



Laparoscopic Resection for Adenocarcinoma of the Stomach or Gastroesophageal Junction Improves Postoperative Outcomes: a Propensity Score Matching Analysis

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Abstract

Background Minimally invasive resection for upper gastrointestinal tumors has been associated with favorable results. However, the role of laparoscopic surgery (LS) in the multimodal treatment of patients with advanced adenocarcinoma of the stomach or gastroesophageal junction needs further investigation.

Methods Clinicopathological data of patients who underwent gastrectomy between 2005 and 2017 were assessed. Outcomes of patients undergoing LS were compared with those of patients treated with a conventional open resection (OR) using a 1:1 propensity score matching analysis.

Results Curative resection for adenocarcinoma of the stomach or gastroesophageal junction was performed in 417 patients during the study period. Beginning in June 2014, the majority of patients underwent LS ($n = 72$) and they were matched with 72 patients who were treated with an OR. The majority of patients treated with LS (89%) had advanced cancer (UICC stages II and III) and 82% of them received neoadjuvant chemotherapy. LS was significantly associated with a higher number of harvested lymph nodes (26 (9–62) vs. 21 (4–46), $P = .007$), a lower 90-day major complication rate (13 vs. 26%, $P = .035$), and a lower length of hospital stay (14 vs. 16 days, $P = .001$). After a median follow-up time of 32 months, 1-year overall survival rate was higher after LS than after OR (93 vs. 74%, $P = .126$); however, results did not reach statistical significance.

Conclusion LS for adenocarcinoma of the stomach or gastroesophageal junction is feasible and significantly reduces major postoperative morbidity resulting in a reduced length of hospital stay. Therefore, LS should be preferably considered for the curative treatment of patients with these malignancies.

Keywords Gastric cancer · Laparoscopic surgery

Introduction

Multimodal treatment including radical resection with extended lymphadenectomy and perioperative chemotherapy provides patients with advanced adenocarcinoma of the stomach or gastroesophageal junction the highest chance for long-term survival and remains the current standard of care.¹ Since the 1990s, minimally invasive surgery was gradually adapted for resection of upper gastrointestinal (GI) cancer,^{2,3} and gained importance especially in Asian countries, where the prevalence of upper GI tumors is higher than in other parts of the world.⁴

Initially, only early gastric cancers have been treated with laparoscopic surgery (LS) resulting in lower postoperative morbidity rates. Lower wound and intraabdominal complication rates, reduced pain, and earlier recovery have been

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reported in patients with stage I gastric cancer who underwent laparoscopic gastric resection.^{5,6} Over time, patients with more advanced tumor burden have also benefited from minimally invasive surgery with similar postoperative morbidity and mortality rates compared to conventional open procedures.⁷

LS for gastric cancer has been also increasingly implemented in western countries.^{8,9} However, studies on this topic have been more often conducted in Asian countries including patients with different characteristics than in Europe or North America.¹⁰ For example, patients with gastric cancer in western countries were shown to be older and more obese than in Asia, and therefore, results from clinical trials cannot be generally transferred without question. In fact, evidence on the advantages of minimally invasive surgery for western patients with gastric cancer is scarce and data based on randomized studies are very limited.^{8,9,11}

Modern statistical methods have been currently introduced to compare different surgical techniques. In this regard, propensity score matched analysis offers a possibility to reduce the impact of treatment selection bias in retrospective studies. To date, propensity score matching for patients with gastric cancer has only been used in three studies comparing the outcomes of LS with those of conventional open resection (OR).^{8,12,13}

Moreover, while previous analyses mainly focused on the technical feasibility and safety of laparoscopic resection for gastric cancer,^{14,15} data on long-term outcomes are lacking. Therefore, the objective of this study was to evaluate and compare postoperative and long-term outcomes of patients with adenocarcinoma of the stomach or gastroesophageal junction undergoing LS with those of patients who underwent OR.

