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Guideline 2-19

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

Staging and Surgical Approaches in Gastric Cancer

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An assessment conducted in December 2023 deferred the review of Guideline 2-19. This means that the document remains current until it is assessed again next year. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

Guideline 2-19 is comprised of 5 sections. You can access the summary and full report here:
https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/37866

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Table of Contents

Staging and Surgical Approaches in Gastric Cancer

Section 1: Recommendations

This section is a quick reference guide and provides the guideline recommendations only. For key evidence associated with each recommendation, see Section 2.

GUIDELINE OBJECTIVES

To develop recommendations on the optimal surgical management of gastric cancer in Ontario.

TARGET POPULATION

These recommendations apply to adult men and women with Stage I to IV gastric cancer (specifically gastric adenocarcinoma) who are being considered for surgery. Gastroesophageal junction tumours and early gastric cancers are excluded because they require additional considerations.

INTENDED USERS

Intended users of this guidance document are surgeons, gastroenterologists, medical oncologists, radiation oncologists, and the multidisciplinary team who treat gastric cancer.

RECOMMENDATIONS

Recommendation 1
Endorsed from Lerut et al., 2012 [1]: • All patients diagnosed with gastric cancer should be discussed at a multidisciplinary team meeting. • In patients with newly diagnosed gastric cancer, CT scan of the chest and abdomen should always be performed. • Endoscopic ultrasound (EUS) can be considered in patients planned for curative treatment on the basis of clinical presentation and/or CT. Fine-needle aspiration cytology of suspicious lymph nodes or metastases can be considered if technically feasible. • The following examinations can be considered for specific indications: positron emission tomography (PET) scan, magnetic resonance imaging (MRI), laparoscopy.
Qualifying Statements for Recommendation 1
• Prior to embarking upon surgery, chemotherapy, or chemoradiation, accurate staging and multidisciplinary discussion are paramount to determine optimal sequencing of therapy. • EUS should only be performed if results may change management plans (e.g., to assess for local invasion, nodal status, or metastatic spread). • As the accuracy for CT scans in detecting M1 disease is only 81% [2], diagnostic laparoscopy may allow patients to avoid a laparotomy in up to 44% of cases of higher stage cancer [3]. Both Scottish Intercollegiate Guidelines Network (SIGN) [4] and Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) [5] guidelines suggest diagnostic laparoscopy in patients with clinically suspected T3 and T4 cancers, or those at higher risk for M1 disease, such as poorly differentiated cancers and those with a higher nodal burden. Diagnostic laparoscopy should be performed prior to

starting chemotherapy for patients in whom a neoadjuvant approach is considered. Peritoneal washings may increase the accuracy of diagnostic laparoscopy.
- PET and MRI may be useful for further characterization of liver lesions, in clinical scenarios in which treatment plans would be changed by the finding of metastatic disease, but should not be routinely performed.

Recommendation 2

- A D2 lymph node dissection is preferred for curative intent resection of gastric cancer. In patients with T1N0 cancers or significant comorbidities a D1 dissection may be performed.

Qualifying Statements for Recommendation 2

- Distal pancreatectomy and/or splenectomy should not be routinely performed, as morbidity and mortality is increased.

Recommendation 3

- A minimum of 16 lymph nodes should be assessed for adequate staging of curative-resected gastric cancer.

Qualifying Statements for Recommendation 3

- American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) guidelines [6] state that 16 lymph nodes are necessary for adequate staging.
- Studies [7,8] suggest that removal and examination of more than 16 nodes may improve survival and increases accuracy of staging by decreasing under-staging, which leads to stage migration.

Recommendation 4

- Surgery for gastric cancer should aim at achieving an R0 margin.

Qualifying Statements for Recommendation 4

- National Comprehensive Cancer Network (NCCN) [9] guidelines suggest 4 cm margins in order to assure negative margins, while the Japanese Gastric Cancer Treatment Guidelines [10] suggest that margins of 3 cm for T1/T2 cancer and 5 cm for T3/T4 cancers be obtained.
- Intra-operative frozen section analysis should be considered in cases where there is concern about a high risk of positive margin.
- Cancers with higher T and N stage, and higher grade tumours, such as diffuse-type histology including signet ring carcinoma, are more likely to have microscopic margins involved, and intra-operative planning or neoadjuvant therapy should take these factors into consideration.
- For patients with poor biology (>5 lymph nodes positive, diffuse-type histology including signet ring carcinoma), an extended resection of the adjacent organs or intra-thoracic esophagus may not result in improved long-term survival, as multivariable analyses in many studies have shown that tumour biology may be a stronger determinant of outcomes than a positive margin.

- Extended resection should be undertaken selectively and with multidisciplinary discussion.

Recommendation 5

- In the metastatic setting, nonsurgical management options are preferred in patients without symptoms.
- In the metastatic setting, surgery should only be considered for palliation of symptoms that cannot be addressed through less-invasive means (i.e., radiation, chemotherapy, stenting).

Qualifying Statements for Recommendation 5

- As the rate of complications appears to be highest in more extensive resections, a palliative total gastrectomy should be performed only in exceptional circumstances, and with multidisciplinary discussion.

Recommendation 6

- Given evidence that higher-volume centres are associated with lower rates of procedure-related mortality, patients should be referred to higher-volume centres for surgical resection.
- Gastric cancer surgery should be performed in centres with sufficient support to prevent or manage complications (e.g., interventional radiology, anesthesia, level 1 intensive care unit).

Qualifying Statements for Recommendation 6

- In most studies, higher-volume centres are associated with improved outcomes. There is no common definition of a high-volume centre compared with medium or low volume within the studies; however, it should be noted that five or fewer annual cases are considered low, or very low volume in all studies.
- An expected 30-day or in-hospital peri-operative mortality should be less than 5%. This is based on published mortality rates from high-volume centres, as well as the "Hepatic, Pancreatic and Biliary Tract (HPB) Surgical Oncology Standards" (EBS#17-2) [11], which recommends a 30-day or in-hospital mortality rate of less than 5% for major pancreatic resection and 3% for anatomical liver resection. As these procedures are more complicated than gastric cancer surgery, it is reasonable to expect a similar or lower mortality rate.
- Hospitals performing gastric cancer surgery should know their mortality rates, and recognize that lower volumes create larger confidence intervals for mortality estimates.

Recommendation 7

- Quality metrics for lymph nodes, margins, peri-operative mortality, and oncologic outcomes should be met regardless of surgical technique (e.g., open or minimally invasive).

Qualifying Statements for Recommendation 7

- While laparoscopic resection has been shown to be equal or superior to open surgery for short-term outcomes, there is no evidence regarding long-term cancer outcomes. Several ongoing randomized trials will report on oncologic survival.

Staging and Surgical Approaches in Gastric Cancer

Section 2: Guideline – Recommendations and Key Evidence

GUIDELINE OBJECTIVES

To develop recommendations on the optimal surgical management of gastric cancer in Ontario.

TARGET POPULATION

These recommendations apply to adult men and women with Stage I to IV gastric cancer (specifically gastric adenocarcinoma) who are being considered for surgery. Gastroesophageal junction (GEJ) tumours and early gastric cancers are excluded because they require additional considerations.

INTENDED USERS

Intended users of this guidance document are surgeons, gastroenterologists, medical oncologists, radiation oncologists, and the multidisciplinary team who treat gastric cancer.

RECOMMENDATIONS, KEY EVIDENCE, AND INTERPRETATION OF EVIDENCE

Recommendation 1

Endorsed from Lerut et al. 2012 [1]:

- All patients diagnosed with gastric cancer should be discussed at a multidisciplinary team meeting.
- In patients with newly diagnosed gastric cancer, CT scan of the chest and abdomen should always be performed.
- Endoscopic ultrasound (EUS) can be considered in patients planned for curative treatment on the basis of clinical presentation and/or CT. Fine-needle aspiration cytology of suspicious lymph nodes or metastases can be considered if technically feasible.
- The following examinations can be considered for specific indications: PET scan, magnetic resonance imaging, laparoscopy.

Qualifying Statements for Recommendation 1

- As the accuracy for CT scans in detecting M1 disease is 81% [2], diagnostic laparoscopy may allow patients to avoid a laparotomy in up to 44% of cases of advanced stage cancer [3]. Both Scottish Intercollegiate Guidelines Network (SIGN) [4] and Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) [5] guidelines suggest diagnostic laparoscopy in patients with clinically suspected T3 and T4 cancers, or those at higher risk for M1 disease, such as poorly differentiated cancers and those with a higher nodal burden. Diagnostic laparoscopy should be performed prior to starting chemotherapy for patients in whom a neoadjuvant approach is considered. Washing may increase the accuracy of diagnostic laparoscopy.
- PET and MRI may be useful for further characterization of liver lesions, in clinical scenarios in which treatment plans would be changed by the finding of metastatic disease, but should not be routinely performed.
- EUS should only be performed if results may change management plans (i.e., to assess for local invasion, nodal status or metastatic spread).

Key Evidence for Recommendation 1

- Key evidence derived from one clinical practice guideline conducted by Lerut at al. [1] of the Belgian Health Care Knowledge Centre.

Interpretation of Evidence for Recommendation 1

- There was agreement among the Working Group members that the overall certainty of the evidence was moderate.
- The Working Group considered accurate staging of each patient to be of paramount importance in order for patients to be provided appropriate treatment. Therefore, the Working Group was unanimous in their opinion that patients would also value the importance of accurate staging, although patient input was not sought.
- The desirable effect (i.e., accurate staging) is large as patients who are improperly staged will not be provided with appropriate treatment. At the same time, the undesirable effects (morbidity of the staging investigations) are manageable in this population. The Working Group believed the desirable effect (accurate staging) is large relative to the undesirable effects (potential increased morbidity) in this population of patients because inaccurate staging will result in patient being treated inappropriately, either by under-treating or over-treating them.
- The evidence is generalizable to the entire population of gastric cancer patients.
- The Working Group believed that all interpretations of the evidence for staging of gastric cancer patients would be similar.

Recommendation 2

- A D2 lymph node dissection (LND) is preferred for curative intent resection of gastric cancer. In patients with T1N0 cancers or significant comorbidities a D1 dissection may be performed.

Qualifying Statements for Recommendation 2

- Distal pancreatectomy and/or splenectomy should not be routinely performed, as morbidity and mortality is increased.

Key Evidence for Recommendation 2

- A systematic review of five studies and 1599 patients [12] demonstrated that five-year survival rate was similar for D2 and D1 LND (47.0% vs. 44.8%; odds ratio [OR], 1.11; 95% confidence interval [CI], 0.84 to 1.47; p=0.14).
- Subgroup analysis by T stage demonstrated a significant survival difference favouring D2 over D1 LND in T3 patients (25.9% vs. 11.5%; OR, 1.64; 95% CI, 1.01 to 2.67; p<0.05).
- 15-year follow-up for the Dutch randomized control trial (RCT) of D1 versus D2 LND showed fewer gastric cancer-related deaths in patients undergoing a D2 LND for all T-stages (gastric cancer related deaths were 48% in D1 vs. 37% in D2, p=0.01, per protocol analysis) [13].

Interpretation of Evidence for Recommendation 2

- See Section after Recommendation 4.

Recommendation 3

- At least 16 lymph nodes should be assessed for adequate staging of curative-resected gastric cancer.

Qualifying Statements for Recommendation 3

- American Joint Committee on Cancer/Union for International Cancer Control (AJCC/UICC) guidelines [6] state that 16 lymph nodes are necessary for adequate staging.
- Studies [7,8] suggest that removal and examination of more than 16 nodes may improve survival and increases accuracy of staging by decreasing under staging which leads to stage migration.

Key Evidence for Recommendation 3

- One systematic review [14] reported significantly improved disease-free survival (DFS) as the number of lymph nodes harvested increased, especially when more than 15 nodes were retrieved, and concluded that 16 lymph nodes should be harvested as a minimum. More current studies of moderate quality [15,16] also report that harvesting more than 15 nodes significantly improved survival.

Interpretation of Evidence for Recommendation 3

- See Section after Recommendation 4.

Recommendation 4

- Surgery for gastric cancer should aim at achieving an R0 margin.

Qualifying Statements for Recommendation 4

- National Comprehensive Cancer Network (NCCN) [9] guidelines suggest 4 cm margins in order to assure negative margins, while the Japanese Gastric Cancer Treatment Guidelines [10] suggest that margins of 3 cm for T1/T2 cancer and 5 cm for T3/T4 cancers be obtained.
- Intra-operative frozen section analysis should be considered in cases where there is concern about a high risk of positive margin.
- Cancers with higher T and N stage, and higher grade tumours, such as diffuse-type histology including signet ring carcinoma, are more likely to have microscopic margins involved, and intra-operative planning or neoadjuvant therapy should take these factors into consideration.
- For patients with poor biology (>5 lymph nodes positive, diffuse-type histology including signet ring carcinoma), an extended resection of the adjacent organs or intra-thoracic esophagus may not result in improved long-term survival, as multivariable analyses in many studies have shown that tumour biology may be a stronger determinant of outcomes than a positive margin.
- Extended resection should be undertaken selectively and with multidisciplinary discussion.

Key Evidence for Recommendation 4

- Data from one study suggest that margins of 5 cm for T3/T4 cancer and 3 cm for T1/T2 cancers are sufficient to obtain resection margins negative for microscopic cancer [17].

- Median overall survival (OS) and median recurrence-free survival (RFS) for patients was significantly better in those with proximal margins of 3.1 to 5.0 cm compared with margins ≤3.0 cm (48.1 vs. 29.3 months, p=0.01; and 38.9 vs. 21.1 months, p=0.02, respectively). Median OS and median RFS for patients with margins >5.0 cm were not significantly different than those with proximal margins of 3.1 to 5.0 cm. However, the OS and RFS advantage of a proximal margin ≥3.1 cm was only associated with Stage I disease only and was not associated with Stage II or III disease [17].

Interpretation of Evidence for Recommendation 4

- See Section after Recommendation 4.

Interpretation of Evidence for Recommendations 2, 3 and 4.

- There was agreement among the Working Group members that the overall certainty of the evidence was moderate based on the entire body of the evidence.
- Although the Working Group looked at survival, mortality, reoperation rates, and RFS, OS was considered to be the most important outcome, followed by RFS. The Working Group was unanimous in their opinion that patients would also value the increased survival benefit associated with each of the surgical parameters evaluated (extent of lymphadenectomy, number of lymph nodes retrieved, and minimal gross margins) although patient input was not sought. The Working Group valued survival when drafting the recommendations as they believed that the morbidities associated with each of these surgical parameters were manageable.
- The desirable effect is increased survival. The undesirable effects (morbidity) are manageable in this population. The Working Group believed the desirable effect (longer survival) is large relative to the undesirable effects (extra morbidity) in the selected group of Stage III patients especially since inadequate LND, positive margins, and retrieval of an inadequate number of lymph nodes are all associated with disease recurrence.
- The evidence is generalizable to the entire gastric cancer population as defined in this guidance document.
- The Working Group believed that there might be an alternate interpretation of the evidence for D2 versus D1 LND if the focus remains on several negative trials available and not on the compelling subgroup analysis of these trials and the emerging long-term survival benefits in ongoing trials.

Recommendation 5

- In the metastatic setting, nonsurgical management options are preferred in patients without symptoms.
- In the metastatic setting, surgery should only be considered for palliation of symptoms that cannot be addressed through less-invasive means (i.e., radiation, chemotherapy, stenting).

Qualifying Statements for Recommendation 5

- As the rate of complications appears to be highest in more extensive resections, a palliative total gastrectomy should be performed only in exceptional circumstances, and with multidisciplinary discussion.

Key Evidence for Recommendation 5

- In one systematic review of 59 studies, procedure-related morbidity occurred in all types of surgical interventions and irrespective of the intent of the surgery. Morbidity ranged from 3.8% to 49% for gastrectomy and 14% to 21% for non-resectional surgeries [18]. In the literature update, procedure-related morbidity in moderate-quality non-curative studies ranged from 15.1% [19] to 88.8% [20]for gastrectomy and 11.5% [21] to 21% [22]for non-resectional surgeries.
- In the systematic review by Mahar et al. [18], procedure-related mortality was lower in palliative resections (0% to 7%) compared with either non-curative (0% to 21%) or not otherwise specified surgeries (0% to 20.4%). The mortality rate for gastrectomy performed for any intent was 0% to 21% whereas the mortality rate for non-resectional surgeries was 0% to 39% [18]. In the literature update, which included all moderate quality studies, procedure-related mortality for gastrectomy performed in non-curative studies was 1.1% [19] to 9.1% [23], whereas the mortality rate for non-resectional surgeries in non-curative studies was 4.8% [21] to 10% [22].
- The REGATTA trial [24] showed no survival benefit of gastrectomy + chemotherapy over chemotherapy alone (25.1% vs. 31.7%) in patients with non-curable gastric cancer (hazard ratio [HR], 1.09; 95% CI, 0.78 to 1.52; p=0.70), and more complications for patients in the gastrectomy + chemotherapy arm.

