Gastric Adenocarcinoma

11

Mohammadali Khorasani, Savtaj S. Brar,
and Natalie G. Coburn

Introduction

In 2017, the Canadian Cancer Society estimated gastric adenocarcinoma to be the 14th most commonly diagnosed malignancy, with 3500 new cases and 2100 deaths. The age-standardized incidence and mortality rate for gastric cancer have decreased from 19.0/100,000 cases and 15.5/100,000 deaths in 1980 to 8.6/100,000 and 5.1/100,000 deaths, respectively, in 2017 [1]. Enormous geographic variation in the incidence of gastric cancer exists with the highest incidence being observed in East Asia. Similarly, wide geographic variation in treatment outcomes is observed with overall 5-year survival rates of 40–60% reported in Asia and Europe, compared to 25–29% in Canada and the USA [1–3].

Risk Factors

Established risk factors for gastric cancer (GC) include *Helicobacter pylori* infection, smoking, alcohol, and dietary factors (such as processed meats and salt-preserved foods). Hereditary gastric cancers represent <5% of all gastric cancers. Main gastric cancer familial predispositions are hereditary diffuse gastric cancer

M. Khorasani
General Surgical Oncology, University of Toronto, Toronto, ON, Canada
e-mail: Mohammadali.Khorasani@alumni.ubc.ca

S. S. Brar
Department of Surgery, University of Toronto, Toronto, ON, Canada
e-mail: sbrar@mtsinai.on.ca

N. G. Coburn (✉)
Department of Surgery, Sunnybrook Health Sciences Centre, University of Toronto, Toronto, ON, Canada
e-mail: Natalie.Coburn@sunnybrook.ca

F. C. Wright et al. (eds.), *Surgical Oncology Manual*,
https://doi.org/10.1007/978-3-030-48363-0_11

(HDFC), gastric adenocarcinoma and proximal polyposis of stomach (GAPPS), familial intestinal gastric cancer (FIGC). Other hereditary cancer syndromes associated with increased risk of gastric cancer include Lynch syndrome, Peutz-Jeghers syndrome (PJS), familial adenomatous polyposis (FAP), Li-Fraumeni syndrome, and BRCA syndromes (BReast CAncer) (see Table 11.1 below).

Table 11.1 Selected familial predispositions to gastric cancer

	Gene mutation	Risk of gastric cancer	Notes
HDGC [4–9]	*CDH-1*[a] (codes for E-cadherin)	70% men, 56% females (by 80 years of age) Average 37 years of age	Autosomal dominant Diffuse-type GCA Prophylactic total gastrectomy + D1 LND recommended at age 20–30 years if CDH-1 positive 87% have microscopic adenocarcinoma on prophylactic gastrectomy specimen CDH-1 positive women: 42% risk of lobular breast cancer by age of 80 years
GAPPS [10, 11]	*APC* promoter IB Variants[a]	12 families have been described with GAPPS to date Youngest reported age of gastric adenocarcinoma is 23 years	Autosomal dominant FGP sparing the antrum. No significant colorectal or duodenal polyps Guidelines not well defined for surveillance or timing of prophylactic gastrectomy
FAP [12, 13]	*APC*	1–2% lifetime risk	Duodenal/peri-ampullary cancer most common extracolonic manifestation ~50% non-adenomatous FGP, ~10% of gastric polyps adenomatous (mostly in antrum) and need to be removed Guidelines recommend surveillance starting at 25–30 years of age Incidence of gastric cancer in FAP patients may be rising [14]
Lynch syndrome [15, 16]	*MMR*, *EPCAM*	Cumulative risk of 7–8%, mean age of 56 years	Autosomal dominant After endometrial cancer, one of the most common extra-colonic manifestations of Lynch syndrome Mostly intestinal type Benefit of surveillance for gastric cancer is unknown[a]
PJS[a] [17, 18]	*STK11*	29% lifetime risk, mean age of 42	Autosomal dominant Surveillance recommended to start in late teens

HDGC hereditary diffuse gastric cancer, *GCA* gastric cancer, *LND* lymph node dissection, *GAPPS* gastric adenocarcinoma and proximal polyposis of stomach syndrome, *APC* adenomatous polyposis coli, *FGP* fundic gland polyps, *FAP* familial adenomatous polyposis, *MMR* mismatch repair, *EPCAM* epithelial cell adhesion molecule, *PJS* Peutz-Jeghers syndrome

[a]See Special Notes below

Special Notes

- *Hereditary Diffuse Gastric Cancer:* criteria for diagnosis of HDGC and genetic testing for *CDH1* mutation are as mentioned below [8]. Of note, in countries with low incidence of sporadic gastric cancer (such as Canada), approximately 10–18% are identified with *CDH-1* mutation.
  1. Two gastric cancer cases in first- or second-degree relatives regardless of age, at least one confirmed to be diffuse gastric cancer (DGC) or
  2. One case of DGC diagnosed below the age of 40 years in a first- or second-degree relative or
  3. Personal or family history of DGC and LBC, one diagnosed below the age of 50 years.
- *Gastric Adenocarcinoma and Proximal Polyposis of Stomach Syndrome*: Proposed criteria for diagnosis are [11] as follows:
  1. Gastric polyps restricted to the body and fungus with no evidence of colorectal or duodenal polyposis
  2. More than 100 polyps in the proximal stomach of the affected patient (or more than 30 polyps in the first-degree relative)
  3. Some FGPs having regions of dysplasia (or a family member with FGP and adenocarcinoma)
  4. Autosomal dominant inheritance
- *Peutz-Jeghers Syndrome*: Clinical diagnosis of PJS is made when any of the following criteria are present [18]:
  1. Two or more histological confirmed Peutz-Jeghers (PJ) polyps
  2. Any number of PJ polyps detected in someone with family history of PJS
  3. Any number of PJ polyps in someone with characteristic mucocutaneous pigmentation
- *Lynch Syndrome* [19–21]:
  1. Patients are at risk of extra-colonic malignancies of endometrium, stomach, ovaries, hepatobiliary, renal pelvis/ureteric, brain and skin
  2. Consensus guidelines for gastric cancer surveillance are variable. In general, a baseline upper GI scope at age of 30–35 years and subsequent scopes every 1–5 years are recommended, especially in patients with risk factors such as intestinal metaplasia, gastric atrophy, family history of gastric cancer, and immigration from countries with high incidence of gastric cancer. In addition, *H. pylori* testing and eradication are recommended.

Classification and Staging

Histopathology

Gastric adenocarcinomas are classified histologically according to the Lauren classification as (1) intestinal (well-differentiated) or (2) diffuse (undifferentiated)

histologic subtypes [22]. Such classification can have clinical implications with respect to prognosis and management decision-making.

Intestinal-type adenocarcinoma of stomach is more sporadic and believed to be causally related to *H. pylori* and environmental risk factors of gastric cancer (GC) [23]. Whereas intestinal-type GC is believed to follow sequential progression of dysplasia to invasive carcinoma, the development of diffuse-type GC is not believed to follow defined preneoplastic stages [23]. Diffuse-type GC has defective intercellular adhesions and tend to spread within deeper layers of gastric wall and in a less coherent fashion [24, 25]. Fashion, which can lead to underestimation of its extent by visual assessment of gastric mucosa. As such, wider gross surgical resection margins may be needed in patients with diffuse-type GC, and if intra-operative frozen sections are being done, full gastric wall thickness assessment of the resection margin should be considered by the pathology team.

In addition, multiple retrospective studies suggest prognostic and predictive value in Lauren classification of gastric adenocarcinoma. Diffuse-type GC has been shown to be associated with worse disease-free survival (DFS) and overall survival (OS) rates [24–26]. Furthermore, in phase 2/3 of the prospective randomized FLOT4 study, comparing pathological response to two different perioperative chemotherapy regimens (ECF/ECX vs. FLOT), analysis of the pooled population of both groups showed that patients with intestinal-type GC had 16% complete pathological response vs. only 3% in patients with diffuse-type GC ($p = 0.004$) [27]. In this study, it was also shown that oxaliplatin-based chemotherapy (FLOT) resulted in more frequent partial tumor response in patients with intestinal-type GC compared to diffuse type (42% vs. 23%, $P = 0.04$), but tumor response between the two Lauren classification subtypes was similar in the non-oxaliplatin group (ECF/ECX).

