Review

Gastric cancer: past accomplishments, present approaches and future aspirations

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Practice Points

- Gastric cancer results in 10,540 annual deaths in the USA.

- On a global scale, gastric cancer has become the second leading cause of cancer-related deaths and demonstrates an estimated 989,600 new cases annually.

- Cancer of the stomach can be broadly categorized into cardia and noncardia anatomic distributions.

- A multitude of risk factors have been identified for the development of gastric carcinoma, including *Helicobacter pylori* infection, elevated BMI and tobacco smoke.

- There are currently no recommendations regarding routine screening for gastric cancer.

- The GASTRIC trial found improved overall survival with postoperative chemotherapy and 5-year overall survival increased from 49.6 to 55.3%.

- The ToGa trial found improved survival with the addition of trastuzumab in patients with Her-2-positive gastric cancer.

- The MAGIC trial demonstrated that perioperative chemotherapy improved overall survival, 5-year survival and progression-free survival.

- The EORTC 40954 trial found neoadjuvant chemotherapy to provide increased rate of R0 resection.

- The Intergroup-0116 trial demonstrated the benefit of postoperative chemoradiotherapy, manifested as improved overall survival and progression-free survival.

- The ARTIST trial found adjuvant chemoradiation to provide improved 3-year disease-free survival among patients with lymph node involvement.

Future Medicine part of fsg

Practice Points (cont.)

- Intensity-modulated radiation therapy may provide reduced organ toxicity, however the clinical benefit in terms of survival remains to be conclusively established.

- Several prognostic factors for gastric cancer have been suggested, such as tumor size and nodal involvement.

- In the incurable setting, radiotherapy can provide a palliative benefit to patients.

- Several trials are currently in either the planning or accrual stages, such as the MAGIC-B, GRANITE-1, TOPGEAR and ARTIST-2 trials.

- A deeper understanding of the biochemistry of gastric cancer combined with improved surgical methods, chemotherapeutic regimens and radiation delivery techniques is necessary for improved patient outcomes.

SUMMARY   The incidence and mortality of gastric cancer has remained largely unchanged since 2005 and approximately 10,540 patients succumb to the disease each year in the USA. The subject of gastric carcinoma is an area of active research by many groups around the world who are investigating the biology of the disease, as well as newer and more efficacious methods of detection and treatment. This review will provide an introduction to gastric cancer epidemiology and biology, and will serve as an overview of the evolution of the treatment of gastric cancer with a focus on present day management, including surgery, chemotherapy, radiation therapy and novel therapeutic modalities.

Despite ongoing research exploring novel therapeutics, gastric cancer continues to pose a significant health concern with an estimated 21,320 new cases in 2012 and 10,540 deaths in the USA – figures that have remained largely unchanged since 2005 [1,2]. However, the incidence of gastric cancer has decreased – probably as a result of changes in diet, food preparation and environmental factors – as demonstrated by the fact that, while stomach cancer was the leading cause of death in the USA a century ago, it is now seventh [3]. On a global scale, gastric cancer has become the second leading cause of cancer-related deaths with approximately 989,600 new cases annually [4]. The highest reported incidences are in eastern Asia, Europe and South America, while the USA and Africa feature the lowest incidence rates [4]. Although Japan does exhibit a greater prevalence of gastric cancer than most western countries, overall survival rates are higher, probably owing to increased screening efforts leading to earlier diagnosis of the disease [3].

In addition to surgery, which forms the cornerstone of gastric cancer management, novel therapeutic regimens have been developed incorporating chemotherapy and radiation therapy. The current review aims to summarize the progress that has been made in this regard and will also specifically address the role that radiotherapy has in the treatment of gastric cancer.

Background
■ Anatomy
The stomach begins at the gastroesophageal junction (GEJ) and terminates at the pylorus. It is bordered superiorly by the diaphragm, esophagus and left lobe of the liver, and inferiorly by the transverse colon. Posterior to the GEJ is the pancreas; the spleen and liver are located laterally, and anterior is the abdominal wall [3]. The volume of the stomach is divided into several anatomic distributions termed the cardia, fundus, body, pylorus and antrum (Figure 1A). The lateral borders of the stomach are the lesser curvature to the right and the greater curvature to the left [5]. The stomach wall consists of four layers – the serosal layer is the outmost portion and is derived from the omentum [5]. The muscular
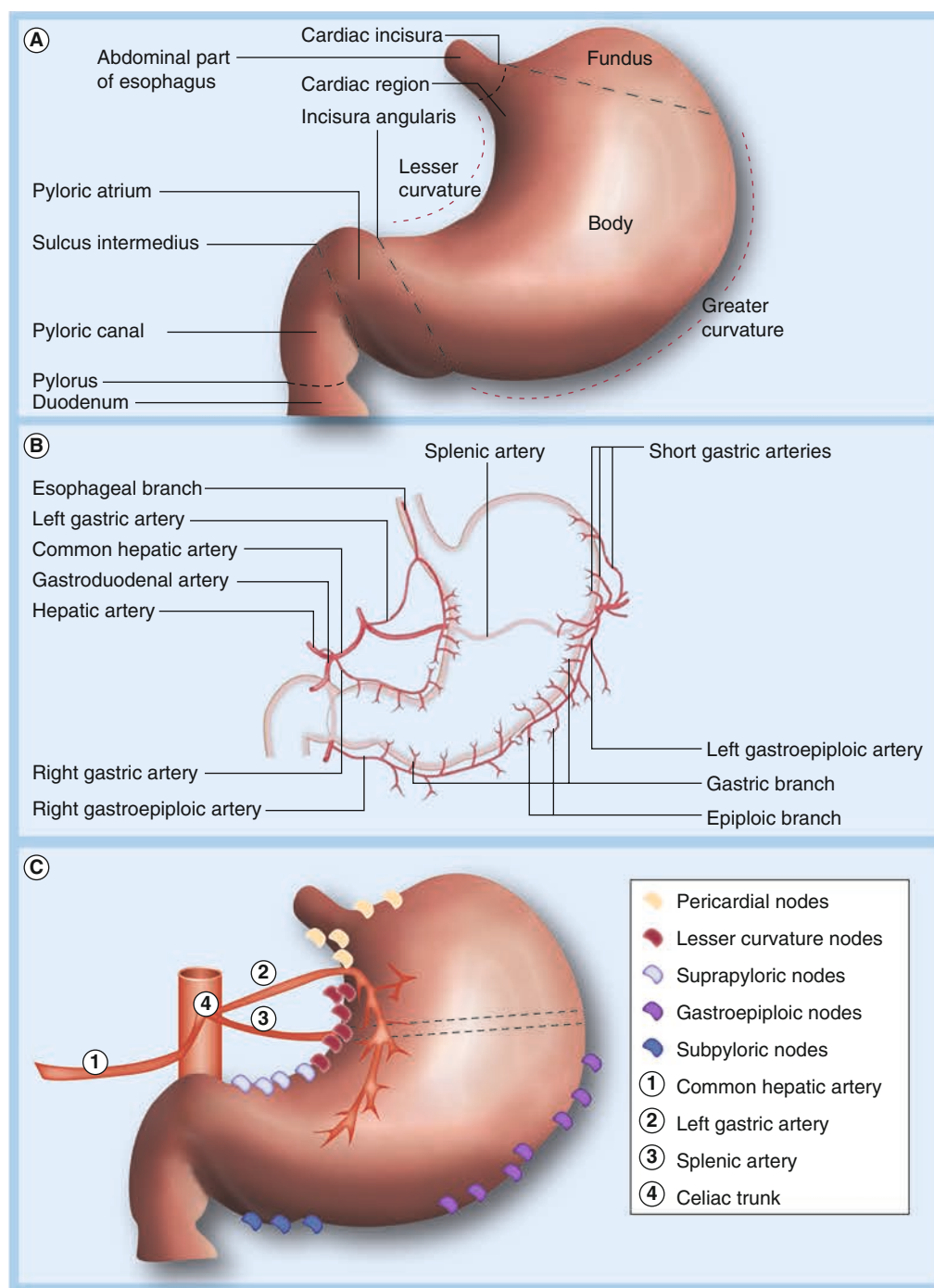
Figure 1. Schematic representations of the stomach. (A) Anatomic distribution, **(B)** blood supply and **(C)** lymphatic drainage.
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layer is beneath the serosa and consists of three types of smooth muscle fibers – longitudinal, circular and oblique [5]. The areolar or submucosal layer connects the muscular layer to the mucosa, which is the innermost portion of the stomach [5]. It is this mucosal layer that contains the glands of the stomach, which function in the production of gastric juices.

The blood supply to the stomach is relatively complex with the lesser curvature supplied by the right gastric artery, derived from the hepatic artery, and the left gastric artery, which

is a branch of the celiac axis **(Figure 1B)** [3]. The greater curvature derives its blood supply from the right gastroepiploic (gastro-omental) arteries, arising from the gastroduodenal artery, and the left gastroepiploic artery, which along with the short gastric arteries, branches directly from the splenic artery [3].

The stomach has an extensive lymphatic system, subdivided into six perigastric groups **(Figure 1C)**. Most proximal are the right and left pericardial lymph nodes, followed by the suprapyloric nodes that are accompanied by the lesser curvature lymph nodes [3]. The greater curvature is supplied by the subpyloric and gastroepiploic nodes [3]. These six lymph node groups drain into the extraperigastric lymph nodes consisting of the common hepatic, left gastric, splenic hilum and splenic artery lymphatics, which in turn drain into the celiac and periaortic lymphatics [3].

■ Symptoms and physical examination findings

Symptoms of gastric cancer include anorexia, weight loss, abdominal pain, anemia, early satiety, nausea, vomiting and melena. The spread of tumor cells along the intrathoracic lymph channels can produce Virchow's node in the left supraclavicular fossa or Irish's node in the left axilla [3]. Palpable nodes in the periumbilical region, termed Sister Mary Joseph's nodes, arise from the spread of tumor cells to the lymphatics along the hepatoduodenal ligament [3].

■ Etiology

Cancer of the stomach can be broadly categorized into cardia and noncardia anatomic distributions. Several studies have identified that while the annual cases of the noncardia subtype have gradually decreased over previous years, the incidence rates of cancers in the gastric cardia have remained either stable or, until recently, steadily increased

since the 1980s [6–11]. The shift in the anatomic distribution of gastric cancer is concerning because cancers of the gastric cardia often present a more complicated and difficult treatment challenge.

Histologically, gastric tumors can be categorized into two subgroups, described by Lauren in 1965: diffuse and intestinal [12]. Cancers of the diffuse subtype often do not arise from precancerous lesions but, rather, appear to have a genetic basis, such as the familial hereditary diffuse gastric cancer syndrome, which is associated with germline mutations in the E-cadherin/*CDH1* gene [12–14]. This is in contrast to cancers of the intestinal histologic type, which are thought to arise from precancerous lesions, such as chronic gastritis [3]. Intestinal-type tumors are also often associated with *Helicobacter pylori* infection and are the more dominant of the histologic subtypes in endemic areas, suggesting a more environmental basis for these cancers [3,15]. Further comparison of these two histologic variants of gastric cancer is provided in **Table 1**.

