

WJG 20<sup>th</sup> Anniversary Special Issues (8): Gastric cancer**Subtotal gastrectomy for gastric cancer**

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**Author contributions:** The idea was proposed by Santoro R; Santoro R and Ettore GM drafted the initial manuscript; Santoro E reviewed and edited the draft; all authors approved the final manuscript before submission.

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Received: October 28, 2013 Revised: June 10, 2014

Accepted: June 26, 2014

Published online: October 14, 2014

**Abstract**

Although a steady decline in the incidence and mortality rates of gastric carcinoma has been observed in the last century worldwide, the absolute number of new cases/year is increasing because of the aging of the population. So far, surgical resection with curative intent has been the only treatment providing hope for cure; therefore, gastric cancer surgery has become a specialized field in digestive surgery. Gastrectomy with lymph node (LN) dissection for cancer patients remains a challenging procedure which requires skilled, well-trained surgeons who are very familiar with the fast-evolving oncological principles of gastric cancer surgery. As a matter of fact, the extent of gastric resection and LN dissection depends on the size of the disease and gastric cancer surgery has become a patient and "disease-tailored" surgery, ranging from endoscopic resection to laparoscopic assisted gastrectomy and conventional extended multivisceral resections. LN metastases are the most important prognostic factor in patients that undergo curative resection. LN dissection remains the most challenging part of the operation due to the location of LN stations around major retroperitoneal vessels and adjacent organs, which are not routinely included in the resected specimen and need to be preserved in

order to avoid dangerous intra- and postoperative complications. Hence, the surgeon is the most important non-TMN prognostic factor in gastric cancer. Subtotal gastrectomy is the treatment of choice for middle and distal-third gastric cancer as it provides similar survival rates and better functional outcome compared to total gastrectomy, especially in early-stage disease with favorable prognosis. Nonetheless, the resection range for middle-third gastric cancer cases and the extent of LN dissection at early stages remains controversial. Due to the necessity of a more extended procedure at advanced stages and the trend for more conservative treatments in early gastric cancer, the indication for conventional subtotal gastrectomy depends on multiple variables. This review aims to clarify and define the actual landmarks of this procedure and the role it plays compared to the whole range of new and old treatment methods.

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**Key words:** Gastric cancer; Gastrectomy; Lymphadenectomy; Laparoscopy; Endoscopy; Quality of life; Gastric stump cancer

**Core tip:** Gastric cancer surgical resection with curative intent is the only treatment providing hope for cure. Gastrectomy with lymph node dissection remains a challenging procedure, which should abide by well-defined oncological principles. Subtotal gastrectomy is the treatment of choice for middle and distal-third gastric cancer; however, due to the necessity of a more extended procedure at advanced stages and the trend for more conservative treatments in early gastric cancer, the indication for conventional subtotal gastrectomy depends on multiple variables. This review aims to define the actual landmarks of this procedure and the role it plays compared to the whole range of new and old treatment methods.

Santoro R, Ettore GM, Santoro E. Subtotal gastrectomy for ga-

stric cancer. *World J Gastroenterol* 2014; 20(38): 13667-13680 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v20/i38/13667.htm> DOI: <http://dx.doi.org/10.3748/wjg.v20.i38.13667>

## INTRODUCTION

Although a steady decline in the incidence and mortality rates of gastric carcinoma has been observed in the last century worldwide, the absolute number of new cases/year is increasing due to the aging of the population<sup>[1]</sup>. In 1990, gastric cancer was the second commonest type of cancer in the world, with 800000 new cases and 650000 deaths per year. In 1997, the number of new cases rose to more than 1 million<sup>[2,3]</sup>. Incidence is higher in East Asia and Eastern Europe, with a smaller number of cases being recorded in North America and Northern Europe<sup>[4]</sup>. The aforesaid decline mainly concerns the Lauren's intestinal (or well differentiated) type, which is more frequently reported in regions where gastric cancer is endemic; it typically arises in the middle and distal third of the stomach, on a background of metaplasia affecting older male patients. On the other hand, the Lauren's diffuse (or poorly differentiated) type is more common in low risk areas. It has a steady incidence and tends to affect younger individuals, mainly females. Moreover, it often shows hereditary characteristics<sup>[5,6]</sup>. Gastric cancer is still a poor prognosis and high mortality disease, second only to lung cancer, especially in countries with lower incidence<sup>[7]</sup>. After Billroth's first successful pylorotomy in 1881 and Schlatte's first total gastrectomy in 1897 for gastric cancer, surgical resection is still the only treatment presently giving hope for cure<sup>[8,9]</sup>. In 1929, MacGuire noted that all the possibilities of partial resection of the stomach and anastomosis with the duodenum and jejunum had been developed<sup>[10]</sup>. He reported excellent results in terms of postoperative morbidity and mortality rates after subtotal gastrectomy in 16 patients. However, a carcinoma of the pylorus with obstruction was described in one patient only, with the others suffering from gastric and duodenal peptic ulcer. MacGuire's report shows that surgeons have been familiar with partial gastrectomy for peptic disease for a very long time; however, the surgical approach to gastric cancer was standardized in Japan in the 1960s<sup>[11]</sup>. The first edition of the General Rules for Gastric Cancer Study was published by the Japanese Research Society for Gastric Cancer (JRSGC) in 1963 and the first English edition was based on the 12<sup>th</sup> Japanese edition and was published in 1995<sup>[12]</sup>. In Japan, the incidence is 20-fold the incidence in United States and, while the incidence of proximal tumors is increasing in the West, distal tumors continue to predominate in the land of the rising sun. Such important epidemiological differences entail different diagnostic and therapeutic strategies and prognosis. In Japan, a mass screening program has been in place since the 1960s and early detection of the disease combined with improved operative techniques has led to a signifi-