Molecular Classification

Recently, as part of the Cancer Genome Atlas (TCGA), a molecular classification for gastric cancer has been developed, dividing gastric cancer into four subtypes: Epstein-Barr virus (EBV) positive, microsatellite unstable (MSI), genomically stable tumors (GS), and those with chromosomal instability (CIN) [28]. These molecular subtypes have been shown to have distinct salient genomic features which may provide guidance in using targeted agents in the future. In Fig. 11.1 below, salient features associated with each subtype, and their distribution in the stomach, are summarized.

Molecular classification is emerging, as potential biomarkers to explore personalized treatment strategies in gastric cancer are in the experimental stages at this time. For instance, studies have shown that EBV-positive and MSI high, gastric cancers have higher PD-L1 expression, making them potential candidates for immunotherapy [28, 29]. In addition, there is data to support prognostic value in this

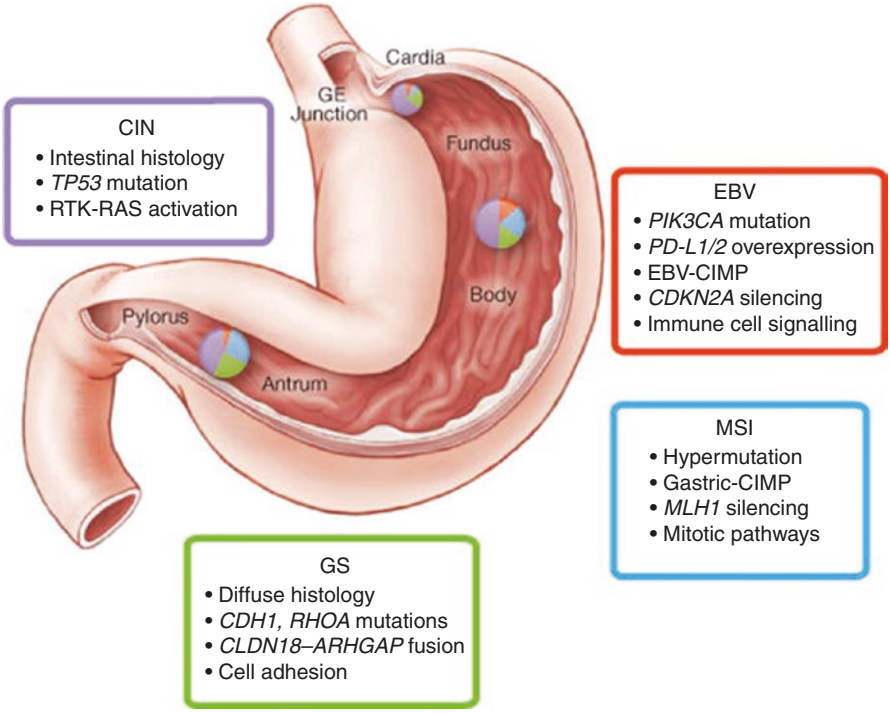

Fig. 11.1 Molecular subtypes of gastric cancer and their distribution within the stomach [28]. (Permission for use of this figure was obtained from Macmillan Publishers Limited)

molecular classification, suggesting EBV-positive tumors have the best prognosis and GS subtype is associated with the worst outcomes [29]. There is also preliminary evidence to suggest that MSI high status may be a negative prognostic marker in patients treated with perioperative chemotherapy [30]. Ongoing research is needed to better define the role of molecular classification in clinical practice.

Staging

Staging of gastric adenocarcinoma is according to the American Joint Committee on Cancer (AJCC), eighth edition. Gastroesophageal junction tumors with their epicenter located less than 2 cm into proximal stomach are classified, staged, and treated as esophageal cancers [31]. This most recent edition of AJCC has separated clinical from pathological staging and has incorporated post-neoadjuvant staging for gastric cancer (see Table 11.2 below).

Table 11.2 Gastric cancer patient outcomes according to the eighth edition of AJCC [32, 33]

Pathological stage[a]	5-year survival (%)
Stage 1a	93.6
Stage 1b	88.0
Stage 2a	81.8
Stage 2b	68.0
Stage 3a	54.2
Stage 3b	36.2
Stage 3c	17.9

Post-neoadjuvant stage[a]	5-year survival (%)
Stage 1	76.5
Stage 2	46.3
Stage 3	18.3
Stage 4	5.7

[a]Pathological stage group patients are without neoadjuvant therapy prior to resection; their survival information is based on the International Gastric Cancer Association data (mostly Japanese and Korean patient data); post-neoadjuvant stage group had either systemic therapy or radiotherapy prior to surgery, and their survival rates in this table are based on the National Cancer Database (US-based database)

Table 11.3 Diagnostic tool accuracy when used for assessment of gastric cancer [34, 35]

	EUS	CT	MRI	PET
T-stage (overall accuracy in %)	75	72	83	–
N-stage (%)				
Overall accuracy	64	66	53	60
Sensitivity	74	77	85	40
Specificity	80	78	75	98
M-stage (overall accuracy (%))	–	81	–	88

Staging Workup

The initial treatment plans are made based on the clinical stage of the patient. There are multiple tools that can be considered to improve the accuracy of the clinical stage and guide clinical decisions. CT scan, MRI, PET scan, endoscopic ultrasound (EUS), and staging laparoscopy ± peritoneal washings are some of these tools.

To evaluate the extent of locoregional disease, diagnostic tools have different accuracies, as summarized in Table 11.3.

According to a meta-analysis [35], EUS was most accurate for T3 disease (85%), followed by T4 and T1 (79% and 77%, respectively). Pooled accuracy of EUS in staging T2 lesions was only 65% in this meta-analysis. CT scan accuracy in assessment of T stage was suggested to be lowest in T1 lesions, being only

63% [34]. When comparing CT against MRI for assessment of T stage [34], MRI's accuracy is statistically significantly higher overall (83% vs. 72%) and when identifying T1 lesions (86% vs. 63%). When assessing for N-Stage, meta-analysis results suggest that both CT and MRI are statistically significantly more sensitive than PET scan, but PET was shown to be more specific than both other techniques [34].

Early vs. Advanced Gastric Cancer

One clinically useful way of classifying gastric cancer is *early* vs. *advanced.* This classification can help guide the management strategy:

Early Gastric Cancer (EGC) tumors confined to the mucosa (Tis or T1a) or submucosa (T1b), independent of the presence of lymph node involvement [36]. EGC is predominately identified by subtle changes in color, vascularity, or texture and is rarely diagnosed outside areas where population-based screening is offered, such as in Japan and Korea.

Advanced Gastric Cancer (AGC) T2 to T4 (invading muscularis propria, subserosa, perforating serosa, or invading adjacent structures), without distant metastasis.

Management

In this section, we discuss the management of gastric cancer classified into *early gastric cancer* and *advanced gastric cancer* (see above for definitions of this classification). Below are definitions of some of the terminologies that are used in the chapter.

Endoscopic Mucosal Resection (EMR) employs endoscopic techniques to elevate (e.g., injection and suction) and resect (e.g., cautery and banding) mucosal lesions en bloc.

Endoscopic Submucosal Dissection (ESD) a variation of EMR that employs submucosal injection and a specialized needle-knife to permit en bloc resection of mucosal and submucosal lesions.

Subtotal Gastrectomy (SG) removal of one-half to three-fourths of the gastric tissue, including omentum and all associated lymph nodes appropriate for a D1 or D2 lymphadenectomy. For distal gastric cancers, SG has been shown to have an equivalent oncological outcome and lesser morbidity when compared to total gastrectomy. SG is also associated with a better nutritional status and quality of life [37].

Total Gastrectomy (TG) removal of all of the gastric tissue and distal esophagus, including omentum and all associated lymph nodes appropriate for a D1 or D2 lymphadenectomy. TG is preferred for tumors confined to the proximal one-third of the stomach.

