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International Journal of Surgery

journal homepage: www.journal-surgery.net

Review

Laparoscopic gastrectomy for gastric cancer: Current evidences



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H I G H L I G H T S

- The laparoscopic approach for gastric cancer is a topic that remains controversial.
- This article provides the current knowledge of laparoscopic treatment for gastric cancer patients.
- Laparoscopic gastrectomy represents a demanding surgical procedure. However, the benefits of this approach are out of question.
- Laparoscopic gastric cancer approach provides an oncologic validity and safety for early gastric cancer patients.
- The near future will tell us if such demanding laparoscopic procedures will be translated into real survival benefit.

A R T I C L E I N F O

Article history:

Received 26 July 2014

Received in revised form

25 September 2014

Accepted 16 October 2014

Available online 31 October 2014

Keywords:

Gastric cancer

Minimally invasive surgery

Laparoscopic surgery

Laparoscopic gastrectomy

Survival

Prognosis

Curative gastrectomy

A B S T R A C T

Nowadays, our understanding of gastric cancer has been improved. The major hope is to increase the survival rates of this aggressive, enigmatic and heterogeneous disease, especially in Western population. Over the past decades, conventional surgery has been the cornerstone of treatment for non metastatic gastric cancer patients. Adequate gastrectomy is recommended for at least T2–4a tumors, while T4b tumors require resection of involved structures. However, in the era of advanced technology, minimally invasive surgical approaches are in the top of the scientific interest. Notably, the laparoscopic approach for gastric cancer is a topic that remain controversial. In this review, we summarize the standard of care according to the current evidences and we provide the latest scientific information assessing safety and efficacy of laparoscopic gastrectomy for gastric cancer.

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1. Introduction

Although the incidence of gastric cancer has been decreased over the past decades, and although the oncologic treatment of gastric cancer has dramatically changed during the last years, mainly due to the advances of chemotherapy, it continues to be a major health problem. Gastric cancer is the fourth most common malignancy and the second cause of death among all cancers [1,2]. There is no doubt that it is an aggressive disease with poor prognosis, that accounts for 800.000–1.000.000 cancer deaths each

year [2,3]. Its prevalence shows wide variability throughout the world. South Korea and Japan are reported to have the highest incidence as well. In China, gastric carcinoma is one of the most common malignant tumors, while Europe and America are considered regions with intermediate incidence. Recent evidences estimate that the 5-year survival rate of gastric cancer in Western countries is 40%, with a median survival time of about 24 months [4]. Interestingly, the 5-year survival rate in Eastern countries is approximately 52%, which is attributed to earlier disease diagnosis after screening programs and more aggressive surgical treatment [5].

It is widely accepted that radical surgery is the cornerstone of therapy in gastric cancer patients; this entails an appropriate gastrectomy with an adequate lymph node dissection. Although nodal status is one of the most critical independent predictors of patient survival after gastrectomy, the extent of lymph node dissection is

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worldwide a matter of debate [6]. For Japanese surgeons, D2 lymphadenectomy in patients with gastric cancer is the gold standard of care from many years, while many Western surgeons nowadays still perform a limited (D1) lymphadenectomy for gastric cancer [7]. Notably, in Western countries and in USA, D2 lymphadenectomy only recently became a recommended surgical option, specifically after the simplification of nodal dissection by the latest Japanese guidelines [7–9]. Over the past years, open surgery has been the standard treatment with much more different comparisons between East and West in terms of survival.

However, in the era of minimally invasive techniques, laparoscopic gastrectomy represents the most promising approach for improving at least short-term quality of life of gastric cancer patients [10,11]. With this article we provide the current knowledge, in terms of feasibility, safety and oncologic efficiency of laparoscopic treatment for patients with gastric cancer at an early and at an advanced stage, with an effort to clarify for whom and when the laparoscopic gastrectomy could be considered a valuable surgical option.

2. Laparoscopic surgery

The last decade surgery has been revolutionized by a continuous effort toward technical and technological research. All these scientific attempts are undoubtedly patient-tailored. What is more, minimally invasive approaches and techniques represent an exciting solution because they are contributing to improve patient's quality of life [12]. However, there is the need of high-quality evidence for the enrollment of new technology and minimally invasive surgical techniques into healthcare system. In this period of economic crisis, more than ever, assessing safety, oncologic efficiency and cost-effectiveness analysis are mandatory [13–15].

Our generation is seeing laparoscopic surgery in the multimodal treatment of solid tumors to expand in clinical practice [14,15]. Nowadays, strong evidences for laparoscopic gastrointestinal cancer resections has only emerged for colon cancer. Current evidences from well conducted randomized controlled trials (RCTs) support the similar safety and efficiency regarding oncological outcomes and the better quality of life for laparoscopic colectomy, compared with open colectomy, for patients with stages I–III colon cancer [15,16].

