# Laparoscopic subtotal gastrectomy for the treatment of advanced gastric cancer: a comparison with open procedure at the beginning of the learning curve

*Federico Marchesi[1], Giuseppina de Sario[1], Stefano Cecchini[1], Francesco Tartamella[1], Matteo Riccò[2], Andrea Romboli[1]*

[1] Dipartimento di Medicina e Chirurgia, sezione di Clinica Chirurgica Generale, Università degli studi di Parma, Parma, Italia;
[2] Azienda provinciale per i servizi sanitari della p.a di Trento, UOPSAL, Trento, Italia

**Summary.** *Background*: In the last decades, after some initial concern, laparoscopic subtotal gastrectomy (LSG) is gaining popularity also for the treatment of advanced gastric cancer (AGC). The aim of this study is to compare a single surgeon initial experience on LSG and open subtotal gastrectomy in terms of surgical safety and radicality, postoperative recovery and midterm oncological outcomes. *Methods*: a case control study was conducted matching the first 13 LSG for AGC with 13 open procedures performed by the same surgeon. Operative and pathological data, postoperative parameters and midterm oncological outcomes were analyzed. *Results:* There was no significant difference in mortality (0%) and morbidity, while the laparoscopic approach allowed lower analgesic consumption and faster bowel movement recovery. Operation time was significantly higher in LSG patients (301.5 vs 232 min, p: 0.023), with an evident learning curve effect. Both groups had a high rate of adequate lymph node harvest, but the number was significantly higher in LSG group (p: 0.033). No significant difference in survival was registered. Multivariate analysis identified age at diagnosis, diffuse-type tumor, pN and LODDS as independent predictors of worse prognosis. *Conclusions:* LSG can be safely performed for the treatment of AGC, allowing faster postoperative recovery. (www.actabiomedica.it)

**Key words:** gastric cancer, laparoscopic gastrectomy, survival, lymphadenectomy

## Introduction

In spite of its declining incidence in the last decades, gastric cancer still represents the second leading cause of cancer-related death in the world (1-3), owing to its poor prognosis (4, 5).

Even though recent progress in adjuvant therapies has led to improvement in the overall survival rate (6, 7) the only curative therapeutic option for gastric cancer is adequate surgical resection

The aim of surgical treatment is to remove the tumour along with the regional lymph nodes, by means of a total or subtotal gastrectomy, depending on tumour site, with an adequate lymphadenectomy (8). In recent years, a minimally invasive approach to gastric cancer has been widely developed mainly in Eastern countries (9). Laparoscopic (laparoscopically-assisted) gastrectomy (LG), since its first description by Kitano (10), has been increasingly adopted, becoming the intervention of choice in many Centres for the treatment of Early Gastric Cancer (ECG). Indeed, many studies have assessed an advantage of LG over open gastrectomy (OG) for EGC in terms of postoperative outcome parameters, with an equivalent rate of recur-

rences (11-14), while data on long-term oncological outcomes, still lacking, are being validated by ongoing phase III clinical trials (15). Despite an initial concern, due to technical and oncological issues, the laparoscopic approach is rapidly gaining popularity also in the treatment of advanced gastric cancer (AGC), but its use as gold standard procedure still needs thorough long-term evaluation (16). As to other types of procedures (17, 18), the potential benefits of the laparoscopic approach to gastric cancer should never be offset by reduced oncological radicality or surgical safety.

The aim of this study is to compare a single surgeon experience on LSG and OSG in terms of surgical safety and radicality, postoperative outcomes and midterm oncological outcomes.

## Methods

### Study Protocol

Starting from 2011 we prospectively enrolled a series of 13 consecutive patients submitted to laparoscopic subtotal gastrectomy (LSG) for AGC at our Institution. All the interventions were performed by a single surgeon (F.M.), experienced in oncological surgery, upper GI laparoscopic surgery and intracorporeal suturing (bariatric surgery), but at his first experience on LSG. Proximal localization of the tumor (requiring total gastrectomy), metastatic disease, neoadjuvant chemotherapy, previous major abdominal surgery or gastric surgery, ASA status >3 and urgency setting were set as exclusion criteria. A series of 13 consecutive patients, previously submitted to open subtotal gastrectomy (OSG) for AGC by the same surgeon, was used as the control group.

