ABSTRACT

The 17th annual Western Canadian Gastrointestinal Cancer Consensus Conference (WCGGC) was held in Edmonton, Alberta, 11–12 September 2015. The WCGGC is an interactive multidisciplinary conference attended by health care professionals from across Western Canada (British Columbia, Alberta, Saskatchewan, and Manitoba) who are involved in the care of patients with gastrointestinal cancer. Surgical, medical, and radiation oncologists; pathologists; radiologists; and allied health care professionals participated in presentation and discussion sessions for the purposes of developing the recommendations presented here. This consensus statement addresses current issues in the management of gastric cancer.

Key Words Gastric cancer, stomach cancer, surgery, neoadjuvant therapy, chemotherapy, radiation


TERMS OF REFERENCE

Purpose
The aim of the Western Canadian Gastrointestinal Cancer Consensus Conference is to develop the consensus opinion of oncologists and allied health professionals from across Western Canada, attempting to define best care practices and to improve care and outcomes for patients with gastrointestinal cancers.

Participants
The conference welcomes medical oncologists, radiation oncologists, surgical oncologists, pathologists, radiologists, gastroenterologists, and allied health professionals from western Canada who are involved in the care of patients with gastrointestinal malignancies (Table 1).

Target Audience
The recommendations presented here are targeted to health care professionals involved in the care of patients with gastric cancer (GC).

Basis of Recommendations
The recommendations are based on presentation and discussion of the best available evidence. Where applicable, references are cited.

RECOMMENDATIONS

Prevention, Screening, and Surveillance in GC

Question 1
Should GC screening be performed in any population group?

Recommendations: Screening for GC is not recommended for the general population. In high-risk patients, screening can be considered on a case-by-case basis. However, the optimal screening method and frequency are not currently known. In patients with CDH1 mutations, screening gastroscopy is not effective, and prophylactic gastrectomy is recommended.

Summary of Evidence: In 2015, 3400 new cases of GC were diagnosed in Canada, making GC the 14th most common gastrointestinal cancer.
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cancer diagnosis. The 5-year relative survival in gc is 25%\(^1\). The geographic incidence shows marked variation, with the highest rates in East Asia, South America, and Eastern Europe, and the lowest rates in the United States and Western Europe\(^2\). Countries with a high gc prevalence, specifically Japan and Korea, have screening programs, because early detection is associated with better outcomes\(^3\)\^-\(^5\). The benefit of screening in average- to low-risk populations has not yet been demonstrated\(^6\).

Hereditary gc is a rare but distinct type of gc that accounts for 1\%-3\% of all gc cases\(^7\). Hereditary diffuse gastric cancer is a subtype of hereditary gc that has been attributed mainly to mutations in CDH1. Carriers of the mutation are at risk of a highly penetrant, aggressive, and early-onset diffuse type of gc\(^8\). Currently, no screening tests are available for early diagnosis in this patient population. Direct visualization with endoscopy tends to detect the cancer late in the disease process, and multiple random endoscopic biopsies often produce false-negative results\(^9\)\^-\(^10\). Therefore, for asymptomatic carriers of CDH1 mutations, prophylactic gastrectomy is recommended\(^7\).

**Question 2**
What is the optimal surveillance strategy for patients with gc after curative resection?

**Recommendations:** Currently, the best strategy for the follow-up of patients who have undergone surgical treatment with curative intent for gc is not known. Patient education and self-referral for abnormal symptoms are important. Periodic assessments are useful to address treatment-related complications, nutrition deficiencies (including vitamin B\(_{12}\) and iron), and psychosocial issues. In patients with a subtotal gastrectomy, eradication of Helicobacter pylori is recommended.

No available data support an improvement in quality of life (qol) or prolongation of survival with early detection of an asymptomatic recurrence by tumour markers or radiologic imaging. Routine imaging studies and bloodwork in asymptomatic patients are therefore not recommended.

