CancerCare Manitoba
ActionCancerManitoba

Practice Guideline: Disease Management

Guideline for the Curative Treatment of Gastric Cancer

Date Updated: December 2018

CancerCare Manitoba Guideline
Disease Management – Gastric Cancer
Developed by: Adopted from CCO

Preface

At CancerCare Manitoba (CCMB) the Clinical Practice Guidelines Initiative (CPGI) seeks to improve patient outcomes through the development, dissemination, implementation and evaluation of guidelines for the management of common clinical scenarios encountered by cancer patients throughout the province.

This clinical practice guideline was created through the efforts of a large interdisciplinary group from CCMB in collaboration with community partners. Members of the CCMB Gastro-Intestinal Disease Site Group (DSG) and Departments of Gastroenterology, Medical Oncology, Radiation Therapy, Thoracic Surgery, and General Surgery have participated in its development.

The Gastro-Intestinal DSG will review and update this document every 3 years, unless emerging evidence from scientific research, or practice issues requiring urgent resolution dictate a need for immediate change in content.

Purpose

This document is intended as a guide to facilitate a common approach to the treatment of gastric cancer.

For this purpose, it may be used by qualified and licensed healthcare practitioners involved with the care of oncology patients, which may include (but is not limited to): physicians, surgeons, nurses, radiation therapists, pharmacists, psychosocial oncology caregivers, and dieticians at CCMB, and Community Oncology Program sites (CCPN sites, Uniting Primary Care and Oncology (UPCON) clinics and WRHA Community Oncology Program sites).

Disclaimer

This guideline document should be viewed as an evidence-based practice tool, and as such, it does not represent an exhaustive text on the subject of adjuvant systemic therapy for gastric cancer. Clinicians are advised to use it in their practice concomitantly with information from other evidence-based sources.

Use of this guideline in the clinical setting should not preclude use of the practitioner's independent clinical judgement, nor should it replace consultation with the appropriate oncology specialist when indicated (example: medical oncologist, radiation oncologist, family practitioner in oncology (FPO), hematologist, nurse practitioner/clinical nurse specialist, pharmacist, psychosocial oncology professional, and dietician).

It is the responsibility of the practitioner to develop an individualized disease or symptom management plan for each patient under his/her care, and ideally, this should take place within the context of a multidisciplinary team. The needs and preferences of the patient and the family should always be reflected in the plan of care.

CONTENTS

Guideline Recommendations

Recommendation #1

The Cancer Care Ontario Guidelines "Staging and Surgical Approaches in Gastric Cancer" [1] recommendations should be adopted in its entirety. The highlights of this document are:

1. Work Up Recommendations:
   - 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.

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.

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

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

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).

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).

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).

Recommendation #2

The Cancer Care Ontario Guidelines "Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer"[2] recommendations are as follows. Updated qualifying statements are addressed on page 10 of this document.

1. Postoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) based on the Macdonald approach[3] or perioperative epirubicin/cisplatin/5- FU (ECF) chemotherapy based on the Cunningham/Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) approach[4] are both acceptable standards of care. Choice of treatment should be made on a case-by-case basis. The panel also recommended the use for perioperative FLOT (fluorouracil plus leucovorin, oxaliplatin and docetaxel) based on preliminary published data at the time of guideline review.
   Note: This recommendation has been suspended in 2021 due to new evidence.

2. Adjuvant chemotherapy is a reasonable option for those patients for whom the Macdonald[3] and MAGIC[4] protocols are contraindicated.
   Note: This recommendation has been suspended in 2021 due to new evidence.

3. Patients with resectable gastric cancer should undergo a pre-treatment multidisciplinary assessment to determine the best plan of care. In addition to surgery, all patients should be considered for neoadjuvant and/or adjuvant therapy.

I. Introduction

Gastric cancer is a low incidence cancer with high mortality rates in Canada.[5] Surgery for gastric cancer is complex and of variable quality, at least in low incident non-Asian countries, with potential for morbidity and mortality.[6] Similarly, the fairly recent advent of adjuvant and neoadjuvant therapies for gastric cancer has made the landscape of treatment of this serious illness complex and at times confusing. Provision of substandard care decreases the survival rates of gastric cancer, and mechanisms to provide clarity, standardization and competence of treatment will be of significant benefit to the Manitoban population.

