.07) in favour of RT NNT=25 <u>5-year survival</u> RR 1.26 (1.08-1.48) (p=0.004) NNT=17 <u>Loco-regional relapse</u> RR 0.72 (0.55-0.96) (p=0.02) NNT=12	Subgroup analysis shows a 5-year survival benefit for the following subgroups: • LQED2 < 40Gy • pre-operative radiotherapy • no intra-operative RT • studies performed after 1990 • studies of low quality	• Per protocol analysis also shows non-significant difference at 3 years and a significant benefit for patients receiving RT at 5 years (NNT 13) • No evidence of publication bias • Type of lymphadenectomy differs between studies
Fiorica 2007[115]	• Design: SR and MA • Sources of funding: none • Search date: December 2006	• Inclusion criteria: RCT's comparing preoperative radiotherapy + surgery or surgery +	• Intervention: preoperative radiotherapy + surgery or surgery + chemora-	<u>3y overall mortality</u> OR 0.67 (0.55-0.82) (p=0.0001) NNT=14	Analysis with exclusion of 2 GTSG trials, confirms results. Subgroup analysis	• In contrast with inclusion criteria, two GTSG studies with surgery + chemotherapy as

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	• Searched databases: Cochrane, Medline, Cancerlit, Embase • Included study designs: RCT • Number of included studies: 9 (1694 patients) Included studies Dent 1979 GTSG 1982 Moertel 1984 GTSG 1990 MacDonald 2001 Shchepotin 1994 Zhang 1998 Skoropad 2000 Skoropad 2002	chemoradiation with surgery alone. Patients with resectable, biopsy-proven gastric cancer without M+ • Exclusion criteria: quasi-randomized trials and observational studies. Control group not surgery alone. Intra-operative radiotherapy only	diation • Comparator: surgery alone	5y mortality OR 0.54 (0.43-0.68) (p<0.00001) NNT=8	shows a significant reduction in 3y and 5y mortality for preoperative radiotherapy, for postoperative radiotherapy only in 5y mortality. 3y mortality significantly decreased when a dose Of > 40 Gy LQED10 was given, not if LEQD10 < 40 Gy. Good compliance with preoperative but not with postoperative radiotherapy No increase of postoperative mortality or anastomotic leakage after preoperative RT. Significant increase ingrade III-IV toxicity with postoperative RT	control arm were included • Quality of surgery, % of curative resection variable and possibly insufficient • Proportion of LN positive patients varies and may differ between control and intervention group in some of the trials • Substantial risk of publication bias

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Bamias 2010[116]	• Design: RCT 2 arms • Research funding: HeCOG research grant • Setting: multicentre, Greece • Sample size: 147 • Period: April 2002-April 2005 • Median FU: 53.7 months (0.1-77.8 months)	• Eligibility criteria: histologically confirmed gastric adenocarcinoma. Operated on by surgeon with volume > 20 operations/year. Negative resection margins, no distant M+, serosal invasion or LN (+). ECOG PS ≤2. > 18y old. No history of other malignancy.No cardiac failure, adequate blood tests, adequate nutritional status	• Intervention: : 6 cycles of adjuvant docetaxel – cisplatin + radiotherapy • Control: 6 cycles of adjuvant docetaxel - cisplatin	<u>Local recurrence rate</u> RT(-):10% RT(+):5% p=0.246 <u>3y Survival</u> RT(-): 61% RT(+):57% <u>3y PFS</u> RT(-): 51% RT(+) : 48% No statistically significant differences in OS or PFS	Significantly higher discontinuation rate in radiotherapy arm	• Under-powered trial as early closure due to slow accrual • 4/147 patients not included in analysis (ineligible)
Kwon 2010[117]	• Design: RCT 2 arms • Research funding: Bio-Signal analysis technology Innovation Program from MEST/NRF and Korea Science and Engineering Foundation • Setting: single centre, Korea • Sample size: 61 • Period: January	• Eligibility criteria: gastric cancer stage IIIA to IV (M0) resected with curative intent (negative margins, D2), adequate blood tests, ECOG PS <2, caloric intake > 1500 kCal, adjuvant treatment started within 4 weeks after surgery. No co-	• Intervention: adjuvant chemptherapy + regional radiation • Control: adjuvant chemotherapy	<u>3y disease-free survival</u> RT(+):80% RT(-):75.2% P= 0.887		• No info on allocation concealment • No blinding • Under-powered trial, early closure due to slow accrual • Baseline character-istics not

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	2002-September 2004	existing malignancy, no morbidity precluding chemotherapy, no distant M+				equally balanced between treatment arms • Loss of FU not reported

5.3.3.3. IP chemotherapy

Systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Yan 2007[118]	• Design: SR and MA • Sources of funding: Foundation for Applied Research in Gastrointestinal Oncology • Search date: December 2006 • Searched databases: Medline,Embase, Pubmed, Cochrane, DARE, Chinese Biomedicine Database, Chinese academic Journals Database • Included study designs: RCT • Number of included studies: 13 (1648 patients)	• Inclusion criteria: patients with biopsy proven adenocarcinoma of the stomach or gastro-oesophageal junction who underwent potentially curative surgery. • Exclusion criteria: studies of low quality	• Intervention: surgery with intra-peritoneal chemotherapy +/- systemic chemotherapy • Comparator: surgery without intra-peritoneal chemotherapy +/- systemic chemotherapy	<u>Overall survival</u> HIIC HR 0.60 (0.43-0.83) (p=0.002) HIIC+EPIC HR 0.45 (0.29-0.68) (p=0.0002) NIIC HR 0.67 (0.44-1.01) (p=0.06) EPIC HR 0.64 (0.37-1.10) (p=0.11) DPIC HR 0.89 (0.51-1.55) (p=0.68) NB results did not change if trial with systemic chemotherapy after NIIC excluded	<u>Perioperative mortality</u> RR 1.03 (0.28-3.75) (p=0.96) <u>Recurrence</u> Very limited evidence shows no significant difference in peritoneal recurrences after HIIC or NIIC and a significant reduction of loco-regional recurrence after EPIC (1 trial).	• No comparison with systemic chemotherapy with or without surgery • No intention-to-treat analysis in several trials • Only one study investigated DPIC • **Studies included considered to be of fair quality**

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Miyashiro 2011[119]	• Design: RCT 2 arms • Research funding: Japanese Ministry of Health • Setting: multicentre, Japan • Sample size: 268 • Period: January 1993-March 1998 • Median FU: not stated (6y planned FU)	• Eligibility criteria: histologically proven gastric cancer T3-T4 macroscopically completed resected, N0-2. Age < 75y. No previous treatment, negative peritoneal cytology. Adequate blood tests and organ function.	• Intervention: adjuvant IP+IV chemotherapy after curative resection for serosa-positieve gastric cancer • Control: curative resection for serosa-positieve gastric cancer	5-year overall survival Surgery alone: 60.9 (52.6-69.2)% Adjuvant chemotherapy: 62 (53.7-70.2)% P=0.482 5-year relapse-free survival Surgery alone: 55.6 (47.2-64.1)% Adjuvant chemotherapy: 57.5 (49.1-65.9)% P=0.512	82/135 patients discontinued chemotherapy, mainly due to toxicity	• Follow-up probably different for the two arms as chemo-therapy patients had more frequent hospital visits during 12 months chemo-therapy • Trial designed to detect a 15% absolute survival difference

5.3.3.4. Immunotherapy

No recently published SR or MA identified

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Jeung 2008[120]	• Design: RCT 2 arms • Research funding: Korea Science and Engineering foundation- Korea government • Setting: single centre, Korea • Sample size: 292 • Period: January 1984-December 1989 • Median FU: 92 months (7-260 months)	• Eligibility criteria: pathologically proven gastric adenocarcinoma treated by curative surgery. No prior chemo- radio- or immunotherapy. ECOG PS < 2. Adequate blood tests. No history of cardiac failure or other malignancy. Early or advanced tumours or presence of ascites excluded. Suficent recovery after surgery within 45 days required	• Intervention: adjuvant chemotherapy (5FU + adriamycin) + polyadenylic-polyuridylic acid (poly A:U) • Control: adjuvant chemotherapy (5FU + adriamycin)	<u>Overall survival</u> 5y : 68.4%vs52.4% 10y : 55.6%vs43.8% 15y : 50.1%vs38.1% Significant better OS with immuno-chemotherapy (p=0.013)		• Loss of FU not reported • 12 ineligible patients excluded after rando-mization • No blinding reported