cant decrease in mortality<sup>[13]</sup>. In a large evaluation of 10000 patients treated between 1962 and 1989 at Kyushu University of Fukuoka, Japan, most carcinomas were found in the distal two thirds of the stomach and a large proportion of patients underwent subtotal distal gastrectomy<sup>[14]</sup>. Total gastrectomy was performed for widespread disease, proximal location, multifocal disease, or due to extensive dissection of the lymph nodes (LNs). According to the Registry of the Japanese Research Society for Gastric Cancer, the incidence of stage-I gastric cancer in 1991 was 55.5%, while subtotal gastrectomy accounted for 69.3%<sup>[15]</sup> of all surgeries. The same registry showed a cumulative 5-year survival rate of 68.2%. In a multi-institutional randomized controlled trial carried out on behalf of the Japan Clinical Oncology Group comparing D2 and extended para-aortic lymphadenectomy in advanced gastric cancer, the incidence of subtotal gastrectomy was 61.1%<sup>[16]</sup>. In Western countries, gastric cancer prognosis has been improving over the last 40 years; however, it remains quite poor<sup>[17]</sup>. In Europe, 5-year survival varies depending on the country, ranging from less than 10% to nearly 25%<sup>[18]</sup>. In the past, gastric cancer located in the distal third of the stomach was treated by total or subtotal gastrectomy, depending on the surgeon's experience. The "en principe" total gastrectomy was proposed in the 1970s to secure better loco-regional tumor control compared to subtotal gastrectomy<sup>[19,20]</sup>. However, the procedure did not gain worldwide acceptance and several surveys carried out at that time showed that the incidence of subtotal gastrectomy varied between 20% and 70%<sup>[21-26]</sup>. Moreover, several non-randomized series published in the 1980s did not show any survival-related benefit of total gastrectomy compared to subtotal gastrectomy<sup>[27-31]</sup>. Lastly, two randomized trials published in 1989 and 1999, respectively, comparing the survival rates for total and subtotal gastrectomy for gastric cancer located in the distal third reported similar survival rates for the two procedures<sup>[32,33]</sup>. Since then, subtotal gastrectomy has been considered the treatment of choice in distal and middle-third gastric cancer, provided that the resection margins fall in healthy tissue, also in Western countries. The extent of a gastric resection is not technically challenging for general surgeons and the extent of the LN dissection required in the treatment of gastric cancer with curative intent is the most challenging part of any operation. In the 1980s and 1990s, the role of LN dissection was also assessed worldwide. The topographic pattern of LN metastases was largely described and the range of the D1, D2, D3 and D4 LN dissections was validated in Japan<sup>[34,35]</sup>. A standardized LN dissection was developed and it was routinely used nationwide with therapeutic benefits and good long-term survival. In Western countries, extended LN dissection was not popular due to higher morbidity and mortality rates and no survival benefits<sup>[36-39]</sup>. Finally, the long-term results of two European studies showed significant improvement in survival rates due to D2 LN dissection in patients with stage-II disease; moreover, the study clearly identified the patients who may benefit from

D2 LN dissection, also in Western countries<sup>[40,41]</sup>. In those years, the benefits of more extended D3 and D4 LN dissections had not been clearly demonstrated compared to D2 lymphadenectomy and they also showed higher incidence of complications<sup>[42,43]</sup>. Based on the aforementioned results, the Japanese Gastric Cancer Association updated the classification of gastric cancer and the guidelines for surgical treatment according to clinical stage in 1998 and in 2011, respectively<sup>[44,45]</sup>. This review aims to point out the role of subtotal gastrectomy in the treatment of gastric cancer, focusing on the extent of gastric resection, the extent of lymphadenectomy, the type of reconstruction in the era of minimal invasive approach and endoscopic resection.

## ONCOLOGICAL PRINCIPLES OF SUBTOTAL GASTRECTOMY: THE RATIONALE

### **Subtotal gastrectomy vs total gastrectomy**

Curative resection is the only chance for cure in patients with resectable gastric cancer. It aims to ensure complete removal of the tumor by providing adequate longitudinal and circumferential resection margins. Subtotal gastrectomy is the gold standard treatment for early-stage gastric cancer located in the distal third of the stomach. The results of two randomized studies carried out in European countries have shown that subtotal gastrectomy for distal-third gastric cancer entails similar long-term survival results as total gastrectomy, with lower morbidity and mortality rates and better postoperative quality of life<sup>[32,33]</sup>. There are several advantages in performing more conservative surgery. Subtotal gastrectomy entails lower short-term morbidity and mortality rates and shorter hospital stay, as well as higher calorie intake and better nutritional status with improved quality of life in the long run. A very large multicentric prospective study on more than 4000 patients carried out in Italy in the 1980s did not find any significant difference in terms of long-term survival between the two procedures<sup>[46]</sup>. However, many years later, surgeons have not reached consensus yet; as a matter of fact, the supporters of the “en principe” total gastrectomy advocate that it allows better local tumor control of the disease. The extent of gastric resection is not a prognostic factor, whereas the adequate LN clearance of the LN stations beyond the perigastric ones is the most important surgical prognostic factor in both early and advanced gastric cancer<sup>[35,47-50]</sup>. In patients with distal-third gastric cancer, total gastrectomy without an adequate lymphadenectomy would be an oncological surgical mistake as it is an overtreatment from the gastric resection standpoint and, at the same time, an undertreatment from the LN dissection standpoint. There is no advantage in extending the resection to the whole stomach; however, the extent of gastric resection depends on the site and size of the primary tumor. According to a prospective randomized study carried out in the 1980s in Italy, the

resection line should provide a safe 3-6 cm resection margin in a case of Lauren’s intestinal or diffuse gastric cancer, respectively<sup>[33]</sup>. However, according to the Japanese Gastric Cancer Association guidelines, a proximal margin of at least 3 cm is recommended for T2 or deeper tumors with an expansive growth pattern (Types 1 and 2) and 5 cm is recommended for those with infiltrative growth pattern (Types 3 and 4)<sup>[45]</sup>. Total gastrectomy may be required in those cases with poorly differentiated histological type located in the angularis portion of the stomach, who are likely to show a submucosal invasion along the lesser curvature towards the cardia with a high risk of microscopic invasion of the transection line<sup>[51]</sup>, or in patients with multicentric disease. Total gastrectomy may also be required in patients suffering from distally located gastric cancer with multiple LN metastases and advanced stages in order to allow an extended D2 or D3 LN dissection. In such cases, an aggressive surgical approach, including multivisceral resections, is the only hope for cure. Total gastrectomy has also been advocated as a prophylactic treatment in the event of E-cadherin gene mutation in association with familial gastric cancer<sup>[52,53]</sup>.

