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Evidence-Based Series 17-4 Version 2 REQUIRES UPDATING

A Quality Initiative of the
Program in Evidence-based Care (PEBC), Cancer Care Ontario (CCO)

Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes

The Expert Panel on Colon and Rectal Cancer Surgery and Pathology

An assessment conducted in December 2021 indicated that Evidence-Based Series 17-4 Version 2 REQUIRES UPDATING. It is still appropriate for this document to be available while this updating process unfolds. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol).

EBS 17-4 is comprised of four sections. You can access the summary and full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/566

Section 1: Guideline Recommendations (ENDORSED)
Section 2: Evidence Summary
Section 3: EBS Development Methods and External Review Process
Section 4: Document Assessment and Review

November 29, 2016

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Guideline Report History

GUIDELINE VERSION	SYSTEMATIC REVIEW		PUBLICATIONS	NOTES AND KEY CHANGES
	Search Dates	Data		
Original Version April 2008	1999-2007	Full Report	Web publication	NA
Current Version November 2016	2007-2015	New data found in section 4: Document Assessment and Review	Updated web publication	2008 recommendations ENDORSED

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Evidence-Based Series #17-4 Version 2: Section 1

Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes: Guideline Recommendations

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A Quality Initiative of Cancer Care Ontario (CCO)'s
Program in Evidence-Based Care (PEBC) and CCO's Surgical Oncology Program (SOP).
Developed by the Expert Panel on Colon and Rectal Cancer Surgery and Pathology

November 29, 2016

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2007 and 2015, and for details on how this Clinical Practice Guideline was ENDORSED.

QUESTIONS

1. What is the recommended technique and extent of surgical resection for curable colorectal cancer (CRC), including extent of bowel resection, extent of lymph node resection, and reporting requirements?
2. What is the recommended approach to processing and reporting the resected specimen, including specimen marking in the operating room, as well as processing and reporting requirements in the pathology laboratory?

TARGET POPULATION

This document applies to all patients with curable colon[1] and rectal[2] cancer in whom surgical management with radical excision is undertaken. This may include selected patients

[1] For the purpose of this document, colon cancers are defined as those that lie within the large intestine from the cecum to the top of the rectum.

[2] Rectal cancers are defined as adenocarcinomas that lie between the termination of the sigmoid colon, usually at the level of the sacral promontory, and the dentate line. The mesorectum and its enveloping mesorectal fascia

with M1 disease. This document does not apply to patients with primary cancers that are managed by polypectomy or full thickness transanal excision, patients treated for recurrent tumours, or patients undergoing surgery with palliative intent.

RECOMMENDATIONS

The recommendations have been organized under two categories: Surgical Issues and Pathology Issues. The foundation for the surgical recommendations is the Guidelines 2000 document sponsored by the National Cancer Institute (NCI) and authored by Nelson et al (1). This report reviews the evidence on surgical issues up to 1999 and provides recommendations based on the reviewed evidence. Section 2 contains the systematic review of the evidence from 1999 to 2007 that was undertaken to supplement the NCI guideline. Where evidence is lacking, the recommendations are based on the consensus of the panel. Recommendations for the pathology issues are based on a systematic review of the published literature up to 2007, as well as a review of four key papers in the field (2-5), also presented in Section 2. The outcomes of interest behind the recommendations are local recurrence, disease-free survival, and overall survival.

The following recommendations are offered by the Expert Panel on Colon and Rectal Cancer Surgery and Pathology, organized as follows:

1. Staging Definitions
2. Tumour Extent and Margin Guidelines
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     - 2.1.1 Margins of Resection: Colon
     - 2.1.2 Margins of Resection: Rectum
     - 2.1.3 Total Mesorectal Excision
     - 2.1.4 En Bloc Multivisceral Resection
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   - 2.2 Pathology
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3. Lymph Node Assessment Guidelines
   - 3.1 Surgery
     - 3.1.1 Extent of Lymphadenectomy
     - 3.1.2 Number of Lymph Nodes Assessed
   - 3.2 Pathology
     - 3.2.1 Technique of Lymph Node Examination
     - 3.2.2 Number of Lymph Nodes Assessed

1. Staging Definitions

- The TNM classification of tumours described by the American Joint Committee on Cancer (AJCC) (6) is recommended for tumour-staging definitions.

2. Tumour Extent and Margin Guidelines

- Resections and Positive Resection Margin Definitions

end at the pelvic floor or top of the puborectalis sling, while the most distal aspect of the rectum ends at the dentate line. The rectum is divided into three sections: lower rectum (0-5 cm from anal verge), mid rectum (5-10 cm from anal verge) and upper rectum (10-15 cm from anal verge). Rectal tumors are classified according to their location relative to the peritoneal reflection anteriorly, i.e., entirely above, astride or entirely below the peritoneal reflection.

- AJCC categorizes resections as R0: no residual tumour; R1: microscopic residual tumour; R2: macroscopic residual tumour.
- Presence of tumour 1 mm or less from a margin should be considered a positive resection margin.

- Surgeons must preoperatively consider the expected R status at the end of an operation. Clinical (e.g., evidence of tumour tethering or fixation on physical exam) and radiological (e.g., cross-sectional imaging with magnetic resonance imaging [MRI] or computed tomography [CT])) assessment is necessary to identify lesions that may have a threatened or involved radial margin. Patients with such a presentation should be considered for neoadjuvant therapy (See Related Guidelines).
- Close consultation between the surgeon and the pathologist is required in the assessment of margins.

2.1 Surgery

2.1.1 Margins of Resection: Colon

Key Recommendation

- Negative margins are the goal of colon resection.

Key Evidence

- The NCI Guidelines 2000 cited numerous studies demonstrating better outcome for patients with margins free of residual tumour.
- In the recent literature, one retrospective study demonstrated no significant association between proximal or distal margin lengths and local recurrence or disease-free survival.

Technical Recommendations

Technical recommendations are based on Expert Panel consensus and endorsement of the NCI Guidelines 2000 and, for recommendations for radial margins, evidence supporting en bloc resection with negative margins for adherent tumours.

Proximal and Distal Margins

- The primary determinant of the extent of bowel resection is the need for adequate removal of lymph nodes and arterial supply that is consistent with the creation of a well-vascularized anastomosis. An adequate minimum length for proximal and distal colon resection margin is 5 cm, although they are generally much greater.

Radial Margins

- Radial, non-peritonealized negative resection margins of the colon should be obtained and must be histologically free of disease (R0) to achieve a curative resection. This does not apply to surfaces of the colon where the tumour has penetrated through a free serosal surface but is not adherent to adjacent structures.
- Ideally, locally advanced adherent tumours should be diagnosed preoperatively through appropriate application of cross-sectional imaging, especially CT scanning, and should be assumed to be malignant in curative-intent operations. En bloc resection of adherent organs or parts of organs should be done where possible to obtain a R0 excision (See En Bloc Multivisceral Resection).

- The specimen must be labelled and areas of possible radial margin involvement, particularly segments not typically associated with a radial margin (e.g. transverse colon), should be marked for correct identification by the pathologist.

2.1.2 Margins of Resection: Rectum

Key Recommendation

- Negative margins are the goal of rectal resection.

Key Evidence

- The NCI Guidelines 2000 cited numerous studies demonstrating better outcome for patients with margins free of residual tumour.
- In the recent literature, retrospective and prospective studies reported decreased local recurrence rates and increased survival in patients with negative margins compared with positive margins.

Technical Recommendations for Proximal and Distal Margins

Technical recommendations are based on the Expert Panel consensus informed by the NCI Guidelines 2000 and evidence emerging in the recent literature update. No data were found to inform proximal rectal resection margin lengths. Distal margin length of 2 cm or greater and a minimally acceptable distal margin length of 1 cm were recommended by the NCI Guidelines 2000. The evidence update yielded 19 studies reporting clinical outcomes by distal margin length or distal tumour spread and provided conflicting findings for adequate distal margin length, ranging from 1 cm to 4 cm.

Proximal Margins

- The primary determinant of the extent of resection of proximal rectum is determined by technical considerations for obtaining adequate lymphadenectomy and reconstruction. The resection margin length should be a minimum 5 cm.

Distal Margins

- The main determinants of distal margin length are adequate clearance of intramural cancer spread and adequate removal of lymph nodes in pericolic fat.
- The distal margin length should be measured in the fresh, anatomically restored ex vivo condition immediately after removal.
- The distal aspect of the tumour should be marked or carefully measured at the time of initial assessment, recognizing that this may change following preoperative therapy.
- For tumours of the proximal and mid rectum, the distal margin length should be a minimum of 5 cm from the distal edge of the primary tumour in most patients to remove positive lymph nodes that are distal to the palpable leading edge of the tumour. The mesorectum and bowel edge must be transected transversely to avoid coning towards the distal resection margin and possible loss of lymph node tissue distal to the primary tumour.
- For tumours at or below the anterior peritoneal reflection, ideally a distal margin length of 2 cm in the fresh specimen should be obtained, not including the circular stapler donut. In expert hands, a negative margin of less than 2 cm can be oncologically adequate to facilitate very low colorectal re-anastomosis. A

negative distal margin must not be compromised in an effort to avoid a permanent colostomy. Please see Section 2 for a full discussion of this issue.

- Intraoperative evaluation of the distal margin by a pathologist may be beneficial but shortcomings of this procedure (e.g., false negative results) must be recognized.

Qualifying Statements regarding the shaded text above – Added to Endorsement in November, 2016

The original 2008 recommendation on distal margin length was modified by the expert panel. The wording "end of the mesorectum" was replaced with "below the anterior peritoneal reflection" to more clearly specify the anatomical location being discussed (see Section 4, *Table 9*, Modification 1 *and Impact on Recommendations*)

The original and the revisions to the recommendation are based on the expert opinion of the guideline panel. In the updated literature review (to February 2016) no new data were identified to inform the recommendation.

General

- Abdominoperineal resection (APR) is indicated for patients in whom the rectal tumour invades or very closely encroaches upon the external anal sphincter.
- The surgeon should scrupulously and systematically document details relevant to the proximal and distal margins on the operative report.
- It is common practice to submit the circular stapler donuts for histological examination; however, histology of the donuts should not be relied on to determine margin status.

Technical Recommendations for Circumferential Radial Margins

These recommendations are informed by numerous retrospective studies and case series cited in the NCI Guidelines 2000 and the updated literature search that demonstrated the importance of negative circumferential radial margins (CRM) to minimize local recurrence and increase disease-free survival and overall survival.

- A CRM is present in the mid-lower rectum, while the upper rectum has a peritonealized anterior surface and a non-peritonealized posterior radial margin similar to the ascending and descending colon.
- All rectal cancers should undergo preoperative workup to assess the extent to which the CRM is threatened. This includes pelvic CT or MRI and, for lesions within reach of the examining finger, a digital rectal exam.
- **Patients with rectal cancer should undergo a high resolution MRI for proper assessment of T and N category and predicted CRM to pre-operatively stage patients (1). Patients with Stage II or Stage III rectal cancer should be offered pre-operative chemoradiotherapy (1, 2)**
- Adherent rectal cancers should be diagnosed preoperatively and en bloc resection may be required to obtain an R0 resection in such cases (See En Bloc Multivisceral Resection).
- The technique of total mesorectal excision (TME) should be employed (See Total Mesorectal Excision).
- The CRM is positive if the tumour is located 1 mm or less from the cut edge of the specimen.

- The surgeon should scrupulously and systematically document details relevant to the CRM on the operative report.

Qualifying Statements regarding the shaded text above – Added to Endorsement in November, 2016

The original 2008 recommendation on high resolution MRI *was modified by the expert panel. The recommendation was updated to align with recommendations in EBS 17-8 and a recent systematic review (see Section 4, Table 9, Modification 2 and Impact on Recommendations)*

The original and the revisions to the recommendation are based on the expert opinion of the guideline panel. In the updated literature review (to February 2016) no new data were identified to inform the recommendation.

2.1.3 Total Mesorectal Excision

Key Recommendations

- For rectal cancer, the technique of TME using sharp dissection under direct visualization in the plane between the parietal fascia of the pelvis and the visceral fascia of the mesorectum should be performed. Careful dissection in this plane offers protection to the pelvic autonomic nerves, which run under the parietal fascia, and offers the best chance for local tumour control.

Key Evidence

- Five out of seven studies comparing TME to conventional resection reported decreased local recurrence rates in patients who underwent TME.

Technical Recommendations

Technical recommendations are based on the Expert Panel consensus informed by the technical issues highlighted in the NCI Guidelines 2000.

- The goal of surgery should be wide anatomic resection to obtain radial clearance of the primary tumour and lymphatic, vascular, and perineural tumour deposits in the mesorectum, preserving the integrity of the mesorectal fascia propria.
- There is evidence that tumours rarely extend in the bowel wall distal to their palpable edge, but deposits in lymph nodes 2-4 cm distal to the palpable edge of a tumour have been observed in a low percentage of cases.
- For tumours of the proximal and mid rectum, the distal margin length should be a minimum of 5 cm from the distal edge of the primary tumour in most patients to remove positive lymph nodes that are distal to the palpable leading edge of the tumour. The mesorectum and bowel edge must be transected transversely to avoid coning towards the distal resection margin and possible loss of lymph node tissue distal to the primary tumour.
- For tumours at or below the anterior peritoneal reflection, ideally a distal margin length of 2 cm in the fresh specimen should be obtained, not including the circular stapler donut. In expert hands, a negative margin of less than 2 cm can be oncologically adequate to facilitate very low colorectal re-anastomosis. A negative distal margin must not be compromised in an effort to avoid a permanent colostomy. Please see Section 2 for a full discussion of this issue.

- Coning-in, or breaching the visceral fascia proximal or just distal to the tumour, should be avoided in both partial and total mesorectal excision to ensure the removal of all mesorectal nodes that are up to 5 cm distal to the leading edge of the tumour.

Qualifying Statements regading the shaded text above – Added to Endorsement in November, 2016

The original 2008 recommendations on TME was modified by the expert panel. For clarification purposes, previous text was replaced by more detailed text appearing earlier in the document (see Section 4, Table 9, Modification 3 and Impact on Recommendations)

The original and the revisions to the recommendation are based on the expert opinion of the guideline panel. In the updated literature review (to February 2016) no new data were identified to inform the recommendation.

2.1.4 En Bloc Multivisceral Resection

Key Recommendations

- Locally advanced, adherent colorectal tumours should be dissected en bloc with histologically negative margins for resection to be considered adequate. If a tumour is transected at the site of local adherence, resection is not complete.

Key Evidence

- Retrospective reviews and case series demonstrated acceptable outcome in patients who underwent en bloc multivisceral resection of adherent tumours when negative resection margins were achieved.
- One large study of registry data reported improved overall survival for colon and rectal cancer patients who had multivisceral resection of locally advanced adherent colorectal cancer compared to standard resection.

Technical Recommendations

Technical recommendations are based on the Expert Panel consensus informed by the technical issues highlighted in the NCI Guidelines 2000.

- Appropriate pre-operative imaging is recommended for proper surgical planning.
- An en bloc multivisceral resection is recommended for all locally advanced tumours involving adjacent structures.
- In the uncommon event that a tumour is unexpectedly found to be adherent to other structures intra-operatively and a multivisceral resection has not been planned, then resection of the primary tumour should be avoided and a proximal stoma should be created.
- The patient should be reviewed at multidisciplinary cancer conference for further surgical planning and opinion regarding possible neoadjuvant therapy.

Qualifying Statements regarding the shaded text above – Added to Endorsement in November, 2016

The original 2008 recommendations on En Bloc Multivisceral Resection *were modified by the expert panel. The original recommendations were updated to*

reflect the recommendations outlined in EBS 17-8 "Optimization of Preoperative Assessment in Patients Diagnosed with Rectal Cancer" and to highlighted a key point that surgeons should NOT routinely be surprised by what is encountered during surgery (see Section 4, Table 9, Modification 4 and Impact on Recommendations).

The original and the revisions to the recommendation are based on the expert opinion of the guideline panel. In the updated literature review (to February 2016) no new data were identified to inform the recommendation.

2.1.5 Inadvertent Tumour Perforation

Key Recommendation

- Every effort should be made to avoid inadvertent perforation of the colon or rectum during dissection.

Key Evidence

- Several retrospective reviews and database audits demonstrated increased local recurrence and decreased survival in patients who had inadvertent perforation of the bowel.

Technical Recommendation

The technical recommendation is based on the Expert Panel consensus informed by the evidence demonstrating a worse outcome for patients with inadvertently perforated tumours.

- Inadvertent perforation should be documented in the operative report and the pathology requisition form.

2.2 Pathology

2.2.1 Margins of Resection: Colon

Technical Recommendations

Technical recommendations are based on the Expert Panel consensus informed by the technical issues highlighted in four key papers in the field (2-5), as well as pathology studies identified in the recent literature search.

Proximal and Distal Margins

- The surgeon should communicate with the pathologist regarding the orientation of the specimen.
- Proximal and distal margins should be sampled for histological examination.
- The distance of the tumour to the proximal and distal margins should be reported in the fresh state, if possible. Measurement in the fixed state must take into account the fact that shrinkage will have occurred; pinning the fresh specimen to a board, under tension, will produce less shrinkage. If the tumour is close to a margin, the distance between the tumour and the margin of concern should be reported as measured microscopically on the glass slide.

Radial Margins

- The surgeon must clearly indicate to the pathologist areas with close contact to other organs or the abdominal wall. The pathologist should be aware of the retroperitoneal margin that exists in certain locations (e.g., proximal ascending colon and descending colon).

- The radial margins of the resected specimen should be inked and sectioned.
- The radial margin distance must be reported. The radial margin should be reported as positive if tumour is located 1 mm or less from the inked nonperitonealized surface of the specimen.

2.2.2 Margins of Resection: Rectum

Technical Recommendations

Technical recommendations are based on the Expert Panel consensus informed by the technical issues highlighted in four key papers in the field (2-5), as well as pathology studies identified in the recent literature search.

Proximal and Distal Margins

- Proximal and distal margins should be sampled for histological examination.
- Pathologists should pay close attention to mesorectal soft tissue, in addition to the mucosa, when assessing the distal margin.

Circumferential Radial Margins

- All rectal cancer specimens should be assessed grossly by the pathologist using the method developed by Quirke (7).
- The mesorectal tissue that constitutes the CRM, including all non-peritonealized bare areas anteriorly and posteriorly, should be inked. The specimen should be fixed with the tumour segment unopened 5 cm above and below the proximal and distal edges of the tumour, respectively, and a gauze wick placed into the unopened segment to facilitate fixation. Following at least 48 hours of fixation, the segment with the tumour should be sliced into transverse sections. The relationship of the tumour to the CRM must be carefully assessed.
- The CRM distance must be reported. The CRM is positive if the tumour is located 1 mm or less from the margin; this includes tumour cells within a lymph node, vein, or nerve, as well as direct tumour extension.
- Note that tumours of the upper rectum have a peritonealized anterior surface and a non-peritonealized posterior radial margin similar to the ascending and descending colon.

Serosal Penetration

- Involvement of the serosa by tumour (pT4a) is not equivalent to involvement of the radial margin by tumour (although there are circumstances in which an advanced tumour has penetrated the serosa and is adherent to adjacent soft tissue).
- Documentation of serosal involvement by tumour requires careful gross and microscopic examination and may require extensive sampling and/or serial sectioning of sampled tissue blocks.
- Serosal penetration is defined as occurring when any of the following criteria are met:
  - Tumor present at the serosal surface
  - Free tumor cells on the serosal surface (visceral peritoneum) with underlying erosion/ulceration of mesothelial lining, mesothelial hyperplasia and/or inflammatory reaction
  - Perforation in which the tumor cells are continuous with the serosal surface through inflammation

- The significance of tumors that are <1 mm from the serosal surface and accompanied by serosal reaction is unclear, with some but not all studies indicating a higher risk of peritoneal recurrence. Multiple level sections and/or additional section of the tumor should be examined in these cases. If the serosal involvement is not present after additional evaluation, the tumor should be assigned to the pT3 category.
- Serosal penetration is an independent prognostic variable and has a strong negative impact on prognosis. The frequency of distant metastasis is greater in cases with perforation of the visceral peritoneum compared to cases with direct invasion of adjacent organs or structures without perforation of the visceral peritoneum, and the median survival time following surgical resection for cure is shorter for patients with pT4b tumours compared to those with pT4a tumours (with or without distant metastasis).

Qualifying Statements regarding the shaded text above – Added to Endorsement in November, 2016

The original 2008 recommendations on serosal penetration were modified by the expert panel. In the first bullet point pT4b was replaced by pT4a to reflect changes in the CAP (see Section 4, Table 9, Modification 5 and Impact on Recommendations). Bullet points 3 and 4 were also updated to align with the recent publication by CAP (based on the AJCC/UICC TNM 7th edition) (see Section 4, Table 9, Modification 6 and Impact on Recommendations)

The original and the revisions to the recommendation are based on the expert opinion of the guideline panel. In the updated literature review (to February 2016) no new data were identified to inform the recommendation.

3. Lymph Node Assessment

3.1 Surgery

3.1.1 Extent of Lymphadenectomy

Technical Recommendations

Technical recommendations are based on Expert Panel consensus informed by the technical issues highlighted in the NCI Guidelines 2000 and evidence suggesting no significant benefit for high arterial ligation over low ligation.

- The goal of colon resection is the removal of the segment of the bowel with the tumour and all the mesentery containing the blood supply and the lymphatics at the level of the primary feeding arterial vessel (e.g., ileocolic, middle colic, left colic, inferior mesenteric artery, and all their branches). When the primary tumour is equidistant from two feeding vessels, both vessels should be excised close to their origin. More radical lymphadenectomy is not supported by available evidence.
- In curative operations, lymph node resection should be en bloc with the main vessel supplying the involved segment of colon.
- Lymph nodes at the origin of feeding vessels (apical nodes) should be included when feasible and tagged for pathologic evaluation.
- Appropriate proximal lymphatic resection and TME of the rectum provides adequate lymphadenectomy for rectal cancer. There is a lack of evidence about the benefit of ligating the inferior mesenteric artery (IMA) at its origin at the aorta, although

nodes should be removed as high as technically possible to allow for complete removal of clinically involved nodes. Suspicious periaortic nodes should be biopsied for staging.
- The surgeon should report the named vessel and lymph node basin resected en bloc. Clinically suspicious nodes should be reported, and any lymph nodes outside the resected basin that are suspicious and biopsied should be reported.

3.1.2 Number of Lymph Nodes Assessed

Technical Recommendations
Technical recommendations are based on Expert Panel consensus and an endorsement of the recommendation in the NCI Guidelines 2000 and are informed by evidence from a published systematic review and a review of the recent literature indicating an improved survival the greater the number of lymph nodes evaluated.

- In general, and particularly for T3/4 neoplasms, a minimum of 12 lymph nodes should be examined to adequately stage colon and rectal cancer, although an effort should be made to identify all lymph nodes. Importantly, the 12-lymph node target may not be achievable in patients with T1 or T2 tumours and/or some patients who receive neoadjuvant therapy.

3.2 Pathology

3.2.1 Technique of Lymph Node Examination

Technical Recommendations
Technical recommendations are based on Expert Panel consensus informed by four key papers in the field (2-5) and pathology studies identified in the recent literature search.

- Pericolic fat should be carefully examined using inspection and palpation. For colonic tumours, examination should occur after pericolic fat has been stripped off the colon and after any appropriate sections have been taken to evaluate the radial margin.
- In the case of rectal tumours, the cross-sectioned slices are examined for lymph nodes, taking care not to double count lymph nodes that might be present in more than one cross-sectional slice.
- All lymph nodes present must be examined histologically. Nodal examination must not stop once 12 nodes have been identified. It is particularly important to find small lymph nodes close to the underlying bowel wall. If less than 12 lymph nodes are found, consideration should be given to placing the fat into a lymph node highlighting solution.
- All grossly negative or equivocal lymph nodes must be submitted in their entirety. However, if a node is grossly positive, partial submission is acceptable.

3.2.2 Number of Lymph Nodes Assessed

Technical Recommendations
Technical recommendations are based on Expert Panel consensus informed by four key papers in the field (2-5) and pathology studies identified in the recent literature search.

- The pathology report should indicate the number of positive lymph nodes as well as the total number of nodes assessed.

- The number of lymph nodes involved by micrometastases (tumour deposits >0.2 mm but <2.0 mm) and isolated tumour cells (ITCs) (single cells or clusters 0.2 mm or less) should be reported separately from typical (macro) metastases. In cases where there are typical (macro) metastases, micrometastases or ITCs do not change the pN stage. Micrometastases without typical (macro) metastases detected by routine histology are reported as pN1, whereas immunohistochemical detection is reported as pN0. The presence of ITCs does not change the pN classification. Note that special measures to detect micrometastases or ITCs (e.g. multiple tissue levels of paraffin blocks, immunohistochemistry [IHC], polymerase chain reaction [PCR]) are not recommended for the routine examination of regional lymph nodes.
- Discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor. (based on the AJCC/UICC TNM 7th edition).

Qualifying Statements regarding the shaded text above – Added to Endorsement in November, 2016

The original 2008 recommendation on lymph node assessment was modified by the expert panel. The recommendation was updated to align with the recent publication by CAP (based on the AJCC/UICC TNM 7th edition) (see Section 4, Table 9, Modification 7 and Impact on Recommendations)

The original and the revisions to the recommendation are based on the expert opinion of the guideline panel. In the updated literature review (to February 2016) no new data were identified to inform the recommendation.

RELATED GUIDELINES

- Evidence-Based Series #17-8: Optimization of preoperative assessment in patients diagnosed with rectal cancer, January 2014.
- Practice Guideline Report #2-20-2: Laparoscopic Surgery for Cancer of the Colon, September 2005
- Practice Guideline Report #2-9: Follow-up of Patients with Curatively Resected Colorectal Cancer, January 2004
- Diagnostic Imaging Recommendations Report: Cross-sectional Imaging in Colorectal Cancer, April 2006
- Multidisciplinary Care Conference Standards, June 2006
- Evidence-Based Series: #2-29 Version 2: Adjuvant Systemic Chemotherapy for Stage II and III Colon Cancer Following Complete Resection, September 2015
- Evidence-Based Series #2-4 Version 2 Preoperative or Postoperative Therapy for the Management of Patients with Stage II or III Rectal Cancer, November 2013

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Evidence-Based Series #17-4 Version 2: Section 2

Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes: Evidentiary Base

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These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2007 and 2015, and for details on how this Clinical Practice Guideline was ENDORSED.