Thus, the purpose of this guideline is to outline the appropriate work-up and treatment of potential curable gastric carcinoma in Manitoba.

The guideline does not cover the following treatment scenarios:

- Carcinoma of the gastro-esophageal junction (GEJ), gastric GIST, gastric neuroendocrine tumours, and gastric lymphoma
- Unresectable and/or metastatic gastric carcinoma
- Gastric metastases from other primary tumours

The guideline is intended to outline the appropriate investigations of a known or suspected gastric carcinoma, as well as an overview of the appropriate use of chemotherapy, radiotherapy and surgery in treating this disease. The reliance on multidisciplinary care is also emphasized.

II. Scope of Guideline

Aim and Purpose

Development of this guideline was undertaken for the purpose of knowledge translation of the current standards in practice for the curative treatment of gastric cancer in Manitoba. The overall aim is to improve the standard of care received by this patient population, through application of evidence-based interventions and promotion of best practices.

Clinical Question #1

What are the appropriate work-ups steps and treatments for potentially curable gastric carcinoma in Manitobans?

Development Panel

Development Panel

Oncology Subspecialties CancerCare Manitoba/University of Manitoba	1 General Surgical Oncologist 1 Medical Oncologist 1 Radiation Oncologist
Gastrointestinal Disease Site University of Manitoba	1 Gastroenterologist
Surgery CancerCare Manitoba/University of Manitoba	1 General Surgeon 1 Thoracic Surgeon

End-Users

This guideline is written for use by clinicians providing care for the above mentioned patient population. Intended primarily for use by medical clinicians, the guideline may be of interest to trainees, allied healthcare staff, healthcare administrators, policy makers and possibly members of the general public.

III. Guideline Methodology

Using standard search strategies, the clinical practice guideline office performed a review of published literature to identify all existing published guidelines. Committee members reviewed each document and assessed for quality and appropriateness. The committee met in person on March 2, 2018 to review this evidence and for in-depth discussion.

The plan of review was as follows:

- Adopt a guideline(s) if deemed appropriate
- Adopt portions of guidelines if no single document was of sufficient quality
- Create a new guideline de novo if guidelines were of poor quality or not appropriate to our patient population or health system

The review meeting consisted of evaluating each guideline on the following criteria:

- Does it cover our stated purpose and scope?
- Is it evidence-based?
- Is it missing any significant areas or evidence with respect to work up and treatment?
- Are there general concerns regarding content or format?

Published Guideline Review

Ten guideline documents were identified in the literature search. On further review, two were found to be frankly out of scope of our goal and discarded. An in-depth discussion of the remaining eight occurred. Two guidelines were essentially a part A and B from the same organization (Cancer Care Ontario) and were considered a single comprehensive document for the purposes of our review. One further guideline (a 2018 guideline from the BC Cancer Agency) was reviewed after the in-person meeting, but was deemed to reflect similar information to the other documents. The ten articles reviewed are listed in Table 1.

Internal and External Review

Internal and external peer reviews were pursued, the results of which are appended to this guideline. The internal review consists of revision by the working group. An external review was undertaken by one radiation oncologist who completed a full review of the guideline document and submitted practitioner feedback comments. Feedback was reviewed and discussed.

Table 1. List of published guidelines reviewed.

Guideline Title	Guideline Group	Year
Gastric Cancer	Alberta Health	April 2016
HER2 Testing and Clinical Decision Making in Gastroesophageal Adenocarcinoma	ASCO	February 1, 2017
Guideline for the Surgical Treatment of Gastric Cancer	BC Cancer	2018
Gastric Cancer: ESMO Clinical Practice guidelines for diagnosis, treatment and follow-up	ESMO	2016
Staging and Surgical Approaches in Gastric Cancer	CCO	January 17, 2017
Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer	CCO	April 5, 2011
Systemic Therapy for Advanced Gastric Cancer	CCO	May 6, 2014
Gastric Cancer	NCCN	2017
Provincial Gastric and Gastro-Esophageal Junction Cancer Treatment Guidelines	SCA	June 2014
Western Canadian GI Cancer Consensus Conference	WC5	2015

Conclusions

The group unanimously agreed to the adoption of the Cancer Care Ontario guidelines for the curable treatment of gastric cancer.[1,2] These guidelines were felt to be comprehensive and evidence-based. Their guideline documents were also found to be easily readable for physicians and surgeons, with an appropriate amount of detail and explanation.

