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Gastric Cancer Etiology and Management in Asia and the West

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Abstract

Regional variation in treatment paradigms for gastric adenocarcinoma has attracted a great deal of interest. Between Asia and the West, major differences have been identified in tumor biology, implementation of screening programs, extent of surgical lymphadenectomy, and routine use of neoadjuvant versus adjuvant treatment strategies. Minimally invasive techniques, including both laparoscopic and robotic platforms, have been studied in both regions, with attention to safety, feasibility, and long-term oncologic outcomes. The purpose of this review is to discuss advances in the understanding of the etiology and underlying biology of gastric cancer, as well as the current state of management, focusing on the differences between Asia and the West.

INTRODUCTION

Gastric cancer is diagnosed in nearly one million new patients each year, and it remains the third leading cause of cancer-related deaths worldwide (1). Its incidence varies widely among global regions, with the highest incidence in East Asia, Eastern Europe, and parts of Latin America. In Western countries, the incidence of gastric cancer is on the rise; approximately 25,000 new cases are diagnosed each year in the United States (1).

In addition to incidence, the clinicopathologic characteristics of gastric cancer also differ among regions, especially between Asia and the West (2–4). These differences have contributed, along with epidemiologic and genetic studies, to the current understanding of gastric cancer as a heterogeneous group of diseases whose development is influenced by a variety of predisposing and etiologic factors (5). Though regional differences have been postulated to result from dissimilarities in epidemiology, tumor biology, screening protocols, and treatment modalities, surgical approach and extent of lymphadenectomy have become increasingly similar between the two regions.

In this review, we describe the differences in the etiology and management of gastric cancer between Asia and the West. We discuss advances in the understanding of the underlying biology of gastric adenocarcinoma and discuss the current state of screening, diagnostic, and treatment strategies.

ETIOLOGY OF GASTRIC CANCER

Gastric cancer represents a heterogeneous group of diseases, including three distinct subtypes: distal intestinal-type gastric cancer associated with chronic gastritis and *Helicobacter pylori* infection; proximal intestinal-type gastroesophageal cancers, which are more aggressive and associated with obesity and gastroesophageal reflux disease; and diffuse signet-ring cell type cancers, which are widely infiltrative and not associated with gastritis (6).

The relative incidence of the various types of gastric cancer is changing in the United States and other Western countries. Tumors located in the gastroesophageal junction and gastric cardia are becoming more common, most likely related to the obesity epidemic and prevalence of gastroesophageal reflux disease (7, 8). While the incidence of noncardia gastric cancer has been declining in almost all ethnic and age groups, the incidence of distal gastric cancer has increased by 70% in Caucasian patients in the 25- to 39-year-old age group (9).

In addition to distribution, the outcomes of some gastric cancer types also vary among global regions. Proximal tumors are more common in the West (4, 10) and are associated with worse outcomes due to more advanced stage at presentation, larger tumor size, and association with poorly differentiated histology (11–13), but patients with these cancers in East Asia seem to have better survival (10). Diffuse histology is also more common in the West (10, 14) and is similarly an independent negative prognostic factor because of its association with lymph node positivity (15).

Given the heterogeneity within histologic categories, the Cancer Genome Atlas research network characterized the molecular drivers of gastric adenocarcinoma (16). This study was intended to develop a robust molecular classification scheme based on dysregulated pathways. Four distinct molecular subtypes of gastric cancer were identified: Epstein-Barr virus–positive tumors, microsatellite-unstable tumors, genomically stable tumors, and tumors with chromosomal instability (16). Microsatellite-unstable and Epstein-Barr virus–positive gastric cancers have been associated with longer survival (17, 18). This new molecular characterization of gastric adenocarcinoma may serve as a clinically useful and prognostic adjunct to routinely obtained histologic and pathologic information and as a basis for targeted therapy trials in the future.