Interpretation of Evidence for Recommendation 5

- There was agreement among the Working Group members that the overall certainty of the evidence was moderate.
- Although the Working Group looked at survival, morbidity, mortality, and quality of life (QOL), morbidity and QOL (where available) were considered to be the most important outcomes. The Working Group was unanimous in their opinion that patients would also likely value these outcomes, although patient input was not sought.
- The Working Group valued OS over toxicity when drafting the recommendations as they felt that the toxicities were manageable.
- The desirable effect (i.e., better QOL, less morbidity) is probably not large, especially for Stage IV patients in whom the goal of surgery is not palliation of symptoms. At the same time, the undesirable effects are moderate. The mortality rates for surgery in Stage IV gastric cancer can be high especially when the surgery is not performed for palliation of symptoms. The Working Group believed the desirable effect (better QOL) was not large relative to the undesirable effects (mortality) and should,

therefore, only be performed for palliation of symptoms. If the surgery is not likely to improve QOL, it should not be done.
- The evidence is not generalizable to the entire Stage IV gastric cancer population as defined in this guidance document.
- The Working Group believed that the REGATTA trial [24] may be interpreted differently by others. REGATTA was stopped early for futility and possible harm in the surgery arm. It is conceivable that these data may be interpreted as meaning that survival was equivalent in the surgery and the surgery + chemotherapy arms, but most are not making this interpretation.

Recommendation 6

- Given evidence that higher-volume centres are associated with lower rates of procedure-related mortality, patients should be referred to higher-volume centres for surgical resection.
- Gastric cancer surgery should be performed in centres with sufficient support to prevent or manage complications (e.g., interventional radiology, anesthesia, level 1 intensive care unit).

Qualifying Statements for Recommendation 6

- In most studies, higher-volume centres are associated with improved outcomes. There is no common definition of a high-volume centre within the studies; however, it should be noted that five or fewer annual cases are considered low or very low volume in all studies.
- An expected 30-day or in-hospital peri-operative mortality should be less than 5%. This is based on published mortality rates from high-volume centres, as well as the "Hepatic, Pancreatic and Biliary (HPB) Tract Surgical Oncology Standards" (EBS#17-2) [11], which recommends a 30-day or in-hospital mortality rate of less than 5% for major pancreatic resection and 3% for anatomical liver resection. As these procedures are more complicated than gastric cancer surgery, it is reasonable to expect a similar or lower mortality rate.
- Hospitals performing gastric cancer surgery should know their mortality rates, and recognize that lower volumes create larger confidence intervals for mortality estimates.

Key Evidence for Recommendation 6

- In one systematic review containing 22 studies looking at institutional volumes, procedure-related morbidity was not significantly different in high-volume compared with low-volume hospitals (19% to 46.5% in high-volume hospitals vs. 19% to 43% in low-volume hospitals). However, meta-analysis of procedure-related mortality favoured high-volume hospitals (OR, 0.73; 95% CI, 0.65 to 0.81; $p<0.00001$). Improved five-year survival was significantly associated with higher institutional volumes in three of seven studies that evaluated this outcome [25].
- In the updated literature search, procedure-related mortality was not significantly different in high- versus low-volume hospitals in four of the five studies evaluating this outcome [26-29]. However, in 2013, Dikken et al. [30] reported that procedure-related mortality significantly favours high-volume hospitals (OR, 0.64; 95% CI, 0.41

to 0.99; p=0.025). The updated literature search only yielded moderate quality non-RCTs.

Interpretation of Evidence for Recommendation 6

- There was agreement among the Working Group members that the overall certainty of the evidence was low to moderate.
- Although the Working Group looked at mortality (especially 30-day and in-hospital mortality) and morbidity, the Working Group was unanimous in their opinion that patients would value mortality as an assessment of surgeon and/or institutional volumes, although patient input was not sought.
- The desirable effect (i.e., lower short-term mortality) is large. At the same time, the undesirable effects (i.e., death) are not small. The Working Group believed the desirable effect (living) was larger relative to the undesirable effects (death).
- The evidence is generalizable to gastric cancer surgery in all institutions.
- The Working Group believed that others may have slightly different interpretations of the volume data by setting definite numerical volume standards, whereas in the present guidance document the focus was on mortality rate instead.

Recommendation 7

- Quality metrics for lymph nodes, margins, peri-operative mortality, and oncologic outcomes should be met regardless of surgical technique (e.g., open or minimally invasive).

Qualifying Statements for Recommendation 7

- While laparoscopic resection has been shown to be equal or superior to open surgery for short-term outcomes, there is no evidence regarding long-term cancer outcomes. Several ongoing randomized trials will report on oncologic survival.

Key Evidence for Recommendation 7

- Short-term outcomes (e.g., blood loss, time to first flatus, length of hospital stay, and post-operative complications) favour laparoscopic compared with open gastrectomy [31-38]. This is based on one systematic review and several more recent primary studies. Long-term cancer-related survival results are currently being examined in several RCTs.

Interpretation of Evidence for Recommendation 7

- There was agreement among the Working Group members that the overall certainty of the evidence was moderate.
- Although the Working Group looked at short-term outcomes (blood loss, time to first flatus, length of hospital stay, post-operative complications, hospital mortality rates, and surgical time) and long-term outcomes (survival), no long-term outcomes have been reported from RCTs to date. The Working Group was unanimous in their opinion that patients would also value both long- and short-term outcomes, although patient input was not sought. Once these longer-term outcome data become more available, the emphasis on short-term outcomes may change.
- The desirable effects (i.e., better short-term outcomes such as blood loss, time to first flatus, length of hospital stay, post-operative complications, hospital mortality

rates) are large. At the same time, the undesirable effects (longer surgical times) are manageable in this population with adequate surgeon training in laparoscopic procedures. The Working Group believed the desirable effect (better short-term surgical outcomes) is large relative to the undesirable effects (longer surgical times). Once these longer-term outcome data become more available, the emphasis on short-term outcomes may change.

- The evidence is generalizable to the entire gastric cancer population as defined in this guidance document.
- The Working Group believed that all interpretations of the evidence regarding laparoscopic versus open surgery in gastric cancer patients would be similar.

FURTHER QUALIFYING STATEMENTS

None.

IMPLEMENTATION CONSIDERATIONS

The Working Group considered the recommendations provided above to be the ideal standard of care and would be feasible to implement. Furthermore, they may improve current health inequities by ensuring the same standards of care for all patients no matter where they are treated in Ontario. Thus, there is the potential for better outcomes for gastric cancer patients across the province. To support in this endeavour it would be useful if hospital mortality rates for gastric cancer surgery were available to hospitals as they are for other types of surgeries such as pancreas, lung, and esophagus. These recommendations may change current practice as many patients are currently only receiving a D1 LND even when a D2 is more appropriate. Moreover, laparoscopic surgeries may occur more often as time goes on and more surgeons are adequately trained in these procedures. These recommendations may come with no additional costs. In fact, overall costs may decrease owing to fewer recurrences, possibly fewer unnecessary surgeries, and reduced length of hospital stays as the number of laparoscopic surgeries performed increases. The Working Group believed the outcomes valued in this guideline would align well with patient values and patients would view these recommendations as acceptable.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-14: *Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer* (available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/351).

- PEBC Evidence-based Series #2-26: *The Role of Chemotherapy in Advanced Gastric Cancer* (available from: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/366

Staging and Surgical Approaches in Gastric Cancer

Section 3: Guideline Methods Overview

This section summarizes the methods used to create the guideline. For the systematic review, see Section 4.

THE PROGRAM IN EVIDENCE-BASED CARE

The Program in Evidence-based Care (PEBC) is an initiative of the Ontario provincial cancer system, Cancer Care Ontario (CCO). The PEBC mandate is to improve the lives of Ontarians affected by cancer through the development, dissemination, and evaluation of evidence-based products designed to facilitate clinical, planning, and policy decisions about cancer control.

The PEBC supports the work of Guideline Development Groups (GDGs) in the development of various PEBC products. The GDGs are composed of clinicians, other healthcare providers and decision makers, methodologists, and community representatives from across the province.

The PEBC is a provincial initiative of CCO supported by the Ontario Ministry of Health and Long-Term Care (OMHLTC). All work produced by the PEBC is editorially independent from the OMHLTC.

BACKGROUND FOR GUIDELINE

A quality problem was identified with respect to surgical approaches to gastric cancer by CCO's Surgical Oncology Program (SOP). The SOP approached the Gastrointestinal (GI) DSG about undertaking this topic. The GI DSG believed this was an important topic and prioritized it.

GUIDELINE DEVELOPERS

This guideline was developed by the Surgical Management of Gastric Cancer GDG (Appendix 1), which was convened at the request of the PEBC GI DSG.

The project was led by a small Working Group of the Surgical Management of Gastric Cancer GDG, which was responsible for reviewing the evidence base, drafting the guideline recommendations, and responding to comments received during the document review process. The Working Group members had expertise in surgical oncology, medical oncology, radiation oncology, and health research methodology. Other members of the Surgical Management of Gastric Cancer GDG served as the Expert Panel and were responsible for the review and approval of the draft document produced by the Working Group. Conflict of interest declarations for all GDG members are summarized in Appendices 2 and 3, and were managed in accordance with the *PEBC Conflict of Interest Policy*.

GUIDELINE DEVELOPMENT METHODS

The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the Practice Guidelines Development Cycle [39].This process includes a systematic review, interpretation of the evidence by the Working Group, draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

The PEBC uses the AGREE II framework [40] as a methodological strategy for guideline development. AGREE II is a 23-item validated tool that is designed to assess the methodological rigour and transparency of guideline development.

The currency of each document is ensured through periodic review and evaluation of the scientific literature and, where appropriate, the addition of newer literature to the original evidence base. This is described in the *PEBC Document Assessment and Review Protocol*. PEBC guideline recommendations are based on clinical evidence, and not on feasibility of implementation; however, a list of implementation considerations such as costs, human resources, and unique requirements for special or disadvantaged populations is provided along with the recommendations for information purposes. PEBC guideline development methods are described in more detail in the *PEBC Handbook* and the *PEBC Methods Handbook*.

Search for Existing Guidelines

A search for existing guidelines is generally undertaken prior to searching for existing systematic reviews or primary literature. This is done with the goal of identifying existing guidelines for adaptation or endorsement in order to avoid the duplication of guideline development efforts across jurisdictions. For this project, the following sources were searched for existing guidelines that addressed the research questions:

- Practice guideline databases: SAGE, National Guidelines Clearinghouse;
- Guideline developer websites: (NICE, SIGN, ASCO)

The following criteria were used to select potentially relevant guidelines:

- Guidelines with recommendations directly related to a question of interest;
- A recent guideline (published in 2010 or later).

Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument[40].

A guideline search uncovered 156 guidelines of which 28 underwent a full-text review. One guideline was retained as an appropriate source document for endorsement for Question 1 only. A search of the primary literature was required for all other questions (see Section 4 and Appendix 3).

Guideline Review and Approval

Internal Review

For the guideline document to be approved, 75% of the content experts who comprise the GDG Expert Panel must cast a vote indicating whether or not they approve the document, or abstain from voting for a specified reason, and of those that vote, 75% must approve the document. In addition, the PEBC Report Approval Panel (RAP), a three-person panel with methodology expertise, must unanimously approve the document. The Expert Panel and RAP members may specify that approval is conditional, and that changes to the document are required. If substantial changes are subsequently made to the recommendations during external review, then the revised draft must be resubmitted for approval by RAP and the GDG Expert Panel.

External Review

Feedback on the approved draft guideline is obtained from content experts and the target users through two processes. Through the Targeted Peer Review, several individuals with content expertise are identified by the GDG and asked to review and provide feedback on the guideline document. Through Professional Consultation, relevant care providers and other potential users of the guideline are contacted and asked to provide feedback on the guideline recommendations through a brief online survey. This consultation is intended to facilitate the dissemination of the final guidance report to Ontario practitioners.

ACKNOWLEDGEMENTS

The members of the Surgical Management of Gastric Cancer GDG would like to thank the following individuals for their assistance in developing this report:

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- Kristy Yiu for conducting a data audit.
- Sara Miller for copyediting.

Staging and Surgical Approaches in Gastric Cancer

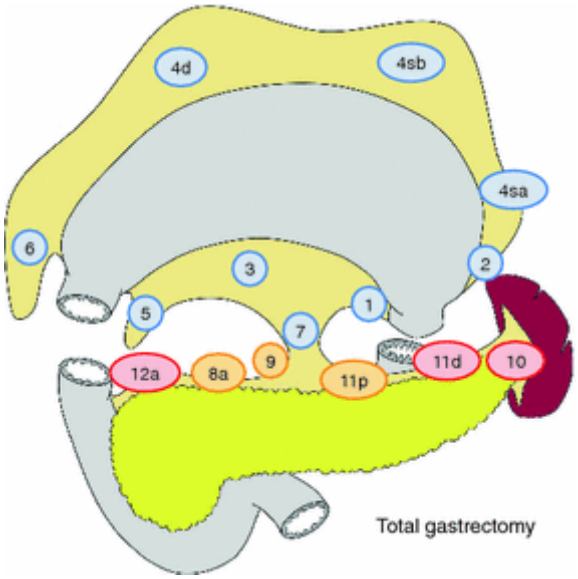
Section 4: Systematic Review

INTRODUCTION

Although the incidence and mortality of gastric cancer has been steadily decreasing in Canadian men and women, this disease remains a global health problem, accounting for 6.8% of all new cancer cases and 8.8% of all cancer deaths worldwide [41] in 2012. In Canada, the annual percent change in age-standardized incidence between 2001 and 2010 is -2.1% and -1.0% in males and females, respectively. The corresponding numbers for the change in age-standardized mortality between 2003 and 2012 is -3.6% and -2.7% for males and females, respectively [42]. In Ontario in 2016, there will be an estimated 1320 new incident cases of stomach cancer (37.7% of the estimated new-incident stomach cancer cases in Canada) and 760 deaths from stomach cancer (37.4% of the estimated stomach cancer deaths in Canada). The five-year relative survival ratio is 25% (95% CI, 23% to 26%) for males and females combined [42]. Concurrently, the rate of incidence of GEJ cancers has increased over the past decade. Most GEJ cancers are now classified as esophageal cancers, given changes in the 7th edition UICC cancer staging system [6], and therefore recommendations in this guideline should not be extrapolated to treatment of GEJ cancers, which require different multidisciplinary considerations. Under select circumstances, early gastric cancer may be curatively treated with endoscopic resection [43]. Discussion of selection of these patients and endoscopic techniques is outside the scope of this guideline.

Resection is the cornerstone for cure for gastric adenocarcinoma; however, several aspects of surgical intervention remain controversial or sub-optimally applied at the population level. Although widely available, staging for gastric cancer is not uniformly performed for patients [44,45]. In addition, the extent of LND with curative gastrectomy continues to be debated. Although D2 lymphadenectomy is considered the standard of care in Asia, D1 lymphadenectomy continues to be routinely performed in Western countries, with some patients receiving a D0 LND in curative-intent cases. A D1 LND includes removal of the omentum with the perigastric lymph nodes (gastric and gastroepiploic arteries, stations 1-6), as well as the left gastric artery (station 7). Station 2 is omitted for a distal gastrectomy. A D2 LND additionally removes lymph nodes along the hepatic artery (station 8a), celiac axis (station 9), splenic artery (stations 10 and 11) and proper hepatic artery (station 12a). A D0 LND is inadequate dissection of one or more of stations 1 to 7 (see Figure 4-1).

Figure 4-1: Lymph node stations for total gastrectomy.



With permission from Springer. Taken from: Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer. 2011;14(2):113-23 (Figure 2.3.1.1). See reference 10.

