Minimally invasive surgery and gastric cancer: where are we now?

The management of gastric neoplasms has undergone numerous changes following the continuous development of new therapies, improvements in endoscopic and surgical technique, as well as following the introduction of combined treatments. This made it possible to guarantee the patient with gastric cancer the best chances of treatment. Today, treatments are often personalized, based on the characteristics of the individual patient as well as the stage and location of the tumor; surgery still remains a key point (1). Technological advances have led to less and less aggressive procedures, while maintaining the effectiveness of traditional treatments. The use of smaller surgical incisions and the consequent reduction in surgical trauma has resulted in a faster postoperative recovery for patients with gastric cancer. Laparoscopy has spread globally in most surgical centers and research is focusing on applying even more sophisticated robotic technologies to gastric cancer surgery. Robotic surgery, which until a few years ago seemed to be only a remote option due to its high costs, is now increasingly used in an increasing number of specialized centers (2).

Importance of screening and minimally invasive treatment

Although the incidence of cancer is decreasing substantially, it still represents the fourth most common cancer and the second cause of death from cancer in the world (3). Thanks to health screening programs and improved diagnostic techniques, the diagnosis of early gastric cancer (EGC) has increased, in fact about 50% of all gastric cancers in Japan and South Korea are EGC (4,5). EGC refers to the presence of neoplastic tissue confined to the mucosa or submucosa, regardless of the presence of lymph node metastases (6). By precancerous lesions we mean anatomic-pathological alterations that have the risk of becoming cancerous over time. Gastric intraepithelial neoplasia (GIN) is an important precancerous lesion, it is subdivided into low-grade intraepithelial neoplasia (LGIN) and high-grade intraepithelial neoplasia (HGIN). Endoscopic treatment of EGC is now possible thanks to technological advances in endoscopic equipment, improvements in technique and increasingly early diagnosis. The most effective and most used technique for the endoscopic treatment of early gastric cancer is endoscopic submucosal dissection (ESD). ESD is both a diagnostic and a therapeutic method, the main incidences are two: undifferentiated intramucosal carcinoma with a diameter of less than two centimeters and differentiated intramucosal carcinoma without ulcerations (7). The main advantages of ESD are represented by reduced costs and rapid recovery due to less trauma with a high percentage of complete resection (8,9). In the face of these undoubted advantages, ESD failure can lead to negative consequences such as the emergence of doctor-patient disputes and the need for additional surgery. Failure of the ESD can occur if there is an inaccurate assessment of the lesion (in terms of type, depth and extent). Even if gastric cancer screening programs have greatly increased the number of EGCs detected, these programs are not feasible (as in Western countries, because of high costs and low incidence). A rapid access to the first endoscopy and a really accurate gastroscopy, should lead to a reduction in the number of missed lesions. When an endoscopic resection results in non-radical or non-curative treatment, or when the risk of lymph node involvement is not negligible, further surgery is recommended. For proximal gastric cancer, the mandatory treatment is represented by gastrectomy, both total and subtotal. As is known, the incidence of early post-operative complications (such as anastomotic dehiscence, intra-abdominal abscesses and surgical wound complications) is much higher in cases of total gastrectomy than in distal stomach resection (10), as is the incidence of nutritional impairments (such as severe reduction in absorption of iron and vitamin B12, anemia and loss of weight) is significantly lower after distal gastrectomy then after complete resection of the stomach (11-13). On the other hand, anastomotic stenosis is less common after distal gastrectomy (14).

Minimally invasive proximal gastrectomy

The number of EGC in the proximal part of the stomach has increased in recent times (15). Cancer of the esophagogastric junction and proximal gastric cancer remain surgical challenges due to perioperative safety and postoperative functional outcome. In the past, even for relatively early cancer, extensive resections (such complete resection of the stomach and

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extensive dissection of lymph nodes) were performed. In recent literature it has been demonstrated that less demolitive resection, as proximal gastrectomy plus regional lymph node dissection, could achieve similar oncological outcomes compared with total gastrectomy (16). In addition to oncological results, the quality of life after gastric surgery has received significant attention. Esophagogastrostomy has very high incidences of reflux esophagitis and anastomotic stenosis. In order to reduce the incidence of reflux esophagitis, which is one of the most redoubtable complications after resection of the proximal part of the stomach, the reconstruction with jejunal interposition has been introduced (17). Unfortunately, none of the numerous published methods of reconstruction after proximal gastrectomy have satisfactory results for establishing a widely accepted routine procedure (18). For the treatment of early gastric cancer, one of the procedures that, thanks to its peculiarity of being a surgical technique capable of preserving digestive functions, is becoming increasingly used, is laparoscopic proximal gastrectomy with reconstruction of the double tract. It would appear that, for the treatment of proximal EGC, this technique offers functional advantages when compared to treatment by total gastrectomy; the Korean study KLASS-05, a prospective randomized study, aims to demonstrate the above-mentioned advantages (19).

Distal gastrectomy: where are we now?

