Review

New treatments for gastric cancer: are they changing clinical practice?

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Practice Points

- Endoscopic mucosal resection and submucosal dissection are showing promising results comparable with conventional surgical approaches for T1 disease.
- Endoscopic therapy for T1 disease is commonly performed in the Far East but is not readily available in most other hospitals in the rest of the world.
- Surgical approaches for cases not amenable to endoscopic therapy include pylorus-preserving gastrectomy or proximal gastrectomy for T1 disease.
- Treatment is contentious since staging can be difficult and unreliable for T2N0 disease.
- Surgical treatment for T2N0 disease should involve D2 dissection, and perioperative chemotherapy may be indicated.
- Current standard of care for T3 cancers is combination perioperative chemotherapy and radical surgery.
- Japanese surgeons advocate a radical D2 gastrectomy. However, two European trials have not shown any survival benefit of D2 over D1 gastrectomy for T3 disease.
- Comparative studies of laparoscopic over open gastrectomy have shown promising results for T3 disease.
- Combination perioperative chemotherapy has become the standard practice for locally advanced gastric cancer in Europe for T3 disease. In the Far East adjuvant chemotherapy, while adjuvant chemoradiotherapy in the USA, remains common practice.
- Novel targeted therapies including trastuzumab and bevacizumab have already shown benefits of improved progression-free survival and response rate in advanced T3 disease.

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SUMMARY Gastric cancer is the second most common cause of cancer-related deaths worldwide. Its treatment is dependent on accurate tumor staging and assessment of a patient's performance status and comorbidities in order to provide optimal individualized management. Improved survival outcomes with reduced recurrence rates became possible thanks to better understanding of appropriate lymphadenectomy and utilization of combination surgery and chemotherapy. For superficial T1 tumors, endoscopic mucosal resection and submucosal dissection are treatment options with promising outcomes similar to surgical approaches. For more invasive gastric tumors, surgery with perioperative chemotherapy is generally regarded as the standard of treatment, with most surgeons advocating D2 node dissection. Nonetheless, many aspects of gastric cancer care remain debated and results from further randomized trials are eagerly awaited.

Gastric cancer is the second most common cause of cancer-related deaths worldwide, with more than 600,000 cases reported annually [1]. The highest rates are shared between Japan, China, Korea, eastern Europe and South America. Over the last two decades, the overall incidence of gastric cancer has declined due to fewer distal gastric tumors. However, adenocarcinoma of the esophagogastric junction (EGJ) and gastric cardia have increased over this same time period. The well-established link between EGJ cancers and chronic gastroesophageal reflux disease, especially in the presence of the growing obesity epidemic, provides a likely explanation. Cancers at or near the EGJ can be difficult to distinguish as either esophageal or gastric. Siewert and Stein classified tumors of the EGJ according to the location of the epicenter of the tumor: type I is a true lower esophageal adenocarcinoma, type II is a junctional or cardia tumor and type III are subcardial or true gastric tumors [2]. Siewert's classification is a clinical classification based on endoscopic and radiological features. The seventh edition of the TNM classification, which is a pathological classification, has stipulated that tumors arising at the EGJ, or arising in the stomach 5 cm or less from the EGJ, are staged as esophageal carcinoma, with those more than 5 cm from the EGJ staged as gastric cancers [3].

The surgical treatment of gastric malignancy has several issues that are subject to debate. The aim of surgical resection is to obtain complete histopathological clearance, which involves radical resection of the primary site as well as resection of affected lymph nodes and adjacent organs if necessary. The appropriate allocation of an individualized approach to gastric cancer treatment is dependent on accurate tumor staging and assessment of a patient's physiological status and comorbidity. Improved survival outcomes with a decreased recurrence rate of disease have become possible thanks to a better understanding of appropriate lymphadenectomy and utilization of a multimodal approach to treatment. Meticulous studies using electron microscopy to track cancers cells spreading into the lymphatic system have allowed the Japanese Classification of Gastric Cancer to identify the pattern of lymph node spread based upon the initial location of the gastric tumor [4]. This in turn has led to the division of lymph nodes into different tiers, with individual stations that attempt to describe the pattern of lymphatic spread from any gastric cancer. The Japanese have specified the nodal stations to be resected for total and distal gastrectomies depending on the specific level of dissection: D0, D1, D1+ or D2 **(Figures 1 & 2)** [5]. Furthermore, the Japanese Classification of Gastric Cancer has also subdivided the nodal tiers according to the tumor site as upper, middle or lower third of the stomach **(Table 1)**. Anatomically, the stations can be considered to fall into three main groups – lymph nodes around the left gastric artery, around the splenic artery and those surrounding the common hepatic artery. Nodal involvement in distant stations from the stomach represents metastatic disease and has a poorer prognosis.

