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PRACTICE GUIDELINE

Staging and surgical approaches in gastric cancer: a clinical practice guideline

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ABSTRACT

Background Resection is the cornerstone of cure for gastric adenocarcinoma; however, several aspects of surgical intervention remain controversial or are suboptimally applied at a population level, including staging, extent of lymphadenectomy (LND), minimum number of lymph nodes that have to be assessed, gross resection margins, use of minimally invasive surgery, and relationship of surgical volumes with patient outcomes and resection in stage IV gastric cancer.

Methods Literature searches were conducted in databases including MEDLINE (up to 10 June 2016), EMBASE (up to week 24 of 2016), the Cochrane Library and various other practice guideline sites and guideline developer Web sites. A practice guideline was developed.

Results One guideline, seven systematic reviews, and forty-eight primary studies were included in the evidence base for this guidance document. Seven recommendations are presented.

Conclusions All patients should be discussed at a multidisciplinary team meeting, and computed tomography (CT) imaging of chest and abdomen should always be performed when staging patients. Diagnostic laparoscopy is useful in the determination of M1 disease not visible on CT images. A D2 LND is preferred for curative-intent resection of gastric cancer. At least 16 lymph nodes 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 be considered only for palliation of symptoms. Patients should be referred to higher-volume centres and those that have adequate support to manage potential complications. Laparoscopic resections should be performed to the same standards as those for open resections, by surgeons who are experienced in both advanced laparoscopic surgery and gastric cancer management.

Key Words Gastric cancer, laparoscopic surgery, lymph node dissection, practice guidelines, staging, surgical margins, surgical volumes, surgery

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INTRODUCTION

Although the incidence of and mortality from gastric cancer have been steadily declining in Canadian men and women, the disease remains a global health problem, accounting for 6.8% of all new cancer cases and 8.8% of all cancer deaths worldwide[1] in 2012. In Ontario in 2016, estimates placed the number of new incident cases of stomach cancer at 1320 (37.7% of the estimated new-incident stomach cancer cases in Canada) and deaths from stomach cancer at 760 (37.4% of the estimated stomach cancer deaths in Canada). The 5-year relative survival ratio was 25% [95% confidence interval (CI): 23% to 26%] for men and women combined[2]. (Concurrently, the incidence rate of gastroesophageal junction cancers has increased since about 2005, but the recommendations in this guideline should not be extrapolated to the treatment of gastroesophageal junction cancers, which are more complex and require different multidisciplinary considerations.) Under select circumstances, early gastric cancer can be curatively treated with endoscopic resection[3]. Discussion of patient selection for such procedures and of endoscopic techniques is outside the scope of this guideline.

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Resection is the cornerstone for cure in gastric adenocarcinoma; however, several aspects of surgical intervention remain controversial or are suboptimally applied at the population level. Although widely available, staging for gastric cancer is not uniformly performed[4,5]. In addition, the extent of lymphadenectomy (LND) accompanying 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.

In a matter closely related to the discussion of the type of lymph node harvest, many patients within North America do not meet the minimum required lymph node assessment for full cancer staging. Moreover, although a positive margin is associated with worse survival, few studies have evaluated the appropriate gross resection margin distances needed for curative-intent resection. Finally, the emergence of laparoscopic techniques has fuelled controversies about whether this minimally invasive surgery provides oncologic results equal to those achieved with traditional open surgical techniques.

Debates also exist with respect to the relationship between surgical volumes (both institutional and for individual surgeons) and outcomes. Volume as a variable has been explored for many surgical procedures because it represents a potentially modifiable factor, and it is an important issue in gastric cancer surgeries, because those surgeries are technically challenging and yet are 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 (obstruction and bleeding, for example), which are amenable to both resection and non-resection interventions (stent, radiation, and so on). Many patients with stage IV disease undergo resection, and yet not all noncurative gastrectomies are performed for symptom control[4]. The percentage of patients in whom an operation could have been avoided, with a concomitant reduction in perioperative morbidity and mortality, is unclear.