It is interesting to note that changes in the diet, for example through immigration, can have a profound impact on the likelihood of developing gastric cancer. Kamineni *et al.* demonstrated a decreased incidence of stomach cancer in Japanese individuals who had immigrated to the USA compared with their counterparts in Japan, in addition to further decreases in second-generation descendants [16]. Another study demonstrated similar decreases in Polish immigrants, while second-generation Japanese individuals, who continued to consume a Japanese-style diet, were found to have high rates of gastric cancer, compared with those who had adopted a more western-style diet [17,18].

■ Genetics

Several genetic factors have been identified as having a potential association with the risk of

Table 1. Lauren classification of intestinal- versus diffuse-type gastric cancer.

Intestinal	Diffuse
Older population [172]	Younger population [12]
Men > women [172]	Women > men [12]
Improved prognosis [12]	Worse prognosis [12]
Associated with *Helicobacter pylori* infection [15]	Genetic etiology (e.g., familial hereditary diffuse gastric cancer) syndrome [13]
Associated with chronic inflammation [173]	Inflammation characteristically absent [13]
Usually arises from precancerous lesion, evidence of glandular dysplasia or *in situ* carcinoma [12,174]	Usually arises from normal mucosa, diffusely infiltrative, signet ring-cell type [12,174]
Usually of the proximal stomach [174]	Usually of the distal stomach [174]

developing gastric cancer. Given the currently accepted notion that *H. pylori* infection confers an increased risk of developing stomach cancer, it is interesting to note that genetic factors leading to a decreased host response to bacterial lipopolysaccharide, such as the Toll-like receptor 4+*896A>G* polymorphism, have been identified as independent risk factors of noncardia gastric cancers [19,20]. Several meta-analyses have also uncovered associations between the risk of gastric cancer and inflammatory mediators such as IL-8, IL-10, non-Asian carriers of the *IL-1RN2* polymorphism, the TNF-α *308A* allele and the *-1195G>A* polymorphism of the *COX-2* gene among Asian populations [20–25]. Mucins that are large extracellular proteins involved in the formation of a protective barrier at epithelial surfaces, such as the stomach, have also been implicated in the development of the diffuse type of gastric cancer through several single nucleotide polymorphisms – *rs2294008* in the prostate stem cell antigen gene and both *rs2070803* and *rs4072037* in the *MUC1* gene [20,26,27]. **Table 2** provides an extensive list of potential genetic parameters associated with the risk of developing stomach cancer [19,21–25,28,29,30–35].

■ Staging
Gastric cancers can be staged according to either the classification guidelines set (American Joint Committee on Cancer/Union for International Cancer Control) **(Table 3)** [36] or the Japanese classification system, which makes a distinction between the clinical, surgical, pathologic and final staging **(Table 4)** [37]. Although the Japanese system is more thorough, the results of one study suggest that the American Joint Committee on Cancer/Union for International Cancer Control system provides more accurate estimates of prognosis [38].

■ Risk factors
Aside from the well-established bacterium *H. pylori*, a multitude of risk factors have been identified for the development of gastric carcinoma. Several studies have demonstrated an association between elevated BMI or increased calorie intake and the risk of developing stomach cancer [39–41]. Another study by Lagergren *et al.* found a positive relationship between symptomatic gastroesophageal reflux disease and the risk of gastric cancer, although this association was relatively weak compared with the risk of developing esophageal cancer [42]. Tobacco smoke and the consumption of nitrate-containing foods have also been identified as risk factors [43–46]. In addition, according to some studies, an excessive amount of salt intake correlates strongly with the incidence rates of gastric cancer, partly accounting for the increased risk among Asian populations, and the decline in the prevalence of this disease may be attributable to the decreased use of

Table 2. Genetic polymorphisms associated with the risk of gastric cancer.		
Gene/genetic polymorphism	Effect on risk	Ref.
Among Caucasians		
TLR4+*896A>G*	Increases	[19]
COX-2 *1195G>A*	Increases	[25]
Prostate stem cell antigen *rs2294008*	Increases	[28]
IL1RN2 carriers	Increases	[23]
IL-8–251A carriers	Increases	[21]
IL10–592	Increases	[22]
TNF-α308A carriers	Increases	[24]
GSTT1-null	Increases	[29]
GSTP1-codon 105	Increases	[30]
p53 codon 72	Increases	[31]
ε2 allele of *ApoE* gene	Decreases	[32]
Among Asians		
TGFB1–509T	Increases	[33]
PARP1 762V>A	Increases	[34]
nt -443 of osteopontin promoter	Increases	[35]
Adapted with permission from [20].		

Table 3. American Joint Committee on Cancer Staging of Gastric Cancer, 7th Edition, 2010.			
Primary tumor (T)			
TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor		
Tis	Carcinoma *in situ*: intraepithelial tumor without invasion of the lamina propria		
T1	Tumor invades lamina propria, muscularis mucosae, submucosa		
T1a	Tumor invades lamina propria or muscularis mucosae		
T1b	Tumor invades submucosa		
T2	Tumor invades muscularis propria		
T3	Tumor penetrates subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. T3 tumors also include those extending into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures		
T4	Tumor invades serosa (visceral peritoneum) or adjacent structures		
T4a	Tumor invades serosa (visceral peritoneum)		
T4b	Tumor invades adjacent structures such as spleen, transverse colon, liver, diaphragm, pancreas, abdominal wall, adrenal gland, kidney, small intestine and retroperitoneum		
Regional lymph nodes (N)			
NX	Regional lymph node(s) cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in 1–2 regional lymph nodes		
N2	Metastasis in 3–6 regional lymph nodes		
N3	Metastases in more than 7 regional lymph nodes		
Distant metastasis (M)			
MX	Presence of distant metastasis cannot be assessed		
M0	No distant metastasis		
M1	Distant metastasis		
Stage Grouping			
Stage 0	Tis	N0	M0
Stage IA	T1	N0	M0
Stage IB	T2	N0	M0
	T1	N1	M0
Stage IIA	T3	N0	M0
	T2	N1	M0
	T1	N2	M0
Stage IIB	T4a	N0	M0
	T3	N1	M0
	T2	N2	M0
	T1	N3	M0
Stage IIIA	T4a	N1	M0
	T3	N2	M0
	T2	N3	M0
Stage IIIB	T4b	N0 or N1	M0
	T4a	N2	M0
	T3	N3	M0
Stage IIIC	T4b	N2 or N3	M0
	T4a	N3	M0
Stage IV	Any T	Any N	M1
Adapted with permission from [36].			

Table 4. Japanese classification of gastric carcinoma, 3rd Edition, 2011.			
Primary tumor (T)			
TX	Depth of tumor unknown		
T0	No evidence of primary tumor		
T1	Tumor confined to the mucosa (M) or submucosa (SM)		
T1a	Tumor confined to the mucosa (M)		
T1b	Tumor confined to the submucosa (SM)		
T2	Tumor invades the muscularis propria (MP)		
T3	Tumor invades the subserosa (SS)		
T4	Tumor invasion is contiguous to or exposed beyond the serosa (SE) or tumor invades adjacent structures (SI)		
T4a	Tumor invasion is contiguous to the serosa or penetrates the serosa and is exposed to the peritoneal cavity (SE)		
T4b	Tumor invades adjacent structures		
Lymph node metastasis (N)			
NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis		
N1	Metastasis in 1–2 regional lymph nodes		
N2	Metastasis in 3–6 regional lymph nodes		
N3	Metastasis in 7 or more regional lymph nodes		
N3a	Metastasis in 7–15 regional lymph nodes		
N3b	Metastasis in 16 or more regional lymph nodes		
Distant metastasis (M)			
MX	Distant metastasis status unknown		
M0	No distant metastasis		
M1	Distant metastasis		
Peritoneal metastasis (P)			
PX	Peritoneal metastasis is unknown		
P0	No peritoneal metastasis		
P1	Peritoneal metastasis.		
Peritoneal lavage cytology (CY)			
CYX	Peritoneal cytology not performed		
CY0	Peritoneal cytology negative for carcinoma cells		
CY1	Peritoneal cytology positive for carcinoma cells		
Hepatic metastasis (H)			
HX	Hepatic metastasis is unknown		
H0	No hepatic metastasis		
H1	Hepatic metastasis		
Stage grouping			
	N0	**N1**	**N2**	**N3**
T1a (M), T1b (SM)	IA	IB	IIA	IIB
T2 (MP)	IB	IIA	IIB	IIIA
T3 (SS)	IIA	IIB	IIIA	IIIB
T4a (SE)	IIB	IIIA	IIIB	IIIC
T4b (SI)	IIIB	IIIB	IIIC	IIIC
M1 (any T, any N)	IV	–	–	–
Adapted with permission from [37].			

salt, made possible by widespread refrigeration of foods [16,47]. Salt is thought to facilitate the development of stomach cancer by producing a state of chronic gastritis and atrophy, and by sensitizing the stomach to nitrate-containing foods [15,43,48–50]. A recent study refined this notion by suggesting that sodium chloride and salted foods may have differing effects on the

gastric mucosa, with the risk of cancer being increased by high consumption of salted foods but not by the intake of sodium chloride as a whole salt [47]. The risk of gastric cancer was also found to have a positive correlation with occupational exposure, especially to fine dust, arsenic dust and low-dose radiation, although inadequate powering of studies makes the drawing of strong associations difficult [51,52]. A report by Eom *et al.* also identified risk factors for multiple gastric cancers, namely advanced age, male gender, family history of cancer, location in the upper third of the stomach and early stage of the tumor with a large size of the main lesion identified as an independent risk factor of additional missed lesions [53]. **Box 1** shows a complete list of risk factors currently believed to be associated with gastric cancer.

Box 1. Risk factors for gastric cancer.