Gastrectomy with lymphadenectomy is still the gold standard for the treatment of early gastric cancer when risk factors are present (such as large tumor size, ulceration, lymph node metastases, poor differentiation, as well as the presence of submucosal, lymphovascular, or submucosal invasion), although endoscopic resection is recognized as the initial treatment for most patients with EGC, at least in countries where there is an effective screening program (20). Kitano was the first surgeon who performed a laparoscopic distal gastrectomy (LDG) in 1991. The LDG has revolutionized the surgical treatment of stomach cancer because it has allowed, with the same surgical quality, a better quality of life, less pain, less blood loss, an earlier recovery and a shorter hospital stay (21). In the early 2000s, for early cancer treatment, minimally invasive gastrectomy appeared to be well established and robotic surgery began to appear in the scene as a safe method. In Japan and Korea, a rapid increase in the number of surgeries for EGC was observed, while in the West, many papers began to appear. In the East the most of the studies were about early tumors, during the same period, Huscher *et al.* published in Italy [2005], a prospective randomized study, in which they confront open distal gastrectomy (ODS) with LDG for treatment of advanced gastric cancer. The KLASS-2 randomized controlled trial was published in 2020 and demonstrated that laparoscopic distal gastrectomy can be used as a standard even for locally advanced cancer (22). After 2010 the studies about robotic distal gastrectomy (RDG) became more frequent. Recently, in 2018, Obama *et al.* analyzed retrospectively 229 RDG and 233 LDG. The free-disease survival and the 5-year survival rates were the same, as well as the pattern of recurrence, demonstrating that the RG is a safe procedure (23). At present, evidence demonstrates that the LADG can be performed safely, for short and long-term outcomes, even in fragile patients (24). About RDG there is no strong evidence at the moment, however many observational studies have shown promising results for robotic approach, however, the cost problem of robotic systems has yet to be solved.

Minimally invasive surgery and chemotherapy

In recent decades, numerous advances have been made in the management of stomach cancer, currently minimally invasive gastrectomies are the most used technique for the treatment of EGC, moreover these minimally invasive methods are becoming increasingly popular even for advanced gastric tumors. In cases of locally advanced gastric carcinoma (LAGC), perioperative chemotherapy has been shown to be capable, in Western countries, of improving the oncological outcomes of this patient setting if compared to surgery alone (25). In terms of oncological outcomes, LDG is considered not inferior to open surgery, and it also allows for a better postoperative course even in patients with LAGC. However, since most of the studies on this topic were conducted in Eastern countries, for this reason, it can be deduced that the patients included in these studies generally did not undergo neoadjuvant or perioperative therapies. Conversely, in Western countries, most patients with LAGC undergo preoperative chemotherapy. Preoperative chemotherapy, which is known to produce cytotoxicity and profibrotic reactions in the tissues, could complicate surgical dissection, especially during the time of lymphadenectomy during minimally invasive surgery (26). For this reason, in the case of patients with locally advanced gastric cancer treated

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with preoperative chemotherapy (NAC), concerns remain regarding the indications for laparoscopic surgery. However, if on the one hand it is not certain that NAC negatively influences the surgical results of laparoscopic gastrectomy, on the other it is evident how a less invasive surgery can facilitate the post-operative course and therefore the subsequent chemotherapy in terms of times and number of cycles.

Mininvasive gastric surgery, complications and how to prevent these

Gastric surgery seems to have accepted the introduction of minimally invasive surgery, this following the scientifically demonstration of the oncological non-inferiority of minimally invasive surgery, at least for most commonly performed procedures: distal and subtotal gastrectomy. Actually, many trained surgeons consider laparoscopic total gastrectomy a safe procedure (27). However, this transition, if compared to colorectal surgery, saw a worsening of short-term post-surgical outcomes (28). Therefore, at present, minimally invasive total gastrectomy

still needs scientific validation and technical improvements. To date a particularly critical point is the jejunal esophagus anastomosis, while all the other technical maneuvers can be reproducible with the same results of open technique, in terms of postoperative complications. Anastomotic leakage after gastric surgery is associated with high morbidity and mortality and is one of the most fearsome complications of gastric cancer surgery, its incidence can reach, according to some authors, up to 9% (29). To evaluate the viability of the anastomosis during surgery, surgeon can rely on some factors such as: the presence of pulsation, peristalsis or bleeding, as well as the color and temperature of the intestine. All these variables have the limit of being based on an evaluation of the single surgeon during the performance of the intervention and therefore they are necessarily subjective. It should also be remembered that intraoperative demarcation of the ischemic bowel can take much longer than expected. Recently, in order to achieve more anatomical information during surgery, fluoroangiography mediated to indocyanine green (ICG) was used in laparoscopic and open surgery (30). Due to the characteristic of ICG to become fluorescent once excited by near-infrared light, this dye can be injected intravenously to obtain a real-time angiography for evaluating tissue perfusion. ICG-enhanced fluorescence was introduced to reduce complications during surgery for gastric tumors, particularly as anastomotic leakage. Currently, ICG-mediated fluorescence can be used, as well as for anastomosis perfusion control, also for intraoperative tumor identification, lymphography for sentinel nodes detection, lymphatic mapping and intraoperative identification of peritoneal carcinomatosis.

Conclusions

The treatment of gastric cancer has undergone a remarkable evolution in the last decades. Driven by technological innovation and emerging scientific evidence gastric cancer surgery is rapidly evolving, both as indications and as surgical techniques. Chemotherapy as well as minimally invasive surgery is expanding the indications supported by evidence and therapeutic results.

However, some aspects still remain to be explored. Many of the topics mentioned in this preface will be dealt with in the following pages.

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Vincenzo Pappalardo
ASST Sette-Laghi, Varese, Italy (*Email: vincenzopappalardo1@gmail.com*)
Stefano Rausei
ASST Sette-Laghi, Varese, Italy (*Email: stefano.rausei@gmail.com*)
Simone Giacopuzzi
University of Verona, Verona, Italy (*Email: simone.giacopuzzi@univr.it*)
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