### **General LN dissection rules**

Lymphatic spread is the most relevant prognostic factor in patients with gastric cancer resected for cure. LN status and ratio are the most important prognostic factors<sup>[35,47-49,54,55]</sup>. The importance of adequate lymphadenectomy as part of a potentially curative resection has been recognized in Western countries as well<sup>[39,41,56-58]</sup>. For absolutely curative resection, lymphatic dissection must be a level higher than the highest echelon of metastatic LNs, in addition to tumor free margin. Appropriate LN dissection is also important for accurate staging. The number of retrieved LNs has been validated as a method of evaluating the adequacy of LN dissection but data collection from each LN station needs considerable effort from both surgeons and pathologists. The number of LN metastases has been validated as a better prognostic indicator compared to the location of the LN metastases<sup>[48,49]</sup> and the staging system was updated in the 2010 UICC/TNM 7<sup>th</sup> edition<sup>[59]</sup>. According to the new system, pN1 is defined as LN metastases in 1 to 2 LNs, pN2 is defined as LN metastases in 3 to 6 LNs, N3a in patients with 7 to 15 metastatic LN, and N3b in patients with more than 16 LNs metastases. The classifications of the LN stations and LN dissections were also updated at the same time.

### **LN stations classification**

In the past, 16 different LN stations were identified surrounding the stomach<sup>[12]</sup>. The perigastric nodes were defined as N1 nodes (station 1 to 6). N2 nodes corresponded to the nodes around the main vessels originating from the celiac trunk (station 9), the left gastric, common hepatic, splenic artery and splenic hilum and arteries (stations 7, 8, 11 and 10, respectively). Nodes at the hepatoduodenal ligament (station 12), the retropancreatic region (station 13) and the root of the mesentery (station 14)

were defined as N3, whereas those along the middle colic vein (station 15) and para-aortic nodes (station 16) were classified as N4. This topographic classification remains very popular among surgeons and still represents a milestone knowledge that helps surgeons perform LN dissection correctly. However, nowadays it has poor clinical significance. As a matter of fact, according to the Japanese classification of gastric carcinoma, LN stations 1-12 and 14v are now defined as “regional” gastric LNs, whereas metastasis to any other nodes is classified as “M1”.

### Definition of LN dissections

LN dissection was initially classified as D1 to D4, depending on the extent and removal of each LN station according to the primary tumor location. In distal subtotal gastrectomy, D1 included removal of only LN stations 1, 3, 4, 5, 6 and 7 surrounding the stomach, whereas D2 included D1 LN dissection and station 8a, 12a, 9 and 11. D3 and D4 LN dissections occur when the other LN stations are removed. This system has been revised and now reflects the number of retrieved LNs rather than their location. Hence, it is as follows: D0 when less than 15 nodes are reported, D1 when 15 to 25 nodes are removed, and D2 when more than 25 nodes are reported in the pathological findings<sup>[12,40,49,60]</sup>. As a matter of fact, the number of LNs itself cannot give any information about the extent of LN dissection. The original N1-3 and D1-3 definitions are far more complicated: LN groups are defined as compartments 1-3 and depend on the location of the primary tumor, according to which each LN station is given a group number (1, 2, 3, or M)<sup>[44]</sup>.

### Oncological principles of LN dissection in distal subtotal gastrectomy

The rate and number of metastatic LNs increases with the depth of tumor invasion through the gastric wall layers and shows a clear relationship with survival<sup>[35,61-63]</sup>. This rate is low in early gastric cancer (EGC) and the Japanese Gastric Cancer Association recommends a D2 LN dissection in most gastric cancer. However, less extensive LN dissection was approved in patients with T1 cancer and clinical node-negative disease. The incidence of LN metastases in lower-third gastric cancer at each LN station according to the depth of tumor invasion was well described in a recent detailed report from the Seoul National University Hospital<sup>[62]</sup>. In this large series, curative resection for gastric cancer located in the distal third of the stomach was carried out with subtotal gastrectomy in 95.2% of the patients, 38.1% of whom suffered from advanced gastric cancer. The mean number of LNs was 37.6 and LN dissection was D2 or more extended in 57.1% of the surgeries. However, extended LN dissection was not performed in EGC, which accounted for 61% of the cases. In the aforementioned study, a D1 +  $\alpha$  (D1 + station 7 and 8a) or D1 +  $\beta$  (D1 + stations 7, 8a and 9) LN dissection was performed in 43% of the patients. The incidence of LN metastases in mucosal EGC (pT1a) was very low, namely 1.1%, and a D1 +  $\beta$  LN dissection

