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Minimally invasive surgery for gastro-oesophageal junction adenocarcinoma: Current evidence and future perspectives

Rodica Bîrlă, Petre Hoara, Florin Achim, Valeriu Dinca, Diana Ciuc, Silviu Constantinoiu, Adrian Constantin

Abstract

Minimally invasive surgery is increasingly indicated in the management of malignant disease. Although oesophagectomy is a difficult operation, with a long learning curve, there is actually a shift towards the laparoscopic/thoracoscopic/robotic approach, due to the advantages of visualization, surgeon comfort (robotic surgery) and the possibility of the whole team to see the operation as well as and the operating surgeon. Although currently there are still many controversial topics, about the surgical treatment of patients with gastro-oesophageal junction (GOJ) adenocarcinoma, such as the type of open or minimally invasive surgical approach, the type of oesophago-gastric resection, the type of lymph node dissection and others, the minimally invasive approach has proven to be a way to reduce postoperative complications of resection, especially by decreasing pulmonary complications. The implementation of new technologies allowed the widening of the range of indications for this type of surgical approach. The short-term and long-term results, as well as the benefits for the patient - reduced surgical trauma, quick and easy recovery - offer this type of surgical treatment the premises for future development. This article reviews the updates and perspectives on the minimally invasive approach for GOJ adenocarcinoma.

Key Words: Gastro-oesophageal adenocarcinoma; Minimally invasive oesophagectomy; Laparoscopic gastrectomy; Abdomino-mediastinal lymph node dissection; Indocyanine green fluorescence imaging
Minimally invasive surgery is increasingly indicated in the management of malignant disease. Although oesophagectomy is a difficult operation, with a long learning curve, there is actually a shift towards the laparoscopic/thoracoscopic/robotic approach, due to the advantages offered to the patient and surgeon. The short- term and long-term results, as well as the benefits for the patient – reduced surgical aggressiveness, quick and easy recovery, offer this type of surgical treatment the premises for future development. This article reviews the updates and perspectives on the minimally invasive approach for gastro-oesophageal junction adenocarcinoma.

INTRODUCTION

In the last decades, the incidence of adenocarcinomas developed in the vicinity of the gastro-oesophageal junction (GOJ) is increasing[1]. Even from the year 1987, some authors recommend an individualized surgical strategy, guided by tumor stage and topographic location of the tumor center or tumor mass, based on the experience with surgical resection of more than 1000 patients with GOJ adenocarcinoma. This required detailed preoperative staging and classification of tumors, arising in the vicinity of the GOJ, into type I - defined when the tumor center was located 1-5 cm above the esophagogastric junction (EGJ), type II when located from 1 cm above to 2 cm below the EGJ, or type III when located 2-5 cm below the EGJ. Type II is also known as "real" carcinoma of the cardia[2].

In patients with type I tumors, transthoracic or transhiatal (TH) oesophagectomy is performed and in patients with type II or type III, an extended total gastrectomy (TG) is more appropriate. In patients with early tumors, staged as uT1 on preoperative endosonography, a limited resection of the proximal stomach, cardia and distal oesophagus, with interposition of a pedicled isoperistaltic jejunal segment, allows a complete tumor removal with adequate lymphadenectomy[3].

Multimodal treatment protocols, with neoadjuvant chemotherapy or combined radiochemotherapy, followed by surgical resection, appear to markedly improve the prognosis, in patients with locally advanced tumors, who respond to preoperative treatment.

Minimally invasive surgery (MIS) is the gold standard in many areas of surgery. The first minimally invasive oesophagectomy was described by Cuschieri[4] in 1993, and one year later, Kitano et al[5] reported the first minimally invasive gastrectomy.

Since 1993, techniques for gastric cancer have evolved from laparoscopic-assisted surgery to total laparoscopic surgery, and oesophagectomy techniques have also evolved from hybrid approaches to a completely minimally invasive manner[6,7].

A 2017 study evaluates worldwide trends in surgical techniques, for oesophageal cancer surgery, comparing it to the 2007 survey[8], among the surgical members of the International Society for Diseases of the Esophagus, the World Organization for Specialized Studies in Diseases of the Esophagus, the International Gastric Cancer Association. Participants completed a web-based questionnaire about surgical strategies for esophageal and GOJ cancer. In 2017, minimally invasive transthoracic approach oesophagectomy was preferred by 43% surgeons, compared to 14% in 2007. In a subgroup analysis of oesophageal surgeons, the number of high-volume surgeons increased from 45% to 54%, over the last seven years. The preferred curative surgical treatment of oesophageal cancer was minimally invasive transthoracic oesophagectomy with two-field lymph node dissection (86%) and gastric tube reconstruction (95%).

Actual, most centers propose a laparoscopic abdominal approach, with gastric mobilization and pull-up through the diaphragmatic hiatus. The thoracic phase includes either an open procedure (hybrid technique)[9] or a thoracoscopic approach.

MIS for GOJ adenocarcinoma is associated with a significant operator-dependent learning curve. Data from the literature show a conversion rate of up to 12.5% from minimally invasive esophagectomy to open surgery, in low volume centers[9].

A recent study recognized that 35-40 MIS are required to acquire proficiency[10]. And another cohort study, analyzing the phases and outcomes of the learning curve, required to master minimally invasive, total adventitial resection of the cardia, suggests that there is a long learning curve[11]. A faster course of the learning curve could be facilitated by: gaining experience in open esophageal surgery and in MIS of the digestive tube, using specific high-performance equipment and carrying out training courses, in centers with great experience in this type of surgery.

