Clinical practice guidelines have been developed after multi-disciplinary consensus based on best available literature. As the name suggests, these are to be used as a guide only. These guidelines do not replace physician judgment which is based on multiple factors including, but not limited to, the clinical and social scenario, comorbidities, performance status, age, available resources and funding considerations. The Saskatchewan Cancer Agency disclaims all liability for the use of guidelines except as expressly permitted by the Agency. No portion of these guidelines may be copied, displayed for redistribution to third parties for commercial purposes or any non-permitted use without the prior written permission from the Agency.

Recommendations for drug treatment presented in the Agency’s guidelines for a cancer site may not reflect provincial cancer drug funding. Please refer to the current Saskatchewan Cancer Agency drug formulary at www.saskcancer.ca for information on cancer drug listing and funding.

Benefits and risk of the proposed treatment should be discussed with patient.

Participating in clinical trials is encouraged when available. Involvement of a multidisciplinary team is strongly recommended.

- Gastric cancer is a heterogeneous disease both biologically and genetically. It is a leading worldwide health problem and a major cause of cancer-related death in the world.

- More than 90 percent of stomach cancers are adenocarcinomas. The incidence of distal gastric carcinoma (gastric body and antrum) has declined dramatically in recent years, while the incidence of adenocarcinoma of the gastroesophageal junction (GEJ) and proximal stomach has increased steadily. The increasing incidence has paralleled the rise in incidence of esophageal adenocarcinoma.

- According to Seventh edition of AJCC Cancer Staging System for Gastric Cancer, tumours arising at the GE junction or in the cardia of the stomach within 5 cm of the GE junction that extend into the GE junction or esophagus (the so-called Siewert III GE junction tumours) are staged as esophageal rather than stomach cancers. However, tumours that arise beyond 5 cm of the GE junction or are within 5 cm of the GE junction but without extension to the esophagus or GE junction are still classified as gastric cancers.

- The term "GEJ tumour" reflects the frequent difficulty in separating the primary location of distal esophageal and proximal gastric cancers; their natural history, response to therapy, and overall prognosis appears to be similar.

- Coincident with these epidemiologic changes in anatomic distribution and histological subtypes, the treatment of advanced gastric and esophageal cancers has converged, and the majority of clinical trials conducted since the mid 1990s now include patients with gastric, esophageal, or GEJ cancer, regardless of histology.
A. ASSESSMENT AND INVESTIGATIONS

- Given the complex nature of gastric cancer management, all patients should be evaluated by a multidisciplinary team including gastroenterologists, pathologists, radiologists, nuclear medicine specialists, surgeons, medical and radiation oncologists, and palliative care specialist (for advanced disease). Staging is based on the AJCC TNM system. T signifies depth of invasion into the gastric wall, N status describes the number of nodes involved and M indicates metastatic disease. Extraperigastric adenopathy including those in the hepatoduodenal, rectorpancreatic, portal, mesenteric, and paraaortic are classified as distant metastases regardless of the number of nodes involved because involvement portends a very poor prognosis. Clinical staging involves a combination of clinical and radiological investigations briefly outlined below. The purpose of which is to determine which patients are potentially curable (Stage I-III) and those that are not (Stage IV).
  - History and physical examination
  - CT scan of chest and abdomen and pelvis
  - Esophagogastroduodenoscopy to identify and biopsy any suspicious intraluminal masses and confirm if the mass arises in the stomach or the esophagus, and if linitis plastica is present.
  - Nutritional evaluation

For multimodality therapy further studies may be required for T and N staging
  - Endoscopic ultrasound examination (EUS): Endoscopic ultrasound (EUS) is helpful to determine the proximal and distal extent of the tumour and to assess tumour depth and lymph node status, although it is less useful in antral tumours. For clinical T1/T2 disease, EUS is recommended to clarify clinical T stage and to ascertain if preoperative chemotherapy is indicated.
  - MRI for T staging and invasion of adjacent structures.
  - PET/CT scan can be considered for patients undergoing multimodality curative treatment. PET may not be helpful in some patients with mucinous or T1 tumours. False negative rates for PET are high in gastric cancer, due to the absence of the GLUT-1 transporter in mucinous and signet ring histologies.
  - Diagnostic laparoscopy for >T1 disease for occult disease. If staging scans are negative, a laparoscopic evaluation - with peritoneal washings for cytology, to rule out peritoneal metastases is suggested prior to surgical resection.
    - 20-30% will have peritoneal metastases.
    - In absence of obvious peritoneal metastases, positive peritoneal cytology is considered to be M1.

