



# The principles of the surgical management of gastric cancer

Elroy P. Weledji, BSc (Hons) Lond, MSc (Lond), MBBchBAO (Ireland), FRCS (Edin)\*

## Abstract

Surgery is the only curative therapy for gastric cancer but most operable gastric cancer presents in a locally advanced stage characterized by tumor 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 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 therapy

## Introduction

Gastric adenocarcinoma are divided into 2 subtypes that are distinct in their natural history and etiology. The subtype that remains endemic in Far East, parts of South 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 *Helicobacter pylori* infection, adverse dietary factors (nitrosamines), and genetic predisposition<sup>[1]</sup>. The increasingly occurring subtype found in western countries is commonly found near the gastro-oesophageal junction (GOJ) and is associated with significant gastritis<sup>[2]</sup>. Associated with the marked increase in incidence of GOJ cancer over the last 30 years is the downward migration of esophageal tumors and proximal shift of gastric tumors. GOJ cancer is the fastest increasing solid malignancy of adult life in the West with an increasing incidence of 3%–4% per annum<sup>[2]</sup>. Siewert et al<sup>[3]</sup> proposed a classification system of GOJ cancers in an attempt to simplify the conundrum (Table 1). However, only specialist esophagogastric surgical centers can accurately classify the tumor of GOJ as arising in distal esophagus, gastric cardia, or subcardinal stomach<sup>[4]</sup>. Being a locoregional disease, the primary objective of surgery is to

excise the primary tumor 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<sup>[5,6]</sup>.

## 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. In total, 65% patients present as advanced cancers (T3, T4), 85% have lymph node metastases, and 40% are metastatic (Table 2)<sup>[4,7]</sup>. A total of 25% will require endoscopic, radiologic, or surgical procedures for hemorrhage, obstruction, pain, or perforation<sup>[2]</sup>. 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 tumors to lymph nodes<sup>[5]</sup>. This may explain the high rate of local recurrence with the poorly differentiated tumors. In all cases microscopic proof of malignancy is required. Once staging investigations are complete, the patient is discussed at the specialized multidisciplinary team, to propose an individually tailored management plan<sup>[6]</sup>. The final pathologic stage, following curative surgery assists in determining prognosis. Survival is significantly poorer among patients with final pathologic stages II, IIIa, and IV (Tables 3, 4)<sup>[8]</sup>.

## Types of gastrectomy and extent of lymphadenectomy

### Historical controversies

During the 1970s, 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 multicentric disease, with gastric mucosal field change, and with subtotal gastrectomy there was inadequate lymphadenectomy (miss left cardia group)<sup>[9]</sup>. In Japan, however

Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Department of Surgery, Faculty of Health Sciences, University of Buea, Buea, Cameroon.

\*Corresponding author. Address: Department of Surgery, Faculty of Health Sciences, University of Buea, P.O. Box 126, Limbe, S.W. Region, Buea, Cameroon. Tel.: +237 699922144. E-mail address: elroyapat@yahoo.co.uk (E.P. Weledji).

Copyright © 2017 The Authors. Published by Wolters Kluwer Health, Inc. on behalf of IJS Publishing Group Ltd. All rights reserved. This is an open-access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

International Journal of Surgery Oncology (2017) 2:e11

Received 18 December 2016; Accepted 18 December 2016

Published online 12 July 2017

<http://dx.doi.org/10.1097/IJS.000000000000011>

**Table 1**  
**Siewert's classification of GOJ adenocarcinomas<sup>[3]</sup>.**

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

With permission from Siewert et al<sup>[3]</sup>.

total gastrectomy was only carried out when required (total gastrectomy “de necessite”) to allow R0 resection to be achieved, while subtotal gastrectomy was carried out for many antral tumors 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 tumors<sup>[5,6]</sup>. 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<sup>[10]</sup>.