Table 1 Anatomic stage/prognostic groups, gastric cancer (27)

Stage	Tumor	Lymph nodes	Metastasis
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	N3a	M0
Stage IIIA	T4b	N0	M0
	T4a	N1	M0
	T4a	N2	M0
	T3	N2	M0
	T2	N3a	M0
Stage IIIB	T4b	N1 or N2	M0
	T4a	N3a	M0
	T3	N3a	M0
	T2	N3b	M0
	T1	N3b	M0
Stage IIIC	T4b	N3a or N3b	M0
	T4a	N3b	M0
	T3	N3b	M0
Stage IV	Any T	Any N	M1

Abbreviation: Tis, tumor in situ.

STAGING AND SCREENING

Accurate clinical staging of gastric cancer is of paramount importance to select the best treatment. Staging employs the TNM model developed by the American Joint Committee on Cancer and updated with an eighth edition in 2016 (19). The most significant modification in the eighth edition was the division of the N3 category into N3a and N3b, with N3a representing 7–15 metastatic regional lymph nodes and N3b representing >15. This change also resulted in some slight modifications to the stage groupings (**Table 1**).

Multiple diagnostic modalities are used to achieve accurate preoperative clinical staging. Information for T and N staging can be obtained using endoscopic ultrasound with or without fine-needle aspiration biopsy. N and M stages are evaluated by computed tomography of the chest, abdomen, and pelvis. In appropriate cases, additional tests and procedures such as a positron emission tomography scan and diagnostic laparoscopy may be pursued to obtain more accurate M staging information. The National Comprehensive Cancer Network (NCCN) consensus guidelines provide further recommendations and explanations of evaluation and workup, as well as treatment for gastric cancer (20).

NCCN: National Comprehensive Cancer Network

Gastric cancer tends to present at later stages because its symptoms are nonspecific (21). As early detection leads to better outcomes, countries with high gastric cancer incidence have implemented screening programs. For example, in Japan, all patients over the age of 40 undergo double contrast

barium study, with subsequent endoscopy if any abnormality is detected. Serum pepsinogen levels are also tested to identify patients at increased risk of developing atrophic gastritis. These screening practices have improved both disease-specific mortality and five-year survival (22). While patients in Japan and South Korea, which also has a large-scale screening program, present with earlier-stage disease than Western patients do, the incidence of early-stage presentation is increasing in the United States; at our high-volume institution, it has risen from 20% to 40% since 1985 (23).

TREATMENT

Surgery is the only curative option for patients with gastric adenocarcinoma. Removal of the tumor is usually accompanied by lymphadenectomy, and the surgical approach depends on the location and stage of the tumor and the experience and preference of the surgeon. Below, we discuss resection options for patients with gastric adenocarcinoma.

Endoscopic Resection for Early Gastric Cancer

Early-stage tumors that have a very low risk of lymph node metastasis are often treatable by endoscopic resection (24). Multiple studies in East Asia have shown that endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are safe and effective for early gastric cancer, with very low rates of early and late complications (25, 26) and local recurrence (27), as well as excellent five-year overall survival (OS) and recurrence-free survival (28). These approaches are now widely used to treat patients with early gastric cancer in that region; specifically, they are indicated for patients with small (<2 cm), stage T1a, well-differentiated adenocarcinomas without ulceration. EMR has also been adopted in Western countries and is recommended by the NCCN to treat tumors smaller than 2 cm that are well or moderately well differentiated, do not penetrate beyond the superficial submucosa or have lymphovascular invasion, and would allow clear lateral and deep margins following resection (20). En bloc excision of small gastric lesions by ESD has been shown to be more effective than EMR in curing small EGCs, but requires greater skills and more advanced instrumentation due to the significant risk of complications including perforation (20, 29). ESD, however, is only just starting to be employed in the West. Recently, Emura et al. (30) reported that a series of patients who underwent EMR in South America had comparable outcomes to those at a major Japanese institution.

Lymph Node Dissection

The extent of lymphadenectomy for gastric cancer depends mostly on stage, though the ideal extent for advanced cases remains controversial. The standard for early gastric cancer is limited D1 dissection, in which only the perigastric lymph nodes are removed. For advanced gastric cancer, D2 lymphadenectomy, removing the nodes along the celiac artery and its branches, is routinely performed in East Asia. In Western countries, surgeons have lower annual caseloads and, except for a few select high-volume centers, tend to perform D1 lymphadenectomy rather than D2 due to the higher morbidity and mortality associated with extended lymph node dissection.