was suggested to be adequate. Instead, the incidence of LN metastases in submucosal EGC (pT1b) was as high as 23%. In particular, metastases to the second level (LN stations 7-11) and third level (LN stations 12-16) were detected in 5% of the patients. The authors concluded that, in patients with distal third submucosal cancer, D1 +  $\beta$  LN dissection entailed a risk of leaving metastatic nodes in 3% of cases and therefore D2 LN dissection was recommended. In other studies, the incidence of micro-metastases in N0 pT1 and pT2 was shown to be as high as 17%-23% and such micro-metastases were correlated with the prognosis<sup>[64,65]</sup>. In a case of EGC, the intraoperative histopathological evaluation of clinically suspected metastatic nodes or the sentinel node technique might be deemed suitable in a tailored LN dissection (D1 +  $\beta$ ) strategy and might avoid extended D2 LN dissection in selected N0 or N1 patients who would not tolerate complications<sup>[66,67]</sup>. In this perspective, the minimally-invasive approach has become the gold standard procedure for the treatment of EGC in Japan. In Western countries, the incidence of gastric cancer is low, no screening program has been approved and most gastric cancer patients are diagnosed with advanced stage gastric cancer. For advanced gastric cancer (pT2-4), extended LN dissection is mandatory because the rate of second level (LN stations 7-11) node metastases ranges between 10% and 20%. Several reports showed that extended LN dissection can be performed with low morbidity and mortality rates<sup>[16,68,69]</sup>. Pancreatosplenectomy, thought to be necessary in the past, remains a source of postoperative complications and is not essential for adequate clearance of nodal stations along the splenic vessels in D2 LN dissection. Accurate dissection along the splenic vessels and the hepatic pedicle is the most challenging part of any gastric surgery for cancer because it requires hepatobiliary and pancreatic surgery technical skills and training. General surgeons without such training are more likely to perform inadequate gastric cancer surgery, especially in the event of advanced gastric cancer when an aggressive surgical procedure is the only chance for cure<sup>[70]</sup>. The higher survival rates after D2 LN dissection compared to D1 surgery as reported by Japanese series have not been confirmed by European randomized trials<sup>[36,37]</sup>. Some skeptics believe that extending LN dissection beyond perigastric stations entails more diagnostic than therapeutic benefit. However, patients with second-level node invasion who undergo D1 gastrectomy are likely to show early local recurrence because of inadequate LN dissection. Furthermore, such patients are understaged at the time of primary surgical treatment which makes comparison with studies that use a more accurate staging inaccurate<sup>[71]</sup>. However, in other major nonrandomized studies, D2 lymphadenectomy was an independent prognostic factor and improved long-term survival in patients with stage-II tumors<sup>[39,56]</sup>. Lastly, the very comprehensive results of the Dutch trial comparing D1 *vs* D2 lymphadenectomy showed that extended LN dissection is associated with lower loco-regional and gastric cancer-related death rates



than D1 surgery<sup>[40]</sup>. This study confirmed that significant long-term survival benefits were observed in stage-II patients (pT2N1 or pT3N0), as had previously been shown by the German Gastric Study Group. The Dutch trial showed higher survival rates in D2 group N2 patients than D1 group patients and as N2 disease is difficult to identify preoperatively, the authors concluded that extended LN dissection might be beneficial when morbidity and mortality rates are very low. As a result, inadequate LN dissection accounts for more than half of the surgical failures due to loco-regional recurrence, especially in those patients with second-level node metastases. A well designed Italian nonrandomized prospective multicentric study on patients with advanced gastric cancer invading the serosa (pT3) located in the gastric antrum showed that subtotal gastrectomy with D2 LN dissection without splenectomy can be performed with low morbidity and mortality rates and survival was even better than that of patients treated with total gastrectomy<sup>[72]</sup>. In the above-mentioned study, the choice of the surgical procedure (total or subtotal gastrectomy) was based on the surgeon's preference. Subtotal gastrectomy was preferentially performed in older patients and when the surgeon believed the disease to be less aggressive, as demonstrated by the higher number of metastatic LN in the TG group. However, the type of surgery had no influence on the number of dissected nodes. The study also confirmed that extended LN dissection can be performed in patients with advanced gastric cancer located in the distal third of the stomach, suitable for subtotal gastrectomy. Total gastrectomy may become necessary when the lymphatic spread is beyond N2 LN stations. In the series reported by the Seoul National University Hospital, the incidence of total gastrectomy in 400 patients with advanced lower-third gastric cancer was 6%<sup>[62]</sup>. In clinical practice, D2 standard LN dissection becomes mandatory in the majority of patients and less extensive lymphadenectomy can be performed in 10 to 20% of cases. Hence, surgeons need to have technical skills and clinical experience in order to treat most gastric cancer patients when surgery is the main treatment option. Results of trials on gastric cancer multidisciplinary management suggested that D2 surgery alone results in much better survival rates than less extensive surgery plus adjuvant chemotherapy and radiotherapy, as shown by the INT0116 trial. The Intergroup randomized trial confirmed that local recurrence of cancer is reduced by 50% after D2 resection<sup>[73,74]</sup>.

With this tailored surgical approach, the Maruyama Index (MI) of unresected disease (as the quantitative measure of sum of the probabilities of metastases to regional LN station 1-12 that were not removed and left behind after primary surgical treatment) may remain low (< 5) within the limits of curative R0 resection, decreasing the risk of loco-regional recurrence and improving survival<sup>[75-78]</sup>. The Dutch D1 vs D2 trial was reanalyzed using the MI as a prognostic tool and the MI < 5 proved to be a strong predictor of survival by both univariate and multivariate analysis. D2 LN dissection should entail

low MI in most patients, particularly in stage II and III gastric cancers<sup>[79]</sup>. Surgical experience and training are essential to perform high quality gastric cancer surgery and advanced gastric cancer patients are more likely to have a low MI curative surgery in high volume institutions rather than in low volume hospitals. Subtotal gastrectomy is the first option in the treatment of middle and lower-third gastric cancer, regardless of the extent of LN dissection required to achieve curative R0 resection with low MI.

