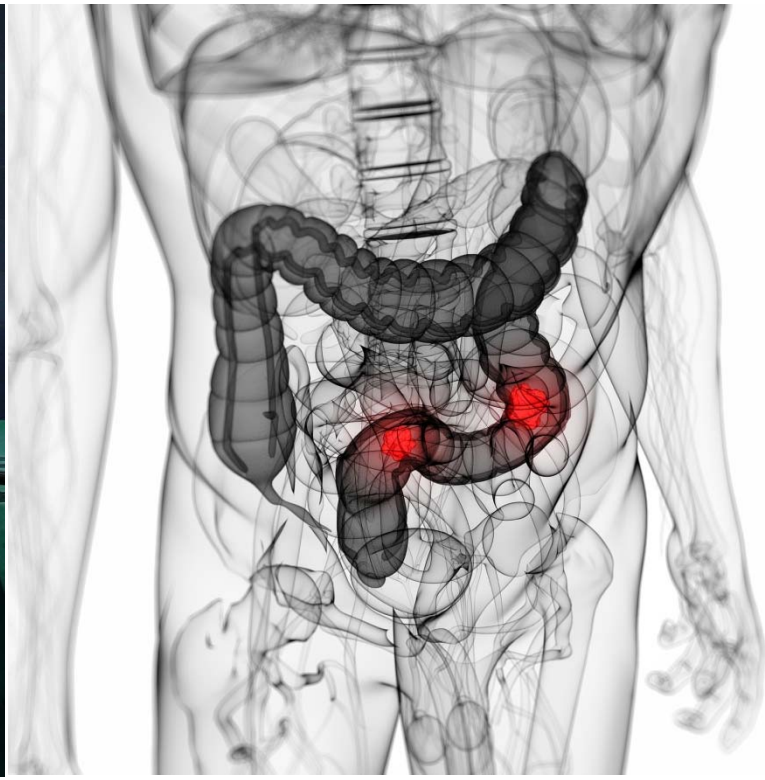
KCE REPORT 218S

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

COLON CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

APPENDIX



KCE REPORT 218S
GOOD CLINICAL PRACTICE

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COLON CANCER: DIAGNOSIS, TREATMENT AND FOLLOW-UP

APPENDIX

MARC PEETERS, ROOS LEROY, JO ROBAYS, GIGI VEEREMAN, DIDIER BIELEN, WIM CEELEN, ETIENNE DANSE, MARC DE MAN, PIETER DEMETTER, PATRICK FLAMEN, ALAIN HENDLISZ, ISABELLE SINAPI, DIRK VANBECKEVOORT, ERIC VAN CUTSEM, DIRK YSEBAERT, PAUL VAN GILS, LAETITIA VEERBEEK, YOLBA SMIT, LEEN VERLEYE

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COLOPHON

Title :	Colon cancer: diagnosis, treatment and follow-up - Appendix
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	Participation in scientific or experimental research as an initiator, principal investigator or researcher: Patrick Flamen, Alain Hendlisz (Principal Investigator PePiTA trial), Marc Peeters (Amgen, Merck Serono), Cornelis Van de Velde (different colorectal trials) Further, it should be noted that all experts and stakeholders, as well as the validators consulted within this report were selected because of their expertise in the field of colon cancer. Therefore, by definition, all consulted experts, stakeholders and validators have a certain degree of conflict of interest to the main topic of this report.
Layout :	Ine Verhulst

Disclaimer :	• **The external experts were consulted about a (preliminary) version of the scientific report. Their comments were discussed during meetings. They did not co-author the scientific report and did not necessarily agree with its content.** • **Subsequently, a (final) version was submitted to the validators. The validation of the report results from a consensus or a voting process between the validators. The validators did not co-author the scientific report and did not necessarily all three agree with its content.** • **Finally, this report has been approved by common assent by the Executive Board.** • **Only the KCE is responsible for errors or omissions that could persist. The policy recommendations are also under the full responsibility of the KCE**
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This document is available on the website of the Belgian Health Care Knowledge Centre

■ APPENDIX REPORT

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1. SEARCH STRATEGIES

1.1. Search for guidelines

Table 1 – Search results - Guidelines on colorectal cancer

Database	# of hits
OVID Medline	305
National Guideline Clearing House	58
G-I-N	8

After removal of duplicate guidelines, 32 guidelines were selected based on title and abstract and retained for full-text evaluation. Of these, 21 guidelines were excluded for the following reasons (see Table 3):

- 15 guidelines were excluded as there was no systematic review of evidence
- 4 guidelines were excluded because of unclear or insufficient methodology
- 1 guideline was a summary of other guidelines
- 1 guideline was the report of an update

Finally, 11 guidelines were retained for an evaluation of the methodological quality.

1.2. Search strategy –PET-CT

Date	6 November 2012
Database	Medline, Medline in progress (via Pubmed)
Search Strategy	Limited to English and published from 2006 onwards: ((deoxyglucose OR desoxyglucose OR deoxy-glucose OR desoxy-glucose OR deoxy-d-glucose OR desoxy-d-glucose OR 2deoxyglucose OR 2deoxy-d-glucose OR fluorodeoxyglucose OR fluorodesoxyglucose OR fludeoxyglucose OR fluordeoxyglucose OR fluordesoxyglucose OR 18fluorodeoxyglucose OR 18fluorodesoxyglucose OR 18fluordeoxyglucose OR fdg* OR 18fdg* OR 18f-dg* OR fluorodeoxyglucose) OR ((fluor OR 2fluor* OR fluoro OR fluorodeoxy OR fludeoxy OR fluorine OR 18f OR 18flu*) AND glucose) AND (*emission AND *tomograph*)) OR *pet$CT* OR (pet AND ct) OR (pet AND cts) OR (*emission AND computed*) OR "Positron-Emission Tomography and Computed Tomography"[Majr] AND "Colorectal Neoplasms/diagnosis"[Mesh] OR "Colorectal Neoplasms/radionuclide imaging"[Mesh] OR ((colorectal OR colon OR colonic OR rectal OR rectum OR rectosigmoid) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*)) AND ("Neoplasm Metastasis/diagnosis"[Mesh] OR "Neoplasm Metastasis/radionuclide imaging"[Mesh] OR metastases OR metastasis OR metastatic OR ((dissemination OR spread OR secondary OR migration) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*)) Run with (13 citations) and without (547 citations) systematic review filter: (“meta-analysis” [pt] OR “meta-anal*” [tw] OR

	"metaanal*" [tw] OR ("quantitativ* review*" [tw] OR "quantitative* overview*" [tw]) OR ("systematic* review*" [tw] OR "systematic* overview*" [tw]) OR ("methodologic* review*" [tw] OR "methodologic* overview*" [tw]) OR ("review" [pt] AND "medline" [tw])

Date	**6 November 2012**
Database	Embase (via Ovid)
Search Strategy	1. colorectal cancer/di [Diagnosis] (10972) 2. (colorectal or colon or colonic or rectal or rectum or rectosigmoid).tw. (325370) 3. (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplasm*).tw. (2513593) 4. 2 and 3 (197545) 5. 1 or 4 (199664) 6. animals/ not humans/ (1353739) 7. 5 not 6 (198030) 8. 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. or Fluorodeoxyglucose F18/ (50039) 9. (fluor or 2fluor* or fluoro or fluorodeoxy or fludeoxy or fluorine or 18f or 18flu*).tw. (46303) 10. glucose.tw. (375377) 11. 9 and 10 (7733) 12. 8 or 11 (50569) 13. (pet or petscan* or pet-ct or pet$ct).tw. or tomography, emission-computed/ (74901) 14. emission.tw. (117756) 15. (tomograph or tomographs or tomographic* or tomography or tomographies).tw. (264951) 16. 14 and 15 (54183) 17. 13 or 16 (99788) 18. 12 or 17 (119739) 19. Positron-Emission Tomography/ (71235) 20. 18 or 19 (138529) 21. animals/ not humans/ (1353739) 22. 20 not 21 (134342) 23. metastasis/di [Diagnosis] (12298) 24. (metastasis or metastases or metastasic or metastatic or dissemination or spread or secondary or migration).tw. (1097790) 25. 23 or 24 (1100863) 26. animals/ not humans/ (1353739) 27. 25 not 26 (1064363) 28. exp Meta Analysis/ (66972) 29. ((meta adj analy$) or metaanalys$).tw. (62030) 30. (systematic adj (review$1 or overview$1)).tw. (47947) 31. or/28-30 (123426) 32. cancerlit.ab. (664) 33. cochrane.ab. (28402) 34. embase.ab. (25238) 35. (psychlit or psyclit).ab. (957) 36. (psychinfo or psycinfo).ab. (6273) 37. (cinahl or cinhal).ab. (8640)

	38. science citation index.ab. (1893) 39. bids.ab. (422) 40. or/32-39 (43207) 41. reference lists.ab. (8561) 42. bibliograph$.ab. (13799) 43. hand-search$.ab. (3946) 44. manual search$.ab. (2262) 45. relevant journals.ab. (722) 46. or/41-45 (26436) 47. data extraction.ab. (10540) 48. selection criteria.ab. (19316) 49. 47 or 48 (28500) 50. review.pt. (1908548) 51. 49 and 50 (17044) 52. letter.pt. (804422) 53. editorial.pt. (419609) 54. animal/ (1808580) 55. human/ (13873115) 56. 54 not (54 and 55) (1353739) 57. or/52-53,56 (2564152) 58. 31 or 40 or 46 or 51 (154334) 59. 58 not 57 (148528) 60. 7 and 22 and 27 and 59 (46) 61. limit 60 to (english language and yr="2006 - Current") (36)
Notes	Also performed without SR filter

Date	6 November 2012
Database	Cochrane Library
Search Strategy	The Cochrane Database of Systematic Reviews was browsed by topic: 1. cancer ->

1.3. Search strategy – MRI liver

Date	15 May 2013
Database	Ovid MEDLINE(R) and PreMedline
Search Strategy	1. exp colorectal neoplasm/ (139087) 2. (colo$ adj5 cancer$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (82789) 3. (colo$ adj5 neoplasm$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (110828) 4. (colo$ adj5 carcin$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (35593) 5. (colo$ adj 5 tumo$).mp. (0) 6. (colo$ adj5 malign$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4748) 7. (colo$ adj5 metast$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol

	supplementary concept, rare disease supplementary concept, unique identifier] (16186) 8. exp neoplasm metastasis/ (148191) 9. (Metasta$ adj3 liver$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (19508) 10. (metasta$ adj3 hepa$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (9583) 11. exp Liver Neoplasms/ (119161) 12. *Liver Neoplasm/sc (9294) 13. 1 or 2 or 3 or 4 or 5 or 6 or 7 (168986) 14. 8 or 9 or 10 or 11 or 12 (262431) 15. 13 and 14 (25853) 16. exp Magnetic Resonance Imaging/mt [Methods] (75858) 17. magnetic.mp. (502108) 18. resonance.mp. (526612) 19. 16 or 17 or 18 (563161) 20. 15 and 19 (921) 21. Meta-Analysis/ (40156) 22. meta analy$.tw. (46497) 23. metaanaly$.tw. (1175) 24. meta analysis.pt. (40156) 25. (systematic adj (review$1 or overview$1)).tw. (37862) 26. exp Review Literature/ (1790824) 27. or/21-26 (1826741)
	28. cochrane.ab. (22318) 29. embase.ab. (20240) 30. science citation index.ab. (1613) 31. or/28-30 (30234) 32. reference list$.ab. (7865) 33. bibliograph$.ab. (10044) 34. hand-search$.ab. (3235) 35. relevant journals.ab. (580) 36. manual search$.ab. (1897) 37. or/32-36 (21117) 38. selection criteria.ab. (16859) 39. data extraction.ab. (7938) 40. 38 or 39 (23430) 41. review.pt. (1787364) 42. 40 and 41 (16464) 43. comment.pt. (499249) 44. letter.pt. (772324) 45. editorial.pt. (315959) 46. animal/ (5156601) 47. human/ (12878801) 48. 46 not (46 and 47) (3753959) 49. or/43-45,48 (4887356) 50. 27 or 31 or 37 or 42 (1831839) 51. 50 not 49 (1675362) 52. 20 and 51 (147) 53. limit 52 to yr="2011 -Current" (24)
Notes	Similar strategy used for EMBASE

Date	15 May 2013
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees #2 MeSH descriptor: [Liver Neoplasms] explode all trees #3 "metastasis":ti,ab,kw (Word variations have been searched) #4 #2 or #3 #5 MeSH descriptor: [Magnetic Resonance Imaging] explode all trees #6 #1 and #4 and #5

1.4. Search strategy – Pathology

Date	20 July 2013
Database	Medline through OVID
Search Strategy	1 lynch syndrome.mp. or exp Colorectal Neoplasms, Hereditary Nonpolyposis/ (3708) 2 (MLH1 or MSH2 or MSH3 or MSH6 or hMSH2 or hMSH1 or hPMS1 or hPMS2 or hMSH6 or hMLH3 or PMS1 or PMS2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (5820) 3 HNPCC.mp. (2042) 4 (lynch$ adj3 syndrome).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1252) 5 ((lynch$ adj3 famil$) and (cancer$ or neoplasm$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (217) 6 hereditary non-polyposis Colorectal Cancer.mp. (877) 7 hereditary nonpolyposis Colorectal Cancer.mp. (1432) 8 (hereditary adj3 nonpolyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4011) 9 (hereditary adj3 non-polyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1140) 10 (familial adj3 nonpolyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (15) 11 (familial adj3 non-polyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (20) 12 (colon or colorectal or lynch$ or HNPCC or hereditary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (276022) 13 2 and 12 (3158) 14 1 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 13 (5863)

15 microsatellite instability.mp. or exp Microsatellite Instability/ (5546)

16 exp Genetic Testing/ or genetic test.mp. or exp Government Regulation/ or exp Genetic Predisposition to Disease/ (129253)

17 15 or 16 (134240)

18 14 and 17 (3021)

19 lynch syndrome.mp. or exp Colorectal Neoplasms, Hereditary Nonpolyposis/ (3708)

20 (MLH1 or MSH2 or MSH3 or MSH6 or hMSH2 or hMSH1 or hPMS1 or hPMS2 or hMSH6 or hMLH3 or PMS1 or PMS2).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (5820)

21 HNPCC.mp. (2042)

22 (lynch$ adj3 syndrome).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1252)

23 ((lynch$ adj3 famil$) and (cancer$ or neoplasm$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (217)

24 hereditary non-polyposis Colorectal Cancer.mp. (877)

25 hereditary nonpolyposis Colorectal Cancer.mp. (1432)

26 (hereditary adj3 nonpolyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4011)

27 (hereditary adj3 non-polyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1140)

28 (familial adj3 nonpolyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (15)

29 (familial adj3 non-polyposis).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (20)

30 (colon or colorectal or lynch$ or HNPCC or hereditary).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (276022)

31 20 and 30 (3158)

32 19 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 31 (5863)

33 colorectal neoplasm.mp. or Colorectal Neoplasms/ (56700)

34 exp Proto-Oncogene Proteins B-raf/ or BRAF.mp. (4566)

35 33 and 34 (854)

36 exp ras Proteins/ (16022)

37 KRAS.mp. (4560)

38 36 or 37 (17807)

39 33 and 38 (1661)

40 limit 39 to yr="2010 -Current" (1087)

Date	19 July 2013
Database	Embase
Search Strategy	#18. 'microsatellite instability'/exp AND 'colorectal cancer'/exp AND ('genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp) #17. 'hereditary nonpolyposis colorectal cancer'/exp AND ('genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp) #16. 'genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp #15. 'nucleotide sequence'/exp #14. 'molecular diagnosis'/exp #13. 'gene amplification'/exp #12. 'gene mutation'/exp #11. 'genetic screening'/exp #10. 'genetic predisposition'/exp #9. 'hereditary nonpolyposis colorectal cancer'/exp OR ('microsatellite instability'/exp AND 'colorectal cancer'/exp) #8. 'microsatellite instability'/exp AND 'colorectal cancer'/exp #7. 'colorectal cancer'/exp #4. 'microsatellite instability'/exp #2. 'hereditary nonpolyposis colorectal cancer'/exp

Date	19 July 2013
Database	Embase
Search Strategy	#4. 'colon cancer'/exp AND 'b raf kinase'/exp 1,181 30 Jul 2013 #3. 'b raf kinase'/exp 5,090 30 Jul 2013 #2. 'colon cancer'/exp 147,583 30 Jul 2013

Date	19 July 2013
Database	Embase
Search Strategy	#18. 'microsatellite instability'/exp AND 'colorectal cancer'/exp AND ('genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp) 1,602 19 Jul 2013 #17. 'hereditary nonpolyposis colorectal cancer'/exp AND ('genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp) 1,022 19 Jul 2013 #16. 'genetic predisposition'/exp OR 'genetic screening'/exp OR 'gene mutation'/exp OR 'gene amplification'/exp OR 'molecular diagnosis'/exp OR 'nucleotide sequence'/exp 1,213,958 19 Jul 2013 #15. 'nucleotide sequence'/exp 412,959 19 Jul 2013 #14. 'molecular diagnosis'/exp 4,057

	19 Jul 2013
	#13. 'gene amplification'/exp 522,981 19 Jul 2013
	#12. 'gene mutation'/exp 402,152 19 Jul 2013
	#11. 'genetic screening'/exp 41,339 19 Jul 2013
	#10. 'genetic predisposition'/exp 77,209 19 Jul 2013
	#9. 'hereditary nonpolyposis colorectal cancer'/exp 4,107 19 Jul 2013
	OR ('microsatellite instability'/exp AND 'colorectal cancer'/exp)
	#8. 'microsatellite instability'/exp AND 'colorectal 2,512 19 Jul 2013
	cancer'/exp
	#7. 'colorectal cancer'/exp 72,385 19 Jul 2013
	#4. 'microsatellite instability'/exp 6,831 19 Jul 2013
	#2. 'hereditary nonpolyposis colorectal cancer'/exp 1,870 19 Jul 2013

Study	Reason for exclusion
Heald et al, 2013	Mix of strategies used over time, results of MSI and IPH testing not reported separately, no family history so Bethesda or othe criteria could not be evaluated.
Van Lier, 2013	results of MSI and IPH testing not reported separately, no family history so Bethesda or othe criteria could not be evaluated.
jerz et al 2013	MSI not consecutive, MSI or IPH, not in paralell
Schofield 2013	only 2/3 of MSI/IHP suspected BRAF negative patients was tested for germline mutation.
Musulen 2012	only abstract available

1.5. Search strategy - Endoscopic treatment stage I

Date	19 November 2012
Database	Medline via OVID
	1. exp Colorectal Neoplasms/ (136562)
	2. exp colonic polyps/ (5743)
	3. (colo$ adj5 polyp$).tw. (9718)
	4. (colo$ adj5 cancer$).tw. (80319)
	5. (colo$ adj5 carcin$).tw. (33009)
	6. (colo$ adj5 neoplas$).tw. (5403)
	7. (colo$ adj5 tumo$).tw. (22774)
	8. (colo$ adj5 metasta$).tw. (15729)
	9. (colo$ adj5 malig$).tw. (4658)
	10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (172858)
	11. exp Endoscopy, Gastrointestinal/ (61242)
	12. endoscop$.mp. (147182)
	13. colonoscop$.mp. (23002)
	14. sigmoidoscop$.mp. (5947)
	15. (colo$ adj5 polyp$ adj5 resect$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (300)
	16. (colo$ adj5 polyp$ adj5 surg$).mp. (226)
	17. (colo$ adj5 polyp$ adj5 excis$).mp. (66)

18. polypectomy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2945)
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (177694)
20. 10 and 19 (19119)
21. exp Colectomy/ (13791)
22. exp laparotomy/ (14832)
23. exp Laparoscopy/ (62311)
24. colectomy.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (14773)
25. colon/su (7430)
26. rectum/su (7925)
27. colonic polyps/su (1759)
28. Colorectal Neoplasms/su (7259)
29. (colo$ adj5 resect$).mp. (10863)
30. (colo$ adj5 surg$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (15434)
31. (colo$ adj5 excis$).mp. (815)
32. (colo$ adj5 remov$).mp. (2992)
33. (surg$ adj5 manag$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (46128)
34. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (164008)
35. exp watchful waiting/ (615)
36. 34 or 35 (164576)
37. 20 and 36 (5515)
38. exp animals/ not humans.sh. (3809969)
39. 37 not 38 (5473)
40. limit 39 to yr="2009 -Current" (1231)
41. meta-analysis/ (37760)
42. metaanaly$.tw. (1128)
43. meta analy$.tw. (43632)
44. meta analysis.pt. (37760)
45. (systematic adj (review$ or overview$)).tw. (35388)
46. exp review literature/ (1759349)
47. 41 or 42 or 43 or 44 or 45 or 46 (1793295)
48. 40 and 47 (156)

Date	5 December 2012
Database	Premedline via Ovid

1. Colorectal Neoplasms.mp (26)
2. colonic polyps.mp (49)
3. (colo$ adj5 polyp$).tw. (447)
4. (colo$ adj5 cancer$).tw. (4784)
5. (colo$ adj5 carcin$).tw. (1243)
6. (colo$ adj5 neoplas$).tw. (240)
7. (colo$ adj5 tumo$).tw. (978)
8. (colo$ adj5 metasta$).tw. (974)
9. (colo$ adj5 malig$).tw. (272)
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (6416)
11. Endoscopy, Gastrointestinal.mp (0)
12. endoscop$.mp . (6833)

13. colonoscop$.mp . (1073)
14. sigmoidoscop$.mp . (136)
15. (colo$ adj5 polyp$ adj5 resect$).mp (16)
16. (colo$ adj5 polyp$ adj5 surg$).mp . (11)
17. (colo$ adj5 polyp$ adj5 excis$).mp . (2)
18. polypectomy.mp (133)
19. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 (7639)
20. 10 and 19 (738)
21. Colectomy.mp (381)
22. laparotomy.mp (1651)
23. Laparoscopy.mp (1074)
24. colectomy.mp (381)
25. colon, surgery.mp (23)
26. rectum, surgery.mp (2)
27. colonic polyps, surgery.mp (0)
28. Colorectal Neoplasms, surgery.mp (0)
29. (colo$ adj5 resect$).mp . (576)
30. (colo$ adj5 surg$).mp (802)
31. (colo$ adj5 excis$).mp . (60)
32. (colo$ adj5 remov$).mp . (214)
33. (surg$ adj5 manag$).mp (3041)
34. 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 (7024)
35. watchful waiting.mp (102)
36. 34 or 35 (7122)
37. 20 and 36 (169)
38. meta-analysis.mp (3951)
39. metaanaly$.tw. (79)
40. meta analy$.tw. (4677)
41. meta analysis.pt. (31)
42. (systematic adj (review$ or overview$)).tw. (5094)
43. review literature.mp (53)
44. 38 or 39 or 40 or 41 or 42 or 43 (8364)
45. randomized controlled trial.pt. (471)
46. controlled clinical trial.pt. (22)
47. randomized.ab. (14505)
48. placebo.ab. (5581)
49. randomly.ab. (13885)
50. trial.ab. (15159)
51. groups.ab. (79716)
52. 45 or 46 or 47 or 48 or 49 or 50 or 51 (105211)
53. 44 or 52 (110852)
54. 37 and 53 (21)

Note: The search for systematic reviews, meta-analyses and randomized controlled trials (RCTs) was performed simultaneously in PreMedline

Date	19 November 2012
Database	EMBASE via Embase.com
Search Strategy	'large intestine cancer'/exp OR 'colon polyp'/exp OR colo* NEAR/5 (polyp* OR cancer* OR carcin* OR neopla* OR tumo* OR metasta* OR malig*) AND 'digestive tract endoscopy'/exp OR endoscop* OR colonoscop* OR sigmoidoscop* OR (colo* AND polyp* NEAR/5 resect*) OR (colo* AND polyp* NEAR/5 remov*) OR (colo* AND polyp* NEAR/5 surg*) OR (colo* AND polyp* NEAR/5 excis*) OR polypectomy AND ('intestine resection'/exp OR 'laparotomy'/exp OR 'laparoscopy'/exp OR colectomy OR (intestine AND resection) OR 'colon surgery'/exp OR 'rectum

	surgery'/exp OR 'colon polyp'/exp/dm_su OR 'large intestine tumor'/exp/dm_su OR colo* NEAR/5 resect* OR colo* NEAR/5 surg* OR colo* NEAR/5 excis* OR colo* NEAR/5 remov* OR surg* NEAR/5 manag* OR 'watchful waiting'/exp) AND [humans]/lim AND [2009-2013]/py AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim)

Date	**19 November 2012**
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees #2 MeSH descriptor: [Intestinal Polyps] explode all trees #3 #1 or #2 #4 MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees #5 endoscop* #6 colonoscop* #7 sigmoidoscop* #8 polypectomy #9 (colo* adj5 polyp*) adj5 (surg* or excis* or remov* or resect*) #10 #4 or #5 or #6 or #7 or #8 or #9 #11 #3 and #10 #12 MeSH descriptor: [Colectomy] explode all trees #13 MeSH descriptor: [Laparotomy] explode all trees #14 MeSH descriptor: [Laparoscopy] explode all trees #15 colectomy #16 MeSH descriptor: [Colon] explode all trees and with qualifiers: [Surgery - SU] #17 MeSH descriptor: [Rectum] explode all trees and with qualifiers: [Surgery - SU] #18 MeSH descriptor: [Colonic Polyps] explode all trees and with qualifiers: [Surgery - SU] #19 MeSH descriptor: [Colorectal Neoplasms] explode all trees and with qualifiers: [Surgery - SU] #20 (colo* or rect*) adj5 (surg* or excis* or remov* or resect*) #21 surg* adj5 manag* #22 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 #23 MeSH descriptor: [Watchful Waiting] explode all trees #24 #22 or #23 #25 #11 and #24 from 2009 to 2012

Date	**19 December 2012**
Database	Medline via OVID
	1. exp Colorectal Neoplasms/ (136731) 2. exp colonic polyps/ (5748) 3. (colo$ adj5 polyp$).tw. (9725) 4. (colo$ adj5 cancer$).tw. (80453) 5. (colo$ adj5 carcin$).tw. (33026) 6. (colo$ adj5 neoplas$).tw. (5406) 7. (colo$ adj5 tumo$).tw. (22794)

8. (colo$ adj5 metasta$).tw. (15751)
9. (colo$ adj5 malig$).tw. (4661)
10. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (173076)
11. exp Endoscopy, Gastrointestinal/ (61323)
12. endoscop$.mp. (147390)
13. colonoscop$.mp. (23047)
14. sigmoidoscop$.mp. (5955)
15. (colo$ adj5 polyp$ adj5 resect$).mp. (302)
16. (colo$ adj5 polyp$ adj5 surg$).mp. (226)
17. (colo$ adj5 polyp$ adj5 excis$).mp. (66)
18. polypectomy.mp. (2946)
19. colonic polyps/su (1762)
20. 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (178291)
21. 10 and 20 (19499)
22. exp animals/ not humans.sh. (3812817)
23. 21 not 22 (19344)
24. limit 23 to yr="2011 -Current" (2131)
25. limit 24 to dutch (6)
26. limit 24 to english (1922)
27. limit 24 to french (10)
28. limit 24 to german (30)
29. 25 or 26 or 27 or 28 (1968)
30. exp Colorectal Neoplasms/ (136731)
31. exp colonic polyps/ (5748)
32. (colo$ adj5 polyp$).tw. (9725)
33. (colo$ adj5 cancer$).tw. (80453)
34. (colo$ adj5 carcin$).tw. (33026)
35. (colo$ adj5 neoplas$).tw. (5406)
36. (colo$ adj5 tumo$).tw. (22794)
37. (colo$ adj5 metasta$).tw. (15751)
38. (colo$ adj5 malig$).tw. (4661)
39. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 (173076)
40. *Endoscopy, Gastrointestinal/ (6780)
41. endoscop$.mp. (147390)
42. colonoscop$.mp. (23047)
43. sigmoidoscop$.mp. (5955)
44. (colo$ adj5 polyp$ adj5 resect$).mp. (302)
45. (colo$ adj5 polyp$ adj5 surg$).mp. (226)
46. (colo$ adj5 polyp$ adj5 excis$).mp. (66)
47. polypectomy.mp. (2946)
48. colonic polyps/su (1762)
49. 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 (166610)
50. 39 and 49 (19092)
51. exp animals/ not humans.sh. (3812817)
52. 50 not 51 (18940)
53. limit 52 to yr="2011 -Current" (2099)
54. limit 53 to english (1894)
55. limit 53 to french (10)
56. limit 53 to german (28)
57. limit 53 to dutch (6)
58. 54 or 55 or 56 or 57 (1938)

Note: This search was simultaneously performed in PreMedline

Date	19 December 2012
Database	EMBASE via Embase.com
Search Strategy	'large intestine cancer'/exp OR 'colon polyp'/exp OR colo* NEAR/5 (polyp* OR cancer* OR carcin* OR neopla* OR tumo* OR metasta* OR malig*) AND ('digestive tract endoscopy'/exp OR endoscop* OR colonoscop* OR sigmoidoscop* OR (colo* AND polyp* NEAR/5 (resect* OR remov* OR surg*)) OR 'polypectomy'/exp OR 'colon polyp'/exp/dm_su) AND 'human'/de AND (2011:py OR 2012:py OR 2013:py) AND ('case control study'/de OR 'clinical article'/de OR 'clinical trial'/de OR 'cohort analysis'/de OR 'comparative study'/de OR 'control group'/de OR 'controlled study'/de OR 'cross-sectional study'/de OR 'diagnostic test accuracy study'/de OR 'intermethod comparison'/de OR 'major clinical study'/de OR 'medical record review'/de OR 'practice guideline'/de OR 'prospective study'/de OR 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de OR 'retrospective study'/de OR 'systematic review'/de) Results: 2733

Date	21 December 2012
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees #2 MeSH descriptor: [Intestinal Polyps] explode all trees #3 #1 or #2 #4 MeSH descriptor: [Endoscopy, Gastrointestinal] explode all trees #5 endoscop* #6 colonoscop* #7 sigmoidoscop* #8 polypectomy #9 colonic polyps, surgery #10 (colo* adj5 polyp*) adj5 (surg* or excis* or remov* or resect*) #11 #4 or #5 or #6 or #7 or #8 or #9 or #10 #12 #3 and #11 from 2011 to 2012

1.6. Search strategy - Laparotomy vs. laparoscopy; single vs. multiple port laparoscopy; robot assisted vs. standard laparoscopy

Date	22 March 2013
Database	Medline via OVID
	1. exp Colorectal Neoplasms/ (136758) 2. (colo$ adj5 cancer$).tw. (80340) 3. (colo$ adj5 carcin$).tw. (32823) 4. (colo$ adj5 neoplas$).tw. (5380) 5. (colo$ adj5 tumo$).tw. (22657) 6. (colo$ adj5 metasta$).tw. (15785) 7. (colo$ adj5 malig$).tw. (4657) 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (169966) 9. exp Colectomy/mt (4448) 10. exp colorectal surgery/mt (493) 11. exp laparotomy/mt (2834) 12. Colonic Neoplasms/su (8819) 13. colon/su (7480) 14. colectomy.mp. (14925) 15. (colo$ adj5 (resect$ or excis$ or surg$ or remov$)).mp. (26857) 16. (surg$ adj5 manag$).mp. (46290) 17. sigmoid/su (2501) 18. exp laparoscopy/mt (21381) 19. robotics/mt (3125) 20. single incision.mp. (1107) 21. single port.mp. (674) 22. single site.mp. (5051) 23. single access.mp. (145) 24. multiport.mp. (203)
	25. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 (122767) 26. 8 and 25 (24829) 27. exp animals/ not humans.sh. (3782732) 28. 26 not 27 (24388) 29. meta-analysis/ (38252) 30. metaanaly$.tw. (1142) 31. meta analy$.tw. (44298) 32. meta analysis.pt. (38252) 33. (systematic adj (review$ or overview$)).tw. (36068) 34. (review adj5 literature).mp. (147565) 35. exp review literature/ (1759617) 36. 29 or 30 or 31 or 32 or 33 or 34 or 35 (1845983) 37. 28 and 36 (3272) 38. limit 37 to yr="2008 -Current" (770)
Comment	The same search was used in premedline (retrieval of 48 references)

Date	22 March 2013
Database	EMBASE via Embase.com
Search Strategy	'large intestine cancer'/exp OR (colo* NEAR/5 neoplasm* OR cancer* OR tumor* OR malig* OR metast* OR carcin*) AND 'colon resection'/exp OR 'colorectal surgery'/exp OR 'laparotomy'/exp OR colonic AND 'cancer'/exp OR 'colectomy'/exp OR colo* NEAR/5 (resect* OR excis* OR surg* OR remov*) OR surg* NEAR/5 manag* OR 'sigmoid'/exp OR 'laparoscopy'/exp OR 'robotics'/exp

	OR single AND 'incision'/exp OR single AND port OR single AND site OR single AND access OR multiport AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [humans]/lim AND [embase]/lim AND [2008-2013]/py
	Number of references retrieved: 658

Date	**22 March 2013**
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees #2 colo* adj5 (cancer* or carcin* or neoplas* or tumo* or malig*) #3 #1 or #2 #4 MeSH descriptor: [Colectomy] explode all trees and with qualifiers: [Methods - MT] #5 MeSH descriptor: [Colorectal Surgery] explode all trees and with qualifiers: [Methods - MT] #6 MeSH descriptor: [Laparotomy] explode all trees and with qualifiers: [Methods - MT] #7 MeSH descriptor: [Colonic Neoplasms] explode all trees and with qualifiers: [Surgery - SU] #8 MeSH descriptor: [Colon] explode all trees and with qualifiers: [Surgery - SU] #9 colectomy #10 colo* adj5 (resect* or excis* or surg* or remov*) #11 surg* adj5 manag* #12 MeSH descriptor: [Colon, Sigmoid] explode all trees and with qualifiers: [Surgery - SU] #13 MeSH descriptor: [Laparoscopy] explode all trees and with qualifiers: [Methods - MT] #14 MeSH descriptor: [Robotics] explode all trees and with qualifiers: [Methods - MT] #15 single incision #16 single port #17 single site #18 single access #19 multiport #20 #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 #21 #3 and #20 #22 #21 from 2008 to 2013, in Cochrane Reviews (Reviews and Protocols) (Word variations have been searched)
	Number of references retrieved: 199

1.7. search strategy enhanced recovery programs

Date	November 2012
Database	Medline via Pubmed
Search Strategy	#1 Search colonic diseases[mh:noexp] OR colonic neoplasms[mh] OR colorectal neoplasms[mh] OR colonic[ti] OR colorectal[ti] OR colon carcinom*[ti] #2 Search surger*[ti] OR resection[ti] OR laparoscop*[ti] OR celioscop*[ti] OR peritoneoscop*[ti] OR laparoscopy[mh] OR surgery[sh] OR "surgical procedures, minimally invasive"[mh] #3 Search #1 AND #2 #4 Search colonic diseases/surgery[mh] OR colorectal neoplasms/surgery[mh] OR colonic neoplasms/surgery[mh] OR colorectal surgery[mh] OR colectom*[tiab] OR colectomy[mh] OR colonoscop*[tiab] OR colonoscopy[mh] OR colorectal surgery[tiab] OR colonic surgery[tiab] #5 Search #3 OR #4 #6 Search enhanced recovery[tiab] OR eras[tiab] OR (enhance*[tiab] AND recovery[tiab]) OR fast track[tiab] OR ft care[tiab] OR ft surgery[tiab] OR faster recovery[tiab] OR early recovery[tiab] OR multimodal perioperative care pathway*[tiab] #7 Search #5 AND #6 #8 Search "outcome and process assessment (health care)"[mh] OR "outcome assessment (health care)"[mh:noexp] OR "treatment outcome"[mh] OR "evaluation studies as topic"[mh] OR "program evaluation"[mh] OR "evaluation studies"[pt] #9 Search effectiveness[tiab] OR outcome*[tiab] OR versus[ti] OR adherence[ti] patient outcome[tiab] OR length of stay[tiab] OR patient discharge[tiab] OR recovery of function[tiab] OR patient readmission*[tiab] OR reoperation*[tiab] OR postoperative hospital stay[tiab] OR morbidity[tiab] OR postoperative pain[tiab] OR postoperative complications[tiab] OR in-hospital mortality[tiab] OR hospital mortality[tiab] OR "quality of life"[tiab] OR patient satisfaction[tiab] OR in-hospital costs[tiab] OR hospital costs[tiab] OR cost saving*[tiab] #10 Search length of stay[mh] OR patient discharge[mh] OR recovery of function[mh] OR patient readmission[mh] OR reoperation[mh] OR pain, postoperative[mh] OR postoperative care/adverse effects[mh] OR postoperative care/mortality[mh] OR postoperative complications[mh] OR hospital mortality[mh] OR hospital costs[mh] OR health care costs[tiab] OR morbidity[mh] OR patient satisfaction[mh] OR "quality of life"[mh] OR "quality adjusted life years"[mh] OR cost savings[mh] #11 Search (((randomized[tiab] OR randomised[tiab] OR controlled[tiab]) AND (study[tiab] OR studies[tiab] OR trial*[tiab])) OR "randomized controlled trial"[pt] OR "controlled clinical trial"[pt] OR "randomized controlled trials as topic"[mh] OR "controlled clinical trials as topic"[mh] OR review[pt] OR meta-analysis[pt] OR review literature as topic[mh] OR metaanalysis as topic[mh] OR review[tiab] OR meta analysis[tiab]) #12 Search #7 AND (#8 OR #9 OR #10 OR #11) #13 Search 2010:2013[dp] AND english[la] #14 Search #12 AND #13 #15 Search "2012/11/22 00.00"[EDAT]:"2012/12/11 06.07"[EDAT] #16 Search #14 NOT #15

Date	November 2012
Database	Embase SciSearch
Search Strategy	1 62698800 ME90; EM90; IS74 2 352036 CT=COLONIC DISEASES OR CT D (COLONIC NEOPLASMS;COLORECTAL NEOPLASMS;COLORECTAL CARCINOMA; COLON CARCINOMA;COLON CANCER;COLORECTAL CANCER) OR FT=(COLONIC;COLORECTAL;COLON CARCINOM*;COLON NEOPLASM*)/TI 3 2982577 FT=(SURGER*;RESECTION;LAPAROSCOP*;CELIOSCOP*;PERITONEOSCOP*) /(TI;CT;UT) OR CT=(LAPAROSCOPY;"SURGICAL PROCEDURES, MINIMALLY INVASIVE";SURGERY) OR QF=SU 4 78611 2 AND 3 5 46860 CT=COLONIC DISEASES/QF=SU OR CT D (COLORECTAL NEOPLASMS;COLORECTAL CARCINOMA; COLON CARCINOMA;COLONIC NEOPLASMS;COLON CANCER;COLORECTAL CANCER)/QF=SU 6 82844 CT=(COLORECTAL SURGERY;COLECTOMY;COLONOSCOPY;COLON SURGERY) OR FT=(COLECTOM*;COLONOSCOP*;COLORECTAL SURGER*;COLONIC SURGERY)/TI 7 138052 4 OR 5 OR 6 8 79832 FT=(ENHANCED RECOVERY;ERAS;FAST TRACK;FT CARE;FT SURGERY;FASTER RECOVERY;EARLY RECOVERY;MULTIMODAL PERIOPERATIVE CARE PATHWAY*)/(TI;AB;CT;UT) OR (FT=ENHANCE*/(TI;AB) AND FT=RECOVERY/(TI;AB)) 9 1261 7 AND 8 10 1800243 CT=("OUTCOME AND PROCESS ASSESSMENT (HEALTH CARE)";"OUTCOME ASSESSMENT (HEALTH CARE)";OUTCOME ASSESSMENT;TREATMENT OUTCOME;"EVALUATION STUDIES AS TOPIC";PROGRAM EVALUATION) OR DT=EVALUATION STUDIES 11 4551674 FT=(EFFECTIVENESS;OUTCOME*;PATIENT OUTCOME;LENGTH OF STAY;PATIENT DISCHARGE;RECOVERY OF FUNCTION;PATIENT READMISSION*;REOPERATION*;POSTOPERATIVE HOSPITAL STAY;MORBIDITY;POSTOPERATIVE PAIN;POSTOPERATIVE COMPLICATIONS)/(TI;AB;CT;UT) 12 1090824 FT=(IN-HOSPITAL MORTALITY;HOSPITAL MORTALITY;"QUALITY OF LIFE";PATIENT SATISFACTION;IN-HOSPITAL COSTS;HOSPITAL COSTS;COST AVING*)/(TI;AB;CT;UT) OR FT=(VERSUS;ADHERENCE)/TI 13 903880 CT=(LENGTH OF STAY;PATIENT DISCHARGE;RECOVERY OF FUNCTION;PATIENT READMISSION;REOPERATION;PAIN, POSTOPERATIVE;POSTOPERATIVE PAIN;POSTOPERATIVE COMPLICATIONS;POSTOPERATIVE COMPLICATION;HOSPITAL MORTALITY) 14 667562 CT=(HOSPITAL COSTS;HOSPITAL COST;HEALTH CARE COSTS;HEALTH CARE COST;MORBIDITY;PATIENT SATISFACTION;"QUALITY OF LIFE";"QUALITY ADJUSTED LIFE YEARS";QUALITY ADJUSTED LIFE YEAR;COST SAVINGS) 15 335 CT=POSTOPERATIVE CARE/QF=AE OR CT=POSTOPERATIVE CARE/QF=MO 16 1326735 FT=(RANDOMIZED;RANDOMISED;CONTROLLED)/(TI;AB) AND FT=(STUDY;STUDIES;TRIAL*)/(TI;AB) 17 439573 DT=(RANDOMIZED CONTROLLED TRIAL;CONTROLLED CLINICAL TRIAL) OR

	CT=("RANDOMIZED CONTROLLED TRIALS AS TOPIC";"CONTROLLED CLINICAL TRIALS AS TOPIC")
	18 5141353 (FT=(REVIEW;META ANALYSIS;META-ANALYSIS)/(TI;AB;CT;UT) OR DT=(REVIEW;SYSTEMATIC REVIEW;LITERATURE REVIEW;META-ANALYSIS)) NOT FT=CHART REVIEW/(TI;AB;CT;UT)
	19 1103 9 AND (10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18)
	20 941 19 AND LA=ENGLISH
	21 505 20 AND PY>2009
	22 291 check duplicates: unique in s=21
	23 190 22 AND BASE=ME90
	24 101 22 NOT 23

Date	November 2012
Database	Cochrane
Search Strategy	((enhanced recovery OR eras OR (enhance* AND recovery) OR (fast AND track) OR ft care OR ft surgery OR faster recovery OR early recovery OR multimodal perioperative care pathway*) AND (surger* OR resection or laparoscop*or celioscop* or peritoneoscol* OR surgical OR procedure) AND (colorectal OR colon* OR rectum OR sigmoid)) in title abstract keywords from 2010 to 2012

Date	November 2012
Database	Centre for Reviews and Dissemination
Search Strategy	((enhanced recovery OR eras OR fast track OR ft care OR ft surgery OR faster recovery OR |arly recovery OR multimodal perioperative care pathway*)) AND ((surger* OR resection or laparoscop*or celioscop* or peritoneoscol* OR surgical OR procedure)) AND ((colorectal OR colon* OR rectum OR sigmoid)) IN DARE, NHSEED, HTA FROM 2010 TO 2012

1.8. Search strategy – treatment of acute obstruction

Date	29 November 2012
Database	Medline, Medline in progress via Pubmed
Search Strategy	Searches limited to studies published in English, from 2005 onwards. Searched combined with a filter for systematic reviews and subsequently with a filter for RCTs. ("Colonic Neoplasms"[Mesh] OR ((colorectal OR colon OR colonic OR (large AND bowel)) AND (cancer* OR carcinoma* OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*)) AND ("Intestinal Obstruction"[Mesh] OR obstructi* OR ileus) SR filter (Hunt D, et al. Ann Intern Med 1997;126:532-538) ("meta-analysis" [pt] OR "meta-anal*" [tw] OR "metaanal*" [tw] OR ("quantitativ* review*" [tw] OR "quantitative* overview*" [tw]) OR ("systematic* review*" [tw] OR "systematic* overview*" [tw]) OR ("methodologic* review*" [tw] OR "methodologic* overview*" [tw]) OR ("review" [pt] AND "medline" [tw]) RCT filter (Cochrane Highly Sensitive Search Strategy for identifying randomized trials (2008)): (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals[mh] NOT (animals[mh] AND humans [mh]))

Date	21 February 2013
Database	Embase via Ovid
Search Strategy	Searches limited to studies published in English, from 2005 onwards. Searched combined with a filter for systematic reviews and subsequently with a filter for RCTs. SRs: 1. exp colon carcinoma/ (18324) 2. (colorectal or colon or colonic or (large and bowel)).tw. (267482) 3. (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplasm*).tw. (2570408) 4. 2 and 3 (172784) 5. 1 or 4 (177307) 6. animals/ not humans/ (1361665) 7. 5 not 6 (175812) 8. colon obstruction/ (1877) 9. (obstructi* or ileus).tw. (235760) 10. 8 or 9 (236365) 11. 7 and 10 (5170) 12. exp Meta Analysis/ (69041) 13. ((meta adj analy$) or metaanalys$).tw. (65160) 14. (systematic adj (review$1 or overview$1)).tw. (50578) 15. or/12-14 (128268) 16. cancerlit.ab. (669) 17. cochrane.ab. (29532) 18. embase.ab. (26616) 19. (psychlit or psyclit).ab. (960) 20. (psychinfo or psycinfo).ab. (6571) 21. (cinahl or cinhal).ab. (8974) 22. science citation index.ab. (1934) 23. bids.ab. (431) 24. or/16-23 (45254) 25. reference lists.ab. (8783) 26. bibliograph$.ab. (14034) 27. hand-search$.ab. (4059) 28. manual search$.ab. (2339) 29. relevant journals.ab. (738) 30. or/25-29 (27023) 31. data extraction.ab. (10792) 32. selection criteria.ab. (19622) 33. 31 or 32 (29057) 34. review.pt. (1934108) 35. 33 and 34 (17228) 36. letter.pt. (813971) 37. editorial.pt. (425841) 38. animal/ (1819017) 39. human/ (14105497) 40. 38 not (38 and 39) (1361665) 41. or/36-37,40 (2587772) 42. 15 or 24 or 30 or 35 (159908) 43. 42 not 41 (153986) 44. exp Meta Analysis/ (69041) 45. ((meta adj analy$) or metaanalys$).tw. (65160) 46. (systematic adj (review$1 or overview$1)).tw. (50578) 47. or/44-46 (128268) 48. cancerlit.ab. (669) 49. cochrane.ab. (29532)

50. embase.ab. (26616)
51. (psychlit or psyclit).ab. (960)
52. (psychinfo or psycinfo).ab. (6571)
53. (cinahl or cinhal).ab. (8974)
54. science citation index.ab. (1934)
55. bids.ab. (431)
56. or/48-55 (45254)
57. reference lists.ab. (8783)
58. bibliograph$.ab. (14034)
59. hand-search$.ab. (4059)
60. manual search$.ab. (2339)
61. relevant journals.ab. (738)
62. or/57-61 (27023)
63. data extraction.ab. (10792)
64. selection criteria.ab. (19622)
65. 63 or 64 (29057)
66. review.pt. (1934108)
67. 65 and 66 (17228)
68. letter.pt. (813971)
69. editorial.pt. (425841)
70. animal/ (1819017)
71. human/ (14105497)
72. 70 not (70 and 71) (1361665)
73. or/68-69,72 (2587772)
74. 47 or 56 or 62 or 67 (159908)
75. 74 not 73 (153986)
76. 11 and 75 (83)
77. limit 76 to (english language and yr="2005 - Current") (54)

RCTs:

1. exp colon carcinoma/ (18324)
2. (colorectal or colon or colonic or (large and bowel)).tw. (267482)
3. (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplasm*).tw. (2570408)
4. 2 and 3 (172784)
5. 1 or 4 (177307)
6. animals/ not humans/ (1361665)
7. 5 not 6 (175812)
8. colon obstruction/ (1877)
9. (obstructi* or ileus).tw. (235760)
10. 8 or 9 (236365)
11. 7 and 10 (5170)
12. Clinical trial/ (879907)
13. Randomized controlled trial/ (339995)
14. Randomization/ (60770)
15. Single blind procedure/ (17042)
16. Double blind procedure/ (115732)
17. Crossover procedure/ (36282)
18. Placebo/ (225894)
19. Randomi?ed controlled trial$.tw. (83949)
20. Rct.tw. (10968)
21. Random allocation.tw. (1253)
22. Randomly allocated.tw. (18609)
23. Allocated randomly.tw. (1889)
24. (allocated adj2 random).tw. (798)
25. Single blind$.tw. (13317)
26. Double blind$.tw. (140729)
27. ((treble or triple) adj blind$).tw. (329)
28. Placebo$.tw. (190592)

	29. Prospective study/ (226205) 30. or/12-29 (1328620) 31. Case study/ (18709) 32. Case report.tw. (248654) 33. Abstract report/ or letter/ (878046) 34. or/31-33 (1140437) 35. 30 not 34 (1292161) 36. 11 and 35 (431) 37. limit 36 to (english language and yr="2005 - Current") (243)

Date	29 November 2012
Database	The Cochrane Library
Search Strategy	The Cochrane Database of Systematic Reviews was browsed by topic: 1. cancer -> colorectal->surgery

1.9. Search strategy – adjuvant chemotherapy stage II colon cancer

Date	02 August 2013
Database	Medline & PreMedline (via OVID)
Search Strategy	1 exp Colonic Neoplasms/ (67813) 2 ((colorect$ or colo rect$) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (82714) 3 ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (85985) 4 1 or 2 or 3 (153411) 5 (high risk$ or high-risk$).tw. (156029) 6 (stage 2$ or stage II$).tw. (48746) 7 5 or 6 (202953) 8 4 and 7 (5828) 9 exp Antineoplastic Combined Chemotherapy Protocols/ (113651) 10 systemic treatment.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4958) 11 exp Chemotherapy, Adjuvant/ (30844) 12 adjuvant$ chemotherap$.tw. (15088)

	13 exp Fluorouracil/ (41426)
	14 (5-fluorouracil$ or 5-FU).tw. (29939)
	15 (leucovorin$ or LV$).tw. (58282)
	16 exp Leucovorin/ (8625)
	17 exp Levamisole/ (4056)
	18 levamisol$.tw. (4062)
	19 exp Cytotoxins/ (22127)
	20 cytotoxic drug$.tw. (6389)
	21 oxaliplatin.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (6622)
	22 bevacizumab.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (12609)
	23 cetuximab.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (5484)
	24 capecitabine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (5874)
	25 panitumumab.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (968)
	26 exp Antineoplastic Agents/ (843603)
	27 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (977432)
	28 exp Colon/su [Surgery] (10232)
	29 surgical resection$.tw. (27157)
	30 (resect$ adj5 colon$).tw. (5904)
	31 (post-operativ$ or post operativ$).tw. (37560)
	32 28 or 29 or 30 or 31 (78715)
	33 4 and 32 (6639)
	34 27 and 33 (1323)
	35 8 or 34 (6840)
	36 limit 35 to yr="2011" (629)

Date	**02 August 2013**
Database	Embase via Embase.com
Search Strategy	'large intestine cancer'/exp AND [2011-2014]/py OR (colo* NEAR/5 cancer AND [2011-2014]/py) OR (colo* NEAR/5 neoplas* AND [2011-2014]/py) OR (colo* NEAR/5 carcin* AND [2011-2014]/py) OR (colo* NEAR/5 tumo* AND [2011-2014]/py) OR (colo* NEAR/5 metasta* AND [2011-2014]/py) OR (colo* NEAR/5 malig* AND [2011-2014]/py) AND (high NEXT/1 risk* AND [2011-2014]/py OR ('high risk' AND [2011-2014]/py) OR (stage NEXT/1 2 OR stage NEXT/1 ii AND [2011-2014]/py)) OR ('adjuvant chemotherapy'/exp AND [2011-2014]/py OR (adjuvant* AND chemotherap* AND [2011-2014]/py) OR 'fluorouracil'/exp OR (5 NEXT/1 fluorouracil* OR 5 NEXT/1 fu* AND [2011-2014]/py) OR ('folic acid derivative'/exp AND [2011-2014]/py) OR (leucovorin* OR lv* AND [2011-2014]/py) OR ('levamisole'/exp AND