Preoperative workup included an endoscopy with biopsy and an abdominal and thoracic CT scan for all the patients. In case of suspected metastatic disease a positron emission tomography (PET) or magnetic resonance imaging (RMI) was added. All patients received IV antibiotic prophylaxis with 3 g of ampicillin/sulbactam and subcutaneous administration of low-weight heparin before surgery (dalteparin sodium 35 UI/kg). Symeticone (400 mg) was administered the day before surgery only to patients in the LSG group.

### Surgical procedure

#### Laparoscopic subtotal gastrectomy

Under general anaesthesia, 12 mmHg pneumoperitoneum was created with a Veress needle. Five trocars were inserted in the upper abdomen (Fig. 1). The first step consisted in lateral to medial colon-epiploic dissection of the greater omentum and of the gastrocolic ligament beyond the gastroepiploic vessels, in order to remove the homonymous lymph node stations (station 4sb). The right gastroepiploic vessels were sectioned too, in order to allow infra-pyloric lymph node stations removal (station 6); nodes along superior mesenteric vein were also removed (station 14 v). Next step was the section of the hepatoduodenal ligament, followed by ligation and section of the right gastric vessels. The duodenum was then divided using a 60 mm endoscopic linear stapler, completing the excision of the right gastro-epiploic (station 4 d) and supra and subpyloric lymph node station (stations 5 and 6). Lymphadenectomy was extended to the common hepatic artery station (station 8) and to the hepatoduodenal ligament (stations 12a). The stomach was mobilized and overturned upward after the ligation of the left gastric artery and vein with lymph node dissection around the celiac trunk and the left gastric artery (stations 7 and 9). The splenic artery lymphadenectomy was then performed (station 11p). Esophago-gastric dissection was then completed and lymphadenectomy



**Figure 1.** Trocar position

was extended up to right crus (stations 3, 1). Gastric resection was performed at a distance of at least 7 cm from the tumour using a 60mm endoscopic linear stapler. An antecolic gastrojejunal side to side anastomosis was performed on the major gastric curvature, using a 45 mm linear stapler. The enterotomy was then closed with a double layer of manual intracorporeal suture using polygalactin 2-0 stitches. Jejunojejunal mechanical side-to-side anastomosis between alimentary and biliary limb was finally performed, at 60 cm from the ligament of Treitz. The specimen was extracted through an enlargement of umbilical trocar incision. A single drain was left in place.

*Open gastrectomy*

The same steps as for laparoscopic approach were carried out through a midline xifo-umbilical laparotomy. Differently from LSG an antecolic, partial oral gastrojejunal anastomosis was performed manually, in double continuous layer. Jejunojejunal anastomosis was performed manually in double layer.

### Postoperative management

The nasogastric tube was normally removed after the first flatus. Early mobilization of the patient is always attempted. Intravenous ketoprofen (100 mg/vial) was used for postoperative pain control. Hospital discharge was scheduled after full recovery from postoperative ileus, feeding on normal diet and after a good level of self-sufficiency had been achieved; however, patients were not discharged before postoperative day 8, which, traditionally, we consider as being the "safety interval" for anastomosis healing (19).

### Data Collection

Patients' demographics, operative parameters (time, blood loss), postoperative data, pathological data (tumor location; histotype according to the Lauren Classification (20); tumor grade; tumor, node, and metastasis (TNM) staging according to the American Joint Committee on Cancer (AJCC) (7th Edition) (21, 22); number of lymph nodes examined; number of lymph nodes positive; lymph nodes ratio) and on-

cological data (recurrence, overall survival) were prospectively collected. Analgesic consumption (vials) was adopted as a postoperative pain parameter. The Clavien-Dindo classification (23) was adopted for surgical complications, and only complications scored > II were matched. The Lymph Node Ratio (LNR) was calculated as a percent value by dividing the total number of lymph nodes harboring metastases by the total number of examined nodes (24, 25).

LODDS were calculated by the empirical logistic formula: log of the ([pLN + 0.5] / [tLN − pLN + 0.5]) where: pLN = positive lymph nodes and tLN = total harvested lymph nodes. In order to avoid an infinite number 0.5 was added to both the numerator and the denominator (26).