Nutritional
- Consumption of salted foods [3,50,175]
- High nitrate consumption [43]
- Low dietary vitamin A and C [50]
- Lack of refrigeration [176]
- Poor drinking water (well water) [3]

Occupational
- Rubber workers [51]
- Coal workers [52]
- Exposure to fine dust/arsenic dust [52]
- Exposure to low dose radiation [52]

Genetic factors
- Type A blood [177]
- Pernicious anemia [177]
- Family history [53]
- Hereditary nonpolyposis colon cancer [178]
- Li–Fraumeni syndrome [178,179]

Precursor lesions
- Adenomatous gastric polyps [176]
- Chronic atrophic gastritis [12,173,176]
- Dysplasia [176]
- Intestinal metaplasia [12,173,176]
- Menetrier's disease [180]

Miscellaneous
- Cigarette smoking [44,45]
- *Helicobacter pylori* infection [20,174,176]
- Epstein–Barr virus [181]
- Advanced age [53]
- Male gender [53]
- Gastroesophageal reflux disease [42]
- BMI/increased caloric intake [39–41]

■ Screening

There are currently no recommendations regarding routine screening for gastric cancer. However, in an early study in Japan, one of the regions with the highest prevalence of this disease, Kaneko *et al.* demonstrated the benefit of a large mass screening effort [54]. This study reported that 90,557 patients were screened and 137 cases of gastric carcinoma were detected. At first glance this may seem to be a small percentage; however, it should be noted that at the time of this study, the death rate from gastric carcinoma in Japan was 122.2 per 100,000 individuals. Moreover, this study reported significantly improved survival rates among patients who underwent mass screening compared with those who did not, owing to the detection of a large number of gastric cancers at the early stage. Although it is possible that improved survival among the Japanese compared with the western population, may be due, in part, to underlying genetic differences, this theory has been called into question by studies reporting survival disparities between Japanese individuals treated with either Japanese techniques or western methods [55]. Since this study by Kaneko and colleagues, numerous groups have explored other potential screening measures for stomach cancer such as photofluography-based techniques and narrow-band imaging magnetic endoscopy [56,57]. A survey of physicians attending the Annual Symposium of the Korean College of *Helicobacter* and Upper Gastrointestinal Research reported that the overwhelming majority of physicians recommended annual endoscopic follow-up for the screening of gastric cancer in patients with intestinal metaplasia and atrophic gastritis [58]. Interestingly, this study also reported no difference in the ability of endoscopy experts and nonexperts in differentiating normal tissue from positive endoscopic findings, suggesting the necessity of a more standardized screening program. To address this need, much work has gone into detecting serum biomarkers that may be used as early indicators of gastric cancer. An early report by Yoshihara *et al.* determined a strong, statistically significant correlation between the risk of gastric cancer and the serum ratio of pepsinogen I and II [59]. Liu *et al.* demonstrated the potential for serum synuclein-γ to serve as a diagnostic indicator of gastric cancer, while another group compiled a panel of 11 protein biomarkers [60,61]. Expanding on earlier work in the field, Ito *et al.* found a strong correlation

between the risk of diffuse-type gastric cancer and the combination of serum pepsinogen level and *H. pylori* antibody positivity [62]. An investigation by Gomceli *et al.* reported on DKK-1, a negative regulator of the Wnt signaling pathway, as a potential novel biomarker of gastric cancer among the Turkish population with a sensitivity and specificity of 100% [63]. These studies represent a small sample of the recently identified potential biomarkers for gastric cancer. A more extensive list adapted from Lin *et al.* is provided in **Table 5**, however, no serum marker is currently considered the standard of care.

■ Survival

While surgery is the mainstay of therapy, early studies have shown an approximate 60% local recurrence rate and long-term survival in only 20–30% of patients in the USA [64–67]. For stage IA patients, 10-year survival rates are approximately 65% and less that 5% for those with more advanced stage IIIB and IV disease with surgery alone [67]. Long-term survival rates are particularly poor for patients with tumors of the gastric cardia as opposed to those of the fundus and more distal sites [67]. Interestingly, survival outcomes reported from Europe and Japan are often higher than what has been found in trials from the USA, with 5-year survival of up to 100% in Japan and 85% in Germany for patients with stage IA disease [68]. The reasons for this discrepancy are unclear with some suggesting that the increased utilization of D2 resections may provide superior outcomes, while others suggest that widespread use of extensive resections leads to upstaging of patients culminating in superior stage-stratified survival for all stages.

■ Diagnosis & workup

The NCCN has published recommendations on the workup of a patient suspected to have gastric cancer, with upper gastrointestinal endoscopy and biopsy serving as the preliminary diagnostic procedure [301]. This is generally followed by CT scans or preferably PET scans of the chest and abdomen to identify the presence of disseminated disease. In cases where M1 disease has not been established, an esophageal ultrasound is warranted to further define tumor size (T-stage), lymph node involvement (N-stage), involvement of distant organs (M-stage) and the presence or absence of ascites. Finally, in patients with evidence of metastatic adenocarcinoma, testing for the

Table 5. Biomarkers associated with gastric cancer.		
Method of detection	**Biomarker**	**Ref.**
Blood	CFI	[182]
	C9	[183]
	IPO-38	[184]
	ITIH3	[185]
	MIF	[186]
Gastric fluid	Pepsin A	[187]
	α1-antitrypsin precursor	[188]
	α-defensin	[189]
	Pepsinogen II	[190]
	GKN1	[190]
Tissue	Selenium-binding protein 1	[187]
	PTEN	[191]
	Cathepsin B	[192]
	HSP27	[193]
	Her2	[194]
Cell lines	Vimentin	[195]
	IL-8	[196]
	ENO1	[197]
	Phospho-p53	[198]
	Galectin 1	[195]
Adapted with permission from [12].		

Her2/neu mutation is carried out. Following this initial workup, additional evaluation for patients with greater than T1a but not M1 disease, who are considering chemoradiation (ChRT) or surgery, may be performed via diagnostic laparoscopy to evaluate the presence of peritoneal metastasis. Those with T1a disease or less are recommended to undergo a multidisciplinary evaluation with consideration given to endoscopic mucosal resection or gastrectomy, while patients with M1 disease are recommended to receive palliative therapy.

Treatment options for gastric cancer

The first gastrectomy for removal of the stomach in the treatment of gastric cancer was performed in 1881 by Theodor Billroth, and complete surgical resection of all gross and microscopic disease continues to be the only proven curative therapy [3,69]. In 2002 Hartgrink *et al.* found that for noncurable cases of stomach cancer, palliative resection also provided a survival advantage over supportive care (8.1 vs 5.4 months); however, on subgroup analysis, this survival benefit was found to only exist among patients with one positive sign of advanced disease (10.5 vs 6.7 months) and not for those patients with two or more signs of incurability. Indicators of advanced disease were defined according to criteria set forth by

the Japanese Research Society for the Study of Gastric Cancer whereby signs of incurability were defined as macroscopically unresectable tumor, hepatic metastasis, peritoneal involvement or distant nodal metastasis [70,71]. It should be noted, however, that resection for palliative purposes is not currently considered standard of care according to the guidelines set forth by the National Cancer Comprehensive Network [301].

An impressive amount of literature has accumulated regarding the treatment of this disease and one study found significant disparity between the treatment alternatives proposed by surgeons, medical oncologists and radiation oncologists, with many physicians not adhering to recommended guidelines [72]. This review will summarize the salient features of the body of knowledge that has accumulated thus far.

■ Surgical management

Open gastrectomy, whether partial or total, is the most commonly employed surgical technique for the removal of stomach cancer [73]. Specifically, total gastrectomy is recommended for the removal of tumors in the proximal or middle third of the stomach, while a more conservative distal gastrectomy is recommended for cancers of the distal third of the stomach [74–76]. Lymph node dissection often accompanies surgery for stomach cancer and can be a matter of debate among surgeons. Delineated according to the Japanese Classification System, the least invasive lymph node evaluation is termed a D1 dissection, consisting of removal of the perigastric lymph nodes (Figure 2) [77]. A D2 dissection consists of the additional removal of nodes along the splenic artery left hepatoduodenal artery, left gastric artery, and common hepatic artery (Figure 2) [77]. The most invasive evaluation, a D3 dissection, includes removal of the para-aortic and posterior hepatoduodenal lymph nodes (Figure 2) [77]. Although multiple studies have demonstrated initially equal survival times between a D1 dissection and the more morbidity-prone D2 dissection, a recent report identified a significant improvement in the gastric cancer-related death rate at a median follow-up of 15.2 years (Box 2) [78–83]. As a result, D2 dissections are now considered to be the recommended operation in western countries, but may be limited by body habitudes. This is in contrast to Japanese practice, in which D2 resections have long been considered the standard of care [84].

■ Postoperative chemotherapy

Although surgery currently offers the only chance for a cure, survival rates with surgery alone are generally poor due to a high rate of local and metastatic relapse [85]. Therefore, much research has gone into the development of adjuvant chemotherapy regimens. In a meta-analysis, Hermans *et al.* concluded that postoperative chemotherapy provided no survival benefit over surgery alone [86]. However, since then, more recent meta-analyses have identified a significant survival advantage with postoperative chemotherapy, especially with combination regimens utilizing 5-fluorouracil (5-FU), an anthracycline and cisplatin [87–95]. These studies reported hazard ratios (HR) for overall survival ranging from 0.78 to 0.85 in favor of postoperative chemotherapy. The most recent meta-analysis, conducted by the Global Advance/Adjuvant Stomach Tumor Research International Collaboration (GASTRIC) Group analyzed 17 randomized controlled trials totaling 3838 patients (Box 3) [94]. This study found a statistically significant improvement in overall survival (HR of death: 0.82; $p < 0.001$) and disease-free survival (HR: 0.82; $p < 0.001$). Median overall survival increased from 4.9 years with surgery alone to 7.8 years with surgery and postoperative chemotherapy, while 5-year overall survival increased from 49.6 to 55.3%.