	[2011-2014]/py) OR (levamisol* AND [2011-2014]/py) OR (oxaliplatin AND [2011-2014]/py) OR (bevacizumab AND [2011-2014]/py) OR (cetuximab AND [2011-2014]/py) OR (capecitabine AND [2011-2014]/py) OR (panitumumab AND [2011-2014]/py) AND ('large intestine cancer'/exp AND [2011-2014]/py OR (colo* NEAR/5 cancer AND [2011-2014]/py) OR (colo* NEAR/5 neoplas* AND [2011-2014]/py) OR (colo* NEAR/5 carcin* AND [2011-2014]/py) OR (colo* NEAR/5 tumo* AND [2011-2014]/py) OR (colo* NEAR/5 metasta* AND [2011-2014]/py) OR (colo* NEAR/5 malig* AND [2011-2014]/py)) AND ('colorectal surgery'/exp AND [2011-2014]/py OR (surgical AND resection AND [2011-2014]/py) OR (resect* NEAR/5 colon* AND [2011-2014]/py) OR (post NEXT/1 operativ* AND [2011-2014]/py))) AND [humans]/lim AND ([cochrane review]/lim OR [controlled clinical trial]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [2011-2014]/py

Date	02 August 2013
Database	The Cochrane Library
Search Strategy	#1 colorectal cancer #2 adjuvant #3 #1 and #2 From 2011 to 2013

1.10. Search strategy – adjuvant chemotherapy in elderly patients

Date	11 April 2013
Database	MEDLINE, MEDLINE in progress via Pubmed
Search Strategy	Aged OR elderly [tiab] OR community-dwelling [tiab] OR geriatric [tiab] OR “mini-mental state” [tiab] OR alzheimer [tiab] OR alzheimer’s [tiab] OR alzheimers [tiab] OR mmse [tiab] OR caregivers [tiab] OR falls [tiab] OR adl [tiab] OR frailty [tiab] OR gds [tiab] OR ageing [tiab] OR “hip fractures “ [tiab] OR elders [tiab] OR frail [tiab] OR mci [tiab] OR cga [tiab] OR acga [tiab] OR mms [tiab] OR mmse [tiab] OR gug [tiab] OR iadl [tiab] OR mna [tiab] OR gds15 [tiab] OR cirs-g [tiab] OR cirsg [tiab] OR mobility [tiab] OR demented [tiab] OR psychogeriatrics [tiab] OR “cognitive impairment” [tiab] OR comorbidit* [tiab] OR dementia [tiab] OR aging [tiab] OR older [tiab] OR “daily living” [tiab] OR “cognitive decline” [tiab] OR “cognitive impairment” [tiab] OR residents [tiab] OR “cognitive functioning” OR “old* people” [tiab] OR nursing homes [mh] OR geriatric assessment [mh] OR aging [mh] OR frail elderly [mh] OR alzheimer disease [mh] OR homes for the aged [mh] OR cognition disorders [mh] OR dementia [mh] OR activities of daily living [mh] OR aged, 80 and over [mh] OR "Age Factors"[Mesh] OR aged [mh] OR "Nutrition Assessment"[Mesh] OR "Psychiatric Status Rating Scales"[Mesh] AND ("Chemoradiotherapy, Adjuvant"[Mesh] OR (adjuvant AND (*therap* OR treatment*)) OR ((chemoradiotherap* OR chemotherap*) AND adjuvant) AND ("Colorectal neoplasms" [Mesh] OR ((colorectal OR colon OR colonic OR (large AND bowel) OR rectal OR rectum OR rectosigmoid) AND (cancer* OR carcinoma*

	OR adenocarcinoma* OR malignan* OR tumor* OR tumour* OR neoplasm*)) Filters: Publication date from 2003/01/01; English SR filter Hunt Ann Int Med 1997: ("meta-analysis" [pt] OR "meta-anal*" [tw] OR "metaanal*" [tw] OR ("quantitativ* review*" [tw] OR "quantitative* overview*" [tw]) OR ("systematic* review*" [tw] OR "systematic* overview*" [tw]) OR ("methodologic* review*" [tw] OR "methodologic* overview*" [tw]) OR ("review" [pt] AND "medline" [tw])

Date	**11 April 2013**
Database	EMBASE via Ovid
Search Strategy	1. aged/ (2120783) 2. aging/ (181798) 3. age/ (387914) 4. exp daily life activity/ or exp elderly care/ or exp geriatrics/ or exp frail elderly/ or exp home care/ (194228) 5. nursing home/ or nursing home patient/ (40824) 6. geriatric assessment/ or geriatric care/ (19639) 7. exp nutritional assessment/ (12803) 8. psychological rating scale/ (15925) 9. exp home for the aged/ (10516) 10. cognitive defect/ (85528) 11. dementia/ or senile dementia/ (72434) 12. exp Alzheimer Disease Assessment Scale/ or exp Alzheimer disease/ (113335) 13. exp Clinical Dementia Rating/ (148) 14. or/1-13 (2773856) 15. colorectal cancer/ (67632) 16. (colorectal or colon or colonic or (large and bowel) or rectum or rectal or rectosigmoid).tw. (345600) 17. (cancer* or carcinoma* or adenocarcinoma* or malignan* or tumor* or tumour* or neoplasm*).tw. (2597566) 18. 16 and 17 (208229) 19. exp colon cancer/ (139805) 20. exp rectum cancer/ (103883) 21. 15 or 18 or 19 or 20 (246420) 22. adjuvant chemotherapy/ (21854) 23. exp adjuvant chemoradiotherapy/ (550) 24. cancer adjuvant therapy/ (31992) 25. (chemotherap* adj5 adjuvant).mp. or (chemoradi* adj5 adjuvant).tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (43101) 26. or/22-25 (67719) 27. 14 and 21 and 26 (3421) 28. limit 27 to ((dutch or english) and yr="2003 - Current") (2418)
Notes	Search also performed with SR filter

Date	**11 April 2013**
Database	Cochrane Library
Search Strategy	The Cochrane Database of Systematic Reviews was browsed by topic: a. cancer -> colorectal -> medical & adjuvant therapy b. cancer -> generic cancer care

1.11. Search strategy – surgery liver-restricted metastatic colorectal cancer

Date	November 2012
Database	Medline via OVID
Search Strategy	1. exp colorectal neoplasm/ (136562) 2. (colo$ adj5 cancer$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (80489) 3. (colo$ adj5 neoplasm$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (108715) 4. (colo$ adj5 carcin$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (35295) 5. (colo$ adj5 tumo$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (25817) 6. (colo$ adj5 malign$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4670) 7. (colo$ adj5 metast$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (15760) 8. exp neoplasm metastasis/ (146094) 9. (Metasta$ adj3 liver$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (19042) 10. (metasta$ adj3 hepa$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (9391) 11. *Liver Neoplasm/sc (9071) 12. 1 or 2 or 3 or 4 or 5 or 6 or 7 (171426) 13. 8 or 9 or 10 or 11 (167564) 14. 12 and 13 (22488) 15. exp antineoplastic agents/ (764651) 16. exp Antineoplastic Combined Chemotherapy Protocols/ (96569) 17. chemotherap$.mp. (286438) 18. colorectal neopl$/dt, th, su (0) 19. systemic therap$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (6518) 20. systemic treatment.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (4377) 21. neo$adjuvant.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (16191) 22. exp Colorectal Surgery/ (1767) 23. colorectal surgery.mp. (3969) 24. exp laparotomy/ (14832) 25. resect$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease

	supplementary concept, unique identifier] (207462) 26. excis$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (135326) 27. metastatec$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (71) 28. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 (1206077) 29. 14 and 28 (12143) 30. Animals/ (5091368) 31. Humans/ (12693665) 32. 30 not (30 and 31) (3717557) 33. 29 not 32 (11614) 34. meta-analysis.mp,pt. or review.pt. or search:.tw. (1902527) 35. 33 and 34 (1899) 36. limit 35 to yr="2009 -Current" (469)

Date	November 2012
Database	Embase via embase.com
Search Strategy	'colorectal cancer'/exp OR (colo* NEAR/3 cancer* AND [2009-2013]/py) OR (colo* NEAR/3 neoplas* AND [2009-2013]/py) OR (colo* NEAR/3 carcin* AND [2009-2013]/py) OR (colo* NEAR/3 tumo* AND [2009-2013]/py) OR (colo* NEAR/3 malign* AND [2009-2013]/py) OR (colo* NEAR/3 metast* AND [2009-2013]/py) AND 'liver metastasis'/exp AND ('liver metastasis'/exp AND [2009-2013]/py OR ('cancer chemotherapy'/exp AND [2009-2013]/py) OR ('cancer combination chemotherapy'/exp AND [2009-2013]/py) OR ('molecularly targeted therapy'/exp AND [2009-2013]/py) OR ('cancer palliative therapy'/exp AND [2009-2013]/py) OR ('surgery'/exp AND [2009-2013]/py) OR (resect* AND [2009-2013]/py) OR (metastatec* AND [2009-2013]/py)) NOT ('animal experiment'/exp AND [2009-2013]/py) AND [2009-2013]/py AND 'systematic review'/de

Date	November 2012
Database	Cochrane library
Search Strategy	#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees #2 MeSH descriptor: [Neoplasm Metastasis] explode all trees #3 #1 and #2 #4 MeSH descriptor: [Drug Therapy] explode all trees #5 MeSH descriptor: [General Surgery] explode all trees #6 MeSH descriptor: [Colorectal Surgery] explode all trees #7 #4 or #5 or #6 #8 #3 and #7 from 2009 to 2012, in Cochrane Reviews (Reviews only), Other Reviews and Cochrane Groups (Word variations have been searched)

1.12. Search strategy other local treatment for liver metastases

Project number	2012-01_GCP_Colon cancer
Project name	Practice guideline Colon Cancer
Search question(s)	Which local therapy should be used in patients with colorectal cancer with lung or liver metastasis? What is the impact of location, number and size of the metastases on the treatment choice?
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)	and related keywords
P (patient)	Patients with stage IV colorectal carcinoma and lung metastases Patients with stage IV colorectal carcinoma and liver metastases
I (Intervention)	Local therapy: Resection (lung/liver) RFA (liver) RT (lung/liver) Radio embolisation (liver)
C (comparison)	Systemic therapy
O (outcome)	Local follow-up, PFS, OS, QoL (incl. complications)

Date	7 November 2012	
Database	Medline OVID (1946 to October Week 1 2012)	
Search Strategy	1	exp Colorectal Neoplasms/ (136077)
	2	(colo$ adj5 cancer$).tw. (79884)
	3	(colo$ adj5 neoplas$).tw. (5382)
	4	(colo$ adj5 carcin$).tw. (32925)
	5	(colo$ adj5 tumo$).tw. (22677)
	6	(colo$ adj5 metasta$).tw. (15658)
	7	(colo$ adj5 malig$).tw. (4641)
	8	1 or 2 or 3 or 4 or 5 or 6 or 7 (169211)
	9	exp Neoplasm Metastasis/ (145489)
	10	(Metasta$ adj5 hepa$).mp. (11558)
	11	(Metasta$ adj5 liver$).mp. (21611)
	12	hepa$.mp. (617480)
	13	9 and 12 (7392)
	14	liver$.mp. (808269)
	15	9 and 14 (14292)
	16	*liver neoplasm/sc (9050)
	17	(Metasta$ adj5 lung$).mp. (20793)
	18	(Metasta$ adj5 pulm$).mp. (9646)
	19	lung$.mp. (576258)
	20	9 and 19 (23306)
	21	pulm$.mp. (486379)
	22	9 and 21 (5727)
	23	*lung neoplasm/sc (6848)
	24	10 or 11 or 13 or 15 or 16 (39963)
	25	17 or 18 or 20 or 22 or 24 (77389)
	26	24 or 25 (77389)
	27	8 and 26 (14658)
	28	liver/su (5471)
	29	lung/su (3849)
	30	exp neoplasm metastasis/th (1147)
	31	resect$.mp. (206282)
	32	surg$.mp. (1359109)
	33	excis$.mp. (134552)

34	remov$.mp. (402602)
35	metastatect$.mp. (69)
36	28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 (1820940)
37	exp Ablation Techniques/ (82879)
38	RFA.mp. (2628)
39	(radiofreq$ adj5 ablat$).mp. (9809)
40	37 or 38 or 39 (84801)
41	exp Radiotherapy/ (126945)
42	radiothera$.mp. (159648)
43	*radiosurgery/ (6103)
44	*stereotaxic techniques/ (5159)
45	(intervention$ adj5 radiol$).mp. (6869)
46	41 or 42 or 43 or 44 or 45 (196212)
47	exp radioisotopes/ (226765)
48	chemoembolization, therapeutic/ (3039)
49	(vena adj3 porta adj3 emboli$).mp. (0)
50	(port$ adj3 vein$ adj3 occlus$).mp. (445)
51	radioembol$.mp. (321)
52	microspheres.mp. (28275)
53	(drug adj3 eluting adj3 beads).mp. (108)
54	(radio$ adj5 isot$).mp. (10250)
55	yttrium$.mp. (5535)
56	47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 (264056)
57	36 or 40 or 46 or 56 (2237149)
58	27 and 57 (7498)
59	exp animals/ not humans.sh. (3799729)
60	58 not 59 (7154)
61	limit 60 to yr="2009 -Current" (1634)
62	meta-analysis/ (37222)
63	meta analy$.tw. (43058)
64	metaanaly$.tw. (1118)
65	meta analysis.pt. (37222)
66	(systematic adj (review$ or overview$)).tw. (34831)
67	exp review literature/ (1752591)
68	62 or 63 or 64 or 65 or 66 or 67 (1786210)
69	61 and 68 (278)

Date	**7 November 2012**	
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations	
Search Strategy	1	(colo$ adj5 cancer$).tw. (4464)
	2	(colo$ adj5 neoplas$).tw. (234)
	3	(colo$ adj5 carcin$).tw. (1174)
	4	(colo$ adj5 tumo$).tw. (931)
	5	(colo$ adj5 metasta$).tw. (905)
	6	(colo$ adj5 malig$).tw. (251)
	7	1 or 2 or 3 or 4 or 5 or 6 (5825)
	8	(neoplasm$ adj5 metasta$).mp. (121)
	9	(Metasta$ adj5 hepa$).mp. (536)
	10	(Metasta$ adj5 liver$).mp. (983)
	11	hepa$.mp. (20081)
	12	8 and 11 (8)
	13	liver$.mp. (20362)
	14	8 and 13 (13)
	15	(liver adj5 neoplasm$ adj5 second$).mp. (2)
	16	(Metasta$ adj5 lung$).mp. (1190)
	17	(Metasta$ adj5 pulm$).mp. (369)

18	lung$.mp. (16995)
19	8 and 18 (26)
20	pulm$.mp. (13470)
21	8 and 20 (8)
22	(lung adj5 neoplasm$ adj5 second$).mp. (2)
23	9 or 10 or 12 or 14 or 15 (1319)
24	16 or 17 or 19 or 21 or 22 (1461)
25	23 or 24 (2605)
26	7 and 25 (513)
27	((colo$ or lung$) adj5 surg$).mp. (1149)
28	((colo$ or lung$) adj5 resect$).mp. (921)
29	((colo$ or lung$) adj5 excis$).mp. (82)
30	((colo$ or lung$) adj5 remov$).mp. (277)
31	metastatect$.mp. (7)
32	(neoplasm$ adj5 metasta$ adj5 therap$).mp. (3)
33	27 or 28 or 29 or 30 or 31 or 32 (2096)
34	(ablat$ adj5 techn$).mp. (268)
35	RFA.mp. (278)
36	(radiofreq$ adj5 ablat$).mp. (701)
37	34 or 35 or 36 (940)
38	(rad$ adj5 therap$).mp. (3188)
39	radiothera$.mp. (4543)
40	radiosurg$.mp. (426)
41	(stereotax$ adj5 techn$).mp. (11)
42	(intervention$ adj5 radiol$).mp. (391)
43	38 or 39 or 40 or 41 or 42 (7483)
44	radioisotop$.mp. (372)
45	radioembol$.mp. (51)
46	(chemoembol$ adj5 therap$).mp. (34)
47	(vena adj3 porta adj3 emboli$).mp. (0)
48	(port$ adj3 vein$ adj3 occlus$).mp. (14)
49	microspheres.mp. (1286)
50	(drug adj3 eluting adj3 beads).mp. (15)
51	(radio$ adj5 isot$).mp. (242)
52	yttrium$.mp. (726)
53	44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 (2657)
54	33 or 37 or 43 or 53 (12880)
55	26 and 54 (195)
56	meta-analysis.mp. (3590)
57	meta analy$.tw. (4265)
58	metaanaly$.tw. (78)
59	meta analysis.pt. (34)
60	(systematic adj (review$ or overview$)).tw. (4703)
61	(review$ adj5 literat$).mp. (11934)
62	56 or 57 or 58 or 59 or 60 or 61 (18399)
63	randomized controlled trial.pt. (462)
64	controlled clinical trial.pt. (22)
65	randomized.ab. (13303)
66	placebo.ab. (5141)
67	randomly.ab. (12997)
68	trial.ab. (13924)
69	groups.ab. (75269)
70	or/63-69 (99077)
71	62 or 70 (114304)
72	55 and 71 (51)

Date	7 November 2012
Database	Embase
Search Strategy	'large intestine cancer'/exp OR colo* NEAR/5 (neoplasm* OR cancer* OR tumo* OR malig* OR metasta OR carcin*) AND (metasta* NEAR/5 (hepa* OR liver*) OR ('metastasis'/exp AND (hepa* OR liver*)) OR metasta* NEAR/5 (lung* OR pulm*) OR ('metastasis'/exp AND (lung* OR pulm*))) AND ('liver resection'/exp OR 'lung surgery'/exp OR resect* OR surg* OR excis* OR remov* OR metastatec* OR 'ablation therapy'/exp OR rfa OR radiofreq* NEAR/5 ablat* OR ('radiofrequency'/exp AND ablation) OR ('tumor'/exp AND ablation) OR 'radiotherapy'/exp OR radiothera* OR 'radiosurgery'/exp OR 'stereotactic procedure'/exp OR intervention* NEAR/5 radiol* OR 'radioisotope'/exp OR 'chemoembolization'/exp OR ('vena'/exp AND porta AND 'embolization'/exp) OR (portal AND 'vein'/exp AND 'occlusion'/exp) OR radioembol* OR 'microspheres'/exp OR ('drug'/exp AND eluting AND beads) OR radio* NEAR/5 isot* OR 'yttrium'/exp) AND 'meta analysis'/exp AND ([cochrane review]/lim OR [meta analysis]/lim OR [systematic review]/lim) AND [humans]/lim AND [2009-2013]/py

Date	7 November 2012
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees #2 MeSH descriptor: [Neoplasm Metastasis] explode all trees #3 hepa* or liver* #4 #2 and #3 #5 metasta* adj5 hepa* #6 metasta* adj5 liver* #7 MeSH descriptor: [Liver Neoplasms] explode all trees and with qualifiers: [Secondary - SC] #8 #4 or #5 or #6 or #7 #9 lung* or pulm* #10 #2 and #9 #11 metasta* adj5 lung* #12 MeSH descriptor: [Lung Neoplasms] explode all trees and with qualifiers: [Secondary - SC] #13 #10 or #11 or #12 #14 #8 or #13 #15 #1 and #14 #16 MeSH descriptor: [Specialties, Surgical] explode all trees #17 MeSH descriptor: [Liver] explode all trees and with qualifiers: [Surgery - SU] #18 MeSH descriptor: [Lung] explode all trees and with qualifiers: [Surgery - SU] #19 MeSH descriptor: [Neoplasm Metastasis] explode all trees and with qualifiers: [Therapy - TH] #20 resect* or surg* or excis* or remov* or metastatect* #21 #16 or #17 or #18 or #19 or #20

#22	MeSH descriptor: [Ablation Techniques] this term only
#23	MeSH descriptor: [Laser Therapy] this term only
#24	MeSH descriptor: [High-Intensity Focused Ultrasound Ablation] this term only
#25	RFA*
#26	radiofreq* adj5 ablat*
#27	#22 or #23 or #24 or #25 or #26
#28	MeSH descriptor: [Radiotherapy] explode all trees
#29	radiothera*
#30	MeSH descriptor: [Radiosurgery] explode all trees
#31	MeSH descriptor: [Stereotaxic Techniques] explode all trees
#32	radiol* adj5 intervention*
#33	#28 or #29 or #30 or #31 or #32
#34	MeSH descriptor: [Radioisotopes] explode all trees
#35	MeSH descriptor: [Chemoembolization, Therapeutic] explode all trees
#36	vena adj3 porta adj3 emboli*
#37	port* adj3 vein* adj3 occlus*
#38	radio* adj5 isot*
#39	radioembol*
#40	MeSH descriptor: [Microspheres] explode all trees
#41	drug adj3 eluting adj3 beads
#42	yttrium*
#43	#34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42
#44	#21 or #27 or #33 or #43
#45	#15 and #44

1.13. Search strategy first-line chemotherapy and targeted therapy

Date	22 October 2012
Database	Medline via OVID
Search Strategy	1. exp Colorectal Neoplasms/ (135940) 2. (colo$ adj5 cancer$).tw. (79753) 3. (colo$ adj5 neoplas$).tw. (5380) 4. (colo$ adj5 carcin$).tw. (32908) 5. (colo$ adj5 tumo$).tw. (22654) 6. (colo$ adj5 metasta$).tw. (15633) 7. (colo$ adj5 malig$).tw. (4638) 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 (169031) 9. exp Neoplasm Metastasis/ (145333) 10. stage IV.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (12982) 11. advanced.ab,ti. (212865) 12. metasta$.tw. (269810) 13. 9 or 10 or 11 or 12 (519270) 14. 8 and 13 (43636) 15. exp Antineoplastic Protocols/ (96176) 16. drug therapy, combination/ or antineoplastic combined chemotherapy protocols/ (225835) 17. exp molecular targeted therapy/ (4215) 18. exp Antineoplastic Agents/ (761288) 19. exp Antibodies, Monoclonal/ (168243) 20. exp Angiogenesis Inhibitors/ (30624) 21. exp Protein Kinase Inhibitors/ (41474)

	22. chemother$.mp. (284983) 23. (systemic therap$ or systemic treatment).mp. (10406) 24. (5-fluorouracil$ or 5-FU).mp. (26744) 25. oxaliplatin$.mp. (4640) 26. irinotecan.mp. (6349) 27. capecitabin$.mp. (3037) 28. FOLFOX$.mp. (1168) 29. FOLFIRI$.mp. (514) 30. XELOX.mp. (177) 31. XELIRI$.mp. (27) 32. (target$ adj3 therap$).mp. (71201) 33. (target$ adj3 treatment).mp. (14951) 34. (target$ adj3 agent$).mp. (10766) 35. EGFR$.mp. (21741) 36. VEGF.mp. (32494) 37. angiogen$.mp. (68039) 38. cetuximab.mp. (2999) 39. bevacizumab.mp. (6461) 40. panitumumab.mp. (600) 41. regorafinib.mp. (0) 42. Colorectal Neoplasms/dt, th [Drug Therapy, Therapy] (10848) 43. 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 (1298249) 44. 14 and 43 (18900) 45. exp animals/ not humans.sh. (3797751) 46. 44 not 45 (17956) 47. limit 46 to yr="2006 -Current" (8061)
	48. meta-analysis.mp,pt. or review.pt. or search:.tw. (1892967) 49. 47 and 48 (1750)
Note	Search for RCTs performed on 29 November 2012 using the following filters: 47. randomized controlled trial.pt. (342334) 48. controlled clinical trial.pt. (85694) 49. randomized.ab. (244919) 50. placebo.ab. (136550) 51. clinical trials as topic.sh. (163815) 52. randomly.ab. (175193) 53. trial.ti. (105840) 54. 47 or 48 or 49 or 50 or 51 or 52 or 53 (791543) 55. 46 and 54 (3283) 56. limit 55 to yr="2011 -Current" (319)

Date	05 December 2012
Database	Premedline via Ovid
Search Strategy	1. (colo$ adj5 cancer$).tw. (4814) 2. (colo$ adj5 neoplas$).tw. (240) 3. (colo$ adj5 carcin$).tw. (1254) 4. (colo$ adj5 tumo$).tw. (984) 5. (colo$ adj5 metasta$).tw. (978) 6. (colo$ adj5 malig$).tw. (273) 7. stage IV.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (595) 8. advanced.ab,ti. (15343) 9. metasta$.tw. (17839) 10. disseminated.tw. (1633) 11. 1 or 2 or 3 or 4 or 5 or 6 (6266) 12. 7 or 8 or 9 or 10 (32956) 13. 11 and 12 (1924) 14. chemother$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (12473) 15. (systemic therap$ or systemic treatment).mp. (739) 16. (5-fluorouracil$ or 5-FU$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1187) 17. oxaliplatin$.mp. (400) 18. irinotecan.mp. (338) 19. capecitabin$.mp. (267) 20. FOLFOX$.mp. (128) 21. FOLFIRI$.mp. (68) 22. XELOX.mp. (27) 23. XELIRI$.mp. (7) 24. (target$ adj3 therap$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (7152) 25. (target$ adj3 treatment).mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1494) 26. (target$ adj3 agent$).mp. (1123) 27. EGFR$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (1980) 28. VEGF$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2644) 29. angiogen$.mp. (3906) 30. cetuximab.mp. (261) 31. bevacizumab.mp. (779) 32. panitumumab.mp. (73) 33. regorafinib.mp. (0) 34. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (27869) 35. 13 and 34 (782)

Date	29 October 2012
Database	EMBASE via Embase.com
Search Strategy	'large intestine cancer'/exp OR colo* NEAR/ cancer OR colo* NEAR/5 neoplas* OR colo* NEAR/5 carcin* OR colo* NEAR/5 tumo* OR colo* NEAR/5 metasta* OR colo* NEAR/5 malig* AND ('metastasis'/exp OR advanced OR 'stage iv' OR metasta* OR disseminated) AND ('molecularly targeted therapy'/exp OR 'protein kinase inhibitor'/exp OR '5 fluorouracil' OR '5 fu' OR irinotecan OR oxaliplatin* OR capecitabin* OR folfox* OR xelox OR xeliris OR egfr OR vegf OR angiogen* OR cetuximab OR bevacizumab OR panitumumab OR regorafinib OR 'cancer chemotherapy'/exp) AND ([cochrane review]/lim OR [meta analysis]/lim OR [randomized controlled trial]/lim OR [systematic review]/lim) AND [humans]/lim AND [2006-2013]/py
Note	Search for RCTs performed on 6 December 2012 using the following filters: [controlled clinical trial]/lim OR [randomized controlled trial]/lim) AND [humans]/lim AND [2011-2013]/py

Date	25 October 2012
Database	Cochrane Library
Search Strategy	#1 MeSH descriptor: [Colorectal Neoplasms] explode all trees #2 colo* near/5 cancer*:ti,ab #3 colo* near/5 neoplas*:ti,ab #4 colo* near/5 carcin*:ti,ab #5 colo* near/5 tumo*:ti,ab #6 colo* near/5 metasta*:ti,ab #7 colo* near/5 malig*:ti,ab #8 #1 or #2 or #3 or #4 or #5 or #6 or #7 #9 MeSH descriptor: [Colorectal Neoplasms] explode all trees and with qualifiers: [Drug therapy - DT] #10 MeSH descriptor: [Antineoplastic Agents] explode all trees #11 MeSH descriptor: [Drug Therapy] this term only #12 MeSH descriptor: [Drug Administration Schedule] this term only #13 MeSH descriptor: [Antineoplastic Protocols] explode all trees #14 MeSH descriptor: [Molecular Targeted Therapy] explode all trees #15 MeSH descriptor: [Maintenance Chemotherapy] explode all trees #16 chemother*.ti,ab #17 systemic therap* or systemic treatment:ti,ab #18 5-fluorouracil* or 5-FU:ti,ab,kw #19 oxaliplatin*:ti,ab,kw #20 irinotecan:ti,ab,kw #21 capecitabin:ti,ab,kw #22 FOLFOX*:ti,ab,kw #23 FOLFIRI:ti,ab,kw #24 XELOX:ti,ab,kw

	#25 XELIRI*:ti,ab,kw #26 target* near/3 therap*:ti,ab #27 target* near/3 treatment:ti,ab #28 target* near/3 agent*:ti,ab #29 EGFR:ti,ab #30 VEGF:ti,ab #31 angiogen*:ti,ab #32 cetuximab:ti,ab #33 bevacizumab:ti,ab #34 panitumumab:ti,ab #35 regorafinib:ti,ab #36 MeSH descriptor: [Neoplasm Metastasis] explode all trees #37 stage IV:ti,ab,kw (Word variations have been searched) #38 advanced:ti,ab,kw (Word variations have been searched) #39 metasta*:ti,ab,kw (Word variations have been searched) #40 MeSH descriptor: [Antibodies, Monoclonal] explode all trees #41 #36 or #37 or #38 or #39 #42 #8 and #41 #43 MeSH descriptor: [Protein Kinase Inhibitors] explode all trees #44 #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #40 or #43 #45 #42 and #44 from 2006 to 2012
Note	Search repeated for RCTs on 6 December 2012 from 2011 to 2012

1.14. Search strategy follow-up

Project number	January 2012
Project name	**CRC**
Search question(s)	**Use of CT in Follow up after treatment with curative intent**
Structured search question(s) (PICO, SPICE, ECLIPSE, ..)	**and related keywords**
P (patient)	CRC patients treated with curative intent
I (Intervention)	CT scan thorax, abdomen
C (comparison)	None or other interventions
O (outcome)	DFS,disease recurrence, metachronous metastases
Note	

Date	16 July 2013
Database	Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>
Search Strategy	1 exp colorectal neoplasms/ (148476) 2 ((colon or colonic) adj3 (cancer$ or neoplas$ or oncolog$ or malignan$ or tumo?r$ or carcinoma$ or adenocarcinoma$)).tw. (61627) 3 1 or 2 (168095) 4 exp Follow-Up Studies/ (488864) 5 (follow up$ or follow-up$).tw. (601837) 6 surveillance*.tw. (103329) 7 monitor*.tw. (515953) 8 4 or 5 or 6 or 7 (1447121) 9 3 and 8 (21269) 10 exp Tomography, X-Ray Computed/ (293564) 11 CT scan.mp. (35970) 12 10 or 11 (310869) 13 9 and 12 (1230) 14 limit 13 to yr="2011 -Current" (223)

The search resulted in 357 hits after discarding duplicates (Medline n= 189, Embase n=168, Cochrane n=0). Selection by title and abstract resulted in 18 publications. Further selection was based on full text and discussed by 2 experts. Inclusion criteria were based on population (CRC patients treated with curative intent) and intervention (at least including CT scan amongst possible other interventions). All types of studies were included. Nine studies did not fulfil the inclusion criteria. Five abstracts were excluded because the related information was insufficient to appraise study quality [1-5]. Note however that the findings of these studies do not contradict the final conclusions. Two retrospective case studies were eliminated because of selection bias, since only suspected recurrences were included (Han 2011, Ozkan 2012). The remaining 2 studies were included, appraised and summarized in the evidence table.

2. CRITICAL APPRAISAL

2.1. Critical appraisal of clinical practice guidelines

Table 2 – AGREE II instrument

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

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

Table 3 – Critical appraisal of clinical practice guidelines - Results

Source	Year	Title	Final appraisal
Cancer Care Ontario (CCO)[6]	2011	Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer after Complete Resection: An Updated Practice Guideline	Recommended
La Société Française de Chirurgie Digestive (SFCD) et de l'Association de Chirurgie Hépatobiliaire et de Transplantation Hépatique (ACHBT)[7]	2011	Management of patients with synchronous liver metastases of colorectal cancer. Clinical practice guidelines. Guidelines of the French society of gastrointestinal surgery (SFCD) and of the association of hepatobiliary surgery and liver transplantation (ACHBT). Short version	Recommended
National Institute for Health and Clinical Excellence (NICE)[8]	2011	Colorectal cancer. The diagnosis and management of colorectal cancer. NICE clinical guideline 131	Recommended
New Zealand Guidelines Group (NZGG)[9]	2011	Management of Early Colorectal Cancer. Evidence-based Best Practice Guideline	Recommended
Scottish Intercollegiate Guidelines Network (SIGN)[10]	2011	SIGN 126. Diagnosis and management of colorectal cancer	Recommended
American Society of Clinical Oncology (ASCO)[11]	2010	American Society of Clinical Oncology 2009 Clinical Evidence Review on Radiofrequency Ablation of Hepatic Metastases From Colorectal Cancer	Recommended
Cancer Care Ontario (CCO)[12]	2010	PET Imaging in Colorectal Cancer	Recommended

Source	Year	Title	Final appraisal
Cancer Care Ontario (CCO)[13]	2008	The Role of Bevacizumab (Avastin®) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer: Guideline Recommendations	Recommended
Integraal Kankercentrum Nederland (IKNL)[14]	2008	Colon cancer. Nation-wide guideline, Version: 2.0	Recommended
Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)[15]	2007	Guidelines for Diagnostic Laparoscopy	Recommended
Integraal Kankercentrum Nederland (IKNL)[16]	2006	Colorectale levermetastasen. Landelijke richtlijn, versie: 1.0	Recommended
Edwards MS et al.	2012	A systematic review of treatment guidelines for metastatic colorectal cancer	Review of published guidelines
Society of American Gastrointestinal and Endoscopic Surgeons (SAGES)	2012	SAGES Evidence-Based Guidelines for the Laparoscopic Resection of Curable Colon and rectal cancer	Not recommended (no systematic review of evidence)
National Comprehensive Cancer Network (NCCN)	2011/ 2012	NCCN Clinical Practice Guidelines in Oncology. Colon Cancer.	Not recommended (unclear methodology)
American College of Radiology	2011	ACR Appropriateness Criteria®. Pretreatment Staging of Colorectal Cancer	Not recommended (no systematic review of evidence)
Aranda E et al.	2011	Treatment recommendations for metastatic colorectal cancer	Not recommended (no systematic review of evidence)
Graña B	2011	SEOM clinical guidelines for hereditary cancer	Not recommended (no systematic review of evidence)
Parmelli E et al.	2011	Updating clinical recommendations for breast, colorectal and lung cancer treatments: an opportunity to improve methodology and clinical relevance	Report on updating process

Source	Year	Title	Final appraisal
Stein A et al.	2011	Current standards and new trends in the primary treatment of colorectal cancer	Not recommended (no systematic review of evidence)
Xu J et al.	2011	Chinese guidelines for the diagnosis and comprehensive treatment of hepatic metastasis of colorectal cancer	Not recommended (no systematic review of evidence)
The AGA institute	2010	AGA Medical Position Statement on the Diagnosis and Management of Colorectal Neoplasia in Inflammatory Bowel Disease	Not recommended (scientific methodology insufficient)
European Society for Medical Oncology	2010	Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment	Not recommended (no systematic review of evidence)
European Society for Medical Oncology	2010	Primary colon cancer: ESMO Clinical Practice Guidelines for diagnosis, adjuvant treatment and follow-up	Not recommended (no systematic review of evidence)
Grávalos Castro C et al.	2010	SEOM clinical guidelines for the adjuvant treatment of colorectal cancer	Not recommended (no systematic review of evidence)
Grávalos Castro C et al.	2010	SEOM clinical guidelines for the treatment of advanced colorectal cancer	Not recommended (no systematic review of evidence)
Schmiegel W et al.	2010	S3 guidelines for colorectal carcinoma. Results of an evidence-based consensus conference on February 6/7, 2004 and June 8/9, 2007	Not recommended (scientific methodology insufficient)
American Society of Clinical Oncology	2009	American Society of Clinical Oncology Provisional Clinical Opinion: Testing for KRAS Gene Mutations in Patients With Metastatic Colorectal Carcinoma to Predict Response to Anti–Epidermal Growth Factor Receptor Monoclonal Antibody Therapy	Not recommended (scientific methodology insufficient)
European Society for Medical Oncology	2009	Advanced colorectal cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up	Not recommended (no systematic review of evidence)

Source	Year	Title	Final appraisal
European Society for Medical Oncology	2009	Primary colon cancer: ESMO Clinical Recommendations for diagnosis, adjuvant treatment and follow-up	Not recommended (no systematic review of evidence)
Nordlinger B et al.	2009	Combination of surgery and chemotherapy and the role of targeted agents in the treatment of patients with colorectal liver metastases: recommendations from an expert panel	Not recommended (no systematic review of evidence)
Papamichael D et al.	2009	Treatment of the elderly colorectal cancer patient: SIOG expert recommendations	Not recommended (no systematic review of evidence)
Sturgeon CM et al.	2009	Use of Tumor Markers in Testicular, Prostate, Colorectal, Breast, and Ovarian Cancers	Not recommended (no systematic review of evidence)

2.2. Critical appraisal of systematic reviews

Table 4 – AMSTAR checklist

Question	Answer
1. Was an 'a priori' design provided? The research question and inclusion criteria should be established before the conduct of the review.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
2. Was there duplicate study selection and data extraction? There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

3. Was a comprehensive literature search performed? At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion? The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
5. Was a list of studies (included and excluded) provided? A list of included and excluded studies should be provided.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
6. Were the characteristics of the included studies provided? In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
7. Was the scientific quality of the included studies assessed and documented? 'A priori' methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
8. Was the scientific quality of the included studies used appropriately in formulating conclusions? The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

9. Were the methods used to combine the findings of studies appropriate? For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi-squared test for homogeneity, I^2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
10. Was the likelihood of publication bias assessed? An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable
11. Was the conflict of interest stated? Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	☐ Yes ☐ No ☐ Can't answer ☐ Not applicable

2.3. Critical appraisal of systematic reviews - Results

Table 5 – Critical appraisal systematic reviews – PET-CT (CoCanCPG checklist)

	Chan 2012	Patel 2011	Brush 2011	Niekel 2010
Internal validity				
The study addresses an appropriate and clearly focused question	Yes	Yes	Yes	Yes
A description of the methodology used is included	Yes	Yes	Yes	Yes
The literature search is sufficiently rigorous to identify all the relevant studies	unclear: no search question is provided	Yes	Yes	Yes, 15 690 hits
Study quality is assessed	unclear: no quality checklist is given, but according to the Appendix it seems that quality assessment has been done.	Yes	Yes	Yes
The method of data extraction is clearly described	Yes	Yes	Yes	Yes
The most important characteristics from the original research are described	Yes	Yes	Yes	Yes
There are enough similarities between the selected studies to make combining them reasonable	No: a priori expectation of heterogeneity	No: planned pooled analyses were not calculated given the heterogeneity in the studies	No	Unknown: Because of the limited number of FDG PET/CT studies, no check for heterogeneity was performed.

	Chan 2012	Patel 2011	Brush 2011	Niekel 2010
Statistical pooling is correctly performed	NA	NA	Unclear, no methodology described	NA
Statistical heterogeneity is adequately taken into account	NA	NA	Unclear, no methodology described	NA
Study quality is taken into account	Unclear, but probably yes, because the authors followed the method of Facey et al.	Yes	Yes	Yes
Overall assessment of the study				
Are the results of the systematic review valid?	No: the poor quality of the studies means that the validity of these estimates is threatened by several biases.	No: the poor quality of the studies means that the validity of these estimates is threatened by several biases.	No: the poor quality of the studies means that the validity of these estimates is threatened by several biases.	No: the poor quality of the studies means that the validity of these estimates is threatened by several biases.
Are the results of the systematic review applicable to the patient group targeted in the search question?	yes	Yes	Yes	Yes
Comments	The search strategies used are available upon request from the corresponding author of this review.	a qualitative summary of results is presented	Because of methodological problems, particularly those caused by the difficulty of estimating within-study variance when patients contribute more than one data point, and when the individual patient data are not available, it was the authors' intention that the 2 × 2 tables should report the lesion-level data, but that the analyses be restricted to patient-level data.	

Table 6 – Critical appraisal systematic reviews – MRI Liver

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
van Kessel 2012[17]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Niekel 2010[18]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Can't answer	Yes	No	Yes
Chan 2012[19]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	NA	No	No	Yes
Xu 2011	No	No	No	No	No	No	No	No	No	No	No	No

[§] *as listed in Table 4*

Table 7 – Critical appraisal systematic reviews - Endoscopic treatment stage I

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Di Gregorio et al. 2012[20]	Can't answer	No	No	No	No	Yes	No	No	No	No	No	(Yes)

[§] *as listed in Table 4*

Table 8 – Critical appraisal systematic reviews - Laparotomy vs. laparoscopy

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Ma et al. 2011	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes
Sammour et al. 2011	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	No	Yes
Ohtani et al. 2012	Can't answer	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes
Ding et al. 2013	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Grailey et al. 2013	Yes	Yes	Yes	Yes	No	Yes	No	No	Yes	Yes	No	Yes

[§] *as listed in Table 4*

Table 9 – Critical appraisal systematic reviews - Single-incision vs. traditional multiport laparoscopic colorectal surgery

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Maggiori et al. 2012[21]	Yes	Yes	No	Yes	No	No	Yes	No	Yes	No	No	Yes
Zhou et al. 2012[22]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes
Lv et al. 2013[23]	Yes	Yes	Yes	No	No	Yes	No	No	Yes	Yes	No	Yes

[§] *as listed in Table 4*

Table 10 – Critical appraisal systematic reviews - Robotic vs. traditional laparoscopic colorectal surgery

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Mirnezami et al. 2009[24]	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No	No	Yes

[§] *as listed in Table 4*

Table 11 – Critical appraisal systematic reviews – acute obstruction (CoCanCPG checklist)

	De Salvo 2008
Internal validity	
The study addresses an appropriate and clearly focused question	Yes
A description of the methodology used is included	Yes
The literature search is sufficiently rigorous to identify all the relevant studies	Yes
Study quality is assessed	NA, no studies included
The method of data extraction is clearly described	NA, no studies included
The most important characteristics from the original research are described	NA, no studies included
There are enough similarities between the selected studies to make combining them reasonable	NA, no studies included
Statistical pooling is correctly performed	NA, no studies included
Statistical heterogeneity is adequately taken into account	NA, no studies included

	De Salvo 2008
Study quality is taken into account	NA, no studies included
Overall assessment of the study	
Are the results of the systematic review valid?	NA, no studies included
Are the results of the systematic review applicable to the patient group targeted in the search question?	Yes
Comments	

Table 12 – Critical appraisal systematic reviews – adjuvant chemotherapy stage II colon cancer

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Figueredo 2008[25]	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes
Wu 2013[26]	yes	no	yes	no	no	no	yes	yes	yes	yes	no	yes

[§] *as listed in Table 4*

Table 13 – Critical appraisal systematic reviews – adjuvant chemotherapy elderly patients (CoCanCPG checklist)

	Sakamoto 2004
Internal validity	
The study addresses an appropriate and clearly focused question	Yes
A description of the methodology used is included	Not completely: not clear whether a systematic review was performed to indentify RCTs
The literature search is sufficiently rigorous to identify all the relevant studies	Not reported
Study quality is assessed	No
The method of data extraction is clearly described	Yes
The most important characteristics from the original research are described	Yes

	Sakamoto 2004
There are enough similarities between the selected studies to make combining them reasonable	Yes
Statistical pooling is correctly performed	Individual patient meta-analysis
Statistical heterogeneity is adequately taken into account	Yes
Study quality is taken into account	No
Overall assessment of the study	
Are the results of the systematic review valid?	Yes
Are the results of the systematic review applicable to the patient group targeted in the search question?	Yes
comments	

Table 14 – Critical appraisal systematic reviews – local treatment

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Rizell et al. 2010[27]	yes	No	yes	yes	yes	yes	yes	yes	yes	no	no	yes
Townsend et al, 2009[28]	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes
Cirocchi et al.[29]	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes
Mocellin et al 2011[30]	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	no	yes

Table 15 – Critical appraisal systematic reviews – cytoreductive surgery and HIPEC

AMSTAR question§	1	2	3	4	5	6	7	8	9	10	11	Included
de Cuba et al. 2013	Yes	Yes	No	No	No	Yes	No	No	No	No	No	No
Chua et al. 2013	Yes	Yes	No	No	No	No	No	No	Not applicable	No	No	No
Weber et al. 2012	Yes	No	No	No	No	Yes	No	No	Not applicable	No	No	No
Newman et al. 2012	Can't answer	No	No	No	No	No	No	No	Not applicable	No	No	No
Chua et al. 2009	Yes	Yes	No	No	No	No	No	No	Can't answer	No	No	No
Cao et al. 2009	Yes	Yes	No	No	No	No	No	No	Can't answer	No	No	No

§ *as listed in Table 4*

Table 16 – Critical appraisal systematic reviews – surgery +/- chemotherapy for isolated liver metastases

AMSTAR question§	1	2	3	4	5	6	7	8	9	10	11	Included
Chen 2011	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Chua 2010	no	yes	yes	yes	yes	yes	no	yes	na	no	no	yes
Ciliberto 2012	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes
Nelson 2009	yes	no	yes	yes	no	yes	yes	yes	yes	yes	yes	yes
Wieser 2010	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes
Quan 2012	yes	yes	yes	yes	yes	yes	no	yes	na	no	no	yes
Lehman 2012	yes	yes	yes	no	yes	yes	no	yes	na	no	yes	yes

§ *as listed in Table 4*

Table 17 – Critical appraisal systematic reviews – first-line chemotherapy and targeted therapy

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
Oral vs IV fluoropyrimidines												
Zhao 2010	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Montagnani 2010	no	yes	**yes**	yes	no	**no**	**no**		yes	no	no	no
Cao 2010	yes	yes	**yes**	yes	yes	**yes**	**yes**	yes	yes	no	no	yes
Ling 2011	yes	yes	**yes**	yes	no	**yes**	**yes**	no	yes	Can't answer	no	yes
Zhang 2012	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Petrelli 2012	yes	no	**yes**	yes	no	**yes**	**no**		yes	no	no	no
Oxaliplatin vs irinotecan												
Liang 2010	yes	yes	**no**[$]	no	no	**yes**	**yes**	yes	yes	no	no	yes
Zhuang 2010	can't answer	yes	**yes**	no	no	**yes**	**yes**	no	yes	yes	no	yes
Bevacizumab												
Cao 2009	yes	yes	**yes**	no	yes	**yes**	**yes**	yes	yes	can't answer	no	yes
Wagner 2009	yes	yes	**yes**	yes	yes	**yes**	**yes**	yes	yes	yes	yes	yes
Welch 2010	yes	yes	**yes**	no	no	**yes**	**yes**	yes	yes	no	no	yes
Loupakis 2010			**no**				**no**					no
Heinemann 2010		no	**no**	no			**no**					no
Galfrascoli 2011	yes	yes	**yes**	yes	yes	**yes**	**yes**	no	yes	no	no	yes
Hompes 2011			**no**	no			**no**					no
Macedo 2012	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	yes	yes
Anti-EGFR therapy												
Nie 2009	yes	yes	**yes**	yes	yes	**yes**	**yes**	can't answer	yes	yes	no	yes
Liu 2010	yes	yes	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Tol 2010	can't	can't	**no**	no			**no**					no

AMSTAR question[§]	1	2	3	4	5	6	7	8	9	10	11	Included
	answer	answer										
Ibrahim 2010		no	**yes**	yes			**no**					no
Qiu 2010			**yes**			**yes**	**no**					no
Petrelli 2011			**no**				**no**					no
Zhang 2011	yes	no	**No**[$]	no	no	**yes**	**yes**	no	yes	no	no	yes
Ibrahim 2011			**yes**			**yes**	**no**					no
Dahabreh 2011	yes	yes	**yes**	no	no	**yes**	**yes**	no	yes	yes	no	yes
Adelstein 2011			**yes**			**yes**	**no**					no
Lin AY 2011			**no**				**no**					no
Loupakis 2012			**no**									no
Vale 2012	yes	can't answer	**yes**	yes	no	**yes**	**yes**	yes	yes	no	no	yes
Wang 2012	yes	can't answer	**yes**	yes	no	**yes**	**can't answer**		yes	yes	no	yes

[§] *as listed in Table 4*

2.4. Critical appraisal of primary studies

Table 18 – Cochrane Collaboration's tool for assessing risk of bias

Domain	Support for judgement	Review authors' judgement
Selection bias		
1. Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Selection bias (biased allocation to interventions) due to inadequate generation of a randomised sequence
2. Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment
Performance bias		
1. Blinding of participants and personnel **2. Assessments should be made for each main outcome (or class of outcomes)**	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Performance bias due to knowledge of the allocated interventions by participants and personnel during the study
Detection bias		
3. Blinding of outcome assessment **4. Assessments should be made for each main outcome (or class of outcomes)**	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective	Detection bias due to knowledge of the allocated interventions by outcome assessors
Attrition bias		
5. Incomplete outcome data **6. Assessments should be made for each main outcome (or class of outcomes)**	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Attrition bias due to amount, nature or handling of incomplete outcome data

Domain	Support for judgement	Review authors' judgement
Reporting bias		
7. Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found	Reporting bias due to selective outcome reporting
Other bias		
8. Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool If particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Bias due to problems not covered elsewhere in the table

2.5. Critical appraisal of primary studies - Results

See last column of evidence tables (4) if not reported hereunder.