This article reviews the updates on the MIS for GOJ adenocarcinoma, in terms of indications, types of MIS and resection, lymph node dissection, anastomosis type, short term and long term outcomes, life quality, and the perspectives, in order to provide reference for clinical treatment and research.
The article is based on the analysis of data considered relevant for the chosen topic from the studies identified in PubMed Central (PMC) and MEDLINE Complete (EBSCO) since 2013, but also on the experience in minimally invasive surgery in the General and Esophageal Surgery Clinic of the Sfanta Maria Clinical Hospital, Bucharest, Romania. Trials were sought and used, as well as data from updates of studies, original articles or reviews, regarding minimally invasive surgery for GOJ adenocarcinoma. For a sensitive search strategy, the terms used in search engines were: “oesophagogastric junction adenocarcinoma” and “oesophagogastric junction adenocarcinoma and minimally invasive surgery”. The article focused on data that have been updated about the types of indications and types of MIS, oesophageo-gastric resection, short-term and long-term results, quality of life, and future perspectives. Only these studies and papers were considered eligible, thus being taken into account in the elaboration of this article. Two authors (Birlă R and Constantin A) selected the articles considered relevant, preferring peer-reviewed articles from highly ranked journals, written in English. The decision to select an item was made by agreement of the two. A number of 195 articles were identified for the period 2013–2023, which included the keywords used in the database search, 11 reviews and systematic reviews, 8 meta-analyses, 5 randomized controlled trials, 10 propensity score-matched studies, 14 comparative studies and 42 observational studies. The reference list from each selected article was screened for additional relevant information. We excluded unpublished data from abstracts, contained in volumes from various congresses or conferences, as we excluded papers that were not in English (Tables 1 and 2).

**INDICATIONS AND TYPES OF MIS FOR GOJ ADENOCARCINOMA**

**Laparo-thoracoscopic surgery**

The indications of MIS in GOJ adenocarcinoma have evolved, initially starting from early cases, currently reaching the choice of the minimally invasive or open approach, for each case, considering the patient’s preference, biological status, and the surgeon’s experience and choice.

Endoscopic resection can be a good therapy for early GOJ adenocarcinoma[12]. When it cannot be applied or fails, the patient is proposed for a minimally invasive surgical resection procedure. In the literature, there are several comparative studies of the results of endoscopic resections and those of MIS. Chen et al[13], performed a propensity study to evaluate the survival of patients treated by the two types of approaches and found that no significant difference was observed in the 5-year cumulative incidence of cancer-specific death between the cohorts and that the type of treatment was not a prognostic factor [hazard ratio (HR) = 1.51, 95% confidence interval (95%CI): 0.81-2.81, \( P = 0.20 \)] in multivariate Cox analysis. Similar results were reported by other authors: Overall survival (OS) rates at 5 years were not statistically significantly different (93.9% vs 97.3%)[14], in another study (93.3 vs 92.9%; \( P = 0.282 \))[15], concluding that endoscopic submucosal dissection (ESD) may be an effective alternative to surgery, for the treatment of early GOJ cancer.

In most cases, with advanced tumors, there is agreement that MIS competes with the open approach. The neoadjuvant treatment can increase the chances of success of MIS, especially in patients with partial or complete clinical response. MIS proves its safety, after neoadjuvant therapy and appears equivalent with the open approach, regarding the perioperative oncologic outcomes[16].

**Robotic surgery**

Robotic surgery has already found its place in minimally invasive methods. The advantages are multiple, from the improved 3-dimensional(3D) visualization, and the 7 degrees of movement of the working tools, to the comfort of the operating surgeon, accompanied by the reduction of the physiologic tremor of the hands. Robotic surgery has the greatest advantage in narrow spaces and for operations with a single field of interest.

Robot-assisted minimally invasive oesophageal surgery is the newest acquisition, in experienced centers being used with results equivalent to laparoscopic and thoracoscopic surgery[17]. However, the learning curve is long for this operation; therefore many cases are needed to obtain the maximum benefits of the method. A recent study found that to perform a minimally invasive oesophagectomy, with intrathoracic anastomosis, in optimal conditions, 119 cases would be needed, which makes this technique not at all easy to implement[18]. Regarding robotically assisted McKeown oesophagectomy, the number of cases required in the learning curve, to be able to operate in optimal conditions, is 70 [19]. The difference is given by the difficulty of performing intrathoracic anastomosis, which is shown to have a lower risk of fistula compared to cervical anastomosis, but with a more serious and disastrous outcome than that associated with the cervical one.

Studies between robot-assisted oesophagectomy and the classic procedure have shown clear benefits in favour of the minimally invasive approach, with a decrease in the number of days of hospitalization, blood loss, and a more complete lymphadenectomy[20]. However, when compared with laparoscopic/thoracoscopic surgery, regarding the number of resected nodes, the amount of blood loss, pulmonary complications or fistulas, and robotic esophagectomy proved to be similar, less in terms of operative time, which was longer in the last case[21].

Other studies have shown the benefits of robotic surgery vs laparoscopic surgery, in terms of lymphadenectomy, at the level of the laryngeal nerve group, with more lymph nodes harvested and fewer recurrent nerve paralysis[22,23].

Currently, robot-assisted Ivor Lewis oesophagectomy can be considered an alternative to laparoscopic/thoracoscopic surgery, with the mention that it is reserved for centers with a large number of cases, which already have experience in minimally invasive oesophageal surgery. Although most centers present robot-assisted oesophagectomy, with one stage of the operation performed laparoscopically, or through a thoracotomy, there are centers where the Ivor Lewis operation...
Table 1 The search strategy summary

<table>
<thead>
<tr>
<th>Items</th>
<th>Specification</th>
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</thead>
<tbody>
<tr>
<td>Databases and other sources searched</td>
<td>PubMed Central (PMC), MEDLINE Complete (EBSCO)</td>
</tr>
<tr>
<td>Search terms used (including MeSH and free text search terms and filters)</td>
<td>Search strategy (see Table 2)</td>
</tr>
<tr>
<td>Timeframe</td>
<td>2013–2023</td>
</tr>
<tr>
<td>Inclusion and exclusion criteria (study type, language restrictions etc.)</td>
<td>Inclusion criteria: Meta-analyses; trials studies; clinical trials &amp; updates of clinical trials; reviews; original articles; only studies/papers/journals written in English Exclusion criteria: Unpublished data from abstracts contained in volumes from various congresses or conferences; papers that were not in English</td>
</tr>
<tr>
<td>Selection process (who conducted the selection, whether it was conducted independently, how consensus was obtained, etc.)</td>
<td>RB performed the search in the databases according to the presented criteria. If a study appears relevant by at least one reviewer - Birla R and Constantin A - the full-text article has been retrieved and checked. The selection of full-text articles was made by two reviewers independently Constantin A and Birla R. Assessing content validity required subjective judgment from the reviewers. The citation number was an important selection criterion. Differences were discussed and if consensus could not be reached between the two reviewers, we requested the consultation and recommendation of a third reviewer (Hoara P). The reference list from each selected article was screened for additional relevant information</td>
</tr>
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Table 2 Systematic literature search for oesophagogastric junction adenocarcinoma and minimally invasive surgery