Materials and Methods

Patient Inclusion Criteria

After authorization by the Institutional Review Board (EA4/052/14), clinicopathological data of 417 patients who underwent resection for adenocarcinoma of the stomach or gastroesophageal junction between 2005 and 2017 at the Department of Surgery, Campus Charité Mitte and Campus Virchow Klinikum, Charité Universitätsmedizin Berlin were collected. Only patients who were eligible for curative intended surgery defined as safe removal of all radiologically and endoscopically evident disease were included in this study. Exclusion criteria included stage IV disease and palliative treatment intent.

Preoperative Assessment

All patients underwent standard preoperative evaluation including medical history, physical examination, laboratory parameter analysis, imaging studies, and anesthesia evaluation.

Esophagogastroduodenoscopy with multiple biopsies and endosonography was performed for diagnosing and staging gastric cancer and cancer of the gastroesophageal junction. Cross-sectional imaging such as computer tomography with triphasic contrast agent protocol or magnetic resonance imaging was used to determine the location and extent of tumor burden as well as the presence of lymph node or distant metastases. If necessary, fluorodeoxyglucose positron emission tomography and diagnostic laparoscopy were carried out to rule out metastatic disease and to define resectability in borderline cases. All cases were presented in a multidisciplinary tumor board, including upper GI surgeons, gastroenterologists, specialized radiologists, medical oncologists, and pathologists, which recommended an individualized treatment strategy. This included perioperative chemotherapy and resection for the adenocarcinoma of the stomach or gastroesophageal junction. In accordance with national guidelines, indications for preoperative chemotherapy included T category of 3 or higher and/or positive N category.¹⁶ Patients received chemotherapy according to the ECF (epirubicin, cisplatin, fluorouracil)¹⁷ or FLOT (fluorouracil, leucovorine, oxaliplatin, docetaxel) regimen.¹⁸ Patients who were administered 4 cycles of preoperative chemotherapy were recommended to complete the course of systemic therapy by receiving 4 cycles of postoperative chemotherapy. This recommendation was defined as “return to intended oncologic therapy” and was dependent on the tumor stage and patient condition.

Surgical Procedure

Since 2014, minimally invasive surgery has been preferably performed for the resection of adenocarcinoma of the stomach or gastroesophageal junction.

In case of OR, the abdominal cavity has been accessed via median laparotomy reaching from the xiphoid to approximately 2 cm below the umbilicus (approximately 35 cm). If LS was performed, the patient was positioned in a supine position with spread legs. An Alexis HandPort system (Applied Medical, Rancho Santa Margarita, CA) was placed in the left middle abdomen via a 7 cm incision. After insertion of a 12 mm trocar, pneumoperitoneum was established and the abdominal cavity was carefully examined to rule out any previously unrecognized peritoneal or other distant metastases. Additional 12 mm trocars were placed in the right upper abdomen and at the umbilicus. Two 5 mm trocars were inserted epigastrically and under the left rib cage.

Transhiatal extended gastrectomy, total gastrectomy with intraabdominal esophagojejunostomy, or subtotal gastrectomy with intraabdominal gastrojejunostomy was performed dependent on the location of the tumor and the histological subtype.

During LS, resected specimens were retrieved via the hand port. Two-field lymphadenectomy (D2) was routinely performed in all cases. Following resection, GI continuity was

restored applying Roux-en-Y reconstruction as previously described.^{19,20} The anastomosis after open total gastrectomy was performed using purse-string suture for 25 mm circular stapled anastomosis. In the laparoscopic setting, the anastomosis was established via 25 mm circular anastomosis performed in double stapling technique using the OrVil system (Medtronic, Dublin, Ireland).

Integrity of the anastomosis was verified by air leak testing during intraoperative endoscopy. Before closing the abdominal cavity, a nasogastric tube and perianastomotic drain were placed in all patients.