Table 19 – Critical appraisal RCT – PET-CT (CoCanCPG checklist)

Study	Study question	Method of randomization	Allocation concealment	Blinding of subjects	Blinding of outcome assessors	Similarity of groups	Only intervention is different	Measuring outcomes	ITT
Ruers 2009	Yes	Yes	Yes	No	No	Yes	Yes	Yes	

Table 20 – Critical appraisal diagnostic accuracy studies – PET-CT (CoCanCPG checklist)

	Mainenti 2010
The index test being studied is clearly specified	Yes
The index test is compared with a reference standard	Yes
The reference standard is likely to correctly classify the target condition	Yes
The spectrum of the included patients is representative of the patients who will receive the test in practice	Yes

Selection criteria are clearly described	Yes
The time period between reference standard and index test is short enough to be reasonably sure that the target condition did not change between the two tests	Yes (4-8 days)
The whole sample or a random selection of the sample received verification using the reference standard of diagnosis	Yes
Patients received the same reference standard regardless of the index test result	Yes
The reference standard is independent of the index test (i.e. the index test did not form part of the reference standard)	Yes
The execution of the index test is described in sufficient detail to permit replication of the test	Yes
The execution of the reference standard is described in sufficient detail to permit its replication	Yes
The index test results were interpreted without knowledge of the results of the reference standard	no: all modalities were randomly performed, but radiologist was not blinded with the results of preoperative imaging modalities.
The reference standard results were interpreted without knowledge of the results of the index test	no: all modalities were randomly performed, but radiologist was not blinded with the results of preoperative imaging modalities.
The same clinical data were available when test results were interpreted as would be available when the test is used in practice	Yes
Uninterpretable/ intermediate test results are reported	Yes
Withdrawals from the study are explained	Yes
Are the results of the study:	
• valid?	Probably yes, but no blinding
• applicable to the patient group targeted in the search question?	Probably yes, but no blinding

Table 21 – Critical appraisal RCTs – Acute obstruction (CoCanCPG checklist)

Study	Study question	Method of randomization	Allocation concealment	Blinding of subjects	Blinding of outcome assessors	Similarity of groups	Only intervention is different	Measuring outcomes	ITT
Alcantara 2011	Yes	Yes – sequence generation not reported	Sealed envelopes, not reported wether these were opaque	No	Not reported	Yes	Yes	Not reported	Yes
Cheung 2009	Yes	Yes	Not reported	Not possible	Not reported	No: more stage IV patients in the open surgery group	Yes	Yes, but time of FU not specified for outcome permanent stoma	Yes
Fiori 2004, 2012	Yes	Yes	Not reported	No	Not reported	Yes	Yes	Not reported	Yes
Ho 2012	Yes	Yes – computer-generated randomisation	Yes – sequentially numbered, opaque sealed envelopes	No	Not reported	No – better stage patients in the stent group	Yes	No	Yes
Kronborg 1995	Yes	Yes – sequence generation not reported on	unclear	No	Not reported	No – 11 vs 6 patients were wrongly diagnosed with cancer; 3 vs 0 had distant spread	Yes	Yes	Yes
Pirlet 2011	Yes	Yes – computer-	Yes – central secured	No	Not	Yes	Yes	Yes	Yes

Study	Study question	Method of randomization	Allocation concealment	Blinding of subjects	Blinding of outcome assessors	Similarity of groups	Only intervention is different	Measuring outcomes	ITT
		generated lists	website		reported				
Sankararajah 2005	Yes	Yes – sequence generation not described	Not described	no	Not reported	Not reported	Yes	Not reported	Not reported
Xinopoulos 2004	Yes	Yes – sequence generation not reported	Not reported	No	Not reported	Not reported	Yes	Not reported	No – 1 patients with unseccesful stent placement was excluded from the analysis
Van Hooft 2008	Yes	Yes – computer generated randomisation sequence	Yes – central randomisation	No	Not reported	Yes	Yes	Not reported	Yes
Van Hooft 2001	Yes	Yes – computer generated randomisation sequence	Yes – web-based allocation	No	No – tough a blinded panel was used to evaluate outcomes	Yes	Yes	Yes	Yes

Table 22 – Critical appraisal RCTs – Enhanced recovery program (CoCanCPG checklist)

Study	Study question	Method of randomization	Allocation concealment	Blinding of investigator and/or participant	Similarity of groups	Only intervention is different	Measuring outcomes	ITT
Ren 2012	yes	yes	unclear	yes	yes	yes	yes	yes
Vlug 2011	yes	yes	unclear	yes	yes	yes	yes	no
Wang G. 2012	yes	unclear	unclear	no	yes	yes	yes	no
Wang Q 2012	yes	yes	yes	unclear	yes	yes	yes	yes
Wang G. 2011	yes	unclear	unclear	unclear	yes	yes	yes	no
Yang 2012	yes	unclear	unclear	unclear	yes	yes	yes	no

Table 23 – Critical appraisal cohort studies – adjuvant chemotherapy in elderly patients (CoCanCPG checklist)

	Abraham 2013	Gross 2007	Hu 2011	Jessup 2005	Kahn 2010	Morris 2007	Van Steenbergen 2012	Wildes 2009	Zuckerman 2009
Internal validity									
The study addresses an appropriate and clearly focused question	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
The cohort being studied is selected from source populations that are comparable in all respects other than the factor under investigation	Appropriate source population, in- and exclusion criteria mentioned	Appropriate source population, in- and exclusion criteria mentioned	Appropriate source population, in- and exclusion criteria mentioned	Appropriate source population, inclusion criteria mentioned, exclusion criteria not	Appropriate source population, in- and exclusion criteria mentioned	Appropriate source population, in- and exclusion criteria mentioned	Appropriate source population, in- and exclusion criteria mentioned	Appropriate source population, in- and exclusion criteria mentioned	Appropriate source population, in- and exclusion criteria mentioned
The likelihood that some eligible subjects might have the outcome at the	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable

time of enrolment is assessed and taken into account in the analysis									
Comparison by exposure status is made between full participants and those lost to follow up	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable	Not applicable
The outcomes are clearly defined	Yes – measurement of outcome not specified. (Possible) loss to follow-up not discussed	Yes – measurement of outcome not specified. (Possible) loss to follow-up not discussed	Yes	Yes – measurement of outcome not specified. (Possible) loss to follow-up not discussed	Yes	Yes	Yes	Yes – measurement of outcome not specified. (Possible) loss to follow-up not discussed	Yes – measurement of outcome not specified. (Possible) loss to follow-up not discussed
The assessment of outcome is made blind to exposure status	Not reported but unlikely to introduce bias	Not reported but unlikely to introduce bias	Not applicable	Not reported but unlikely to introduce bias	Not reported but unlikely to introduce bias	Not reported but unlikely to introduce bias	Not reported but unlikely to introduce bias	Not reported but unlikely to introduce bias	Not reported but unlikely to introduce bias
The measure of assessment of exposure is reliable	Yes	Yes	Yes	Yes	Yes – medical records	Yes – medical records	Yes – medical records	Yes	Yes
The main potential confounders are identified and taken into account in the design and analysis	Yes – year of diagnosis, patient- and tumor-related factors	Yes – all factors available in the registry	Not applicable	No, unadjusted analysis	Yes	No, unadjusted analysis	No, unadjusted analysis	Yes- limited adjustment applied. Data from propensity score analysis not shown but	Yes – adjusted analysis, for large number of patient- and tumor-related

								reported to be similar	variables
Overall assessment of the study									
Are the results of the study: • valid? • applicable to the patient group targeted in the search question?	Yes Yes	Yes Yes	Yes Yes	± unadjusted analysis Yes	Yes Yes	± unadjusted analysis Yes	± unadjusted analysis Yes	Yes Yes	Yes Yes

Table 24 – Critical appraisal RCTs - First-line chemotherapy and targeted therapy

RoB tool question[§]	1	2	3	4	5	6	7
Guan 2011	low	low	high	high	high	low	No ITT analysis
Fuchs 2007	low	low	high	high	low	unclear	sponsored by Pfizer, early closure of capeIRI arm, 3X2 design with simultaneous testing of celecoxib
Köhne 2008	low	low	high	high	low	unclear	sponsored by Roche, Pfizer, Aventis
Cassidy 2011	low	low	high	high	low	low	sponsored by Roche. Cross-over allowed, censored in analysis.
Pectasides 2012	low	low	high	high	unclear	unclear	no ITT analysis
Souglakos 2012	low	low	high	high	unclear	unclear	no ITT analysis
Hochster 2008	low	low	high	high	unclear	unclear	sponsored by Sanofi-aventis
Ducreux 2011	low	low	high	high	unclear	unclear	sponsored by Roche
Van Cutsem 2011	low	low	high	low	high	low	19 untreated patients (reasons unspecified) not included in ITT. KRAS status known for

RoB tool question[§]	1	2	3	4	5	6	7
							1063/1198 pts. Sponsored by Merck
Tveit 2012	low	unclear	high	high	high	low	KRAS status known for 88% of patients only. 5 ineligible patients excluded from ITT. Sponsored by Merck serono and Sanofi-Aventis
Ducreux 2011 (S vs C)	low	low	high	high	low	low	early closure due to slow accrual after the introduction of bevacizumab
Koopman 2007	low	low	high	high	low	low	Sonsored by Sanofi-Aventis, Roche and pfizer. 17 ineligible patients excluded from analysis
Seymour 2007	low	low	high	high	low	low	Sponsored by Sanofi-synthelabo, Aventis, Wyeth-Lederle, Baxter

$ see Table 18

Table 25: Cochrane collaboration risk of bias tool on RCT on CT chest abdomen in follow-up (Mant, 2013)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	• Low risk of bias	Independent allocation
Allocation concealment (selection bias)	• Low risk of bias	Computerised algorithm
Blinding of participants and personnel (performance bias)	• Low risk of bias	No blinding but unlikely effect on outcome
Blinding of outcome assessment (detection bias)	• Low risk of bias	Analysis by independent researchers
Incomplete outcome data (attrition bias)	• Low risk of bias	Complete report
Selective reporting (reporting bias)	• Low risk of bias	Complete report
Other bias	• Unclear risk of bias	

3. GRADE – LEVEL OF EVIDENCE

Table 26 – Laparotomy versus laparoscopy: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall mortality OR: 0.90, 95% CI: 0.70-1.01	7	0	0	0	-1	0	4: Consistent with clinically important reduction in mortality	Moderate
Local recurrence OR: 0.82, 95% CI: 0.51-1.31	6	0	0	0	-2	0	4: CI includes both considerable benefit and considerable harm	Low
Distant metastases OR: 0.97, 95% CI: 0.78-1.21	8	0	0	0	-2	0	4: CI includes both considerable benefit and considerable harm	Low
Operative time WMD: 42.08, 95% CI : 29.87-54.30, favouring open surgery	5	0	0	0	0	0		High
Hospital stay WMD: -2.28, 95% CI: -4.05 - -0.52, favouring laparoscopy	6	0	0	0	-1	0	4: Consistent with clinically irrelevant reduction	Moderate
Peri-operative overall complications OR: 0.73, 95% CI: 0.56-0.95, favouring laparoscopy	9	0	-1	0	0	-1	2: Consistent with no difference 4: More imprecise studies give larger effects	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 27 – Single-incision vs. traditional multiport laparoscopic colorectal surgery: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall complication rate OR: 0.82, 95% CI: 0.63-1.08 [Lv]	19	-1	0	-1	-1	0	1: Majority of included studies not randomized; no blinding 3: Sample includes patients with other pathologies than CRC 4: Consistent with clinically important reduction in complications; most studies have small sample size	Very low
Overall conversion rate OR: 1.71; 95% CI: 0.97-3.00 [Lv]	18	-1	0	-1	-1	0	1: Majority of included studies not randomized 3: Sample includes patients with other pathologies than CRC 4: Consistent with clinically important reduction in conversion rate; most studies have small sample size	Very low
Operative time MD: -3.59, 95% CI: -10.59 - 3.77 [Lv]	20	-1	0	-1	-1	0	1: Majority of included studies not randomized 3: Sample includes patients with other pathologies than CRC 4: CI includes both considerable reduction and increase in operative time; most studies have small sample size	Very low
Post-operative hospital stay MD: -0.54, 95% CI: -0.95 - -0.12, favouring single incision laparoscopy [Lv]	20	-1	0	-1	-1	0	1: Majority of included studies not randomized 3: Sample includes patients with other pathologies than CRC 4: Consistent with clinically irrelevant reduction; most studies have small sample size	Very low

Table 28 – robotic versus laparoscopic surgery: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Total morbidity rate RAC: 6/35 vs. LAC: 7/35 (p=0.500)	1	-1	0	0	-2	0	1: No blinding 4: Small sample size (n=70)	Very low
Overall conversion rate (to open surgery) RAC: 0/35 vs. LAC: 0/35 (p=1.000)	1	0	0	0	-2	0	4: Small sample size (n=70)	Low
Operative time RAC: 195 min vs. LAC: 130 (p<0.001)	1	-1	0	-1	0	0	1: No blinding 3: Only 1 study; there may be a learning curve for the surgeon	Low
Post-operative hospital stay RAC: 7.9 days vs. LAC: 8.3 days (p=0.130)	1	0	0	-1	-1	0	3: Studied sample differed significantly from the population of interest 4: Small sample size (n=70)	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 29 – Enhanced recovery programs: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Mortality RD: 0, 95% CI: -0.01-0.02	7	0	0	-1	0	0	3: High variability in ERAS programs and not clear what ERAS really consisted of	moderate
Complications RR: 0.67, 95% CI: 0.52-0.86	11	0	0	-2	0	0	3: High variability in ERAS programs and not clear what ERAS really consisted of, pooling of variable complications	low
Readmissions RR: 076, 95% CI: 0.45-1.28	6	0	0	-1	-2	0	3: High variability in ERAS programs and not clear what ERAS really consisted of 4: Consistent with clinically important increase and decrease in readmissions	Very low
Hospital stay No pooled effect calculated	6	0	-1	-1	0	-1	2: Larger effect in smaller studies 3: High variability in ERAS programs and not clear what ERAS really consisted of 5: Funnel plot in favour of publication bias	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Overall grade: Very low

Table 30 – Stent as a bridge to surgery: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Morbidity Alcantara: in-hospital morbidity: 2/15 (13.3%) vs. 7/13 (53.8%) (p=0.042) Chueng: successful 1-stage operations: 67% vs. 38% (0.04) Ho: Complication rate: 35% vs. 58% (p=0.152) Pirlet: Abdominal complications: 7/30 vs. 7/30 (p=1.00) Sankararajah : 24% post-stenting + 14% post-elective surgery vs. 66% (numbers not reported) Van Hooft 2011: SAE RR 1.46 (95%CI 1.06-2.01) (p=0.02)	6	-1	-1	0	-1		1: four trials closed early for conflicting reasons 2: conflicting results 4: small trials, low number of events	Very low
Definitive colostomy OR 0.699; 95%CI 0.374 – 1.308	4	-1	0	0	-2	0	1: trials closed early for conflicting reasons 4: 95%CI includes both appreciable benefit and harm	Very low
Peri-procedural mortality OR 0.84; 95%CI 0.35 – 2.02	5	-1	0	0	-2	0	1: trials closed early for conflicting reasons 4: 95%CI includes both appreciable benefit and harm, low number of events	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 31 – Stent as palliative treatment for obstruction due to left sided colorectal cancer: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Morbidity Fiori: no significant difference Xinopoulos: no significant difference Van Hooft: large number of SAE in stent group	3	0	-1	0	-2	0	2: conflicting results 4: small sample size, low number of events	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 32 – Adjuvant chemotherapy stage II colon cancer: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Disease-free survival Meyers RR 0.84: 95%CI 0.75-0.94 Wu HR 0.86; 95%CI 0.75-0.98	 6 7	-1	0	0	-1	0	1:allocation concealment adequate in five trials only, often subgroup analysis 3: not downgraded in view overall LoE in spite of lack of uniform definition of patient selection 4: CIs includes clinical decision threshold	Low
Overall survival Meyers HR 0.87; 95%CI 0.78-0.97 Wu HR 0.81; 95%CI 0.71-0.91	 9 7	-1	0	0	-1	0	1:allocation concealment adequate in five trials only, often subgroup analysis 3: not downgraded in view overall LoE in spite of lack of uniform definition of patient selection 4: CIs includes clinical decision threshold	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 33 – Adjuvant chemotherapy for elderly patients: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Cancer specific survival (adjusted analysis) Abraham 2013, Zuckerman 2009: colon cancer specific mortality lower with the use of adjvant chemotherapy in each age stratum ≥ 65 years.	2 observational studies	0	0	0	0	0		Low
Safety Gross 2007 : no difference in 1-year hospitalisation rate in elderly patients with a chronic condition with or without adjuvant chemotherapy Kahn 2010: statistically significant difference in yearly late adverse event rate	2 observational studies	0	-1	0	0	0	2: contradicting results based on different outcome measures 4: not down-graded as already downgraded for heterogeneity	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 34 – Systemic chemotherapy with or without radiofrequency ablation for unresectable liver metastases: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
PFS at 3 years HR 0.63; 95%CI 0.42-0.95	1 RCT	0	-1	0	-1	0	2: single study 4: CI includes clinical decision threshold, sample size < 400	Low
OS 61.7% (95%CI 48.2-73.9%) in the RFA group versus 57.6% (95%CI 44.1-70.4%) in the CT only group	1 RCT	0	-1	0	-1	0	2: single study 4: sample size < 400, wide overlapping CI for OS estimations	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 35 – hepatic artery infusion (HAI) in unresectable CRCliver metastases: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Risk of death HR 0.90; 95%CI 0.76 to 1.07 (P = 0.24)	10	-1	-1	0	-1	0	1: only 2/10 high quality trials, 4/10 crossover trials 2: unexplained heterogeneity 4: CI includes effect and no effect	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 36 – Chemo-embolization for unresectable colorectal liver metastases: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Chemo-embolization versus chemotherapy								
Overall survival HR 0.60; 95%CI 0.08-0.97	1	0	-1	-1	-1	0	2: Only one study 3. Control chemotherapy was less performing 4: OIS not met and CI compatible with clinically unimportant effect	Very Low
Progression-free survival HR 0.51; 95%CI 0.32, 0.82	1	-1	-1	-1	-1	0	1. outcome assessment not blinded 2: Only one study 3. Control chemotherapy was less performing 4: OIS not met	Very Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 37 – Radio-embolization for unresectable colorectal liver metastases: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
SIRT + chemotherapy versus chemotherapy								
Progression-free survival HR 0.23; 95%CI 0.08-0.68	1	0	-1	-1	-1	0	2: Only one study 3. Control chemotherapy was less performing 10 years ago. 4: OIS not met	Very Low
Overall survival HR 0.22; 95%CI 0.07-0.74	1	0	-1	-1	-1	0	2: Only one study 3. Control chemotherapy was less performing 10 years ago 4: OIS not met	Very Low
SIRT + HAI vs. HAI								
Progression-free survival **HR: 0.72; 95%CI 0. 43-1.21**	1	0	-1	0	-2	0	2: Only one study 4: OIS not met+ confidence interval compatible with considerable harm or considerable benefit	Very Low
Overall survival **HR 0.62; 95%CI 0.37-1.05**	1	0	-1	0	-2	0	2: Only one study 4: OIS not met+ CI includes effect and no effect	Very Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

SIRT after failed chemotherapy

We attribute a moderate level of evidence based on the study of Hendlisz et al. 2010[31], despite the fact that an effect on progression free survival but no effect on overall survival could be demonstrated, due to cross over after progression.

Table 38 – Radio-embolization for unresectable colorectal liver metastases refractory to systemic chemotherapy: GRADE profile

SIRT + chemotherapy versus chemotherapy								
Progression-free survival HR = 0.51; 95% CI, 0.28 to 0.94	1	0	-1	0	0	0	2: only one study	moderate
Overall survival HR = 0.92; 95% CI, 0.47 to 1.78	1	0	-1	0	-1	0	2: only one study 4 CI includes no effect	Low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 39 – cytoreductive surgery and HIPEC: GRADE profile

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Median overall survival *(no pooled estimate)*	3	-1	0	0	0	0	1: all studies have serious methodological limitations	Very low
Median disease-free survival *(22.8 (HIPEC) vs. 13.0 months, p=0.02)*	1	-1	0	0	0	0	1: all studies have serious methodological limitations	Very low
Postoperative mortality 37% *(HIPEC)* vs. 19%, p=0.2	1	-1	0	0	0	0	1: all studies have serious methodological limitations	Very low
Morbidity 37% *(HIPEC)* vs. 19%, p=0.2	1	-1	0	0	0	0	1: all studies have serious methodological limitations	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Overall grade: Very low

Table 40 – Oral versus IV fluoropyrimidines: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Oral versus IV pyrimidines + oxaliplatin								
Progression-free survival HR 1.07; 95%CI 0.98-1.16	4	-1	0	0	-1	0	1: blinding in none of the studies 4: CI includes significant benefit for 5FU (HR > 1.1)	Low
Overall survival HR 1.01; 95%CI 0.93-1.11	5	0	0	0	-1	0	4: CI includes significant benefit for 5FU (HR > 1.1)	Moderate
Oral versus IV pyrimidines + irinotecan								
Progression-free survival HR 1.35; 95%CI 1.07-1.70	2	-2	0	0	-1	0	1: both trials closed early 4: CI includes no significant effect and appreciable benefit 5FU	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 41 – Oxaliplatin-based versus irinotecan-based chemotherapy: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival WMD -2.04 months; 95%CI -3.54 to -0.54 months	6	-1	-1	0	-1	0	1: allocation concealment unclear in all studies 2: heterogeneity visible on forest plot 4: upper boundary of CI includes clinically no significant effect	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 42 – Sequential versus combined first-line chemotherapy for mCRC: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Overall survival HR 1.01; 95%CI 0.93-1.11	3	0	0	0	0	0		High

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 43 – Adding bevacizumab to first-line chemotherapy for mCRC: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Progression-free survival HR 0.59; 95%CI 0.46 to 0.74	6	-1	0	0	0	0	1: no blinding, no ITT in 3/6 studies	Moderate
Overall survival HR 0.82; 95%CI 0.71 to 0.94	7	0	0	0	-1	0	1: blinding considered as not introducing risk of bias for OS 4: CI includes clinical decision threshold (0.94 clinically non-significant effect)	Moderate

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

Table 44 – – Adding cetuximab or panitumumab to first-line chemotherapy +/- bevacizumab for mCRC: GRADE profiles

Results	No. of studies	1	2	3	4	5	Reasons for downgrading	GRADE
Cetuximab/panitumumab added to chemotherapy								
Progression-free survival HR 0.82; 95%CI 0.69-0.96	6	-1	0	0	-1	0	1: No blinding in all studies, possible selection bias for KRAS status 2: statistical heterogeneity but explained 4: CI includes clinical decision threshold	Low
Overall survival HR 0.89; 95%CI 0.80-0.99	6	-1	0	0	-1	0	1: possible selection bias for KRAS status 4: CI includes clinical decision threshold	Low
Cetuximab/panitumumab added to chemotherapy + bevacizumab								
Progression-free survival HR 1.27; 95%CI 1.06-1.51	3	-2	0	0	0	0	1: unclear allocation concealment and no blinding in both studies, possible selection bias for KRAS status	Low
Overall survival HR 1.51; 95%CI 0.74-3.08	2	-1	0	0	-2	0	1: unclear allocation concealment, possible selection bias for KRAS status 4: CI includes appreciable harm and appreciable benefit	Very low

1. Limitations 2. Inconsistency 3. Indirectness 4. Imprecision 5. Reporting bias

4. EVIDENCE TABLES

4.1. Guidelines

4.1.1. Diagnosis

Colonoscopy

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	In the diagnosis of colorectal cancer, the gold standard for making the diagnosis is a biopsy, which can only be achieved by colonoscopy.		
SIGN 2011[10]	March 2011	Colonoscopy is recommended as a very sensitive method of diagnosing colorectal cancer, enabling biopsy and polypectomy.		Recommendation D
IKNL 2008[14]	February 2006	To confirm or rule out colon cancer, colonoscopy (preferably in conjunction with histological confirmation) is the technique of choice.	Colonoscopy has a sensitivity of 79-100% for detecting colon cancer B De Zwart 2001	2
		Tattooing the tumour during colonoscopy facilitates perioperative localisation of the tumour.	Tumour demarcation using submucosal tattooing during colonoscopy prior to laparoscopic surgery provides adequate visualisation and localisation of the tumour in 86-98% of patients.C Feingold 2004; B Fu 2001	3
		If complete visualisation of the colon is not performed preoperatively due to stenosing tumour or other reasons, colonoscopy should be performed within 3 months after surgery.		
New Zealand guidelines group[9]	2011	Preoperative assessment should include colonoscopy of the entire large bowel. If proximal parts of the colon are not directly visualised preoperatively, postoperative repeat colonoscopy should be undertaken within 12 months.		C

Computed tomographic colonography versus barium enema and other imaging modalities

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	If the endoscope cannot pass the cancer, the rest of the colon has not been imaged and this should be done using the best alternative investigation, usually barium enema or CT colonography. It may be that radiological investigations can make the diagnosis and allow a decision to operate and the histology is obtained from the pathology specimen.		
SIGN 2011[10]	March 2011	CT colonography can be used as a sensitive and safe alternative to colonoscopy.		Recommendation C
IKNL 2008[14]	February 2006	CT colonography or barium enema is indicated as a diagnostic or adjuvant diagnostic test for patients with incomplete colonoscopy without diagnosis, when colonoscopy is not possible, or when precise tumour localisation is needed and not sufficiently determined by colonoscopy.		Level 2
		As a second-line diagnostic test to detect or rule out colorectal carcinoma, CT colonography is preferred over barium enema.		Level 3
		MR colonography is to be considered in young patients and pregnant women in order to avoid radiation but experience is limited.		Level 3
New Zealand guidelines group[9]	2011	Where complete examination is not possible, imaging of the proximal colon with CT colonography (or with barium enema if CT colonography is not available) is recommended.		C

4.1.2. Staging

CT chest-abdomen-pelvis

Table 45 – Evidence table: guidelines staging CT thorax-abdomen

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IKNL Colorectale levermetastasen 2006[16]	2005	At diagnosis a chest X ray is sufficient to screen for lung metastases because of their low prevalence. CT has higher sensitivity and results in more false positive examinations.	Observational studies	3
		CT or MRI of the liver are indicated prior to resection of the primary tumour. In doubt, the examination is to be repeated after 3 months. A CT should examine the entire abdomen. If the liver cannot be visualized well by sonography, or in case of unexplained elevated CEA, CT or MRI are indicated. The choice of either examination, with intravenous contrast, will depend on the local situation, cost and available expertise.	Cross-sectional studies	3
IKNL 2008[14]	February 2006	**Loco-regional staging**: abdominal CT is indicated for patients suspected of having a locally advanced tumour or if laparoscopic resection is planned. Due to practical considerations (choice and sequence of therapy), abdominal/hepatic CT can be used routinely for staging. Screening for **distant metastases** should be done with abdominal CT and chest x-ray	Observational studies	Level 2 Level 3
NICE 2011[8]	February 2011	Offer contrast enhanced CT of the chest, abdomen and pelvis, to estimate the stage of disease, to all patients diagnosed with colorectal cancer unless it is contraindicated. No further routine imaging is needed for patients with colon cancer.	SR of (low quality) observational studies	
SIGN 2011[10]	March 2011	All patients with colorectal cancer should be staged by contrast enhanced CT of the chest, abdomen and pelvis unless the use of intravenous iodinated contrast is contraindicated.	Cohort studies with a high risk of bias	Recommendation D

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
SFCD et ACHBT[7]	2011	During the diagnostic workup for synchronous LMCRC, the imaging investigation should be identical to that for metachronous LMCRC and should include a CT scan of the chest, abdomen, and pelvis, with contrast enhancement; a liver MRI should be performed in the case of diagnostic doubt.		C
		When curative resection of LMCRC is possible, 18-FDG scintigraphy and CT should be performed,as well as the CT scan of chest, abdomen,and pelvis, to look for extrahepatic lesions.		C

PET-CT

Table 46 – Evidence table: guidelines staging PET-CT

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
New Zealand guidelines group[9]	2011	PET-CT scanning is not recommended as part of routine preoperative assessment of non-metastatic colon cancer		C
NICE 2011[8]	February 2011	If the CT scan shows metastatic disease only in the liver and the patient has no contraindications to further treatment, a specialist hepatobiliary MDT should decide if further imaging to confirm surgery is suitable for the patient – or potentially suitable after further treatment – is needed	MA of diagnostic accuracy studies	
		Research recommendation: a prospective trial should be conducted to investigate the most clinically effective and cost-effective sequence in which to perform MRI and PET-CT, after an initial CT scan, in patients with colorectal that has metastasised to the liver, to determine whether the metastasis is resectable. The outcomes of interest are reduction in inappropriate laparotomies and improvement in overall survival.		
		Research recommendation: a prospective, multi-centre		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		observational study of the quality, sensitivity, specificity and cost-effectiveness of using PET-CT in the management of patients with colorectal cancer should be conducted.		
SIGN 2011[10]	March 2011	In patients with apparently organ-restricted liver or lung metastases (either at primary presentation or during follow up) who are being considered for resection, a PET/CT scan should be considered prior to the administration of cytoreductive chemotherapy. The identification of occult metastatic disease prior to resection or chemotherapy may render resection inappropriate or may alter patient's management. FDG PET/CT should be used in the evaluation of patients with raised tumour marker CEA with negative or equivocal conventional imaging or assessment of possible pelvic recurrence and pre-sacral mass following treatment.		Recommendation C Recommendation D
IKNL Colorectale levermetastasen 2006[16]	2005	PET/CT is not first choice for the detection of liver metastases but can be considered when CT or MRI do not allow clear definition of lesions. PET/CT can be considered to rule out extra hepatic disease in patients with resectable metastases diagnosed with CT. When PET/CT is available it can replace other imaging techniques for detection of liver and extra hepatic lesions.		Level 1 Level 1 Level 3
Cancer Care Ontario 2010[12]	May 2008	The routine use of PET is not recommended for the diagnosis or staging of clinical Stage I-III colorectal cancers. PET is recommended for determining management and prognosis if conventional imaging is equivocal for the presence of metastatic disease.	Observational studies	
SFCD et ACHBT[7]	2011	When curative resection of LMCRC is possible, FDG PET and CT should be performed, as well as the CT of chest, abdomen,and pelvis, to look for extrahepatic lesions.		C

MRI Liver

Table 47 – Evidence table: guidelines staging MRI Liver

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	If the CT scan shows metastatic disease only in the liver and the patient has no contraindications to further treatment, a specialist hepatobiliary MDT should decide if further imaging to confirm surgery is suitable for the patient – or potentially suitable after further treatment – is needed	MA of diagnostic accuracy studies	
		Research recommendation: a prospective trial should be conducted to investigate the most clinically effective and cost-effective sequence in which to perform MRI and PET-CT, after an initial CT scan, in patients with colorectal that has metastasised to the liver, to determine whether the metastasis is resectable. The outcomes of interest are reduction in inappropriate laparotomies and improvement in overall survival.		
IKNL Colorectale levermetastasen 2006[16]	2005	If the liver cannot be visualized well by sonography, or in case of unexplained elevated CEA, CT or MRI are indicated. The choice of either examination, with intravenous contrast, will depend on the local situation, cost and available expertise.		

4.1.3. Multidisciplinary team meeting (MDT)

Table 48 – Evidence table: guidelines MDT

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IKNL Colorectale levermetastasen 2006[16]	2005	Medical centers in charge of diagnosing CRC should have multidisciplinary teams consisting of specialists in internal medicine, surgery, radiology, nuclear mediciane, interventional radiology and radiotherapy.		

4.1.4. Pathology

Table 49 – Evidence table: guidelines pathology reporting

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
SIGN 2011[10]	March 2011	Pathological reporting of colorectal cancer resection specimens should include information on: tumour differentiation, staging (Dukes and TNM systems),margins (peritoneal and CRM), extramural vascular invasion All reporting of colorectal cancer specimens should be done according to, or supplemented by, the Royal College of Pathologists' minimum data set.		Recommendation B
IKNL 2008[14]	February 2006	The pathology report should include at least the following information: • histological tumour type • histological tumour grade • extent of invasion (T stage) • distance between the tumour and the nearest resection margin, and the completeness of resection • number of excised and affected lymph nodes (N stage) • tumour size The following information is optional: • perineural invasion • macroscopic description of the tumour • vascular invasion • lymphatic invasion		NA

Table 50 – Evidence table: guidelines evaluation of lymph nodes

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IKNL 2008[14]	February 2006	Determining the lymph node status of a patient requires evaluating as many lymph nodes as possible using conventional techniques (HE without pre-treatment). A minimum of 10 lymph nodes is recommended to establish a negative lymph node status.	There is evidence that a better estimation of stage and prognosis can be made as the number of lymph nodes examined increases. C Cserni 2002 Recommendations regarding the minimum number of lymph nodes that must be evaluated range from nine to as many as possible. C.Cianchi 2002, Yosihimatsu 2002, Cserni 2002	Level 3 Level 4

4.1.5. Endoscopic treatment stage I

Table 51 – Evidence table: guidelines endoscopic treatment stage I

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	The colorectal MDT should consider further treatment for patients with locally excised, pathologically confirmed stage I cancer taking into account pathological characteristics of the lesion, imaging results and any previous treatments.	Expert opinion	No evidence
		Offer further treatment to patients whose tumour had involved resection margins (less than 1 mm).	Retrospective case series	
		Discuss the risks and benefits of all treatment options with the patient after discussion in the MDT.	Expert opinion	No evidence
SIGN 2011[10]	March 2011	Further surgery for pedunculated polyp cancers that have been removed endoscopically is indicated if: • there is histological evidence of tumour at, or within 1 mm of, the resection margin • there is lymphovascular invasion	2 cohort studies	2^{+}

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		• the invasive tumour is poorly differentiated.		
NZGG 2011[9a]	June 2004	Adenomas with focal malignancy may be managed safely by endoscopic polypectomy provided strict criteria for patient selection and histopathological assessment are adhered to. In particular, adenomas with focal malignancy should be well or moderately differentiated and excision should be complete.		III-2 (NHMRC)
NHMRC, 2011[32b]	December 2009	Management of malignant polyps by polypectomy alone is standard practice and is acknowledged to be safe, providing that there is adherence to a strict policy of case selection and histopathological assessment recognising four key features that together identify a very low risk of lymph node metastasis: • a clear margin of excision (1 to 2mm) • cancer which is well- or moderately-differentiated • absence of lymphatic or venous invasion • complete removal as assessed endoscopically	1 case-control study 5 case series 1 narrative review	
		Malignant polyps with unfavourable features may require further treatment, but this decision should be made on the basis of the age, site, health and wishes of the patient. For colonic polyps, excision can be achieved successfully by laparotomy with colonic resection or laparoscopically assisted colectomy.	1 systematic review[34] (based on Medline search only; no quality appraisal; only retrospective case series retrieved) 1 RCT[35] 2 narrative reviews	
IKNL 2008[14]	February 2006	Not covered		

[a] The New Zealand Guidelines Group clinical guideline on the Management of Early colorectal Cancers (2011[9]) is based on the 2005 National Health and Medical Research Council (NHMRC) guideline.

[b] First full version published in 1999, updated in 2005[33]; (partial) update "Clinical Practice Guidelines for Surveillance Colonoscopy - in adenoma follow-up, following curative resection of colorectal cancer, and for cancer surveillance in inflammatory bowel disease" in December 2011, and online available on regularly updated wiki platform (last update: 24 November 2012).

4.1.6. Laparoscopic treatment

Table 52 – Evidence table: guidelines laparoscopic treatment

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8] (recommendations copied from NICE 2006[36c])	February 2011	Laparoscopic (including laparoscopically assisted) resection is recommended as an alternative to open resection for individuals with colorectal cancer in whom both laparoscopic and open surgery are considered suitable.		
		Laparoscopic colorectal surgery should be performed only by surgeons who have completed appropriate training in the technique and who perform this procedure often enough to maintain competence. The exact criteria to be used should be determined by the relevant national professional bodies. Cancer networks and constituent trusts should ensure that any local laparoscopic colorectal surgical practice meets these criteria as part of their clinical governance arrangements.		
		The decision about which of the procedures (open or laparoscopic) is undertaken should be made after informed discussion between the patient and the surgeon. In particular, they should consider: o the suitability of the lesion for laparoscopic resection o the risks and benefits of the two procedures o the experience of the surgeon in both procedures.	Expert opinion	No evidence
SIGN 2011[10]	March 2011	Laparoscopic and open surgery can be offered for resection of colorectal cancer.	2 systematic reviews	$1^{+}/1^{++}$
		Surgery for colorectal cancer should only be carried out by appropriately trained surgeons whose work is audited.	2 SR	2^{++}

[c] The recommendations formulated in NICE 2006 'Laparoscopic surgery for colorectal cancer' were formulated by the technology appraisal and not by the guideline developers.

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NZGG 2011[9]	June 2004	In experienced hands, laparoscopic surgery for colon cancer has equivalent outcomes to conventional surgery.		I (NHMRC)
		Elective surgery for colon cancer should be performed by a surgeon with specific training and experience in colorectal surgery, and with sufficient caseload to maintain surgical skills		B (NZGG)
IKNL 2008[14]	February 2006	Laparoscopic surgery for colon cancer is safe and at least as effective as open surgery, provided that the surgeon has sufficient expertise.	Short-term: 2 SR & 1 RCT Long term: 2 SR	
		Given the prolonged learning curve associated with laparoscopic surgery, it is very important that the surgeon is adequately trained before practicing this technique on his or her own. (The American Society of Colon and Rectal Surgeons (ASCRS) and the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) have developed minimum requirements that surgeons must meet before they can perform laparoscopic surgery with curative intent in patients with cancer.)	1 case series	
		Surgeons must perform at least 20 laparoscopic colon operations for benign or incurable diseases before starting laparoscopic colon surgery with curative intent. The working group is of the opinion that these international guidelines should also be applied in the Netherlands. It should be noted that the first 20 procedures are performed preferably under the supervision of an expert surgeon. Under these conditions, both benign and curative laparoscopic colorectal resections can be performed.	1 case series	

4.1.7. Treatment of acute obstructions

Table 53 – Evidence table: guidelines: treatment of acute obstruction

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	If considering the use of a colonic stent in patients presenting with acute large bowel obstruction offer CT of the chest, abdomen and pelvis to confirm the diagnosis of mechanical obstruction, and to determine whether the patient has metastatic disease or colonic perforation.	2 case series	
		Do not use contrast enema studies as the only imaging modality, in patients presenting with acute large bowel obstruction.		
		A consultant colorectal surgeon should consider inserting a colonic stent in patients presenting with acute large bowel obstruction. They should do this together with an endoscopist or a radiologist (or both) who is experienced in using colonic stents.		
		Resuscitate patients with acute large bowel obstruction, then consider placing a self-expanding metallic stent to initially manage a left-sided complete or near-complete colonic obstruction.		
		Do not place self-expanding metallic stents: o in low rectal lesions **or** o to relieve right-sided colonic obstruction **or** o if there is clinical or radiological evidence of colonic perforation or peritonitis.	Case series	
		Do not dilate the tumour before inserting the self-expanding metallic stent.		
		Only a healthcare professional experienced in placing colonic stents who has access to fluoroscopic equipment and trained support staff should insert colonic stents.		

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		If a self-expanding metallic is suitable, attempt insertion urgently and no longer than 24 hours after patients present with colonic obstruction.	Case series	
SIGN 2011[10]	March 2011	Mechanical large bowel obstruction should be distinguished from pseudo-obstruction before surgery.	1 case-control or cohort study (only title available)	2^+
		Patients with malignant obstruction of the large bowel should be considered for immediate resection.	1 review	2^+
		If immediate reconstruction after resection is deemed feasible, segmental resection is preferred for left-sided lesions.	1 RCT	1^{++}
		Where facilities and expertise are available, colonic stenting can be considered for the palliation of patients with obstructing colon cancer, ie in those who are not fit for immediate resection or in those with advanced disease. The risk of colonic perforation should be taken into account.	1 SR & 3 RCTs	2^+
		Stenting as a bridge to surgery in patients fit for immediate resection should only be performed as part of a randomised controlled trial.	Expert opinion	4
NZGG 2011[9]	June 2004	Primary anastomosis should be considered as a colectomy, with an ileocolic or ileorectal anastomosis.	SR (based on (historical) case-control studies)	III-2 (NHMRC)
		Primary anastomosis could be considered for left-sided obstruction and may need to be preceded by on table colonic lavage.	SR (based on (historical) case-control studies)	III-2 (NHMRC)
		Primary resection of obstructing carcinoma is recommended unless the patient is moribund.	SR (based on (historical) case-control studies)	B (NZGG)
		Colonic stenting for palliation of left-sided bowel obstruction in people with colorectal cancer is recommended, if endoscopic expertise can be readily accessed.	SR (based on (historical) case-control studies)	B (NZGG)
		Colonic stenting as a bridge to surgery for left-sided bowel obstruction in people with colorectal cancer may be considered for an individual, if endoscopic expertise can be readily accessed.	SR (based on (historical) case-control studies)	C (NZGG)

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		People with colorectal cancer who have bowel obstruction and are being considered for colonic stenting should be invited to participate in randomised controlled trials, where these are available.	Expert opinion	
IKNL 2008[14]	February 2006	The gastroenterologist and the surgeon should consult before treating patients with acute obstruction in the colon due to colon cancer. Stent placement should be discussed, particularly if there is evident colon dilatation proximal to the obstruction and if acute stent placement is feasible.	Expert opinion	No evidence
		Enrolment of patients with acute colon obstruction in a clinical trial, in which surgical treatment is compared with stent placement with or without subsequent surgery, should be encouraged as much as possible.	Expert opinion	No evidence
		If participation in a study is not possible, then primary stent placement followed within a few weeks by resection with primary anastomosis is preferred over immediate surgical treatment, provided that sufficient expertise with acute decompression of the obstructed colon when stent placement is available.	1 review (based on 29 case series), 1 review (based on 54 studies), 1 RCT, 1 prospective study, 3 cohort studies and 1 decision-theory analysis	Moderate
		For patients undergoing primary surgical correction of an acute colon obstruction, resecting the tumour during the first operation is recommended.	1 SR (based on 1 low-level comparative study)	
		For patients with an albumin level < 20 mmol/l, ascites, or poor nutritional status (> 5% weight loss in 1 month or > 10% over the last 6 months), a very conservative approach should be used with regard to primary anastomosis following resection.	1 RCT, 1 comparative study and 1 case series	

4.1.8. Adjuvant chemotherapy stage II-III colon cancer

Table 54 – Evidence table: guidelines adjuvant chemotherapy stage II

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Consider adjuvant chemotherapy after surgery for patients with high-risk stage II colon cancer. Fully discuss the risks and benefits with the patient.	RCTs	Low to very low (downgraded for inconsistency, indirectness and imprecision)
SIGN 2011[10]	March 2011	*The evidence identified was of insufficient quality to determine the use of any novel prognostic or predictive marker to aid decision making in this group of patients.*		
NZGG 2011[9]	June 2004	People with resected node negative colon cancer (Stage II) with poor prognostic features may be offered postoperative chemotherapy. Discussion of risks and benefits of treatment should include the potential but uncertain benefits of treatment and the potential side effects.	3 SR & 4 RCTs	C (NZGG)
		Irinotecan should not be given as postoperative adjuvant chemotherapy for people with Stages I, II and III colon cancer.		A
CCO 2011[37]	November 2010	The routine use of adjuvant chemotherapy for all patients with stage II colon cancer is not recommended. However, the subset of patients with high-risk stage II disease who should be considered for adjuvant therapy includes patients with inadequately sampled nodes, T4 lesions, perforation or poorly differentiated histology.	Not clear	
		The ultimate clinical decision should be based on discussions with the patient about the nature of the evidence supporting treatment, the anticipated morbidity of treatment, the presence of high-risk prognostic features on individual prognosis and patient preferences.	Expert opinion	
		When treated with adjuvant therapy, high-risk stage II patients should receive similar regimens to those	Not clear	

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		recommended for stage III patients.		
		The enrolment of resected high-risk stage II patients in clinical trials is encouraged. Additional trials comparing adjuvant therapy with observation are needed and are ethically acceptable in stage II colon cancer.	Expert opinion	
IKNL 2008[14]	February 2006	For patients with high-risk stage II colon cancer, adjuvant chemotherapy should be considered. With regard to the choice of chemotherapy, the same considerations apply here as for stage III disease.	1 meta-analysis (based on 5 studies), 1 SR (based on 37 RCTs and 11 meta-analuses) and pooled data-set from 7 RCTs)	High

Table 55 – Evidence table: guidelines adjuvant chemotherapy stage III

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8] **(recommendations copied from NICE 2006**[38d]**)**	February 2011	The following are recommended as options for the adjuvant treatment of patients with stage III (Dukes C) colon cancer following surgery for the condition: • capecitabine as monotherapy • oxaliplatin in combination with 5-fluorouracil and folinic acid.		
		The choice of adjuvant treatment should be made jointly by the individual and the clinicians responsible for treatment. The decision should be made after an informed discussion between the clinicians and the patient; this discussion should take into account contraindications and the side-effect profile of the agent(s) and the method of administration as well as the clinical condition and preferences of the individual.	Expert opinion	No evidence
SIGN 2011[10]	March 2011	All patients with Stage III colorectal cancer should be considered for adjuvant chemotherapy.	SR & RCTs	$1^{++}/1^{+}$

[d] The recommendations formulated in NICE 2006 'Capecitabine and oxaliplatinin the adjuvant treatment of stage III (Dukes' C) colon cancer. Technology Appraisal 100' were formulated by the technology appraisal and not by the guideline developers.

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		Decisions concerning adjuvant therapy for patients over the age of 75 with Stage III colorectal cancer should be based on a balance between the risks and the potential benefits of treatment. Biological age may be more relevant than chronological age in making these decisions.	Expert opinion	4
NZGG 2011[9]	June 2004	People with resected node positive colon cancer (Stage III) should be offered postoperative chemotherapy unless there is a particular contraindication, such as significant co-morbidity or poor performance status.	1SR & 1 RCT	A (NZGG)
		For people with colon cancer who are to receive single agent postoperative chemotherapy, either capecitabine or bolus fluorouracil plus leucovorin are appropriate regimens.	1 RCT	B (NZGG)
		For people with resected node positive colon cancer (Stage III) who are to receive postoperative chemotherapy, combination chemotherapy with oxaliplatin and a fluoropyrimidine is recommended.	1 RCT	A
		Irinotecan should not be given as postoperative adjuvant chemotherapy for people with Stages I, II and III colon cancer.	3 RCTs	A
CCO 2011[37]	November 2010	The Gastrointestinal Cancer DSG recommends that patients with completely resected stage III colon cancer should be offered adjuvant chemotherapy and that this treatment should start within 8 weeks of surgery.	Meta-analyses of RCTs	
		Treatment should depend on factors such as patient suitability and preference, and patients and clinicians must work together to determine the optimal course of treatment.	Expert opinion	
		The recommended treatment option is 5-FU given intravenously in combination with LV and oxaliplatin in the regimens known as FOLFOX or FLOX. These 5-FU/LV/oxaliplatin regimens have shown superior DFS when compared with 5-FU plus LV and are the recommended regimens. Oxaliplatin administration is	RCTs	

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		associated with a 1% risk of persistent grade 3 neuropathy, which needs to be considered in conjunction with expected benefits of therapy.		
		Some patients would not be considered appropriate for oxaliplatin regimens. Examples include patients with underlying neurological conditions or at increased risk of neuropathy, patients at increased risk for infections and patients likely to poorly tolerate infections as a result of chemotherapy. For these patients, the treatment options are: • Oral capecitabine administered for 6 months, which has equivalent efficacy to intravenous 5-FU/LV. Capecitabine results in significantly less diarrhoea, stomatitis, neutropenia, nausea/vomiting and alopecia, but significantly more hand-foot syndrome when compared with 5-FU/LV. • 5-FU in combination with LV given for 6 months using either the weekly or monthly schedule.	RCTs	
		Suitable patients should be offered entry into clinical trials testing neoadjuvant treatments for resected stage III colon cancer.	Expert opinion	
IKNL 2008[14]	February 2006	FOLFOX is the adjuvant chemotherapy regimen of choice for stage III colon cancer.	1 RCT and 1 conference abstract	Moderate
		The oral 5-FU analogue capecitabine is at least as effective as 5-FU in the metastatic setting and has a more favourable toxicity profile than 5-FU when used alone or in combination with other agents; therefore, capecitabine may also replace 5-FU in the adjuvant setting.	1 RCT	Moderate
		Patients with advanced age and/or comorbidity may receive monotherapy with capecitabine or UFT/LV.	RCT	

Table 56 – Evidence table: guidelines resection of synchronous or metachronous CRC liver metastases

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IKNL 2008[14]	February 2006	No commentary		
IKNL Colorectale levermetastasen 2006[16]	June 2006	Resection of liver metastases (+/- other local treatment modalities) should preferably be performed in centres with sufficient expertise and experience and the availability of the necessary infrastructure.	none	
		Resection of CRC liver metastases should be registered in order to evaluate outcomes and better define clear indications for surgery in the future.	none	
		Resection of synchronous liver metastases should be considered. Simultaneous resection if primary tumour and synchronous liver metastases is discouraged. OS is comparable for simultaneous and staged resection in case of minimal interval of 2 to 3 mo – in case of a shorter interval surgery could be avoided in 2/3 of patients b/o disease progression	Lyass S 2001, Vogt P 1991; Lambert LA 2000	LoE 3
SIGN 2011[10]	February 2011	Surgical resection should be considered for all patients with resectable liver metastases	Case series	LoE 4
		Patients with resectable liver metastases should be considered for perioperative chemotherapy with a combination of oxaliplatin and 5-FU/leucovorin for a total period of six months.	1 RCT	LoE 4
NICE 2011[8]	February 2011	If both primary and metastatic tumours are considered resectable, anatomical site-specific MDTs should consider initial systemic treatment followed by surgery, after full discussion with the patient. The decision on whether the operations are done at the same time or separately should be made by the anatomical site-specific MDTs in consultation with the patient.	1 SR (1 on non resectable metastases), 1 RCT, 3 retrospective case series studies, 2 case matched, 1 non-matched case series	Very low (GRADE):
Cancer Care Ontario 2012[39]	June 2012 (report date)	Peri-operative chemotherapy, either before and after resection, or after resection, is recommended in patients with resectable liver metastatic disease.	Systematic review of 3 RCT's and 28 case series	

Table 57 – Evidence table: guidelines cytoreductive surgery and HIPEC

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Not covered		
SIGN 2011[10]	March 2011	Not covered		
NZGG 2011[40]	June 2004	Not covered		
IKNL 2008[14]	February 2006	Treatment with HIPEC may be considered for patients with metastases limited to the abdominal cavity, provided that the number of metastatic sites is limited and the metastases can be removed radically by surgery.	Non-randomized comparative study	Low

Table 58 – Evidence table: guidelines first-line systemic treatment of metastatic colorectal cancer

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
IKNL 2008[14]	02-2006	In asymptomatic patients with irresectable, measurable disease, systemic therapy should not be delayed	3 RCTs	
		Combined fluoropyrimidine-based chemotherapy and bevacizumab is the standard first-line treatment for patients in good general condition (WHO PS 0-1) without contraindications for the use of bevacizumab	3 RCTs	
		Oral fluoropyrimines are preferred above IV 5-FU/LV as side effects are less common and oral administration is also safe in combination therapy	4 RCTs	
		Both oxaliplatin or irinotecan are considered valuble options for first line treatment. If 5FU is given in combination with irinotecan,it should be administered as continuous infusion and not as a bolus infusion as the latter is associated with increased toxicity.	Review based on 7 RCTs	
		Combination therapy of fluoropyrimidines with irinotecan or oxaliplatin has no significant benefit compared to sequential treatment with these agents.	2 prospective studies	
SIGN 2011[10]	February 2011	All patients with metastatic colorectal cancer should be considered for chemotherapy.	Several SRs	1++

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		Combination treatment with 5-FU/Leucovorin/oxaliplatin or capecitabine and oxaliplatin or 5-FU/leucovorin/irinotecan are the preferred options in patients with with good performance status and organ function.	RCTs, MA	1+/1++
		Consider raltitrexed for patients with metastatic colorectal cancer who are intolerant to 5-FU and leucovorin, or for whom these drugs are not suitable.	RCT	1+
		Although the use of bevacizumab is associated with improved outcomes in patients with metastatic colorectal cancer , it is currently not recommended by the Scottish Medicines Consortium (due to insufficient evidence of cost effectiveness).		
NICE 2011[8]	February 2011	When offering multiple chemotherapy drugs to patients with advanced and metastatic colorectal cancer, consider one of the following sequences of chemotherapy unless they are contraindicated: FOLFOX as first-line treatment then single agent irinotecan as second line treatment OR FOLFOX as first-line treatment then FOLFIRI as second-line treatment OR XELOX as first-line treatment then FOLFIRI as second-line treatment	Mixed treatment comparison (indirect modelling)	
		Decide which combination and sequence of chemotherapy to use after full discussion of the side effects and the patient's preferences.		
		Consider raltitrexed only for patients with advanced colorectal cancer who are intolerant to 5-FU and leucovorin, or for whom these drugs are not suitable (for example, patients who develop cardiotoxicity). Fully discuss the risk and benefits of raltitrexed with the patient.	1 RCT with indirect evidence, one randomized phase II trial and some non-randomized phase II trials	

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
		Oral therapy with either capecitabine or tegafur with uracil (in combination with folinic acid) is recommended as an option for the first-line treatment of metastatic colorectal cancer.	NICE technology appraisal 61 (2003)[$]	
		The choice of regimen (intravenous 5-fluorouracil and folonic acid or one of the oral therapies) should be made jointly by the individual and the clinician(s) responsible for treatment. The decision should be made after an informed discussion between the clinician(s) and the patient; this discussion should take into account contraindications and the side-effect profile of the agents as well as the clinical condition and preferences of the individual.		
		The use of capecitabine or tegafur with uracil to treat metastatic colorectal cancer should be supervised by oncologists who specialize in colorectal cancer.		
		Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine is not recommended for the treatment of metastatic colorectal cancer.	NICE technology appraisal 212 (2010)[$]	

4.1.9. Follow-up

Table 59 – Evidence table: general guidelines on follow-up

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Offer follow-up to all patients with primary colorectal cancer undergoing treatment with curative intent. Start follow-up at a clinic visit 4 to 6 weeks after potentially curative treatment.	Not clear	NA
		Start reinvestigation if there is any clinical, radiological or biochemical suspicion of recurrent disease.	Not clear	NA
		Stop regular follow-up when the patient and healthcare professional have discussed and agreed that the likely benefits no longer outweigh the risks of further tests **or** when the patient cannot tolerate further treatments.	Expert opinion	No evidence
SIGN 2011[10]	March 2011	Patients who have undergone curative resection for colorectal cancer should undergo formal follow up in order to facilitate the early detection of metastatic disease.	3 SRs & MAs, 3 RCTs, 1 comparative study, 1 cost-benefit study	$1^{+}/1^{++}$
		Clinicians should be aware of the need to have symptoms and signs of metastatic recurrence promptly investigated.	Expert opinion	No evidence
NZGG 2011[9]	June 2004	All people who have undergone colorectal cancer resection should be followed up intensively.	Expert opinion	No evidence
		All people who have undergone colorectal cancer resection and develop relevant symptoms should undergo clinical assessment.	Expert opinion	No evidence
		For people with colon cancer at high risk of recurrence (Stages IIb and III), clinical assessment is recommended at least every six months for the first three years after initial surgery and then annually for a further two years or when symptoms occur.		B
		For people with colon cancer at lower risk of recurrence (Stages I and IIa) or for people with co-morbidities restricting future surgery, clinical assessment is recommended when symptoms occur or by annual review for five years after initial surgery.		B

		All people with colorectal cancer Stages I to III should have liver imaging between years 1 and 3.		B
		The use of faecal occult blood testing as part of colorectal cancer follow-up is not recommended.		B
		Follow-up should be under the direction of the multidisciplinary team and may involve follow-up in primary care.	Expert opinion	No evidence
		People with colorectal cancer should be given written information outlining planned follow-up (eg, discharge report) at discharge from treatment, including what they should expect regarding the components and the timing of follow-up assessments.	Expert opinion	No evidence
IKNL 2008[14]	February 2006	The person responsible for coordinating follow-up must be clearly defined per hospital and per patient.	Expert opinion	No evidence
		T1N0: Check-ups every 6 months for the first 2 years after surgery, then annually for up to 5 years after surgery, followed by colonoscopy every 6 years. Physical examination only as indicated.	Expert opinion	No evidence
		All other tumours without distant metastases: Check-ups every 6 months for the first 2 to 3 years after surgery, then annually for up to 5 years after surgery.	2 SR & 1 practice guideline	
		Stage IV: Individual follow-up policy, depending primarily on the type of therapy (chemotherapy or no chemotherapy).	Expert opinion	No evidence

Table 60 – Evidence table: CEA in follow-up

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Offer patients regular serum CEA tests (at least every 6 months in the first 3 years).	Expert opinion	No evidence
SIGN 2011[10]	March 2011	Interval CEA estimation (and CT scanning) may be of value in the follow up of patients who have undergone curative resection for colorectal cancer but further studies are required to define an optimum approach.	Expert opinion	No evidence
NZGG 2011[9]	June 2004	Follow-up should include physical examination and CEA.		B
IKNL 2008[14]	February 2006	T1N0: Routine CEA assessment and diagnostic imaging are not indicated due to their low diagnostic yield.	Unclear	Low
		All other tumours without distant metastases: CEA assessment every 3 to 6 months for the first 3 years after treatment, then every 6 months for up to 5 years after treatment.	2 SR & 1 practice guideline	
IKNL 2006[16]	2005	CEA is useful in follow-up after resection of the primary tumour if it was elevated at diagnosis.	Expert opinion	

Table 61 – Evidence table: colonsocopy in follow-up

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Offer a surveillance colonoscopy at 1 year after initial treatment. If this investigation is normal consider further colonoscopic follow-up after 5 years, and thereafter as determined by cancer networks. The timing of surveillance for patients with subsequent adenomas should be determined by the risk status of the adenoma.	Not clear	NA
SIGN 2011[10]	March 2011	If complete visualisation of the colon is not performed preoperatively due to stenosing tumour or other reasons, colonoscopy should be performed within 3 months after surgery.		
		Colonoscopic follow up is advised five-yearly after curative resection for colorectal cancer.	Expert opinion	No evidence
		Where the clinician suspects intraluminal recurrence, colonoscopy is indicated.	Expert opinion	No evidence
NZGG 2011[9]	June 2004	All people with colorectal cancer should have a colonoscopy before surgery or within 12 months following initial surgery.		B
		For people with colon cancer at lower risk of recurrence (Stages I and IIa), follow-up colonoscopy every three to five years is recommended.		B
IKNL 2008[14]	February 2006	**T1N0**: colonoscopy every 6 years	Expert opinion	No evidence
		All other tumours without distant metastases: Colonoscopy within the first 3 months after surgery if complete colonoscopy was not possible before surgery.	Expert opinion	No evidence
		Colonoscopy 2 to 3 years after surgery, according to the consensus on follow-up of colon polyps (6 years for 0-2 polyps, 3 years for 3 or more polyps). If complete colonoscopy is not possible, CT colonography is an alternative.	2 SR & 1 practice guideline	

Table 62 – Evidence table: ultrasound in follow-up

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Not covered		
SIGN 2011[10]	March 2011	Not covered		
NZGG 2011[9]	June 2004	Not covered		
IKNL 2008[14]	February 2006	**All other tumours without distant metastases**: Hepatic ultrasound every 6 months for the first year after surgery, then annually for up to 5 years after surgery.	2 SR & 1 practice guideline	
IKNL 2006[16]	2005	After resection of the primary tumour, sonography can be sufficient for follow-up if the liver can be well visualized.		

