Overview on Gastric Cancer

Chapter 3

The Principles of the Surgical Management of Gastric Cancer

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Abstract

Surgery is the only curative therapy for gastric cancer but most operable gastric cancer presents in a locally advanced stage characterized by tumour infiltration of the serosa or the presence of regional lymph node metastases. Surgery alone is no longer the standard treatment for locally advanced gastric cancer as the prognosis is markedly improved by perioperative chemotherapy. The decisive factor for optimum treatment is the multidisciplinary team (MDT) specialized in gastric cancer. However, despite multimodal therapy and adequate surgery only 30% of gastric cancer patients are alive at 3 years. This article reviewed the principles of the surgical management of gastric cancer (minimally-invasive or open) and how this may optimize multimodal treatment.

Keywords: gastric cancer; surgery; multimodal treatment

Abbreviations: EMR: endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; ECF: epirubicin, cisplatin and infusional fluorouracil; ECX: epirubicin, cisplatin and capecitabine; OTG: open total gastrectomy; LATG: laparoscopy-assisted total gastrectomy; BMI: Body mass index; AUGIS: association of upper gastrointestinal surgeons; BSG: British Society of gastroenterology; BASO: British Association of surgical oncologists

1. Introduction

Gastric adenocarcinoma are divisible into two subtypes which are distinct in their natural history and aetiology. The subtype that remains endemic in Far East, parts of S America and Eastern Europe is principally a disease of the distal stomach associated with chronic gastritis, intestinal metaplasia and atrophy of mucosa. The high incidence rates in these regions is thought to be due to continuing high rate of *H. pylori* infection, adverse dietary factors (nitrosamines) and genetic predisposition [1]. The increasingly occurring subtype found in Western countries is commonly found near the GOJ and is associated with significant gastritis [2]. Associated with the marked increase in incidence of GOJ cancer over the last 30 years is

the downward migration of oesophageal tumours and proximal shift of gastric tumours. GOJ cancer is the fastest increasing solid malignancy of adult life in the West with an increasing incidence of 3-4% per annum [2]. Siewert and Stein proposed a classification system of GOJ cancers in an attempt to simplify the conundrum. (**Table 1**) [3]. However, only specialist oesophagogastric surgical centres can accurately classify the tumour of GOJ as arising in distal oesophagus, gastric cardia or subcardinal stomach [4]. Being a loco-regional disease, the primary objective of surgery is to excise the primary tumour with clear longitudinal and circumferential resection margin, with combined organ resection as required (R0 resection) and resection of associated lymph nodes; then safely restoring intestinal and biliary continuity to allow adequate nutritional intake [5,6].

2. Patient Pathway and Selection for Gastric Surgery

Only 40% of early gastric cancer are associated with symptoms and 80% of gastric cancer patients present with > T1 disease. 65% patients present as advanced cancers (T3,T4), 85% have lymph node metastases and 40% are metastatic (**Table 2**) [4,7]. 25% will require endoscopic, radiological or surgical procedures for haemorrhage, obstruction, pain or perforation [2]. Physical signs develop late and most commonly associated with locally advanced or metastatic disease. Evidence from studies of early gastric cancers from Japan suggest that well-differentiated cancers may metastasize more frequently to the liver and poorly-differentiated tumours to lymph nodes [5]. This may explain the high rate of local recurrence with the poorly-differentiated tumours. In all cases microscopic proof of malignancy is required. Once staging investigations are complete, the patient is discussed at the specialized MDT, to propose an individually tailored management plan [6]. The final pathological stage, following curative surgery assists in determining prognosis. Survival is significantly poorer among patients with final pathological stages II,IIIa and IV (**Tables 3,4**) [8].