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## ONCOLOGICAL PRINCIPLES OF SUBTOTAL GASTRECTOMY: HOW TO PERFORM IT

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### *Extent of gastric resection and the resection margin*

Nowadays, this procedure accounts for 23%-70% of all cancer gastrectomies performed in specialized centers in European and Far Eastern countries<sup>[15,23-25,43,55]</sup>. Subtotal gastrectomy can also be performed in patients with gastric cancer arising in the middle part of the stomach as the length of proximal resection margin is currently the single most important factor in deciding the final gastric resection extent<sup>[33,72]</sup>. Although total gastrectomy was recommended in the past as the standard surgery for middle-third gastric cancer, it has been shown that subtotal gastrectomy can be carried out in middle-third gastric cancer patients when a 3-6 cm tumor proximal free margin can be achieved, according to the Lauren histological type<sup>[33]</sup>. In early gastric cancer, subtotal gastrectomy is the gold standard treatment, whereas in case of advanced gastric cancer, the intraoperative frozen section histopathological evaluation of the transection line is useful to detect positive margins and proceed to total gastrectomy. Other more recent studies supported this stomach sparing strategy in the treatment of gastric cancer located in the middle third. Subtotal gastrectomy was performed in 39.3% of the 402 patients with middle-third advanced gastric cancer at the Korea University College in Seoul, compared to 83.3% of the 172 patients with lower-third cancer<sup>[80]</sup>. In this study, as expected, the patients who underwent total gastrectomy had more advanced T stage; however, there was no difference in stage-stratified survival rate based on the extent of curative gastric resection. Multivariate analysis revealed that the type of gastric resection and the length of the proximal resection margin, using cut-off value from 1-5 cm in intervals of 1 cm, had no impact on 5-year survival. Similar results were reported in another study from the same region<sup>[81]</sup>. In order to prevent local recurrence of cancer, a > 6.5 cm gross margin was recommended in the past<sup>[82]</sup>. More recently, > 3 cm a margin in the final pathology for advanced gastric cancer has been considered adequate. However, according to the Japanese Classification of Gastric Cancer Carcinoma (2<sup>nd</sup> English edition), high chances of cure are achieved when the resection margin is > 1 cm. The resection line infiltration is an unfavorable prognostic factor at any stage of the disease and patients in good general

condition for whom radical surgery is possible should be considered for reoperation<sup>[51]</sup>. Since long-term oncological outcome does not seem to be affected by the type of gastric resection or by the length of the proximal resection margin, patients with middle-third advanced gastric cancer can be safely treated with subtotal gastrectomy with curative intent. Such patients will benefit in terms of postoperative morbidity and mortality rates, as well as quality of life.

### **“Two thirds” of “four fifths” subtotal gastrectomy and the destiny of the left gastric artery**

The extent of gastric resection is usually defined as “two thirds” or “four fifths” of the stomach. From an oncological standpoint, this is not relevant provided that the proximal margin of the resection falls in healthy tissue and adequate LN dissection is performed; however, the size of the remnant stomach is important for the reconstruction phase following partial gastrectomy. If the gastric stump is too short, reconstruction is preferably done by using Billroth II or Roux-en-Y methods. The Billroth I method can be performed when the size of the remaining stomach allows obtaining a tension-free gastroduodenal anastomosis. In addition, the length of the gastric remnant may cause concern about the vascularization of the distal end of the gastric stump. The extensive resection and LN dissection disrupting the arterial branches surrounding the stomach, including LN station #1, that provide the blood supply to the gastric stump may contribute to postoperative necrosis of the distal part of the gastric stump and unfavorable outcome. After standard D2 subtotal gastrectomy for advanced gastric cancer, the blood supply of the gastric stump is maintained up to the level of resection by the esophagocardio-tuberal branches and the short gastric arteries. However, the gastric stump might show poor vascularization in the resection area if the stump is too long, thus entailing possible risk of late ischemia not detected during surgery and postoperative fistula at the gastroduodenal or gastro-jejunal anastomosis. Hence, when the left gastric artery is divided at the root from the celiac trunk and radical lymphatic clearance is performed, the short gastric vessels should be preserved and a “four fifth” subtotal gastrectomy performed; the type of reconstruction will depend on the surgeon’s choice and the remaining stomach length. In a case of EGC without gross LN metastases, D1 +  $\beta$  or D2 LN dissection can be performed with preservation of the left gastric artery and its “ascending branch”, especially if the tumor is distally located on the greater curvature<sup>[83]</sup>. In this setting, adequate LN dissection can be performed by skeletonizing the hepatic artery, the celiac trunk and then the left gastric artery, as in transplant surgery, by removing the adipose tissue containing the lymphatics along these arteries. Similarly, extended LN dissection can be carried out along the splenic artery by preserving the pancreatic tail and spleen. Only the stem of the left gastric artery and the “ascending branch” can be preserved as the feeding artery for the gastric remnant

by dividing the “descending branch” at the root<sup>[84]</sup>. The blood supply provided by this artery to the gastric remnant allows safely performing two-third subtotal gastrectomy, thus making it possible to proceed to reconstruction by tension-free Billroth I anastomosis after dividing the short gastric vessels.