B. TREATMENT

- Radical resection in gastric cancer is an integral part of treatment for curative intent. Unfortunately the rates of local and distant failures are high following surgery alone. Therefore adjuvant or perioperative regimens of chemo-radiotherapy or chemotherapy respectively have been investigated. Both progression free and overall survival are improved with either protocol compared to surgery alone (Figure 1 Appendix).
- 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 need to be considered for neoadjuvant and/or adjuvant therapy.
- Indicators of unresectability include metastatic disease, encasement of major vascular structures such as the aorta or celiac axis or non-perigastric lymph node involvement. Extensive involvement of the submucosal lymphatic plexus with tumour (linitis plastic)
occurs in about 5% of gastric cancers. It is associated with a very poor prognosis and may not be amenable to curative resection.

- Patients with tumours that invade the submucosa (T2 or higher) or suspicious perigastric lymph node involvement should be reviewed by a multidisciplinary team to determine the best course of multimodality therapy.
- Treatment for \textit{H. pylori} infection is recommended because \textit{H. pylori} infection is a well-defined risk factor for both early and invasive gastric cancer, and chronic infection is associated with tumour recurrence and the development of metachronous dysplasia or cancer following treatment.

C. MANAGEMENT BY STAGE

C1. Stage 0 Tis (Carcinoma in situ- no invasion into lamina propria)
- Endomucosal resection
- Subtotal gastrectomy
- Gastrectomy

C2. Stage IA (T1N0)
T1a- Tumour invades lamina propria or muscularis mucosae-
- Endomucosal resection
- Subtotal gastrectomy
- Gastrectomy
T1b- tumour invades submucosa
- Gastrectomy

C3. Stage IB-Stage IIIC
- For gastric and gastro-esophageal cancer pre-operative chemotherapy with ECF/ECX (epirubicin, cisplatin, 5-fluorouracil /epirubicin, cisplatin, capecitabine), for 3 cycles followed by surgery followed by 3 cycles of chemotherapy as per MAGIC protocol is one of the standard options (see section G). Gastro-esophageal cancer should be treated as per CROSS protocol in a timely fashion.
- Alternatively for patients who undergo upfront surgery, adjuvant chemoradiation as per the Inter-group 0116 protocol is preferred approach in patients with good performance status. INT-0116 involved adjuvant 5FU/LV x 1 cycle, then 2 cycles concurrent with RT to 45Gy, then a further 2 cycles (see section G1).
- Postoperative -adjuvant chemotherapy alone may be an option for selected patients with node-negative disease following D2 resection who are not candidates for adjuvant chemoradiation (ARTIST- Six courses of postoperative capecitabine plus cisplatin).
- For GE junction cancers, patients may be treated with neoadjuvant Carbo/Taxol concurrent with radiotherapy, followed by surgical resection according to the CROSS trial protocol, which included primarily distal esophageal (58%) and GE junction (24%) tumours. Eligible patients were those with primary tumours < 8cm in length and ≤ stage T3N1.
- The value of pre-operative chemoradiation for patients with resectable gastric cancer (excluding GE junction) remains unclear. While some good Phase 2 and 3 results have been demonstrated, it has yet to be evaluated in a randomized fashion.
- For patients with poor performance status who are not candidate for radical surgery palliative radiotherapy (40Gy/16 fractions, 36Gy/12 fractions, 30Gy/10 fractions, 20Gy/5 fractions, 8Gy/1 fraction and or palliative chemotherapy in combination with best supportive care can be considered.
C4. Stage IV