More recently, studies have suggested that the actual number of nodes affected by the disease is a major prognostic factor. In the current seventh edition of the TNM classification the nodal (N) categories have been modified according to number of lymph nodes involved:

- N1 = 1 or 2 positive lymph nodes;
- N2 = 3–6 positive lymph nodes;
- N3 = ≥7 positive lymph nodes.

The classification also stipulates that the minimum number of lymph nodes that should be resected in order to provide accurate pathological staging of the tumor is 15. However, for a D2 resection, it has been suggested that a minimum of 25 nodes should be resected in order to collect sufficient lymph nodes to include those with microscopic metastatic foci and improve overall prognosis [6].

This review article describes the current commonly applied treatment strategies for different tumor stages of disease, including newer techniques and practices adopted. Current ongoing trials will also be discussed with their implications for further optimal treatment for gastric cancer.

T1 disease

Early gastric cancers involve superficial tumors that either invade the lamina propria or muscularis mucosae (T1a), or invade the submucosal layer (T1b). They can be classified according to their endoscopic appearance as protruding, superficial elevated, superficial flat, superficial depressed or excavated lesions. Endoscopic therapies, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), have been increasingly employed for T1 gastric tumors. In 2009, a Cochrane review systematically considered the published evidence and concluded that there were no randomized comparisons of endoscopic resection and gastric resection in early gastric cancers and that such trials were needed [7]. Nevertheless, there have been extensive large series presented from the Far East, and the National Cancer Centre in Japan has defined the current criteria for endoscopy therapy to include [8]:

- Intestinal type adenocarcinoma;
- No lymphatic or venous invasion;
- Intramucosal cancer regardless of size without ulceration;
- Intramucosal cancer <30 mm with ulceration;
- Minute submucosal penetration (sm1) and <30 mm.

ESD is generally preferred to EMR in the Far East as it provides a more complete pathological specimen, allowing depth of penetration to be analyzed, as opposed to the piecemeal sample usually obtained with EMR **(Figure 3)**. In a retrospective study up to 98% completeness of resection was possible with ESD with a subsequent better 3-year recurrence-free survival of 97.6%, compared with 92.5% with EMR [9]. Early retrospective studies also compared EMR with surgery for T1 disease and have shown similar results between the two groups in terms of long-term disease-free survival (under 65 years: EMR 92.8%, surgery 91.9%; over 65 years: EMR 80.8%, surgery 75%) [10]. Long-term survival data comparing ESD with surgery is pending but likely to show promising results given its already appreciated superiority to EMR. However, endoscopic therapies, especially ESD, do require an experienced endoscopist and well-equipped facilities to perform the procedure. Although the approach is well established in Japan, Korea and China, ESD is not widely available in many European hospitals. In the UK, NICE recommends that such endoscopic procedures must be carefully audited in