Closely related to the discussion of the type of lymph node harvest, many patients within North America do not meet the minimum requirement of lymph node assessment for full cancer staging. Moreover, although a positive margin is associated with worse survival, there are very few studies evaluating the appropriate distance for gross resection margins needed for curative-intent resection. Finally, the emergence of laparoscopic techniques have fuelled controversies about whether or not this minimally invasive surgery provides equal oncologic results to traditional open surgical techniques.

Debates also exist with respect to the relationship between surgical volumes (both institutional and on an individual surgeon level) and outcomes. This issue has been explored for many surgical procedures because they are potentially modifiable factors. It is an important issue for gastric cancers as these surgeries are technically challenging, yet infrequently performed because of the relatively low incidence of gastric cancer in Ontario.

The management of Stage IV gastric cancer is difficult. Most new-incident cases of gastric cancer in Canada are not potentially curable with surgery. However, advanced gastric cancer can have life-threatening symptoms (e.g., obstruction, bleeding), which are amenable to both resection and non-resectional interventions (e.g., stent, radiation). Many patients with Stage IV disease undergo resection, yet not all non-curative gastrectomies are performed for symptom control [44]. It is unclear in what percentage of patients an operation could have been avoided, with a concomitant reduction in peri-operative morbidity and mortality.

The Working Group of the Surgical Management of Gastric Cancer GDG developed this evidentiary base to inform recommendations as part of a clinical practice guideline. Based on the objectives of this guideline (Section 2), the Working Group derived the research questions outlined below.

RESEARCH QUESTIONS

1) What is/are the optimal techniques(s) to adequately stage gastric cancer?

2) What is the optimal technique of gastric cancer surgery with curative intent with respect to:
    a. D2 lymph node dissection?
    b. D1 lymph node dissection?
    c. The minimal number of lymph nodes needed to be dissected for curative-intent resection?
    d. The minimal gross margin for curative-intent resection?
    e. Laparoscopic versus open resection?

3) What are the indications for surgery for Stage IV gastric cancer in:
    a. Asymptomatic patients?
    b. Symptomatic patients?

4) What is the relationship between surgical volumes and outcomes?

METHODS

This evidence review was conducted in two planned stages, including a search for systematic reviews followed by a search for primary literature. These stages are described in subsequent sections.

Search for Existing Systematic Reviews

A search was conducted for existing systematic reviews. Methods for locating and evaluation of existing systematic reviews are described here:

- Databases searched (MEDLINE, EMBASE, Cochrane Database of Systematic Reviews)
- Years covered
    - Question 2a/b – 1995 – present
    - Question 2c – 2000 – present
    - Question 2d – 1980 – present
    - Question 2e – 2010 – present
    - Question 3- 2000 – present
    - Question 4 – 2000 - present
- Search terms – see Appendix 3
- Selection criteria
    - English language and all included studies in English
    - Directly related to one or more guideline questions

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item Assessment of Multiple Systematic Reviews (AMSTAR) [46] tool to determine whether or not existing systematic reviews met a minimum threshold for methodological quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

A relevant systematic review was available for Question 2a/b, c, d, 3 and Question 4. A search for primary studies was undertaken from the point in time at which each systematic review was ended until June 10, 2016 in MEDLINE and until Week 24 of 2016 in EMBASE. The newer relevant primary studies are included for each of these questions. If more than one publication was available for a given trial only the most recent publication was included.

No relevant systematic review was available for Question 3e and a search for primary studies was undertaken. Recall from Section 3 that an endorsable guideline was available for Question 1.

Literature Search Strategy

Please see Appendix 3 for the primary literature search strategy for each question.

Study Selection Criteria and Process

Question 2a/b

Inclusion Criteria

- English language
- Adult gastric cancer patients with Stage I to III disease
- D2 versus D1 LND
- Includes at least one outcome of interest (morbidity, DFS, OS)
- Systematic reviews and randomized trials in which N=30 minimally.

Exclusion Criteria

- Case studies, commentaries, editorials
- Includes GEJ tumours and these data cannot be parsed out
- Includes T1N0 cases and these data cannot be parsed out

Question 2c

Inclusion Criteria

- English language
- Adult gastric cancer patients with Stage I to III disease
- Comparison of number of lymph nodes dissected
- Includes at least one outcome of interest (morbidity, DFS, OS)
- Systematic reviews, randomized trials, other prospective or retrospective comparative studies (cohort, case-control, historically controlled) in which N=30 minimally.

Exclusion Criteria

- Case studies, commentaries, editorials
- Includes GEJ tumours and these data cannot be parsed out
- Includes T1N0 cases and these data cannot be parsed out

Question 2d

Inclusion Criteria

- English language
- Adult gastric cancer patients with Stage I to III disease
- Comparison of sizes of negative margins
- Includes at least one outcome of interest (DFS, OS)
- Systematic reviews, randomized trials, other prospective or retrospective comparative studies (cohort, case-control, historically controlled) in which N=30 minimally.

Exclusion Criteria

- Case studies, commentaries, editorials
- Includes GEJ tumours and these data cannot be parsed out
- Includes T1N0 cases and these data cannot be parsed out

Question 2e

Inclusion Criteria

- English language
- Adult gastric cancer patients with Stage I to III disease
- Laparoscopic versus open gastrectomy with D2 LND
- Includes at least one outcome of interest
    - Short-term outcomes – hospital length of stay, blood loss, short-term 30-day mortality
    - Long-term outcomes – DFS, OS
- Systematic reviews, randomized trials, other prospective or retrospective comparative studies (cohort, case-control, historically controlled) in which N=30 minimally.

Exclusion Criteria

- Case studies, commentaries, editorials
- Includes GEJ tumours and these data cannot be parsed out
- Includes T1N0 cases and these data cannot be parsed out

Question 3

Inclusion Criteria

- English language
- Adult gastric cancer patients with Stage IV disease
- Surgery versus observation or surgery + chemotherapy versus chemotherapy alone
- Includes at least one outcome of interest (palliation outcomes such as QOL, median survival, do they leave the hospital)
- Systematic reviews, randomized trials of any size, other prospective or retrospective comparative studies (cohort, case-control, historically controlled) in which N=30 minimally.

Exclusion Criteria

- Case studies, commentaries, editorials

Question 4

Inclusion Criteria

- English language
- Adult gastric cancer patients with Stage I to III disease
- Comparison of various hospital or surgeon volumes
- Includes at least one outcome of interest (expected perioperative mortality, morbidity, OS)
- Systematic reviews, randomized trials, other prospective or retrospective comparative studies (cohort, case-control, historically controlled) in which N=30 minimally.

Exclusion Criteria

- Case studies, commentaries, editorials

A review of the titles and abstracts that resulted from the search was independently conducted by one reviewer (RC). For those items that warranted full-text review, one reviewer reviewed each item (RC) for all questions except Question 3, for which two reviewers (RC and NC) reviewed each item in collaboration.

Data Extraction and Assessment of Study Quality and Potential for Bias

Data from the included guideline, systematic reviews, and primary studies were extracted by one member of the Working Group (RC). All extracted data and information were audited by an independent auditor.

Important quality features, such as industry funding, control details, blinding, and power calculations, for each non-RCT study were extracted. RCTs were evaluated using the Cochrane Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/). Systematic reviews were evaluated using the AMSTAR tool [46] and guidelines were evaluated using AGREEII [40].

Synthesizing the Evidence

Meta-analysis was not planned as many of the studies included in this systematic review were quite varied and retrospective.

RESULTS

Search for Existing Systematic Reviews

A search for systematic reviews uncovered 1821 documents. Of these, 88 underwent full-text review and eight were retained that represented seven systematic reviews (Table 4-1).

Search for Primary Literature

A search for primary literature was conducted for Questions 2a/b, c, e, 3 as well as Question 4. For these questions, the literature search was an update from wherever the systematic review identified for a given question left off. No systematic review was identified for Question 2d; therefore, a de novo literature search was undertaken. As an endorsable guideline was available for Question 1, no search for primary literature was undertaken for this question.

Literature Search Results

For the individual study literature search there were 23,290 hits. Of these, 211 underwent a full-text review and 47 were retained. One study was obtained through reference mining. For a summary of the full literature search results (including guidelines and systematic reviews), please refer to Figure 4-2, which is a flow diagram depicting the inclusion and exclusion of all studies for this guidance document. A summary of all included studies can be found in Table 4-1.

Figure 4-2. Literature search results flow diagram.

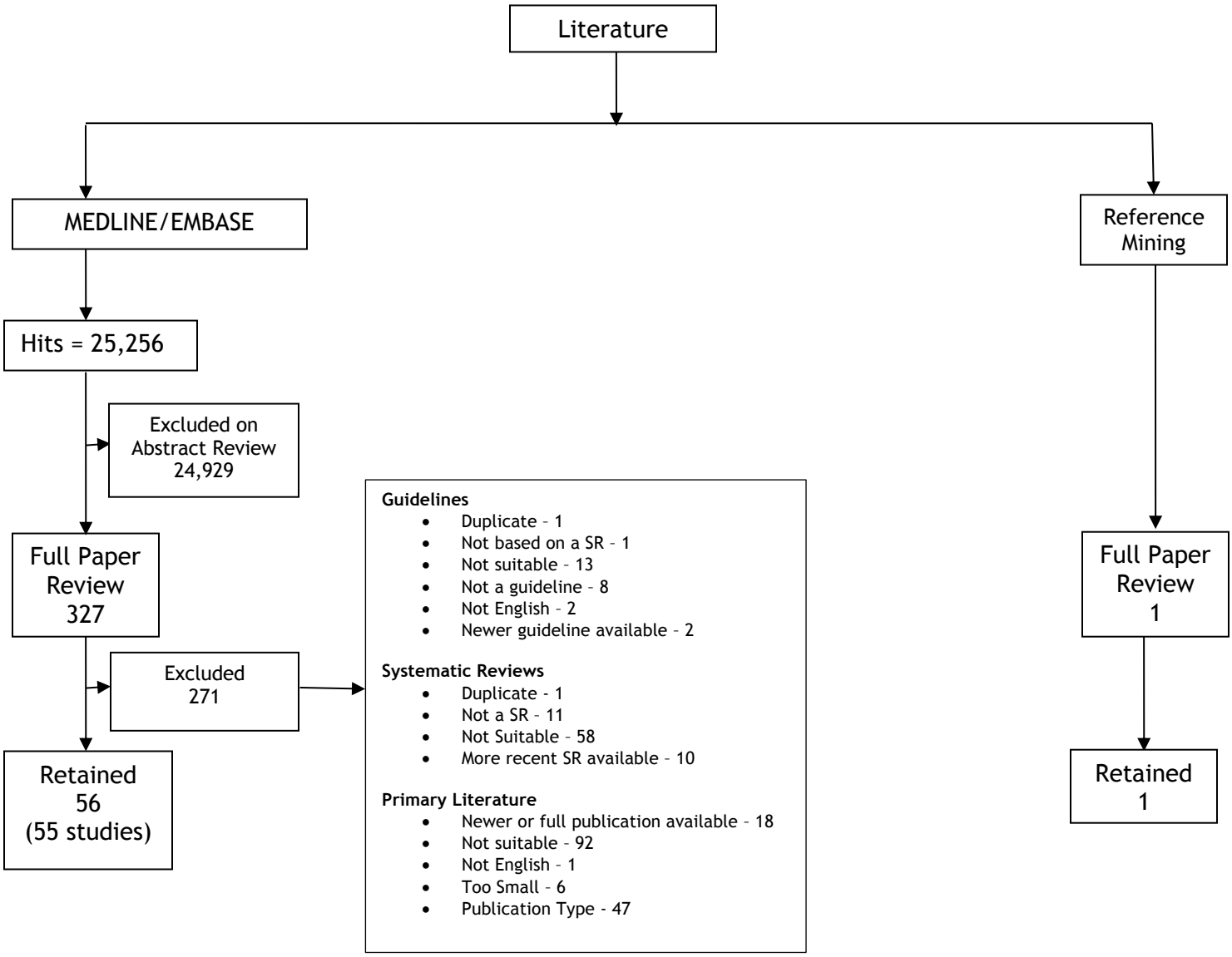


Table 4-1. Studies selected for inclusion.

QUESTION	GUIDELINES*	SYSTEMATIC REVIEWS	INDIVIDUAL STUDIES				REFERENCES
	NUMBER OF GUIDELINES RETAINED	NUMBER OF SYSTEMATIC REVIEWS (PAPERS) RETAINED	NUMBER OF HITS	FULL TEXT REVIEW	NUMBER OF STUDIES (PAPERS) RETAINED	REFERENCE MINING	
Q1 - Staging	1	NA	NA	NA	NA	0	[1]
Q2a/b – D2 vs. D1 LND	0	3	6547	30	0	1	[12,13,47,48]
Q2c – Min. no. LNs dissected	0	1	101	17	8	0	[7,8,14-16,49-52]
Q2d – Min. margins	0	0	11495	30	4	0	[17,53-55]
Q2e – Laparosopic vs. Open	0	1	2451	45	15	0	[31-38,56-63]
Q3 – Surgery in Stage IV patients	0	1(2)	2099	62	13	0	[18-24,64-71]
Q4 – Surgical volumes	0	1	597	27	7	0	[25-30,72,73]

*see Section 3

Abbreviations: LN=lymph nodes; LND=lymph node dissection; min.=minimum; NA=not available; no.=number

Study Design and Quality

Various study designs are included in this guidance document. The guideline being endorsed for Question 1 [1] was assessed using the AGREE II tool [40] (see Table 4-2). All systematic reviews were assessed using AMSTAR [46] (see Table 4-3). RCTs were assessed using the Cochrane Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/) (see Table 4-4) and all non-RCTs were assessed using A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NSRI) tool (https://sites.google.com/site/riskofbiastool/) (see Table 4-5).

Guideline

The Lerut et al. [1] guideline was assessed by four independent reviewers using the AGREE II tool [40]. It scored well on several domains including scope and purpose, rigour of development, and clarity of presentation. In addition, each reviewer gave this guideline an overall assessment of 5 or 6 on a Likert scale of 7 (Table 4-2).

Table 4-2: Evaluation of included guideline using AGREE II

DOMAIN	ITEM	APPRAISER 1	APPRAISER 2	APPRAISER 3	APPRAISER 4	DOMAIN SCORE
Scope and Purpose	1	6	6	7	6	68%
	2	6	7	7	7	
	3	7	2	5	5	
Stakeholder Involvement	4	4	2	5	3	42%
	5	1	1	4	2	
	6	6	5	5	4	
Rigour of Development	7	7	7	7	6	72%
	8	5	2	2	6	
	9	5	6	6	6	
	10	6	7	7	6	
	11	7	4	4	6	
	12	7	6	6	6	
	13	7	6	6	6	
	14	1	1	2	2	
Clarity of Presentation	15	7	6	6	6	88%
	16	7	6	6	6	
	17	7	6	6	6	
Applicability	18	1	1	1	2	17%
	19	4	4	4	4	
	20	1	2	1	2	
	21	1	2	1	1	
Editorial Independence	22	1	1	1	2	48%
	23	7	7	6	6	
Overall Assessment		5	6	5	5	

Systematic Reviews

All systematic reviews used in this guidance document were assessed using the AMSTAR tool [46]. Overall, all included systematic reviews scored well on those items that were applicable. All seven systematic reviews provided an a priori design, conducted duplicate study selection and data extraction, performed a comprehensive literature search, used the status of publication as an inclusion criterion, and provided the characteristics of each included study. One of the included systematic reviews provided a list of excluded studies and only three provided information regarding conflicts of interest of the authors (Table 4-3).

Table 4-3: Evaluation of included systematic reviews using AMSTAR.