Of mention, the ESMO guideline was deemed to be of equivalent quality and scope. We favoured the Ontario guideline for its depth of explanation, including methodology, and readability, as well as its Canadian origin (and thus applicable to our health system). The BC guideline was similarly of good quality but only covered the surgical aspects of care, so not as comprehensive as required for our purposes. It should be noted that all three guidelines deliver essentially the same message.

The CCO guideline relating to staging and surgery dates from 2017 and is contemporaneous in all aspects. No alterations, or qualifying statements, were recommended by the committee. In regards to the non-surgical aspects of treatment, however, this aspect of the guideline is dated, with no other published guidelines in our search to replace it. Thus the committee felt it appropriate to adopt the 2011 guideline as a base for our recommendation and then add further data to it, as an informal mechanism of updating. The qualifying statements agreed to are listed below:

1. Clinical Trials. We wish to encourage enrollment of gastric cancer patients into clinical trials when feasible, and locally available. The landscape of gastric cancer treatment has seen significant improvements over the last two decades, since the publication of the first major randomized control trial showing benefit of adjuvant therapy in gastric cancer[3]; yet there is significant work still needed to improve our survival statistics and quality of life. Clinical trial enrolment is felt to be beneficial in that it ensures current high quality care and allows for the development of new treatment paradigms. It does require uncoerced and informed consent of the patient, with their acceptance of the inherent unknowns in experimental regimens, and often has strict enrolment criteria as well as limitations to where care can be delivered; as such, trial enrolment is not for everyone.

2. FLOT perioperative chemotherapy. The choice of perioperative chemo in stage 1B to 3 cancers should include the option of the FLOT (docetaxel, oxaliplatin, and fluorouracil/leucovorin) regimen.[7] The German AIO group published their results on this regimen in abstract form at ASCO 2017. These results show a dramatic improvement over the previous standard of ECF (epirubicin, cisplatin, and fluorouracil).[4] As the abstract results are extraordinarily compelling, the Canadian gastric cancer medical oncology community has widely adopted this protocol and we concur with that approach. FLOT should be considered for all advanced stage gastric cancer patients who are healthy enough for aggressive chemotherapy. As this data is still preliminary, review of patients through P and T or case conference mechanisms is prudent. Upon publication of final results, strong consideration to placing this regimen on formulary is recommended, assuming the final publication is congruent with the published abstract.

3. Additional trials. Several non-practice changing trials were discussed at our committee meeting. The CRITICS trial was one such trial.[8] This trial randomized patients to post-operative chemoradiotherapy versus chemotherapy alone in patients receiving preoperative chemotherapy and surgery for gastric cancer. The study found that a postoperative chemoradiotherapy regimen did not improve overall survival compared to chemotherapy therapy alone. It did note poor compliance to both postoperative regimens and sits as a reminder that all studies show patients to be less apt to tolerate therapy in the postoperative period. The ARTIST trial was also briefly discussed.[9] This trial compared postoperative chemotherapy to postoperative chemoradiotherapy in patients who had recovered from a D2 lymphadenectomy. This trial did not find an advantage to chemoradiotherapy in the intention-to-treat analysis, but post hoc analysis did reveal a potential advantage to that strategy in node positive patients, as well as those with intestinal-type histology. The relevance of this trial to our local population is also uncertain, as a majority of patients do not receive extended lymphadenectomy currently; as such, it does not supplant the information gained for the SWOG trial[3], but does provide for some reflection in the utility of radiation in the minority of patients with extended lymphadenectomies. Finally, there must be some note that many of our gastric cancer studies come from Asian populations, and in general, they report survival rates well in excess of what is seen in Western populations, regardless of what treatment protocol is used. The differences in patient population, screening, centralization of care, and treatment strategies make applicability of many Asian trials to be challenging to our provincial context. Thus, we must exercise caution in interpreting such data.

