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Surgical Management of Malignant Gastric Tumours: A Practical Guide

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Additional information is available at the end of the chapter

Abstract

Gastric cancer is one of the most common gastrointestinal malignancies, known also for its dismal prognosis, except early cases. Despite the advances in systemic therapy, surgery remains the cornerstone of treatment. The majority of gastric cancers are carcinomas, while neuroendocrine tumours and gastrointestinal stromal tumours (GISTs) rank next by frequency. Tumour biology, disease course and prognosis differ amongst the aforementioned gastric cancers; thus, surgical treatment has to be adjusted as well. Accumulation of evidence ensures an individualised approach in all aspects of surgical treatment. Specific criteria are set to choose the best surgical treatment while maintaining postoperative function and acceptable life quality. Minimally invasive techniques continue to gain acceptance, while usage is still highly variable. Endoscopic resection is suitable for very early adenocarcinomas, whereas more advanced tumours require standard gastrectomy. Despite the initial concerns, subtotal gastrectomy (SG) is feasible and safe, especially for distal adenocarcinomas. In recent years, D2 lymphadenectomies have become more frequent in Western countries, and evidence supports this tendency. Surgery for gastric neuroendocrine tumours is type-specific and will be discussed in detail. Gastrointestinal stromal tumours are treated by local resection without wide margins or extensive lymph node dissection. Novel targeted therapy can aid surgical treatment by downstaging larger GISTs.

Keywords: gastric cancer, gastric carcinoma, neuroendocrine tumours, GIST, surgery, gastrectomy, lymphadenectomy, laparoscopy

1. Introduction

Despite significant reduction in incidence, important advances in understanding of tumour biology and improvements of complex management of this disease, gastric cancer is still a major and in many aspects poorly resolved oncological problem. Thus, the title 'silent killer' still remains.

Gastric cancer is the fourth most common cancer and second leading cause of cancer death in the world, with nearly a million of new cases in 2012 [1]. There are substantial geographical variations in gastric cancer incidence and survival, with half of all cases diagnosed in East Asia (GLOBOCAN data). This is related to the prevalence of risk factors, mainly *Helicobacter pylori* infection (**Table 1**) [2].

Similarly, stage at diagnosis is also dependent on geographical factors and local screening policies. In most countries, the majority of cases are still diagnosed at an advanced stage (see **Figure 1**).

There are many classifications for gastric cancer. Anatomically, it can be divided in true gastric (noncardia) cancers and gastro-oesophageal (cardia) cancers, which differ in epidemiology and surgical treatment [1]. Histologically, the majority of gastric cancers are malignant epithelial tumours, namely, carcinomas (>90%), while neuroendocrine tumours (NETs) and gastrointestinal stromal tumours (GISTs) rank next by frequency [3].

Surgery is still the only potentially curative treatment of gastric cancer. Despite adequate surgical resection, gastric cancer has a high recurrence rate after operation [4]. Survival parameters have traditionally been higher in Asian countries due to screening and higher proportion of early disease [5]. A 5-year overall survival of 72.3% has been reported in one Korean study, whereas European studies report survival of 28.0–44.3% [2]. To improve these figures, a systematic and evidence-based approach must be used to treat gastric cancer.

Since gastric carcinomas, NETs and GISTs have different characteristics, natural history and prognosis, the cornerstone of treatment, surgical resection, has to be adjusted as well. In this chapter, we discuss the common features and differences in surgical treatment of different gastric cancers according to TNM stage as well as the latest advances in minimally invasive and endoscopic surgical techniques.

Risk factor	Influence and relative risk
H. pylori infection	↑ 3.02
Pernicious anaemia	↑ 6.8
Cigarette smoking	↑ 1.53
Heavy alcohol consumption	↑ 1.20
High dietary salt	↑ 1.07
Dietary fruit and vegetables	↓ 0.81

**Table 1.** Risk factors of gastric cancer.
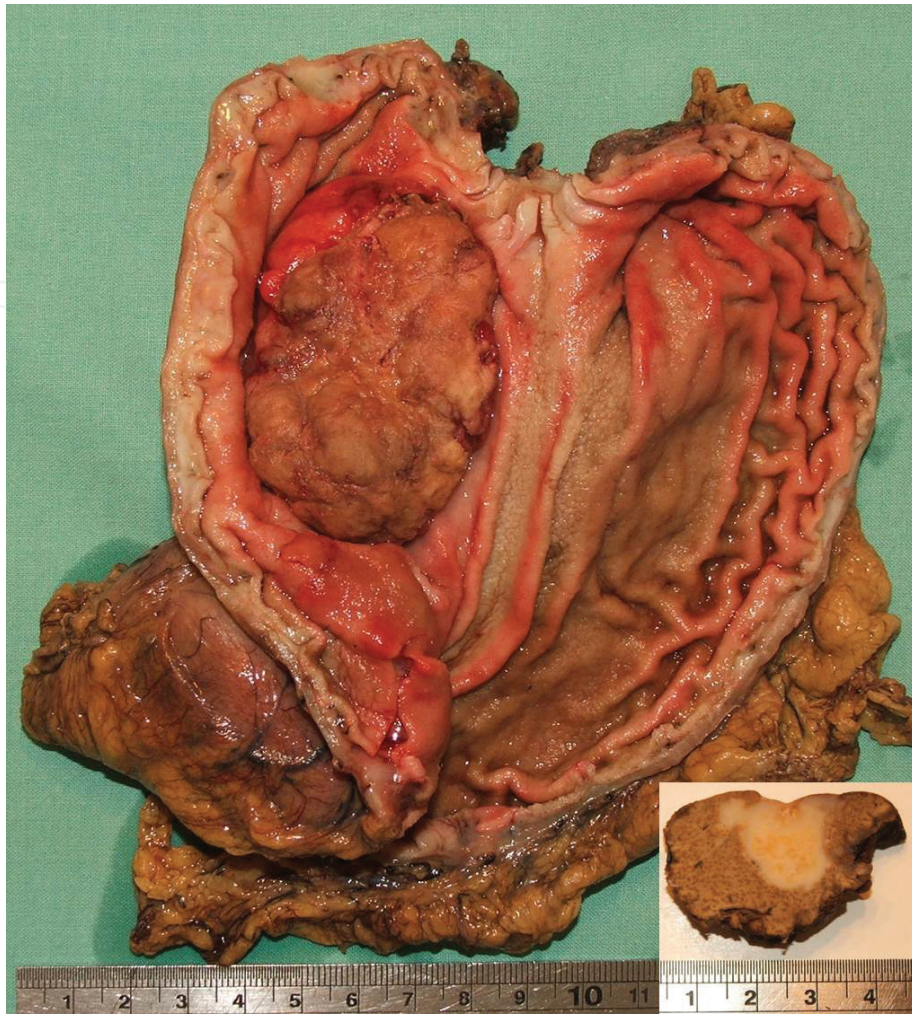
Figure 1. Haematogenous spread of intestinal gastric cancer. Gastrectomy showing a dominant mass lesion. Inset: synchronously resected liver metastasis.