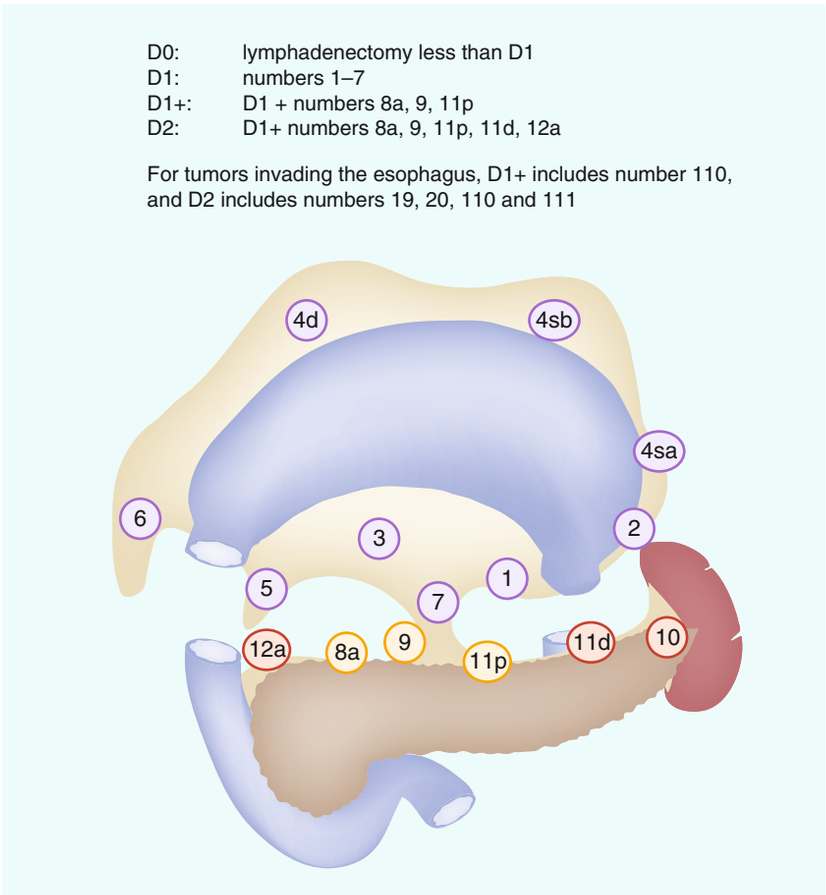

Figure 1. Total gastrectomy. Nodal stations resected depending on the extent of dissection performed.
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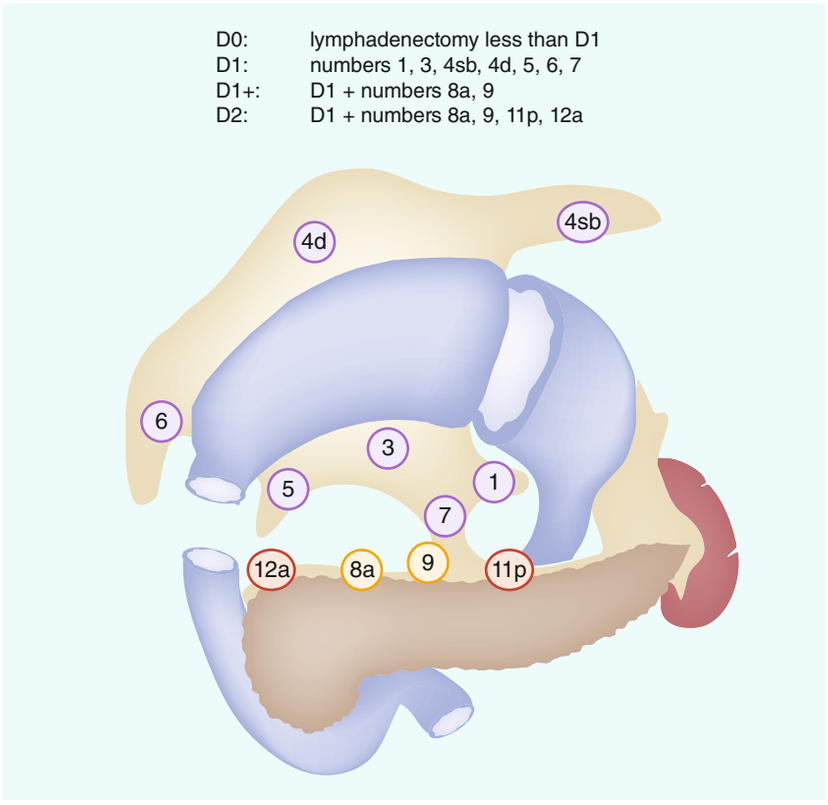

Figure 2. Distal gastrectomy. Nodal stations resected depending on the extent of dissection performed.
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high-volume tertiary referral centers, performed by a trained healthcare professional and patients managed by a multidisciplinary team [11].

If the cancer invades the submucosa as in T1b, the risk of lymph node metastasis is too high to be considered for ESD/EMR. In addition, T1a gastric cancers that do not fulfill the endoscopic criteria or have diffuse histology should be considered for surgical resection. Traditionally, a radical surgical approach was taken. However, current practice involves a more conservative resection depending on tumor size and location. Midbody tumors are usually suitable for pylorus preserving gastrectomy while a proximal gastrectomy is performed for early proximal third cancers. An antireflux procedure is commonly combined with proximal gastrectomy as patients can suffer from severe symptomatic reflux. An alternative is the Meredino procedure with a jejunal interposition loop between the esophagus and the distal gastric remnant. Laparoscopic ± open wedge excision is an option for T1a tumors that are unresectable via the endoscopic route, particularly in patients unfit for major surgery. Attention must be paid to obtaining adequate resection margins as retrospective series have reported resection margin recurrence following this procedure [12].