5.4. Treatment gastric cancer beyond mucosa: advanced (un)resectable gastric cancer

5.4.1. Surgery: gastrectomy +/- Multivisceral resection (MVR)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Brar 2011[121]	• Design: SR • Sources of funding: Canadian cancer Society, Ontario Ministry of Health, Long-term care career scientist Award. Hanna family chair in Surgical Oncology. • Search date: 1 January 1998 – 31 December 2009 • Searched databases: Medline, Embase • Included study designs: all > 29 patients • Number of included studies: 17 (1343 patients)	• Inclusion criteria: newly diagnosed, biopsy proven gastric adenocarcinoma. Patients underwent surgery, reported on survival. Sample size ≥ 30 patients. Published in English in peer reviewed journals; • Exclusion criteria: animal or ex vivo studies, other cancer populations without separate results for gastric cancer; Insufficient information. Studies investigating pancreatico-duodenectomy	• Intervention: multivisceral resection for locally advanced gastric cancer • Comparator: not stated	5y survival R0 resection: 32-35%	Complications 3% anastomotic leak 2% pancreatic fistula 10% (range 0-15%) perioperative death Overall complication rate range 11.8-910.5%	• No info on non-surgical peri-operative treatment • No direct comparison with chemotherapy alone • Limited info on end-result of surgery (removal of all macroscopic tumour??)
Mahar 2011[122]	• Design: SR and MA • Sources of funding: Canadian cancer Society, Ontario Ministry of Health, Long-term care career scientist Award. Hanna family chair in	• Inclusion criteria: primary reports in English. Reporting on morbidity, mortality, median or 1y survival • Exclusion criteria: 75% of data collection < 1985, duplicates,	• Intervention: non-curative surgery for advanced gastric cancer • Comparator: not stated *NB non-curative*	30d mortality Gastrectomy: 0-21% Bypass: 0-33% Exploratory laparotomy: 8-39% Median Survival	Morbidity Gastrectomy : 3.8-49% Non-resectional interventions : 14-21%	• No critical appraisal of included studies but only very low level of evidence available • Due to overall low methodological

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Surgical Oncology. • Search date: 1 january 1985 – 1 December 2009 • Searched databases: Medline, Embase, Cochrane • Included study designs: all > 30 patients • Number of included studies: 58	mixed cancer population without separate results for gastric cancer.	*surgery defined as surgery for advanced gastric cancer with regional or distant M+ without the explicit goal of symptom relive* *NB surgery seems to be restricted to gastrectomy without MVR*	Palliative gastrectomy: 9-13 months Non-curative surgery: 5-24 months NOS: 3-20.6 months 1y survival Non-curative surgery: 12-66.7% NOS : 26.6-80.3%		quality and heterogeneity between studies, no meta-analysis possible • Reported proportion of stage IV patients: range 12-100% • No info on non-surgical treatment, no direct comparison with chemotherapy without surgery
Kerkar 2010[123]	• Design: SR • Sources of funding: Intramural Research program of the Center for Cancer Research, NCI, Bethesda, USA • Search date: 1990-2009 • Searched databases: Pubmed, Scopus • Included study designs: all > 9 patients • Number of included studies: 19 (436 patients)	• Inclusion criteria: studies investigating the long-term survival following hepatic resections for metastatic gastric adenocarcinoma, published in English. • Exclusion criteria: < 10 patients, no long term FU, duplicate data • Patient characteristics: median age: 55-67y. 58 synchronous liverM+. 61% single hepatic M+, 77 unilobar liverM+.	• Intervention: hepatic resection for gastric adenocarcinoma metastatic to the lvier • Comparator: not stated	Survival Median survival: 17 months Median 1y: 62.0% Median 3y: 30.0% Median 5y: 26.5% Postoperative mortality Overall in hospital: 3.5% Overall 30d: 0.9%	Morbidity Minimal data available: Reported numbers: 4/24, 7/15 and 3/10. Prognostic factors for survival Worse outcome if Positive resection margins, primary tumor lymphatic, venous or serosal invasion, synchronous presentation, higher number of liver M+, liver M+ > 4cm, disease in both hemi-livers	• No critical appraisal of included studies • Also 'metachronous disease' included with median disease-free interval 12.5 months (10.1-21 months) • No direct comparison with chemotherapy only

5.4.2. IP chemotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Gill 2011[124]	• Design: SR • Sources of funding: • Search date: 2000-2010 • Searched databases: Medline, Embase, Scopus, BIOSIS previews, Cochrane Library • Included study designs: randomized and non-randomized controlled trials, prospective cohort studies • Number of included studies: 10 (0 RCT, 1 non-RCT, 6 prospective, 3 retrospective)	• Inclusion criteria: adult patients with gastric cancer and peritoneal carcinomatosis (PC) • Exclusion criteria: other, distant metastasis of gastric cancer. • Median FU: 46 months	• Intervention: cytoreductive surgery (CRS) + heated intraperitoneal chemotherapy (HIPEC) • Comparator: not stated (historical controls have a reported median survival of 1-3 months) *NB open and closed HIPEC procedures are used, most common agents are cisplatin and mitomycin*	Median OS 7.9 (range 6.1-9.2) months 15 (range 9.5-43.4) months for patients with complete cytoreduction 1y survival 43% (22-68%) 5y survival 13% (?)	Mortality 4.8% Morbidity 21.5%	• No formal critical appraisal of included studies but only low level of evidence available • No direct comparison with systemic chemotherapy or surgery + systemic chemotherapy

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Yang 2011[125]	• Design: RCT 2 arms • Research funding: • Setting: single centre, Japan • Sample size: 68 • Period: not stated • Median FU: 32 (7.5-83.5) months	• Eligibility criteria: gastric cancer with peritoneal carcinomatosis. age 20-75y, karnofsky PS >50, life expectancy > 8 weeks, adequate blood tests and cardiopulmonary function, no lung liver or prominent lymph node M+	• Intervention: cytoreductive surgery (CRS) + HIPEC • Control: CRS Detailed description of surgery in protocol	<u>Disease-specific survival</u> CRS: median 6.5 (4.8-8.2) months CRS+HIPEC: median 11.0 (10.0-11.9) months P=0.046	No significant difference in (selected) serious adverse events (SAE)	• No report on concealment of allocation • No blinding reported

5.4.3. Chemotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Montagnani 2011[126]	• Design: SR and MA • Sources of funding: Azienda Unita Sanitaria Locale 11 • Search date: not stated • Searched databases: Pubmed, Cancerlit, Embase, Cochrane, ESMO, ASCO abstracts • Included study designs: RCT • Number of included studies: 3 Included studies: Cunningham 2008 Al-Batran 2008 Popov 2008	• Inclusion criteria: unresectable locally advanced or metastatic gastric or gastroesophageal adenocarcinoma. • Exclusion criteria: crossover from control to experimental arm	• Intervention: Oxaliplatin-based chemotherapy for patients with advanced unresectable gastric cancer • Comparator: cisplatin-based chemotherapy for patients with advanced unresectable gastric cancer	Risk of death HR 0.88 (0.78-0.99) (p=0.04) Risk of progression HR 0.88 (0.80-0.98) (p=0.02)	Toxicity **Gr 3-4 neutropenia** OR 0.53 (0.41-0.69) **Gr 3-4 diarrhea** 2.73 (1.66-4.49) **Gr 3-4 neurotoxicity** 6.91 (3.08-15.46)	• No clear description of in- and exclusion criteria • No description of requirements of comparator; however, in the three included trials, the two compared groups only differ in oxaliplatin versus cisplatin • Jadad score: 3-2-2
Ma 2011[127]	• Design: SR and MA • Sources of funding: The Leading Academic Discipline Porject of the Shangai Municipal Education Committee and The Shangai Municipal Natural Science Foundation.	• Inclusion criteria: RCT comparing capecitabine-based chemotherapy with 5FU-based chemotherapy for advanced gastric cancer • Exclusion criteria: not original research,	• Intervention: capecitabine-based chemotherapy for advanced gastric cancer • Comparator: 5-FU based chemotherapy for advanced gastric cancer *NB majority of trials compares XELOX with*	Survival Western countries OS 10.7m versus 9.5 months (p=0.03) PFS 6.6m vs. 6.1 months (p=0.09) Response rate OR 1.32 (1.11-1.57) (p=0.002)	Toxicity (gr3-4) Leukopenia OR 0.42 (0.23-0.78) (p=0.005) Stomatitis OR 0.43 (0.24-0.76) (p=0.004) N&V OR 0.60 (0.44-0.83) (p=0.002) Hand-foot OR 2.45	• In Caucasian patients, difference in stomatitis and N&V not significantly different in the two groups • Results critical appraisal (Jadad score) not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	• Search date: 20 September 2010 • Searched databases: Pubmed, ASO, ECCO, ESMO, Wanfang database, CNKI Weipu database, J-STAGE • Included study designs: RCT • Number of included studies: 18 (2175 patients)	no adequate response and survival data available	*FOLFOX*	Caucasian patients: OR 1.32 (1.05-1.66) (p=0.02)	(1.46-4.10) (p=0.0007) Mortality OR 1.00 (p=0.98)	
Huang 2011[128]	• Design: SR and MA • Sources of funding: not stated • Search date: April 1966-December 2009 • Searched databases: Pubmed, Embase, Cochrane Library • Included study designs: RCT • Number of included studies: 4 (1 RCT + 3 abstracts) (2115 patients) Included studies: Boku 2009 Ajani 2009 Fuse 2008	• Inclusion criteria: patients with AGC at baseline. RCT comparing S1-based with 5FU-based chemotherapy, no other differences between treatment arms. Prospective phase II-III RCT's	• Intervention: S1-based chemotherapy for advanced gastric cancer • Comparator: 5FU-based chemotherapy for advanced gastric cancer	<u>Overall Survival</u> HR 0.87 (0.79-0.96) (p=0.007) <u>Overall response rate</u> OR 1.25 (0.31-5.09) (p=0.754)	<u>Safety</u> neutropenia OR 0.37 (0.29-0.48) (p<0.001) Anemia, diarrhea, nausea, stomatitis, treatment-related deaths: no significant difference	• Limited evidence, RCT + 2 abstracts from Asia, one abstract from USA • No obvious publication bias