2. Gastric adenocarcinomas

Carcinomas, representing malignant epithelial tumours, arise from epithelial cells in the most superficial, mucosal layer of gastric wall. Traditionally, carcinomas have been divided, according to Lauren classification, in diffuse and intestinal type (**Figure 2**). The former is poorly differentiated, lacks glands, has a more pronounced genetic component, spreads via transmural and lymphatic route and generally has a worse prognosis. Intestinal type is characterised by glandular structures, well or moderately differentiated tumours with haematogenous spread and more pronounced environmental risk factor influence [6]. More recently, the WHO produced a classification that was in concert with histological division of gut tumours—tubular, papillary, mucinous adenocarcinomas, poorly cohesive carcinoma and rare variants [1]. However, there is very little evidence that the aforementioned classifications have additional prognostic value compared to TNM staging [6]. Therefore, for this practical guide, only TNM stage will be taken into consideration.
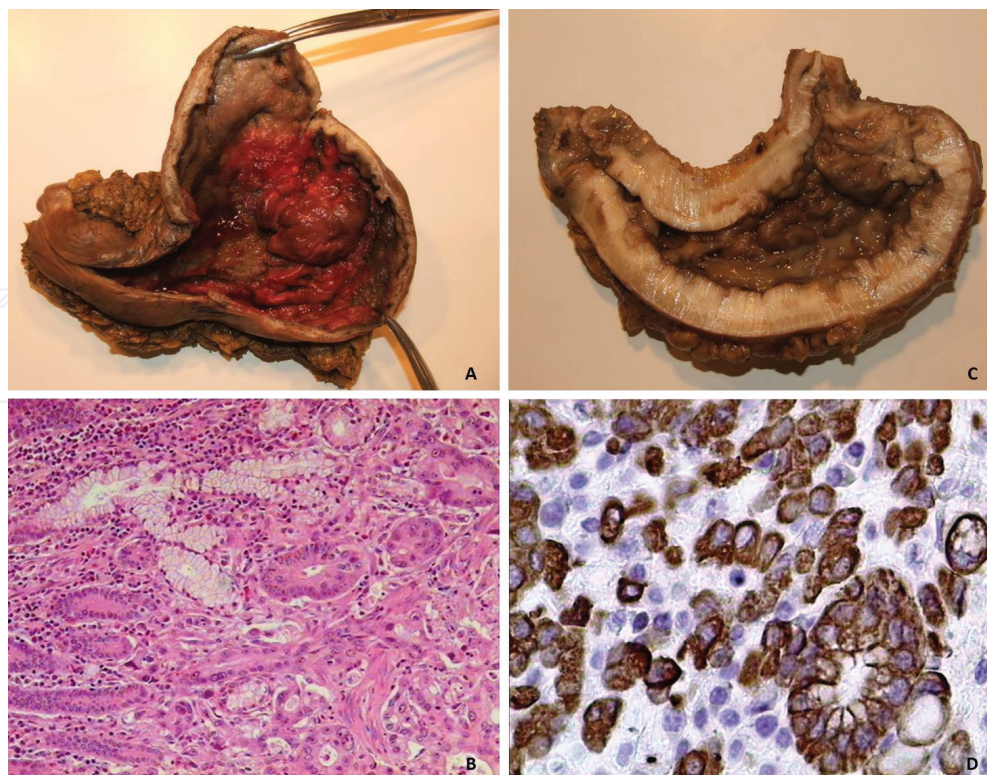
Figure 2. Types of gastric carcinoma by Lauren classification. (A and B) Intestinal type: (A) gross view in gastrectomy and (B) morphological structure showing adenocarcinoma. Haematoxylin-eosin, original magnification (OM) 100×. (C and D) Diffuse type: (C) gross view in gastrectomy and (D) morphological structure showing signet ring cells. Immunoperoxidase, cytokeratin AE1/AE3, OM 400×.

2.1. Early gastric adenocarcinomas

For very early gastric carcinomas (T1a), endoscopic treatment is possible. Precise patient selection is essential to avoid suboptimal treatment. The target is to identify a subgroup of patients for whom the risk of lymph node metastases is virtually zero [5]. Both Japanese and European guidelines have similar criteria for patient selection for endoscopic treatment [5, 7]:

1. Confined to mucosa (T1a)

2. Well differentiated

3. Non-ulcerated

4. Diameter of ≤2 cm

However, in the guidelines, issued by european society for medical oncology (ESMO), these criteria are necessary to consider endoscopic treatment [III, B], whereas Japanese guidelines state them as an absolute indication for endoscopic resection [5, 7]. This underlines the experience of Japanese doctors in endoscopic treatment of very early gastric cancer. The resection is considered curative when a meticulous pathologic examination of specimen reveals an en bloc resection of a tumour with previously mentioned features, negative resection margins and no lymphovascular invasion [7].

There are two principal methods for endoscopic removal of gastric cancer. In endoscopic mucosal resection (EMR), a saline injection is used to elevate the tumour and is followed by an excision with a snare device using electrocautery [6] (**Figure 3**). This is generally indicated for lesions smaller than 10–15 mm [5].

In endoscopic submucosal dissection (ESD), electrocautery is used to mark the borders of the tumour followed by hydrodissection with epinephrine and indigo carmine. The lesion is then removed en bloc by dissecting the submucosal layer from the proper muscle layer using insulation-tipped electric knife [6, 7] (**Figure 4**).
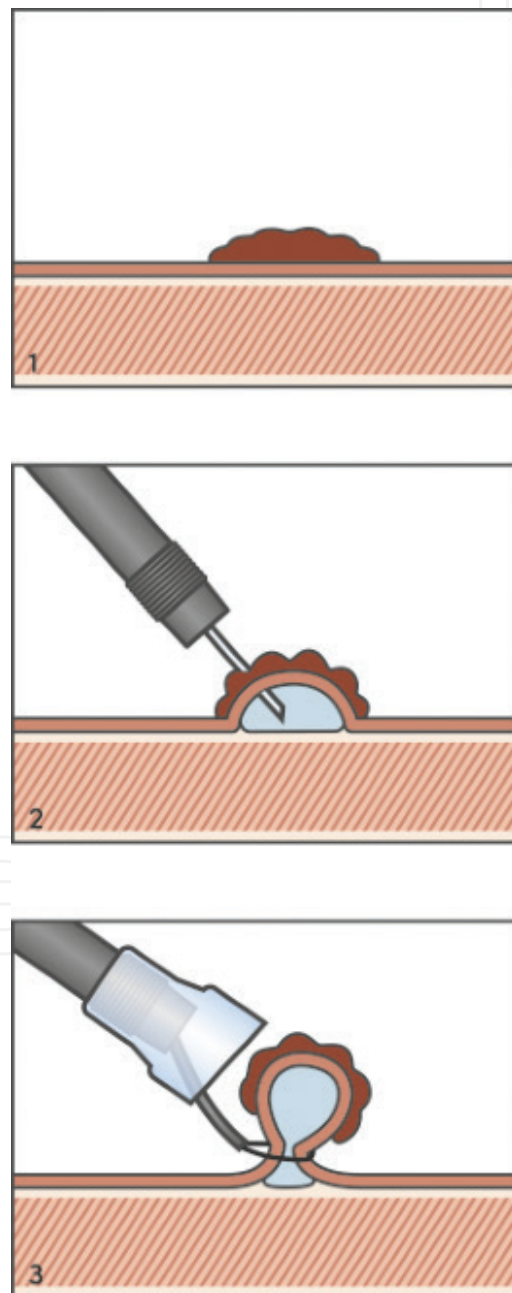
Figure 3. Endoscopic mucosal resection: (1) Localisation of tumour, (2) submucosal injection of saline to elevate the area and (3) electrocautery is applied through snare device to perform resection followed by removal of the lesion.
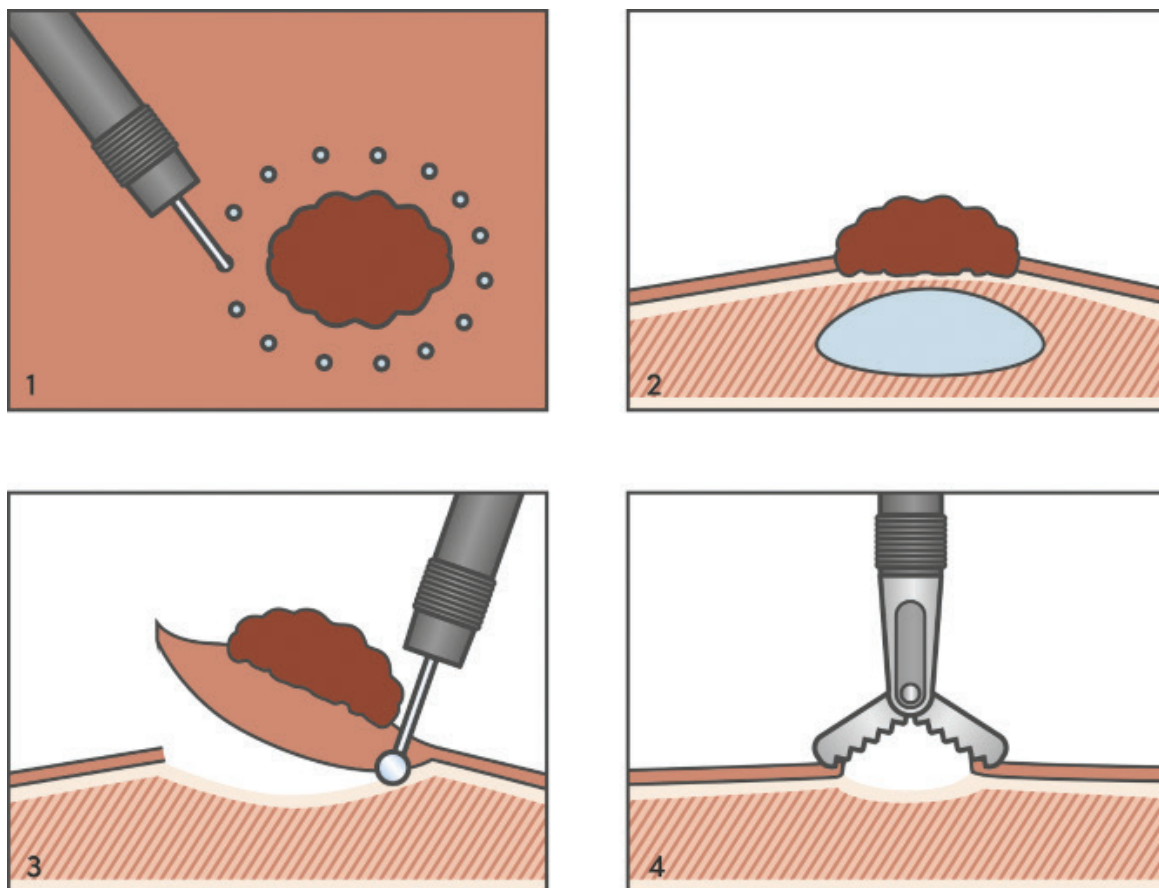
Figure 4. Endoscopic submucosal dissection. (1) Marking borders of the tumour with electrocautery, (2) submucosal injection of a lifting agent, (3) circumferential mucosal incision followed by submucosal dissection with insulation-tipped electric knife and (4) haemostasis.