References

1. Coburn N, Cosby R, Klein L, Knight G, Malthaner R, Mamazza J, Mercer D, Ringash J. Staging and Surgical Approaches in Gastric Cancer. Toronto (ON): Cancer Care Ontario; 2017 January 17. Program in Evidence-based Care Guideline No.: 2-19. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer (accessed March 2, 2018)

2. Knight G, Earle CC, Cosby R, Coburn N, Youssef Y, Spithoff K, et al. Neoadjuvant or adjuvant therapy for resectable gastric cancer (ARCHIVED 2018). Toronto (ON): Cancer Care Ontario; 2011 Apr 5. Program in Evidence-based Care Evidence-based Series No.: 2-14 version 3.2011. Available at: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer (accessed March 2, 2018)

3. Macdonald JS, Smalley SR, Benedetti J, Hundahl SA, Estes NC, Stemmermann GN, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345(10):725-30.

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6. Mahar AL et al. A systematic review of the effect of institution and surgeon factors on surgical outcomes for gastric cancer. J Am Coll Surg. 2012 May;214(5):860-

7. Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. The Lancet 2019; 393(10184):1948-1957.

8. Cats A, Jansen EPM, van Grieken NPT, et al. Chemotherapy versus chemoradiotherapy after surgery and preoperative chemotherapy for resectable gastric cancer (CRITICS): an international, open-label, randomised phase 3 trial. Lancet Oncol. 2018 May;19(5):616-628.

9. Park SH, Sohn TS, Lee J, et al. Phase III Trial to Compare Adjuvant Chemotherapy With Capecitabine and Cisplatin Versus Concurrent Chemoradiotherapy in Gastric Cancer: Final Report of the Adjuvant Chemoradiotherapy in Stomach Tumors Trial, Including Survival and Subset Analyses. J Clin Oncol. 2015 Oct 1;33(28):3130-6.

IV. Cancer Care Ontario Staging and Surgical Approaches in Gastric Cancer (Guideline 2-19)

Guideline – Recommendations and Key Evidence

Ontario
Cancer Care Ontario
Action Cancer Ontario

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

N. Coburn, R. Cosby, L. Klein, G. Knight, R. Malthaner, J. Mamazza, D. Mercer, J. Ringash and the Surgical Management of Gastric Cancer Guideline Development Group

Report Date: January 17, 2017

An assessment conducted in October 2019 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

Section 1: Recommendations
Section 2: Guideline - Recommendations and Key Evidence
Section 3: Guideline Methods Overview
Section 4: Systematic Review
Section 5: Internal and External Review

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 Tstages (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.1
- 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/guidelinesadvice/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/guidelinesadvice/types-of-cancer/366

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V. Cancer Care Ontario Neoadjuvant Therapy for Resectable Gastric Cancer (Evidence-Based Series 2-14 Version 3.2011 ARCHIVED 2018)

Updated Guideline Recommendations

cancer care ontario | program in evidence-based care
action cancer ontario | programme de soins fondé sur des preuves

Evidence-Based Series 2-14 Version 3.2011: Section 1

Neoadjuvant or Adjuvant Therapy for Resectable Gastric Cancer: Updated Guideline Recommendations

G. Knight, C.C. Earle, R. Cosby, N. Coburn, Y. Youssef, K. Spithoff, R. Malthaner, R.K.S. Wong, and the Gastrointestinal Cancer Disease Site Group

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

Report Date: April 5, 2011

An assessment conducted in December 2018 ARCHIVED Evidence based Series (EBS) 2-14 Version 3. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes. The PEBC has a formal and standardized process to ensure the currency of each document (PEBC Assessment & Review Protocol)

EBS 2-14 Version 3 is comprised of 3 sections. You can access the full report here: https://www.cancercareontario.ca/en/guidelines-advice/types-of-cancer/351

Section 1: Updated Guideline Recommendations
Section 2A: Updated Evidentiary Base 2011
Section 2B: Original Evidentiary Base 2002
Section 3: EBS Development Methods and External Review Process

The guideline recommendations contained in Section 1 of this Evidence-based Series replace recommendations in previous versions of Guideline 2-14. These updated recommendations are based on a new systematic review of the relevant data from January 2002 to June 2010 (Section 2A) plus the original evidence up to January 2002 (Section 2B).

QUESTION

Should patients with resectable gastric cancer (Stage 1B [invasion of the muscularis propria] and above) receive neoadjuvant or adjuvant therapy in addition to surgery? Outcomes of interest are overall survival (OS), disease-free survival (DFS), and adverse events.

TARGET POPULATION

These recommendations apply to adult patients with potentially curable, surgically resectable (Stage 1B [invasion of the muscularis propria] and above) gastric cancer.