## **ROLE OF CONVENTIONAL SURGERY IN EARLY-STAGE GASTRIC CANCER VS MINIMALLY INVASIVE TECHNIQUES**

### **Subtotal gastrectomy vs endoscopic resection**

Although gastrectomy with LN dissection is still the gold standard treatment for early gastric cancer, endoscopic surgical techniques such as endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been proposed in selected patients as alternative treatments to maintain good quality of life<sup>[85-87]</sup>. Typically, EMR of large lesions require piecemeal resection. ESD is an alternative technique which enables en bloc resection. With this technique, LN dissection is not performed and regional LNs remain untreated. Therefore, patient selection is mandatory and this conservative technique can only be proposed for patients with low risk of LN metastases. According to the Japanese gastric cancer treatment guidelines of the Japanese Gastric Cancer Association (2010, ver.3), EMR or ESD are indicated as the standard treatment for differentiated-type adenocarcinoma without ulcerative findings whose depth of invasion is clinically diagnosed as T1a and with  $\leq 2$  cm diameter. This group of tumors show very low incidence of LN metastases. In a large study on 5265 patients who underwent gastrectomy with LN dissection for EGC, the incidence of LN invasion was observed in only 2.7% of mucosal cancers and 18.6% of EGC invading the submucosa<sup>[83]</sup>. None of the 1230 well differentiated intramucosal cancers with less than 30 mm diameter were associated with LN metastases. Other risk factors for LN metastases were lymphatic-vascular involvement, undifferentiated histological type and tumor diameter larger than 30 mm. The endoscopic resection of tumors with the aforementioned features is under investigation and those tumors are considered as an expanded indication. In 1091 submucosal invasive tumors, the incidence of LN metastases was 20.3%<sup>[83]</sup>. As for intramucosal cancer, the presence of LN metastases had a significant correlation with tumor size larger than 30 mm, undifferentiated histological type and lymphatic-vascular involvement. The incidence of LN metastases in patients negative for these three risk factors was 5.6%; the authors suggested that in this subset of patients, LN dissection may not be necessary and EMR or ESD should be performed. However, these criteria are based on the full histological examination of the resected specimen. Therefore, it is of paramount importance that the EMR or ESD is technically well performed and the specimen fully examined. Resection is deemed curative when the tumor size is  $\leq 2$  cm and en-bloc resection

with negative margins is performed for pT1a histologically differentiated-type without lymphovascular infiltration. When EMR or ESD is deemed non curative, additional surgical treatment should be recommended. Gastrectomy is also required when EMR or ESD are not feasible and since most tumors are located in the middle and distal thirds of the stomach, subtotal gastrectomy with LN dissection remains the treatment of choice.

### **Laparoscopic-assisted distal gastrectomy vs open procedure**

Laparoscopic surgery for gastric cancer has gained popularity since its first application in 1991<sup>[88]</sup>. With the improvement of laparoscopic instruments and techniques, minimally invasive surgery has recorded increasing clinical application to treat early-stage gastric cancer<sup>[89]</sup>. In Asian countries such as Japan and South Korea, laparoscopic-assisted distal gastrectomy (LADG) has become a standard therapy for early gastric cancer (EGC) located in the distal and middle thirds<sup>[90,91]</sup>. Furthermore, the development of this technique also entailed wide acceptance for other types of gastrectomies. The results of a retrospective multicenter study carried out in South Korea by the Korean Laparoscopic Gastrointestinal Surgery Study (KLASS) group showed that laparoscopic-assisted gastrectomy (LAG) provided satisfactory long-term oncological outcomes, similar to those of open surgery<sup>[92]</sup>. In the above-mentioned study, indication for LAG was gastric cancer patients with preoperative stage Ia (cT1N0M0) diagnosis, except those who were suitable for endoscopic resection. However, as experience accumulated, indications were expanded to preoperative diagnosis of more advanced early-stage disease (cT1N1M0, cT2N0M0 and cT2N1M0). The incidence of recurrence was 1.6% (19/1186) in EGC and 13.4% (31/231) in advanced gastric cancer (AGC)<sup>[93]</sup>. The study suggests that LAG is a good alternative to open gastrectomy in patients with relatively early-stage gastric cancer. LAG has several significant advantages, including less intraoperative blood loss, less postoperative pain, earlier postoperative recovery and shorter hospital stay. However, adequate lymphadenectomy is the most important prognostic factor in gastric cancer and the reliability of a laparoscopic approach depends on performing D2 dissection correctly, as in open surgery, following the criteria of the Japanese Gastric Cancer Association guidelines. It is estimated that a laparoscopic approach is employed in about 20% of gastric cancer surgeries in Japan; nevertheless, according to the Japanese Gastric Cancer Guidelines (2010, ver.3), this minimally invasive technique should be considered an investigational treatment. At present, although the long-term results of the phase III KLASS trial are yet to be published, LAG is considered to be accepted for EGC<sup>[94]</sup>. In intramucosal cancer not suitable for endoscopic resection or after non-curative endoscopic resection, surgical treatment is recommended and the laparoscopic approach seems to be a good alternative to conventional open surgery as a D1 +  $\beta$  LN dissection can be safely performed

with curative intent. The application of LAG for AGC remains controversial due to the technical difficulty of performing a complete D2 lymphadenectomy. Extended LN dissection was shown to be technically feasible with a high number of retrieved nodes in both laparoscopic and robotic approaches<sup>[95,96]</sup>. However, the preoperative diagnosis of AGC with obvious node metastases is not an indication for the minimally invasive approach. In several series, preoperative understaging of EGC conceals the presence of AGC in 4.6%-7.6% of cases. The retrospective analysis of the KLASS group regarding 239 patients who were diagnosed with AGC on final pathological examination showed that the long-term survival outcome rates were comparable to those previously reported for open gastrectomy<sup>[92]</sup>. In this study, a D2 LN dissection was performed in 68.2% of the procedures; however, only 23% of the patients were diagnosed with stage III or IV disease. A recent meta-analysis of LADG showed that the short-term outcome of LADG for EGC is better than that of the open procedure<sup>[97]</sup>. However, LADG performed significantly less well compared to open distal gastrectomy in terms of operative time and also showed a smaller number of harvested LNs. The long-term outcome should be proven by further results of ongoing randomized clinical trials.