Given the number of issues with respect to staging and surgical approaches in gastric cancer, a clinical practice guideline was warranted.

RESEARCH QUESTIONS

1. Which technique or techniques are optimal for the adequate staging of gastric cancer?
2. Which technique of gastric cancer surgery with curative intent is optimal with respect to
   a) D2 versus D1 lymph node dissection?
   b) the minimal number of lymph nodes that have to be dissected?
   c) the minimal gross margins?
   d) laparoscopic versus open technique?
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 volume and outcomes?

METHODS

The present guideline was developed by the Surgical Management of Gastric Cancer Guideline Development Group (GDG), which was convened at the request of the Gastrointestinal Disease Site Group of Cancer Care Ontario's Program in Evidence-Based Care (PEBC). The PEBC produces evidence-based and evidence-informed guidance documents using the methods of the practice guidelines development cycle[6]. That process includes a systematic review, interpretation of the evidence by the GDG, draft recommendations, internal review by content and methodology experts, and external review by Ontario clinicians and other stakeholders.

Overall Literature Search

The evidence review for the present guideline was conducted in three planned stages: a search for guidelines, for systematic reviews, and for primary literature. All search strategies are available on request to the corresponding author.

Search for Existing Guidelines

A search for recent guidelines (published in 2010 or later) that have addressed the research questions was undertaken first, with the goal of identifying existing guidelines for adaptation or endorsement. Practice guideline databases (the Standards and Guidelines Evidence Directory of Cancer Guidelines, the U.S. National Guidelines Clearinghouse) and guideline developer Web sites (the U.K. National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network, the American Society of Clinical Oncology) were searched. Guidelines that were considered relevant to the objectives and the research questions were then evaluated for quality using the AGREE II instrument[7].

Search for Existing Systematic Reviews

A search was then conducted for existing English-language systematic reviews that were directly related to one or more guideline questions. Databases searched were MEDLINE, EMBASE, and the Cochrane Database of Systematic Reviews.

Identified systematic reviews were evaluated based on their clinical content and relevance. Relevant systematic reviews were assessed using the 11-item AMSTAR[8] tool to determine whether the existing systematic reviews met a minimum threshold for methodologic quality and could be considered for inclusion in the evidence base.

Search for Primary Literature

A relevant systematic review was available for questions 2(a), 2(b), 2(d), 3, and 4. A search for primary studies was then undertaken from the point in time at which each available systematic review ended up to 10 June 2016 in MEDLINE and up to week 24 of 2016 in EMBASE. For each of the research questions, the newer relevant primary

studies are included. If more than one publication was available for a given trial, only the most recent publication is included.

No relevant systematic review was available for question 2(c), and a search for primary studies was undertaken. A review of the titles and abstracts that resulted from the search was independently conducted by one reviewer (RC). For items that warranted full-text review, one reviewer reviewed each item (RC) for all questions except question 3, for which two reviewers (RC, NC) reviewed each item in collaboration.

Studies that were not randomized controlled trials (RCTs) were evaluated using the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (http://methods.cochrane.org/bias/risk-bias-non-randomized-studies-interventions). Evaluations of RCTs were conducted using the Cochrane Risk of Bias tool (http://handbook.cochrane.org/, Chapter 8.5).

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.

Internal Review

All PEBC guidelines are reviewed by a panel of content experts (the Expert Panel) and a methodology panel [the Report Approval Panel (RAP)]. Both panels must approve the document. The Working Group was responsible for incorporating the feedback and changes required by both panels.

External Review

The PEBC external review process is two-pronged. It includes a targeted peer review that is intended to obtain direct feedback on the draft report from a small number of specified content experts and a professional consultation that is intended to facilitate dissemination of the final guidance report to Ontario practitioners.

RESULTS

Literature Search Results

Guidelines

The 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.

