VIA MEDICA

Review article

Surgical treatment of gastric cancer: then and now

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Gastric cancer is one of the most commonly diagnosed cancers found in the world (980,000 new cases in 2008), but its treatment outcomes are poor, particularly in the European Union (EU); only a 25% survival after 5 years. Despite advances made in combination therapy, the only effective treatment that remains is surgery. The extent of gastric resection and lymphadenectomy, along with reconstruction methods, have systematically evolved over the last 100 years. This paper discusses both present day recommendations and the pathways that were taken enabling modern gastric surgery to develop.

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Introduction

Although gastric cancer (GC) morbidity has been steadily falling over the last 100 years or so, it still remains the fourth most common cancer in the world; in 2008 there were 980,000 new cases globally, of which 83,000 occurred in the EU and over 5,000 in Poland [1, 2]. Enduring dietary changes and decreases in chronic Helicobacter Pylori infections have led to decreased morbidity in all developed countries of the world within the last 50 years [1]. This however does not translate into a satisfactory rates of those surviving; the 5 year survival for GC in Europe is around 25%, whereas in Japan it is 70% [3, 4]. A significant cause for this large difference is that Japan undertakes a screening programme that enables 70% of diagnoses to be made of early GC, whilst in Poland the rates are never higher than 6.7%. The promising advances made in chemo-/radio-therapies have not altered the fact that still the only method remaining for successfully treating GC is surgery.

Historical outline

In spite of the centuries old tradition of performing stomach operations, a breakthrough occurred with the advent of when antiseptics and anaesthesia were discovered. Before the introduction of anaesthesia, attention was however only focused on making a gastric fistula which could extend patient life/survival and halt the spectre of the patient starving to death. The first such fistula was made by an American army doctor, William Beamont in 1822, who was treating a trapper with a bullet wound. A partial gastrectomy, because of cancer, was first performed in Paris on April 1879 by Jules Pean, however the patient died shortly afterwards. Another attempt at removing a gastric tumour was made in Celm on November 1880 by Ludwig Rydygier [5, 6]; also with no success. It was only Theodor Billroth on January 1881, who managed to successfully undertake a pylorus resection, including the tumour, followed by anastomy of the proximal stomach to the duodenum; this type of reconstruction is to this day termed a 'Billroth I'. Even though the operation was successful, the patient later died because of recurrence. Billroth then encouraged by the experimental work by his pupil Wolffler, subsequently performed an anastomy of the stomach to the jejunum after shutting off and resecting a cancer of the duodenum, thus duodenal passage is bypassed; this procedure being termed the 'Billroth II'. The first successful total gastrectomy (TG) was undertaken in 1897 by Schlatter on a 56 year-old patient who survived for 14 months but then died of metastases. Subsequent attempts however did not proceed so smoothly, where the mortality after such operations was high. It should be remembered that the extent of such interventions relies on

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just removing parts of the pyloric antrum, and it should also be noted that a lymphadenectomy was not even considered. A therapeutic success was then considered as one reducing symptoms and prolonging life by 2–3 years [5, 6]. Attempts to improve outcomes were based on changing surgical techniques and methods of reconstruction; but to no avail. For many years the Hoffmeister method remained one of the most popular ways of reconstruction, involving the closing of the stomach at its lesser curvature and anastomy to the greater curvature of the intestinal loop.

High mortality rates, preoperatively, meant that until the 1940s of the last century gastrectomies were performed extremely rarely. Until 1929, only 62 cases of TG were published throughout the world and the mortality rate exceeded 50% [7]. The decrease in perioperative mortality occurred due to the introduction of antibiotics, blood transfusion and advances made in analgesia and anaesthesia. Nonetheless, up to the 1970s, the post-TG mortality risk reached 20%. It was not until advances had been made in enteral and parenteral nutrition, as well as in intensive care, at the end of the 1980s that the mortality rate fell below 5% [8, 9].

The extent of resection

The beginnings of gastric surgery were mainly devoted to dealing with disease symptoms. Developments in pathological anatomy, physiology and oncology led an evolutionary change in the approach and scope of surgical operations, eventually leading to the concept of regional operating theatres. The aim of surgery is to remove both the tumour and lymph nodes, thereby minimising the risk of relapse. Nevertheless, the growing importance of chemo- and radio-therapy used in combination therapy does not relieve the surgeon of responsibility for curing GC. Following the time when the extent of resection was being maximised, (arising from pinning excessive hopes for curing cancer by these means), compromise solutions are now sought for in trade-offs between the risk of relapse and quality of the patient's life (QoL) after treatment. What then should be the extent of gastric resection/gastrectomy? This should depend on the size, type and location of the tumour. The QoL in TG patients is worse than those when SG is used [10, 11].