Because of the differences in morbidity between D1 and D2/D3 lymphadenectomy, several clinical trials have compared their outcomes (**Table 2**). These trials, in the Netherlands (31–33), Italy (34, 35), and the United States (36, 37), have found acceptable morbidity and mortality at high-volume cancer centers, as well as improved survival after gastrectomy with removal of 16 or more lymph nodes. Thus, D2 lymphadenectomy is becoming the gold standard in specialized centers in the United States and Europe, where it can be safely performed by highly skilled and experienced surgeons.

Table 2 Randomized studies on the extent of lymphadenectomy

References	Country	Comparison	*n*	Morbidity (%)	*p*	Mortality (%)	*p*	OS (%)	*p*
75	UK	D1	200	28.0	<0.001	6.5	0.04	35	>0.05
		D2	200	46.0		13.0		33	
31–33	Netherlands	D1	380	25.0	<0.001	4.0	0.004	21[a]	0.340
		D2	331	43.0		10.0		20	
34, 35	Italy	D1	133	12.0	0.178	3.0	0.722	66.5	0.695
		D2	134	17.9		2.2		64.2	
76	Taiwan	D1	110	7.3	0.012	0	NA	53.6	0.041
		D3	111	17.1		0		59.5	
77	Japan	D2	263	20.9	0.067	0.8	>0.05	69.2	0.850
		D2 + PAND	111	28.1		0.8		70.3	
78	Japan	D2+LTA	85	49.0	0.060	4.0	0.25	24.0[b]	0.060
		D2+TH	82	34.0		0.0		37.0	

Abbreviations: OS, overall survival; LTA, left thoracoabdominal approach; NA, not applicable; PAND, para-aortic node dissection; TH, transhiatal approach; UK, United Kingdom. [a]15-year; [b]10-year; all other survival values are for 5 years.

Laparoscopic Gastrectomy

Since Kitano et al. (38) reported the first laparoscopic gastrectomy (LAG) for early gastric cancer in 1994, the technique has become an alternative option for the treatment of gastric cancer. Multiple retrospective studies, prospective studies including randomized clinical trials (RCTs), and meta-analyses from Asia, Europe, and the United States have shown that minimally invasive and open gastrectomy (OG) have oncologically equivalent outcomes (**Table 3**) (39). Many of these studies have highlighted the benefits of minimally invasive techniques, which include decreased estimated blood loss, shorter hospital stay, more expeditious return of bowel function, lower analgesic requirements, more rapid recovery time, and improved overall quality of life compared with OG. Perhaps most importantly, postoperative recovery is more rapid after minimally invasive gastrectomy, allowing a higher proportion of patients to receive indicated adjuvant systemic therapy (40). Despite this robust body of data, the steep learning curve associated with advanced minimally invasive techniques and patient selection has limited their use in the United States outside of high-volume centers.

Two large multicenter RCTs are currently under way to demonstrate the long-term oncologic results of LAG for early gastric cancer: the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS)-01 trial (41) and the Japan Clinical Oncology Group 0912 trial (42, 43). The KLASS-01 trial is the first multicenter RCT to compare OG ($n = 711$) and LAG ($n = 705$) for stage I gastric cancer (41). Short-term outcomes from this trial showed a slightly higher average number of lymph nodes retrieved in the OG group (40.5 versus 43.7; $p = 0.001$) and a significantly lower overall complication rate in the LAG group (13.0% versus 19.9%; $p = 0.001$). Mortality rates, however, were similar between the two groups (0.6% versus 0.3%; $p = 0.687$) (44).