INTENDED USERS

These guidelines are intended for use by clinicians and healthcare providers involved in the management and referral of patients with resectable gastric cancer.

RECOMMENDATIONS

- Postoperative 5-fluorouracil (5-FU)-based chemoradiotherapy (CRT) based on the Macdonald approach (1) (Section 2A, Appendix 6) or perioperative epirubicin/cisplatin/5- FU (ECF) chemotherapy based on the Cunningham/Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) approach (2) (Section 2A, Appendix 6) are both acceptable standards of care. Choice of treatment should be made on a case-by-case basis.
- Adjuvant chemotherapy is a reasonable option for those patients for whom the Macdonald (1)□and MAGIC (2) protocols are contraindicated.
- Patients with resectable gastric cancer should undergo a pre-treatment multidisciplinary assessment to determine the best plan of care. In addition to surgery, all patients should be considered for neoadjuvant and/or adjuvant therapy.

KEY EVIDENCE

- Two secondary analyses of the Southwestern Oncology Group (SWOG)/Intergroup trial (1) were identified that reported updated survival data (3,4). These results are consistent with earlier data reported in Section 2B of this report. Updated results from Hundahl (3) indicated a median survival of 36 months for patients who received postoperative chemoradiotherapy (5-FU/Leucovorin) versus (vs.) 27 months for patients who underwent surgery alone (p=0.003). Relapse-free survival was 30 months vs. 19 months (p<0.001). A further update of this trial (4) demonstrates that the original SWOG/Intergroup trial results reported in 2001 are robust with almost identical results, even with more than 11 years of follow-up for both OS (hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.63 to 0.92; p=0.005) and DFS (HR, 0.66; 95% CI, 0.55 to 0.80; p<0.001), favouring postoperative CRT over surgery alone.

- The MAGIC trial (2) is the largest trial incorporating preoperative therapy to date and the only randomized trial with a perioperative approach. A significant benefit for perioperative ECF was reported for overall survival (HR, 0.75; 95% CI, 0.60 to 0.93; p=0.009) and progression-free survival (PFS) (HR, 0.66; 95% CI, 0.53 to 0.81; p<0.001).
- A meta-analysis by Fiorica (5) of five trials that provided 3-year mortality data indicated a non-significant benefit for postoperative chemoradiotherapy over surgery (odds ratio [OR], 0.79; 95% CI, 0.59 to 1.05; p=0.10). However, the meta-analysis of three trials that provided 5-year mortality data indicated a significant benefit for postoperative CRT over surgery (OR, 0.45; 95% CI, 0.32 to 0.64; p<0.00001).
- An individual patient data meta-analysis by the Global Advanced/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) group (6) found a modest advantage for postoperative chemotherapy for OS (HR, 0.82; 95% CI, 0.76 to 0.90; p<0.001) and for DFS (HR, 0.82; 95% CI, 0.75 to 0.90; p<0.001).

QUALIFYING STATEMENTS

- The Macdonald (1) and MAGIC (2) protocols have never been compared to each other in a single trial to determine if one is superior to the other.
- The mix of tumour sites in the Macdonald (1) and MAGIC (2) protocols were not the same. In the MAGIC trial (2), 74% of participants had a stomach tumour, 11.5% had a gastroesophageal junction (GEJ) tumour, and 14.5% had a lower esophageal tumour. In the Macdonald (1) trial, most participants had a tumour in the distal stomach. However, approximately 20% of participants had lesions present in the GEJ. There were no esophageal tumours.
- The Boige et al. (7) study comparing preoperative 5-FU/cisplatin vs. surgery alone demonstrated a significant improvement in OS and DFS with preoperative chemotherapy. Since these data are currently only available in abstract form, the Gastrointestinal Disease Site Group (Gastrointestinal DSG) does not recommend this treatment at this time. However, should these stated benefits be maintained when published in full and there are no material differences in reported toxicities, the DSG would consider recommending the Boige protocol in patients with resectable gastric cancer.
- Technical considerations pertaining to the delivery of radiation therapy are provided in the Discussion in Section 2A of this report.

COMPARISON FROM PREVIOUS GUIDELINE RECOMMENDATIONS

- The Macdonald (1) approach of postoperative chemoradiation continues to be recommended.
- Perioperative ECF chemotherapy based on the MAGIC protocol is now currently recommended, whereas in the previous version (Version 2) there was insufficient evidence to recommend a particular regimen.
- Adjuvant chemotherapy continues to be an option for those for whom the main recommended treatments options (i.e., the Macdonald or MAGIC protocols) are contraindicated.