- Palliative chemotherapy may be given to help improve symptoms and quality of life, and extend survival in appropriately selected patients.
- Currently approved chemotherapeutic agents for advanced gastric carcinoma (HER2 negative) include: 5-fluorouracil (5-FU), capecitabine, cisplatin, epirubicin, docetaxel, and irinotecan.
  - The most commonly used regimens are:
    - 5-FU and cisplatin
    - Epirubicin, cisplatin and 5-FU (ECF) or Epirubicin, cisplatin capecitabine (ECX) or Epirubicin, oxaliplatin, capecitabine (EOX)
    - 5FU and oxaliplatin (FOLFOX)
- The choice and sequence of chemotherapy is determined by disease-related factors, patient factors and patient preferences as assessed by the medical oncologist. In patients with good performance status combination therapy can be considered (see section H). In patients with poor performance status or impaired creatinine clearance, consider carboplatin instead of cisplatin (See appendix and refer to Saskatchewan Cancer Agency Gastrointestinal Cancer Chemotherapy protocols for indications, dosing and eligibility criteria).
  - First line combination therapy – Cisplatin/5FU and the three drug combinations with ECF, ECX, EOX, or FOLFOX are acceptable regimens for HER2 negative tumour. DCF has been associated with substantial grade 3-4 toxicities and is not routinely recommended. Response rates and survival are modestly better with the three drug combinations. Cisplatin /5-fluorouracil /Herceptin for adenocarcinoma of stomach and GE junction cancer. Patients who are responding after 6 cycles of chemotherapy with trastuzumab may continue with maintenance single agent trastuzumab until disease progression.
  - 2nd line –Taxanes (docetaxel or paclitaxel) or irinotecan alone or in combination with 5FU (FOLFIRI) can be considered in patients with good performance status. Ramucirumab alone or in combination with paclitaxel is an option for patients with good performance status who have disease progression on prior treatment with 5-FU or platinum-containing chemotherapy and can be considered if access is available.
- Palliative radiotherapy (40Gy/16 fractions, 36Gy/12 fractions, 30Gy/10 fractions, 20Gy/5 fractions, 8Gy/1 fraction) may be given to relieve dysphagia, obstruction or bleeding.
- Palliative gastrectomy in highly selected patients with recurrent bleeding or obstruction following palliative radiation attempts.
- Palliative care team should be involved, early in patients care, for pain and symptoms management. Nutrition and psychosocial support should be provided to the patients and their family.

D. FOLLOW UP AFTER CURATIVE THERAPY

Follow-up investigations should be tailored based on disease stage, adjuvant treatment provided, performance status, and clinical signs and symptoms. There is lack of level 1 evidence with respect to optimal follow up of patients with stomach and GE junction cancer who are treated with curative intention. All patients should be educated to seek medical attention if they developed abnormal symptoms.
- In patients treated with curative intent: history and physical examination every 3–6 months for the first 3 years then every 6–12 months for the next 2 years and annually thereafter.
- Routine imaging studies such as thoracoabdominal CT scan, abdominal ultrasound and chest x-ray are not recommended and can be performed as clinically indicated.
- Endoscopic examination as clinically indicated.
- Laboratory testing including CBC, serum chemistry, LFT, and CEA only as clinically indicated.
Nutritional counseling for all; vitamin B12 supplementation in patients who have had proximal or total gastrectomy

E. SURGICAL APPROACHES

E1. Primary Tumour
- Total gastrectomy with regional lymphadenectomy -if tumour arises in the body and extends to within 6 cms of cardia or antrum.
- Proximal subtotal gastrectomy or total gastrectomy with distal esophagectomy-for tumours arising within the gastric cardia or involving the gastroesophageal junction (epicentre of tumour within stomach- Siewert type III)
- Distal subtotal gastrectomy-distal tumours
- Early gastric cancers (T1a) may be amenable to endoscopic resection if they are well-differentiated, ≤2 cm, confined to the mucosa and not ulcerated.

E2. Level of lymphadenectomy
- The degree of lymphadenectomy that is required for gastric resection is a point of controversy between surgeons in Eastern Asia and the Western world. Lymph node dissection can be classified as D0, D1, or D2.
- D0 involves incomplete resection of locoregional nodes. D1 refers to the removal of greater and lesser omental lymph nodes (perigastric). D2 is a much more involved dissection including D1 nodes as well as nodes along the celiac plexus, common hepatic artery, splenic hilum and artery.
- Experience from both observational and randomized trials in Asian population has demonstrated that D2 dissection leads to superior outcomes compared with D1. The Dutch and MRC ST01 trials failed to demonstrate any initial survival advantage with D2 resection. However, fifteen year follow-up results from the Dutch trial demonstrated fewer locoregional recurrences and gastric cancer-related deaths (37% vs. 48%) with D2 resection, as well as a non-statistically significant OS benefit (29% vs. 21%, p = 0.34). This was slightly offset by an increase in postoperative mortality and morbidity. A meta-analysis of 12 randomized, controlled trials confirmed no overall survival benefit for D2 lymphadenectomy, although a benefit was seen among patients who had resection without a splenectomy and/or pancreatectomy.
- It has been therefore argued that if the morbidity and mortality of D2 resection can be decreased by performing resections in high volume centres, this can translate to better outcomes. At present most guidelines recommend a D1 lymphadenectomy with the goal of evaluating at least 15 lymph nodes.