A large randomized controlled Phase III trial compared surgery alone with surgery plus chemotherapy consisting of eight 3-week cycles of capecitabine and 6 months of oxaliplatin, following gastrectomy with D2 dissection among patients with stage II–IIIB gastric cancer [96]. The authors reported that at a median follow-up time of approximately 34 months, the addition of chemotherapy to surgery had resulted in a 3-year progression-free survival of 74% compared with 59% in the surgery only group ($p < 0.0001$). Another large Phase III trial by Sasako *et al.* compared surgery alone with surgery plus chemotherapy consisting of 4 weeks of S-1 (an oral fluoropyrimidine antitumor agent designed from a prodrug of 5-FU) followed by 2 weeks of rest, with this cycle being repeated for 1 year [97]. The overall 5-year survival for this ongoing trial was reported to be 61.1% in the surgery-only group compared with 71.7% in the surgery plus chemotherapy cohort and progression-free survival rates were 53.1 and 65.4%, respectively. Although many of the published reports involved
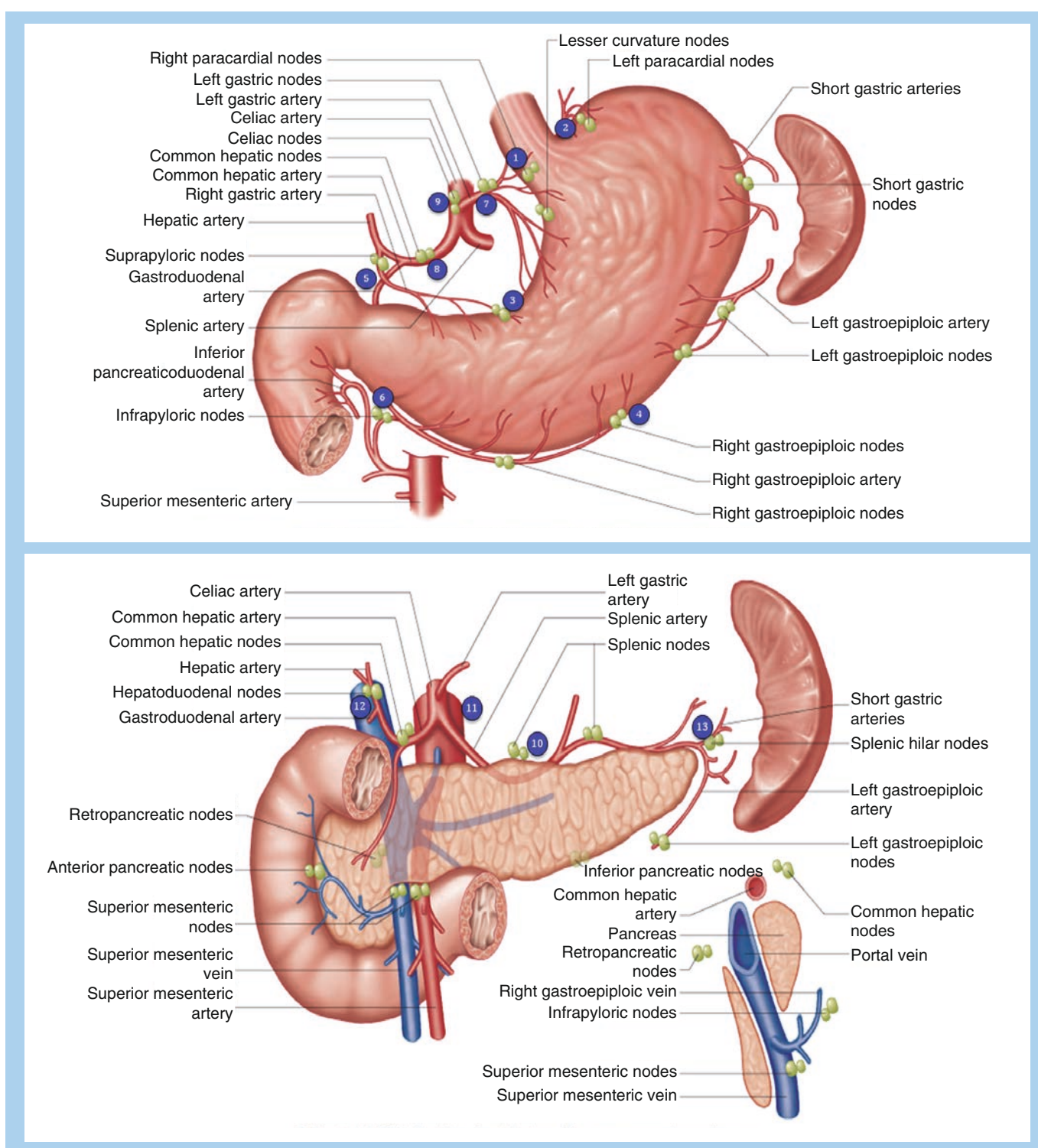
Figure 2. Location of lymph nodes involved in D1–D3. D1 dissections involve the perigastric lymph nodes (locations 1–6). D2 dissections involve lymph nodes along the splenic artery (location 10), splenichilum (location 13), celiac artery (location 9), left gastric artery (location 7), and common hepatic artery (location 8). D3 dissections include para-aortic (location 11) and posterior hepatoduodenal lymph nodes (location 12).
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Box 2. Randomized Dutch trial of D1 versus D2 lymphadenectomy.

A randomized Dutch trial that included 1078 patients who underwent either D1 or D2 lymphadenectomy demonstrated that at a median follow-up of 15.2 years, patients who received D2 resections experienced fewer deaths due to gastric cancer (37 vs 48%; p = 0.01), greater freedom from recurrence (28 vs 22%; p = 0.015) and lower rates of locoregional recurrence (22 vs 12%; p = 0.015)

Data taken from [82].

D2 lymphadenectomies and many others do not explicitly specify the type of surgery performed, the results of the meta-analysis by Sun *et al.* suggests that the benefit of postoperative chemotherapy can also be attained following D1 resection [92].

Chemotherapy for unresectable gastric cancer

In the case of advanced inoperable gastric cancer, early studies demonstrated a clear and substantial benefit to chemotherapy compared with best supportive care. A seminal report by Murad *et al.* investigated a regimen consisting of 5-FU, doxorubicin and methotrexate (FAMTX) and found a median overall survival of 9 months compared with only 3 months in the control group (p = 0.001), with a very acceptable toxicity profile **(Box 4)** [98]. Randomization was interrupted in the middle of this study once the benefit provided by the chemotherapy regimen became apparent. A randomized Phase III trial by another group explored the benefit of a similar regimen consisting of 5-FU, epidoxorubicin and methotrexate versus the best supportive care and found a median time to progression of 5.4 months in the treatment group and only 1.7 months in the control group (p = 0.0013), with an equally impressive improvement in median overall survival, which was reported to be 12.3 months in the treatment group compared with 3.1 months in the control group (p = 0.0006) [99]. Another randomized trial by Glimelius *et al.* found a statistically significant advantage to chemotherapy versus the best supportive care in terms of overall survival, progression-free survival and quality of life [100]. A meta-analysis by Wagner *et al.* confirmed these findings by reporting chemotherapy provided a significant survival advantage of approximately 6 months compared with supportive care (HR: 0.39–0.49), while also leading to a significant improvement in the quality of life [95]. This study also found a survival advantage with combination chemotherapy regimens versus single agent therapy (HR: 0.82) with the best overall survival achieved through the three-drug combination of 5-FU, cisplatin and an anthracycline. Another group conducting a pooled analysis of irinotecan-containing treatment regimens in comparison with those lacking this agent found a statistically significant benefit in terms of time-to-treatment failure, as well as decreased incidence of gastrointestinal and high-grade hematologic toxicity [101]. However, this study did not find an improvement in overall survival with the inclusion of irinotecan.

An important Phase III international study published in 2010, termed the ToGa trial incorporated both gastric (82% of patients) and gastroesophageal cancers (18% of patients) and compared the clinical outcomes between chemotherapy alone, consisting of either capecitabine plus cisplatin or 5-FU plus cisplatin, with chemotherapy plus trastuzumab in patients with gastroesophageal/gastric cancer positive for Her2, which has been reported to occur in 7–34% of cases, although as Gravalos and colleagues have suggested, Her2 positivity is less frequent with gastric tumors (9.5%) compared with tumors of the GEJ (25%) [102–105]. The ToGa study found a significant increase in median overall survival with the addition of trastuzumab (13.8 months) versus chemotherapy alone (11.1 months), with comparable rates of adverse events between the two treatment regimens **(Box 4)**. A summary of various chemotherapeutic regimens that have been investigated for the treatment of unresectable gastric cancer is provided in **Table 6**. First-line chemotherapy regimens are most often either taxane- or 5-FU-based with irinotecan as a second-line agent to be used in combination with other drugs [301].

Preoperative chemotherapy

One of the most important drawbacks of a combination regimen involving both surgery

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Box 3. GASTRIC meta-analysis of survival with postoperative chemotherapy.

Meta-analysis of 17 trials totaling 3838 patients demonstrating adjuvant chemotherapy provided improved overall survival (hazard ratio: 0.82; p < 0.001) and improved disease-free survival (hazard ratio: 0.82; p < 0.001). Estimated median overall survival was 4.9 years in the surgery only group versus 7.8 years in the surgery + chemotherapy group, while 5-year survival increased from 49.6 to 55.3%

Data taken from [94].

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and postoperative chemotherapy is the morbidity resulting from gastrectomy, which leads to poor compliance with postoperative chemotherapy [69]. To address this issue, several groups have explored the possibility of neoadjuvant and perioperative chemotherapy. A Phase III study, termed the MAGIC trial, investigated the clinical outcomes between patients with resectable cancer receiving either surgery alone or perioperative chemotherapy in addition to surgery [106]. This trial included 503 patients, 253 of whom received surgery alone and the other 250 received perioperative chemotherapy consisting of three preoperative and three postoperative cycles of epirubicin (50 mg/m^2) and cisplatin (60 mg/m^2) on day 1, and a continuous infusion of 5-FU (200 mg/m^2) for 21 days. The patient population included in the study consisted of those with stomach cancer (76%) as well as patients with lower esophageal and esophagogastric cancers (26%). While no differences in postoperative complications were detected, resected tumors among the patients receiving preoperative chemotherapy were found to be significantly smaller and less advanced compared with those in patients who did not receive chemotherapy. The MAGIC trial also reported improvement in overall survival among the patients receiving perioperative chemotherapy (HR: 0.75), 5-year survival (36 vs 23% for surgery alone) and progression-free survival (HR: 0.66). Of note, patients were not routinely staged in a modern fashion with neither esophageal ultrasound nor PET in this trial. In addition, of the 250 patients treated with perioperative chemotherapy, no patient achieved a pathological complete response, which has been suggested to confer a survival benefit [107].

Despite the influential nature of the MAGIC trial, it does not make it possible to determine the relative contributions of pre- and post-operative chemotherapy, an important issue considering the substantial difficulty patients often experience with postoperative treatment. To address this concern, a study from the European Organization for Research and Treatment of Cancer (EORTC) conducted by Schuhmacher *et al.,* randomized 144 patients to receive either surgery alone or preoperative chemotherapy followed by surgery **(Box 5)** [108]. Approximately 37% of patients treated with neoadjuvant therapy had cardia or GEJ tumor locations. These researchers found improved R0 resection

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Box 4. Chemotherapy for inoperable gastric cancer.

A randomized prospective Phase II–III trial examined FAMTX therapy versus best supportive care in 40 patients with advanced gastric cancer. The treatment group demonstrated an increase in median OS (9 vs 3 months; p = 0.001) with randomization interrupted in the middle of the study due to the overwhelming improvement in patient outcome with FAMTX therapy;
ToGa Trial: randomized, international, Phase III trial involving 594 patients and conducted across 24 countries examining the effect of chemotherapy versus chemotherapy + trastuzumab for *Her2*-expressing gastric or GEJ cancer. Chemotherapy consisted of either capecitabine + cisplatin or 5-FU + cisplatin. Median OS was improved in the trastuzumab plus chemotherapy group (13.8 vs 11.1 months; p = 0.0046). Rates of grade 3 or 4 adverse events did not differ between the chemotherapy only arm and the chemotherapy + trastuzumab arm

5-FU: 5-Fluorouracil; FAMTX: 5-Fluorouracil, doxorubicin and methotrexate; GEJ: Gastroesophageal junction; OS: Overall survival.
Data taken from [92,102].

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following neoadjuvant therapy compared with surgery alone (81.9 vs 66.7%), but did not find an overall survival benefit. However, the authors reported that 95.8% of patients were able to complete both the chemotherapeutic regimen and undergo surgery. Pathological complete response rate was 7.1% and lymph nodes were positive in 76.5% in the surgery-alone group versus 61.4% in the neoadjuvant group (p = 0.018). Lymphatic invasion was absent in 41 patients (58.6%) in the neoadjuvant group versus 23 patients(33.8%) in the surgery-alone group (p = 0.01).