QUESTIONS

1. What is the recommended technique and extent of surgical resection for curable colorectal cancer (CRC), including extent of bowel resection, extent of lymph node resection, and reporting requirements?
2. What is the recommended approach to processing and reporting the resected specimen, including specimen marking in the operating room, as well as processing and reporting in the pathology laboratory?

TARGET POPULATION

This document applies to all patients with curable colon and rectal cancer in whom surgical management with radical excision is undertaken. This may include selected patients with M1 liver or lung metastases. This document does not apply to patients with primary cancers that are managed by polypectomy or full thickness transanal excision, patients treated for recurrent tumours, or patients undergoing surgery with palliative intent.

INTRODUCTION

In 2007, an estimated 20,800 people will be diagnosed with colorectal cancer per year in Canada, with approximately 7,800 of these cases occurring in Ontario (1). Nationally, colorectal cancer is the third most common cancer site in both males and females, following

prostate and lung cancer in males and breast and lung cancer in females. Colorectal cancer is the second most common cause of cancer death in Canada, following lung cancer, with an estimated 8,700 deaths in Canada and approximately 3,250 deaths in Ontario (1).

Surgical resection of the disease site remains the cornerstone of curative management of colorectal cancer. Pathological assessment is inextricably linked to surgical management and communicates the tumour extent (T-stage) and the absence or presence and degree of lymph node metastases (N-stage). In addition, pathological assessment defines, among other parameters, the quality of surgical management, including critical information on the completeness of resection (R-stage). This information, together with preoperative, intraoperative, and postoperative assessment for metastases (M-stage) is essential for accurate staging, treatment planning, and prediction of prognosis.

Surgical and pathological management and assessment are complemented by preoperative and/or postoperative radiological assessment and medical and radiation oncology evaluation and/or management. Moreover, a host of other professionals working in close communication, with co-coordinated collaboration, are often required to achieve optimal results.

The National Cancer Institute (NCI) sponsored an expert panel to review the literature to 1999 and formulate guidelines on resection techniques for colon and rectal cancer surgery. The NCI Guidelines 2000 (2) forms the basis for the surgical components of this document. A decision was made to adopt the evidence cited in the NCI Guidelines 2000 as a summary of the available evidence published before 1999 and perform updated searches of the literature for selected topics considered relevant for this CCO document. The quality of the NCI document was evaluated using the Appraisal of Guidelines Research & Evaluation (AGREE) Instrument, and results are reported in Appendix 4. Recommendations for pathology techniques and reporting requirements are based on publications by Quirke et al (3), Burroughs et al (4), and Ludeman et al (5) and are in accordance with pathology reporting protocols developed by the College of American Pathologists (CAP) (6). In addition, studies on pathology methods identified in the systematic search of recent literature are included in this review.

This document focuses narrowly on the surgical and pathological considerations for the radical resection of colorectal cancer and refers the reader to other CCO and/or PEBC documents where appropriate, for details on complementary aspects of optimal multidisciplinary care. The document is structured around sections on critical surgical and pathological performance markers, related in an evidence-based manner to patient oncological outcome.

METHODS

The evidence-based series (EBS) guidelines developed by Cancer Care Ontario's Program in Evidence-Based Care (PEBC) use the methods of the Practice Guidelines Development Cycle (7). For this project, the core methodology used to develop the evidentiary base was the systematic review. Evidence was selected and reviewed by members of the CCO Expert Panel on Colon and Rectal Cancer Surgery and Pathology and two methodologists.

The systematic review is a convenient and up-to-date source of the best available evidence on surgical and pathological quality performance in radical surgery for colon and rectal cancer. The body of evidence in this review is primarily comprised of retrospective chart reviews and database audits. The systematic review and companion recommendations are intended to promote evidence-based practice in Ontario, Canada. The PEBC is supported

by the Ontario Ministry of Health and Long-Term Care through Cancer Care Ontario. All work produced by the PEBC is editorially independent from its funding source.

Literature Search Strategy

The MEDLINE database (1999 to February week 1, 2007) was systematically searched for evidence, using the following Medical Subject Heading (MeSH) terms "colonic neoplasms/su,pa", "rectal neoplasms/su,pa", "colorectal neoplasms/su,pa", "intestinal perforation", and "lymph node excision". These MeSH terms were combined with text words for margins of resection, en bloc multivisceral resection, inadvertent tumour perforation, total mesorectal excision, and lymphadenectomy. The results were limited by using search words for the following publication types: randomized controlled trials, prospective studies, case-series, retrospective studies, and pathology studies. Personal reprint files were also searched and citations from retrieved articles were reviewed.

Inclusion Criteria (Table 1)

Studies were considered eligible for inclusion if they were:

1. Randomized controlled trials (RCTs), non-randomized prospective studies, case-series or retrospective reviews reporting relevant outcome data for patients undergoing surgical resection for primary colon or rectal cancer.
2. Syntheses of evidence in the form of systematic reviews or meta-analyses.
3. Published in the English language.

Exclusion Criteria (Table 1)

Studies were not considered for inclusion if they were:

1. Case reports or narrative review articles.
2. Studies of patients undergoing surgical resection for recurrent colon or rectal cancer.

Table 1. Inclusion criteria and outcomes of interest.

Topic	Inclusion Criteria	Outcomes of Interest
Tumour extent and margin guidelines		
Colon and rectum margins of resection	Comparative outcome data for proximal, distal, radial and circumferential margin status	LR, DFS, OS
Total mesorectal excision	TME vs conventional surgery without preoperative radiotherapy	LR
En bloc multivisceral resection	Studies reporting outcome data for patients undergoing en bloc resection	Margin status, LR, DFS, OS
Inadvertent tumour perforation	Perforated vs not perforated	LR, DFS, OS
Lymph node assessment		
Lymphadenectomy	High versus low ligation	DFS, OS
	# of lymph nodes analyzed	DFS, OS
	Occult tumour cells in lymph nodes	DFS, OS

Notes: DFS, disease-free survival; LR, local recurrence; OS, overall survival; TME, total mesorectal excision; vs, versus.

Synthesis of Data

Data have been summarized in tables in Appendix 1. No data were pooled in a meta-analysis due to the absence of randomized data and the heterogeneity of the included studies in terms of patients, surgery and pathology procedures, measurement of outcomes, and choice of outcome comparisons.

RESULTS

Literature Search Results

The following results (Table 2) were obtained from the systematic literature review:

Table 2. Literature search results (1999 to February week 1, 2007)

Topic	Number of MEDLINE hits	Number ordered for full-publication review	Number of articles included in this report	Table #
Tumour extent and margin guidelines				
Colon and rectum margins of resection				
R status	504 total	83 total	8	3
Proximal and distal margins			15	4
Radial/circumferential margins			20	5
Pathology methods			7	-
Total mesorectal excision	344	33	8	6
En bloc multivisceral resection	297	65	30	7
Inadvertent tumour perforation	136	6	5	8
Lymph node assessment				
Lymphadenectomy	884 total	123 total		
Extent of lymphadenectomy			2	9
# of lymph nodes			17[a]	10
Occult tumour cells in lymph nodes			4[b]	11
Pathology methods			6	-

Notes:

a. 17 additional studies were included in a systematic review (8) and are not reported individually in Table 10.
b. 38 additional studies were included in a systematic review (9) and are not reported separately in Table 11.

Study Quality

In general, the quality of evidence for studies identified in the literature search was poor. No RCTs have been performed to specifically address the extent of tumour resection, resection margins, extent of lymphadenectomy, or lymph node evaluation techniques. For this reason, the evidence currently available on which recommendations are based is limited to retrospective reviews of charts or databases, case series, subgroup analyses of RCTs, and non-randomized prospective studies. In evaluating the evidence, it is important to take the inherent limitations of these study designs into consideration. The available studies were often small and underpowered to detect statistically significant differences in relevant outcomes between patient subgroups. As these studies were not controlled, confounding factors such as adjuvant therapy and patient baseline characteristics could often not be taken into account. Statistical methods used to determine the effect of surgical and pathological variables on outcome varied between studies and are therefore difficult to compare. In addition, details regarding pathological techniques for the assessment of resection margins and evaluation of lymph nodes were frequently not reported.

The NCI Guidelines 2000 (2) were assessed for quality independently by three reviewers, using the AGREE instrument. While the guideline scored well for the Scope and Purpose and Clarity and Presentation domains, it scored lower for the Stakeholder Involvement, Applicability, and Editorial Independence domains. These lower scores were due in part to the fact that patients' views and preferences were not sought, the guideline was not piloted among target users, potential costs and barriers to implementation were not discussed, and editorial independence from the funding body and conflicts of interest were not explicitly stated. Problems in the domain of Rigour of Development included the lack of details regarding strategies used to search for the evidence, unclear criteria for including or excluding evidence, no description of external review of the guideline by experts not involved in developing the guideline, and no procedure reported for updating the guideline. Despite these issues, the authors did not feel that these shortcomings should preclude the use of this guideline as a basis for the current update of the evidence.

Tumour extent and margin guidelines ("T" issues)

Extent of Resection (R status)

NCI Guidelines 2000

The NCI Guidelines 2000 (2) adopted the definitions for extent of resection ("R" status) recommended by the AJCC Prognostic Factors Consensus Conference Colorectal Working Group (10). R0 is defined as no residual tumour, R1 is defined as microscopic residual tumour, and R2 is defined as macroscopic residual tumour. If surgical or pathological reports describe non-en bloc resection, positive radial or bowel margins, residual lymph node disease, or incomplete staging, the resection is not considered complete.

Recent Evidence

A literature search of the evidence since the publication of the NCI Guidelines 2000 (2) identified eight studies that reported outcome data as a function of overall margin status or "R" stage (11-18), including four single-centre retrospective reviews (11-13,15), one multicentre retrospective review (16), one prospective cohort (14), one retrospective analysis of pathology specimens from a phase II study (17), and one national database audit (18) (Table 3). Six studies included only patients with rectal tumours (11,12,15-18), and two included patients with both rectal and colon tumours (13,14). Only four studies reported details on the method of margin assessment and criteria for margin positivity (11,12,14,18).

Where data were available, all studies demonstrated increased local recurrence rates and decreased survival for patients who had positive resection margins (R1 or R2) compared to patients with negative resection margins (R0), although some studies did not report statistical comparison data or were small and unable to detect a statistically significant difference in outcome between groups. A large retrospective review of 2,452 colorectal cancer patients by Staib et al (13) reported that five-year survival was 77.6% in patients with R0 resections, 45.7% in patients with R1 resections, and 3.8% in patients with R2 resections, suggesting that the aim of surgery should be to achieve an R0 resection. A national database audit by Eriksen et al (18) reported local recurrence in 18% of 348 rectal cancer patients with R0 resections and 40% of 159 patients with R1 resections, although no statistical comparison data were reported.

Colon: Margins of Resection

Proximal and Distal Margins

NCI Guidelines 2000

Proximal and distal resection margins of the colon are closely linked to the extent of lymphadenectomy, and the length of colon removed is determined by the removal of the arterial supply of the colon. The NCI Guidelines 2000 (2) cited two studies supporting the resection of a minimum of five to 10 cm on either side of the tumour in order to remove the epicolic and paracolic lymph nodes and minimize anastomotic recurrences. One retrospective analysis of pathologic specimens and one study on mapping of lymphatic metastases indicated that the length of ileum resected did not appear to affect local recurrence in tumours of the ascending colon, supporting the recommendation that a minimum length of ileum should be removed to avoid malabsorption syndromes.

Recent evidence

Only one study was identified that provided data for proximal and distal resection margins in patients with tumours of the colon (19) (Table 4). In a multivariate analysis, this retrospective review by Read et al reported no significant association between the length of proximal or distal margin and local recurrence or disease-free survival.

Radial/Circumferential Margins

The NCI Guidelines 2000 (2) did not cite studies on radial or circumferential margins in patients with tumours of the colon, and no relevant studies were identified in a search of the literature published since 1999.

Rectum: Margins of resection

Proximal and Distal Margins

NCI Guidelines 2000

Proximal and distal resection margins of the rectum are influenced by the level of vascular ligation and excision of the mesorectum. The NCI Guidelines 2000 (2) indicated that the recommendation of a 5 cm margin is based on a study that demonstrated that intramural extension occurred in an estimated 12% of cases. Four studies were cited that showed distal intramural spread to be rare and found beyond 1 cm in 4% to 10% of cases. One of these studies reported that distal spread beyond 1.5 cm was usually observed in poorly differentiated tumours and prognosis was poor regardless of distal resection margin length. Four studies demonstrated acceptable survival and local recurrence with a distal resection margin at least 2 cm, and two of these studies indicated that a 1 cm distal margin might be adequate. One study was cited to support the statement that a negative margin might be adequate with preoperative radiotherapy and chemotherapy.

Recent evidence

A search of the literature published since 1999 identified 14 studies of distal resection margin length in patients with rectal tumours (12,20-32) (Table 4). Four studies did not report any details on the method of margin assessment or criteria for margin positivity (21,25,27,32). No studies provided relevant outcome data as a function of proximal resection margin length.

Eight studies were identified that compared outcomes for distal margin length less than 2 cm versus greater than 2 cm (20-22,26-29,31). Of the four largest studies (20,22,27,31), two reported no significant difference in local recurrence rates between distal margins less than versus greater than 2 cm (20,22), one reported significantly increased five-year local recurrence rates in patients with margins less than 2 cm (17.2% versus [vs] 5.4%; $p<0.001$) (27), and one reported increased overall survival in patients with margins less than 2 cm (85% vs 70%; $p=0.025$) (31).

Five studies were identified that compared outcomes for distal margin length less than 1 cm versus greater than 1 cm (12,22,24,26,32). A large retrospective series by Bokey et al (22) reported increased five-year local recurrence in patients with margins less than 1 cm compared with greater than 1 cm (27.2% vs 9.9%; p=0.01) and another study (32) reported similar results at three years (16% vs 7%; p=0.014). The other studies that reported results for this comparison were small and likely underpowered to detect a difference between groups (12,24,26). No studies reported comparative overall survival data.

Two retrospective studies provided further data for specific margin length categories (23,25). Bufalari et al reported local recurrence-free survival data for 73 patients: 43% for distal margins less than or equal to 1 cm, 100% for 1 to 2 cm, 89% for 2 to 4 cm, and 93% for greater than 4 cm (p=0.0002) (23). No significant difference in overall survival was reported. In an analysis of 352 patients, Stocchi et al reported no significant difference in local recurrence or overall survival between patients with distal margin lengths less than 1 cm, between 1 and 2 cm, and greater than 2 cm (25).

Radial/Circumferential Margins

NCI Guidelines 2000

The NCI Guidelines 2000 (2) reported that numerous studies, including the landmark 1986 study by Quirke et al (33), demonstrated the importance of pathological assessment of radial and circumferential resection margins and the association between positive margins and increased local and distal treatment failure rates. Three studies were cited that reported local recurrence rates ranging from 29% to 85% in margin-positive cases and 3% to 10% in margin-negative cases. An additional study was cited that indicated a clinically significant relationship between disease-free and overall survival and margin involvement.

Recent evidence

A review of the literature published since 1999 identified twenty studies reporting relevant outcome data as a function of radial or circumferential resection status in patients with rectal tumours (24,29,31,32,34-48) (Table 5). Nine papers considered margins to be involved if a tumour was present within 1 mm of the cut edge (31,37-41,45-47), while one study considered margins to be involved if a tumour was present within 2 mm (29). Six studies did not provide details on the method of radial or circumferential margin assessment or criteria for margin positivity (25,32,34-36,48).

Fifteen studies compared positive or involved radial or circumferential margins to negative margins (29,31,32,35-40,42,44-48). Of the nine studies that reported statistical comparison data for local recurrence (29,32,37,39,40,42,44,46,48), seven reported significantly decreased local recurrence rates in patients with uninvolved radial or circumferential margins (37,39,40,42,44,46,48). A retrospective review by Wibe et al of 686 patients reported local recurrence in 5% of patients with negative circumferential margins and 22% of patients with positive margins (39). Another retrospective analysis of 586 patients by Birbeck et al reported local recurrence in 15% of patients with negative margins compared with 56% of patients with positive margins (40). All four of the studies that reported statistical comparison data for disease-free survival demonstrated improved outcome for patients with negative radial or circumferential margins (42,46,47,31). Of the ten studies that reported statistical comparison data for overall survival (29,31,35,36,38,40,42,44,47,48), nine reported significantly improved survival in patients with negative radial or circumferential margins compared to those with positive margins (29,31,36,38,40,42,44,47,48). One retrospective analysis of 586 patients reported overall survival of 79% in patients with negative circumferential margins compared with 40% in

patients with positive margins ($p<0.0001$) (40). An analysis of 656 patients from the control arm of a randomized trial reported a two-year survival of 90% in patients with negative circumferential margins compared with 67.9% in patients with positive margins (38).

Several studies provided outcome data for more specific categories of circumferential margin length (25,34,38-41), two of which were based on the analysis of patients from the same RCT (38,41). Nagtegaal et al reported two-year local recurrence in 16.4% of patients for margins up to 1 mm, 14.9% for 1 to 2 mm, and 10.3% for 2 to 5 mm (38). Two-year overall survival was 69.7% for margins up to 1 mm, 84.8% for 1 to 2 mm, and 87.0% for 2 to 5 mm. Based on these data, Nagtegaal et al recommended that minimum circumferential margin length should be 2 mm rather than 1 mm. Marijnen et al reanalyzed data from the same RCT, but included patients who received preoperative radiotherapy and reported two-year local recurrence in 13.1% for margins up to 1 mm, 8.5% for 1 to 2 mm, and 3.3% for greater than 2 mm (41). A graph included in the report by Birbeck et al (40) showed a high local recurrence rate for patients with circumferential margins less than 1 mm and low local recurrence rate for patients with margins between 1 and 2 mm.

Pathology

Seven pathology studies were identified that were relevant to the discussion of colon or rectal resection margins (49-55). Goldstein et al (55) examined 26 resected sigmoid and rectal specimens for organ shrinkage after removal and fixation. On average, specimens shrank 40% of their original in vivo length after being removed and left unfixed for 10 to 20 minutes and 57% after fixation overall. The study concluded that margin measurement must be performed immediately after the specimen is removed from the patient in order to be precise. Six studies were identified that examined regional spread of tumour cells to determine adequate resection margins (49-54). One study reported that distal intramural spread greater than 1 cm has poor prognosis regardless of excision margin length and status (50). One study reported distal mesorectal spread in four of 31 specimens with distance ranging from 1 to 3.5 cm (53). Based on observations of tumour spread, three studies recommended distal mesorectal clearance of 4 cm (49,51,53), while one reported that 3 cm may be adequate (54). One study recommended a 1.5 cm distal margin for the rectal wall (51), one recommended 2 cm (52), one recommended 3 cm (54), and one recommended 4cm (53).

Total Mesorectal Excision

NCI Guidelines 2000

The goal of total mesorectal excision is to sharply dissect the lymphovascular, fatty, and neural tissue that surrounds the rectum, under direct visualization of the mesorectal plane. Two studies were cited by the NCI Guidelines 2000 (2) that demonstrated the presence of tumour deposits in the mesorectum remote from the primary tumour and a strong correlation between the extent of mesorectal tumour spread and cancer outcomes. Five studies were cited that reported increased failure rates in patients treated for local disease whose lateral resection margins were positive for disease, demonstrating the importance of radial clearance techniques. One study reported that most failures are extrarectal rather than anastomotic, and four studies were cited that reported low rates of local recurrence in patients who underwent mesorectal excision. Two studies of mesorectal deposits in pathological specimens suggested that mesorectal clearance of at least 4 cm distal to the tumour should be sufficient.

Recent evidence

The literature review identified eight studies reporting local recurrence data for comparisons between TME and conventional resection (43,88-94) (Table 6). One study was a prospective series with retrospective control (43), one was a comparison between two RCTs (93), one was an audit of a national prospective database (92), and five were retrospective reviews (88-91,94). Local recurrence ranged from 6% (92) to 12% (90) in patients who underwent TME versus 12% (92) to 30% (43) in patients who underwent conventional resection. Of the seven studies that provided statistical comparisons between TME and conventional resection (43,88,89,91-94), five reported significantly decreased local recurrence in patients who underwent TME (43,91-94).

En Bloc Multivisceral Resection

NCI Guidelines 2000

Resection is considered complete if tumours adherent to adjacent organs are resected en bloc with no histological involvement of resection margins. The NCI Guidelines 2000 (2) reported that colorectal tumours are adherent to adjacent structures in 15% of cases and most often involve the uterus, adnexa, posterior vaginal wall, and urinary bladder. Tumour adhesion to adjacent structures can be a result of inflammatory processes or malignant invasion. Seven studies were cited that reported incidence of histologically proven malignant adhesions in 49% to 84% of cases. Eight studies were cited that reported improved survival for patients whose adherent tumours were resected en bloc compared to those whose adhesions were surgically separated (five-year survival 61% vs. 23% in one study), and two studies reported decreased recurrence rates for patients who underwent en bloc resections (local recurrence 36% vs 77% in one study). The NCI Guidelines 2000 (2) reported that, although partial or total removal of the urinary bladder as part of the en bloc resection is associated with increased morbidity, such procedures were shown in one study to increase survival when resections margins were negative for tumour.

Recent evidence

The search of the recent literature identified 30 studies reporting outcome data for patients who underwent en bloc resection of adherent tumours (25,56-84), the majority of which were retrospective reviews of databases or charts (Table 7). Studies were heterogeneous with respect to organs involved by tumour, extent of surgical resection, procedures ranging from partial resection of a single adjacent organ to total pelvic exenteration, and percentage of patients with negative margins following resection. Sixteen studies included only patients with rectal tumours (25,56,60,64,66-72,76-79,83), four included only patients with colon tumours (59,65,74,82), and 10 included patients with both colon and rectal tumours (57,58,61-63,73,75,80,81,84).

Local recurrence in patients who underwent en bloc resection of adherent tumours was reported in 16 studies (25,56,60,63,64,67-69,71-73,76,78,79,83,84) and ranged from 0% (67) to 45% (83). Statistical comparisons against standard resection were reported in only two studies (25,83), and neither was able to detect a significant difference in local recurrence between groups. Disease-free survival was reported in six studies (61,71,75-77,82), five of which reported five-year results for patients undergoing en bloc resection for adherent tumours, ranging from 49% (61) to 66.8% (75). Only one study provided statistical comparisons for disease-free survival between en bloc resection and standard resection (75), and no significant difference was detected. Five-year overall survival was reported in 19 studies (25,57,58,60, 62,64-66,68,70,72,74-76,79-81,83,84) and ranged from 31.2% (58) to 76.6% (75) for patients who underwent en bloc resection. Three studies reported five-year

overall survival separately by surgical margin status (57,74,84), ranging from 51% (57) to 61% (84) in patients with negative margins and from 0% (57,74) to 17% (84) in patients with positive margins. Six papers reported results separately for en bloc versus standard resection (25,58,75,76,81,83), and statistical comparisons were performed in four (25,75,81,83). One study demonstrated that multivisceral resection was independently associated with improved overall survival among both colon (HR=0.89; 95%CI, 0.83 to 0.96) and rectal (HR=0.81; 95% CI, 0.70 to 0.94) cancer patients compared to standard resection (81).

Inadvertent Tumour Perforation

NCI Guidelines 2000

The NCI Guidelines 2000 (2) reported that the incidence of inadvertent perforation during surgery has been reported in 7.7% to 25.6% of cases. Four retrospective studies were cited that demonstrated a statistically significant reduction in five-year survival and an increase in local recurrence for patients with inadvertent perforations. One of these studies further demonstrated that perforation at the site of the tumour had a greater impact on survival and local recurrence than perforation at a site remote from the tumour.

Recent evidence

Five studies published since 1999 were identified that reported outcome data for patients with and without inadvertent bowel perforation (25,44,85-87) (Table 8). All five studies included only patients with rectal cancer. Two were single-centre audits of prospective databases (85,86), one was a retrospective review (25), and two were audits of a Norwegian national prospective database (44,87). Of the two Norwegian database audits, one included patients who underwent Hartmann's resection (87), while the other included only patients who underwent anterior resection or abdominoperineal resection (44).

The incidence of inadvertent perforation ranged from 2.6% (85) to 9% (44). In patients with perforation, local recurrence ranged from 7% (85) to 28.8% (87), while local recurrence occurred in 8% (85) to 16% (25) in patients without perforation. A statistically significant increase in local recurrence rate was reported for patients with inadvertent perforation in three studies (44,86,87), while one study was not able to detect a significant difference between patients with and without perforation (25). Of the three studies that reported statistical comparisons for overall survival data (25,44,87), the two studies of the Norwegian national database reported a statistically significant decrease in survival for patients with inadvertent perforation (44,87).

Lymph Node Assessment ("N" Issues)

Level of Ligation

NCI Guidelines 2000

The NCI Guidelines 2000 (2) identified one randomized trial assessing radical lymphadenectomy for left-sided colon cancer, with no benefit for wider lymphadenectomy being reported. Five retrospective studies were cited that reported conflicting results on the value of extended lymphadenectomy. The reports of one study suggested that the status of the apical node might have prognostic significance. The NCI Guidelines 2000 (2) identified several studies supporting the recommendation that the level of proximal vascular ligation be the origin of the primary feeding vessel. One multicentre RCT showed no significant difference in long-term survival between left colectomy with ligation of the inferior mesenteric artery (IMA) and segmental colectomy with ligation of the primary feeding vessel. A large series was cited that showed increased survival with high IMA ligation for patients with stage II rectal cancer but not for patients with stage III disease. An additional study

suggested that high ligation resulted in more accurate staging but not increased survival. One study reported that metastases beyond an uninvolved sentinel lymph node were present in only 5% of cases. The NCI Guidelines 2000 (2) reported that there were no controlled trials demonstrating a benefit for extended lateral pelvic lymph node dissection.

Recent evidence

Two retrospective reviews comparing outcome for patients with high versus low arterial ligation were identified in the recent literature (35,107) (Table 9). One study reported no significant benefit for high ligation on overall survival (35), and one study reported no significant benefit for high ligation on disease-free survival (107).

Number of Lymph Nodes Evaluated

NCI Guidelines 2000

One study was cited by the NCI Guidelines 2000 (2) to support the recommendation that at least 12 lymph nodes negative for disease must be examined to achieve greater than 90% accuracy in staging.