A more conservative approach to lymph node dissection has also been adopted following the advent of careful lymph node mapping which identifies the lymph node groups at risk of lymphatic spread. Hence, for mucosal disease resection should include N1 tier lymph nodes, including those along the left gastric (station 7) and anterior hepatic nodes (station 8), known as D1α resection. For submucosal disease, a D1α with inclusion of the celiac axis nodes (station 9) should be performed – this is a D1β resection.

Sentinel lymph node mapping has been assessed as an alternative to surgical lymphadenectomy to determine whether less invasive surgery is appropriate [13]. Early reports confirmed that applying techniques developed in melanoma and breast cancer surgery can detect the first tier of draining nodes in early gastric cancer. Further reports began to demonstrate limitations, and similar difficulties identified in breast cancer and melanoma sentinel node surgery were observed in gastric cancer. First, there is the selection of single or dual techniques (radioisotope and blue dye) and the timing of administration in relation to timing of surgery. The majority of surgeons undertaking this procedure would now use endoscopic administration using dual tracers. Second, there is the selection of histopathological techniques for diagnosis of metastatic nodal involvement. Conventional hematoxylin and eosin may fail to detect micrometastases, which are considered more significant in gastric cancer than in breast cancer. Addition of immunohistochemical techniques has been shown to increase accuracy. The use of intraoperative reverse transcription-PCR (one-step nucleic acid amplification) remains to be investigated to determine whether the equivalent value to its use in breast cancer can be replicated. Third, there is the selection of patients for sentinel node mapping. Unlike breast cancer, gastric lymphatic pathways are multidirectional. As a result, sentinel nodes can be identified in multiple sites, which mainly relate to the tumor site and involve lesser curve nodal stations or greater curve stations but occasionally can affect stations on both curvatures. In the majority of studies the sentinel node does appear to allow identification of the 'at-risk' lymphatic basin of peritumoral nodes. Studies have also shown, in more locally advanced disease,

Table 1. Nodal tiers according to site of tumor as defined by the Japanese Classification of Gastric Cancer.

Tumor site	N1	N2	N3	M
Upper third	1, 2, 3, 4sa, 4sb	4d, 7, 8a, 9, 10, 11p, 11d	5, 6, 12a, 16	14v
Upper/middle third	1, 2, 3, 4sa, 4sb, 4d, 5, 6	7, 8a, 9, 10, 11p, 11d, 12a	14v, 16	–
Middle/lower third	1, 3, 4sb, 4d, 5, 6	7, 8a, 9, 11p, 12a	2, 4sa, 19, 11d, 14v, 16	–
Lower third	3, 4d, 5, 6	1, 7, 8a, 9, 11p, 12a, 14v	4sb, 16	2, 10, 11d

that metastases can 'skip' nodal pathways due to lymphatic obstruction thus making the technique unreliable in T3 tumors. The current consensus is that sentinel node surgery has a role in T1 disease if being treated with local excision or limited resection, as it can identify the nodal basin, which needs to be excised [13].

T2N0 disease

Gastric tumor invasion through the muscularis propria with no nodal involvement defines the T2N0 category. An expert panel including surgeons, gastroenterologists, pathologists, radiation and medical oncologists attended the first St Gallen EORTC Gastrointestinal Cancer Conference in March 2012 and debated at length the best treatment option for T2N0 tumors [14]. Pretreatment lymph node staging was judged to be highly unreliable and hence subsequent difficulties in knowing how aggressive treatment needed to be. A slight majority concluded that perioperative chemotherapy in addition to surgery was the best approach while others declared surgery alone as the treatment of choice. All panel members agreed that an extended lymphadenectomy (D2) was indicated for this group of patients if there were no contraindications from associated comorbidity.

T3 disease

T3 disease is defined as a tumor penetrating the subserosal connective tissue without invasion of visceral peritoneum or adjacent structures. Also included are tumors that extend into the gastrocolic or gastrohepatic ligaments, or into the greater or lesser omentum, without perforation of the visceral peritoneum covering these structures [3]. The current standard of care for these cancers is combination perioperative chemotherapy and radical surgery.

Surgery

Surgery for locally advanced gastric cancer has been evaluated in a number of studies, applying experience from the Far East in western patients. Most surgeons agree on a D2 gastrectomy with at least 5 cm proximal and distal clearance for intestinal type gastric adenocarcinomas [15]. An 8 cm margin should be achieved for diffuse and signet ring cell types of gastric cancer owing to their submucosal permeation of cancer cells contributing to a poorer prognosis. Surgeons in Japan advocate D2 lymphadenectomy, which involves removing the perigastric nodes and the second tier of nodes along the left gastric artery, splenic artery and common hepatic artery. The exact nodes to be resected depend on the site of the tumor (Table 1). The results from Japan reflect a standard approach originally documented in the Japanese Rules [5].