Systematic Reviews

A search for systematic reviews uncovered 1821 documents. Of those documents, 88 underwent full-text review, and 8 that represented 7 systematic reviews were retained.

Primary Literature

The search for primary literature (updates to the systematic reviews and a *de novo* search) produced 23,290 hits. Of the located publications, 211 underwent a full-text review, and 47 were retained. Additionally, 1 individual study was obtained through reference mining. Table I summarizes the included studies.

Internal Review

Expert Panel Review and Approval

Of the 34 members of the GDG Expert Panel, 28 members cast votes, and none abstained, for an 82% response during March–April 2016. Of the members who cast votes, 25 approved the document (89%).

RAP Review and Approval

Three RAP members, including the PEBC director, reviewed the draft guideline in February–March 2016. The RAP approved the document on 3 March 2016.

External Review

Targeted Peer Review

Eight targeted peer reviewers from Ontario, Quebec, British Columbia, the United States, and Italy who were considered to be clinical or methodology experts on the topic were identified by the Working Group. Three agreed to be reviewers, and three responses were received.

Professional Consultation

Feedback was obtained through a brief online survey of health care 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 had identified gastric cancer as an interest were contacted by e-mail to inform them of the survey. The 138 health care providers contacted included 132 who practiced in Ontario and 6 who practiced outside Ontario. Of 11 responses received (8%), 8 indicated that the provider did not have an interest in this area or was unavailable to review the guideline at the time.

RECOMMENDATIONS AND KEY EVIDENCE

Recommendation 1

Recommendation 1 is endorsed directly from Lerut *et al.*[9].

All patients diagnosed with gastric cancer should be discussed at a multidisciplinary team meeting. In patients with newly diagnosed gastric cancer, CT imaging of chest and abdomen should always be performed. Endoscopic ultrasonography can be considered in patients planned for curative treatment on the basis of clinical presentation or CT imaging, or both. 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, magnetic resonance imaging, laparoscopy.

Qualifying Statements for Recommendation 1

Given that the accuracy of CT imaging in detecting M1 disease is 81%[66], diagnostic laparoscopy could allow patients to avoid a laparotomy in up to 44% of cases of advanced-stage cancer[67]. Guidelines from both the Scottish Intercollegiate Guidelines Network[68] and the Society of American Gastrointestinal and Endoscopic

TABLE I Publications selected for inclusion

Research question	Publications retained (*n*)			Reference
	Guidelines	Systematic reviews	Primary studies	
1. Staging	1	NA	NA	9
2. Optimal technique				
a) D2 compared with D1 lymph node dissection	0	3	1	10–13
b) Minimal number of lymph nodes dissected	0	1	8	14–22
c) Minimal surgical margins	0	0	4	23–26
d) Laparoscopic compared with open surgery	0	1	15	27–42
3. Surgery in stage IV patients	0	1 (2)	13	43–57
4. Surgical volumes	0	1	7	58–65

NA = not applicable.

Surgeons[69] suggest diagnostic laparoscopy in patients with clinically suspected T3 and T4 cancers or in those at higher risk for M1 disease, such as those with poorly differentiated cancers and with a higher nodal burden. Diagnostic laparoscopy should be performed before the start of chemotherapy for patients in whom a neoadjuvant approach is considered. Washing might increase the accuracy of diagnostic laparoscopy.

Positron-emission tomography and magnetic resonance imaging could be useful for the 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.

Endoscopic ultrasonography should be performed only if the results could change management plans (that is, to assess for local invasion, nodal status, or metastatic spread).

Key Evidence for Recommendation 1

The key evidence is derived from one clinical practice guideline authored by Lerut *et al.*[9] of the Belgian Health Care Knowledge Centre.

Recommendation 2

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

Qualifying Statements for Recommendation 2

Distal pancreatectomy or splenectomy (or both) should not be routinely performed because of increased morbidity and mortality.