Palliative Gastrectomy (PG) gastrectomy performed with the intent to alleviate symptoms from the primary gastric cancer in the context of metastatic disease. A gastrectomy performed otherwise in a patient with metastatic disease is considered a non-curative gastrectomy [38].

D1 Lymph Node Dissection includes removal of the omentum with perigastric lymph nodes (stations 1–6) and lymph nodes along the left gastric artery (station 7). *It is important to note that station 1 (right paracardial) is part of a D1 LND, but station 2 (left paracardial) is not removed for SG* [39]. See Fig. 11.2 for schematic of the lymph node stations.

D2 Lymph Node Dissection D1 nodes and lymph nodes along the common hepatic artery (station 8a), celiac axis (station 9), splenic artery (stations 10 and 11), and hepatic artery proper (station 12a) [39]. Clearance of station 10 and 11 nodes may require splenectomy (See Special Notes – Extent of Lymphadenectomy) (Fig. 11.2) [39].

Bursectomy Removal of anterior leaflet of the transverse mesocolon and the pancreatic capsule, along with total omentectomy.

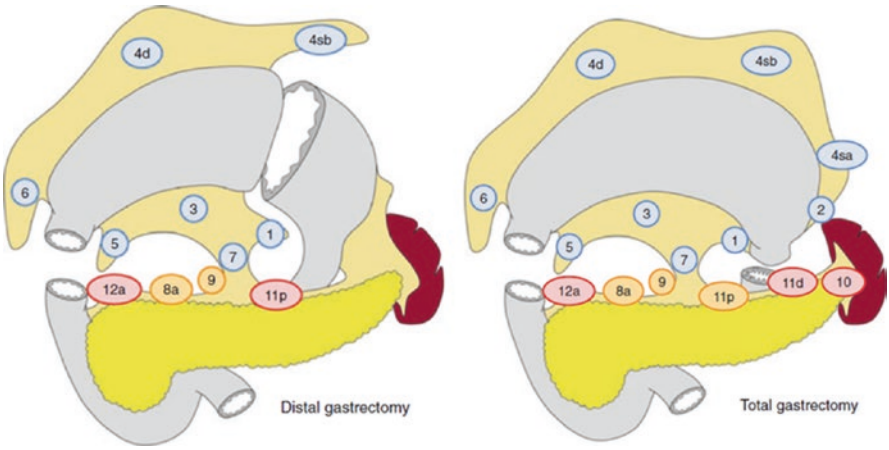

Fig. 11.2 Lymph node stations according to the Japanese gastric cancer treatment guidelines. (Figure adopted from 2014 Japanese gastric cancer treatment guidelines, Springer publications [40]). Numbers in *blue* color: D1 lymphadenectomy stations; numbers in *orange* color: D1+ lymphadenectomy stations; numbers in *red* color: D2 lymphadenectomy stations

Early Gastric Cancer (EGC)

Workup	Surgery	Adjuvant therapy	Follow-up (f/u)
Recommended: History and physical exam Upper endoscopy Imaging: CT abdomen/pelvis EUS Staging laparoscopy[a] *Optional:* CT chest PET is not indicated for EGC	*Gastrectomy* with D1 lymph node dissection[a] OR *Endoscopic resection* can be considered for lesions fulfilling all of the following [41][a]: Intestinal type Confined to mucosa (Tis or T1a) and cN0 Elevated lesions <20 mm or flat lesions <10 mm in diameter Absence of high-risk features (ulceration, poorly differentiated, lymphovascular invasion) Clear lateral and deep margins after excision	Indicated for all node-positive disease, and those who are found to be T2 or higher after resection (please see section on "Advanced Gastric Cancer")	*Recommended:* Iron, B12, calcium supplements Every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years, and yearly thereafter with: History and physical exam B12, Fe, bone density if TG was performed *Optional:* CT abdomen/pelvis[a] EGD[a]

EGC early gastric cancer, *EUS* endoscopic ultrasound, *EMR* endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *SG* subtotal gastrectomy, *TG* total gastrectomy, *RCT* randomized controlled trials, *EGD* esophago-gastro duodenoscopy

[a]See Special Notes

Special Notes: Early Gastric Cancer

Endoscopic resection EMR/ESD may be used in appropriately selected lesions amenable to en bloc resection that have minimal or no risk of nodal metastasis by experienced providers. Expanded criteria for ESD outside of the criteria listed above are considered investigational. ESD expertise and regional outcomes should be considered when choosing ESD as the treatment strategies, as recent meta-analysis has suggested worse endoscopic outcomes in Western countries compared to Eastern countries [42]. If after endoscopic resection it is revealed that the lesion is outside of the above-mentioned criteria (i.e. non-curative endoscopic resection), further treatment with gastrectomy and lymphadenectomy should be considered [43].

In the case of T upstage after endoscopic resection, management as per recommendations in the section "Advanced Gastric Cancer" should be considered.

Staging Laparoscopy (SL) Limited use in EGC. In cases where the tumor is reliably felt to be clinically T1 and N0, then SL can be omitted.

Extent of Lymphadenectomy Considerable controversy surrounds the role of extended lymphadenectomy (D1 vs. D2 resection) in early gastric cancer. Adequate staging requires 15 or more lymph nodes to be harvested. For cT1N0 tumors, D1 with splenopancreatic preservation is generally recommended. Worse outcomes have been associated with D2 lymphadenectomy in patients with EGC [44]. If clinically node positive, the staging should be reassessed to ensure not AGC.

Resection Margin (Early and Advanced Gastric Cancer) Positive microscopic margins after gastrectomy are associated with inferior outcomes when compared to those in whom R0 status was achieved [45–48]. When subtotal gastrectomy is performed, in general a gross proximal margin of at least 4 cm is recommended to ensure R0 resection [48–50]; however, guidelines differ in their recommendation (see table below). Likely, smaller gross margins can be used in resection of EGC (T1), advocated by Japanese gastric cancer treatment guidelines, suggesting a 2 cm gross proximal margin in such cases [36]. Of note, diffuse or signet ring cell subtypes are at higher risk of positive margin, and in these cases a greater gross resection margin can be considered. Recommendations from three different guidelines for surgical resection margins in gastric cancer are outlined in Table 11.4 below.

Intra-operative frozen sections of resection margin can be considered selectively, and in retrospective studies, they have been shown to be associated with low (1.7%) false-negative rates [52]. However, patients with signet ring cell or diffuse-type histology are at higher risk of false-negative intra-operative frozen section assessment [52].

To address a microscopically positive margin (R1 resection), consideration for re-resection *or* post-op CRT is recommended by clinical guidelines [50, 51] in selected cases.

Table 11.4 Recommended gastric cancer macroscopic proximal resection margin based on guidelines

	Recommended proximal gross margin
JGCG [40]	EGC: 2 cm AGC: 3–5 cm (depending on the growth pattern)
NCCN [50]	4 cm
ESMO [51]	5 cm (stage 1b-3) Consider 8 cm in diffuse type

JGCG Japanese Gastric Cancer Treatment Guidelines, *NCCN* National Comprehensive Cancer Network, *ESMO* European Society for Medical Oncology, *EGC* early gastric cancer, *AGC* advanced gastric cancer

- Decision to re-resect in this scenario is complex and requires careful consideration of anatomical feasibility, patient factors, and disease factors. Microscopically positive margins in gastric cancer may not be an independent predictor of outcomes in patients with more advanced disease [45, 48, 53]; therefore, re-resection after a microscopically positive margin, when technically feasible, may only be considered in patients who have favorable stage of disease.
- Demonstrated recurrence and survival benefits of post-operative CRT after R1 resection are based on retrospective studies only [54–57], and its potential risks/benefits should be carefully discussed in multidisciplinary cancer conferences on a case by case basis.

Laparoscopic Gastrectomy (LG) LG is appropriate for EGC in experienced, high-volume centers, where results are monitored and assessed against international benchmarks [58]. It is safe and improved short-term outcomes have been demonstrated, but oncologic outcomes are currently being evaluated with ongoing RCTs [59].