<table>
<thead>
<tr>
<th>Search terms</th>
<th>Number of articles</th>
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<tbody>
<tr>
<td>1 Search: Oesophagogastric junction adenocarcinoma</td>
<td>2939</td>
</tr>
<tr>
<td>2 Search: (Oesophagogastric junction adenocarcinoma) AND (minimally invasive surgery)</td>
<td>429</td>
</tr>
<tr>
<td>3 Search: (Oesophagogastric junction adenocarcinoma) AND (minimally invasive surgery) Filters: English, from 2010-2023</td>
<td>230</td>
</tr>
<tr>
<td>4 Search: (Oesophagogastric junction adenocarcinoma) AND (minimally invasive surgery) Filters: English, from 2013-2023</td>
<td>195</td>
</tr>
<tr>
<td>Final number after review for inclusion and exclusion criteria and addition of articles from review of references¹</td>
<td>126</td>
</tr>
</tbody>
</table>

¹Exclusion criteria: No abstract available; non minimally invasive surgery; gastro-oesophageal junction adenocarcinoma not a major focus of article; not published in English; case reports without on minimally invasive surgery.

is performed exclusively with the robot, with very good results, on over 200 cases[24].

There are ongoing studies that try to demonstrate the superiority of robotic oesophagectomy over conventional MIS [25].

**OESOPHAGO-GASTRIC RESECTION**

For type I and II GOJ adenocarcinomas, there are different minimally invasive techniques, based on transthoracic or TH approaches, as in open surgery. Usually, the minimally invasive Ivor Lewis technique is the primary choice, although intrathoracic anastomosis is sometimes difficult. The operation starts with a laparoscopy, proximal gastrectomy and abdominal lymphadenectomy. Although pyloroplasty was indicated in open surgery, as a mandatory procedure, to improve gastric tube evacuation after vagotomy, in MIS, current studies do not show differences in terms of postoperative gastric evacuation, regardless of whether the pyloroplasty was performed[26].

The second phase right thoracoroscopy, includes mobilization of the oesophagus and mediastinal lymph node dissection between the area from the carina to the azygos vein and down to the diaphragm. The oesophagus is divided at least 5 cm proximal to the cranial pole of the tumor, and the specimen is extracted; the gastric tube is pulled up into the thorax through the hiatus, to create an intrathoracic anastomosis. Methods of anastomosis include end-to-side anastomosis, manual or mechanical with a circular stapler[27], or side-to-side anastomosis with a linear stapler[28].
The minimally invasive McKeown procedure begins with a right thoracotomy, with oesophageal and mediastinal lymph node dissection, which are similar to the previously described Ivor Lewis technique. Subsequently, the patient's position is changed to supine and then a laparoscopic small curvature resection and lymph node dissection are performed. The creation of the gastric tube is also similar to that described in the Ivor Lewis technique. After laparoscopy, a left cervical incision is made and the oesophagus is divided, the specimen is extracted in the abdomen and then outside and the gastric tube is pulled up through the mediastinum, in the cervical region where an end-to-side manually sutured anastomosis, with the proximal oesophagus, is performed.[29]

The minimally invasive TH procedure consists of a laparoscopy and a left cervical incision, followed by a longitudinal gastrectomy with lymph nodes dissection and laparoscopic TH dissection of the distal oesophagus. The gastric tube is created extracorporeally and then pulled up in the cervical area, where the anastomosis is done.[30].

Also, Ebihara et al.[31] report considerable advantages, such as securing the proximal margin, intrathoracic oesophago-jejunostomy, and increased exposure in the operative field of the lower mediastinal area for GOJ Siewert type II, through minimally invasive abdominal and left thoracic approach.

For type III cancers, a laparoscopic TG is indicated. A TG with DII lymph node dissection is performed, the duodenum is closed using a linear stapler and a Roux-en-Y limb of the jejunum, is fashioned for the anastomosis with the oesophagus. The diaphragm is opened and the distal oesophagus is mobilized. Only the distal peri oesophageal lymph nodes are resected, and the oesophageal resection is limited. The jejunum is transected at 25 cm distal to the Treitz ligament, distal limb of the jejunum is lifted to prepare the oesophago-jejunostomy. Due to the limited size of the hiatus, the use of OrVil® (Medtronic, Inc., Minneapolis, MN, United States) facilitates the performance of the end-to-side oesophagus-jejunal anastomosis.[32]. Finally, a side-to-side jejuno-jejunostomy is performed at 45-50 cm below the oesophago-jejunostomy.

**Complete mesenteric resection - new concepts**

A new concept, about the type of oesophagogastric resection, extrapolated from the complete resection of the mesorectum, is also configured in resections for GOJ tumors. Zhu et al.[33], propose a study to evaluate the efficacy and safety of TH laparoscopic surgery of complete mesenteric resection (CME) in comparison with those of the traditional laparoscopic TH approach in the treatment of Siewert II/III GOJ adenocarcinoma, following the short term results. They found that intraoperative blood loss and hospitalization were significantly reduced ($P < 0.05$) in the CME-TH group (patients with CME through TH laparoscopic surgery) compared with those in the TH group (patients without CME through TH laparoscopic surgery), while significantly more lymph nodes were harvested ($P < 0.05$) in the CME-TH than in the TH group, with no significant differences in complications ($P > 0.05$) between two groups. It was concluded that the meso of the stomach and the lower oesophagus can be completely resected, together with the tumor, lymph nodes, adipose tissue and blood vessels blood as an "intact package" GOJ adenocarcinoma, leading to better short-term results.

In the same direction, Lorenzi et al.[34] propose a minimally invasive technique of circumferential hiatal dissection for the distal oesophagus and GOJ adenocarcinoma in the context of hybrid Ivor Lewis oesophagogastrectomy (laparoscopic/thoracotomy) or minimally invasive procedure. The hiatus dissection included the surrounding peri-oesophageal tissues in a cylindrical fashion, maximizing the distance from the oesophageal wall. Bilateral crural muscle fibers and pleura, anterior pericardial fat, and posterior pre-aortic tissue were excised en bloc. The pathological findings were particularly focused on the involvement of the circumferential resection margin. The results obtained (R0 resection in 92.5%, and negative circumferential resection margin in 91% of patients with pT3 tumors) support the authors' conclusions that the adoption of this technique could reduce the incidence of involvement of the circumferential resection margin and improve the pathological results.

