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REVIEW ARTICLE

Technical aspects, short- and long-term outcomes of laparoscopic and robotic D2-lymphadectomy in gastric cancer

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Summary

Purpose: *Gastric cancer is a common malignancy and its radical excision with an adequate lymph node resection provides an improved oncologic outcome. D2 lymphadenectomy in distal or total gastrectomy is considered a highly desirable technique for curable early or locally advanced gastric cancer. Many studies with high-level of evidence confirm the importance of the application of minimally invasive techniques in improving the short-and long-term outcomes of patients who undergo gastrectomy.*

Methods: *A MEDLINE search was performed with the following keywords; "d2 gastrectomy open laparoscopic", "d2 gastrectomy open robotic" and "d2 gastrectomy laparoscopic robotic". The search was narrowed on randomized control trials (RCT).*

Results: *6 studies in total are included in the present study; 5 RCTs on open vs laparoscopic group and 1 RCT on open vs robotic group. There is currently no RCT comparing the laparoscopic vs robotic techniques.*

Conclusions: *The superiority of laparoscopic gastrectomy towards the open technique is widely accepted, yet the proven acceptance of minimally invasive robotic techniques is still debated and not scientifically established. Technical challenges are the main point of discussion among the experts on the field, as well as the advantages of laparoscopic and robotic-assisted gastrectomy over the conventional open. This review provides a comparison on technical aspects, the short-and long-term outcomes of open and minimally invasive gastrectomy with D2 lymphadenectomy in early and advanced gastric cancer.*

Key words: *gastric cancer, gastrectomy, minimally invasive surgery, D2 lymphadenectomy*

Introduction

Gastric cancer is the fourth most common malignancy and one the most significant causes of cancer death nowadays [1]. Gastrectomy is the recommended and definite treatment of gastric cancer, usually accompanied by lymph node dissection [2]. Up until 1994, the surgical option for gastrectomy was an open-abdomen procedure, when Kitano et al. performed the first laparoscopic-assisted gastrectomy for early gastric cancer [3,4]. Since then, laparoscopic-assisted distal gastrectomy (LADG), particularly for early stage gastric cancer, has become a widely accepted standard procedure in many centers around the world, predominantly in Asian countries [5]. In the West, most often gastric cancer is diagnosed in a later stage and this complicates the surgical technique needed for an oncological resection [6]. Laparoscopic gastrectomy, when compared to open surgery, is generally associated with fewer early complications, such as less blood loss, lesser pain, earlier return to proper bowel movement and patient mobilization [2,7].

Robotic surgery seems to be able to succeed surgical techniques far more advanced than laparoscopic surgery, hence it is lately introduced in

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the upper gastrointestinal track procedures. Robot-assisted gastrectomy is currently suggested as a safer and more efficient method in reconstructing the alimentary tract, as well as achieving a more curative treatment, oncologically speaking, by retrieving higher number of possibly affected lymph nodes [5,8]. D2 lymphadenectomy is currently the standard of care in all types of gastric cancer except for the very early type.

The aim of the article is to compare the technical aspects, the short-term outcomes and the long-term outcomes of open, laparoscopic and robotic assisted distal or total gastrectomy with D2 lymphadenectomy in early and advanced gastric cancer.

Methods

A MEDLINE search was performed on randomized control trials (RCT) on the following keywords: "d2 gastrectomy open laparoscopic", "d2 gastrectomy open robotic" and "d2 gastrectomy laparoscopic robotic". There was no chronological restriction. Only peer-reviewed full-text RCT articles published in the English language were included. Safety of the procedures and the oncological outcome of each were the two major criteria of investigation on the present study.

Results

The search term "d2 gastrectomy open laparoscopic" returned 14 results. Five of these were RCTs comparing the open vs the laparoscopic technique and were included in our study. Similarly, only one RCT comparing the open versus the robotic technique was retrieved with the use of the search term "d2 gastrectomy open robotic". No results were returned with the use of the search term "d2 gastrectomy laparoscopic robotic". These results are presented on Tables 1 and 2 respectively.

Open surgery versus laparoscopic surgery

Technical aspects

For a laparoscopic gastrectomy, the patient is placed in a reverse Trendelenburg position with legs abducted. Apart from the camera, which is placed in the peri-umbilical area, another 4 ports are placed, two 12mm and two 5mm, one in each quadrant; upper right, lower right, upper left, and lower left for the first assistant [6].