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	Jin 2008					
Wagner 2010[129] (update Wagner 2006)	• Design: SR and MA • Sources of funding: German Ministry of Education & Research • Search date: March 2009 • Searched databases: CENTRAL, Medline, Embase + databases of ongoing trials + abstracts ESMO, ECCO, ASCO • Included study designs: RCT • Number of included studies: 3	• Inclusion criteria: randomized controlled trials with or without blinding, abstracts and unpublished data if sufficient information • Exclusion criteria: cross-over studies, quasi-randomized studies. Combined radio-chemotherapy. • Patient characteristics: biopsy proven T3-T4 inoperable or M1, recurrent or metastatic gastric or gastro-oesophageal adenocarcinoma without prior chemotherapy or radiotherapy	• Intervention: Chemotherapy for advanced gastric cancer + best supportive care • Comparator: best supportive care (BSC)	<u>Overall Survival</u> HR 0.37 (0.24-0.55) Median OS 11 months vs. 4.3 months <u>Time to progression</u> HR 0.31 (0.22-0.43)		• Sensitivity analysis with only 2 high quality studies included confirms results for OS
	• Number of included studies: 13 (1914 patients)		• Intervention: Single-agent chemotherapy • Comparator: combination	<u>Overall survival</u> HR 0.82 (0.74-0.90) Median survival 8.3	<u>Tumour response</u> OR 2.91 (2.15-3.93)	• Sensitivity analysis with exclusion of trials with high rate of 2nd

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
			chemotherapy	months versus 6.7 months Time to progression HR 0.67 (0.49-0.93)	Treatment related death OR 1.22 (0.52-2.85)	line treatment or Asian trials confirms results for OS
	• Number of included studies: 3 (501 pts)		• Intervention: 5-FU/cisplatin/anthracycline • Comparator: 5-FU/cisplatin	Overall survival HR 0.77 (0.62-0.95) WMD +/- 2 months		• 2 months to be considered as a clinically meaningful difference? • No heterogeneity between studies • Adequate allocation concealment
	• Number of included studies: 7 (1147 patients)		• Intervention: FU/cisplatin/anthracycline • Comparator: FU/anthracycline	Overall survival HR 0.82 (0.73-0.92) WMD +/- 1 month		
	• Number of included studies: 4 (640 patients)		• Intervention: irinotecan-containing chemotherapy • Comparator: chemotherapy without irinotecan	Overall survival HR 0.86 (0.73-1.02) Median survival irinoteca, (+): 9.8 months Median survival irinotecan (-): 8.3 months Time to progression HR 0.86 (0.71-1.04)	Tumour response OR 1.77 (0.85-3.69) Treatment-related death OR 0.29 (0.08-1.05) 0.6% versus 2.9% Treatment discontinuation due to toxicity OR 0.60 (0.30-1.20)	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
					10.1% versus 16.8%	
	• Number of included studies: 3 (805 patients)		• Intervention: docetaxel containing regimens • Comparator: non-docetaxel-containing regimens	Overal survival HR 0.93 (0.75-1.15) Time to progression HR 1.06 (0.85-1.32)	Response rate OR 1.30 (0.98-1.72) Treatment-related death OR 0.80 (0.34-1.84) 1.9% versus 2.5% Treatment discontinuation due to toxicity OR 0.72 (0.42-1.22) 16.7% versus 20.6%	
	• Number of included studies: 1 (316 patients)		• Intervention: oral 5-FU prodrugs • Comparator: IV fluoropyrimidines	Overall survival HR 0.85 (0.65-1.11) Median survival 10.4 versus 9.3 months in favour of capecitabine Time to progression HR 0.80 (0.62-1.03) Median PFS 5.6 versus 5.0 months	Response rate OR 1.80 (1.11-2.94) Treatment related deaths 0.6% versus 1.3% (only 3 deaths reported in total Treatment discontinuation due to toxicity 18% in both arms	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	• Number of included studies: 2 (292 patients)	•	• Intervention: oxaliplatin containing regimen • Comparator: same regimen with oxaliplatin replaced by cisplatin	Overall survival HR 0.82 (0.47-1.45) Median overall survival 10.5 versus 8.4 months Time to progression HR 0.67 (0.43-1.04) Median PFS 5.8 versus 3.9 months	Response rate 39% versus 27% Toxic death 2 patients (1.4%) died in the cisplatin arm, no toxic deaths in the oxaliplatin arm Treatment discontinuation due to toxicity 10.7% versus 10.8%	
Zagouri 2011[130]	• Design: SR and MA • Sources of funding: • Search date: • Searched databases: medline • Included study designs: all • Number of included studies: 47	• Inclusion criteria: studies examining the efficacy and safety of targeted therapies in metastatic gastric cancer. • Exclusion criteria: language other than English, French, German. Duplicate data.	• Intervention: molecularly targeted therapy +/- chemotherapy • Comparator: placebo +/- chemotherapy	Bevacizumab OS HR 0.87 (0.73-1.03) (p=0.1002) Trastuzumab OS HR 0.74 (0.60-0.91) (p=0.0046) PFS HR 0.71 (0.59-0.85) (p=0.0002)		• Medline search only • No critical appraisal of included studies • Only results of phase III RCTs presented in evidence table • Both RCTs sponsored by company • Results trastuzumab based on interim analysis after 75% of events, possibly underpowered

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Narahara 2011[131]	• Design: RCT 2 arms • Research funding: Yakult Honsha Co. And Daiichi Sankyo Co. • Setting: multicentre, Japan • Sample size: 326 (315 included in analysis) • Period: June 2004-November 2005 • Median FU: not stated	• Eligibility criteria: histologically confirmed unresectable or recurrent gastric adenocarcinoma, oral food intake possible. Age 20-75y. No prior chemotherapy or radiotherapy. Expected survival > 12 weeks. ECOG PS 0-2. Adequate blood tests. No massive ascites, no concurrent other malignancy, no pregnancy or lactation	• Intervention: irinotecan + S-1 in unresectable or recurrent cancer (IRI-S) • Control: S-1 in unresectable or recurrent cancer (IRI-S)	Median survival time IRI-S 12.8 months S-1 10.5 months P=0.233	Response-rate IRI-S 41.5% S-1 26.9% P=0.035	• ITT analysis • No info on maturity of data at time of analysis
Curran 2009[132] **QoL results of Dank et al. 2008**	• Design: RCT 2 arms • Research funding: Pfizer • Setting: multicentre, international • Sample size: 337 • Period: June 2000-March 2002 • Median FU: not stated	• Eligibility criteria: histologically confirmed gastric adenocarcinoma with measurable metastatic disease or locally recurrent disease with at least 1 measurable LN. 18-75 years old. Karnofsky PS > 70%, life expectancy	• Intervention: IF: irinotecan + 5-FU + folinic acid • Control: CF: cisplatin + 5-FU • Treatment was administered unti disease progression, unacceptable toxicity or withdrawal of	Quality of Life No signficiant difference in QoL scores or minimum global health status	Physical functioniçng scale significant better results for IF group	• Analyses based on time windows, independent of cycle duration • Median duration of treatment 21 weeks in IF

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		> 3 months and adequate blood tests	consent			arm, 17 weeks in CF arm
Ohtsu 2011[133]	• Design: RCT 2 arms • Research funding: Genentech, F. Hoffman-La Roche, Chugai Pharmaceutical • Setting: multicentre, international • Sample size: 774 • Period: September 2007 – December 2008 • Median FU: 11.4 months in intervention group, 9.4 months in placebo group	• Eligibility criteria: age > 17y, histologically confirmed, unresectable locally advanced or metastatic adenocarcinoma of the stomach, ECOG PS 0-2, evaluable disease according to RECIST. No prior platinum or antiangiogenic therapy. Adequate blood tests.	• Intervention: bevacizumab + cisplatin + capecitabine • Control: placebo + cisplatin + capecitabine	<u>Overall survival</u> Bevacizumab: median OS 12.1 (11.1-13.8) months Placebo: 10.1 (9.0-11.3) months HR = 0.87 (0.73-1.03) P=0.1002	<u>Progression-free survival</u> Bevacizumab: median PFS 6.7 (5.9-7.1) months Placebo: 5.3 (4.4-5.6) months HR = 0.80 (0.68-0.93) P=0.0037	• Double blind study, no independent radiology review performed • Only patients with measurable disease included in analysis of response
Bang 2010[134]	• Design: RCT 2 arms • Research funding: F. Hoffmann-La Roche • Setting: multicentre, international • Sample size: 594 (584 included in analysis) • Period: September 2005-December 2008 • Median FU: 18.6 months in	• Eligibility criteria: >18y, histologically confirmed inoperable, metastatic or recurrent gastric cancer. ECOG PS 0-2. Adequate organ function. Measurable or non-measurable disease. HER2 3+ on immunohisto-chemistry or FISH	• Intervention: trastuzumab + cisplatin + capecitabine or 5-FU • Control: cisplatin + capecitabine or 5-FU	<u>Median overall survival</u> Trastuzumab: 13.8 (12-16) months Control: 11.1 (10-13) months HR 0.74 (0.60-0.91) P=0.0046 <u>Progression-free survival</u> Trastuzumab 6.7 (6-8) months		• No intention-to –treat analysis • No blinding of patients, investigators and assessors • Results based on interim analysis after