Postoperative Management

After resection, all patients were admitted to a specialized intensive care unit where they were closely monitored for postoperative complications including bleeding, anastomotic leak, intraabdominal or wound infections, pneumonia, and organ failure. Postoperative surgical feeding tubes in form of percutaneous endoscopic jejunostomies have not been routinely used in our department. Traditionally, GI decompression via nasogastric tube and nil per os diet was routinely maintained for 5 days. If an oral radiologic contrast agent examination (RCE) on the fifth postoperative day (POD) excluded anastomotic leak, the nasogastric tube was removed and oral diet was started.²⁰ However, in the current era of minimally invasive surgery and modern perioperative protocols of enhanced recovery after surgery (ERAS), nasogastric tubes are removed on the first POD. Early return to oral intake as well as early mobilization is pursued.²¹ Anastomotic leak was diagnosed upon clinical signs of infection or remarkable discharge through the perianastomotic drains using computed tomography, endoscopy, or oral contrast agent study.²⁰ Perianastomotic drains were removed if discharge was unremarkable and less than 500 cc per day.

Any complication within 90 days after surgical procedure defined postoperative morbidity. Postoperative complications were graded according to the classification of Clavien and Dindo.^{22,23} Postoperative mortality was defined by any death within 30 and 90 days after resection.

Histological Evaluation

All resected specimens were routinely histologically evaluated to confirm the diagnosis of adenocarcinoma of the stomach or gastroesophageal junction, to define the tumor category according to the TNM classification and to examine resection margins with regard to the presence of tumor cells. R0 resection was defined if surgical margins were microscopically negative for malignant cells.²⁴

Statistical Analysis

Patients were stratified according to the type of surgical procedure and propensity score analysis was performed to match patients who underwent LS with patients treated with OR. This allowed for significant reduction of differences in baseline characteristics between the two patient cohorts, thus minimizing the impact of treatment-related selection bias. A 1:1 propensity score matching using a logistic regression model with a match tolerance of 0.1 was performed including the following matching parameters: patient age, sex, American Society of Anesthesiologists (ASA) status, Union for International Cancer Control (UICC) tumor stage, extent of resection, and the administration of preoperative chemotherapy.

Quantitative and qualitative variables were expressed as medians (range), means (range), and frequencies. The chi-square or Fisher's exact test, and the Mann-Whitney *U* test were used to compare categorical and continuous variables, as appropriate. Overall survival (OS) rates were calculated from the date of resection to the date of death or last follow-up using the Kaplan-Meier method and were compared between the two technique-related patient groups using log-rank tests.

P values < .05 were considered statistically significant. For statistical analysis, SPSS software package, version 23, by IBM (Armonk, NY) was used.

Results

Patient Characteristics

During the study period, 417 patients underwent resection for adenocarcinoma of the stomach or gastroesophageal junction. Since June 2014, LS has been predominantly performed ($n = 72$) and this cohort was matched with 72 patients who underwent OR. After matching, baseline characteristics did not significantly differ between the two groups, as shown in Table 1. The proportion of male gender was comparable between the groups of patients undergoing OR and LS, respectively (25 vs. 31%, $P = .457$). Median age at time of resection was 65 and 68 years in the OR and LS group, respectively ($P = .151$). Interestingly, body mass index was significantly higher in the LS group than in the OR group (27 vs. 25 kg/m², $P = .037$). Physical status according to ASA was comparable between the groups and comorbidities such as diabetes, cardiovascular disease, pulmonary disease, and renal insufficiency, did not significantly differ between the groups except for liver cirrhosis which was more prevalent in patients undergoing LS (10 vs. 1%, $P = .029$). Postoperative C-reactive protein levels were comparable between the groups (145 vs. 158 mg/dL, $P = .334$) and the majority of patients received preoperative chemotherapy in both groups (OR 82% vs. LS 85%, $P = .655$). Moreover, preoperative chemotherapy regimens