Follow-Up Surveillance
Evidence to support the benefit of early detection of recurrence is lacking. Most providers perform surveillance with serial CT scans. Surveillance EGD should be offered to patients at risk of local recurrence (e.g., following endoscopic resection) when complete gastrectomy would be considered.

Advanced Gastric Cancer

Workup	Surgery	Perioperative/adjuvant therapy	Follow-up (f/u)
Recommended tests: History and physical exam Upper endoscopy Imaging: CT abdomen/pelvis Staging laparoscopy[a] *Optional tests*: CT chest EUS[a] PET is not indicated	*Gastrectomy* D2 LND SG or TG depending on location of tumor[a] Consider intraoperative margin assessment[a] Multi-visceral resection should be performed if the patient is considered a candidate for curative resection	Options are: Perioperative FLOT chemo (preferred) [56, 60] *OR*[a] Adjuvant 5-FU-based CRT (if D1 LND or less) [61] *OR*[a] If no pre-op therapy, consider adjuvant chemo after D2 LND (If N+ may consider addition of CRT to the post-op regimen) Each of the options above has been shown to be superior to resection alone in RCTs [62]. For guidance on choice of multimodality therapy, see Special Notes below	Every 3–6 months for 1–2 years, then every 6–12 months for 3–5 years, and yearly thereafter with: History and physical exam B12, Fe, bone density if TG was performed *Optional tests:* CT abdomen/pelvis[a] EGD[a]

EUS endoscopic ultrasound, *SG* subtotal gastrectomy, *TG* total gastrectomy, *RCT* randomized controlled trial, *ECF* epirubicin, cisplatin and fluorouracil (5-FU), FLOT docetaxel, oxaliplatin, fluorouracil, and leucovorin, *CRT* chemoradiotherapy, *EGD* esophago-gastro duodenoscopy

[a]See Special Notes

Special Notes: Advanced Gastric Cancer

Staging Laparoscopy (SL) Radiologically occult peritoneal metastases are found in 20–30% of patients with T2 or higher disease [63]. SL is indicated in patients with clinical T2 or higher, or node positive on clinical staging to rule out radiologically occult peritoneal metastasis or positive peritoneal cytology [50]. Patients with positive peritoneal washings experience outcomes comparable to those with overt metastatic disease and should be considered palliative [64]. In patients who are being considered for preoperative therapy, SL with peritoneal washings should be obtained prior to preoperative therapy. Even though there are some data to suggest that patients who are converted from cytology positive to negative with systemic therapy have better outcomes [50, 65], role of surgery (gastric resection ± intra-peritoneal chemotherapy) is considered experimental and not the standard of care. Further studies are ongoing to better define the role of surgery in patients with peritoneal disease [66, 67].

Endoscopic Ultrasound (EUS) EUS is valuable in the distinction between EGC and AGC and is critical if considering EMR/ESD. In patients with an established diagnosis of AGC, EUS is unlikely to change management and is not routinely required.

Resection Margin:
Please refer to the "Resection Margin" section under Early Gastric Cancer management.

Extent of Lymphadenectomy Evidence suggests improved cancer-specific outcomes with D2 resection, particularly in higher staged tumors (T2–4) [44, 68]. Splenopancreatectomy is clearly associated with higher operative morbidity and is avoided unless required to achieve R0 resection margins [39, 69]. Involvement of nodes beyond a D2 resection (i.e., mesenteric, para-aortic, retroperitoneal) is classified as distant metastases [31]. The role of "D3" resections is not supported in the management of gastric cancer [70].

Bursectomy Bursectomy was routinely considered/performed for serosa-positive gastric cancers according to Japanese guidelines, but has been studied further in JCOG 1001 randomized control trial in patients with resectable cT3/T4a GC [60]. The results of the study were published early, after second interim analysis in 2017, on the basis of futility. Based on these results, bursectomy did not provide survival advantage over non-bursectomy and was significantly associated with more pancreatic fistula [60]. A recent meta-analysis also was consistent with the results of JCOG

1001, but did not demonstrate superior overall or recurrence-free survival in patients with resectable cT3/T4 GC who received bursectomy [71].

Laparoscopic Gastrectomy (LG) LG is not recommended for AGC due to limited available evidence on oncologic outcome [40, 50]. A Korean RCT is investigating oncologic outcomes of LG in AGC [72].

Combined Modality Treatment:
Strong evidence exists to support adding systemic therapy or chemoradiotherapy (CRT) to surgical resection as part of the treatment for patients with advanced GC improves outcomes [61, 73–75]. Below, we discuss peri-operative vs. postoperative therapy treatment strategies, as well as roles of chemotherapy and CRT in treatment of advanced GC. This is followed by Fig. 11.3, which summaries this discussion.

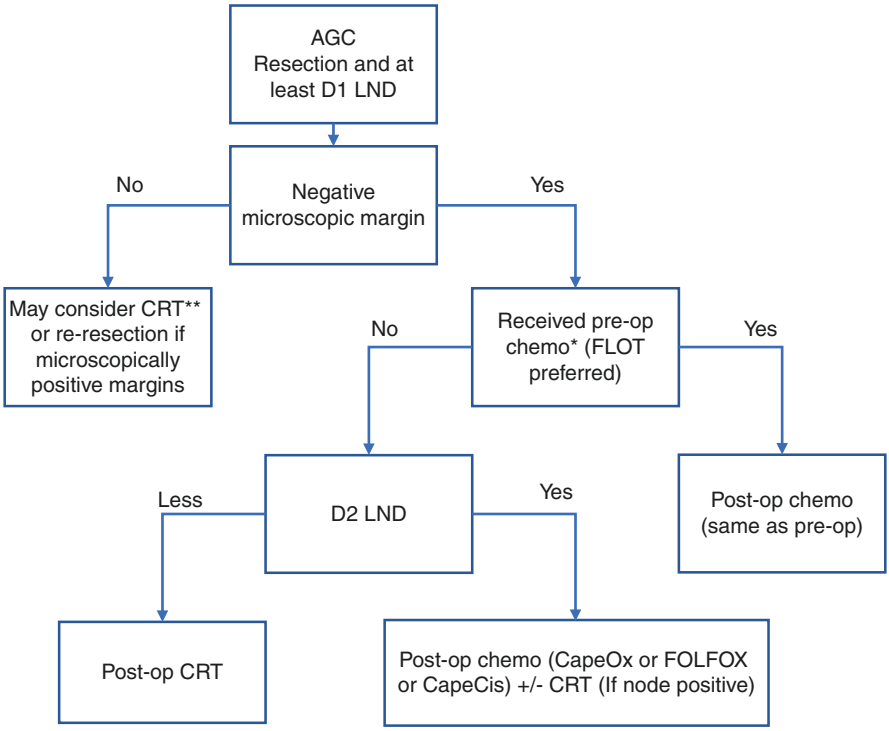

Fig. 11.3 Peri-operative/postoperative therapy decision tree for advanced gastric cancer (AGC). Please see section above on "Combined Modality Treatment" for further details. *For treatment of AGC, we advocate for peri-operative chemotherapy approach over adjuvant therapy only, given low compliance rate with adjuvant therapy post-gastric surgery. **The benefit of post-op CRT in this scenario is only demonstrated in retrospective studies. Its risk/benefit or indication should be discussed on a case-by-case basis in multidisciplinary rounds. *R1 resection* microscopically positive margin, *CRT* chemoradiotherapy, *LND* lymphadenectomy, *AGC* advanced gastric cancer, *FLOT* docetaxel, oxaliplatin, fluorouracil, and leucovorin, *CapeOx* capecitabine and oxaliplatin, *CapeCis* capecitabine and cisplatin, *FOLFOX* FOLinic acid, fluorouracil, oxaliplatin