FUTURE RESEARCH

Future trials should examine new molecular targets in patients with gastric cancer to account for the genetic and molecular variation in this disease. In addition, given the

results of S-1 trials in Asia as well as the improved safety profile of S-1 in the First-Line Advanced Gastric Cancer Study (FLAGS) trial in advanced gastric cancer (8), a trial of S-1 in the neoadjuvant and adjuvant setting in North America may be warranted. Finally, a trial of neoadjuvant chemoradiation would be helpful.

RELATED GUIDELINES

- PEBC Evidence-based Series #2-26: *Chemotherapy for Advanced Gastric Cancer* (available from: http://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=75973)

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VI. Implementation and Dissemination

The value of guidelines truly lies in their implementation and use. For that purpose, consideration was given to implementation during the drafting of this guideline document.

CancerCare Resources

It was recognized that resources would be needed to distribute these guidelines to the community. For that purpose, the guideline will be accessible online through the CancerCare Manitoba website. Online availability will be preceded by an e-blast notification with the website embedded. Announcement of the guideline and updates will be through established provincial communication channels: Community Oncology Program to CCPN rural sites, UPCON clinics and WRHA Community Oncology Program sites. Use of the guideline in clinic will be through the online version.

Educational Events

The guideline's recommendations were presented at Disease Site Group Meetings and the Cancer Surgery Update (2019).

Concordance Measurement and Performance Audit

A plan is being developed regarding the guideline concordance measurement and will be presented to the CCMB standards committee for approval. Briefly, a panel will review each gastric cancer case at CCMB and provide a confidential feedback form covering the key recommendations to the treating physicians/surgeons. Suggestions will be presented in an encouraging format. The audit and feedback process will be done under the auspices of the CCMB standards committee, and include the protections therein. This plan will be finalized and implemented after the settling of the Covid-19 pandemic.

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CCO Gastric Guideline used with permission December 2018.

VIII. Conflicts of Interest

In accordance with the CCMB policy no. 01.001, "Conflict of Interest", the authors of this guideline disclosed no conflicts of interest and declares that no commercial support was received during the development of this guideline.

IX. Appendix

Appendix 1

External Review:

Dr. Rebecca Wong, a Radiation Oncologist from the Princess Margaret Center in Toronto, Ontario, who was an author on the adopted CCO guidelines, was contacted to act as an external reviewer. Her completed checklist, comments, and our responses are included herein.

External Guideline Review Results

Dr. Rebecca Wong *Radiation Oncologist* *Princess Margaret Center* *Toronto, Ontario, Canada*	1. Scope of the guideline The stated purpose of the guideline is to outline the appropriate work up and treatment of potentially curable gastric carcinoma in Manitoba. On page 6, it is stated that the group agrees to adapt the CCO guideline (1,2). However, in the document provided, only guideline 2-14 was included. I do not see information for guideline 2-19 represented in this document. If it is only guideline 2-14 that is being included, then the recommendations will not be addressing the appropriate workup part of the objective. 2. Recommendations There is no section where I am able to review the actual recommendations from the panel to the practitioner. Is it the intention for the reader to refer to page 11-12 and use the statements provided here as the recommendation for Manitoba? The format used by the ITP guideline is more explicit – i.e. Having a section that states "Summary of recommendations". 3. Guideline Methodology (for adaptation) The main concern I would raise for the guideline as presented is the lack of a literature search for primary evidence when the guideline 2-14 in its current form is archived. "An assessment conducted in December 2018 ARCHIVED Evidence based Series (EBS) 2-14 Version 3. This means that the recommendations will no longer be maintained but may still be useful for academic or other information purposes". I agree providing a discussion on key evidence as on page 7 is a reasonable way of addressing any practice changing trials that should be considered, as an evidence based guided document, it seems inadequate (especially when the source document is listed as archived). If the guidelines panel is happy to limit the literature

	review to existing guidelines as use that as the reference point as stated, including the literature search strategy employed would enhance the methods employed. A statement to the effect that the references of existing guideline, expert panel was used to identify potential practice changing trials that may be missed may be worth including in the methods section. A "matrix" aligning the questions and recommendations from the published guideline review may serve to provide support that the recommendations are consistent with other existing guidelines that you have reviewed. 4. Documents & references I would like to point out that the version included in the documents is titled Evidence-Based Series 2-14 Version 3.2011. The most recent version posted on the CCO website is titled Evidence-Based Series 2-14 Version 3 ARCHIVED 2018) The reference for FLOT perioperative chemotherapy can also be updated to the full published article Lancet 2019; 393: 1948–57 +/- the accompanying commentary (Published Online April 11, 2019 http://dx.doi.org/10.1016/ S0140-6736(18)33189-1)