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
	intervention group, 17.1 months in control group.	positive • Exclusion criteria: prior chemotherapy for metastatic disease, insufficient cardiovascular function, malabsorption syndrome, GI bleeding, brain metastasis		Control: 5.5 (5-6 months HR 0.71 (0.59-0.85) P=0.0002		75% of events (boundery crossed)
Lee 2009[135]	• Design: RCT 2 arms • Research funding: • Setting: multicentre, Korea • Sample size: 147 pts • Period: July 2000-January 2004	• Eligibility criteria: pathologically proven unresectable locally advanced or metastatic gastric cancer; Evaluable disease. 20-70 years. ECOG PS 0-2. Life expectancy > 3 months, adequate blood tests, no serious cardio-pulmonary co-morbidity • Exclusion criteria: prior systemic chemotherapy, uncontrolled infection, metastasis to central nervous system, psychiatric disorders,	• Intervention: Heptaplatin + 5-FU • Control: cisplatin + 5-FU	<u>Median overall survival</u> Heptaplatin 7.3 (6.0-8.6) months Cisplatin 7.9 (6.8-9.0) months P=0.24 <u>Median time to progression</u> Heptaplatin 2.5 (range 0.7-6.1) months Cisplatin 2.3 (range 0.6-5.3) months	<u>Toxicity</u> Grade 3-4 haematological toxicity: no significant difference Grade 3-4 nausea & vomiting more frequent in heptaplatin arm (p=0.01/p=0.05)	• Central rando-mization • No information on blinding • ITT analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
		hypersensitivity to study treatment.				
Kuramoto 2009[136]	• Design: RCT 2 arms • Research funding: • Setting: Ministry of education, Science and culture, Japan • Sample size: 88 • Period: 1995-2005	• Eligibility criteria: patients with gastric cancer who underwent R0 resection with D2 lymphadenectomy. No macroscopic involvement of peritoneum and cytology of peritoneal lavage positive for tumour cells.	• Intervention: Surgery + extensive intraoperative peritoneal lavage (EIPL) + IP chemotherapy • Control: Surgery alone / surgery + IP chemotherapy	<u>5y overall survival</u> EIPL 43.8% IP chemotherapy: 4.6% Surgery alone: 0% P<0.0001	<u>Peritoneal recurrence</u> EIPL 40% IP chemotherapy 79.3% Surgery alone 89.7% P<0.0001	• Small sample size, no power calculation

5.4.4. Surgery for gastric perforation

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Mahar 2011[137]	• Design: SR (qualitative review) • Sources of funding: Canadian Cancer Society • Search date: 1 January 1985 – 1 January 2010 • Searched databases: Medline, Embase, Cochrane • Included study designs: all • Number of included studies: 8 retrospective studies (127 patients)	• Inclusion criteria: studies reporting on reporting on procedure-related morbidity, mortality or survival in perforated gastric cancer cases, published in English • Exclusion criteria: reviews, MA, SR, abstracts, letters, care-reports, guidelines	• Intervention: surgery 35 simple repair 41 subtotal gastrectomy 15 total gastrectomy 7 gastrectomy NOS Few simple repair • Comparator: none	<u>Overall operative mortality</u> 8-40% 8-100% for simple repaire 0-50% resection <u>Survival</u> Median OS 9.8-36 months R0 resection: 75.2 months	<u>Procedure related morbidity</u> 15-57%	• No critical appraisal of included studies, however only very low level of evidence available • All surgery was performed in an emergency setting

5.4.5. Surgery or stenting for malignant gastric outlet obstruction

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
Zheng 2011[138]	• Design: SR and MA • Sources of funding: not stated • Search date: 5 December 2010 • Searched databases: Pubmed, Embase, Chinese Biomedical Database, Cochrane Library • Included study designs: RCT + non-randomized controlled trials • Number of included studies: 6 (3 RCT + 3 CCT) Included trials: Jeurnink 2010 Mehta 2006 Fiori 2004 Guo 2010 Schmidt 2009 Johnsson 2004	• Eligibility criteria: controlled clinical trials and RCTs • Patients characteristics: • Median FU:	• Intervention: endoscopic stenting (ES) • Comparator: gastrojejuno-stomy (GJ)	<u>Time to oral intake</u> Mean time after procedure 3.6 days shorter for ES <u>Survival</u> Mean survival 78 days after ES, 81 days after GJ (no statistical significance) <u>QoL</u> No combination of data possible, overall no clear difference between ES and GJ	<u>Complications</u> ES: 0-40% GJ: 22.2-57.1% <u>Mortality</u> ES: 4.2-28.6% GJ: 21.4-26.7% OR 0.58 (0.18-1.86) <u>Hospital stay</u> All studies show a significantly shorter hospital stay after ES vs. GJ (idem for costs)	• Limited, low level of evidence available • Also other cancer types included, mainly cancer of the pancreas
• **Ly 2010**[139]	• Design: SR and MA • Sources of funding: • Search date: January 1990 – May 2008 • Searched databases: Medline, Embase, Google	• Clinical studies directly comparing endoscopic stenting (ES) with gastrojejunostomy for palliative management of gastric or duodenal obstruction	• Intervention: endoscopic stenting • Comparator: laparoscopic (LGJ) or open (OGJ) gastrojejuno-	<u>ES versus OGJ</u> **Oral intake** OR 2.62 (1.17-5.86) (p=0.02) **Mean time to oral intake** WMD 7 days (5.02-	<u>ES versus OGJ</u> **Length of hospital stay** WMD 12 days (7.94-15.65) shorter for ES **Major complications** OR 1.04 (0.47-2.29)	• No critical appraisal of included studies, but only low level of evidence available • Also other cancer types

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of review quality
	scholar, ISI proceedings, Cochrane library, online registers of controlled clinical trials • Included study designs: RCT, prospective and retrospective cohort comparisons • Number of included studies: 13 (2 RCT, 1 prospective, 10 retrospective cohort comparisons) (514 patients, 94 gastric cancer) Included studies: Jeurnink 2007 El-Shabrawi 2006 Mehta 2006 Espinel 2006 Mejia 2006 Del piano 2005 Maetani 2005 Fiori 2004 Mittel 2004 Maetini 2004 Johnnson 2004 Wong 2002 Yim 2001	• Exclusion criteria: only abstract available, duplicate data	stomy	8.75) earlier for ES **Mortality 30 days** OR 0.83 (0.32-2.18) (p=0.71) **Survival** WMD 26 days (-69.03-16.40) (p=0.23) <u>ES versus LGJ</u> No MA possible, results suggest shorter hospital stay, shorter time to oral intake and fewer complications after ES versus LGJ but possible shorter survival	(p=0.93)	included

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Jeurnink 2010[140]	• Design: RCT 2 arms • Research funding: (ZonMW) • Setting: multicentre, the Netherlands • Sample size: 39 • Period: January 2006-May 2008	• Eligibility criteria: Obstructive cancer from the distal one third of the stomach to the distal duodenum. No oral intake or liquids only. Unresectable or metastatic disease. • Exclusion criteria: other strictures of GI tract, previous surgery or treatment for the same condition. WHO PS 4. Unable to complete QoL questionnaires	• Intervention: endoscopic stent placement • Control: open or laparoscopic gastrojejuno-stomy	More rapid improvement after stent vs. surgery ($p<0.01$) but long term food intake (30days, 60 days), better after surgery ($p=0.05$). More days alive with good food intake (GOOSS score >1) after surgery compared to stents No significant difference in overall survival	More re-interventions, major complications and recurrent obstructive symptoms after stent placement. Shorter hospital stay after stent placement	• Mainly other cancer types (e.g. pancreatic cancer) included • Small sample size

5.5. Treatment of recurrent disease

Randomized controlled trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcomes	Results secondary and other outcomes	Critical appraisal of quality
Thuss-Patience 2011[141]	• Design: RCT 2 arms • Research funding: Aventis, Pfizer • Setting: Mutlicentre, Germany • Sample size: 40 • Period: October 2002-December 2006 • Median FU: not stated (FU completed after death of last patient)	• Eligibility criteria: histologically proven adenoca of the stomach with progression during or within 6 months after first-line chemotherapy. No more than 1 prior line of chemotherapy. Age < 76y, adequate blood tests. ECOG PS <3. Measurable or evaluable disease	• Intervention: irinotecan 2nd line chemotherapy • Control: best supportive care	Overall survival HR for death 0.48 (0.25-0.92)		• No clear concealment of allocation • Early closure due to slow accrual