Laparoscopic total gastrectomy with D2 lymphadenectomy was first used for advanced gastric cancer in 1999 (45), and multiple studies in East Asia have found it to be oncologically efficacious and safe for these patients. Survival outcomes of LAG and OG among patients with advanced gastric cancer were found to be similar in a systematic review and meta-analysis of one RCT and nine non-RCTs including a total of 1,819 patients (46). Similarly, a retrospective cohort study

LAG: laparoscopic gastrectomy

OG: open gastrectomy

Table 3 Selected studies on minimally invasive gastrectomy

References	Inclusion	Surgery	*n*	No. of LN	*p*	Morbidity (%)	*p*	Mortality (%)	*p*
41, 44, 79–81 (Asia)	cT1–2N0	LADG	705	43.7	0.001	13.0	0.001	0.6	0.687
		ODG	711	40.5		19.9		0.3	
42 (Asia)	cT1N0–1	LADG	462	39	NA	3.3[a]	0.720	0.0	NA
	cT2N0	ODG	459	39		3.7[a]		0.0	
49 (Asia)	cT2–4a N0–1	LADG	525	Recruiting	NA	Recruiting	NA	Recruiting	NA
		LADG	525	Finished		Finished		Finished	
50 (Asia)	cT2–4a N0–2	LADG	250	Recruiting	NA	Recruiting	NA	Recruiting	NA
		LADG	250						
48 (Asia)	cT2–4a N0–3	LADG	528	36.1	0.738	15.2	0.285	0.4	0.249
		ODG	528	36.9		12.9		0.0	
52 (United States)	Stage I–IIIb	LADG	30	18	0.03	26	0.07	0	NA
		ODG	30	21		43		0	
40 (United States)	Stage 0–III	LAG	87	20	0.47	14[a]	0.57	1	NA
		OG	87	20		13[a]		0	

Abbreviations: LADG, laparoscopy-assisted distal gastrectomy; LAG, laparoscopic gastrectomy; LN, lymph nodes; NA, not applicable; ODG, open distal gastrectomy; OG, open gastrectomy. [a]Grade 3–4.

found comparable five-year disease-free survival (LAG 65.8% versus OG 62.0%; $p = 0.737$), five-year OS (LAG 68.1% versus OG 63.7%; $p = 0.968$), mortality rates (LAG 1.1% versus OG 0%; $p = 0.519$), morbidity rates (LAG 24.2% versus OG 28.5%; $p = 0.402$), and patterns of recurrence for LAG ($n = 186$) and OG ($n = 123$) (47). Finally, a large multicenter retrospective study from the Chinese Laparoscopic Gastrointestinal Surgery Study (CLASS) group showed that in addition to being safe and technically feasible, LAG also yields acceptable short-term oncologic outcomes for locally advanced gastric cancer ($n = 1{,}184$) (48).

At present, three large RCTs are under way on the use of laparoscopic distal gastrectomy with D2 lymphadenectomy to treat advanced gastric cancer in Korea, Japan, and China. Recruiting is now finished for the KLASS-02 trial in Korea, a phase III study to evaluate efficacy (49). An initial report from the JLSSG0901 trial from Japan, after the recruitment of 180 patients, demonstrated the technical safety of the procedure for locally advanced gastric cancer (50). Recently, the CLASS group reported the morbidity and mortality of a phase III study from China (CLASS-01) including patients with clinical stage T2–4aN0–3M0 disease ($n = 528$ per group) and 15 experienced surgeons from 14 institutions. Both postoperative morbidity (LAG 15.2% versus OG 12.9%; $p = 0.285$) and overall mortality (LAG 0.4% versus OG 0%; $p = 0.249$) were equivalent, indicating that experienced surgeons can safely perform LAG with D2 lymphadenectomy for advanced gastric cancer (51).

Few studies have examined LAG outside Asia, and all have been limited to short-term outcomes. A retrospective, case-matched study ($n = 30$ per group, all undergoing distal gastrectomy) from our high-volume cancer center found that LAG was associated with a trend toward fewer early (26 versus 43%; $p = 0.07$) and late (0 versus 20%; $p = 0.03$) complications, as well as equivalent surgical outcomes (margin status and lymph node retrieval) (52). A later, larger study ($n = 87$ per group) from our institution found significant differences in minor (27% versus 16%; $p < 0.01$) and late (17% versus 7%; $p < 0.01$) complications (40). A meta-analysis of RCTs and high-quality

non-RCTs (mostly conducted in Asia) also determined that the overall incidence of complications following LAG was lower than for OG (odds ratio = 0.59; $p < 0.001$) (39).