### **LADG technical aspects**

From a technical standpoint, several techniques have been described to perform minimally invasive distal gastrectomy, including laparoscopic-assisted and robotic-assisted techniques with extracorporeal anastomosis, which are the most frequently described ones, and the entirely intracorporeal technique. In the laparoscopic and robotic-assisted techniques, minilaparotomy is performed after mobilization of the stomach and division of the gastric vessels at the root together with LN dissection. The mobilized stomach is pulled out through the minilaparotomy site and resected. Billroth I or II or Roux-en-Y anastomosis can be performed extracorporeally by using stapling devices or hand-sewing techniques, depending on the surgeon's choice<sup>[98-100]</sup>. In addition, LN dissection of the nodes behind the hepatic artery or portal vein that are not easily harvested by laparoscopy can be safely removed through this minilaparotomy before reconstruction. In entirely intracorporeal subtotal gastrectomy, side-to-side gastrojejunal anastomosis is usually performed using laparoscopic linear cutter staples through two access openings of the jejunal limb and the posterior wall of the gastric stump. Then, the openings are closed with running suture or extracorporeal slipknots, depending on surgeon's preference<sup>[95]</sup>. Then, the resected stomach is extracted using a polyethylene endobag through the enlarged umbilical incision or, preferably, from a suprapubic incision. Since most of the tumors treated by LADG are EGC and the tumor border is often unclear, preoperative endoscopic marking of the proximal margin of the tumor is recommended in order to obtain a proximal resection margin of at least 2 cm in pT1 tumors.



## RECONSTRUCTION AFTER DISTAL SUBTOTAL GASTRECTOMY AND LONG-TERM OUTCOME

The extent of gastric resection does not influence survival when patients are matched for stage groups and the type of reconstruction after SG for gastric cancer has never been associated with any prognostic value<sup>[15,24,40]</sup>. After subtotal gastrectomy, the following reconstruction methods are usually employed: Billroth I gastroduodenostomy, Billroth II gastrojejunostomy with or without Braun anastomosis, Roux-en-Y gastrojejunostomy, uncut Roux-en-Y gastrojejunostomy and jejunal interposition. Distal subtotal gastrectomy entails risks of symptomatic gastroesophageal reflux disease (GERD) and cancer of the gastric stump (CGS); however, in the past, the impact of partial gastrectomy for benign peptic disease on survival was found to be so weak that prophylactic endoscopic monitoring was unrewarded until 15 to 20 years postoperatively<sup>[101]</sup>. In Far Eastern countries where the incidence of gastric cancer is high and subtotal gastrectomy is the most frequently performed procedure, all types of reconstructions are routinely performed depending on surgeon and/or institution choice and the Japanese Gastric Cancer Treatment Guidelines 2010 (ver.3) do not recommend any type of reconstruction after distal gastrectomy. Each type has advantages and disadvantages. A choice should be based on personal experience and surgical results, as well as the functional outcome and postoperative quality of life. The most important factor influencing postoperative quality of life is symptomatic bile reflux esophagitis and various reconstruction methods have been introduced in order to reduce bile reflux and prevent symptoms; however, this complication occurs in 5% of patients, regardless of the type of reconstruction<sup>[102]</sup>. Billroth I and Billroth II reconstructions are the preferred method of anastomosis across Japan, whereas reconstruction using Roux-en-Y anastomosis is more common in Europe and North America, with a view to preventing GERD, reducing the risk of CGS, and improving the functional outcome<sup>[99,103-106]</sup>. However, there is no convincing evidence proving that one method is better than the other from both carcinogenetic and functional standpoints<sup>[100,107-109]</sup>.

### Risk of cancer of the gastric stump

The interval between subtotal gastrectomy for gastric cancer and detection of CGS is significantly shorter compared to previous gastrectomy for benign ulcer disease, with the first one being 5-10 years from primary operation, while the latter is more than 15-20 years<sup>[110,111]</sup>. CGS within 5 years from gastrectomy was shown to occur only in patients who had primary surgery for gastric cancer, even at an early stage; however, such early recurrence probably results from incorrect initial diagnosis of multicentric disease or from non-curative initial gastrectomy. Unfortunately, such types of recurrences may occur despite accurate pre- and intraoperatively

patient selection and they are not related to the type of reconstruction; rather they are due to the surgical choice to perform partial gastrectomy instead of total gastrectomy. On the other hand, true primary CGS occurs later, more than 5 years postoperatively, and can result from the same pathogenetic pathway that leads to CGS after resection for benign disease where the role of reflux and type of reconstruction remain controversial. The incidence of true primary CGS is less than 1% in the long-term<sup>[15,111,112]</sup>. In Far Eastern countries, surgeons adopted a radical approach to LN dissection but not to the extent of gastric resection and SG accounts for two thirds of all cancer gastrectomies, with early carcinoma affecting 60% of all patients<sup>[15,113]</sup>. In Japan, CGS was observed after both Billroth I and Billroth II procedures, but also after a Roux-en-Y procedure<sup>[110,111,114,115]</sup>, and the type of reconstruction after SG has never been recognized as a prognostic factor. In our previous study, the incidence of CGS after Billroth I SG was 0.7% in the very long-term<sup>[112]</sup>. Therefore, the impact of the type of reconstruction on CGS development remains most theoretical than practical. The theoretical 1% long-term risk of CGS does not justify “*en principe*” TG, even in young patients with long-term life expectancy, unless they have a history of familial gastric cancer. In our previous study, SG in young patients with favorable pathological staging was confirmed to improve long-term survival and have favorable functional outcome<sup>[116]</sup>. However, lifelong endoscopic monitoring is recommended after initial gastrectomy for all patients, especially those operated on at an early stage because early diagnosis of CGS entails hope for cure<sup>[111,115,117]</sup>.