**Proximal resection margin –additional procedures**

Due to the propensity for intramural invasion of the proximal oesophagus, a clear proximal resection margin is crucial to minimize the rate of anastomotic recurrence, its length being a prognostic factor for survival in multivariate analyses.[35]. A length of more than 2 cm of the proximal margin, in resected specimens has been recommended[36] but was difficult to assess because the surgeon cannot estimate the location of the tumor by tactile sense. In most studies, the method of determining the proximal section line of the oesophagus is not described.

Sugita et al.[37] routinely used intraoperative endoscopy to visualize the tumor location and establish the proximal resection level. In addition, intraoperative pathological examination of frozen sections was performed in all cases or suspected cases.[37,38]. Indeed, the combination of intraoperative endoscopy and frozen section analysis may be the perfect way to confirm negative resection margins, but these methods are not always available in all institutions. Therefore, it is essential to carefully assess preoperatively, the extent of oesophageal invasion by preoperative upper endoscopy, upper gastrointestinal barium swallow, and enhanced computed tomography.

**Lymph node dissection - current controversies**

The extent of lymphadenectomy for GOJ adenocarcinoma has been continuously the subject of discussion. The extent of lymphadenectomy associated with oesophagectomy should be adequate because the number of lymph nodes removed is an independent predictor of survival. To maximize the survival benefit, according to one report, a minimum of 23 lymphadenectomy associated with oesophagectomy should be adequate because the number of lymph nodes removed is an independent predictor of survival. To maximize the survival benefit, according to one report, a minimum of 23 lymph nodes should be removed.[39]

Current German guidelines[40] specify that the standard of care should be a two-field lymph node dissection, both abdominal and mediastinal. In oesophageal cancer, standard two-field lymph node dissection involves: In the chest-posterior mediastinal lymph node dissection from the diaphragm up to the subcarinal nodes and aortopulmonary window; and in the abdomen - D2 Lymphadenectomy: Lymph nodes along the celiac trunk, common hepatic and splenic
arteries, along the lesser gastric curvature, in the lesser omentum. The extended dissection involves the lymph nodes included in the standard two-field lymphadenectomy (2FND) and the right paratracheal nodes along the right recurrent nerve and the brachiocephalic trunk.

Therefore, for oesophageal adenocarcinoma, the advantage of adding a third field during lymph node dissection is less clear; the survival benefit of three-field lymphadenectomy (3FND) applies only to patients with upper- and middle-third oesophageal cancer[41].

Giacopuzzi et al[42], in the study published in 2017, pointed out that in Siewert I tumors, the involvement of the middle and upper mediastinal nodes was 5%; for this reason, 3FND should be considered an overtreatment for patients with Siewert I tumors.

In a multicenter prospective study, Kurokawa et al[43] evaluated the distribution of lymph node metastases from GOJ tumors and the optimal extent of lymph node dissection in the abdominal and mediastinal fields. If the oesophageal invasion has exceeded 2.0 cm, excision of the lower mediastinal area, which includes the lower thoracic para oesophageal nodes (station 110) is strongly recommended; if oesophageal invasion exceeds 3.0 cm, excision of the upper and middle mediastinal lymph nodes (stations 106recR and 108) is poorly recommended; if the oesophageal involvement exceeds 4.0 cm, excision of the 44 upper mediastinal lymph nodes group (station 106recR) is strongly recommended.

The investigation of lymph node metastasis patterns, proposed by Li et al[44], led to the following results: The percentage of patients with positive celiac and lower mediastinal lymph nodes reached 58.3% (42/72) and 8.3%, respectively (6/72). The disease-free survival (DFS) and disease-specific survival of these 72 patients was 94% and 93.4% at 1 year after surgery and 59.8% and 62% at 3 years after surgery, respectively, suggesting the need for inferior mediastinal and celiac D2 Lymph node dissection, to improve oncologic outcome.

The rates of lymph node metastases, for both Siewert type II and type III tumors, were relatively low, but not negligible, at lower mediastinal nodal stations, particularly station 110[45]. In addition, metastatic involvement in middle and upper mediastinal lymph nodes was significantly higher, when the length of oesophageal invasion was >3 cm[46]. Of note, mediastinal lymph node metastases can be an independent survival factor and are associated with distant metastases and poor survival outcomes[47].

Therefore, special attention should be paid to these nodal stations to anticipate better survival and dissection of stations 110 and 111 have been recommended in Japanese guidelines for tumors invading the oesophagus.

To easily and safely perform lymph node dissection around the lower oesophagus, at a higher level in the lower mediastinal space, it is crucial to ensure a sufficient view, with adequate space for manoeuvres. Even in the open technique, the complex topographical anatomy of the GOJ leads to a narrow and deep surgical field, as well as a rather limited surgical view, which often makes the surgeon unable to see and access the dissection area properly, if the assistant fails to help with a correct exposure. All of these can lead to the failure of a complete lymphadenectomy. In contrast, the laparoscopy can provide both the surgeon and the assistant with a better, magnified surgical view. In addition, fine vascular sealing devices allow for more meticulous dissection under a bloodless field. Sugita et al[37], Huang et al[48] and Juntilla et al[49] reported that the number of harvested lymph nodes was significantly higher in the laparoscopic group, for Siewert type II tumors.

Sakaguchi et al[50] and Pang et al[51], reported a method of dissection of the lower mediastinal lymph nodes en bloc, through a laparoscopic TH approach, by sectioning the tendinous center of the diaphragm, with the excision of the periesophageal tissue, harvesting an average of five lymph nodes, and observing the correlation of the length of tumor invasion of the oesophagus with the number of metastatic nodes.

To minimize perioperative complications, in the absence of metastatic nodal involvement proximal to the carina and for patients with Siewert type II adenocarcinoma, TH oesophagectomy should therefore be considered a valid surgical approach, transthoracic oesophagectomy should be considered a valid surgical tool in patients with distal oesophageal cancer or Siewert type I cancer, associated with limited metastatic lymph nodal involvement[41].