External Guideline Review Checklist

1. Are you responsible for the care of patients for whom this draft guideline report is relevant? This may include the referral, diagnosis, treatment, or follow-up of patients.	Yes ☒	No ☐	Unsure ☐
If you answered "*No*" or "*Unsure*", please return this questionnaire to the address on the reverse side. If you answered "*Yes*", please answer the questions below and return to the address on the reverse side.			
	Strongly agree	Neither agree or disagree	Strongly disagree
2. The rationale for developing a guideline, as stated in the *Preface and Introduction* sections of this draft report, is clear.	☒	☐	☐
3. There is a need for a guideline on this topic.	☒	☐	☐
4. The literature search is relevant and complete (e.g., no key trials were missed nor any included that should not have been) in this draft guideline.	☐	☒	☐
5. I agree with the methodology used to summarize the evidence included in this draft guideline.	☒	☐	☐
6. The results of the trials described in this draft guideline are interpreted according to my understanding of the data.	☒	☐	☐
7. The draft recommendations in this report are clear.	☒	☐	☐
8. I agree with the draft recommendations as stated.	☒	☐	☐
9. The draft recommendations are suitable for the patients for whom they are intended.	☒	☐	☐
10. The draft recommendations are too rigid to apply to individual patients.	☐	☐	☒
11. When applied, the draft recommendations will produce more benefits for patients than harms.	☒	☐	☐
12. The draft guideline report presents options that will be acceptable to patients.	☒	☐	☐
13. To apply the draft recommendations will require reorganization of services/care in my practice setting.	☐	☒	☐
14. To apply the draft recommendations will be technically challenging.	☐	☐	☒
15. The draft recommendations are too expensive to apply.	☐	☐	☒
16. The draft recommendations are likely to be supported by a majority of my colleagues.	☒	☐	☐
17. If I follow the draft recommendations, the expected effects on patient outcomes will be obvious.	☒	☐	☐
18. The draft recommendations reflect a more effective approach for improving patient outcomes than is current usual practice. (if they are the same as current practice, please tick NA). NA ☒	☐	☐	☐
19. When applied, the draft recommendations will result in better use of resources than current usual practice (if they are the same as current practice, please tick NA). NA ☒	☐	☐	☐
20. I would feel comfortable if my patients received the care recommended in the draft guideline.	☒	☐	☐
21. This draft report should be approved as a practice guideline.	☒	☐	☐
22. If this draft report were to be approved as a practice guideline, how likely would you be to make use of it in your own practice?	☒	☐	☐
23. If this draft report were to be approved as a practice guideline, how likely would you be to apply the recommendations to your patients?	☒	☐	☐

Response to External Review:

Dr. Pamela Hebbard

I kindly thank Dr. Wong for her time and insightful feedback on our guideline process. Her comments are all well taken and used to strengthen the guideline document and process.

Modifications/Actions	
1	The Manitoba guideline references CCO guidelines 2-19 and 2-14. We will ensure that this is more clearly noted in our document.
2	A recommendation section will be added to the MB document so that clinicians do not have to flip between the CCO guidelines and our own.
3	The guideline committee was given instructions to review existing guidelines first and adopt or adapt one if possible. As all committee members are practicing in gastric cancer treatment, we did have a good working knowledge of missing studies due to the age of the guidelines reviewed and included this in our discussion portion. The guideline literature search was performed by staff no longer under the employment of CancerCare Manitoba and given the length of time since we did the exercise, I do not have a memory of the search strategy. Unfortunately, this item will remain unreconciled, but I do take the comment under advisement to employ during any future update of the guideline.
4	The reference updates will be noted and have been made.

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CCMB Clinical Practice Guideline: Disease Management
Guideline for the Curative Treatment of Gastric Cancer