The reasons for the lack of survival benefit in the EORTC study in contrast to the MAGIC trial are unclear; however, among the possible explanations is the inclusion of only T3 and T4 tumors in the EORTC study, whereas a substantial fraction of the MAGIC trial participants had tumors of stage T1 and T2. Furthermore, the EORTC trial demonstrated a high proportion of R0 resections with low rates of postoperative complications even in the surgery-only group, and these resections may have provided substantial survival with little additional benefit possible through the incorporation of preoperative chemotherapy. Furthermore, the MAGIC trial included a substantial portion of patients with cancers of the esophagus and GEJ, which have been demonstrated in the literature to benefit from preoperative chemotherapy. Alternatively, this discrepancy in survival between the two studies can be attributed to the postoperative chemotherapy in the MAGIC trial and the ensuing eradication of metastatic disease, some of which may have resulted from intraoperative seeding. In addition, the lack of survival

Table 6. Phase II studies examining various chemotherapy regimens for unresectable gastric cancer.						
Chemotherapeutic agents	CR (%)	PR (%)	Disease control rate (CR + PR + SD; %)	Median progression-free survival (months)	Median overall survival (months)	Ref.
FOLFIRI	0	18.2	36	2.3	5.1	[199]
FOLFIRI	0	21	46	2.5	7.6	[200]
FOLFIRI	5.2	23.7	63	3.7	6.4	[201]
FOLFIRI	0	10	46.7	3.3	10.9	[202]
FOLFOX	3	50	70.6	9.4	12.1	[203]
XELIRI	3.1	40.6	68.8	5.6	11	[204]
Irinotecan	0	9.3	62.8	2.8	8.0	[175]
S-1 + paclitaxel	NA	NA	NA	7.5	15	[205]
S-1 + cisplatin	2.6	42.1	79.6	6.4	13.4	[206]
S-1 + docetaxel + cisplatin	0	81	98.3	8.7	18.5	[207]
S-1 + oxaliplatin	0	53.7	90.2	4.6	7.8	[208]
NK105 (micellar paclitaxel)	3.6	21.4	55.4	3.0	14.4	[209]
5-FU, cisplatin, doxorubicin	12.8	51.3	NA	7.93	12.1	[210]
5-FU, cisplatin, mitomycin-C	10.3	28.2	NA	5.14	8.3	[210]
TIROX	14	61	79.5	10.2	17.6	[211]
Irinotecan, cisplatin	0	21	63	3.6	7.4	[212]
Docetaxel, S-1	NA	46	NA	7.3	16.0	[213]
Docetaxel, cisplatin	NA	24	NA	4.9	8.3	[213]
Cetuximab, irinotecan, leucovorin, 5-FU	NA	46	79	9	16.5	[214]
Oxaliplatin, capecitabine	4.1	58.1	83.8	5.9	10.8	[215]
Paclitaxel, 5-FU, leucovorin	3.3	46.7	78.3	7.7	14.3	[216]
Docetaxel (75 mg/m^2), capecitabine (1000 mg/m^2)	5	45	87.5	5.6	10.1	[217]
Docetaxel (60 mg/m^2), capecitabine (800 mg/m^2)	0	23.5	70.6	3.7	7.2	[217]
Docetaxel, cisplatin, 5-FU	7.1	71.4	92.1	NA	13	[218]
Docetaxel, oxaliplatin	4.7	27.9	79.1	4.2	8.3	[219]
Sunitinib	0	2.6	34.6	2.3	6.8	[220]

5-FU: 5-Fluorouracil; CR: Complete response; FOLFIRI: Irinotecaan, 5-Fluorouracil, leucovorin; FOLFOX: Leucovorin, fluorouracil and oxaliplatin; NA: Not available; PR: Partial response; SD: Stable disease; TIROX: S-1, irinotecan and oxaliplatin; XELIRI: Capecitabine and irinotecan.

advantage in the EORTC trial, similar to that observed in the MAGIC trial, could be related to the power of the study, being that the MAGIC study evaluated 503 patients while the EORTC trial included 144 patients.

Another study utilizing a neoadjuvant docetaxel-based regimen reported 75% of patients in the preoperative arm tolerating both surgery and chemotherapy, while only 34% of those in the postoperative arm were able to receive both modalities [109]. This study also reported similar postoperative morbidity between the two arms but a tendency for greater incidence of chemotherapy-related serious adverse events in the postoperative chemotherapy arm (23%) versus the preoperative chemotherapy arm (11%; p = 0.07).

A Phase III trial by Ychou and colleagues reported findings similar to the MAGIC trial [110]. This investigation consisted of 224 patients, 111 assigned to surgery alone and 113 to surgery with perioperative chemotherapy consisting of two or three preoperative cycles of cisplatin (100 mg/m^2) on day 1 and a continuous infusion of 5-FU (800 mg/m^2) on days 1–5 every 28 days with three or four postoperative cycles of the same regimen. This trial found an improvement over surgery alone in 5-year survival (38 vs 24%), 5-year disease-free survival (34 vs 19%) and curative resection rate (84 vs 73%) with similar rates of postoperative morbidity. However, it should be noted that the original design of this study was meant to include only tumors of the esophagus and GEJ, with inclusion criteria later expanded to include gastric cancers. The authors of this study reported a beneficial effect of chemotherapy only in patients with tumors of the GEJ, which

comprised approximately two-thirds of the patients in the study. The other two patient groups – those with cancers of the esophagus and noncardia stomach – were deemed too small to be able to distinguish between a small effect of chemotherapy and no effect at all. Likewise, the aforementioned MAGIC trial also did not evaluate a purely homogenous group, with approximately 15% of patients with cancers of the lower esophagus and 12% with cancers of the GEJ.

Several pilot studies and Phase II trials have been conducted utilizing a variety of chemotherapeutic agents in combination with surgery. A summary of these is provided in **Table 7**. It should be noted that according to the guidelines of the NCCN, the current standard of care for localized operable stomach cancer is either preoperative chemotherapy or ChRT followed by surgery and additional postoperative treatment, with similar systemic treatment guidelines in the case of inoperable gastric cancer [301].

■ **Hyperthermic intraperitoneal chemotherapy**

Several groups have also addressed the incorporation of cytoreductive surgery (CRS) followed by hyperthermic intraperitoneal chemotherapy (HIPEC) into the management of peritoneal carcinomatosis from gastric cancer. A recent

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Box 5. EORTC 40954 preoperative chemotherapy trial.

The European Organization for Research and Treatment of Cancer Trial 40954 randomized 144 patients with locally advanced carcinoma of the stomach or GEJ to receive surgery alone or neoadjuvant chemotherapy followed by surgery. Chemotherapy consisted of two 48-day cycles of cisplatin (50 mg/m^2) followed by continuous infusion 5-FU (2000 mg/m^2). Among patients receiving neoadjuvant chemotherapy, complete and partial clinical responses were seen in 5.8 and 30.4%, respectively. The rate of R0 resection was significantly improved, 66.7% in the surgery alone arm versus 81.9 in those receiving neoadjuvant chemotherapy (p = 0.036). HR for median overall survival was 0.84 in favor of chemotherapy, but this was not statistically significant (p = 0.466). HR for progression-free survival was also in favor of chemotherapy (HR: 0.76) but was also not of statistical significance (p = 0.20)

5-FU: 5-Fluorouracil; GEJ: Gastroesophageal junction; HR: Hazard ratio.
Data taken from [108].

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study from Brazil reported on the treatment of patients with a combination of preoperative chemotherapy (docetaxel, cisplatin and 5-FU), D2 resection, HIPEC with mitomycin C and three more cycles of postoperative chemotherapy with the same three agents [111]. At a median follow-up of 25 months, the authors reported seven out of ten patients without evidence of disease. Yang *et al.* carried out a Phase III trial with patients randomized to CRS alone or CRS + HIPEC [112]. At a median follow-up of 32 months, the authors reported a mortality rate of 97.1% in patients receiving CRS compared with 85.3% in those receiving the combined therapy. Median overall survival in this study was

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Table 7. Early phase clinical trials utilizing various chemotherapy regimens in combination with surgery.

Study (year)	Chemotherapy	AC/NAC	pCR (%)	RR (%)	OS	DFS	Remarks	Ref.
Inoue *et al.* (2012)	S-1 + cisplatin	NAC	0	63	Median 50.1 months	17.4 months	NA	[221]
Li *et al.* (2012)	FOLFOX	AC vs NAC	6	69.7	74 months	Median DFS not reached	4-year survival: neoadjuvant (78%), adjuvant (51%) 4-year DFS: neoadjuvant (78%); adjuvant (51%)	[222]
Oyama *et al.* (2012)	Docetaxel + cisplatin + S-1	NAC	0	68.8	2-year survival: DCS (93.8%), no DCS (32.9%)	2-year DFS: DCS (75.0%), no DCS (28.7%)	100% DCR	[223]
Fushida *et al.* (2012)	Docetaxel + cisplatin + S-1	NAC	NA	NA	Ongoing	NA	NA	[224]
Fujiwara *et al.* (2012)	NIPS: docetaxel + S-1	NAC	0	78	Median 24.6 months 1 year: 76% 2 years: 54%	NA	Survival: 1 year (76%), 2 years (54%)	[225]

AC: Adjuvant chemotherapy; DCR: Disease control ratio; DCS: Docetaxel + cisplatin + S-1; DFS: Disease-free survival; FOLFOX: Leucovorin, fluorouracil and oxaliplatin; NA: Not available; NAC: Neoadjuvant chemotherapy; NIPS: Neoadjuvant intraperitoneal and systemic chemotherapy; OS: Overall survival; pCR: Pathologic complete response; RR: Response rate.

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significantly improved with CRS-only patients surviving 6.5 months and CRS + HIPEC patients surviving 11.0 months (p = 0.046), with no significant difference in serious adverse effects between the two groups [112]. Due to the increased morbidity associated with CRS and HIPEC therapy, the value of this treatment has been a source of controversy; however, a recent study has suggested that despite an initial reduction in the quality of life, patients will often return to their baseline level of functioning within the first 6 months to 1 year [113].

■ Postoperative radiation therapy

Given the high local recurrence rate of resected gastric cancer of 50–60%, many groups have studied radiation therapy with or without chemotherapy, as a means of attaining improved locoregional control of disease. An early prospective, randomized controlled trial by the British Stomach Cancer Group allocated patients to receive either surgery alone, surgery and adjuvant radiation or surgery and adjuvant chemotherapy [114]. This study did not find any benefit in the administration of either adjuvant radiation or chemotherapy versus surgery alone and proposed that surgery remains the standard of care. Similarly, with the exception of a small study by the Gastrointestinal Tumor Study Group with a 4-year follow-up, several other early studies did not detect a benefit with the combination of radiation and chemotherapy compared with chemotherapy alone in terms of patient survival [115–117].

However, other early Phase III trials suggested a potential role for postoperative radiation therapy [118,119]. One such trial, by Zhang and colleagues, investigating the potential benefit of preoperative radiation therapy without chemotherapy, noticed improvements in 5-year (30.10 vs 19.75%) and 10-year (20.26 vs 13.30%) survival rates, as well as decreases in local relapse (38.6 vs 51.7%) and regional lymph node metastasis (38.6 vs 54.6%) when comparing surgery with postoperative radiotherapy with surgery alone [119].