If an appropriate macroscopic margin is preserved, then any partial surgical resection does not lower the chances for effecting a cure and it improves the QoL. Evidence for this was provided by prospective studies of Gouzi, Bozzetti and Davies [11–14]. Most researchers consider that 4–5 cm is a safe enough margin for intestinal tumours, but 6–8 cm for diffuse tumours; according to Lauren [11, 14–16]. A retrospective study by Harrison et al. evaluated 98 patients with cancer in the proximal part of the stomach, (65 after SG and 33 after TG), and found no differences in survival or recurrence rates, however the QoL had not been measured. Indeed, there is no prospective study data in the literature that takes into account QoL in both such groups.

Hundhal et al. summarised treatment outcomes for patients operated on in the USA, during 1985–1996. Only 18% patients underwent D2 lymphadenectomy; in line with UICC classification of > 15 lymph nodes/sample. More than half the patients were at clinical stages III and IV of advancement and less than 1/3 had a tumour located in the distal part of the stomach. In spite of the limited indications for partial gastrectomy, a complete excision was undertaken in only 40% cases [17]. Siewert reported on treatment outcomes in 1654 patients from German and Austrian centres: 30% tumours were located in the distal part of the stomach, 39.9% in the middle and 26% in the proximal [18]. A subtotal distal gastrectomy was performed only in 23.1% of patients, whilst the others underwent total or total extended gastrectomies for tumours of the gastroesophageal junction. Extending the extent of resection to those neighbouring organs that are infiltrated, increases the risk of complications and mortality during the perioperative period [19, 20]. However in certain cases of infiltration/invasion, particularly for node-negative stage patients, the chances of recovery are significantly affected [21–24]. Splenectomy and splenopancreatectomy had no effect on survival compared to resection limited by an analogous lesion progression according to the UICC classification [21]. Prospective studies have not yielded any data on the effects of splenectomy on treatment outcomes. Nonetheless, removing lymph nodes from the splenic cavity whilst preserving the organ can prove difficult. A vitally important and still much debated issue is the extent of the lymphadenectomy. The success of Japanese surgeons in treating GC was initially confirmed by retrospective studies and led to defining the range of the so-called standard (D1) and the extended (D2) lymphadenectomies. Furthermore, it is accepted that for correctly assessing the tumour stage, at least 15 lymph nodes are required present for a D1 and at least 25 for a D2. The classification of lymphadenectomy ranges made by the Japanese Research Society for Gastric Cancer is shown in Figure 1. Studies by Maruyama et al. have proved the advantage of performing a D2 lymphadenectomy over D1. The difference in 5-year survival rates was significant; 61.6% vs 44.3% [25, 26].

The difficult-to-replicate Japanese studies in Western countries have prompted prospective European studies to be undertaken. The largest of these was a study by Bonenkamp et al. (Dutch Gastric Cancer Group), in which 632 patients were randomised into two lymphadenectomy groups: D1 or D2. The differences in 5-year survival proved to be insignificant, nevertheless significant differences were respectively observed for the following: complications (25% vs 43%) and perioperative mortality (4% vs 10%) [19]. One drawback pointed out for the Dutch study is the limited experience of surgeons performing the extended lymphadenectomies, which may also increase the risk of complications, including deaths; most of the centres performing less

than 10 gastric operations annually. The D2 operation was similarly found to be inferior in a study by Cushieri et al. on 400 patients [20]. Upon investigating the sub-groups from these two studies, then the increasing complications and perioperative mortality rates were found to apply to those patients that underwent extended resection for splenectomy and/or distal pancreatectomy. If such cases are excluded from the assessment, then mortality and complications become similar for both groups. Moreover, at clinical stage II and III A, the survival is significantly longer in the D2 group. This is confirmed by an extended lymph node dissection study from Holland [27], a study by Edwards et al. (5-year survival 32% vs 59% in favour of D2), Siewert and a German group, where patients at clinical stage II showed 49.2% vs 19.9% rates (i.e. a 30% difference favouring D2) as well as by other Japanese researchers [18, 26–28]. A study by Sano [29] surveyed selected centres specialising in gastric surgery

(i.e. above 80 gastrectomies annually) and showed that both D2 and D2+ lymphadenectomies (extended by the para-aortic nodes) can be safely performed by experienced surgeons (mortality 0.8%). Evidence is lacking that any further extension of lymphadenectomy improves patient survival, which was confirmed by studies from the Cracow-based centre; Kulig et al. [30, 31].