Key Evidence for Recommendation 2

A systematic review of five studies and 1599 patients[10] demonstrated that the 5-year survival rate was similar for D2 and D1 LNDs [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; $p < 0.05$).

The 15-year follow-up from the Dutch RCT of D1 compared with D2 LND showed fewer gastric cancer–related deaths in patients undergoing a D2 LND for all T stages (48% with D1 LND vs. 37% with D2 LND, $p = 0.01$ per protocol analysis)[11].

Recommendation 3

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

Qualifying Statements for Recommendation 3

The guideline published by the American Joint Committee on Cancer and the Union for International Cancer Control[70] states that 16 lymph nodes are necessary for adequate staging.

Studies suggest that removal and examination of more than 16 nodes might improve survival and increases the accuracy of staging by reducing understaging, which leads to stage migration[14,15].

Key Evidence for Recommendation 3

One systematic review[16] reported that disease-free survival significantly improves as the number of lymph nodes harvested increases, especially when more than 15 nodes are retrieved, and concluded that 16 lymph nodes at minimum should be harvested. More current studies of moderate quality also report that harvesting more than 15 nodes significantly improves survival[17,18].

Recommendation 4

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

Qualifying Statements for Recommendation 4

The guideline from the U.S. National Comprehensive Cancer Network[71] suggests a 4 cm distance to assure negative margins. The Japanese Gastric Cancer Treatment Guidelines[72] suggest that a distance of 3 cm for T1/2 cancer and 5 cm for T3/4 cancer be obtained.

Intraoperative frozen-section analysis should be considered in cases in which a high risk of a positive margin is a concern.

Cancers with higher T and N stages, and tumours of higher grade (for example, diffuse-type histology, including signet-ring carcinoma), are more likely to have involved

microscopic margins, and intraoperative planning or neoadjuvant therapy should take those factors into consideration.

For patients with poor biology (>5 positive lymph nodes; diffuse-type histology, including signet-ring carcinoma), an extended resection of the adjacent organs or intrathoracic esophagus might not result in improved long-term survival. Multivariable analyses in many studies have shown that, compared with a positive margin, tumour biology could be a stronger determinant of outcome.

Extended resection should be undertaken selectively and with multidisciplinary discussion.

Key Evidence for Recommendation 4

Data from one study suggests that margin distances of 5 cm for T3/4 cancer and 3 cm for T1/2 cancer are sufficient to obtain resection margins negative for microscopic cancer[23].

Median overall and recurrence-free survival were significantly better in patients with proximal margin distances of 3.1–5.0 cm than with distances of 3.0 cm or less (48.1 months vs. 29.3 months, $p = 0.01$, and 38.9 months vs. 21.1 months, $p = 0.02$, respectively). Median overall and recurrence-free survival were not significantly different for patients with proximal margin distances greater 5.0 cm than for those with proximal margin distances of 3.1–5.0 cm. However, the overall and recurrence-free survival advantage of a proximal margin distance of 3.1 cm was associated only with stage I disease and not with stage II or III disease[23].

Recommendation 5

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

Qualifying Statements for Recommendation 5

Given that the complication rate 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 fifty-nine studies, procedure-related morbidity occurred in all types of surgical interventions and regardless of the intent of the surgery. Morbidity ranged from 3.8% to 49% for gastrectomy and from 14% to 21% for non-resection surgeries[43]. In the literature update, procedure-related morbidity in moderate-quality noncurative studies ranged from 15.1%[44] to 88.8%[45] for gastrectomy and from 11.5%[46] to 21%[47] for non-resection surgeries.

In the systematic review by Mahar *et al.*[43], procedure-related mortality was lower in palliative resections (0%–7%) than in either noncurative (0%–21%) or not-otherwise-specified surgeries (0%–20.4%). The mortality rate for gastrectomy performed for any intent was 0%–21%; the mortality rate for non-resection surgeries was 0%–39%[43]. In the literature update, which included all moderate-quality studies, procedure-related mortality for gastrectomy performed in noncurative studies was 1.1%–9.1%[44,48]; the mortality rate for non-resection surgeries in noncurative studies was 4.8%–10%[21,47].