**Summary of Evidence:** To date, all of the surveillance guidelines are based on low-level evidence or no evidence at all, because randomized controlled trials on this subject are lacking. Very few trials report anything other than the detection of recurrence or death as their primary endpoints, and the prognostic effect of early detection seems doubtful, given the poor survival of patients with recurrent gc\(^11\). The limited studies available to date have not shown a survival benefit for the detection of asymptomatic recurrence compared with patient-reported symptomatic recurrence\(^12\)\^-\(^13\). Furthermore, qol constitutes an important omission in the current literature. Whether ongoing surveillance improves or reduces patient qol is unclear because the available studies did not evaluate this outcome. Importantly, benign postsurgical complications, nutrition disorders, and the need for psychosocial support can be detected during follow-up visits. However, the effects of return visits and extra diagnostic tests—and the associated stress—must be also assessed\(^13\).

In patients requiring a gastrectomy, approximately 30\% subsequently experience feeding problems, with severe symptoms presenting in 1\%-2\%. The main symptoms are early postprandial satiety, loss of appetite, alteration of taste, reflux, dyspepsia, nausea or vomiting (or both), and diarrhea\(^14\). Weight loss is a frequent finding after gastric surgery, but is often temporary. Malabsorption can occur, related to the accelerated passage of a large bolus into the jejunum, vagal denervation (which increases the rapidity of oro-cecal transit), and bacterial overgrowth because of the decrease in gastric acid secretion, and pancreatic insufficiency\(^15\)\^-\(^16\). Nearly 30\% of patients present with microcytic (iron deficiency) or megaloblastic anemia (vitamin B\(_{12}\) deficiency). Iron deficiency is the most common anemia after gastric resection because of both acid and pepsin reduction, which are needed for iron absorption. Moreover, because of a lack of intrinsic factor secretion, vitamin B\(_{12}\) deficiency is common after gastric resection (typically after total gastrectomy)\(^17\). Bone diseases such as osteoporosis, osteopenia, and osteomalacia are commonly reported in gastrectomy patients. However, osteoporosis symptoms might not occur for 10 years or more after gastric surgery\(^18\).

The Maastricht iv/Florence Consensus Conference guidelines strongly recommend eradication of H. pylori in patients with previous gastric neoplasia who have undergone gastric surgery\(^19\)\^-\(^20\). However, the effect of H. pylori eradication in the prevention of metachronous gastric cancer remains a controversial issue. The two published randomized trials with short-term follow-up produced conflicting results\(^21\)\^-\(^22\). The effects of H. pylori eradication in preventing metachronous gc should be evaluated in well-designed long-term follow-up studies\(^23\).

**Issues in the Surgical Management of GC**

**Question 3**
What is the optimal surgical treatment of gc?

**Recommendations:** The choice of surgery depends on tumour location, clinical stage, and histologic type. The oncologic procedure should achieve clear margins with removal of the tumour. Intraoperative frozen section (irs) assessment of the margins is highly recommended. An extensive lymphadenectomy (at least 15 lymph nodes, as put forward by surgeons with expertise in gc) should be performed. Optimal surgical management can be guided by a diagnostic laparoscopy, particularly for patients at high risk of peritoneal disease.

**Summary of Evidence:** Complete resection with negative surgical margins and adequate lymph node dissection has been accepted as the only possible curative treatment for gc\(^24\). Multiple studies have demonstrated that microscopically positive (R1) margins after resection can be associated with worse prognosis, although the prognostic effect can differ between early- and advanced-stage gc\(^25\)\^-\(^31\). On multivariate analysis, the predictors for a positive margin include higher T stage, higher N stage, larger tumour size, and diffuse histologic type\(^24\)\^-\(^28\)\^-\(^30\). Use of irs of the resection lines is common for the assessment of margin status. The
accuracy of IRS has been reported to be approximately 98%, with both sensitivity and specificity being high. Few studies have examined whether conversion of a positive IRS to a microscopic negative margin (R0) is associated with improved outcomes. Based on the limited data available, converting patients with a positive IRS to an R0 margin was significantly associated with decreased local recurrence, but improvement in recurrence-free survival or overall survival (OS) has not been confirmed.