Table 63 – Evidence table: CT chest abdomen in follow-up

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Offer patients regular surveillance with: a minimum of two CTs of the chest, abdomen and pelvis in the first 3 years.	Expert opinion	No evidence
SIGN 2011[10]	March 2011	Interval CT scanning (and CEA estimation) may be of value in the follow up of patients who have undergone curative resection for colorectal cancer but further studies are required to define an optimum approach.	Expert opinion	No evidence
NZGG 2011[9]	June 2004	Not covered		
IKNL 2008[14]	February 2006	T1N0: Routine CEA assessment and diagnostic imaging are not indicated due to their low diagnostic yield.	Unclear	
		All other tumours without distant metastases: Hepatic ultrasound every 6 months for the first year after surgery, then annually for up to 5 years after surgery. CT scan is indicated if ultrasound cannot be performed easily for technical reasons, e.g. patients with obesity or air in the intestines.	2 SR & 1 practice guideline	

Table 64 – Evidence table: PET-CT in follow-up

Reference	Search date	Recommendations/conclusions	Evidence base	Level of evidence
NICE 2011[8]	February 2011	Not covered		
SIGN 2011[10]	March 2011	FDG PET/CT should be used in the evaluation of patients with raised tumour marker CEA with negative or equivocal conventional imaging or assessment of possible pelvic recurrence and pre-sacral mass following treatment.		Recommendation D
IKNL 2008[14]	February 2006	Not covered		
IKNL Colorectale levermetastasen 2006	2005	Not covered		

4.2. Additional evidence

4.2.1. Diagnosis

Table 65 – Evidence table diagnosis: RCTs

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Atkin 2013[41]	• Design: RCT • Sources of funding: NIHR HTA programme, Cancer Research UK. Medicsight, viatronix, Bracco UK and barco provided equipment • Setting: multicentre, UK	• Eligibility criteria: 55 years or older, , fit to undergo full bowel preparation, no genetic predisposition or history of inflammatory bowel disease, no whole-colon examination in the previous 6 months, not in follow-up for previous bowel cancer	• Index test(s) Computed tomographic colonography (CTC) (533 pts) • Reference standard: colonoscopy (1047 pts)	• Overall detection rate colorectal cancer or large polyps: RR 0.94; 95%CI 0.70-1.27 (p=0.69) • Miss rate for colorectal cancer: 1 (3.4%) vs 0 (0%) • Pats died: 11.8% vs 14.7% after a median FU of 5.2 years (p= 0.11) • Referrals for additional colonic investigations: 30% vs 8.2%. RR 3.65;	Other colorectal findings: • Diverticulosis significantly more frequently diagnosed in the CTC group (p<0.0001); colitis (p=0.0022) and anal pathology (p=0.0002) more frequently diagnosed in the colonoscopy group Extracolonic findings: • at least one	• Dropouts: 2.3% and 0.9% respectively withdrew consent • Results critical appraisal: adequate random sequence generation and allocation concealment. No blinding of participants,

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Sample size: 1610 pts • Duration: March 2004-December 2007	• Patients characteristics: median age 68 years, 55% women. 72-73% presented with change in bowel habit • Prevalence of disease: 11% colorectal cancer		95%CI 2.87-4.65 • Serious adverse events: 4 unplanned hospital admission within 30 days possibly attributable to a randomized procedure, three after colonoscopy and 1 after CTC. No confirmed perforations were reported.	diagnosed in 60.4% of CTC patients without colorectal cancer • extracolonic cancers during 3 year FU: IRR 0.94; 95%CI 0.59-1.49 (p=0.79)	care givers or outcome assessors. Low risk for attrition bias.
Von wagner 2013[42]	• Design: RCT • Sources of funding: NIHR HTA programme, Cancer Research UK. Medicsight, viatronix, Bracco UK and barco provided equipment • Setting: multicentre, UK • Sample size: 1610 pts • Duration: March 2004-December 2007	• Eligibility criteria: 55 years or older, , fit to undergo full bowel preparation, no genetic predisposition or history of inflammatory bowel disease, no whole-colon examination in the previous 6 months, not in follow-up for previous bowel cancer • Patients characteristics: median age 68 years, 55% women. 72-73% presented with change in bowel habit	• Index test(s) Computed tomographic colonography (CTC) (533 pts) • Reference standard: colonoscopy (1047 pts)	• Colonoscopy patients slightly less satisfied overall (p=0.008) • Colonoscopy reported more worry overall (p=0.007) • Physical discomfort significantly worse for patients undergoing colonoscopy (p=0.001) • No significant difference in psychologic consequences at 3 months	• Receiving results more often on the same day for colonoscopy patients, and more often by a face-to-face conversation, leading to higher patients satisfaction (p<0.0005) •	• Dropouts: 2.3% and 0.9% respectively withdrew consent • Results critical appraisal: adequate random sequence generation and allocation concealment. No blinding of participants, care givers or outcome assessors. Low risk for attrition bias.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		• Prevalence of disease: 11% colorectal cancer				
Halligan 2013[43]	• Design: RCT • Sources of funding: NIHR HTA programme, Cancer Research UK. Medicsight, viatronix, Bracco UK and barco provided equipment • Setting: multicentre, UK • Sample size: 3838 pts • Duration: March 2004-December 2007	• Eligibility criteria: 55 years or older, , fit to undergo full bowel preparation, no genetic predisposition or history of inflammatory bowel disease, no whole-colon examination in the previous 6 months, not in follow-up for previous bowel cancer • Patients characteristics: median age 69 years, 61% women. 76% presented with change in bowel habit. • Prevalence of disease: 3-4% colorectal cancer	• Index test(s): computed tomographic colonography (CTC) (285 pts) • Reference standard: barium enema (2553 pts)	• Overall detection rate colorectal cancer or large polyps: RR 1.31; 95%CI 1.01-1.68 (p=0.0390) • Miss rate for colorectal cancer: 7% vs 14% (p=0.21) • Pts died: 15.7% vs 15.8% after a median FU of 5.4 years (p= 0.94) • Referrals for additional colonic investigations: 23.5% vs 18.3%. RR 1.28; 95%CI 1.12-1.46 • Serious adverse events: 5 unplanned hospital admission within 30 days possibly attributable to a randomized procedure, 1 after colonoscopy and 4 after barium enema.	Extracolonic findings: • at least one diagnosed in 57.8% of CTC patients without colorectal cancer • extracolonic cancers during 3 year FU: IRR 1.18; 95%CI 0.89-1.57 (p=0.24)	• Dropouts: 0.6% and 1% respectively withdrew consent • Results critical appraisal: see Atkin 2013

4.2.2. Staging

Table 66 – Evidence table: staging PET-CT vs CT - SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of review quality
Chan 2012[19]	Design: SR. Source of funding: Ontario Ministry of Health Search date: May 2010 Searched databases: MEDLINE, EMBASE (Aug 2005- May 2010) Included study designs: 8 SR 28 primary studies (randomised study, non-randomised studies) in different settings Included studies: Rappeport 2007 Lubezky 2007 Adie 2009 Orlacchio 2009	Eligibility criteria (see also Facey et al.): SR: FDG-PET in CRC in humans evidence related to diagnostic accuracy, change in patient management, clinical outcomes or treatment response Primary studies: Prospective Full article available evidence related to diagnostic accuracy, change in patient management, clinical outcomes or treatment response 12 patients or more included Suitable	Index test(s): (Whole body) (FDG)-PET-CT Comparison test: CT, MRI, CT and FDG-PET, intraoperative gamma probe, none Reference test: histopathology or clinical (radiological) follow-up, (intraoperative) ultrasound morphology, surgical exploration, none	Detection of hepatic metastases: FDG-PET/CT: TP / FP / FN / TN / Se / Sp / PPV / NPV Adie, 2009: 28 / 7 / 18 / 0 / 61% / 0% / 80% / 0% Lubezky, 2007: / / / / 93% / / / / Rappeport, 2007: / / / / 66% / 99% / 98% / 76% Orlacchio, 2009: / / / / 97% / 98% / 99% / 95% CT: TP / FP / FN / TN / Se / Sp / PPV / NPV Adie, 2009: / / / / / / / / Lubezky, 2007: / / / / 88% / / / / Rappeport, 2007: / / / / 89% / 67% / 72% / 86% Orlacchio, 2009: / / / / 91% / 95% / 98% / 81% Detection of extra hepatic metastases: Rappeport, 2007: TP / FP / FN / TN / Se / Sp / PPV / NPV PET-CT: / / / / 84% / 96% / / CT: / / / / 95% / 87% / / Other outcomes: Staging primary tumour Treatment response RT planning Recurrence Cost effectiveness Patient management	One randomized study showed a change in treatment plan: decrease in futile surgery from 48% to 28%(p=0,042). Sensitivity of PET in detecting liver metastases decreases following neoadjuvant chemo-therapy. PET is less sensitive but more specific than MRI for detection of hepatic metastases.	Results critical appraisal: Adequate search Quality appraisal performed, but level of evidence not shown Heterogeneity not clearly reported Probably (high) risk of bias due to: Partial verification Differential verification Blinding not always reported Analysis by lesion (one study)

		Comparison test Patient characteristics: CRC				
Patel 2011[44]	Design: SR Source of funding: University of Alberta, Canada. Search date: March 30, 2009. Searched databases: MEDLINE, EMBASE, Scopus, Web of Science, Cochrane Library, PubMed (limited to the last 6 months), DARE, grey literature including Conference Papers Index, American College of Radiology, American College of Surgeons, Royal College of Radiologists, Canadian Association of General Surgeons, American Society of Clinical Oncology,	Included if: Index test 2-18-F-fluoro-2-deoxyglucose PET/CT scan Comparison test CT scan histological gold standard, sufficient data to populate a 2 × 2 table. Excluded if: clearly irrelevant, intact primary tumours, previous hepatic therapy for cancer, pregnant patients, alternate radio-compound, separate PET and CT scans. Patient characteristics: adults (≥18 years) colorectal liver	Index test(s): 2-18-F-fluoro-2-deoxyglucose PET/CT Comparison test: CT, MRI	PET-CT has a higher accuracy for detection of extra-hepatic and hepatic colorectal metastatic disease than CT alone. For hepatic lesions (5 studies; 316 patients), PET/CT had higher SN and SP than CT (PET/CT SN = 91%–100% and SP = 75%–100%; CT SN = 78%–94% and SP = 25%–98%). For extra-hepatic lesions (3 studies; 178 patients), PET/CT was more sensitive than CT, but specificities were similar (PET/CT sensitivity [SN] =75%–89% and specificity [SP] = 95%–96% vs. CT SN = 58%–64% and SP = 87%–97%). Detection of hepatic metastases:	Change in treatment plan (different type of surgery, surgery avoided) Overall: PET/CT affected clinical practice in 8% to 20% of patients. Chemotherapy effect PET-CT: With chemo: Se: 98%, Sp: 100% Without chemo: Se: 95%, Sp: 60% Chemo did not confound PET-CT No FDG uptake in extrahepatic meta's : With chemo: 66% Without chemo: 8%	Results critical appraisal: Adequate search One study did not describe their population. Differential verification in one study. Statistical assessments of heterogeneity and reporting bias were planned but not executed because of the small number of studies. Planned pooled analyses were not calculated given the heterogeneity in the studies.

	Google Scholar, Clinical Trials Registry, health technology websites, reference lists of all included studies. Included study design: Prospective, retrospective, cross sectional. 6 studies: Bellomi 2007 Chen 2007 Chua 2007 Ramos 2008 Rappeport 2007 Selzner 2004 Sample sizes ranged from 35 to 131.	metastases being assessed for liver resection		PET-CT TP FP FN TN Se Sp PPV NPV Bellomi, 2007 17 0 0 50 100% 100% 100% 100% Chua, 2007 63 2 4 6 94% 75% 97% 60% Ramos, 2008 69 0 56 9 55% 100% 100% 14% Rappeport, 2007 26 0 2 3 93% 100% 100% 60% Selzner, 2004 60 1 6 9 91% 90% 98% 60% CT TP FP FN TN Se Sp PPV NPV Bellomi, 2007 16 1 1 50 94% 98% 94% 98% Chua, 2007 61 6 6 2 91% 25% 91% 25% Ramos, 2008 98 4 27 5 78% 56% 96% 16% Rappeport, 2007 28 2 0 1 100% 33% 93% 100% Selzner, 2004 61 1 7 7 90% 88% 98% 50% Detection of extrahepatic metastases: PET-CT TP FP FN TN Se Sp PPV NPV Bellomi, 2007 6 0 2 0 75% NA 100% 0% Rappeport, 2007 10 1 2 22 83% 96% 91% 92% Selzner, 2004 32 2 4 38 89% 95% 94% 90% CT TP FP FN TN Se Sp PPV NPV Bellomi, 2007 8 0 0 59 100% 100% 100% 100% Rappeport, 2007 7 3 5 20 58% 87% 70% 80% Selzner, 2004 23 1 13 39 64% 98% 96% 75%		
Brush 2011[45]	Design: SR/HTA Source of funding: National Institute for Health Research Health Technology Assessment programme (HTA). Search date: May 2009. Searched databases: BIOSIS Previews;	Inclusion: Adults with known or suspected primary cancer of the colon or rectum; undergoing pre-operative staging prior to curative surgery; in a secondary care setting	Index tests: integrated FDG PET/CT with both contrast-enhanced and non contrast-enhanced CT. Comparator tests: standard imaging tests including	Target condition: known or suspected primary, recurrent or metastatic CRC. FDG PET-CT sensitivity, range: 87%–100%, specificity, range: 75%–100% CT sensitivity, range: 75%–98%, specificity, range: 25%–100%	Changes in patient management. Adverse effects Economic evaluation	Results critical appraisal: Adequate search The poor quality of the studies means that the validity of these estimates is threatened by several biases, and the lack of paired data prevented statistical tests from eliminating chance

CINAHL Plus; The Cochrane Library; Compendex; ProQuest Dissertations and Theses; EMBASE; Global Health; Global Health Library regional indexes (comprising LILACS, AFRO, EMRO, PAHO, WHOLIS); Index to Theses; Inspec; MEDLINE; Meta Register of Current Controlled Trials; National Technical Information Services; OpenSIGLE (System for Information on Grey Literature in Europe); UK Clinical Research Network;

Web of Science, including Conference Proceedings Citation Index; EMBASE.

Included study designs: prospective and retrospective patient series

Studies that combined patients with colorectal and anal cancer, only if < 20% of patients had anal cancer.

Exclusion:

Studies solely in patients with anal cancer.

Patient characteristics:

age 58-65 years

CRC

ultrasound, diagnostic CT, MRI and PET, alone or in combination.

Reference standards: histopathology of surgical resected specimens (gold standard), histopathology based on biopsy, or follow-up (clinical examination or imaging tests).

Detection of hepatic metastases, patient level:

PET-CT	TP	FP	FN	TN	Se	Sp	PPV	NPV
D'Souza, 2009	7	0	1	0	88%	NA	100%	0%
Chua, 2007	63	2	4	6	94%	75%	97%	60%
Kong, 2008	60	0	1	4	98%	100%	100%	80%
Rappeport, 2007	26	0	2	3	93%	100%	100%	60%
Coenegrachts, 2009	23	0	1	0	96%	NA	100%	0%
Wildi, 2008	10	3	3	0	77%	0%	77%	0%
CT								
D'Souza, 2009	6	0	2	0	75%	NA	100%	0%
Chua, 2007	61	6	6	2	91%	25%	91%	25%
Kong, 2008	60	0	1	4	98%	100%	100%	80%
Rappeport, 2007	28	2	0	1	100%	33%	93%	100%
Coenegrachts, 2009	NR	NR	NR	NR	NA	NA	NA	NA
Wildi, 2008	NR	NR	NR	NR	NA	NA	NA	NA

Detection of hepatic metastases, lesion level:

PET-CT	TP	FP	FN	TN	Se	Sp	PPV	NPV
Lubezky, 2007	29	2	2	0	94%	0%	94%	0%
Cantwell, 2008	67	4	33	6	67%	60%	94%	15%
Rappeport, 2007	47	1	24	74	66%	99%	98%	76%
CT								
Lubezky, 2007	28	1	4	0	88%	0%	97%	0%
Cantwell, 2008	85	0	15	10	85%	100%	100%	40%
Rappeport, 2007	63	25	8	50	89%	67%	72%	86%

Detection of hepatic metastases, lesion level, after neo adjuvant chemotherapy:

Lubezky, 2007	TP	FP	FN	TN	Se	Sp	PPV	NPV
PET-CT	48	4	50	20	49%	83%	92%	29%
CT	64	6	34	18	65%	75%	91%	35%

Detection of extra hepatic metastases, patient level:

PET-CT	TP	FP	FN	TN	Se	Sp	PPV	NPV
Selzner, 2004	32	2	38	4	46%	67%	94%	10%
Rappeport, 2007	10	1	2	22	83%	96%	91%	92%
CT								
Selzner, 2004	23	1	39	13	37%	93%	96%	25%
Rappeport, 2007	NR	NR	NR	NR	NA	NA	NA	NA

Per patient basis (pooled estimate), hepatic

findings.

	(diagnostic cohort), cross-sectional, before and after studies and RCTs. Number of included studies: 16 prospective (5) and retrospective patient series (10), unclear design (1). In total 890 patients. Included studies			metastases: The pooled accuracy data showed FDG PET/CT to have a sensitivity of 91% (95% CI 87% to 94%) and a specificity of 76% (95% CI 58% to 88%).		
Niekel 2010[18]	Design: SR and Meta analysis Source of funding: unknown, but authors stated no financial relationship to disclose. Search date: Jan 2010. Searched databases: MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Review, and Web of Science (articles published from Jan 1990 – Jan 2010). Included study designs:	Inclusion criteria: Prospective study design Study population > 10 patients Imaging techniques: CT, MR imaging, FDG PET, or FDG PET-CT. reference standard: intraoperative findings (palpation and/or US) or histo-pathologic examination or follow-up. retrievable data were present for calculating	Index test(s): CT, MR imaging, FDG PET, or FDG PET-CT Comparison test: intraoperative findings (palpation and/or US) or histo-pathologic examination or follow-up.	Detection of liver metastases, per patient basis (pooled estimate): FDG PET-CT (n=3): Se: 96.5 (94.2, 97.9) Sp: 97.2 (92.8, 99.0) CT (n=9): Se: 83.6 (66.9, 92.8) Sp: 94.9 (92.9, 96.3) FDG PET-CT | TP | FP | FN | TN | Se | Sp | PPV | NPV Zelzner et al (28) | 60 | 1 | 6 | 9 | 91% | 90% | 98% | 60% Rappeport et al (38)* | 26 | 0 | 2 | 3 | 93% | 100% | 100% | 60% Orlacchio et al (47)* | 329 | 3 | 7 | 128 | 98% | 98% | 99% | 95%	Data about FDG PET/CT were limited, with a per-lesion sensitivity of 66.2% and a per-patient sensitivity of 96.5%. On a per-patient basis, the sensitivity of CT was significantly lower than that of FDG PET (P = .025); specificity estimates were comparable. Per-lesion basis (pooled estimate): FDG PET-CT (n=1): Se: 66.2 (54.5, 76.2) CT (n=38): Se: 74.4 (68.7, 79.3) FDG PET/CT | TP | FP | FN | TN | Se | Sp | PPV | NPV Rappeport et al (38)* | 47 | | 24 | | 66% | NA | 100% | 0%	Results critical appraisal: Adequate search Prospective studies only. Quality appraisal performed: level 4 of evidence (according to Oxford Centre for Evidence Based Medicine) Because of the limited number of FDG PET/CT studies, no check for heterogeneity was performed. Probably (high) risk of bias due to: Partial verification

	prospective. Number of included studies: 39 (3391 patients). Pooled data were calculated with 3 studies for FDG PET/CT and with 9 studies for CT.	sensitivity and specificity. Exclusion: data about a single modality could not be extracted. Studies including patients who had previously undergone treatment Patient characteristics: Mean age: 61 years (range: 20-93 years), 1863 males, 1317 females. Imaging modalities were evaluated for both patients suspected of having colorectal metastases and those known to have colorectal liver metastases.		Differential verification Blinding not always reported.

Facey 2007	Design: SR Source of funding: National Institute for Health Research Health Technology Assessment programme (HTA). Search date: August 2005 English systematic reviews published since the search for the ultra rapid review (May 2004) Systematic reviews published in a Western European, non-English language since 1966 (with those prior to 2000 deselected by hand) English and non-English primary studies since 2000. Searched databases: MEDLINE,MEDLINE in process and other non-indexed citations and EMBASE, The Cochrane Database of Systematic Reviews, Database	Eligibility criteria: SR inclusion criteria: dedicated FDG-PET in the stated cancers in humans evidence related to diagnostic accuracy, change in patient management, clinical outcomes, treatment response or RT planning robust qualitative or quantitative systematic reviews studies in English, French, German, Spanish or Italian. SR exclusion criteria: gamma PET (dual-headed camera) coincidence detection emission tomography (CDET)	Index test(s): PET-(CT) Comparison test: PET, CT, MRI, US Reference test: histopathology, core biopsy, or clinical follow-up, (min. 6 months).	Detection of hepatic metastases: Zelsner, 2004 TP FP FN TN Se Sp PPV NPV PET-CT 60 1 6 9 91% 90% 98% 60% CT 61 3 5 7 92% 70% 95% 58% Other outcomes: Staging primary tumor Treatment response RT planning Recurrence Cost effectiveness Patient management	Staging/restaging: FDG-PET more sensitive than CT to detect hepatic and extrahepatic metastases. 13 studies report some form of patient management changes affecting 9–59% of patients. PET correctly upstaged 12/58 patients (21%), so liver resection was not undertaken and chemo or no further therapy was given (Rosa, 2004). Change in surgery: 8% Avoided surgery based on the PET/CT: 13%. PET-CT 10–15% more sensitive or specific than FDG-PET. PET sensitivity much better than CT, particularly for multiple CLM and extrahepatic disease 23% patients avoided surgery and associated surgical morbidity (lots of bias in this study: Arulampalam, 2004)	Level of evidence: B Adequate search Quality appraisal performed, but level of evidence not shown Heterogeneity not clearly reported Probably (high) risk of bias due to: Partial verification Differential verification Blinding not always reported Analysis by lesion (one study)

	of Abstracts of Reviews of Effectiveness (DARE) and the HTA database international database of HTA reports. Members of the International Network of Agencies for Health Technology Assessment (INAHTA) were contacted in August 2005 for details of systematic reviews not yet listed on the HTA database, or to clarify incomplete HTA database entries. Sources searched for primary studies. The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, MEDLINE in-process and other non-indexed citations, and EMBASE. Included study	tracers other than FDG systematic reviews that have been superseded reports that cost more than £50 to obtain no English abstract available published as (conference) abstract only. Primary studies inclusion criteria: prospective study of dedicated FDG-PET in a single cancer of interest published after the search date of a robust systematic review covering that management decision clinical study published as a full article in a peer-reviewed journal evidence related to diagnostic accuracy, change in patient	

PET	TP	FP	FN	TN	Se	Sp	PPV	NPV
Kinkel, 2002					> 84%			
Arulampalam, 2004	17	1	0	10	100%	91%	94%	100%
Truant, 2005	78	1	21	4	79%	80%	99%	16%
CT								
Kinkel, 2002					72%			
Arulampalam, 2004	8	1	9	10	47%	91%	89%	53%
Truant, 2005	78	3	21	1	79%	25%	96%	5%

	designs: :prospective comparative and retrospective 1 SR and 1(Selzner, 2004) primary studies were of interest to the research question.	management or clinical outcomes at least 12 human patients with the cancer of interest patient pathway similar to that used in the UK suitable reference standard used in diagnostic studies studies in English, French, German, Spanish or Italian. Primary studies exclusion criteria: evaluations of gamma PET or CDET abstracts from conferences, etc. preliminary or interim analyses or case series that were later augmented retrospective studies tracers other than FDG cancers other than the eight specified		

	mixed cancers that were not reported separately with at least 12 patients in one cancer review/editorial PET technical papers (e.g. SUVs, FDG uptake, phantom studies, quantitation papers) abstract does not allow study characteristics to be determined reports that cost more than £50 to obtain no English abstract available studies in non-English languages that were duplicated in English papers. Patient characteristics: CRC	

Table 67 – Evidence table: staging PET-CT vs CT – primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Mainenti 2010[46]	Design: prospective Source of funding: unknown Setting: hospital Sample size: 34 patients. Duration: July 2005 – March 2007.	Eligibility criteria: Inclusion: Histologically proven diagnosis of colorectal adenocarcinoma. Scheduled for surgery. Exclusion: Refusal to participate Known contraindications to one of the examinations Patient characteristics: Mean Age: 63 years (range 29-81years) Male/female ratio: 20:14. Prevalence of disease: Six out of 34 (17.6%) patients presented at least one hepatic metastasis. Multiple liver metastases were present in four out of the six patients;	Index test(s): PET-CT. Reference standard: CE-US, MDCT and SPIO enhanced MRI (all patients). Gold standard: Surgical palpation, IOUS, histopathology and follow-up MDCT (all patients).	Detection of hepatic metastases, patient based analysis PET-CT Se: 100% Sp: 96% PPV: 86% NPV: 100% Accuracy: 97%. CT Se: 83% Sp: 96% PPV: 83% NPV: 96% Accuracy: 94%.		Dropouts: none Results critical appraisal: All modalities were randomly performed, but radiologist was not blinded with the results of preoperative imaging modalities.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
		The maximum number of lesions in a patient was six. A total of 6/34 were classified as patients with metastasis 28/34 patients were free from metastases. A diffuse fatty infiltration involving the right hepatic lobe was observed in a patient. No malignant lesions different from colo-rectal Metastasis.				

Table 68 – Evidence table: staging MRI liver– systematic reviews

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Van Kessel 2012[17]	• Design: SR and MA • Sources of funding: Not reported • Search date: May 2011 • Searched databases: Medline & Embase • Included study	• Eligibility criteria: Pts diagnosed with initially unresectable CRLM, who had been treated with neoadjuvant chemotherapy	• Index test(s): CT, PET-CT, MRI or FDG PET • Comparison test: intraoperative US and histo-pathologic	• Effectiveness for detection of CRC liver metastases: Pooled sensitivities in *pts who had neoadjuvant chemo*: MRI: 85.7% (3 trials; sign heterogeneity) CT: 69.9% (5 trials) FDG-PET: 54.5% (6 trials;		• No critical appraisal

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	designs: Prospective (n=6) and retrospective (n=5) cohort studies • Number of included studies: 11 • Included studies: Akhurst 2005, Lubezky 2007, Rappeport 2007, Carnaghi 2007, Ramos 2008, Angliviel 2009, Adie 2009, Bacigalupo 2010, Spatz 2011, Kulemann 2010, van Kessel 2011	(for downsizing in order to render resectable) • Patients characteristics: mean age: 62 (range: 28-82); male/female ratio: 542/344 • Median FU: not reported	examination (for those who had surgery - 835 lesions) or follow-up imaging (71 lesions)	sign heterogeneity) PET-CT: 51.7% (2 trials; sign heterogeneity) Pooled sensitivities in *pts who had no neoadjuvant chemo*: MRI: no data		
Niekel 2010[18]	• Design: SR and Meta analysis • Source of funding: unknown, but authors stated no financial relationship to disclose. • Search date: Jan 2010. • Searched	• Eligibility criteria: Inclusion: o Prospective study design o Study population > 10 patients o Imaging techniques: MRI, CT, FDG PET, or FDG	• Index test(s): MRI,CT, FDG PET, or FDG PET-CT • Comparison test: intraoperative findings (palpation and/or US) or histo-pathologic	• *Detection of hepatic liver metastases, per patient basis (pooled estimate):* o) Modality : *I* 2 Index of Sensitivity (%) / Mean Sensitivity (%)/ *I* 2 Index of Specificity (%)/ Mean Specificity (%) MR imaging (*n* = 6)	*Direct comparison MRI vs PET-CT (based on 1 study*[47]*)* Per lesion sensitivity and specificity 66% and 83% for PET/CT, 82% and 82% for SPIO-enhanced MR I MRI superior to PET CT (p <0.05) Per patient sensitivity	Critical appraisal: • Adequate search • Prospective studies only. • Quality appraisal performed: level 4 of evidence (according to Oxford Centre

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	databases: MEDLINE, EMBASE, CINAHL, Cochrane Database of Systematic Review, and Web of Science (articles published from Jan 1990 – Jan 2010). • Included study designs: prospective. • Number of included studies with MRI : 18 • Pooled data were calculated with 61 datasets for MRI	PET-CT. o reference standard: intra operative findings (palpation and/or US) or histo-pathologic examination or follow-up. o retrievable data were present for calculating sensitivity and specificity. Exclusion: o Combination of imaging modalities presented o data about a single modality could not be extracted. o Studies including patients who had previously undergone treatment	examination or follow-up.	43.3 (0.0, 69.9)/ 88.2 (64.8, 96.8) /61.8 (21.3, 81.4)/ 92.5 (89.5, 94.6) CT (*n* = 9) 92.9 (88.9, 95.4)/ 83.6 (66.9, 92.8) /52.5 (10.3, 74.9)/ 94.9 (92.9, 96.3) FDG PET (*n* = 6) 0.0 (0.0, 0.7) /94.1 (91.6, 95.9)/ 0.0 (0.0, 0.6)/ 95.7 (92.7, 97.6) FDG PET/CT (*n* = 3) NA/ 96.5 (94.2, 97.9)/ NA /97.2 (92.8, 99.0) • *Detection of hepatic liver metastases, per lesion basis (pooled estimate):* **Modality: *I* 2 Index of Sensitivity (%) / Mean Sensitivity (%)** MR imaging (*n* = 61) 83.4 (79.4, 86.7) / 80.3 (74.6, 85.0) CT (*n* = 38) 70.9 (60.0, 78.9) / 74.4 (68.7, 79.3) FDG PET (*n* = 8) 86.4 (76.2, 92.2) / 81.4 (66.5, 90.6) FDG PET/CT (*n* = 1) NA 66.2	and specificity:93% and 83% for PET-CT, 100% and 82% for SPIO-enhanced MRI *Subgroup of lesions by size:sensitivity (%)* <10 mm: 60.2(54.4,65.7)(n=8) for MRI vs 47.3 (40.1,54,5)(n=5) for CT >=10 mm: 89.0(81.7,93.7)(n=8) for MRI vs 86.7 (77.6,92.5)(n=5) for CT	for Evidence Based Medicine) • Because of the limited number of • Probably (high) risk of bias due to: o Partial verification o Differential verification o Blinding not always reported.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		(surgery, radiation therapy, and/or chemotherapy) . • Patient characteristics (for the entire report): o Mean age: 61 years (range: 20-93 years), 1863 males, 1317 females. o Histopath proven primary CRC		(54.5, 76.2) (NA= not available)		

4.2.3. Pathology

Table 69 – Evidence table: KRAS testing - SRs

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Adelstein 2010	• Design: SR and MA • Sources of funding: not mentione • Search date: 2009 • Searched databases: Medline embase Cochrane ASCO annual proceedings • Included study designs: RCT • Number of included studies: 1	• Eligibility criteria: Patients for colorectal cancer •	• Role of KRAS in prediciting effectiveness of treatment	KRAS status was reported in 7555 cases. In subgroup analysis, the progression HR for KRAS wild patients assigned to anti-EGFR antibodies was 0.80 (4436 patients 95%CI: 0.64, 0.99) and for mutant cases 1.11 (3119 patients, 95%CI: 0.97, 1.27). A significant treatment effect interaction between KRAS status and addition of anti-EGFR antibodies to standard treatment was found for PFS (ratio of HRs 0.71, 95%CI: 0.57, 0.90 p=0.005) and response rate difference (difference in RDs 15%, 95%CI: 8, 22%, p<0.001).	• There was no evidence that the extent of effect modification differed between chemotherapeutic partners for both PFS (p=0.3) and response rate (p=0.6).	• No double selection. •
Des Guetz 2009	• Design: SR and MA • Sources of funding: not mentione • Search date: 2009 • Searched	• Eligibility criteria: Patients for colorectal cancer stage II and III •	• Intervention: receiving adjuvant treatment • Comparator: • No adjuvant	HR RFS: 0.96 (95% confidence interval (CI): 0.62– 1.49); HR OS (6 studies): 0.70 (95% CI: 0.44–1.09; p = 0.12). •	• They found a significant interaction between MSI status (MSI-H or MSS) and therapeutic status suggesting a lesser benefit for MSI-H than for MSS	• No double selection. •

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	databases: Medline embase Cochrane ASCO annual proceedings • Included study designs: RCT • Number of included studies: 7		treatment • Role of MSI in effectivness		patients (HR interaction RFS: 0.77 (95% CI: 0.67–0.87)).	
Des Guetz 2009	• Design: SR and MA • Sources of funding: not mentione • Search date: 2009 • Searched databases: Medline embase Cochrane ASCO annual proceedings • Included study designs: RCT • Number of included studies: 6	• Eligibility criteria: Patients for Metastatic colorectal cancer	• Intervention: 5FU based chemotherapy and combination therapy • Comparator: • No therapy • Role of MSI in effectivness	. The global hazard ratio (HR) for RR was 0.82 (95% confidence interval, CI: 0.95; 0.65-1.03; p=0.09) •	• Effect size secondary outcome	• No double assessment selection • Pooling of rather hetergenuous studies

Table 70 – Evidence table: KRAS testing subgroup analyses

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Tejpar 2012	• Design: subgroup analysis • Sources of funding: Merck KGaA Darmstadt, • Germany) 1,378 evaluable patients from the CRYSTAL and OPUS studies	• Eligibility criteria: Patients with colorectal cancer	KRAS mutation status (wild-type, G13D, G12V, or other mutations	Within KRAS mutation subgroups, cetuximab plus chemotherapy versus chemotherapy alone significantly improved PFS (median, 7.4 v 6.0 months; hazard ratio [HR], 0.47; P = .039) and tumor response (40.5% v 22.0%; odds ratio, 3.38; P = .042) but not survival (median, 15.4 v 14.7 months; HR, 0.89; P = .68) in patients with G13D-mutant tumors.	• Patients with G12V and other mutations did not benefit from this treatment combination	• Retrospective subgroup analysis
Peeters 2013	• Design: retrospective analysis of three randomized phase III studies • Sources of funding: Amgen	• Eligibility criteria: Patients for colorectal cancer	Patients were randomly assigned 1:1 to FOLFOX4 (infusional fluorouracil, leucovorin, and oxaliplatin) in study 20050203, FOLFIRI (fluorouracil, leucovorin, and irinotecan) in study 20050181, or best supportive care in study 20020408 with or without panitumumab 6.0 mg/kg once every 2 weeks. In all,	No mutant KRAS allele in patients treated on the control arm emerged as a consistent prognostic factor for PFS or overall survival (OS). In addition, no mutant KRAS allele was consistently identified as a predictive factor for PFS or OS in patients receiving panitumumab treatment.		• Retrospective subgroup analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
			441 (20050203), 486 (20050181), and 126 (20020408) patients with mutant KRAS codon 12 or 13 alleles were included in the analysis.			
Perez-Carbonell 2012	• Design: prospective cohort study • Sources of funding: not mentione • 2093 patients	• Eligibility criteria: Patients for colorectal cancer	• IHC for loss of MMR proteins or MSI • MMR sequencing on positive patients	• Of the 14 (0.7%) patients who had a MMR gene mutation, 12 fulfilled at least one of the revised Bethesda criteria and two (14.3%) did not	• 80 patients (8.6%) showed loss of expression of some of the MMR proteins and/or MSI. Four hundred and eighty-six patients (23.2%) met some of the revised Bethesda criteria.	• No comparison MSI or IHC possible, only sensitivity of Bethesda criteria compared to universal testing.

Table 71 – Evidence table: tests for defective mismatch repair genes – primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Canard 2012	• Design: prospective cohort study • Sources of funding: not mentione • 1,040 patients	• Eligibility criteria: Patients for colorectal cancer	• IHC for loss of MMR proteins • MSI • MMR sequencing on positive patients • Promoter methylationwas assessed in tumors with a loss of MLH1 expression	Sensitivity of IHC and MSI testing for detecting identifiedLS patients were, respectively, 92% (23 of 25) and 84% (21 of 25). After exclusion of patients not tested for an MMR mutation, the positive predictive value of IHC and MSI testing were 29.1% (23 of 79) and 27.3% (21 of 77),respectively.	• 12% of the patients with proven LS and 37.1% of the patients with possible LS did not fulfil the revised Bethesda criteria; moreover, a restriction of screening to patients younger than 50 years would havemissed about half of patients with proven LS.	• Prospective cohort with all patients tested for reference and screening test
Moreira 2012	• Design: prospective cohort study • Sources of funding: not mentione • 10019 patients underwent tumor MMR testing	• Eligibility criteria: Patients for colorectal cancer	• IHC for loss of MMR proteins or MSI • MMR sequencing on positive patients	f 312 (3.1%) were MMR gene mutation carriers. In the population-based cohorts (n = 3671 probands), the universal screening approach (sensitivity, 100%; 95% CI, 99.3%-100%; specificity, 93.0%; 95% CI, 92.0%-93.7%; diagnostic yield, 2.2%; 95% CI, 1.7%-2.7%) was superior to the use of Bethesda guidelines (sensitivity, 87.8%; 95% CI, 78.9%-93.2%; specificity, 97.5%; 95% CI, 96.9%-98.0%; diagnostic yield, 2.0%; 95% CI, 1.5%-2.4%; P < .001),	• 12% of the patients a selective strategy based on tumor MMR testing of cases with CRC diagnosed at age 70 years or younger and in older patients fulfilling the Bethesda guidelines (sensitivity, 95.1%; 95% CI, 89.8%-99.0%; specificity, 95.5%; 95% CI, 94.7%-96.1%; diagnostic yield, 2.1%; 95% CI, 1.6%-2.6%; P < .001). This selective strategy	• No comparison MSI or IHC possible, only sensitivity of Bethesda criteria compared to universal testing.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					missed 4.9% of Lynch syndrome cases but resulted in 34.8% fewer cases requiring tumor MMR testing and 28.6% fewer cases undergoing germline mutational analysis than the universal approach.	
Perez-Carbonell 2012	• Design: prospective cohort study • Sources of funding: not mentione • 2093 patients	• Eligibility criteria: Patients for colorectal cancer	• IHC for loss of MMR proteins or MSI • MMR sequencing on positive patients	• Of the 14 (0.7%) patients who had a MMR gene mutation, 12 fulfilled at least one of the revised Bethesda criteria and two (14.3%) did not	• 80 patients (8.6%) showed loss of expression of some of the MMR proteins and/or MSI. Four hundred and eighty-six patients (23.2%) met some of the revised Bethesda criteria.	• No comparison MSI or IHC possible, only sensitivity of Bethesda criteria compared to universal testing.

4.2.4. Endoscopic treatment stage I

Table 72 – Evidence table: management of malignant adenomas after polypectomy - review

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Di Gregorio 2012[20]	• Design: Clinical study and literature overview • Sources of funding: Non reported • Search date: Not reported • Searched databases: Not reported • Included study designs: Not reported • Number of included studies: 13 (incl. present study) • Included studies: Cranley 1986 Coverlizza 1987 Muller 1989 Sughiara 1989 Geraght 1991 Kyzer 1992 Whitlow 1996 Netzer 1998 Seize 2004 Choi 2009 Pizzaro 2009 Boinike 2010 Di Gregorio 2012	• Eligibility criteria: Patients with malignant polyps • Patients characteristics: M/F: 380/259; mean age: 64.3 y.o. • Median FU: Not reported	• Intervention: endoscopic polypectomy • Comparator: endoscopic polypectomy followed by surgery • High risk polyps were defined by the presence of at least one of the following histological features: positive resection margin, poorly differentiated adenocarcinoma, lymphatic/vascular invasion or tumour budding. • Adverse outcome was defined as a local recurrence of adenocarcinoma or metastatic neoplasia detected during follow-up.	Low risk polyps • Di Gregorio 2012: 10/105 underwent surgery: no residual disease. 0/105 patients adverse outcome due to bowel cancer • Pooled analysis: 53/345 were treated surgically. 1/53 residual cancer reported. 1/345 death due to cancer High risk polyps: • Di Gregorio 2012: 23/50 underwent surgery. 5/23 residual tumour. 3/50 died of disease progression. 2/3 underwent polypectomy only. • Pooled analysis: 335/471 underwent surgery; 49/335 (14.6%) residual tumour. 23/471 (4.9%) death due to cancer.	Pooled analysis: Positive vs negative resection margins • Residual disease: 22.7% vs 1.7% • Recurrent disease: 5.1% vs 0.6% • LN metastasis: 9.04% vs 4.85% • Death due to cancer: 6.53% vs 1.16% Poorly differentiated vs well/moderately differentiated: • Residual disease: 10.6% vs 4.0% • Recurrent disease: 9.1% vs 0% • LN metastasis: 4.17% vs 5.17% • Death due to cancer: 21.87% vs 0.78% Vascular invasion vs no vascular invasion • Residual disease: 15.2% vs 5.5% • Recurrent disease: 5.8% vs 0.9% • LN metastasis:	• Results critical appraisal: literature search limited to Medline; no study design criteria reported for included studies; no quality appraisal of included studies; Unclear if consecutive inclusion of patients. Completeness of FU unclear. For analysis of individual risk factors, selection for treatment unclear, no correction for other risk factors.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					21.83% vs 2.48% • Death due to cancer: 10.38% vs 0.6%	

Notes: Di Gregorio et al., 2012[20] was not retrieved through the literature search as the publication was not available through Ovid Medline, Embase nor Cochrane Library at the time of the search; the article was suggested as "Golden Hit" for Research Question 3 by IKNL experts. An e-mail was sent to the first author in order to get some more details on the applied methodology of the literature search and review process.

Fitzgerald et al., 2011[48] ("Golden Hit") is a summary of the New Zealand Guideline on the management of early colorectal cancer (2011), which was based on the Australian NHMRC guideline of 2005 (with regard to Research Question 3, no adaptations were adopted in the New Zealand Guideline).

Seitz et al., 2004[49] ("Golden Hit") is a clinical study and literature overview, but the review was not systematically performed, there was no critical appraisal of the literature.