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

The type of gastrectomy depends on the site of the primary tumor with the resection margin aimed at a 5 cm minimum from the palpable edge of the tumor. Total gastrectomy is for the “diffuse” type tumors that are more prone to lateral spread<sup>[5,6,11]</sup>. Total gastrectomy may not be necessary for distal tumors as long as adequate staging, mapping biopsies, careful radiologic review, and on-table esophagogastroduodenoscopy with or without frozen section are satisfactory<sup>[5,12]</sup>. There are several methods of restoring intestinal continuity posttotal gastrectomy. The simple and most commonly used is Roux-en-Y reconstruction. Distal third cancers (tumors 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<sup>[6]</sup>. Total gastrectomy is performed only when there is a large distal third tumor or when submucosal tumor infiltration is within 7–8 cm of GOJ<sup>[5]</sup>. Limited gastric resections are suggested only for palliation or in the very elderly<sup>[12]</sup>. 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<sup>[12]</sup>. The middle third cancers (tumors of the gastric body) often requires total gastrectomy as it depends on the proximal margin of the

**Table 2**  
**TNM 7 classification of gastric cancer<sup>[6]</sup>.**

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

With permission from Wiley-Blackwell<sup>[7]</sup>.

**Table 3**  
**TNM 7 staging of gastric cancer<sup>[6]</sup>.**

Stage 0	Tis, NO, MO
Stage 1A	T1, NO, MO
Stage 1B	T1, N1, MO
	T2, NO, MO
Stage IIA	T3, NO, M1
	T2, N1, MO
	T1, N2, MO
Stage IIB	T4a, NO, MO
	T3, N2, MO
	T2, N3, MO
Stage IIIA	T4a, N1, MO
	T3, N2, MO
	T2, N3, MO
Stage IIIB	T4b, NO, N1, MO
	T4a, N2, MO
	T3, N3, MO
Stage 111C	T4a, N3, MO
	T4b, N2, N3, MO
Stage IV	Any T, any N, M1

tumor. The amount of stomach remaining below GOJ should be a minimum of 2 cm. Serosa-negative cancer requires 7 cm margin from GOJ and serosa-positive cancer requires 8 cm from GOJ. Smaller margins are acceptable in elderly patients especially if “intestinal type”<sup>[11,12]</sup>. Proximal third cancers are tumors of the gastric cardia. Siewert 3 GOJ tumors may be amenable to total gastrectomy if enough proximal clearance is possible. True junctional tumors (Siewert 2) is treated with extended total gastrectomy or cardio-esophagectomy<sup>[13]</sup>. All patients with proximal gastric tumors, should be made aware that at time of dissection/resection, it may be necessary to proceed to cardio-esophagectomy 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, periesophageal nodes), and an uncomplicated anastomosis with low morbidity<sup>[5,6,12]</sup>. Ex vivo proximal margin of > 3.8 cm of normal esophagus (5 cm 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 tumors 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<sup>[5,12,14]</sup>. There is marked health-related quality of life (HRQL) deterioration after gastrectomy, and total gastrectomy

**Table 4**  
**5-year survival rates<sup>[6]</sup>.**

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

With permission from Wiley-Blackwell<sup>[7]</sup>.

has greater long-term HRQL deficit than subtotal surgery<sup>[15,16]</sup>. However, 95% near total gastrectomy, which includes complete resection of the gastric fundus and complete cardinal lymphadenectomy (groups 1 and 2) with a little (2 cm) 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 esophagogastric junction<sup>[17]</sup>. In addition, the anastomosis of the distal stomach to the esophagus following a proximal subtotal gastrectomy may produce a poor functional result because of alkaline reflux that can be very troublesome and difficult to control.