Nodal status in resected GC is one of the most important independent predictors of patient survival. In areas without screening programs, such as North America, patients often present late and have a high frequency of nodal involvement. Nodal dissection in GC varies internationally, with surgeons in countries such as Japan and Korea routinely performing the most extensive lymphadenectomies (D2 or greater); most surgeons in North America and many other Western countries perform more limited lymphadenectomies (D1 or less). The Japanese Gastric Cancer Association published detailed guidelines for the pathologic assessment and staging of GC, describing 4 nodal stations (N1–N4) with the D level of lymphadenectomy based on those definitions of lymph-node station level. A D1 lymphadenectomy is defined as removal of all N1 nodes, and a D2 dissection, as removal of all N1 and N2 nodes. Nonrandomized Asian series have demonstrated improved OS with D2 lymphadenectomy, making it the standard of care in East Asia. However, randomized Western studies and a meta-analysis of D1 compared with D2 lymphadenectomy failed to reproduce the OS benefit observed in the retrospective Eastern studies. In 1997, the Union for International Cancer Control and the American Joint Committee on Cancer, in the 5th edition of their staging manual, recommended that a minimum of 15 lymph nodes be assessed per patient. That recommendation was based on the nodal classification of N1 indicating 1–6 positive lymph nodes, N2 indicating 7–15 positive nodes, and N3 indicating more than 15 positive nodes, which was derived from outcomes based on retrospective databases. The 7th edition of the manual in 2010 revised the nodal classification system, with N1 indicating 1–2 positive nodes, N2 indicating 3–6 positive lymph nodes, N3 indicating 7–15 positive lymph nodes, and N3b indicating more than 16 positive nodes. With those changes, the Union for International Cancer Control and the American Joint Committee on Cancer now recommend that at least 16 lymph nodes be assessed per patient. Many groups have suggested that the number of lymph nodes assessed should vary according to stage and should be fewer than 15 in early GC and more than 15 in advanced cancers. A recent review of the current literature suggested that the more lymph nodes assessed, the less the stage migration and possibly the better the long-term outcomes, especially in more advanced GC.

**Question 4**
Should gastrectomy be limited to high-volume centres?

**Recommendations:** There is an association between higher-volume centres and improved outcomes. However, the definition of a “higher-volume centre” is controversial.

Surgeries should be performed in centres with adequate resources and supports, and by surgeons with training and expertise in oncologic gastric surgery. Centres performing GC surgery should actively participate in provincial programs to monitor quality.

**Summary of Evidence:** Given that the GC incidence is relatively low in Western countries, the annual hospital volume for GC resections in non-centralized regions might be low. Centralization could offer a chance to increase the volume. Increased hospital volume is associated with improved outcomes, which in turn are associated with lower short-term mortality and improved survival. An optimal hospital volume setpoint for oncologic gastrectomies has not been established. Improvement in hospital mortality based on cases per year has ranged from 9 or more cases per year to more than 63 cases per year. The variables that assist high-volume hospitals in improving mortality rates have been difficulty to study. For example, high-volume hospitals might be better equipped to manage postoperative complications. One study found that adverse event rates were similar in high- and low-volume hospitals after gastrectomy for GC; however, inpatient mortality was associated with the number and availability of intensive care beds and licensed nurses. That phenomenon is addressed as “failure to rescue” and is described not only for gastrectomy but also for other gastrointestinal operations. Other institutional variables that have been associated with improved outcomes in high-volume centres include preoperative investigations such as laparoscopy, endoscopic ultrasonography, and cardiac stress testing, which suggests improvement in patient selection for high-risk surgery.

**Neoadjuvant and Adjuvant Therapy for Early-Stage GC**

**Question 5**
What is the preferable adjuvant or neoadjuvant therapy for patients with operable GC?

**Recommendations:** It is not possible to define whether adjuvant or neoadjuvant therapy is preferable for patients with operable GC. The choice is defined by patient preference, patient characteristics, and surgical techniques. Evidence-based options included perioperative and postoperative therapy. In patients unable to receive...
postoperative radiation, adjuvant fluoropyrimidine-based chemotherapy (ctx) could be considered.