Table 1 Comparison of clinicopathologic characteristics of 144 patients who underwent resection for adenocarcinoma of the stomach or gastroesophageal junction according to the surgical technique (open vs. laparoscopic procedure) after propensity score matching

Characteristics	Open resection (<i>N</i> = 72)	Laparoscopic surgery (<i>N</i> = 72)	<i>P</i> *
Male sex, <i>n</i> (%)	18 (25)	22 (31)	.457
Median age at resection (range), years	65 (33–89)	68 (31–86)	.151
Age > 65 years, <i>n</i> (%)	38 (53)	41 (57)	.615
Median BMI (range)	25 (16–39)	27 (20–36)	.037
Resection type, <i>n</i> (%)			.593
Transhiatal extended gastrectomy	19 (26)	17 (24)	
Total gastrectomy	46 (64)	44 (61)	
Subtotal gastrectomy	7 (10)	22 (15)	
Diabetes, <i>n</i> (%)	13 (18)	17 (24)	.412
Cardiovascular disease, <i>n</i> (%)	42 (58)	44 (61)	.734
Pulmonary disease, <i>n</i> (%)	10 (14)	9 (13)	.806
Liver cirrhosis, <i>n</i> (%)	1 (1)	7 (10)	.029
Renal insufficiency, <i>n</i> (%)	2 (3)	2 (3)	1.00
ASA physical status, <i>n</i> (%)			.610
I	2 (3)	4 (5)	
II	33 (46)	30 (42)	
III	36 (50)	35 (49)	
IV	1 (1)	3 (4)	
Preoperative chemotherapy, <i>n</i> (%)	61 (85)	59 (82)	.655
Median duration of resection (range), min	264 (143–415)	345 (129–756)	< .0001
T category, <i>n</i> (%)			.211
T1	4 (6)	4 (6)	
T2	8 (11)	12 (16)	
T3	48 (66)	36 (50)	
T4	12 (17)	20 (28)	
N category, <i>n</i> (%)			.001
N0	23 (32)	13 (18)	
N1	11 (15)	33 (46)	
N2	20 (28)	15 (21)	
N3	18 (25)	11 (15)	
Median number of lymph nodes removed (range)	21 (4–46)	26 (9–62)	.007
UICC stage, <i>n</i> (%)			.958
I	7 (10)	8 (11)	
II	28 (39)	27 (38)	
III	37 (51)	37 (51)	
Lymphangiosis carcinomatosa, <i>n</i> (%)	30 (42)	21 (29)	.117
Venous invasion, <i>n</i> (%)	10 (14)	6 (8)	.289
Tumor grading (G), <i>n</i> (%)			.798
G1	1 (1)	1 (1)	
G2	32 (45)	36 (50)	
G3	39 (54)	35 (49)	
Positive resection margins (R1), <i>n</i> (%)	7 (10)	2 (3)	.085
Anastomotic leak, <i>n</i> (%)	4 (5.6)	2 (2.8)	.404
Median highest postoperative CRP (range), mg/dL	145 (30–352)	148 (63–341)	.334
Median duration of hospital stay (range), days	16 (10–83)	14 (6–133)	.001
Return to intended oncologic treatment, %	81	82	.876
Postoperative morbidity, <i>n</i> (%)	26 (36.1)	19 (26.4)	.208

Table 1 (continued)

Characteristics	Open resection (<i>N</i> = 72)	Laparoscopic surgery (<i>N</i> = 72)	<i>P</i> *
Major postoperative morbidity, <i>n</i> (%)	19 (26.4)	9 (12.5)	.035
30-day mortality, <i>n</i> (%)	1 (1.4)	2 (2.8)	.560
90-day mortality, <i>n</i> (%)	5 (6.9)	3 (4.2)	.467
Readmission rate, <i>n</i> (%)	3 (4.2)	2 (2.8)	.649

BMI, body mass index; UICC, Union for International Cancer Control; ASA, American Society of Anesthesiologists; CRP, C-reactive protein

*Comparison of patients undergoing open resection vs. laparoscopic surgery

(ECF or FLOT) did not differ between the groups. The proportion of patients undergoing transhiatal extended gastrectomy, total gastrectomy, and subtotal gastrectomy was also comparable between the patient cohorts ($P = .593$). Median duration of resection was significantly longer in the LS group than in the OR group (345 vs. 264 min, $P < .0001$).