### D1 versus D2 lymphadenectomy

D1 lymphadenectomy is when all N1 nodes (perigastric nodes closest to primary) are removed en bloc with the stomach (limited) and D2 is when all N1 and N2 (distant perigastric 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<sup>[18]</sup>. Excision of the primary lesion with omenta, and N1 and N2 lymph nodes can cure patients even in presence of lymph node metastasis<sup>[12,15]</sup>. Originally, to ensure full nodal clearance along the splenic artery a routine en bloc resection of spleen and distal pancreas was performed. The western nonradical view is that more radical lymphadenectomy only gives more accurate pathologic staging, rather than confer improved survival benefit. The Medical Research Council (MRC) D1 versus 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<sup>[6,15]</sup>. 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%) versus D2 group (37%). Local recurrence of 22% D1 group versus 12% D2. Operative mortality of D2 was significantly higher 10% versus 4%, and complication rate 43% versus 25%, D2 versus D1. In total, 20% of D2 group with N2 nodes were still alive at 11 years; unlikely if D1 alone was performed<sup>[12]</sup>. Overall D2 has lower locoregional recurrence and gastric cancer–related death rates. It has significantly higher postoperative mortality, morbidity, and reoperation rates. Spleen-preserving D2 resection is thus recommended for

resectable gastric cancer<sup>[15,19]</sup>. The current European description of D2 lymphadenectomy involves removal of > 15 lymph nodes, irrespective of node stations<sup>[5,6]</sup>. Extended D3 lymphadenectomy is a more radical en bloc resection including N3 nodes outside normal lymphatic pathways from stomach, involved in advanced stages, for example, 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 maneuver is probably worthwhile in distal cancers where N2 nodes appear involved. There is no advantage of D3 versus D2, but D3 versus D1 showed improved overall survival<sup>[20–22]</sup>. Uptake of radical resection remains poor in the West due to relative technical difficulty of achieving nodal clearance, more GOJ tumors, adiposity, and lack of formalized training in systematic lymphadenectomy. Practice is likely to change as training is increasingly centralized at high volume centers with lower operative mortality and lower failure to rescue rates due to astute management of complications<sup>[10,23]</sup>. The future trend is toward lymphadenectomy being tailored to individual preoperative and operative staging, age, and fitness<sup>[6,15,18]</sup>. 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 celiac axis nodes (station 9)(D1b) for submucosal disease is recommended. Japanese experience has confirmed that it achieved the same outcome as standardized D2 lymphadenectomy.

### Strategies to minimize locoregional 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 defining the aims and limitations of radical surgery. Gastric cancer is a locoregional disease with 80% recurrence rates in patients with T4 serosal-positive disease. Thus, radical surgery in T4 disease produces little benefit<sup>[14]</sup>. The majority of recurrences occur locally either in gastric bed, retroperitoneum, or anastomosis, rather than distant metastases<sup>[24]</sup>. 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 subset that micrometastasizes early<sup>[14]</sup>. 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<sup>[15]</sup>. Two successful strategies are available to improve outcomes in patients with localized gastric cancer<sup>[6,25]</sup>. 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<sup>[26]</sup>. There is less enthusiasm in the United Kingdom and in Europe because of the toxicity of abdominal chemoradiotherapy such as nausea and vomiting, myelosuppression including neutropenia, fatigue, mucositis, and diarrhea. In addition, the benefit is uncertain post “optimum” surgery. It may, however, be considered in patients at high risk of

recurrence, that is no neoadjuvant therapy and/or suboptimal surgery, for example, in emergency context and in selected patients after an R0 resection<sup>[15]</sup>.