### Functional outcome

Postoperative quality of life is an important goal when treating gastric cancer surgically. After partial gastrectomy, some patients report disorders such as reflux esophagitis and alkaline gastritis, as well as dumping syndrome, delayed gastric emptying and malabsorption, which are defined as functional dyspepsia. Duodenogastric reflux is recognized to be a major cause of clinical symptoms after resection. 5% incidence of functional failure (Visick grade of III or IV)<sup>[118]</sup> has been reported after all different types of reconstructions but symptoms are not always correlated with reflux disease<sup>[102,104,113,119]</sup>. Our previous study on the functional outcome after Billroth I SG showed that functional failure is not only related to reflux disease, but also to functional dyspepsia that is a multifactorial disorder<sup>[112]</sup>. Bile reflux into the gastric remnant following Billroth I and II reconstruction has been reported to be a frequent event. The endoscopic evidence of bile reflux or chronic superficial gastritis is not directly correlated with symptoms and the latter may be similar to those shown by healthy subjects. The conclusions of several studies comparing the functional outcome of the different reconstructive procedures remains controversial<sup>[101,103-109]</sup>. Roux-Y reconstruction seems to be effective in reducing bile reflux into the stomach, compared



to Billroth I and II procedure<sup>[100,103,106]</sup>, and conversion to this procedure has been reported in patients with symptomatic uncontrolled reflux disease. However, other studies showed limited benefits from Roux-Y over Billroth I or II anastomosis because of frequent complications, including Roux-Y stasis syndrome or gallstones formation, and they failed to demonstrate that there is any significant difference in the long-term postoperative functional outcome<sup>[104,105,107-109,120]</sup>. A large study on the endoscopic evaluation of the remnant stomach failed to find significant long-term difference in terms of bile reflux for the three types of reconstructions and confirmed that only reflux esophagitis is the real gold standard for symptomatic reflux disease<sup>[102]</sup>; endoscopy showed that only a minority of the patients (less than 5%) reported signs of reflux esophagitis, independent of the type of partial gastrectomy, thus confirming that other functional disorders, such as the decrease in lower esophageal sphincter pressure, the presence of a hiatus hernia, or the accommodation of the remnant stomach to a meal, can lead to post-gastrectomy functional dyspepsia. In our previous study on the very long-term functional outcome of Billroth I SG followed up to 18 years, we found encouraging results in terms of the absence of meal-related discomfort and normal number of meals per day and we were surprised to record that the majority of our patients had completely recovered from surgery and could hardly see any difference compared to their preoperative conditions<sup>[112]</sup>. Postoperative endoscopy showed no evidence of mucosal changes in 85% of patients, including those who had been operated on more than 10 years before. Similar results have been reported for the other type of reconstructions<sup>[100,106,109]</sup>.

## FOLLOW-UP

Pre- and intraoperative accurate patient selection remains mandatory and this procedure can be considered a valid option in patients with favorable pathological staging. After resection, no specific diagnostic method has been identified to detect recurrence. Recurrence is usually diagnosed through a combination of exams, including ultrasound, computed tomography, positron emission tomography and tumor marker evaluation. Computed tomography seems to be essential in the follow-up of patients. Consensus has not been reached as to the optimal frequency; it is usually performed every 3 to 12 mo, depending on the stage of the disease and time elapsed since surgery. Furthermore, after subtotal gastrectomy, lifelong endoscopic monitoring is recommended to detect possible mucosal changes at an early stage.

## COST-EFFECTIVENESS

The clinical research that has been carried out in the last thirty years was promoted with a view to define the clinical benefits of subtotal gastrectomy compared to

total gastrectomy in terms of quality of life, including nutritional status, functional dyspepsia and long-term survival. Moreover, it has placed special focus on gastric stump recurrence. In the last decade, new studies have been conducted comparing open conventional distal gastrectomy with the laparoscopic approach or endoscopic resection in the case of EGC, and other studies compared conventional postoperative care with the fast-track program<sup>[94,121-123]</sup>. However, the main focus of such studies was on the clinical outcome and long-term results and, although these novel approaches are still considered as investigational according to the Japanese Gastric Cancer Treatment Guidelines 2010 (ver.3), their clinical applications are gaining more and more popularity among specialized surgeons. Little is known about the cost-effectiveness of subtotal gastrectomy for gastric cancer. The cost-effectiveness of the procedures is yet to be calculated and no specific information can be provided as multiple and different variables contribute to the cost analysis of such an intriguing surgical procedure and its variants, including the social organization and the health system of each individual country. In particular, the phase III controlled randomized multicenter KLASS 01 trial carried out in South Korea on 1415 patients included cost-effectiveness among its secondary endpoints<sup>[124]</sup>. However, the trial is currently ongoing and the cost analysis is still being conducted.

The cost-effectiveness analysis focused mainly on primary and secondary preventive strategies and on postoperative adjuvant chemotherapies for resectable gastric cancer. *Helicobacter pylori* (*H. pylori*) infection is estimated to carry a significant lifetime risk of developing peptic ulcer and gastric cancer. Screening the population for the presence of *H. pylori* infection and treating *H. pylori*-positive subjects may reduce mortality and morbidity in the future decades<sup>[125]</sup>. The serology screening and 13C-urea breath test for *H. pylori* were shown to achieve more health benefit at a lower cost compared to no screening in the Chinese population. The serology screening was found to be cost-effective<sup>[126]</sup>. A well designed study on a limited and controlled population in Taiwan showed that a once-only chemoprevention program should be initiated earlier in life and suggested that primary prevention dominates on secondary prevention strategy for high risk groups<sup>[127]</sup>. *H. pylori* eradication at an early stage can effectively ameliorate the infiltration of acute inflammatory cells and protect the gastric mucosa from irreversible damage. Early-stage gastric cancer detection in the secondary prevention strategy is a critical issue to improve prognosis. Endoscopic screening of the population for gastric cancer is generally deemed not to be cost effective, except in Japan where prevalence is very high. However, stomach screening in moderate to high-risk population subgroups was shown to be cost-effective<sup>[128]</sup>. Patients that are diagnosed with gastric cancer at an early stage are more likely to undergo partial gastrectomy than total gastrectomy, thus making moderate-high risk population screening results cost-effective, even from a surgi-

cal standpoint.

## CONCLUSION

This article on subtotal gastrectomy for gastric cancer aimed to clarify the actual landmarks of this procedure and the role it plays compared to the whole range of new and old treatment methods. Since the clinical application of the study is very helpful for patient evaluation and decision making, we recommend that the readers apply this knowledge into routine clinical practice.

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ISSN 1007-9327



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