ITEM	Seevaratnam 2012a [48]	El-Sedfy 2014 [12]	Mocellin 2015 [47]	Seevaratnam 2012b [14]	Huang 2014[31]	Mahar 2012a,b [18,64]	Mahar 2012c[25]
1. Was an 'a priori' design provided?	Y	Y	Y	Y	Y	Y	Y
2. Was there duplicate study selection and data extraction?	Y	Y	Y	Y	Y	Y	Y
3. Was a comprehensive literature search performed?	Y	Y	Y	Y	Y	Y	Y
4. Was the status of publication (i.e., grey literature) used as an inclusion criterion?	Y	Y	Y	Y	Y	Y	Y
5. Was a list of studies (included and excluded) provided?	N	N	Y	N	N	N	N
6. Were the characteristics of the included studies provided?	Y	Y	Y	Y	Y	Y	Y
7. Was the scientific quality of the included studies assessed and documented?	Y	Y	Y	N	Y	N	Y
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	Y	Y	Y	NA	Y	NA	Y
9. Were the methods used to combine the findings of the studies appropriate?	Y	Y	Y	NA	Y	NA	Y
10. Was the likelihood of publication bias assessed?	N	N	Y	NA	N	NA	N
11. Was the conflict of interest stated?	N	N	Y	N	Y	N	Y
TOTAL AMSTAR POINTS	8	8	11	5	9	5	9

Abbreviations: N=no; NA=not applicable; Y=yes

Randomized Controlled Trials

Four RCTs were included in this guidance document and were assessed using Cochrane's Risk of Bias tool (chapter 8.5) (http://handbook.cochrane.org/). All included RCTs were fully published. Four of the items were scored as either high risk of bias or unclear in three of the trials [13,20,56] trials and three of the items were scored as either high risk of bias or unclear in two of the trials [24,57].

Table 4: Evaluation of included randomized controlled trials using Cochrane's Risk of Bias tool.

Question	Study	Selection Bias		Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
		Random Sequence Generation	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Incomplete Outcome Data	Selective Reporting	Other Sources of Bias
2a/b - D2 vs. D1 lymph node dissection	Songun 2010 [13]	Low	Low	High	High	High	Low	Unclear
2e - Open vs. laparoscopic surgery	Cui 2015 [56]	Low	Low	Unclear	Unclear	High	Low	Unclear
	Hu 2016 [57]	Low	High	High	Unclear	Low	Low	Low
3 - Surgery in stage IV patients	GYMSSA 2014 [20]	Low	Unclear	High	High	Low	Low	High
	REGATTA 2016 [24]	Low	High	High	High	Low	Low	Low

Non-Randomized Controlled Studies

This guidance document includes 43 non-randomized controlled studies that were each assessed using A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) tool (https://sites.google.com/site/riskofbiastool/). This tool assesses each trial on seven domains of bias (Table 4-5). Each of the included studies had at least one domain that was assessed as having a moderate risk of bias and almost all of the studies had as least one other domain that was assess as having a moderate risk of bias or for which no information was available to assess that domain. Overall, each included non-randomized study was assessed as having a moderate risk of bias.

Table 4-5: Evaluation of included non-randomized controlled studies using Cochrane's ACROBAT-NSRI.

Question	Study	Bias due to confounding	Bias in selection of participants into the study	Bias in measurement of interventions	Bias due to departures from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported result	Funding[b]	Overall
2c – Lymph Nodes	Biffi 2011 [15]	Mod	Low	Low	Low	Low	Low	Low	NI	Mod
	Xu 2012 [16]	Mod	Low	Mod	Low	Low	Low	Low	Low	Mod
	Kim 2014 [8]	Mod	Low	Mod	Low	NI	Low	Low	NI	Mod
	Biondi 2015 [49]	Mod	Low	Low	Low	Mod	Low	Low	NI	Mod
	Chen 2015 [7]	Mod	Low	Low	Low	NI	Low	Low	Low	Mod
	Chu 2015 [50]	Mod	Low	Low	Low	NI	Low	Low	NI	Mod
	Gholami 2015 [51]	Mod	Low	Low	Low	NI	Low	Low	NI	Mod
	He 2016 [52]	Mod	Low	Low	Low	Low	Low	Low	Low	Mod
2d – Surgical Margins	Kim 2014 [53]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	Lee 2014 [54]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
	Ohe 2014 [55]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	Squires 2015 [17]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod
2e – Open versus Laparoscopic Surgery	Bo 2013 [32]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
	Kim 2014 [58]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod
	Wang 2013 [33]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod
	Fang 2014 [34]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
	Lee JH 2014 [59]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
	Lee SR 2014 [60]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
	Lin 2014 [35]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod
	Lu 2015 [61]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod
	Wang 2015 [62]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod
	Zhang 2015 [63]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
	Ji 2016 [36]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
	Li 2016 [37]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod
	Zhang 2016 [38]	Mod	Low	Low	Low	Low	[a]See below	Low	NI	Mod
3 – Surgery in Stage IV	Huang 2010 [19]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	Lupascu 2010 [23]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	Al-Amawi 2011 [21]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	Kokkola 2012 [68]	Mod	Mod	Mod	Low	NI	[a]See below	Low	NI	Mod
	Kulig 2012 [22]	Mod	Mod	Mod	Low	Low	[a]See below	Low	NI	Mod
	Miki 2012 [70]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	He 2013 [65]	Mod	Low	Mod	Low	Mod	Low	Low	Low	Mod
	Ikeguchi 2013 [66]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	Mariette 2013 [69]	Mod	Low	Mod	Low	Mod	[a]See below	Low	Low	Mod
	Ikeguchi 2016 [67]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
	Yamada 2016 [71]	Mod	Low	Mod	Low	Low	[a]See below	Low	NI	Mod
4 – Surgical Volumes	Reavis 2009 [26]	Mod	Low	Low	Low	NI	[a]See below	Low	Low	Mod
	Skipworth 2009 [27]	Mod	Low	Mod	Low	NI	[a]See below	Low	Low	Mod
	Dikken 2012 [28]	Mod	Low	Low	Low	Low	Low	Low	Low	Mod
	Yun 2012 [73]	Mod	Low	Low	Low	NI	[a]See below	Low	Low	Mod
	Dikken 2013 [30]	Mod	Low	Low	Low	Mod	Low	Low	Low	Mod
	Ichikawa 2013 [72]	Mod	Low	Mod	Low	NI	[a]See below	Low	NI	Mod
	Murata 2015 [29]	Mod	Low	Low	Low	Low	[a]See below	Low	Low	Mod

Abbreviations: ACROBAT-NRSI=A Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions; Mod=moderate risk of bias; NI=no information

[a]Low risk for mortality and survival; No information for other outcomes

[b]Low risk = non-industry funding.

Outcomes

Question 1: What is/are the optimal technique(s) to adequately stage gastric cancer?

Guidelines

One guideline produced by the Belgian Health Care Knowledge Centre [1] was retained from the guideline search as it sufficiently addressed the issue of adequate staging in gastric cancer and was therefore endorsed by the surgical gastric Working Group. Only the section pertaining to staging is being endorsed (see page 52 of the Lerut et al. guideline). The authors of this guideline conclude that: (a) all gastric cancer patients should be discussed at a multidisciplinary case conference, (b) newly diagnosed patients should have a CT scan of the chest and abdomen, (c) patients planned for curative treatment can be considered for EUS as well as fine-needle aspiration of suspicious lymph nodes if feasible, and (d) PET scan, MRI, and laparoscopy can be considered for specific indications.

Question 2: What is the optimal technique of gastric cancer surgery with curative intent with respect to:

a. D2 lymph node dissection?
b. D1 lymph node dissection?
c. The minimal number of lymph nodes needed to be dissected for curative-intent resection?
d. The minimal gross margin for curative-intent resection?
e. Laparoscopic versus open resection?

Question 2a/b – D2 versus D1 Lymph Node Dissection

Systematic Reviews

Three systematic reviews with meta-analyses were retained that pertained to D2 versus D1 LND. Seevaratnam et al. [48] and Mocellin & Nitti [47] are the most recent reports of mortality and morbidity outcomes. El-Sedfy et al. [12] is an update of Seevaratnam et al. [48] with respect to five-year survival. Seevaratnam et al. [48] covers the literature from 1985 to 2010 inclusive and includes five RCTs comprising 1642 patients reported in nine papers. Mocellin & Nitti [47] covers the literature up to January 2015 and includes five RCTs comprising 1653 patients. Four of the five RCTs in both Seevaratnam et al.[48] and Mocellin & Nitti [47] are the same.

<u>Mortality</u>

Overall hospital mortality was consistently significantly higher for patients undergoing D2 compared with D1 LND in both the Seevaratnam et al. [48] systematic review (7.5% vs. 3.8%; relative risk [RR], 2.02; 95% CI, 1.30 to 3.14; p=0.002) and the Mocellin & Nitti [47] systematic review (RR, 2.007; 95% CI, 1.336 to 3.015; p=0.001). Seevaratnam et al. [48] went on to divide studies into early and more recent trials. They demonstrated that hospital mortality, while significantly worse in early trials comparing D2 with D1 (10.5% vs. 4.6%; RR, 2.23; 95% CI, 1.44 to 3.44; p=0.0003), is no longer significantly different in more recent trials comparing D2 with D1 LND (1.2% vs. 1.5%; RR, 0.74; 95% CI, 0.17 to 3.26; p=0.70). This was also true in the early trials if spleen and/or pancreas were preserved rather than resected [48].

<u>Reoperation Rate</u>

The reoperation rate was significantly higher in those undergoing D2 compared with D1 LND (11.4% vs. 5.1%; RR, 2.24; 95% CI, 1.52 to 3.32; p<0.0001) [48].

Survival

Survival data reported in El-Sedfy et al. [12] cover the literature from 1985 to February 1, 2015 and includes four RCTs comprising 1599 patients reported in five papers. The five-year survival rate was similar for D2 and D1 LND (47.0% vs. 44.8%; OR, 1.11; 95% CI, 0.84 to 1.47; p=0.14). Not surprisingly, OS for D2 versus D1 was also similar in Mocellin & Nitti [47] (HR, 0.911; 95% CI, 0.708 to 1.172; p=0.471).

El-Sedfy et al. [12] conducted subgroup analysis by T stage and demonstrated a significant survival difference favouring D2 compared with D1 LND in T3 patients (25.9% vs. 11.5%; OR, 1.64; 95% CI, 1.01 to 2.67; p<0.05). Subgroup analysis by N stage did not demonstrate any survival differences (OR, 1.36; 95% CI, 0.98 to 1.87; p=0.06) [12], but the trials were not powered for this analysis.

Updated Literature

The updated literature search yielded no new RCTs. However, 15-year follow-up data of the Dutch trial included in El-Sedfy et al. [12] were available. The update demonstrated fewer gastric cancer-related deaths in patients undergoing a D2 LND. Gastric cancer-related deaths were 48% in D1 versus 37% in D2 (p=0.01, per protocol analysis) [13].

Question 2c - The minimal number of lymph nodes needed to be dissected for curative-intent resection

Systematic Review

One systematic review without meta-analysis was retained [14]. This paper is the most recent systematic review pertaining to the number of lymph nodes (LNs) that should be harvested for curative-intent resection in gastric cancer. Seevaratnam et al. [14] covers the literature from 1998 to 2010 inclusive and includes 25 retrospective studies comprising 74,228 patients. DFS was significantly longer with more LNs assessed in the two studies that reported this outcome. OS was reported in 18 studies and was significantly improved as number of LNs harvested increased especially when more than 15 nodes were retrieved. These authors conclude that although current guidelines suggest that 16 LNs is adequate, a higher number of nodes should be harvested and assessed.

Updated Literature

The updated literature search yielded eight additional studies [7,8,15,16,49-52]; all were retrospective studies. Three studies [15,16,49] reported that harvesting more than 15 LNs significantly improves survival. Chu et al. [50] specifically studied T stage and reported that OS is significantly better in T3/T4 patients when more than 15 LNs were assessed (p<0.001) but not in T1/T2 patients (p=0.44). Chu et al. [50] also reported that the removal of more than 25 LNs was not significantly better with respect to survival than removal of 25 LNs or less. He et al. [52] reported than harvesting at least 18 LNs improved OS in all patients (HR, 0.383; 95% CI, 0.195 to 0.755; p=0.006), but particularly in patients with T3 disease (HR, 0.292; 95% CI, 0.088 to 0.974; p=0.045) and T4 disease (HR, 0.352; 95% CI, 0.146 to 0.851; p=0.020). Gholami et al. [51] found no overall disease-specific survival (DSS) difference when more than 15 LNs were harvested. However, subgroup analysis demonstrated significant improvement in DSS when harvesting more than 15 LNs in patients with Stage IA through IIIA disease (10-year DSS

74% vs. 57%; p=0.018), as well as in patients with N0-2 disease (10-year DSS 72% vs. 55%; p=0.023). Chen et al. [7] specifically studied N2 and N3 disease and reported that the five-year OS rates were significantly better for both cohorts of patients when more than 25 LNs were assessed compared with the assessment of 15 to 24 LNs. Finally, Kim et al. [8] concluded that five-year survival was significantly better when more than 40 compared with 15 to 39 LNs were assessed in those with differentiated gastric cancer.

Question 2d - The minimal gross margin for curative-intent resection

Systematic Review

No systematic review was found that pertained to the minimal gross margin needed for curative-intent resection.

Updated Literature

A de novo literature search for primary studies was undertaken and four retrospective studies were retained [17,53-55]. Kim et al. [53] studied the appropriate resection margins for gastrectomy in early gastric cancer in 2081 patients. They subdivided tumours into six categories according to the distance from the proximal margin: ≤1 mm, >1 mm, ≤10 mm, >10 mm, ≤30 mm and >30 mm. Only five patients had margins ≤1 mm and three of these had microscopically positive margins and underwent re-resection. There were no statistically significant differences between those with margins >1 but ≤10 mm, >10 but ≤30 mm, or >30 mm with respect to tumour recurrence or disease-related death [53].

Lee et al. [54] studied whether or not the length of a negative resection margin affects local recurrence and survival in both early (N=1001) and advanced (N=787) gastric cancer patients. These authors conclude that the length of the proximal or distal margins did not significantly affect survival or local recurrence in both early and advanced gastric cancer, if the margins were pathologically negative.

Ohe et al. [55] evaluated the relationship between the distance of the proximal resection margin and recurrence in 744 gastric cancer patients undergoing curative resection. Of these patients, 529 underwent distal gastrectomy and 245 underwent total gastrectomy. In the total gastrectomy group, the mean distance of the proximal resection margin was 4.03 cm and was correlated with recurrence (p=0.032), but not locoregional recurrence (p=ns). In the distal gastrectomy group, the mean distance of the proximal resection margin was 6.4 cm and did not affect either recurrence or locoregional recurrence.

Squires et al. [17] studied resection margins in distal gastric adenocarcinoma in 465 patients at seven institutions from the U.S. Gastric Cancer Collaborative. The mean proximal margin was 4.8 cm. Median OS and median RFS for patients was significantly better in those with proximal margins of 3.1 to 5.0 cm compared with margins ≤3.0 cm (48.1 vs. 29.3 months, p=0.01; and 38.9 vs. 21.1 months, p=0.02, respectively). Median OS and median RFS for patients with margins >5.0 cm were not significantly different than those with proximal margins of 3.1 to 5.0 cm. However, the OS and RFS advantage of a proximal margin ≥3.1 cm was only associated with Stage I disease only and was not associated with Stage II or III disease [17].

Question 2e – Laparoscopic versus Open Surgery

Systematic Review

One systematic review with meta-analysis was retained [31]. This paper is the most recent systematic review of laparoscopy versus open gastrectomy with D2 LND for advanced gastric cancer. Huang et al. [31] covers the literature from January 2000 to September 2013 inclusive and includes 11 studies comprising 1904 patients.

Short-term Outcomes

Short-term outcomes including blood loss (weighted mean difference [WMD], -144.47; 95% CI, -194.01 to -94.93; p<0.05), time to first flatus (WMD, -0.91; 95% CI, -1.19 to -0.62; p<0.05), length of hospital stay (WMD, -2.69; 95% CI, -4.96 to -1.58; p<0.05) and post-operative complications (RR, 0.70; 95% CI, 0.57 to 0.86; p<0.05) all favoured laparoscopic compared with open gastrectomy. There was no statistically significant difference with respect to hospital mortality rates (RR, 0.82; 95% CI, 0.23 to 2.88; p=0.76) or with respect to the number of LNs harvested (WMD, 1.85; 95% CI, -0.32 to 4.02; p=0.09). Each of these outcomes had high heterogeneity (78% to 95%) except for post-operative complications and hospital mortality rates, which had no heterogeneity [31].

Surgical time was significantly longer for the laparoscopic procedure compared with the open procedure (WMD, 41.78; 95% CI, 14.49 to 69.08; p<0.05) with high heterogeneity (95%) [31].

Long-term Outcomes

Three-year survival rate, based on three non-randomized studies involving 315 patients, demonstrated no statistically significant difference between the laparoscopic and open procedures (RR, 1.09; 95% CI, 0.96 to 1.23; p=0.18). This outcome had no heterogeneity [31].