Two European trials, the Dutch [16] and the UK Medical Research Council (MRC) trial [17] did not show improved survival with D2 gastrectomy compared with D1 resection, but showed increased short- and long-term mortality if the spleen and/or pancreas were removed. However, several constraints at the time of execution of the two trials that challenge their conclusions should be taken into account. The annual average number of cases per hospital was 1.0 and 1.5 resections in the Dutch and MRC trials, respectively. Appoximately 82 and 75% of patients in the Dutch and MRC trials had less lymphadenectomy than specified. Also, the high operative mortality reported in these two trials implied limited experience in European surgeons compared with the Japanese surgeons.

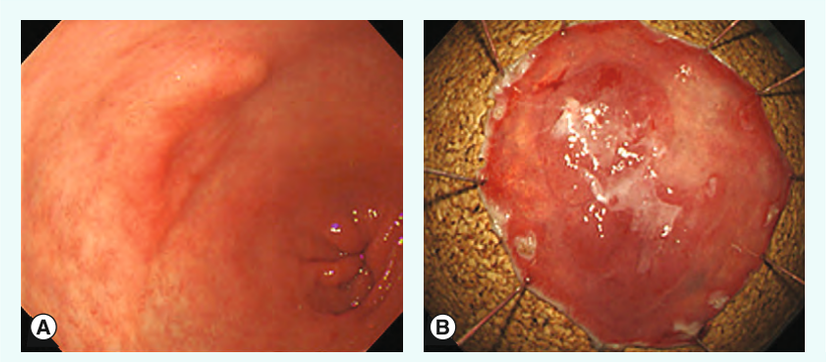

Figure 3. Endoscopic appearance of (A) early gastric cancer and (B) endoscopic submucosal dissection specimen.

However, long-term follow-up in the Dutch trial has shown a reduction in gastric cancer deaths in the D2 group [18].

Subsequent studies published from Europe have shown improved results almost matching those from Japanese counterparts. Hanna *et al.* demonstrated that, in a cohort of 100 patients undergoing gastrectomy, the outcomes achieved matched the high standards reported in Japanese studies [19]. There were no deaths in the gastrectomy group with a 5-year survival of 58.4% and an anastomotic leak rate of approximately 2%. The Italian gastric cancer study group has reported similarly with 30-day mortalities of 3% for D1 and 2.2% for D2 gastrectomies [20]. It is now recommended by most European centers to perform a D2 lymphadenectomy in suitably fit patients and with low operative morbidity and mortality.

In the UK, centralization of cancer surgery has lead to improved mortality and morbidity rates following esophagogastric cancer resections. The Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland recommended that there should be 4–6 surgeons per esophagogastric unit with each surgeon carrying out a minimum of 15–20 resections per year [21]. In 2009, the National Esophago-Gastric Cancer Audit showed that the 30-day mortality was reduced to 4.2% for gastric resection [22]. Furthermore, a recent study by Coupland *et al.* identified 62,811 patients diagnosed with esophageal or gastric cancer on the UK national cancer register [23]. Associations between hospital volume, resection rate and survival were assessed. Results showed that increasing hospital volume correlated well with lower operative mortality (HR: 0.87; 95% CI: 0.79–0.95 for hospitals with >80 resections per year compared with those with <20 per year). The association was particularly significant during the first 30 days after surgery, but remained clinically relevant beyond 12 months. The authors therefore supported and encouraged further centralization of cancer services in England.

More extensive lymphadenectomy has been studied in randomized trials. Wu *et al.* demonstrated better survival after extended D3 lymph node dissection [24]. By contrast, a trial of extended lymphadenectomy including the paraaortic nodes did not show any advantage over standard D2 dissection [25]. Subsequent studies have suggested there may be an advantage for more extensive nodal dissection in specific situations. Roviello *et al.* have shown a potential advantage for para-aortic nodal dissection [26]. In 286 patients with locally advanced disease, 13% had para-aortic node involvement. The 5-year survival for this group was 17.1% compared with 52% with T2–4 cancer. de Manzoni *et al.* have defined from this group a high risk for para-aortic disease of 42% for T3/4 tumors with mixed or diffuse histology arising in the upper third of the stomach [27]. This group may benefit from more extensive nodal dissection but this would be best defined in a randomized trial.