**Summary of Evidence:** Although surgery remains the cornerstone of curative therapy in gc, fewer than 25% of patients present with early-stage disease. The survival of patients with potentially curable nonmetastatic disease falls below 50% when the tumour invades through the muscularis propria, and below 20% with involvement of regional lymph nodes32. High rates of locoregional and distant relapse with subsequent poor survival have led to attempts to improve outcomes. In Western countries, randomized trials have now established either postoperative ccrt or perioperative ctx as standard adjuvant therapies. The approach taken in Asia, which has the highest incidence of gc, uses a different standard of care, consisting of extended resection followed by postoperative ctx alone.

Adjuvant ccrt was established in 2001, when the INT0116 trial reported by MacDonald et al.75 demonstrated a significant survival advantage for the use of postoperative ccrt, with the 10-year update76 demonstrating a persistent median os advantage for patients who received ccrt after surgery compared with those who received surgery alone. Criticisms of the INT0116 trial include substantial rates of acute toxicity, lower rate and extent of nodal dissections (54% received a D0 resection, 36% a D1 resection, and only 10% a D2 resection), relatively simple (and outdated) radiotherapy techniques, and the choice of ctx regimen [bolus 5-fluorouracil (5fu)]77. More recently, the ARTIST trial, a phase ii Korean study that required patients to have received a D2 resection or better, randomized patients to either postoperative capecitabine–cisplatin or capecitabine–cisplatin and radiotherapy. That trial failed to meet its primary endpoint, disease-free survival88. However, in an unplanned subgroup analysis, the patients with lymph node involvement and intestinal-type histology were observed to experience a statistically significant disease-free survival advantage. Furthermore, a more detailed analysis of first site of failure demonstrated a clinically relevant difference in patterns of relapse, with locoregional relapse occurring more frequently in the capecitabine–cisplatin arm than in the capecitabine–cisplatin and radiation arm (13% vs. 7%, p = 0.0033), but no difference in the rate of distant metastasis79. The Cancer and Leukemia Group B 80101 trial attempted to improve the ctx regimen, comparing postoperative epirubicin–cisplatin–5fu before and after ccrt with 5fu before and after ccrt (per the INT0116 regimen); on interim reporting, the authors did not find a survival benefit80.

A benefit with perioperative ctx was established by the British MAGIC trial, which demonstrated a statistically and clinically significant reduction in death and cancer recurrence for epirubicin–cisplatin–5fu administered before and after surgical resection compared with surgery alone81. A subsequent French trial reported similar results with the use of a perioperative regimen of cisplatin–5fu (cp)82. However, most of the patients enrolled in the French study had adenocarcinomas of the lower one third of the esophagus and of the gastroesophageal junction (75%), with only 25% of the randomized patients having gc.

An individual patient-level meta-analysis of adjuvant ctx in gc confirmed a 6% absolute benefit for 5fu-based ctx compared with surgery alone in all subgroups tested83. Historically, Asian studies have noted a greater benefit with adjuvant ctx than Western studies have. More recently, in a Japanese study (ACTS–gc), an os benefit was confirmed in stage ii and iii gc patients who, compared with their counterparts who received D2 resection alone, received a D2 resection followed by S1 (an oral dihydropyrimidine dehydrogenase inhibitor fluoropyrimidine not currently available in North America)84,85. The classic trial randomized stage ii or iii gc patients from South Korea, China, and Taiwan who underwent a D2 resection to observation or to 8 cycles of capecitabine–oxaliplatin86. Patients in the capecitabine–oxaliplatin arm experienced improved 3-year disease-free survival and os. However, more than half of those patients experienced grade 3 or 4 toxicities. Based on those two studies, the current standard of care in Asian countries is adjuvant ctx. Whether those data are applicable to gc patients in Western countries is unknown.