Updated Literature

The updated literature search yielded 15 additional studies [32-38,56-63] (Table 4-6). Overall, blood loss, time to first flatus, and length of hospital stay all favoured the laparoscopic arm and post-operative morbidity was either the same or favoured the laparoscopic arm compared with the open arm. Surgical time was significantly longer in the laparoscopic arm compared with the open surgical arm in all but three studies [35,36,61] that reported this outcome. Post-operative mortality, number of LNs harvested, and survival were not significantly difference in the laparoscopic compared with the open arms. Nine studies in the updated literature search provided information on oncologic survival (see Table 4-6).

Table 4-6. Outcomes from studies included in the updated literature search regarding laparoscopic versus open gastrectomy with curative intent.

Study	Design	N	Blood Loss (mL)	Time to First Flatus (days)	Length of Hospital Stay (days)	Post-operative Morbidity (%)	Post-operative Mortality (%)	Number of Lymph Nodes Harvested	Surgical Time (minutes)	Survival (%)
Bo 2013 [32]	Retro	Lap – 117 Open - 117	196.9 358.2 p=0.024	3.4 3.9 p=ns	7.4 10.7 p=0.047	11.1 16.3 p=0.045	NR	35.2 37.4 p=ns	292.8 242.1 p=0.039	**5-year** 49.3 46.5 p=ns T2 – p=ns T3 – p=ns
Kim 2014 [58]	Retro	Lap – 60 Open - 60	NR	3.1 4.0 p<0.001	With complications 10.1 9.8 p=ns Without complications 8.1 8.7 p=ns	Minor 5.0 15.0 p=ns	0 3.3 p=NR	44.9 43.7 p=ns	255.3 200.9 p<0.001 (mean)	**5-year** 95.9 94.7 p=ns
Wang 2013 [33]	Retro	Lap – 54 Open - 54	160.2 257.8 p<0.01	3.9 4.4 p=0.03	9.5 11.1 p=0.02	13.0 24.1 p=0.03	0.0 0.0 p=ns	27.9 27.7 p=ns (mean)	259.3 199.8 p<0.01	**1-year** 98.0 91.5 p=ns **3-year** 91.9 86.9 p=ns **5-year** 81.1 82.1 p=ns
Fang 2014 [34]	Retro	Lap – 87 Open -87	220 310 p<0.05 (median)	NR	12 18 p<0.01	6.9 5.7 p=ns	0.0 0.0 p=ns	32 36 p=ns (median)	337 224 p<0.01 (median)	**5-year** 59 54 p=ns
Lee JH 2014 [59]	Retro	Lap – 391 Open - 715	NR	NR	NR	NR	NR	Distal Gast 49.0 51.0 p=ns Total Gast 55.0 58.0 p=ns	NR	NR

Lee SR 2014 [60]	Retro	Lap – 34 Open - 50	NR	NR	9.0 10.0 p=0.031	17.6 16.0 p=ns	0.0 4.0 p=ns	28.5 40.0 p<0.001	NR	**5-year** 93.2 77.5 p=ns
Lin 2014 [35]	Retro	Lap – 58 Open - 58	74.0 218.4 p=0.000	2.6 3.7 p=0.028	14.2 18.1 p=0.012	12.1 15.5 p=ns	0.0 1.7 p=ns	30.8 29.0 p=0.114 (mean)	235.7 245.4 p=ns	NR NR p=ns
Cui 2015 [56]	RCT	Lap – 148 Open - 148	99 125 p=0.018	4.1 4.7 p=0.002	14.4 18.2 p=0.005	21.8 19.0 p=ns	0.0 0.0	29.3 30.1 p=ns	258 194 p<0.0001	NR
Lu 2015 [61]	Retro	Lap – 252 Open - 252	92 204 p<0.001	3.7 4.0 p=ns	14.4 16.6 p=0.001	17.1 23.4 p=ns	0.4 0.8 p=ns	32 29 p=ns	194 267 p<0.001	3-year 56.3 55.2 p=ns (matched samples)
Wang 2015 [62]	Retro	Lap – 188 Open - 233	347 320 p=0.019	NR	8.2 16.3 p=0.017	10.1 9.0 p=ns	NR	24.3 25 p=ns	287 210 p=0.021	NR
Zhang 2015 [63]	Retro	Lap – 86 Open - 86	200 260 p=0.003	NR	8 12 p=0.010	10.5 15.1 p=ns	0.0 0.0	20 21 p=ns	210 180 p=0.001	5-year 59 56 p=ns
Hu 2016 [74]	RCT	Lap – 528 Open - 528	105.5 117.3 p=0.001	3.5 3.6 p=0.011	10.8 11.3 p<0.001	15.2 12.9 p=ns	0.4 0.0 p=ns	36.1 36.9 p=ns	217.3 186.0 p<0.001	NR
Ji 2016 [36]	Retro	Lap – 103 Open -114	100.0 400.0 p=0.00	2.0 5.0 p=0.00	7.4 14.9 p=0.00	4.9 18.4 p=0.00	0.0 1.8 p=ns	26 25 p=ns	216.6 205.7 p=ns	NR
Li 2016 [37]	Retro	Lap – 101 Open - 101	131.9 129.5 p=ns	2.8 3.6 p<0.001	10.5 11.9 p<0.001	22 38 p=0.019	1.0 2.0 p=ns	33.7 33.1 p=ns	297.4 198.1 p<0.001	NR
Zhang 2016 [38]	Retro	Lap – 92 Open - 92	230 290 p=0.010	NR	7 10 p=0.008	15.2 21.7 p=ns	0.0 0.0	17 18 p=ns	230 200 p=0.020	5-year 57 50 p=ns

Abbreviations: Gast=gastrectomy; lap=laparoscopic; NR=not reported; ns=non-significant; RCT=randomized controlled trial; Retro=retrospective

Question 3: What are the indications for surgery for Stage IV gastric cancer in:

a. Asymptomatic patients?

b. **Symptomatic patients?**

Systematic Reviews

One systematic review, which reported outcomes in two papers, was retained [18,64]. This systematic review included 59 articles, none of which were RCTs. Each study was categorized as palliative (PAL), non-curative (NC) or not otherwise specified (NOS). The intent of surgery in PAL studies was defined as the alleviation of symptoms or improvement in QOL. In NC studies, the intent of surgery was defined as not for palliation of symptoms and in NOS studies the definitions for palliative or non-curative were not provided but surgery was carried out in patients with advanced disease.

Morbidity

Procedure-related morbidity occurred in all surgical interventions and irrespective of the intent of the surgery. Morbidity ranged from 3.8% to 49% for gastrectomy and 14% to 21% for non-resectional surgeries [18].

Mortality

Procedure-related mortality was reported much more often than morbidity. Mortality was lower in PAL resections (0% to 11.3%) compared with either NC (0% to 21%) or NOS (0% to 20.4%). The mortality rate for gastrectomy performed for any intent was 0% to 21% whereas the mortality rate for non-resectional surgeries was 0% to 39% [18].

Survival

Median survival for PAL gastrectomy was consistent across studies and ranged from nine to 13 months. Median survival for NC and NOS gastrectomies were less consistent and ranged from five to 24 months and three to 20.6 months, respectively. Median survival for NC non-resectional surgery was three to 12 months [18].

One-year survival was not reported for any of the PAL-intent gastrectomy studies. However, one-year survival was 12% to 66.7% for NC resections and 26.6% to 80.3% for NOS resections. One-year survival for non-resectional surgery was 3% to 37.5% [18].

Quality of Life

QOL for this systematic review was reported in a separate publication [64]. None of the included studies used validated QOL instruments. Nine studies reported on various measures of palliation effectiveness. Mean time to oral intake ranged from 2.9 to eight days. Mean length of hospital stay ranged from seven to 13 days and one study reported a median length of hospital stay of 28 days. Other surrogate QOL measures included, but were not limited to re-admission to hospital, hospital-free survival, hospitalization index, and ingestion index but these were evaluated in only one study each.

Updated Literature

The updated literature search yielded 13 additional studies: 11 retrospective studies [19,21-23,65-71] and two RCTs [20,24]. Of these, 12 were considered to be NC intent [19-24,65,66,68-71] and one was considered to be PAL [67].

Morbidity

Procedure-related morbidity in NC studies ranged from 15.1% to 88.8% for gastrectomy [19,20] and 11.5% to 21% for non-resectional surgeries [21,22] (Table 4-7).

Mortality

Procedure-related mortality for gastrectomy performed in NC studies was 1.1% to 9.1% [19,23] whereas the mortality rate for non-resectional surgeries in NC studies was 4.8% to 10% [21,22] (Table 4-7).

Survival

Median survival for PAL gastrectomy was 14 months [67]. Median survival for NC gastrectomies ranged from 8.5 to 33.4 months [21,70]. Median survival for NC non-resectional surgeries ranged from 4.4 to 10.8 months [22,71] (Table 4-7).

Two-year survival for the PAL intent gastrectomy study was 16.3% [67]. One-year survival was 43% to 73.9% for NC resections [21,70] and 16% for non-resectional surgeries in the one paper that reported this outcome [21] (Table 4-7).

Quality of Life

QOL was poorly reported. One measure of palliation effectiveness that was reported the most was length of hospital stay. Four papers provided data for this outcome [19-21,23]. For gastrectomies, the median length of hospital stay ranged from 13 to 17 days and the mean ranged from 16.9 to 23 days.

Table 4-7. Outcomes from studies included in the updated literature search regarding palliative and non-curative surgery in Stage IV gastric cancer patients.

Study	Design	Intent of Surgery	N	Procedure-related morbidity N(%)	Procedure-related Mortality N(%)	Median Survival (months)	Mean Survival (months)	1-year Survival (%)	Length of Hospital Stay (days)
Huang 2010 [19]	Retro	NC	Gastrectomy - 365 Non-resectional Sx - 151	55(15.1) NR	4(1.1) NR	10.2 4.5	NR	NR	Median – 15-17 NR
Lupascu 2010 [23]	Retro	NC	Gastrectomy alone – 25 Gastrectomy/chemo – 30	In total 19(34.5)	In total 5(9.1)	NR	8.9 17.8	NR	Mean - 23
Al-Amawi 2011 [21]	Retro	NC	Gastrectomy – 44 Non resectional Sx - 61	11(25.0) 7(11.5%)	2(4.5) 3(4.8)	8.5 6.0	10.5 5.5	43 16	Mean – 16.9 Median – 13 Mean – 13 Median -12
Kokkola 2012 [68]	Retro	NC	Gastrectomy – 23 Non-resectional Sx – 32 Gastrectomy/chemo Gastrectomy alone Non resectional Sx/chemo None resectional Sx alone	'Comparable in both groups'	NR	10.8 5.7 14.3 1.9 13.5 1.9	NR	NR	NR
Kulig 2012 [22]	Retro	NC	Gastrectomy – 415 Non-resectional Sx - 536	135(33) 114(21)	18 (4) 52(10)	10.6 4.4	NR	NR	NR
Miki 2012 [70]	Retro	NC	Gastrectomy/hepatic resection - 25 Gastrectomy - 13 Chemotherapy alone - 12	NR	NR	33.4 10.5 8.7	NR	73.9 (1-year) 42.8 (3-year) 36.7 (5-year) 46.2 (1-year) 23.1 (3-year) 15.4 (5-year) 36.7 (1-year) 12.2 (3-year) 0.0 (5-year)	NR
He 2013 [65]	Retro	NC	Gastrectomy/chemo – 224[a] Chemo alone - 323	NR	NR	23.9 10.4	NR	NR	NR
Ikeguchi 2013 [66]	Retro	NC	Gastrectomy – 54 Non-resectional Sx/other - 42	10(18.5) NR	1(1.9) NR	NR	NR	2-year 23.2 6.6	NR
Mariette 2013 [69]	Retro	NC	Gastrectomy – 677 No surgery - 532	NR	8.6	11.9 8.5	NR	NR	NR
Fujitani 2016 [24] (REGATTA)	RCT	NC	Gastrectomy/chemo – 89 Chemo alone – 86	14(16)	1(1.1) 1(1.2)	14.3 16.6	NR	2-year 25.1 31.7	NR

Rudloff 2014 [20](GYMSSA)	RCT	NC	Sx/chemo - 9 Chemo alone - 8	8(88.8) NA	NR	11.3 4.3	NR	44.4 0.0	Median – 17 NA
Ikeguchi 2016 [67]	Retro	PAL	Gastrectomy - 37 Non-resectional Sx - 41	4(10.8) 0(0.0)	0(0.0) 0(0.0)	14 10	NR	2-year 16.3 11.0	NR
Yamada 2016 [71]	Retro	NC	Gastrectomy or Gastrostomy - 44 Non-resectional Sx - 28	NR	NR	22.8 10.8	NR	NR	NR

[a]N=224 reported in text of paper but N=223 reported in the table in the paper.

Abbreviations: Chemo=chemotherapy; NA=not available; NC=non-curative; NR=not reported; PAL=palliative; RCT=randomized controlled trial; Retro=retrospective; Sx=surgery

Question 4 - What is the relationship between surgical volumes and outcomes?

Systematic Review

One systematic review was retained [25]. This paper is a comprehensive systematic review pertaining to the effect of institutional volume and surgeon experience on surgical outcomes in gastric cancer. Mahar et al. [25] covers the literature from 1985 to 2009 inclusive and includes 28 mostly retrospective studies. Of these, 22 studies evaluated institutional volumes on gastric cancer surgery outcomes and eight studies evaluated surgeon training or volumes on gastric cancer surgery outcomes. Definitions of hospital volume were dichotomized into high-volume hospitals (≥10 to 13 gastric cancer-related surgeries per year) and low-volume hospitals (<10 gastric cancer-related surgeries per year).

Institution Volume

Overall, the range of procedure-related morbidity was not significantly different in high-volume compared with low-volume hospitals (19% to 46.5% in high-volume hospitals vs. 19% to 43% in low-volume hospitals). Meta-analysis of procedure-related mortality favoured high-volume hospitals (OR, 0.73; 95% CI, 0.65 to 0.81; p<0.00001). Improved five-year survival was significantly associated with higher institutional volumes in three of seven studies that evaluated this outcome [25].

Surgeon Volume and/or Training

Lower procedure-related morbidity was significantly associated with increased surgeon volume based on one study. Lower procedure-related mortality was significantly associated with higher surgeon volumes (two studies) and more surgeon training (one study). Improved five-year survival was associated with more surgeon experience (training, age, or volume) in one of five studies that evaluated this outcome [25].

Updated Literature

The literature search update yielded seven additional retrospective studies [26-30,72,73] evaluating hospital volumes on gastric cancer surgery outcomes (Table 4-8). No additional studies evaluating surgeon training and/or volumes were identified. Each study defined institutional volume differently. Only two studies [26,29] evaluated procedure-related morbidity and it was not significantly different in high- versus low-volume hospitals. Procedure-related mortality was not significantly different in high- versus low-volume hospitals in four of the five studies evaluating this outcome [26-29]. Dikken et al. 2013 [30], however, reported that procedure-related mortality significantly favours high-volume hospitals (OR, 0.64; 95% CI, 0.41 to 0.99; p=0.025). Survival was not significantly improved in three of the four studies evaluating this outcome [28,30,72]. Yun et al. 2012 [73] report significantly better five-year survival in high- versus low-volume hospitals (adjusted HR, 1.36; 95% CI, 1.29 to 1.44) although a specific p-value is not reported (Table 4-8).

Skipworth et al. [27] calculated the number of procedures needed to be performed per year in order to achieve published recommended mortality rates. Using inverse power functions, they reported that a minimum of 16 gastrectomies per year must be performed in a hospital to ensure an average mortality rate of less than 10% and that a minimum of 41 gastrectomies per year must be performed in a hospital to ensure an average mortality rate of less than 5%.

Table 4-8. Outcomes from studies included in the updated literature search regarding the relationship between hospital surgical volumes and outcomes in gastric cancer patients.