Recent evidence

A systematic review by Chang et al (8) of studies published from 1990 to 2006 reporting survival data for patients who underwent curative resection of colon cancer as a function of the number of lymph nodes evaluated was identified. Seventeen studies, including two secondary analyses of multicentre RCTs, five population-based observational studies, and 10 single-institution retrospective cohort studies, were included in the systematic review. These studies were heterogeneous with respect to quality, methodology, and threshold numbers of lymph nodes used in comparisons (range six to 40 lymph nodes), thus precluding quantitative pooling of data or determination of a minimum number of lymph nodes to be evaluated for optimal survival results. Eleven of the seventeen studies included patients with both colon and rectal cancer, and separate results by disease site were not available. Sixteen of the 17 studies reported improved survival the greater the number of lymph nodes evaluated in patients with stage II colon cancer, and four of six studies reported improved survival in patients with stage III colon cancer.

Seventeen additional studies reporting overall or disease-free survival data for patients with colon or rectal cancer as a function of the number of lymph nodes evaluated were identified (15,19,23,25,31,95-106) (Table 10). Five studies included patients with both colon and rectal tumours (98,100,102,105,106), seven included only patients with rectal tumours (15,23,25,31,95-96,101), and five included only patients with colon tumours (19,97,99,103,104). Similar to the studies included in the systematic review by Chang et al (8), these 17 reports were heterogeneous with respect to study design, patient population, adjuvant therapy administered, lymph node retrieval techniques, and thresholds of lymph node numbers for comparison. Of the twelve studies reporting overall survival data with statistical comparisons (15,23,25,31,96-98,100,102-104,106), seven demonstrated a significant survival benefit for patients with the more lymph nodes evaluated (15,98,100,102-104,106). Of the seven studies reporting disease-free survival data with statistical comparisons (19,31,97,99,101,103,105), only two reported a statistically significant benefit for patients with the more lymph nodes evaluated (103,105).

Occult Tumour Cells in Lymph Nodes

Recent evidence

A literature search for evidence on the prognostic significance of occult tumour cells in lymph nodes was conducted to determine whether special measures such as polymerase chain reaction (PCR) or immunohistochemistry (IHC) should be used as standard laboratory techniques. A systematic review by Doekhie et al (9) of studies published from 1953 to 2004 on the clinical relevance of occult tumour cells, including isolated tumour cells (ITCs) and micrometastases, in lymph nodes was identified. Four studies used the PCR method to detect occult tumour cells through identification of K-ras or p53 gene mutations in hematoxylin- and eosin-negative lymph nodes. Three out of the four studies showed increased recurrence rates or mortality from disease for patients with occult tumour cells detected by PCR compared to patients with no occult tumour cells detected. Six studies using reverse transcriptase PCR (RT-PCR) to detect carcinoembryonic antigen (CEA), cytokeratin 20 (CK20), or guanylyl cyclise C (GCC) demonstrated that positive RT-PCR results negatively impacted survival. Two studies showed no prognostic value of real-time RT-PCR. Results from one study indicated that there is a narrow window of PCR cycles in which reliable results can be obtained. Only nine of 28 studies showed a significantly worse outcome in patients with lymph nodes containing occult tumour cells identified by IHC.

Four additional studies using immunohistochemistry to detect occult tumour cells in lymph nodes that reported overall or disease-free survival were identified (108-111) (Table 11). Only one study reported overall survival data, and patients without occult tumour cells floating freely in lymph node sinuses had significantly increased five-year overall survival compared to patients with occult tumour cells (108). Three out of the four studies reported no significant difference in disease-free or relapse-free survival between patients with and without occult tumour cells (109-111).

Pathology Techniques

Six studies were identified that examined various pathology techniques to improve lymph node retrieval (112-117). Two studies evaluated whether the examination of multiple lymph node sections detected significantly more nodal metastases than the examination of a single section (112-114). One prospective study of 72 colorectal specimens concluded that the assessment of multiple sections of lymph nodes led to only a small number of additional nodal metastases (112). An average of six extra tissue blocks were processed for each case, and only four cases had nodal metastases that might have gone undetected with the conventional examination of a single section. A retrospective study of 100 colorectal specimens demonstrated that examination of three sections detected extra metastases in 11 cases, resulting in altered staging classification in two patients (114). One study demonstrated that submission of the entire mesenteric fat for dehydration and microscopic examination was more accurate in sampling lymph nodes than standard manual dissection (116). Another study (113) suggested that satisfactory lymph node retrieval was possible without fat clearance if mesenteric fat was suitably fixed prior to dissection. In this study, specimens in the experimental group receiving at least an additional 24-hour fixation in 10% aqueous formaldehyde were compared to cases that underwent conventional fixation. A study of colorectal specimens demonstrated that significantly more lymph nodes ($p=0.05$) could be detected after re-fixation in lymph node-revealing solution containing ethanol, diethyl ether, glacial acetic acid, and formalin than conventional fixation in formalin with no further treatment (115). Another retrospective study of 67 colonic specimens compared lymph node identification using glacial acetic acid, ethanol, distilled water, and formaldehyde (GEWF solution) to conventional sectioning, inspection, and palpation (117). For specimens processed in GEWF, significantly more lymph nodes were identified compared to conventional processing (mean 10.2 vs. 6.8 lymph nodes per case; $p=0.002$). The average size of lymph nodes containing a metastatic tumour was significantly smaller in cases processed by GEWF

compared to conventional processing.

DISCUSSION

The evidence currently available in the literature on surgical and pathology quality performance is primarily comprised of retrospective reviews of charts or databases, case series, subgroup or exploratory analyses of RCTs, and non-randomized prospective studies. In developing the recommendations in this report, the Expert Panel on Colon and Rectal Cancer Surgery and Pathology took into consideration existing guidelines and key papers in the field (2-6) in addition to studies published since 1999. The available studies were often small and likely underpowered to detect differences in outcome between patient subgroups, and details regarding surgical and pathology methods were often poorly reported. In addition, results were complicated by confounding factors, varying statistical methods to detect associations between surgical and pathological variables and outcome, and varying comparisons. Where evidence was not available or was not sufficient to reach definitive conclusions, recommendations are based on the expert opinion of the panel.

MARGINS OF RESECTION

Extent of Resection

Of the eight reports providing outcome data by extent of resection (R status) that were identified in a search of the literature since 1999, most were retrospective studies and most included few patients with positive resection margins for comparison, with the exception of a large review by Staib et al (13) and a national database audit (18). However, in those studies that reported local recurrence, disease-free survival, or overall survival, results were similar, demonstrating decreased local recurrence and increased overall survival for patients with negative resection margins. The panel unanimously agreed that achieving negative resection margins is a primary goal of surgical resection. It is important that surgeons preoperatively identify tumours that may present a threatened margin, through clinical and radiological assessment, and consider referring these patients for possible neoadjuvant therapy.

Colon Proximal and Distal Margins

The evidence for colon proximal and distal resection margin length is minimal; therefore, recommendations are based on expert opinion and panel consensus. The NCI Guidelines 2000 document (2) cited several retrospective studies of pathological specimens and lymphatic metastasis mapping to support a recommendation that resection of 5 cm on either side of the primary tumour appeared to be adequate in order to minimize anastomotic recurrences. The literature search of studies published since 1999 identified only one study, and that study reported no significant association between proximal or distal margin length and local recurrence or disease-free survival (19). While the Expert Panel recognized that the removal of 5 cm on either side of the primary tumour has historically been considered sufficient, members agreed that modern thinking suggests that a minimum of 10 cm should be resected in order to perform adequate lymphadenectomy and removal of arterial supply and create a well-vascularized anastomosis.

Rectal Proximal and Distal Margins

No studies were identified that reported outcome data as a function of proximal resection margin length in patients with rectal cancer. The proximal margin for a rectal resection depends primarily on technical considerations for obtaining adequate lymphadenectomy and reconstruction. The Expert Panel agreed that the proximal rectal resection margin length should be a minimum of 5 cm.

The evidence available for distal resection margin length is limited to retrospective studies and non-randomized prospective series, and results are conflicting. The majority of the studies reported comparisons of distal margin length greater than 2 cm versus less than 2 cm or greater than 1 cm versus less than 1 cm. It is difficult to conclude from such comparisons whether a distal margin length of 1 cm or 2 cm is adequate, although the majority of studies demonstrated that greater margin lengths improved outcome. Only two studies compared outcome in patient subgroups with margins less than 1 cm, between 1 and 2 cm, and greater than 2 cm (23,25). One small study reported higher local recurrence-free survival in patients with margins between 1 and 2 cm or greater than 2 cm compared to margins less than 1 cm, but no significant difference in overall survival was observed (23). A larger retrospective analysis reported no significant difference in either local recurrence or survival between patients with distal margins less than 1 cm, between 1 and 2 cm, and greater than 2 cm (25). Further evidence for rectal distal resection margin length is provided by pathology series measuring the extent of distal intramural spread. Recommendations for distal rectal wall margin length presented in these studies varied from 1.5 cm to 3 cm.

For tumours of the proximal and mid rectum, the Expert Panel agreed that the distal margin length should be a minimum of 5 cm from the distal edge of the primary tumour in most patients. After much discussion, the panel agreed that the ideal minimum distal margin length for tumours at or below the mesorectum is 2 cm; however, margin lengths less than 2 cm may be adequate in appropriately selected patients, for intestinal continuity. These recommendations are in accordance with the NCI Guidelines 2000 (2). The primary goal should be the achievement of negative resection margins in order to minimize the chance of local recurrence, and negative margins should not be compromised in order to avoid a permanent colostomy. Good results in patients with minimal distal margins are dependent on the expertise of the surgeon in employing a technically accurate sharp mesorectal excision and not coning in on the distal aspect of the mesorectum. It is crucial that surgeons document any details relevant to the proximal and distal margins on the operative report.

Rectal Circumferential Radial Margins

Evidence for the importance of negative CRM and CRM length is limited to retrospective chart reviews, database audits, non-randomized prospective series, and secondary analyses of patients selected from RCTs; however, there is consistency across the reports regarding the value of a negative CRM. Several early studies cited in the NCI Guidelines 2000 (2) also established the importance of obtaining negative lateral, radial, and circumferential resection margins to decrease treatment failure (33,118,119). In the majority of studies published since 1999 that reported outcomes as a function of CRM status or length, tumours less than or equal to 1 mm from the cut edge were classified as positive margins and were associated with decreased survival, decreased disease-free survival, and increased local recurrence compared to those with negative margins. One study recommended that CRM length should be a minimum of 2 mm, based on data demonstrating higher local recurrence in patients with margins less than 1 mm or between 1 and 2 mm compared to margins greater than 2 mm (38).

The Expert Panel unanimously agreed that obtaining a negative CRM is critical in order to minimize local recurrence and improve survival. A discussion was held regarding whether CRM length greater than 1 mm is sufficient in order to be considered a negative margin. Based on the observation that the majority of studies used 1 mm clearance as a criterion for a negative CRM and the evidence that margins greater than 1 mm showed improved overall survival, disease-free survival, and local control compared to margins less than 1 mm, the

panel recommended that CRM be reported as positive if tumour is located 1 mm or less from the cut edge of the specimen.

Pathology Techniques and Reporting Requirements

Accurate and detailed reporting of resection margins by pathologists is necessary in order to determine the adequacy of surgical resection and to guide further treatment decisions. For colon and rectal specimens, proximal and distal margins should be routinely sampled for histological examination. If a tumour is close to a margin, the margin length should be measured microscopically on the glass slide. For rectal specimens, pathologists should pay close attention to mesorectal soft tissue in addition to the mucosa for the assessment of the distal margin. The panel recommended that all rectal specimens be assessed by the pathologist, using the method developed by Quirke (3).

In the assessment of radial margins, pathologists should pay particular attention to areas of the colon where the surgeon has indicated close contact between the tumour and other organs or the abdominal wall. For rectal specimens, the mesorectal tissue that constitutes the CRM should be inked, and the relationship between the tumour and the CRM must be carefully assessed. The presence of a tumour, including a tumour within a lymph node, vein, or nerve, located 1 mm or less from the margin should be reported as a positive CRM.

It is important to note that serosal penetration of the tumour (pT4b) is not equivalent to radial margin involvement. Careful gross and microscopic examination is required to properly document serosal involvement by tumour, and this may include extensive sampling or serial sectioning of sampled tissue blocks. Serosal penetration is an independent prognostic variable and has a strong negative impact on prognosis (14,120,121). The frequency of distant metastasis is greater in cases with perforation of the visceral peritoneum compared to cases with direct invasion of adjacent organs or structures without perforation of the visceral peritoneum. The median survival time following surgical resection for cure is shorter for patients with pT4b tumours compared to those with pT4a tumours with or without distant metastasis.

TOTAL MESORECTAL EXCISION

No RCTs have been published that compare conventional surgery to total mesorectal excision in patients with rectal cancer; therefore, evidence is limited to retrospective reviews, database audits, prospective series with historical controls, and comparisons between RCTs. Although these study designs are not the highest quality, results were consistent across studies. In all studies, local recurrence rate was lower in patients who received total mesorectal excision than in those who had conventional surgery, although not all studies were able to detect a statistically significant difference.

High-quality data regarding adverse effects associated with TME compared with conventional resection is not available. Two studies compared leak rates of TME procedures with conventional resection. One study reported no significant difference in anastomotic dehiscence between patients who underwent TME and those who underwent conventional surgery (92). A second study reported a higher incidence of anastomotic leakage in patients in the TME trial compared to patients in the conventional surgery trial (12% vs 6%; p=0.046); however, the type of resection was not an independent predictor for anastomotic leakage in a multivariate analysis after adjustment for differences in case mix between trials (93).

The Expert Panel unanimously agreed that the technique of TME using sharp dissection under direct visualization of the mesorectal plane should be performed to reduce local recurrence. The goal of rectal cancer resection should be a wide anatomic resection to

obtain radial clearance of mesorectal tissue, including the primary tumour and lymphatic, vascular, and perineural tumour deposits. The integrity of the mesorectal fascia propria should be preserved, and at least 5 cm clearance of attached mesorectum attached to the bowel, distal to the tumour, should be achieved. For upper rectal and some middle rectal cancers, it is satisfactory to resect 5 cm of mesorectum and rectal tube beyond the distal edge of the palpable tumour, as opposed to completing dissection of the mesorectum to the pelvic floor.

En Bloc Multivisceral Resection of Locally Advanced Adherent Tumours

The majority of the evidence for en bloc resection of locally advanced adherent colorectal cancer is retrospective with small numbers of patients. Many studies reported results for multivisceral resections in subgroup analyses, and few studies provided statistical comparison data between en bloc multivisceral resection and resection through an adherent structure. In general, the evidence suggests that multivisceral resection of adherent structures can result in satisfactory survival outcomes when negative margins are achieved.

Of particular note are the results of the population-based registry review by Govindarajan et al (81). In an analysis of 8,380 patients with T4 colorectal cancer invasive to adjacent organs, only 33.3% of patients underwent multivisceral resection. An independent association between multivisceral resection and overall survival was reported for both colon and rectal cancer patients. In patients with adherent tumours, multivisceral resection was not associated with increased mortality at either one month or six months after diagnosis.

Based on the evidence available, the Expert Panel agreed that locally advanced, adherent colorectal tumours should be resected en bloc in order for resection to be considered complete. By consensus, the panel further stated that, if a surgeon finds a locally advanced adherent tumour in an otherwise curable patient and is not prepared to perform a multivisceral resection, the surgeon should consider either aborting the operation or creating a proximal stoma and then referring the patient for multidisciplinary opinion regarding neoadjuvant therapy and more radical surgery.

Inadvertent Perforation

The studies that provide evidence for the effects of inadvertent perforation of the bowel generally report consistent results suggesting increased local recurrence and decreased overall survival for patients with perforation. The Expert Panel unanimously agreed that extreme care should be taken by surgeons to avoid perforation of the bowel during surgery, and all instances of perforation should be reported on the operative report and pathology requisition form.

Extent of Lymphadenectomy

The evidence supporting recommendations for the extent of lymphadenectomy and level of ligation is limited; therefore, recommendations are based on a combination of Expert Panel consensus and the evidence available. In the recent literature, two studies reported no significant benefit for high arterial ligation compared to low ligation.

The panel agreed that the goal of colon resection is the removal of the segment of colon with the tumour and all the mesentery containing the blood supply and the lymphatics at the level of the primary feeding arterial vessel. In curative resections, lymph nodes should be resected en bloc with the main vessel supplying the involved segment of the colon, and apical nodes should be included when feasible.

For rectal cancer, the panel concluded that adequate lymphadenectomy is achieved through appropriate proximal lymphatic resection and TME. Panel members agreed that high

ligation of the superior rectal artery should be performed but that there is insufficient evidence about the benefit of ligating the IMA at its origin. Lymph nodes should be removed as high as technically possible to allow for complete removal of clinically involved nodes and suspicious periaortic nodes should be biopsied for staging.

Number of Lymph Nodes for Examination

The studies assessing the number of lymph nodes to be examined were heterogeneous with respect to threshold comparisons and study design. In general, the evidence demonstrates that overall survival improves the greater the number of lymph nodes evaluated. Based on consensus, the Expert Panel recommended the examination of a minimum of 12 lymph nodes, but not all Panel members were in agreement with the recommendation. This number is in accordance with the recommendations provided by the NCI Guidelines 2000 document (2) and with ongoing initiatives in Ontario to increase the number of lymph nodes examined. In patients with T1 and T2 tumours or patients who have undergone preoperative therapy, the assessment of 12 lymph nodes may not be possible. The panel was in agreement that examination of lymph nodes should not stop at 12 but that all available lymph nodes should be examined.

Pathology Methods

For rectal and colonic tumours, all lymph nodes should be histologically examined. Examination should not halt after 12 nodes have been evaluated. If less than 12 lymph nodes are identified, the pathologist should consider placing the fat into a lymph node highlighting solution. It is important that small lymph nodes close to the bowel wall are also examined.

Currently the available evidence on the prognostic significance of lymph node involvement by micrometastases, defined as tumour deposits between 0.2 mm and 2.0 mm, or by isolated tumour cells (ITCs), defined as single cells or clusters 0.2 mm or less, is conflicting. For this reason, the Expert Panel does not recommend the use of immunohistochemistry or polymerase chain reaction for the routine examination of regional lymph nodes. However, lymph node involvement by micrometastases or isolated tumour cells detected by routine histology must be reported. Sentinel node biopsy remains an experimental procedure while there is insufficient evidence that the presence of occult tumour cells results in poorer prognosis.

CONCLUSIONS

This guideline addresses the optimization of performance concerning margin status and lymph node assessment in colorectal cancer. Achieving this requires the coordinated efforts of surgeons and pathologists, as well as other medical professionals. In addition to such collaboration, system changes in individual institutions are often required to achieve best results. Surgeons, pathologists, and the teams in which they are involved should focus on ensuring that colorectal cancers are resected with negative (R0) margins and that an adequate number of lymph nodes are assessed to allow for accurate decision making relating to prognosis and adjuvant therapy.

CONFLICT OF INTEREST

Members of the Expert Panel on Colon and Rectal Cancer Surgery and Pathology who were involved in the writing of this document were polled for potential conflicts of interest. No conflicts were declared.

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Appendix 1. Evidence tables.

Table 3. Colon and rectum margins of resection: positive vs negative margins.

Author, Year (reference)	Study Design (tumour type)	Margin	N	Local recurrence	Disease free Survival	Overall survival	Pathology Details
Singh, 2000 (11)	Single centre retrospective review (rectal) [a]	Positive margins Negative margins	3 10	Local failure 33% 40%	NR	NR	In 5 pts, radial margin status was unknown.
Andreola, 2001 (12)	Single centre retrospective review (rectal)	Positive margins Negative margins	8 68	60% 3.3%	NR	NR	Distal margin measured after fixation in 10% formalin for 24 hours. CRM measured by sampling a 1-mm thick slice of adipose tissue from the whole surface of the margin. CRM considered positive when tumour <1 mm from margin.
Staib, 2002 (13)	Single centre retrospective review (colorectal)	R0 R1 R2 unresectable	1293 529 497 118	NR	NR	5-year 77.6% 45.7% 3.8% 0% p<0.0001	Details of margin assessment and criteria for margin positivity not reported.
Petersen, 2002 (14)	Prospective cohort (colorectal)	Positive Negative	8 232	NR	NR	HR=2.61 (1.42-4.79) p=0.002 [b]	Mean number of tumour blocks 5.7. ≥2 blocks taken where tumour closest to peritoneal surface and where tumour closest to any surgical margin. Minimum distance between tumour and CRM ≤1 mm considered involved.
Kuru, 2002 (15)	Single centre retrospective review (rectal)	Positive Negative	4 175	LRFS 50% 67% p=0.30	NR	5-year 50% 59% p=0.60	Details of margin assessment and criteria for margin positivity not reported.
Wulf, 2004 (16)	Multicentre retrospective review (rectal)	R0 R1/R2	502 32 [c]	Local control HR=1.63 [b] p=0.005	HR=1.19 p=0.05	HR=1.38 p=0.015	Details of margin assessment and criteria for margin positivity not reported.
Movsas, 2006 (17)	Retrospective review of pathology material from phase II study (rectal)	Positive Negative	3 17	p<0.001	p=0.02	p=NS	Details of margin assessment and criteria for margin positivity not reported.
Eriksen, 2006 (18)	National database audit (rectal)	R0 R1 R2	348 159 217	5-year 18% 40%	NR	5-year 49% 20% 12%	Circumferential resection margin >1 mm considered to be uninvolved.

Notes: CRM, circumferential resection margin; HR, hazard ratio; LRFS, local recurrence-free survival; NR, not reported; N, number of patients evaluated.
a All patients had localized pelvic non-nodal metastatic foci.

b Based on multivariate analysis
c Estimated from data reported as percentages.

Table 4. Colon and rectum margins of resection: proximal and distal.

Author, Year (reference)	Study Design (tumour type)	Margin	N	Local recurrence	Disease free Survival	Overall survival	Pathology Details
COLON							
Read, 2002 (19)	Single centre retrospective review	Distal	316 total	Locoregional control HR=0.90 (95% CI 0.69-1.18) p=0.44 [d]	HR=0.99 (95% CI 0.96-1.03) p=0.60 [c]	NR	Tumours staged according to TNM staging system (AJCC/UICC)
		Proximal		HR=1.09 (95% CI 0.90-1.32) p=0.38 [d]	HR=1.0 (95% CI 0.97-1.02) p=0.91 [c]		
RECTUM							
Jatzko, 1999 (20)	Single centre retrospective review	Distal <2 cm >2 cm [a]	 89 339	5/10 year 11.1% 10.8% p=0.138	NR	NR	WHO, UICC, AJCC criteria used for pathological classification Only pts with R0 resection according to UICC/AJCC were included
Merchant, 1999 (21)	Single centre retrospective review	 ≥2 cm <2 cm	 76 19	 12% 0% p=0.15	NR	NR	NR
Bokey, 1999 (22)	Single centre retrospective review	Distal >2 cm ≤2 cm >1 cm ≤1 cm	 472 124 557 39	5-year 11.0% 11.5% p=0.92 9.9% 27.2% p=0.01 HR (≤1 cm) =3.8, p<0.01[c]	NR	NR	Distal margin clearance measured in fresh unfixed specimen
Bufalari, 2000 (23)	Single centre retrospective review	Distal ≤1 cm 1.1-2.0 cm 2.1-4.0 cm >4 cm Negative Positive	 7 16 35 15 70 3	LRFS 43% 100% 89% 93% p=0.0002 [b] 89% 67% p=NS	NR	 57% 81% 57% 87% p=NS 69% 67% p=NS	Distal margins measured in formalin-fixed specimens. Infiltration of margins by tumour cells measured histologically with H&E staining.
Kuvshinoff, 2001 (24)	Case series	Distal ≤1 cm >1 cm	 16 12	NR	log-rank p=0.06	NR	Distal margins measured in fixed specimens. Tumour involvement also assessed by intraoperative frozen section.

Author, Year (reference)	Study Design (tumour type)	Margin	N	Local recurrence	Disease free Survival	Overall survival	Pathology Details
Andreola, 2001 (12)	Single centre retrospective review	Distal All patients: <1 cm ≥1 cm R0 patients: <1 cm ≥1 cm	 35 41 29 NR	 11.4% 7.3% 3.4% 5.1%	NR	NR	Distal margin measured after fixation in 10% formalin for 24 hours. Circumferential margin measured by sampling a 1-mm thick slice of adipose tissue from the whole surface of the margin. Circumferential margin considered positive when tumour <1 mm from margin.
Stocchi, 2001 (25)	Retrospective analysis of patients enrolled in 3 RCTs	Distal <1 cm 1-2 cm >2 cm	 54 113 185	 13% 16% 13% p=0.31	NR	 64% 58% 65% p=0.23	NR
Moore, 2003 (26)	Case series?	Distal ≤1 cm >1 cm ≤2 cm >2 cm	 17 77 53 41	3-year 12% 9% p=0.99 8% 11% p=0.93 HR=1.1 (95% CI 0.87-1.5) p=0.34	3-year RFS 82% 85% p=0.80 88% 82% p=0.88 HR=1.1 (95% CI 0.91-1.4) p=0.29	NR	Distal margin length assessed before tumour fixation in unpinned specimen. "Donuts" created by circular intraluminal staplers not included in the measurement of distal margin length, but examined and negative in all cases.
Law, 2004 (27)	Prospective study	Distal >2 cm <2 cm	 380 183	5-year 5.4% 17.2% p<0.001	NR	NR	NR
Safioleas, 2005 (28)	Single centre retrospective review	Distal <2 cm >2 cm	 15 37	 53.3% 10.8% p=0.000488	NR	NR	Proximal and distal margins measured before specimen was fixed.
Luna-Perez, 2005 (29)	Case series	Distal <2 cm >2 cm	 15 46	 6.7% 10.9% p=0.53	NR	5-year 42% 81% p=0.006	Specimens mapped and sliced.

Author, Year (reference)	Study Design (tumour type)	Margin	N	Local recurrence	Disease free Survival	Overall survival	Pathology Details
Benzoni, 2006 (30)	Case series	Distal	58 total	NR	NR	p=0.04 [c]	Specimens fixed in buffered 10% formalin for 24 hours. If no macroscopically obvious tumour, whole suspect area sliced (5-8 mm slices) and paraffin embedded. If macroscopically obvious tumour, at least 4 paraffin blocks sampled with additional fragment from surrounding area. Measured distance between deepest point of infiltration and corresponding inked margin.
Laurent, 2006 (31)	Case series	Distal ≤2 cm >2 cm	 38 262		5-year 75% 59% p=0.141	5-year 85% 70% p=0.025	Distal resection margin assessed by surgeon in operating room. Specimen immediately sent to pathologist and pinned on corkboard. Mesorectal surface inked before slicing to measure circumferential resection margin. Distal and circumferential resection margins assessed microscopically. Circumferential resection margin considered positive if ≤1 mm.
Chiappa, 2006 (32)	Case series	Distal <1 cm ≥1 cm	 48 151	3-year 16% 7% p=0.014	NR	NR	NR

Notes: AJCC, American Joint Committee on Cancer; CI, confidence interval; H&E, hematoxylin and eosin; HR, hazard ratio; LRFS, local recurrence-free survival; N, number of patients evaluated; NR, not reported; NS, not significant; RCT, randomized controlled trial; TNM, Tumour, Node, Metastasis; UICC, International Union Against Cancer; WHO, World Health Organization.

a All patients had R0 resection. 124 patients with unknown distal margin clearance are not included.

b Based on multivariate analysis, p=0.02.

c Based on multivariate analysis.

d Based on multivariate analysis of 131 patients undergoing left-sided colonic resection, stratified by tumour stage.