Based on currently available trial results, evidence about the treatment modality that is preferred choice (perioperative ctx, ccrt, or adjuvant ctx) is lacking. Clinical trials that are currently ongoing, including the ARTIST ii trial (Asian population) and the CRITICS and TOPGEAR trials (both in Western populations), might answer that question in the future.

**Systemic Therapy Options for Advanced Disease**

**Question 6**

What is the role of anti–vascular endothelial growth factor (vegf) or immune therapy in metastatic gc?

**Recommendations:** Bevacizumab has no demonstrated benefit compared with ctx alone in first-line therapy for metastatic gc. Ramucirumab monotherapy or ramucirumab with paclitaxel have level 1 evidence for benefit in second-line therapy.

Currently, immune therapy is considered investigational.

**Summary of Evidence:** Angiogenesis is the process by which blood vessels grow in an uncontrolled manner from the pre-existing vasculature, promoting tumour growth, development, and metastasis87–92. The members of the vegf family—vegfa, vegfb, vegfc, vegfd, vegfe, and placental growth factor—are involved in continually encouraging angiogenesis in neoplasms87–92,93. By binding to 1 of 3 vegf receptors, vegf results in receptor dimerization, phosphorylation, and downstream stimulation of cell growth and angiogenesis84–96. Expression of vegf is seen in 42%–49% of gc and has been associated with increased disease burden and worse clinical outcomes92,97–102. Bevacizumab is a humanized monoclonal antibody against vegfa. In the phase iii randomized controlled AVAgast trial, bevacizumab was added to capecitabine–cisplatin to study its effect on os in patients receiving first-line therapy for advanced gc103. Although an increased response rate and longer median progression-free survival (prs) were observed, there was no statistically significant difference in median os. Similarly, the AVAtor study,
conducted in China, also randomized advanced GC patients to first-line treatment with capecitabine–cisplatin and either bevacizumab or placebo, finding that the outcomes of interest, OS and PFS, were not different between the two arms. Bevacizumab is therefore not in routine clinical use in advanced GC.

Ramucirumab is a fully human monoclonal antibody against VEGF receptor 2. It has been shown to be beneficial as a single agent or in combination with CTX as second-line treatment in patients with metastatic GC. Ramucirumab as a single agent was associated with an increased median OS of 5.2 months compared with 3.8 months in patients receiving placebo. In the phase III RAINBOW trial, patients receiving second-line paclitaxel for metastatic GC were randomized to ramucirumab or placebo. The patients who received paclitaxel with ramucirumab experienced a median OS of 9.63 months, compared with 7.36 months in patients who received paclitaxel with placebo. Patients in the RAINBOW trial were required to have an excellent Eastern Cooperative Oncology Group performance status of 1 or 0. Among patients who received ramucirumab, increases in neutropenia, leucopenia, and hypertension were observed.

Interest in developing immunotherapeutic strategies for the treatment of GC is increasing. Immune checkpoints are one targeted pathway of interest. Immune checkpoints are inhibitory pathways hardwired into the immune system that are essential for maintaining self-tolerance and modulating the duration and amplitude of physiologic immune responses so as to minimize collateral tissue damage. However, those checkpoints can also allow for immune escape in cancer. Checkpoint pathways are regulated by ligand–receptor interactions. For example, programmed death-1 receptor (PD-1) and CTL-associated antigen 4 are inhibitory molecules whose presence on lymphocytes signifies a blunted immune response. The PD-1 molecule negatively regulates and downregulates T cell responses, and eventually apoptosis is initiated after a PD-1 ligand binds with PD-1. The PD-1 ligands PD-L1 and PD-L2 are negatively regulated and downregulates T cell responses, and eventually apoptosis is initiated after a PD-1 ligand binds with PD-1. The PD-1 ligands PD-L1 and PD-L2 are frequently expressed on tumour cells and can thus thwart the immune response. One approach to overcome that is the immune response inhibition has been to target immune checkpoints with blocking monoclonal antibodies. Early-phase studies in GC using antibodies such pembrolizumab and nivolumab showed encouraging results, but further studies are needed to confirm activity.

