Mid- and Long-Term Outcomes of Totally Laparoscopic Gastrectomy for Gastric Cancer. Prospective Study

Juan Carlos Martín del Olmo (jcmlolmo@gmail.com)
Medina del Campo Hospital

Juan Ramón Gómez López
Medina del Campo Hospital

Cristina López Mestanza
Hospital Virgen de la Concha

Pilar Concejo Cutolí
Medina del Campo Hospital

María Luz Martín Esteban
Medina del Campo Hospital

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Abstract

Purpose. The laparoscopic approach for gastric carcinoma (GC) is being increasingly implemented. Although recent evidence suggests that this surgical approach is associated with improvements in short-term outcomes, mid- and long-term outcomes have not been well studied. This study aimed to evaluate the mid- and long-term outcomes of laparoscopic gastrectomy (LG) with D1-D2 lymph node dissection for all stages of GC.

Methods. A prospective study of GC treated by laparoscopic approach between January 2004 and December 2019 was performed. The demographics, perioperative data, operation details, length of hospital stay, morbidity, mortality and pathologic and oncological outcomes were analyzed.

Results. A total of 70 patients met the inclusion criteria. The median age was 73 years old. Subtotal gastrectomy was performed in 52 cases (74.3%), and total gastrectomy was performed in 18 cases (25.7%). The median operative time was 270 minutes. The median postoperative stay was 10 days. Morbidity was 35.7%, with a mortality of 7.1%. The disease-free survival (DFS) was 61.2% at three years and 52.3% at five years.

Conclusions: LG is a feasible and secure surgical procedure for GC with good mid- and long-term results. Advanced age should not be considered a contraindication for LG.

Introduction

Although there is a global decrease in its incidence, gastric carcinoma (GC) is the fifth most common cancer and the third most common cause of cancer-related mortality worldwide [1, 2, 3]. Gastrectomy with adequate lymph node dissection, in combination with neoadjuvant or adjuvant therapies, remains the most effective treatment for nonmetastatic gastric cancer [4, 5, 6].

Currently, there are two surgical options for potentially curable patients: laparoscopic gastrectomy (LG) and open gastrectomy (OG). However, it is still not clear whether one of these options is superior [2].

The first LG was performed by Kitano [7] in 1994. Since then, laparoscopic gastric surgery has rapidly spread in Asia, but in Western countries, its development has been slower than laparoscopic colorectal surgery [8, 9]. Demographic and technical reasons can explain this situation. First, patients’ profiles are quite different, with a globally lower number but more advanced cases in Western countries and frequently with a higher prevalence of patients with high body mass index (BMI). These factors make the procedure technically more demanding with a longer learning curve for a limited total number of cases. Nonetheless, this approach is gaining acceptance in these countries, and successive series including all TNM stages have been reported [6, 9, 10].

In general, the data reported show that LG for GC is associated with better early postoperative outcomes than open surgery [4, 11]. The operative procedure for laparoscopic subtotal gastrectomy (LSG) with D1-
D2 lymph node dissection is relatively well standardized, and its surgical and oncological results have been supported in different studies [1, 12, 13]. Laparoscopic total gastrectomy (LTG) is still considered a more demanding surgical procedure, especially due to extended lymphadenectomy, esophagojejunal anastomosis and its related postoperative complications [11, 14]. Recent studies have shown that the minimally invasive surgical approach (MIS) to GC is feasible and safe [4, 15]. However, there are still discrepancies regarding the suitability of the procedure for all stages of the disease, mainly with regard to long-term outcomes [16, 17]. In addition, there is controversy regarding the application of surgically aggressive procedures, such as total gastrectomy with extended lymphadenectomy, in aged patients who often have high rates of comorbidities, a situation that may compromise the short- and long-term results, with a possible increase in the incidence of postoperative complications and the mortality rate [18, 19].

The aim of this study was to evaluate the mid- and long-term outcomes of LG with D1-D2 lymph node dissection for all stages of GC.