F. PATHOLOGY & BIOMARKERS IN GASTRIC CANCERS

F1. Pathology
Specimen: specify
- Type
- Procedure
Tumour: specify
- Site
- Size
- Histologic type
- Histologic grade
- Microscopic tumour extension
- Margins: proximal, distal, omental (radial), deep (for endoscopic resections)
- Treatment effect (if neo-adjuvant therapy given)
- Lymph-Vascular invasion
• Perineural invasion
• TNM
  o Lymph nodes: number examined, number involved
• BHer2/neu status in patients with adenocarcinoma of gastro-esophageal junction or gastric cancer with distant metastasis (See biomarkers).

F2. Biomarkers
• Biomarkers can be investigated at various levels: genetic analysis including polymorphism evaluation, gene expression profiling or DNA sequencing; transcriptional assays such as reverse transcriptional polymerase chain reaction (RT-PCR) for mRNA level detection and transductional tests such as immunohistochemistry for protein detection with the latter being the most cost effective.
• Despite recent developments in gene sequencing and molecular diagnostics, the role of biomarkers remains controversial. Biomarkers in gastric cancer GC can be described as diagnostic, prognostic, predictive and therapeutic markers.

F2A. Diagnostic Biomarkers
• Unlike markers for colon (CEA) and pancreatic cancer (Ca 19-9), a specific biomarker suggestive of gastric carcinoma that may be used for screening has yet to be elucidated. Currently, there remains a paucity of noninvasive biomarker-mediated techniques for early detection of gastric carcinoma.

F2B. Prognostic Biomarkers
Certain proteins when overexpressed have been identified to confer an increased invasiveness and poorer survival. These include urokinase-type plasminogen activator (uPa), VEGF, MET, MYC, tie-1, protein tyrosine kinase, CD44v6, PDGF-A, TGF-beta, and cyclin D2. Underexpressed proteins that confer this same result include loss of p27 (Kip1), p21 (CIP1), plasminogen activator inhibitor type-1, and tissue-type plasminogen activator [T].
• Elevated serum concentrations of tissue inhibitor metalloproteinase (TIMP)-1, interleukin 10, hepatocyte growth factor, soluble receptor for IL-2, and soluble fragment of E-cadherin are associated with a greater invasiveness and poorer survival.

F2C. Predictive Biomarkers
• Identification of molecular markers of chemosensitization would provide information allowing prediction of the patient’s likely response to treatment. Overexpression of p53 by immunohistochemistry of locally advanced GCs was found to indicate a lower response rate to neoadjuvant cytotoxic therapy. Expression of thymidine phosphorylase and thymidine synthase predict response to fluorouracil agents, and expression of BAX and Bcl-2 confer chemoresistance.

F2D. Therapeutic Biomarkers
• Current regimens in the treatment of gastric cancer have limited impact on improving prognosis and overall survival. A greater understanding into the molecular carcinogenesis of GC is required to optimally stratify patients and to guide targeted therapy. Currently targeted therapy is limited to the HER2 biomarker.

F2D1. HER1 & HER2
• The Human epithelial growth factor receptor (HER) family is composed of four receptors: HER1 (EGFR or ErbB1), HER2 (ErbB2), HER3 (ErbB3) and HER4 (ErbB4).
• Overexpression of EGFR is reported to be a poor prognostic factor, associated with the presence of lymph node metastases, higher stage, and poor survival. This biomarker is a therapeutic target, and monoclonal antibodies against EGFR (cetuximab, panitumumab) have been developed.
• There remains controversy whether a separate scoring system is required for immunohistochemical expression of Her2 positivity in GC or whether the well-recognized scoring system for breast is acceptable. In gastric cancer patients, HER2 overexpression is generally correlated with an aggressive disease course, shorter survival and an overall poor outcome. A meta-analysis including 42 publications found that the majority (72%) of publications concluded HER2 positivity confers a poor survival and/or clinicopathological characteristics including serosal invasion, lymph node metastases, disease stage and/or distant metastases. There are, however, studies that reported no difference in prognosis between HER2 positive and negative tumours.