- *Peri-operative Chemotherapy*
  - Currently, in North America, peri-operative chemotherapy is the favored multi-modality approach for treatment of AGC. Peri-operative FLOT has been recently adopted as the standard of care in North America for management of patients with cT2 or greater and/or cN-positive patients [75].
  - Three preoperative and three postoperative cycles of ECF/ECX were compared against four pre- and 4 postoperative cycles of FLOT in a phase 3 randomized trial. The results showed that FLOT was associated with improved OS and PFS, with no increased complications rates [75]. More patients in the FLOT arm were able to complete all allocated treatment cycles compared to ECF/ECX. Peri-operative FLOT also resulted in improved R0 resection rates.
  - In the phase 2 of the same trial, four cycles of preoperative FLOT was associated with significantly higher rates of pathological complete regression (16%) compared to three cycles of preoperative ECF/ECX (6%) [27].
  - The role of replacing postoperative chemotherapy with CRT after preoperative chemo and adequate surgery (at least D1+) in patients with stage 1B-4a was investigated in the CRITICS trial [76]. There was no improvement in outcomes with incorporating CRT postoperatively in the treatment of these patients.
  - The CRITICS trial [76] once again highlighted the poor compliance with post-operative therapies after gastric resection (59% and 62% in the two groups) regardless of whether chemo or CRT was used postoperatively. In the FLOT study [75], only 52% of patients in the ECF/ECX arm and 60% of patients in the FLOT arm started the allocated postoperative chemotherapy. Low compliance has been seen in other gastric cancer adjuvant therapy trials as well, and should be a factor considered when deciding between peri-operative or adjuvant therapy approach in treatment of patients with GC. CRITICS-2 trial will be looking at the value of incorporating CRT in the neoadjuvant setting, in an attempt to find the most effective therapy that can be administered preoperatively, when patients have higher chance of tolerating the therapy [77].
- *Postoperative Chemoradiotherapy*
  - The landmark INT-0116 trial showed long-term, improved, relapse-free survival and overall survival in patients with resectable stage 1B-4 disease who received postoperative CRT compared to those with surgery alone [61]. However, in this study, only 10% of patients had D2 lymph node dissections, and 54% did not even have complete D1 lymphadenectomy [19].
  - A phase 3 randomized trial in Korea investigated the role of postoperative CRT after curative resection of advanced gastric cancer with D2 lymphadenectomy, and did not demonstrate benefit with addition of adjuvant CRT in this group of patients compared to adjuvant chemotherapy alone [78, 79]. Unplanned subgroup analysis [79] suggested improved disease-free survival in node-positive patients who received concurrent adjuvant CRT compared to

adjuvant chemotherapy alone. Benefits of adjuvant CRT in this subset of patients will be explored further in ARTIST-2 trial.
  - There may be a role for considering postoperative radiation in the case of microscopically positive resection margins. Please see the section "Resection Margin" above for more details.
  - To summarize the role of radiotherapy, patients with resected advanced GC who had curative resection but only D1 lymphadenectomy and no neoadjuvant chemo should be considered for adjuvant CRT [61]. In patients who receive neoadjuvant chemo followed by curative resection and at least D1 lymphadenectomy, no clear benefit has been demonstrated in post-op CRT compared to post-op chemo [76]. Lastly, in node-positive patients with completely resected gastric cancer and D2 lymphadenectomy who did not receive preoperative chemotherapy, there may be benefit in incorporating CRT in their adjuvant regimen [79].
- *Postoperative Chemotherapy:*
  - Following curative resection (R0) and D2 lymphadenectomy of advanced GC, in patients who did not receive preoperative chemo, the results of phase 3 randomized trials as well as meta-analysis support use of adjuvant chemotherapy over surgery alone, when possible [74, 78, 80–83]. However, the role of adjuvant chemotherapy in this patient population who have received D1 lymphadenectomy (or less) is not well defined, and adjuvant CRT tends to be the treatment of choice [50, 61].

Unresectable or Metastatic Gastric Cancer

Workup	Management	Follow-up (F/U)
Recommended tests: History and physical exam Upper endoscopy HER-2 status Imaging: CT abdomen/pelvis *Optional tests:* Staging laparoscopy[a] CT chest	Consider chemotherapy, radiotherapy, and nonoperative management for symptomatic patients Palliative gastrectomy should be avoided and only performed for symptomatic patients, for whom all nonsurgical and less morbid options have been considered Stenting is associated with less morbidity than resection or bypass for palliation of obstruction and is typically preferred Radiation or angioembolization can be effective for transfusion-dependent bleeding	As symptoms warrant

[a]See Special Notes

Special Notes: Unresectable or Metastatic Gastric Cancer

Staging Laparoscopy may have utility in confirming metastatic disease, especially carcinomatosis, if suspected on imaging.

Criteria for Nonoperative Management

- Unresectable
  - Level 3 or 4 suspicious nodes on imaging or confirmed by biopsy. Level 3 nodes include the posterior surface of the pancreas (nodal station 13), superior mesenteric artery, and vein (station 14). Level 4 nodes are middle colic vessels (station 15) and the para-aortic nodes (station 16).
  - Invasion or encasement of major vascular structures, such as celiac axis and its branches, is considered unresectable. Isolated left gastric artery involvement can be treated with curative intent if an R0 margin is obtainable.
- Metastatic spread or peritoneal seeding (including positive peritoneal cytology) identified at surgical resection is considered incurable. Unless symptoms exist, systemic therapy should be considered rather than resection.
- Non-curative gastrectomy has been demonstrated to impart no benefit in the setting of metastatic disease and exposes patients to unnecessary surgical procedures and risks of complications. In a phase 3 trial, survival of gastrectomy (followed by postoperative chemotherapy) in patients with advanced gastric cancer and one non-curative factor was compared against modern chemotherapy only, showing no survival benefit from gastrectomy and higher serious adverse events [84].

Landmark Surgical Publications (D1 vs. D2 Lymphadenectomy)

Study	Methods	Results
Dutch Trial Bonenkamp et al. [69]	RCT $N = 711$ D1 vs. D2 resection D2 resection included distal pancreatectomy (30%) and splenectomy (38%)	Morbidity: 43% D2 vs. 25% D1 ($p < 0.001$) Mortality: 10% D2 vs. 4.0% D1 ($p = 0.004$) Median postoperative stays: D2 25 days vs. D1 18 days; $p < 0.001$ *5-year update* [39]*:* No difference in 5-year OS rates: 35% D1 vs. 33% D2 *15-year update* [68]*:* Overall 15-year survival: 22% D1 vs. 28% D2; $p = 0.34$ Deaths from gastric cancer: 48% D1 vs. 37% D2; $p = 0.01$

Study	Methods	Results
Medical Research Council (MRC) ST01 Cuschieri et al. [85]	RCT $N = 400$ D1 vs. D2 resection D2 resection includes distal pancreatectomy and splenectomy (56%), or only splenectomy (66%)	Morbidity: 46% D2 vs. 28% D1; $p < 0.001$ Mortality: 13% D2 vs. 6.5% D1; $p = 0.04$ *5-year update* [86]*:* No difference in 5-year OS rates: 35% D1 vs. 33% D2
Italian Gastric Cancer Surgical Group (IGCSG) Degiuli et al. [87]	RCT $N = 267$ D1 vs. D2 resection In the D2 arm, spleen and pancreas were preserved unless direct tumor extension. Splenectomy was performed for T1 or higher tumors on the greater curvature of the proximal or middle one-third of the stomach	No difference in 5-year OS: 66.5% D1 vs. 64.2% D2 Morbidity: 10.5% D1 vs. 16.3% D2; $p < 0.29$ In-hospital mortality: 0% D2 vs. 1.3% D1; not statistically significant *5-year update* [44]*:* Trend toward improved 5-year OS for advanced disease (T2-4; N+): 59% D2 vs. 38% D1; $p = 0.055$ 5-year DSS for pT1 cancers were worse in the D2 arm compared to the D1 group (83% vs. 98%; $p = 0.015$)

CRT chemoradiotherapy, *OS* overall survival, *RCT* randomized control trial

Landmark Chemotherapy and Chemoradiation Publications

Study	Methods	Results
FLOT Trial Al-Batran et al. [75]	RCT $N = 716$ Stage ≥cT2 and/or cN+, M0 resectable gastric and GEJ adenocarcinoma 3 preoperative and 3 postoperative 3-week cycles of ECF/ECX or 4 preoperative and 4 postoperative 2-week cycles of FLOT	*Peri-op FLOT improved overall survival and progression-free survival compared to peri-op ECF/ECX* Median OS 50 months vs. 35 months (HR 0.77 [0.63–0.94]; $p = 0.012$) PFS 30 vs. 18 months (HR 0.75 [0.62–0.91]; $p = 0.004$) More grade 3 and 4 nausea/vomiting within ECF/ECX group compared to FLOT