**Material And Methods**

This is a single-center prospective study. All gastric adenocarcinoma patients operated on between January 2004 and December 2019 who underwent laparoscopic resection with D1-D2 lymphadenectomy were considered.

The exclusion criteria were patients who were lost to follow-up, were unfit for surgery, underwent palliative surgery or had T4b lesions or gastric neoplasms other than adenocarcinoma.

The preoperative evaluation included laboratory tests, upper digestive endoscopy with biopsy, computed tomography scans (chest, abdomen, and pelvis), and endoscopic ultrasound in selected cases. Since 2015, all cases of T≥ 2 and any N≥ 1 have been recommended to undergo neoadjuvant therapy. The extension of gastric resection and lymphadenectomy was determined by tumor location to obtain free margins. Informed consent was obtained from all patients.

The TNM protocol of the College of American Pathologists was used for staging [20]. In the preoperative workup, the patients were classified according to the American Anesthesiology Association (ASA) [21]. Perioperative and postoperative complications were classified according to the Clavien-Dindo system [22]. The operative procedure for LG and D1-D2 lymph node dissection was performed in the same way as that previously reported [1].

Gastrojejunostomy was performed in a side-by-side fashion with a linear stapler, and esophagojejunal anastomosis was conducted with a circular stapler in most cases and, occasionally, a hand-sewn anastomosis was performed. The specimens were retrieved with a specimen retrieval bag through an assistance incision, usually the Pfannenstiel incision, covered by a wound protector.

Surgical mortality was considered when death occurred up to 30 days after surgery or during the hospital stay. Length of hospital stay, age, sex, comorbidities, extent of surgery, pTNM stage, and disease-free
survival (DFS) were analyzed. The patients were followed-up at one, three and six months after surgery and every 6 months later until the fifth year, then once a year.

Statistical analyses were performed using SPSS, ver. 25.0 (SPSS Inc., Chicago IL, USA). The demographics, perioperative data, operation details, length of hospital stay, morbidity, mortality and pathologic and oncological outcomes are expressed as numbers and percentages for qualitative variables and medians and interquartile ranges (IQRs) for quantitative variables. Factors associated with recurrence risk at 12, 36 and 60 months were evaluated using univariate and multivariate Cox regression analyses. Variables with $P < 0.1$ in the univariate analysis were further introduced into the multivariate analysis using the Wald selection method. TNM stage was analyzed for its impact on DFS using the Kaplan-Meier method and the log-rank test at 12, 36 and 60 months.

To determine the risk factors for the development of serious morbidity (Clavien-Dindo $\geq$ III), we first performed univariate and multivariate logistic regression analyses. Again, variables with $P < 0.1$ in the univariate analysis were further introduced into the multivariate analysis with the Wald selection method. P values $< 0.05$ were considered statistically significant.

This study involved the use of data from clinical records. To guarantee the proper handling of the information, the data were treated confidentially and anonymously according to the provisions of the Spanish Organic Law 15/1999, of 13 December 1999, on Personal Data Protection (LOPD). All methods were performed in accordance with the guidelines and regulations established by the Declaration of Helsinki (1964, revised in 1983) on biomedical research in humans, the Spanish Royal Decree 1090/2015, of December 4, which regulates clinical trials with drugs, the Research Ethics Committees with drugs and the Spanish Registry of Clinical Studies.

The present study is a clinical trial that was approved by Ethics Committee of Valladolid University (reference number PI 20-1964).

Results

The patient characteristics are summarized in Table 1. A total of 70 patients met the inclusion criteria. The median age was 73 years (65.8-78.0), with male predominance (51.4%). Preoperative comorbidities were present in 93% of the patients (47.1% were classified as ASA II and 44.3% as ASA III). A total of 24.3% of the patients had a history of previous abdominal surgery. Regarding lesion location, 36 lesions were located in the antrum (51.4%), 28 in the body (40%), and the remaining 6 (8.6%) in the 1/3 proximal stomach.