• Based on the result of ToGA trial (see D6a), trastuzumab should thus be offered to patients with IHC grade 3+ and those with 2+ that showed positivity on FISH (a HER2/CEP17 ratio of 2.0). Several trials have targeted HER2 using a combination of different drugs including lapatinib (EGFR and HER2 inhibitor) and pertuzumab which binds a different area on HER2 than trastuzumab.

F2D2. EGFR2, MET, EGFR2

• Human epidermal growth factor receptor 2, MET and FGFR2 oncogenic driver alterations (gene amplification and overexpression) occur in three largely distinct molecular segments in GC. A significant proportion of HER2-negative patients may potentially benefit from MET- or FGFR2-targeted therapies.

G. ADJUVANT AND NEOADJUVANT THERAPY IN LOCALIZED GASTRIC AND GE JUNCTION CANCERS

G1. Adjuvant chemoradiation therapy

• Following potentially curative resection of gastric or GE junction cancer (T1-4, N0-1), 556 patients were randomly assigned to observation alone or adjuvant combined chemoradiotherapy. The majority of tumours were T3/T4, and 85 percent had nodal metastases. Treatment comprised of one cycle of FU (425 mg/m² per day) and leucovorin (20 mg/m² per day) daily for five days, followed one month later by RT (45 Gy in daily 1.8 Gy fractions) given with concurrent FU and leucovorin (400 mg/m² and 20 mg/m², respectively) on days 1 through 4, and on the last three days of RT. Two more five-day cycles of chemotherapy (FU 425 mg/m² per day and leucovorin calcium 20 mg/m² per day) were given at monthly intervals beginning one month after completion of chemoradiotherapy.

• Three-year disease-free (48 versus 31 percent) and overall survival rates (50 versus 41 percent) were significantly better with combined modality therapy, and median survival was significantly longer (36 versus 27 months). Benefits were maintained with longer follow-up (five-year overall survival 43 versus 28 percent, HR 1.32 (95% CI 1.10-1.60).

• CALGB 80101, a US Intergroup study, compared the INT0116 protocol regimen (infusional 5FU with RT) versus postoperative ECF before and after FU plus concurrent RT in 546 patients with completely resected gastric or EGJ tumours that extended beyond the muscularis propria or were node positive. Overall survival, the primary endpoint, was not significantly better with ECF (at three years, 52 versus 50 percent for ECF and FU/LV, respectively).

G2. Peri-operative chemotherapy

• In the United Kingdom Medical Research Council MAGIC trial, 503 patients with potentially resectable gastric (74 percent), distal esophageal (11 percent), or EGJ adenocarcinomas (15 percent) T2 or higher were randomly assigned to surgery alone or surgery plus perioperative chemotherapy (three preoperative and three postoperative cycles of ECF).

• A higher proportion of chemotherapy-treated patients with gastric cancer who underwent radical surgery had a potentially curative procedure (79 versus 70 percent), and significantly
more had T1/2 tumours (52 versus 37 percent) and N0/N1 disease (84 versus 71 percent). Chemotherapy was well tolerated overall and fewer than 12 percent of all patients had serious (grade 3 or 4) toxic effects. However, only 104 (42 percent) were able to complete protocol treatment, including surgery and all three cycles of the postoperative chemotherapy.

- Despite this, overall survival was significantly better in the chemotherapy group (HR for death 0.75, 95% CI 0.60-0.93) as was progression-free survival (HR for progression 0.66). The 25 percent reduction in the risk of death favoring chemotherapy translated into an improvement in five-year survival from 23 to 36 percent. Local failure occurred in 14 percent of the chemotherapy-treated patients compared to 21 percent of those undergoing surgery alone. Distant metastases developed in 24 and 37 percent of patients, respectively.