A seminal Phase III report was published with the results of the Intergroup-0116 trial 3 years later **(Box 6)** [120]. This trial included 556 patients who were assigned to receive either surgery alone or surgery plus adjuvant 5-FU and leucovorin for one cycle followed by 5-FU and leucovorin during the first and last weeks of radiation (4500 at 180 cGy per day given 5 days per week for 5 weeks) followed by additional 5-FU and leucovorin. The results demonstrated a statistically significant benefit of postoperative ChRT manifested as improved overall survival (36 vs 27 months; p = 0.005) and progression-free survival, with a HR for relapse of 1.52 against the surgery-only arm of the study (p < 0.001) [120]. Of note, patients were required to maintain a caloric intake of at least 1500 kcal/day by either oral or enterostomal alimentation, highlighting the importance of adequate nutrition during treatment for the results of this trial to be generalizable. In a recently published 10-year follow-up, the Intergroup-0116 trial reported nearly unchanged HRs with a HR of overall survival and progression-free survival of 1.32 and 1.51, respectively, against the surgery-only arm [121]. Moreover, the authors noted a significant difference in the patterns of relapse with locoregional failures occurring in 24% of patients receiving surgery and ChRT and in 47% of those who received surgery alone (p = 0.012). Rates of distant metastases were comparable between the two cohorts [121]. It is noteworthy that a majority of patients in the Intergroup-0116 trial underwent either D0 or D1 resection with only 10% receiving the more extensive D2 resection, suggesting the benefit of postoperative ChRT in the cases of less extensive lymph node dissection.

Similarly, ChRT following D2 resection was found by Kim *et al.* to be superior to surgery alone, yielding increases in overall survival (95.3 vs 62.6 months), progression-free survival (75.6 vs 52.7 months) and consistently greater 5-year survival rates among patients with higher-stage cancers [122]. In addition, the authors of this prospectively designed study reported significantly lower locoregional recurrence in the combination treatment arm (14.9 vs 21.7%). This study is noteworthy since while adjuvant ChRT had become standard practice for D0 and D1 resections following the INT-0116 trial, the additional benefit that ChRT may provide following D2 resection was a matter of debate. Dikken *et al.* compared Phase I/II trials employing postoperative ChRT with surgery-only studies by the Dutch Gastric Cancer Group Trial (DGCT), which randomly assigned patients to either a D1- or D2-type resection. Dikken and colleagues found that local recurrence after 2 years was significantly lower in the ChRT group versus the surgery only group, 5 and 17%, respectively [123]. However,

following subgroup analysis, this study concluded that while a significant difference in local recurrence was present between D1-resection patients receiving ChRT and DGCT-D1 resection-only patients (2 vs 8%), no such decrease in local recurrence rates was found when D2-resection patients receiving ChRT were compared with DGCT-D2 resection-only patients, a finding that appears to contradict the results reported by Kim *et al.* [122].

This apparent contradiction seems to be reconciled by the recently completed Phase III ARTIST trial **(Box 6)** [124]. This study consisted of 458 post-D2 resection patients randomized to receive either capecitabine plus cisplatin or capecitabine plus cisplatin with concurrent ChRT consisting of radiotherapy and capecitabine. This study did not find a significant improvement in 3-year disease-free survival with ChRT (78.2%) or without (74.2%). However, on subgroup analysis, the patients who had lymph node involvement were found to derive a significant benefit in terms of 3-year disease-free survival (77.5 vs 72.3%). It is plausible that because the Kim *et al.* and Dikken *et al.* studies did not differentiate between node-positive and node-negative patients, the former study (which excluded T1N0 and T2N0 patients) detected a benefit among patients receiving D2 resection, while the latter study (in which 44.7% of surgery only patients were N0) did not. The ARTIST trial also demonstrated that when the patients were stratified by stage (IB/II and III/IV), the addition of ChRT conferred a significant prolongation in disease-free survival across all stages (HR: 0.6865). Therefore, despite a short follow-up period, there were relatively high survival rates and further evaluation of these patients is necessary for recurrence and survival.

Intraoperative radiation therapy

Zhang *et al.* compared patients receiving surgery and adjuvant ChRT with patients receiving surgery, intraoperative radiation and adjuvant ChRT [125]. These investigators found a significant increase in 5-year locoregional control rates (50 vs 35%) and decreased recurrence within the external-beam radiotherapy field for patients receiving intraoperative radiation. However, as would be expected, the authors reported a higher incidence of grade 3 and 4 late toxicity in patients receiving intraoperative radiation, namely enteritis and hemorrhage.

Box 6. Postoperative radiation therapy for gastric cancer.

The Intergroup-0116 trial randomized 556 patients with cancer of the stomach or gastroesophageal junction to either surgery alone or surgery + postoperative ChRT, with adjuvant therapy consisting of 5-FU, leucovorin and 45 Gy radiation. Median OS was increased in the cohort receiving combination therapy (36 vs 27 months) with HR for death = 1.35 in the surgery only group (p = 0.005). HR for relapse in patients receiving surgery alone was 1.52 (p < 0.001). A 10-year update continued to demonstrate improved median OS (HR: 1.32; p = 0.0046) and recurrence-free survival (HR: 1.51; p < 0.001). Locoregional failures occurred in 47% of patients who underwent surgery alone compared with 24% in patients receiving surgery plus postoperative ChRT (p = 0.012)

The ARTIST trial randomized 458 patients to postoperative chemotherapy alone (capecitabine + cisplatin) or chemotherapy plus 45 Gy radiotherapy. Although the addition of radiotherapy did not increase DFS in the study population as a whole, on subgroup analysis, patients with metastatic lymph node involvement did demonstrate improved 3-year DFS with radiation therapy (77.5 vs 72.3%; p = 0.0365)

5-FU: 5-Fluorouracil; ChRT: Chemoradiation; DFS: Disease-free survival; HR: Hazard ratio; OS: Overall survival. Data taken from [120,121,124].

Preoperative radiation therapy

An important prospective study conducted by Skoropad *et al.* analyzed the outcome of using a combination of preoperative radiotherapy, surgery and intraoperative radiotherapy compared with surgery alone [126]. This study found that while the combined modality did not lead to a survival benefit in lymph node negative and T1–T2 cases, there was a statistically significant survival advantage among patients with lymph node-positive and T3–T4 cancers, a finding also reported by earlier studies [127,128]. However, it should be noted that despite the radiotherapy regimen, 20 Gy in five fractions preoperatively and 20 Gy intraoperative radiation as a single fraction, is not standard. A follow-up study by the same group also found no increase in the rate of surgical complications such as anastomotic leakage and wound infection, a complementary finding to that of Valenti *et al.* who found similar rates of postoperative complications between patients receiving chemotherapy and those receiving chemotherapy followed by ChRT [129,130]. Ajani and colleagues demonstrated a 26% pathologic complete response rate and 77% R0 resections following preoperative chemotherapy (leucovorin, 5-FU and cisplatin) followed by 45 Gy radiation with concurrent chemotherapy (5-FU and paclitaxel). The authors reported grade 3 late radiation effects in only 5% of patients and 21% experienced grade 4 toxicity, notably thrombosis, fatigue, anorexia, diarrhea and vomiting [107]. Another recent meta-analysis by Valentini and colleagues analyzed nine

randomized controlled trials to find a clear benefit in 5-year overall survival following preoperative radiotherapy (Box 7) [131].

A study performed at the MD Anderson Cancer Center (TX, USA) retrospectively analyzed clinical outcomes among patients who received preoperative ChRT, but were then unable to undergo surgery due to clinical deterioration, predominantly due to the development of metastatic disease [132]. The authors reported a local control of 11.0 months and an overall survival of 10.1 months, with most patients receiving a dose of 45 Gy. This study and others described in **Table 8** suggest a benefit of ChRT for gastric cancer for patients with resectable gastric cancer treated with ChRT compared with patients treated with chemotherapy alone, in terms of pathological complete response rates which are two- to three-times higher with CRT compared with chemotherapy alone.

An important point of any preoperative regimen is that it allows for the selection of patients who may experience metastatic disease during this time and may not benefit from surgery. There is ongoing work investigating novel combinations of radiation and chemotherapy. **Table 8** provides details on the more recent trials.

Radiation therapy for unresectable gastric cancer

While radiotherapy has been demonstrated to be beneficial in the treatment of resectable gastric cancer, several studies have also demonstrated a benefit of radiation in combination with chemotherapy in the management of patients with inoperable disease. Moertel *et al.* randomized patients with unresectable gastric cancer to either radiotherapy alone or 5-FU with concurrent radiation and found a median survival of 6 months among patients receiving radiation alone compared with 13 months among patients receiving combined treatment [133]. The 5-year

survival was also found to be improved to 12% with combined modality therapy compared with 0% in the radiation-alone cohort [133]. Another study by the Gastrointestinal Tumor Study Group compared chemotherapy alone with MeCCNU (semustine) and 5-FU to a regimen consisting of radiation concurrent with 5-FU followed by maintenance therapy with MeCCNU and 5-FU [115]. This study demonstrated a statistically significant improvement among patients receiving the combined ChRT regimen with regard to 4-year survival (18 vs 7%; p < 0.05) [115].

■ Intensity-modulated radiation therapy

The INT-0116 trial utilized radiation delivered in the form of photons of at least 4 MV and, although a groundbreaking study, the authors of this trial reported significant grade 3 or greater treatment-related toxicity, with hematologic and gastrointestinal adverse events experienced by 54 and 33% of patients, respectively [120]. These side effects prompted investigation into other modalities of radiation delivery that may potentially reduce therapy-associated toxicity. Intensity-modulated radiation therapy (IMRT) is a recent advance in radiation therapy that allows for more conformal treatment plans, while also making it possible to deliver varying radiation doses within a single treatment session. Several recent studies have investigated the therapeutic value of IMRT for the management of stomach cancer. A relatively early study, which retrospectively analyzed and compared multiple plans for each of the 15 gastric cancer patients who were treated with postoperative radiotherapy, concluded that IMRT plans for gastric cancer resulted in lower doses to the left kidney and especially avoided the possible ablation of one kidney that can result with more conventional anteroposterior/posteroanterior (AP/PA) fields of radiation [134]. However, the authors also reported higher doses to the right kidney using IMRT compared with AP/PA plans. IMRT dose constraints, with respect to the kidneys, included a V12 of 25% with maximum dose of 45 Gy. This study addresses the importance of avoiding excessive, even low-dose, irradiation of the kidney as long-term, clinically significant nephropathy can occur with a latency of up to 15 years [135].

Ringash and colleagues demonstrated the superiority of IMRT compared with 3D conformal radiotherapy (3D-CRT) in terms of

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Box 7. Meta-analysis of pre-, intra- and post-operative radiation for gastric carcinoma.

A meta-analysis of nine randomized controlled trials taking place over a total of 25 years evaluated the effect radiotherapy (pre-, post- or intra-operative) on 3- and 5-year survival. Preoperative radiotherapy was found to have a statistically significant effect on 5-year survival, by both intention to treat (relative risk of survival: 1.39; p = 0.002) and per protocol (relative risk of survival: 1.29; p = 0.04) analyses

Data taken from [131].