Nine patients (12.8%) underwent neoadjuvant treatment. Subtotal gastrectomy was performed in 52 patients (74.3%), and total gastrectomy was performed in 18 (25.7%). All patients underwent D1-D2 lymphadenectomy, which was determined by the extent of gastrectomy. The reconstruction technique was performed in an intracorporeal manner by Billroth II (32.9%) and mainly by Roux-en-Y (67.1%).
Conversion to open surgery was performed in 4 cases (5.7%), in three due to the presence of severe adherences of previous abdominal surgery and in the other due to intraperitoneal bleeding.

The median operative time was 270 minutes (IQR: 230-300). Postoperative adjuvant therapy was administered to 56 patients (80%). T3 (31.4%) lesions were predominant, and the incidence of T4 lesions was 22.9%. Regarding stage, IIB was the most frequent (21.4%) (Table 2). Lymph node metastasis was present in 51.4%. The median length of hospital stay was 10 days (IQR: 7.8-17.3). Major postoperative complications (Clavien-Dindo classification grade ≥ III) were observed in 23 (32.8%) patients (Table 2). The multivariate analysis identified the coexistence of cardiopathy (odds ratio (OR) 4.4, p=0.038) and the presence of anemia (OR 4.6, p=0.040) at the time of diagnosis, and lymph node metastasis in the preoperative evaluation (OR 9.8, p=0.008), as independent prognostic factors for serious morbidity. Regarding the cause of complications, six cases were related to reconstruction problems: four were related to anastomosis leakage, and two were related to duodenal stump dehiscence. Minor complications (Clavien-Dindo grades I and II) occurred in 27.1% (19 patients). Morbidity was higher in the LTG group than in the LSG group (61% vs 47.1%). The surgical mortality was 7.1% (5 patients: 1 LTG and 4 LSG).

With a median follow-up of 34 months, the local recurrence rate was 12.5%, and the metastatic recurrence rate was 15.7%. Four cases presented both types of recurrence.

Ninety percent (63 patients) of our cohort was followed up for one year, and the DFS rate was 86.2%. Eighty percent (56 patients) of the cohort was followed up for three years, and the DFS rate was 61.2%. Finally, 70% (49 patients) of the cohort was followed up for five years, and the DFS rate was 52.3%. Twenty-five (35.7%) patients died during follow-up, and seven of the deaths were from unrelated pathologies (25.9%).

Multivariate Cox regression analysis identified present tumoral mass at diagnosis (HR 13.1, p=0.007), CEA level (HR 1.1, p<0.001) and median positive lymph nodes (HR 1.1, p=0.001) as independent prognostic factors for decreased DFS at 12 months. Moreover, CEA level (HR 1.1, p=0.005) and median positive lymph nodes (HR 1.1, p<0.001) were independent prognostic factors for decreased DFS at 36 months. Finally, CEA level (HR 1.1, p=0.039), T4 (HR 4.5, p=0.012) and stage IIIB (HR 17.4, p=0.035) were independent prognostic factors for decreased DFS at 60 months. The Kaplan-Meier curves showed that advanced TNM stages translated into shorter DFS times at 12, 36 and 60 months (Fig. 1).

**Discussion**

By definition, gastric cancer is a systemic disease [23] and requires a multidisciplinary approach [24]. Currently, gastrectomy with negative margins and adequate perigastric lymph node dissection is the basis of treatment for GC [4, 10]. Since the initial report of Kitano [7], the application of laparoscopy has allowed the implementation of the obvious advantages of minimally invasive access for GC surgery [2, 25, 26, 27]. Initially, LG was indicated for early distal gastric cancer [7], and progressively accumulated evidence has demonstrated the equivalence of laparoscopic distal gastrectomy and open surgery, with
several studies that confirmed satisfactory long-term outcomes [25, 26]. However, concerns about the oncological outcomes of LG have delayed its application in advanced gastric cancer, especially in Western countries [2, 10].