RAG: robotic-assisted-gastrectomy

Robotic-Assisted Gastrectomy

The use of robotics for gastric adenocarcinoma was first described in 2003 (53, 54), and the first use in the United States was reported in 2007 (55). Though multiple retrospective studies of robotic-assisted gastrectomy (RAG) for gastric cancer have been published, only limited conclusions can be drawn regarding its efficacy because of considerable variability in inclusion criteria, surgeon experience, type of reconstruction performed, and outcomes evaluated.

Many studies have demonstrated the feasibility and safety of RAG for gastric cancer (**Table 4**). A multicenter prospective study reported similar rates of overall complications, mortality, and number of harvested lymph nodes for RAG ($n = 223$) and LAG ($n = 211$) (56). RAG, however, was associated with longer operating time and higher costs. A recent meta-analysis of eight studies including 1,875 patients undergoing RAG showed lower estimated blood loss but similar complication rates and similar numbers of harvested lymph nodes compared with LAG (57).

The robotic surgery platform offers several technical advantages over laparoscopy. Most important is that the camera provides three-dimensional, high-definition, stable, and magnified views of the operative field. Additionally, robotic instruments can articulate and provide seven degrees of freedom, facilitating suturing and difficult dissections. Nonetheless, successful robotic surgery requires institutional support and coordinated teamwork; the familiarity of all surgical team members with the procedure and the robotic platform is critically important.

According to some studies, RAG may be easier to learn than LAG due to the robotic platform's ergonomic and technical advantages, especially for surgeons who have experience in advanced laparoscopy. Learning RAG may require as few as 20 to 25 cases (43, 58), especially if surgeons have laparoscopic experience (59), though another study of a single surgeon's learning curve found that 95 cases were required for learning RAG versus 270 cases for LAG (60). Early robotic cases appear to yield nearly equivalent outcomes to late laparoscopic cases, and are associated with less blood loss, increased lymph node retrieval, shorter hospital stay, and earlier initiation of diet compared with early laparoscopic cases (61). No studies have prospectively compared the learning curves of surgeons for RAG versus LAG at the beginning of their laparoscopic experience. Experienced open surgeons may be able to shift directly to the robotic platform without laparoscopic experience (62), but formal simulation training on the robotic platform in both dry and wet labs is imperative.

Because operating time for RAG is longer than for LAG or OG, surgeons must be careful to select appropriate patients for this surgical approach, especially early in their experience. Ideal candidates for RAG are those with minimal medical comorbidities, low or normal body mass index, small tumors, distal tumors, and those who have not received neoadjuvant chemotherapy. RAG is also suitable for patients with a CDH1 mutation, as these patients are recommended to undergo prophylactic total gastrectomy due to their ~70% lifetime risk of developing gastric adenocarcinoma (63). While there are no absolute contraindications for RAG, relative contraindications may include significant intra-abdominal adhesions, large tumor size, or invasion into adjacent organs. As for any minimally invasive surgery, dense intra-abdominal adhesions can prevent clear visualization of important structures and therefore compromise the operation.

Data on the long-term outcomes of RAG are limited but suggest acceptable survival and recurrence rates (64). Additional studies are needed to fully appreciate the clinical benefits of the robotic approach, particularly as they relate to recurrence-free survival, which may be improved because of robotics' facilitation of more precise lymphadenectomy. As surgeons gain more experience with