G3. Adjuvant chemotherapy
- The benefit of adjuvant therapy using oxaliplatin based therapy was evaluated in the multicentre CLASSIC trial, in which 1035 patients with stage II, IIIA, or IIIB gastric cancer were randomly assigned to eight 21-day cycles of capecitabine (1000 mg/m² twice daily in days 1 to 14) plus oxaliplatin (130 mg/m² on day 1) or surgery alone after D2 gastrectomy. At a median follow-up of 34 months, chemotherapy was associated with a significant improvement in three-year disease-free survival (74 versus 59 percent, HR for death 0.56, 95% CI 0.44-0.72), with only a borderline statistically significant improvement in overall survival (83 versus 78 percent, HR 0.72, 95% CI 0.52-1.00). However, with longer follow-up, the improved overall survival with chemotherapy was statistically significant (five-year overall survival 78 versus 69 percent, HR for death 0.66 percent, 95% CI 0.51-0.85).
- In ARTIST trial, 458 patients with complete resected gastric cancer and a D2 lymph node dissection were randomly assigned to six courses of postoperative capecitabine plus oxaliplatin or two courses of postoperative XP followed by chemoradiotherapy (45 Gy RT with concurrent daily capecitabine [825 mg/m² twice daily]) and two additional courses of XP. Compared to chemotherapy alone, the addition of RT to XP chemotherapy did not significantly reduce recurrence rates, although in unplanned subgroup analysis, patients with nodal metastases had superior disease-free survival with combined therapy as compared to XP alone.

H. SYSTEMIC THERAPY IN ADVANCED GASTRIC & GE JUNCTION CANCERS

H1. Chemotherapy versus best supportive care
- In a meta-analysis of three trials comparing chemotherapy versus best supportive care, there was a significant benefit in overall survival in favor of chemotherapy (hazard ratio [HR] 0.37; 95% CI 0.24 -0.55), which translated into an improvement in median survival from 4.3 to 11 months. Chemotherapy should be considered for patients with appropriate performance status.

H2. Single agent chemotherapy
- Doxorubicin, cisplatin, 5-fluorouracil (5-FU) and etoposide are associated with modest response rates of short duration (usually less than six months). Carboplatin has not been as widely studied as cisplatin, but it appears to be significantly less active. Single agent paclitaxel or docetaxel produces response rates in less than a quarter of the patients (typically 15-25% range).

H3. Combination chemotherapy
- Combination chemotherapy leads to higher response rates but it remains unclear if this leads to improved survival. Randomized trials show no clinically meaningful survival improvements with combination chemotherapy. A meta-analysis that included trials performed in patients with advanced gastric cancer (predominantly using older combination
regimens) indicated that first-line combination therapy was associated with a modest but statistically significant survival benefit when compared to single agent therapy. However, these trials were done with older regimens and modern regimens such as ECF (epirubicin, cisplatin, 5-fluorouracil) have not been tested in such studies and combination chemotherapy represents the standard of care for most patients.

- The combination of cisplatin plus 5-FU is one the best studied and the most commonly used regimens in due to its proven activity and well-established toxicity profile. Response rates can be seen in 25 percent of patients and toxicity may be improved if the cisplatin is split over 3-5 days.

- Capecitabine and infusional 5-FU were compared in the REAL-2 trial, a randomized phase III study. Oxaliplatin was also substituted for cisplatin in two of the arms ECF (epirubicin /cisplatin /5FU), EOF (epirubicin /oxaliplatin /5FU), ECX (epirubicin /cisplatin /capecitabine), and EOX (epirubicin /oxaliplatin /capecitabine), respectively. There were no significant differences among the groups in terms of objective response rate (41, 42, 46, and 48 percent with ECF, EOF, ECX, and EOX, respectively) or progression-free survival or toxicity. There was a statistically significant improvement in overall survival when outcomes of both capecitabine-containing arms were combined and compared to both 5-FU-containing arms. A meta-analysis of two trials (including REAL-2) concluded that, compared to 5-FU combinations, capecitabine combinations were associated with higher response rates (odds ratio 1.38, 95% CI 1.10-1.73) and better overall survival (hazard ratio for death 0.87, 95% CI 0.77-0.98). This plus the need for a central venous line have resulted in many experts favoring the capecitabine arms.

- The ECF remains the reference regimen for first-line treatment of advanced upper G1 cancer, at least in the US and Europe and is one of the accepted regimens. However when both oxaliplatin and capecitabine are substituted in the ECF regimen, outcomes are at least as good as with ECF. Median survival in patients treated with EOX was modestly longer when compared to ECF (median 11.2 versus 9.9 months) leading some experts to suggest that EOX is preferred over ECF for first-line therapy. FOLFOX has also been compared to ECF with comparable results.

- Docetaxel plus cisplatin and 5-FU (DCF) has been compared to cisplatin and 5-FU alone in the TAX-325 trial. DCF showed significant improvement compared to cisplatin/5-FU in measures of clinical benefit as defined in the trial. Whether DCF is more effective or safer than ECF or similar regimens is not entirely clear but it appears to be more toxic.