Nevertheless, in recent years, several prospective studies have demonstrated that the laparoscopic approach could be implemented in advanced gastric cancer with adequate oncological results [4, 15], but data about mid- and long-term outcomes and recurrence patterns are still scarce [4]. Furthermore, most of these studies come from Asia, with little data on the application of MIS in GC from the USA and European countries, and it seems evident that the patient populations differ with differing geographic areas. With the data registered in the IMIGASTRIC trial, Lin et al [8] found that in the Western cohort, the patients were more elderly, with higher BMI values and ASA scores, factors that can have an important influence on the immediate results of surgery, which was confirmed in our cohort.

Additionally, most of these studies were mainly based on early stages of the disease because they were based on a screening program for gastric cancer, which is not routinely implemented in Western countries.

Another factor to consider is that a selection bias in the cases treated could occur, mainly in comparative studies with open surgery, with a higher frequency of early stages in the laparoscopic arm [4, 6]. Moreover, many of the published series are based on mixed laparoscopic procedures (assisted) [4, 16, 27]. To avoid this issue, we opted for the total laparoscopic approach in all patients who met the inclusion criteria previously described so that this was a single-arm study.

The gradual aging of the population in different areas of the world implies that a larger number of elderly patients will require surgery for GC [28]. It is logical to speculate that the laparoscopic approach will allow the implementation of the advantages of MIS in this group of patients.

Although the incidence of GC is higher in these stages of life, most available studies include a wide range of ages, especially those from Asian countries, and few focus on the specific outcomes of aged patients. In this regard, Pan [28], in a study published in 2018, concluded that LG in elderly patients with GC obtained similar results to those observed in nonelderly patients, which was confirmed by other authors [19, 29, 30]. Our research, although with a limited number of cases but with more than 77% of patients over 75 years old, aims to confirm that the laparoscopic approach for GC is feasible and appropriate from an oncological point of view and that it is not conditioned by advanced age.

To assess the data of our study in the proper context, the first point to considerer involves the characteristics of the treated patients, which includes a population with a high average age (median 73 years) associated with a significant level of comorbidities (93%) when compared with other published data [4, 15, 29]. Clearly, these two factors are especially important in assessing the short-term outcomes of surgery.
The reported overall morbidity in aged patients who underwent open gastrectomy was 27.6%, with a mortality of 12% [31]. In regard to MIS, the morbidity associated with LG currently ranges from 6–25% [32]. Elderly patients had a higher risk of postoperative complications, mainly due to their comorbidity index and the decrease in functional reserve. A meta-analysis performed by Pan [28] including over 3275 patients treated with LG found that the morbidity in the elderly group ranged between 10% and 30%. We reported a morbidity (Clavien-Dindo grade ≥ III) of 32.8%, similar to the data of Yasukawa [30], who reported a morbidity of 44.6% in patients with a mean age of 76.6 years; however, these rates were higher than those reported by other authors [15, 33], although the mean age and the level of comorbidities of our cohort were higher. These findings partially confirm those reported by Jeong [11], who, in a retrospective study of more than 300 cases published in 2018, found that old age, male sex and number of comorbidities were associated with a higher incidence of postoperative complications. Moreover, as previously mentioned, our data show that anemia on admission, cardiopathy and lymph node metastasis in the preoperative workup were independent prognostic factors of major postoperative morbidity. For these reasons, we established a presurgical prehabilitation program to improve the baseline situation of patients. Another factor that can influence morbidity is the extent of surgery. In agreement with other authors [15], we found that the morbidity is higher in LTG than in LSG (61.1% vs 41.1%), and the more extended lymphadenectomy can partially justify these data.