Study	Design	Country	Volume Category (No. cases per year)	Number of Hospitals	Number of Patients	Procedure-related morbidity N(%)	Procedure-related Mortality N(%)	Survival (%)
Reavis 2009 [26]	Retro	USA	High (≥13) Medium (6-12) Low (≤5)	10 36 75	593 1076 500	NR (46.5) NR NR (42.8) p=ns	NR (2.4) NR NR (4.4) p=ns	NR
Skipworth 2010 [27]	Retro	Scotland	1st quartile (1-3) 2nd quartile (4-5) 3rd quartile (6-9) 4th quartile (≥10)	61 total	416 678 1463 2032	NR	37 (8.9) 74 (10.9) 137 (9.4) 175 (8.6) p=ns	NR
Dikken 2012 [28]	Retro	Netherlands	Very low (1-5) Low (6-10) Medium (11-20) High (≥ 21)	NR	3411 6099 4356 355	NR	6-month mortality HR (95%CI) 1.00 0.95 (0.84-1.07) 0.95 (0.83-1.08) 1.10 (0.82-1.49) p=ns	3-year HR (95%CI) 1.00 0.99 (0.91-1.07) 0.99 (0.90-1.08) 0.98 (0.86-1.12) p=ns
Yun 2012[73]	Retro	Korea	Low-medium (≤ 55) High (≥ 56)	NR	NR	NR	NR	5-year HR (95%CI) 1.63 (1.55-1.70)[a] 1.36(1.29-1.44)[b]
Dikken 2013 [30]	Retro	Netherlands Sweden Denmark England	1-10 11-20 ≥ 21	NR	9010 (total)	NR	OR (95%CI) 1.00 0.84 (0.67-1.05) 0.64 (0.41-0.99) p=0.025	2-year HR (95%CI) 1.00 1.04 (0.93-1.15) 1.01 (0.84-1.22) p=ns
Ichikawa 2013 [72]	Retro	Japan	High Low	1 total	321 99	NR	NR	NR NR p=0.045 (favouring high-volume group)
Murata 2015 [29]	Retro	Japan	High (≥ 40 in 3 years) Low (< 40 in 3 years)	71 670	1830 4111	OR (95%CI) 0.96 (0.79-1.16) 1.00 p=ns	OR (95%CI) 0.53 (0.20-1.41) 1.00 p=ns	NR

Abbreviations: CI=95% confidence interval; HR=hazard ratio; NR=not reported; ns=not significant; OR=odds ratio; Retro=retrospective
[a]Unadjusted HR
[b]Adjusted HR

Ongoing, Unpublished, or Incomplete Studies

Laparoscopic staging for locally advanced gastric cancer in Chinese patients	
Protocol ID:	NCT02172690
Date last modified:	December 6, 2014
Type of trial:	Single group, open label
Primary endpoint:	Peritoneal metastasis or positive cytology
Accrual:	A total of 450 patients will be accrued for this study over 2 years.
Sponsorship:	Peking University
Status:	Recruiting
Endoscopic ultrasonographic staging and conventional endoscopic staging for depth of invasion for early gastric cancer	
Protocol ID:	NCT01832246
Date last modified:	November 17, 2014
Type of trial:	Observational study
Primary endpoint:	Diagnostic accuracy between endoscopic ultrasonographic staging and endoscopic staging
Accrual:	560 patients will be accrued within 1 year
Sponsorship:	Seoul National University Hospital
Status:	Not yet recruiting
A comparison between D1 and D2 lymphadenectomy in gastric cancer: A prospective randomized controlled trial	
Protocol ID:	NCT00447746
Date last modified:	March 14, 2007
Type of trial:	Randomized study, parallel assignment, active control, open label
Primary endpoint:	5-year overall survival
Accrual:	600 will be accrued
Sponsorship:	Tata Memorial Hospital
Status:	Recruitment status unknown
A clinical trial of D1+ versus D2 gastrectomy for stage IB and II advanced gastric cancer (ADDICT)	
Protocol ID:	NCT02144727
Date last modified:	April 18, 2016
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint:	5-year overall survival
Accrual:	1880 will be accrued
Sponsorship:	National Cancer Center, Korea
Status:	Recruiting
Laparoscopic versus open gastrectomy for gastric cancer (LOGICA)	
Protocol ID:	NCT02248519
Date last modified:	December 1, 2015
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint:	Post-operative hospital stay
Accrual:	210 will be accrued
Sponsorship:	UMC Utrecht
Status:	Recruiting

Comparison of laparoscopic versus open gastrectomy for advanced gastric cancer: A prospective randomized trial	
Protocol ID:	NCT01043835
Date last modified:	June 4, 2012
Type of trial:	Randomized, parallel assignment, active control, double blind
Primary endpoint:	3-year disease-free survival
Accrual:	328 will be accrued
Sponsorship:	Yan Shi
Status:	Unknown

Comparison of laparoscopic versus open gastrectomy for gastric cancer: A prospective randomized trial (KLASS)	
Protocol ID:	NCT00452751
Date last modified:	September 20, 2010
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Overall survival
Accrual:	1400 will be accrued
Sponsorship:	National Cancer Center, Korea
Status:	Unknown

Efficacy of laparoscopic subtotal gastrectomy with D2 lymph node dissection or locally advanced gastric cancer (KLASS-02-RCT)	
Protocol ID:	NCT01456598
Date last modified:	June 23, 2015
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	3-year relapse free survival
Accrual:	1050 will be accrued
Sponsorship:	Ajou University School of Medicine, Korea
Status:	Ongoing, but not recruiting participants

Laparoscopy-assisted total gastrectomy for clinical stage 1 gastric cancer (KLASS-03)	
Protocol ID:	NCT01584336
Date last modified:	February 5, 2014
Type of trial:	Single group, open label
Primary endpoint	Incidence of postoperative morbidity and mortality
Accrual:	168 will be accrued
Sponsorship:	Soonchunhyang University Hospital, Korea
Status:	Unknown

A comparison of laparoscopic with open distal gastrectomy in advanced gastric cancer after neoadjuvant chemotherapy (REALIZATION)	
Protocol ID:	NCT02404753
Date last modified:	March 30, 2015
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	3-year progression-free survival
Accrual:	96 will be accrued
Sponsorship:	Peking University
Status:	Recruiting

Prospective randomized trial of laparscopy-assisted distal gastrectomy (LADG) versus open distal gastrectomy (ODG) in patients with early gastric cancer (EGC) (COACT_0301)	
Protocol ID:	NCT00546468
Date last modified:	May 22, 2012
Type of trial:	Randomized, parallel assignment, active control, open-label
Primary endpoint	5-year disease free survival
Accrual:	164 accrued
Sponsorship:	National Cancer Center, Korea
Status:	Completed

A multicenter randomized phase II clinical trial of laparoscopy assisted versus open distal gastrectomy with D2 lymph node dissection for advanced gastric cancer (COACT_1001)	
Protocol ID:	NCT01088204
Date last modified:	October 5, 2015
Type of trial:	Randomized, parallel assignment, active control, open label
Primary endpoint	Noncompliance rate
Accrual:	204 accrued
Sponsorship:	National Cancer Center, Korea
Status:	Ongoing, but not recruiting
Surgical technique, open versus minimally-invasive gastrectomy after chemotherapy (STOMACH)	
Protocol ID:	NCT02130726
Date last modified:	December 21, 2015
Type of trial:	Randomized, parallel assignment, active control, double blind
Primary endpoint	Extent of lymph node dissection
Accrual:	200 will be accrued
Sponsorship:	Stichting Nuts Ohra
Status:	Recruiting
Laparascopic versus open resection of cancer stomach	
Protocol ID:	NCT02789826
Date last modified:	May 29, 2016
Type of trial:	Randomized, parallel assignment, active control, double blind
Primary endpoint	Number of lymph nodes in postoperative sample
Accrual:	100 will be accrued
Sponsorship:	Assiut University
Status:	Not yet open for recruitment

DISCUSSION

Gastric cancer is a relatively rare disease within Ontario, but has a large impact owing to high cancer-related mortality. As supported in the CCO Standards Guideline [75], all patients should be discussed at a multidisciplinary meeting to "ensure that all appropriate diagnostic tests, all suitable treatment options, and the most appropriate treatment recommendations are generated for each cancer patient". Input from medical and radiation oncology prior to embarking upon surgical resection is crucial, given the complexity of the disease and multitude of treatment options. Multi-modal treatment has been shown to improve survival in numerous studies; neoadjuvant chemotherapy [76] and post-operative chemoradiation [77] are examined in PEBC guideline #2-14 [78,79].

Staging

Thorough staging of gastric cancer allows for the best selection of treatment options. A CT scan of the chest, abdomen, and pelvis has a relatively high accuracy (71% for T-staging, 66% for N-staging, and 81% for M-staging), and should be performed for all patients [2]. As CT scan may miss peritoneal disease and small liver metastases in up to 44% of cases [3], a diagnostic laparoscopy is indicated in patients at risk for these findings, and will have the highest yield for clinically suspected T3/T4, poorly differentiated tumours, and those with a high nodal burden. Importantly, diagnostic laparoscopy has been found to change management plans in up to 60% of patients [3]. Additionally, the 30-day mortality rate and length of stay is much lower for patients undergoing a diagnostic laparoscopy, compared with those undergoing an exploratory (open) laparotomy. Further, laparoscopy may allow for starting chemotherapy sooner than an open laparotomy for those patients found to have Stage IV disease. Peritoneal washings may increase the accuracy of laparoscopy, as any finding of malignant cells within washings would render the patient Stage IV [6,80]. An EUS, PET, or MRI may be indicated to answer specific clinical questions regarding CT findings (e.g., unclear liver lesions, or possible invasion into the pancreas), but none are routinely indicated.

D1 versus D2 Lymph Node Dissection

Appropriate surgical management represents an opportunity to improve patient outcomes and overall survival. While the short-term outcomes of the Dutch and British D1 versus D2 RCTs [81,82] showed higher peri-operative morbidity and mortality, the 15-year follow-up of the Dutch trial showed a decrease in gastric cancer locoregional recurrence in the D2 group with improved death from gastric cancer rates (37% for D2, vs. 48% for D1, p=0.01) [13]. Much of the peri-operative morbidity and mortality in the Dutch and British RCTs has been attributed to the distal pancreatectomy and splenectomy, which were recommended in the older trial protocols, and are no longer endorsed as a routine part of a D2 LND. Additionally, surgical training and subsequent case volume within the trials have been highlighted as a possible reason for the higher rate of complications within the D2 arm.

A subsequent RCT from the Italian Gastric Cancer Study Group has been conducted with increased training, higher case volumes, and modification of the protocol, eliminating the distal pancreatectomy and splenectomy. In this trial, the complication and peri-operative mortality rates were similar for D1 and D2 LND [83]. Although the overall trial showed no improvement for patients undergoing the D2 LND, subgroup analysis showed improved five-year DSS with the D1 LND for pT1 patients (98% in the D1 group vs. 83% in the D2 group, p=0.015) [84]. For pT2-4 and LN-positive patients in the D2 arm (38% in the D1 group vs. 59% in the D2 group, p=0.055), there was no statistically significant difference in survival; however, the trial was not adequately powered to detect survival differences in subgroup analyses. Subsequent meta-analysis supports the survival benefit for advanced stage patients. However, as the D2 LND is

associated with increased complication rates, it should not be selected for patients undergoing non-curative-intent surgery, or patients with significant co-morbidities.

Lymph Node Assessment

The AJCC/UICC staging [6] recommends that at least 16 lymph nodes be assessed for appropriate staging. While the systematic review shows improved survival associated with patients in whom more LNs are assessed, given that all studies were retrospective or prospective cohorts, there is no ability to infer causality. Further confounding this issue, assessment of too few LNs may create stage migration. For example, a designation of N3b is given for patients with 16 or more positive LNs. If a patient does not have at least 16 LNs assessed, it is impossible to be staged N3b. Bouvier et al. [85] estimated that the risk of misclassification is 47% when fewer than 10 LNs are examined, while Bando et al. [86] report that 45% of patients with LN involvement would have been under-staged if only a D1 LND had been performed. Many of the authors suggested thresholds higher than 16 LN to be assessed for adequate staging, and stage migration occurred in many series to a threshold above 40 LNs assessed. However, given the non-randomized data, no firm conclusions may be made.

The median number of LNs assessed in the United States (US) is 10 [87,88]. In the Intergroup 0116 trial conducted in the US [77], investigators found that 54% of patients had a D0 LND, 36% had a D1 LND, and 10% had a D2 LND. As studies have shown that a D1 LND will remove a mean of 26 LNs (range, 8 to 55), while a D2 LND will remove 37.4 LN (range, 15 to 72) [89], many patients may still be undergoing a D0 LND in Ontario and the US.

Margins

As a primary tenet of cancer surgery, resections should aim to have R0 margins. No randomized data exist to inform recommendations regarding the length of stomach necessary to achieve negative margins. Three issues exist: the minimum amount of grossly negative stomach necessary to ensure R0 resection, the minimum amount of grossly negative stomach necessary to impact survival for patients with an R0 resection, and the impact of an extended resection on patient outcomes and QOL.

Recommendations for a minimum resection length arise from the 1982 report by Bozetti et al. [90], who found a minimum margin of 6 cm led to consistently negative microscopic margins on final pathology report. Subsequent studies have found lengths of 2 cm to 5 cm were needed to decrease the likelihood of positive margins, dependent upon histology and depth of invasion [91,92]. This has led to the recommendations from the NCCN [9] to have a minimum of 4 cm margins for T1b or greater cancers, and from the Japanese Gastric Cancer Treatment guidelines [10] to have a 3 cm margin for T1/T2 cancers and 5 cm for T3/T4 cancers.

Most adjusted analyses show that positive margins have independent impact on OS in multivariable models; therefore, achieving negative margins is important in optimal patient outcomes. However, in many of these studies, other biologic factors such as nodal burden and histology had stronger impact on survival than positive margins, leading some authors to question the need for multivisceral or thoracic resections in order to achieve a negative margin in patients with other markers of advanced biology. Only one study has examined the potential benefit for re-resection of positive margin, with Kim et al. [53] showing that only in patients with ≤5 positive LNs is a repeat resection beneficial to the survival outcomes.

As most patients will have an R0 resection, and as a more extensive resection is likely to impact the patient in terms of increased complications, and decreased quality of life post-operatively, the routine amount of grossly negative margin resected is an important question. Some groups have found that in the absence of positive margins, there is no demonstrated survival benefit for extended resection [54,55], while the US Gastric Cancer Collaborative found that a negative margin less than 3 cm [17] was associated with survival differences.

For patients in whom consideration is being made for an extended or multivisceral resection in order to obtain negative margins, multidisciplinary discussion should be held, with consideration of other factors (signet ring histology, nodal burden) that may impact upon patient survival.

Management of Stage IV Disease

Patients with Stage IV gastric cancer have a predicted median survival of nine to 13 months for resection performed for palliation, five to 24 months for non-curative resection and three to 20.6 months for resections in which the indication for surgery was not clear. Unfortunately, many of these patients present with significant symptoms of bleeding, obstruction, pain, and cachexia [18]. Currently, treatment for these patients is variable across the province, with rates of gastrectomy ranging from 32% to 53%, chemotherapy ranging from 24% to 51%, and radiation from 18% to 41% [93]. Review of the literature showed a significant number of publications of retrospective cohorts. While these studies cannot assess the impact of surgery on patient survival, they are useful to define the complication rate following surgery for Stage IV gastric cancer, with reported peri-operative morbidity of 2% to 49% and operative mortality up to 21% [18].

The REGATTA trial [24] gives the best evidence for treatment of Stage IV gastric cancer patients. In this multi-institutional RCT, patients with limited M1 disease were randomized to either upfront chemotherapy or surgery with post-operative chemotherapy. After enrolment of 164 patients, the trial was stopped by the Data Safety Monitoring Committee owing to futility of achieving the primary endpoint. Grade 2 to 4 toxicities were higher in the surgery arm than the chemotherapy arm and fewer cycles of chemotherapy were received in the surgery arm, with the group experiencing the worst outcomes in the surgery arm being upper gastric cancers.

Unfortunately, patient QOL data are lacking for patients treated with chemotherapy compared with surgery. Given the high rate of complications and peri-operative mortality, demonstrated lack of benefit in survival, and no information regarding QOL differences for the two treatments, resection cannot be recommended for Stage IV patients, with the exception of treatment of symptoms.

Surgical Volume

Many studies have examined the relationship between volume and patient outcomes, with each study creating slightly different definitions of morbidity and mortality, and various cut-points for volume considerations. Most of the studies were retrospective cohorts, and patient and hospital characteristics varied significantly. Given the heterogeneity of these studies, interpretation of the volume-outcome relationship is difficult; however, a clear improvement in peri-operative mortality is found. Therefore, patients should be referred to higher-volume centres with the ability to manage post-operative complications. Although an absolute volume cut-point cannot be defined owing to heterogeneity of the literature, it should be noted that all non-Asian trials considered less than five cases per year to be low- or very low-volume hospitals.