Table 73 – Evidence table: management of malignant adenomas after polypectomy - observational studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Benizri et al. 2012[50]	• Design: Retrospective case series • Sources of funding: None reported • Setting: University Hospital Nice • Sample size: 64 • Period: 2000 - 2010	• Eligibility criteria: Patients with T1 CRC that had been removed during endoscopic polypectomy, all polyps **had at least 1 of the following adverse criteria** (1) inadequate excision with cancer free distance ≤ 1 mm, (2) lymphovascular invasion, (3) poorly differentiated carcinoma (grade III), (4) SM 2-3 involvement, (5) tumour budding, (6) sessile morphology, (7) piecemeal	• Intervention(s): resection (either by laparotomy or laparoscopy) and regional lymphadenectomy • Comparator(s): /	• Survival rate: 100% (immediately after colectomy) • Rate of lymph node metastasis and/or residual adenocarcinoma at resection: 7/64 (11%)(residual adenocarcinoma: 2, lymph node metastasis: 5)(rectum: 2, colon: 5);	• postoperative complications: 16/64 (25%); • benefit-risk balance =0 when only 1 criterion indicated surgery and =2.3 when at least two criteria indicated additional surgery (grade 3-4 complications considered as serious as the long-term risk measured by the presence by of residual carcinoma at the time of surgery. Surgery is considered beneficial if the ratio is greater	• Results critical appraisal: retrospective study; also rectal cancer included; sessile morphology and piecemeal resection also considered risk factor; no data reported on the number of lymph node metastasis and/or residual adenocarcinoma in patients with negative histological

		resection • Patients characteristics: 30 (47%) female ; median age 65 (43-82). n=52 colon, n=12 rectum • Median FU: not reported			than 1)	features; no correction for multiple testing; no long time outcome data; small sample size
Butte et al. 2012[51]	• Design: Retrospective case series • Sources of funding: None reported • Setting: Tertiary teaching centre, USA • Sample size: 143 • Period: 1990-2007	• Eligibility criteria: patients with T1 CRC undergoing polypectomy followed by colectomy • Patients characteristics: 73 (51%) female; mean age 60.4 +/- 12 y.o. • Median FU: 63 months	• Intervention(s): polypectomy followed by colectomy • Comparator(s): /	• Survival without evidence of disease: 122/143 (15 died of unknown causes and 6 died of other causes). • At colectomy: residual disease in the colonic wall in 19 (13%) pts (invasive in 16 (11%) and noninvasive in 3 (2.1%)) and lymph node metastasis in 10 (7%) pts (combination of residual disease in the colonic wall and lymph node metastasis in 2 (1.4%) pts.	• Rate residual invasive disease diagnosed at colectomy: in case of positive or unknown margin at polypectomy 16% vs. 0% in case of R0,; • Residual disease in the colonic wall associated with older age (p=0.02), left-sided polyps (p=0.04) and polypectomy margin status (p=0.02), but after Bonferroni correction none remain significant • Lymph node metastasis associated with young age (0.03) and lymphovascular invasion (p=0.018), but after Bonferroni	• Dropouts: not reported • Results critical appraisal: retrospective study; pts who did not get colectomy were also excluded (low risk pts and pts with sever comorbidity); submucosal invasion could not be reliably evaluated in the study; most polypectomies were performed in other clinics; no measure of treatment effect estimation (e.g. OR), only X^2 and Wilcoxon tests were

					correction none remain significant.	performed; no multivariable analyses performed; no correction for multiple testing
Kim et al. 2011[52]	• Design: Retrospective case series • Sources of funding: none reported • Setting: University hospital, Korea • Sample size: 129 (64 with intramucosal CRC and 65 with submucosal CRC) • Period: 2005-2007	• Eligibility criteria: pts with early CRC (i.e. limited to mucosa or submucosa) who had EMR or ESD • Patients characteristics: mean age: 63.23 +/- 9.78 y.o.; male: 89 (69%) • Mean FU: 19 months	• Intervention(s): EMR or ESD (not the aim to compare results of both) • Comparator(s): / • Adverse outcome defined as residual cancer or lymph node metastasis at the post-surgical pathologic evaluation or the local recurrence or distant metastasis. • Cave: 7 pts with submucosal cancer underwent subsequent surgical resection: 5 had lymphovascular involvement or positive margin, one perforation	Survival rate: • Intramucosal CRC: 62/64 (2 pts died of unrelated diseases) • Submucosal CRC: not reported. Adverse outcomes: • 7/129 patients of which 5 high risk and 2 low risk. 3 • 3/5 high risk pts underwent surgical resection after EMR.Two of them had no recurrence during FU • 2/5 high risk patients had a positive margin and had no further surgery. Both showed local recurrence • 2/7 low risk patients had local recurrence and liver metastasis respectively	Recurrence (i.e. local recurrence and distant metastasis) rate: • Intramucosal CRC: 0/64 • Submucosal CRC: 7/65: (3/7 who had EMR/ESD + colectomy vs. 4/58 who only had EMR/ESD),	• Dropouts: unclear • Results critical appraisal: retrospective study; also rectal cancer included; no correction for two different methods (EMR and ESD) used; short FU (mean: 19 months); definition and total number of high risk and low risk patients unclear.

			and one requested resection			
Meining et al. 2011[53]	• Design: prospective cohort study • Sources of funding: not reported • Setting: 1 hospital in Germany • Sample size: n=141 (polypectomy and surgical removal of T1 CRC) and n= 249 (polypectomy of T1 CRC) • Period: 1974-2002	• Eligibility criteria: pT1 CRC • Patients characteristics: mean age of all patients: 63.8 +/- 10.74 y.o.; 54% men • Mean FU: 87.2 +/- 50.77 months.	• Group A: polypectomy and surgical removal of T1 CRC. • Intervention B: polypectomy of T1 CRC • Decision in favour of or against surgery based on risk patterns, patients' personal wishes and patients' fitness. • **Unfavourable outcome** was defined if 1 or more of the following occurred: locoregional relapse, distant M+, lymph node M+, death related to colorectal cancer or disease detected during	• No survival data reported • Unfavourable outcome: 2.8% in intervention group A and 6.8% in B	For intervention group B: • Rate of unfavourable outcome when tumour was incompletely resected: 20% (vs. 4% in case of R0), resulting in a RR of 6, Sens: 0.59, Spec: 0.82, npv: 0.96; • Rate of unfavourable outcome when tumour was poorly differentiated: 43% (vs. 6% in other cases) resulting in a RR of 7, Sens: 0.18, Spec: 0.98, NPV: 0.94; • Rate of unfavourable outcome in case of lymphovascular infiltration: 44% (vs. 5% in other cases) resulting in a RR of 8, Sens: 0.24, Spec: 0.98, NPV: 0.95.	• Dropouts: complete FU data available for 390/474 (83%) patients • Results critical appraisal: long duration of the study; unclear criteria for allotment in additional surgery group hence comparison bw groups not recommended; 64 pts for whom no FU were available not included in the study; short follow-up (at least 2 years); unclear reliability of follow-up data ("patients' hospital files, referring physicians, patients' relatives were

			surgery			contacted"
Oka et al. 2011[54]	• Design: Retrospective case series (questionnaire survey) • Sources of funding: none reported • Setting: Multicentre (n=15) , Japan • Sample size: 792 • Period: not reported	• Eligibility criteria: Patients with submucosal CRC with surveillance after endoscopic resection • Patients characteristics: female: 236 (30%); mean age: 72.9 +/- 12.3 y.o.; • Mean FU: 38.7 +/- 83.0 months **Tumour characteristics:** • 588/792 colon; 204792 rectum • Average size 16.2mm (range 3-60mm) • Lateral positive margin 50/792, 238 cases not mentioned • Vertical margin positive 34/792; 195 cases not mentioned • Well or moderately differentiated: 787 cases, 2 poorly differentiated, 3 not reported • Submucosal	• Intervention(s): endoscopic resection (en bloc resection (n=569), piecemeal resection (n=114), ER technique not mentioned (n=109)) • Comparator(s): /	• Survival data not reported. Survival rate in recurrence group: 10/18 (56%) • Recurrence rate: 18/792 (2.3%)	• local recurrence in 11 cases and metastatic recurrence in 13 cases • Recurrence rate after en bloc resection: 14/569 (2.5%), after piecemeal resection: 4/114 (3.5%) • multivariate logistic regression analysis for recurrence after ER for submucosal CRC (n=387): lymphatic invasion OR: 6.36 (95% C.I. 1.46-27.79); mean interval between ER and recurrence: 19.7 +/- 9.2 months	• Dropouts: not reported. • Results critical appraisal: retrospective study; non-response to questionnaire survey was high (13/28 invited institutions); histopatho-logical data only available for 387/792 (49%) cases; histopathological data come from different institutions; short FU

		invasion less than 1000µm 324/792 cases, deeper than 1000µm 315/792, not reported 153/792 cases				

4.2.5. Laparoscopy versus laparotomy

Table 74 – Evidence table: laparoscopy versus laparotomy: SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Grailey 2013[55]	• Design: SR & MA • Sources of funding: partial support from NIHR Biomedical Research Centre funding scheme • Search date: Dec 2011 • Searched databases: Medline, Embase, Web of Science, Cochrane Databases and grey literature • Included study designs: comparative or RCTs	• Eligibility criteria: **Pts of 70 y.o. or older** • Patients characteristics: mean/median ages ranged between 75 and 93 y.o.; number of pts receiving ASA score 1-2 vs. 3-4 • Median FU: not reported	• Intervention: laparoscopy • Comparator: open surgery	• Operative mortality (i.e. 30-day mortality and in-hospital mortality taken together; 9 trials), OR: 0.92, 95% CI: 0.45-1.87	• Anastomotic leak (8 trials), OR: 0.94, 95% CI: 0.46-1.91 • Postoperative pneumonia (10 trials), OR: 0.57, 95% CI: 0.32-1.03 • **Length of hospital stay** (9 trials), WMD: -1.23, 95% CI -1.78- -0.67, favouring laparoscopy • **Return to normal bowel function** (5 trials), WMD: -1.23, 95% CI: -1.84 - -0.61, favouring laparoscopy (but statistically significant heterogeneity) • **Operative time** (8 trials), WMD: 3.46, 95% CI: 1.55-5.37, favouring open	Results critical appraisal: • Only 1 RCT included; selection bias for other trials cannot be excluded • Only age and ASA score reported as pt characteristic • Critical appraisal of individual studies performed but not reported • No evaluation of long-term outcomes (hence no OS, PFS data) • Conflicts of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Number of included studies: 11 • Included studies: Vignali 2005 Tei 2009 Tuech 2000 Stocchi 2000 Stewart 1999 Sklow 2003 Senagore 2003 Lin 2010 Lian 2010 Law 2002 Frasson 2008				surgery (but statistically significant heterogeneity) • **Intra-operative blood loss** (6 trials), WMD: -2.79, 95% CI -4.18 - -1.39, favouring laparoscopy (but statistically significant heterogeneity) • **Postoperative cardiac morbidity**, OR: 0.58, 95% CI: 0.34-0.99, favouring laparoscopy • Postoperative ileus, OR: 0.65, 95% CI: 0.37-1.12 • **Postoperative wound infection**, OR: 0.45, 95% CI: 0.28-0.71, favouring laparoscopy	interest of included trials not reported
Ding 2013[56]	• Design: SR & MA • Sources of funding: no competing financial interests • Search date:	• Eligibility criteria: pts with **right-sided** colon cancer • Patients characteristics: only number of pts according to Dukes' stages reported	• Intervention: laparoscopic right hemicolectomy • Comparator: open right hemicolectomy	• Mortality rate (6 trials), OR: 1.00, 95% CI: 0.38-2.58 • Recurrence rate (5 trials), OR: 0.83, 95% CI: 0.51-1.34 • Conversion rate: range between 0-21.4%	• **Operative time** (6 trials), WMD: 33.37, 95% CI : 14.23-52.51, favouring open surgery (but statistically significant heterogeneity)	Results critical appraisal: • Only 1 RCT included; selection bias for other trials cannot be excluded

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	April 2012 • Searched databases: Medline, Embase, Cochrane library • Included study designs: RCT & retrospective nonrandomized trials • Number of included studies: 12 • Included studies: Abdel-Halim 2010 Guan 2010 Nakamura 2009 Ramacciato 2008 Tong & Law 2007 Lohsiriwat 2007 Del Rio 2006 Zheng 2005 Baker 2004 Lezoche 2002 Leung 1999 Bokey 1996	• Median FU: not reported			• **Blood loss** (4 trials), WMD, -128.97, 95% CI: -232.01 - -25.94, favouring laparoscopy (but statistically significant heterogeneity) • Number of harvested lymph nodes (7 trials), WMD: 0.51, 95% CI: -1.96-2.97 • Postoperative pain: data too heterogenous for MA (3 trials reported significantly less postoperative pain after laparoscopic surgery) • **Time to first flatus** (4 trials), WMD: -0.96, 95% CI: -1.25 - -0.66, favouring laparoscopy • **Postoperative hospital stay** (5 trials), WMD: -1.62, 95% CI: -2.98 - -0.26, favouring laparoscopy (but statistically significant heterogeneity)	• Only Dukes staging reported as pt characteristic • Only few studies including pts with Dukes stage D • No evaluation of long-term outcomes (hence no OS, PFS data) • Both right and extended right hemicolectomies included (which may have cuased heterogeneity) • No detailed data on surgeons' experience • Conflicts of interest of included trials not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					• Postoperative complications: pneumonia, OR: 1.02, 95% CI: 0.50-2.08; urinary tract infection, OR: 0.78, 95% CI: 0.25-2.44; anastomotic leak, OR: 0.82; 95% CI: 0.33-2.04; ileus, OR: 0.63, 95% CI: 0.35-1.14; hemorrhage, OR: 0.72, 95% CI: 0.21-2.49; deep vein thrombus, OR: 0.72, 95% CI:0.18-2.97; wound infection, OR: 0.56, 95% CI: 0.31-1.01.	
Ohtani 2012[57]	• Design: SR & MA • Sources of funding: no conflict of interest • Search date: October 2011 • Searched databases: Medline, Embase,	• Eligibility criteria: pts with colon cancer • Patients characteristics: not reported • FU (10 trials): range 30 - 95 months	• Intervention: laparoscopic surgery • Comparator: open conventional surgery	• Overall mortality (7 trials), OR: 0.90, 95% CI: 0.70-1.01 • Cancer-related mortality (5 trials), OR:0.79, 95% CI: 0.55-1.11 • Peri-operative mortality (6 trials), OR: 0.72, 95% CI: 0.35-1.48 • Overall recurrence (9 trials), OR: 0.96, 95% CI: 0.81-1.15	• **Operative time** (5 trials), WMD: 42.08, 95% CI : 29.87-54.30, favouring open surgery (but statistically significant heterogeneity) • **Blood loss** (4 trials), WMD, -103.90, 95% CI: -180.88 - -26.91, favouring laparoscopy (but	Results critical appraisal: • No patient characteristics reported • No detailed data on surgeons' experience • Conflicts of interest of included trials

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Cochrane library, Science citation index • Included study designs: 12 RCTs • Number of included studies: 12 • Included studies: Braga 2010, CLASICC trial 2005-2007-2010, COLOR trial 2005-2009, COST trial 2004, Curet 2000, ALCCaS trial 2008, Kaiser 2004, Barcelona trial 2008, Liang 2006, Mirza 2008, Pascual 2011, Winslow 2002			• Local recurrence (6 trials), OR: 0.82, 95% CI: 0.51-1.31 • Wound-site recurrence (7 trials), OR: 2.40, 95% CI: 0.87-6.61 • Distant metastases (8 trials), OR: 0.97, 95% CI: 0.78-1.21 • Conversion rate (12 trials): range between 3-46.4%	statistically significant heterogeneity) • Number of dissected lymph nodes (3 trials), WMD: -0.48, 95% CI: -1.27-0.31 • **Time to oral resumption** (3 trials), WMD: -0.81, 95% CI: -1.03 - -0.60, favouring laparoscopy (but statistically significant heterogeneity) • **Hospital stay** (6 trials), WMD: -2.28, 95% CI: -4.05 - -0.52, favouring laparoscopy (but statistically significant heterogeneity) • **Peri-operative overall complications** (9 trials), OR: 0.73, 95% CI: 0.56-0.95, favouring laparoscopy (but statistically significant heterogeneity) • **Ileus** (8 trials), OR:	not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					0.40, 95% CI: 0.25-0.66, favouring laparoscopy • Positive circumferential resection margin (2 trials), OR: 1.29, 95% CI: 0.65-2.54 • Cost of surgery (2 trials), WMD: 1048.48, 95% CI: -590.29-2687.24 (but statistically significant heterogeneity)	
Sammour 2011[58]	• Design: SR & MA • Sources of funding: 1st author is supported by the Surgeon Scientist Scholarship from the Royal Australasian College of Surgeons; The 2nd author is supported by the Ruth Spencer Fellowship from the	• Eligibility criteria: pt with an indication for any colonic or rectal surgery • Patients characteristics: not reported • Median FU: not reported	• Intervention: laparoscopic colorectal surgery • Comparator: open colorectal surgery	• **Intra-operative complication** (10 trials), OR: 1.37, 95% CI:1.06-1.76, favouring open surgery (with low heterogeneity) • **Intra-operative complication - colon cancer only** (5 trials), OR: 1.557, 95% CI:1.12-2.15, favouring open surgery (with moderate heterogeneity)	• **Intra-operative bowel injury** (10 trials), OR: 1.88, 95% CI: 1.10-3.21, favouring open surgery (with moderate heterogeneity) • Intra-operative haemorrhage (10 trials), OR: 1.25, 95% CI: 0.84-1.84 • Intra-operative solid organ injury (10 trials), OR: 0.77, 95% CI: 0.36-1.65	Results critical appraisal: • Patients with acutely, with a transverse colon, synchronous or invading neoplastic lesion were excluded from studies • No patient characteristics reported • 20 trials (also large ones) were excluded since intra-

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Auckland Medical Research Foundation • Search date: Aug 2009 • Searched databases: Medline and Cochrane Central Register of controlled trials • Included study designs: RCTs (published and unpublished) • Number of included studies: 10 • Included studies: Basse 2005, COST trial 2004, CLASICC trial 2005, ALCCaS trial 2008, King 2006, Klarenbeek 2009 (diverticulitis), Lujan 2009					operative complications not separately reported • Conflicts of interest of included trials not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	(rectal cancer), Maartense 2006 (Crohn), Tang 2001, Veldkamp 2005					
Ma 2011[59]	• Design: SR & MA • Sources of funding: not reported • Search date: 2008 • Searched databases: Medline, Embase and Cochrane Library • Included study designs: RCTs • Number of included studies: 15 • Included studies: Araujo 2003, Braga 2005, COST 2004, Curet 2000, Jayne 2007, Kaiser 2004, Lacy 2002, Leung 2004,	• Eligibility criteria: Patients with colorectal cancer in need of colorectal surgery • Patients characteristics: proportion males: 36-78%; mean age: 44-73 y.o. • FU: 1-59 months	• Intervention: laparoscopy • Comparator: open colorectal resection	• Overall mortality (8 trials), OR: 0.84, 95% CI: 0.73-1.03 • Cancer related mortality (7 trials), OR: 0.82, 95% CI: 0.66-1.02 • Cancer related mortality - colon only (6 trials), OR: 0.85, 95% CI: 0.66-1.09	• Overall recurrence (12 trials), OR: 0.92, 95% CI: 0.77-1.10 • Local recurrence (10 trials), OR: 0.81, 95% CI: 0.59-1.12 • Wound-site recurrence (6 trials), OR: 1.97, 95% CI: 0.77-5.02 • Distant metastases (9 trials), OR: 0.26, 95% CI: 0.02-2.88 • **Overall complication** (11 trials), OR: 0.71, 95% CI: 0.58-0.87, favouring laparoscopy	Results critical appraisal: • Critical appraisal of individual studies performed but not reported • Some studies included stage IV • Patients lost to FU were excluded from meta-analysis, which may have have caused bias • No detailed data on surgeons' experience • Conflicts of interest of included trials not reported

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Liang 2006, Milsom 1998, Mirza 2008, Park 2008, Stage 1997, Winslow 2002, Zhou 2004					

Table 75 – Evidence table: laparoscopy versus laparotomy: RCT

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Green 2013[60]	• Design: RCT • Sources of funding: UK MRC • Setting: UK, multi-centre, CLASICC trial (27 centres) • Sample size: 794 • Duration: July 1996- July 2002	• Eligibility criteria: pts suitable for left or right hemicolectomy, sigmoid colectomy, anterior resection or abdominoperineal resection • Patients characteristics[e]: mean age: 69 y.o.; proportion female: 44-46%; mean BMI: 25-26; ASA grade I-III • Median FU: 62.9 months (IQR: 22.9-92.8)	• Intervention: laparoscopically assisted colorectal resection (n=526) • Comparator: open colorectal resection (n=268)	• Median overall survival (only pts with colonic cancer): Intervention: 81.9, 95% CI: 61.0-103.3 vs. control 105.7 months, 95% CI: 72.9- - ; no significant difference • Median disease free survival (only pts with colonic cancer): Intervention: 86.6, 95% CI: 67.3-108.7 vs. control: 106.6 months, 95% CI: 72.7- - ; no significant difference	• Local recurrence rate: no significant differences between intervention and control; 10-year local recurrence rate significantly higher for right colonic cancers (14.7%) vs. left colonic cancers (5.2; p=0.019) • Distant recurrence rate: no significant differences between intervention (22.7%) and control (19.8%) • Wound/port-site recurrence rate: no significant differences in time to	• Dropouts: NA • Results critical appraisal: no blinding, unclear allocation concealment

[e] Data retrieved from earlier publication on CLASICC trial (Guillou et al., 2005)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					wound/port-site recurrence between intervention (n=10) and control (n=2) • Intraoperative conversion: 144/526 (27%)	
Li 2012[61]	• Design: RCT • Sources of funding: not reported • Setting: Hong Kong, single-centre • Sample size: 145 • Duration: July 1996-October 2005	• Eligibility criteria: pts with carcinomas of **right-sided colon** (i.e. cecum, ascending colon, hepatic flexure or transverse colon) confirmed on colonoscopic biopsy • Patients characteristics: mean age: 68 y.o.; proportion female: 54-57%; ASA grade II-III; stages I-IV • Median FU: 99.7 months	• Intervention: laparoscopic colorectal resection (n=71) • Comparator: open colorectal resection (n=74)	• Probability of survival at 5 yrs: Intervention: 75.0%, SE: 7.1% vs. control 74.2%, SE: 7.1%; no significant difference; probability of 5yr survival for stage I: 100% vs. 83.3% (NS), stage II: 68.7% vs. 83.3% (NS), stage III: 74.5% vs. 64.4% (NS) • Probability of being disease free at 5 yrs: Intervention: 82.3%, SE: 6.9% vs. control 84.1%, SE: 6.2%; no significant difference	• Total morbidity rate: Intervention: 23.9% vs. 35.1%, p=0.14 • **Mean operative time**: intervention: 198.4 vs. control 129.7 minutes, p=0.002 • **Hospital stay**: Intervention: 7.8 vs. control 10 days, p=0.033 • **Median time to resumption of normal diet**: Intervention: 4 vs. control 5 days, p=0.045 • Mean number of lymph nodes removed: Intervention: 18.7 vs. 20.7, p=0.30 • Median time to 1st flatus: Intervention: 3 vs. control 3.5 days, p=0.33	• Dropouts: NA • Results critical appraisal: no blinding, inadequate sample size for survival comparison

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					• Median time to 1st bowel motion: Intervention: 5 vs. control 4 days, p=0.94 • Postoperative pain VAS score: Intervention: 4.2 vs. control 4.5, p=0.54 • Analgesic requirement (median number of injections): Intervention: 7 vs. control 8, p=0.69 • Median time to ambulation: Intervention: 4 vs. control 4 days, p=0.11 • Intraoperative conversion: 11/71 (16%)	
Bagshaw 2012[62]	• Design: RCT • Sources of funding: Bobby Moore fund, cancer research UK and Ethicon Endo-surgery (Europe)	• Eligibility criteria: pts with a single adenocarcinoma of the right, left or sigmoid colon, presenting for elective treatment • Patients characteristics[f]:	• Intervention: laparoscopic colon resection (n=294) • Comparator: open colon resection (n=298)	• 5-year survival rate: hazard ratio: 0.988, 95% CI:0.732-1.335 • 5-year disease free survival rate: hazard ratio: 0.968, 95% CI: 0.729-1.286 • 5-year colon cancer freedom from	• Recurrence rate: Intervention: 13.7% vs. control: 14.8%, p=0.73 • Intraoperative conversion: 43/294 (15%)	• Dropouts: NA • Results critical appraisal: no blinding, significant difference in tumor pathology (distal resection

[f] Data retrieved from earlier publication on ALCCaS trial (Hewett et al., 2008)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	GmbH • Setting: Australia and New Zealand multi-centre (n=31 centres) • Sample size: 587 • Duration: January 1998-April 2005	mean age: 69.4-71.15 y.o.; proportion female: 52-53%; mean BMI: 26; ASA grade I-IV • Median FU: 5.2 years (5-yr confirmed follow-up for survival and recurrence for 567 (97%) pts)		recurrence rate: hazard ratio: 1.023, 95% CI: 0.670-1.562		margin, perineural invasion of the tumor, positive harvested lymph nodes and difference in N-stage) between intervention and control group
Kaltoft 2011[63]	• Design: double blinded RCT • Sources of funding: none • Setting: Denmark, University hospital • Sample size: 18 • Duration: not reported	• Eligibility criteria: pts with verified cancer at least 20 cm above the anal sphincter, between 40 and 90 y.o., scheduled for sigmoid resection without a planned stoma • Patients characteristics: mean age: 65 (control) - 73 (intervention) y.o.; proportion female: 75-90%; ASA grade I-III • Median FU: 30 days	• Intervention: laparoscopic colorectal resection (n=10) • Comparator: open colorectal resection (n=8)	• No report of OS, PFS, DFS	• **Median hospital stay**: Intervention: 4.5 vs. control 7 days, p=0.006 • Nursing time spent (day -1 to day 3 or entire admission): no significant difference • Pain: no significant difference • **Number of pts returning to normal activity**: *) after 14 days: no significant difference; *) **after 30 days**: Intervention: 10/10 vs. control: 4/8, p=0.023 • **Fatigue** (VAS score): Intervention:	• Dropouts: none • Results critical appraisal: small sample size, no intention-to-treat protocol (if surgery was converted from laparoscopic to open surgery pts were excluded), incomplete recruitment for the study (due to reorganisation of the hospital structure), no correction for multiple testing

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					7 vs. control 46, p=0.033 • **Sleep during the day after 30 days**: Intervention: 0.5 vs. control: 1.5 hr, p=0.036	

Table 76 – Evidence table: Single-incision vs. traditional multiport laparoscopic colorectal surgery - SRs

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Lv 2013[23]	• Design: SR and MA • Sources of funding: Not reported • Search date: June 2012 • Searched databases: Pubmed, Cochrane Library • Included study designs: RCTs and comparative studies • Number of included studies: 20 (2 RCTs) • Included studies: Champagne 2012, Fujii 2012,	• Eligibility criteria: Patients in need of colorectal surgery (not only CRC) • Patients characteristics: proportion males: 29%-64%; mean ages: 31.6-73.0 y.o.; ASA score 1 and 3; mean BMI: 21.2-29.0 • Median FU: not reported	• Intervention: Single-incision laparoscopic colorectal surgery (SILC)(n=670 pts) • Comparator: traditional multiport laparoscopic colorectal surgery (MLC)(n=838 pts)	• Overall conversion rate (14 trials), OR: 1.71, 95% CI: 0.97-3.00 (*among 627 SILC procedures: 38 (6%) were needed to convert to MLC and 12 (2%) to laparotomy or hand-assisted laparoscopic surgery; among 754 MLC procedures, 31 (4%) were needed to convert to laparotomy or other procedures*) • Overall complication rate (19 trials), OR: 0.82, 95% CI: 0.63-1.08	• Operative time (20 trials), MD: -3.59, 95% CI: -10.59-3.77 (but statistically significant heterogeneity) • **Estimated blood loss** (13 trials), MD: -18.61, 95% CI: -31.33 - -5.90, favouring SILC (but statistically significant heterogeneity) • **Post-operative hospital stay** (20 trials), MD: -0.54, 95% CI: -0.95 - -0.12, favouring SILC (but statistically significant heterogeneity)	Results critical appraisal: • Only 2 RCTs included; selection bias for other trials very plausible since SILC tends to be performed in "selected pts" by "experienced laparoscopic surgeons" • Most included studies have small samples • No critical appraisal of individual studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Gaujoux 2012, Huscher 2012, Kanakala 2012, Lai 2012, Lu 2012, Poon 2012, Ramos-Valadez 2012, Rijcken 2012, Champagne 2011, Chen 2011, Kim 2011, Lee 2011, McNally 2011, Papaconstantinou 2011, Papaconstantinou 2011 (a), Wolthuis 2011, Adair 2010, Waters 2010					• No evaluation of long-term outcomes (hence no OS, PFS data) • Different single port systems may also lead to heterogeneity • Conflicts of interest of included trials not reported
Zhou 2012[22]	• Design: SR and MA • Sources of funding: not reported • Search date: January 2012 • Searched databases: Medline, Embase, Cochrane	• Eligibility criteria: Patients in need of colorectal surgery (not only CRC) • Patients characteristics: proportion males: 29%-66%; mean ages: 31.6-70.0 y.o.; mean BMI: 21.2-29.0	• Intervention: Single-incision laparoscopic colorectal surgery (SILS)(n=521 pts) • Comparator: conventional laparoscopic colorectal	• Overall conversion rate (14 trials), OR: 0.63, 95% CI: 0.33-1.22 • Overall morbidity rate (12 trials), OR: 0.85, 95% CI: 0.63-1.14 • Postoperative mortality: SILS: 0.1% vs. CL: 0.3%; p=0.75 • 1-year disease-free survival (1 trial): SILS:	• Operative time (9 trials), WMD: -1.29, 95% CI: -7.35-4.76 • **Operative blood loss** (4 trials), WMD: -33.71, 95% CI: -50.59 - -16.83 • **Need for blood transfusion** (3 trials), OR: 0.42, 95% CI: 0.19-0.94, favouring SILS	Results critical appraisal: • Only 1 RCT included; selection bias for other trials very plausible since SILC tends to be performed in "selected pts"

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	database • Included study designs: RCTs and comparative studies • Number of included studies: 14 (1 RCT) • Included studies: Champagne 2012, Fujii 2012, Gaujoux 2012, Huscher 2012, Kanakala 2012, Lu 2012, Ramos-Valadez 2012, Rijcken 2012, Chen 2011, Kim 2011, Lee 2011, Papaconstantinou 2011, Papaconstantinou 2011 (a), Adair 2010, Waters 2010	• Median FU: not reported	surgery (CL)(n=634 pts)	92% vs. CL: 92% • Port-site recurrence (1 trial): SILS: 0 (after a mean of 13 months)	• **Hospital stay** (10 trials), MD: -0.32, 95% CI: -0.52 - -0.12, favouring SILS (but statistically significant hetergeneity, likely been introduced by variation in discharge criteria) • **Time to first flatus** (2 trials), WMD: -0.58, 95% CI: -0.85 - -0.30 • **Length of largest incision** (5 trials), WMD: -0.84, 95% CI: -1.54 - -0.14, favouring SILS • Number of harvested lymph nodes (6 trials), WMD: 1.71, 95% CI: -0.41-3.83	by "experienced laparoscopic surgeons" • Most included studies have small samples • Only 1 study with 1-year oncologic outcomes • Lack of long-term oncologic outcomes (hence no pooled OS, PFS data) • Pooled analysis of pathologic resection margin status not possible • No studies comparing the systemic stress response of SILS vs. CL • Different single port systems may also lead to heterogeneity • Conflicts of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
						interest of included trials not reported

Table 77 – Evidence table: Robotic vs. traditional laparoscopic colorectal surgery - SRs

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Mirnezami 2010[24]	• Design: SR • Sources of funding: not reported • Search date: January 2009 • Searched databases: Medline, Embase, Cinahl, Cochrane library • Included study designs: RCT (n=1), comparative studies (n=7) and case series (n=9) • Number of included studies: 17 • Included studies: Baik 2008, Spinoglio 2008, Hellan 2007, Rawlings 2007,	• Eligibility criteria: pts who had robotic colorectal surgery • Patients characteristics: not reported • Median FU: not reported	• Intervention: robotic colorectal surgery • Comparator: conventional laparoscopic surgery (for RCT and comparative studies)	• Conversion rate: overall rate for robotic surgery: 6%; • Complication rate: overall rate for robotic surgery: 11%; 30-day mortality: 0 • Number of lymph nodes harvested: comparable results • Resection margin clearance: comparable results	• **Operative time**: increased with robotic procedure (statistically significant in 3 studies) • **Hospital stay**: *comparative studies*: conflicting results; *RCT*: significant reduction after robotic surgery (6.9 vs. 8.7 days, p<0.001) • Intra-operative blood loss: *comparative studies*: conflicting results; *RCT*: non-significant differences	Results critical appraisal: • Only 1 RCT included; selection bias for other trials very plausible • Study heterogeneity precluded meta-analysis of the data • Most included studies have (very) small samples (n=2-53), which may account for the lack of statistical differences • Inconsistent reporting of data

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	De Noto 2006, Pigazzi 2006, Sebajang 2006, Brauman 2005, Ruurda 2005, Woeste 2005, Anvari 2004, D'Annibale 2004, Delaney 2003, Giulianotti 2003, Vibert 2003, Hashizume 2002, Weber 2002					• No evaluation of long-term (oncological) outcomes (hence no OS, PFS data) • Patient characteristics of included studies not reported • Publication bias not assessed • Conflicts of interest of included trials not reported

Table 78 – Evidence table: robotic vs. traditional laparoscopic colorectal surgery - SRs

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Mirnezami 2010[24]	• Design: SR • Sources of funding: not reported • Search date: January 2009 • Searched databases: Medline, Embase, Cinahl, Cochrane library	• Eligibility criteria: pts who had robotic colorectal surgery • Patients characteristics: not reported • Median FU: not reported	• Intervention: robotic colorectal surgery • Comparator: conventional laparoscopic surgery (for RCT and comparative studies)	• Conversion rate: overall rate for robotic surgery: 6%; • Complication rate: overall rate for robotic surgery: 11%; 30-day mortality: 0 • Number of lymph nodes harvested: comparable results • Resection margin	• **Operative time**: increased with robotic procedure (statistically significant in 3 studies) • **Hospital stay**: *comparative studies*: conflicting results; *RCT*: significant reduction after	Results critical appraisal: • Only 1 RCT included; selection bias for other trials very plausible • Study heterogeneity precluded

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Included study designs: RCT (n=1), comparative studies (n=7) and case series (n=9) • Number of included studies: 17 • Included studies: Baik 2008, Spinoglio 2008, Hellan 2007, Rawlings 2007, De Noto 2006, Pigazzi 2006, Sebajang 2006, Brauman 2005, Ruurda 2005, Woeste 2005, Anvari 2004, D'Annibale 2004, Delaney 2003, Giulianotti 2003, Vibert 2003, Hashizume 2002, Weber 2002			clearance: comparable results	robotic surgery (6.9 vs. 8.7 days, p<0.001) • Intra-operative blood loss: *comparative studies*: conflicting results; *RCT*: non-significant differences	meta-analysis of the data • Most included studies have (very) small samples (n=2-53), which may account for the lack of statistical differences • Inconsistent reporting of data • No evaluation of long-term (oncological) outcomes (hence no OS, PFS data) • Patient characteristics of included studies not reported • Publication bias not assessed • Conflicts of interest of included trials not reported

Table 79 – Evidence table: robotic vs. traditional laparoscopic colorectal surgery - RCT

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Park 2012[64]	• Design: RCT • Sources of funding: National Research Foundation of Korea • Setting: Sout-Korea, Single-Centre • Sample size: 70 • Duration: September 2009 - July 2011	• Eligibility criteria: pts with newly disgnosed right-sided clonic carcinoma • Patients characteristics: mean age: 62.8-66.5 y.o.; proportion female: 46-60%; BMI: 23.8-24.4; ASA grade I-III • Median FU: 30 days (?)	• Intervention(s): robot-assisted colectomy • Comparator(s): laparoscopically assisted colectomy	• No report of OS, PFS, DFS	• Mean hospital stay: Intervention: 7.9 vs. control 8.3 days, p=0.130 • **Mean operating time**: Intervention: 195 min vs. control: 130 min, p<0.001 • Pain: no significant difference (assessed at day 1 and day 5) • Mean estimated blood loss: Intervention: 35.8 vs. control: 56.8 ml, p=0.211 • Mean time to first flatus: Intervention: 2.6 vs. control: 2.9 min, p=0.502 • Morbidity rate: Intervention: 6/35 vs. control: 7/35, p=0.723 • Mean number of retrieved lymph nodes: Intervention: 29.9 vs. control: 30.8, p=0.265 • Conversion rate: 0% • **Total cost**: significantly higher for robot-assisted colectomy	• Dropouts: none • Results critical appraisal: no blinding, small sample, surgeon had more experience with laparoscopy than robot-assisted surgery,

4.2.6. Enhanced recovery after surgery

Table 80 – Evidence table: ERAS – study characteristics

Study ID	Intervention	Randomized (n)	Analysed (n)	M/F	Median age (years)	Stage	ASA	Surgery	Procedure
Ren 2012	ERAS	299	299	190 male	61 (21-80)	Not reported	1.4 (0.4)	Open surgery	Right hemicolectomy: 71 Transverse colon: 3 Left hemicolectomy: 20 Sigmoid resection: 11 Lower anterior resection: 140 Rectosigmoid resection with colostomy: 16 Abdominoperineal resection: 37
	Standard care	298	298	178 male	59 (24-78)	Not reported	1.4 (0.3)	Open surgery	Right hemicolectomy: 95 Transverse colon: 3 Left hemicolectomy: 15 Sigmoid resection: 14 Lower anterior resection: 125 Rectosigmoid resection with colostomy: 9 Abdominoperineal resection: 38
Vlug 2011	Laparoscopy + ERAS	106	100	53% male	66 (SD 8.6)	T0: 13 T1: 10 T2: 4 T3: 48 T4: 5	Grade I or II: 53%	laparoscopy	Right-sided: 45% Left-sided: 55%
	Laparoscopy + standard care	110	109	62% male	68 (SD 8.8)	T0: 15 T1: 5 T2: 27 T3: 50	Grade I or II: 62%	laparoscopy	Right-sided: 44% Left-sided: 56%

Study ID	Intervention	Randomized (n)	Analysed (n)	M/F	Median age (years)	Stage	ASA	Surgery	Procedure
						T4: 3			
	Open surgery + ERAS	103	93	58% male	66 (SD 10.3)	T0: 16 T1: 7 T2: 19 T3: 55 T4: 3	Grade I or II: 58%	Open surgery	Right-sided: 35% Left-sided: 65%
	Open surgery + standard care	108	98	60%	66 (SD 701)	T0: 16 T1: 5 T2: 21 T3: 53 T4: 5	Grade I or II: 0%	Open surgery	Right-sided: 55% Left-sided: 45%
G. Wang 2012	Laparoscopy + ERAS	54	49	32 male	55 (33-65)	Duke A: 9 Duke B: 26 Duke C: 14	ASA I: 13 ASA II: 27 ASA III: 9	laparoscopy	Right colectomy: 16 Left colectomy: 14 Sigmoid colectomy: 19
	Laparoscopy + standard care	53	50	27 male	53 (37-67)	Duke A: 11 Duke B: 29 Duke C: 10	ASA I: 15 ASA II: 24 ASA III: 11	laparoscopy	Right colectomy: 18 Left colectomy: 12 Sigmoid colectomy: 20
Q. Wang 2012	Laparoscopy + ERAS	40	38	22 male	57 (38-69)	TNM 1: 19 TNM 2: 56 TNM 3: 31	ASA I: 27 ASA II: 60 ASA III: 19	laparoscopy	Right hemicolectomy: 7 Sigmoid colectomy: 18 Left hemicolectomy: 1 Transverse colectomy: 1 Anterior resection: 13
	Laparoscopy + standard care	40	38	20 male	55 (40-67)		ASA I: 32 ASA II:	laparoscopy	Right hemicolectomy: 6 Sigmoid colectomy: 16 Left hemicolectomy: 2

Study ID	Intervention	Randomized (n)	Analysed (n)	M/F	Median age (years)	Stage	ASA	Surgery	Procedure
							56 ASA III: 16		Transverse colectomy: 2 Anterior resection: 12
G. Wang 2011	ERAS	115	106	65 male	57 (38-69)	TNM 1: 19 TNM 2: 56 TNM 3: 31	ASA I: 27 ASA II: 60 ASA III: 19	Not reported	Right hemicolectomy: 30 Left hemicolectomy: 18 Sigmoid colectomy: 28 Anterior resection: 30
	Standard care	115	104	60 male	55 (40-67)	TNM 1: 19 TNM 2: 56 TNM 3: 31	ASA I: 32 ASA II: 56 ASA III: 16	Not reported	Right hemicolectomy: 24 Left hemicolectomy: 26 Sigmoid colectomy: 32 Anterior resection: 22
Yang 2012	Open surgery + ERAS	35	32	20 Male	57.2 (SD 11.7)	TNM 1: 5 TNM 2: 18 TNM 3: 9		Open surgery	Right hemicolectomy: 6 Left hemicolectomy: 2 Sigmoid colectomy: 6 Dixon procedure: 18
	Open surgery + standard care	35	30	22 Male	59.5 (SD 12.1)	TNM 1: 7 TNM 2: 16 TNM 3: 7		Open surgery	Right hemicolectomy: 7 Left hemicolectomy: 3 Sigmoid colectomy: 7 Dixon procedure: 13

Table 81 – Evidence table: ERAS – outcomes

Study ID	Intervention	Randomized (n)	Analysed (n)	Mortality (n)		Complications (n)		readmissions		Hospital stay (days)	
Ren 2012	ERAS	299	299	0		29	p=0.900	NA		5.7 (1.6°	p<0.001
	Standard care	298	298	0		28		NA		6.6 (2.4)	
Vlug 2011	Laparoscopy + ERAS	106	100	2	p=0.65	34	p=0.20	6	p=0.97	5	p<0.001
	Laparoscopy + standard care	110	109	2		37		7		6	
	Open surgery + ERAS	103	93	4		43		7		7	
	Open surgery + standard care	108	98	2		41		7		7	
G. Wang 2012	Laparoscopy + ERAS	54	49	1	p=0.31	6	p=0.295	2	p=0.663	4(2-12)	p<0.01
	Laparoscopy + standard care	53	50	0		10		3		5(3-48)	
Q. Wang 2012	Laparoscopy + ERAS	40	38	NA		2	p=0.045	NA		5.5 (5-6-	p<0.001
	Laparoscopy + standard care	40	38	NA		8		NA		7(6-8)	

Study ID	Intervention	Randomized (n)	Analysed (n)	Mortality (n)		Complications (n)		readmissions		Hospital stay (days)	
G. Wang 2011	ERAS	115	106	2	p=0.572	20	p=0.015	4	Not statistically significant	5 (2-41)	p<0.01
	Standard care	115	104	1		39		9		7 (3-55)	
Yang 2012	Open surgery + ERAS	35	32	NA		Infectious:2 Not infections: 4	Infectious: p<0.05 Not infectious: p=1.000	0		6 (1)	p<0.05
	Open surgery + standard care	35	30	NA		Infectious:8 Not infections: 4		0		11.7 (3.82)	

4.2.7. Adjuvant chemotherapy stage II

Table 82 – Evidence table: adjuvant chemotherapy stage II - SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Wu 2012[26]	• Design: SR and MA • Sources of funding: Grant support 2010 NSFC proposal • Search date: 1985-2010 • Searched databases: Medline, Embase, Web of Science,	• Eligibility criteria: (1) RCTs (2) colorectal cancer stage Dukes B or stage II (T3-T4 N0 M0) (3) no prior cancer therapy • Patients characteristics: not stated • Median FU:42 to >.60 months	• Intervention: surgery + adjuvant chemotherapy • Comparator: surgery alone	• 5-year OS stage II colon cancer: HR 0.81; 95%CI 0.71-0.91 • 5-year DFS stage II colon cancer: HR 0.86; 95%CI 0.75-0.98		• Results critical appraisal: HR was reported in text of the original study in three studies only. For the other studies, HR estimate was extrapolated (calculated from data using a

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	SciFinder Scholar, Clinical Evidence Online, Biosis, Cochrane Library, Ebsco, MD consult • Included study designs: RCTs • Number of included studies: 12 • Included studies: Wolmark 1988 Wolmark 1990 Group of Japan 1995 Zaniboni 1998 Vaillant 2000 Kato 2002 Watanabe 2004 Glimelius 2005 Hartung 2005 Watanabe 2006 Quasar 2007 Schippinger 2007					hierarchical series of steps presented by Tieny et al. or extracted from graphical representation).

4.2.8. Adjuvant chemotherapy elderly patients

Table 83 – Evidence table: adjuvant chemotherapy elderly patients: MA of 3 RCTs

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Sakamoto 2004[65]	MA Support: not reported; Setting: Japan Databases searched: not reported Search date: not reported Languages: not reported Included studies: 3 RCTs including 5233 patients	Inclusion: trials initiated before 1990, that randomly assigned patients by central randomisation to either long-term (12 months) administration of oral fluorinated pyrimidines or no further treatment after curative resection of colorectal tumours Exclusion: not reported Patient characteristics: Dukes A (11%), B (44%) or C (45%) rectal (46%) or colon (55%) carcinoma	Surgery + chemotherapy (at least oral fluorinated pyrimidines) vs. surgery with no chemotherapy	**mortality** 65-69 years: HR ±0.9 (95%CI ±0.6-1.2), 6% better in chemotherapy group (SE 13%) 70-75 years: HR ±1.1 (95%CI: ±0.7-1.6), 9% worse in chemotherapy group (SE 21%) **DFS**: 65-69 years: HR ±1.1 (95%CI ±0.8-1.4), 8% better in chemotherapy group (SE 11%) 70-75 years: HR ±1.1 (95%CI ±0.8-1.7), 18% better in chemotherapy group (SE 6%)	**OS colon cancer (all age groups)**: HR 0.86; 95%CI 0.73-1.00	Individual patient data meta-analysis of Koidara 1998 and Yasutomi 1997 Unclear whether a systematic review was performed to identify studies Analysis per Dukes stage not available Some analyses available in figures only (denoted with ´±´ here) Trials using sealed envelopes were excluded.

Table 84 – Evidence table: adjuvant chemotherapy elderly patients: observational studies

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Abraham 2013[66]	Observational study Support: Veterans of Foreign Wars and its Ladies Auxiliary Surgical Oncology Research Award; CoI: no disclosures Setting: California Cancer Registry, United States Sample size: N= 20537 ≥65 years Duration: patients diagnosed between 1994-1998 Follow-up: not reported	Inclusion: patients diagnosed with colon cancer; aged 50-94 years; AJCC stage III; undergone resection; known chemotherapy status Exclusion: in situ disease; unknown T-classification and lymph node and chemotherapy status; negative lymph nodes; metastatic disease; cases identified via death certificates or nursing home records Patient characteristics: 62% of patients aged 65-74 received chemotherapy vs. 38% of those aged 75-84; and 11% of those aged 85-94 years; around 70% of patients had a T2 tumour	Surgery + chemotherapy (unspecified) vs. surgery with no chemotherapy	Cancer specific mortality, propensity-adjusted: 65-74 years: HR 0.80 (95%CI does not include 1) 75-84 years: HR 0.71 (95%CI does not include 1) 85-94 years: HR 0.73 (95%CI does not include 1) 5-Year cancer-specific survival rates: 65-74 years: not reported ≥75 years: 55% vs. 43% (p<0.0001) 85-94 years: 43% vs. 38% (p=0.0002)	A model predicting chemotherapy refusal suggests that increasing age strongly predicted refusal.	Retrospective analysis of cancer registry data No data on specific chemotherapy agents, dosages and duration/completion of therapy available. Hazard ratio´s propensity-adjusted for year of diagnosis, tumour grade, T-stage, sex, race and insurance status. 1630 out of 29 435 patients were excluded from the analysis because of unknown chemotherapy status.

Gross 2007[67]	Observational study Support: Beeson Career Development Award; Claude D. Pepper Older Americans Independence Center at Yale; CoI: not reported on Setting: SEER-MEDICARE database, United States Sample size: N= 5330 (2807 patients with either heart failure, diabetes or COPD) Duration: diagnosed 1993-1999 Follow-up: maximum 10 years	Inclusion: ≥67 years; diagnosed with primary adenocarcinoma stage III who lived longer than 6 months after their diagnosis (5490/6637 pts). Exclusion: date of death was recorded as prior to or the same month as the month of their cancer diagnosis; the data source was autopsy or death certificate; missing information regarding their race (115 pts); ineligible for Medicare Part A and B coverage or fee-for-service coverage during the 2-year period prior to their cancer diagnosis; not received chemotherapy and had died within 6 months of surgery; no lymph nodes that were positive for malignancy Patient characteristics: 36% patients with heart failure received	Surgery + chemotherapy (unspecified) vs. surgery with no chemotherapy	<u>mortality, propensity-adjusted</u>: Chronic heart failure: HR 0.70 (95%CI ±0.56-0.87) COPD: HR ±0.69 (95%CI ±0.56-0.85) Diabetes: HR ±0.60 (95%CI ±0.47-0.74) One chronic condition: HR ±0.65 (95%CI ±0.55-0.78) ≥2 chronic conditions: HR ±0.72 (95%CI ±0.60-0.88) <u>5-year survival probability</u>: Chronic heart failure: 43% (95%CI 40-47%) vs. 30% (95%CI 27-34%) COPD: 46.2% vs. 32.9% (CIs not reported) Diabetes: 47.4 vs. 34.1% (CIs not reported) <u>1-year probability of having any hospitalization</u>: Chronic heart failure: 54.7% (95%CI 49.0–60.3%) vs. 52.4% (95%CI 48.1–56.6%)	Whether patients had completed chemotherapy or not did not influence the analyses (data not reported) The total number of co-morbidity conditions was not related significantly to toxicity related hospitalizations for patients who received chemotherapy (data not presented) Increasing age and number of chronic conditions are inversely related with the receipt of chemotherapy.	Retrospective analysis of cancer registry data linked with administrative claims data. Hazard ratio´s propensity-adjusted for year of diagnosis, patient-related and tumour-related factors Not all reported in numbers (but reported in a figure, denoted by: ±)

		chemotherapy; 58% of diabetes patients and 55% of COPD patients; vs. 60% of all patients		COPD: ± 55% vs. 53% Diabetes: ± 53% vs. 54% Adjusted OR 1-year hospitalization: Chronic heart failure: 1.06; 95% CI, 0.75–1.50 COPD: p=0.48 Diabetes: p=0.85		
Hu 2011[68]	Observational study Support: Agency for Healthcare Research and Quality; CoI: not reported Setting: SEER-MEDICARE database, United States Sample size: N= 7903 patients that received chemotherapy Duration:1991-2005 Follow-up: not reported	Inclusion: patients aged ≥65 diagnosed with stage III colon cancer between 1991-2005; Medicare beneficiaries with both Medicare Part A and Part B for 12-month period after primary cancer diagnosis Exclusion: death within 3 months after diagnosis; non-microscopic confirmed diagnosis; reporting source from autopsy or death certificate Patient characteristics: older patients were less likely to receive	Surgery + chemotherapy	Proportion of patients that completed chemotherapy (%): 65-69 years: 74% 70-74 years: 65% 75-79 years: 59% 80-84 years: 49% ≥85 years: 46%	-	Retrospective analysis of cancer registry data linked with administrative claims data.

		chemotherapy				
Jessup 2005[69]	Observational study Support: American College of Surgeons and the American Cancer Society; CoI: none Setting: National Cancer Database (database of 1430 United States hospitals) Sample size: N= 85934 (unclear how many patients aged ≥70 were in the 1997 cohort) Duration: 1990-2002 Follow-up: 5 years for the outcome 5-year survival	Inclusion: stage III adenocarcinoma of the colon Exclusion: not reported Patient characteristics: 63% of patients aged 70-79 received chemotherapy vs. 28% of those aged ≥80 years in 1995-1996	Surgery + chemotherapy (unspecified) vs. surgery with no chemotherapy	5-year survival in the 1997 cohort: 70-79 years: ±70% vs. 50% ≥80 years: ±70% vs. 50%	-	Retrospective analysis of hospital registry data No data on specific chemotherapy agents, dosages, or information concerning the duration/completion of therapy available 5-year survival data depicted in a figure (denoted by ±) 5-year survival data not adjusted for confounders
Kahn 2010[70]	Observational study Support: National Cancer Institute, Department of Veterans Affairs grant; CoI: none Setting: multiple centres, United States Sample size: N= 373 aged ≥65 years Duration: 2003-2005 Follow-up: not	Inclusion: patients diagnosed with stage III colon cancer from 2003 - 2005 who underwent surgical resection and were followed up for as long as 15 months post diagnosis Exclusion: non-responders, rectal cancer, other stages, unclear whether	Surgery + adjuvant chemotherapy (unspecified) vs. surgery with no chemotherapy	Unadjusted yearly late adverse event rate: 65-74 years: 0.42 (95%CI: 0.28-0.56) vs. 0.16 (95%CI: 0.01-0.31) ≥75 years: 0.34 (95%CI: 0.20-0.48) vs. 0.21 (95%CI: 0.09-0.32)	-	Analysis based on retrospective hospital based data and base line survey Adjusted events rates were adjusted for patients´ characteristics and chemotherapy characteristics

	reported	received adjuvant chemotherapy Patient characteristics: 84% of patients aged 65-74 years used chemotherapy vs. 50% of those ages ≥75 years		Adjusted yearly late adverse event rate: depicted in a figure 65-74 years: 0.45 vs. ±0.16 (p<0.01) ≥75 years: 0.28 vs. ±0.14 (p<0.01)		
Morris 2007[71]	Observational study Support: Royal Australasian College of Surgeons; CoI: not reported Setting: four hospitals, Australia Sample size: N= 464 aged 65-75 years Duration: 1993-2003 Follow-up: mean 60 months	Inclusion: patients diagnosed with stage II colorectal cancer during 1993–2003 Exclusion: age >75 years; metachronous colon cancer; concomitant inflammatory bowel disease; familial polyposis coli; previous malignancies; positive surgical margins Patient characteristics: 20% of patients aged 65-69 years received chemotherapy vs. 7% of those aged 70-75 years	Surgery + adjuvant chemotherapy (5-FU) vs. surgery with no chemotherapy	Unadjusted hazard ratio mortality: 65-69 years: 1.08 (95%CI: 0.43–2.69, p=0.87) 70-75 years: 0.71 (95%CI: 0.26–1.95; p= 0.51)	-	Retrospective analysis of hospital records Data on the doses administered not reported Perioperative deaths within 4 weeks of surgery were excluded from the analysis Very few patients in the groups that received chemotherapy (33 and 20 respectively) Unadjusted analysis
Van Steenbergen 2012[72]	Observational study Support: Dutch Cancer Society; CoI: none	Inclusion: patients aged ≥75 years with resected stage III primary colon cancer, diagnosed in the	Surgery + adjuvant chemotherapy (unspecified) vs. surgery with no chemotherapy	Unadjusted 5-year survival: 75-79 years: 57 vs. 33% (p<0.0001)	-	Retrospective analysis of population-based cancer registry data Data on the

	Setting: the Netherlands Cancer Registry, the Netherlands Sample size: N=6290 aged 75-84 Duration: 1997-2009 Follow-up: not reported	period 1997–2009 in The Netherlands Exclusion: no surgery Patient characteristics: 22-44% of patients aged 75-79 received chemotherapy vs. 4-10% of those aged 80-84 years and vs. 0-1% of those aged ≥85 years		80-84 years: 41 vs. 28% (ns)		chemotherapeutic agents and doses administered not reported Only 190 patients aged 80-84 years received chemotherapy Unadjusted analysis
Wildes 2010[73]	Observational study Support: National Institutes of Health; CoI: none Setting: Barnes-Jewish Hospital Oncology Data Services registry, United States Sample size: N= 435 Duration: 1996-2006 Follow-up: not reported	Inclusion: colorectal cancer patients stage III, diagnosed 1996-2006 Exclusion: no surgery Patient characteristics: 72% of patients in the alpha subgroup received chemotherapy, vs. 69 and 29% in the beta and gamma subgroups	Surgery + (neo)adjuvant chemotherapy (unspecified) vs. surgery with no chemotherapy	3-year overall survival: Alpha subgroup: 70 vs. 42% Beta subgroup:71 vs. 59% Gamma subgroup: 62 vs. 35% Adjusted hazard ratio for death: Alpha subgroup: 0.44 (95%CI: 0.34-0.57) Beta subgroup: 0.45 (95%CI: 0.28-0.72) Gamma subgroup: 0.48 (95%CI: 0.28-0.81)	Propensity score analysis confirmed these results. Within each quintile, chemotherapy was associated with increased survival. There was no significant difference in survival for those who received chemotherapy across the quintiles (data not shown)	Retrospective analysis of hospital cancer registry data Data on the chemotherapeutic agents and doses administered were not available Hazard ratio´s adjusted for gender, race and cancer site The Adult Co-morbidity Evaluation-27 (ACE-27) was used to categorise co-morbidity as none, mild, moderate or severe Patients were then stratified according to increasing age and co-morbidity:

						Alpha subgroup: patients aged 65-74 years with no or mild co-morbidity, or aged 75-84 with no co-morbidity Beta subgroup: patients aged 65-74 years with moderate to severe co-morbidity, or aged 75-84 with mild co-morbidity Gamma subgroup: patients aged 75-84 with moderate to severe co-morbidity, or patients aged ≥85 with no to severe co-morbidity
Zuckerman 2009[74]	Observational study Support: Sanofi-Aventis; Setting: SEER-MEDICARE database, United States Sample size: N= 7182 (and 3016 propensity matched patients) Duration: 1997-2002 Follow-up:	Inclusion: diagnosis stage III colon cancer, aged ≥66 years; continuous Medicare Part A and B enrolment without health maintenance organization (HMO) enrolment during the 12 months before diagnosis Exclusion: claims for other cancer diagnoses, human immunodeficiency virus or acquired	Surgery + chemotherapy (unspecified) vs. surgery with no chemotherapy	Hazard ratio colon cancer related death, adjusted: 66-69 years: 0.47 (95%CI: 0.33–0.65) p<0.001 70-74 years: 0.32 (95%CI: 0.25–0.40) p<0.001 75-79 years: 0.41 (95%CI:0.34–0.50) p<0.001 80-84 years: 0.41 (95%CI:0.34–0.50)	Similar results were obtained when all-cause mortality was used instead of colon cancer–specific mortality, completion of chemotherapy instead of a dummy for treatment receipt, and age quintiles instead of 4-year groups (data not reported)	Retrospective analysis of cancer registry data Hazard ratio´s adjusted for tumour an patients´ characteristics, including co-morbidity Propensity matching undertaken to make a new cohort of patients with a balance in covariates between patients who did receive chemotherapy

	immunodeficiency syndrome; organ transplant during the 5 years before the colon cancer diagnosis; missing, incomplete, or inconsistent information; colon cancer diagnosed at autopsy; stage III diagnosis but no reported positive nodes; treated with capecitabine or irinotecan Patient characteristics: receipt of chemotherapy: 66-69 years: 19%; 70-74 years: 30%; 75-79 years: 30%; 80-84 years: 17%; ≥85 years: 5%	p<0.001 ≥85 years: 0.54 (95%CI: 0.41–0.71) p<0.001 Hazard ratio colon cancer related death, propensity matched and adjusted: 66-69 years: 0.54 (95%CI: 0.35–0.84) p=0.006 70-74 years: 0.36 (95%CI: 0.26–0.50) p<0.001 75-79 years: 0.36 (95%CI: 0.27–0.46) p<0.001 80-84 years: 0.65 (95%CI: 0.50–0.84) p<0.001 ≥85 years: 0.51 (95%CI: 0.36–0.72) p<0.001	and those who did not