Study (year)	Chemotherapy	Radiation	pCR (%)	RR (%)	Survival	Remarks	Ref.
Table 8. Clinical trials using combinations of chemotherapy and radiation†.							
Trials incorporating preoperative ChRT							
Kim *et al.* (2009)	5-FU	SBRT 45–51 Gy	71	100	3-year MOS: 43% 3-year DFS: 29%	Limited to para-aortic lymph node recurrence	[149]
Inoue *et al.* (2012)	S-1	3D-CRT 50 Gy	8.3	83.3	3-year MOS: 58.3%	NA	[226]
Chakravarty *et al.* (2012)	5-FU/FA/oxaliplatin or docetaxel/5-FU/oxaliplatin	IMRT 45–50.4 Gy	20	80	80% survival at 14-month follow-up	NA	[145]
Pera *et al.* (2012)	Oxaliplatin, cisplatin, 5-FU	45 Gy	16	58	Median PFS 23.2 months MOS: 28.4 months	Included esophageal, GE and gastric cancers	[227]
Lee *et al.* (2012)	Dose level -1: S-1 60 mg/m²/day + oxaliplatin 40 mg/m² on days 1, 8, 15 and 22 Dose level 1: S-1 80 mg/m²/day + oxaliplatin 40 mg/m²	3D-CRT 41.4 Gy	8.3	50	NA	Dose level 1: 1 DLT S-1 dose at Dose level 1 was reduced to 60 mg/m²/day during study because of toxicity	[228]
Trials incorporating postoperative ChRT							
Boda-Heggemann *et al.* (2009)	5-FU/FA or oxaliplatin/ capecitabine	45 Gy 3D-CRT or IMRT	NA	NA	MOS: 3D-CRT 18 months, IMRT not reached 2-year survival: 3D-CRT 37%, IMRT 67%	NA	[144]
Zhang *et al.* (2012)	5-FU + cisplatin + docetaxel + leucovorin	3D-CRT 45 Gy vs IOERT 12–15 Gy + 3D-CRT 39.6 Gy	NA	5-year LRC: IOERT – 50%, No IOERT – 35%	5-year survival: IOERT – 28%, No IOERT – 26%	NA	[229]
Papadimitriou *et al.* (2012)	Adjuvant leucovorin + 5-FU	45 Gy	NA	NA	MOS: 32 months DFS: 25.2 months	NA	[230]
Kofoed *et al.* (2012)	Adjuvant 5-FU + leucovorin	45 Gy, locoregional	NA	NA	3-year AC: 37%, Surgery alone: 24% MOS: adjuvant – 26 months, surgery alone – 16 months	Limited to cancer of GEJ; T0N0 and T1N0 excluded	[231]

†Pathologic complete response rates with chemoradiation regimens **(Table 7)** are often greater than with chemotherapy alone regimens **(Table 6)**, ranging from 8.3 to 71% versus 0 to 6%.
5-FU: 5-Fluorouracil; AC: Adjuvant chemotherapy; ChRT: Chemoradiation; CRT: Conformal radiation therapy; DFS: Disease-free survival; DLT: Dose-limiting toxicity; FA: Folinic acid; GE: Gastroesophageal; GEJ: Gastroesophageal junction; IMRT: Intensity-modulated radiation therapy; IOERT: Intraoperative electron beam radiotherapy; LRC: Locoregional control; MOS: Median overall survival; NA: Not available; pCR: Pathologic complete response; PFS: Progression-free survival; RR: Response rate; SBRT: Stereotactic body radiosurgery.

target volume coverage and sparing of critical organ, such as the spinal cord, kidneys, liver and heart **(Box 8)** [136]. In a case report comparing IMRT with AP/PA and three field treatments, Knab *et al.* noted that IMRT plans resulted in a significantly lower mean and maximum radiation dose to the whole kidney [137]. Additional benefits included a lower volume of the liver receiving radiation, a lower volume of irradiated small bowel, and a lower dose delivered to the spinal cord [137]. Several other studies have also supported the findings of these investigators, suggesting that IMRT may be superior to 3D-CRT for treating cancers of the stomach [138,139]. Minn *et al.* reported reduced liver V30 for IMRT versus 3D-CRT (p < 0.001), as well as no increase in serum creatinine (p = 0.02), suggesting sparing of renal function, although kidney V20 (p = 0.17) and mean liver dose (p = 0.19) were not significantly improved and mean kidney dose was found to be higher in the IMRT cohort (13.9 vs 11.1 Gy;

Box 8. Intensity-modulated radiation therapy versus 3D-conformal radiation therapy for gastric cancer.

Twenty patients with gastric cancer underwent treatment planning with IMRT and 3D-CRT to evaluate whether or not one treatment modality provided a superior plan. Plans were evaluated by two different radiation oncologists with disagreements being resolved by a third oncologist. IMRT was found to provide superior planning target volume coverage in 86% of cases with improved sparing of the spinal cord in 74%, kidneys in 69%, liver in 71% and heart in 69% of cases. The maximal dose to the spinal cord and median dose to 50% of the liver, heart and left kidney were lower with IMRT compared with 3D-CRT

CRT: Conformal radiation therapy; IMRT: Intensity-modulated radiation therapy.
Data taken from [136].

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p = 0.05) [138]. Two-year overall survival rates in this study were improved, but not of statistical significance (65 vs 51%; p = 0.5) [138]. A study from The Netherlands confirmed reports that IMRT improves organ sparing compared with 3D-CRT; however, the group did not detect further benefit with the addition to the IMRT of respiration-gated radiotherapy, in which radiation delivery is synchronized to the patient's respiratory cycle [140]. Another study by Tillman *et al.* concluded that preoperative radiation therapy compared with postoperative radiotherapy provided benefits such as significant reduction in target volume, lung irradiation and radiation dose to the heart [141]. However, they did not detect any difference in radiation dose to the kidney, spinal cord and liver.

Despite the apparent improved critical organ sparing afforded by IMRT compared with 3D-CRT, a crucial issue to consider is that of normal tissue exposure to low-dose radiation. An important article by Hall and Wuu made the argument that due to a combination of more fields being used for IMRT plans and increased radiation leakage, IMRT results in a greater percentage of normal tissue exposed to low-dose radiation [142]. The authors estimate that this will lead to a near doubling of the second malignancy rate from 1% for conventional radiotherapy to 1.75% for IMRT, for patients surviving 10 years. A similar increase in the rate of second malignancies with IMRT was also reported in a recent study on prostate, as well as head and neck, cancers [143]. It can be argued that due to the poor long-term survival of gastric cancer patients, second malignancies arising after a period of 10 years may not be clinically relevant.

Several studies have also conducted single-arm and double-arm evaluations of IMRT-based treatments. A report from Germany compared 3D-CRT with conventional chemotherapy (5-FU/folinic acid) to IMRT with intensive chemotherapy (oxaliplatin/capecitabine) to find markedly improved patient survival in the IMRT cohort [144]. These authors also reported no adverse events greater than grade 2 in either treatment group. A recent study from the MD Anderson Cancer Center has demonstrated the utility of IMRT as a preoperative therapeutic option in providing excellent target coverage and fewer, albeit not statistically significant, hospitalizations and instances of feeding tube use compared with 3D-CRT [145]. Another report by Hofheinz *et al.* presented evidence for the tolerability of combining IMRT with two potent cytostatic chemotherapeutics, oxaliplatin and capecitabine [146]. Although the available data suggests the possibility of reduced normal tissue doses to certain critical organs through the use of IMRT, whether or not this translates into measurable clinical benefit in reducing short- and long-term toxicity has yet to be established, necessitating further work in this area.

■ **Stereotactic body radiosurgery**

Stereotactic body radiosurgery (SBRT) is an advanced form of radiation therapy and is defined by the American Society for Radiation Oncology as "an external-beam radiation therapy method used to very precisely deliver a high dose of radiation to an extracranial target within the body, using either a single dose or a small number of fractions" with the goal being "high target dose and steep dose gradients beyond the target" [147]. Targets usually treated with this technique are small, approximately 6 cm or less, so this technique could not be applied to standard postoperative radiation fields that treat draining lymph node basins, anastomotic sites and preoperative tumor volumes. As a relatively new technique, research into the application of SBRT is sparse. Bignardi *et al.* compared conformal radiation therapy, IMRT and SBRT for abdominal lymph node metastases from gastric cancer and reported improved target volume coverage and lower irradiation of organs at risk with SBRT, relative to IMRT and conformal radiation therapy [148]. However, given the very low involvement of organs at risk with all three modalities, it remains to be seen whether or not such reduction in healthy tissue irradiation will confer a clinical benefit. Although, a clear

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benefit of SBRT, as noted by these authors, is the improved treatment efficiency in the form of fewer fractions compared with IMRT and conformal radiation therapy.

Para-aortic lymph node recurrence of gastric cancer poses an important therapeutic challenge from a radiotherapy perspective in that the proximity of these lymph nodes to critical structures, such as the spinal cord, small intestine and colon, hinder the delivery of effective doses of radiation with standard regimens [149]. A small study consisting of seven patients utilizing SBRT for salvage therapy after recurrence to para-aortic lymph nodes reported, at a follow-up of 14–33 months, only two patients died of their disease (at 14 and 32 months) [149]. Of the remaining patients, all of whom survived at least 20 months, two were disease free at the time of follow-up (26 and 33 months) and five were alive with disease. A case study from Japan reported on incorporation of SBRT in the treatment of liver metastases in an elderly man with gastric cancer. The authors reported a reduction in tumor size with the patient alive and disease free after 2 years [150]. Although these are small studies, they suggest the possibility that SBRT may prove very effective in managing certain aspects of gastric cancer and underscore the necessity for further work in this area.

Prognostic/predictive factors of survival & response to therapy

In recent years, several groups have attempted to identify predictive factors that would indicate the likelihood of recurrence. Zhang *et al.* reported on the differing efficacy of 5-FU-based treatments based on the expression of polymorphisms for the gene encoding dihydropyrimidine dehydrogenase, a key enzyme involved in the metabolism of 5-FU [151]. Shitara *et al.* uncovered evidence for a potential role in delaying recurrence for two polymorphisms of IGF-1, rs1520220 and rs2195239, with rs1520220 being particularly protective among patients with Stage III–IV disease [152]. Peritoneal recurrence is the most common site of failure in patients with stage II/III gastric cancer and although the introduction of chemotherapeutic regimens incorporating S-1 has improved survival rates, a report by Aoyama and colleagues indicated that tumor diameter ≥70mm and pathologic N3 stage are risk factors of peritoneal recurrence [153]. This

study also identified tumor size and lymph node metastases as being prognostic of survival with only 37.2% of patients with tumor size ≥70mm, as opposed to 79.2% of those with tumor size <70mm, surviving 5 years and only 46.0% of N3 patients versus 74.7% of N0–N2 patients surviving 5 years [153].