**Antireflux anastomosis**

A recent study proposes a semi-embedded valve anastomosis, associated with proximal gastrectomy, to improve postoperative reflux disease, as well as nutritional status, associated with TG[52].

Significant reductions in gastrointestinal reflux (60.7% vs 4.2%, \( P < 0.001 \)), postoperative reflux oesophagitis, and improvement of the overall health status were reported by a study[53], comparing the use of an esophago-gastric anastomosis by lateral overlap with fundoplication, by Yamashita (SOFY), with antireflux function, associated with laparoscopic proximal gastrectomy and respectively Roux-en-Y esophago-jejunoanastomosis for laparoscopic TG, in patients with Siewert II/III tumors.

Another study reported acceptable results, for the prevention of reflux oesophagitis, with a side-to-side esophago-gastric anastomosis, using a linear stapler – the new technique of esophagogastric tube reconstruction with lateral overlap, which can be performed either after laparoscopic proximal gastrectomy, or after minimally invasive Ivor Lewis oesophagectomy[54].

Lateral anastomosis has been considered a promising approach for creating an intrathoracic esophago-gastrostomy in minimally invasive oesophagectomy. Manual suturing of the hole left at the level of the anastomosis is a technical challenge in thoracoscopic Ivor Lewis oesophagectomy. Wang et al[55] presented initial experience using autostatic suture (barbed suture), with promising short-term results.

**Additional intraoperative procedures – indocyanine green fluorescence imaging**

Parallel to the improvement of minimally invasive techniques, the development of intraoperative real-time imaging evaluation has brought an additional benefit, regarding the safety of the operative technique, with a direct impact on intraoperative morbidity and the improvement of postoperative results.
Tissue details that cannot be visualized under normal conditions can be highlighted by fluorescence techniques, following the administration of indocyanine green (ICG). The technique shows encouraging results, regarding the evaluation of lymphadenectomy, optimization of the dissection and viability of anastomotic partners[56].

**Fistula risk improvement**

A specific complication is the anastomotic fistula, which is responsible for decreasing the survival rate and increasing the risk of local recurrence[57]. An important risk factor is inadequate blood perfusion at the level of the anastomosis[38]. Usually, this aspect is evaluated subjectively, through the macroscopic inspection of the tissues, the bleeding at the level of the anastomotic organ's margins and the palpation of the pulse of the vascular pedicles. In the context of a minimally invasive technique, with the use of stapling devices, these manoeuvres are technically very limited. In this sense, different fluorescence imaging methods have been introduced, and among them, ICG angiography (ICG-FA), seems to bring the most benefits. Due to its fluorescent properties, it allows visualization of tissue perfusion in real-time. After endovascular administration, the dye quickly binds to plasma proteins, remaining in the vascular space. With the help of a near-infrared (NIR) light source, the surgeon can observe in detail the diffusion of the dye, at the tissue level. However, the evaluation by ICG-FA is still subjective. By visual assessment, a consensus regarding the quantification of tissue perfusion is not established[59], but an objective parameter can be determined, which is the perfusion speed of the dye in cm/S.

Some authors observed that, even though, fluorescence angiography using ICG, in the evaluation of the vascularization of the gastric stump shows specificity of over 94%, with a negative predictive value of almost 80%, the sensitivity is still below 22%, with a positive predictive value of almost 64%, which suggests that this method does not detect the risk of fistula, instead the measurement of the perfusion speed of the dye in the gastric tube can help to assess this risk[60,61]. Shimada et al[62], evaluating the usefulness of ICG-FA for reconstruction after esophagectomy, state that the technique is useful in evaluating the vascularization of the graft and helps to choose the correct site for the anastomosis. However, the rate of fistulas did not change. It can be speculated that the microvascularization highlighted by fluorescence, is not necessarily sufficient for a viable anastomosis. A recent meta-analysis confirms this result[63]. On the other hand, Campbell et al[64] reported a decrease in the fistula rate from 20% to 0%, after the introduction of ICG-FA. Koyanagi et al [65], confirm the improvement of results after the use of ICG.

**Modulation of lymph node dissection and thoracic duct**

Logically, the fluorescence evaluation was also taken into account for the intraoperative evaluation of the lymphatic network (node mapping). Several studies have presented encouraging data in this direction by injecting peritumoral ICG, aiming at a better highlight of the lymphatic network and an improvement in specific morbidity of lymphadenectomy[66-68]. Although strongly supported by theoretical foundations, the data provided by the literature in this direction are insufficient and inconclusive.

Although small, the risk of damage to the thoracic duct remains a reality, especially in obese patients[69]. The injection of ICG at the level of the mesentery or bilateral groin, offers the possibility of optimal highlighting of the thoracic duct, allowing its identification during dissection or its ligation in the event of a suspected injury[70].

**Limit of oesophageal resection**

Last but not least, the use of ICG fluorescence seems to be useful in establishing the resection limit, especially proximal, but also distal, in oncological surgery of the GOJ. The Gastroesophageal Junction Carcinoma Working Group in Japan established that for junctional tumors that invade the esophagus less than 4 cm, the TH approach can be used[43].

However, the challenge arises from the exact establishment of the topography and the tumor boundary intraoperatively. In MIS, such as laparoscopic and robotic, locating the tumor during surgery is difficult, due to the lack of tactile sensation. Currently, ICG fluorescence imaging can be used for the exact localization of the GOJ tumor[71,72]. In this direction, Sagawa et al[73] use the Firefly mode of the da Vinci Xi system, through the capability of NIR visualization and simultaneous intraoperative upper gastrointestinal endoscopy, that precisely indicates the positioning and limits of the tumor injected with ICG.

In conclusion, the need to quantify the data provided by ICG-FA, to issue clear protocols, becomes imperative, and the data from the literature, due to their lack of homogeneity, does not yet provide a close perspective of such an objective. However, the potential of these techniques is obvious.

**SHORT-TERM AND LONG-TERM RESULTS**

**Short-term outcomes**

The development of minimally invasive techniques for resection of GOJ adenocarcinoma has the potential advantage of minimizing morbidity. The first randomized controlled trial was conducted in the Netherlands, enrolling 200 patients with the minimally invasive McKeown and Ivor Lewis approach. This clinical trial aimed to identify differences in morbidity, severity of complications and quality of life[74].