3. Types of gastrectomy and extent of lymphadenectomy

3.1. Historical controversies

During the 1970's, enthusiast in West suggested the concept of total gastrectomy as appropriate radical surgical management of gastric cancer- *'total gastrectomy 'de principe'*. They argued there was less risk of positive proximal resection margin, that gastric cancer is mmulticentric disease, with gastric mucosal field change, and with subtotal gastrectomy there was inadequate lymphadenectomy (misss left cardia group). In Japan, however, total gastrectomy was only carried out (*total gastrectomy 'de necessite'*) when required to allow R0 resection to be achieved, whilst subtotal gastrectomy was carried out for many antraltumours with satisfactory results. The pattern of lymphatic spread in antral cancers should indicate that removal of left cardiac, short gastric, splenic hilum, and distal splenic artery nodes are unlikely to improve outcome (5% involved and, if positive, poor prognostic sign). The issue of positive

margins is mainly due to inaccurate diagnosis of proximal extent of tumours [5,6]. Several RCTs were carried out which showed no difference in post-operative morbidity or mortality, or difference in 5-year survival. Indeed, some showed that 5-year survival after subtotal was better than after total gastrectomy. Total gastrectomy has greater long-term HRQL deficit than subtotal surgery [11].

3.2 Western radical: (AUGIS/BSG/ BASO) guidelines 2011

The type of gastrectomy depends on the site of the primary tumour with the resection margin aimed at a 5cm minimum from the palpable edge of the tumour. Total gastrectomy is for the 'diffuse' (according to the Lauren classification) type tumours which are more prone to lateral spread [5,6,14]. Total gastrectomy may not be necessary for distal tumours as long as adequate staging, mapping biopsies, careful radiological review, on- table oesophagogastroduodenoscopy (OGD) with or without frozen section are satisfactory [5,15]. Distal third cancers (tumours of the gastric antrum) will require a subtotal (80%) gastrectomy, including division of the left gastric artery and vein, and excision of regional lymphatic tissue [6]. Total gastrectomy is performed only when there is a large distal third tumour or when submucosaltumour infiltration is within 7-8cm of GOJ [5]. Limited gastric resections is suggested only for palliation or in the very elderly [15]. Distal pancreas and spleen is not to be resected for a cancer in the distal two-third of stomach as there is no oncological advantage but increased morbidity [15]. The middle third cancers (tumours of the gastric body) often requires total gastrectomy as it depends on the proximal margin of the tumour. The amount of stomach remaining below GOJ should be a minimum of 2cm. Serosa negative cancer requires 7cm margin from GOJ and serosa positive cancer requires 8cm from GOJ. Smaller margins are acceptable in elderly patients especially if 'intestinal type' (according to the Lauren classification) [14,15]. Proximal third cancers are tumours of the gastric cardia. Siewert 3 GOJ tumours may be amenable to total gastrectomy if enough proximal clearance is possible. True junctional tumours (Siewert 2) is treated with extended total gastrectomy or cardio-osophagectomy [10]. All patients with proximal gastric tumours, should be made aware that at time of dissection/resection, it may be necessary to proceed to caedio-oesophagectomy with possible thoracotomy, so as not to compromise resection margins. The overall aim of surgery is adequate local clearance, appropriate lymphadenectomy (formal D2 and posterior mediastinal, perioesophageal nodes) and an uncomplicated anastomosis with low morbidity [5,6,15]. Ex vivo proximal margin of > 3.8cm of normal oesophagus (5cm *in vivo*) is associated with minimal risk of anastomotic recurrence and an independent predictor of survival. Intraoperative frozen section is standard. Splenic and hilar node resection should only be considered in patients with tumours of proximal stomach located on greater curvature/ posterior wall of stomach close to splenic hilum where incidence of splenic hilar nodal involvement is likely to be high [5,13,15]. There is marked health-related quality of life (HRQL) deterioration after gastrectomy, and total gastrectomy has greater

long-term HRQL deficit than sub-total surgery [16,17]. However, 95% near total gastrectomy which includes complete resection of the gastric fundus and complete cardial lymphadenectomy (groups 1 & 2) with a little (2cm) gastric pouch has similar oncological outcome but offer best short-term results such as lower anastomotic leak rate and a better quality of life than total gastrectomy. This is because of the limited disruption of the oesophagogastric junction [18]. In addition, the anastomosis of the distal stomach to the oesophagus following a proximal subtototal gastrectomy may produce a poor functional result because of alkaline reflux that can be very troublesome and difficult to control.