Data of the control group were obtained from the Parma Tumor Registry and the patient clinical charts.

### Statistical analysis

Because of the reduced number of cases included in the study, the nonparametric Mann-Whitney rank test for two independent variables were used for the comparison of continuous variables, whereas association of dichotomous variables was assessed through the Fishers' exact test. Univariate survival analysis was performed through Kaplan-Meier statistics: LSG and OSG were compared through the Log-rank (Mantel-Cox) test, with calculation of respective Hazard Ratio (HR) for LSG vs. OSG, and respective survival curves were elaborated. Statistical analysis was performed by using software package SPSS 24.0 (IBM Corp. Armonk, NY). A difference with p<0.05 was considered statistically significant.

### Ethical issues

The study was approved by the institutional review board, and informed consent was obtained from all participants.

## Results

As shown in table 1, cases and controls were similar for demographics, biometric parameters and ASA status.

**Table 1.** Patients demographic and tumor characteristics

| Approach | VL (N = 13) | Open (N = 13) | P value |
|---|---|---|---|
| Age (yrs) | | | |
| *Median (range)* | 74 (52 to 88) | 75 (69 to 82) | 0.424 |
| Sex | | | |
| *Male* | 8, 61.5% | 8, 61.5% | 1.000 |
| *Female* | 5, 38.5% | 5, 38.5% | |
| BMI (kg/m²) | | | |
| *Median, range* | 25.2 (21.9 to 34.5) | 26.7 (21.9 to 30.2) | 0.745 |
| *<25.0 kg/m²* | 5, 38.5% | 6, 46.1% | 0.920 |
| *25.0 – 29.9 kg/m²* | 7, 5.4% | 6, 46.1% | |
| *30.0 kg/m² or more* | 1, 7.7% | 1, 7.7% | |
| ASA | | | 0.480 |
| *ASA2* | 2, 15.4% | 0, - | |
| *ASA3* | 11, 84.6% | 13, 100% | |
| Histologic type | | | 0.251 |
| *Intestinal* | 4, 30.8% | 8, 61.5% | |
| *Diffuse* | 5, 38.5% | 2, 15.4% | |
| *Mixed* | 4, 30.8% | 3, 23.1% | |
| *Grading* | | | 0.013 |
| *G1* | 0, - | 0, - | |
| *G2* | 1, 7.7% | 8, 61.5% | |
| *G3* | 12, 92.3% | 5, 38.5% | |
| *Staging (AJCC)* | | | 0.229 |
| IA | 0, - | 0, - | |
| IB | 0, - | 0, - | |
| IIA | 3, 23.1% | 3, 23.1% | |
| IIB | 0, - | 2, 15.4% | |
| IIIA | 2, 15.4% | 1, 7.7% | |
| IIIB | 6, 46.2% | 2, 15.4% | |
| IIIC | 2, 15.4% | 5, 38.5% | |

In patients submitted to LSG tumor grade was higher (p: 0.013) while stage did not significantly differ among the groups, as well as nodal involvement (LNR, LODDS). Intestinal type tumor was more frequent in OSG group (61% vs 31%).

Operation time was significantly higher in LSG patients (301.5 ± 84.2 vs 232.0 ± 58.9 p: 0.023), even though such a difference seems to decrease with a "learning curve" effect (Fig. 2). No conversion to open occurred.

Blood loss was similar in cases and controls (table 2). Harvested lymph nodes were higher in patients undergone LSG (26.3 ± 8.1vs18.5 ± 9.2; p: 0.033), and
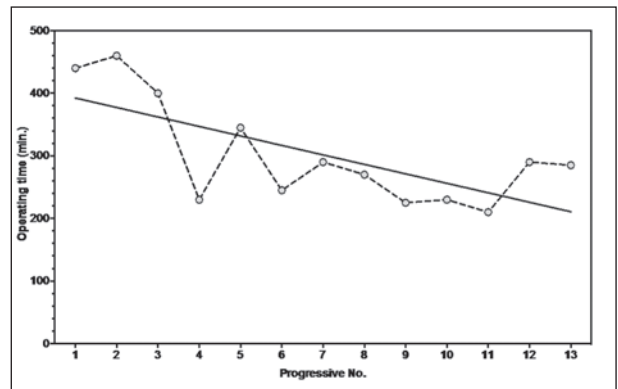


**Figure 2.** Operative times (laparoscopic gastrectomy)

92% of the LSG group and 77% of the OSG group had adequate lymphadenectomy (more than 15 nodes according to the AJCC and NCCN guidelines (8, 20)).