4.2.9. Treatment acute obstruction

Table 85 – Evidence table: treatment of acute obstruction: RCTs

I Study ID	II Method	III Patient characteristics	IV Intervention(s)	V Results primary outcome	VI Results secondary and other outcome(s)	VII Critical appraisal of study quality
Alcantara 2011[75]	RCT Support: Parc Taulí Foundation; CoI: not reported Setting: single centre, Spain Sample size: N= 28 Duration: February 2004-December 2006 Follow-up: mean 37.6 months (SD: 16.1)	Inclusion: obstructive left-sided colonic cancer; age ≥18 years Exclusion: unresectable lesion (intraoperative); severe ischemia or cecal perforation; fecal or advanced purulent peritonitis; hemodynamic instability during surgery; immunodepressed state; septic shock Patient characteristics: 43% male Mean age ±71 years 14% stage IV, with resectable hepatic metastases which were operated on as scheduled surgery during follow-up	Stent placement before surgery **vs**. emergency surgery with intraoperative colonic lavage and primary anastomosis	In-hospital mortality: 0 vs. 1 (p=0.464) Overall in-hospital morbidity: 2/15 (13.3%) vs. 7/13 (53.8%) (p=0.042) Anastomotic dehiscence: 0 vs. 4/13 (30.7%) (p=0.035) Surgical site infection: 2 (13.3%) vs. 6 (46.1%) (p=0.096) Complications related to stent placement: 0% (1 pt had hartmann procedure due to inflammatory phlegmon throughout the stent area) (actual data not reported, survival depicted in a figure)	No differences were found with respect to long term survival or disease-free period. There were more relapses in the stent group, although the number was not significant (p=0.055)	Patients probably treated with curative intent. Unclear how intraoperative exclusion criteria after randomization were handled. Suspended early because of excess morbidity in the emergency surgery group Sequence generation not reported on Allocation concealment through sealed envelopes Blinding of patients and personnel not possible Blinded outcome assessment not reported ITT analyses
Cheung 2009[76]	RCT Support: none Setting: single	Inclusion: Adult patients with an obstructing tumour between the splenic flexure and recto	Self-expanding metal stent followed by laparoscopic resection **vs**.	*All results reported stent + laparoscopy vs. emergency open surgery*	Four patients had failed endoluminal stenting owing to failed cannulation	Not reported whether patients were treated with curative or palliative intent. Small

	centre, Hong Kong Sample size: N= 48 Duration: January 2002-May 2005 Follow-up: not reported	sigmoid junction Exclusion: peritonitis, right lower quadrant tenderness, or a grossly distended cecum (>10 cm in maximal dimension) on plain abdominal radiography; patients who were considered unfit for operative treatment; patients with a previous laparotomy; and patients with a clinically palpable tumour on abdominal examination Patient characteristics: 54% male 25% stage IV (3/24 vs. 9/24 patients had stage IV; p=0.02 using STATA´s prtesti command)	emergency open surgery (Hartmann, primary anastomosis after either subtotal or total colectomy or segmental colectomy with on-table lavage) In both treatment arms, a defunctioning stoma was constructed if considered appropriate by the surgeon	Successful 1-stage operations: 67% vs. 38% (0.04) Permanent colostomy: 0% vs. 25% (p=0.03) Stent related complications: 0% Anastomotic leakage: 0/24 vs. 2/24 (p=0.45) Wound infection: 2/24 vs. 8/24 (p=0.04) Chest infection: 0/24 vs. 1/24 (p=0.99) Intra-abdominal sepsis: 0/24 vs. 1/24 (p=0.99) Other morbidities: 0/24 vs. 5/24 (p=0.02) Peri-procedural mortality: 0/24 vs. 0/24		study Time of follow-up not reported One patient from each group was excluded from analysis: one because of withdrawal of consent and one because of extensive disease precluding surgery after stent placement. Computer-generated randomisation Allocation concealment not reported Blinding of patients and personnel and outcome assessment not reported
Fiori 2004, Fiori 2012[77, 78]	RCT Support: not reported; Setting: single centre, Italy Sample size: N= 22 Duration: January 2001-May 2003 Follow-up: 4 to 6 years, until death of all patients	Inclusion: malignant sub acute obstruction of the rectom or sigmoid colon presenting an advanced unresectable stage Patient characteristics: 59% male Mean age: ±76 years Site of obstruction: 8 sigmoid; 14 rectum 100% stage IV	Stenting vs. proximal diverting colostomy	Stent related complications: 0% Peri-procedural mortality: 0% vs. 0% There were no statistically significant differences between the 2 groups concerning peri-procedural morbidity	Long term FU stent: 2 patients had fecal impaction at the stent site, which was resolved by removing mechanically the stool; in the 3rd patient, there was tumour in-growth, which was resolved with laser	Patients were treated with palliative intent Small trial Suspended early because no stent-related complications were found (which was considered to occur à priori) Randomisation with random-number tables

				Crude median survival: 297 days (range: 125–612 days) vs. 280 days (range: 135–591 days) (not significant) No case of mortality during long-term follow-up was related to the procedures	treatment and the insertion of a new stent. One patient had chronic anemia requiring blood transfusion 1 stoma prolapsed after 9 months, which was well tolerated by the patient without surgical revision. One patient had significant skin inflammation and irritation around the stoma. Two patients had chronic anemia requiring blood transfusion	Allocation concealment procedure not reported Blinding of patients and personnel not possible Blinded outcome assessment not reported ITT analyses, no loss to follow-up
Ho 2012[79]	RCT Support: not reported; Setting: single centre, Singapore Sample size: N= 39 Duration: October 2004-February 2008 Follow-up: 60 days	Inclusion: acute left-sided malignant colonic obstruction with no evidence of peritonitis Exclusion: obstruction due to non-colonic malignancy Patient characteristics: 56% male Median age: ±68 years 26% stage IV 10/20 vs. 5/19 patients were stage III (p=0.13	Stenting + elective surgery vs. emergency surgery For both study arms, surgical options at the discretion of the individual surgeon included resection and primary anastomosis, Hartmann's procedure, (sub)total	*All results reported stent + surgery vs. emergency surgery* Complication rate: 35% vs. 58% (p=0.152) Mortality: 0% vs. 16% (p=0.106) Defunctioning stomas: 2/20 vs. 6/19 (p=0.127) Permanent stoma 1 year post-surgery: 1/20 vs. 2/19	Six out of twenty patients (30%) failed stenting (of which technical stent failure occurred in five patients) and underwent emergency surgery.	Small trial Computer-generated randomisation Allocation concealment: sequentially numbered, opaque, sealed envelopes 1 patient developed peritonitis before stenting and was excluded Blinding of patients and personnel not

		with Stata´s prtesti command); 3/20 vs. 7/19 patients were stage IV (p=0.12)	colectomy, diverting stoma formation and laparoscopic colectomy			possible Blinded outcome assessment not reported
Kronborg 1995[80]	RCT Support: not reported; Setting: single centre, Denmark Sample size: N= 121 Duration: 1978-1993 Follow-up: 4 months to 15 years	Inclusion: patients presenting with signs of left-sided obstructive colorectal tumours; no synchronous tumour in the right colon; complete resection of tumour possible Exclusion: distant spread; low rectal tumours; intestinal gangrene; inflammatory bowel disease Patient characteristics: 42% male Mean age: ±71 years 22% Dukes C	Transverse colostomy followed by planned resection with anastomosis **vs**. Acute resection with colostomy and anastomosis in a later stage *7/63 patients in the immediate resection without anastomosis group had an anastomosis at the time of resection with an intracolonic bypass by an intraluminal tube (coloshield).*	*All results reported staged resection vs. immediate resection* ≥1 postoperative complication: 31/58 vs. 42/63 (p=0.19) Post-operative mortality: 10/58 vs. 8/63 Patients surviving curative resection for cancer who have no permanent colostomy: 32/35 vs. 36/50 (p=0.05) (excluding the patients with a coloshield: 32/35 vs. 30/44, p=0.01) Local recurrence: 9/34 vs. 5/50 (p=0.09) Overall recurrence: 16/34 vs. 22/50 Median disease-free interval: 18 vs. 12 months (p=0.02) Cancer-specific survival: no significant difference	-	Sequence-generation not described Allocation concealment not described Blinding of patients and personnel not possible Blinded outcome assessment not reported 11 vs. 6 patients did not have cancer. These patients were not included in the survival analyses. 3 vs. 0 patients had unexpected distant spread

Pirlet 2011[81]	RCT Support: metallic stent devices were provided free of charge by BARD France SAS; hospital clinical research program, Montpellier University Hospital, Agence Française de Sécurité sanitaire des produits de santé.; Setting: multicentre, France Sample size: N= 60 Duration: December 2002-October 2006 Follow-up: not reported	Inclusion: acute left-sided malignant large bowel obstruction; age ≥ 18 years, fit for both emergency surgery and colonic stenting Exclusion: symptoms suggesting bowel perforation; stage IV carcinoma Patient characteristics: 48% male Mean age: ±73 years 0% stage IV	Stent + surgery **vs**. emergency surgery (laparotomy) For both study arms, surgical options at the discretion of the individual surgeon included segmental or subtotal resection and primary anastomosis with or without intraoperative colonic washout, Hartmann's procedure, diverting stoma formation, two-stage and three-stage procedures	*All results reported stent + surgery vs. emergency surgery* Stoma placement: 43% vs. 57% (p=0.30) Permanent stoma: 9/30 vs. 8/30 Overall primary anastomosis rate without leakage: 53% vs. 43% (p=0.45) In-hospital mortality: 3/30 vs. 1/30 In-hospital morbidity: - Abdominal complications: 7/30 vs. 7/30 (p=1.00) - Extra abdominal complications: 8/30 vs. 10/30 (p=0.57)	14/30 (47%) stent insertions were technically successful, of which 2 clinical failures of colonic decompression. Two colonic perforations directly related to the stent placement procedure occurred (7%)	Prematurely closed trial (intended to randomise 80 patients) because of 2 colonic perforations during stent placement and high technical failure rates. 10/70 randomized patients were excluded from analysis because of protocol violations (treatment before randomisation, no surgery after stent placement, benign lesions) Randomisation sequence generation through computer-generated lists Allocation concealment procedure: secured web site Blinding of patients and personnel not possible Blinded outcome assessment not reported

Sankararajah 2005[82]	RCT (abstract) Support: not reported; Setting: not reported, United Kingdom Sample size: N= 19 Duration: 2000-2004 Follow-up: median 12 months	Inclusion: patients with a large bowel obstruction Exclusion: not reported Patient characteristics: 58% male Median age: 79 years 58% of the lesions were Dukes B or C; 32% had liver metastases	Stent with or without elective surgery vs. emergency surgery	*All results reported stent + surgery vs. emergency surgery* Post-procedural (≤30 days) mortality: 1/9 vs. 1/9 Post-procedural morbidity: 24% post-stenting + 14% post-elective surgery vs. 66% (numbers not reported) Estimated 1-year survival: 54% vs. 57% (numbers not reported) Median survival: 23 months vs. 19 months	78% of stenting procedures were successful, 57% of the stented patients went on to have elective surgery.	Interim analysis in abstract form 1 patient randomised to emergency surgery refused treatment 57% of stented patients underwent elective surgery Randomisation sequence generation not reported Allocation concealment procedure not reported Blinding of patients and personnel not possible Blinded outcome assessment not reported unclear whether ITT analysis was performed
Xinopoulos 2004[83]	RCT Support: not reported; Setting: single centre, Greece Sample size: N= 30 Duration: March 1998-April 2002 Follow-up: not reported but up until	Inclusion: inoperable malignant partial colon obstruction, from colon (n=24) or ovarian cancer (n=6) Patient characteristics: 53% male Mean age: 72 years Site of obstruction:	Stent vs. colostomy	Stent-related complications: 0% Surgery was performed without serious complications Peri-procedural morbidity: 0% vs. 0%	Technical success rate stent placement 93.3% A moderate occlusive in-growth of tumour into the stent was documented in 6 patients and was treated with internal laser	Small trial 1 patient in whom stent placing was not possible was excluded from the trial Randomisation sequence generation not reported Allocation concealment procedure not

	all patients died	rectosigmoid colon in 18 patients and sigmoid colon in 12 patients.		Median survival: 21.4 vs. 20.9 weeks	application. After 44 weeks of follow-up and internal application of a laser, 1 stent was expelled to the anal side of the lesion without complication	reported Blinding of patients and personnel not possible Blinded outcome assessment not reported no ITT analysis
Van Hooft 2008[84]	RCT Support: ZonMw; CoI: none Setting: multicentre, the Netherlands Sample size: N= 21 Duration: December 2004-January 2006 Follow-up: until death or at least 1 year	Inclusion: incurable, metastatic left−sided colorectal cancer and imminent obstruction; age ≥18 years Exclusion: ileus; Karnofsky performance status <50% or an American Society of Anaesthesiologists class of IV or V Patient characteristics: 52% male Mean age: ±65 years 100% stage IV	Stent vs. palliative surgery (palliative resection or fecal diversion).	Median survival out of hospital with WHO PS 0-1 during the first year: 38 days (interquartile range: 5.25±288.75 days) vs. 56 days (interquartile range: 7.5±338.5 days) (p=0.68) Adverse events including long-term follow-up: 11 vs. 1 (p<0.001) Stent-related complications within 30 days: 2 perforations, 1 hospital admission for diarrhea and 1 hospital admission for severe pain that spontaneously resolved Peri-procedural mortality: 2 vs. 0 Colostomy: 0 vs. 2	Surgical arm: 8/10 patients underwent surgery, 6/8 had resection with primary anastomosis. Attempt of stenting undertaken in 10/11 pts, successful in 9/10. Two perforation 12 days after placement and 4 late perforations at day 44, 106, 351 and 355. Three patients had a second stent placed, two because of stent obstruction and one because of stent migration.	A high number of serious adverse events in the nonsurgical arm led to premature closure of the trial. Computerised, central randomisation Blinding of patients and personnel not possible Blinded outcome assessment not reported (complications were masked for group assignment) ITT analysis

Van Hooft 2011[85]	RCT Support: none; Setting: multiple centres, the Netherlands Sample size: N= 98 Duration: March 2007- August 2009 Follow-up: 6 months	Inclusion: acute obstructive left-sided colorectal cancer; age ≥18 years Exclusion: signs of peritonitis, perforation, fever, sepsis, or other serious complications demanding urgent surgery; physical status of class 4 or 5 according to the American Society of Anaesthesiologists; obstruction caused by a non-colonic malignancy or a benign disease; distal tumour margin of less than 10 cm from the anal verge; inability to complete self-report quality-of-life questionnaires Patient characteristics: 52% male Mean age: ±71 years	Stenting + surgery vs. emergency surgery Type and extent of surgery were selected by the surgeon in the stenting group. Emergency surgency was performed according to conventional standards.	*All results reported stent + surgery vs. emergency surgery. RR < 1 favours emergency surgery.* 30-day mortality: 5/47 vs. 5/51 RR 0.92 (95%CI 0.28-2.98) (p=0.89) Overall mortality: 9/47 vs. 9/51 RR 0.92 (95%CI 0.40-2.12) (p=0.84) Patients with SAE: 25/47 vs. 23/51 RR 0.85 (95%CI 0.57-1.27) (p=0.43) Stoma rates post-surgery: 24/47 vs. 38/51 RR 1.46 (95%CI 1.06-2.01) (p=0.02) Stoma rates at latest follow-up: 27/47 vs. 34/51 RR 1.16 (95%CI 0.85-1.59) (p=0.35) Six stent associated perforations at 6 months; additionally 3 silent stent perforations detected in the operative specimen	Stent placement was technically and clinically successful in 33/47 patients No significant differences according to EORTC-QLQ-C30, including subscales, based on available data and corrected for differences at baseline No significant differences according to EORTC-QLQ-CR38, based on available data and corrected for differences at baseline, except for the stoma-related problems subscale where the emergency surgery group scored better (–12.0 (–23.7 to –0.2) (p=0.046)	A higher morbidity in the stent arm led to premature stopping of the trial (98/120 planned patients enrolled) Computer-generated randomisation Web-based allocation Blinding of patients and personnel not possible Blinded outcome assessment: blinded assessors evaluated outcomes ITT analysis

4.2.10. Surgery +/- chemotherapy for isolated liver metastases

Table 86 – Evidence table: systematic reviews synchronous CRC liver metastases

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Chen 2011[86]	• Design: MA • Sources of funding: not stated • Search date: 1/1966-12/2009 • Searched databases: PubMed, • Embase, Cochrane Library, Ovid, and Web of Science • Included study designs: comparative • Number of included studies: 14	• Eligibility criteria: CRC with resectable synchronous hepatic metastasis • Patients characteristics: 2204 patients: 1384 (ages 56-64.9) having received simultaneous resection, 817 (ages 58-61) staged resection • Median FU: 2.5 yrs (total 5 yrs)	• Intervention: • simultaneous resection • Comparator: staged resection	3. Overall survival no statistical difference at 1 year (OR, 0.77; 95% CI, 0.51–1.16, P=.21), 3 years (OR, 1.12; 95% CI, 0.85–1.47, P=.43), 5 years (OR, 1.14; 95% CI, 0.86–1.50, P=.37)	1. Operative factors: A:operative time (weighted mean difference [WMD], −34.19; 95% confidence interval [CI], −81.32–12.95, P=.16) B:intraoperative blood loss (WMD, −161.33; 95% CI, −351.45–28.79, P=.10). C:hospital stay (WMD, −4.77; 95% CI, −7.26–2.28, P<.01) 2.Postoperative complications: lower morbidity rate (odds ratio [OR], 0.71; 95% CI, 0.57–0.88, P=.002	• Results critical appraisal • High quality studies • heterogeneity

Table 87 – Evidence table: systematic reviews synchronous and metachronous CRC liver metastases

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Chua 2009	• Design: SR • Sources of funding: not stated • Searched databases and dates: MEDLINE, PubMed • Included study designs: RCT and non randomized trials • Number of included studies: 23	• Eligibility criteria: -publications where systemic CT was used in patients with resectable CLM, more than 20 patients, English • Patient characteristics: 3,278 patients with majority of hepatic-only metastases (5 studies including patients with extra-hepatic disease) median number of lesions: 2 (range 2-7), median maximum size of the lesion 4 cm (range 3-5).	• Intervention: neoadjuvant CT • Comparator: none	• DFS (reported in 12 studies):median 21 mo (range 11–40 mo) • OS (reported in 13 studies): median 46 mo (range 20–67 mo) • peri-operative mortality: median rate: 2% (range 0–5%) • peri-operative morbidity: median rate: 27% (range 11–50%)	**radiological assessment:** (reported in 14 studies): median rate of objective response • (complete/partial) 64% (range 44–100%);. • Median rate of complete response: 4% (range 0–38%). • median rate of partial response 52% (range 10–90%). • median rate of stable disease 26% (range 0–47%). • median rate of disease progression: 15% (range 0–37%) **hepatectomy:** • median rate of complete resection: 93% (range 39–100%);	Results critical appraisal • No comparator • Various types of chemotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
					• median rate of hepatectomy involving resection of 3 or more segments: 68% (range 23–97%)	
Nelson, 2009	• Design: meta-analysis • Sources of funding: not stated • Search date:1966 to December 2008 • Searched databases: MEDLINE,Embase, Cochrane Central Register of Controlled Trials, the Cochrane Hepato-Biliary Group Controlled Trials Register. • Included study designs: RCT • Number of included studies: 7 • Included studies: • Kemeny 1999 • Kemeny 2002 • Lorenz 1998 • Lygidakis 1995 • Rudroff 1999 • Tono 2000 • Wagman 1990	• Eligibility criteria: resectable hepatic mCRC synchronous and metachronous • Patients characteristics: Total of 592 patients with in 289 intervention group • Median FU: 81 months	• Intervention: Postoperative intra arterial chemotherapy • Comparator: No postoperative chemotherapy	1)overall survival HR (Fixed, 95% CI) 1.09 [0.89, 1.34] 8.9% survival advantage in favour of control group 2) adverse events related to the chemotherapy No result	1)Intra-hepatic tumour recurrence 2)time to recurrence 3)extra-hepatic tumour recurrence 4)time to recurrence and disease specific survival : for all: no results (lack of denominator)	Includes 1 poor quality study Results lack significance

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Wieser, 2010	• Design: SR and MA • Sources of funding: P.U.R.E Research Program funded by the State Ministry for Innovation, Science, Research and Technology of Northrhine-Westfalia and the FoRUM foundation of the Ruhr-University Bochum. • Search date: • 1980- 23 January 2009 • Searched databases: Medline (PubMed), the Cochrane Library, the Latin American and Caribbean Literature on Health Sciences (LILACS) • Included study designs: RCTs • Number of included studies: 8 • Included studies: Nordlinger,2008 Lorenz,1998 Portier,2006 Langer,2002 Kemeny,2002 Rudroff,1999 Lygidakis,1995	• Eligibility criteria: Resectable stage IV CRC synchronous and metachronous • Patients characteristics:, median/mean age <65 yrs • Median FU: 81 months	• Intervention: peri-operative chemotherapy • Comparator: surgery alone	OS: • HR, 0.94; 95%CI, 0.8-1.10; *p* = 0.43. • subset analysis HAI: HR, 1.0; 95% CI, 0.84-1.21; *p* = 0.96; I^2 = 30% • subset analysis systemic chemotherapy: HR, 0.74; 95% CI, 0.53-1.04; *p* = 0.08; I^2 = 0% RFS: • HR, 0.77; 95%CI, 0.67-0.88; p = 0.0001 • subset analysis HAI: HR, 0.78; 95%CI, 0.65-0.95; *P* = 0.01 • subset analysis systemic chemotherapy HR 0.75; 95%CI 0.62-0.91; p= 0.003	• mild and acceptable toxicities: grade 3-4 leucopoenia in 4.9%, grade 3-4 neutropenia in 13 %, grade 3 nausea and vomiting in 13.9%, diarrhoea in 7.3% and hepatic toxicity in 6.4%. • Treatment related deaths in HAI: 12%	Results critical appraisal: • Results based on abstracted data • Corrections for heterogeneity did not alter results • Includes HAI studies reviewed by Nelson 2009

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Wagman,1990					
Ciliberto, 2012	• Design: SR and MA • Sources of funding: not stated • Search date:1982 to May 2010 • Searched databases: Pubmed,CancerLit,Embase,Medscape,Cochrane, abstracts from cancer meetings • Included study designs:RCT • Number of included studies:3 • Studies included: • Langer,2002 • Portier,2006 • Nordlinger,2008	• Eligibility criteria: • CRC with resected/resectable liver metastases, ages18-80yrs,no co morbidities, adequate staging, minimum of 24 mo follow up • Patients characteristics: total of 666 patients included • Median FU: not stated	• Intervention: systemic chemotherapy (peri and post resection) • Comparator: Resection only	• DFS:HR 0.71; 95%CI 0.582-0.878;P=0.001 • PFS:HR 0.75; 95%CI 0.620-0.910; P=0.003 • OS:HR 0.743; 95%CI 0.527-1.045; P=0.088		• Good quality RCTs • Various chemotherapy regimens • All 3 RCT s were included in MA by Wieser 2010, reaching similar conclusions
Lehman, 2012	• Design: SR • Sources of funding: not stated • Search date: not noted • Searched databases:Pubmed, • Included study designs: full papers, all study designs • Number of included studies:14	• Eligibility criteria: resectable metastases, chemotherapy in combination with liver surgery • Patients characteristics:NA • Median FU:NA	• Intervention: Neoadjuvant CT • Comparator: surgery alone or none	• Effect size primary outcome: NA	• Effect size secondary outcome: NA • PFS (3 studies): 23-40 mo • OS (5 studies):34-56 mo • 5yr survival (5 studies) 28 -60%	• Level of evidence:very low • Narrative review
Quan, 2012	• Design: SR • Sources of funding: not	• Eligibility criteria: • Patients	• Intervention: chemotherapy	• for RCT see Ciliberto 2012	• for RCT see Ciliberto 2012	• Results critical appraisal:

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	stated • Search date:1995-January 2010 • Searched databases: Medline, Embase • Included study designs :RCT, prospective or retrospective case series with> 50 cases • Number of included studies:30	characteristics: CRC liver metastases with or without lung metastases, portal node metastases or other extrahepatic disease, resectable and non-resectable metastases • Median FU: not reported	before or post surgery • Comparator: surgery alone	• for non randomized trials: no significant difference in mortality in any of the reported studies, all operative mortality <5% • 5 yr survival (%) available from 10 studies in which at least a part of the patients received neo-adjuvant CT: range 25-53 %	• for non randomized trials: resectability rates were comparable (14 studies) • complication rates ranging from 0-51% (24 studies) • significantly more complications 38% vs. 13.5% p=0.03 (1 study)	heterogeneity preventing meta-analysis

Table 88 – Evidence table: surgery +/- chemotherapy synchronous CRC liver metastases (primary studies)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
Goyer 2012	Design:retrospective,comparative study Sources of funding: none Setting: single referral centre comparing own patients (group 1) and referred patients (group 2) Sample size: 47 own and 32 referred patients Duration:NA	Eligibility criteria: CRC with resectable liver metastases Patients characteristics: • median ages: group 1: 62(47-87), group 2: 60 (34-79); • M/F group 1 31/13, group 2 16/16; • primary tumour in rectum group 1: 8, group 2:7 Median FU: 43 mo	Intervention(s): Group 1: neoadjuvant CT in 11; combined surgery in 30 (64%) with 5 needing a second liver resection. Interval CT in 19 patients Comparator(s): Group 2: no neoadjuvant CT or combined surgery; Interval CT in all 32-patients: 24 one line, 7 two lines and 1 three lines.	Effect size primary outcome; OS at 3 and 5 yrs : 73.8 % and 57.3 % vs. 74.9% and 61.2% p=0.360 PFS at 3 and 5 yrs: 40.3% and 25.9% vs. 34.8% and 23.2% p=0.422 QoL: morbidity rates: 47% vs. 75%, P = 0.023.	Effect size secondary outcome: Significant difference in time between diagnosis and hepatic resection: 5 (1-23) vs. 9(2-35) mo p=0.0008 Significant difference in time between resection primary tumour and hepatic metastasis:: 0 (0-20) vs. 8 (2-34) mo p<0.0001 Significant difference between number of CT cycles before liver resection: 6 (4-13) vs. 12 (2-51) p=0.0009.	Dropouts : not reported Results critical appraisal: no confounders taken into account for analysis, blinding not possible

Table 89 – Evidence table: surgery +/- chemotherapy synchronous and metachronous CRC liver metastases (primary studies)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal
Nordlinger 2012	• Design:RCT • Sources of funding: none • Setting: multicenter EORTC study (78 centres) • Sample size: 182 subjects in each arm • Duration: enrolment September 2000 -July 2004	• Eligibility criteria: CRC with resectable liver metastases (max 4). • Patients characteristics: 18-80 yrs old, WHO performance <=2 or less, exclusion of patients with previous chemotherapy with oxaliplatin, cancer in the past 10 yrs and various medical conditions, pregnant or breastfeeding women • Patients characteristics: 18-80 yrs old, • Median FU: 8.5 yrs	• Intervention(s): peri-operative CT (6 cycles before and 6 cycles post) + surgery • Comparator: Surgery alone	• PFS reported in 2008 and included in Ciliberto 2012	5 yr OS: • 51.2% (CT) vs. 47.8% (S) • HR 0.88, 95% CI 0.68 - 1.14,	• Dropouts: none • Results critical appraisal: Abstract only

4.2.11. Radiofrequency ablation: evidence tables

Table 90 – Evidence table: radiofrequency ablation (RFA) – SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Cirrochi 2012[29]	• Design: SR and MA • Sources of funding: Not mentioned • Search date: January 2012 • Searched databases: Medline, Embase, Lilacs, Cochrane, Cochrane register of trials, the Clinical-Trials.gov site • Included study designs: Randomized clinical trials (RCTs), quasi-randomised or controlled clinical trials (CCTs) Observational study designs including comparative cohort studies	• Patients with colorectal lung metastases (CRLMs) who have no contraindications for RFA. Patients with unresectable extra-hepatic disease • Median FU: not stated	• Intervention: RFA • Comparator: hepatic resection (HR)	• Overall survival: - Aloia 2006 27% in RFA group (30 patients) vs 71% HR group (150 patients) (P < 0.001).. - Berber 2008 30% in RFA group (27 patients) vs 40% in HR group (30 patients) (P = 0.35). - Hur 2009 89.7% in RFA group (25 patients) vs 50.1% in HR group (42 patients) (P = 0.0263). - Kim 2011 31.2% in RFA group (177 patients) vs 45.3% in HR group (278 patients) (P < 0.001). - Lee 2008 38.5% in RFA group (37 patients) vs 65.7% in HR group (116 patients) (P = 0.227). - Otto 2010 48% in RFA group (28 patients) vs 51% in HR	• Marginal recurrence The marginal recurrence was higher in the RFA group vs HR group, respectively: 11/30 vs 8/150 (P = 0.001) Aloia 2006, 8/25 vs 6/42 (P = 0.85) Hur 2009, 3/28 vs 2/82 (P < 0.001) Otto 2010, 7/30 vs 1/59 (P < 0.01) Park 2008, 5/46 vs 2/95 Schiffman 2010, 8/22 vs 0/30 White 2007. • Intrahepatic recurrence The intrahepatic recurrence was higher in the RFA group vs HR group, respectively: 5/30 vs 27/150 Aloia 2006, 8/25 vs 6/42 Hur 2009, 13/30 vs 10/59 Park 2008, 11/46 vs 10/95 (P=0.026)	• Results critical appraisal: High quality review, no pooling attempted due to heterogeneity in population and interventions and the fact that most studies are observational and of relatively poor quality

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	comparing RFA to another intervention, single arm cohort studies or case control studies have been included if they have: prospectively collected data, ten or more patients; and have a mean or median follow-up time of 24 months • Number of included studies: 18		RFA systemic plus CT versus systemic CT alone	group (82 patients) (P = 0.930). - Reuter 2009 49% in RFA group (66 patients) vs 45% in HR group (126 patients) (P = 0.31). In the Ruers study 119 patients were randomised to RFA plus systemic CT or CT alone as first line therapy for metastatic colorectal cancer (Ruers 2010). The median progression free survival was 16.8 months in the RFA + CT group (95% CI, 11.7-22.1) and 9.9 months (9.3- 13.7) in the CT group (P = 0.025). Overall survival (30-months) was 61.7% (95% CI, 48.21-73.93) in the RFA + CT group and 57.6% (44.07-70.39) in the CT group. In eligible patients (RFA + CT; 57 pts, CT; 58 pts) these rates were 64.9% (95% CI, 51.13-77.09) and 56.9% (43.23-69.84),	Schiffman 2010, 1/22 vs 8/30 White 2007.	

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				respectively.		
			RFA plus HAI versus RFA plus adjuvant HAI and HR	One study compared RFA with HAI or RFA, adjuvant HAI, and surgical resection alone as first line therapy for metastatic colorectal cancer in 50 patients (Scaife 2003). There was no evidence of disease In 26% (5/19) of patients underwent RFA with HAI and in 35% (11/31) of patients underwent RFA with surgical resection and HAI. Overall survival was 73% (14/19) in RFA with HAI group and 61% (19/31) in patients underwent RFA with surgical resection and HAI.		
			RFA plus HR vs HR vs RFA alone vs chemiotherapy	In 190 patients underwent HR there are the best survival (3-year survival 73%, 4-year 65%, 5-year 58%, P 0.0001). RFA (57 pts.) showed a higher incidence of local recurrence: 84% in RFA only, 63% in RHA + HR,		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				52% in HR. The survival rate was similar in RFA + hepatic resection (101 pts.) and RFA groups (3 years survival 43% vs. 37%, 4-years 36% vs. 22%, P not significant). The poor results in patients underwent RFA was a consequence of the more advanced stage ("unresectable" CR LM). In RFA resection or RFA the survival was better than after chemotherapy alone (70 pts.) (P 0.0017) (Abdalla 2004)		
			RFA with HR vs CSA plus HR	The use of intraoperative RFA was associated with a lower blood loss (median 500 ml vs 200 ml). The incidence of postoperative complications ablation technique related was higher in patients underwent CSA. In CSA group 3 patients developed a hepatic abscess resolved after percutaneous drainage; in		

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				RFA group there was not present complications ablation technique related. The local recurrence was similar in both groups: 14% in the RFA arm and 12% in the CSA arm (Kornprat 2007) .		
			RFA vs HR plus RFA	Four studies (Gleisner 2008, Vyslouzil 2009, McKay 2009; Kim 2011) comparing RFA with HR evaluated the overall survival (OS). In McKay's trial the median survival for RFA and resection in combination with RFA was 2.6 years (95% CI = 1.8 to 3.3 years) vs 2.3 (95% CI = 1.6 to 3.2 years), respectively (McKay 2009).		

4.2.12. Hepatic arterial infusion (HAI) for unresectable liver metastases

Table 91 – Evidence table: hepatic arterial infusion – SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Mocellin et al, 2012[30]	• Design: SR and MA • Sources of funding: not mentioned • Search date: Jan 2012 • Searched databases: medline embase Cochrane clinical trials, • Included study designs: RCT • Number of included studies: 10	• Eligibility criteria: Patients with colorectal cancer and unresectable liver metastases • Median FU: not given	• Intervention: HAI • Comparator: systemic chemotherapy	**Overall survival** • All studies Hazard Ratio (Random, 95%CI) 0.90 [0.76, 1.07] • subgroup 99 pts 7 studies Hazard Ratio (Random, 95% CI) 0.81 [0.64, 1.03] • subgroup 65% treated 8 studies Hazard Ratio (Random, 95% CI) 1.02 [0.90, 1.15] • subgroup no crossover 6 studies Hazard Ratio (Random, 95% CI) 0.86 [0.67, 1.10] • subgroup high quality 2 dtudies Hazard Ratio (Random, 95% CI) 0.88 [0.54, 1.44]	**Tumour response** 9 studies 901 patients Risk Ratio (M-H, Fixed, 95%CI) 2.26 [1.80, 2.84]	• Level of evidence: Low level of evidence • Results critical appraisal Good systematic review, large heterogeneity amongst studies together with evolution in control systemic chemotherapy, which has considerably improved

4.2.13. Selective internal radiation therapy (SIRT) for unresectable liver metastases

Table 92 – Evidence table: SIRT – SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Townsend, 2009[28]	• Design: SR and MA • Sources of funding: not mentioned • Search date: • Searched databases: • medline embase Cochrane clinical trials, ASCO • Included study designs: RCT • Number of included studies: 2	• Eligibility criteria: • Patients with colon cancer & hepatic metastases • Patient characteristics	SIRT & Systemic chemotherapy OR versus Systemic chemotherapy alone	Van Hazel 2004 (n=21): **Progression Free Survival** Chemo + SIRT: 11.5 months vs. Chemo: 4.6 months. HR: 0.23 (CI 0.08-0.68) **Median Survival** Chemo + SIRT: 29.4 months vs. Chemo: 11.8 months. HR: 0.22 (CI 0.07-0.74) **1-year survival** Chemo + SIRT:82% vs. hemo: 50% **2-year survival** Chemo + SIRT: 64% vs. Chemo: 20% **5-year survival** Chemo + SIRT: 0% vs. Chemo: 0% **Response Rate** Chemo + SIRT: 73% vs. Chemo:0%	Van Hazel 2004 (n=21): increased toxicity with the addition of SIRT to systemic chemotherapy with fluorouracil (with 13 grade 3 or 4 events in the combination group compared with 5 grade 3 or 4 events in the chemotherapy alone group. No effect on quality of life	• Level of evidence: low • High quality review that included 2 small studies with different comparisons of moderate quality, both studies were industry sponsored.
			SIRT & HAI Versus HAI alone	Gray 2001 (n=63) **Progression Free Survival** Chemo + SIRT:7.3 months vs. Chemo: 5.9 months. HR: 0.72 (CI 0. 43-1.21) **Median Survival** Chemo + SIRT:17.6 months vs. Chemo: 15.6 months. HR: 0.62 (CI 0.37-1.05) **1-year survival** Chemo + SIRT:71% vs.	Gray 2001 (n=63) no significant increase in toxicity with the addition of SIRT to regional chemotherapy with 23 grade 3 or 4 events reported in both groups, although slightly more patients in the SIRT and	

				Chemo:61% **2-year survival** Chemo + SIRT: 37% vs. Chemo: 29% **5-year survival** Chemo + SIRT: 6% vs. Chemo:0% **Response Rate** Chemo + SIRT: 37% vs. Chemo:14%	regional chemotherapy group experienced grade 1 or 2 nausea or diarrhoea (16 compared with 11 in the regional chemotherapy alone group). No effect on quality of life	
Rizell, 2010[27]	• Design: SR and MA • Sources of funding: Swedisch government • Search date: jan 2010 • Searched databases: medline, embase, Cochrane, CRD • Included study designs: • RCT & observational • Number of included studies: 24	• Eligibility criteria: • Patients with colon cancer & hepatic metastases	SIRT & Systemic chemotherapy OR SIRT & HAI • Reference standard: Systemic chemotherapy OR SIRT	• 2 RCT's: see Townsend et al, above • Controlled trial: Hong 2009 (n=36) **Median Survival** TACE 7,7 months 90Y-RE 6,9 months **1-year survival** TACE 43% 90Y-RE 34% **2-year survival** TACE 10% 90Y-RE 18% **5-year survival** TACE 10% 90Y-RE 18% • **Case series** Cianni 2009 **Median Survival** 12 months **Complete response Rate** 5 % Gray 2000 **Median Survival** 9.9 months **Complete response Rate** 0 %	The dominating adverse effects of radioembolization were nausea, mild abdominal pain and fatigue. Grade 3 - 4 liver toxicity was reported in 2 - 4 % of patients, grade 3 - 4 gastrointestinal toxicity in 5 - 8 %, and grade 3 - 4 bilirubin toxicity in 12 % of patients	• Level of evidence: • Very low • Results critical appraisal HTA report based on a good quality review

				Kennedy 2006 **Complete response Rate** 0 % Mulcahy 2009 **Median Survival** 14.5 months **Complete response Rate** 0 % Stubbs 2006 **Median Survival** 11 months **1-year survival** 48% **2-year survival** 18% **Complete response Rate** 1 %	

Table 93 – Evidence table: radio-embolisation of unresectable liver metastases – primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Seidensticker, 2012[87]	• Design: retrospectively matched cohort • Sources of funding: not mentioned • Setting: 3 centres in Germany • • Sample size:29 matched pairs	Patients with chemotherapy-refractory liver dominant metastatic colorectal cancer	• Intervention(s): radioembolization plus best supportive care (BSC) • Comparator(s): *BSC*	• Overall survival: prolonged survival (median, 8.3 vs. 3.5 months; P\0.001) with a hazard ratio of 0.3 (95% confidence interval, 0.16–0.55; P\0.001) in a multivariate Cox proportional hazard model	Treatment-related adverse events: included: grade 1–2 fatigue (n = 20,69%), grade 1 abdominal pain/nausea (n = 14, 48.3%), and grade 2 gastrointestinal ulceration (n=3, 0.3%). Three cases of grade 3 radiation-induced liver disease	• Level of evidence: Low • Results critical appraisal matching criteria: retrospectively matched synchronous/metachronous metastases, tumor burden, increased ALP, and/or CEA [200 U/ml]]

Martin, 2012[88]	• Design: case serie • Sources of funding: Not mentioned • Setting: The Ohio State University (US) • Sample size:24	• Eligibility criteria: Patients with metastatic colorectal cancer	Yttrium-90 (90Y) radioembolization	• Effect size primary outcome Median PFS : 3.9 months (95% CI, 2.4-4.8 months) OS :8.9 months (95% CI, 4.2-16.7 months),		Very low level of evidence Case series
Hendlisz, 2010[31]	• Design: open-label RCT • Sources of funding: last author received honoraria from Sirtex Medical • Setting: Multicenter (n=3), Belgium • Sample size: 44 (after exclusion of 1 pt with bone metastases and 1 pt in whom ^{90}Y was technically not possible • Duration: inclusion of pts between December 2004 and November 2007	• Eligibility criteria: • Patients with unresectable chemotherapy-refractory liver-limited metastatic CRC, not amenable to curative surgery or local ablation and resistant or intolerant to standard chemotherapy; pst had and ECOG performance status of min 2 and had adequate bone marrow, renal and liver function • Patients characteristics: male: 28/44 (64%); median age 66 y.o.(range:	• Intervention(s): Yttrium-90 (^{90}Y) radioembolizatio n (once) + 5FU protracted IV infusion (225mg/m² D1-14, cycle 1 and 300mg thereafter (arm B); n=21 • Comparator(s): 5FU protracted IV infusion (300mg/m² D1-14) (arm A); n=23 • Chemotherapy endpoint: disease progression, unacceptable toxicity or withdrawal of consent • cave: pts in arm A with	• Effect size primary outcome: Median OS: 7.3 months (arm A) vs. 10.0 months (arm B), with a hazard ratio of 0.92, 95% CI: 0.47-1.78; median time to liver progression (TTLP): 2.1 months (arm A; with 23 events, all situated in the liver) vs. 5.5 months (arm B; with 18 events), with a hazard ratio of 0.38, 95% CI: 0.20-0.72; median time to tumor progression at any site (TTP): 2.1 months (arm A) vs. 4.5 months (arm B), with a hazard ratio of 0.51, 95% CI: 0.28-0.94; best	• Effect size secondary outcome: grade 3 or 4 toxicities observed in 6/22 (27%) pts (arm A; 2 pts who did not receive therapy were not included) vs. 1/21 (5%) pts (arm B); 16 pts from arm A received further therapies (n=10 ^{90}Y radioembolization monotherapy, n=5 cetuximab + chemo and n=1 chemo) vs. 9 pts from arm B (n=3 cetuximab + chemo, n=4 chemo, n=1 palliative brain radiotherapy and n=1 unspicified	• Level of evidence: very low • Dropouts/ cross-over: cross-over of 16 pts from arm A to arm B (to receive ^{90}Y radioembolization); local progression in 4 pts from arm B after unjustified change in the treatment allocated by randomization. • Results critical appraisal: trial was prematurely closed (with the number of enrolled patients lower than required (based on power analysis)); open-label design; liver progression not documented in 3 pts of arm B; in 4 pts from arm B there was an unjustified change in the treatment allocated by randomization;

		45-91); 41/44 (93%) had more than 1 hepatic lesion • Median FU: 24.8 months (range: 2-41 months)	documented progression were permitted to cross-over to receive ^{90}Y radioembolizatio n	overall hepatic response: 0/23 (0%) pts vs. 2/21 (9.5%) and disaese control rates (i.e. partial response and stable disease): 8/23 (35%) vs. 18/21 (86%).	therapy)	
Bester, 2012[89]	• Design: comparative retrospective cohort study • Sources of funding: first author is a paid consultant of Sirtex Medical • Setting: referral centre for radioembolizati on, Australia • Sample size: n= 224 with metastatic CRC who underwent radioembolizati on and n= 29 with metastatic CRC who underwent standard care (also data on non-CRC pts reported in	• Eligibility criteria: "salvage" patients with CRC with inoperable liver metastasis, with sufficient hepatic reserve and adequate renal function • Patients characteristics: radioembolization group: male: 142/224 (63%); median age 67 y.o. (range: 27-89) • Median FU: immediate, 1 month and 3 months FU data presented (for all patients, i.e. also for those pts who had a non-CRC primary tumor)	• Intervention(s): radioembolizatio n (n= 224) • Comparator(s): standard care (i.e. conservative treatment or continued supportive care)(n= 29)	• median OS: embolization group 11.9 months (95% CI: 10.1-14.9 months) vs. standard care group: 6.6 months (no 95% CI mentioned), log-rank test: P=0.001.	• outcome: adverse effects only reported for CRC and non-CRC pts together	• Level of evidence: Very low • Dropouts: not mentioned • Results critical appraisal: retrospective design; some (exact number not reported) pts received more than one radioembolization session and only the first treatment was considered in the analysis; no data on drop-out; data on adverse effects not reported for CRC pts only; short FU (i.e. 3 months); comparison group is very small (and good comparator?)

	manuscript) • Duration: inclusion of pts bw February 2006 and February 2011					
Kosmider, 2012[90]	• Design: retrospective case series • Sources of funding: 2 co-authors are paid members of the advisory board of Sirtex Medical • Setting: 2 hospitals in Australia • Sample size: n= 19 • Duration: treatment bw Jan 2002 and Oct 2008	• Eligibility criteria: Pts with unresectable liver metastases from CRC, with good performance status, with adequate renal, hemopoietic and liver function • Patients characteristics: male: 16/19 (84%); median age: 62 (range: 44-75); 18 pts had stage IV disease and 1 pat had had FOLFOX chemo for node-positive colon cancer and after 16 months he had a liver meta; median metastatic liver envolvement: 40%; n= 5 with lung meta • FU at 1, 3 and 6 months	• Intervention(s): ^{90}Y radioembolization (on day 3 or 4 of cycle 1) in combination with chemotherapy (oxaliplatin-based (n= 12) or 5-fluorouracil (n=7), at clinician's discretion and according to local protocols); chemo was continued for a maximum of 6 months. • Comparator(s): /	• Effect size primary outcome: median OS: 29.4 months (in liver-only disease: 37.8 months vs. 13.4 months in pts with extra-hepatic disease, p=0.03); median PFS: 10.4 months (in liver-only disease: 10.7 months vs. 3.6 months in pts with extra-hepatic disease, p=0.09); overall tumor response: complete response in 2 pts (11%), partial in 14 (74%), stable disease in 1 (5%) and progressive disease in 1 (5%).	• Effect size secondary outcome: median time to best response: 4.4 months; adverse effects after 0-4 weeks: fever as part of the post-RE syndrome febrile (n=7), neutropenia (n=1, gr 3), abdominal pain (n=4, gr 2 and n=3 gr 3), fatigue (n=6, gr 2 and n=4, gr 3); after 4-12 weeks: bilirubin (n=4, gr 2 and n=1, gr 3), aspartate aminotransferase (n=4, gr 2, n=1, gr 3), alkaline phophatase (n=4, gr 2 and n=1, gr 3), gastritis (n=2, gr 2 and n=4, gr 3), gastric ulceration (n=1, gr	• Results critical appraisal: retrospective design; small sample size; no control arm; short term follow-up;

					4), liver dysfunction (n=4, gr 2 and n=1, gr 5 (=death)), anorexia (n=6, gr 2, n=3, gr 3 and n=1, gr 4), ascites (n=4, gr 2 and n=1, gr 3); after 12-24 weeks (mainly related to chemotherapy): neuropathy (n=2, gr 2 and n=1, gr 3), hand-foot disease (n=1, gr 3)	
Chua, 2011[91]	• Design: prospective cohort study • Sources of funding: none reported • Setting: tertiary radioembolization treatment center in Sydney • Sample size: 140 consecutive pts • Period of recruitment: March 2006-May 2009	• Eligibility criteria: Pts with unresectable (i.e. insufficient estimated future liver remnant, vascular invasion, progression under chemotherapy or an unresectable extrahepatic lesion) CRC liver metastases, ECOG performance status of 0-2, adequate hematology, renal and hepatic	• Intervention(s): ^{90}Y radioembolization (n=133: single treatment and n=7: repeated treatments) with (n= 48/140, 34%) or without (n=92/140, 66%) concomitant or post-radioembolization chemotherapy • Comparator(s): /	median overall survival: 9 months (95% CI: 6.4-11.3); 1-year survival: 42%, 2-year survival: 22% and 3-year survival: 20%; at last follow-up: 103 (74%) pt had died; complete response in 2 (1%) pts, partial response in 43 (31%) pts, stable disease in 44 (31%) and progressive disease in 51 (37%) pts; based on multivariable analysis sign more favorable treatment response	• no treatment related mortality; early complications (i.e. days 1-30) in 36 (26%) pts: nausea in 7 (5%) pts, vomiting in 1 pt (1%), gastritis in 3 pts (2%), intestinal ulceration in 1 pt (1%) and abdominal pain in 20 (14%) pts; delayed complications in 7 (5%) pts: radiation induced liver	• Results critical appraisal: not explained based on what rationale some pts received chemotherapy; no control arm; short term follow-up;

	function • Patients characteristics: male: 88/140 (63%); median age: 64 (range: 37-85); colon n=112/140 (80%); extent of liver metastases: 0-25%: 78 (55%), 26-50%: 50 (36%) and 51-75%: 12 (9%) • Median FU: 9 months (range: 1-43)	(i.e. complete or partial response) in case of concomitant or post-radioembolization chemotherapy (p= 0.007); based on multivariable analysis sign better overall survival in case of location of primary site in colon (vs. rectum, HR: 1.7, 95%CI: 1.1-2.7, absence of extrahepatic disease (HR: 0.6, 95% CI: 0.4-1.0) and favorable treatment response (HR: 4.6, 95%CI: 2.7-7.8)	dysfunction in 3 (2%) pts, intestinal ulceration in 4 (3%) pts and gall bladder and biliary related complication in 1 (1%) pt

4.2.14. Chemo-embolisation unresectable liver metastases

Table 94 – Evidence table: chemo-embolisation for unresectable liver metastases – SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Carter, 2010[92]	• Design: SR Sources of funding: • Search date: 2009 • Searched databases: MEDLINE, EMBASE, Science Citation Index, Current Contents and PubMed • Included study designs: RCT & case series • Number of included studies: 2	• Eligibility criteria: Patients with liver metastases from colorectal cancer	• Intervention: *TACE* • Comparator: Any comparator	• Effect size primary outcome Only overall response and side effect reported for two case series: (Aliberti 2006 & Fiorentini 2007)	• Effect size secondary outcome	• Level of evidence: Very low • Results critical appraisal Adequate search strategy but only response rates reported, review only used for reference tracking

Table 95 – Evidence table: chemo-embolization for unresectable liver metastases – primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Fiorentini, 2012[93]	• Design: RCT • Sources of funding: not mentioned • Setting: Italy • Sample size:74	• liver metastases in patients with colorectal cancer. • characteristics:	• Intervention(s): chemoembolization with Irinotecan eluding beads	• Overall survival Median survival was 22 (95% Confidence Interval CI=21-23) months, for DEBIRI and 15 (95% CI=12-18) months for FOLFIRI Log rank test: 0.031, HR 0.60 (95 CI 0.37, 0.97)	Progression-free survival 7 (95% CI=3-11) months in the DEBIRI group compared to 4 (95% CI=3-5) months in the FOLFIRI group (p=0.006, log-rank). The median time for duration of improvement to quality of life was 8 (95% CI=3-13) months in the DEBIRI group and 3 (95% CI=2-4) months in the FOLFIRI group. (p=0.00002, log-rank).	• Level of evidence: low Unclear randomisation, no or unclear allocation concealment, no outcome blinding Effect on overall survival borderline significant, OIS not fulfilled
Vogl, 2009[94]	• Design: case serie • Sources of funding: not mentioned • Setting: Germany • Sample size:463	• Eligibility criteria: • palliative treatment of liver metastases in patients with colorectal cancer. • • characteristics: • Median FU:29 months	• Intervention(s): 3 different chemo-embolization protocols	• Effect size primary outcome The 1-year survival rate after chemo-embolization was 62%, and the 2-year survival rate was 28%. Median survival from date of diagnosis of liver metastases was 38 months and from the start of chemo-embolization treatment was 14 months. There was no statistically significant	• Effect size secondary outcome partial response (68 patients [14.7%]), stable disease (223 patients [48.2%]), and progressive disease (172 patients [37.1%]).	• Level of evidence: very low • followed untill death • Results critical appraisal Case series consisting of patients treated with different protocols with different patients characteristics,

				difference between the three treatment protocols.		
Martin, 2009[95]	• Design: case serie • Sources of funding: not mentioned • Setting: multi-site (US, Chechia Serbia • Sample size:55 • Duration:	• Eligibility criteria: palliative treatment of unresectable liver metastases in patients with colorectal cancer. • Patients characteristics: • Median FU	• Intervention(s): Transarterial chemoembolization (TACE) using irinotecan-loaded beads	• Effect size primary outcome Median disease free survival from the time of first treatment: 247 days Overall survival from the time of first treatment : 343 days	• Effect size secondary outcome Treatment response, judged by the RECIST criteria, 71% responded at 3 months, 56% at 6 months, and 40% at 12months	• Very low level of evidence • Results critical appraisal Case serie with adequate follow up
Albert, 2011[96]	• Design: case serie • Sources of funding: not mentioned • Setting: US • Sample size: 121	palliative treatment of unresectable liver metastases in patients with colorectal cancer.	• Intervention(s): Chemoembolization with cisplatin, doxorubicin, mitomycin C, ethiodized oil, and polyvinyl alcohol particles,performed at monthly intervals for 1 to 4 sessions	Median time to disease progression (TTP) in the treated liver was 5 months, and median TTP anywhere was 3 months. Median survival was 33 months from diagnosis of the primary colon cancer, 27 months from development of liver metastases, and 9 months from chemoembolization	2 (2%) partial esponse, 39 (41%) stable disease, and 54 (57%) progression	• Very low level of evidence • Results critical appraisal Case series with adequate follow up
Aliberti 2012[97]	• Design: case serie • Sources of funding: not mentioned • Setting: US • Sample size: 82	metastatic colorectal carcinoma to the liver after failing chemotherapy • Median FU:29 months	DC Bead, drug-eluting bead, loaded with irinotecan	• median survival was 25 (range 6-34) months, with progression free survival at 8 (range 4-16) months	• Adverse observed effects were: right upper quadrant pain (40%), fever (80%), nausea (27%) and increased transaminases (70%)	• Very low level of evidence, case series with reported adequate follow up