A meta-analysis comparing both methods was performed, and the results indicated significantly higher en bloc and complete histologic resection rates for ESD (odds ratio, OR = 9.69 vs. OR = 5.66, $p < 0.001$). This increased radicality and also resulted in lower recurrence rate (OR = 0.009, $p < 0.001$). On the other hand, perforation rate was significantly higher for ESD (OR = 4.67, $p < 0.001$) [8]. The European Society of Gastrointestinal Endoscopy Guidelines recommend ESD as the standard procedure for most early gastric tumours [IV, B] [5].

Extended criteria for ESD also are known. One Korean study found no statistically significant differences in recurrence rates between absolute indication and extended indication groups (7.7% vs. 9.3%, $p = 0.524$). However, due to the lack of high-quality evidence, these indications remain investigational and will not be discussed in detail here [7].

Surgical resection is indicated in patients with T1 tumours that do not meet the criteria for endoscopic treatment. However, the extent of resection can be reduced compared to more advanced cancers [5]. For patients with clinical T1 and N0 who require surgical resection for middle gastric cancer, a pylorus-preserving gastrectomy can be offered if the distal extent of tumour is at least 4 cm proximal to pylorus (see **Figure 5**). For early proximal gastric tumours, proximal gastrectomy is an option if more than half of the distal stomach can be preserved (**Figure 6**) [4]. As for segmental gastrectomy and local resection under sentinel navigation,

these are still considered investigational [7]. If the above-mentioned criteria are not met, early gastric cancer is treated with a standard gastrectomy. In addition, lymphadenectomy is required because of the risk of lymph node metastases due to submucosal invasion. The extent of lymphadenectomy in early gastric cancer will be discussed in the following chapter.
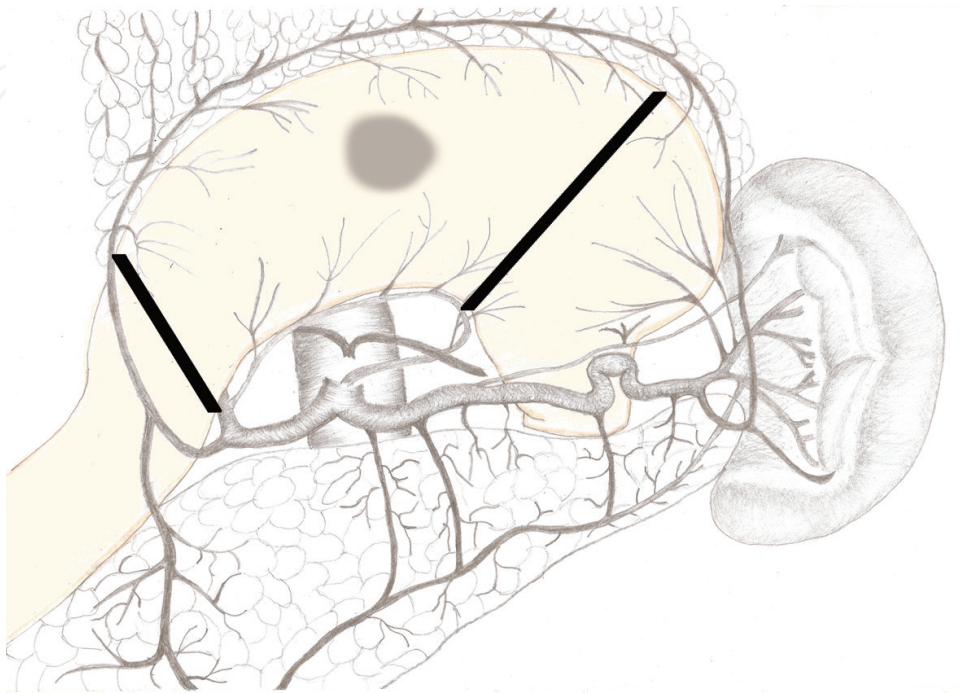
Figure 5. Pylorus-sparing gastrectomy.
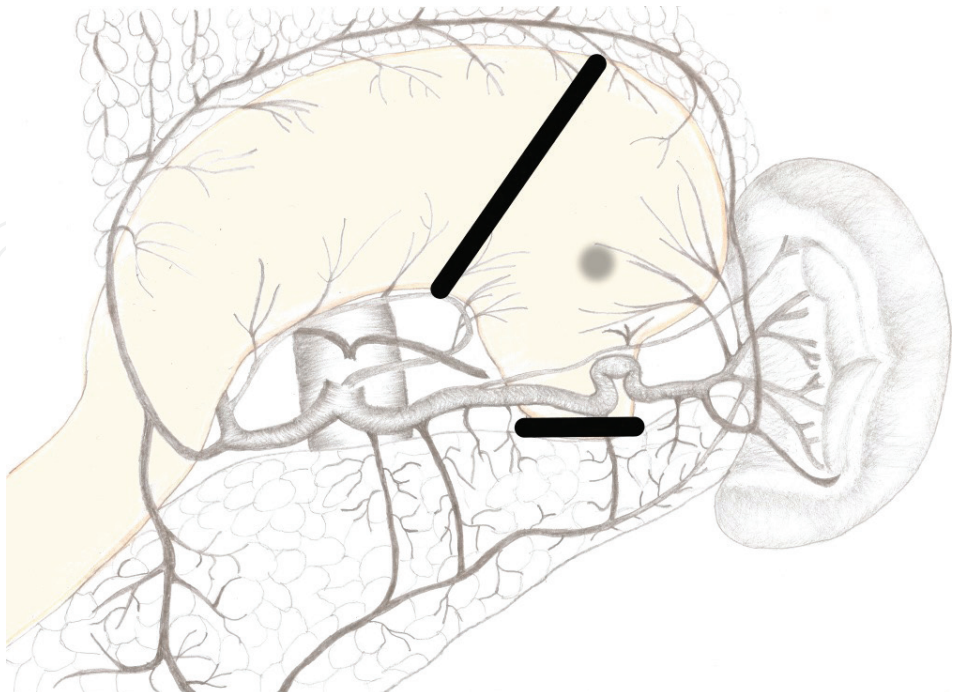


Figure 6. Proximal gastrectomy.