Question 7
What is the optimal sequence of CTX for metastatic GC?

Recommendations: For patients appropriate for systemic therapy, the choice and sequence of CTX is determined by the patient’s performance status, comorbidities, prior therapies, response to and duration of prior therapies, and patient preferences. Enrolment in a clinical trial should be considered where possible.

In patients with HER2-positive disease, first-line treatment with fluoropyrimidine, cisplatin, and trastuzumab should be offered. For disease without HER2 overexpression, there is evidence for the use of fluoropyrimidine–platinum combinations or fluoropyrimidine–irinotecan combinations in the first-line setting.

Acceptable second-line therapies include fluoropyrimidine–platinum combinations, fluoropyrimidine–irinotecan combinations, irinotecan monotherapy, docetaxel monotherapy, paclitaxel monotherapy, ramucirumab–paclitaxel, or ramucirumab monotherapy.

Summary of Evidence: Unfortunately, most patients with GC present with advanced disease, and of those who present at an earlier stage, many experience relapse or metastatic disease. Treatment options for advanced GC must take into account comorbidities, organ function, performance status, prior therapies, and patient preferences, and should include best supportive care (BSC) with or without CTX. A meta-analysis demonstrated a significant survival benefit when patients with advanced GC were treated with CTX compared with BSC alone. It also showed that the survival benefit with first-line combination therapy exceeded the benefit with single-agent therapy and that 3-drug regimens, adding either an anthracycline to CF or cisplatin to a 5FU–anthracycline regimen, also showed a survival benefit. The V325 study confirmed the benefit of triplet CTX by showing additional survival benefit when the 3-drug regimen of docetaxel, cisplatin, and 5FU was compared with CF in the first line; however, that benefit came at the expense of increased toxicity, particularly febrile neutropenia. Subsequently, a randomized phase III trial comparing epirubicin–cisplatin–capecitabine with FOLFIRI (5FU–leucovorin–irinotecan) met its primary endpoint, demonstrating improved time to treatment failure with the FOLFIRI regimen, with no difference in PFS, OS, or overall response rate. In addition, patients receiving the FOLFIRI regimen experienced significantly fewer grade 3 and 4 toxicities overall, with significantly fewer high-grade hematologic adverse events.

Based on the current evidence, no regimen is internationally recognized as standard or superior for the first-line management of advanced GC. However, in an estimated 10%–15% of patients with HER2-positive GC, the phase III TOGA trial demonstrated significantly improved OS, PFS, and overall response rate with the addition of trastuzumab to a CF doublet (median OS: 13.8 months vs. 11.1 months; hazard ratio: 0.74; 95% confidence interval: 0.60 to 0.91). The benefits were even more pronounced in the patients with a HER2 immunohistochemistry score of 3+ or 2+ and fluorescence in situ hybridization positivity (median OS: 16.0 months vs. 11.8 months; hazard ratio: 0.65). That regimen now represents a standard of care for such patients.

In patients with advanced GC and adequate performance status, improvements in OS and QoL are also associated second-line CTX compared with BSC. Monotherapy agents that have shown modest clinical benefits (compared with BSC) include irinotecan, paclitaxel, and docetaxel. A randomized phase III trial comparing weekly paclitaxel with irinotecan demonstrated similar efficacy for both regimens, but with different toxicities: increased grade 3 neuropathies in the paclitaxel arm and increased grade 3–4 febrile neutropenia in the irinotecan arm. As already described, ramucirumab has been shown to be beneficial as both a single agent and in combination with paclitaxel as second-line treatment in patients with metastatic GC.
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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: HL has served on advisory boards for Eli Lilly, Leo Pharma, Amgen, Celgene, Sirtex Medical, and Bayer; KEM has served on advisory boards for Eli Lilly and Leo Pharma; SG and JPM have served on advisory boards for Eli Lilly. The remaining authors declare that they have no conflicts to disclose.

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