The standard treatment of gastric adenocarcinoma is currently the complete/almost complete excision of the stomach (a margin/boundary of at least 5 cm) together with regional D2 lymphadenectomy. The area of lymphadenectomy can be limited to D1 (lymph nodes around the stomach) for T1N0 advancement. The area of D2 lymphadenectomy includes the lymph nodes of the celiac artery, the left gastric artery, common hepatic artery and the surroundings of the splenic artery along with the hilus lienis (splenic cacity) which in isolated cases may require selective removal of
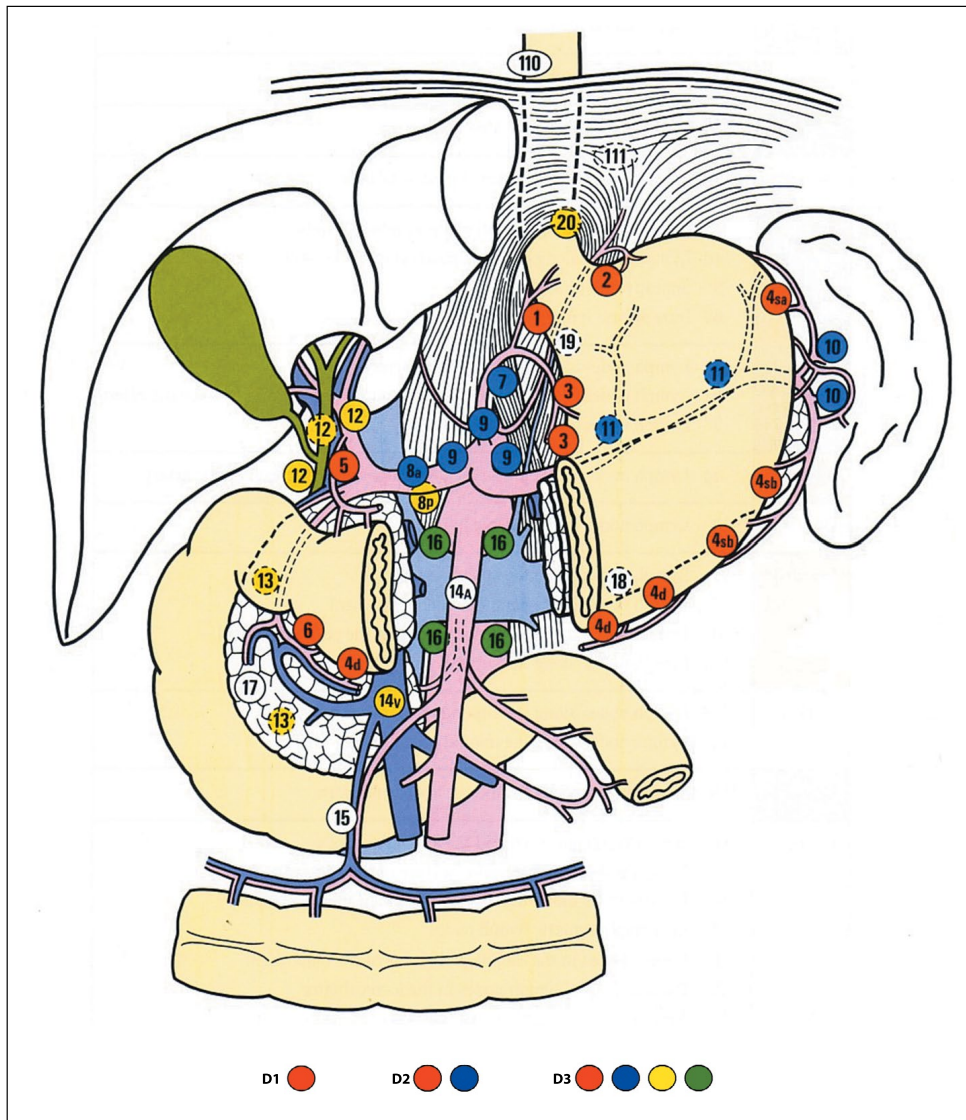
Figure 1. Extent of resected gastric lymph nodes (according to the Japanese Research Society for Gastric Cancer)