While T category was comparable between all patients ($P = .211$), N category did significantly differ between the groups ($P = .001$), as shown in Table 1. However, the UICC stage was comparable ($P = .958$) between the two groups. The proportion of patients with lymphatic (42 vs. 29%, $P = .117$) and venous tumor invasion (14 vs. 8%, $P = .289$) was also similar between the two groups. Histopathologic evaluation of tumor grading revealed no differences when comparing the two techniques ($P = .798$). Interestingly, LS was significantly associated with a higher median number of harvested lymph nodes (26 (9–62) vs. 21 (4–46), $P = .007$). Resection margins were more frequently positive for malignant cells (R1) among patients undergoing OR compared to patients undergoing LS; however, differences did not reach statistical significance (10 vs. 3%, $P = .085$). Administration of

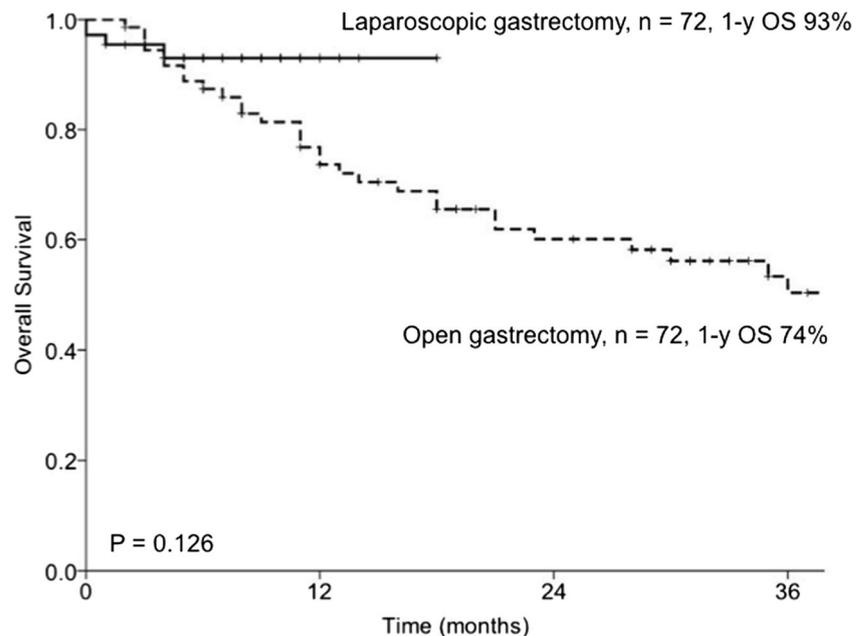
postoperative chemotherapy was comparable between the groups (81 vs. 82%, $P = .876$).

Postoperative Outcomes and Overall Survival

While the overall postoperative morbidity rate was not different between the groups (OR 26% vs. LS 19%, $P = .208$), the major postoperative complication rate was lower in the LS than in the OR group (9 vs. 19%, $P = .035$). Anastomotic leak was found in four patients after OR and in two patients after LS ($P = .404$). Median duration of hospital stay was shorter for patients who underwent LS than for patients treated with OR (14 vs. 16 days, $P = .001$). Postoperative 30- and 90-day mortality rates did not significantly differ between the OR and LS group (1.4 vs. 2.8%, $P = .560$, and 6.9 vs. 4.2%, $P = .467$, respectively).

After a median follow-up of 32 months, 1-year OS rates were higher in the LS group (93%) than in the OR group (74%), although this difference failed to reach statistical significance (Fig. 1, $P = .126$).