3. Laparoscopic surgery for gastric cancer

It is widely known that the first early distal gastric cancer series treated by laparoscopic-assisted gastrectomy (LAG) was described by Kitano et al., in 1991 [17]. After this report, the procedure has rapidly achieved popularity in Eastern countries.

It is out of question that laparoscopic gastrectomy represents a demanding surgical procedure. Experts believe that it is very difficult to perform a subtotal and much more a total gastrectomy in a laparoscopic way, especially in patients with high body mass index (BMI) and cardiovascular or respiratory comorbidities [18,19]. Moreover, it is very difficult to perform laparoscopic lymphadenectomy and really experienced hands are needed for this purpose. As for the alimentary reconstruction after a laparoscopic gastrectomy, the grade of difficulty raises from the Billroth I approach to Billroth II approach and to the gastro-jejunostomy according to the Roux en Y approach [18,20]. Although these difficulties, in order to additionally reduce the invasiveness, an effort is made by advanced laparoscopic surgeons, to reduce more the length of the surgical incisions [21].

Although there are many difficulties, most of the researchers agree that the benefits of the laparoscopic approach are out of question. Indeed, decreased pain, reduced cosmetic disfigurement,

shorter length of hospital stay, less postoperative pain and short term outcomes with better quality of life are some of the expected benefits for the patients treated via laparoscopic gastrectomy. Although these benefits, the therapeutic effects in gastric adenocarcinoma in terms of surgical safety, oncological efficacy and long term outcomes still remain unclear [12].

Indeed, laparoscopic approach for gastric cancer patients is widely routinely used by Japanese experienced surgeons. Differently, laparoscopic gastrectomy is performed only in some high volume centers in Western countries [22]. However, many controversies and doubts still exist due to no prospective large clinical studies to evaluate and describe the rates of overall survival and the rates of disease free survival of patients with gastric cancer treated with laparoscopic gastrectomy, especially in Western countries. On the other hand, more and more controversy exist for patients treated via total laparoscopic gastrectomy for cancer that constitutes a very demanding and long lasting surgical procedure [23].

As for the current guidelines for laparoscopic treatment and gastric cancer, we have to highlight that there is not exist an unanimous consensus. The main recommendation is that laparoscopic approach should be used only for early gastric cancer and only by experienced surgeons already highly skilled in gastric surgery [24,25].

3.1. Current evidence on laparoscopic gastrectomy for cancer

Nowadays, not only the surgical techniques and procedures in laparoscopic gastrectomy are improving but also the attempt of adequate lymph node dissection is implementing. Furthermore, the last two years the East surgeons have dealt with advanced and demanding procedures including total gastrectomy and extended lymph node dissection. Recently, some prospective well-conducted trials have been conducted in Japan and Korea in order to evaluate the safety and oncological feasibility of laparoscopic gastrectomy for early or advanced gastric cancer [26–28].

Up to date, there are published several randomized-controlled trials and metaanalysis that have robustly confirmed that laparoscopic gastrectomy is safe, feasible, with efficient oncologic outcomes and better short-term outcomes than those of open gastrectomy in patients with early gastric cancer [29,30]. The latest metaanalysis on this issue was offered by Zhang CD [31]. Pubmed, Embase, CINAHL, AMED, the Cochrane controlled Trials Register and the China National Knowledge electronic databases were systematically evaluated between 1992 and 2012. Operative time, incision length, blood loss, number of lymph nodes dissected, time to flatus, time to first oral time assumption, use of analgesics, complications, length of postoperative stay, recurrence, and mortality were the examined parameters. An amount of 1665 patients were enrolled from five RCTs and 11 case controls studies. Nine hundred patients with early gastric cancer were treated with laparoscopic gastrectomy, while 746 patients were treated with open gastrectomy. The results were amazing in favor of laparoscopic gastrectomy for early gastric cancer in eastern patients. Indeed, laparoscopic gastrectomy was associated with less trauma (incision length: weighted mean differences (WMDs) –12.91 cm; $P < 0.00001$), less blood loss (WMD –121.04 mL, $P < 0.00001$), less postoperative pain (number of times to use analgesics: WMD –1.64; $P = 0.001$), faster bowel recovery (time to flatus: WMD –0.62 d; $P = 0.0001$), fewer complications (OR 0.57; $P = 0.01$) and shorter period of postoperative stay (WMD –3.73 d; $P = 0.0007$). On the other hand, although it was not statistically significant, laparoscopic gastrectomy was associated with longer operative time and minor number of total dissected lymph nodes (WMD –3.43 lymph nodes; $P = 0.04$). No difference in recurrence rate (OR 0.58; $P = 0.33$) and mortality rate was observed