6. REFERENCES

1. (UICC) IUAC. TNM classification of malignant tumours. 7th ed. ed. Sobin LH, Gospodarowicz MK, Wittekind C, editor.: Wiley-Blackwell; 2009.
2. Thosani N, Singh H, Kapadia A, Ochi N, Lee JH, Ajani J, et al. Diagnostic accuracy of EUS in differentiating mucosal versus submucosal invasion of superficial esophageal cancers: a systematic review and meta-analysis. Gastrointest Endosc. 2012;75(2):242-53.
3. Tranchemontagne J. Stadification initiale du cancer de l'oesophage : revue systématique sur la performance des méthodes diagnostiques. Québec: Agence d'évaluation des technologies et des modes d'intervention en santé; 2009. 5 Available from: www.aetmis.gouv.qc.ca.
4. van Vliet EP, Heijenbrok-Kal MH, Hunink MG, Kuipers EJ, Siersema PD. Staging investigations for oesophageal cancer: a meta-analysis. Br J Cancer. 2008;98(3):547-57.
5. Puli SR, Reddy JB, Bechtold ML, Antillon D, Ibdah JA, Antillon MR. Staging accuracy of esophageal cancer by endoscopic ultrasound: a meta-analysis and systematic review. World J Gastroenterol. 2008;14(10):1479-90.
6. Yen TJ, Chung CS, Wu YW, Yen RF, Cheng MF, Lee JM, et al. Comparative study between endoscopic ultrasonography and positron emission tomography-computed tomography in staging patients with esophageal squamous cell carcinoma. Dis Esophagus. 2012;25(1):40-7.
7. Ba-Ssalamah A, Matzek W, Baroud S, Bastati N, Zacherl J, Schoppmann SF, et al. Accuracy of hydro-multidetector row CT in the local T staging of oesophageal cancer compared to postoperative histopathological results. Eur Radiol. 2011;21(11):2326-35.
8. Eloubeidi MA, Cerfolio RJ, Bryant AS, Varadarajulu S. Efficacy of endoscopic ultrasound in patients with esophageal cancer predicted to have N0 disease. Eur J Cardiothorac Surg. 2011;40(3):636-41.
9. Shum WY, Hsieh TC, Yeh JJ, Chen JH, Su CC, Liang JA, et al. Clinical usefulness of dual-time FDG PET-CT in assessment of esophageal squamous cell carcinoma. Eur. J. Radiol. 2011.
10. Smith BR, Chang KJ, Lee JG, Nguyen NT. Staging accuracy of endoscopic ultrasound based on pathologic analysis after minimally invasive esophagectomy. Am Surg. 2010;76(11):1228-31.
11. Choi J, Kim SG, Kim JS, Jung HC, Song IS. Comparison of endoscopic ultrasonography (EUS), positron emission tomography (PET), and computed tomography (CT) in the preoperative locoregional staging of resectable esophageal cancer. Surg Endosc. 2010;24(6):1380-6.
12. Hsu WH, Hsu PK, Wang SJ, Lin KH, Huang CS, Hsieh CC, et al. Positron emission tomography-computed tomography in predicting locoregional invasion in esophageal squamous cell carcinoma. Ann Thorac Surg. 2009;87(5):1564-8.
13. Noble F, Bailey D, Panel SUGT, Tung K, Byrne JP. Impact of integrated PET/CT in the staging of oesophageal cancer: a UK population-based cohort study. Clin Radiol. 2009;64(7):699-705.
14. Kato H, Kimura H, Nakajima M, Sakai M, Sano A, Tanaka N, et al. The additional value of integrated PET/CT over PET in initial lymph node staging of esophageal cancer. Oncol Rep. 2008;20(4):857-62.
15. Mennigen R, Tuebergen D, Koehler G, Sauerland C, Senninger N, Bruewer M. Endoscopic ultrasound with conventional probe and miniprobe in preoperative staging of esophageal cancer. J Gastrointest Surg. 2008;12(2):256-62.
16. Schreurs LM, Verhoef CC, van der Jagt EJ, van Dam GM, Groen H, Plukker JT. Current relevance of cervical ultrasonography in staging cancer of the esophagus and gastroesophageal junction. Eur J Radiol. 2008;67(1):105-11.
17. Arnott SJ, Duncan W, Gignoux M, Girling D, Hansen H, Launois B, et al. Preoperative radiotherapy for esophageal carcinoma. Cochrane Database of Systematic Reviews 2005, Issue 4. Art. No.: CD001799. DOI: 10.1002/14651858.CD001799.pub2.; 2010.

18. Boughrassa F. Traitement curatif du cancer de l'oesophage : revue systématique sur la thérapie néoadjuvante et la chimioradiothérapie seule. Québec: Agence d'évaluation des technologies et des modes d'intervention en santé; 2009. 5 Available from: www.aetmis.gouv.qc.ca
19. Sjoquist KM, Burmeister BH, Smithers BM, Zalcberg JR, Simes RJ, Barbour A, et al. Survival after neoadjuvant chemotherapy or chemoradiotherapy for resectable oesophageal carcinoma: an updated meta-analysis. Lancet Oncol. 2011;12(7):681-92.
20. Kranzfelder M, Schuster T, Geinitz H, Friess H, Buchler P. Meta-analysis of neoadjuvant treatment modalities and definitive non-surgical therapy for oesophageal squamous cell cancer. Br J Surg. 2011;98(6):768-83.
21. Ando N, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, et al. A Randomized Trial Comparing Postoperative Adjuvant Chemotherapy with Cisplatin and 5-Fluorouracil Versus Preoperative Chemotherapy for Localized Advanced Squamous Cell Carcinoma of the Thoracic Esophagus (JCOG9907). Ann Surg Oncol. 2011.
22. Hirao M, Ando N, Tsujinaka T, Udagawa H, Yano M, Yamana H, et al. Influence of preoperative chemotherapy for advanced thoracic oesophageal squamous cell carcinoma on perioperative complications. Br J Surg. 2011;98(12):1735-41.
23. Jin HL, Zhu H, Ling TS, Zhang HJ, Shi RH. Neoadjuvant chemoradiotherapy for resectable esophageal carcinoma: a meta-analysis. World J Gastroenterol. 2009;15(47):5983-91.
24. Lv J, Cao XF, Zhu B, Ji L, Tao L, Wang DD. Long-term efficacy of perioperative chemoradiotherapy on esophageal squamous cell carcinoma. World J Gastroenterol. 2010;16(13):1649-54.
25. Chen YM, Pan XF, Tong LJ, Shi YP, Chen T. Can 18F-fluorodeoxyglucose positron emission tomography predict responses to neoadjuvant therapy in oesophageal cancer patients? A meta-analysis. Nucl Med Commun. 2011;32(11):1005-10.
26. Kwee RM. Prediction of tumor response to neoadjuvant therapy in patients with esophageal cancer with use of 18F FDG PET: a systematic review. Radiology. 2010;254(3):707-17.
27. Ngamruengphong S, Sharma VK, Nguyen B, Das A. Assessment of response to neoadjuvant therapy in esophageal cancer: an updated systematic review of diagnostic accuracy of endoscopic ultrasonography and fluorodeoxyglucose positron emission tomography. Dis Esophagus. 2010;23(3):216-31.
28. Misra S, Choi M, Livingstone AS, Franceschi D. The role of endoscopic ultrasound in assessing tumor response and staging after neoadjuvant chemotherapy for esophageal cancer. Surg. Endosc. 2011:1-5.
29. van Heijl M, Omloo JM, van Berge Henegouwen MI, Hoekstra OS, Boellaard R, Bossuyt PM, et al. Fluorodeoxyglucose positron emission tomography for evaluating early response during neoadjuvant chemoradiotherapy in patients with potentially curable esophageal cancer. Ann Surg. 2011;253(1):56-63.
30. van Heijl M, Phoa SS, van Berge Henegouwen MI, Omloo JM, Mearadji BM, Sloof GW, et al. Accuracy and reproducibility of 3D-CT measurements for early response assessment of chemoradiotherapy in patients with oesophageal cancer. Eur J Surg Oncol. 2011;37(12):1064-71.
31. McCann P, Stafinski T, Wong C, Menon D. The safety and effectiveness of endoscopic and non-endoscopic approaches to the management of early esophageal cancer: a systematic review. Cancer Treat Rev. 2011;37(1):11-62.
32. Boughrassa F. Traitement du cancer de l'oesophage : revue systématique sur les techniques chirurgicales. Québec: Agence d'évaluation des technologies et des modes d'intervention en santé; 2011. 7 Available from: www.aetmis.gouv.qc.ca
33. Chou SH, Chuang HY, Huang MF, Lee CH, Yau HM. A prospective comparison of transthoracic and transhiatal resection for esophageal carcinoma in Asians. Hepatogastroenterology. 2009;56(91-92):707-10.