More recently the MAGIC/UK MRC trial demonstrated that perioperative chemotherapy resulted in an improvement in overall survival and progression-free survival. Perioperative chemotherapy is the standard of care in United Kingdom and most of Europe for localized gastric cancer with the accepted regimens of ECF or ECX<sup>[15,27]</sup>. 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 3 cycles after surgery were compared with surgery alone. Perioperative chemotherapy showed an increased 5-year survival rate from 23% to 36%<sup>[27,28]</sup>. Similar results were achieved in the French study of perioperative cisplatin and FU<sup>[29,30]</sup>. Adjuvant chemotherapy alone may confer a survival benefit and should be considered in patients at high risk of recurrence who have not received neoadjuvant therapy (Japanese ACTS-GC trial)<sup>[31,32]</sup>. However, despite multimodal therapy and adequate surgery only 30% of gastric cancer patients are alive at 3 years<sup>[15,27]</sup>. As approximately 15% of gastric and esophageal junctional adenocarcinoma overexpress 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, esophagus, or junction of stomach and esophagus [stage 1b (T1N1) II, III or stage IV (T4, N1, or N2MO), type III GOJ adenocarcinoma]. Chemotherapy is given in 3 cycles over 9 weeks, with 5–6 weeks break followed by surgery. The safety was marred by perforations at primary tumor, cardiac toxicity, wound healing complications, and GI bleeding<sup>[33,34]</sup>. 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%)<sup>[35]</sup>. Currently trials are underway in the west to try and replicate this. Postoperative chemoradiation is the standard of care in the United States and for all patients with positive resection margins. With longer-term (> 11 y) follow-up, the benefits of both the overall survival (35 vs. 27 mo) and disease-free survival (27 vs. 19 mo) were maintained<sup>[6]</sup>.

## Laparoscopic versus open gastrectomy

### Principles

The same principles that govern open surgery is applied to laparoscopic surgery. To ensure the same effectiveness of laparoscopic gastrectomy (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<sup>[33–37]</sup>. As laparoscopic experience has accumulated, the indications for LG have been broadened to patients with advanced gastric cancer.

### Indications

LG may be considered as a safe procedure with better short-term and comparable long-term oncological results compared with open gastrectomy<sup>[31]</sup>. In addition, there is HRQL advantages to

minimal access surgery<sup>[38]</sup>. There is a general agreement that a laparoscopic approach to the treatment of gastric cancer should be chosen only by surgeons 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<sup>[32]</sup>. 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<sup>[33,34]</sup>. As laparoscopic experience has accumulated, the indications for 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<sup>[34]</sup>. The Japanese Gastric Cancer Association guidelines in 2004 suggested endoscopic mucosal resection or endoscopic submucosal dissection for stage 1a (cT1N0M0) diagnosis; patients with stage 1b (cT1N1M0) and cT2N0M0 were referred for LG<sup>[35]</sup>. 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. Laparoscopy-assisted total gastrectomy shows better short-term outcomes compared with open total gastrectomy in eligible patients with gastric cancer. There was a significant reduction of intraoperative blood loss, a reduced risk of postoperative complications, and a shorter hospital stay<sup>[36]</sup>. 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<sup>[37]</sup>. However, obesity is not a risk factor for survival of patients but it is independently predictive of postoperative complications. Careful approach is being needed, especially for male patients with high body mass index<sup>[6,10]</sup>.

### Robotic surgery

Robotic surgery will become an additional option 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. A multicenter study with a large number of patients is needed to compare the safety, efficacy, value (efficacy/cost ratio) as well as the long-term outcomes of robotic surgery, traditional laparoscopy, and the open approach<sup>[33,39]</sup>.

### 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 postoperative pain, rapid return of gastrointestinal function, and 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 esophago-gastric multidisciplinary team following the staging and assessment of fitness for treatment or palliation.

### Conflict of interests

The author declares that there is no financial conflict of interest with regard to the content of this report.