4.2.15. Resection lung metastases

Table 96 – Evidence table: resection lung metastases – SR

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Gonzalez, 2012[98]	• Design: SR Sources of funding: • Search date: nov 2011 • Searched databases: MEDLINE, Included study designs: & case series • Number of included studies: 25	• Eligibility criteria: • Patients with lung metastases and colorectal cancer	• Intervention: *Metastatectomy*	Overall 5-year survival after complete resection of LM ranged from 27 to 68 % Median survival from 18 to 72 months	Associated with poor survival: (1) a short disease-free interval between primary tumor resection and development of LM (HR 1.59, 95 % confidence interval [CI] 1.27–1.98); (2) multiple LM (HR 2.04, 95 % CI 1.72–2.41); (3) positive hilar and/or mediastinal lymph nodes (HR 1.65, 95 % CI 1.35–2.02); (4) elevated prethoracotomy carcinoembryonic antigen (HR 1.91, 95 % CI 1.57–2.32).	• Level of evidence: very low • Results critical appraisal Only case series identified

Table 97 – Evidence table: resection lung metastases – primary studies

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Schule, 2012[99]	• Design: case serie • Sources of funding: not mentioned • Setting: Germany • Sample size:65	• Patients with liver and lung metastases in patients with colorectal cancer.	Patients who underwent liver and lung resection for colorectal metastases	Five- and 10-year survival rates for all patients are 57 and 15 % from diagnosis of the primary tumour, 37 and 14 % from resection of the first metastasis and 20 and 15 % from resection of the second metastasis. After complete resection, 5- and 10-year survival rates increased to 61 and 18 %, 43 and 17 % as well as 25 and 19 %, respectively. Long-term survivors ((greater-than or equal to)10 years) were seen only after complete resection of both metastases.	Negative margins (p00.002), the absence of pulmonary involvement in synchronous metastases (p00.0003) and single metastases in both organs (p00.036) were associated with a better prognosis	• Level of evidence: very low Patients with lung and liver metastases
Hirosawa, 2012[100]	• Design: case serie • Sources of funding: not mentioned • Setting: Japan • Sample size:266	Patients with lung metastases and colorectal cancer	Complete resection of the lung metastases	The cumulative 2- and 5-year survival rates of the patients who underwent pulmonary resection were 76.6 and 46.7 %, respectively	T4 tumor stage and N2 tumor stage as primary cancer-related risk factors, and the number of metastases greater than three, bilateral distribution of pulmonary metastases, DFI less than 2 years, CEA level higher than 5.0	• Very low level of evidence • Case series

					ng/mL prior to pulmonary resection as primary cancer-related risk factors, were significant predictors of worse survival	
Gonzalez 2012[101]	• Design: case serie • Sources of funding: not mentioned • Setting: Lausanne/Geneva (Switzerland) • Sample size: 23	• patients who underwent prior resection of hepatic CRC metastases • Median follow-up was 32 months (range:3–69 months)	Metastatectomy in the lung	Three- and 5-year overall survival rates after lung surgery were 56 and 39%, respectively, Median survival: 46 months (95% CI 35–57). Median diseasefree survival after metastasectomy : 13 months (95% CI 5–21)	Factors associated with mortality (None statistically significant) : (1) age [60 years; (2) primary tumor stage III/IV; (3) presence of multiple lung metastases, .	Low level of evidence, case series with reported adequate follow up
Tampellini 2012[102]	• Design: Retrospective cohort • Sources of funding: not mentioned • Setting: University of Torine, Italy) • Sample size: 309	• G1, comprised of 155 patients with pulmonary and extrapulmonary metastases; G2, comprised of 104 patients with LM only and no surgery; G3, comprised of 50 patients with LM only and submitted to surgery	Metastatectomy in the lung	No difference in response rates emerged between G1 and G2. Median progression-free survival (PFS) times were: 10.3 months, 10.5 months, and 26.2 months for G1, G2, and G3, respectively. No difference in PFS times was observed between G1 and G2, whereas there was a statistically significant difference between G2 and G3. Median overall survival	Survival times were longer in resected patients: 17 survived >5 years and three survived >10 years. In patients with LM only and no surgery, four survived for 5 years and none survived >10 years	Low level of evidence, Retrospective cohort with adjustment for confounders, characteristics of patients undergoing lung surgery and not undergoin lung surgery is very different and it is unclear how much residual confounding

				times were 24.2 months, 31.5 months, and 72.4 months, respectively. Survival times were longer in resected patients: 17 survived >5 years and three survived >10 years. In patients with LM only and no surgery, four survived for 5 years and none survived >10 years In a Cox regression model, adjusting for some confounders lung surgery was associated with longer progression free survival HR (0.46, CI.0.31 - 0.57) and overall survival HR (0.26, CI.0.06 0.47)		persists.
Marin 2013[103]	• Design: case serie • Sources of funding: not mentioned • Setting: Lausanne/Geneva (Switzerland) • Sample size: 44	• Patients with lung metastases from colorectal cancer, strict selection criteria established by a panel of liver surgeons, chest surgeons, oncologists, and radiologists	Lung metastatectomy	Overall survival was 93% at 1 year, 81% at 3 years, and 64% at 5 years.	Factors related to poor prognosis in the univariate analysis were presence of more than 1 pulmonary metastasis (p = 0.04), invasion of the surgical margin (p = 0.006), and administration of neoadjuvant chemotherapy (p = 0.01 for hepatic metastases and p = 0.02 for pulmonary	Low level of evidence, case series with reported adequate follow up

					metastases).	
Lida 2012[104]	• Design: case serie • Sources of funding: not mentioned • Setting: Japan • Sample size: 1013	• patients with CRC lung metastases	Metastatectomy in the lung	Overall 5-year survival was 53.5%. Median survival time was 69.5 months.	Univariate analysis showed tumor number (P < 0.0001), tumor size (P < 0.0001), prethoracotomy serum carcinoembryonic antigen (CEA) level (P < 0.0001), lymph node involvement (P < 0.0001), and completeness of resection (P < 0.0001) to significantly influence survival. In multivariate analysis, all remained independent predictors of outcome..	Low level of evidence, case series with reported adequate follow up

4.2.16. Stereotactic body radiation therapy (SBRT)

Table 98 – Evidence table: Stereotactic body radiotherapy (SBRT)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Chang 2011	Case series	Patients with colorectal cancer and liver metastases	*SBRT*	12-month, 18-month, and 24-month OS rates of 72%, 55%, and 38%, respectively	and12-month, 18-month, and 24-month local control rates of 67%, 65%, and 55%, respectively	• Very low level of evidence • Case series

4.2.17. Cytoreductive surgery and HIPEC

Table 99 – Evidence table: SR cytoreductive surgery and HIPEC

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
de Cuba 2013[105]	• Design: SR and MA • Sources of funding: none reported • Search date: April 2012 • Searched databases: Medline (through Pubmed) • Included study designs: observational studies • Number of	• Eligibility criteria: pts with CRC with peritoneal AND liver metastases, treated with a combination of CRS & HIPEC and curative treatment of the liver metastases • Patient characteristics: not reported • FU: 1 month - 5 yrs	• Intervention: cytoreductive surgery (CRS) + hyperthermic intraperitoneal chemotherapy (HIPEC)(n=3) +/- early postoperative intraperitoneal chemotherapy (EPIC)(n=3) • Comparator: /	• Median overall survival: 6-36 months		Results critical appraisal: • Observational studies, hence selection bias cannot be excluded • No systematic critical appraisal of individual studies performed • Small number of pts included (n: 7-70; 6-59% of the total sample of the primary study) • Considerable difference in BL characteristics of the population undergoing CRS + HIPEC • Difference in reporting

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	included studies: 6 • Included studies: Elias 2010 Cavaliere 2010 Varban 2009 Chua 2009 Kianmanesh 2007 Carmignani 2004					total intra-abdominal disease burden • 1 study also included pts with malignant ascites and occlusive syndrome, which negatively impact survival • Varying methods of HIPEC administration (coliseum, closed, combination of both) and not reported in 2 trials • Per-operative chemo used in 2 trials and not reported in 4 trials • Varying methods for CRLM treatment (resection, left in situ, cryosurgery, RFA) and not reported in 2 trials • No patient characteristics reported • Conflicts of interest of included trials not reported

Table 100 – Evidence table: primary studies cytoreductive surgery and HIPEC

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Cashin 2012[106]	• Design: Comparative study • Sources of funding: Non reported • Setting: University hospital Uppsala (Sweden) • Sample size: 32 (16 vs. 16) • Duration: treatment performed between 1993-2008	• Eligibility criteria: R1 surgery (i.e. macroscopically complete surgery) for peritoneal carcinomatosis from colon cancer • Patients characteristics: mean age: 53 (HIPEC) vs. 56 (SPIC) y.o.; proportion female: 12/16 vs. 7/16; peritoneal cancer index: 14.4 (HIPEC) vs. 13.2 (SPIC) • Median FU: 38 (HIPEC) vs. 66 months (SPIC)	• Intervention(s): cytoreductive surgery (CRS) + peroperative hyperthermic intraperitoneal chemotherapy (HIPEC; oxaliplatin in 15 pts; mitomycin C in 1pt who did not get i.v. chemo) + i.v. chemotherapy (5-FU + leucovorin) • Comparator(s): CRS + normothermic sequential postoperative intraperitoneal chemotherapy (SPIC)	• Mortality: 6% (HIPEC) vs. 6% (SPIC) • Median OS: 36.5 (HIPEC) vs. 23.9 months (SPIC), p=0.01 • Median DFS: 22.8 (HIPEC) vs. 13.0 months (SPIC), p=0.02	• Grade III-IV 90-day morbidity: 37% (HIPEC) vs. 19% (SPIC), p= 0.2	• Dropouts: not reported • Results critical appraisal: no randomisation; no blinding; retrospective analysis of database; low number of patients; significant difference between groups in date of treatment (HIPEC: 2004-2008 vs. SPIC: 1996-2007), hence improved surgical skills favouring HIPEC group; CRS more extensive in HIPEC group; great diversity in chemotherapy used in both groups; significant difference in chemotherapy before surgery (HIPEC: 13/16) vs. SPIC: 7/16); postoperative chemo: missing data for 4/16 (I) vs. (5/16); 2 different SPIC regimens on the 1st day (5-FU i.p. (n=10)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
						vs. oxaliplatin i.p. (n=6); 2 different HIPEC regimens (oxaliplatin i.p. + 5-FU and leucovorin i.v. (n=15) vs. mitomycin i.p. and no i.v. chemo); 9/16 HIPEC pts received additional early postoperative intraperitoneal chemotherapy (EPIC); only 3/16 SPIC pts received ≥ 6 treatments (of 8 cycles planned); SPIC was stopped because of tumour progression (31%), catheter problems (20%), toxicity (12%), abdominal pain (12%), bowel perforation (6%)
Franko 2010[107]	• Design: Comparative study • Sources of funding: Non reported • Setting: University of Pittsburgh	• Eligibility criteria: pts with peritoneal carcinomatosis from colorectal cancer; limited liver involvement allowed • Patients characteristics: mean age: 51	• Intervention(s): CRS + HIPEC (with mitomycin 100') + i.v. chemo (n=67) • Comparator(s): i.v. chemo (n=38)	• Median OS: 34.7 (HIPEC) vs. 16.8 months (SPIC), p<0.001		• Dropouts: not reported • Results critical appraisal: no randomisation; no blinding; retrospective analysis of control (and intervention?)

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Medical Centre Cancer Centres Network • Sample size: 105 (67 vs. 38) • Duration: diagnosis between 2001-2007	(HIPEC) vs. 59 y.o. (control), p<0.001; no sign differences in gender distribution, tumour grade, site of origin (colon vs. rectum)(no absolute date presented) • Median FU: not reported				data; control group was statistically older (mean age: 59 y.o. vs 51 y.o., p<0.001), had a higher proportion of pts diagnosed with carcinomatosis at initial presentation (76% vs. 42%, p< 0.001) and a higher proportion of pts with liver lesion (35% vs. 15%, p=0.014); significantly less oxaliplatin in controls (47% vs. 78%, p=0.001); significantly less bevacizumab and/or cetuximab in controls (18% vs. 59%, p<0.001); no median FU reported
Elias 2009[g109]	• Design: Comparative study • Sources of funding: partial funding from the French government	• Eligibility criteria: pts with peritoneal carcinomatosis from colorectal cancer; HIPEC group: no huge and symptomatic PC, no extra-abdominal	• Intervention(s): CRS + i.v. FU and leucovorin + HIPEC (oxaliplatin, 30') • Comparator(s): palliative chemo	• Median survival: 62.7 (HIPEC) vs. 23.9 months (control), p<0.05;	• 5-year survival: 51% (95% CI: 36–65%, HIPEC) vs 13% (95% CI 6–26%, controls) • 2-year survival: 81% (95% CI: 68–90%,	• Level of evidence: • Dropouts • Results critical appraisal: no randomisation; no blinding; HIPEC pts were significantly younger (46 vs. 51

g This study was also adopted in the NICE Guidance NICE Guidance[108]

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Setting: France; HIPEC group: 1 centre; controls: 5 centres • Sample size: 96 (48 vs. 48) • Duration: 1998 - 2003 (surgery for HIPEC group vs. diagnosis of colorectal peritoneal carcinomatosis for control group)	malignancy, good general status and < 66 y.o.; control group: WHO performance status of 1 to 2, <65 y.o., no extra-obdominal, no evidence of bowel obstruction, no tumour larger than 2 cm on CT and no rapid progression of peritoneal carcinomatosis under systemic chemotherapy • Patients characteristics: mean age: 46 (HIPEC) vs. 51 y.o. (control), p=0.01; proportion females: 36% vs. 34 % • Median FU: 63 (HIPEC) vs. 96 months (control)	+/- palliative surgery		HIPEC) vs 65% (95% CI 55–74%, controls)	y.o., p=0.01); significantly more HIPEC pts had well differentiated tumours (37/48 vs. 29/48, p=0.02); prospective inclusion of cases based on HIPEC procedure vs. retrospective inclusion of controls based on diagnosis, hence selection bias is possible; data missing only in control group on initial pT stage, lymph node status, tumour differentiation and extension of PC; also rectal cancer included (HIPEC: 8/48 vs. control 7/48); great diversity of chemotherapy used in both groups

4.2.18. First-line chemotherapy and targeted therapy

Table 101 – Evidence table: SRs oral versus IV fluoropyrimidines

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Zhang 2012	• Design: SR and MA • Sources of funding: not stated • Search date: April 2011 • Searched databases: CENTRAL, Pubmed, Ovid Sciencedirect, EBSCO, EMBASE and conference proceedings • Included study designs: RCTs • Number of included studies: 7 • Included studies: Rothenberg 2008 Porschen 2007 Ducreux 2010 Van Cutsem 2009 Diaz-Rubio	• Eligibility criteria: RCTs published in English. Histologically confirmed CRC. Experimental arm consists of cpecitabine plus oxaliplatin • Patients characteristics: mean age between 59-66 years. • Median FU: not stated	• Intervention: XELOX or CAPOX or OXXEL • Comparator: FOLFOX(4)(6)	• OS: no meta-analysis performed • PFS: no meta-analysis performed	• Overall response rate (5 trials): OR 0.85; 95%CI 0.70-1.02 • Complete response (4 trials): OR 0.78; 95%CI 0.47-1.31 • Partial response (4 trials): OR 0.81; 95%CI 0.65-1.00	Results critical appraisal: • none of the trials had any description of concealment allocation and blinding methods. • Publication bias not assessed, possible conflicts of interest not reported • Unclear if all trials included first-line patients only.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	2007 Comella 2009 Cassidy 2008					
Cao 2010	• Design: SR and MA • Sources of funding: not stated • Search date: September 2008 • Searched databases: Pubmed, Embase, Cochrane library, abstracts of ASCO meetings • Included study designs: RCTs • Number of included studies: 6 • Included studies: Cassidy 2008 Diaz-Rubio 2007 Porschen 2007 Martoni 2007 Comella 2009	• Eligibility criteria: RCTs including patients with metastatic colorectal cancer or advanced colorectal cancer. Capecitabine plus oxaliplatin versus FU plus oxaliplatin for first line treatment • Patients characteristics: median age between 61-67 years • Median FU: between 12.3-29.7 months	• Intervention: Capecitabine plus oxaliplatin • Comparator: FU plus oxaliplatin	• Overall survival (4 trials): HR 1.04; 95%CI 0.95-1.14 • Progression-free survival (3 trials): HR 1.08; 95%CI 0.98-1.18	• Time to treatment failure: HR 1.10; 95%CI 1.01-1.20 • Overall response rate: OR 0.87; 95%CI 0.73-1.03 • Toxicity: • Grade 3-4 thrombocytopenia: OR 1.87; 95%CI 1.24-2.81 (p=0.003) • Grade 3-4 neutropenia: OR 0.20; 95%CI 0.07-0.53 (p=0.001) • Grade 3-4 hand-foot syndrome: OR 3.90; 95%CI 2.13-7.12 (p<0.001)	Results critical appraisal: • publication bias not assessed, possible conflicts of interest not reported • Generation of sequence of randomization described in only 3 out of 6 trials, only one study double blind

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Bennouna 2007					
Ling 2011	• Design: SR and MA based on individual patient data • Sources of funding: Shanghai Municipal Education Committee, Shanghai Municipal natural Science Foundation • Search date: March 2010 • Searched databases: Medline CENTRAL, Highwire press, conference proceedings ASCO - ECCO • Included study designs: phase III RCT • Number of included studies: 10	• Eligibility criteria: phase III RCT including metastatic CRC, trials in adjuvant setting excluded. Trials comparing capecitabine-based chemotherapy and infusional 5-FU-based chemotherapy with ITT analysis • Patients characteristics: advanced or metastatic CRC undergoing first-line treatment except in Skof 2009 (neoadjuvant) and Rothenberg 2008 (2nd line); Median age between 60.5-67 years. • Median FU: not stated	• Intervention: capecitabine-based chemotherapy • Comparator: infusional 5-FU-based chemotherapy	• Overall survival: WMD 0.29 months (p=0.75) • Progression-free survival: WMD 1.24 months (p=0.04) (in favour of capecitabine)	• Response rate: OR 1.02; 95%CI 0.90-1.14 • Response rate for trials comparing oxaliplatin combinations: OR 0.93; 95%CI 0.82-1.06 • Response rate capecitabine monotherapy versus 5-FU monotherapy: OR 1.56; 95%CI 1.16-2.06 • Severe adverse events: OR 0.73: 95%CI 0.59-0.92 (p=0.007) in favour of capecitabine	Results critical appraisal: • funnel plots for assessment of publication bias not reported. Possible conflicts of interest for included trials not reported. • Unclear if trials reporting on neoadjuvant chemotherapy or second line treatment are included in survival analysis.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	• Included trials: Kohne 2008 Eduardo 2007 Van Cutsem 2001 Skof 2009 Cassidy 2008 Rothenberg 2008 Martoni 2006 Comella 2009 Hoff 2001 Porschen 2007					

Petrelli 2012[110]: no critical appraisal of included studies, second line study included in meta-analysis. Reference list checked for additional studies: Fuchs 2007 included in meta-analysis KCE.
Montagnani 2010[111]: no critical appraisal of included studies, study in neo-adjuvant setting included in meta-analysis. Fuchs 2007 and Köhne 2008 included in meta-analysis KCE

Table 102 – Evidence table: RCTs oral versus IV fluoropyrimidines

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Fuchs 2007	• Design: RCT • Sources of funding: Pfizer • Setting: multicentre, USA, Canada, Australia, New Zealand • Sample size: 430 patients • Duration: February 2003-December 2004	• Eligibility criteria: histologically confirmed metastatic colorectal adenocarcinoma with measurable disease, ECOG PS 0-1, adequate organ function, no previous chemotherapy for metastatic disease, prior adjuvant chemotherapy completed 12 months befor includion. CNS metastases excluded, cardiovascular comorbidity excluded. • Patients characteristics: median age 61-62y, primary tumour colonca 64.5-71% • Median FU: 34 months	• Intervention(s): FOLFIRI (infusional 5FU + irinotecan) versus mIFL (bolus 5FU + irinotecan) versus CapeIRI (capecitabin + irinotecan)	**Median PFS** • FOLFIRI 7.6 months • mIFL: 5.9 months • CapeIRI 5.8 months • FOLFIRI versus mIFL: HR 1.51; 95%CI 1.16-1.97 (p=0.004) • FOLFIRI versus CapeIRI : HR 1.36 ; 95%CI 1.04-1.80 (p=0.015) • mIFL versus CapeIRI : HR 1.05 ; 95%CI 0.81-1.38 (p=0.46) **Median OS** • FOLFIRI 23.1 months • mIFL 17.6 months • CapeIRI 18.9 months • These differences in OS between chemotherapy arms did not achieve statistical significance (p=0.09 for FOLFIRI versus mIFL)	**Tolerability**: • Discontinuation of study treatment for unacceptable toxicity: CapeIRI 25.5%, FOLFIRI 14.6% mIFL 13.9% • Death rates within the first 60 days of treatment: FOLFIRI 3.6%, mIFL 5.1%, CapeIRI 3.5%	• Dropouts: not stated • Results critical appraisal: early closure of CapeIRI arm due to toxicity and introduction of bevacizumab for second episode of the trial. Trial designed as 3X2 randomization with simultaneous evaluation of celecoxib versus placebo. No blinding of patients, carers or outcome assessors.
Köhne 2008	• Design: RCT • Sources of funding:	• Eligibility criteria: previously untreated metastatic,	• Intervention(s): CAPIRI (capecitabine	• Median PFS: CapIRI 5.85 months versus FOLFIRI 9.6	• Frequency of grade 3/4 adverse events: CAPIRI 74% versus	• Dropouts: 3 patients did not receive study

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Roche, Pfizer, Aventis • Setting: Multicentre, Belgium, Germany, Hungary • Sample size: 85 • Duration: May 2003 – April 2004	histologically verified colorectal adenocarcinoma. WHO PS 0-2. • Patients characteristics: 62% male; 52% coloncancer; Median age 64.0y (range 42-78) • Median FU: 14.6 months	+ irinotecan) • Comparator(s): FOLFIRI (infusional 5FU + irinotecan) • 2X2 design with comparison celecoxib versus placebo	months HR 0.76; 95%CI 0.48-1.21 in favour of FOLFIRI • Median OS: CapIRI 14.75 months versus FOLFIRI 19.9 months HR 0.31; 95%CI 0.14-0.71 in favour of FOLFIRI	FOLFIRI 49%	drugs, excluded from safety analysis • Results critical appraisal: early closure after randomization of 85 (planned 692 patients) due to seven toxic deaths, five in the CAPIRI arm and two in the FOLFIRI arm.
Cassidy 2011	• Design: RCT • Sources of funding: Roche • Setting: multicentre, worldwide • Sample size: 2034 pts • Duration: July 2003 – May 2004	• Eligibility criteria: histologically confirmed, unresectable metastatic colorectal cancer, ECOG PS 0-1, life expectancy > months. No previous systemic therapy for metastatic disease. Adequate organ function. Excluded: clinically detectable ascites, known CNS metastases • Patients characteristics:	• Intervention(s): XELOX (capecitabine + oxaliplatin) • Comparator(s): FOLFOX4 (5FU + oxaliplatin) • 2X2 design with comparison bevacizumab versus placebo (second phase of trial) • Treatment continued until disease progression or for 48 weeks. (continuation in	• Median overall survival: (all) XELOX 19.8 months versus (all) FOLFOX4 19.5 months. HR 0.95; 97.5%CI 0.85-1.06) • Median overall survival bevacizumab patients excluded: XELOX 19.0 months versus FOLFOX4 18.9 months. HR 0.95: 97.5%CI 0.83-1.09 • Median overall survival chemotherapy-bevacizumab: XELOX-bevacizumab 21.6 months versus FOLFOX4-	• Frequency of grade 3/4 adverse events: XELOX 72% versus FOLFOX4 78% • Frequency of grade 3/4 adverse events XELOX-bevacizumab 75% versus FOLFOX4-bevacizumab 85%	• Dropouts: ITT analysis performed but no info on loss of follow-up • Results critical appraisal: no blinding reported. Study insufficiently powered for overall survival as primary outcome PFS (non-inferiority design).

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		median age between 60-62y, primary coloncancer between 63-67% • Median FU: 14.6 months	post-study phase or surgery allowed)	bevacizumab 21.0 months. HR 0.95; 97.5%CI 0.78-1.15		
Ducreux 2011	• Design: RCT • Sources of funding: Roche • Setting: multicentre, France • Sample size: 306 pts • Duration:May 2003-August 2004	• Eligibility criteria: previously untreated, histologically confirmed mCRC, measurable disease. ECOG PS 0-2. Prior (neo)adjuvant chemotherapy allowed if completed at least 6 months prior to enrolment. Adequate organ function. • Patients characteristics: median age 66-64y. Male 64-60%. Primary site colon cancer 60-63%. • Median FU: 18.8 months	• Intervention(s): XELOX (oxaliplatin+ capecitabine) • Comparator(s): FOLFOX6 (oxaliplatin + leucovorin + IV 5FU) *Treatment was continued for maximum 24 weeks*	• Progression-free survival: HR 1.00; 90%CI 0.82-1.22 • Overall survival HR 1.02; 90%CI 0.81-1.30	• 20% of XELOX- and 22% of FOLFOX6-treated patients discontinued treatment due to toxicity • Grade 3/4 adverse events: XELOX associated with significantly less grade3/4 neuropathy, neutropenia, and febrile neutropenia but more diarrhoea and thrombocytopnia	• Dropouts: 22 ineligible patients included in ITT population. No information on loss of follow-up • Results critical appraisal: sample size calculation for response rate as primary outcome. No blinding reported.
Pectasides 2012	• Design: RCT • Sources of funding:	• Eligibility criteria: histologically or cytologically	• Intervention(s): Bevacizumab + irinotecan +	• Median PFS: XELIRI-bev 10.2 months versus	Toxicity: • Neutropenia more frequent in the	• Dropouts: 17 ineligible patients

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Hellenic Cooperative Oncology Group for translational research • Setting: multicentre, Greece • Sample size: 302 (285) • Duration: January 2006 – January 2008	confirmed stage IV CRC with measurable disease. Previous adjuvant treatment should be completed at least 4 months before enrolment. ECOG PS 0-2. Adequate organ function • Patients characteristics: • Median FU: 42 months	capecitabine • Comparator(s): bevacizumab + irinotecan + capecitabine *Bevacizumab was not administered if a contra-indication was present and optionally in elderly patients > 75 years old*	FOLFIRi-bev 10.8 months (p=0.74) Median OS: XELIRI-bev 20 months versus FOLFIRi-bev 25.3 months (p=0.099	FOLFIRI-bev group (13% versus 22%; p=0.053) • Diarrhoea more frequent in the XELIRI group (19% versus 11%; p=0.082) • Vomiting more frequent in the XELIRI group (5% versus 0%; p=0.014)	excluded from analysis • Results critical appraisal: no blinding. Only 117pts in the intervention group and 120 pts in the control group received bevacizumab
Souglakos 2012	• Design: RCT • Sources of funding: non stated • Setting: multicentre, Greece • Sample size:336 • Duration: June 2005 – June 2008	• Eligibility criteria: Untreated patients with mCRC, adjuvant treatment completed at least 6 months before study enrolment. ECOG PS 0-2. Measurable disease, adequate organ function. Excluded: liverM+ > 50% of the livern chronic diarrhoea, contraindication for bevacizumab • Patients characteristics: median age 66-67y. Male 62-66%.	• Intervention(s): CAPIRI-bev (capecitabine, irinotecan, bevacizumab) • Comparator(s): bolus 5FU + FA, irinotecan, bevacizumab • Treatment continued until disease progression or unacceptable toxicity	• Median PFS: FOLFIRI-bev 10.0 months versus CAPIRI-Bev 8.9 months. HR 0.99: 95%CI 0.90-1.09 (p=0.85) • Median OS: FOLFIRI-bev 25.7 months versus CAPIRI-Bev 27.5 months. HR 1.08: 95%CI 0.94-1.24 (p=0.30)	• Toxicity: patients treated with CAPIRI-Bev had a significantly higher incidence of grade ¾ febrile neutropenia (p<0.001), diarrhoea (p=003) and hand-foot skin reaction (p=0.03). • Death rates within the first 60 days of treatment were 2.4% for FOLFIRI-Bev patients and 4.1% for CAPIRI-Bev patients (p=0.42)	• Dropouts: 3 ineligible patients excluded from the analysis • Results critical appraisal: no blinding reported.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		Primary tumour location colon 74-80% • Median FU: 32 months				
Hochster 2008	• Design: RCT • Sources of funding: sanofi-aventis • Setting: multicentre, USA • Sample size: 150+223 • Duration: December 2002 – November 2003 and November 2003 – April 2004	• Eligibility criteria: histologically documented mCRC or recuurent CRC without prior chemotherapy for metastatic cancer. Prior adjuvant chemotherapy allowed if completed at least 6 months prior to enrolment. ECOG PS 0-1. Measurable disease. Adequate organ function. • Patients characteristics: median age 57-64y, male 57-65%primary coloncancer 55-75% • Median FU: not stated	• Treatment arms TREE 1: mFOLFOX6 versus bFOL versus CapeOx • Treatment arms TREE 2: mFOLFOX6-bev + bFOL-bev + CapeOc-bev	Median overall survival: • mFOLFOX6 19.2 months (95%CI 14.2-24.9 months) • bFOL 17.9 months (95%CI 11.5-24.6) • CapeOX 17.2 months (95%CI 12.5-22.3 months) • mFOLFOX6-bev 26.1 months (95%CI 18.0 to NE months) • bFOL-bev 20.4 months (95%CI 18.4-25.3 months) • CapeOX-bev 24.6 months (21.4-31.6 months) Median TTP: • mFOLFOX6 8.7 months (95%CI 6.5-9.8 months) • bFOL 6.9 months (95%CI 4.2-8.0) • CapeOX 5.9 months (95%CI 5.1-7.4 months) • mFOLFOX6-bev 9.9	• Incidence of Grade3-4 AE during the first 12 weeks of treatment • mFOLFOX6 76% (95%CI 61-87%) • bFOL 44% (95%CI 30-59%) • CapeOx 73% (95%CI 58-85%) • mFOLFOX-bev: 65% (95%CI 53-76%) • bFOL-bev: 60% (95%CI 48-72%) • CapeOx 58% (95%CI 46-70%)	• Dropouts: not reported • Results critical appraisal: no blinding reported. Completeness of follow-up unclear. No conclusions on survival data, insufficient reporting for inclusion in meta-analysis.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
				months (95%CI 7.9-11.7 months) • bFOL-bev 8.3 months (95%CI 6.6-9.9 months) • CapeOX-bev 10.3 months (8.6-12.5 months)		

Table 103 – Evidence table: oxaliplatin versus irinotecan based chemotherapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Liang 2010	• Design: SR and MA • Sources of funding: not stated • Search date: January 2010 • Searched databases: Medline, OVID, Springer, Cochrane Controlled Trials register, Chinese Biology and Medicine disc • Included study designs: RCT • Number of	• Eligibility criteria: metastatic colorectal cancer diagnosed by pathological examination. First-line studies. Outcomes: clinical efficacy, adverse effects. ITT. • Patients characteristics: comparable between treatment arms • Median FU: not stated	• Intervention: irinotecan in combination with fluorouracil/leucovorin • Comparator: oxaliplatin in combination with fluorouracil/leucovorin	Overall survival: • WMD -2.04 months; 95%CI -3.54 to -0.54 months (p=0.008) in favour of oxaliplatin-based chemotherapy Time to progression: • -1.07 months; 95%CI 0.70 to 0.26 months (p=0.12)	Response rate: • RR 0.82; 95%CI 0.70-0.96 (p=0.01) in favour of oxaliplatin-based chemotherapy Grade 3-4 toxicity: • Diarrhoea: RR 1.71; 95%CI 1.22-3.09 • Neurotoxicity: RR 0.06; 95%CI 0.03-0.14 • Neutropenia: RR 0.70; 95%CI 0.55-0.91 • Thrombocytopenia: RR 0.18; 95%CI 0.05-0.61 • Alopecia: RR 14.56; 95%CI 4.11-51.66	Results critical appraisal: • Several databases were searched but no 'additional search strategy' such as checking reference lists, search of trial databases or consultation of experts • Included studies considered to be of poor quality as no blinding and

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	included studies: 7 • Included studies: Goldberg 2004 Tournigand 2004 Delaunoit 2004 Kalofonos 2005 Comella 2005 Colucci 2005 Goldberg 2006					allocation concealment unclear in all trials.

Zhuang 2010: search date may 2008; all studies included in meta-analysis Liang 2010

Table 104 – Evidence table: RCTs sequential versus combination therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Koopman 2007	• Design: RCT • Sources of funding: Dutch Cancer Foundation, Roche, Aventis, Sanofi and Pfizer • Setting: multicentre, the Netherlands • Sample size: 820 pts • Duration: January 2003-December 2004	• Eligibility criteria: histologically proven colorectal cancer, advanced stage not amenable to surgery. Measurable disease. No prior chemotherapy for metastatic disease, previous adjuvant chemotherapy allowed if las administration at least 6 months before randomization; WHO PS 0-2. Adequate organ function. • Patients characteristics: median age 63 years, 63% male, 60% primary colon cancer • Median FU: 31.5 months	• Intervention(s): Sequential treatment = capecitabine, then irinotecan, then capecitabine + oxaliplatin • Comparator(s): combination therapy = capecitabine + irinotecan then capectiabine + oxaliplatin Treatment was continued until disease progression or intolerable toxicity for at least six months.	• Overall survival: HR 0.92; 95%CI 0.79-1.08	• PFS after first line treatment: HR 0.77; 95%CI 0.67-0.89 in favour of the combination group	• Dropouts: 17 ineligible patients excluded from analysis. • Results critical appraisal: no blinding.
Seymour 2007	• Design: RCT • Sources of funding: UK Medical research	• Eligibility criteria: histologically confirmed colorectal cancer with	• Strategy A: 5FU until treatment failure then irinotecan	• Overall survival: HR 1.06; 95%CI 0.97-1.17 for strategy B versus C (non-inferiority		• Dropouts: • Results critical appraisal: no blinding

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	council, sanofi-synthelabo, Aventis, Wyeth-Lederle, Baxter • Setting: multicentre, UK + Cyprus • Sample size: 2135 pts • Duration: May 2000-December 2003	inoperable locoregional or metastatic disease. Measurable disease. WHO PS 0-2. No prior chemotherapy for metastatic disease. Adequate organ function. • Patients characteristics: 66-70% male, median age 63-64 years, 65-69% primary colon cancer • Median FU: 26.5 months	• Strategy B: 5FU until treatment failure then 5FU + irinotecan (B-Ir) or 5FU + oxaliplatin (B-Ox) • Strategy C: 5FU + irinotecan (C-Ir) or 5FU + oxaliplatin (C-Ox) All strategies could be followed by salvage chemotherapy	analysis).		
Ducreux 2011	• Design: RCT • Sources of funding: Sanofi-Aventis • Setting: multicentre, France • Sample size: 410 pts • Duration:February 2002 – February 2006	• Eligibility criteria: histologically proven metastatic colorectal cancer with measurable disease. WHO PS 0-2. No prior chemotherapy for metastatic disease, adjuvant chemotherapy allowed if ended 6 months before enrolment. • Patients	• Intervention(s): Sequential treatment = 5FU continued until treatment failure, then FOLFOX6 until treatment failure then FOLFIRI until treatment failure. • Comparator(s): combination treatment = FOLFOX6 until treatment failure,	• Overall survival: HR 1.02; 95%CI 0.82-1.27	• PFS after first line treatment: HR 0.70; 95%CI 0.57-0.85 in favour of combination treatment • PFS after first and second-line treatment: HR 0.95; 95%CI 0.77-1.16 • PFS after first, second and third line of treatment: HR 0.95; 95%CI 0.77-1.16	• Dropouts: 9 pts (2%) lost of follow-up • Results critical appraisal: no blinding. Early closure due to low accrual after the approval of bevacizumab

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
		characteristics: 60-63% male, median age 66-68y. 76-79% primary colon cancer • Median FU: 36 months	then FOLFIRI until treatment failure. Further lines in both treatment groups were at the investigator's discretion			

Table 105 – Evidence table: SRs chemotherapy +/- bevacizumab

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Macedo 2012	• Design: SR and MA • Sources of funding: • Search date: March 2011 • Searched databases: Pubmed, Embase, Lilacs, Cochrane library, Meeting websites ASCE, ESMO, World congress on GI cancer • Included study designs: RCTs • Number of included studies:	• Eligibility criteria: RCTs comparing chemotherapy with or without bevacizumab in previously untreated patients with metastatic colorectal cancer. Studies including other targeted agents were excluded. • Patients characteristics: first line treatment, 2 two trials exclusively	• Intervention: Chemotherapy + bevacizumab • Comparator: chemotherapy	• Overall survival: HR 0.84; 95%CI 0.77-0.91 (p=0.04) • Progression-free survival: HR 0.72; 95%CI 0.66-0.78 (p=0.01) • Overall response rate: OR 1.12; 95%CI 0.94-1.33 (p=0.21) • Treatment interruptions: HR 1.47; 95%CI 1.19-1.83 • Treatment related mortality: OR 1.00; 95%CI 0.61-1.63	Irinotecan based chemotherapy • Overall survival: HR 0.78; 95%CI 0.68-0.89 • Progression-free survival: HR 0.66; 95%CI 0.58-0.76 Oxaliplatin based chemotherapy • Overall survival: HR 0.89; 95%CI 0.79-1.00 • Progression-free survival: HR 0.83; 95%CI 0.74-0.93	• Results critical appraisal: No results of tests for publication bias reported.

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	6 **Phase II** Kabinnavar 2003 Kabinnavar 2005 **Phase III** Hurwitz 2004 Stathopoulos 2010 Saltz 2008 Tebutt 2010	elderly patients. • Median FU: not stated		Toxicity • Hypertension (grade 3-5): OR 4.90; 95%CI 2.16-11.11 • Bleeding: OR 1.78; 95%CI 1.07-2.95 • Perforation: OR 1.80; 95%CI 0.78-4.17 • Tromboembolic events: OR 1.30; 95%CI 1.01-1.67	Fluorouracil monotherapy • Overall survival: HR 0.84; 95%CI 0.69-1.03 • Progression-free survival: HR 0.58; 95%CI 0.49-0.70	

Welch 2010: all first-line studies included in Macedo et al.
Galfrascoli 2011: all first-line studies included in Macedo et al.
Cao 2009: all first-line studies included in Macedo et al.

Table 106 – Evidence table: Treatment metastatic colorectal cancer: RCTs chemotherapy +/- bevacizumab

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Guan 2011	• Design: RCT • Sources of funding: Sponsored by Shangai Roche Pharmaceuticals • Setting: Multicentre, China • Sample size: 214 pts • Duration:July	• Eligibility criteria: unresectable, histologically proven, measurable mCRC ECOG PS 0-1, no previous therapy for metastatic disease, life expectancy ≥ 3 months, adequate organ function. • Exclusion criteria: previous irinotecan or anti-VEGF therapy, untreated	• Intervention(s): Bevacizumab + irinotecan + 5FU/LV • Comparator(s): irinotecan + 5FU/LV • Treatment continued until documented progressive disease, death or unacceptable toxicity	• PFS rate at six months: 62.6% (95%CI 54.5-70.6%) in the intervention group versus 25.0% (95%CI 14.4-35.6%) in the comparator group (p<0.001) • Median PFS: 8.3 months (95%CI 7.4-8.9 months) in the intervention group versus 4.2 months (95%CI 3.7-4.9) months	• Incidence of grade 3-4 adverse events: 69% intervention group versus 61% control group	• Dropouts: 11 patients excluded due to no tumour assessment or survival information (7) or not received study treatment (4) • Results critical appraisal: no ITT analysis

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	2007-August 2008	brain metastases or evidence of central nervous system disease, clinically significant cardiovascular disease. • Patients characteristics:median age 50-53 years, colon cancer 48%, 35.9-41.7% single metastatic site • Median FU: not stated		in the comparator group • Risk of death: HR 0.62; 95%CI 0.41-0.95 (p=0.014)		

Table 107 – Evidence table: SRs chemotherapy +/- anti-EGFR therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Vale 2012	• Design: SR and MA • Sources of funding: UK Medical Research Council • Search date: not stated • Searched databases: Medline, CENTRAL, PDQ, clinicaltrials.gov and conference	• Eligibility criteria: completed RCTs comparing chemotherapy + cetuximab or panitumumab with the same standard treatment alone in patients of any age with advanced colorectal cancer.	• Intervention: Anti-EGFR MAbs + chemotherapy • Comparator: identical chemotherapy alone	• Overall survival first and second line KRAS wild type patients: HR 0.89; 95%CI 0.82-0.97 • Progression-free survival first and second line KRAS wild type patients: HR 0.83; 95%CI 0.76-0.90 • Progression-free survival for patients with wild-type KRAS	• Progression-free survival first and second line KRAS wild type patients, including trials using bevacizumab + chemotherapy + anti-EGFR therapy: HR 1.27; 95%CI 1.06-1.51 (poorer PFS associated with the addition of bevacizumab)	• Results critical appraisal: publication bias not assessed, possible conflict of interest of included studies not stated. Risk of bias for included trials low or unclear. • Baseline

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	proceedings ASCO, ASCO GI, ESMO, ECCO, World GI congress) • Included study designs: completed RCTs • Number of included studies: 5+2 • Included first-line RCTs: CRYSTAL (Van Cutsem 2008) OPUS (Bokemeyer 2008) PRIME (Douillard 2009 COIN (Maughan 2011) • Nordic VII (Tveit 2010) • CAIRO2 (Tol 2009) • PACCE (Hecht 2009	Separate analysis for first –line trials as reported here. Trials including bevacizumab (CAIRO2, PACCE) included in the sensitivity analysis only. • Patients characteristics: Median age between 61-63y, % male between 54-66% • Median FU: not stated		status, including results for all randomized patients from three trials where KRAS subgroup data are unavailable: HR 0.78; 95%CI 0.72-0.863		characteristics for the subset of patients in whom KRAS status was assessed were similar to those for all randomised patients (low risk of selection bias)

NB: as cetuximab and panitumumab are registered in Europe for wild type KRAS advanced colorectal cancer only, results are reported exclusively for this group of patients
Wang 2012: all first-line trials included in Vale et al.
Dahabreh 2011: reports HR of patients with KRAS wild type tumours versus KRAS mutated tumours. No data on treatment outcome within the KRAS wild type group
Zhang 2011: all first-line trials included in Vale et al.
Nie 2009: all first-line trials included in Vale et al.
Liu 2010: all first-line trials included in vale et al.

Table 108 – Evidence table: RCTs chemotherapy +/- anti-EGFR therapy

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
Van Cutsem 2011 (updated results CRYSTAL, Van Cutsem 2009)	• Design: RCT • Sources of funding: Merck • Setting: multicentre, Europe - Asia • Sample size: 1217 pts • Duration: July 2004 – November 2005	• Eligibility criteria: histologically confirmed colorectal adenocarcinoma with EGFR expression, unresectable disease at first occurrence of metastatic disease. ECOG PS 0-2. No prior therapy for metastatic disease. • Patients characteristics KRAS WT pts: 60.3-62.0% male, median age 59-61y. 84.3-87.7% M+ at one or two sites, 20.6-21.5% confined to liver • Median FU: 46 months	• Intervention(s): Cetuximab + FOLFIRI • Comparator(s): FOLFIRI	For WT KRAS tumours: • PFS: HR 0.696; 95%CI 0.558-0.867 (p=0.0012) • OS: HR 0.796; 95%CI 0.670-0.946 (p=0.0093)	For WT KRAS tumours: • Overall response rate: OR 2.096; 95%CI 1.515-2.826 (p=0.0093)	• Dropouts: 19 untreated patients (reasons unspecified) excluded from the ITT • Results critical appraisal: no ITT. No blinding of patients and carers but blinding of oucome assessors. Incomplete outcome data as KRAS status known for 1063/1198 patients only (baseline characteristics comparable to overall population).
Tveit 2012	• Design: RCT • Sources of funding: Merck Serono, Sanofi-Aventis, Norwegian Cancer	• Eligibility criteria: previously untreated metastatic colorectal adenocarcinoma, measurable disease, ECOG PS 0-2. FU-based adjuvant	• Intervention A: Continued bolus FU + folinic acid + oxaliplatin + • Intervention B: continued bolus FU + folinic acid	For KRAS wild-type patients: • Overall survival: arm B versus A: HR 1.14; 95%CI 0.80-1.61 arm C versus A : HR 1.08 ; 95%CI 0.77-1.52	For KRAS wild type: • Overall response rate: HR 0.96; 95%CI 0.55-1.69	• Dropouts: 5 ineligible patients excluded from ITT. KRAS status known for 88% of

Study ID	Method	Patient characteristics	Intervention(s)	Results primary outcome	Results secondary and other outcome(s)	Critical appraisal of review quality
	Society, Swedish Cancer Society • Setting: multicentre, Northern Europe • Sample size: 571 pts • Duration: May 2005 – October 2007	chemotherapy allowed if ended more than six months before inclusion • Patients characteristics for KRAS WT population: median age 60y, 51-66% male, 64-57% colon cancer	+ oxaliplatin + continued cetuximab • Intervention C: intermittent bolus FU + folinic acid + oxaliplatin + continued cetuximab Continued: treatment continued until progressive disease or unacceptable toxicity Intermittent: stopped after 16 weeks of treatment and reintroduced after recording progressive disease	• Progression-free survival: arm B versus A: HR 1.07; 95%CI 0.79-1.45		patients only • Results critical appraisal: unclear allocation concealment (although probably central randomization), no blinding.