Table 5. Colon and rectum margins of resection: radial and circumferential.

Author, Year (reference)	Study Design (tumour type)	Margin	N	Local recurrence	Disease free Survival	Overall survival	Pathology Details
Willett, 1999 (34)	Retrospective review (rectal)	Radial		10-year local control	10-year RFS	NR	Proximal and distal margins ≥ 1 cm
		>4 mm	33		70%		
		1-4 mm	37	80%	60%		
		≤ 1 mm	19	76%	60%		
				73%, p=NS	p=NS		
Fleshman, 1999 (35)	Retrospective review (rectal)	Radial		NR	NR	Open APR: p=0.1	NR
		Positive	24			Lap APR: p=0.78	
		Negative	170				
Kuvshinoff, 2001 (24)	Case series (rectal)	Radial		NR		NR	Radial margin assessed to nearest mm from viable tumour to closest radial inked surface.
		>3 mm	17		log-rank p<0.02		
		≤3 mm	15				
Ueno, 2001 (36)	Retrospective review (rectal)	Circumferential		NR	NR	5-year	NR
		Negative	36			39.1%	
		Positive	8			0%	
						p<0.0001	
Sanfilippo, 2001 (37)	Retrospective review (rectal)	Radial			NR	NR	Specimen first evaluated grossly. Areas closest to tumour were inked and sectioned for microscopic evaluation. Close margin defined as ≤1 mm from inked margin.
		Positive or close (<1 mm)	4	75%			
		≥1 mm	41	29% (5-year) p<0.00001			
Stocchi, 2001 (25)	Retrospective review (rectal)	Radial [a]			NR		NR
		0-5 mm	93	20%		53%	
		6-10 mm	46	24%		49%	
		>10 mm	76	3% p=0.01		56% p=0.93	
		<1 mm	NR	25%			
Nagtegaal, 2002 (38)	Pts selected from 1 arm of RCT [d] (rectal)	Circumferential		2-year	NR	2-year	Standardized pathology examination using protocol of Quirke. Lateral resection margin inked and specimen fixed for 48 hours. Sliced transversely to provide multiple coronal sections. Macroscopic CRM measured with a ruler. Sufficient blocks taken. When tumour approached margin (<1 cm), measurements repeated microscopically. Any tumour ≤1 mm from CRM recorded as tumour margin involvement. If tumour >1 mm but <2 mm from CRM, deeper levels cut to exclude involvement.
		≤1 mm	120	16.4%		69.7%	
		1.1-2 mm	53	14.9%		84.8%	
		2.1-5 mm	139	10.3%		87.0%	
		5.1-10 mm	155	6.0%		91.2%	
		>10 mm	189	2.4% p=0.0007		92.8% p<0.0001	
		0 mm	65	30.7%			
		≤1 mm	55	7.9% p=0.0004			
		Positive				67.9%	
		Negative				90.0% p<0.0001	

Author, Year (reference)	Study Design (tumour type)	Margin	N	Local recurrence	Disease free Survival	Overall survival	Pathology Details
Wibe, 2002 (39)	Retrospective review (rectal)	Circumferential Positive Negative 0-1 mm 2-5 mm 6-10 mm 11-19 mm ≥20 mm	 65 621 65 170 168 127 156	 22% 5% p<0.001 22% 8% 7% 4% 1%	NR	 63% 87% 63% 81% 84% 91% 94%	Circumferential margin >1mm was classified as an uninvolved margin. Fresh specimens opened along antimesenteric border and fixed in formalin. Specimens sectioned in transverse plane to identify lateral resection margin.
Birbeck, 2002 (40)	Retrospective review (rectal)	Circumferential 0 mm >0, <1 mm >1 mm Involved Not involved	 66 97 421 165 421	 54.5% 27.8% 10% 56% [b] 15% [b] log-rank p<0.0001 HR=3.68 (95% CI 2.32-5.83) [c]	NR	 40% [b] 79% [b] log-rank p<0.0001 HR=2.16 (95% CI 1.53-3.05) [c]	Complete transverse slicing of the tumour and segments above and below at 3- to 5-cm intervals. Technique based on Quirke. Minimum distance between tumour and CRM ≤1 mm considered involved.
Marijnen, 2003 (41)	Pts selected from an RCT [d] (rectal)	Circumferential >2 mm 1-2 mm ≤1 mm	 987 100 227	2-year 3.3% 8.5% 13.1% p<0.0001	NR	NR	See pathology details for Nagtegaal 2002.
Bouzourene, 2003 (42)	Analysis of phase II data (rectal)	Radial Positive Negative <2 mm ≥2 mm	 25 79 NR NR	 p=0.001 p=0.005	 p=0.0007 p=0.7	 p=0.001 p=0.9	Specimens opened through anterior wall. Fixed in 10% buffered neutral formalin for 24 hours. External surface of specimen inked. Tumour and attached mesorectum serially sliced at 3- to 4-mm intervals perpendicular to longitudinal axis of rectum. Tissue samples embedded in paraffin, cut, and stained with H&E.
Bulow, 2003 (43)	Prospective cohort (rectal)	Circumferential 1mm ≥2 mm	14 259	36% 8% p=0.030	NR	NR	According to the principles of Quirke.
Wibe, 2004 (44)	Prospective national cohort (rectal)	Circumferential Involved Not involved	 163 1,973	HR=1.6 (95% CI 1-2.4) p=0.043 [c]	NR	HR=1.4 (95% CI 1.1-1.8) p=0.003 [c]	According to the principles of Quirke
Luna-Perez, 2005 (29)	Case series (rectal)	Circumferential <2 mm >2 mm	 12 49	 16.7% 8.2% p=0.33	NR	5-year 42% 81% p=0.006	Circumferential margin <2 mm was considered positive. Specimens mapped and sliced.

Author, Year (reference)	Study Design (tumour type)	Margin	N	Local recurrence	Disease free Survival	Overall survival	Pathology Details
Beresford, 2005 (45)	Database audit (rectal)	Circumferential Positive Negative	 21 125	NR	NR	HR=3.36 (95% CI 1.79-6.29) p<0.001	Anterior and posterior surfaces were inked. Specimens were fixed in formalin for 72 hours. Circumferential margin ≤1 mm was considered positive.
Macadam, 2005 (46)	Retrospective review (rectal)	Circumferential Positive Negative	 NR [e]	 p<0.001	 p<0.001	NR	Circumferential margin was considered positive if tumour was present at or within 1 mm of the cut surface.
Mawdsley, 2005 (47)	Database audit (rectal)	Circumferential Positive Negative	 24 98	 62% 10%	3-year 9% 52% p<0.001	3-year 25% 64% p=0.0001	Anterior and posterior nonperitonealized surfaces inked. Specimen fixed in formalin for 72 hours. Area above tumour cut transversely in 5-mm slices from 20 mm above to 20 mm below the tumour. Circumferential margin was considered positive if tumour was present at or within 1 mm of the cut surface.
Das, 2006 (48)	Single centre retrospective review (rectal)	Radial Positive Negative	 6 464	HR=5.02 (95% CI 1.21-20.81) p=0.026	NR	HR=3.71 (95% CI 1.37-10.07) p=0.010 HR=4.85 (95% CI 1.64-14.38), p=0.004 [c]	NR
Laurent, 2006 (31)	Case Series (rectal)	Circumferential ≤1 mm >1 mm	 23 203	 22% 3%	5-year 20% 68% p<0.001	5-year 29% 78% p<0.001	Specimen immediately sent to pathologist and pinned on cork board. Mesorectal surface inked before slicing to measure circumferential resection margin. Distal and circumferential resection margins assessed microscopically. Circumferential resection margin considered positive if ≤1 mm.
Chiappa, 2006 (32)	Case Series (rectal)	Circumferential Positive Negative	 16 86	3-year 21% 11%, p=0.07	NR	NR	NR

Notes: CI, confidence interval; CRM, circumferential resection margin; H&E, hematoxylin and eosin; HR, hazard ratio; NR, not reported; N, number of patients evaluated; NS, not significant; RFS, recurrence-free survival;
a P value for test of association between radial free margin and local recurrence rate is 0.01.
b Only includes patients with potentially curative resection, n=488.
c Based on multivariate analysis.
d Nagtegaal analyzed patients from the surgery-alone arm of the Dutch TME trial and Marijnen analyzed patients from the same trial including patients who received preoperative radiotherapy in addition to surgery.
e Not clear if analysis based on all patients (n=168) or only patients with potentially curative resection (n=120). 19% of all patients had positive circumferential radial margins and 14% of potentially curative resections had positive margins.

Table 6. Comparative studies of total mesorectal excision versus conventional resection.

Author, Year (reference)	Study Design	Treatment	N	Local recurrence
Bokey, 1999 (88)	Retrospective review	Total anatomical dissection (TME for lower or mid-rectal tumours and mesorectum ligated and divided for upper rectal tumours)	274	5 year 8%
		Non-total anatomical dissection	322	14% p=0.06
Di Matteo, 2000 (89)	Retrospective review	TME in extraperitoneal localisations	98	11.2%
		Conventional surgery, partial mesorectal excision in anterior resection for extra peritoneal neoplastic localisation	41	21.9%, p>0.05
Shirouzu, 2001 (90)	Retrospective review	TME, some patients had lateral lymphadenectomy and/or autonomic nerve preservation	381	12%
		Conventional surgery	77	27%
Nesbakken, 2002 (91)	Retrospective review			5-year
		Curative TME for lower and mid-rectal tumours, PME for upper rectal tumours, 6% had adjuvant RT	134	9%
		Conventional curative resection, 2% had adjuvant RT	178	24%, p=0.02
Wibe, 2002 (92)	National audit	Curative TME [a]	1395	6% [b]
		Conventional curative resection [a]	229	12% [b] HR (non-TME vs TME) =2.7 (95% CI 1.7-4.2), p<0.0001
Kapiteijn, 2002 (93)	Comparison between RCTs			2-year
		Curative TME, no preoperative RT [c]	661	9%
		Conventional curative resection, no preoperative RT [d]	269	16% HR=0.02 (95% CI 0.00-0.22) [e] log-rank p=0.002
Bulow, 2003 (43)	Prospective series with retrospective control			3-year
		Curative resection, laparotomy, TME for lower two thirds of rectum, optional PME for tumours in upper third of rectum, various anastomosis techniques decided by surgeon	311	11%
		Conventional curative resection [f]	246	30% HR=0.33 (95% CI 0.21-0.52), p<0.001 [g]
Bernardshaw, 2006 (94)	Retrospective review			5-year
		TME, all R0	181	9%
		Conventional curative resection, all R0	139	18% p=0.046

Notes: N, number of patients; NR, not reported; HR, hazard ratio; CI, confidence interval; RT, radiotherapy; PME, partial mesorectal excision; TME, total mesorectal excision.
a 5% of all patients who received curative resection received adjuvant radiotherapy
b Includes both local and local plus distant recurrence
c Patients from the control arm of the Dutch TME trial (2001) comparing TME with preoperative radiotherapy with TME alone.
d Patients from the CRAB trial (1994) comparing transfusion of leucocyte-depleted or buffy coat-depleted blood.
e From a multivariate Cox regression model
f Patients from the Danish RANX05 Study evaluating the effect of ranitidine on postoperative complications and survival.
g Adjusted for differences in age.

Table 7. En bloc multivisceral resection of adherent tumours.

Author, year (reference)	Design	Treatment	N	Margin Status	Local recurrence	Disease-free survival	Overall survival
Sokmen, 1999 (56)	Retrospective review Avg f/u:33 months	Multivisceral resection for primary rectal cancer (LAR (13), APR (4), AR (3))	20 (rectal)	Negative: 17 (85%) Positive: 3 (15%)	15% (after an avg. of 8 months)	NR	Median: 28 months (without histopathologically confirmed invasion to adjacent organs); 22 months (with confirmed invasion)
Gebhardt, 1999 (57)	Unclear – likely retrospective review f/u NR	Multivisceral resection for primary colorectal cancer (colonic resection (119), rectal resection (30), rectal extirpation (24))	173 (total) 51 (rectal) 58 (sigmoid) 64 (colon)	Negative: 140 (81%) Positive: 33 (19%)	NR	NR	5-year Overall: 42% Negative margins:51% Positive margins: 0%
Hermanek, 2000 (58)	Prospective Observation Median f/u: 60 months	Multivisceral resection en bloc for adherent tumours. Standard surgery (not defined) for adherent tumours.	45 (34 colon/ 11 rectal) 24 (19 colon/ 5 rectal)	R0:100%	NR	NR	5-year Rectal: 31.2% v. 20% Colon: 72.7% v. 44.4%
Koea, 2000 (59)	Retrospective Review Median f/u: 26 months	En bloc pancreaticoduodenectomy (4); en bloc duodenectomy (4)	8 (colon)	Negative: 100%	NR	NR	75%
Law, 2000 (60)	Retrospective Review Mean f/u: 49.8 months	Total pelvic exenteration (removal of entire bladder and lower ureters en bloc with the rectum)	15 (rectal)	Negative: 100%	7%	NR	5-year 64%
Stocchi, 2001 (25)	Retrospective Review Median f/u: 6.7 years	En bloc resection of the rectum and adjacent structure Dissection of the area of adherence	39 (rectal) 40	NR	27% 43% p=0.88	NR	5-year 33% 28% p=0.97
Chen, 2001 (61)	Retrospective Review f/u NR	Total pelvic exenteration for primary colorectal cancer	49 (12 colon/ 37 rectal)	Negative: 100%	NR	5-year 49%	NR
Stief, 2002 (62)	Retrospective Review Median f/u: 63 months	Surgery for CRC with total or partial extirpation of at least one urological organ, resected en bloc.	40	Negative: 58% Positive: 43%	NR	NR	5-year 44% (median 39 months)
Lehnert, 2002 (63)	Retrospective Review Median f/u: 71 months	Multivisceral resection for locally advanced primary colon and rectal cancer	201 (139 colon/ 62 rectal)	Negative: 65% Positive: 35%	11% overall; 9% colon, 16% rectal	NR	5-year UICC stage: II – 63% III – 38% IV – 12%

Author, year (reference)	Design	Treatment	N	Margin Status	Local recurrence	Disease-free survival	Overall survival
Wiig, 2002 (64)	Prospective case series Mean f/u: 60 months	Total pelvic exenteration for rectal cancer (primary and recurrent – only primary cases included in table)	25 (rectal)	Negative: 80% Positive: 20%	5-yr: 18%	NR	5-year 36%
Luna-Perez, 2002 (65)	Retrospective Review Median f/u: 36.8 months	Multivisceral resection for colon cancer.	40 (colon)	NR	NR	NR	5-year 45%
Yamada, 2002 (66)	Retrospective Review Median f/u NR	Pelvic exenteration and sacral resection for rectal cancer (primary and recurrent – only primary cases included in table)	22 (rectal)	Negative: 95% Positive: 5%	NR	NR	5-year Dukes B: 74.1% Dukes C: 47.4%
Ike, 2003 (67)	Retrospective Review Mean f/u: 8 months	Extended APR with partial prostatectomy for rectal cancer (en bloc)	4 (rectal)	Negative: 100%	0%	NR	NR
Ruo, 2003 (68)	Retrospective Review Median f/u: 22 months	Rectal cancer resection with in-continuity partial vaginectomy and TME	64 (rectal)	Negative: 94% Positive: 6%	16% (Med TTR: 11 months) Positive: 50% (2/4) Negative: 13% (8/60)	NR	5-year 46% (med. 44 months)
Gohl, 2003 (69)	Prospective Case Series Median f/u: 34 months	Multivisceral resection of advanced rectal cancer	113 (rectal)	Negative: 89% (101/113) Positive: 11%	3-yr: 12.7% (only –ve margin pts.)	NR	3-year 73% (only negative margin pts.)
Kecmanovic, 2003 (70)	Unclear – likely retrospective review Median f/u NR	Total pelvic exenteration (n=10), posterior pelvic exenteration (n=2)	12 (rectal)	NR	NR	NR	5-year 32%; median 50 months
Moriya, 2003 (71)	Retrospective Review Median f/u: 68 months	Total pelvic exenteration (n=48), abdomino-perineal exenteration (n=4) Partial resection (n=137)	52 (rectal) 137	TPE/APE: Negative: 79%; Positive: 21% Partial: Negative: 64%; Positive: 36%	TPE/APE: Negative: 4.8% Partial: Negative: 12%	5-year 57% (whole group with –ve margins)	NR

Author, year (reference)	Design	Treatment	N	Margin Status	Local recurrence	Disease-free survival	Overall survival
Ike, 2003 (72)	Retrospective Review Mean f/u: 147.6 months	Total pelvic exenteration for primary rectal cancer	71 (rectal)	Negative: 100%	5.6% (crude)	NR	5-year Overall: 54.1% T3: 65.7% T4: 39% 10-year Overall: 50% T3: 58.8% T4: 39%
Carne, 2004 (73)	Retrospective Review Mean f/u: 62 months	No bladder resection (n=4) Partial cystectomy (n=45) Total cystectomy en bloc (n=4)	53 (2 rectal/ 51 colon)	NR	No – 100% Partial – 18% Total – 0%	Crude: No—0% Partial—56% Total—50%	Crude: No—0% Partial – 71% Total – 75%
Vieira, 2004 (74)	Retrospective Review Median f/u: 47.7 months	Extended resection of locally advanced colon cancer (en bloc surgery of tumour together with 1 or more organs and/or structures).	95 (colon)	Negative: 91% Positive: 9%	NR	NR	5-year Overall: 52.6% Negative: 58.3%; Positive: 0% 10-year 47.4%
Nakafusa, 2004 (75)	Unclear, likely retrospective. Median f/u: 62 months.	Multivisceral resection Standard operation (surgery for colorectal cancer without a resection of other organs or structures).	53 (33 colon/ 20 rectal) 270 (174 colon/ 96 rectal)	Negative: 100%	NR	5-year 66.8% 72.9% p=0.896	5-year 76.6% 79.5% p=0.9347
Oledzki, 2004 (76)	Retrospective review Median f/u: 24 months.	Resection of rectum with total cystectomy. Resection of rectum without cystectomy.	18 (rectal) 65	Negative: 100% NR	6% 14%	5-year 53% 42.5%	5-year 56.6% 58.2%
Amshel, 2005 (77)	Retrospective review. Mean f/u: 32 months.	APR (n=10), LAR (n=8), total proctectomy with coloanal anastomosis (n=5), or pelvic exenteration (n=1)	24 (rectal)	Positive: 25% Negative: 75%	NR	54%	75%
Liang, 2006 (78)	Phase II (abstract) Median f/u: 18 months	Laparoscopic APR	22 (rectal)	NR	9% (Crude)	NR	NR

Author, year (reference)	Design	Treatment	N	Margin Status	Local recurrence	Disease-free survival	Overall survival
Smedh, 2006 (79)	Retrospective Review Median f/u: 37 months	APR with TME + en bloc resection of other organs or structures APR + TME	23 (rectal) 40	Overall: Curative: 81% Indeterminate: 11% Palliative: 8%	Overall: 1.7% (curative / indeterminate only)	NR	Overall: 5-year 75%[a]
Visokai, 2006 (80)	Retrospective Review Mean f/u: 21.6 months	Multivisceral resection – removal of colorectal tumour en bloc with adherent structures.	28 (type NR)	R0: 100%	NR	NR	5-year 45%
Govindarajan, 2006 (81)	Population-based Registry Review[b]	Multivisceral resection for locally advanced adherent colorectal cancer. Standard resection.	2789 (type NR) 5591	NR	NR	NR	5-year 35.1% 27.7%
Kapoor, 2006 (82)	Retrospective Review Median f/u: 54 months	En bloc resection of right-sided colon cancer with adjacent organ invasion.	11 (colon)	NR	9%	Median: 54 months	NR
Bannura, 2006 (83)	Retrospective Review Median f/u: 32 months	Posterior pelvic exenteration Standard resection	30 (rectal) 75	NR	45% 24% p=0.06	NR	5-year 48% 62% p=0.09
Winter, 2007 (84)	Prospective Study Median f/u: 7 years	En bloc total or partial cystectomy.	63 (46 colon/ 17 rectal)	R0:89% R1:11%	14% (3/56 R0, 6/7 R1)	NR	5-year 57% (61% R0, 17% R1; p=0.018)

Notes: APR, abdominoperineal resection; AR, anterior resection; CRC, colorectal cancer; f/u, follow-up; LAR, low anterior resection; N, number of patients evaluated; NR, not reported; TME, total mesorectal excision; TTR, time to recurrence; UICC, International Union Against Cancer.
a Estimated from survival curve.
b Surveillance, Epidemiology, and End Results (SEER) Registry

Table 8. Inadvertent perforation.

Author, year (reference)	Design	N (tumour type)	Inadvertent Perforation	Local recurrence	Overall survival
Kagda, 1999 (85)	Case series	572 [a] (rectal)	15 perforated (2.6%) [b] 557 not perforated	7% (at last follow-up) 8%	58% (5-year) NR [c]
Stocchi, 2001 (25)	Retrospective review of pts accrued to 3 RCTs	670 (rectal)	33 perforated (5%) 637 not perforated	26% 16% p=0.16	60% 59% p=0.72
Bonadeo, 2001 (86)	Case series	417 (rectal)	12 perforated (2.9%) [d] 405 not perforated	Local failure in 6 of 12 perforated cases Perforation associated with LR p<0.0001	NR
Eriksen, 2003 (87)	National database audit	2,873 (rectal)	234 perforated (8.1%) [e] 2,639 not perforated	28.8% (5-year) [f] 9.9% HR=3.0 (95% CI 2.2-4.1) p<0.001	41.5% [f] 67.1% HR=2.0 (95% CI 1.6-2.4), p<0.001
Wibe, 2004 (44)	National database audit	2,136 (rectal)	184 perforated (9%) [h] 1,952 not perforated	HR=2.9 (95% CI 2-4.2) p<0.001	HR=1.3 (95% CI 1.1-1.7), p=0.017)

Notes: CI, confidence interval; HR, hazard ratio; LR, local recurrence; RCT, randomized controlled trial; N, number of patients evaluated; NR, not reported.
a Only includes patients with potentially curative resection. 260 additional patients who underwent palliative surgery for metastatic disease are excluded.
b If patients who underwent palliative surgery are included, 42 of 832 patients (5%) had perforation.
c Survival curves reported as "similar"
d Incidence of intraoperative perforation varied by type of resection: 13.8% for abdominoperineal resection, 1.7% for anterior resection (p=NR).
e In multivariate analysis, incidence of intraoperative perforation was significantly greater for abdominoperineal resection compared to anterior resection (odds ratio 5.6, 95% CI 3.5-8.8, p<0.001) and in those age ≥80 years (odds ratio 2.0, 95% CI 1.2-3.5)
f Based on analysis of 2650 patients who did not receive preoperative or postoperative radiotherapy.
g Eriksen and Wibe data both from Norwegian Rectal Cancer Project database but inclusion criteria differed between studies.
h Incidence of intraoperative perforation varied by distance of tumour from the anal verge: 5% at 9-12 cm, 8% at 6-8 cm, 13% at 0-5 cm (p<0.001); Incidence of intraoperative perforation also varied by type of resection: 15% for abdominoperineal resection, 4% for anterior resection (p<0.001).

Table 9. Studies reporting outcomes by extent of lymphadenectomy.

Author, Year (reference)	Study Design	Extent of lymphadenectomy	N	Overall survival	Disease-free survival	Study Details
Fleshman, 1999 (35)	Three centre retrospective review	High ligation of IMA No high ligation of IMA	121 73	Open APR: p=0.53 Lap APR: p=0.86	NR	Rectal tumours. All patients had APR, either open or Lap.
Kawamura, 2000 (107)	Single centre retrospective review	Limited nodal involvement Low ligation High ligation Intermediate nodal involvement Low ligation High ligation Central node involvement Low ligation High ligation	379 132 35 12 2 4	NR	 p=0.29 p=0.47 p=0.64	Colon tumours. Extent of nodal dissection dictated by the certified surgeon's policy. The surgeon examined the resected specimen, collected lymph nodes immediately after the operation, and submitted them for histopathological examination. Pathologists examined excised nodes microscopically. Patients whose dissection was confined to the pericolonic nodes were excluded.

Notes: APR, abdominal perineal resection; IMA, inferior mesenteric artery; Lap, laparoscopic; N, number of patients evaluated; NR, not reported.

Table 10. Studies reporting outcomes as a function of number of lymph nodes evaluated.

Author, Year (reference)	Study Design	# of lymph nodes removed/examined	N	Overall survival	Disease-free survival	Study Details
Bufalari, 2000 (23)	Single-centre retrospective review	7-14 >14	54 19	52% 67% p=NS	NR	Stage II/III rectal tumours. Specimens formalin-fixed.
Tepper, 2001 (95)	Retrospective nested cohort [b]	Node-negative 0-4 5-8 9-13 ≥14 Node-positive 0-5 6-9 10-14 ≥15	 127 138 129 133 270 306 264 297	5-year 68% 73% 72% 82% 61% 58% 57% 61%	NR	High-risk rectal tumours (T3, T4, or node-positive).
Tocchi, 2001 (96)	Case series	Mean 19.3 ± 8.8	53 total	p=0.08	NR	Mesorectum and open rectum pinned to corkboard and fixed in 10% formaldehyde. Transverse sections carried along the rectal wall and mesorectum at 5 mm intervals. Lymph nodes detected by clearing method.
Stocchi, 2001 (25)	Retrospective nested cohorts [c]	Range 0-56 ≤4: 18% <12:68%	673 total	p=0.46	NR	Stage II/III rectal tumours.
Read, 2002 (19)	Single-centre retrospective review	Mean 14 ± 12	316 total	NR	No significant difference in DFS in univariate or multivariate analysis for number of lymph nodes analyzed.	Patients underwent curative treatment for colon tumours.
Kuru, 2002 (15)	Single-centre retrospective review	5-14 >14	120 59	5-year 57% 67% p=0.53 Survival prognosis: total resected nodes (>14) HR=0.49, p=0.038 [a]	NR	Rectal tumours.
Joseph, 2003 (97)	Retrospective nested cohort [d]	Node-negative pts 10-30 >30	300 total	5-year 80% 100% p=0.03 8-year 72% 92%	5-year 78% 91% p=0.09 8-year 74% 87%	High-risk stage II and III colon tumours.