The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland demonstrated an in-hospital mortality rate of approximately 5% for gastric resections in 2004 [94]. Additionally, current CCO standards for hepatopancreaticobiliary surgery (EBS #17-2) [11] state that a 30-day/in-hospital mortality rate of 5% is expected for major pancreas resections, with less than a 3% expected 30-day/in-hospital mortality rate for anatomical liver resections, guiding our recommendation for a mortality rate <5% for gastric resections.

The ability to reliably assess perioperative mortality is inversely linked to volume, as the confidence interval around a mortality estimate must increase as the volume decreases. If a hospital performs 100 cases with five mortalities, the mortality rate will be 5% with a 95% CI

of 1.8% to 11.8%, while a hospital performing 20 cases with one death would have a 95% CI of 0.26% to 26.9%. A hospital performing five resections, with no deaths has a 95% CI of 0% to 53.7%.

Laparoscopic Resection

Numerous retrospective, prospective, and randomized trials have reported short term outcomes for laparoscopic compared to open gastric resection for cancer. Short-term outcomes of blood loss, time to flatus, hospital length of stay, and peri-operative morbidity either favour laparoscopic resection, or find no difference, albeit with an increase in operative time. Long-term oncologic outcomes are currently being examined in the KLASS, KLASS-2, and KLASS-3 trials (see section labeled ***Ongoing, Unpublished, or Incomplete Studies***).

Although there is no Level 1 evidence regarding oncologic outcomes for laparoscopic gastric cancer surgery, many other abdominal cancers are approached laparoscopically (i.e., colon, rectum, liver, pancreas) [95-97]. All quality recommendations above should be met, regardless of open or laparoscopic surgical technique.

CONCLUSIONS

Staging in gastric cancer should follow the recommendations outlined by Lerut et al. [1] in that all patients should be discussed at a multidisciplinary team meeting and a CT of the chest and abdomen should always be performed. All other imaging can be considered based on clinical presentation. As radiologic staging may miss carcinomatosis and small-volume liver metastasis, diagnostic laparoscopy should be considered in patients at high risk for Stage IV disease. A D2 LND is preferred for curative-intent resection in advanced non-metastatic gastric cancer, whereas a D1 LND is preferred in patients with T1 cancers, palliative cases, or in patients with significant comorbidities. Moreover, at least 16 LNs should be assessed for adequate staging of curative-resected gastric cancer. Gastric cancer surgery should aim to achieve an R0 resection margin. In the metastatic setting, surgery should only be considered for palliation of symptoms. As higher-volume centres have a lower peri-operative mortality rate, patients should be referred to higher volume centres, and those with adequate support to manage potential complications. An expected 30-day or in-hospital peri-operative mortality rate should be less than 5%. To this end, an adequate annual volume should exist in order to determine whether a hospital is achieving this standard. Laparascopic resections should be performed to the same standards as open resections by surgeons who are experienced in both advanced laparoscopic surgery and gastric cancer management.

Staging and Surgical Approaches in Gastric Cancer

Section 5: Internal and External Review

INTERNAL REVIEW

The guideline was evaluated by the GDG Expert Panel and the PEBC Report Approval Panel (RAP) (Appendix 2). The results of these evaluations and the Working Group's responses are described below.

Expert Panel Review and Approval

Of the 34 members of the GDG Expert Panel, 28 members cast votes and none abstained, for a total of 82% response in March/April 2016. Of those that cast votes, 25 approved the document (89%). The main comments from the Expert Panel and the Working Group's responses are summarized in Table 5-1.

Table 5-1. Summary of the Working Group's responses to comments from the Expert Panel.

Comments	Responses
T1NO tumours should be addressed.	The discussion was amended to address these rare tumours.
The intended users should be broadened.	This was modified.
Several suggestions regarding the wording and content of Recommendation 1 dealing with staging.	As this recommendation was an endorsement from another guideline, the wording cannot be changed. However, issues of concern were added to the qualifying statements for clarification purposes.
Add in a description of D2 versus D1 LND.	This was added in.
In the qualifying statement for Recommendation 4, make it clear that signet ring is a subtype of diffuse histology.	This change was made.
In Recommendation 5, clarify that surgery in Stage IV patients for palliation of symptoms should only be considered if less-invasive means cannot address the problem.	This change was made.
Recommendation 6 should be more strongly worded with respect to encouraging gastric surgery being performed at higher-volume centres.	This recommendation was modified.
A few small editorial revisions were suggested.	These changes were made.

RAP Review and Approval

Three RAP members, including the PEBC Director, reviewed this document in February/March 2016. The RAP approved the document March 3, 2016. The main comments from the RAP and the Working Group's responses are summarized in Table 5-2.

Table 5-2. Summary of the Working Group's responses to comments from RAP.

Comments	Responses
Add in a description of D2 versus D1 LND.	This was added in.
Much of the evidence is non-randomized and retrospective.	The Working Group agrees. However, these are the data that are currently available.
There was one comment that Recommendation 6 (volumes question) should be more strongly worded with respect to encouraging gastric surgery being performed at higher-volume centres and defining what a high-volume centre is. However, another comment indicated that the recommendation was quite clear given the current evidence.	A compromise was reached and the recommendation modified. However, it was not possible to provide a clear definition of a high-volume centre.

EXTERNAL REVIEW

External Review by Ontario Clinicians and Other Experts

Targeted Peer Review

Eight targeted peer reviewers from Ontario, Quebec, British Columbia, USA, and Italy who are considered to be clinical and/or methodological experts on the topic were identified by the Working Group. Three agreed to be the reviewers (Appendix 2). Three responses were received. The recommendations submitted for external review can be found in Appendix 4. Results of the feedback survey are summarized in Table 5-3. The comments from targeted peer reviewers and the Working Group's responses are summarized in Table 5-4.

Table 5-3. Responses to nine items on the targeted peer reviewer questionnaire.

	Reviewer Ratings (N=3)				
Question	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the guideline development methods.				1	2
2. Rate the guideline presentation.			1		2
3. Rate the guideline recommendations.				1	2
4. Rate the completeness of reporting.				1	2
5. Does this document provide sufficient information to inform your decisions? If not, what areas are missing?				2	1
6. Rate the overall quality of the guideline report.					3
	Strongly Disagree (1)	(2)	Neutral (3)	(4)	Strongly Agree (5)
7. I would make use of this guideline in my professional decisions.					3
8. I would recommend this guideline for use in practice.					3
9. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Implementing changes in referral patterns and physician practices so that patients are referred to higher-volume centres. • Ability to obtain a PET scan for gastric cancer in Ontario unless the cancer involves the GEJ. • Dissemination to front-line surgeons to make them aware of the recommendations.				

Table 5-4. Responses to comments from targeted peer reviewers.

Comments	Responses
1. A comment that the qualifying statement that EUS should only be performed if results may change management plans should be reworked.	The qualifying statement was amended.
2. A comment that the recommendation regarding LND needs to be reworked, especially regarding those with significant comorbidities.	The recommendation was amended.
3. A comment that the recommendation regarding staging laparoscopy should be more strongly supported	This recommendation was from the endorsement of the Lerut et al. [1] guideline; therefore, it cannot be changed. Also, the Working Group thought that the recommendation along with the accompanying qualifying statement was strong enough.
4. An idea that a checklist should be developed for those performing gastric cancer surgery regarding the services available at each hospital.	This is beyond the scope of this guideline.

Professional Consultation

Feedback was obtained through a brief online survey of healthcare professionals and other stakeholders who are the intended users of the guideline. All surgeons, gastroenterologists, medical oncologists, and radiation oncologists in the PEBC database who identified gastric cancer as an interest were contacted by email to inform them of the survey. In total, 138 healthcare providers were contacted: 132 who practice in Ontario and six who practice outside Ontario. Eleven (8%) responses were received. Eight stated that they did not have interest in this area or were unavailable to review this guideline at the time. The results of the feedback survey from 11 people are summarized in Table 5-5. The main comments from the consultation and the Working Group's responses are summarized in Table 5-6.

Table 5-5. Responses to four items on the professional consultation survey.

	Number (%)				
General Questions: Overall Guideline Assessment	Lowest Quality (1)	(2)	(3)	(4)	Highest Quality (5)
1. Rate the overall quality of the guideline report.			1 (9)	4 (36)	6 (55)
	Strongly Disagree (1)	(2)	(3)	(4)	Strongly Agree (5)
2. I would make use of this guideline in my professional decisions.				4 (36)	7 (64)
3. I would recommend this guideline for use in practice.				6 (55)	5 (45)
4. What are the barriers or enablers to the implementation of this guideline report?	Barriers: • Dissemination of the guideline to healthcare providers caring for people with gastric cancer • Uptake and acceptance of the guideline • Timely access to CT • Access to surgeons prepared to perform D2 lymphadenectomies may be a challenge in certain regions • Lack of EUS, which is more sensitive for T staging and CT scan.				

Table 5-6. Modifications/Actions taken/Responses regarding main written comments from professional consultants.

Comments	Responses
1. A comment that the recommendation regarding D1 versus D2 lymphadenectomy may need to be amended.	The recommendation was amended.
2. A comment that the role of the family physician in the workup of the patient is not addressed	This was beyond the scope of this guideline.
3. A comment that CT should be performed at an institution with experience in gastric cancer staging and where radiologists actively participate in multidisciplinary oncology rounds.	The Working Group agrees this would be ideal but it is not practical unless these are resource allocation changes.
4. A comment that the guideline should be updated as new evidence becomes available.	All PEBC guidance documents are assessed yearly for currency and relevancy.

CONCLUSION

The final guideline recommendations contained in Section 2 and summarized in Section 1 reflect the integration of feedback obtained through the external review processes with the document as drafted by the GDG Working Group and approved by the GDG Expert Panel and the PEBC RAP.

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Appendix 1. Members of the Surgical Management of Gastric Cancer Guideline Development Group

Name	Specialty	Affiliation
Belal Ahmad	RO	London Regional Cancer Program London, ON
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Scott Berry	MO	Odette Cancer Centre Toronto, ON
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Christine Brezden-Masley	MO	St. Michael's Hospital Toronto, ON
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON
Natalie Coburn	SO	Odette Cancer Centre Toronto, ON
Craig Earle	MO	Odette Cancer Centre Toronto, ON
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON
Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON
Laz Klein	SO	Humber River Regional Hospital Toronto, ON
Gregory Knight	MO	Grand River Regional Cancer Centre Kitchener, ON
Jennifer Knox	MO	Princess Margaret Hospital Toronto, ON
Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON
Richard Malthaner	SO	London Regional Cancer Program London, ON

Joseph Mamazza	SO	Ottawa Civic Hospital Ottawa, ON
Dale Mercer	SO	Hotel Dieu Hospital Kingston, ON
Brandon Meyers	MO	Juravinski Cancer Centre Hamilton, ON
Jason Pantarotto	RO	Ottawa Hospital Cancer Centre Ottawa, ON
Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON
Marko Simunovic	SO	Juravinski Cancer Centre Hamilton, ON
Simron Singh	MO	Odette Cancer Centre Toronto, ON
Stephen Welch	MO	London Regional Cancer Progam London, ON
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON
Youssef Youssef	RO	Durham Regional Cancer Centre Oshawa, ON
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON
Roxanne Cosby	HRM	Program in Evidence-Based Care McMaster University Hamilton, ON

Abbreviations: HR=health research methodologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Appendix 2. Members of the Surgical Management of Gastric Cancer Working Group, Expert Panel, Report Approval Panel and Target Reviewers and their COI declarations.

In accordance with the PEBC Conflict of Interest (COI) Policy, the guideline authors (Working Group) Surgical Management of Gastric Cancer Expert Panel members, and internal and external reviewers were asked to disclose potential conflicts of interest.

Members of the Surgical Management of Gastric Cancer Working Group

Name	Specialty	Affiliation	Declarations of interest
Natalie Coburn Working Group Chair	SO	Odette Cancer Centre Toronto, ON	Within the past five years has published many scholarly papers and commentaries related to gastric cancer management.
Laz Klein	SO	Humber River Regional Hospital Toronto, ON	Within the past five years received $5000 or more in a single year to act as proctor with Medtronic, Ethicon, and Conmed.
Gregory Knight	MO	Grand River Regional Cancer Centre Kitchener, ON	Within the past five years received $5000 or more in a single year for travel support and to be on advisory boards for multiple companies.
Richard Malthaner	SO	London Regional Cancer Program London, ON	Declared they had no conflicts of interest.
Joseph Mamazza	SO	Ottawa Civic Hospital Ottawa, ON	Declared they had no conflicts of interest.
Dale Mercer	SO	Hotel Dieu Hospital Kingston, ON	Declared they had no conflicts of interest.
Jolie Ringash	RO	Princess Margaret Hospital Toronto, ON	Within the past five years has been a principal investigator in gastric cancer clinical trials.
Roxanne Cosby	HR	Program in Evidence-Based Care McMaster University Hamilton, Ontario	Declared they had no conflicts of interest.

Abbreviations: HR=health research methodologist; MO=medical oncologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Surgical Management of Gastric Cancer Expert Panel

Name	Specialty	Affiliation	Declarations of interest
Belal Ahmad	RO	London Regional Cancer Program London, ON	Declared they had no conflicts of interest
Tim Asmis	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest
Scott Berry	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Jim Biagi	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest
Sav Brar	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest
Christine Brezden-Masley	MO	St. Michael's Hospital Toronto, ON	Declared they had no conflicts of interest
Kelvin Chan	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Charles Cho	RO	Stronach Regional Cancer Program Newmarket, ON	Declared they had no conflicts of interest
Craig Earle	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Tarek Elfiki	MO	Windsor Regional Cancer Centre Windsor, ON	Declared they had no conflicts of interest
Rachel Goodwin	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Within the past five years received $5000 or more in a single year from Novartis and Sanofi to support travel costs to conferences.
Robert Gryfe	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest
Nazik Hammad	MO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest
Derek Jonker	MO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest
Maria Kalyvas	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest
Paul Karanicolas	SO	Odette Cancer Centre Toronto, ON	Within the past five years received $5000 or more in a single year to be on Bayer advisory board and a consultant to Sanofi. Neither of these positions was relevant to the topic of this guideline.
Erin Kennedy	SO	Mt. Sinai Hospital Toronto, ON	Declared they had no conflicts of interest
Jennifer Knox	MO	Princess Margaret Hospital Toronto, ON	Within the past five years received research support from Pfizer, AstraZeneca, and Novartis

Aamer Mahmud	RO	Cancer Centre of Southeastern Ontario Kingston, ON	Declared they had no conflicts of interest
Celia Marginean	Path	The Ottawa Hospital General Campus Ottawa, ON	Declared they had no conflicts of interest
Caitlin McGregor	Radio	Sunnybrook Health Sciences Centre Toronto, ON	Declared they had no conflicts of interest
Brandon Meyers	MO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest
Jason Pantarotto	RO	Ottawa Hospital Cancer Centre Ottawa, ON	Declared they had no conflicts of interest
Fayez Quereshy	SO	Princess Margaret Hospital Toronto Western Hospital Toronto, ON	Declared they had no conflicts of interest
Mark Rother	MO	Peel Regional Cancer Centre Mississauga, ON	Declared they had no conflicts of interest
Marko Simunovic	SO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest
Simron Singh	MO	Odette Cancer Centre Toronto, ON	Declared they had no conflicts of interest
Chris Teshima	GE	St. Michael's Hospital Toronto, ON	Declared they had no conflicts of interest
Alice Wei	SO	Cancer Care Ontario Toronto, ON	Within the past five years received $5000 or more in a single year to act in a consulting capacity to CCO's Surgical Oncology Program
Stephen Welch	MO	London Regional Cancer Program London, ON	Declared they had no conflicts of interest
Raimond Wong	RO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest
Rebecca Wong	RO	Princess Margaret Hospital Toronto, ON	Declared they had no conflicts of interest
Youssef Youssef	RO	Durham Regional Cancer Centre Oshawa, ON	Declared they had no conflicts of interest
Kevin Zbuk	MO	Juravinski Cancer Centre Hamilton, ON	Declared they had no conflicts of interest