Table 109 – Evidence table: CT chest abdomen in follow-up

Reference	Methodology	Patient characteristics	Intervention	Results primary outcome	Results secondary and other outcomes	Critical appraisal of study quality
Fora 2012	• Design: retrospective case series • Source of funding:not mentioned • Setting:university hospital • Sample size: n= 177 • Duration: median follow-up 81 months	• Eligibility criteria: CRC patients after curative resection +/- adjuvant chemotherapy • Patient characteristics: stage II (48) and III(129), median age 57.5 (22-88) yrs	CT chest, abdomen and pelvis q 6 mths for 2 yrs followed by yearly for 3 – 5 yrs, CEA q 3 mths for 2 yrs followed by q 6 mths for 3-5 yrs and full colonoscopy at 1 and 3 yrs	Recurrence detected in n=44 based on CEA in 8, CT in 30 (68%), colonoscopy in 1, symptoms in 3, peroperative finding (colostomy closure) in 2. CEA was normal in 20/44 (45%)	25 (57%) of detected recurrence came to surgery of which 12 are cancer free after 81 mths 15/19 unresected patients died, median survical 20.7 mths	Based on Quadas : no major biases
Mant 2013	• Design: RCT, factorial design with independent allocation • Source of funding: UK National Istitute for Health Research Health Technology Assessment (project nr 99/10/99) • Setting:multicenter: 39 NHS hospitals • Sample size: n= 1211 • Duration:mean follow-up 3.7 yrs (3-5)	• Eligibility criteria: CRC patients after curative resection +/- adjuvant chemotherapy – residual disease was excluded by imaging (CT, MRI) and CEA • Patient characteristics: Dukes A :18.7%, B: 49.8%,C:31.5% - median age 69 yrs (63-75)	Allocation to1 of 4 groups: 1) CEA q 3 mths for 2 yrs, then q 6 mths for 3 yrs + 1 CT at 12-18 mths. 2) CT chest, abdomen, pelvis q 6 mths for 2 yrs, then annually for 3 yrs. 3) CEA and CT as above. 4) Minimum follow-up:1 CT scan at 12-18 mths if requested at study entry by the hospital clinician.	*adjusted OR for detection 2.7 for CEA only (p=0.035) and 3.4 for CT only (p=0.007), 2.9 for CT+CEA *absolute differences in detection rate in the more intensive arms (1, 2and 3) compared to 4) :4.3-5.7% (5.8-8.0% per protocol)	*absolute difference in proportion of recurrences treated surgically 1.4% for CEA (p=0.28) and 2.8% for CT (p=0.04) * no differences in DFS or OS	Level of evidence: 1 Dropouts: 1) 203/300 2) 47/299 3) 57/302 4) 101/301 Results critical appraisal: low risk of bias

5. EXTERNAL REVIEW BY STAKEHOLDERS

5.1. Summary of feedback by the representatives of the professional societies

Section	Draft recommendations	Strength of Recommendation (weak, strong)	GRADE Level of Evidence (Very low to High)	SH1	SH2	SH3	SH4	SH5	SH6	SH7		Report stakeholder meeting
diagnosis												
	To confirm or rule out colon cancer, colonoscopy (preferably in conjunction with histological confirmation) is the technique of choice in fit patients	strong	NA	5	5	3	5	5	5	5		strong recommendation
	If colonoscopy is considered not feasible or contra-indicated, CT colonography is recommended.	strong	NA	5	5	5	4	4	5	5		strong recommendation. Change to "is recommended", barium enema deleted
staging of invasive colon cancer												
	A CT scan including the chest and abdomen is recommended for all patients diagnosed with colon cancer	strong	NA	5	5	5	5	2	5	5	not for early colon cancer	strong recommendation
	PET-CT is not recommended as part of routine preoperative assessment of non-metastatic colon cancer	strong	NA	5	5	5	5	5	5	5		strong recommendation
	PET-CT is recommended to detect additional metastasis in colorectal cancer patients	strong	NA	5	5	5	5	5	5	5		delete "liver", one recommendation for all resectable

	with potentially resectable liver metastases										metastases
	PET-CT should be considered in patients with potentially resectable lung or peritoneal metastases		NA	5	5	4	5	5	5	5	With the intention to detect distant metastases that would render surgery futile. PET/CT has not enough accuracy for peritoneal staging to determine peritoneal operability and should not be considered as a routine imaging modality when peritoneal metastases are detected.	recommendation deleted, see previous recommendation
	MRI of the liver should be considered for patients who are eligible for resection of liver metastases based on CT and PET-CT	strong	NA	5	5	5	5	5	5	5		strong recommendation
	Treatment decisions should be discussed by a multidisciplinary team	strong	ADAPTE	5	5	5	5	5	5	5		
Pathology												
	KRAS mutation status should be assessed in all patients when anti-EGFR treatment is considered.	strong	NA	5	5	3	5	5	5	3		
	Pathology reports should at least contain the minimal datasets as defined by (inter)national professional organizations; it should always include the	strong	ADAPTE	5	5	3	5	5	5	5		

	pathological TNM classification.											
	For the pathological examination of resection specimens for colorectal cancer, as much lymph nodes as possible should be assessed for the presence of tumour cells. Only routine hematoxylin and eosin stained samples should be used.	strong	ADAPTE	5	5	3	5	5	5	3		
surgical treatment stage 0-I-II												
	In patients in whom Tis is diagnosed after polypectomy, no additional treatment is indicated on the condition that: (1) there is a clear margin of excision (1 to 2mm), (2) the tumour is well or moderately differentiated and (3) there is no lymphatic or venous invasion	weak	very low	5	2	3	4	5	5	3	ok if complete resection in one specimen,,,	change to strong recommendation

	In patients in whom T1 is diagnosed after polypectomy, surgical resection is recommended	strong	very low	5	1	3	4	4	3	3	polypectomy alone if pedonculated polyp, well or moderately differentiated, no lymphatic or venous invasion, clear margin>1mm. Idem non pedonculated polyp with T1SM1 and same caracteristics,	change to should be considered
	In the absence of contra-indications,	weak	low	3	5	3	5	5	5	3	strength of	change to a
	laparoscopy is a preferable option for surgery in patients with resectable stage I-III colon cancer										recommendation should be strong: there is overwhelming evidence on short-term benefits and long-term beneifit s of a laparoscopic approach with equal oncological outcome	"valid option in patients"
	Single incision laparoscopy can be considered an alternative to multiple incision laparoscopy	weak	very low	2	1	3	4	2	2	3	proven????? too few data	no change as it is a weak recommendation
	Robot-assisted colectomy is not recommended in colon cancer patients	strong	very low	NA	5	3	5	1	2	3	robot-assisted = laparoscopic	add: "given its high cost"

	There is insufficient evidence to formulate any recommendation regarding the use of complete mesocolic excision in colon cancer	NA	NA	3	5		4	1	5	3	more data are available and it seems the technique of choice for advanced colonic cancer	no change, only intermediate outcomes available in the literature. Data mainly from one centre only
	An enhanced recovery program is recommended after surgery for colon cancer.	strong	very low	4	5	3	5	4	5	3	there are PRT data in support. (do not agree with the very low level of evidence)	no change, additional information in the text
	The use of an intraluminal stent as a bridge to surgery in patients with acute obstruction due to curable colorectal cancer is not recommended	strong	very low	4	1	3	4	4	5	3	recommended ASCRS, ACPGBI, systematic review BERNSTEIN	no change, see more recent RCTs published after the review of Bernstein
	For the treatment of patients with acute obstruction due to incurable colorectal cancer intraluminal stenting can be considered in selected patients.	weak	very low	NA	5	3	4	4	2	3		
adjuvant chemotherapy stage II-III colon cancer												
	Adjuvant chemotherapy can be considered for stage II colon cancer taking into account the presence of high risk features in the tumour, co-morbidities and patients preferences	weak	low	3	5	**3**	**4**	**2**	**5**	3	define the risk factors	no change. Trials in meta-analysis include Dukes B or stage II without furhter specifications. Often considered (non-validated) risk factors will be

										mentioned in the text.
	If a patient is considered for adjuvant 5FU-monotherapy, MSI testing should be performed. If the tumour is MSI-high, no 5FU-monotherapy should be given.	strong	NA	4	5	**3**	**4**	**4**	**5**	3	Although data mainly in stage II, recommendation applies to stage III as data are considered "prove of principle"
	Adjuvant chemotherapy is recommended for stage III colon cancer. In fit patients, fluoropyrimidine and oxaliplatin is the combination of choice	strong	ADAPTE	4	5	3	5	4	5	3	
	Adjuvant chemotherapy for stage II or III colon cancer should not be omitted in elderly patients based on age alone	weak	low	5	5	3	4	4	5	3	
surgical treatment of liver metastases											
	Liver metastases should be resected if imaging techniques indicate that surgery is an option	strong	ADAPTE	5	5	3	5	5	5	5	
	Simultaneous resection of the primary colon tumour and liver metastases can be considered if the patient is sufficiently fit and a simultaneous operation is judged technically feasible	weak	moderate	NA	5	3	4	5	5	3	

	Systemic peri-operative or adjuvant chemotherapy can be considered in patients with resectable colorectal liver metastasis	weak	moderate	NA	4	**3**	**4**	**4**	**5**	3		
	(Neo)adjuvant hepatic arterial infusion chemotherapy is not recommended in patients with resectable colorectal liver metastasis	strong	very low	NA	3	3	3	4	5	3		
Local treatment modalities for unresectable liver metastases												
	Radiofrequency ablation (RFA) can be considered in addition to surgery in patients with liver metastases in order to achieve complete response and sufficient liver function	weak	ADAPTE	NA	4	3	4	2	5	5	should be a strong recommendations	change to" should be considered", strong recommendation. Move to chapter on surgery.
	Radiofrequency ablation (RFA) is not recommended in patients with unresectable liver metastases	strong	low	NA	5	3	5	4	5	4		
	Hepatic artery chemotherapy (HAI) is not recommended as treatment of liver metastases from colorectal cancer	strong	very low	NA	4	**3**	**3**	**4**	**5**	4		
	Chemoembolisation of liver metastases from colorectal cancer is not recommended outside the framework of clinical research	weak	very low	NA	4	3	3	4	5	4		

	Adding radioembolistation to systemic chemotherapy in patients with unresectable liver metastases is not recommended	weak	very low	NA	4	3	4	3	5	4		
	Radioembolistation can be considered in patients with unresectable liver metastases refractory to systemic chemotherapy	weak	low	NA	4	3	3	3	5	4		
	The use of stereotactic body radiation therapy in the treatment liver metastases from colorectal cancer is not recommended outside the framework of clinical research	strong	very low	NA	4	3	4	3	5	4		
Local treatment of lung metastases												
	Resection of lung metastases can be considered if complete resection can be achieved and if the patient accepts the uncertain benefits and risks.	strong	very low	NA	4	3	4	5	5	5	rephrase to should be considered	change to "should be considered", strong recommendation
	The use of stereotactic body radiation therapy can be considered for unresectable or inoperable limited lung metastases from colorectal cancer	weak	very low	NA	4	**3**	**3**	**3**	**5**	4		
Treatment of peritoneal metastases												
	Cytoreductive surgery and HIPEC may be considered for patients with metastases	weak	very low	NA	5	3	5	4	5	4	recommendation should be strong for the patient who has limited	change to should be offered to highly selected fit patients,

	limited to the abdominal cavity, provided that the number of metastatic sites is limited and the metastases can be removed radically by surgery. HIPEC should only be used with special arrangements for clinical governance, consent and audit or research, since it carries significant risks of morbidity and mortality which needs to be balanced against the benefit (i.e. improvement in survival for patients with colorectal cancer).										intraperiotneal disease or a Krukenberg tumour.(PCI <11-15)	delete percieved. Strong recommendation for highly selected cases.
Treatment of metastatic colon cancer: first-line chemotherapy +/- targeted therapy												
	Combination chemotherapy containing oral or intravenous fluoropyramidines and oxaliplatin or irinotecan is considered the first choice regimen for first–line treatment of metastatic colorectal cancer	strong	very low	NA	4	3	5	4	5	3		
	If combination chemotherapy contains flruoropyrimidines and irinotecan, fluoropyrimidines should be administered intravenously	weak	very low	NA	2	3	3	3	5	3	consider the use of Xeloda??	
	Sequential or combined first-line chemotherapy can be considered in patients with metastatic colon cancer	weak	high	NA	5	3	5	4	5	3		

	In RAS wild type patients, the addition of anti-EGFR therapy (cetuximab or panitumumab) or bevacizumab to first-line chemotherapy should be considered	strong	low	NA	5	3	5	4	5	3	change to RAS
	In RAS mutated patients, the addition of bevacizumab to first-line chemotherapy should be considered	strong	moderate	NA	5	3	4	4	5	3	change to RAS
Second line chemotherapy											
	Second-line chemotherapy should be considered for patients with metastatic colorectal cancer with good performance status and adequate organ function	strong	ADAPTE	NA	5	3	5	4	5	3	
	In fit patients treated in first line with oxaliplatin or irinotecan containing chemotherapy, a change in the cytotoxic regimen from oxaliplatin to irinotecan or from irinotecan to oxaliplatin should be considered	strong	ADAPTE	NA	5	3	5	4	5	3	
Follow-up after treatment with curative intent											
	Identify a coordinator who communicates a follow-up plan to the patient following curative resection.		ADAPTE	5	5	3	5	4	5	5	
	A full colonoscopy should be performed within a year after		NA	5	2	3	5	4	5	3	within 6 months: ASCO and French guidelines	change to 'as soon as possible and no

	curative surgery in cases where complete colonoscopy was impossible preoperatively									later than within 6 months'
	Surveillance colonoscopy is recommended one and five years after curative treatment	NA	2	2	3	5	4	5	3	Waarschijnlijk frequenter in de eerstvolgende jaren, 1-3-8 years according to NCCN	no change
	Propose regular clinic visits starting 4 -6 weeks after surgery and intensive follow-up plan with CT chest, abdominal and pelvis every 6 months for 2 years, then annually for 3 years. A cheaper effective follow-up plan is to perform CEA measurement 3 monthly for 2 years, then 6 monthly for 3 years, with a single chest, abdominal and pelvic CT scan at 12-18 months. A positive CEA is an indication for CT	NA	2	2	**3**	**4**		**5**	4	Is dergelijke hoge frequentie van CT scans altijd nodig? Quid echo abdomen? French guidelines: regular clinic visits + CEA + echography or CT abdo every three months the 2 first years, every 6 month for the next 3 years, chest CT once a year,	change to: "After curative treatment, propose: • a first clinic visit (including baseline CT and CEA) 4-6 weeks after treatment; these data will serve as baseline for further FU • during the first 2 years 3-monthly clinical exams and CEA and 6-monthly CT • during follow-up years 3-5: 6-monthly clinical exams and CEA and annual CT "
	Do not rely on CEA	NA	4	4	**3**	**4**		**5**	4	contradictory to the previous recommendation	delete recommendation

	Although readily available, do not rely on hepatic ultrasound	NA	3	3	3	4		3	5	delete recommendation
	Occult blood testing has no role in CRC follow-up	NA	3	5	3	4	4	5	4	

5.2. Summary feedback patient representatives

The following remarks were received from the Flemish cancer league:

- It is important to involve general practitioners and psychosocial caregivers in the multidisciplinary team discussions.
- A coordinator who ensures the patients is informed about the disease and treatment decisions is important during all stages of the disease, not only during follow-up. An example of a recommendations for which this particularly important is: “Adjuvant chemotherapy for stage II or III colon cancer should not be omited for elderly patients based on age alone “.
- Psycosocial care should be an integral part of care for cancer patients and should thus be addressed in the guideline.

6. PATHOLOGY REPORTS: MINIMAL DATA SETS

6.1. College of American pathologysts

Surgical Pathology Cancer Case Summary

Protocol web posting date: June 2012

COLON AND RECTUM: Resection, Including Transanal Disk Excision of Rectal Neoplasms

Select a single response unless otherwise indicated.

Specimen (select all that apply) (Note A)
___ Terminal ileum
___ Cecum
___ Appendix
___ Ascending colon
___ Transverse colon
___ Descending colon
___ Sigmoid colon
___ Rectum
___ Anus
___ Other (specify): _____
___ Not specified

Procedure
___ Right hemicolectomy
___ Transverse colectomy
___ Left hemicolectomy
___ Sigmoidectomy
___ Rectal/rectosigmoid colon (low anterior resection)
___ Total abdominal colectomy
___ Abdominoperineal resection
___ Transanal disk excision (local excision)
___ Other (specify): _____
___ Not specified

+ Specimen Length (if applicable)
+ Specify: ___ cm

Tumor Site (select all that apply) (Note A)
___ Cecum
___ Right (ascending) colon
___ Hepatic flexure
___ Transverse colon
___ Splenic flexure
___ Left (descending) colon
___ Sigmoid colon
___ Rectosigmoid
___ Rectum
___ Ileocecal valve
___ Colon, not otherwise specified
___ Cannot be determined (see Comment)

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+ Tumor Location
+ ___ Tumor is located above peritoneal reflection
+ ___ Tumor is located below the peritoneal reflection
+ ___ Not specified

Tumor Size
Greatest dimension: ___ cm
+ Additional dimensions: ___ x ___ cm
___ Cannot be determined (see Comment)

Macroscopic Tumor Perforation (Note G)
___ Present
___ Not identified
___ Cannot be determined

+ Macroscopic Intactness of Mesorectum (Note H)
+ ___ Not applicable
+ ___ Complete
+ ___ Near complete
+ ___ Incomplete
+ ___ Cannot be determined

Histologic Type (Note B)
___ Adenocarcinoma
___ Mucinous adenocarcinoma
___ Signet-ring cell carcinoma
___ High-grade neuroendocrine carcinoma
    ___ Large cell neuroendocrine carcinoma
    ___ Small cell neuroendocrine carcinoma
___ Squamous cell carcinoma
___ Adenosquamous carcinoma
___ Medullary carcinoma
___ Undifferentiated carcinoma
___ Other (specify): _____
___ Carcinoma, type cannot be determined

Histologic Grade (Note C)
___ Not applicable
___ Cannot be assessed
___ Low-grade (well-differentiated to moderately differentiated)
___ High-grade (poorly differentiated to undifferentiated)
___ Other (specify): _____

+ Histologic Features Suggestive of Microsatellite Instability (Note I)

+ Intratumoral Lymphocytic Response (tumor-infiltrating lymphocytes)
+ ___ None
+ ___ Mild to moderate (0-2 per high-power [X400] field)
+ ___ Marked (3 or more per high-power field)

+ Peritumor Lymphocytic Response (Crohn-like response)
+ ___ None
+ ___ Mild to moderate
+ ___ Marked

+ Tumor Subtype and Differentiation (select all that apply)
+ ___ Mucinous tumor component (specify percentage: ____)
+ ___ Medullary tumor component
+ ___ High histologic grade (poorly differentiated)

Microscopic Tumor Extension
___ Cannot be assessed
___ No evidence of primary tumor
___ No invasion of lamina propria
___ Intramucosal carcinoma, invasion of lamina propria/muscularis mucosae
___ Tumor invades submucosa
___ Tumor invades muscularis propria
___ Tumor invades through the muscularis propria into the subserosal adipose tissue or the nonperitonealized pericolic or perirectal soft tissues but does not extend to the serosal surface
___ Tumor penetrates to the surface of the visceral peritoneum (serosa)
___ Tumor is adherent to other organs or structures (specify: _____)
___ Tumor directly invades adjacent structures (specify: _____)
___ Tumor penetrates to the surface of the visceral peritoneum (serosa) *and* directly invades adjacent structures (specify: _____)

Margins (select all that apply) (Note J)

If all margins uninvolved by invasive carcinoma:
Distance of invasive carcinoma from closest margin: ___ mm *or* ___ cm
Specify margin: _____

Proximal Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ No adenoma or intraepithelial neoplasia / dysplasia identified
___ Adenoma (low-grade intraepithelial neoplasia / dysplasia) present
___ High-grade intraepithelial neoplasia / dysplasia or intramucosal carcinoma present (specify): _____
___ Involved by invasive carcinoma

Distal Margin
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ No adenoma or intraepithelial neoplasia / dysplasia identified
___ Adenoma (low grade intraepithelial neoplasia / dysplasia) present
___ High-grade intraepithelial neoplasia / dysplasia or intramucosal carcinoma present (specify): _____
___ Involved by invasive carcinoma

Circumferential (Radial) or Mesenteric Margin
___ Not applicable
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma (tumor present 0-1 mm from margin)

Deep Margin (endoscopic mucosal resections) (required only if applicable)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Mucosal Margin (noncircumferential transanal disk excision) (required only if applicable)
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
Distance of invasive carcinoma from closest mucosal margin: ___ mm *or* ___ cm
+ Specify location (eg, o'clock position), if possible: _____
___ Involved by invasive carcinoma
+ Specify location (eg, o'clock position), if possible: _____
___ Uninvolved by adenoma
___ Involved by adenoma

Other Margin(s) (required only if applicable)
Specify margin(s): _____
___ Cannot be assessed
___ Uninvolved by invasive carcinoma
___ Involved by invasive carcinoma

Treatment Effect (applicable to carcinomas treated with neoadjuvant therapy) (Note K)
___ No prior treatment
___ Present
+ ____ No residual tumor (complete response, grade 0)
+ ____ Moderate response (grade 1, minimal residual cancer)
+ ____ Minimal response (grade 2)
___ No definite response identified (grade 3, poor response)
___ Not known

Lymph-Vascular Invasion (Note E)
___ Not identified
___ Present
___ Indeterminate

Perineural Invasion (Note E)
___ Not identified
___ Present
___ Indeterminate

Tumor Deposits (discontinuous extramural extension) (Note L)
___ Not identified
___ Present (specify number of deposits: ____)
___ Indeterminate

+ Type of Polyp in Which Invasive Carcinoma Arose (Note F)
+ ___ None identified
+ ___ Tubular adenoma
+ ___ Villous adenoma
+ ___ Tubulovillous adenoma
+ ___ Traditional serrated adenoma
+ ___ Sessile serrated adenoma
+ ___ Hamartomatous polyp
+ ___ Indeterminate

Pathologic Staging (pTNM) (Note M)

TNM Descriptors (required only if applicable) (select all that apply)
___ m (multiple primary tumors)
___ r (recurrent)
___ y (posttreatment)

Primary Tumor (pT)
___ pTX: Cannot be assessed
___ pT0: No evidence of primary tumor
___ pTis: Carcinoma in situ, intraepithelial (no invasion of lamina propria)
___ pTis: Carcinoma in situ, invasion of lamina propria/muscularis mucosae
___ pT1: Tumor invades submucosa
___ pT2: Tumor invades muscularis propria
___ pT3: Tumor invades through the muscularis propria into pericolorectal tissues
___ pT4a: Tumor penetrates the visceral peritoneum
___ pT4b: Tumor directly invades or is adherent to other organs or structures

Regional Lymph Nodes (pN)
___ pNX: Cannot be assessed
___ pN0: No regional lymph node metastasis
___ pN1a: Metastasis in 1 regional lymph node
___ pN1b: Metastasis in 2 to 3 regional lymph nodes
___ pN1c: Tumor deposit(s) in the subserosa, or non-peritonealized pericolic or perirectal tissues without regional lymph node metastasis
___ pN2a: Metastasis in 4 to 6 regional lymph nodes
___ pN2b: Metastasis in 7 or more regional lymph nodes

___ No nodes submitted or found

Number of Lymph Nodes Examined
Specify: ____
___ Number cannot be determined (explain): _____

Number of Lymph Nodes Involved
Specify: ____
___ Number cannot be determined (explain): _____

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Distant Metastasis (pM)
___ Not applicable
___ pM1: Distant metastasis
+ Specify site(s): _____
___ pM1a: Metastasis to single organ or site (eg, liver, lung, ovary, nonregional lymph node)
___ pM1b: Metastasis to more than 1 organ/site or to the peritoneum

+ Additional Pathologic Findings (select all that apply)
+ ___ None identified
+ ___ Adenoma(s)
+ ___ Chronic ulcerative proctocolitis
+ ___ Crohn disease
+ ___ Dysplasia arising in inflammatory bowel disease
+ ___ Other polyps (type[s]): _____
+ ___ Other (specify): _____

+ Ancillary Studies (select all that apply) (Note N)

+ ___ Microsatellite Instability (specify testing method: _____)
+ ___ Stable
+ ___ Low
+ ___ High

+ Immunohistochemistry Studies for Mismatch Repair Proteins
+ ___ MLH1
+ ___ Intact nuclear positivity, tumor cells
+ ___ Loss of nuclear positivity, tumor cells
+ ___ Pending
+ ___ Other (specify): _____
+ ___ MSH2
+ ___ Intact nuclear positivity, tumor cells
+ ___ Loss of nuclear positivity, tumor cells
+ ___ Pending
+ ___ Other (specify): _____
+ ___ MSH6
+ ___ Intact nuclear positivity, tumor cells
+ ___ Loss of nuclear positivity, tumor cells
+ ___ Pending
+ ___ Other (specify): _____
+ ___ PMS2
+ ___ Intact nuclear positivity, tumor cells
+ ___ Loss of nuclear positivity, tumor cells
+ ___ Pending
+ ___ Other (specify): _____

+ Mutational Analysis
+ ___ *BRAF* V600E mutational analysis (specify testing method: _____)
    + ___ Mutant *BRAF* detected
    + ___ No mutant *BRAF* detected (wild type *BRAF* allele)
    + ___ Other (specify):_____

+ ___ *KRAS* mutational analysis (specify testing method: _____)
    + ___ Mutant *KRAS* detected (specify mutation_____)
    + ___ No mutant *KRAS* detected (wild type KRAS allele)
    + ___ Other (specify):_____

+ Other, specify: _____

+ ____ Not performed

+ Comment(s)

6.2. Royal college of pathologists

APPENDIX C PROFORMA FOR COLORECTAL CANCER RESECTIONS

Surname: ..... Forenames: ..... Date of birth: .....

Hospital..... Hospital no: ..... NHS no: .....

Date of receipt: ..... Date of reporting: ..... Report no: .....

Pathologist: ..... Surgeon: ..... Sex: .....

Specimen type: Total colectomy / Right hemicolectomy / Left hemicolectomy / Sigmoid colectomy / Anterior resection / Abdominoperineal excision / Other (state) .....

Gross description

Site of tumour .....

Maximum tumour diameter: .....mm

Distance of tumour to nearer cut end .....mm

Tumour perforation (pT4) Yes ☐ No ☐

If yes, perforation is serosal ☐ retro/infra peritoneal ☐

For rectal tumours:

Relation of tumour to peritoneal reflection (tick one):

Above ☐ Astride ☐ Below ☐

Plane of surgical excision (tick one):

Mesorectal fascia ☐

Intramesorectal ☐

Muscularis propria ☐

For abdominoperineal resection specimens:

Distance of tumour from dentate line .....mm

Histology

Type

Adenocarcinoma Yes ☐ No ☐

If No, other type .....

Differentiation by predominant area

Well / moderate ☐ Poor ☐

Local invasion

No carcinoma identified (pT0) ☐

Submucosa (pT1) ☐

Muscularis propria (pT2) ☐

Beyond muscularis propria (pT3) ☐

Tumour invades adjacent organs (pT4a) ☐

AND/OR

Tumour cells have breached the serosa (pT4b) ☐

Maximum distance of spread beyond muscularis propria .....mm

Response to neoadjuvant therapy

Neoadjuvant therapy given Yes ☐ No ☐ NK ☐

If yes:

No residual tumour cells / mucus lakes only ☐

Minimal residual tumour ☐

No marked regression ☐

Tumour involvement of margins

	N/A	Yes	No
Doughnuts	☐	☐	☐
Margin (cut end)	☐	☐	☐
Non-peritonealised 'circumferential' margin	☐	☐	☐

Histological measurement from tumour to non-peritonealised margin .....mm

Metastatic spread

No of lymph nodes present .....

No of involved lymph nodes .....

(pN1 1–3 nodes, pN2 4+ nodes involved)

Highest node involved (Dukes C2) Yes ☐ No ☐

Extramural venous invasion Yes ☐ No ☐

Histologically confirmed distant metastases (pM1):

Yes ☐ No ☐ If yes, site: .....

Background abnormalities: Yes ☐ No ☐

If yes, type: (delete as appropriate)

Adenoma(s) (state number .....)

Familial adenomatous polyposis / Ulcerative colitis / Crohn's disease / Diverticulosis / Synchronous carcinoma(s) (complete a separate form for each cancer)

Other .....

Pathological staging

Complete resection at all surgical margins

Yes (R0) ☐ No (R1 or R2) ☐

TNM (5th edition)

(y) pT ..... (y) pN .....(y) pM .....

Dukes

Dukes A ☐ (Tumour limited to wall, nodes negative)

Dukes B ☐ (Tumour beyond M. propria, nodes negative)

Dukes C1 ☐ (Nodes positive and apical node negative)

Dukes C2 ☐ (Apical node involved)

Signature: ..... **Date** ...../...../..... **SNOMED Codes** T..... / M.....

APPENDIX D PROFORMA FOR LOCAL EXCISION SPECIMENS

Surname: ..... Forenames: ..... Date of birth: .....

Hospital..... Hospital no: ..... NHS no: .....

Date of receipt: ..... Date of reporting: ..... Report no: .....

Pathologist: ..... Surgeon: ..... Sex: .....

Specimen type

Polypectomy / Endoscopic mucosal resection / Transanal endoscopic microsurgical (TEM) excision / Other

Comments: .....

Gross description

Site of tumour .....

Maximum tumour diameter (if known) ..... mm

Histology

Tumour type

Adenocarcinoma Yes ☐ No ☐

If No, Other .....

Differentiation

Well/moderate ☐ Poor ☐

Local invasion

Confined to submucosa (pT1) ☐

Into muscularis propria (pT2) ☐

Beyond muscularis propria (pT3) ☐

For pT1 tumours:

Maximum thickness of invasive tumour from muscularis mucosae .....mm

Haggitt level (polypoid tumours) 1 / 2 / 3 / 4

Kikuchi level (for sessile/flat tumours) sm1 / sm2 / sm3

Lymphatic or vascular invasion:

None ☐

Possible ☐

Definite ☐

Background adenoma: Yes ☐ No ☐

Margins

Not involved ☐

Involved by adenoma only ☐

Deep margin Involved by carcinoma ☐

Peripheral margin Involved by carcinoma ☐

Histological measurement from carcinoma to nearest deep excision margin.....mm

Pathological staging

Complete resection at carcinoma at all margins

Yes (R0) ☐ No (R1 or R2) ☐

pT stage .....

Signature: ..... **Date** ...../...../..... **SNOMED codes** T..... / M.....

REFERENCES

1. Anannamcharoen S, Boonya-Ussadol C. Identification of patients with high-risk for pulmonary metastases after curative resection of colorectal cancer. Journal of the Medical Association of Thailand. 2012;95(5).
2. Leventakos K, Lu SS, Perry DJ. Intensive CT scan surveillance for patients who have undergone curative intent treatment for colorectal cancer: The Medstar Washington Hospital Center experience. J Clin Oncol. 2013;31(15).
3. Penney N, Lisa S, Pye G. Colorectal cancer follow-up at a District General Hospital. Colorectal Dis. 2011;13:46.
4. Robertson FPC, Robertson JHP, Stewart A, Mander BJ. The impact of the introduction of a routine 2 year CT scan in patients undergoing curative resections for colorectal cancer. Colorectal Dis. 2012;14:24.
5. Walter CJ, Al-Allak A, Borley N, Goodman A, Wheeler J. The role of fifth-year surveillance computed tomography scanning after potentially curative resections for colorectal cancer. Gut. 2011;60:A76.
6. Jonker D, Spithoff K, Maroun J, Group. atGCDS. Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer after Complete Resection: An Updated Practice Guideline. 2011
7. Zalinski S, Mariette C, Farges O, Sfcd-Achbt evaluation committee, French Society of Gastrointestinal Surgery, Association of Hepatobiliary Surgery, et al. Management of patients with synchronous liver metastases of colorectal cancer. Clinical practice guidelines. Guidelines of the French society of gastrointestinal surgery (SFCD) and of the association of hepatobiliary surgery and liver transplantation (ACHBT). Short version. J Visc Surg. 2011;148(3):e171-82.
8. NICE. Clinical Guideline Colorectal cancer: the diagnosis and management of colorectal cancer. 2011.
9. New Zealand guidelines group. Management of Early Colorectal Cancer. Evidence-based Best Practice Guideline. 2011.
10. SIGN. SIGN 126: Diagnosis and management of colorectal cancer. 2011.

11. Wong SL, Mangu PB, Choti MA, Crocenzi TS, Dodd GD, 3rd, Dorfman GS, et al. American Society of Clinical Oncology 2009 clinical evidence review on radiofrequency ablation of hepatic metastases from colorectal cancer. J Clin Oncol. 2010;28(3):493-508.
12. Chan K, Welch S, Walker-Dilks C, Raifu AO. PET Imaging in Colorectal Cancer. Cancer Care Ontario program in evidence-based care. 2010.
13. Welch S, Kocha W, Rumble RB, Spithoff K, Maroun J. The Role of Bevacizumab (Avastin®) Combined With Chemotherapy in the Treatment of Patients With Advanced Colorectal Cancer: Guideline Recommendations. Cancer Care Ontario Evidence-based series. 2008.
14. IKNL. Coloncarcinoom. Landelijke richtlijn met regionale toevoegingen. 2008.
15. Society of American Gastrointestinal and Endoscopic Surgeons (SAGES). Diagnostic Laparoscopy Guidelines. In; 2007.
16. IKNL. Colorectale levermetastasen. 2006.
17. van Kessel CS, Buckens CF, van den Bosch MA, van Leeuwen MS, van Hillegersberg R, Verkooijen HM. Preoperative imaging of colorectal liver metastases after neoadjuvant chemotherapy: a meta-analysis. Ann Surg Oncol. 2012;19(9):2805-13.
18. Niekel MC, Bipat S, Stoker J. Diagnostic imaging of colorectal liver metastases with CT, MR imaging, FDG PET, and/or FDG PET/CT: a meta-analysis of prospective studies including patients who have not previously undergone treatment. Radiology. 2010;257(3):674-84.
19. Chan K, Welch S, Walker-Dilks C, Raifu A. Evidence-based guideline recommendations on the use of positron emission tomography imaging in colorectal cancer. Clin Oncol (R Coll Radiol). 2012;24(4):232-49.
20. Di Gregorio C Fau - Bonetti LR, Bonetti Lr Fau - de Gaetani C, de Gaetani C Fau - Pedroni M, Pedroni M Fau - Kaleci S, Kaleci S Fau - Ponz de Leon M, Ponz de Leon M. Clinical outcome of low- and high-risk malignant colorectal polyps: results of a population-based study and meta-analysis of the available literature. Intern Emerg Med. 2012;27:27.
21. Maggiori L, Gaujoux S, Tribillon E, Bretagnol F, Panis Y. Single-incision laparoscopy for colorectal resection: A systematic review and meta-analysis of more than a thousand procedures. Colorectal Dis. 2012;14(10):e643-e54.
22. Zhou YM, Wu LP, Zhao YF, Xu DH, Li B. Single-incision versus conventional laparoscopy for colorectal disease: A meta-analysis. Dig. Dis. Sci. 2012;57(8):2103-12.
23. Lv C, Wu S, Wu Y, Shi J, Su Y, Fan Y, et al. Single-incision laparoscopic versus traditional multiport laparoscopic colorectal surgery-a cumulative meta-analysis and systematic review. Int. J. Colorectal Dis. 2013.
24. Mirnezami AH, Mirnezami R, Venkatasubramaniam AK, Chandrakumaran K, Cecil TD, Moran BJ. Robotic colorectal surgery: hype or new hope? A systematic review of robotics in colorectal surgery. Colorectal Dis. 2010;12(11):1084-93.
25. Figueredo A, Coombes ME, Mukherjee S. Adjuvant therapy for completely resected stage II colon cancer. Cochrane Database Syst Rev. 2008(3):CD005390.
26. Wu X, Zhang J, He X, Wang C, Lian L, Liu H, et al. Postoperative adjuvant chemotherapy for stage II colorectal cancer: a systematic review of 12 randomized controlled trials. J Gastrointest Surg. 2012;16(3):646-55.
27. Rizell M, Hultborn R, Bernhardt P, Svensson J, Sternby EM, Samuelsson O, et al. 90Yttrium radioembolisation for hepatocellular carcinoma and colorectal liver metastases (Structured abstract). Health Technology Assessment Database. 2010(3).

28. Townsend A, Price T, Karapetis C. Selective internal radiation therapy for liver metastases from colorectal cancer. Cochrane Database of Systematic Reviews. 2009(4).
29. Cirocchi R, Trastulli S, Boselli C, Montedori A, Cavaliere D, Parisi A, et al. Radiofrequency ablation in the treatment of liver metastases from colorectal cancer. Cochrane Database of Systematic Reviews. 2012(6).
30. Mocellin S, Pasquali S, Nitti D. Fluoropyrimidine-HAI (hepatic arterial infusion) versus systemic chemotherapy (SCT) for unresectable liver metastases from colorectal cancer. Cochrane Database of Systematic Reviews. 2011(3).
31. Hendlisz A, Van Den Eynde M, Peeters M, Maleux G, Lambert B, Vannoote J, et al. Phase III trial comparing protracted intravenous fluorouracil infusion alone or with yttrium-90 resin microspheres radioembolization for liver-limited metastatic colorectal cancer refractory to standard chemotherapy. J. Clin. Oncol. 2010;28(23):3687-94.
32. Australian Government - National Health and Medical Research Council. Clinical Practice Guidelines for Surveillance Colonoscopy - in adenoma follow-up, following curative resection of colorectal cancer, and for cancer surveillance in inflammatory bowel disease. 2011.
33. Australian Government - National Health and Medical Research Council. Clinical Practice Guideline for the prevention, early detection and management of colorectal cancer. 2005.
34. Hassan C, Zullo A, Risio M, Rossini FP, Morini S. Histologic risk factors and clinical outcome in colorectal malignant polyp: a pooled-data analysis. Diseases of the Colon & Rectum. 2005;48(8):1588-96.
35. Liang J-T, Shieh M-J, Chen C-N, Cheng Y-M, Chang K-J, Wang S-M. Prospective evaluation of laparoscopy-assisted colectomy versus laparotomy with resection for management of complex polyps of the sigmoid colon. World Journal of Surgery. 2002;26(3):377-83.
36. NICE. Laparoscopic surgery for colorectal cancer. Review of NICE technology appraisal 17. 2006.
37. Jonker DJ, Spithoff K, Maroun J, Gastrointestinal Cancer Disease Site Group of Cancer Care Ontario's Program in Evidence-based Care. Adjuvant systemic chemotherapy for Stage II and III colon cancer after complete resection: an updated practice guideline. Clin Oncol (R Coll Radiol). 2011;23(5):314-22.
38. NICE. Capecitabine and oxaliplatinin the adjuvant treatment of stage III (Dukes' C) colon cancer. Technology Appraisal 100. 2006.
39. Gallinger S, Biagi JJ, Fletcher GG, Nhan C, Ruo L, McLeod RS, et al. The role of liver resection in colorectal cancer metastases. Toronto (ON): 2012, June15. Program in Evidence-based Care - Evidence-based Series
40. New Zealand Guidelines Group. Management of early colorectal cancer. 2011.
41. Atkin W, Dadswell E, Wooldrage K, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. Lancet. 2013.
42. von Wagner C, Ghanouni A, Halligan S, Smith S, Dadswell E, Lilford RJ, et al. Patient acceptability and psychologic consequences of CT colonography compared with those of colonoscopy: results from a multicenter randomized controlled trial of symptomatic patients. Radiology. 2012;263(3):723-31.
43. Halligan S, Wooldrage K, Dadswell E, Kralj-Hans I, von Wagner C, Edwards R, et al. Computed tomographic colonography versus barium enema for diagnosis of colorectal cancer or large polyps in symptomatic patients (SIGGAR): a multicentre randomised trial. Lancet. 2013.
44. Patel S, McCall M, Ohinmaa A, Bigam D, Dryden DM. Positron emission tomography/computed tomographic scans compared to computed tomographic scans for detecting colorectal liver metastases: a systematic review. Ann Surg. 2011;253(4):666-71.

45. Brush J, Boyd K, Chappell F, Crawford F, Dozier M, Fenwick E, et al. The value of FDG positron emission tomography/computerised tomography (PET/CT) in pre-operative staging of colorectal cancer: a systematic review and economic evaluation. Health Technol Assess. 2011;15(35):1-192, iii-iv.

46. Mainenti PP, Mancini M, Mainolfi C, Camera L, Maurea S, Manchia A, et al. Detection of colo-rectal liver metastases: prospective comparison of contrast enhanced US, multidetector CT, PET/CT, and 1.5 Tesla MR with extracellular and reticulo-endothelial cell specific contrast agents. Abdom Imaging. 2010;35(5):511-21.

47. Rappeport ED, Loft A, Berthelsen AK, von der Recke P, Larsen PN, Mogensen AM, et al. Contrast-enhanced FDG-PET/CT vs. SPIO-enhanced MRI vs. FDG-PET vs. CT in patients with liver metastases from colorectal cancer: a prospective study with intraoperative confirmation. Acta Radiol. 2007;48(4):369-78.

48. Fitzgerald A Fau - Frizelle F, Frizelle F Fau - Jeffery M, Jeffery M Fau - Balasingam A, Balasingam A Fau - Casey J, Casey J Fau - Collett J, Collett J Fau - Lynch T, et al. Summary of guidance for the management of early bowel cancer. 2011;124(1337):90-9. PMID- 15622570 OWN - NLM STAT- MEDLINE.

49. Seitz U Fau - Bohnacker S, Bohnacker S Fau - Seewald S, Seewald S Fau - Thonke F, Thonke F Fau - Brand B, Brand B Fau - Braiutigam T, Braiutigam T Fau - Soehendra N, et al. Is endoscopic polypectomy an adequate therapy for malignant colorectal adenomas? Presentation of 114 patients and review of the literature. 2004;47(11):1789-96; discussion 96-7.

50. Benizri EI, Bereder JM, Rahili A, Bernard JL, Vanbiervliet G, Filippi J, et al. Additional colectomy after colonoscopic polypectomy for T1 colon cancer: A fine balance between oncologic benefit and operative risk. Int. J. Colorectal Dis. 2012;27(11):1473-8.

51. Butte JM, Tang P, Gonen M, Shia J, Schattner M, Nash GM, et al. Rate of residual disease after complete endoscopic resection of malignant colonic polyp.[Erratum appears in Dis Colon Rectum. 2012 Apr;55(4):498 Note: Nash, Garret M [corrected to Nash, Garrett M]]. Dis Colon Rectum. 2012;55(2):122-7.

52. Kim MN, Kang JM, Yang JI, Kim BK, Im JP, Kim SG, et al. Clinical features and prognosis of early colorectal cancer treated by endoscopic mucosal resection. J Gastroenterol Hepatol. 2011;26(11):1619-25.

53. Meining A, von Delius S, Eames TM, Popp B, Seib HJ, Schmitt W. Risk factors for unfavorable outcomes after endoscopic removal of submucosal invasive colorectal tumors. Clin Gastroenterol Hepatol. 2011;9(7):590-4.

54. Oka S, Tanaka S, Kanao H, Ishikawa H, Watanabe T, Igarashi M, et al. Mid-term prognosis after endoscopic resection for submucosal colorectal carcinoma: summary of a multicenter questionnaire survey conducted by the colorectal endoscopic resection standardization implementation working group in Japanese Society for Cancer of the Colon and Rectum. DIG. ENDOSC. 2011;23(2):190-4.

55. Grailey K, Markar SR, Karthikesalingam A, Aboud R, Ziprin P, Faiz O. Laparoscopic versus open colorectal resection in the elderly population. Surg. Endosc. Interv. Tech. 2013;27(1):19-30.

56. Ding J, Liao GQ, Xia Y, Zhang ZM, Liu S, Yan ZS. Laparoscopic versus open right hemicolectomy for colon cancer: A meta-analysis. J. Laparoendosc. Adv. Surg. Techn. 2013;23(1):8-16.

57. Ohtani H, Tamamori Y, Arimoto Y, Nishiguchi Y, Maeda K, Hirakawa K. and long-term results of randomized con-trolled trials that compared laparoscopy-assisted and open colectomy for colon cancer. J. Cancer. 2012;3(1):49-57.

58. Sammour T, Kahokehr A, Srinivasa S, Bissett IP, Hill AG. Laparoscopic colorectal surgery is associated with a higher intraoperative complication rate than open surgery. Ann. Surg. 2011;253(1):35-43.

59. Ma Y, Yang Z, Qin H, Wang Y. A meta-analysis of laparoscopy compared with open colorectal resection for colorectal cancer. Med Oncol. 2011;28(4):925-33.

60. Green BL, Marshall HC, Collinson F, Quirke P, Guillou P, Jayne DG, et al. Long-term follow-up of the Medical Research Council CLASICC trial of conventional versus laparoscopically assisted resection in colorectal cancer. Br J Surg. 2013;100(1):75-82.
61. Li JC, Leung KL, Ng SS, Liu SY, Lee JF, Hon SS. Laparoscopic-assisted versus open resection of right-sided colonic cancer--a prospective randomized controlled trial. Int J Colorectal Dis. 2012;27(1):95-102.
62. Bagshaw PF, Allardyce RA, Frampton CM, Frizelle FA, Hewett PJ, McMurrick PJ, et al. Long-term outcomes of the australasian randomized clinical trial comparing laparoscopic and conventional open surgical treatments for colon cancer: the Australasian Laparoscopic Colon Cancer Study trial. Ann Surg. 2012;256(6):915-9.
63. Kaltoft B, Gogenur I, Rosenberg J. Reduced length of stay and convalescence in laparoscopic vs open sigmoid resection with traditional care: a double blinded randomized clinical trial. Colorectal Dis. 2011;13(6):e123-30.
64. Park JS, Choi GS, Park SY, Kim HJ, Ryuk JP. Randomized clinical trial of robot-assisted versus standard laparoscopic right colectomy. Br J Surg. 2012;99(9):1219-26.
65. Sakamoto J, Ohashi Y, Hamada C, Buyse M, Burzykowski T, Piedbois P. Efficacy of oral adjuvant therapy after resection of colorectal cancer: 5-year results from three randomized trials. J Clin Oncol. 2004;22(3):484-92.
66. Abraham A, Habermann EB, Rothenberger DA, Kwaan M, Weinberg AD, Parsons HM, et al. Adjuvant chemotherapy for stage III colon cancer in the oldest old: results beyond clinical guidelines. Cancer. 2013;119(2):395-403.
67. Gross CP, McAvay GJ, Guo Z, Tinetti ME. The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. Cancer. 2007;109(12):2410-9.
68. Hu CY, Delclos GL, Chan W, Du XL. Assessing the initiation and completion of adjuvant chemotherapy in a large nationwide and population-based cohort of elderly patients with stage-III colon cancer. Med Oncol. 2011;28(4):1062-74.
69. Jessup JM, Stewart A, Greene FL, Minsky BD. Adjuvant chemotherapy for stage III colon cancer: implications of race/ethnicity, age, and differentiation. JAMA. 2005;294(21):2703-11.
70. Kahn KL, Adams JL, Weeks JC, Chrischilles EA, Schrag D, Ayanian JZ, et al. Adjuvant chemotherapy use and adverse events among older patients with stage III colon cancer. JAMA. 2010;303(11):1037-45.
71. Morris M, Platell C, McCaul K, Millward M, van Hazel G, Bayliss E, et al. Survival rates for stage II colon cancer patients treated with or without chemotherapy in a population-based setting. Int J Colorectal Dis. 2007;22(8):887-95.
72. van Steenbergen LN, Lemmens VE, Rutten HJ, Wymenga AN, Nortier JW, Janssen-Heijnen ML. Increased adjuvant treatment and improved survival in elderly stage III colon cancer patients in The Netherlands. Ann Oncol. 2012;23(11):2805-11.
73. Wildes TM, Kallogjeri D, Powers B, Vlahiotis A, Mutch M, Spitznagel EL, Jr., et al. The Benefit of Adjuvant Chemotherapy in Elderly Patients with Stage III Colorectal Cancer is Independent of Age and Comorbidity. J Geriatr Oncol. 2010;1(2):48-56.
74. Zuckerman IH, Rapp T, Onukwugha E, Davidoff A, Choti MA, Gardner J, et al. Effect of age on survival benefit of adjuvant chemotherapy in elderly patients with Stage III colon cancer. J Am Geriatr Soc. 2009;57(8):1403-10.
75. Alcantara M, Serra-Aracil X, Falco J, Mora L, Bombardo J, Navarro S. Prospective, controlled, randomized study of intraoperative colonic lavage versus stent placement in obstructive left-sided colonic cancer. World J Surg. 2011;35(8):1904-10.
76. Cheung HY, Chung CC, Tsang WW, Wong JC, Yau KK, Li MK. Endolaparoscopic approach vs conventional open surgery in the treatment of obstructing left-sided colon cancer: a randomized controlled trial. Arch Surg. 2009;144(12):1127-32.
77. Fiori E, Lamazza A, De Cesare A, Bononi M, Volpino P, Schillaci A, et al. Palliative management of malignant rectosigmoidal obstruction. Colostomy vs. endoscopic stenting. A randomized prospective trial. Anticancer Res. 2004;24(1):265-8.

78. Fiori E, Lamazza A, Schillaci A, Femia S, Demasi E, Decesare A, et al. Palliative management for patients with subacute obstruction and stage IV unresectable rectosigmoid cancer: colostomy versus endoscopic stenting: final results of a prospective randomized trial. Am J Surg. 2012;204(3):321-6.

79. Ho KS, Quah HM, Lim JF, Tang CL, Eu KW. Endoscopic stenting and elective surgery versus emergency surgery for left-sided malignant colonic obstruction: a prospective randomized trial. Int J Colorectal Dis. 2012;27(3):355-62.

80. Kronborg O. Acute obstruction from tumour in the left colon without spread. A randomized trial of emergency colostomy versus resection. Int J Colorectal Dis. 1995;10(1):1-5.

81. Pirlet IA, Slim K, Kwiatkowski F, Michot F, Millat BL. Emergency preoperative stenting versus surgery for acute left-sided malignant colonic obstruction: a multicenter randomized controlled trial. Surg Endosc. 2011;25(6):1814-21.

82. Sankararajah D, Forshaw MJ, Parker MC. Multicentre prospective randomised controlled trial of pre-operative endoluminal stenting vs. surgery in large bowel obstruction – interim analysis of short term outcomes. Colorectal diseases. 2005;7 (suppl. 1):45-143.

83. Xinopoulos D, Dimitroulopoulos D, Theodosopoulos T, Tsamakidis K, Bitsakou G, Plataniotis G, et al. Stenting or stoma creation for patients with inoperable malignant colonic obstructions? Results of a study and cost-effectiveness analysis. Surg Endosc. 2004;18(3):421-6.

84. van Hooft JE, Fockens P, Marinelli AW, Timmer R, van Berkel AM, Bossuyt PM, et al. Early closure of a multicenter randomized clinical trial of endoscopic stenting versus surgery for stage IV left-sided colorectal cancer. Endoscopy. 2008;40(3):184-91.

85. van Hooft JE, Bemelman WA, Oldenburg B, Marinelli AW, Holzik MF, Grubben MJ, et al. Colonic stenting versus emergency surgery for acute left-sided malignant colonic obstruction: a multicentre randomised trial. Lancet Oncol. 2011;12(4):344-52.

86. Chen J, Li Q, Wang C, Zhu H, Shi Y, Zhao G. Simultaneous vs. staged resection for synchronous colorectal liver metastases: A metaanalysis. International Journal of Colorectal Disease. 2011;26(2):191-9.

87. Seidensticker R, Denecke T, Kraus P, Seidensticker M, Mohnike K, Fahlke J, et al. Matched-pair comparison of radioembolization plus best supportive care versus best supportive care alone for chemotherapy refractory liver-dominant colorectal metastases. Cardiovasc. Intervent. Radiol. 2012;35(5):1066-73.

88. Martin LK, Cucci A, Wei L, Rose J, Blazer M, Schmidt C, et al. Yttrium-90 radioembolization as salvage therapy for colorectal cancer with liver metastases. Clin. Colorectal Cancer. 2012;11(3):195-9.

89. Bester L, Meteling B, Pocock N, Pavlakis N, Chua TC, Saxena A, et al. Radioembolization versus standard care of hepatic metastases: Comparative retrospective cohort study of survival outcomes and adverse events in salvage patients. J. Vasc. Intervent. Radiol. 2012;23(1):96-105.

90. Kosmider S, Tan TH, Yip D, Dowling R, Lichtenstein M, Gibbs P. Radioembolization in combination with systemic chemotherapy as first-line therapy for liver metastases from colorectal cancer. J Vasc Interv Radiol. 2011;22(6):780-6.

91. Chua TC, Bester L, Saxena A, Morris DL. Radioembolization and systemic chemotherapy improves response and survival for unresectable colorectal liver metastases. J. Cancer Res. Clin. Oncol. 2011;137(5):865-73.

92. Carter S, Martin Ii RCG. Drug-eluting bead therapy in primary and metastatic disease of the liver. HPB. 2009;11(7):541-50.

93. Fiorentini G, Aliberti C, Tilli M, Mulazzani L, Graziano F, Giordani P, et al. Intra-arterial infusion of irinotecan-loaded drug-eluting beads (DEBIRI) versus intravenous therapy (FOLFIRI) for hepatic metastases from colorectal cancer: final results of a phase III study. Anticancer Res. 2012;32(4):1387-95.

94. Vogl TJ, Gruber T, Balzer JO, Eichler K, Hammerstingl R, Zangos S. Repeated transarterial chemoembolization in the treatment of liver metastases of colorectal cancer: Prospective study. Radiology. 2009;250(1):281-9.

95. Martin RCG, Robbins K, Tomalty D, O'Hara R, Bosnjakovic P, Padr R, et al. Transarterial chemoembolisation (TACE) using irinotecan-loaded beads for the treatment of unresectable metastases to the liver in patients with colorectal cancer: An interim report. World J. Surg. Oncol. 2009;7:80.

96. Albert M, Kiefer MV, Sun W, Haller D, Fraker DL, Tuite CM, et al. Chemoembolization of colorectal liver metastases with cisplatin, doxorubicin, mitomycin C, ethiodol, and polyvinyl alcohol. Cancer. 2011;117(2):343-52.

97. Aliberti C, Fiorentini G, Muzzio PC, Pomerri F, Tilli M, Dallara S, et al. Trans-arterial chemoembolization of metastatic colorectal carcinoma to the liver adopting DC Bead(registered trademark), drug-eluting bead loaded with irinotecan: Results of a phase II clinical study. Anticancer Res. 2011;31(12):4581-7.

98. Gonzalez M, Poncet A, Combescure C, Robert J, Ris HB, Gervaz P. Risk Factors for Survival after Lung Metastasectomy in Colorectal Cancer Patients: A Systematic Review and Meta-Analysis. Ann Surg Oncol. 2012.

99. Schule S, Dittmar Y, Knosel T, Krieg P, Albrecht R, Settmacher U, et al. Long-term results and prognostic factors after resection of hepatic and pulmonary metastases of colorectal cancer. Int. J. Colorectal Dis. 2012:1-9.

100. Hirosawa T, Itabashi M, Ohnuki T, Yamaguchi N, Sugihara K, Kameoka S. Prognostic factors in patients undergoing complete resection of pulmonary metastases of colorectal cancer: a multi-institutional cumulative follow-up study. Surg. Today. 2012:1-6.

101. Gonzalez M, Robert JH, Halkic N, Mentha G, Roth A, Perneger T, et al. Survival after lung metastasectomy in colorectal cancer patients with previously resected liver metastases. World J Surg. 2012;36(2):386-91.

102. Tampellini M, Ottone A, Bellini E, Alabiso I, Baratelli C, Bitossi R, et al. The role of lung metastasis resection in improving outcome of colorectal cancer patients: Results from a large retrospective study. Oncologist. 2012;17(11):1430-8.

103. Marin C, Robles R, Conesa AL, Torres J, Flores DP, Parrilla P. Outcome of strict patient selection for surgical treatment of hepatic and pulmonary metastases from colorectal cancer. Dis. Colon Rectum. 2013;56(1):43-50.

104. Iida T, Nomori H, Shiba M, Nakajima J, Okumura S, Horio H, et al. Prognostic factors after pulmonary metastasectomy for colorectal cancer and rationale for determining surgical indications: A retrospective analysis. Ann. Surg. 2012.

105. de Cuba EM, Kwakman R, Knol DL, Bonjer HJ, Meijer GA, Te Velde EA. Cytoreductive surgery and HIPEC for peritoneal metastases combined with curative treatment of colorectal liver metastases: Systematic review of all literature and meta-analysis of observational studies. Cancer Treat Rev. 2013;39(4):321-7.

106. Cashin PH, Graf W, Nygren P, Mahteme H. Intraoperative hyperthermic versus postoperative normothermic intraperitoneal chemotherapy for colonic peritoneal carcinomatosis: a case-control study. Ann Oncol. 2012;23(3):647-52.

107. Franko J, Ibrahim Z, Gusani NJ, Holtzman MP, Bartlett DL, Zeh Iii HJ. Cytoreductive surgery and hyperthermic intraperitoneal chemoperfusion versus systemic chemotherapy alone for colorectal peritoneal carcinomatosis. Cancer. 2010;116(16):3756-62.

108. NICE. Interventional procedure overview of cytoreduction surgery followed by hyperthermic intraoperative peritoneal chemotherapy for peritoneal carcinomatosis. 2009.

109. Elias D, Lefevre JH, Chevalier J, Brouquet A, Marchal F, Classe JM, et al. Complete cytoreductive surgery plus intraperitoneal chemohyperthermia with oxaliplatin for peritoneal carcinomatosis of colorectal origin. J Clin Oncol. 2009;27(5):681-5.

110. Petrelli F, Cabiddu M, Barni S. 5-Fluorouracil or capecitabine in the treatment of advanced colorectal cancer: a pooled-analysis of randomized trials. Med Oncol. 2012;29(2):1020-9.

111. Montagnani F, Chiriatti A, Licitra S, Aliberti C, Fiorentini G. Differences in efficacy and safety between capecitabine and infusional 5-fluorouracil when combined with irinotecan for the treatment of metastatic colorectal cancer. Clin Colorectal Cancer. 2010;9(4):243-7.