Author, Year (reference)	Study Design	# of lymph nodes removed/examined	N	Overall survival	Disease-free survival	Study Details
Mukai, 2003 (98)	Single centre retrospective review	All pts ≥17 ≤16 Dukes B pts ≥17 ≤16 Dukes C pts ≥17 ≤16	 119 312 54 113 39 76	10-year 80.8% 64.0% p=0.0374 97.9% 78.8% p=0.0173 70.0% 43.4% p=0.1419	NR	Colorectal tumours.
Radespiel-Troger, 2004 (99)	Single centre retrospective review	 ≤37 >37	 326 315	NR	3-year 82% 80% p=0.53 5-year 80% 77%	Colon tumours. Formal lymph node dissection or extended hemicolectomy or subtotal colectomy with dissection of 2 lymphatic drainage areas.
Wang HS, 2005 (100)	Single centre retrospective review	 <7 ≥7	 70 89	5-year 21.7% 57.9% p<0.00001	NR	T1 colorectal tumours. Formalin-fixed and paraffin-embedded specimens stained with H&E reviewed at time of study. Specific lymph node dissection technique unknown. Adipose clearance solutions not used. All pericolonic and perirectal adipose dissected.
Beresford, 2005 (101)	Single centre retrospective review	Node-negative <3 ≥3	 31 71	3-year 62% 70% 5-year 31% 62%	3-year 26% 58% p=0.43	Rectal tumours. Patients received preoperative synchronous chemoradiotherapy. Specimens inked and fixed in formalin for 72 hours. Highest lymph node found by slicing across the main vascular pedicle just distal to its ligature, and continuing with serial slices at millimetre intervals until a lymph node was found. Other lymph nodes were found by serial slicing though the remainder of the fat and connective tissue. All lymph nodes were submitted for histological examination.

Author, Year (reference)	Study Design	# of lymph nodes removed/examined	N	Overall survival	Disease-free survival	Study Details
Wong, 2005 (102)	Multicentre retrospective case series	Node-negative ≤7 ≥8 ≤8 ≥9 ≤9 ≥10 ≤10 ≥11 ≤11 ≥12 ≤12 ≥13 ≤13 ≥14 ≤14 ≥15	2149 total	5-year 58.5% 84.2% p<0.001 62.3% 85.0% p<0.001 69.2% 84.5% p<0.001 73.5% 84.1% p=0.04 75.1% 84.0% p=0.02 75.3% 84.5% p=0.01 75.7% 84.8% p=0.02 78.2% 83.7% p=0.18	NR	Specimen delivered to pathology fresh and grossly examined. External surface was examined and inked over the palpable tumour. Mesenteric and adventitial fat carefully displaced by manual pressure, visually inspected for lymph nodes, and palpated for the presence of firm tissue that was indicative of a lymph node. No fat clearance used. Representative sections were examined in all grossly involved lymph nodes. Grossly uninvolved lymph nodes smaller than 3 mm were submitted whole and those 3 mm or larger were bivalved and submitted for routine H&E examination.
Berger, 2005 (103)	Retrospective Nested cohort [d]	Mean 13	3411 total	HR=0.980 p<0.0001 [a]	HR=0.985 p=0.0008 [a]	High risk stage II and III colon tumours.
Asaad, 2005 (104)	Single centre retrospective review	≥7 <7	Stage II 112 57 Stage III 130	5-year OS 64.0% 37.8% p<0.001 41.0%	NR	Stage II and III colon tumours.
Koch, 2006 (105)	Prospective study	≥12 <12	80 10	NR	5-year RFS 88% 69% p=0.04 HR=1.7 (95% CI 0.8-3.2) p=0.16 [a]	Stage II colorectal tumours.
George, 2006 (106)	Prospective observational study	0-4 5-10 >10	1104 1717 771	5-year p<0.001	NR	Colorectal tumours. Dukes' stage A-D

Author, Year (reference)	Study Design	# of lymph nodes removed/examined	N	Overall survival	Disease-free survival	Study Details
Laurent, 2006	Single centre			5-year OS	5-year DFS	Rectal tumours.
(31)	retrospective	≤12	141	76%	61%	Microscopic assessment of lymph nodes.
	review	>12	145	70%	60%	
				p=0.53	p=0.86	

Notes: CI, confidence interval; DFS, disease-free survival; H&E, hematoxylin and eosin; HR, hazard ratio; N, number of patients evaluated; NR, not reported; NS, not significant; OS, overall survival; RFS, relapse-free survival.

a Based on multivariate analysis.

b Patients from GI Intergroup trial of adjuvant therapy for patients with resected, high-risk (T3,T4, or node-positive) rectal cancer.

c Patients from three adjuvant study protocols conducted by the North Central Cancer Treatment Group (NCCTG).

d Patients from INT0089, an intergroup trial of adjuvant chemotherapy for high-risk stage II and III colon cancer.

e Patients from North Carolina Colon Cancer Study (NCCCS), a population-based case-control study of environmental and genetic risk factors for colon cancer..

f Cochrane-Armitage test for trend.

h Pooled results of proximal colon, distal colon, and rectal cancer.

Table 11. Prognostic effects of occult tumour cells in lymph nodes.

Author, Year (reference)	Study Design	Occult tumour cell status	N	Overall survival	Disease-free survival	Study Details
Mukai, 2005 (108)	Retrospective review	Positive Negative	21 103	5-year OS 62.3% 91.8% p=0.0003	5-year RFS 34.9% 90.2% p=0.0000	Stage II/Dukes B colorectal tumours without lymph node metastases. Immunohistochemical detection of cytokeratin using AE1/AE3 antibodies. Only occult neoplastic cells floating freely in the lymph node sinuses were counted. Presence of ≥3 cytokeratin-positive cells defined as positive while 0-2 cytokeratin-positive cells defined as negative.
Messerini, 2006 (109)	Single centre retrospective review	Positive Negative ITC positive Micrometastasis positive Negative	151 244 112 39 244	NR	12-year 74.2% 78.3% p=0.39 77.7% 64.1% 78.3% p=0.14	Stage IIA colorectal tumours. Specimens fixed in 10% buffered formalin for 24 hours. Lymph nodes searched using a manual technique without fat clearing. Lymph nodes >5 mm were bisected and lymph nodes ≤5 mm were entirely processed. Tissue samples were embedded in paraffin and stained with H&E. Original histologic slides were reviewed and confirmed to be free of metastases. 12 new serial 5 µm-thick sections were obtained from the original paraffin blocks for each case. Sections were deparaffinized, rehydrated, and incubated with the anti-cytokeratin 20 antibody using an automated immunostainer.
Lee, 2006 (110)	Single centre retrospective review	ITC positive ITC negative	60 61	NR	DFS p=0.809 RR=1.001 (95% CI 0.365-2.745) [a] p=0.998	Stage I and II colorectal tumours. Specimens fixed in formalin and embedded in paraffin. H&E staining and IHC staining were performed in the immediate operative period. One 4- section cut for H&E staining, another 4-section cut for IHC staining with cytokeratin antibody. Paraffin sections were deparaffinized and rehydrated. Original slides were reviewed by a pathologist.
Mukai, 2006 (111)	Prospective cohort?	Stage II/III Positive Negative Stage III Positive Negative	 15 47 9 24	NR	3-year RFS 76.2% 89.0% p=0.4131 62.5% 80.8% p=0.4006	Stage II and III colorectal tumours. Immunohistochemical detection of cytokeratin using AE1/AE3 antibodies. Only occult neoplastic cells floating freely in the lymph node sinuses were counted. Presence of ≥3 cytokeratin-positive cells defined as positive while of 0-2 cytokeratin-positive cells defined as negative.

Notes: CI, confidence interval; DFS, disease-free survival; H&E, hematoxylin and eosin; ITC, isolated tumour cell; IHC, immunohistochemistry; N, number of patients evaluated; NR, not reported; OS, overall survival; RFS, relapse-free survival; RR, risk ratio.
a Based on multivariate analysis

Appendix 2. Appraisal of guidelines using the AGREE Instrument.

The Appraisal of Guidelines Research & Evaluation (AGREE) Instrument provides a framework for assessing the quality of clinical practice guidelines. It consists of 23 items organised in six domains. Three appraisers independently assessed the NCI Guidelines 2000 (2) using all six domains of the AGREE Instrument.

I. NCI Guidelines 2000

Domain	Domain Score
Scope and Purpose	70.4%
Stakeholder Involvement	47.2%
Rigour of Development	50.8%
Clarity and Presentation	83.3%
Applicability	33.3%
Editorial Independence	11.1%

The AGREE Instrument is accessible at http://www.agreecollaboration.org/instrument/. Accessed September 14, 2007.

Appendix 3: Expert Panel on Colon and Rectum Cancer Surgery & Pathology membership.

Dr. Andy Smith, Chair Surgical Oncologist Odette Cancer Centre, Sunnybrook	**Dr. David Driman**, Chair Pathologist London Health Sciences Centre
Dr. Bernard Langer Consultant Cancer Care Ontario	**Dr. Robin McLeod,** Surgical Lead, Quality Improvement Cancer Care Ontario
Karen Spithoff Research Coordinator Program in Evidence-based Care	**Amber Hunter** Quality Coordinator Cancer Care Ontario
Dr. Nancy Baxter Surgical Oncologist St. Michael's Hospital	**Dr. Paul Belliveau** Surgical Oncologist Hotel-Dieu Hospital
Linda Boich Vice President Clinical Services Niagara Health System	**Dr. Mahmoud Khalifa**, Pathologist Odette Cancer Centre, Sunnybrook
Dr. Angus Maciver Surgical Oncologist Stratford General Hospital	**Dr. Craig McFadyen** Surgical Oncologist Grand River Regional Cancer Centre
Dr. Ken Newell Pathologist Grey Bruce Health Services	**Bryan Rumble** Research Coordinator Program in Evidence-based Care
Dr. Marko Simunovic Surgical Oncologist Hamilton Regional Cancer Centre	

program in evidence-based care
a cancer care ontario program

programme de soins fondé sur des preuves
un programme de action cancer ontario

Evidence-Based Series #17-4 Version 2: Section 3

Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes: EBS Development Methods and External Review Process

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A Quality Initiative of Cancer Care Ontario (CCO)'s
Program in Evidence-Based Care (PEBC) and CCO's Surgical Oncology Program (SOP).
Developed by the Expert Panel on Colon and Rectal Cancer Surgery and Pathology.

Report Date: April 17, 2008

These guideline recommendations have been ENDORSED, which means that the recommendations are still current and relevant for decision making. Please see Section 4: Document Assessment and Review for a summary of updated evidence published between 2007 and 2015, and for details on how this Clinical Practice Guideline was ENDORSED.

THE SURGICAL ONCOLOGY PROGRAM AND THE PROGRAM IN EVIDENCE-BASED CARE COLLABORATION

The Surgical Oncology Program (SOP) and the Program in Evidence-based Care (PEBC) are initiatives of Cancer Care Ontario (CCO). The mandate of the SOP is to improve the delivery of cancer surgery in Ontario through initiatives designed to increase access to care, improve the quality of care, support the recruitment and retention of cancer surgeons, support knowledge transfer and evidence-based practice, and foster research and innovation. The mandate of the PEBC is to improve the lives of Ontarians affected by cancer, through the development, dissemination, implementation, and the evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer care. The SOP and PEBC have worked collaboratively on a number of occasions to develop evidence-based materials relevant to the surgical community in Ontario.

The PEBC is well known for producing evidence-based guidelines, known as Evidence-based Series (EBS) reports, using the methods of the Practice Guidelines Development Cycle (1,2). The EBS report consists of an evidentiary base (typically a systematic review), an interpretation of and consensus agreement on that evidence by our Groups or Panels, the

resulting recommendations, and an external review by Ontario clinicians and other stakeholders in the province for whom the topic is relevant. The PEBC has a formal standardized process to ensure the currency of each document, through the periodic review and evaluation of the scientific literature and, where appropriate, the integration of that literature with the original guideline information.

As part of its quality improvement mandate, the SOP convenes expert panels for the selection of quality indicators and the development of clinical guidelines and organizational standards. The panels are comprised of surgeons, other clinicians, health care administrators, other health care professionals, and methodologists and are established on an as-needed basis for specific quality initiatives.

The Evidence-Based Series

Each EBS is comprised of three sections:

- *Section 1: Guideline Recommendations*. Contains the clinical recommendations derived from a systematic review of the clinical and scientific literature and its interpretation by the Group or Panel involved and a formalized external review in Ontario by review participants.
- *Section 2: Evidentiary Base.* Presents the comprehensive evidentiary/systematic review of the clinical and scientific research on the topic and the conclusions reached by the Group or Panel.
- *Section 3: EBS Development Methods and External Review Process.* Summarizes the evidence-based series development process and the results of the formal external review of the draft version of Section 1: Recommendations and Section 2: Evidentiary Base.

DEVELOPMENT OF THIS EVIDENCE-BASED SERIES

Development and Internal Review

This EBS was developed by the Expert Panel on Colon and Rectal Cancer Surgery and Pathology of CCO. See Section 2, Appendix 3 for a complete list of Expert Panel members. The series is a convenient and up-to-date source of the best available evidence on surgical and pathological quality performance in radical surgery for colon and rectal cancer, developed through review of the evidentiary base, evidence synthesis, and input from external review participants in Ontario.

Report Approval Panel

Prior to the submission of this EBS draft report for external review, the report was reviewed and approved by the PEBC Report Approval Panel, which consists of two members, including an oncologist, with expertise in clinical and methodology issues. Key issues raised by the Report Approval Panel included:

- The structure of Section 1 should be reworked to separate key recommendations for which there is supporting evidence from technical and process recommendations that in general are based on Expert Panel consensus.
- The AGREE instrument should be used to assess the quality of guidelines on which this document is based.
- The authors should clarify why data were not pooled in a meta-analysis for some of the results and outcomes.

- The authors should clarify that the outcomes of interest driving the recommendations are local recurrence and overall survival. The authors should consider providing statements about the adverse effects associated with different surgical approaches.

Modifications in Response to Report Approval Panel Feedback:

- The authors restructured the recommendations and evidence in Section 1 to clarify which are the key recommendations directly supported by evidence and which are technical recommendations based on Expert Panel consensus.
- The AGREE instrument was used to assess the quality of the NCI Guidelines 2000 (3). Results are reported in Appendix 2.
- The authors did not feel that meta-analyses were appropriate because of the high degree of heterogeneity between study designs, reporting of outcomes and outcome comparisons. A paragraph was added to the methods section to indicate that no meta-analyses were performed.
- A statement was added to Section 1 that the outcomes driving the recommendations are local recurrence and overall survival. A review of adverse events associated with the surgical approaches discussed would be complex and likely of poor quality. Where available, general statements about adverse effects were added.

External Review by Ontario Clinicians

Following the review and discussion of Section 1: Recommendations and Section 2: Evidentiary Base of this EBS and review and approval of the report by the PEBC Report Approval Panel, the Expert Panel on Colon and Rectal Cancer Surgery and Pathology circulated Sections 1 and 2 to external review participants in Ontario for review and feedback.

Methods

Feedback was obtained through a mailed survey of 168 external review participants in Ontario (92 surgeons, 48 pathologists, 12 radiation oncologists, and 16 medical oncologists). The survey consisted of items evaluating the methods, results, and interpretive summary used to inform the draft recommendations and whether the draft recommendations should be approved as a guideline. Written comments were invited. The survey was mailed out on December 10, 2007. Follow-up reminders were sent at four weeks (post card) and six weeks (complete package mailed again). The Expert Panel on Colon and Rectal Cancer Surgery and Pathology reviewed the results of the survey.

Results

Eighty responses were received out of the 168 surveys sent (48% response rate). Responses include returned completed surveys as well as phone, fax, and email responses. Of the participants who responded, 62 indicated that the report was relevant to their practice or organizational position, and 63 completed the survey (79%). Results of the feedback survey are summarized in Table 12.

Table 12. Responses to items on the external review feedback survey.

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Disagree or disagree strongly**
The rationale for developing a guideline, as stated in the "*Introduction*" section of the draft report, is clear.	60 (97)	2 (3)	
There is a need for a guideline on this topic.	61 (97)		2 (3)
The literature search is relevant and complete (i.e., no key trials were missed nor any included that should not have been).	52 (85)	9 (15)	
I agree with the methodology used to summarize the evidence.	57 (92)	5 (8)	
The results of the trials described in the draft report are interpreted according to my understanding of the data.	60 (98)	1 (2)	
The draft recommendations in the report are clear.	61 (98)		1 (2)
I agree with the draft recommendations as stated.	60 (97)	1 (2)	1 (2)
The draft recommendations are suitable for the patients for whom they are intended.	61 (98)	1 (2)	
The draft recommendations are too rigid to apply to individual patients.	7 (11)	8 (13)	46 (75)
When applied, the draft recommendations will produce more benefits for patients than harms.	58 (95)	2 (3)	1 (2)
The draft report presents options that will be acceptable to patients.	52 (88)	5 (8)	2 (3)
To apply the draft recommendations will require reorganization of services/care in my practice setting.	9 (15)	13 (22)	38 (63)
To apply the draft recommendations will be technically challenging.	17 (27)	4 (6)	41 (66)
The draft recommendations are too expensive to apply.	4 (6)	10 (16)	48 (77)
The draft recommendations are likely to be supported by a majority of my colleagues.	52 (84)	6 (10)	4 (6)
If I follow the draft recommendations, the expected effects on patient outcomes will be obvious.	40 (67)	19 (32)	1 (2)
The draft recommendations reflect a more effective approach for improving patient outcomes than is current usual practice. †	27 (44)	8 (13)	1 (2)
When applied, the draft recommendations will result in better use of resources than current usual practice. †	16 (26)	16 (26)	3 (5)
I would feel comfortable if my patients received the care recommended in the draft report.	58 (94)	3 (5)	1 (2)
This draft report should be approved as a practice guideline.	55 (92)	4 (7)	1 (2)
To apply the draft recommendations would require an increase in pathology technical staff.	25 (41)	25 (41)	11 (18)
To apply the draft recommendations would require training/mentoring of surgeons.	45 (75)	11 (18)	4 (7)
Which do you foresee as the biggest obstacles to implementing these recommendations in your hospital setting?			
a) Not enough pathologists		21 (36)	15 (25)
b) Not enough pathologist assistants	23 (39)	22 (37)	8 (14)
c) Not enough surgeons	29 (49)	22 (38)	30 (52)
d) Lack of training (technical skills)	6 (10)	21 (37)	21 (37)
e) Too many other competing priorities	15 (26)	16 (28)	25 (43)
f) Poor collaboration between surgeons and pathologists	17 (29) 16 (27)	16 (27)	27 (46)

Item	Number (%)*		
	Strongly agree or agree	**Neither agree nor disagree**	**Disagree or disagree strongly**
I see myself playing an active role in contributing towards the implementation of this guideline.	37 (73)	11 (22)	3 (6)
If the draft report were to become a practice guideline, how likely would you be to make use of it in your own practice?	**Likely or very likely**	**Unsure**	**Not at all likely or unlikely**
	55 (92)	3 (5)	2 (3)
If the draft report were to become a practice guideline, how likely would you be to apply the recommendations to your patients?	56 (95)	2 (3)	1 (2)

***** Percentages reported are percentages of practitioners who provided an answer to the question.

† 26 respondents answered that the draft recommendations are the same as current practice and checked "not applicable".

Summary of Written Comments and Expert Panel Responses

Twenty-one respondents (33%) provided written comments. The main points contained in the written comments are summarized in Table 13.

Table 13. Summary of external review comments and Expert Panel responses.

TARGET POPULATION:
One respondent commented that the target population for the guideline should not be limited to selected M1 lung or liver metastases, given that overall survival for patients with resectable M1 lesions at other sites may reach 15-20%.
Response: The Target Population in Section 1 was modified to include "selected patients with M1 disease", instead of "selected patients with M1 liver or lung metastases".
COLON AND RECTUM DEFINITIONS:
Three respondents commented on the definitions of the colon and rectum in the draft Section 1. One respondent liked that the rectum was anatomically defined to a structure that could be identified on preoperative scans and was consistent with criteria for adjuvant therapy. A second respondent questioned the definition of the rectum, since the anorectal ring is the anatomic landmark most readily judged on a physical exam and is applied practically in assigning lesions as arising in the anal cavity versus the rectum. A third respondent commented that a definition of tumour location with respect to the anterior peritoneal reflection should be included.
Response: The definitions of the colon and rectum were replaced by definitions of colon and rectal cancers in Section 1. A comment regarding tumour location with respect to the anterior peritoneal reflection was added to the footnote in section 1.
PREOPERATIVE IMAGING:
One respondent requested further clarification regarding preoperative imaging, particularly criteria for MRI, for colorectal cancer. Another respondent commented that this guideline provides an opportunity to set a standard for preoperative imaging in rectal cancer. Two additional respondents commented that the availability of preoperative imaging in a timely manner is an obstacle to implementing the guideline recommendations.
Response: Imaging for colorectal cancer has been addressed in more depth in a separate CCO PEBC Recommendations Report, "Cross-sectional imaging in colorectal cancer". More specific recommendations for preoperative imaging are beyond the scope of this guideline.
PROXIMAL AND DISTAL MARGINS:

Three respondents requested clarification regarding proximal and distal resection margins. One respondent questioned whether the stapler donut should be included in the distal margin of rectal cancer. Another respondent felt that recommending resection of 10 cm on either side of colon tumours but a 5 cm proximal margin for rectal tumours seems inconsistent. The third respondent requested clarification of what defines proximal, mid- and low rectum and commented that all patients with mid-rectal tumours would be submitted to coloanal anastomosis if a 5 cm distal margin was attempted.

Response: Statements were added to the recommendations to clarify that measurement of the distal rectal margin should not include the stapler donut and the donut should not be relied on to determine margin status. The recommendation for adequate proximal and distal colon margin length was changed from 5-10 cm to 5 cm to be consistent with recommendations for rectal cancer. A definition of upper-, mid- and low rectum was added to the footnotes in Section 1. The phrase "in most patients" was added to the recommendation that the distal margin length should be a minimum of 5 cm from the distal edge of the primary tumour for tumours of the proximal and mid rectum, to recognize that a 5 cm margin may not be possible in all patients.

CIRCUMFERENTIAL RADIAL MARGINS:

One respondent commented that the wording of the statement "the upper rectum has a non-circumferential posterior radial margin" (2.1.2 *Technical Recommendations for Circumferential Radial Margins*) was confusing.

Response: The statement "the upper rectum has a non-circumferential posterior radial margin" was changed to "the upper rectum has a peritonealized anterior surface and a non-peritonealized posterior radial margin similar to the ascending and descending colon."

PATHOLOGICAL ASSESSMENT OF RESECTION MARGINS:

Several respondents commented on the recommendations for pathological assessment of resection margins. Two respondents commented that leaving the rectal tumour segment unopened results in poor fixation and one commented that the risks and benefits of the Quirke method should be further evaluated. One respondent commented that pathologists are sometimes requested to open the specimen and report the distal margin intraoperatively. One respondent expressed concern that the recommendation that the "distal margin length should be measured in the fresh, anatomically restored ex vivo condition immediately after removal" would lead surgeons to open the specimen to assess distal margins immediately after removal. Another respondent requested clarification regarding how T stage should be reported for tumours associated with discontinuous extramural extension.

Response: Additional processing details to ensure adequate fixation, including placement of a gauze wick into the unopened specimen and fixation for a minimum of 24 hours, were added to the recommendations (2.2.2). A note was added to the recommendations that discontinuous extramural extension should be classified as pT3 (3.2.2).

SEROSAL PENETRATION:

One respondent requested a clear definition of serosal penetration.

Response: A definition of serosal penetration was added to the recommendations (2.2.2).

EN BLOC MULTIVISCERAL RESECTION:

One respondent objected to the use of the term "standard resection" to refer to non-en bloc resection.

Response: The term "standard resection" was retained, as this term was used in the literature cited.

LYMPHADENECTOMY:

Several comments were received regarding lymphadenectomy and examination of lymph nodes. One respondent commented that there is no evidence for the recommendation to sample suspicious lymph nodes outside the field of resection and another felt that separating routinely identified micrometastases should not be recommended. One respondent requested further information on the role of sentinel lymph nodes and

another requested clarification regarding whether larger nodes should be bisected or trisected before submitting in their entirety.
Response: The recommendation to sample suspicious lymph nodes outside the field of resection was removed. Sentinel lymph node biopsy remains an experimental procedure, as stated in the Discussion of Section 2, and is not included in the recommendations. Additional details regarding identification of micrometastases and isolated tumour cells were added to the recommendations (3.2.2). The panel did not feel that additional details regarding bisecting or trisecting larger nodes was required.
PREOPERATIVE THERAPY:
Two respondents commented that recommendations for consideration of preoperative therapy should apply to rectal cancer only.
Response: The recommendation to consider preoperative therapy for colon and rectal tumours not initially considered resectable (i.e., threatened or involved radial margin) was retained.
VOLUME-RELATED OUTCOMES:
One respondent commented that the recommendations did not address volume-related outcomes in rectal cancer, presuming that referral to high volume centres further optimizes outcome.
Response: Volume-related outcomes were beyond the scope of this guideline and were not addressed.
OBSTACLES TO IMPLEMENTATION:
Several respondents suggested obstacles to implementing the guideline recommendations, other than those identified in the questionnaire (Table 12). These included availability of preoperative imaging, surgical communication to pathologists regarding circumferential radial margins, serosal adhesions and identification of proximal and distal margins, and the submission of fresh specimens at appropriate times.
Response: No response was required.

Conclusion

This EBS report reflects the integration of feedback obtained through the external review process with final approval given by the Expert Panel on Colon and Rectal Cancer Surgery and Pathology and the Report Approval Panel of the PEBC. Updates of the report will be conducted as new evidence informing the questions of interest emerges.

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REFERENCES

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3. Nelson H, Petrelli N, Carlin A, Couture J, Fleshman J, Guillem J, et al. Guidelines 2000 for colon and rectal cancer surgery. J Natl Cancer Inst. 2001;93:583-96.