We had no mortality in both groups. No major complication (Clavien Dindo >2) was registered in in LSG group, while 1 patient submitted to OSG was re-operated on postoperative day 7 due to acute bleeding. Postoperative course was better for LSG, with lower analgesic consumption (11.9 vs 15.3 p: 0.047) and faster bowel movement recovery (mean: 2.3 vs 3.89 p: 0.042), while time to oral feeding was not significantly different between the groups (table 2). Mean hospital stay was 10.7 days in LSG and 12.3 in OSG (p: 0.419).

Both LSG and OSG allowed for a free margin resection in all cases. No early recurrence (<12 months) was registered.

Overall survival (KM analysis) was higher for LSG (57.0 months 95%CI 41.2 to 72.8 vs. 51.2 months 95%CI 22.2, p = 0.022; HR 0.139, 95%CI 0.059 to 0.809) (Fig. 3).

## Discussion

Over the last decades, laparoscopic surgery has gained increasing popularity in several fields of oncologic surgery, allowing a proven postoperative advantage without affecting oncological outcome. Unlike colonic cancer surgery, though, the laparoscopic approach to gastric cancer is still source of debate, being accepted, and not widely adopted, only for EGC (27-29) or undiagnosed lesions (30).

**Table 2.** Outcomes

| Approach | VL (N = 13) | Open (N = 13) | P value |
|---|---|---|---|
| **Operation time (minutes, range)** | 285 (210 to 460) | 230 (155 to 360) | 0.023 |
| **Post-Operative Complications (CD>2)** | 0, - | 1, 7.7% | 1.000 |
| **Blood Loss (ml, range)** | 78 (22 to 190) | 89 (60 to 150) | 0.685 |
| **Pain Vials (range)** | 11.9 (9 to 18) | 15.3 (13 to 22) | 0.047 |
| **Post-operative Ileum (days, range)** | 3 (2 to 6) | 3 (3 to 12) | 0.042 |
| **Time to oral feeding (days, range)** | 4 (3 to 9) | 5 (4 to 8) | 0.205 |
| **Hospital Stay (days, range)** | 9 (6 to 28) | 10 (8 to 23) | 0.419 |
| **Harvested Lymph nodes** | | | |
| Median (range) | 27 (10 to 36) | 16 (11 to 44) | 0.033 |
| < 15 | 1, 7.7% | 3, 23.1% | 0.593 |
| 15 or more | 12, 92.3% | 10, 76.9% | |
| **Positive Lymph nodes** | | | |
| Median (range) | 10 (0 to 16) | 6 (0 to 21) | 0.551 |
| **LN ratio** | | | |
| Median (range) | 38.2 (0 to 100) | 45.5 (0 to 73.3) | 0.954 |
| **LODDS** | | | |
| Median (range) | -0.2021 | | |
| (-1.7559 to 1.3222) | -0.7255 | | |
| (-1.5185 to 0.4074) | 0.795 | | |
| **Short term (<1 year) recurrence%** | 0 | 0 | 1.000 |