3.3. D1 versus D2 lymphadenectomy

D1 lymphadenectomy is when all N1 nodes (peri-gastric nodes closest to primary) removed enbloc with the stomach (limited) and D2 is when all N1 and N2 (distant peri-gastric nodes and nodes along main arteries supplying stomach) are systematically removed en bloc with stomach. The observation that gastric cancer commonly remained localized to stomach and adjacent lymph node corroborates the Japanese view that radical systemic D2 lymphadenectomy has an increased survival benefit [19]. Excision of the primary lesion with omenta, and N1 and N2 lymph nodes can cure patients even in presence of lymph node metastasis [15,16]. Originally, to ensure full nodal clearance along the splenic artery a routineen bloc resection of spleen and distal pancreas was performed. The Western non-radical view is that more radical lymphadenectomy only gives more accurate pathological staging, rather than confer improved survival benefit. The MRC D1 vs D2 lymphadenectomy trial concluded in 1999 that the classical Japanese D2 had no survival benefit over D1. However D2 resection without pancreaticosplenectomy may be better than standard D1 [6,16]. The Dutch D1D2 trial 15-year results of 2010 demonstrated an overall survival in 15 years of 21% D1 and 29% D2 group. The gastric cancer-related death rate was significantly higher in the D1 group 48% vs D2 group 37%. Local recurrence of 22% D1 group *vs* 12% D2. Operative mortality of D2 was significantly higher 10 vs 4%, and complication rate 43% vs 25%, D2 vs D1. 20% of D2 group with N2 nodes were still alive at 11years; unlikely if D1 alone was performed [15]. Overall D2 has lower locoregional recurrence and gastric cancer-related death rates. It has significantly higher post-operative mortality, morbidity and reoperation rates. Spleen-preserving D2-resection is thus recommended for resectable gastric cancer [16,20]. The current European description of D2 lymphadenectomy involves removal of >15 lymph nodes, irrespective of node stations [5,6]. Extended D3 lymphadenectomy is a more radical en bloc resection including N3 nodes outside normal lymphatic pathways from stomach, involved in advanced stages e.g. station 12 (hepatoduodenal ligament) or by retrograde lymphatic flow due to blockage of normal pathways. Station 12 nodes are involved in 9% of lower third and 4% of middle third cancers. Five-year survival rates of up to 25% have been reported in Japan for patients who have had positive station 12 nodes resected. This manoeuvre is probably worth while in

distal cancers where N2 nodes appear involved. There is no advantage of D3 *vs* D2, but D3 vs D1 showed improved overall survival [21-23]. Uptake of radical resection remains poor in the West due to relative technical difficulty of achieving nodal clearance, more GOJ tumours, adiposity and lack of formalized training in systematic lymphadenectomy. Practice is likely to change as training is increasingly centralized at high volume centres with lower operative mortality and lower failure to rescue rates due to astute management of complications [11,24]. The future trend is towards lymphadenectomy being tailored to individual preoperative and operative staging, age and fitness [6,16,19]. For early gastric cancer not suitable for endoscopic resection, proximal or distal partial resection with limited lymphadenectomy (N1 tier LN plus station 7 and 8a (D1a)) for mucosal disease and coeliac axis nodes (station 9) (D1b for submucosal disease is recommended. Japanese experience has also confirmed that it achieved the same outcome as standardised D2 lymphadenectomy).