A 2017 multicenter study, evaluating short-term results after a minimally invasive Ivor Lewis approach, showed that the rate of anastomotic fistulas is still high (15.2%), possibly due to the technical diversity of anastomotic techniques and a high percentage of patients treated with neoadjuvant chemoradiotherapy (90.2%); an aggressive approach of the complications (thoracotomy for decortications in 13 patients with empyema) have led to low mortality (2.1%), concluding that further improvements and standardization in anastomotic technique are needed to achieve a safe intrathoracic
anastomosis [75].

Other studies claim that, once the experience is gained in the minimally invasive approach, the results are excellent. In their review of over 1000 MIs, Luketich et al. [76] reported an overall mortality of 1.7%, vocal cord paresis in 4% of the patients, and an anastomotic fistula rate of 5%. The average duration of lymph nodes removed was 20, and 98% of patients obtained a negative histological margin. The average duration of hospitalization was 8 d, with 2 d in the intensive care unit. These numbers speak about what can be achieved, in the context of a dedicated program, with substantial experience and expertise in perfecting a new surgical approach.

There are a few randomized controlled trials, which have compared minimally invasive esophagectomy with open transthoracic esophagectomy. In the TIME trial, conventional thoraco-laparoscopic oesophagectomy was compared with the open approach [76], with a lower incidence of pulmonary infections reported in patients with MIS. In the MIRO trial, hybrid oesophagectomy was compared with transthoracic open oesophagectomy, with the hybrid approach being associated with a lower incidence of major complications [77]. In the MIOMIE trial [78], the hybrid approach was compared with the open approach, with equal results being reported, in terms of morbidity and mortality.

Additional studies found no significant difference in oesophagectomy-related morbidity (anastomotic fistula, anastomotic stricture rate, gastric tube ischemia, chylothorax, vocal cord paralysis) and reduced use of narcotics, due to less postoperative pain. The pain score in the laparoscopic group decreased faster, making it evident that the small wounds generated less stress and pain, which justified the faster recovery [76,79-82]. Similar results have been reported in meta-analysis [83,84], systematic review [85,86], propensity analysis [87], or clinical trials [88-92] comparing MIE with open and hybrid resections.

Zhang et al. [93] presented in a study the comparative results of open vs laparoscopically assisted TH approach and observed that the rate of pleural perforation, requiring the prolonged use of mechanical ventilation, for more than 12 h, was lower in the laparoscopic group, but this lesion, in laparoscopic surgery, may affect the recovery of lung function, possibly due to tension pneumothorax.

Danetc et al. [94] studied the oncological outcomes of patients who underwent minimally invasive oesophagectomy. He analyzed 1586 patients (in 17 studies) in which the minimally invasive approach was compared with the open approach. The number of lymph nodes removed was significantly higher in the minimally invasive approach (median of 16 nodes compared to 10 nodes harvested in open oesophagectomies, P = 0.03). Similar results were reported after hand-assisted laparoscopic surgery [95], or in other studies that used the minimally invasive approach [48,96].

Other authors conclude that for patients with Siewert type II adenocarcinoma, modified Ivor Lewis surgery, thoraco-laparoscopic oesophago-gastroctomy, 2FND, and intrathoracic anastomosis, is safe and feasible [97].

The use of MIS, in patients with neoadjuvant treatment, did not lead to different short-term results, compared to those of patients with primary surgery. Compared to the group with open surgery, it was found that MIS patients had shorter median intensive care unit time (P = 0.002) and hospital lengths of stay (p < 0.0001), but the incidence of postoperative complications (open: 54.8% vs MIS: 41.1%, P = 0.155), mortality at 30 d (open: 2.7% vs MIS: 0%, P = 0.506) and anastomotic leak rates (open: 1.4% vs MIS: 0%, P = 1.00) were similar. However, the respiratory complications were significantly reduced after MIS (8.9%) compared with open (29.7%; P = 0.004) [98].

Long-term results

Data on long-term survival are limited but encouraging. Several studies compared long-term surgical and oncological outcomes after laparoscopic and open gastroctomy, for GOJ adenocarcinoma, reporting similar 5-year OS and DFS survival rates (44.6% vs 42.1%, P = 0.403; 40.1% vs 37.6%, P = 0.321, respectively) [99]. Similar results were reported in another study, after minimally invasive or open esophagectomy, for 5-year OS (12.5% in MIS vs 16% in open approach) and DFS (67% in MIS vs 16%-57% in open approach, P = 0.33) [96]. Other studies found longer but not significantly different 5-year OS and DFS rates between patients in the laparoscopic group vs open group, in patients with Stage III disease (HR = 0.42, (95%CI: 0.05-3.47) vs HR = 0.47, (95%CI: 0.10-2.12)) [100], or a median survival for the laparoscopic approach of 56 mo and 47 mo, respectively, with 5-year OS of 40% and 29.1%, respectively [83].

Another study identified a significantly different five-year survival in oesophagectomy patients (64%-MIS vs 35%-open approach, P < 0.001), and multivariate analysis demonstrated that patients with an open approach had significantly poorer survival, compared with the minimally invasive procedure, independent of age, rate of excised lymph nodes, radiochemotherapy and pathologic stage (HR=2.00, P = 0.019) [101].

Two studies used propensity score matching analysis to adjust for selection bias, leading to more reliable comparisons between laparoscopic and open approach [83,101]. In the stratified analysis, a better survival was observed in the laparoscopic group for Siewert type II, which may be due to a more thorough lymph node dissection around the lower oesophagus, and a significantly longer median DFS and better OS than the open approach, for types Siewert II/III [83].

The rate and pattern of recurrence did not differ between the two groups, during the follow-up phase [102,103]. Another study reports that, in terms of recurrence, the most common site was the peritoneum [38].

In a comparative study of neoadjuvant vs adjuvant therapy, with a median follow-up period of 37.5 mo, a pathological complete responder rate of 26% was reported in the neoadjuvant chemoradiotherapy group and a greater rate of R0 resection than in the adjuvant group (95 % vs 76%; P = 0.002). The multivariable analysis of OS showed lower hazards of death independently associated with neoadjuvant vs adjuvant therapy (HR = 0.57, 95%CI: 0.36-0.91; P = 0.0200) [104].

Another study showed that preoperative radiochemotherapy determined improvement in R0 resection rate, compared to surgery and preoperative chemotherapy, but there is no significant difference in OS. Both neoadjuvant strategies remain clinically meaningful options for patients with resectable gastroesophageal junction tumors [105,106].