Table I. Surgical treatment of gastric cancer NCCN *vs* ESMO Consensus Am Coll Surg 2013 [16]

Resection extent	Proximal tumour — TG
	Distal tumour — SG/TG
Lymphadenectomy	T1N0 — D1
	T > 1N > 0 — D2
	Minimum 15 lymph nodes in surgical sample after radical surgery 25 lymph nodes
Organ resection	Splenectomy — electively NO
	Bursectomy — electively NO
	Cholecystectomy — electively NO, only for cholelithiasis
Margins	< 5 cm ad-hoc studies, cutting into positive margins (R1)
Reconstruction	After SG — Roux-en-Y
	After TG — Roux-en-Y
	— Roux-en-Y + reservoir
Post-surgery nutrition	Jejunostomy — after TG
	TPN — Lack of consesus
Others	Poll — lack of consensus
	Routine sealing — lack of consensus

the spleen, whilst sparing the pancreas. Obligatory standards of conduct for treating gastric cancer are summed up by the American College of Surgeons (Tab. I) [16]. Despite attempts for globally harmonising standards, there are important differences in how the extents of radical resection are approached between Asia with the US and Europe. In Western countries, the recommended margins for achieving a curative resection (RO) through TG or SG is a 4 cm minimum according to the NCCN or 5–8 cm by ESMO or a D1 or D2 lymphadenectomy (without elective pancreatic resection/splenectomy) at a minimum of 15 lymph nodes being present [32–33]. Japanese recommendations give a margin of 2–5 cm depending on the T and G tumour characteristics [34]. Other differences are in the extent of lymphadenectomy. In contrast to the Japanese, recommendations for D1 according to Western countries does not include the lymph nodes of left gastric artery. Such differences make it indeed difficult to compare treatment outcomes (Fig. 1).

Reconstruction methods following total gastrectomy

The aim of reconstruction in the GI tract is to restore the function of a given resected organ by as far as is possible, so enabling a reversion back to an independent status. Up till now there are 50 ways proposed for reconstruction, post--gastrectomy, but all can be divided into two basic groups according to whether duodenal passage has been preserved or not. Both these approaches can be performed in straight-forward fashion and are complemented by constructing an intestinal reservoir pouch. A third group uses double-tract methods which reduces the risk of ischemia as well as linking the benefits arising both from retaining duodenal passage and in constructing an intestinal reservoir pouch.

The method of reconstruction after TG as proposed by Schlatter, [7] consisted of oesophageal anastomosis with the intestinal loop pulled up and when completed by intra-intestinal anti-reflux anastomosis, this procedure dominated the 1940s. Unfortunately, most patients reported symptoms of reflux oesophagitis [35, 36]. Likewise, for these same reasons duodenoesophagostomies, as proposed in 1898 by Brigham and then propagated by Nakayama and Hinze, have now been abandoned. It was only in 1909 that a reconstruction of the Y-loop improved the QoL as proposed by Cesar Roux in Lausanne (originally for SG and later adapted for TG) (Fig. 2). The favourable outcomes achieved by this method had been confirmed by numerous studies in the 1940s. A modification proposed by Orr in 1947 involving anastomosis of the end of the oesophagus to the side of the intestinal loop (intended to reduce tension and improve the blood supply to the anastomosis), ultimately determined today's most popular method for reconstruction of the digestive tract after total gastrectomy [9]. Its main advantage is that it is simple to perform and it effectively prevents reflux of bile into the oesophagus, whereas its disadvantage is the absence of duodenal passage. A reconstruction procedure that preserved duodenal passage was (jejunal segment interposition first undertaken in 1941 by Seo and subsequently modified and propagated by Longmire and Henley (Fig. 3). Maintaining the passage of food through the duodenum allows at least to partially preserve the hormonal regulation of the gastrointestinal tract function as well as providing endoscopic access to the duodenum and bile ducts (Figs. 2, 3) [37–40].