Abbreviations: GE=gastroenterologist; MO=medical oncologist; Path=pathologist; Radio= radiologist; RO=radiation oncologist; SO=surgical oncologist

Members of the Surgical Management of Gastric Cancer Report Approval Panel

Name	Specialty	Affiliation	Declarations of interest
Melissa Brouwers	HR	Program in Evidence-Based Care	Declared they had no conflicts of interest
Bill Evans	MO	Juravinski Cancer Centre, retired	Declared they had no conflicts of interest
Donna Maziak	SO	Ottawa General Hospital	Declared they had no conflicts of interest

Abbreviations: HR=health research methodologist; MO=medical oncologist; SO=surgical oncologist

Members of the Surgical Management of Gastric Cancer Targeted Peer Reviewers

Name	Specialty	Affiliation	Declarations of interest
Eric Frechette	Surgeon	London Health Sciences Centre	Declared they had no conflicts of interest
Trevor Hamilton	Surgeon	British Columbia Cancer Agency	Declared they had no conflicts of interest
Grant Moffat	Surgeon	Mississauga Halton Central West Regional Cancer Program	Declared they had no conflicts of interest

The COI declared above did not disqualify any individuals from performing their designated role in the development of this guideline, in accordance with the PEBC COI Policy. To obtain a copy of the policy, please contact the PEBC office by email at ccopgi.mcmaster.ca

Appendix 3 – Search strategies for Clinical Practice Guidelines, Systematic Reviews and Primary Literature

Clinical Practice Guidelines

MEDLINE

1. gastric cancer.mp. or Stomach Neoplasms/
2. (guideline or practice guideline).pt.
3. (guideline: or recommend: or consensus or standards).ti.
4. 2 or 3
5. 1 and 4

EMBASE

1. gastric cancer.mp. or Stomach Neoplasms/
2. (guideline or practice guideline).pt.
3. (guideline: or recommend: or consensus or standards).ti.
4. 2 or 3
5. 1 and 4
6. limit 6 to english language

Systematic Reviews

MEDLINE

1. meta-analysis as topic/
2. meta analysis.pt.
3. (meta analy$ or metaanaly$).tw.
4. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s or quantitative overview).tw.
5. (systematic adj (review$ or overview$)).tw.
6. (exp Review Literature as topic/ or review.pt. or exp review/) and systematic.tw.
7. or/1-6
8. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
9. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
10. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
11. (study adj selection).ab.
12. 10 or 11
13. review.pt.
14. 12 and 13
15. 7 or 8 or 9 or 14
16. (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.
17. 15 not 16
18. gastric cancer.mp. or Stomach Neoplasms/
19. 17 and 18
20. limit 19 to english language

EMBASE

1. exp Meta-Analysis/ or exp "Systematic Review"/
2. (meta analy$ or metaanaly$).tw.
3. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s or quantitative overview).tw.
4. (systematic adj (review$ or overview$)).tw.
5. exp "Review"/ or review.pt.
6. (systematic or selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
7. (study adj selection).ab.
8. 5 and (6 or 7)
9. or/1-4,8

10. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
11. (reference list$ or bibliograph$ or hand-search$ or relevant journals or manual search$).ab.
12. 9 or 10 or 11
13. (editorial or note or letter or erratum or short survey).pt. or abstract report/ or letter/ or case study/
14. 12 not 13
15. gastric cancer.mp. or stomach cancer/
16. stomach neoplasms.mp.
17. 15 or 16
18. 14 and 17
19. limit 18 to english language

Primary Studies
Question 2a/b
MEDLINE
1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. or/1-5
7. lymphadenectomy.mp. or exp Lymph Node Excision/
8. lymph node/
9. (D1 or D2).mp.
10. cancer staging/
11. or/7-10
12. 6 and 11
13. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report).mp. or historical article.pt. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
14. exp Meta-Analysis as Topic/
15. meta-analysis.pt.
16. (meta analy$ or metaanaly$).tw.
17. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s).mp. or quantitative overview.tw. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
18. (systematic adj (review$ or overview$)).tw.
19. (exp review literative as topic/ or review.pt. or exp review/) and systematic.tw.
20. or/14-19
21. (cochrane or embase or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids of sigle or cancerlit).ab.
22. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
23. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
24. (study adj selection).ab.
25. 23 or 24
26. review.pt.
27. 25 and 26
28. 13 or 20 or 21 or 22 or 27
29. 12 not 28
30. limit 29 to english language

EMBASE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. or/1-5
7. lymphadenectomy.mp. or exp Lymph Node Excision/
8. lymph node/
9. (D1 or D2).mp.
10. cancer staging/
11. or/7-10
12. 6 and 11
13. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report).mp. or historical article.pt. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
14. exp Meta-Analysis as Topic/
15. meta-analysis.pt.
16. (meta analy$ or metaanaly$).tw.
17. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s).mp. or quantitative overview.tw. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
18. (systematic adj (review$ or overview$)).tw.
19. (exp review literative as topic/ or review.pt. or exp review/) and systematic.tw.
20. or/14-19
21. (cochrane or embase or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids of sigle or cancerlit).ab.
22. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
23. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
24. (study adj selection).ab.
25. 23 or 24
26. review.pt.
27. 25 and 26
28. 13 or 20 or 21 or 22 or 27
29. 12 not 28
30. limit 29 to english language

Question 2c

MEDLINE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. or/1-5
7. ((negative or resection) adj2 margin$).mp.

8. exp Frozen Sections/
9. exp Gastrectomy/
10. ((gastric or stomach) adj2 resect$).mp.
11. omentectom$.mp.
12. multivisceral resection$.mp.
13. or/7-12
14. (number of lymph nodes or lymph node assessment or lymph node examination or total lymph node count).mp.
15. 6 and 13 and 14
16. limit 15 to english language

EMBASE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. or/1-5
7. ((negative or resection) adj2 margin$).mp.
8. exp Frozen Sections/
9. exp Gastrectomy/
10. ((gastric or stomach) adj2 resect$).mp.
11. omentectom$.mp.
12. multivisceral resection$.mp.
13. or/7-12
14. (number of lymph nodes or lymph node assessment or lymph node examination or total lymph node count).mp.
15. 6 and 13 and 14
16. limit 15 to english language

Question 2d

MEDLINE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp.
3. ((gastric or stomach) adj1 carcinoma).mp.
4. ((gastric or stomach) adj1 adenocarcinoma).mp.
5. ((gastric or stomach) adj1 neoplasm$).mp.
6. or/1-5
7. ((negative or resection) adj2 margin$).mp.
8. exp frozen sections/
9. exp gastrectomy/
10. ((gastric or stomach) adj2 resect$).mp.
11. omentectom$.mp.
12. multivisceral resection$.mp.
13. (surgical adj2 margin$).mp.
14. or/7-13
15. 6 and 14
16. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report).mp. or historical article.pt.
17. exp meta-analysis as topic/
18. meta-analysis.pt.
19. (meta analy$ or metaanaly$).tw.
20. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s).mp. or quantitative overview.tw.
21. (systematic adj (review$ or overview$)).tw.
22. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.

23. (cochrane or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids of sigle or cancerlit).ab.
24. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
25. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
26. (study adj selection).ab.
27. review.pt.
28. or/16-27
29. 15 not 28
30. limit 29 to english language

EMBASE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp.
3. ((gastric or stomach) adj1 carcinoma).mp.
4. ((gastric or stomach) adj1 adenocarcinoma).mp.
5. ((gastric or stomach) adj1 neoplasm$).mp.
6. or/1-5
7. ((negative or resection) adj2 margin$).mp.
8. exp frozen sections/
9. exp gastrectomy/
10. ((gastric or stomach) adj2 resect$).mp.
11. omentectom$.mp.
12. multivisceral resection$.mp.
13. (surgical adj2 margin$).mp.
14. or/7-13
15. 6 and 14
16. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report).mp. or historical article.pt.
17. exp meta-analysis as topic/
18. meta-analysis.pt.
19. (meta analy$ or metaanaly$).tw.
20. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s).mp. or quantitative overview.tw.
21. (systematic adj (review$ or overview$)).tw.
22. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
23. (cochrane or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids of sigle or cancerlit).ab.
24. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
25. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
26. (study adj selection).ab.
27. review.pt.
28. or/16-27
29. 15 not 28
30. limit 29 to english language

Question 2e

MEDLINE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp.
3. ((gastric or stomach) adj1 carcinoma).mp.
4. ((gastric or stomach) adj1 adenocarcinoma).mp.
5. ((gastric or stomach) adj1 neoplasm$).mp.
6. or/1-5
7. laparoscopy-assisted gastrectomy.mp.
8. laparoscopic-assisted gastrectomy.mp.
9. Laparoscopy/ or Hand-Assisted Laparoscopy/ or laparoscopy.mp.
10. open gastrectomy.mp.
11. conventional gastrectomy.mp.
12. gastrectomy.mp. or Gastrectomy/

13. or/7-12
14. 6 and 13
15. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report).mp. or historical article.pt.
16. exp meta-analysis as topic/
17. meta-analysis.pt.
18. (meta analy$ or metaanaly$).tw.
19. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s).mp. or quantitative overview.tw.
20. (systematic adj (review$ or overview$)).tw.
21. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
22. (cochrane or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
23. (reference lists$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
24. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
25. (study adj selection).ab.
26. review.pt.
27. or/15-26
28. 14 not 27
29. limit 28 to english language

EMBASE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp.
3. ((gastric or stomach) adj1 carcinoma).mp.
4. ((gastric or stomach) adj1 adenocarcinoma).mp.
5. ((gastric or stomach) adj1 neoplasm$).mp.
6. or/1-5
7. laparoscopy-assisted gastrectomy.mp.
8. laparoscopic-assisted gastrectomy.mp.
9. laparoscopy/ or Hand-assisted Laparoscopy/ or laparoscopy.mp.
10. open gastrectomy.mp.
11. conventional gastrectomy.mp.
12. gastrectomy/ or Gastrectomy.mp.
13. or/7-12
14. 6 and 13
15. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report).mp. or historical article.pt.
16. exp meta-analysis as topic/
17. meta-analysis.pt.
18. (meta analy$ or metaanaly$).tw.
19. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative systhes$s).mp. or quantitative overview.tw.
20. (systematic adj (review$ or overview$)).tw.
21. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
22. (cochrane or psyclit or psychinfo or cinahl or cinhal or science citation index or scisearch or bids or sigle or cancerlit).ab.
23. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
24. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
25. (study adj selection).ab.
26. review.pt.
27. or/15-26
28. 14 not 27
29. limit 28 to english language

Question 3

MEDLINE

1. stomach cancer.mp. or exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. 1 or 2 or 3 or 4 or 5
7. exp Palliative Care/
8. exp Terminal Care/
9. palliat$.mp.
10. "stage IV".mp.
11. advanced disease.mp.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. limit 13 to english language
15. (comment or letter or editorial or note or erratum or short survey or news or newspaper article or patient education handout or case report or historical article).pt.
16. 14 not 15
17. meta-analysis as topic/
18. meta-analysis.pt.
19. (meta analy$ or metaanaly$).tw.
20. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s or quantitative overview).tw.
21. (systematic adj (review$ or overview$)).tw.
22. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
23. 17 or 18 or 19 or 20 or 21 or 22
24. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids of sigle or cancerlit).ab.
25. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
26. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
27. (study adj selection).ab.
28. 26 or 27
29. review.pt.
30. 28 and 29
31. 23 or 24 or 25 or 30
32. 16 not 31

EMBASE

1. stomach cancer.mp. or exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. 1 or 2 or 3 or 4 or 5
7. exp Palliative Care/
8. exp Terminal Care/
9. palliat$.mp.
10. "stage IV".mp.

11. advanced disease.mp.
12. 7 or 8 or 9 or 10 or 11
13. 6 and 12
14. limit 13 to english language
15. (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.
16. 14 not 15
17. meta-analysis as topic/
18. meta-analysis.pt.
19. (meta analy$ or metaanaly$).tw.
20. (systematic review$ or pooled analy$ or statistical pooling or mathematical pooling or statistical summar$ or mathematical summar$ or quantitative synthes$s or quantitative overview).tw.
21. (systematic adj (review$ or overview$)).tw.
22. (exp review literature as topic/ or review.pt. or exp review/) and systematic.tw.
23. 17 or 18 or 19 or 20 or 21 or 22
24. (cochrane or embase or psychlit or psyclit or psychinfo or psycinfo or cinahl or cinhal or science citation index or scisearch or bids of sigle or cancerlit).ab.
25. (reference list$ or bibliograph$ or hand-search$ or relevant journals of manual search$).ab.
26. (selection criteria or data extraction or quality assessment or jadad scale or methodological quality).ab.
27. (study adj selection).ab.
28. 26 or 27
29. review.pt.
30. 28 and 29
31. 23 or 24 or 25 or 30
32. 16 not 31

Question 4

MEDLINE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
6. or/1-5
7. (resources or health care planning).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier]
8. ("ancillary service$" or "support service$" or "hospital adj2 (laborator$ or radiology or pharmac$)").mp.
9. interventional radiology/
10. coronary care unit/ or intensive care unit/
11. exp intensive care/
12. recovery room/
13. interventional radiology.mp.
14. (respiratory care unit$ or ICU or pediatric intensive care unit).mp.
15. preoperative care/ or perioperative period/ or peroperative care/ or postoperative care/
16. or/7-15
17. 6 and 16
18. (requirement$ or outcome$).mp.
19. 17 and 18
20. (hospital volume or surgeon volume or volume outcome or facility volume or institution volume or center volume or centre volume).mp.
21. 6 and 20
22. 19 or 21
23. limit 22 to english language

EMBASE

1. exp Stomach Neoplasms/
2. ((gastric or stomach) adj1 cancer$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
3. ((gastric or stomach) adj1 carcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
4. ((gastric or stomach) adj1 adenocarcinoma).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
5. ((gastric or stomach) adj1 neoplasm$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
6. or/1-5
7. (resources or health care planning).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword]
8. ("ancillary service$" or "support service$" or "hospital adj2 (laborator$ or radiology or pharmac$)").mp.
9. interventional radiology/
10. coronary care unit/ or intensive care unit/
11. exp intensive care/
12. recovery room/
13. interventional radiology.mp.
14. (respiratory care unit$ or ICU or pediatric intensive care unit).mp.
15. preoperative care/ or perioperative period/ or peroperative care/ or postoperative care/
16. or/7-15
17. 6 and 16
18. (requirement$ or outcome$).mp.
19. 17 and 18
20. (hospital volume or surgeon volume or volume outcome or facility volume or institution volume or center volume or centre volume).mp.
21. 6 and 20
22. 19 or 21
23. limit 22 to english language

Appendix 4. Recommendations submitted for external review on June 6, 2016.

RECOMMENDATIONS

Recommendation 1
Endorsed from Lerut et al., 2012 [1]: • All patients diagnosed with gastric cancer should be discussed at a multidisciplinary team meeting. • In patients with newly diagnosed gastric cancer, CT scan of the chest and abdomen should always be performed. • Endoscopic ultrasound (EUS) can be considered in patients planned for curative treatment on the basis of clinical presentation and/or CT. Fine-needle aspiration cytology of suspicious lymph nodes or metastases can be considered if technically feasible. • The following examinations can be considered for specific indications: PET scan, magnetic resonance imaging, laparoscopy.
Recommendation 2
• A D2 lymph node dissection is preferred for curative intent resection of gastric cancer. A D1 lymph node dissection is preferred in patients with T1N0 cancers, M1 disease, or significant comorbidities.
Recommendation 3
• A minimum of 16 lymph nodes should be assessed for adequate staging of curative-resected gastric cancer.
Recommendation 4
• Surgery for gastric cancer should aim at achieving an R0 margin.
Recommendation 5
• In the metastatic setting, nonsurgical management options are preferred in patients without symptoms. • In the metastatic setting, surgery should only be considered for palliation of symptoms that cannot be addressed through less-invasive means (i.e., radiation, chemotherapy, stenting).
Recommendation 6
• Given evidence that higher volume centres are associated with lower rates of procedure-related mortality, patients should be referred to higher volume centres for surgical resection. • Gastric cancer surgery should be performed in centres with sufficient support to prevent or manage complications (e.g., interventional radiology, anesthesia, level 1 intensive care unit).
Recommendation 7
• Quality metrics for lymph nodes, margins, peri-operative mortality, and oncologic outcomes should be met regardless of surgical technique (e.g., open or minimally invasive).