4. Strategies to Minimize Loco-Regional Recurrence

A rational approach to surgery for gastric cancer requires an understanding of the modes of spread of this cancer and how it recurs after surgery. This knowledge is essential in defininging the aims and limitations of radical surgery. Gastric cancer is a loco-regional disease with 80% recurrence rates in patients with T4 serosal positive disease. Thus radical surgery in T4 disease produces little benefit [13]. The majority of recurrences occur locally either in gastric bed, retroperitoneum or anastomosis, rather than distant metastases [25]. The median time to recurrence is 2 years. T1/T2 serosal negative disease as expected show fewer recurrences , but those that recur does so later. Distant liver failure (liver metastases) is potentially due to the aggressive sub-set that micrometastasizes early [13]. Strategies to prevent gastric bed recurrence include a meticulous surgical technique with en-bloc resection of stomach, affected adjacent organs and intact gastric lymphatic chains to prevent iatrogenic cell spillage and prevent peritoneal dissemination [16]. Two successful strategies are available to improve outcomes in patients with localized gastric cancer [6,26]. The results of a large North American study (Gastrointestinal Cancer Intergroup Trial INT 0116) reported that postoperative chemoradiotherapy conferred a survival advantage compared with surgery alone, which led to the regimen being adopted as a standard of care [27]. More recently the MAGIC/UK Medical Research Council (MRC) trial demonstrated that perioperative chemotherapy resulted in an improvement in overall survival and progression free survival. Peri-operative chemotherapy is the standard of care in UK and most of Europe for localized gastric cancer with the accepted regimens of ECF or ECX [16,28]. The MRC MAGIC trial have recommended neoadjuvant/ adjuvant chemotherapy in conjunction with adequate surgery (multimodal therapy) to improve outcomes in gastric cancer. Three cycles ECF chemotherapy before and three cycles after surgery were compared to surgery alone. Peri-operative chemotherapy showed an increased 5-year survival rate from 23 to 36% [28,29]. Similar results were achieved in the French study of periopera-

tive cisplatin and FU [30,31]. Adjuvant chemotherapy alone may confer a survival benefit and should be considered in patients at high risk of recurrence who have not received neo-adjuvant therapy (Japanese ACTS-GC trial) [32,33]. However, despite multimodal therapy and adequate surgery only 30% of gastric cancer patients are alive at 3 years [16,28]. As approximately 15% of gastric and oesophagealjunctional adenocarcinoma over express human epidermal growth factor receptor- 2 (HER2) on the cell membrane HER2 a tyrosine kinase receptor can be targeted by monoclonal antibody bevacizumab. The MRC ST03 trial compared ECX and bevacizumab with ECX alone for cancer of the stomach, oesophagus, or junction of stomach and oesophagus (stage 1b (T1N1) II,III or stage IV (T4,N1 or N_2MO), Type III GOJ adenocarcinoma). Chemotherapy in three cycles over 9weeks, 5-6 weeks break then surgery. The safety was marred by perforations at primary tumour, cardiac toxicity, wound healing complications and GI bleeding [34,35]. Trials are underway to assess the usefulness of this regime. Recent randomized trials from China revealed a survival benefit with preoperative radiotherapy (30 vs 20%) [36]. Currently trials are under way in the west to try and replicate this. Post- operative chemoradiation is the standard of care in the USA and for all patients with positive resection margins. With longer-term (>11years) follow-up, the benefits of both the overall survival (35 vs 27 months) and disease- free survival (DFS) (27 vs 19 months) were maintained [6]. There is less enthusiasm in the UK and in Europe because of the toxicity of abdominal chemoradiotherapy such as nausea and vomiting, myelosuppression including neutropenia, fatigue, mucositis and diarrhoea. In addition, the benefit is uncertain post 'optimum' surgery. It may, however, be considered in patients at high risk of recurrence i.e. no neoadjuvant therapy and/or suboptimal surgery, e.g. in emergency context and in selected patients after an R0 resection [16].