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Evidence-Based Series #17-4: Version 2: Section 4

A Quality Initiative of the
Program in Evidence-Based Care (PEBC), Cancer Care Ontario

Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes:

The Expert Panel on Colon and Rectal Cancer Surgery and Pathology

November 29, 2016

The 2008 guideline recommendations are

ENDORSED

This means that the recommendations are still current and relevant for decision making.

OVERVIEW

The original version of this guidance document was released by Cancer Care Ontario's Program in Evidence-based Care in 2008.

In December 2014, this document was assessed in accordance with the PEBC Document Assessment and Review Protocol and was determined to require a review. As part of the review, a PEBC methodologist conducted an updated search of the literature. Two clinical experts reviewed and interpreted the new eligible evidence and proposed the existing recommendations could be endorsed. The Expert Panel on Colon and Rectal Cancer Surgery and Pathology endorsed the recommendations found in Section 1 (Clinical Practice Guideline) on November 29, 2016.

DOCUMENT ASSESSMENT AND REVIEW RESULTS

Question Considered

1. What is the recommended technique and extent of surgical resection for curable colorectal cancer (CRC), including extent of bowel resection, extent of lymph node resection, and reporting requirements?

2. What is the recommended approach to processing and reporting the resected specimen, including specimen marking in the operating room, as well as processing and reporting requirements in the pathology laboratory?

Literature Search and New Evidence

The new search from February 2007 to February 2016 yielded 76 references evaluating the optimization of surgical and pathological quality performance in radical surgery for colon and rectal cancer. Nineteen studies reported on colon and rectum margins of resection; of these, five examined positive versus negative margins, four looked at proximal and distal margins, and 10 examined radical and circumferential margins. Two studies compared total mesorectal excision to conventional resection and one examined En bloc multivisceral resection of adherent tumours. Three studies reported on inadvertent perforations and one study reported on outcomes by extent of lymphadenectomy. Finally, 52 studies examined outcomes as a function of number of lymph nodes evaluated (some studies reported on more than one outcome).

Impact on Guidelines and Its Recommendations

The Expert panel agreed that no new recommendations are required and that the 2008 recommendations cover all relevant subjects areas identified in the new evidence; therefore, the Expert Panel ENDORSED the recommendations on optimization for surgical and pathological quality performance in radical surgery for colon and rectal cancer.

In the 2008 version, along with key recommendations, "technical recommendations" were made based on the Expert Panel consensus informed by, the AJCC/UICC TNM, 6th edition, NCI Guidelines 2000, and other literature sources as described in the guideline. Since 2008, the publication of the College of American Pathologists (CAP) "Protocol for the Examination of Specimens from patients with Primary Carcinoma of the Colon and Rectum" (based on AJCC/UICC TNM, 7th edition)(1), along with other relevant documents (2, 3), has prompted an update in the wording and structure of seven of these technical recommendations. These changes are outlined in Table 9 below and described with qualifying statements in the appropriate areas in "Section 1: Guideline recommendations."

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Document Review Tool

Number and title of document under review	17-4: Optimization of Surgical and Pathological Quality Performance in Radical Surgery for Colon and Rectal Cancer: Margins and Lymph Nodes
Current Report Date	April 17, 2008
Clinical Expert	Dr. Erin Kennedy and Dr. David Driman
Research Coordinator	Sarah Kellett (until Oct 7, 2015) and Judy Brown
Date Assessed	March 10, 2016

Approval Date and Review Outcome (once completed)	November 29, 2016 ENDORSED

Original Question(s):

1. What is the recommended technique and extent of surgical resection for curable colorectal cancer (CRC), including extent of bowel resection, extent of lymph node resection, and reporting requirements?
2. What is the recommended approach to processing and reporting the resected specimen, including specimen marking in the operating room, as well as processing and reporting requirements in the pathology laboratory?

Target Population:

Patients with curable colon and rectal cancer in whom surgical management with radical excision is undertaken. This may include selected patients with M1 disease. This document does not apply to patients with primary cancers that are managed by polypectomy or full thickness transanal excision, patients treated for recurrent tumours, or patients undergoing surgery with palliative intent.

Study Section Criteria:

Inclusion Criteria
Studies were considered eligible for inclusion if they were:
1. Randomized controlled trials (RCTs), non-randomized prospective studies, case-series or retrospective reviews reporting relevant outcome data for patients undergoing surgical resection for primary colon or rectal cancer.
2. Syntheses of evidence in the form of systematic reviews or meta-analyses.
3. Published in the English language.

Exclusion Criteria
Studies were not considered for inclusion if they were:
1. Case reports or narrative review articles.
2. Studies of patients undergoing surgical resection for recurrent colon or rectal cancer.

Search Details:

- February 2007 to February 2016 (Medline Aug wk 4 and Embase wk 32)
- February 2007 to February 2016(ASCO Annual Meeting)
- February 2007 to February 2016 (clinicaltrials.gov)

Brief Summary/Discussion of New Evidence:

The new search from February 2007 to September 2015 yielded 76 references evaluating the optimization of surgical and pathological quality performance in radical surgery for colon and rectal cancer. Nineteen studies reported on colon and rectum margins of resection; of these, five examined positive versus negative margins, four looked at proximal and distal margins, and 10 examined radical and circumferential margins. Two studies compared total mesorectal excision to conventional resection and one examined En bloc

multivisceral resection of adherent tumours. Three studies reported on inadvertent perforations and one study reported on outcomes by extent of lymphadenectomy. Finally, 52 studies examined outcomes as a function of number of lymph nodes evaluated (some studies had more than one outcome).

Clinical Expert Interest Declaration:

None declared.

Instructions. Instructions. For each document, please respond YES or NO to all the questions below. Provide an explanation of each answer as necessary.

1. Does any of the newly identified evidence, on initial review, contradict the current recommendations? (i.e., the current recommendations may cause harm or lead to unnecessary or improper treatment if followed)	No.
2. Does the newly identified evidence support the existing recommendations?	Yes.
3. Do the current recommendations cover all relevant subjects addressed by the evidence, such that no new recommendations are necessary?	Yes.

4. Is there a good reason (e.g., new stronger evidence will be published soon, changes to current recommendations are trivial or address very limited situations) to postpone updating the guideline? Answer Yes or No, and explain if necessary:	No. There will be an updated colorectal cancer pathology reporting protocol from AJCC/CAP within the next year or so. There will be changes in that document but we predict that these will not affect the current recommendations.

Review Outcome	ENDORSE
DSG/GDG Approval Date	November 29, 2016
DSG/GDG Commentary	The Expert Panel suggested updating the wording and structure of seven of the technical recommendations to align them with current practice.

Rererences

1. Tang LH, Berlin J, Branton P, Burgart LJ, Carter DK, Fitzgibbons PL, et al. Protocol for the examination of specimens from patients with primary carcinoma of the colon and rectum. College of American Pathologists. 2016;Based on AJCC/UICC TNM, 7th edition; Protocol web posting date: January 2016(https://www.google.ca/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&uact=8&ved=0ahUKEwj4zdrqjs7QAhWl24MKHamSArMQFgghMAE&url=http%3A%2F%2Fwww.cap.org%2FShowProperty%3FnodePath%3D%2FUCMCon%2FContribution%2520Folders%2FWebContent%2Fpdf%2Fcp-colon-16protocol-3400.pdf&usg=AFQjCNGD14BIdVjzMZIA29UFZbFHLa_3bw&sig2=ekws6s8ouRcn-jBuSyXY6A).
2. Kennedy A, Vella E, MacDonald D, Wong S, McLeod R. Optimization of preoperative assessment in patients diagnosed with rectal cancer. . In: Program in Evidence-Based Care E-BSN-, editor. Toronto (ON): : Cancer Care Ontario; 2014 January 15.
3. Wong RKS, Jang R, Darling G. Postoperative chemoradiotherapy vs. preoperative chemoradiotherapy for locally advanced (operable) gastric cancer: clarifying the role and technique of radiotherapy. J Gastrointest Oncol. 2015 07/08/received 09/20/accepted;6(1):89-107.

Table 1. Colon and rectum margins of resection: positive vs. negative (5 studies)			
Author, year	**Study Characteristics**	**Results**	**Author's conclusion**
(Angelsen et al. 2014)	**Design:** A combined retrospective and prospective cohort study of consecutive patients with CLM without extrahepatic disease treated with primary resection at a medium volume centre. **Groups:** margin width A: R1, <1 mm (n=48), B: 1 to 4 mm (n=77), C: 5 to 9 mm (n=46) and D: >10 mm (n=71).	**LR:** R1, <1 mm 14.6% OR=24.89 (4.77, 129.69) p=0.0001 1-4 mm 3.9% OR=16.00 (3,22, 79.56) p=0.001 5-9 mm 6.5% OR=5.25 (0.95, 29.15) p=0.058 ≥10 mm 1.3% OR=1.00 (ref) **DFS:** NR **OS:** RM status: 42.5% in R0 (ref), 16.1% in R1 p=0.011; resections HR=1.53 (0.98, 2.39) p=0.067	R1 resections for CLM predict adverse outcome. RMs below 5 mm increased the risk for LR and shortened the time to recurrence. Preoperative chemotherapy did not alter an adverse outcome in R1 vs. R0 patients.
(Dassanayake et al. 2011)	**Design:** A case-control study of patients with rectal cancer having surgery with curative intent **Groups:** patents with local recurrence (n=21) and controls without local recurrence (n=78)	**LR:** PRM model 1 OR=4.81 (p<0.01) and Model 2 OR= 5.51 respectively (p<0.01), PRM only factors associated with LR for both models (OR 4.81 and 5.51 respectively) **DFS:** NR **OS:** NR	A PRM is the single factor affecting local recurrence of rectal cancer in patients not receiving neo-adjuvant therapy.
(Hamady et al. 2014)	**Design**: Observational prospectively collected data for 2715 patients who underwent primary resection of CLM from 2 major hepatobiliary units in the UK. **Groups:** RM <1 mm, (n=663), ≥1 mm (n=2052)	**LR:** NR **DFS**: RM <1 mm 5-yr DFS 20%, median 15mo; ≥1 mm 5-yr DFS 33%, median 28mo; HR=1.4 (1.2-1.5) p<0.001 **OS:** NR	One-mm cancer-free RM achieved in patients with colorectal liver metastases should now be considered the standard of care.
(Sadot et al. 2015)	**Design:** A single-institution prospectively maintained database metastatic CRC - liver hepatic resection **Groups**: Margin status 0mm (n=245), R0 (0.1 to 0.9 (n= 160) mm, 1 to 9 mm (n=1191) and ≥10 mm (n=765)	**LR:** NR **DFS:** NR **OS:** Nodal status of primary, negative 39%, positive 61%: HR=1.6(1.4-1.7); p<0.001. Margin status: 0mm (ref); 0.1-0.9mm, HR=0.7(0.6-0.9) p=0.03; 1-9mm, HR=0.6(0.5-0.7), p<0.001; >10mm, HR=0.5(0.4-0.6) p=<0.001.	Resection margin width is independently associated with OS. Wide margins should be attempted whenever possible. However, resection should not be precluded if narrow margins are anticipated, as submillimeter margin clearance is associated with improved survival.
(Wu et al. 2014)	**Design**: Patients with resectable adenocarcinoma and treated with TME selected from a single institution in Japan 2003 to 2011 **Groups:** Number of lymph nodes retrieved (NLNR) <5 (n=66) ≥5 (n=75); Lymph-vascular invasion (LNI) yes (n=9)/no (n=132)	**LR:** NR **DFS:** Number of retrieved lymph nodes <5 3 yr 68.2%, 5yr 57.4%, ≥5 3yr 93%, p= 0.000; LNI Yes 3yr 85.7% 5yr 22.4%, 3yr 81.6 5yr 71.9%, p=0.768 **OS:** NR	For the patients with pT3N0 rectal cancer, addition radiation after TME surgery made no significant differences in survival rate and local recurrence rate.
CLM=colorectal liver metastases; CRC=colorectal cancer; CRM=cirumferential resection margin; CRT=preoperative chemoradiotherapy; DFS=disease free survival; DSS=disease specific survival; HR=hazard ratio; LR=local recurrence; nCRT=neoadjuvant chemoradiotherapy; NR=not reported; OR=odds ratio;			

Table 1. Colon and rectum margins of resection: positive vs. negative (5 studies)			
Author, year	**Study Characteristics**	**Results**	**Author's conclusion**
OS=overall survival, RC=rectal cancer; RM=resection margin; ROD=risk of death; TME=Total Mesorectal Excision;			

Table 2. Colon and rectum margins of resection: proximal and distal (4 studies)			
Author, year	**Study Characteristics**	**Results**	**Author's conclusion**
(Bernstein et al. 2012)	**Design:** Prospective cohort of a national study consisted of 3571 patients receiving anterior resection for RC without preoperative RT **Groups:** DRM ≥11mm (n=543), ≤10mm (n=3028)	**LR:** DRM ≥11mm (ref), ≤10mm HR=2.20(1.5-3.24)p<0.001; 5 yr DRM≤10 mm 14.5% (11.1–17.9), ≥11 mm 8.6% (7.4–9.8) p<0.001 **DFS:** NR **OS:** DRM ≥11mm (ref), ≤10mm HR=1.08 (0.89-1.31)p=0.46; 5 yr DRM ≤10 mm 68.5% (64.3–72.7) ≥11 mm 68.8% (67.0–70.6) p<0.641	For rectal cancer patients treated without RT, a DRM of >10 mm is recommended.
(Kim et al. 2014)	**Design:** 368 patients with locally advanced RC. All underwent preoperative CRT and sphincter-sparing surgery **Groups:** Distal Margin (DM) ≤3 (n=84), >3 (n=284)	**Pelvic tumour control:** ≤3 mm: 66.7%, >3 mm: 86.2% with a ypT3-4 tumour (P=0.049), ≤3 mm: 70.0%, >3 mm: 89.1% in patients who showed no response to CRT (P=0.039) **DFS:** 5-yr DRM ≤3 mm: 75.8%, >3 mm: 77.2%, p=0.816 **OS:** NR	The results suggest that a distal margin of ≤3 mm in the surgical specimen after preoperative CRT is associated with a lower rate of pelvic tumour control at 5 years in patients with Stage ypT3-4 tumours or in those who do not respond to CRT
(Lin et al. 2013) 2013	**Design:** Prospective review of medical records of patients who underwent potentially curative surgery for RC **Groups:** Positive (n=13), negative (n=335)	**LR:** Distal margin ≥2 cm HR=1.00 (.42–10.23) Distal margin <2 cm HR=2.07, p=.375 **DFS:** NR **OS:** NR	Circumferential resection margin of ≤1 mm adversely affects cancer-specific survival, local recurrence, and distant metastasis.
(Pacelli et al. 2013)	**Design:** Prospectively collected hospital records of 338 patients surgically treated for RC **Groups**: DRM Negative (n=332), Positive (n=6)	**LR 5-yr:** DRM positive 20% vs negative 4.7%, p=0.01 **DFS 5-yr:** DRM positive 16.7% vs negative 72.8%, p<0.001;DRM positive 62.5% vs negative 79.9%, p<0.001 **OS:** NR	The extent of mesorectal excision should be tailored depending on tumor location and the use of neoadjuvant chemotherapy, combined with IORT in advanced middle and low rectal cancer, leading to remarkable tumor down staging with excellent prognosis in responding patients.
CLM=colorectal liver metastases; CRC=colorectal cancer; CRM=cirumferential resection margin; CRT=preoperative chemoradiotherapy; DFS=disease free survival; DRM = distal resection margin; DSS=disease specific survival; HR=hazard ratio; IORT = intraoperative radiotherapy; LR=local recurrence; nCRT=neoadjuvant chemoradiotherapy; NR=not reported OR=odds ratio; OS=overall survival, RC=rectal cancer; RM=resection margin; ROD=risk of death; TME=Total Mesorectal Excision			

Table 3. Colon and rectum margins of resection: radical and circumferential (10 studies)			
Author, year	**Study Characteristics**	**Results**	**Author's conclusion**
(Bernstein et al. 2009)	**Design:** A national population-based rectal cancer registry for CRC **Groups:** CRM 0-2 mm (n=496), CRM 2+ (n=2700)	**LR:** 5-yr CRM 0-2 mm 23.7%, CRM 2+ 8.9%, p<0.001 **DFS:** NR **OS:** 5-yr CRM 0-2 mm 44.5%, CRM 2+ 66.0%, p<0.001	A CRM of 2 mm or less confers a poorer prognosis and patients should be considered for neoadjuvant treatment.
(Hwang et al. 2014)	**Design:** Retrospectively analyzed data from patients who underwent preoperative CRT and curative surgery for locally advanced rectal cancer **Groups:** CRM>2 mm (n=487), CRM=1.1-2.0 mm (n=36), CRM=0.1-1.0 mm (n=200, CRM=0 mm (n=18)	**LR**5-yr: CRM=0 mm: 63.0%, HR=1.00 (ref); CRM=0.1-1.0 mm: 24.4%, HR=0.28 (0.08–0.91) p= 0.035; CRM=1.1–2.0 mm: 10.3%, HR=0.11 (0.03–0.46) p= 0.002; CRM>2.0 mm:10.1% HR=0.18 (0.08–0.42) p=0.0001 **DFS:**5-yr: CRM=0 mm: 22.2%, HR=1.00 (ref); CRM=0.1-1.0 mm: 51.8%, HR=0.32 (0.13–0.75) p=0.009; CRM=1.1–2.0 mm: 70.1%, HR=0.24 (0.10–0.54) p= 0.001; CRM>2.0 mm: 77.7%, HR=0.26 (0.14–0.48) p<0.0001 **OS:** NR	After preoperative CRT, CRM distance provides useful information for risk stratification in the recurrence of rectal cancer.
(Kang et al. 2013)	**Design:** Prospectively collected data of 449 patients who underwent curative resection followed by complete adjuvant CRT for stage III RC located within 12 cm from the anal verge **Groups:** CRM-positive group (n=79) and a CRM-negative group (n=370)	**LR:** CRM≤1 mm 13%, CRM>1 mm 13.5%, p=0.677 **RFS:** HR=1.5, CI: 1.0-2.2, p=0.017 **DFS:** NR **OS:** NR	Local recurrence rate did not differ according to CRM involvement status in stage III rectal cancer patients, although CRM involvement was shown to be an independent poor prognostic factor.
(Kelly et al. 2011)	**Design:** 1561 patents undergoing curative excision of RC **Groups:** CRM ≤1 (n=232), CRM=1-5 mm (n=370), CRM=5-10 mm (n=288), CRM>10 mm (n=671)	**LS:** NR **DFS:** NR **OS:** 5-yr: CRM≤1 43.2%, CRM=1-5 mm 51.7%, CRM=5-10 mm 66.6%, CRM>10 mm 66.0% **ROD:** >10mm vs ≤1mm HR=1.61, p<0.001; >10mm vs 1mm-5mm HR=1.35, p=0.005; >10mm vs 5-10mm HR=1.02, p=0.873	A predicted CRM of 5 mm or less on preoperative staging should be considered for neoadjuvant treatment.
(Kennelly et al. 2013)	**Design:** retrospectively collected data from patients from five hospital databases treated for RC **Groups:** CRM-negative (n=260), CRM-positive (n=42)	**LR:** CRM positivity OR=3.63 (1.42-9.75) p=0.016; time to node positivity OR=1.78 (0.68, 4.65) p=0.324 **DFS:** NR **OS:** death CRM positivity OR=2.94, (1.22-9.65) p=0.017	In patients undergoing APE by appropriately trained surgeons using a standardized approach, margin positivity was dictated by tumour stage, but not by centre or surgeon.

Table 3. Colon and rectum margins of resection: radical and circumferential (10 studies)			
Author, year	**Study Characteristics**	**Results**	**Author's conclusion**
(Lin et al. 2013)	**Design:** 348 patients who underwent potentially curative surgery for RC **Groups:** Positive (n=13), negative (n=335)	**LR:** CRM>1 mm HR=1.00 (ref), CRM≤1 mm HR=7.38 (1.42–38.41) p=0.018; No lymphovascular invasion HR=1.00, Lymphovascular invasion HR=1.28 (0.16-10.42) p=0.816 **DFS:** NR **CSS:**5-yr: Circumferential resection margins: negative 75.8%, positive 0%, p=0.001 **OS:** NR	Circumferential resection margin of ≤1 mm adversely affects cancer-specific survival, local recurrence, and distant metastasis.
(Nikberg et al. 2015)	**Design:** A multidisciplinary, prospective, population-based, single institution study for RC. **Groups:** CRM≤1mm (n=32), CRM>1mm (n=416)	**LR:** NR **DFS:** CRM>1mm HR=1.00 (ref), ≤1mm HR=0.87 (0.36-2.07) p=0.749; Num of lymph nodes HR=0.97(0.94-1.00) p=0.088 **OS:** NR	CRM is an important measurement in rectal cancer pathology, but the correlation to local recurrence is much less than previously stated, probably because of oncological treatment and surgery that respects the mesorectal fascia and, when required, en bloc resections. CRM should not be used as a prognostic marker in the modern multidisciplinary management of rectal cancer.
(Pacelli et al. 2013)	**Design:** Prospectively collected hospital records of 338 patients surgically treated for RC **Groups:** CRM Negative (n=265), Positive (n=4)	**LR:** 5-yr: CRM positive 100% vs negative 4.2%, p<0.001 **DFS:** 5-yr: CRM positive 0% vs negative 75.6%, p<0.001 **DSS:** 5-yr: CRM positive 0% vs negative 88.3%, p<0.001 **OS:** NR	The extent of mesorectal excision should be tailored depending on tumor location and the use of neoadjuvant chemotherapy, combined with IORT in advanced middle and low rectal cancer, leading to remarkable tumor down staging with excellent prognosis in responding patients.
(Park et al. 2014)	**Design:** A retrospective review of prospectively collected data of a single tertiary care hospital for RC **Groups:** CRM <0.5 mm (n=NR), <1.0, <2.0mm(n=NR), and <3.0 mm (n=NR)	**LR:** NR **DFS:** CRT(-) CRM≤1 mm, HR=2.33 (1.16–4.70) p=0.018 CRT(+) CRM≤1 mm, HR=3.42 (1.10–10.62) p=0.034 **OS:** CRT(-) CRM≤1 mm, HR=2.20 (1.10–4.41) p=0.026; CRT (+) CRM, ≤1 mm, HR=5.35 (1.81–15.83) p=0.002	A CRM of <1 mm had a strong association with DFS compared with CRM <0.5, <2.0, and <3 mm. A CRM <1 mm was an independent predictor of a poor outcome in both the non CRT and CRT groups.
(Tilney et al. 2009)	**Design:** Prospectively collected data from single tertiary care referral centre (n=435) for RC **Groups:** >10 mm (n=262), 3-10 mm (n=96), 2 mm (n=21), and ≤1mm (n=56)	**LR:** >10 mm 9.0% , 2-10 mm 14.7%, ≤1mm 25.8%, p<0.001; ≤1 mm HR=2.29, p=0.041 **CSS:** >10 mm 80.8%, 3-10 mm 69.2%, 2 mm 59.2%, ≤1mm 34.1%, p<0.001; CSM CRM ≤1 mm vs. >10 mm HR=3.38, p=0.014, CRM ≤1 mm vs. 2 mm HR=2.24, p=0.029 **OS:** NR	CRM ≤2 mm are associated with significantly reduced CSS, and margins ≤1 mm with increased LR, when other factors are accounted for, challenging the assumption that a circumferential resection margin of ≤1 mm is safe.

Table 3. Colon and rectum margins of resection: radical and circumferential (10 studies)			
Author, year	**Study Characteristics**	**Results**	**Author's conclusion**
(Wang et al. 2009)	**Design:** 106 RC patients prospectively followed **Groups:** CRM involvement (CRMI) n=20, CRM negative (CRMN) n=86	**LR:** CRMI n=3, CRMN n=7, p<0.002 **DFS:** CRMI 15%, CRMN 73.3%, p<0.001 **OS:** CRMI 45%, CRMN 79.1%, p<0.001	Detailed pathologic examination, including status of CRM, is advocated since it provides accurate prognostic information. Surgeons could maximize the probability of cure by following the principle of TME. Preoperative adjuvant therapy was essential for advanced staged and lower-located lesions, which implied likelihood of CRMI.
CSS = cancer specific survival; CRM=cirumferential resection margin; DFS=disease free survival; DSS = disease specific survival; ; LR = local recurrence; nCRT=neoadjuvant chemoradiotherapy; ROD = risk of death; RC = rectal cancer; RFS = relapse free survival			

Table 4. Comparative studies of total mesorectal excision versus conventional resection (2 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Petronella et al. 2010)	**Design: Retrospective** comparison of two groups of patients operated for rectal carcinoma **Groups:** RC/ TME (n=47), historical control no TME (n=46)	**LR:** 6% vs 13%	TME patients, complications are lower than in no TME patients; the site of the tumour affects the appearance of complications which are more frequently in distal localizations. An important result is the minor incidence of local recurrences after TME, which brings us to the conclusion that TME can be considered a valid method with an acceptable risk for the surgery of rectal tumour.
(Shihab et al. 2010)	**Design:** Retrospectively analyzed medical records of 126 patients with middle and low rectal carcinomas **Groups: b**TME (n=80), conventional methods (n=46)	**LR:** NS **OS:** 5-yr 75% vs 47% (p=0.0346)	TME appears to improve long-term survival in patients with middle and low rectal carcinomas. The incidence of locoregional recurrence is also reduced by TME.
CLM=colorectal liver metastases; CRC=colorectal cancer; CRT=preoperative chemoradiotherapy; DFS=disease free survival; DSS=disease specific survival; HR=hazard ratio; LR=local recurrence; NR=not reported OR=odds ratio; OS=overall survival, RC=rectal cancer; RM=resection margin; ROD=risk of death; TME=Total Mesorectal Excision; CRM=cirumferential resection margin; DFS=disease free survival; nCRT=neoadjuvant chemoradiotherapy;			

Table 5. En bloc multivisceral resection of adherent tumours (1 study)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Chen et al. 2011)	**Design:** Retrospective analysis of patients with stage T4N0M0 lesions following MVR for colorectal cancer. CRC **Groups:** adhesion patterns inflammatory adhesion (IA)(n=128) and malignant invasion (MI)(n=159)	**LR:** NR **DFS:** NR **OS:** MI colon (HR=2.028; P=0.0001); rectal MI (HR=0.451; P=0.0002)	MI was validated as an adverse prognostic factor for stage T4N0M0 colorectal cancer following MVR suggesting that it may be classified as a T4-subgroup in order to reinforce practice guidelines.