Fig. 1 Comparison of overall survival of 144 patients who underwent resection for adenocarcinoma of the stomach or gastroesophageal junction according to the surgical technique (open vs. laparoscopic procedure) after propensity score matching



Discussion

This study examined postoperative and long-term outcomes of patients who underwent OR or LS for adenocarcinoma of the stomach or gastroesophageal junction in a propensity score matching analysis. We found that LS was significantly associated with a lower 90-day major complication rate and a lower length of hospital stay. Additionally, OS rates were comparable between the two techniques.

Resection is currently considered as the mainstay of curative-intended treatment for patients with gastric and esophageal cancer^{25,26} and has been performed with low postoperative morbidity and mortality.^{8,27} Resection combined with perioperative chemotherapy or chemoradiation within the framework of multimodal treatment strategies^{17,28} has achieved 5-year OS rates up to 59%.¹⁹

Since minimally invasive surgery for upper GI tumors has been introduced,² the feasibility, safety, and oncologic value of this approach have been evaluated.^{6,29–35} In a Korean randomized study, 1416 patients with stage I gastric cancer were randomly assigned to receive either open or laparoscopic distal gastrectomy.⁵ The authors found lower morbidity rates, including lower wound infections and intraabdominal complications after laparoscopic distal gastrectomy compared to open distal gastrectomy. In contrast, our cohort included patients with all tumor stages but mostly patients with advanced gastric cancer (T3 and T4), which more accurately represents a western gastric cancer patient population. Patients with more advanced gastric cancer were included in another randomized controlled trial conducted by Hu et al. including 1056 patients who underwent either laparoscopic or open gastrectomy with D2 lymphadenectomy. The authors found similar postoperative morbidity and mortality rates in both groups.⁷ Importantly, this cohort differed from ours regarding BMI and patient age, which were both lower than in our study. Additionally, a higher rate of patients with well-differentiated tumors (G1) was included in this study in comparison to our study, indicating that tumor biology may differ between the two studies as well.⁷ Therefore, comparisons between our results and those from Asian centers should be very carefully made.

In a current multicentric study from the Netherlands using propensity score matching analysis, 442 patients who underwent minimally invasive resection for gastric cancer were compared to 442 patients who underwent open gastrectomy. Brenkman et al. showed that both surgical techniques resulted in similar rates of postoperative morbidity (37 vs. 40%, $P = .489$) and mortality (6 vs. 4%, $P = .214$).⁸ The patient cohort analyzed by the authors was comparable to ours concerning age, BMI, disease stage, and comorbidities. However, preoperative chemotherapy was less frequently administered than in our patients, which may have significantly influenced the postoperative and long-term outcomes.

In our study, we indicated that postoperative morbidity rates were similar after LS and OR (26.4 vs. 36.1%,

$P = .208$). However, major postoperative morbidity was lower after LS than after OR (12.5 vs. 26.4%, $P = .035$) underlining the advantages of the minimally invasive approach over the conventional open procedure. Additionally, 30- and 90-day mortality did not differ between the two techniques.

A major concern when performing LS is the risk for anastomotic leak, due to the more technically challenging procedure.³⁶ In our study, LS was not associated with a higher rate of anastomotic leaks compared to OR (2.8 vs. 5.6%, $P = .404$). This finding may also have a positive impact on the oncologic outcomes following LS, since anastomotic leak has been significantly associated with diminished long-term survival in patients undergoing resection for gastric and esophageal cancer in a previous study from our institution.¹⁹

While statistically not significant, we reported higher rates of anastomotic leak after OR (5.6%) than after LS (2.8%, $P = .404$). Moreover, the incidence of positive resection margins (R1) tended to be higher in the open resection group than in the minimally invasive resection group (10 vs. 3%, $P = .085$). Part of the patients in the OR cohort have been treated in an older era when centralized cancer surgery and ERAS principles were not fully established. Currently, the fact that resections are performed by only two specialized upper GI surgeons in our center may have contributed to reduced R1 rates and lower complication rates including anastomotic leaks following laparoscopic resection. In addition, R1 resection rates have been reduced due to standardized and routinely performed intraoperative frozen sections of the resected specimen allowing for further margin resection. The lower R1 rate among patients undergoing LS (3 vs. 10%, $P = .085$) may emphasize the advantage of this technique in enabling curative treatment.