Studies suggest that an indication for laparoscopic gastrectomy is an early stage cancer, preferably a clinical stage lower than T2N1M0 [9,10]. Although many studies suggest that patient selection for laparoscopic gastrectomy is targeted to patients mainly without any lymph node metastases, others do select patients with affected lymph nodes since a D2 lymphadenectomy is to be performed, eliminating any lesser resection for patients with advanced disease [2,11].

Laparoscopic-assisted gastrectomy is a major challenge is obese patients, as any laparoscopic procedure is expected to be. Added to that, the intraperitoneal fat creates difficulties in proper lymphadenectomy [12]. Operating time on patients with increased BMI is higher than those who are not obese.

As far as the type of gastrectomy is concerned, it is widely agreed that the laparoscopic total gastrectomy has many technical challenges, especially the anastomosis between oesophagus and jejunum which is far more difficult to perform laparoscopically. Anyway, in total gastrectomy, regardless of the type of approach, the oesophagojejunal anastomosis is considered insecure and most surgeons keep the patients fasted until the 5th postoperative day, thus minimizing any advantage of the laparoscopic technique.

A major factor concerning the comparison of the two techniques is the learning curve of the surgeon. The surgical technique is optimized after a certain number of procedures which might be different for each surgeon. Various studies have been published on this aspect with high deviation of results among them. Two of them suggest that the learning curve for competence in performing D2 laparoscopic gastrectomy improves dramatically after 50 and 60 cases respectively [13,14].

Short-term outcomes

Intraoperative complications of laparoscopic surgery are considered comparable to open surgery [12]. Regarding the immediate postoperative outcome, many advantages can be stated upon laparoscopic gastrectomies. Lesser manipulation of the abdominal wall and the small bowel, better pain management with lesser need for opioids, less discomfort and nausea, and earlier return to normal bowel function, leading to earlier oral intake postoperatively are the main advantages to be taken into consideration [15-17]. In addition, cosmetic outcome on the patient's surgical wound, as well as the future risk of hernias are to be considered.

Currently there are five randomized control trials that directly compare the two techniques on distal gastrectomies. The results of these trials are summarized in Table 1. All these studies confirm that the advantages as stated above exist, and laparoscopic procedures do have comparable or

Table 1. Randomized clinical trials on distal gastrectomy comparing the open versus laparoscopic technique

Study	*No patients*	*Type of operation*	*Stage*	*Lymph nodes*	*Perioperative complications*	*Long-term survival*
Cai et al. 2011 [18]	LAG 61/ OG 62	Proximal gastrectomy, distal gastrectomy or total gastrectomy Reconstruction B-I, B-II anastomosis, esophagogastrostomy and esophageal jejunostomy on both groups	IB-IIIB on both groups	LAG 22.98±2.704 OG 22.87±2.428 (p =0.839)	-2 conversions from LAG to OG - no postoperative deaths -postoperative morbidity LAG 12.24% OG 19.15% -pulmonary infection more frequent in group OG (p=0.038)	Overall survival rates: LAG 67.1% OG 53.8% (mean follow-up time of 22.1354 months)
Inaki et al. 2015 [35]	LAG 91/ OG 89	Distal gastrectomy with D2 lymph node dissection on both groups Reconstruction B-I, B-II or Roux-en-Y anastomosis	IB-IIIB on both groups	LAG 47 (range 10-104) No data recorded on OG group	-1 conversion from LAG to OG -1 re-surgery due to leakage -15% postoperative complications (pancreatic fistula, stenosis, surgical site infection) -0% mortality rate	No long-term data recorded. No re-admission 6 months after discharge
Cui et al 2015 [33]	LAG 148/ OG 148	Proximal, distal or total gastrectomy on both groups Reconstruction B-I, B-II anastomosis, esophagogastrostomy or esophageal jejunostomy on both groups	IA-IIIC on both groups	LAG 29.3±11.8 OG 30.1±11.4 (p=0.574)	-11 conversions from LAG to OG -Post operational morbidity LAG 21.8% OG 19.0% (p=0.560) -delayed gastric emptying more often in the LAG group (p=0.022) -0% mortality rate	No long-term data recorded
Hu et al. 2016 [36]	LAG 519/ OG 520	Distal or total gastrectomy with D2 lymph node dissection on both groups Reconstruction B-I, B-II or Roux-en-Y anastomosis	IA-IV on both groups	No data recorded	-33 conversions from LAG to OG - postoperative morbidity LAG 15.2% OG 12.9% (p=0.285) -0.4% mortality rate in the LAG group/0% in OG	No long-term data recorded
Shi et al. 2017 [7]	LAG 162/ OG 160	Distal or total gastrectomy with D2 lymph node dissection on both groups Reconstruction B-I, B-II or Roux-en-Y anastomosis	IB-IV on both groups	LAG 31.59 ± 5.87 OG 32.18 ± 6.07 (P=0.377)	-6 conversions from LAG to OG - postoperative morbidity LAG 11.72% OG 14.38% (p=0.512) -0% mortality rate	No long-term data recorded