5. Laparoscopic versus opengastrectomy

5.1. Principles

The same principles that govern open surgery is applied to laparoscopic surgery. In order to ensure the same effectiveness of LG as conventional open gastrectomy, all the basic principles such as properly selected patients, sufficient surgical margins, standardized D2 lymphadenectomy, no-touch technique etc, should be followed [34-38]. As laparoscopic experience has accumulated, the indications for laparoscopic gastrectomy (LG) have been broadened to patients with advanced gastric cancer.

5.2. Indications

Laparoscopic gastrectomy may be considered as a safe procedure with better short-term and comparable long-term oncological results. compared to open gastrectomy [32]. In addition, there is HRQL advantages to minimal access surgery [12]. There is a general agreement that a laparoscopic approach to the treatment of gastric cancer should be chosen only by sur-

geons already highly skilled in gastric surgery and other advanced laparoscopic interventions. Furthermore, the first procedures should be carried out during a tutoring program. Diagnostic laparoscopy is strongly recommended as the first step of laparoscopic as well as open gastrectomies [33].The advantage of early recovery because of reduced surgical trauma would allow earlier commencement of adjuvant chemotherapy and the decreased hospital stay and early return to work may offset the financial costs of laparoscopic surgery. The first description of LG was given by Kitano, Korea in 1994 and was initially indicated only for early gastric cancer patients with a low risk lymph node metastasis [34,35]. As laparoscopic experience has accumulated, the indications for laparoscopic gastrectomy (LG) have been broadened to patients with advanced gastric cancer. However, the role of LG remains controversial, because studies of the long-term outcomes of LG are insufficient [35]. The Japanese Gastric cancer Association guidelines in 2004 suggested EMR or ESD for stage 1a (cT1N0M0) diagnosis; Patients with stage 1b (cT1N1M0) and cT2N0M0) were referred for LG [36]. Totally laparoscopic D2 radical distal gastrectomy using Billroth II anastomosis with laparoscopic linear staplers for early gastric cancer is considered to be safe and feasible. LTG shows better short term outcomes compared with OTG in eligible patients with gastric cancer. There was significant reduction of intraoperative blood loss, a reduced risk of post-operative complications and shorter hospital stay [37]. Western patients are relatively obese and there is an increased risk of bleeding if lymphadenectomy is performed. LG is technically difficult in the obese than in the normal weight due to reduced visibility, difficulty retracting tissues, dissection plane hindered by adipose tissue, and difficulty with anastomosis. Open gastrectomy is thus preferable for the obese [38]. Obesity is not a risk factor for survival of patients but it is independently predictive of post-operative complications. Careful approach is being needed, especially for male patients with high BMI [6,11].

5.3. Robotic surgery

Robotic surgery will become additional options in minimally invasive surgery. The importance of performing effective extended lymph node dissection may provide the advantage of using robotic systems. Such developments will improve the quality of life of patients following gastric cancer surgery. However, a multicenter study with a large number of patients is needed to compare the safety, efficacy, value (cost/efficacy ratio) as well as the long-term outcomes of robotic surgery, traditional laparoscopy and the open approach [34,39].

6. Conclusions

Gastric cancer is a locoregional disease and adequate surgery is for locoregional control which is mostly ‘treatment’ only. ‘Cure’ requires neoadjuvant/adjuvant chemotherapy to attack the putative micrometastases and prevent local recurrence. Perioperative chemotherapy is currently standard treatment for resectable gastric cancers but neoadjuvant and adjuvant therapies

are no substitute for inadequate surgery. Minimally-invasive surgery has the advantage over open gastrectomy in reducing surgical trauma, improved nutrition, reduced post-operative pain, rapid return of gastrointestinal function, shorter hospital stays with no reduction in curability. The optimization of multimodal therapy is by ensuring adequate surgery for an individual patient. This is based on the decision of the specialist oesophagogastric multidisciplinary team (MDT) following the staging and assessment of fitness for treatment or palliation