34. Sgourakis G, Gockel I, Radtke A, Musholt TJ, Timm S, Rink A, et al. Minimally invasive versus open esophagectomy: meta-analysis of outcomes. Dig Dis Sci. 2010;55(11):3031-40.
35. Nederlof N, Tilanus HW, Tran TC, Hop WC, Wijnhoven BP, de Jonge J. End-to-end versus end-to-side esophagogastrostomy after esophageal cancer resection: a prospective randomized study. Ann Surg. 2011;254(2):226-33.
36. Dai JG, Zhang ZY, Min JX, Huang XB, Wang JS. Wrapping of the omental pedicle flap around esophagogastric anastomosis after esophagectomy for esophageal cancer. Surgery. 2011;149(3):404-10.
37. Aly A, Jamieson GG, Watson DI, Devitt PG, Ackroyd R, Stoddard CJ. An antireflux anastomosis following esophagectomy: a randomized controlled trial. J Gastrointest Surg. 2010;14(3):470-5.
38. Wouters MWJM, Gooiker GA, Van Sandick JW, Tollenaar RAEM. The volume-outcome relation in the surgical treatment of esophageal cancer: A systematic review and meta-analysis. Cancer. 2011.
39. Liu CX, Li XY, Gao XS. Meta-analysis of late course accelerated hyperfractionated radiotherapy combined with FP chemotherapy for esophageal carcinoma. Chin. 2010;29(10):889-99.
40. Crehange G, Maingon P, Peignaux K, N'Guyen T D, Mirabel X, Marchal C, et al. Phase III trial of protracted compared with split-course chemoradiation for esophageal carcinoma: Federation Francophone de Cancerologie Digestive 9102. J Clin Oncol. 2007;25(31):4895-901.
41. Cunningham D, Starling N, Rao S, Iveson T, Nicolson M, Coxon F, et al. Capecitabine and oxaliplatin for advanced esophagogastric cancer. N Engl J Med. 2008;358(1):36-46.
42. Rosenblatt E, Jones G, Sur RK, Donde B, Salvajoli JV, Ghosh-Laskar S, et al. Adding external beam to intra-luminal brachytherapy improves palliation in obstructive squamous cell oesophageal cancer: a prospective multi-centre randomized trial of the International Atomic Energy Agency. Radiother Oncol. 2010;97(3):488-94.
43. Sgourakis G, Gockel I, Radtke A, Dedemadi G, Goumas K, Mylona S, et al. The use of self-expanding stents in esophageal and gastroesophageal junction cancer palliation: a meta-analysis and meta-regression analysis of outcomes. Dig Dis Sci. 2010;55(11):3018-30.
44. Rupinski M, Zagorowicz E, Regula J, Fijuth J, Kraszewska E, Polkowski M, et al. Randomized comparison of three palliative regimens including brachytherapy, photodynamic therapy, and APC in patients with malignant dysphagia (CONSORT 1a) (Revised II). Am J Gastroenterol. 2011;106(9):1612-20.
45. Blomberg J, Wenger U, Lagergren J, Arnelo U, Agustsson T, Johnsson E, et al. Antireflux stent versus conventional stent in the palliation of distal esophageal cancer. A randomized, multicenter clinical trial. Scand J Gastroenterol. 2010;45(2):208-16.
46. Shenfine J, McNamee P, Steen N, Bond J, Griffin SM. A randomized controlled clinical trial of palliative therapies for patients with inoperable esophageal cancer. Am J Gastroenterol. 2009;104(7):1674-85.
47. Guo JH, Teng GJ, Zhu GY, He SC, Fang W, Deng G, et al. Self-expandable esophageal stent loaded with 125I seeds: initial experience in patients with advanced esophageal cancer. Radiology. 2008;247(2):574-81.
48. Javed A, Pal S, Dash NR, Ahuja V, Mohanti BK, Vishnubhatla S, et al. Palliative Stenting With or Without Radiotherapy for Inoperable Esophageal Carcinoma: A Randomized Trial. J. Gastrointest. Cancer. 2010:1-7.
49. Verschuur EM, Steyerberg EW, Tilanus HW, Polinder S, Essink-Bot ML, Tran KT, et al. Nurse-led follow-up of patients after oesophageal or gastric cardia cancer surgery: a randomised trial. Br J Cancer. 2009;100(1):70-6.
50. Roedl JB, Harisinghani MG, Colen RR, Fischman AJ, Blake MA, Mathisen DJ, et al. Assessment of treatment response and recurrence in esophageal carcinoma based on tumor length and standardized uptake value on positron emission tomography-computed tomography. Ann Thorac Surg. 2008;86(4):1131-8.

51. Mocellin S, Marchet A, Nitti D. EUS for the staging of gastric cancer: a meta-analysis. Gastrointest Endosc. 2011;73(6):1122-34.
52. Kwee RM, Kwee TC. The accuracy of endoscopic ultrasonography in differentiating mucosal from deeper gastric cancer. Am J Gastroenterol. 2008;103(7):1801-9.
53. Choi J, Kim SG, Im JP, Kim JS, Jung HC, Song IS. Is endoscopic ultrasonography indispensable in patients with early gastric cancer prior to endoscopic resection? Surg. Endosc. Interv. Tech. 2010;24(12):3177-85.
54. Hye SA, Lee HJ, Yoo MW, Sang GK, Jong PI, Se HK, et al. Diagnostic accuracy of T and N stages with endoscopy, stomach protocol CT, and endoscopic ultrasonography in early gastric cancer. J. Surg. Oncol. 2009;99(1):20-7.
55. Zheng Z, Yu Y, Lu M, Sun W, Wang F, Li P, et al. Double contrast-enhanced ultrasonography for the preoperative evaluation of gastric cancer: a comparison to endoscopic ultrasonography with respect to histopathology. Am J Surg. 2011;202(5):605-11.
56. Seevaratnam R, Cardoso R, McGregor C, Lourenco L, Mahar A, Sutradhar R, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. 2011:1-16.
57. Wang Z, Chen JQ. Imaging in assessing hepatic and peritoneal metastases of gastric cancer: a systematic review. BMC Gastroenterology. 2011;11(19).
58. Kwee RM, Kwee TC. Imaging in assessing lymph node status in gastric cancer. Gastric Cancer. 2009;12(1):6-22.
59. Anzidei M, Napoli A, Zaccagna F, Di Paolo P, Zini C, Cavallo Marincola B, et al. Diagnostic performance of 64-MDCT and 1.5-T MRI with high-resolution sequences in the T staging of gastric cancer: a comparative analysis with histopathology. Radiol Med (Torino). 2009;114(7):1065-79.
60. Bilici A, Ustaalioglu BB, Seker M, Kefeli U, Canpolat N, Tekinsoy B, et al. The role of 18F-FDG PET/CT in the assessment of suspected recurrent gastric cancer after initial surgical resection: can the results of FDG PET/CT influence patients' treatment decision making? Eur J Nucl Med Mol Imaging. 2011;38(1):64-73.
61. Cidon EU, Cuenca IJ. Gastric Adenocarcinoma: Is Computed Tomography (CT) Useful in Preoperative Staging? Clinical Medicine Oncology. 2009;3:91-7.
62. Graziosi L, Bugiantella W, Cavazzoni E, Cantarella F, Porcari M, Baffa N, et al. Role of FDG-PET/CT in follow-up of patients treated with resective gastric surgery for tumour. Ann Ital Chir. 2011;82(2):125-9.
63. Ha TK, Choi YY, Song SY, Kwon SJ. F18-fluorodeoxyglucose-positron emission tomography and computed tomography is not accurate in preoperative staging of gastric cancer. J Korean Surg Soc. 2011;81(2):104-10.
64. Hwang SW, Lee DH, Lee SH, Park YS, Hwang JH, Kim JW, et al. Preoperative staging of gastric cancer by endoscopic ultrasonography and multidetector-row computed tomography. J Gastroenterol Hepatol. 2010;25(3):512-8.
65. Kawaguchi T, Ichikawa D, Komatsu S, Okamoto K, Murayama Y, Shiozaki A, et al. Clinical evaluation of JCGC and TNM staging on multidetector-row computed tomography in preoperative nodal staging of gastric cancer. Hepato-Gastroenterology. 2011;58(107-108):838-41.
66. Kim DW, Park SA, Kim CG. Detecting the recurrence of gastric cancer after curative resection: comparison of FDG PET/CT and contrast-enhanced abdominal CT. J Korean Med Sci. 2011;26(7):875-80.
67. Kim EY, Lee WJ, Choi D, Lee SJ, Choi JY, Kim BT, et al. The value of PET/CT for preoperative staging of advanced gastric cancer: Comparison with contrast-enhanced CT. Eur. J. Radiol. 2011;79(2):183-8.