between groups [31]. What is more, Vinuela EF. et al. and Sun J. et al. [32,33] reported recently the advances of laparoscopic gastrectomy versus open gastrectomy for patients with early gastric cancer. We have to highlight that all these data should be carefully validated and analyzed from a critical point of view also in Western patients with well conducted prospective trials, but early gastric cancer in these countries is a rare occasional finding. Actually, it is known that most gastric cancer patients in West are diagnosed at an advanced stage.

As for advanced gastric cancer, a prospective randomized controlled multicenter trial in order to evaluate the safety and feasibility of laparoscopic-assisted D2 gastrectomy for advanced gastric cancer was conducted by Nam BH. et al. and was published recently [34]. This study enrolled patients with distal gastrectomy for advanced gastric cancer staged by endoscopy and computed tomography. Patients were randomized in two groups, either to laparoscopic distal gastrectomy group or open distal gastrectomy group. The statistical analyses with power sample size calculation showed that 102 patients were enough to be included in the two groups. This trial had as primary end point the non-compliance rate of D2 dissection. As for the secondary endpoints were the 3-year disease free survival, surgical and postoperative complications, hospital stay and rate of D2 dissection evaluated by the intra-operative video documentation. The main topic for laparoscopic distal gastrectomy treatment of advanced gastric cancer is the oncologic safety. Therefore, the non-compliance rate of clearing the defined N2 area was selected by the authors as the most important factor for the technical feasibility of the laparoscopic procedure-approach. This study is underway and the first results will offer promising and exciting evidence of the oncologic feasibility and safety of laparoscopic-assisted distal gastrectomy for patients with advanced gastric cancer, which is the main matter of debate today in Eastern patients [34].

Recently, another meta-analysis by Choi Y.Y et al. was published regarding laparoscopic gastrectomy and its oncologic safety and efficacy in patients with advanced gastric cancer [35]. The main end point of this meta-analysis was to compare laparoscopic gastrectomy and open gastrectomy in terms of long-term outcomes in patients with advanced gastric cancer. The authors selected studies from three major databases, PubMed, Embase, and the Cochrane Central, and the search was performed using keywords related to advanced gastric cancer and laparoscopic approach until July 31, 2012. Specifically, ten studies (one RCT and nine retrospective studies) with a total of 1.816 patients were included in this large meta-analysis; there were 859 patients were treated with laparoscopic gastrectomy for advanced gastric cancer, while 960 patients were treated via open gastrectomy for the same reason. Nine studies compared the overall survival rate between laparoscopic gastrectomy and open gastrectomy for advanced gastric cancer, and five studies reported the disease-free survival rates. The authors concluded that there was no statistical difference in the overall survival (hazard ratio [HR]: 0.90, 95% confidence interval [CI]: 0.76–1.06, $P = 0.22$) and in the disease-free survival (HR: 1.03, 95% CI: 0.76–1.40, $P = 0.86$) between the two groups of patients for advanced gastric cancer [35]. In the setting of laparoscopic approach and its oncologic efficacy for patients with advanced gastric cancer the most recent meta-analysis was conducted by Chen K. et al. [36]. A careful search was performed by the authors until June 2013 to identify all the comparative studies analyzing all survival rates, recurrence rates, surgical outcomes and surgical complications. In this meta-analysis a total of 15 trials (two RCTs and 13 observational studies) with a total of 2.519 patients were enrolled. Of these patients, 1327 underwent laparoscopic gastrectomy (52.7%) and 1192 underwent open gastrectomy (47.3%). The researchers reported that laparoscopic gastrectomy was

characterized by less blood loss [95% CI 174.57 to 103.44, $P < 0.001$], earlier time to first flatus [95% CI 1.14 to 0.44, $P < 0.001$], shorter length of postoperative hospital stay [95% CI 4.13 to 2.09, $P < 0.001$] and a decrease in complications [95% CI 0.61 to 0.90, $P = 0.003$]. The only drawback of laparoscopic gastrectomy compared to open surgery was the longer operative time involved [95% CI 34.09 to 63.26, $P < 0.001$]. We have to highlight that the main topic of this meta-analysis was that no significant difference in the number of total lymph nodes dissected, margin distance, mortality, cancer recurrence rate and long-term survival rate was observed between the patients with advanced gastric cancer treated with laparoscopic or open gastrectomy as well ($P > 0.05$). The most important aspect to keep in mind is that although a longer operation is needed, laparoscopic gastrectomy is a safe and oncologically efficient approach for advanced gastric cancer with a lower complication rate and improved postoperative length of stay compared to open gastrectomy. In addition, similar rates in terms of cancer recurrence and long-term survival was observed for laparoscopic and open gastrectomy and this highlights the fact that laparoscopic gastrectomy is at least a safe patient-friendly method [37,38].