Values expressed as medians
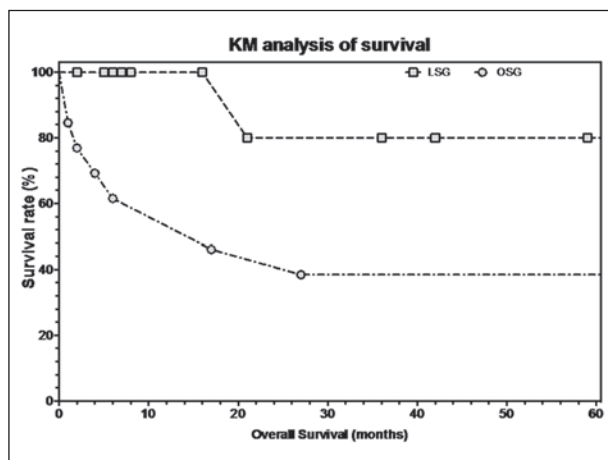


**Figure 3.** Overall survival post operation (KM analysis)

Despite many studies assessed an advantage on clinical outcome for LSG (11-14), a recent meta-analysis (12) showed the absence of significant differences in postoperative outcome parameters in the few randomized studies included. In fact, LSG seems to allow shorter hospital stay and lower postoperative pain, while refeeding time can be biased by a variable number of unpredictable prolonged gastroparesis, which seems to be poorly influenced by the type of surgical approach or reconstruction. Differently from what Kim et al. stated (11), postoperative benefits seem not so evident as for colonic surgery, where the difference on abdominal invasiveness between the open and laparoscopic approach is probably higher (12). Moreover, some authors (31) perform a laparoscopically-assisted procedure, using a wide "service" laparotomy to perform the anastomosis: in a frequently not obese abdomen (as the case of gastric cancer patients), the difference in laparotomy length between LSG and OSG ends up as being often not relevant.

Moreover, many technical issues about LSG safety have been raised. In particular, given the supposed oncological superiority of D2 dissection in AGC treatment (32, 33), the initial concern about the feasibility of an adequate laparoscopic dissection D2 has limited the routinely use of LSG for gastric cancer in advanced

stages (12). In fact, in western countries, D2 dissection is considered a recommended but not required procedure, even though there is uniform consensus that removal of an adequate number of lymph nodes (>15) is beneficial for staging purposes (8). A recent meta-analysis (34) based on non-randomized trials seems to suggest that D2 lymphadenectomy performed laparoscopically is as effective as an open procedure, even in AGC.

The anastomose technique represents another important technical issue for laparoscopic gastrectomy. A specific skill in intracorporeal suturing is required for LSG, whereas even major, and apparently non-solved, technical problems are related to intracorporeal esophagojejunal anastomosis after laparoscopic total gastrectomy, where a gold standard technique has not yet been identified. In fact, due to the higher anastomosis-related complication rate, as reported by Lee (31), LTG is still under investigation.

In our series, LSG seems to confirm the postoperative outcome benefits reported by previous studies, even though a prolonged gastroparesis may delay the refeeding thus affecting the recovery of patients in both groups.

The number of harvested lymph nodes was significantly higher in LSG, and, in most of cases (92%), oncologically adequate, confirming that lymphadenectomy should not be considered a technical issue for a surgeon trained in laparoscopic and oncological surgery, even at his first experience on laparoscopic gastric resection for AGC. On the other hand, as reported in most series (14, 16), operative times were longer for LSG (301.5 ± 84.2 vs 232.0 ± 58.9 p:0.023), but did not entail any higher blood loss or complication rate. Some authors suggested a learning curve of 50 cases for LSG (35); as shown in graphic 1, considerable reduction of surgical times can be achieved after few procedures if the surgeon is experienced in intracorporeal suturing and anastomosis, as already demonstrated, for instance, in colonic surgery (36, 37).

Oncological outcomes cannot be clearly evaluated by our series, because of the few cases matched and the relatively short follow-up. However, LSG allowed adequate resection in terms of free margin and lymphadenectomy in all the patients; therefore, it can be assumed that survival difference depends only on

cancer stage and biology, as per the prognostic factors of multivariate analysis (Age, tumour type, pN, LODDS). Moreover, former concerns on cell seeding in laparoscopic oncologic resection (38, 39) seem to be overtaken by the extremely low number of port site implant reported and by the absence of short-term recurrence in the major studies (13), as well as in our series.

## Conclusions

Our study confirms that LSG for AGC can be safely performed by a surgeon experienced in oncological and laparoscopic surgery, allowing faster recovery of the patient. Future randomized trials should confirm the equivalence on surgical outcomes.

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Correspondence:
Federico Marchesi
Università degli Studi di Parma,
Dipartimento di Scienze Chirurgiche
Sezione di Clinica Chirurgica, Generale e Terapia Chirurgica
Via Gramsci n.14, 43100 Parma
Tel. +39 0521 702156
Fax +39 0521 940125
E-mail: fede53@lycos.com