68. Kim JW, Shin SS, Heo SH, Choi YD, Lim HS, Park YK, et al. Diagnostic performance of 64-section CT using CT gastrography in preoperative T staging of gastric cancer according to 7th edition of AJCC cancer staging manual. Eur. Radiol. 2011:1-9.
69. Kim SJ, Kim HH, Kim YH, Hwang SH, Lee HS, Park do J, et al. Peritoneal metastasis: detection with 16- or 64-detector row CT in patients undergoing surgery for gastric cancer. Radiology. 2009;253(2):407-15.
70. Kim YH, Lee KH, Park SH, Kim HH, Hahn S, Park do J, et al. Staging of T3 and T4 gastric carcinoma with multidetector CT: added value of multiplanar reformations for prediction of adjacent organ invasion. Radiology. 2009;250(3):767-75.
71. Lee ES, Kim SH, Lee JY, Kim SJ, Kim MA, Lee JM, et al. Radiologist performance in differentiating polypoid early from advanced gastric cancer using specific CT criteria: Emphasis on dimpling sign. Am. J. Roentgenol. 2009;193(6):1546-55.
72. Lee SM, Kim SH, Lee JM, Im SA, Bang YJ, Kim WH, et al. Usefulness of CT volumetry for primary gastric lesions in predicting pathologic response to neoadjuvant chemotherapy in advanced gastric cancer. Abdom. Imaging. 2009;34(4):430-40.
73. Makino T, Fujiwara Y, Takiguchi S, Tsuboyama T, Kim T, Nushijima Y, et al. Preoperative T staging of gastric cancer by multi-detector row computed tomography. Surgery (USA). 2011;149(5):672-9.
74. Marrelli D, Mazzei MA, Pedrazzani C, Di Martino M, Vindigni C, Corso G, et al. High accuracy of multislices computed tomography (MSCT) for para-aortic lymph node metastases from gastric cancer: A prospective single-center study. Ann. Surg. Oncol. 2011;18(8):2265-72.
75. Moschetta M, Stabile Ianora AA, Anglani A, Marzullo A, Scardapane A, Angelelli G. Preoperative T staging of gastric carcinoma obtained by MDCT vessel probe reconstructions and correlations with histological findings. Eur. Radiol. 2010;20(1):138-45.
76. Pan Z, Zhang H, Yan C, Du L, Ding B, Song Q, et al. Determining gastric cancer resectability by dynamic MDCT. Eur. Radiol. 2010;20(3):613-20.
77. Park MJ, Lee WJ, Lim HK, Park KW, Choi JY, Kim BT. Detecting recurrence of gastric cancer: The value of FDG PET/CT. Abdom. Imaging. 2009;34(4):441-7.
78. Sim SH, Kim YJ, Oh DY, Lee SH, Kim DW, Kang WJ, et al. The role of PET/CT in detection of gastric cancer recurrence. BMC Cancer. 2009;9.
79. Yan C, Zhu ZG, Yan M, Zhang H, Pan ZL, Chen J, et al. Size of the largest lymph node visualized on Multi-Detector-Row Computed Tomography (MDCT) is useful in predicting metastatic lymph node status of gastric cancer. J. Int. Med. Res. 2010;38(1):22-33.
80. Leake PA, Cardoso R, Seevaratnam R, Lourenco L, Helyer L, Mahar A, et al. A systematic review of the accuracy and indications for diagnostic laparoscopy prior to curative-intent resection of gastric cancer. 2011:1-10.
81. Mahadevan D, Sudirman A, Kandasami P, Ramesh G. Laparoscopic staging in gastric cancer: An essential step in its management. J. 2010;6(4):111-3.
82. Power DG, Schattner MA, Gerdes H, Brenner B, Markowitz AJ, Capanu M, et al. Endoscopic Ultrasound Can Improve the Selection for Laparoscopy in Patients with Localized Gastric Cancer. J. Am. Coll. Surg. 2009;208(2):173-8.
83. Wang Z, Dong ZY, Chen JQ, Liu JL. Diagnostic Value of Sentinel Lymph Node Biopsy in Gastric Cancer: A Meta-Analysis. Ann. Surg. Oncol. 2011:1-10.
84. Cozzaglio L, Bottura R, Di Rocco M, Gennari L, Doci R. Sentinel lymph node biopsy in gastric cancer: Possible applications and limits. Eur. J. Surg. Oncol. 2011;37(1):55-9.
85. Tajima Y, Murakami M, Yamazaki K, Masuda Y, Kato M, Sato A, et al. Sentinel node mapping guided by indocyanine green fluorescence imaging during laparoscopic surgery in gastric cancer. Ann. Surg. Oncol. 2010;17(7):1787-93.
86. Toth D, Kincses Z, Plosz J, Torok M, Kovacs I, Kiss C, et al. Value of sentinel lymph node mapping using a blue dye-only method in gastric cancer: a single-center experience from North-East Hungary. 2011:1-5.

87. Park YM, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. Surg Endosc. 2011;25(8):2666-77.
88. Bennett C, Wang Y, Pan T. Endoscopic mucosal resection for early gastric cancer. Cochrane Database Syst Rev. 2009(4):CD004276.
89. Li W, Qin J, Sun YH, Liu TS. Neoadjuvant chemotherapy for advanced gastric cancer: a meta-analysis. World J Gastroenterol. 2010;16(44):5621-8.
90. Biffi R, Fazio N, Luca F, Chiappa A, Andreoni B, Zampino MG, et al. Surgical outcome after docetaxel-based neoadjuvant chemotherapy in locally-advanced gastric cancer. World J Gastroenterol. 2010;16(7):868-74.
91. Memon MA, Subramanya MS, Khan S, Hossain MB, Osland E, Memon B. Meta-analysis of D1 versus D2 gastrectomy for gastric adenocarcinoma. Ann Surg. 2011;253(5):900-11.
92. Zheng B, Ma B, Yang K, Mi D. Meta-analysis of randomized controlled trials comparing D2 and D4 lymphadenectomy for gastric cancer. Eur. Surg. Acta Chir. Austriaca. 2011.
93. Chen XZ, Hu JK, Zhou ZG, Rui YY, Yang K, Wang L, et al. Meta-analysis of effectiveness and safety of D2 plus para-aortic lymphadenectomy for resectable gastric cancer. J Am Coll Surg. 2010;210(1):100-5.
94. Wang Z, Chen JQ, Cao YF. Systematic review of D2 lymphadenectomy versus D2 with para-aortic nodal dissection for advanced gastric cancer. World J Gastroenterol. 2010;16(9):1138-49.
95. Yang SH, Zhang YC, Yang KH, Li YP, He XD, Tian JH, et al. An evidence-based medicine review of lymphadenectomy extent for gastric cancer. Am J Surg. 2009;197(2):246-51.
96. McCulloch P, Nita ME, Kazi H, Gama-Rodrigues J. Extended versus limited lymph nodes dissection technique for adenocarcinoma of the stomach.[update in Cochrane Database Syst Rev. 2004;(4):CD001964; PMID: 15495024]. Cochrane Database of Systematic Reviews. 2003(4):CD001964.
97. Lustosa SA, Saconato H, Atallah AN, Lopes Filho Gde J, Matos D. Impact of extended lymphadenectomy on morbidity, mortality, recurrence and 5-year survival after gastrectomy for cancer. Meta-analysis of randomized clinical trials. Acta cir. 2008;23(6):520-30.
98. Brar SS, Seevaratnam R, Cardoso R, Law C, Helyer L, Coburn N. A systematic review of spleen and pancreas preservation in extended lymphadenectomy for gastric cancer. 2011:1-11.
99. Roberts P, Seevaratnam R, Cardoso R, Law C, Helyer L, Coburn N. Systematic review of pancreaticoduodenectomy for locally advanced gastric cancer. 2011:1-8.
100. Yang K, Chen XZ, Hu JK, Zhang B, Chen ZX, Chen JP. Effectiveness and safety of splenectomy for gastric carcinoma: a meta-analysis. World J Gastroenterol. 2009;15(42):5352-9.
101. Fujita J, Kurokawa Y, Sugimoto T, Miyashiro I, Iijima S, Kimura Y, et al. Survival benefit of bursectomy in patients with resectable gastric cancer: interim analysis results of a randomized controlled trial. 2011:1-7.
102. Imamura H, Kurokawa Y, Kawada J, Tsujinaka T, Takiguchi S, Fujiwara Y, et al. Influence of bursectomy on operative morbidity and mortality after radical gastrectomy for gastric cancer: results of a randomized controlled trial. World J Surg. 2011;35(3):625-30.
103. Zorcolo L, Rosman AS, Pisano M, Marcon F, Restivo A, Nigri GR, et al. A meta-analysis of prospective randomized trials comparing minimally invasive and open distal gastrectomy for cancer. J Surg Oncol. 2011;104(5):544-51.
104. Martinez-Ramos D, Miralles-Tena JM, Cuesta MA, Escrig-Sos J, Van der Peet D, Hoashi JS, et al. Laparoscopy versus open surgery for advanced and resectable gastric cancer: a meta-analysis. Rev Esp Enferm Dig. 2011;103(3):133-41.