Consistent with the central role that surgical resection maintains in the treatment of gastric carcinoma, cancers of the middle or upper third of the stomach, if treated with D2 resection, often necessitate dissection of the splenic hilar lymph nodes, which in turn requires a splenectomy [154]. However, given the already advanced nature of disease involving the splenic hilar lymph nodes, the efficacy of splenectomy has been a subject of debate. Zhu *et al.* addressed this issue in a recent study examining the prognostic significance of splenic hilar lymph node involvement, discovering that for patients with metastases to these lymph nodes, there was no survival difference following either R0 resection or R1–R2 resection [154]. In addition, the presence of splenic hilar lymph node involvement was found to be a independent risk factor of both distant metastases following R0 resection, as well as reduced survival, further lending support to the notion that splenic hilar lymph node metastases may be an indication of incurable disease and splenectomy, given the associated morbidity, may not be justified in patients with involvement of these lymph nodes [154]. Expression of histone deacetylase 1 in gastric carcinoma has been suggested to confer worse prognosis among patients with an initial response to platinum-based chemotherapy according to a study by Mutze *et al.,* while expression of the serine protease HtrA1 appeared to improve response to platinum-based chemotherapy in a report by Catalano and colleagues [155,156].

Research efforts have also attempted to identify prognostic factors of recurrence and survival with the aim of determining a more individually tailored approach to treatment. A study from China by Liu *et al.* identified three independent prognostic factors that correlated with reduced survival among patients with node-negative gastric cancer, namely T stage (HR: 2.735), lymphatic tumor emboli (HR: 7.270) and vascular tumor emboli (HR: 3.010) [157]. Liver–intestine cadherin, CDH17, was identified by Wang and colleagues as bearing prognostic significance among pN0 cancers, especially

with regard to larger tumor size, deeper invasion, lymphatic invasion, lymph node micrometastasis and overall survival, with only 54.1% of CDH17-positive patients surviving 5 years compared with 89.1% of those not expressing CDH17 [158].

Radiation therapy for palliation

Despite the survival advantage afforded by radiation therapy, gastric cancer is often an incurable disease, particularly in advanced disease. However, for terminally ill patients, radiotherapy has been shown to provide a palliative benefit in several studies. A study from the MD Anderson Cancer Center by Kim *et al.* demonstrated that a significant proportion of patients benefit from a radiation dose of 35 Gy in terms of bleeding (70%), dysphagia/obstruction (81%) and pain (86%) [159]. Furthermore, the palliation received from each of these symptoms was of considerable duration, lasting a median of 70, 81 and 49% of the remainder of the patient's life, respectively [159]. This report confirmed the results of an earlier retrospective analysis from Singapore that used a variety of radiation regimens ranging from 8 Gy in a single fraction to 40 Gy in 16 fractions. Following radiotherapy, 54.3% of patients experienced control of bleeding (median duration of response: 140 days), 25% of patients experienced control of obstruction (median duration of response: 102 days) and 25% of patients experienced pain control (median duration of response: 105 days) [160]. Asakura *et al.* demonstrated that 30 Gy delivered in ten fractions is adequate to control gastric bleeding and found that patients who received concurrent chemotherapy had a significantly reduced rate of bleeding, exhibiting a median rebleeding survival-free time of 5.5 months compared with 1.7 months for radiotherapy alone [161]. These findings were further confirmed by a Japanese study that reported hemostasis rates of up to 92% with radiation therapy of a median dose of 40 Gy [162].

Ongoing clinical trials & novel targets in gastric cancer

Research into the mechanistic biochemistry, the predictive proteomics and the multidisciplinary management of gastric cancer is widespread and ongoing. A large multicenter trial is currently underway, recruiting patients from The Netherlands, Sweden and Denmark. Termed the CRITICS trial, this Phase III study will treat patients with three cycles of preoperative epirubicin, cisplatin and capecitabine (ECC), followed by surgery with lymph node dissection [163]. The patients will then be randomized to either an additional three cycles of ECC or concurrent ChRT (45 Gy, cisplatin and capecitabine). Primary end points will be overall survival with secondary end points of disease-free survival, toxicity and quality of life.

Another study that is currently in the process of accruing, termed the MAGIC-B trial, will be similar to the original MAGIC study, but will randomize patients to perioperative ECC with or without the addition of bevacizumab, an antibody directed against the VEGF receptor, intended for antiangiogenetic effect. This antibody was also utilized in the AVAGAST trial, which randomized patients to either chemotherapy alone (capecitabine plus cisplatin) or chemotherapy with bevacizumab [164]. Although overall survival between the two groups was not significantly different (12.1 months with bevacizumab vs 10.1 months), the addition of bevacizumab led to a statistically significant improvement in progression-free survival (6.7 vs 5.3 months; p = 0.0037) and response rate (46 vs 37.4%; p = 0.0315) [164].

The aforementioned ToGA trial demonstrated improved survival with the incorporation of the Her2 monoclonal antibody, trastuzumab, in patients with gastric cancer positive for overexpression of the Her2 receptor, making trastuzumab the first targeted agent that yielded a survival benefit for gastric cancer patients. Indeed, targeted molecular therapeutics will most likely play an everincreasing role as adjuvant agents in the management of cancer and several recent studies have undertaken the effort to identify potential candidate compounds. The mTOR and the associated PI3K pathway of growth, proliferation and survival has been an active area of cancer research for several years. Yoon and colleagues, along with several other groups, have explored the potential benefit of inhibiting the kinase activity of mTOR, thus preventing downstream activation of the ribosomal protein S6K1 and subsequent protein synthesis [165]. Although the report by Yoon *et al.* only demonstrated median progression-free and overall survival of 1.7 and 8.3 months, respectively, this trial consisted of very advanced gastric cancer cases with patients who had previously failed multiple regimens.

However, a clear and direct relationship was noted between the phosphorylation of S6K1 and survival, culminating in a twofold increase in overall survival over patients who did not display phosphorylation of S6K1. The results of this trial suggest that while inhibition of the mTOR pathway with agents such as everolimus may not be successful as monotherapy for all cases of gastric cancer, incorporation of these compounds as adjuvant therapeutics may provide substantial benefit in select populations demonstrating expression of the appropriate biomarkers. Two important Phase III trials are currently underway to more clearly define a role for the mTOR inhibitor, everolimus. The GRANITE-1 study will examine the safety and efficacy of everolimus in patients with advanced gastric cancer by comparing best supportive care with best supportive care plus everolimus [302]. The GRANITE-2 study, which is currently accruing, will compare everolimus alone versus everolimus plus paclitaxel, among patients initially treated with a fluoropyrimidine containing regimen, with the primary end point being progression-free survival [303].

Among the planned sequels to the aforementioned studies is the ARTIST-2 trial, which will further explore the interesting finding that patients in the ARTIST trial with metastatic disease in the lymph nodes appeared to derive a greater benefit from D2 lymphadenectomy and ChRT. The Phase III ARTIST-2 trial will include patients with pathologic lymph node involvement and randomize patients to receive either D2-resection alone or D2 resection with postoperative ChRT.

An Australian Phase II–III trial is currently open to recruitment to elucidate the benefit of neoadjuvant ChRT therapy. Termed TOPGEAR, this study will compare the control arm, consisting of preoperative chemotherapy, surgery and postoperative chemotherapy with a treatment arm consisting of preoperative chemotherapy followed by preoperative ChRT, surgery and postoperative chemotherapy [304]. Preoperative chemotherapy will consist of epirubicin 50 mg/m^2 and cisplatin 60 mg/m^2 on day 1 with a continuous 21-day infusion of 5-FU 200 mg/m^2/day. Preoperative ChRT will consist of a continuous 200 mg/m^2/day infusion of 5-FU throughout the entire period of radiotherapy, which will be 45 Gy given over 25 fractions, 5 days per week for 5 weeks. Alternatively, preoperative ChRT may consist of capecitabine 825 mg/m^2 twice per day on days 1–5 of each week during the same regimen of radiotherapy. Postoperative chemotherapy in both the control and treatment arms will be comprised of three cycles of epirubicin, cisplatin and 5-FU 4–10 weeks following surgery. The surgical procedure will be a D1 lymphadenectomy at a minimum with D2 resection recommended. The trial is aiming to recruit a total of 752 patients with the primary outcome being overall survival.

Lapatinib, another kinase inhibitor with activity against both the Her2 and EGF receptor kinase domains, has also been the subject of active investigation with regard to gastric cancer. Currently approved for use in breast cancer patients who have failed trastuzumab, anthracyline and taxane therapy, lapatinib has demonstrated activity in preclinical studies against gastric cancer cell lines [166–168]. A current Phase III study is in progress to determine if the addition of lapatinib to chemotherapy consisting of capecitabine plus oxaliplatin extends time to progression and overall survival versus chemotherapy alone [305]. Other cellular targets of anticancer agents that are currently being investigated include the c-Met tyrosine kinase, which is involved in cellular proliferation and angiogenesis, as well as inhibitors of Polo-like kinase 1, which is involved in various stages of mitosis, such as centrosome maturation, spindle formation, chromosome separation and cytokinesis [169,170].

Conclusion

The management of gastric cancer is a complex and multi-faceted issue. Surgery, in the form of a partial or total gastrectomy, still remains as the only curative approach, however long-term survival is complicated by relapse and metastases [85]. Several important studies, such as the GASTRIC, MAGIC, and EORTC 40954 trials, have demonstrated the benefit of chemotherapy, both in the preoperative and postoperative settings, and others have shown this benefit to extend to the management of inoperable gastric cancer [94,98,99,106,108]. HIPEC therapy and novel combination of chemotherapeutic agents are an area of active research [111,112].

Interest in the incorporation of radio-therapy into the treatment of gastric cancer has led to several seminal studies such as the

Intergroup-0116 and ARTIST trials, which suggested improved patient outcomes following chemoradiation versus chemotherapy alone [120,124]. Modified radiotherapy regimens have been explored including preoperative and intraoperative approaches, both of which appear to provide a survival advantage [125,131]. Preoperative radiation has also been suggested to confer improved survival to patients who were unable to undergo subsequent surgery as a result of metastatic disease and this ability to select out patients who will not benefit from surgery, due to distant metastases, serves to illustrate an additional advantage of the preoperative approach [132]. More sophisticated radiation delivery techniques such as IMRT and SBRT are being actively research with the goal of providing improved targeting of the cancer with reduced normal tissue radiation exposure [136,149,150].

Current guidelines established by the National Comprehensive Cancer Network suggest, for the medically fit patient, preoperative chemotherapy or chemoradiation followed by surgery and either observation or additional postoperative treatment based on the degree of tumor resection achieved [301]. Current and future studies, such as the CRITICS, MAGIC-B, and ARTIST-2 trials will further refine the management of gastric cancer [163].

Future perspective
Since Theodor Billroth performed the first gastrectomy in 1881, the repetoire of therapeutic options available in the treatment of gastric cancer has expanded considerably. The introduction and continued discovery of various cytotoxic agents has resulted in considerable improvement in patient survival. The combined treatment modality of such agents, together with rapidly advancing radiation technology, has provided a powerful adjuvant tool following surgical resection. Despite such formidable advances, gastric cancer continues to pose a considerable therapeutic challenge and a poor, albeit improved, patient outcome. Moreover, while cytotoxic chemotherapeutics are a critical component of stomach cancer management, the efficacy of such agents appears to have reached a plateau. The future of gastric cancer therapy will most likely revolve not around a single modality, but will draw upon the individual potencies of cytotoxins for systemic treatment, as well as improved radiation targeting and delivery for locoregional control with the incorporation of novel targeted agents, made possible by an ever increasing understanding of the biological mechanics of gastric cancer.

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