From the time when the Roux-en-Y syndrome was first described by Mathias, greater weight is given to retaining the continuity used to reconstruct the intestinal loop, which is designed to protect against peristaltic wave disorders in the intestine and symptoms of pronounced pseudo-intestinal obstruction. In the opinion of this study group, such measures when taken improves the patient's QoL, especially in the first year after TG [41]. Apart from restoring gastrointestinal passage another important issue after TG it is to prevent reflex disease arising from the lack of the pylorus and lower oesophageal sphincter. The most effective safeguard appears to be in keeping sufficient distance between the oesophageal-intestinal and biliary anastomosis. A distance of around 7 cm was originally proposed by Roux for the reconstruction; in the 1950s Wells and Johnston lengthened this to 20–25 cm, whilst nowadays the majority of workers suggest 40–60 cm. In reconstructing intestinal interpositions, whilst maintaining duodenal passage, it was initially postulated that the loop length be is less than 20 cm.
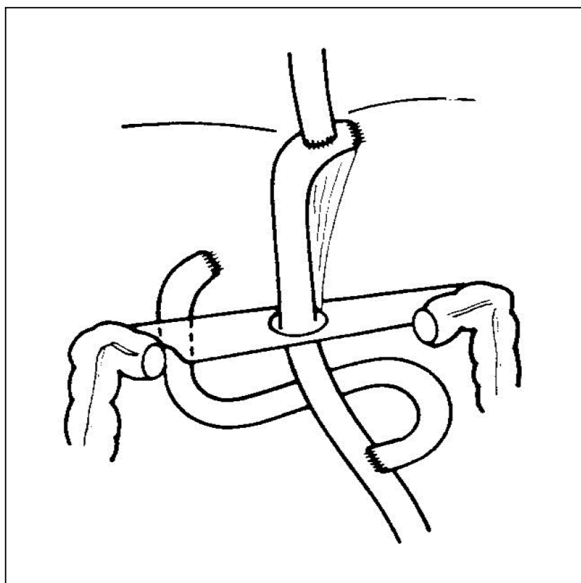
Figure 2. Roux-en-Y reconstruction. No duodenal passage
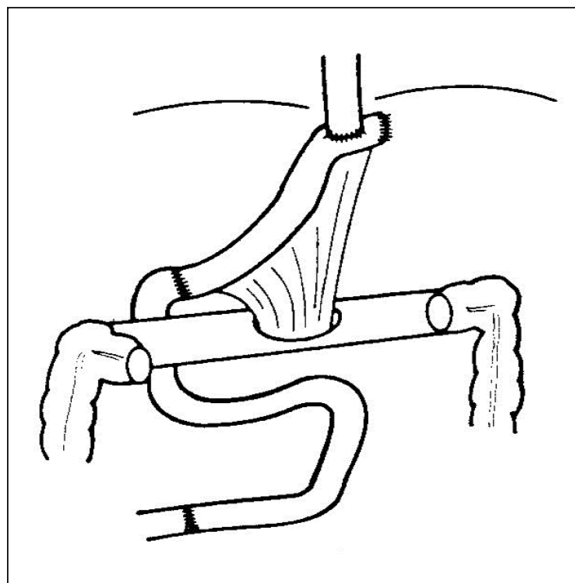
Figure 3. Longmire-Henley reconstruction. Duodenal passage retained

In 1952, Longmire proposed a longer length, whilst Gutgenam in 1966 confirmed that a loop of 30–35 cm significantly reduced the risk of reflux disease [38, 39, 42, 43]. An anti-reflux role for jejunoplication was proposed by Schreiber and performed by an end-to-side esophagojejunostomy and using the 'blind' intestinal loop [44, 45]. Gorka however proposed an invagination technique when performing end-to-end esophagojejunostomy through extending the anastomosis to the first line of the intestine at a depth of 4–5 cm, which both protects against leakage during the perioperative period and creates/affords an anti-reflux mechanism [46]. A favourable anti-reflex outcome can also be obtained by a reconstruction using the ileo-caecal segment and Bauhin's valve. This method was propounded by Lee and Hunnicutt in the early 1950s which at the same time allowed restoration of the stomach's function as a gastric food reservoir [47, 48]. Prospective studies have indeed confirmed the efficacy of this anti-reflux procedure, however other adverse consequences are diarrhoea or halitosis and no gains in QoL nor in other nutritional parameters over other technically much simpler ways of reconstructing; this now leading a decreased popularity of this method [49].