105. Yakoub D, Athanasiou T, Tekkis P, Hanna GB. Laparoscopic assisted distal gastrectomy for early gastric cancer: is it an alternative to the open approach? Surg Oncol. 2009;18(4):322-33.
106. Chen XZ, Hu JK, Yang K, Wang L, Lu QC. Short-term evaluation of laparoscopy-assisted distal gastrectomy for predictive early gastric cancer: a meta-analysis of randomized controlled trials. Surg Laparosc Endosc Percutan Tech. 2009;19(4):277-84.
107. Gertler R, Rosenberg R, Feith M, Schuster T, Friess H. Pouch vs. no pouch following total gastrectomy: meta-analysis and systematic review. Am J Gastroenterol. 2009;104(11):2838-51.
108. Group G, Paoletti X, Oba K, Burzykowski T, Michiels S, Ohashi Y, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA. 2010;303(17):1729-37.
109. Sun P, Xiang JB, Chen ZY. Meta-analysis of adjuvant chemotherapy after radical surgery for advanced gastric cancer. Br J Surg. 2009;96(1):26-33.
110. Liu TS, Wang Y, Chen SY, Sun YH. An updated meta-analysis of adjuvant chemotherapy after curative resection for gastric cancer. Eur J Surg Oncol. 2008;34(11):1208-16.
111. Di Costanzo F, Gasperoni S, Manzione L, Bisagni G, Labianca R, Bravi S, et al. Adjuvant chemotherapy in completely resected gastric cancer: a randomized phase III trial conducted by GOIRC. J Natl Cancer Inst. 2008;100(6):388-98.
112. Kulig J, Kolodziejczyk P, Sierzega M, Bobrzynski L, Jedrys J, Popiela T, et al. Adjuvant chemotherapy with etoposide, adriamycin and cisplatin compared with surgery alone in the treatment of gastric cancer: a phase III randomized, multicenter, clinical trial. Oncology. 2010;78(1):54-61.
113. Zhang XL, Shi HJ, Cui SZ, Tang YQ, Ba MC. Prospective, randomized trial comparing 5-FU/LV with or without oxaliplatin as adjuvant treatment following curative resection of gastric adenocarcinoma. Eur J Surg Oncol. 2011;37(6):466-72.
114. Valentini V, Cellini F, Minsky BD, Mattiucci GC, Balducci M, D'Agostino G, et al. Survival after radiotherapy in gastric cancer: systematic review and meta-analysis. Radiother Oncol. 2009;92(2):176-83.
115. Fiorica F, Cartei F, Enea M, Licata A, Cabibbo G, Carau B, et al. The impact of radiotherapy on survival in resectable gastric carcinoma: a meta-analysis of literature data. Cancer Treat Rev. 2007;33(8):729-40.
116. Bamias A, Karina M, Papakostas P, Kostopoulos I, Bobos M, Vourli G, et al. A randomized phase III study of adjuvant platinum/docetaxel chemotherapy with or without radiation therapy in patients with gastric cancer. Cancer Chemother Pharmacol. 2010;65(6):1009-21.
117. Kwon HC, Kim MC, Kim KH, Jang JS, Oh SY, Kim SH, et al. Adjuvant chemoradiation versus chemotherapy in completely resected advanced gastric cancer with D2 nodal dissection. Asia Pac J Clin Oncol. 2010;6(4):278-85.
118. Yan TD, Black D, Sugarbaker PH, Zhu J, Yonemura Y, Petrou G, et al. A systematic review and meta-analysis of the randomized controlled trials on adjuvant intraperitoneal chemotherapy for resectable gastric cancer. Ann Surg Oncol. 2007;14(10):2702-13.
119. Miyashiro I, Furukawa H, Sasako M, Yamamoto S, Nashimoto A, Nakajima T, et al. Randomized clinical trial of adjuvant chemotherapy with intraperitoneal and intravenous cisplatin followed by oral fluorouracil (UFT) in serosa-positive gastric cancer versus curative resection alone: final results of the Japan Clinical Oncology Group trial JCOG9206-2. Gastric Cancer. 2011;14(3):212-8.
120. Jeung HC, Moon YW, Rha SY, Yoo NC, Roh JK, Noh SH, et al. Phase III trial of adjuvant 5-fluorouracil and adriamycin versus 5-fluorouracil, adriamycin, and polyadenylic-polyuridylic acid (poly A:U) for locally advanced gastric cancer after curative surgery: final results of 15-year follow-up. Ann Oncol. 2008;19(3):520-6.
121. Brar SS, Seevaratnam R, Cardoso R, Yohanathan L, Law C, Helyer L, et al. Multivisceral resection for gastric cancer: a systematic review. 2011:1-8.

122. Mahar AL, Coburn NG, Singh S, Law C, Helyer LK. A systematic review of surgery for non-curative gastric cancer. 2011:1-13.
123. Kerkar SP, Kemp CD, Avital I. Liver resections in metastatic gastric cancer. HPB. 2010;12(9):589-96.
124. Gill RS, Al-Adra DP, Nagendran J, Campbell S, Shi X, Haase E, et al. Treatment of gastric cancer with peritoneal carcinomatosis by cytoreductive surgery and HIPEC: a systematic review of survival, mortality, and morbidity. J Surg Oncol. 2011;104(6):692-8.
125. Yang XJ, Huang CQ, Suo T, Mei LJ, Yang GL, Cheng FL, et al. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy improves survival of patients with peritoneal carcinomatosis from gastric cancer: final results of a phase III randomized clinical trial. Ann Surg Oncol. 2011;18(6):1575-81.
126. Montagnani F, Turrisi G, Marinozzi C, Aliberti C, Fiorentini G. Effectiveness and safety of oxaliplatin compared to cisplatin for advanced, unresectable gastric cancer: a systematic review and meta-analysis. Gastric Cancer. 2011;14(1):50-5.
127. Ma Y, Tang L, Wang HX, Xu YC, Zhang FC. Capecitabine for the treatment for advanced gastric cancer: Efficacy, safety and ethnicity. J. Clin. Pharm. Ther. 2011.
128. Huang J, Cao Y, Wu L, Liao C, He Y, Gao F. S-1-based therapy versus 5-FU-based therapy in advanced gastric cancer: a meta-analysis. Med. Oncol. 2010:1-8.
129. Wagner AD, Unverzagt S, Grothe W, Kleber G, Grothey A, Haerting J, et al. Chemotherapy for advanced gastric cancer. Cochrane Database Syst Rev. 2010(3):CD004064.
130. Zagouri F, Papadimitriou CA, Dimopoulos MA, Pectasides D. Molecularly targeted therapies in unresectable-metastatic gastric cancer. A systematic review. Cancer Treat. Rev. 2011;37(8):599-610.
131. Narahara H, Iishi H, Imamura H, Tsuburaya A, Chin K, Imamoto H, et al. Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer. 2011;14(1):72-80.
132. Curran D, Pozzo C, Zaluski J, Dank M, Barone C, Valvere V, et al. Quality of life of palliative chemotherapy naive patients with advanced adenocarcinoma of the stomach or esophagogastric junction treated with irinotecan combined with 5-fluorouracil and folinic acid: results of a randomised phase III trial. Qual Life Res. 2009;18(7):853-61.
133. Ohtsu A, Shah MA, Van Cutsem E, Rha SY, Sawaki A, Park SR, et al. Bevacizumab in Combination With Chemotherapy As First-Line Therapy in Advanced Gastric Cancer: A Randomized, Double-Blind, Placebo-Controlled Phase III Study. J Clin Oncol. 2011;29(30):3968-76.
134. Bang YJ, Van Cutsem E, Feyereislova A, Chung HC, Shen L, Sawaki A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial.[Erratum appears in Lancet. 2010 Oct 16;376(9749):1302]. Lancet. 2010;376(9742):687-97.
135. Lee KH, Hyun MS, Kim HK, Jin HM, Yang J, Song HS, et al. Randomized, multicenter, phase III trial of heptaplatin 1-hour infusion and 5-fluorouracil combination chemotherapy comparing with cisplatin and 5-fluorouracil combination chemotherapy in patients with advanced gastric cancer. Cancer Res. 2009;41(1):12-8.
136. Kuramoto M, Shimada S, Ikeshima S, Matsuo A, Yagi Y, Matsuda M, et al. Extensive intraoperative peritoneal lavage as a standard prophylactic strategy for peritoneal recurrence in patients with gastric carcinoma. Ann Surg. 2009;250(2):242-6.

137. Mahar AL, Coburn NG, Karanicolas PJ, Viola R, Helyer LK. Effective palliation and quality of life outcomes in studies of surgery for advanced, non-curative gastric cancer: a systematic review. 2011:1-8.
138. Zheng B, Wang X, Ma B, Tian J, Jiang L, Yang K. Endoscopic stenting versus gastrojejunostomy for palliation of malignant gastric outlet obstruction. Dig. Endosc. 2011.
139. Ly J, O'Grady G, Mittal A, Plank L, Windsor JA. A systematic review of methods to palliate malignant gastric outlet obstruction. Surg Endosc. 2010;24(2):290-7.
140. Jeurnink SM, Steyerberg EW, van Hooft JE, van Eijck CH, Schwartz MP, Vleggaar FP, et al. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): a multicenter randomized trial. Gastrointest Endosc. 2010;71(3):490-9.
141. Thuss-Patience PC, Kretzschmar A, Bichev D, Deist T, Hinke A, Breithaupt K, et al. A randomised phase III study of the Arbeitsgemeinschaft Internistische Onkologie (AIO). Eur. J. Cancer. 2011;47(15):2306-14.