An original article on the issue of long term results after laparoscopic or open gastrectomy for advanced resectable gastric cancer is provided by Kim et al. [39]. In this study, that is the largest original trial published up to date, ten experienced surgeons from multiple high-volume centers performing at least 80 gastrectomies annually were enrolled. The authors report that in total, approximately 1.500 laparoscopic and 1.500 open gastrectomies over a period of seven years, were performed for about 3.000 patients. The authors analyzed 5-year survival rates, morbidity, mortality, and learning curve for laparoscopic gastrectomy. They report [39,40] that overall survival, disease-specific survival, and recurrence-free survival were no significantly different among groups. A better overall survival rate in the laparoscopic group was observed only for patients with disease stage IA. There was no significant difference in morbidity or mortality and the mean number of required learning curve was 42 patients [40]. Interesting issues are raised by this work, but also more and more questions. These valuable results can be reproduced in a safe way for Western patients? It is widely known that there has been a long matter of debate and is still ongoing that gastric cancer is 'different' in the East and the West. Various studies report that cancer-related survival is better in Japan and South Korea, and various reasons have been discussed. Maybe the explanation key is the different genetic background among East and West population [41–43].

As for total gastrectomy the criticism and skepticism for laparoscopic gastrectomy is much more exciting. A very recent meta-analysis conducted by Chen K. et al. [44] included nine comparative observational studies. RCTs were not included in this meta-analysis. A total of 1221 patients were enrolled; 436 patients were treated with laparoscopic assisted total gastrectomy and 785 patients were treated with open total gastrectomy. The results for the patients enrolled in the group of laparoscopic total gastrectomy were characterized by a longer operating time [95% CI: 30.48–84.88; $P < 0.001$], less blood loss [95% CI: 2.48 – 0.49; $P < 0.001$], earlier time to flatus [95%CI: –1.22 –0.30; $P < 0.001$], shorter hospital stay (95%CI:3.96 – 1.38, $P < 0.001$) and a decrease in medical complications (95%CI:0.19–0.90, $P = 0.03$). Moreover, the researchers concluded that the total number of lymph nodes dissected, mortality, surgical complications, recurrence rate and long-term survival rate of patients between the open and laparoscopic group were similar [45]. From this further representative meta-analysis, we can deduct that despite a longer operation, laparoscopic assisted total gastrectomy can be performed safely in high volume surgical centers, but are needed well-conducted

prospective, multicentric, clinical trials in order to be able to draw safe conclusions [46–49].

4. Conclusions-future perspectives

In conclusion, we have to highlight the fact that as laparoscopic experience has been accumulated between surgeons of the eastern countries, the indications for laparoscopic approaches have included also more 'difficult' and demanding cases with advanced gastric cancer patients. On the other hand, in Western countries laparoscopic gastrectomy is in the very beginning stage and when performed is performed for early gastric cancers. But the early gastric cancers in Western countries is a very rare event. As it is known, more than 90% of gastric cancers in the West are diagnosed at an advanced stage.

The 'established' knowledge up to date is that laparoscopic approach for gastric cancer provides an oncologic validity and safety for patients with early gastric cancer in experienced hands and in high volume centers, while for advanced gastric cancer more prospective trials are needed. The most important aspect to keep in mind is that laparoscopic gastrectomy constitutes a demanding operation and for the achievement of valuable long-term results a real learning curve requires hard training. Given the low quality of some studies considered in the metaanalyses, the near future with well-conducted prospective multicenter trials also from Western countries will tell us if such advanced-demanding laparoscopic procedures will be translated into real survival benefit for gastric cancer patients. It seems that new horizons are ahead for laparoscopic surgery as the current clinical evidence revealed that the laparoscopic gastrectomy performed by 'experienced hands' is not inferior to open gastrectomy for early gastric cancer and for advanced gastric cancer in eastern populations.

Ethical approval

None.

Sources of funding

None.

Author contribution

Georgios D. Lianos, Stefano Rausei, Laura Ruspi, Federica Galli, Alberto Mangano: study design, writing.

Dimitrios H. Roukos, Gianlorenzo Dionigi, Luigi Boni: writing, final approval of the manuscript.

Conflicts of interest

None.

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