Table 6. Inadvertent perforation (3 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Belt et al. 2012)	**Design:** Prospective follow up data of 448 patients with colon cancer that underwent resection **Groups:** Stages I/II colon cancer Perforated (n=25) not perforated (n=423)	**LR:** 36.0% vs. 16.1%; p=0.01 **DFS:** 5 yr 15.1% vs. 8% ; log rank 8.1, p=0.004 **OS:** 5-yr 16.3% vs. 8%, log rank 7.4, p=0.006	Peri-operative bowel perforation is associated with increased recurrence rates and impaired disease-free survival in early-stage colon cancer patients.
(Bulow et al. 2011)	**Design:** Study based on the Danish National Colorectal Cancer Database of 1125 patients **Groups:** Stage 1-4 rectal cancer / abdominoperineal resection / perforated (n=108)	**LR:** Perforation yes vs. no HR=2.39 (1.42–4.05) p=0.011 **DFS**: NR **OS**: Perforation yes vs. no HR=1.43 (1.10–1.86) p=0.0079 **CSS:** Perforation yes vs. no HR=1.47 (1.07–2.03) p=0.017	Intra-operative perforation is a major risk factor for local and distant recurrence and survival and therefore should be avoided.
(Rodriguez-Gonzalez et al. 2013)	**Design:** Retrospective analysis of oncologic outcomes of patients **Groups:** outcomes of patients with T4a CRC, nonperforated (NP) (n=51), perforated (P) (n=49)	**LR:** NR **DFS:** NR **OS:** NP med. 21.06 mos (8.6–35.5), P 68.63 mos (22.06–115.16); 2-yr: P 77.55%, NP 54.9%; 5-yr: P 77.55%, NP 30.61%;	Perforated cancers had higher survival rates and metastasis-free interval that non-perforated cancers, probably by a lower number of metastatic lymph nodes, smaller LNR and better TNM stage. Moreover the predictive value, in mortality rate, of metastatic lymph nodes and LNR was similar.
CLM=colorectal liver metastases; CRC=colorectal cancer; CRT=preoperative chemoradiotherapy; DFS=disease free survival; DSS=disease specific survival; HR=hazard ratio; LR=local recurrence; NR=not reported OR=odds ratio; OS=overall survival, RC=rectal cancer; RM=resection margin; ROD=risk of death; TME=Total Mesorectal Excision; CRM=cirumferential resection margin; DFS=disease free survival; nCRT=neoadjuvant chemoradiotherapy;			

Table 7. Studies reporting outcomes by extent of lymphadenectomy (1 study)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Georgiou et al. 2009)	**Design:** meta-analysis to assess the value of extended lateral pelvic lymphadenectomy in the operative management of rectal cancer. (20 studies) **Groups:** EL vs standard resection	**LR:** OR=0.83, 95% CI 0.61-1.13; p=0.23; DR OR=0.93, 95% CI 0.72-1.21; p=0.60 **DFS:** 5-yr HR=1.23, 95% CI 0.75-2.03, p=0.41 **OS:** 5-yr HR=1.09, 95% CI 0.78-1.50, p=0.62	Extended lymphadenectomy does not seem to confer a significant overall cancer-specific advantage, but does seem to be associated with increased urinary and sexual dysfunction.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Ahmadi et al. 2015)	**Design:** Retrospective analysis of clinico-pathological and survival data for patients retrieved from the New Zealand Cancer Registry **Groups:** LNY ≥12 (n=NR)	**LR:** NR **DFS:** NR **OS** stage I-III: LNY≥12 HR=0.67 (0.64-0.72) p<0.001; stage III-IV HR=0.56, (0.51-0.62) p<0.001	LNY is influenced by patient age, site of disease and T stage. LNY (Stage I-II) and LNR (Stage III-IV) have independent prognostic value in CRC
(Akagi et al. 2013)	**Design:** Review articles on literature on large, population-based, prospective clinical studies of the evaluation of lymph nodes in CC **Groups:** LNR (n=NR)	**LR:** NR **DFS:** LNR stage III pooled HR=3.71 (2.36-5.38) **OS:** LNR Stage IIII pooled HR=2.36 (2.14-2.61)	To improve lymph node evaluation and the quality of clinical practice, daily collaboration between surgeons and pathologists is important. Scientific evidence for reasonable and practical LNH and LNR values should be identified based on large, well-controlled, prospective studies.
(Blaker et al. 2015)	**Design:** Population based case-control study Stage I–IV CRC **Groups:** ≥12 lymph nodes (n=1492), <12 lymph nodes (n=406)	**LR:** ≥12 LN 31%, <12 LN 28% **RFS:** ≥12 LN Ref HR=1.00, <12 LN HR=1.06 (0.84–1.33) **OS:** ≥12 LN Ref HR=1.00,<12 LN HR=1.04 (0.85–1.27)	Previously reported effect of a low lymph node count on the patients' outcomes is eliminated by improved lymph node examination quality and thus question the general applicability of a 12 lymph node cut off for adjuvant chemotherapy decision making in stage II disease.
(Ceelen et al. 2010)	**Design:** systematic search was performed for studies examining the prognostic significance of the LNR in CRC **Groups:** LNR (n=NR)	In all identified studies, the LNR was identified as an independent prognostic factor in patients with stage III cancer of the colon or rectum. The prognostic separation obtained by the LNR was superior to that of the number of positive nodes (N stage). **OS:** LNR pooled HR=2.36 (95% CI, 2.14-2.61) **DFS**: LNR pooled HR=3.71 (95% CI, 2.56-5.38)	The LNR allows superior prognostic stratification in stage III colorectal cancer and should be validated in prospective studies.
(Chandrasinghe et al. 2014)	**Design:** 131 prospectively followed patients, having five or more lymph nodes harvested from the specimen stages II and III CRC **Groups:** LNH≥14 (n=38), LNH<14 (n=73)	**LR:** NR **DFS:** NR **OS:** LNH HR=0.197 (0.066–0.593) p=0.004	LNH of 14 or more resulted in better survival outcome from CRC. Staging of the disease could be accurate with increased nodal harvesting effect remained significant (HR=0.19, p=0.004) after adjusting, for other factors.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Chang et al. 2012)	**Design:** Based on surgical patients with newly diagnosed colon adenocarcinoma registered in the Taiwan Cancer Database colon adenocarcinoma stage III **Groups:** LNT, LNP, LNN, LNR, LODDS	**LR:** NR **DFS:** Stage III - AUC: LNT 0.560 (0.537–0.582); LNP 0.687 (0.666–0.708); LNN 0.621 (0.599–0.643); LNR 0.700 (0.679–0.721); LODDS 0.696 (0.676–0.717); **OS:** Stage III - AUC: LNT 0.580 (0.558–0.603); LNP 0.677 (0.656–0.698); LNN 0.639 (0.618–0.661); LNR 0.704 (0.684–0.725); LODDS 0.702 (0.681–0.723)	For patients undergoing resection for colon cancer, LNR, LODDS, and LNP are better prognostic factors for those with stage III disease than LNT is for patients with stage III disease.
(Chen et al. 2011)	**Design:** Surveillance Epidemiology and End Results registry (1992-2004) Stage III colon cancer **Groups:** <12 nodes (n=18028) vs ≥12 nodes (n=18,684)	**LR:** NR **DFS:** NR **OS:** med. 53 mos vs 66 mos, p<0.001; LNR ≥12 nodes HR=1.32 (LNR=10%-24%) to 5.12 (LNR=100%); LNR <12 nodes HR=1.23(LNR=10%-24%) to 2.28 (LNR=100%)	Metastatic LNR independently estimates survival in Stage III colon cancer, irrespective of number of nodes examined. However, statistically significant differences in each LNR stratum between those with resection of fewer than 12 or 12 nodes or more would indicate that a 12-node minimum may still be necessary for accurate staging.
(Chin et al. 2009)	**Design:** Prospective study of patients featuring stage III adenocarcinoma of the colon underwent curative resection Stage III CC **Groups:** LNR1 (LNR≤0.44) LNR2 (LNR≤0.77) LNR3 (LNR>0.7)	**LR:** NR **DFS:** 5-yr: LNR1 66.7%, LNR2 35.1%, LNR3 0% (p<0.0001); T3/4LNR1 patients vs N1 or N2 NS; **OS:** NR	LNR is a more precise predictor of 5-year DFS than number of positive lymph nodes (N stage) in patients with stage III colon cancer.
(de Campos-Lobato et al. 2013)	**Design:** A single-center colorectal cancer database 237 cancer patients undergoing neoadjuvant CRT c-stage II–III RC **Groups:** <12 lymph nodes (n=167), ≥12 lymph nodes (n=70)	**LR:** 5-yr <12 nodes 0% (0), ≥12 nodes 11% (SE=2.8) p=0.008 **DFS:** 5-yr cancer specific mortality <12 nodes 8.8% (SE=4), ≥12 nodes 15.6% (SE=3.4) p=0.45; cancer-free survival <12 77.1% (SE=6.4) ≥12 75.2% (3.7) p=0.11 **OS:** 5-yr <12 nodes 89% (SE=4.4) ≥12 nodes 81.4% (SE=3.6) p=0.53	Retrieval of less than 12 nodes in the proctectomy specimen of RC patients treated with neoadjuvant CRT does not affect OS, CSM, CFS, or DR and may be a marker of higher tumor response and, consequently, decreased LR rate.
(Dedavid e Silva and Damin 2013)	**Design:** 70 patients who underwent resection of a primary CRC in a single institution stage CC **Groups**: LNR<0.15 (superior line) (n=38),>0.15 (inferior line) (n=32)	**LS:** tumor recurrence, positive lymph node HR=0.965 (0.721-1.291) p=0.808 **DFS:** 3-yr LNR<0.15 and >0.15 90% vs 64%, p=0.011; stage IIIB LNR<0.15 and >0.15 ~90% vs ~52%, p=0.016 **OS:** LNR<0.15 (superior line) and >0.15 (inferior line) ~84% vs ~45%, p=0.024.	Lymph node ratio is a strong predictor for tumor recurrence in stage III colon cancer.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Del Rio et al. 2012)	**Design:** 200 patients with CRC **Groups:** LNR% and Quartiles	**LR:** NR **DFS:** NR **OS:** q1 27.12%, q2 9.38%, q3 16.67%, q4 1.56%; LNR 50% vs. 51%-100% p=0.025; LN 1%-25% vs 26%-50% p=0.025; NR 1-25% vs 76%-100% p=0.001; LNR 1-25% vs. 51%-75% p=0.025	LNR is a reliable prognostic index in post surgical colorectal cancer staging.
(Duraker et al. 2014)	**Design:** 461 CRC patients prospectively collected, plus 74 N1 disease patients who had at least 12 lymph nodes removed CRC & 74N1 **Groups:** LNR 1-7 LNR (n=128), 8-11 (n=108) LNR, ≥12 (n=225) (grouping A); 1-11 (n=236), ≥12 (n=225) (grouping B)	**LR:** NR **CSS:** LN removed (grouping A) 1-7 60.9% 8-11 63.9% ≥12 75.1%, p=0.014; LN removed (grouping B - patients with N1 disease, n=71) 1-11 62.3%, ≥12 75.1%, p=0.004; LN removed (grouping A) 1-7 RR=1.00 (ref), 8-11 RR=0.76 (0.49-1.17), ≥12 RR=0.52, p=0.006; LN removed (grouping B) 1-11 RR=1.00 (ref), ≥12 RR=0.59 (0.41-0.84), p=0.004 **DFS:** NR **OS:** NR	In colorectal cancer patients whose removed lymph nodes are non-metastatic, removal of at least 12 lymph nodes will determine the lymph node status reliably.
(Elias et al. 2012)	**Design**: Retrospectively collected clinicopathological data of 535 patients from single institution for CRC **Groups:** pLNR<0.4 (n=116), LNR>0.4 (n=41)	**LR:** NR **DFS:** NR **OS:** 10 yr IIIA 76%, IIIB 56%, IIIC 0%, p=0.014; Stage III pLNR<0.4 vs pLNR>0.4 HR=5.25 (1.2-22.1) p=0.02	The ratio-based staging (pLNR) of CRC is a more accurate and clinically useful prognostic method than the number of positive LNs resected or the total number of LNs retrieved for predicting the course of patients with stage III CRC.
(Galizia et al. 2009)	**Design:** Prospective study of consecutive patients with node-positive CC **Groups:** Node-positive CC / LNR pN1 patients, ≤0.1818 (n=81), >0.1818 (n=26), pN2 ≤0.1818 (n=4), >0.1818 (n=34)	**LR:** NR **DFS:** NR **OS:** 5-yr pN1 patients low vs. high HR=0.25 (0.05–0.42) p=0.0003; pN2 patients, HR=0.17 (0.11–0.93) p=0.0373; LNR HR=8.07 (2.41–26.99) p=0.0007	LNR was a robust prognostic indicator for node-positive CC undergoing curative surgery. Because this ratio-based staging was demonstrated to reduce stage migration and to aid in identifying high-risk patients, it should be proposed as a standard tool for colon cancer staging.
(Gill et al. 2015)	**Design**: Retrospective cohort study of 4790 patients with stage I to III rectal cancer using California Cancer Registry stage I - III CRC patients who underwent tri-modality therapy consisting of surgery CT and RT **Groups:** nodes examined 0-2 (n=283), 3-5 (n=569), 6-8 (n=571), 9-11 (n=469), 12+ (n=941); Neoadjuvant and adjuvant cohort	**LR:** NR **DFS:** NR **CSS:** Nodes examined: 0-2 neoadjuvant HR=1.67 (1.10-2.54) p=0.0168, adjuvant HR= 1.74 (1.10-2.54) p=0.0680; 3-5 neoadjuvant HR=1.77 (1.28-2.46) p=0.0006, adjuvant HR= 2.19 (1.48-3.23) p=<0.0001; 6-8 neoadjuvant HR=1.68 (1.23-2.29) p=0.0111, adjuvant HR= 1.79 (1.26-2.53) p=0.0010; 9-11 neoadjuvant HR=1.35 (0.97-1.88) p=0.0747, adjuvant HR=1.30 (0.92-1.85) p=0.1401	In this large cohort of rectal cancer patients treated with tri-modality therapy, reduced lymph node retrieval in node negative patients did not provide additional prognostic information in patients treated with neoadjuvant therapy.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Hashiguchi et al. 2010)	**Design:** Prospectively followed patients who had undergone surgical treatment from 1980 to 2000 from single institution Localized colon cancer **Groups:** cut-off value of 18 for node-negative and 20 for node-positive patients	**LR:** NR **CSS:** cutoff value 20 NLNE (node-positive) patients 5-year stage IIIB 79.3% with 20 or more NLNE and 63.3% with less than 20 NLNE (P=0.0052). **OS:** IIB patients was 96.5% with 18 or more NLNE and 67.5% with NLNE less than 18 (P[r]=0.0067)	The clinical significance of NLNE is not limited to being a benchmark for quality care, but has a definite benefit as a prognostic indicator across the stages. Patients could be stratified more efficiently by the integration of NLNE to TNM staging.
(Hayes et al. 2014)	**Design:** Case control study of patients in a large tertiary referral center CRC **Groups:** Nodes examined ≥12 (n=42), <12 (n=29); rectal vs non-rectal	**Systematic recurrence:** ≥12 Nodes examined p<0.0001 Node positive p=0.0113; Suboptimal node yield RR=1.6 (1.332-2.163) p=0.013 rectal vs non-rectal **DFS:**NR **OS:** NR	Rectal cancers have greater risk of SR than colon cancers. A lower yield of lymph nodes in rectal cancer specimens may contribute to this.
(Homma et al. 2015)	**Design:** 154 patients at a single institution. T1–4 lower rectal adenocarcinoma radical resection **Groups**: Lymphatic invasion Negative (n=19), positive (n=65)	**LR:** Lymphatic invasion negative (ref) HR=1.00, positive HR=1.27 (0.58–2.79) p=0.55; Venous invasion Negative (ref) HR=1.00, Positive HR=1.87 (0.41–8.55) p0.42; total number of lymph node metastases 0–3 (ref) HR=1.00, >3 HR=2.52 (1.12–5.64) p=0.02; LLN metastasis, Negative (ref) HR=1.00, Positive HR=1.10 (0.35–3.40) p=0.87 **DFS:** NR **OS:** NR	The presence of one or two LLN metastases in patients who have undergone LLN dissection with surgery for lower rectal cancer is not associated with poor prognosis. The number of LLN metastases is a more significant risk factor for poor prognosis.
(Jiang et al. 2014)	**Design**: Prospectively reviewed data of consecutive patients who underwent radical resection for stage III CRC radical resection **Groups:** LNR< 0.167 (n=72), 0.167<LNR< 0.562 (n=140), and LNR>0.562 (n=76)	**LR:** NR **DFS:** LNR <0.167 80.00%, 0.167-0.562 57.14%, ≥0.562 38.71%, p=0.005; Metastatic lymph node 1-3 64.20%, ≥4 46.51%, p=0.057 **OS:** LNR <0.167 86.67%, 0.167-0.562 66.67%, ≥0.562 41.94%, p=0.001; Metastatic lymph node 1-3 71.60%, ≥4 53.49%, p=0.044	Both LNR and the number of metastatic LNs were significant prognostic factors for 5-year DFS and OS in stage III CRC patients. LNR was an independent prognostic factor for 5-year OS. LNR remained an independent prognostic factor in patients with fewer than 12 lymph nodes examined. LNR was a potent independent prognostic predictor for OS and DFS in stage III CRC patients, especially for patients with fewer than 12 lymph nodes examined.
(Kang et al. 2011)	**Design:** Prospectively followed patients diagnosed as node-positive after undergoing preop-CRT followed by curative resection. **Groups:** among ypN1 lower LNR (N1G1), higher LNR (N1G2).	**LR:** NR **DFS:** NR **OS:** NIG1 better OS than N1G2, p=0.018, no difference between the survival rates of the N1G2 and the ypN2 groups (p=0.987)	LNR is an independent prognostic factor after preop-CRT for rectal cancer. LNR showed better prognosis stratification than the ypN stage. Therefore, LNR should be considered as an additional prognostic factor in node-positive rectal cancer after preop-CRT