Study	Methods	Results
CRITICS Trial Cats et al. [76]	RCT *N* = 788 Stage 1B-4. Induction. 3 cycles of pre-op ECX, then curative gastrectomy and at least D1 LND, then randomized to post-op chemo (3 cycles of ECX) or CRT (45 Gy + weekly and daily capecitabine) Post-op only 59% of chemo group and 62% of CRT group started post-op therapy	*Post-op CRT did not improve overall survival* vs. *post-op chemo* Median OS 43 months (95% CI 31–57) in chemo group and 37 months (30–48) in CRT group (HR 1.01 m, 95% CI 0.84–1.22; $p = 0.90$). Median follow-up 61.4 months No mortality in post-op period. Grade 3 and 4 complications during post-op were 48% and 9% in chemo group vs. 41% and 4% in CRT group
INT-0116 Trial MacDonald et al. [61]	RCT *N* = 556 Surgery plus adjuvant CRT vs. surgery alone Adjuvant treatment was 5-FU + leucovorin followed by 4500 cGy All patients received curative-intent surgery: Only 10% received D2 resection 54% received D0 resection	*Improved overall and relapse-free survival with adjuvant CRT* Median OS: 36-month CRT vs. 27-month surgery alone; $p = 0.005$ Median RFS: 30-month CRT vs. 19-month surgery alone; $p < 0.001$ 3-year OS: 50% CRT vs. 41% surgery alone; $p = 0.005$
MAGIC Trial Cunningham et al. [73]	RCT *N* = 503, T2 or higher Surgery with perioperative ECF vs. surgery alone ECF was administered for 3 cycles preoperatively and 3 cycles postoperatively	*Improved PFS and OS with perioperative ECF* 5-year OS: 36% ECF vs. 23% surgery alone; HR 0.75 (95% CI 0.60–0.93), $p = 0.009$ PFS: HR 0.66 (95% CI 0.53–0.81), $p < 0.001$
GASTRIC Study Paoletti et al. [74]	Patient-level meta-analysis of 17 RCTs *N* = 3838 Chemotherapy after complete resection vs. surgery alone	*Improved OS and DFS with adjuvant chemotherapy in resectable gastric cancer* OS: HR = 0.82 (95% CI 0.76–0.90; $P < 0.001$) DFS: HR = 0.82 (95% CI 0.75–0.90; $P < 0.001$)
CLASSIC Trial Noh et al. [80]	Multicenter RCT *n* = 1035 patients, stage II–IIIB Surgery plus adjuvant capecitabine and oxaliplatin vs. surgery alone All patients underwent D2 resection	*Improved DFS and OS with chemo* 5-year DFS: 68% vs. 53%; HR 0.58 (95% CI 0.47–0.72) 5-year OS: 78% vs. 69%; HR 0.66 (95% CI 0.51–0.85)

Study	Methods	Results
ARTIST-I Trial Park et al. [78, 79]	RCT $n = 458$ All patients underwent D2 gastrectomy Chemotherapy alone (6 cycles capecitabine + cisplatin) vs. CRT (4 cycles chemo; 45 Gy with concurrent capecitabine)	*No difference in DFS and OS at 7years of median follow-up* 5-year DFS: HR 0.74 (95% CI 0.52–1.05; $p = 0.092$) 5-year OS: 73% vs. 75%, HR 1.13 (95% CI 0.78–1.65; $p = 0.53$) Subgroup analysis suggests benefit of CRT for node-positive disease and intestinal subtype (awaiting results of ARTIST-II trial)

CRT chemoradiotherapy, *OS* overall survival, *RFS* relapse-free survival, *PFS* progression-free survival, *DFS* disease-free survival, *HR* hazard ratio, *RCT* randomized control trial, *ECF* epirubicin/cisplatin/5-fluorouracil, *FLOT* docetaxel, oxaliplatin, fluorouracil, and leucovorin

Landmark Palliative Publications

Study	Methods	Results
Chemotherapy vs. best supportive care in non-curable gastric cancer Glimelius et al. [88]	RCT $N = 61$, unresectable Chemotherapy + best supportive care vs. best supportive care alone Chemotherapy was ELF-regimen consisting of 5-fluorouracil, leucovorin, and etoposide	*Improved or prolonged high-quality life at 4 months*: 45% chemotherapy group vs. 20% best supportive care group; $p < 0.05$
TOGA Trial Bang et al. [89]	RCT $N = 584$, inoperable or metastatic, HER-2+ gastric cancer Chemotherapy alone (capecitabine or 5-FU + cisplatin) vs. chemotherapy + trastuzumab	*Improved median OS in HER2+ patients treated with trastuzumab*: median OS 13.8-month trastuzumab vs. 11.1-month chemotherapy alone ($p = 0.0046$) 22% of patients assessed were HER2+
REGATTA Trial Fujitani et al. 2016 [84]	RCT $N = 175$ (planned $N = 330$) Eligibility: gastric cancer (cT1-3), single non-curable site of disease confined to liver, peritoneum or para-aortic lymph node, PS 0-1 Gastrectomy (D1 without resection of metastases) followed by chemotherapy (S-1 plus cisplatin) vs. chemotherapy alone	Terminated early by DSMC based on futility: 2-year OS 25.1% for gastrectomy followed by chemotherapy vs. 31.7% for chemotherapy alone ($p = 0.68$)

OS overall survival, *RCT* randomized control trial, *5-FU* fluorouracil, *PS* performance status, *DSMC* data safety monitoring committee

Referral to Medical Oncology and Radiation Oncology

- As the decision regarding adjuvant treatments should be made preoperatively, all patients should be referred to medical oncology and radiation oncology prior to resection and discussed at a multidisciplinary care conference.
- Relative contraindications to chemotherapy [62]
  - Impaired cardiac function such as congestive heart failure, baseline left ventricular ejection fraction less than 50%, transmural myocardial infarction, valvular heart disease, high-risk arrhythmias
  - Impaired renal function (Cr clearance of <60 ml/min)
  - Disorders of the nervous system and diabetes are relative contraindications for chemotherapy with neuropathic agents (e.g., platinums)
- Relative contraindications to radiation
  - Prohibitive toxicities anticipated due to volume or adjacent structures
  - Connective tissue disease
  - Previous irradiation to area

Referral to Multidisciplinary Cancer Conference

- All cases of advanced gastric cancer should be discussed at a Multidisciplinary Cancer Conference (MCC), before surgical intervention to devise an individual plan for each patient.
- Gastric cancer cases that were not discussed at MCC preoperatively should be discussed if the final pathology is >T1N0.

References

1. Canadian Cancer Society. Canadian Cancer Society's Steering Committee: Canadian Cancer Statistics 2018. http://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2018-EN.pdf?la=en.
2. Kim JP. Surgical results in gastric cancer. Semin Surg Oncol. 1999;17:132–8.
3. Jim MA, Pinheiro PS, Carreira H, et al. Stomach cancer survival in the United States by race and stage (2001-2009): findings from the CONCORD-2 study. Cancer. 2017;123(Suppl):4994–5013.
4. Fitzgerald RCCC. Clinical implications of E-Cadherin associated hereditary diffuse gastric cancer. Gut. 2004;53:775–8.
5. Gayther SA, Gorrini's KL, Ramos SJ, et al. Identification of germ-line E-Catherine mutations in gastric cancer families of European Origin. Cancer Res. 1998;58:4086–9.
6. Seevaratnam R, Coburn N, Cardozo R, et al. A systematic review of the indications for genetic testing and prophylactic gastrectomy among patients with hereditary diffuse gastric cancer. Gastric Cancer. 2012;15(Suppl 1):S153–63.
7. Pharoah PD, Guilford PCC. Incidence of gastric cancer and breast cancer in CDH1 (E-cadherin) mutation carriers from hereditary diffuse gastric cancer families. Gastroenterology. 2001;121:1348–53.