### References

- [1] Forman D. Gastric cancer: global pattern of the disease an overview of environmental risk factors. *Best Pract Res Clin Gastroenterol* 2006;20: 633–49.
- [2] Jemal A, Siegel R, Ward E, *et al.* Cancer statistics. *CA Cancer J Clin* 2006;56:106–30.
- [3] Siewert JR, Feith M, Werner M, *et al.* Adenocarcinoma of the esophago-gastric junction: results of surgical therapy based on anatomical/topographic classification in 1002 consecutive patients. *Ann Surg* 2000; 232:353–61.
- [4] Pal N, Axisa B, Yusof S, *et al.* Volume and outcome for major upper GI surgery in England. *J Gastrointest Surg* 2008;12:353–7.
- [5] Roukos DH, Kappas AM. Perspectives in the treatment of gastric cancer. *Nat Clin Pract Oncol* 2005;2:98–107.
- [6] Rajdev L. Treatment options for surgically resectable gastric cancer. *Curr Treat Options Oncol* 2010;11:14–23.
- [7] The TNM Classification of malignant tumours 7th edn; eds Leslie H Sabin, Mary K. Gospodarowicz, Christian Wittekind, copyright 2009 with permission of Wiley-Blackwell.
- [8] Barchi LC, Yagi OK, Jacob CE, *et al.* Predicting recurrence after curative resection for gastric cancer: external validation of the Italian Research Group for Gastric Cancer (GIRCG) prognostic scoring system. *Eur J Surg Oncol* 2016;42:123–31.
- [9] Lauren P. The two histological main types of gastric carcinoma: diffuse and so-called intestinal-type carcinoma. An attempt at a histo-clinical classification. *Acta Pathol Microbiol Scand* 1965;64:31–49.
- [10] Allum WH, Blazeby JM, Griffin SM, *et al.* Association of upper gastrointestinal surgeons—guidelines for the management of oesophageal and gastric cancer. *Gut* 2011;60:1449–72.
- [11] Xu YY, Huang BJ, Sun Z, *et al.* Risk factors for lymph node metastasis and evaluation of reasonable surgery for early gastric cancer. *World J Gastroenterol* 2007;13:5133–8.
- [12] Vasilescu C, Herlea V, Tidor S, *et al.* D2 lymph node dissection in gastric cancer surgery: long term results—analysis of an experience with 227 patients. *Chirurgia (Bucur)* 2006;101:375–84.
- [13] Songun I, Putter H, Kranenberg EM, *et al.* Surgical treatment of gastric cancer: 15-year follow follow-up results of the randomized nationwide Dutch D1D2 trial. *Lancet Oncol* 2010;11:439–9.
- [14] Arru L, Azagra JS, Facy O, *et al.* Totally laparoscopic 95% gastrectomy for cancer: technical considerations. *Langenbecks Arch Surg* 2015;400: 387–93.
- [15] Cho BC, Jeung HC, Choi HJ, *et al.* Prognostic impact of resection margin involvement after extended (D2/D3) gastrectomy for advanced gastric cancer: a 15-year experience at a single institute. *J Surg Oncol* 2007;95: 461–8.
- [16] Yonemura Y, Wu CC, Fukushima N, *et al.* East Asia Surgical Oncology Group. Operative morbidity and mortality after D2 and D4 extended dissection for advanced gastric cancer: a prospective randomized trial conducted by Asian surgeons. *Hepatogastroenterology* 2006;53:389–94.
- [17] Sasako M, Sano T, Yamamoto S, *et al.* D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med* 2008; 359:453–62.
- [18] Weledji EP, Verla V. Failure to rescue patients from early critical complications of oesophagogastric cancer surgery. *Ann Med Surg (Lond)* 2016; 2:34–41.
- [19] Sano T. Adjuvant and neoadjuvant therapy of gastric cancer: a comparison of three pivotal studies. *Curr Oncol Rep* 2008;10:191–8.
- [20] Kozak KR, Moody JS. The survival impact of the intergroup 0116 trial on patients with gastric cancer. *Int J Radiat Oncol Biol Phys* 2008;72: 517–21.
- [21] Yoshikawa T, Omura K, Kobayashi O, *et al.* A phase II study of pre-operative chemotherapy with S-1 plus cisplatin followed by D2/D3 gastrectomy for clinically serosa-positive gastric cancer (JACCRO GC-01 study). *Eur J Surg Oncol* 2010;36:546–1.