2.1.1. Extent of lymphadenectomy for early gastric tumours

Lymphadenectomy is an essential part of radical gastric cancer surgery. According to the latest UICC/AJCC TNM classification (seventh edition), at least 15 lymph nodes must be harvested to perform adequate staging [5]. However, in a USA-based study comprising more than 3000 patients, it was found that only 23.8% of cases had more than 15 lymph nodes harvested [6].

All of the relevant lymph nodes are divided in 16 stations (see **Figure 7**). The first six stations, perigastric nodes, are grouped together as N1. Stations 7–11, coeliac axis, are grouped as N2 [4]. Depending on the extent of lymph node removal, the term D1 (perigastric nodes) or D2 (perigastric nodes plus clearance of coeliac axis) is used [5]. However, traditionally, the extent of lymphadenectomy was classified relative to the location of tumour [6]. In the latest Japanese gastric cancer treatment guidelines (2014), a more rational approach is suggested. What constitutes D1 or D2 lymphadenectomy is actually dependent on the extent of gastrectomy, regardless of tumour location [7]. For example, in total gastrectomy (TG), D1 means removal of the first seven nodal stations, whereas in distal gastrectomy, D1 constitutes removal of stations 1, 3, 4sb, 4d and 5–7 [7].

For all cT1a tumours which are not amenable to endoscopic treatment as well as cT1b tumours, D1 lymphadenectomy is necessary. If the tumour is well differentiated and does not exceed 1.5 cm in diameter, D1 lymphadenectomy is sufficient. For larger and less differentiated tumours, an extended D1+ lymphadenectomy is required based on the tumour localisation and the extent of gastric resection. Several but not all of the D2 nodes are included in this lymphadenectomy [7].
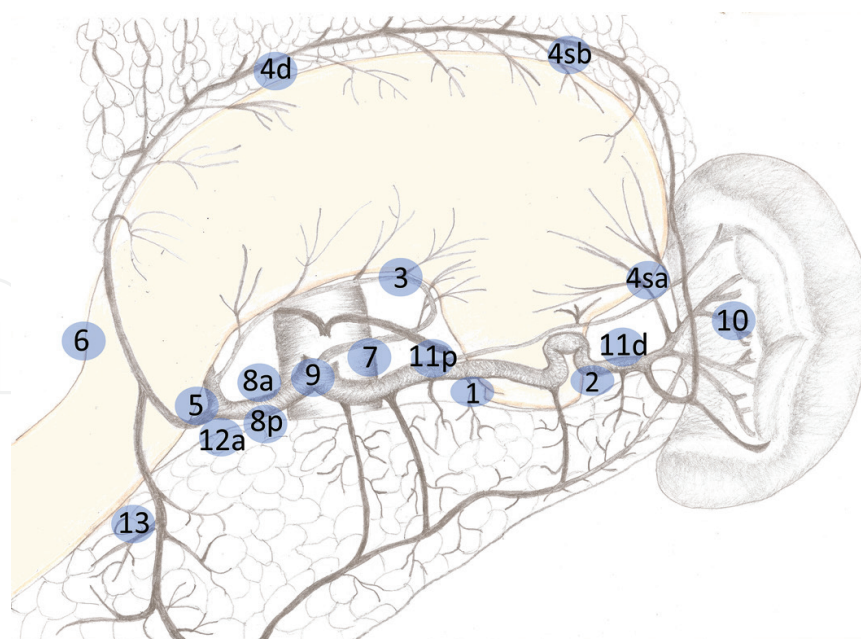
**Figure 7.** Lymph node stations: (1) right paracardial, (2) left paracardial, (3) lesser curvature, (4sa) short gastric, (4sb) left gastroepiploic, (4d) right gastroepiploic, (5) suprapyloric, (6) infrapyloric, (7) left gastric artery, (8a) anterior common hepatic, (8p) posterior common hepatic, (9) celiac trunk, (10) splenic hilum, (11p) proximal splenic, (11d) distal splenic, (12a) left hepatoduodenal and (13) retropancreatic.

2.2. Gastric carcinoma stage IB–III

There is a consensus amongst specialists and societies that gastric carcinoma invading proper muscular layer or having positive lymph nodes requires a standard gastrectomy [4–7]. A standard gastrectomy means either total gastrectomy (**Figure 8**) or distal subtotal gastrectomy removing at least two-thirds of the stomach (**Figure 9**) [4]. In Japanese guidelines, a D2 lymphadenectomy is an integral part of standard gastrectomy. However, in Western countries this recommendation is not so strict. General recommendation is that a D2 dissection should be performed in high-volume specialised centres with appropriate experience if the patient is medically fit [5].