Some authors think that surgical treatment could also be used in tumors with small-volume metastatic disease. A clinical trial evaluated the feasibility and effectiveness of using induction chemotherapy with fluorouracil, leucovorin, oxaliplatin and docetaxel followed by surgical resection, with curative intent, for patients with oligometastatic GOJ cancer.
Rigorous criteria were used to include cases, in the group of patients with surgical treatment after 4 chemotherapy sessions. The results showed better survival for patients with surgical resection (gastrectomy and metastasectomy), the OS is 31.3 mo, compared to 9-11 mo for non-operated patients[107].

In patients with neoadjuvant treatment, the long-term results are similar regardless of the approach, OS rates at 5 years (open: 61% vs MIS: 50%, \( P = 0.933 \)); MIS was not a significant predictor of OS (HR=1.07; 95%CI: 0.61-1.87; \( P = 0.810 \)[98].

QUALITY OF LIFE

The surgery of GOJ cancer, due to its amplitude, has a major impact on the quality of life. The specific element, around which the quality of life revolves, is postoperative reflux, with all its consequences. Oesophago-gastrostomy is the traditional and most widespread reconstruction method after proximal gastrectomy with distal oesophagectomy, the accepted technique in the oncological approach to GOJ tumors[103]. The main deficiency of the technique could be the high incidence of reflux oesophagitis, which varies between 9.1% and 35.3%[108,109].

The increased incidence is due to surgical resection, which alters the anatomy of the digestive tube, leading to disruption of anti-reflux mechanisms. In addition, the absence of the gastrointestinal pacemaker and the section of the vagus nerve leads to the impairment of gastric motility, with a direct impact on gastric emptying[110]. Studies have documented that reflux can wake patients from sleep, while sleep disturbances can worsen reflux symptoms, creating a true vicious circle[111]. Long-term sleep disturbances can impair cognitive function and severely impact the quality of life[112].

The long-term postoperative impact is mainly due to the mediastinal adhesion syndrome, with pulmonary involvement, but also in connection with reflux symptoms. Thus, dyspnea, even two years after surgery, seems to be due to pulmonary adhesions, secondary to the thoracic phase of the Ivor Lewis technique. On the other hand, it is known that gastric acidity, even after vagal denervation, normalizes over time. More than three years after surgery, the 24-hour gastric pHmetry in most patients is similar to that of healthy subjects[113]. This phenomenon is associated with an increasing incidence of reflux esophagitis, metaplasia and the need for effective anti-reflux treatment. Some reports indicate that the choice between gastrectomy, oesophagectomy or oeso-gastroctomy, does not have a significant influence on the quality of life, for patients with GOJ adenocarcinoma, six months after surgery[114]. Other studies document higher quality of life parameters, after minimally invasive oesophagectomy than after minimally invasive gastrectomy. Moreover, after thoracoscopic oesophagectomy, it seems to be close to that of the general population[115]. In addition, a meta-analysis of nine studies showed that patients, who underwent minimally invasive transthoracic oesophagectomy, had superior parameters than patients who underwent open transthoracic oesophagectomy, regarding general condition, fatigue, pain, and quality of life[116]. It should be mentioned that these differences were no longer present 6 mo and 1 year after the operation. In this meta-analysis, however, no difference was made between hybrid oesophagectomy or minimally invasive total oesophagectomy, nor between Ivor Lewis, McKeown or Orringer oesophagectomy. In a recent Swedish national study, quality of life was not statistically different at 1 year and 2 years after minimally invasive total oesophagectomy, hybrid oesophagectomy, and open oesophagectomy[117]. Because the robotic technique is relatively new, there are no studies on long-term results using this technique. A recent study reports significant benefit in terms of quality of life 4 mo postoperatively after the robotically assisted Ivor Lewis technique compared with open oesophagectomy[118]. Sarkaria et al[119] compared early postoperative quality of life after robotic oesophagectomy and open transthoracic oesophagectomy and reported significantly superior outcomes for the robotic technique. However, they included both the Ivor Lewis and McKeown techniques and reported results only for a four-month follow-up, during which 20% of patients were lost.

The search for technical artifacts, to restore the continuity of the digestive tract, after proximal gastrectomy with distal oesophagectomy, and improve postoperative reflux is thus a justifiable objective. In the Japanese Gastric Cancer Treatment Guidelines, in addition to the traditional oesophagus-gastro anastomosis, double tract reconstruction is specified as a possible technical alternative[120].

For double tract reconstruction, the jejunum is transected 25 cm distal to the Treitz ligament, distal limb of the jejunum is lifted to prepare the oesophageo-jejunalostomy. An end-to-side oesophageo-jejunalostomy is performed with a circular stapler, and the jejunal stump is closed with a linear stapler. Next, a side-to-side gastro-jejunalostomy is performed 15 cm below the oesophageo-jejunalostomy. Finally, a side-to-side jejunoo-jejunalostomy is performed 15-20 cm below the gastro-jejunalostomy[121].

Some studies have reported that this procedure could reduce the incidence of reflux oesophagitis after proximal gastrectomy[122]. A comparative study documents an incidence of reflux oesophagitis of 30.8% in the group with oesophageo-gastrostomy and 8.0% for double tract reconstruction. Patients in the group with double tract reconstruction complained less often of dysphagia, pain, reflux, loss of appetite, anxiety, dry mouth and unpleasant taste than those with oesophageo-gastrostomy[122]. However, the technique requires additional studies to confirm the advantages.

Another technique that aims to improve postoperative reported reflux is super MIS, through ESD and endoscopically submucosal tunnel dissection which, for the early stages, are equally effective from a curative point of view, with the advantage of avoiding major anatomical changes, secondary to classic surgery[123]. The quality of life is greatly improved, especially regarding reflux and sleep quality. It is believed that this is the result of the less aggressive surgical approach, in that the endoscope does not damage the integrity of the gastrointestinal tract, with relatively few changes in digestive physiology. Moreover, the proportion of patients with postoperative acid reflux, in the group treated by super MIS, is lower than that reported in the healthy group[124]. This may be due to scar contraction after endoscopic manoeuvres, with increased lower oesophageal sphincter pressure[125]. This technique requires confirmation through
additional studies and is indicated in the early stages of the disease.