The surgical approach for tumors affecting the cardia, subcardia and Siewert type II EGJ tumors has also been studied, comparing either a transhiatal extended total gastrectomy or an esophagogastrectomy. Sasako *et al.* conducted a randomized trial comparing transhiatal with a left thoracoabdominal approach for total gastrectomy [28]. The transhiatal method conveyed greater survival and less morbidity compared with its counterpart, possibly because of the greater physiological insult caused by the thoracoabdominal approach.

Minimally invasive approaches to gastric resection have been evaluated in a number of studies. Since the first reported laparoscopic distal gastrectomy for gastric cancer in 1994 [29], the number of laparoscopic gastrectomies performed has increased, especially in Japan and Korea. Small comparative studies, mainly focusing on distal gastrectomies, have shown a potential benefit of laparoscopic over open gastrectomy including less postoperative pain and reduced chest infections [30–32]. Cianchi *et al.* recently reported decreased blood loss, reduced incidence of surgery-unrelated complications and shorter length of hospital stay with laparoscopic versus open total and distal gastrectomies in a matched cohort study of 82 patients [33]. However, operative time for both procedures was significantly greater in the laparoscopic group. Most cases underwent a D2 lymph node dissection and only short-term follow-up data was collected.

A large case–control study from Korea specifically focused on total gastrectomy and analyzed the short-term surgical outcomes between laparoscopic total gastrectomy (LTG) versus open approaches [34]. Results suggest that LTG is a safe and feasible procedure for total gastrectomies involving D1+ lymph node dissection. However, in the D2 subgroup, the LTG group

showed a significantly increased risk of postoperative morbidity (52.6 vs 18.4%; p = 0.003) and even mortality (10.5 vs 0%; p < 0.001) compared with D1 dissection.

The main area of concern is in esophagojejunal anastomoses, with more anastomotic leakage and luminal bleeding seen in the LTG group. Newer techniques have been developed in an attempt to reduce complications at the esophagojejunal anastomoses. These include techniques for laparoscopic purse-string suturing, a transorally inserted anvil for circular stapling and an overlapping hemidouble stapling technique. Two randomized controlled trials, JCOG 0912 in Japan and KLASS in Korea, are currently ongoing and comparing the long-term survival after open and laparoscopic gastrectomy for early gastric cancer. These and subsequent trials will specifically need to take into account the extent of lymph node dissection performed to a standardized level, the technique used to create the gastrojejunal anastomosis and separate results for distal and total gastrectomies. Until the results of these studies are known, laparoscopic resection cannot be recommended.

A more recent development in minimally invasive surgery is the introduction of robot-assisted procedures. Published evidence comparing robot-assisted with conventional laparoscopic and open gastrectomies for gastric cancer is gradually increasing. The frequently documented benefits of robotics over laparoscopy include wristed instruments that allow seven degrees of freedom, 3D stereoscopic vision, elimination of hand tremor with finer manipulation and also surgeon comfort. A comparative study by Kang and colleagues showed that during the initial learning curve for robotic gastrectomy (usually 20 cases) the operative time and hospital stay is significantly greater compared with the conventional laparoscopic approach [35]. However, surgical outcomes were similar between the two groups as surgeon experience grew. Furthermore, the robotic gastrectomy cases had significantly less blood loss (93.25 ± 84.59 ml vs 173.45 ± 145.19 ml; p < 0.001) suggesting possible superiority of the newer technique.

In contrast, Hyun *et al.* reported that postoperative complications were more commonly seen in the robotic gastrectomy group as opposed to the laparoscopic group, although this difference did not reach statistical significance (47.3 vs 38.5%; p = 0.361) [36]. Importantly, Hyun's study showed that in obese patients fewer lymph nodes were harvested by the robotic procedure than the laparoscopic (23.4 vs 32.2; p = 0.006). This obviously gives rise to an important area of concern, especially when dealing with more advanced disease where greater lymph node involvement is suspected; the likelihood of obtaining complete histopathological clearance of all possible sites of disease may be significantly compromised. However, the data is based on the experience of only a single surgeon and robotic gastric resection remains experimental. More reproducible results should be obtained from larger multicenter trials involving several experienced robotic surgeons.

Chemotherapy & chemoradiotherapy

Combination perioperative chemotherapy has become the standard practice for locally advanced gastric cancer in Europe. In the UK, the MAGIC trial compared perioperative epirubicin, cisplatin and infused 5-fluorouracil (ECF) with surgery alone in patients with gastric, EGJ and lower esophageal adenocarcinoma [37]. ECF was administered as three cycles before and after surgery. Significant benefits were noted with neoadjuvant chemotherapy causing substantial downstaging of the tumor without increasing the rate of postoperative complications. The overall survival also increased from 23 to 36%. Similar results were also seen in the French FFCD trial that used the combination treatment of cisplatin and 5-fluorouracil [38].