2.2.1. Extent of lymphadenectomy for stage IB–III gastric carcinoma

There used to be a fierce debate between Asian and Western surgeons about the extent of lymphadenectomy. Asian specialists advocated D2 lymphadenectomy because of superior oncologic outcomes. However, Western surgeons argued that D2 lymphadenectomy only added to perioperative morbidity and mortality with no significant survival benefit [4]. There were three randomised controlled trials (RCTs) that addressed this issue. The Dutch trial randomised 711 patients in D1 and D2 lymphadenectomy groups. It has to be noted that distal pancreatectomy with splenectomy was performed in all cases with D2 dissection but only selectively in D1 dissection. This trial reported a significantly higher morbidity (42% vs. 4%, $p < 0.001$) and mortality (10% vs. 4%, $p < 0.004$) in D2 group. Furthermore, there was no 5-year survival benefit in D2 group (D1 = 34% vs. D2 = 33%). However, this study was criticised because of many shortcomings. One of them was the fact that surgeons participating in this trial had no previous experience in D2 lymphadenectomies and they were trained using video
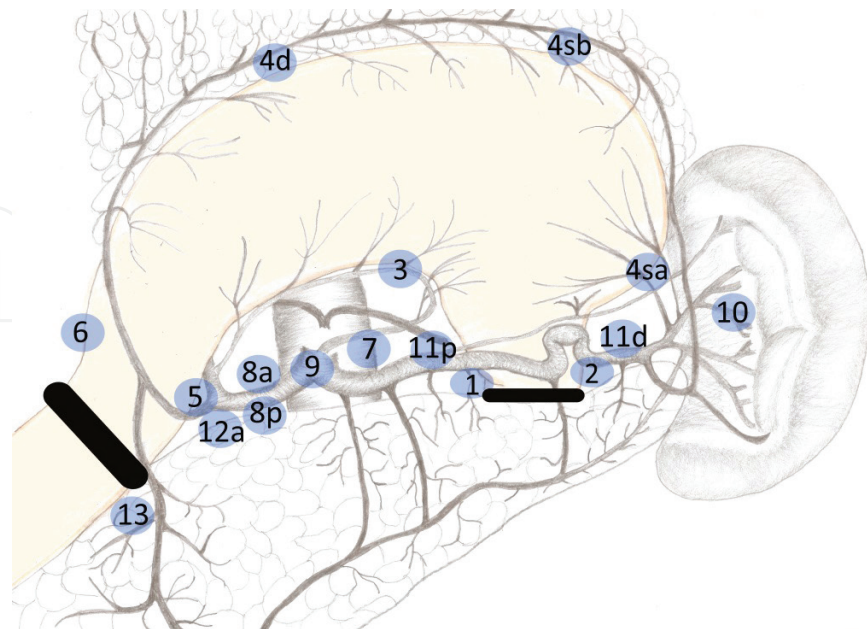
Figure 8. Total gastrectomy. In total gastrectomy, D1 lymphadenectomy constitutes dissection of nodal stations 1–7. D2 lymphadenectomy constitutes dissection of D1 + stations 8a, 9, 10, 11p, 11d and 12a.
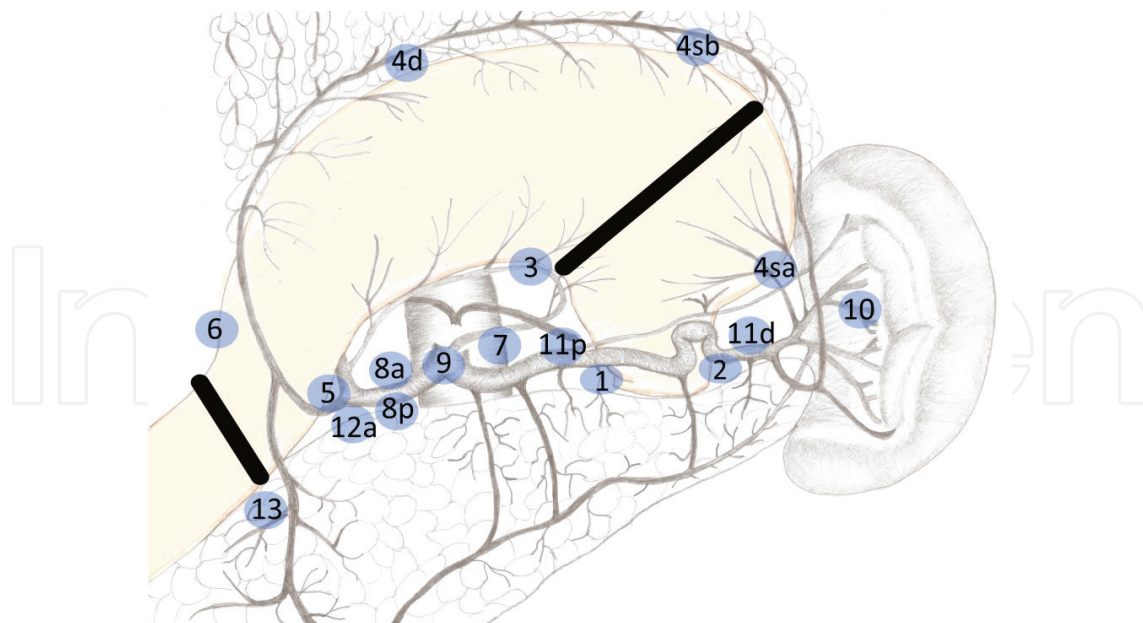
Figure 9. Distal subtotal gastrectomy. In distal subtotal gastrectomy, D1 lymphadenectomy constitutes dissection of nodal stations 1, 3, 4sb, 4d, 5, 6 and 7. D2 lymphadenectomy constitutes dissection of D1 + stations 8a, 9, 11p and 12a.

materials and booklets. It was only after the 15-year survival data were analysed that the evidence showed positive results for D2 dissection. Gastric cancer-related deaths were significantly lower in D2 group (37% vs. 48%). Local (12% vs. 22%) and regional (13% vs. 19%) recurrence rates were also lower in D2 group. The overall 15-year survival was 21% in D1 group and 29% in D2, without statistically significant difference ($p = 0.34$) [4, 9].

Another famous study that questioned the usefulness of D2 dissection was Medical Research Council trial. The results of this study drew similar conclusions – there was no evidence to support routine use of D2 lymphadenectomy. Again, distal pancreatectomy with splenectomy was performed in D2 dissections just as it was in the Dutch study. Significantly, lower survival on subgroup analysis was noted in both studies for patients with distal pancreatectomy and splenectomy. The third landmark RCT on this subject, the Italian study, found comparable overall morbidity (12.0% in D1 vs. 17.9% in D2, $p = 0.178$) and no significant difference in 30-day postoperative mortality rate (3.0% in D1 vs. 2.2% in D2, $p = 0.72$). The essential difference was that only experienced surgeons participated in this trial and that distal pancreatectomy with splenectomy was not routinely performed [4, 9]. The main conclusion is that in Western countries D2 lymphadenectomy can be safely performed in high-volume centres by experienced surgeons. Distal pancreatectomy and splenectomy are no longer considered an integral part of modern D2 lymphadenectomy and are considered beneficial only if the primary tumour or metastatic nodes invade these organs [4, 7, 9].

2.2.2. Extent of resection

Microscopically, negative resection margins are required to qualify any gastric resection as curative. Although not all patients with positive resection margins develop cancer recurrence,

this undoubtedly worsens prognosis [10]. There seems to be a lack of agreement about what is an adequate margin from gastric carcinoma with different articles suggesting slightly different numbers. There are studies that have illustrated tumour cell spread as far as 5 cm laterally from the primary tumour. Therefore, a margin of at least 6 cm seems necessary [6]. However, according to other experts, a 4 cm margin is sufficient [1, 4].

Discussion about distal resection margin is simpler. This margin is limited by the papilla of Vater and is generally 2–4 cm from the pylorus. If the tumour invades papilla or further down the duodenum, a metastatic disease is expected, and gastrectomy alone will not suffice [10].

Regarding proximal resection margin, the Japanese guidelines have specific recommendation. For T1 gastric carcinoma, a gross resection margin of 2 cm is recommended. In case the tumour margins are equivocal on preoperative endoscopy, a biopsy-guided marking with clips can be used to aid in intraoperative decision-making [7]. If the cancer is invading proper muscular layer or deeper, a 3 cm margin is needed for expansively growing tumours, and 5 cm are necessary for infiltrating tumours [7]. The idea that optimal proximal margin distance is stage-dependent is highlighted by a multicentre US study reporting on 465 patients who underwent gastric resection due to distal gastric carcinoma. Authors found that in stage I there was no difference in overall survival between 3.1–5.0 cm and >5.0 cm proximal margin [11]. For a diffuse gastric carcinoma, an 8 cm margin is recommended [5]. If the resection margin is negative, the distance from the tumour does not per se influence the prognosis [10]. Therefore, in case the aforementioned criteria regarding proximal margin distance cannot be followed, frozen section examination is highly recommended [7]. In case of positive resection margins on the final histology, the benefits of reoperation must be weighed against the risks of repeated operation. Reoperation is usually warranted in low-stage cases with minimal (N0–N1) nodal involvement [10].

2.2.3. Total vs. subtotal gastrectomy

Unlike the debate regarding lymphadenectomy, total gastrectomy (TG) vs. subtotal gastrectomy (SG) is a less polarising topic. Since the 'en principle' total gastrectomy was suggested in the 1970s, several large studies have provided evidence to support the role of distal subtotal gastrectomy [12]. Currently, it is the procedure of choice for early gastric cancer located in the distal and middle third of the stomach if the resection margins are located well within the healthy stomach (distances discussed previously). The advantages of subtotal gastric resection are the following: several studies have reported lower morbidity and mortality, reduced hospital stay and superior nutritional status with better quality of life in long term [12]. Two large randomised trials performed in Europe found no significant difference in long-term survival between TG and SG for distal gastric cancer but lower morbidity, mortality and better quality of life in SG group [12]. A recently performed meta-analysis of six trials also found no significant difference in 5-year survival between TG and SG groups (p = 0.18). However, it did not show higher postoperative complication rates (p = 0.30) or hospital mortality (p = 0.12) in TG group which was in contrast to previously mentioned studies [13].