8. van der Post RS, Vogelaar IP, Carneiro F, et al. Hereditary diffuse gastric cancer: updated clinical guidelines with an emphasis on germline CDH1 mutation carriers. J Med Genet. 2015;52(6):361–74.
9. Caldas C, Carneiro F, Lynch HT, et al. Familial gastric cancer: overview and guidelines for management. J Med Genet. 1999;36:873.
10. Rudloff U. Gastric adenocarcinoma and proximal polyposis of the stomach: diagnosis and clinical perspectives. Clin Exp Gastroenterol. 2018;11:447–59.
11. Worthley DL, Phillips KD, Wayte N, et al. Gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS): a new autosomal dominant syndrome. Gut. 2012;61(5):774–9.
12. Anaya DA, Chang GJ, Rodriguez-bigas MA. Extracolonic manifestation of hereditary colorectal cancer syndrome. Clin Colon Rectal Surg. 2008;21(4):263–72.
13. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol. 2015;110:223.
14. Mankaney G, Leone P, Cruise M, et al. Gastric cancer in FAP: a concerning rise in incidence. Familial Cancer. 2017;16:371–6.
15. Møller P, Seppaia TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the prospective lynch syndrome database. Gut. 2018;67(7):1306–16.
16. Vasen HF, Blanco I, Astana-Collin K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013;62(6):812–23.
17. Tomlinson IP, Houlston RS. Peutz-Jeghers Syndrome. J Med Genet. 1997;34:1007–11.
18. Van Lier MG, Wagner A, Mathus-Vliegen EM, et al. High cancer risk in Peutz-Jeghers syndrome: a systematic review and surveillance recommendations. Am J Gastroenterol. 2010;105(6):1258–64.
19. Gupta S, Provenzale D, Regenbogen SE, et al. NCCN guidelines ® insights: genetic/familial high-risk assessment: colorectal, version 3.2017 featured updates to the NCCN guidelines. J Natl Compr Canc Netw. 2017;15:1465–75.
20. Balmaña J, Balaguer F, Cervantes A, Arnold D. Familial risk-colorectal cancer: ESMO clinical practice guidelines. Ann Oncol. 2013;24(Suppl 6):vi73–80.
21. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American society of clinical oncology clinical practice guideline endorsement of familial risk-colorectal cancer: European Society for medical oncology clinical practice guidelines. J Clin Oncol. 2015;33:209–17.
22. Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. Acta Pathol Microbiol Scand. 1965;64:31–49.
23. Correa P. Human gastric carcinogenesis: a multistep and multifactorial process--First American Cancer Society Award Lecture on Cancer Epidemiology and Prevention. Cancer Res. 1992;52(24):6735–40.
24. Qiu M, Cai M, Zhang D, et al. Clinicopathological characteristics and prognostic analysis of Lauren classification in gastric adenocarcinoma in China. J Transl Med. 2013;11:58.
25. Chen YC, Fang WL, Wang RF, et al. Clinicopathological variation of Lauren classification in gastric cancer. Pathol Oncol Res. 2016;22(1):197–202.
26. Kung PL, Gubens M, Fisher GA, Ford JM, et al. Long-term survivors of gastric cancer: a California population-based study. J Clin Oncol. 2012;30(28):3507–15.
27. Al-Bartan SE, Hofheinz RD, Pauligk C, et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. Lancet Oncol. 2016;17(12):1697–708.

28. Cancer Genome Atlas Research Network, Bass AJ, Thorsson V, Shmulevich I, et al. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–9.
29. Sohn BH, Hwang JE, Jang HJ, et al. Clinical significance of four molecular subtypes of gastric cancer identified by the cancer genome atlas project. Clin Cancer. 2017. https://doi.org/10.158/1078-0432.CCR-16-2211.
30. Smyth EC, Wotherspoon A, Peckitt C, et al. Mismatch repair deficiency, microsatellite instability, and survival: an exploratory analysis of the Medical Research Council adjuvant gastric infusional chemotherapy (MAGIC) trial. JAMA Oncol. 2017;3(9):1197–203.
31. Amin MB, Edge S, Greene F, et al. American Joint Committee Cancer staging manual. New York: Springer; 2017.
32. Sano T, Coit DG, Kim HH, et al. Proposal of a new stage grouping of gastric cancer for TNM classification: International Gastric Cancer Association staging project. Gastric Cancer. 2017;20:2017.
33. In H, Ravetch E, Langdon-Embry M, et al. The newly proposed clinical and post-neoadjuvant treatment staging classifications for gastric adenocarcinoma for the American Joint Committee on Cancer (AJCC) staging. Gastric Cancer. 2018;21(1):1–9.
34. Seevaratnam R, Cardoso R, Mcgregor C, et al. How useful is preoperative imaging for tumor, node, metastasis (TNM) staging of gastric cancer? A meta-analysis. Gastric Cancer. 2012;15(Suppl):S3–S18.
35. Cardoso R, Coburn N, Seevaratnam R, et al. A systematic review and meta-analysis of the utility of EUS for preoperative staging for gastric cancer. Gastric Cancer. 2012;15(Suppl):S19–26.
36. Association Gastric Cancer Association. Japanese classification of gastric carcinoma – 2nd English edition. Gastric Cancer. 1998;1(1):10–24.
37. Gouzi JL, et al. Total versus subtotal gastrectomy for adenocarcinoma of the gastric antrum. A French prospective controlled study. Ann Surg. 1989;209:162–6.
38. Mahar AL, et al. A systematic review of surgery for non-curative gastric cancer. Gastric Cancer. 2012;15(Suppl 1):S125–37.
39. Bonenkamp JJ, et al. Extended lymph-node dissection for gastric cancer. N Engl J Med. 1999;340:908–14.
40. Association JGC. Japanese gastric cancer treatment guidelines 2014 (ver. 4). Gastric Cancer. 2017;20:1–19.
41. Gotoda T. Endoscopic resection of early gastric cancer: the Japanese perspective. Curr Opin Gastroenterol. 2006;22(5):561–9.
42. Daoud DC, Suter N, Durand M, et al. Comparing outcomes for endoscopic submucosal dissection between Eastern and Western countries: a systematic review and meta-analysis. World J Gastroenterol. 2018;24(23):2518–36.
43. Jeon MY, Park JC, Hahn KY, et al. Long-term outcomes after noncurative endoscopic resection of early gastric cancer: the optimal time for additional endoscopic treatment. Gastrointest Endosc. 2018;87(4):1003–1013.e2.
44. Degiuli M, et al. Randomized clinical trial comparing survival after D1 or D2 gastrectomy for gastric cancer. Br J Surg. 2014;101:23–31.
45. Morgagni P, La Barba G, Colciago E, et al. Resection line involvement after gastric cancer treatment: handle with care. Updat Surg. 2018;70(2):213–23.
46. Bria E, De Manzoni G, Beghelli S, et al. A clinical-biological risk stratification model for resected gastric cancer: prognostic impact of Her2, Fhit, and APC expression status. Ann Oncol. 2013;24(3):693–701.
47. Songun I, Bonenkamp JJ, Hermans J, et al. Prognostic value of resection-line involvement in patients undergoing curative resections for gastric cancer. Eur J Cancer. 1996;32A:433–7.
48. Kim SH, Karpeh MS, Klimstra DS, et al. Effect of microscopic resection line disease on gastric cancer survival. J Gastrointest Surg. 1999;3:24–33.
49. Ito H, Clancy TE, Osleen RT, et al. Adenocarcinoma of the gastric cardia: what is the optimal surgical approach? J Am Coll Surg. 2004;199(6):880–6.