In the Far East there have been two randomized controlled trials of adjuvant chemotherapy after standard D2 resection for locally advanced gastric cancer. The Japanese ACTS-GC trial evaluated S-1 (a fluoropyrimidine) as a single oral agent, and reported that patients who received 12 months of S-1 after gastrectomy had better overall survival (3-year overall survival: 80.1 vs 70.1%; p = 0.0024) [39]. Combinations of S-1 with other cytotoxic agents have been studied in advanced disease with variable results. A combined Korean and Chinese trial, the CLASSIC trial, included combination capecitabine and oxaloplatin [40]. This study again reported a better overall disease-free survival at 3 years in the treated group (79 vs 59%; p < 0.0001).

In the USA, the Intergroup 116 trial demonstrated a significant benefit in overall survival and local control rates in patients receiving chemoradiotherapy postoperatively compared with those who had surgery alone [41].

The Western trials have however been criticized because of the quality of surgery. Furthermore, in the MAGIC trial patients were included with potentially resectable disease and survival may have been influenced because a proportion did not undergo curative-intent resection after randomization. The striking feature comparing the three trials (Table 2) is the survival in the control surgery groups. In the Japanese and the CLASSIC trials it is 70 and 59%, respectively at 3 years, compared with 23% at 5 years in MAGIC and 41% at 3 years in Intergroup 116. Despite this, the chemotherapy and chemoradiotherapy combinations do have a biological effect that results in a survival benefit.

Targeted therapies are currently under investigation in advanced disease as novel approaches to tailor treatment according to individual tumor characteristics. Amplification or overexpression of the human EGF receptor 2 (HER2) has been reported in 7–34% of gastric cancers. HER2 has a role in tumor cell proliferation, apoptosis, adhesion, migration and differentiation. Its role in prognosis is uncertain with some reports suggesting that HER2-expressing gastric cancers have a poorer prognosis and are a more aggressive disease with others suggesting no effect. In an attempt to emulate the beneficial effect of trastuzumab (a monoclonal antibody to HER2) observed in breast cancer expressing HER2, a trial was designed adding trastuzumab to conventional chemotherapy in advanced gastric and gastro–esophageal junctional cancers overexpressing HER2 [42]. The median overall survival for the combination of trastuzumab and chemotherapy was 13.8 months compared with 11.1 months for chemotherapy alone. As a result the combination of trastuzumab and chemotherapy has been recommended to be the standard of care for patients with advanced HER2 positive gastric and gastroesophageal junctional cancer. It remains to be seen if including anti-HER2 agents in the perioperative setting can improve outcome in patients with more locally advanced disease.

Expression of VEGF has also been shown to have a poor prognosis in gastric cancer [43] as it promotes angiogenesis and tumor growth. The monoclonal antibody bevacizumab has been raised against VEGF and has been evaluated in the double-blind randomized Phase III AVAGAST trial in advanced gastric cancer [44]. A cohort of 774 patients with advanced gastric or gastroesophageal cancer were treated with a cisplatin plus capecitabine chemotherapy doublet and randomized to either the addition of bevacizumab or placebo. Patients received bevacizumab or placebo followed by cisplatin on day 1 plus capecitabine twice daily for 14 days every 3 weeks. Cisplatin was given for six cycles, while capecitabine and bevacizumab were administered until disease progression or unacceptable toxicity. Results showed that the addition of bevacizumab to chemotherapy led to a significant improvement in progression-free survival (6.7 months vs 5.3 months; hazard ratio: 0.80; 95% CI: 0.68–0.93; p = 0.0037) and overall response rate (46.0 vs 37.4%; p = 0.0315) but was not associated with significant improvements in overall survival (12.1 vs 10.1 months; hazard ratio [HR]: 0.87; 95% CI: 0.73–1.03; p = 0.1002); thus failing to meet its primary end point. Comparable toxicity profiles were noted between the two arms.

More recently, prospectively collected biomarker data from the AVAGAST study has shown that angiogenic markers may have predictive value for bevacizumab efficacy in gastric cancer [45]. Prespecified biomarkers included plasma VEGF-A, protein expression of neuropilin-1 and

Table 2. Comparison of MAGIC, Intergroup 116, ACTS-GC and the CLASSIC trials.