There are several proposed advantages of TG. It could reduce the risk of inadequate lymph node harvest, thus lowering local recurrence risk. Due to removal of all gastric tissue, it eliminates

the risks of multicentric synchronous or metachronous carcinoma [13]. TG is recommended for gastric carcinoma located in the upper third of the stomach, signet ring cell cancers (*linitis plastica*), cancer arising on the background of atrophic gastritis, multicentric cancers, advanced distally located tumours with lymph node metastasis to allow extended lymphadenectomy, invasion of pancreas (which requires pancreaticosplenectomy) and patients with inherited E-cadherin mutation as a prophylactic measure (due to 80% lifetime risk of developing gastric cancer) [1, 6, 7, 12, 13].

2.2.4. Laparoscopic vs. open gastrectomy

Laparoscopic gastric cancer surgery is technically demanding and is currently performed more routinely by Asian surgeons. Nevertheless, more and more specialists around the globe are becoming more confident in laparoscopic surgery, and, with the help of technological advancements, usage of laparoscopy will certainly increase [14]. As discussed previously, very early gastric carcinomas are preferably treated by endoscopic resection. However, criteria for endoscopic treatment are very strict, and these methods are more widely used in high-incidence countries with high proportion of early cases. Therefore, the most solid indication for laparoscopic surgery is gastric carcinoma located in the distal or middle third of the stomach and limited to submucosa without evidence of lymph node involvement or mucosal cancers not amenable to endoscopic treatment [14]. In case of laparoscopic total gastrectomy, the more widely accepted indication is T1N0 tumour of proximal third of the stomach [14]. There is evidence that laparoscopy is a safe and feasible option even for advanced gastric carcinomas if performed in high-volume specialised centres [1]. A systematic review comprising 3411 patients revealed similar lymph node harvest and long-term survival for laparoscopic distal gastrectomy compared to open approach. Hospital stay, analgetic consumption, postoperative complication rate and blood loss in surgery were all reduced in laparoscopic approach group [1]. Surgeons in Eastern Asia have expanded the use of laparoscopy to advanced cancers even with limited involvement of perigastric nodes [14]. There is still a small amount of high-quality evidence to support these expanded indications [4, 14]. However, one large systematic review analysing 23 studies with 7336 patients was recently published. Authors found comparable 5-year overall survival ($p = 0.45$), recurrence ($p = 0.08$) and gastric cancer-related death rates ($p = 0.28$) between laparoscopic and open gastrectomy groups. These results led them to conclude that laparoscopic gastrectomy was comparable to the open approach and did not worsen oncologic results [15]. To evaluate the role of laparoscopy in advanced gastric cancer, a meta-analysis comprising 11 studies and 1904 patients was performed. A D2 dissection was performed in both open and laparoscopic cases. Researchers found reduced blood loss, morbidity, shorter postoperative ileus and length of hospital stay in laparoscopic group, although the operation time was longer by almost 42 min ($p < 0.05$). No significant difference was noted in lymph node harvest, intrahospital mortality, recurrence rate and 3-year overall survival rates. This indicates that laparoscopy has several advantages in short-term results and is equivalent from oncologic standpoint [16].

While many surgeons perform the so-called laparoscopy-assisted gastrectomy which requires mini-laparotomy incision and extracorporeal anastomosis, several options for totally laparoscopic gastrectomy are available. Even single-port laparoscopy is being performed frequently

in high-volume centres. A small study comparing 50 single-port laparoscopies with 50 multi-port surgeries indicated superior short-term results for single-port surgery. However, this did not lead to reduced hospital stay. Most specialists use at least five ports for laparoscopic gastrectomy [14].

Despite the aforementioned studies, the present state of laparoscopic gastric surgery is not entirely clear. A lot of the evidence comes from Asian countries, high-volume specialised centres with considerable experience. Current studies have been criticised for bias and hetero-geneity, for example, not including the most advanced gastric cancers in studies comparing open with laparoscopic approach. Some authors have found reduced lymph node harvest at specific nodal stations during laparoscopic D2 dissection. This has raised the question of robotic surgery as a valid tool to overcome some of the technical difficulties that comes with laparoscopic surgery. Robotic system has superior manoeuvrability and visualisation, which is essential in performing dissection along the celiac axis, spleen and pancreas. Another advantage is the relatively easier restoration of gastrointestinal continuity using robotic sys-tem. As with other procedures, robotic gastrectomy seems to take less time to master than conventional laparoscopic surgery although this could in part be related to previous experi-ence in laparoscopic approach. There is currently not enough high-quality evidence to draw any definitive conclusions on robotic gastric cancer surgery in comparison with conventional laparoscopic and open surgery [17].

3. Gastric neuroendocrine tumours (NETs)

NETs arise from the cells of the diffuse neuroendocrine system that are scattered all around the body and have both neural and endocrine characteristics (**Figure 10**). This is a heteroge-neous group of tumours with wide variations in biologic behaviour, clinical picture and opti-mal management. Despite the fact that these tumours are typically indolent in nature, often
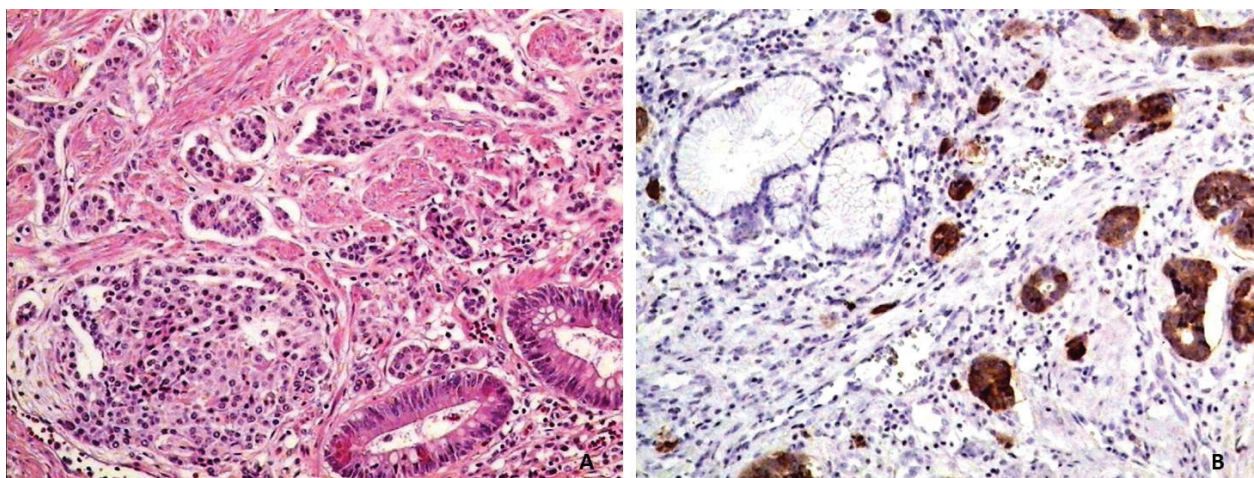
Figure 10. Gastric NET. (A) Haematoxylin-eosin, original magnification (OM) 100×. (B) Synaptophysin expression. Immunoperoxidase, OM 100×.

described as slowly growing, they all have malignant potential. Therefore, surgical resection is the only definitive treatment [18].

Gastric NETs (GNETs) are rare tumours, but their incidence is growing. The proportion of GNETs amongst all gastrointestinal NETs also increases. The current incidence is 1–2 per 100,000 persons per year which accounts for 8.7% of all gastrointestinal NETs. This increase of incidence is at least partly related to more widespread use of gastrointestinal endoscopy [18, 19].