Table 4 Short-term outcomes of robotic, laparoscopic, and open gastrectomy

Reference	Approach	*n*	Total gastrec-tomies	Operative time (min)	Blood loss (mL)	Number retrieved lymph nodes	Conversion to open (%)	Morbidity (%)	Mortality (%)
82	R	18	0	344	90	25	2	6	6.2
	L	52	0	235	148	31	3	12.5	2
83	R	16	0	259.2	30.3	41.1	0	0	0
	L	11	0	203.9	44.7	37.4	0	9	0
	O	12	0	126.7	78.8	43.3	NA	16	-
84	R	29	12	290	197.6	28.0	NR	41.4	0
	O	120	37	222	386.1	31.7	NA	42.5	3.3
85	R	236	62	219.5	91.6	39.0	0	11	0.3
	L	591	108	170.7	147.9	37.4	0	13.7	0.4
86	R	30	0	229.1	152.8	30.2	0	13	0
	L	62	0	189.4	88.3	33.4	0	6	0
58	R	100	16	202	93.2	NR	NR	14.0	0
	L	282	37	173	173.4	NR	NR	10.3	0
87	R	36	36	305.8	214.2	42.8	0	16.7	0
	L	65	65	210.2	150.3	39.4	0	15.4	0
88	R	39	7	430	50	32	NR	15.4	2.6
	L	64	7	350	100	26	NR	15.6	1.6
	O	586	179	320	400	34	NA	14.7	1.4
89	R	436	109	226	85	40.2	NR	10.1	0.5
	L	861	158	176	112	37.6	NR	9.4	0.3
	O	4,542	1,232	158	192	40.5	NA	10.7	0.5
90	R	30	0	218	75	34	0	5	0
	L	120	0	140	60	35	0	9	0
91	R	25	0	361	51.8	44.3	0	11.2	0
	L	225	0	345	81.0	43.2	0	16.9	0
92	R	38	9	234.4	131.3	32.8	0	47.3	0
	L	83	18	220.0	130.5	32.6	0	38.5	0
93	R	88	30	381	46	40	0	2.3	1.1
	L	438	136	361	34	38	0	11.4	0.2
94	R	51	51	264.1	163.4	47.2	0	15.7	2.0
	L	58	58	210.3	210.7	42.8	NR	22.4	0
95	R	21	0	439	96	44	0	9.5	0
	L	161	0	315	115	40	0	10.0	0
96	R	120	26	234.8	118.3	34.6	0	5.8	NR
	L	394	118	221.3	137.6	32.7	0	4.3	NR
97	R 72	72	8	357.9	79.6	30.6	NR	12.5	1.4
	L 73	73	10	319.8	116.0	28.1	NR	8.2	1.4

Abbreviations: R, robotic; L, laparoscopic; NA, not applicable; NR, not reported; O; open. Table adapted from reference 98 with permission. All studies were nonrandomized and retrospective.

Table 5 Summary of trials of perioperative adjuvant therapy

References	Country	Treatment	*n*	5-y DFS (%)	*p*	5-y OS (%)	*p*
69	United States	45 Gy + 5-FU	281	48[a]	<0.001	50[d]	0.005
		Surgery	275	31[a]		41[d]	
66	United Kingdom	ECF	250	38[b]	<0.001	36	0.009
		Surgery	253	25[b]		23	
67	France	5-FU + Cis	113	34	0.003	38	0.02
		Surgery	111	19		24	
68	Germany	FLOT	128	16[c]	0.02	NR	NA
		ECF/ECX	137	6[c]		NR	
71, 72	Japan	S1	529	65	NR[e]	72	NR[e]
		Surgery	530	53		61	
73, 74	Korea, China, Taiwan	XELOX	520	68	<0.001	78	0.002
		Surgery	515	58		69	
99, 100	Korea	XP	228	65	0.092	73	0.484
		XPRT	230	73		75	

Abbreviations: 5-FU, 5-fluorouracil; Cis, cisplatin; DFS, disease-free survival; ECF, epirubicin, cisplatin, 5-FU; ECX, epirubicin, cisplatin, capecitabine; NR, not reported; OS, overall survival; XELOX, capecitabine + oxaliplatin; XP, capecitabine + cisplatin; XPRT, XP + radiotherapy.
[a]3-year recurrence-free survival, [b]5-year progression-free survival, [c]pathologic complete response, [d]3-year OS, [e]95% confidence interval for hazard ratios: DFS, 0.537 to 0.793; OS, 0.540 to 0.828.

the robotic platform, inclusion criteria will likely expand to include patients with more advanced disease and higher body mass index.