Another concern is the possible negative effects of pneumoperitoneum on cardiorespiratory function during a time-demanding surgical procedure and its influence on the development of cardiorespiratory complications [11, 15, 34]. We usually maintain a 12 mm Hg pneumoperitoneum during surgery, and none of the patients in our cohort had severe cardiac or lung complications during the procedure.

LG is associated with a prolonged surgical time and has been reported to be related to an increase in surgical mortality [35]. We reported a median operative time of 270 minutes, which is approximate to that published by other authors [30, 33], and this number grows in parallel with the increase in the number of harvested lymph nodes (Fig. 2-3).

The surgical mortality associated with LG ranged between 0% and 7% [6, 19]. We reported a mortality of 7.1% (five cases: 7.8% in LSG and 5.6% in LTG). In agreement with previously reported data [4, 11], we found that these mortality rates, which were somewhat higher than those recorded by other authors, are associated with advanced stage (≥ III).

The mean length of hospital stay (10 days) is similar to the data reported by other authors [11, 33], and we believe this confirms that LG implements the benefits of MIS in GC surgery.

Regarding the conversion to open surgery, the rates were between 0% and 12% [11, 15, 24, 30]; we reported a rate of 5.7% (4 cases), mainly in patients with previous abdominal surgery and severe adhesions (3 cases). Approximately 25% of our patients had a history of previous abdominal surgery, and like other authors [23], we consider that this was not a contraindication for LG.
Regarding the medium- and long-term oncological results, only a few studies have reported the long-term outcomes of LG for GC, and they show similar rates to those recorded for open surgery [9, 6, 29, 36], but most of them included wide ranges of age and a predominance of early stages. The three-year overall survival (3y-OS) varies significantly in published series, ranging between 60% and 80%, with a five-year overall survival (5y-OS) of approximately 50% [9, 15, 16]. We reported a DFS rate of 86.2% at twelve months, 61.2% at three years and 52.3% at five years, which were consistent with the findings of previous reports [6, 9, 27, 33, 37], but inferior to the 73.5% 3y-OS reported by Nakauchi [15]. This discrepancy may be due to the differences in tumoral stage presented in both series (> IIB: 23.7% vs 51.4%). Similar to other reported data [4, 27], we found that large tumors, advanced T stage and lymph node metastasis are associated with decreased DFS. The cause of death in the majority of cases was tumor recurrence, with different presentation patterns, but in 25%, it was caused by unrelated illnesses associated with advanced age.

The limitations of our study include that it is a single-arm and single-center study with a limited number of patients. However, taking into account the relatively low incidence of GC in our area, we believe that it provides valid information on the MIS approach for this disease.

**Conclusions**

LG for gastric cancer could be performed in a secure way. The technique is feasible and associated with acceptable morbidity and mortality rates. Its oncological results in the medium and long term are similar to those reported for open surgery. Despite a higher risk of postoperative complications, advanced age should not be considered a contraindication for LG.

**Declarations**

**Author Contributions**

Dr. J. C. Martín-del Olmo: study conception and design; drafting of manuscript.

Dr. J. R. Gómez-López: acquisition data; critical revision of manuscript.

Dra. M. L. Martín-Esteban: acquisition data.

Dra. P. Concejo-Cutoli: acquisition data.

Dra. C. López-Mestanza: analysis and interpretation of data.

**Data availability statement:** The authors declare that the data recorded in this study correspond to reality and are accessible in the clinical records of our center. For additional information, contact with J.C. Martín del Olmo (jcmolmo@gmail.com).
Ethical approval from the Ethics Committee of Valladolid University was granted and the study protocol is registered in ClinicalTrials.gov with the identifier NCT04652986.

**Competing Interests Statement:** The authors have no relevant financial or non-financial interests to disclose.

**References**


Tables

Table 1, 2 is available in the Supplemental Files section.

Figures
Figure 1

Kaplan-Meyer curves of DFS for all stages.
Figure 2

Lymph node count according to case number.
Figure 3

Operative time according to case number.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.jpg
- Table2.jpg