There are three to four types of GNETs which differ significantly in terms of biologic behaviour, malignancy, prognosis and optimal treatment [18–20]. Some discrepancy in literature regarding classification of GNETs is noted. Although the latest European Neuroendocrine Tumour Society (ENETS) guidelines still divide GNETs in three types, a further subclassification of type 3 tumours is considered appropriate [20]. A comparison of different GNET types is depicted in **Table 2**.

Tumour characteristics	Type 1 GNET	Type 2 GNET	Type 3 GNET
Proportion of GNETs (%)	70–80	5–6	10–15
Associated diseases/syndromes	Chronic atrophic gastritis	MEN1-ZES	Sporadic
Typical tumour size (cm)	<1–2 cm	<1–2 cm	>2 cm
Tumour number	Multiple	Multiple	Solitary
Location	Fundus, corpus	Fundus, corpus	Any
Serum gastrin	↑	↑	N
Histology (most common)	NET G1	NET G1/G2	NEC G3
Invasion	Mucosa, submucosa	Mucosa, submucosa	Any
Frequency of metastasis (%)	2–5	10–30	>50
Prognosis	Excellent	Good	Poor

GNET, gastric neuroendocrine tumour; MEN1-ZES, multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome; N, normal; NET, neuroendocrine tumour; G, grade; NEC, neuroendocrine carcinoma.

Table 2. Features of different gastric NETs.

3.1. Type 1 GNETs

This is the most common type of GNETs (70–80%) and is more frequently seen in female patients. Type 1 GNETs develop from enterochromaffin-like (ECL) cells and are associated with chronic gastric mucosal atrophy caused by *H. pylori* or autoimmune gastritis. These tumours are well differentiated, usually small (<1 cm), multiple, located in the fundus or corpus, limited to mucosa or submucosa and have an excellent prognosis [18–20]. They have a very low mitotic rate and metastatic potential (2–5%) [18, 19]. Pathophysiological mechanism of type 1 GNET development is achlorhydria caused by atrophic gastritis, which stimulates gastrin production, which in turn evokes ECL cell hyperplasia [19].

These tumours are best treated with conservative approach, with surgery reserved for selected cases. In ENETS guidelines, endoscopic surveillance every 1–2 years is recommended

for lesions <1 cm without evidence of invasion into the proper muscular layer or metastasis. However, other specialists have recently suggested removal of all visible lesions with biopsy forceps or EMR (>5 mm tumours). This approach has to be compared with the previously mentioned less aggressive management in randomised trials to support its use. Any GNET with size close to 10 mm or threatening proper muscular layer has to be resected to avoid metastatic spread [18–20]. Research has shown superior complete resection rates for ESD compared to EMR in the treatment of GNETs [19].

Surgical resection is recommended for type 1 GNETs that are invading the proper muscular layer (T2), have recurred after endoscopic removal and are poorly differentiated or in case of positive resection margins after endoscopic resection [18–20]. Depending on the location and number of lesions as well as potential involvement of lymph nodes, local excision, partial or total gastrectomy is selected. Antrectomy to reduce hypergastrinemia is questionable and is rarely performed [18, 20].

3.2. Type 2 GNETs

These tumours are less frequently encountered (5–6%) and are associated with multiple endocrine neoplasia type 1 and Zollinger-Ellison syndrome (MEN1-ZES). Just like type 1 GNETs, they are gastrin-dependent, consist of ECL cells, are small, multiple and relatively benign. These are equally distributed amongst genders and in 10–30% of cases are metastatic at presentation. Although type 2 GNETs are asymptomatic per se, they can present with peptic ulcer disease due to hypersecretion of gastric acid caused by ZES [18–20].

According to the National Comprehensive Cancer Network (NCCN) guidelines, the treatment of type 2 GNETs is similar to type 1 tumours. In ENETS guidelines, however, only local surgical excision is recommended. The fact that the patient has multiple tumours does not alter surgical treatment by itself. Local or limited resection of the coexisting gastrinoma is recommended, but decision has to be made in a multidisciplinary setting in high-volume centres [18, 20].

3.3. Type 3 GNETs

Type 3 NETs (10–15%) are sporadic, usually poorly differentiated, single tumours >10 mm in size not associated with gastrin hypersecretion. These tumours have the tendency to invade proper muscular layer and are frequently metastatic (in regional lymph nodes, liver) at the time of diagnosis [18–20].

There are reports that suggest that in selected cases (<2 cm, well differentiated, submucosal, without lymphovascular invasion) type 3 GNETs should be treated with endoscopic or wedge resection. Despite that, ENETS guidelines strictly recommend type 3 GNETs to be treated like gastric carcinomas with distal or total gastrectomy and lymphadenectomy [18, 20].

4. Gastric gastrointestinal stromal tumours (GISTs)

GISTs are mesenchymal tumours that develop from the interstitial cells of Cajal (gastrointestinal pacemakers) anywhere in the GI tract. GISTs are rare constituting only less than 1% of all GI malignancies. Although the annual reported incidence is just 10 cases per million, the

actual Incidence is believed to be much higher [22]. The stomach is the most common location for GISTs (70%). The driving force for GIST development is a gain-of-function mutation in tyrosine kinase receptor gene *c-KIT* [21].

Although the discovery of tyrosine kinase inhibitor imatinib has been the most significant change in GIST treatment over recent years, surgery as the only potentially curative method remains the cornerstone of treatment [23].

Gastric GISTs start their growth in deeper layers, mostly in the smooth muscle layer of gastric wall; expand intra- or extraluminally and eventually produce haematogenous metastasis in solid organs or peritoneum. They can also cause sarcomatosis by perforating into peritoneal cavity [21].

Any patient who is medically fit should undergo complete surgical resection of gastric GIST. However, NCCN and ESMO guidelines recommend endoscopic surveillance for small (<1 cm and <2 cm, respectively) gastric lesions if high-risk features are not present by endoscopic ultrasound investigation (ulcerations (see **Figure 11**), cystic spaces, irregular borders, echogenic foci and heterogeneity). All other cases and patients who do not want to undergo endoscopic surveillance should be treated by surgical resection [21, 24].

Unlike for carcinoma, a wide resection margin of healthy tissue is not necessary for GISTs. It is of paramount importance to be meticulous and remove the entire lesion without damaging tumour pseudocapsule or causing tumour spillage or bleeding as this would increase the risk of locoregional recurrence and sarcomatosis. GISTs rarely spread via lymphatics; therefore, lymphadenectomy is not necessary. If noted, enlarged lymph nodes near the tumour can selectively be dissected. Either wedge resection or full-thickness partial gastrectomy is usually sufficient for lesser and greater curvature tumours, whereas a transgastric resection after anterior gastrotomy incision is performed for posterior wall gastric GISTs. Total or subtotal gastrectomy is only required for tumours occupying large portions of the stomach. If the tumour is borderline resectable or a extensive operation

Figure 11. Gastrointestinal stromal tumour. Note the umbilicated ulceration.

(total gastrectomy, en bloc resection of adjacent organs) is predicted, neoadjuvant treatment with imatinib is used to downstage the tumour and perform less extensive surgery in advanced cases [21–24].

Laparoscopic surgery is considered a feasible and safe option for the treatment of small (<5 cm) gastric GISTs as long as the general oncologic principles are followed. This statement is supported by evidence from several retrospective cohort studies [23]. Direct manipulation of the tumour with instruments is contraindicated, and a plastic bag must be used on extraction to reduce the risk of spillage. Both ESMO and NCCN guidelines support the use of laparoscopic technique for small gastric GISTs (<5 cm) [23]. Although there are studies that indicate feasibility for larger tumours [25], more high-quality research is needed to widen this indication. A hybrid procedure, endoscopy-assisted laparoscopic resection, can aid in tumour localisation and preservation of gastric volume. While it is currently performed in a limited amount of centres, it will probably take a more prominent place amongst minimally invasive gastric procedures [21].