50. National Comprehensive Cancer Network. NCCN clinical practice guideline in oncology gastric cancer. v2.2018. http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf http://www.nccn.org/professionals/physician_gls/pdf/gastric.pdf.
51. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(Suppl 5):38–49.
52. McAuliffe JC, Tang LH, Kamrani K, et al. Prevalence of false-negative results of intraoperative consultation on surgical margins during resection of gastric and gastroesophageal adenocarcinoma. JAMA Surg. 2018;154:126.
53. Squires MH 3rd, Kooby DA, Pawlik TM, et al. Utility of the proximal margin frozen section for resection of gastric adenocarcinoma: a 7-Institution Study of the US Gastric Cancer Collaborative. Ann Surg Oncol. 2014;21(13):4202–10.
54. Stiekema J, Trip AK, Jansen EPM, et al. Does adjuvant chemoradiotherapy improve the prognosis of gastric cancer after an R1 resection? Results from a Dutch cohort study. Ann Surg Oncol. 2015;22:581–8.
55. Stiekema J, Trip AK, Jansen EPM, Boot H, Cats A, Ponz OB, et al. The prognostic significance of an R1 resection in gastric cancer patients treated with adjuvant chemoradiotherapy. Ann Surg Oncol. 2014;21:1107–14.
56. Rhome RM, Moshier E, Sarpel U, et al. Predictors of positive margins after definitive resection for gastric adenocarcinoma and impact of adjuvant therapies. Int J Radiat Oncol Biol Phys. 2017;98:1106–15.
57. Dikken JL, Jansen EPM, Cats A, Bakker B, Hartgrink HH, Kranenbarg EMK, et al. Impact of the extent of surgery and postoperative chemoradiotherapy on recurrence patterns in gastric cancer. J Clin Oncol. 2010;28:2430–6.
58. Brar S, Law C, McLeod R, et al. Defining surgical quality in gastric cancer: a RAND/UCLA appropriateness study. J Am Coll Surg. 2013;217(2):347–57.e1.
59. Kim W, Kim HH, Han SU, et al. Decreased morbidity of laparoscopic distal gastrectomy compared with open distal gastrectomy for stage I gastric cancer: short-term outcomes from a multicenter randomized controlled trial (KLASS-01). Ann Surg. 2016;263:28–35.
60. Kurokawa Y, Doki Y, Mizusawa J, et al. Bursectomy versus omentectomy alone for resectable gastric cancer (JCOG1001): a phase 3, open-label, randomised controlled trial. Lancet Gastroenterol Hepatol. 2018;3(7):460–8.
61. Macdonald JS, Smalley SR, Benedetti J, et al. Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. N Engl J Med. 2001;345:725–30.
62. Knight G, Earle CC, Cosby R, TGCDSG, et al.. Neoadjuvant or adjuvant therapy for resectable gastric cancer, Evidence-based series 2–14 version 3. Toronto Cancer Care Ontario; 2011.
63. Lowy AM, Mansfield PF, Leach SD, et al. Laparoscopic staging for gastric cancer. Surgery. 1996;119:611–4.
64. Oh CA, Bae JM, Oh SJ, et al. Long-term results and prognostic factors of gastric cancer patients with only positive peritoneal lavage cytology. J Surg Oncol. 2012;105:393–9.
65. Mezhir JJ, Shah MA, Jacks LM, et al. Positive peritoneal cytology in patients with gastric cancer: natural history and outcome of 291 patients. Ann Surg Oncol. 2010;17(12):3173–80.
66. Newhook TE, Agnes A, Blum M, et al. Laparoscopic hyperthermic intraperitoneal chemotherapy is safe for patients with peritoneal metastases from gastric cancer and may Lead to gastrectomy. Ann Surg Oncol. 2019;26(5):1394–400.
67. Badgwell B, Blum M, Das P, et al. Phase II trial of laparoscopic hyperthermic intraperitoneal chemoperfusion for peritoneal carcinomatosis or positive peritoneal cytology in patients with gastric adenocarcinoma. Ann Surg Oncol. 2017;24(11):3338–44.
68. Songun I, Putter H, Kranenbarg EM, et al. Surgical treatment of gastric cancer: 15-year follow-up results of the randomised nationwide Dutch D1D2 trial. Lancet Oncol. 2010;11:439–49.
69. Bonenkamp JJ, Songun I, Hermans J, et al. Randomised comparison of morbidity after D1 and D2 dissection for gastric cancer in 996 Dutch patients. Lancet. 1995;345:745–8.

70. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. N Engl J Med. 2008;359:453–62.
71. Xiong B, Ma L, Huang W, et al. Efficiency of bursectomy in patients with resectable gastric cancer: an updated meta-analysis. Eur J Surg Oncol. 2019;45:1483.
72. Kim HI, Hur H, Kim YN, et al. Standardization of D2 lymphadenectomy and surgical quality control (KLASS-02-QC): a prospective, observational, multicenter study [NCT01283893]. BMC Cancer. 2014;14:209.
73. Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355:11–20.
74. GASTRIC, Paoletti X, Oba K, et al. Benefit of adjuvant chemotherapy for resectable gastric cancer: a meta-analysis. JAMA. 2010;303:1729–37.
75. Al-Bartan 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 gastricor gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet. 2019;393:1948.
76. Cats A, Jansen EPM, van Grieken NCT, 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;19(5):616–28.
77. Slagter AE, Jansen EPM, van Laarhoven HWM, et al. CRITICS-II: a multicentre randomised phase II trial of neo-adjuvant chemotherapy followed by surgery versus neo-adjuvant chemotherapy and subsequent chemoradiotherapy followed by surgery versus neo-adjuvant chemoradiotherapy followed by surgery in resectable gastric cancer. BMC Cancer. 2018;18(1):877.
78. Lee J, Lim DH, Kim S, et al. Phase III trial comparing capecitabine plus cisplatin versus capecitabine plus cisplatin with concurrent capecitabine radiotherapy in completely resected gastric cancer with D2 lymph node dissection: the ARTIST trial. J Clin Oncol. 2012;30:268–73.
79. 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;33(28):3130–6.
80. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. Lancet Oncol. 2014;15:1389–96.
81. Diaz-Nieto R, Orti-Rodríguez R, Winslet M. Post-surgical chemotherapy versus surgery alone for resectable gastric cancer. Cochrane Database Syst Rev. 2013;(9):CD008415.
82. Grau JJ, Martín M, Fuster J, et al. Impact of adjuvant chemotherapy in the long-term outcome of patients with resected gastric cancer. J Surg Oncol. 2003;82(4):234–40.
83. Sasako M, Sakuramoto S, Katai H, et al. Five-year outcomes of a randomized phase III trial comparing adjuvant chemotherapy with S-1 versus surgery alone in stage II or III gastric cancer. J Clin Oncol. 2011;29:4387.
84. Fujita J, Yang HK, Mizusawa J, et al. Gastrectomy plus chemotherapy versus chemotherapy alone for advanced gastric cancer with a single non-curable factor (REGATTA): a phase 3, randomised controlled trial. Lancet Oncol. 2016;17(3):309–18.
85. Cuschieri A, Fayers P, Fielding J, et al. Postoperative morbidity and mortality after D1 and D2 resections for gastric cancer: preliminary results of the MRC randomised controlled surgical trial. The Surgical Cooperative Group. Lancet. 1996;347:995–9.
86. Cuschieri A, Weeden S, Fielding J, et al. Patient survival after D1 and D2 resections for gastric cancer: long-term results of the MRC randomized surgical trial. Surgical Co-operative Group. Br J Cancer. 1999;79:1522–30.
87. Degiuli M, Sasako M, Calgaro M, et al. Morbidity and mortality after D1 and D2 gastrectomy for cancer: interim analysis of the Italian Gastric Cancer Study Group (IGCSG) randomised surgical trial. Eur J Surg Oncol. 2004;30(3):303–8.

88. Glimelius B, Ekström K, Hoffman K, et al. Randomized comparison between chemotherapy plus best supportive care with best supportive care in advanced gastric cancer. Ann Oncol. 1997;8(2):163–8.
89. Bang YJ, Van Cutsem E, Feyereislova A, et al. Trastuzumab in combination with chemotherapy versus chemotherapy alone for treatment of HER2-positive advanced gastric or gastro-oesophageal junction cancer (ToGA): a phase 3, open-label, randomised controlled trial. Lancet. 2010;376(9742):687–97.