LAG: Robotic-assisted gastrectomy, OG: open gastrectomy

Table 2. Randomized clinical trials on robotic versus open gastrectomy

Study	*No patients*	*Type of operation*	*Stage*	*Lymph nodes*	*Perioperative complications*	*Long-term survival*
Wang et al. 2016 [37]	RAG 158/ OG 153	Distal or total gastrectomy with D2 lymph node dissection on both groups Reconstruction B-I, B-II or Roux-en-Y anastomosis	IA-IIIC on both groups	OG 29.1±6.7 RAG 30.1±7.2, (P=0.447)	-3 conversions to OG - postoperative morbidity RAG 9.3% OG 10.3% (p=0.756) -Leak: RAG 4, OG 3. Total 7 re-surgeries -no intraoperative robotic procedure-related complications	No long-term data recorded

RAG: Robotic-assisted gastrectomy

lower complications compared to the open surgery. Only one RCT records a higher rate of pulmonary infections on laparoscopic surgeries compared to open [18]. The main drawback still remains the prolonged surgical time.

Long-term outcomes

All RCT concerning the comparison of open and laparoscopic surgery include limited number of patients, thus minimizing the strength of evidence and obscuring the safe extraction of results in the long-term. Group 1 of the studies stated above claim that in D2 lymphadenectomy, the number of lymph nodes retrieved in the open method is higher compared to the laparoscopic procedure [5]. The same result is issued by the meta-analysis studies of Group 2. This finding is attributed to the technical complexity of the extended D2 lymphadenectomy procedure. This raises questions on the safe oncologic outcome of the laparoscopic assisted distal gastrectomies with D2 lymph node resection. Currently there is only one prospective study comparing the survival (5-year and disease free) between these two, concluding that there is not any statistical difference in the survival of patients on which either open or laparoscopic distal gastrectomy was performed [19].

A systematic review on the assessment of the reviews currently published on comparison of open and laparoscopic surgeries states that many of these studies appear to have some methodological flaws, especially as far as blindness and randomization are concerned [20].

The main aspect of these findings that needs not to be oversighted is the fact that most of these refer to early gastric cancer and cannot be generalized to advanced-stage disease. Furthermore, most of these studies are undertaken in specialized centers in the East with high volume of patients and do not refer to current practice in the Western countries [5].

In early cancer patients, laparoscopic assisted distal gastrectomy is the standard therapy, especially in eastern countries [21]. In advanced cancer, the acceptance of laparoscopic surgery with D2 lymphadenectomy is not wide, due to the technical difficulties that might occur. The Korean Laparoscopic Gastrointestinal Surgery Study Group published a study comparing the long-term outcomes of patients with advanced cancer who underwent laparoscopic resection, stating that this technique is adequate for a safe oncologic outcome and is comparable to open surgery [22].

In advanced cancer, the studies published that refer to D2 gastrectomy compare the number of lymph nodes resected in open and laparoscopic procedure and do not find a significant difference between the two groups. The same result refers to tumor recurrence and survival rates. This is feasible though on the expense of the longer operation time [23,24]. As already stated above, this is reversely proportional to the experience of the surgeon to perform a laparoscopic D2 lymphadenectomy and is tightly associated with the learning curve of this procedure.

Open surgery versus robotic surgery

Technical aspects

For the robotic assisted gastrectomy, the patient is placed in a supine position. A total of 5 ports are placed; one for the camera, in the periumbilical region, one on the left axillary line on the upper abdomen, one on the right axillary line on the upper abdomen, one along the right midclavicular line and the last between the previous one and the camera port for the first assistant. Then the patient is placed in a reverse Trendelenburg position. This technical aspect is proposed by Bonapasta et al. [25]. Others place the last port in the lower left quadrant [6].

It is currently accepted that the most difficult part of the D2 lymph node resection is around the major vessels, the hepatic, celiac and splenic. The robotic
surgery provides an advantage on the surgical handling of tissues as well as in the management of bleeding from the vessels, especially around the ones mentions above, where the field of view is limited and the possibility of tissue injury is high.