5. Conclusions

Gastric cancer at present remains one of the most difficult oncological problems the surgeon has to deal with. Despite extensive research in novel systemic therapeutic options, surgery is still the only potentially curative treatment. Accumulation of evidence has made surgical treatment of gastric cancer more personalised allowing to select the extent of resection and lymphadenectomy according to specific tumour. Increased skills combined with technological advances have further improved the postoperative function by making minimally invasive approach safe and effective. Even complex procedures like D2 lymph node dissection are nowadays performed laparoscopically in specialised centres. Despite being rare, gastric NETs and GISTs need special consideration when it comes to surgical treatment because these tumours differ from adenocarcinomas in biology and best management. Robotic surgery and hybrid endoscopic surgical procedures will probably have a more prominent role in the future because of their potential advantages over conventional laparoscopic surgery.

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References

[1] Van Cutsem E, Sagaert X, Topal B, Haustermans K, Prenen H. Gastric cancer. Lancet. 2016;388(10060):2654-2664. DOI: 10.1016/S0140-6736(16)30354-3

[2] Thrumurthy SG, Chaudry MA, Hochhauser D, Mughal M. The diagnosis and management of gastric cancer. BMJ. 2013;347:f6367. DOI: 10.1136/bmj.f6367

[3] Karimi P, Islami F, Anandasabapathy S, Freedman ND, Kamangar F. Gastric cancer: Descriptive epidemiology, risk factors, screening, and prevention. Cancer Epidemiol Biomarkers Prev. 2014;23(5):700-713. DOI: 10.1158/1055-9965.EPI-13-1057

[4] Kuo CY, Chao Y, Li CP. Update on treatment of gastric cancer. Journal of the Chinese Medical Association. 2014;77(7):345-353. DOI: 10.1016/j.jcma.2014.04.006

[5] Smyth EC, Verheij M, Allum W, Cunningham D, Cervantes A, Arnold D; ESMO Guidelines Committee. Gastric cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2016;27(Suppl. 5):v38-v49. DOI: 10.1093/annonc/mdw350

[6] Townsend CM Jr., Beauchamp RD, Evers BM, Mattox KL. Sabiston Textbook of Surgery: the Biological Basis of Modern Surgical Practice. 20th ed. Philadelphia: Elsevier Sounders; 2017. 1213-1231 p.

[7] Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines. Gastric Cancer. 2017;20(1):1-19. DOI: 10.1007/s10120-016-0622-4

[8] Facciorusso A, Antonino M, Di Maso M, Muscatiello N. Endoscopic submucosal dissection vs endoscopic mucosal resection for early gastric cancer: A meta-analysis. World J Gastrointest Endosc. 2014;6(11):555-563. DOI: 10.4253/wjge.v6.i11.555

[9] Garg PK, Jakhetiya A, Sharma J, Ray MD, Pandey D. Lymphadenectomy in gastric cancer: Contentious issues. World J Gastrointest Surg. 2016;8(4):294-300. DOI: 10.4240/wjgs.v8.i4.294

[10] Shin D, Park SS. Clinical importance and surgical decision-making regarding proximal resection margin for gastric cancer. World J Gastrointest Oncol. 2013;5(1):4-11. DOI: 10.4251/wjgo.v5.i1.4

[11] Squires MH 3rd, Kooby DA, Poultsides GA, Pawlik TM, Weber SM, Schmidt CR, Votanopoulos KI, Fields RC, Ejaz A, Acher AW, Worhunsky DJ, Saunders N, Levine EA, Jin LX, Cho CS, Bloomston M, Winslow ER, Russell MC, Cardona K, Staley CA, Maithel SK. Is it time to abandon the 5-cm margin rule during resection of distal gastric adenocarcinoma? A multi-institution study of the U.S. Gastric Cancer Collaborative. Ann Surg Oncol. 2015;22(4):1243-1251. DOI: 10.1245/s10434-014-4138-z

[12] Santoro R, Ettorre GM, Santoro E. Subtotal gastrectomy for gastric cancer. World J Gastroenterol. 2014;20(38):13667-13680. DOI: 10.3748/wjg.v20.i38.13667

[13] Kong L, Yang N, Shi L, Zhao G, Wang M, Zhang Y. Total versus subtotal gastrectomy for distal gastric cancer: Meta-analysis of randomized clinical trials. Onco Targets Ther. 2016;9:6795-6800. DOI: 10.2147/OTT.S110828.

[14] Son T, Hyung WJ. Laparoscopic gastric cancer surgery: Current evidence and future perspectives. World J Gastroenterol. 2016;22(2):727-735. DOI: 10.3748/wjg.v22.i2.727

[15] Chen XZ, Wen L, Rui YY, Liu CX, Zhao QC, Zhou ZG, Hu JK. Long-term survival outcomes of laparoscopic versus open gastrectomy for gastric cancer: A systematic review and meta-analysis. Medicine (Baltimore). 2015;94(4):e454. DOI: 10.1097/MD.0000000000000454

[16] Huang YL, Lin HG, Yang JW, Jiang FQ, Zhang T, Yang HM, Li CL, Cui Y. Laparoscopy-assisted versus open gastrectomy with D2 lymph node dissection for advanced gastric cancer: A meta-analysis. Int J Clin Exp Med. 2014;7(6):1490-1499

[17] Caruso S, Patriti A, Roviello F, De Franco L, Franceschini F, Coratti A, Ceccarelli G. Laparoscopic and robot-assisted gastrectomy for gastric cancer: Current considerations. World J Gastroenterol. 2016;22(25):5694-5717. DOI: 10.3748/wjg.v22.i25.5694

[18] Li TT, Qiu F, Qian ZR, Wan J, Qi XK, Wu BY. Classification, clinicopathologic features and treatment of gastric neuroendocrine tumors. World J Gastroenterol. 2014;20(1):118-125. DOI: 10.3748/wjg.v20.i1.118

[19] Sato Y, Hashimoto S, Mizuno K, Takeuchi M, Terai S. Management of gastric and duodenal neuroendocrine tumors. World J Gastroenterol. 2016;22(30):6817-6828. DOI: 10.3748/wjg.v22.i30.6817

[20] Delle Fave G, O''Toole D, Sundin A, Taal B, Ferolla P, Ramage JK, Ferone D, Ito T, Weber W, Zheng-Pei Z, De Herder WW, Pascher A, Ruszniewski P; Vienna Consensus Conference participants. ENETS consensus guidelines update for gastroduodenal neuroendocrine neoplasms. Neuroendocrinology. 2016;103(2):119-124. DOI: 10.1159/000443168

[21] Roggin KK, Posner MC. Modern treatment of gastric gastrointestinal stromal tumors. World J Gastroenterol. 2012;18(46):6720-6728. DOI: 10.3748/wjg.v18.i46.6720.

[22] Kong SH, Yang HK. Surgical treatment of gastric gastrointestinal stromal tumor. J Gastric Cancer. 2013;13(1):3-18. DOI: 10.5230/jgc.2013.13.1.3

[23] Nishida T, Blay JY, Hirota S, Kitagawa Y, Kang YK. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer. 2016;19(1):3-14. DOI: 10.1007/s10120-015-0526-8

[24] ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014;25(Suppl. 3):iii21-iii26. DOI: 10.1093/annonc/mdu255

[25] Kasetsermwiriya W, Nagai E, Nakata K, Nagayoshi Y, Shimizu S, Tanaka M. Laparoscopic surgery for gastric gastrointestinal stromal tumor is feasible irrespective of tumor size. J Laparoendosc Adv Surg Tech A. 2014;24(3):123 -129. DOI: 10.1089/lap.2013.0433