- [22] Messenger M, Lefevre JH, Pichot-Delahaye V, *et al.* FREGAT Working Group. The impact of perioperative chemotherapy on survival in patients with gastric signet ring cell adenocarcinoma: a multicenter comparative study. *Ann Surg* 2011;254:684–93; discussion 693.
- [23] Robb WB, Messenger M, Goere D, *et al.* FREGAT Working Group. Predictive factors of postoperative mortality after junctional and gastric adenocarcinoma resection. *JAMA Surg* 2013;148:624–31.
- [24] Gunderson LL, Sosin H. Adenocarcinoma of the stomach- areas of failure in a reoperation series (second or symptomatic look). Clinicopathological correlation and implications for adjuvant therapy. *Int J Radiol Oncol Biol Phys* 1982;8:1–11.
- [25] Sasako M, Saka M, Fukagawa T, *et al.* Adjuvant chemotherapy using S-1 for curatively resected gastric cancer—the nationwide clinical trial. *Gan To Kagaku Ryoho* 2006;33(suppl 1):110–6.
- [26] Shitara K, Chin K, Yoshikawa T, *et al.* Phase II study of adjuvant chemotherapy of S-1 plus oxaliplatin for patients with stage III gastric cancer after D2 gastrectomy. *Gastric Cancer* 2015. [Epub ahead of print].
- [27] Mongan AM, Kalachand R, King S, *et al.* Outcomes in gastric and junctional cancer using neoadjuvant and adjuvant chemotherapy (epirubicin, oxaliplatin and capecitabine) and radical surgery. *Ir J Med Sci* 2015;184:417–23.
- [28] Bouché O, Penault-Llorca F. HER2 and gastric cancer: a novel therapeutic target for trastuzumab. *Bull Cancer* 2010;97:1429–40.
- [29] MacDonald JS, Smalley SR, Benedetti J, *et al.* Chemoradiotherapy after surgery compared with surgery alone for adenocarcinoma of the stomach or gastroesophageal junction. *N Eng J Md* 2001;345:725–30.
- [30] Jackson C, Mochlinski K, Cunningham D. Therapeutic options in gastric cancer: neoadjuvant chemotherapy vs postoperative chemoradiotherapy. *Oncology (Williston Park)* 2007;21:1084–7; discussion 1090, 1096–8, 1101.
- [31] Zhang ZX, Gu XZ, Yin WB, *et al.* Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of adenocarcinoma of gastric cardia (AGC)—report on 370 patients. *Int J Radiat Oncol Biol Phys* 1998;42:929–34.
- [32] National Institute for Health and Clinical Excellence (NICE). Laparoscopic gastrectomy for cancer: National institute for health and clinical excellence july2008 ISBN 1-84629-629-753–2.
- [33] Parisi A, Nguyen NT, Reim D, *et al.* Current status of minimally invasive surgery for gastric cancer: a literature review to highlight studies limits. *Int J Surg* 2015;17:34–40.
- [34] Bracale U, Pignata G, Lirici MM, *et al.* Guideline Committee Of The Italian Society Of Hospital Surgeons-ACOI and Italian Hi-Tech Surgical Club-IHTSC. Laparoscopic gastrectomies for cancer: the ACOI-IHTSC national guidelines. *Minim Invasive Ther Allied Technol* 2012;21:313–9.
- [35] Koeda K, Nishizuka S, Wakabayashi G. Minimally invasive surgery for gastric cancer: the future standard of care. *World J Surg* 2011;35: 1469–77.
- [36] Usui S, Yoshida T, Ito K, *et al.* Laparoscopy-assisted total gastrectomy for early gastric cancer: comparison with conventional open total gastrectomy. *Surg Laparosc Endosc Percutan Tech* 2005;15:309–14.
- [37] Haverkamp L, Weijs TJ, Van Der Sluis PC, *et al.* Laparoscopic total gastrectomy versus open total gastrectomy for cancer: a systematic review and meta-analysis. *Surg Endosc* 2013;27:1509–20.
- [38] Kim YW, Baik YH, Yun YH, *et al.* Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. *Ann Surg* 2008;248:721–7.
- [39] Huang KH, Lan YT, Fang WL, *et al.* Initial experience of robotic gastrectomy and comparison with open and laparoscopic gastrectomy for gastric cancer. *J Gastrointest Surg* 2012;16:1303–10.