**FUTURE PERSPECTIVES**

In recent years, with the improvement of technology, MIS technology has developed rapidly. MIS has wide prospects for use in GOJ adenocarcinoma and its application is the current trend.

Today, MIS uses high-definition 3D imaging systems and 2-dimensional imaging systems with 4K ultra-high-definition cameras. Shortly, this high-definition technology will be available in every dedicated operating room and will help surgeons perform these complex surgical procedures safely.

Although robot-assisted minimally invasive oesophagectomy is indeed attractive to many surgeons, its high cost still limits the use of this technology. As more companies develop robot-assisted surgical systems, in competition with the da Vinci systems, further technical development of less expensive robotic surgical systems is expected shortly.

The role of sentinel node biopsy in the surgical treatment of GOJ adenocarcinoma is still debated. The application of the sentinel node concept could limit the extension of the node dissection, avoiding all associated complications. Undoubtedly, this surgical strategy should be applied only to patients with cT1N0. Shortly, sentinel node mapping and nodal navigation surgery could be considered a promising and interesting tool for early-stage oesophageal cancer, identifying patients who could be treated with individualized, less invasive surgery. However, such complex surgery will be concentrated in high-volume centers and performed by dedicated surgeons, to minimize postoperative complications and improve oncological outcomes.

**CONCLUSION**

Surgery is still the most important method in the comprehensive treatment of GOJ adenocarcinoma. There is a strong worldwide trend towards MIS, endoscopic methods being used for superficial cancers and robotic and laparo-thoracoscopic methods for early tumors, or locally advanced tumors after neoadjuvant therapy.

The preferred MIS of GOJ tumors is oesophagectomy for Siewert type I tumors and gastrectomy for Siewert type III tumors. Most surgeons favor an extended gastrectomy for Siewert type II tumors. Although pyloroplasty was usually performed in open surgery, in the current MIS, most surgeons have given up on it. The clearly improved visualization and the possibility of fine dissection in narrow spaces, offered by MIS gives the possibility of a much more rigorous lymph node dissection compared with open surgery. Many methods can be adopted for anastomosis, such as manual, circular stapler, linear stapler, and even robot-assisted anastomosis, with comparable results in terms of fistula rate. The use of ICG-FA as an adjunct method for lymph node dissection, or for intraoperative visualization of the vascularization of the gastric tube, is proven to bring important improvement in the performance of the method.

Minimally invasive oesophagectomy may improve short-term results with fewer complications, compared to traditional open oesophagectomy. Most authors note, along with the indisputable benefits of the patient with a minimally invasive approach (quick recovery, reduced need for analgesics, decreased length of hospitalization, etc.), the decrease in the incidence of pulmonary complications, and with regard to the rate of anastomotic fistulas, its decrease is especially noticeable when intraoperative ICG-FA was used. In the long term, in advanced cases, the results are similar regardless of the type of approach; some studies, however, note better long-term results in patients with a minimally invasive approach. Also, the quality of life is better after the minimally invasive approach, and with regard to the appearance of reflux symptoms, a lower incidence is noted after the use of double tract reconstruction.

However, there is still no consensus on the ideal type of MIS for GOJ adenocarcinoma. Large randomized controlled trials are still needed to test which minimally invasive technique is best for this tumor.

**FOOTNOTES**

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Minimally invasive surgical techniques have been increasingly adopted in the treatment of esophageal cancer, aiming to reduce postoperative morbidity and mortality while maintaining oncological efficacy.

One such technique is minimally invasive Ivor Lewis esophagectomy after neoadjuvant therapy. This procedure involves resection of distal esophagus and gastroesophageal junction cancers, often with better cosmetic outcomes compared to open surgery. However, the outcomes following this procedure have been subject to varying reports.

A study by Pratschke J, Biebl M. Laparoscopic Resection for Adenocarcinoma of the Stomach or Gastroesophageal Junction Improves Postoperative Outcomes assessed the impact of laparoscopic surgery on these outcomes. The results supported the use of laparoscopic resection for this type of cancer, indicating improved postoperative outcomes.

Another study, Minimally Invasive Ivor Lewis Esophagectomy After Neoadjuvant Therapy, by C. Zhang et al., also highlighted the benefits of minimally invasive surgery, noting reduced hospital mortality in patients with resectable oesophageal cancer.

In a systematic review and meta-analysis, Reducing In-Hospital Mortality of Patients with Resectable Oesophageal Cancer: A Meta-Analysis, pooling data from multiple studies, it was concluded that minimally invasive surgery can lead to a reduction in mortality for patients undergoing esophagectomy.

Furthermore, the significance of reducing morbidity and mortality has been a focus in several studies. For instance, Morbidity in open versus minimally invasive hybrid esophagectomy (MIOMIE): Long-term results of a randomized controlled clinical study, by Peschaud F, Prudhomme M, Triboulet JP, Mariette C., suggest that hybrid approaches may offer improved outcomes.

A larger-scale study, Minimally Invasive Esophagectomy for Esophageal Cancer, by N. Zhou et al., confirmed the clinical superiority of minimally invasive surgery, demonstrating better outcomes for patients undergoing esophagectomy.

The importance of surgical technique in reducing short- and long-term complications has also been emphasized. For example, in Minimally Invasive Total Gastrectomy for Advanced Siewert Type, by J. Zhang et al., the authors highlighted the feasibility and outcomes of this approach.

Overall, these studies and reviews underscore the potential benefits of minimally invasive surgery in esophageal cancer treatment, with ongoing efforts to improve patient outcomes and reduce surgical morbidity. Further research is needed to continue refining surgical techniques and improving patient outcomes.
Radical Proximal Gastrectomy for Patients with Upper Gastric or Esophagogastric Adenocarcinoma.

Oesophagectomy for oesophageal cancer.

Reconstruction after proximal gastrectomy for early gastric cancer in the upper third of the stomach: an analysis of our 13-year experience.

Esophagogastrostomy reconstruction after limited proximal gastrectomy.

Perioperative chemo(radio)therapy versus primary surgery for resectable adenocarcinoma of the stomach, gastroesophageal junction, and lower gastroesophageal junction cancer: a systematic review of randomized clinical trials across three decades.

With Resectable Gastric and Gastroesophageal Cancer.

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