- Irinotecan based FOLFIRI also appears superior to cisplatin/5FU in response rates and survival being in the 10-12 month range. Similar outcomes were obtained using irinotecan in combination with oral capecitabine.

H4. BIOLOGICAL THERAPY

H4A. Her-2 positive Gastric cancers

- Approximately 22 percent of gastric and GE junction tumours overexpress the type II EGFR (HER2). The benefit of trastuzumab in advanced HER2-positive adenocarcinoma of the stomach or GE junction was addressed in the phase III ToGA trial, which compared standard chemotherapy (six courses of cisplatin plus either infusional 5-FU or capecitabine) with and without trastuzumab every three weeks until disease progression. Patients were eligible if their tumour was positive by either IHC (ie, showing 3+ expression) or FISH (ie, showing a HER2/CEP17 ratio of 2 or greater). Response rate was significantly higher with trastuzumab (47 versus 35 percent). Median overall survival (the primary endpoint) was significantly better with trastuzumab (13.8 versus 11.1 months) with 26% relative reduction in mortality. The survival of patients was even higher for the subgroup with samples that have been scored either IHC 2+/FISH+ or IHC 3+ in the trastuzumab plus chemotherapy arm There are no data addressing the benefit of continuing trastuzumab with the second-line regimen.
H4B. Other Biological Agents

- Ramucirumab is a monoclonal antibody that binds to the VEGFR-2. Two randomized phase III trials have shown a survival benefit of ramucirumab, either as monotherapy or in combination with paclitaxel in patients with previously treated advanced gastric or GE junction adenocarcinoma. For instance, patients with advanced gastric cancer following disease progression on first-line platinum or fluoropyrimidine-based chemotherapy were randomly assigned to ramucirumab, intravenously once every 2 weeks or placebo. Median overall survival was 5.2 months for the ramucirumab group and 3.8 months for placebo.

- Sunitinib and sorafenib are small molecule multitargeted TKIs. Early studies have shown mixed results and there are no phase three trials to support their use. Small molecule TKIs tested includes gefitinib and erlotinib. A survival benefit for gefitinib could not be shown in the only phase III trial, which randomized patients to gefitinib 500 mg daily or placebo in the second line setting.

- Bevacizumab has also not shown a survival benefit in the phase III AVAGAST study where bevacizumab was added to capecitabine plus cisplatin and is not recommended.

- Agents targeting the EGFR pathway including Cetuximab and panitumumab have been studied and results have been disappointing. Phase III trials involving both these agents have been negative.

H5. Second line therapy

- Second-line chemotherapy regimens after failure of the first-line regimen have generally shown lower response rates and greater toxicity. In patients with good performance both docetaxel/paclitaxel and irinotecan are options. The benefit appears to be modest with a survival benefit of 5.3 months seen with chemotherapy vs. 3.8 months with best supportive care.

- Ramucirumab alone or in combination with paclitaxel is an option for patients with good performance status who have disease progression on prior treatment with 5-FU or platinum-containing chemotherapy and can be considered if access is available.

I. Radiotherapy Techniques and Dose

- Radiation therapy should be preceded by CT simulation in every patient. The patient is placed supine, comfortable, with the neck in a neutral position. The arms should be out of the treatment field. Additional immobilization is optional. Reproducibility is improved with an empty stomach, best accomplished by having the patient fast 3-4 hours prior to simulation and each treatment. This also reduces the likelihood of nausea and/or vomiting, and reduces the size of the treatment volume. Planning is pursued using conventional 3DCRT techniques. A 4-field technique is preferable in most cases. In some cases an APPA technique may be adequate. IMRT is an option on a case by case basis when dose constraints cannot be met. IV contrast is optional, and not standard at this time.

- Adjuvant chemoradiotherapy: The postoperative treatment paradigm when including radiotherapy is largely based on the results of the INT-0116 trial. 85% of patients in the trial were lymph node positive. The following lymph node regions were included: perigastric, celiac, para-aortic, splenic, porta hepatitis and pancreaticoduodenal. This was performed in the era of 2D planning, which is no longer common practice. In most postoperative cases, there is no discernable GTV. The following structures, when present, should be routinely included in the CTV:
  - Residual stomach
  - Any known or suspected residual gross disease
  - Surgical resection bed
  - Duodenal stump
  - Anatomoses
Lymph node regions from which positive nodes were retrieved, if known, should be covered in the CTV. Elective lymph node coverage is at the discretion of the treating physician. It should be based on local drainage as it relates to the tumour location. Suggestions for elective coverage are as follows:

- **GE junction:** 3-5 cm of distal esophagus, periseophageal, celiac, and perigastric LN regions
- **Proximal stomach:** Perigastric, periesophageal, celiac, peripancreatic and porta hepatitis LN regions
- **Body of stomach:** Perigastric, splenic, celiac, peripancreatic, porta hepatitis LN regions
- **Distal stomach:** Perigastric, periduodenal, peripancreatic, porta hepatitis, celiac LN regions

Dose range: 45 – 50.4 GY in 1.8Gy fractions

The PTV is a 1cm uniform expansion from the CTV, or according to institutional tolerances for setup variability and patient factors.

An atlas for lymph node region delineation is available from the practical radiation oncology journal, PMID: 24674268

- **Neoadjuvant chemoradiotherapy (GE junction):** Neoadjuvant treatment for GE junction cancer is based on the CROSS trial. The GTV was defined as grossly visible primary tumour and enlarged regional lymph nodes. The PTV was defined as a proximal and distal margin of 4 cm (3 cm distal when tumour extending into stomach) and radial margin of 1.5cm from the GTV. No CTV was defined. Extrapolating from CROSS, a reasonable CTV would be 3cm proximal, 2cm distal (into stomach) and 1cm radial from GTV, edited as appropriate. Findings from EUS and upper GI endoscopy should be incorporated along with axial imaging to define the appropriate GTV. PTV is expanded 1cm from the CTV in all directions, or according to institutional tolerances accounting for setup variation and patient factors. The trial dose was 41.4Gy, elective lymph node regions were not included. Dose prescription is variable at Canadian centres, ranging from 41.4 to 50.4 Gy in 1.8 Gy fractions. Elective lymph node coverage is at the discretion of the treating physician, recommendations are listed in the above section for adjuvant chemoradiotherapy.

**J. REFERENCES**


Additional resources

www.cancer.gov

www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13970


www.esmo.org/Guidelines-Practice/Clinical-Practice-Guidelines/Gastrointestinal-Cancers/Gastric-Cancer

www.bccancer.bc.ca/HPI/CancerManagementGuidelines/Gastrointestinal/02.Stomach/default.htm


www.uptodate.com

Canadian Cancer Trial www.canadiancancertrials.ca/Default.

Chairperson: Dr. Shahid Ahmed.

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K. APPENDIX

K1. FIGURE 1. FRAMEWORK OF MANAGEMENT OF GASTRIC CANCER

K2. Regimens used in advanced gastric and GEJ tumours

**ECF** - Epirubicin 50mg/m², Cisplatin 60mg/m², 5FU 200 mg/m² CVI (q21 Days, up to 6 cycles).

**ECX** - Epirubicin 50mg/m², Cisplatin 60mg/m², Capecitabine 625mg/m² daily (q21 Days, up to 6 cycles).

**5FU/Cisplatin** Cisplatin 75mg/m² D1 or 25mg/m² D1-3, 5FU 1000 mg/m² D1-4 (q21 Days, up to 6 cycles)

**EOX** Epirubicin 50mg/m², Oxaliplatin 130mg/m², Capecitabine 625mg/m² daily (q21 Days, up to 6 cycles).

**FOLFOX** Leucovorin 400 mg/m² iv day1 5-FU 400 mg/m² iv bolus day 1 followed by 2400 mg/m² iv over 46 hrs Oxaliplatin 85 mg/m² iv day1 Every 2 weeks for 12 cycles

**DCF** Docetaxel 75mg/m² D1, Cisplatin 75mg/m² D1, 5FU 1000 mg/m² D1-4 (q21 Days, up to 6 cycles)

**FOLFIRI** Leucovorin 400 mg/m² iv day1 5-FU 400 mg/m² iv bolus day1, and then 2400 mg/m² iv over 46 hrs Irinotecan 180 mg/m² iv over 90 min day1

**5FU/Cisplatin/Herceptin** Cisplatin 80 mg/m² D1, 5FU 800mg/m² D1-5 CVI, Herceptin 8mg/kg LD after 6 cycles if no progression, Herceptin 6mg/kg MD (q21 Days, up to 6 cycles. Herceptin can be continued after 6 cycles if no progression). Capecitabine can be substituted for 5FU.