In assessing QoL after TG, a significant problem is that it is the size of meals consumed that often prolongs the period of convalescence. The next step in the development of gastric surgery was thereby focused on reconstructing the gastrointestinal tract so that a food reservoir was created. For the aforementioned reconstruction methods, only the ileo-caecal segment fulfils this role. Just as reconstruction without food reservoirs, such methods can be divided into two groups according to whether duodenal passage is retained or not. In 1952, Hunt and Lawrence were the first to propose creating a J-shaped reservoir (J-Pouch) which did not preserve duodenal passage, but was modified in 1976 by Herfarth through the jejunoplication anastomosis; this still being successfully used up till now [50–52]. Reconstructions that create an intestinal reservoir by duodenal closure were also suggested by Tomoda and Nakayama [53] whilst Lygidakis proposed avoiding intestinal dilation and slowing passage by forming two reservoirs separated by a 5 cm segment without anastomosis [54]. Horwath proposed creating a 15cm long reservoir with two anti-peristaltic anastomised loops forming a Y-shaped pouch (i.e. aboral pouch) [55]. Methods for constructing food reservoirs are more complex and time consuming, and thereby require extensive experience in gastric surgery by the surgeon. Upon reviewing the literature, the observed effects of improving QoL and nutritional parameters in patients after TG for reconstruction without any reservoirs do not meet the desired outcomes. Thus, reconstructions using R-Y methods and L-H interpositions are still the simplest and most commonly used methods for restoring the continuity of the gastrointestinal tract after TG.

Minimally invasive surgery

Access via minimally invasive surgery was pioneered using GC surgery at a Japanese centre. The first laparoscopy-assisted distal gastric resection was performed in 1994 Kitano et al. [56], and the first TG (due to cancer) by Azagra et al. (Belgium) in 1995 [57]. At present, using laparoscopy is uncontroversial when making pre-operative diagnoses of gastric cancer particularly in advanced disease stages. According to NCCN recommendations, using laparoscopy for diagnostic purposes are made in cases whenever diagnos-

ing T3–4 or N + tumours is in any doubt. At lower stages of clinical advancement, the chances of diagnosing metastases is low (4% vs 25%), even when aided by laparoscopic-ultrasound examination; Power et al. [58]. Laparoscopic access in GC surgery is slowly gaining more and more adherents. Nevertheless it is difficult to unequivocally address all concerns about minimally invasive surgery because most publications report short series cases.

For this reason, both ESMO and NCCN recommends that minimally invasive access requires further prospective studies for due consideration. Husher et al. [59] reported on the first prospective study which compared open techniques in conjunction with laparoscopy to distal gastrectomy [59]. Long-term results have shown no differences in OS, but have however demonstrated shorter hospital stays, reduced blood loss and the starting of oral nutrition earlier for those undergoing laparoscopy. Controversies abound on questions concerning the completeness of resection as well as that of regional lymphadenectomy with local recurrences occurring or implants in such areas after trocar puncture. Laparoscopic gastric surgery undoubtedly requires the surgeon to be extensively experienced. Initially, such surgical access was preferred when dealing with less advanced (T1–T2) tumours in the distal part of the stomach. This procedure is widely supported in Japan, where the incidence of contracting early gastric cancer (EGC) reaches 50%. Concerns over retaining a QoL are reasons for considering wedge resection for Tis or T1a tumours, although for such patients endoscopic dissection can also be a surgical treatment option [60–62]. For T1b tumours located in the body of the stomach, wedge resection is considered while maintaining the prepyloric area, gastro-intestinal anastomosis and D1 lymphadenectomy [63]. In Japan in 2010, 42% of SGs are performed through laparoscopic access [64]. It is currently believed that minimally invasive surgery can also used in more advanced cases [65–68], where its outcomes largely depend on the experience of the centre. Some practitioners tend to gain laparoscopic access using a port for lending the hand assistance, especially that the wound needed for removal has a similar size [69, 70]. The risk of local recurrence or implants in the post-trocar channel occurs mainly in advanced cases and can be limited by an appropriate surgical technique. It should be remembered though that laparoscopic access cannot reduce the oncological extent of the resection.

Conclusions

In spite of the progress made in other areas of oncology, the surgeon and the quality of their experience are still the only sure guarantee for treating GC. The effectiveness of combination therapy does not obviate the surgeon of responsibility for resecting to the correct extent (partial or total gastric removal with at least a 5 cm macroscopically healthy margin) taking into account regional lymph nodes removal (D2 lymphadenectomy excepting T1N0–D1 tumours). Minimally invasive access, if keeping to oncological standards, is equivalent to open cancer surgery, particularly for less advanced tumours of the distal stomach. A correct//appropriate reconstruction of the digestive tract still remains a determinant for the QoL after TG.

Conflicts of interest: none declared

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