Perioperative Adjuvant Treatment

Approaches to adjuvant therapy differ between Asia and the West on the basis of perioperative adjuvant therapy trials conducted in the two regions (**Table 5**). The standard of care in the United States and Europe for gastric cancer that is either T2 or greater or node positive, set forth in the NCCN guidelines, is either perioperative chemotherapy, based on the results of RCTs, or preoperative chemoradiotherapy, based on category 2b evidence, prior to curative-intent surgery (20, 65). In Asia, preoperative chemotherapy is rarely employed, as trials performed there support postoperative chemotherapy over surgery alone.

Neoadjuvant chemotherapy is the standard approach for locally advanced gastric cancer in Europe and the United States primarily on the basis of the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) Trial (performed in the United Kingdom), which demonstrated that treatment with perioperative epirubicin, cisplatin, and fluorouracil (ECF) improved OS to 36%, compared with 23% for surgery alone ($p = 0.009$), as well as progression-free survival (66). A similar benefit was seen in the contemporary French FFCD9703 trial (67); neoadjuvant fluorouracil and cisplatin improved five-year OS (38% versus 24%; $p = 0.02$), five-year disease-free survival (34% versus 19%; $p = 0.003$), and curative resection rate (84% versus 73%; $p = 0.04$) compared with surgery alone. More recently, the phase II results of the German FLOT-4 trial suggest that four preoperative and four postoperative cycles of docetaxel, oxaliplatin, leucovorin, and fluorouracil (FLOT; $n = 148$) may be superior to three preoperative and three postoperative cycles of epirubicin, cisplatin, and either fluorouracil or capecitabine (ECF/ECX;

$n = 152$) (68). Analysis of the intent-to-treat population showed that FLOT led to a significantly higher rate of pathologic complete regression (16% versus 6%; $p = 0.02$).

Support for perioperative chemoradiotherapy for gastric cancer comes from the Intergroup (INT) 0116 trial, which showed that postoperative chemoradiotherapy improved median OS compared with surgery alone (50% versus 41%; $p = 0.005$) (69). Chemoradiotherapy may also be administered preoperatively, but the few studies that have compared this approach to surgery alone, which showed promise for survival benefit, were prone to bias (70).

In Asia, postoperative chemotherapy is standard for stage II/III gastric cancer on the basis of two major trials. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) demonstrated that one year of oral S-1 following surgery improved five-year OS compared with surgery alone (71.7% versus 61.1%) (71, 72). The CLASSIC trial found a similar survival advantage for patients with stage II–IIIB disease with adjuvant capecitabine and oxaliplatin (XELOX); five-year OS was 78% versus 69% for surgery alone ($p = 0.0015$), and five-year disease-free survival was 68% versus 58% ($p < 0.0001$) (73).

Ongoing RCTs are testing the efficacy of adjuvant chemoradiotherapy after neoadjuvant chemoradiotherapy, intensified chemotherapy, and targeted therapy plus chemotherapy.

CONCLUSION

The management of gastric cancer, as well as understanding of the underlying biology, is constantly evolving. The adoption of screening programs in Asian countries with high gastric cancer incidence has led to earlier detection and wider use of endoscopic mucosal resection. Multiple RCTs showing favorable surgical and oncologic outcomes have led to the adoption of minimally invasive surgery. As experience with these techniques and long-term follow-up data accumulate, the indications for LAG and RAG will likely become more refined over time. Also based on RCT results, the use of adjuvant chemotherapy and chemoradiotherapy has improved survival of patients with more advanced gastric cancer, though strategies vary geographically. Neoadjuvant chemotherapy and adjuvant chemoradiotherapy are employed in the United States and Europe, while adjuvant chemotherapy is standard in Asia. Simultaneously, the identification of distinct genetic signatures promises to facilitate the development of targeted therapies and identification of patients who will benefit from specific treatment strategies. These and other advances in understanding of the molecular underpinnings of gastric cancer should improve disease-specific outcomes in the long term.

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