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Junginger et al. 2014)	**Design:** Prospectively followed patients who have not undergone neoadjuvant therapy for stage III RC **Groups:** >12 (n=178) vs. <12 lymph (n=59) nodes examined; LNR1 ≤0.1 (n=62), LNR2 ≤ 0.2 (n=57), LNR3 ≤ 0.394 (n=59), LNR>0.394 (n=59)	**LR:** NR **DFS:** LNR1 (ref), LNR2 HR=2.338 p=0.011, LNR3 HR=2.588 p=0.014, LNR4 HR=4.515 p<0.001 **OS:** LNR1 (ref), LNR2 HR=2.351 p=0.015, LNR3 HR=2.716 p= 0.014, LNR4 HR=5.252 p<0.001	In patients with adequate lymph node dissection, LNR staging does not add substantial information to the predictions of updated TNM lymph node staging. However, in patients with inadequate lymph node harvesting, the LNR compensates for the under-staging of the TNM classification and provides a better estimation of prognosis than the updated TNM system.
(Huh et al. 2010)	**Design:** Prospectively followed patients who underwent curative surgery for CRC with proven lymph node metastases CRC **Groups:** LNR1 (<0.09) (n=128), LNR2 (between 0.09 and 0.18) (n=130), LNR3 (>0.18 and <0.34) (n=135), and LNR4 (>0.34)(n=121)	**LR:** NR **DFS:** 5-yr LNR1 73%, LNR2 67%, LNR3 54%, LNR4 42%, p<0.001; LNR >0.18 HR=1.596 (1.122-2.268) p=0.009 **OS:** 5-yr LNR1 79%, LNR2 72%, LNR3 62%, LNR4 55%, p<0.001; LNR >0.18 HR=1.589 (1.106-2.284) p=0.012	In addition to the conventional pT and pN categories, the LNR was a predictor of both the overall and DFS in patients with node-positive CRC. It may compensate for an inadequate lymph node dissection in surgery for CRC.
(Kelder et al. 2009)	**Design:** Data from 2,281 patients retrospectively reviewed with Localized CC **Groups:** Node negative <6 examined (n=713), 6-11 (n=545), ≥12 (n=295); Node positive <6 examined (n-230), 6-11 (n=310), ≥12 (n=198)	**LR:** NR **DFS:** NR **OS:** 5-yr node-positive 51.3 node-negative 68.2%; Node positive: <6 nodes examined OS=46.3% (39.4-52.9), 6-11 OS=53.9% (47.9-59.6), ≥12 OS=53.1% (45.5-60.1), p=0.0756; Node negative: <6 nodes examined OS=63.5% (59.5-67.2), 6-11 OS=70.2% (65.9-74.1), ≥12 OS=75.9% (70-80.8) p=0.0013	T stage, localization, and patient age were predictive for the number of nodes examined. A higher number of examined nodes was associated with an increase in node positivity. The survival benefit can be explained by stage migration. Eventually this may lead to an overall survival benefit, as more patients are classified as node-positive, and therefore will receive adjuvant therapy.
(Kim et al. 2009)	**Design:** Retrospectively collected data from of RC patients who have had TME followed by CRT **Groups:** LNR≤0.1 (n=69), 0.1-0.2 (n=49), 0.2-0.4 (n=54), and >0.4 (n=60)	**LR:** NR **DFS:** NR **OS:** ≤0.1 89%, 0.1-0.2 67%, 0.2-0.4 64%, >0.4 50%, p<0.001; ≤0.1 (ref) HR= 1.0, 0.1-0.2 HR=1.3 p=0.623, 0.2-0.4 HR=2.4 p=0.047, >0.4 HR=3.7, p=0.005; N1 (p=0.032) and N2 (p=0.034) tumors.	Lymph node ratio was the most significant predictor of survival in the patients with Stage III rectal cancer who had undergone postoperative chemoradiation.
(Kim et al.2009a)	**Design:** Prospectively collected data on patients with RC who received neoadjuvant CRT. RC **Groups:** absence of lymph nodes (ypNx, n=9), node-negative status (ypN(-) n=150), node-positive status (ypN(+), n=99)	There was no significant difference of oncological outcomes among ypNx patients and a subset of ypN(-) patients based on the number of nodes retrieved using three cutoff values (1-11, 12-25, and 25-65 nodes).	In a neoadjuvant setting, ypN(+) disease was an independent risk factor for oncological outcomes. An absence of nodes does not represent an inferior oncological outcome. The number of nodes does not seen to impact survival and recurrence in ypN(-) patients.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Kim et al.2009b)	**Design**: 900 patients who underwent tumor-specific mesorectal excision for stage II&III CRC **Groups:** number of lymph nodes retrieved	In multivariate analysis, stage II disease with less than 15 nodes retrieved was an adverse factor for CSS and RFS. In Kaplan-Meier survival analysis, using cutoff values, the difference for CSS was not significant with 22 and more nodes and the difference for RFS was not observed with 23 and more nodes.	The number of lymph nodes retrieved is closely associated with survival and recurrence in patients with stage II rectal cancer and, for more accurate prognostic stratification, at least 22 and 23 nodes seem to be necessary, respectively, for CSS and for RFS.
(Klos et al. 2011)	**Design:** Retrospectively collected data from consecutive patients in a tertiary care referral center who underwent neoadjuvant CRT and TME for RC **Groups:** LNR: low (0.09 (n=NR), medium 0.09-0.36 (n=NR), and high ≥0.36 (n=NR); LNP Med 1–3 (n=NR), High ≥4 (n=NR)	**LR:** NR **DFS:** NR **ROD:** LNR Med HR=2.5 (1.36–4.600) p=0.003 High HR=3.43 (1.72–6.84) p=0.001, LNP Med HR=2.67 (1.42–5.00) p=0.002, High HR=2.96 (1.44–6.09) p=0.003	Patients who undergo neoadjuvant chemoradiation before rectal cancer surgery frequently have fewer than 12 lymph nodes harvested despite maintaining vigorous surgical standards. Lymph node ratios may provide excellent prognostic value and are possibly a better independent staging method than absolute positive lymph node counts when less than 12 lymph nodes are harvested after neoadjuvant treatment.
(Kobayashi et al. 2011)	**Design:** Patients with Stage III distal RC prospectively followed at 12 institutions **Groups:** LNR G1<0.04 (n=126), G2 0.04–0.079 (n=126), G3 0.08–0.15 (n=111), G4 0.151–1 (n=130)	**LR:** NR **DFS:** NR **OS:** 5 yr G1 80.5% (ref) HR=1.00, G2 74.4% HR=1.26 (0.75–2.14) p= 0.39, G3 50.3% HR=2.43 (1.42–4.17) p=0.0012, G4 36.4%, HR=3.11 (1.82–5.32) p<0.0001	Adding the LNR concept to the AJCC cancer staging system will improve accuracy in evaluating the nodal status of distal rectal cancer.
(Kotake et al. 2012)	**Design:** Retrospectively collected data on patients with Stage II-III CRC **Groups:** NLNR 1-9 (n=2294), 10-16 (n=2333), 17-26 (n=2290), 27+ (n=2226)	**LS:** NR **DFS:** NR **OS:** Stage II NLNR 1-9 (ref) HR=1.00, 10-16 HR=0.63 (0.53-0.76) p<0.01, 17-26 HR=0.59 (0.49-0.72) p<0.01, 27+ HR=0.46 (0.37-0.57) p<0.01 Stage III NLNR 1-9 (ref) HR=1.00, 10-16 HR=0.91 (0.80-1.03) p=0.14, 17-26 HR=0.92 (0.81-1.05) p=0.23, 27+ HR=0.75 (0.65-0.86) p<0.01	The number of lymph nodes retrieved was shown to be an important prognostic variable not only in Stage II but also in Stage III colorectal cancer, and it was most prominently determined by the scope of nodal dissection. A cut-off value for the number of lymph nodes retrieved was not found, and it is necessary to carry out appropriate nodal dissection and examine as many lymph nodes as possible.
(Kritsanasakul et al. 2012)	**Design:** Pathological reports of 533 consecutive patients retrospectively reviewed with stages I–III CRC **Groups:** nLN<12 (n=315), ≥12 (n=218)	**LR:** NR **DFS:** NR **OS:** LNR>0.35 HR= 1.67 (1.07–2.62) p=0.02; nLN<12 HR=1.47 (1.06–2.06) p=0.02	Our data emphasize the importance of lymph node harvesting during the surgical resection of CRCs. In addition, LNR is a strong independent factor associated with CRC survival.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Li et al. 2014)	**Design:** SEER-registered rectal cancer patients treated with preoperative radiotherapy (preop-RT) with LN metastasis **Groups:** number LN dissected >12 (n=1,124), ≥12 (n=748)	**LR:** NR **DFS:** NR **OS:** No. of LNs dissected <12 (ref) HR=1.000, ≥12 HR=0.875 (0.747–1.026) p=0.099	The yp-rN stage can be used together with the yp-N stage to select high-risk patients for postoperative treatment.
(Liu et al. 2014)	**Design:** Retrospectively collect data on patients diagnosed with synchronous mCRC and treated with lymphadenectomy CRC **Groups**: regional lymph nodes pN0 (n=140), pN1 (n=223), pN2 (n=133)	**LR:** NR **DSS:** median mos. pN0 34.992 ± 2.14, pN1 27.145 ±1.715, pN2 17.273 ±1.020; p= <0.001, pN2 and pN1 vs. pN0 17.273_1.020 and 27.145_1.715 vs. 34.992_2.143 months; P<0.001 **OS:** cancer-specific mortality regional lymph nodes HR=1.630 (1.422–1.868);<0.001	Our findings indicate that optimal TNM staging for mCRC should incorporate lymph node status to provide a more effective and predictive model.
(Lu et al.)	**Design:** Prospectively collected data on patients with stage III patients with CRC who underwent curative-intent surgery **Group:** LNR ≥17 (n=322), <17% (n=290)	**LR:** NR **DFS 5-yr:** LNR ≥17 vs.<17% HR=1.53 (1.05–2.23) p= 0.028 **OS: 5-yr:** LNR ≥17 vs.<17% HR=1.54 (1.05–2.22) p= 0.026	The LNR, set at the median value or 17 %, could be an independent prognostic factor for stage III CRC patients.
(Lykke et al. 2013)	**Design:** Retrospectively collected data from a large nationwide Danish cohort of CC **Groups:** LNC<12 (n=3,254), 12+ (n=5,329), LNR quartiles - cut-off points 1/12 (n=NR), ¼ (n=NR), and ½ (n=NR)	**LR:** NR **DFS:** NR **OS:** 5-year LNC<12 57.8%, 12+ 66.6%, p<0.0001; Stage III 5-year LNR1 68.1%, LNR2 57.4%, LNR3 49.35%, LNR4 32.4%	Our data emphasize the importance of lymph node harvesting during the surgical resection of CRCs. In addition, LNR is a strong independent factor associated with CRC survival.
(Moro-Valdezate et al. 2013)	**Design:** Retrospectively collected data of all patients diagnosed with CRC who underwent oncological resection consecutively in a single institution **Groups:** ≥12 LNs (n=NR), <12 (n=NR)	**LR:** NR **DFS:** A recovery of ≥12 LNs did not show significant differences in DFS 5-year survival, but the factor of colorectal surgeon did. **OS:** A recovery of ≥12 LNs did not show significant differences in OS 5-year survival, but the factor of colorectal surgeon did.	Number of LN metastases, lymphocyte response, type of surgical resection, age of patient and colorectal surgeon can predict the LN harvest. Survival in colorectal cancer, however, is probably more influenced by the performance of the operation by an expert surgeon than by recovery of more than 12 LNs.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Nadoshan et al. 2013)	**Design:** Retrospectively collected data on patients with stage III RC who underwent curative resection **Groups:** Total lymph nodes examined 7-11 (n=NR), <7 (n=NR); LNR: >0.2 (n=28) ≤0.2 (n=100)	**LR:** Total lymph node examined: 7-11 vs. <7 HR=1.7(0.8-3.4), ≥12 vs. <7 HR=1.8 (0.8-4.1), LNR: >0.2 vs. ≤0.2 HR=8.4 (2.9-24.0) **DFS:** NR **OS:** Total lymph node examined: 7-11 vs. <7 HR=2.8(1.3-6.2), ≥12 vs. <7 HR=4.5 (1.9-10.6), LNR: >0.2 vs. ≤0.2 HR=5.0 (2.1-11.6); 5 yr LNR≤0.2 69%, >0.2 19%, log rank p<0.001	Total number of examined lymph nodes and LNR were significant prognostic factors for survival in patients with stage III rectal cancer undergoing preoperative CRT.
(Ng et al. 2009)	**Design:** Retrospectively collected data from the SEER cancer registry with Node positive CRC **Groups:**, % positive nodes ≤0.19 (n=912), 0.20-0.39 (n=459), 0.40-0.59 (n=163), 0.60-0.79 (n=74), and 0.80-1.0 (n=109)	The mean number of nodes examined was 10.4 (range, 1-89) for N0, 11.0 (range, 1-72) for N1, and 14.6 (range, 4-79) for N2 (p<0.0001). N1 and N2 patients were stratified according to the percentage of positive nodes into quintiles (≤0.19, 0.20-0.39, 0.40-0.59, 0.60-0.79, and 0.80-1.0). In both N1 and N2 disease, a lower percentage of lymph nodes involved with metastatic disease was associated with improved survival (p<0.0001).	The increasing ratio of positive to total nodes was the result of a decrease in the total number of nodes examined in N1 disease and a steeper decline in total nodes examined in relation to the increase in the number of positive nodes in N2 disease. The ratio of positive to total nodes has prognostic significance in node-positive colorectal cancer.
(Norwood et al. 2010)	**Design:** Prospectively collected data from patients in single centre with Dukes' A and B CC (n=2,449) **Groups:** LNH <12 (n=NR), 12+ (n=NR)	**LR:** NR **DFS:** NR **OS:**<12 LNR sign. shorter survival compared with at least 12 nodes (p=0.001)	As a unit, we are achieving the national standard for lymph node harvest. This standard was maintained whether the surgeon performing the surgery was a consultant or a trainee, and also when the surgery was performed in the emergency setting. These data support the concept of 12 nodes being required for accurate staging.
(Parnaby et al. 2015)	**Design;** Patients receiving colon cancer resection from a prospective database for CC **Groups:** LNR0 (n=510), LNR1 (0.01–0.17) (n=243), LNR2 (0.18–0.41) (n=105), LNR3 (0.42–0.69) (n=42), LNR4 (40.7) (n=21)	**LR:** NR **DFS:** LNR0 n=510 (55.4%) (ref) HR=1.00, LNR1 n=243 (26.4%) HR=1.78 (1.25-1.82), LNR2 n=105 (11.4%) HR=3.79 (2.56-5.61), LNR3 n=42 (4.6%) HR=2.60 (1.50-4.48), LNR4 n=21 (2.3%) HR=4.76 (2.21-10.27); Proximal n=540 (58.3%) ref HR=1.00, Distal n=381 (41.2%) HR=0.95 (0.72-1.25) **OS:** LNR0 (ref) HR=1.00, LNR1 HR=1.37 (1.03-1.82), LNR2 HR=2.37 (1.70, 3.30), LNR3 HR=2.40 (1.57-3.65), LNR4 HR=5.51 (3.16-9.58), p<0.001	This study demonstrated, in the presence of high surgical, oncology and pathological standards, EMVI and increasing LNR were independent predictors of decreased overall and disease-free survival for patients undergoing curative colon cancer resection. LNR was superior to pN stage in predicting overall and disease-free survival.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Ren et al. 2012)	**Design:** Cases with Stage III CRC analyzed retrospectively **Groups:** LNR (continuous variable)	**LR:** NR **DFS:** LNR Exp(B) 11.748 (3.200-43.122) p<0.0001 **OS:** NR	We confirmed that lymph node ratio was a prognostic factor in stage III CRC and had a better prognostic value than did N stage
(Rivadulla-Serrano et al.)	**Design:** Retrospective study of patients with CC (pN0 of TNM classification) **Groups:** Number of analysed lymph nodes (<7, (n=NR) 7-14 (n=NR),>14 (n=NR)	**LR:** NR **DFS:** NR **OS:** 5-yr <7 lymph nodes 63.0%; 7-14 lymph nodes: 80.6%, >14 lymph nodes: 91.8%, p<0.01	In our centre, harvesting a larger number of lymph nodes is related to improved rates of 5-years survival for patients with colon cancer staged as pN0. It seems reasonable to recommend obtaining as many lymph nodes as possible, and not to establish a minimum number of lymph nodes to be harvested.
(Rosenberg et al. 2010)	**Design:** Retrospectively collected data from a population database of CRC patients **Groups:** LNR 0 (n=9,657) LNR 0.01 to 0.17 (n=3,383), LNR 0.18 to 0.41 (n=2,222), LNR 0.42 to 0.69 (n=1,217), LNR ≥ 0.70 (n=830)	**LR:** NR **DFS:** NR **OS:** 5-yr LNR=0 (71.4%,) LNR 0.01 to 0.17 (52.4%), LNR 0.18 to 0.41 (33.3%), LNR 0.42 to 0.69 (19.8%), and LNR>or=0.70 (8.3%) P<0.001	The 3 cut-off values of LNRs had strong independent prognostic value in a population-based collective of patients with colorectal cancer. The LNR should be routinely reported and included in the American Joint Committee on Cancer staging system.
(Sato et al. 2011)	**Design:** Retrospective study of 149 patients node positive low rectal carcinoma **Groups:** with positive LNs (group II, n=64)) ,without positive LLNs (group I,(n=85)	**LR:** G1 31 (36.5), GII 42 (65.6); p<0.01 **DFS:** NR **OS:** 5-yr group I 69.8%, group II 36.2%, HR = 2.41 (1.37, 4.26) p=0.002	LLN dissection for low rectal carcinoma was effective for patients with fewer than four positive unilateral LLNs in either area B or C.
(Sjo et al. 2012)	**Design:** A prospective, observational study of patients treated in in a single institution with stage I-III CC **Groups**: number of examined lymph nodes <8 (n=254), 8-11 (n=166), ≥12 (n=530)	**LR:** Time to recurrence - No lymph nodes <8 (ref) HR=1.0, 8–11 HR=0.8 (0.5–1.1) p=0.2, ≥12 HR=0.5 (0.4–0.7) p<0.001; stage I p=0.09, stage II p=0.03, stage III p=0.02 **DFS:** NR **OS:** No of lymph nodes <8 Reference, 8–11 HR=0.7 (0.5–0.9) p=0.04 ≥12 HR=0.6 (0.5–0.8) p<0.001; stage I p=0.08, stage II 2 p=0.004, stage III p=0.06	The number of examined lymph nodes increased in the study period. A stage migration was observed, and time to recurrence improved in patients with stage I to III disease. In patients with stage III disease, lymph node ratio was a stronger prognostic factor than the total number of lymph nodes examined.
(Storli et al. 2011)	**Design**: National surveillance program of colon cancer treatment **Groups:** NLN, LNR 1 <0.25 (n=NR), LNR 2 0.25–0.50 (n=NR), LNR 3 0.51–0.75 (n=NR), LNR 4 0.76–1(n=NR)	**LR:** NR **DFS:** NR **OS:** No. of sampled lymph nodes per increments of 10 HR=0.82 (0.57, 1.17) p=0.266; stage III LNR 1 83.5%, LNR 2 63.3%, LNR 3 18.8%, and LNR 4 18.2% (log-rank test p<0.001).	The lymph node count did not have a significant impact on outcome overall, whereas the LNR proved significant for stage III. A prospective protocol using overall lymph node yield as a surrogate measure for more radical surgery, nevertheless, seems warranted to improve the lymph node harvest according to international recommendations.

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Tsai et al. 2011)	**Design:** RC patients with non-metastatic disease received preoperative chemoradiation followed by mesorectal excision and had ypN0 disease. **Groups:** #LN examined <7 LN (n=188), >7 LN (=184)	**LR:** 5-yr FFR: 86% vs 72%; HR=0.39 p=0.003 **DFS:** 5-yr CSS: 95% vs 86%; HR=0.45 p=0.04 **OS:** 5-yr: 87% vs 81%; HR=0.75 (0.46-1.20) p=0.23	The number of lymph nodes examined was associated independently with disease relapse and cancer-specific survival in patients with rectal cancer who had ypN0 disease after receiving preoperative chemoradiation. Hence, the authors concluded that the number of negative lymph nodes examined may be a prognostic factor in patients with rectal cancer who receive preoperative chemoradiation
(Tuna et al. 2011)	**Design:** 125 patients retrospectively followed in a single institution Stage II CC **Groups:** metastatic LNR, LNR <0.2 (n=NR), LNR >0.2 (n=NR)	**LR:** NR **DFS:** Mean duration LNR <0.2 was 100.6±8.6 months LNR >0.2 it was 71.7±8.3 months (p=0.017); 5-year DFS rate in patients with a LNR>0.2 was 42.3%; it was 64.1% in those with LNR<0.2 **OS:** mean OS LNR <0.2 120.5±7.3 months, with a LNR>0.2 92.8±9.0 months, p=0.074	The determination of the optimal cut-off value for the LNR in future prospective studies will help defining prognosis with better accuracy in colon cancer patients.
(Vaccaro et al. 2009)	**Design:** 362 patients Stage IIIL CC followed prospectively **Groups:** NR <0.25 (n=274) , ≥0.25 (n=88)	**LR:** NR **DFS:** 5-yr: LNR<0.25 (68.3% (61.5–75.2), LNR≥0.25 31.5% (19.4–43.5), p=0.001; 5-yr CSS: LNR<0.25 74.5% (67.9–80.9), LNR ≥0.25 40.1% (27.1–53.1), p=0.001 **OS:** 5 yr LNR<0.25 (n=274) 64.9% (58.1–71.9), LNR≥0.25 (n=88) 38.3% (25.5–51.1), p=0.001	A lymph node ratio ≥0.25 was an independent prognostic factor in Stage III colon adenocarcinoma regardless of the number positive nodes. It modified outcomes predicted by the current staging system.
(Vather et al. 2009)	**Design:** New Zealand Cancer Registry data for stage II-III CC **Groups:** number of nodes (n=NR)	**LR:** NR **DFS:** NR **ACM:** Number of nodes>25 p=0.0001 1–4 RC=1.659 (1.376–2.000) p=0.0001 5–8 RC=1.443 (1.229–1.694) p=0.0001 9–12 RC=1.310 (1.118–1.535) p=0.001 13–16 RC=1.063 (0.893–1.265) p=0.491 17–20 RC=1.030 (0.845–1.256) p=0.769 21–24 RC=1.103 (0.892–1.364) p=0.366	Increased rates of nodal examination are associated with a significantly lower 5-year mortality for Stage II and III colonic cancer, but this survival advantage appears to be minimal after the 16-node mark. The lymph node ratio has been validated as a powerful predictor of survival in Stage III cancer. Our results support the current practice of harvesting and examining as many nodes as possible during attempted curative resection.
(Zekri et al. 2015)	**Design**: Prospectively followed patients with stage II & III CRC **Groups:** Group 1: LNR<0.05 (n=NR), Group 2: LNR=0.05-0.19 (n=NR) & Group 3>0.19 (n=NR); NILN (continuous)	**RFS:** HR=NILN 1.15, 95% CI 1.055-1.245; P=0.001; LNR continuous variable p=0.002 **DFS:** NR **OS:** LNR p=0.02	LNR may predict RFS and OS in patients with resected stage II & III CRC. Studies with larger cohorts and longer follow up are needed to further examine and validate theprognostic value of LNR

Table 8. Studies reporting outcomes as a function of number of lymph nodes evaluated (49 studies)			
Author, year	**Study characteristics**	**Results**	**Author's conclusion**
(Zeng et al. 2014)	**Design:** 131 patients who received neoadjuvant chemoradiotherapy (CRT) followed by curative resection. RC **Groups**: LNR≤0.2 (n=86) , >0.2 (n=45)	**LR:** NR **DFS:** LNR≤0.2 s >0.2, HR=3.637(1.838-7.195) p<0.001 **OS:** LNR≤0.2 vs >0.2, HR=3.778 (1.741-8.198) p=0.001	LNR is an independent prognostic factor in ypN-positive rectal cancer patients, both in patients with <12 harvested LNs, and as well as in those ≥ 12 harvested LNs. LNR provides better prognostic value than pN staging. Therefore, it should be used as an additional prognostic indicator in ypN-positive rectal cancer patients.
(Zhang et al. 2013)	**Design:** 265 patients with colorectal cancer CRC stage II/III **Groups:** number of lymph nodes harvested	**LR:** NR **DFS:** NR **OS:** higher in patients with 12 or more lymph nodes harvested, adjusted RR=0.215 (0.102-0.456).	The number of lymph nodes harvested was a prognostic variable to evaluate outcome in patients with colorectal cancer. However, most patients did not receive adequate lymph node evaluation. More efforts should be done to improve quality of care in this area.
ACM AUC=area under the curve; CLM=colorectal liver metastases; CRC=colorectal cancer; CRT=preoperative chemoradiotherapy; CSS=cancer specific survival; DFS=disease free survival; DSS=disease specific survival; HR=hazard ratio; LR=local recurrence LNH= lymph node harvest; LPLN=lateral pelvic lymph nodes; FFR=freedom from relapse; LNT = total number of lymph nodes , LNP = number of positive lymph nodes , LNYN = number of negative lymph nodes, RPLN = ratio of positive lymph nodes; LNR = lymph node harvest; LNN=lymph node number; LNR = lymph node ration; LNY = lymph node yield; LODDS = log odds of positive lymph nodes; RC = regression coefficient; NILN = number of involved LNs NR = not reported OR = odds ratio; OS = overall survival, RC = rectal cancer; RM = resection margin; ROD = risk of death; TME = Total Mesorectal Excision; CRM = cirumferential resection margin; DFS = disease free survival; nCRT = neoadjuvant chemoradiotherapy			

Table 9: Modifications to Original Technical Recommendations (see Section 1: Guideline Recommendations and Impact on Recommendations)				
No.	**Section of Guideline & Page**	**Original Recommendation**	**Suggested Revision**	**Rationale for Revision**
1	2.1 Surgery 2.1.2 Margins of Resection: Rectum Page 4	For tumours at or below the end of the end of the mesorectum, ideally a distal margin length of 2 cm in the fresh specimen should be obtained, not including the circular stapler donut."	For tumours at or below the anterior peritoneal reflection, ideally a distal margin of 2 cm in the fresh specimen should be obtained, not including the circular stapler donut.	The wording "end of the mesorectum" was replaced with "'below the anterior peritoneal reflection" to more clearly specify the anatomical location being discussed.
2	2.1 Surgery 2.1.2 Margins of Resection: Rectum Page 5	For lesions that are stage II (i.e., T3 or T4) or III (i.e., likely positive lymph nodes on cross sectional imaging), neoadjuvant therapy should be considered. Such determinations demand a high-quality MRI and, ideally for T status, a trans-rectal ultrasound (See Related Guidelines, p.10)	Patients with rectal cancer should undergo a high resolution MRI for proper assessment of T and N category and predicted CRM to pre-operatively stage patient. Patients with Stage II or Stage III rectal cancer should be offered pre-operative chemoradiotherapy	Updated to align with recommendations in EBS 17-8 "Optimization of Preoperative Assessment in Patients Diagnosed with Rectal Cancer" and by Wong et al. "Postoperative chemoradiotherapy vs. preoperative chemoradiotherapy…"
3	2.1 Surgery 2.1.3 Total Mesorectal Excision Page 6	While tumours of the high rectum do not require TME, in all cases at least 5 cm of mesorectum distal to the leading edge of the tumour should be removed if possible.	For tumours of the proximal and mid rectum, the distal margin length should be a minimum of 5 cm from the distal edge of the primary tumour in most patients to remove positive lymph nodes that are distal to the palpable leading edge of the tumour. The mesorectum and bowel edge must be transected transversely to avoid coning towards the distal resection margin and possible loss of lymph node tissue distal to the primary tumour For tumours at or below the anterior peritoneal reflection, ideally a distal margin length of 2 cm in the fresh specimen should be obtained, not including the circular stapler donut. In expert hands, a negative margin of less than 2 cm can be oncologically adequate to facilitate very low colorectal re-anastomosis. A negative distal margin must not be compromised in an effort to avoid a	For clarification purposes, the original "Technical Recommendation" in 2.1.3 was replaces with two paragraphs from 2.1.2 "Technical Recommendations for Proximal and Distal Margins"

Table 9: Modifications to Original Technical Recommendations (see Section 1: Guideline Recommendations and Impact on Recommendations)				
No.	**Section of Guideline & Page**	**Original Recommendation**	**Suggested Revision**	**Rationale for Revision**
			permanent colostomy. Please see Section 2 for a full discussion of this issue.	
4	2.1 Surgery 2.1.4 En Bloc Multivisceral Resection Page 6	If a surgeon finds a locally advanced, adherent tumour in an otherwise curable patient and is not prepared to perform a multivisceral resection, then consideration should be given to either aborting the operation or creating a proximal stoma and then referring the patient for multidisciplinary opinion regarding possible neoadjuvant therapy and more radical surgery.	Appropriate pre-operative imaging is recommended for proper surgical planning. An en bloc multivisceral resection is recommended for all locally advanced tumours involving adjacent structures. In the uncommon event that a tumour is unexpectedly found to be adherent to other structures intra-operatively and a multivisceral resection has not been planned, then resection of the primary tumour should be avoided and a proximal stoma should be created. The patient should be reviewed at multidisciplinary cancer conference for further surgical planning and opinion regarding possible neoadjuvant therapy.	Updated to reflect the recommendations outlined in EBS 17-8 "Optimization of Preoperative Assessment in Patients Diagnosed with Rectal Cancer" to highlighted a key point that surgeons should NOT routinely be surprised by what they encounter during surgery.
5	2.2 Pathology 2.2.2 Margins of Resection: Rectum Page 8	Involvement of the serosa by tumour (pT4b) is not equivalent to involvement of the radial margin by tumour (although there are circumstances in which an advanced tumour has penetrated the serosa and is adherent to adjacent soft tissue).	pT4b should be replaced with pT4a.	Updated to align with recent publication by the College of American Pathologists(CAP) (based on the AJCC/UICC TNM 7th edition)

Table 9: Modifications to Original Technical Recommendations (see Section 1: Guideline Recommendations and Impact on Recommendations)				
No.	**Section of Guideline & Page**	**Original Recommendation**	**Suggested Revision**	**Rationale for Revision**
6	2.2 Pathology 2.2.2 Margins of Resection: Rectum Page 8	Serosal penetration is defined as occurring when any of the following criteria are met: •Free tumour cells are present on the serosal surface with underlying ulceration. •Tumour is present at the serosal surface with an associated inflammatory reaction, mesothelial hyperplasia, and/or erosion or ulceration.	Serosal penetration is defined as occurring when any of the following criteria are met: Tumor present at the serosal surface Free tumor cells on the serosal surface (visceral peritoneum) with underlying erosion/ulceration of mesothelial lining, mesothelial hyperplasia and/or inflammatory reaction Perforation in which the tumor cells are continuous with the serosal surface through inflammation The significance of tumors that are <1 mm from the serosal surface and accompanied by serosal reaction is unclear, with some but not all studies indicating a higher risk of peritoneal recurrence. Multiple level sections and/or additional section of the tumor should be examined in these cases. If the serosal involvement is not present after additional evaluation, the tumor should be assigned to the pT3 category.	Updated to align with recent publication by the CAP (based on the AJCC/UICC TNM 7th edition)
7	3.2 Pathology 3.2.2 Number of Lymph Nodes Assessed Page 10	A tumour nodule in the pericolonic/perirectal fat without histologic evidence of residual lymph node tissue is classified as a lymph node replaced by tumour if the nodule has the form and smooth contour of a lymph node. If the nodule has an irregular contour, the nodule should be classified as a discontinuous extramural extension, pT3.	Discrete tumor deposits in pericolic or perirectal fat away from the leading edge of the tumor and showing no evidence of residual lymph node tissue, but within the lymphatic drainage of the primary carcinoma, are considered tumor deposits or satellite nodules and are not counted as lymph nodes replaced by tumor.	Updated to align with recent publication by CAP (based on the AJCC/UICC TNM 7th edition)

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Literature Search Strategy

MEDLINE only:

Search run on September 24 2015.

General Colorectal Search

1. colonic neoplasms/su,pa
2. rectal neoplasms/su,pa
3. colorectal neoplasms/su,pa
4. or/1-3

Margins of Resection

5. margin:.mp.
6. CRM.mp.
7. or/5-6

Occult Neoplastic Lesions

8. occult tumo:r cells.mp.
9. isolated tumo:r cells.mp.
10. micrometastas:.mp.
11. ITC.mp.
12. or/9-11

Intersphincteric Resection

13. Intersphincteric.mp

Inadverdent Perforation

14. Intestinal perforation/
15. (perforat: adj3 (surg: or intestin: or interaoperative or inadverdent:)).mp.
16. *neoplasm seeding/
17. Or/14-16

Total Mesorectal Excision

18. (mesorectal excision or TME).mp.
19. (sharp adj3 (dissect: or exis: or resect:)).mp.
20. or/18-19

En Bloc Resection

21. en bloc.mp.
22. adherent.mp.
23. ((extend: or extens:) adj3 (surg: or operat: or resect:)).mp.
24. multivisceral resect:.mp.
25. multiorgan resect:.mp.
26. or/21-25

Lymphadenectomy

27. lymph node.mp.
28. lymphadenectomy.mp.
29. lymph node excision/
30. (lateral node: or lateral pelvic node).mp.
31. (node adj3 (dissect: or excis: or resect:)).mp.
32. or/27-31

Combine Outcomes of Interest

33. **4 and (7 or 12 or 13 or 17 or 20 or 26 or 32)**

Limits

34. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
35. (case report$ or editorial$ or comment$ or letter$).pt.
36. 34 or 35
37. 33 not 36
38. Limit 37 to (humans and English language)
39. (200702$ or 200703$ or 200704$ or 200705$ or 200706$ or 200707$ or 200708$ or 200709$ or 200710$ or 200711$ or 200712$ or 2008$ or 2009$ or 2010$ or 2011$ or 2012$ or 2013$ or 2014$ or 2015$).ed.
40. 38 and 39
41. remove duplicates from 40

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1. **EDUCATION AND INFORMATION** – An archived document is a document that will no longer be tracked or updated but may still be useful for academic or other informational purposes. The document is moved to a separate section of our website, each page is watermarked with the word "ARCHIVED".

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3. **DELAY –** A delay means that there is reason to believe new, important evidence will be released within the next year that should be considered before taking further action.

4. **UPDATE** – An Update means that the DSG/GDG recognizes that there is new evidence that makes changes to the existing recommendations in the guideline necessary but these changes are more involved and significant than can be accomplished through the Document Assessment and Review process. The DSG/GDG will rewrite the guideline at the earliest opportunity to reflect this new evidence. Until that time, the document will still be available as its existing recommendations are still of some use in clinical decision making.