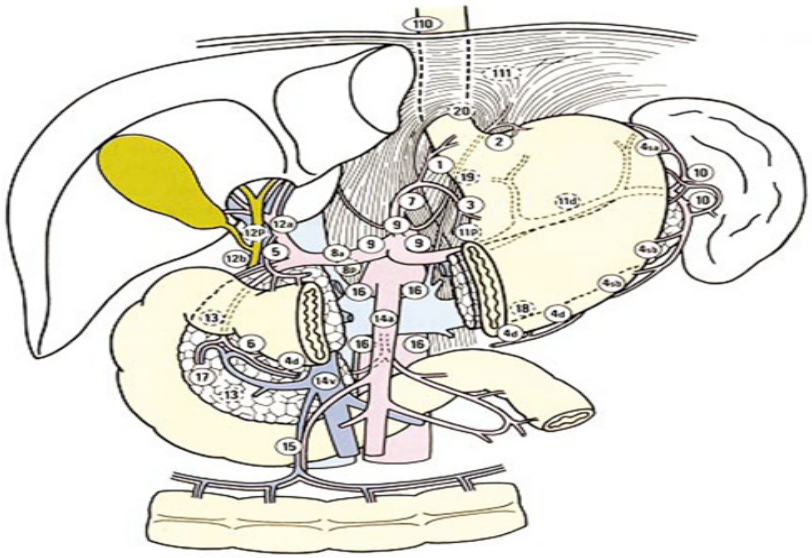

Figure 1: The lymph node stations according to the Japanese classification.

Table 1: Siewert's classification of GOJ adenocarcinomas [3] (with permission fromSiewert JR, Feith M., Werner M., Stein H.J.Ann. Surg. 2000; 232(3): 353-3(61).

Type 1	Adenocarcinoma of distal oesophagus arising in Barrett's segment, which may infiltrate GOJ fro above
Type 2	True junctional carcinoma of the cardia
Type 3	Subcardinal carcinoma, which may infiltrate GOJ from below

Table 2: TNM 7 classification of gastric cancer [6]. (With permission from: The TNM Classification of malignant tumours 7thedn; eds Leslie H Sabin, Mary K. Gospodarowicz, Christian Wittekind, copyright 2009 with permission of Wiley- Blackwell.)

T	N	M
T1: invades lamina propria or submucosa	N0 : no involved regional lymph nodes	M0: no distant metastases
T1a- invades lamina propria or muscularismucosa		
T1b- invades submucosa		
T2: invades muscularispropria	N1: 1-2 regional lymph nodes involved	M1: distant metastases
T3: invades sub serosa	N2: 3-6 regional lymph nodes involved	
T4: invadesserosa	N3a: 7-15 lymph nodes involved	
T4a-perforate serosa		
T4b- invades adjacent structures	N3b: >15 regional lymph nodes involved	

Table 3: TNM 7 staging of gastric cancer [6]

Stage 0	Tis, N0, M0
Stage 1A Stage 1B	T1, N0, M0 T1, N1, M0 T2, N0, M0
Stage IIA	T3, N0, M1 T2, N1, M0 T1, N2, M0.
Stage IIB	T4a, N0, M0 T3, N2, M0 T2, N3, M0
Stage IIIA	T4a, N1, M0 T3, N2, M0 T2, N3, M0
Stage IIIB	T4b, N0, N1, M0 T4a, N2, M0 T3, N3, M0
Stage 111C	T4a, N3, M0 T4b, N2, N3, M0
Stage IV	Any T, Any N, M1

Table 4: 5-year survival rates [6]. (With permission from: The TNM Classification of malignant tumours 7thedn; eds Leslie H Sabin, Mary K. Gospodarowicz, Christian Wittekind, copyright 2009 with permission of Wiley- Blackwell.)

Stage 0	>90%
Stage 1A	60-80%
Stage 1B	50-60%
Stage 11	30-40%
Stage 111B	20%
Stage 111C	10%
Stage 1V	< 5%

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