The REGATTA trial[49] showed no survival benefit of combined gastrectomy and chemotherapy over chemotherapy alone (25.1% vs. 31.7%) in patients with noncurable gastric cancer (hazard ratio: 1.09; 95% CI: 0.78 to 1.52; $p = 0.70$). Moreover, patients in the combined gastrectomy and chemotherapy arm experienced more complications.

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 (for example, interventional radiology, anesthesia, level 1 intensive care unit).

Qualifying Statements for Recommendation 6

In most studies, higher-volume centres are associated with improved outcomes. The studies have no common definition of a high-volume centre; however, 5 or fewer annual cases is considered low-volume or very low-volume in all studies.

The expected 30-day or in-hospital perioperative mortality should be less than 5%. That rate is based on published mortality rates from high-volume centres, and on standards published by Cancer Care Ontario[73], which recommend a 30-day or in-hospital mortality rate of less than 5% for major pancreatic resection and 3% for anatomic liver resection. Given that those 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 should recognize that lower volumes create larger confidence intervals for mortality estimates.

Key Evidence for Recommendation 6

In one systematic review (22 studies) looking at institutional volumes, procedure-related morbidity was not significantly different in high-volume compared with low-volume hospitals (19%–46.5% in high-volume hospitals vs. 19%–43% in low-volume hospitals). However, a meta-analysis of procedure-related mortality favoured high-volume hospitals (OR: 0.73; 95% CI: 0.65 to 0.81; $p < 0.00001$). Improved 5-year survival was significantly associated with higher institutional volumes in three of seven studies evaluating that outcome[58].

In the updated literature search, procedure-related mortality was not significantly different in high-volume compared with low-volume hospitals in four of the five studies evaluating that outcome[60–63]. However, in 2013, Dikken *et al.*[63] 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 yielded only moderate-quality non-RCTs.

Recommendation 7

Quality metrics for lymph nodes, margin distances, perioperative mortality, and oncologic outcomes should be

met regardless of surgical technique (for example, open or minimally invasive).

Qualifying Statements for Recommendation 7

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

Key Evidence for Recommendation 7

Short-term outcomes (for example, blood loss, time to first flatus, length of hospital stay, and postoperative complications) favour laparoscopic compared with open gastrectomy[27–34]. Those observations are based on one systematic review and several more recent primary studies. Long-term cancer-related survival results are currently being examined in several RCTs.

CONCLUSIONS

Staging in gastric cancer should follow the recommendations outlined by Lerut *et al.*[9], in that all patients should be discussed at a multidisciplinary team meeting and CT imaging of chest and abdomen should always be performed. All other imaging can be considered based on clinical presentation. Because radiologic staging can 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 nonmetastatic gastric cancer, whereas a D1 LND is preferred in patients with T1 cancer, in palliative patients, and in patients with significant comorbidities. Moreover, at least 16 lymph nodes 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 be considered only for palliation of symptoms. Because higher-volume centres have a lower perioperative mortality rate, patients should be referred to higher-volume centres and those with adequate support to manage potential complications. The expected 30-day or in-hospital perioperative mortality rate should be less than 5%. To that end, the annual volume should be adequate to allow for determination of whether a hospital is achieving the standard. Laparoscopic resections should be performed to the same standards as those for open resections, by surgeons who are experienced in both advanced laparoscopic surgery and gastric cancer management.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: NC has published many scholarly papers and commentaries related to gastric cancer management; LK has received funds to act as a proctor with Medtronic, Ethicon, and CONMED Corporation; GK has received funds for travel support and to participate in advisory boards for multiple companies; and JR has been a principal investigator in gastric cancer clinical trials. All other authors declare that they have no conflicts of interest.

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