Short-term outcomes

One of the largest series [9] of patients comparing open with robotic gastrectomy (39 robotic versus 586 open) states that the robotic gastrectomy is superior to open as far as the blood loss and hospitalization time are concerned, but inferior to the operation time.

There is currently only one randomized control trial on robotic-assisted gastrectomy with D2 lymphadenectomy that record the short-term outcomes and the safety of the procedure, compared to the open technique, but do not provide data on the long-term outcomes (Table 2).

Long-term outcomes

A study by Guzman et al. suggests that the robotic assisted surgery is comparable to the open one concerning the number of lymph nodes resected in D2 lymphadenectomies [26]. The same result was found by Huang et al. [9], who also noted no

significant difference in the postoperative morbidity rate between the two techniques.

Most of the studies published state that the resected specimen has free resection margins in all cases after robotic surgery. This comes in line with a careful selection of patients and a meticulous preoperative staging and tumor marking [10].

Laparoscopic surgery versus robotic surgery

Technical aspects

The theoretical advantages of the robotic gastrectomy compared to the laparoscopic procedure are the improved ergonomics for the surgeon, the optimized view by the three dimensional aspect that can be provided by the robotic panel, the minimization of tremor and the increased degrees of freedom provided by the instruments. It is also stated that the learning curve of the procedure when it is robotic assisted is steeper [12]. On the contrast, major disadvantages are stated; the overall cost, the restricted field of view and the prolonged operating time.

Furthermore, in robotic assisted total gastrectomy, the restoration of the alimentary tract continuity can be easily performed with intraperitoneal suture anastomosis minimizing the technical complications of the laparoscopic procedure. In laparoscopy, the performance of a handsewn anastomosis is also feasible but far more technically demanding than in robotic assisted technique.

Thereafter, the use of a circular or end-to-end stapler or even a hybrid open technique is proposed to facilitate the performance of the anastomosis [10]. The robotic sewn technique, where the anastomosis is performed by single intracorporeal sutures, is a promising alternative to other techniques, providing a result comparable to open surgery handsewn anastomosis and minimizing the possible complications [10].

Short-term outcomes

One of the first series of patients published concerning robotic assisted gastrectomy, including 100 patients with D1+ and D2 lymph node resection, states similar short-term outcomes (feeding time, bowel movement and length of hospitalization) to laparoscopic gastrectomy [27].

These studies confirm that the short-term outcomes of robotic-assisted techniques are better than the ones of open and laparoscopic procedures. Shorter hospital stay and less blood loss are the main advantages, all against to longer operating times.

There is none randomized control trial comparing the robotic technique to the laparoscopic technique up to the date that this article was written.

Long-term outcomes

It is not well known up to now whether the robotic procedure can indeed provide a better oncologic outcome.

Current data suggests that the robotic surgery is superior to the laparoscopic as far as the number of lymph nodes resected is concerned in a D2 lymphadenectomy. This may be the case since the second tier lymph node stations are better exposed in the operation field provided by the robotic camera [9]. Other non-randomized control trials suggest that the number of lymph nodes between the two groups is not statistically significant [5]. A recent retrospective comparative single-institutional study from Italy reports a higher number of lymph nodes dissected in D2 lymphadenectomy in the robotic technique compared to the laparoscopic technique [6].

One of the few studies that report the long-term survival of patients, states that patients after D2 lymphadenectomy had 97% 5-year survival rate for early and 67% for advanced stage gastric cancer, similar to the survival rates after open or laparoscopic procedures [28]. A recent comparative study states that the postoperative complications and the disease-free survival are comparable between laparoscopic and robotic total D2 gastrectomy. The total number of lymph nodes resected did not have any statistical difference. However, in technical challenging areas, such as along the splenic artery, the number of lymph nodes resected was significantly higher in the robotic assisted group [29].

Discussion

Up to recently, there has been a prolonged debate on the need of D2 lymph node resection on curable gastric cancer. D2 lymphadenectomy includes all lymph nodes on D1 level (the greater and lesser omental lymph nodes, which are the right and left cardiac lymph nodes, along lesser and greater curvature, and suprapyloric along the right gastric artery and infra-pyloric area) plus the removal of all the nodes along the left gastric artery, common hepatic artery, celiac artery, splenic hilum, and splenic artery. This requires a significant degree of training and expertise. There has been an assumption that the high level of lymphadenectomy may provide better staging and higher survival rate but creates a higher perioperative risk. Currently, D2 gastrectomy is a standard therapy in the East, and

a strongly recommended one in the West. This is the result of many studies that proved the perioperative mortality rate did not increase in the hands of experienced surgeons and indeed the long-term survival of patients is better than those who underwent D1 resection for advanced gastric cancer. This also depicts in the current NCCN guidelines. Summarizing this debate, D2 lymphadenectomy is a risk worth taken in improving the survival of patients [30].