Trial	Inclusion	D2 rate (%)		Stage				Survival		Ref.
				T1	*T2*	*T3*	*T4*	*3-year*	*5-year*	
MAGIC	Stage II–IIIb	41.8	C (%)	15.7	36.0	43.6	4.7	–	36.3	[37]
			S (%)	8.3	28.5	54.9	8.3	–	23.0	
INTERGROUP 116	T1/T2, T3 & T4	10	C (%)	–	31†	62	7	50	–	[41]
			S (%)	–	31	61	8	41	–	
ACTS-GC	Stage II–IIIb	100	C (%)	0.2	54.6	42.5	2.6	80.1%	–	[39]
			S (%)	0	54	43.8	2.3	70.1	–	
CLASSIC	Stage II–IIIb	100	C (%)	1	55	44	<1	74	–	[40]
			S (%)	2	54	44	1	59	–	

†T1 and T2 combined rate.
C: Chemotherapy; S: Surgery.

VEGF receptors-1 and -2. There was a beneficial trend for overall survival in those with raised baseline levels of plasma VEGF-A (HR: 0.72; 95% CI: 0.57–0.93) versus low levels (HR: 1.01; 95% CI: 0.77–1.31; p = 0.07), and for those with low baseline expression of neuropilin-1 (HR: 0.75; 95% CI: 0.59–0.97) versus high levels (HR: 1.07; 95% CI: 0.81–1.40; p = 0.06). Although neither of these results reached statistical significance, the authors concluded that VEGF-A and neuropilin-1 may prove to be significant biomarkers for predicting prognosis in treatment with bevacizumab in advanced gastric cancer and should be further evaluated in future studies.

Two important trials currently underway that are likely to provide further valuable insight into these novel aspects of gastric cancer treatment include the ST03 trial [101] and the CRITICS trial [102]. The ST03 trial, currently in progress in the UK, is comparing perioperative combination chemotherapy (epirubicin, cisplatin and capecitabine [ECX]) with or without bevacizumab in operable gastric or EGJ adenocarcinoma [101]. The primary end point is overall survival, with secondary end points including treatment-related morbidity, response rates, resection rates, disease-free survival, quality of life and cost–effectiveness. Recently, an additional arm has been included in this trial assessing the feasibility of randomizing patients with HER2-expressing tumors to receive lapatinib, an oral small molecule inhibitor of HER2.

The Dutch Gastric Cancer Group is conducting the CRITICS trial [102]. The aim of the trial is to assess overall survival by effectively combining the approaches of the MAGIC trial with perioperative chemotherapy and the US Intergroup 116 trial with postoperative chemoradiotherapy. Patients are randomized to either postoperative chemoradiotherapy or postoperative chemotherapy after having adequate gastric resection with neoadjuvant ECX chemotherapy. Surgeons are recommended to carry out at least a standardized D1+ gastric resection with removal of 15 lymph nodes and avoiding pancreatosplenectomy. The primary end point is overall survival, with secondary end points including disease-free survival, toxicity and quality of life. The results are expected shortly.

Future perspective

The management of early and locally advanced gastric cancer has seen many advances in endoscopic and surgical technique over the last few decades, as well as developments in chemotherapeutic regimens. The growing use of endoscopic mucosal resection and, more recently, endoscopic submucosal dissection for T1 disease are showing very promising results in terms of safety and disease-free survival. However, such endoscopic procedures should be carefully audited in high volume tertiary referral centers, performed by experienced endoscopists and patients managed by a multidisciplinary team; all of which are not readily available in all countries.

Minimally invasive techniques including laparoscopic and robot-assisted surgery are being evaluated in gastric cancer surgery. Commonly reported benefits of laparoscopic surgery, such as reduced postoperative pain and less chest infection, have emerged for laparoscopic gastrectomies. However, operative time is significantly longer and, more importantly, for laparoscopic D2 gastrectomies there appears to be an increased risk of morbidity and mortality associated with esophagojejunal anastomotic leakage or luminal bleeding. Further larger-scale studies are therefore needed before this technique can be recommended.

With regard to chemotherapy, the large trials in the 1990s and 2000s have demonstrated the role of perioperative chemotherapy as a standard of care. The most significant recent introduction to treatment has been the targeted therapies with specific monoclonal antibodies including trastuzumab and bevacizumab. Their true potential is still under investigation.

Gastric cancer is the second most common cause of cancer-related deaths worldwide, hence the continual drive to provide accurate, reliable staging and achieve the optimal treatment that is likely to encompass advanced surgical procedures as well as combinations of chemotherapeutic, radiation and biological agents.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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