Laparoscopic gastrectomy has been an established procedure for the past 20 years. It has been rapidly evolved since the first laparoscopic assisted gastrectomy in 1994 and nowadays it provides a non-inferior oncologic outcome, but with superior short-term outcomes. Despite that, there are certain limitations in that procedure, such as the technical difficulty of D2 lymphadenectomy, that the robotic assisted surgery comes to expand. The possible advantages of robotic surgery seem to be endless; but it is yet to be confirmed whether all these come true to advancing minimally invasive gastrectomies one step further. The current review comes to compare open, laparoscopic, and robotic D2 gastrectomies as far as technical aspects, short-term and long-term outcomes are concerned.

Technically speaking, the major aspect to be carefully considered is the creation of the anastomosis. In a laparoscopic gastrectomy, the anastomosis can be done via a stapler or a semi-open procedure, where the two ends are pulled through a mini incision extracorporeal and are hand-sutured or stapled, like in an open procedure. The robotic procedure provides an extra option; intracorporeal hand-suture, in the expense of prolonged surgical time. Anastomosis is a crucial part of the procedure, since a possible leakage may lead to increased postoperative morbidity, leading to extended hospital stay. A recent prospective study reports that the anastomotic leaks are statistically more common to laparoscopic and robotic procedures compared to open, but without statistical difference in related deaths and reoperation between these [31].

Another important aspect between the three techniques is the cost. Apparently, the robotic gastrectomy is a highly costly operation, exceeding the same procedure done laparoscopically by almost twice the amount, as many studies state [32], without even considering the original acquiring cost of the robot. The point that should be noted and further investigated though is the reduction of the indirect costs (hospital stay, return to work) that are associated with the better short-term outcomes that minimally invasive surgery provides.

Furthermore, a technical point mentioned in the robotic assisted gastrectomy is the advantage of a three-dimensional view but with a small field of vision. This is obviously proposed as an advantage since it is compared to a standard two-dimensional view that the laparoscopic technique provides. There is currently no study that compares the visualization that the robot provides to the visualization that the newer three-dimensional laparoscopic towers can depict. This could be an excellent alternative with significantly fewer costs compared to the robotic surgical systems.

As far as the short-term outcomes are concerned, both laparoscopic and robotic procedures tend to outweigh the open gastrectomy. Postoperative pain, first time to passing flutus, feeding time and hospital stay are superior in the minimally invasive techniques. Intraoperative parameters and especially blood loss is a major advantage [7]. The main disadvantage remains the longer operating time, as laparoscopic being a longer procedure than open and robotic being even more prolonged than laparoscopic. For the latter, the main reason is the time for setup and docking the robotic arms.

Complication rates are low in any type of gastrectomy; wound complications, bleeding events, pancreatitis, ileus, delayed gastric emptying and anastomotic stricture [33].

The long-term outcomes are still uncertain and need further research. All preliminary results state that the 5-year survival rate in patients treated laparoscopically is comparable to those of open procedures. Even in advanced cancer patients, a large scale study with 1485 patients who underwent laparoscopic gastrectomy proved that the 5-year survival rate was similar to open procedure [22]. In early cancer patients, the survival rate is considered high and comparable between these two surgical options. Very few studies currently state the long-term survival of patients who underwent robotic assisted gastrectomy, possibly due to the fact that this is a rather new modality and more time is needed for the safe extraction of results.

In addition, an interesting point that can be noted is that minimally invasive gastrectomy with D2 lymphadenectomy seems an attractive preventive surgery in patients with CDH1 mutations which lead to hereditary diffuse gastric cancer [34].

Concluding, the minimally invasive techniques for treating gastric cancer seem to be rather promising, rapidly improving the short-and long-term outcomes of patients with early and advanced gastric cancer. Technical aspects are more challenging in laparoscopic and robotic gastrectomy, but this seem to be related with the surgeon's expertise and experience [35]. There is a need for further well-designed randomized control trials with large

sample size comparing the laparoscopic and robotic procedure to the open, especially on the long-term outcomes of patients.

Authors' contributions

EK: review design, review supervision, data collection, analysis, interpretation, introduction, review, and discussion sections, and critical revision for important intellectual content. MP: data collection, introduction, review, and discussion sections. DT: data collection, analysis, introduction and discussion sections.

Conflict of interests

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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