Resection of regional lymph nodes is an important prognostic factor for patients with upper GI tumors (D2).³⁷ In our study, LS was significantly associated with a higher number of harvested lymph nodes (26 (9–62) vs. 21 (4–46), $P = .007$). In contrast, previous studies showed that the number of retrieved lymph nodes was significantly lower during laparoscopic-assisted distal gastrectomies in comparison to open gastrectomies (40.5 ± 15.3 vs 43.7 ± 15.7 , $P < .001$).⁵ Whereas, other studies found comparable lymph node yields between laparoscopic and open gastrectomy.^{6–9} Of note, the median number of lymph nodes harvested during laparoscopic gastrectomies increased from 12 to 20 ($P < .001$) over a time period of 4 years as shown in a recent study by Brenkman et al.⁹ Our results underline the radicalness and oncologic value of the minimally invasive compared to open approach in upper GI cancer surgery.

In our study, OS was not significantly different between patients treated with LS and those treated with OR, even though 1-year OS was higher after LS than after OR (93 vs. 78%, $P = .126$). Previous studies have also shown comparable long-term results between the two techniques.⁹ However, in the current era of multimodal treatment strategies, patients treated with LS may return earlier to intended oncologic

treatments and thus benefit more from modern chemotherapy regimens resulting in improved long-term survivals.

LS was associated with a significantly shorter postoperative hospital stay than OR in our study (14 vs. 16 days, $P < .001$) and this finding was in accordance with results from previous studies.⁸ However, other groups have reported lower durations of hospital stay.^{9,38} Patients in our cohort generally remained in hospital after surgery until mobilization and gradual reintroduction to solid oral intake was completed, since this cannot be reliably provided by our national outpatient health care system. However, the longer duration of hospital stay in our cohort has contributed to a lower readmission rate due to postoperative complications compared to other studies with shorter length of hospital stay.^{39–41} Readmission rates after discharge in our study were 4.2 and 2.8% in the open and laparoscopic resection group, respectively ($P = .649$).

Traditionally, our postoperative protocol for patients undergoing surgery for gastric cancer suggested a 5-day period of postoperative fasting. On POD 5, the integrity of the anastomosis was tested via a routine oral RCE. If anastomotic leak was excluded, oral diet was started. Recently, we have shown that routinely performed RCE was not helpful to detect anastomotic leak as this happens mostly before or after POD 5.²⁰ Additionally, ERAS protocols have currently proposed an early return to oral intake.⁴² However, the utilization of LS in the multimodal treatment of patients with gastric cancer represents only one feature of the ERAS concept and extended implementation of the ERAS protocols including items such as preoperative diet optimization, opioid-sparing analgesia, and balanced fluid economy is needed in order to achieve more significant reduction of postoperative complication rates and length of hospital stay.⁴³ We have been gradually adapting our perioperative patient care in accordance with the ERAS guidelines^{21,44} and therefore expect a significant reduction of the length of hospital stay after gastrectomy in the near future.

Similarly, patients who underwent colorectal,⁴⁵ pancreatic,⁴⁶ or liver surgery procedures^{47,48} were also able to benefit from the implementation of ERAS programs in regard to postoperative outcomes. In the case of colorectal cancer, improved 5-year survival rates have also been associated to ERAS.⁴⁹ Therefore, the establishment of ERAS principles in minimally invasive surgery for upper GI tumors is expected to improve both postoperative and long-term results.

Moreover, the use of LS for the treatment of upper GI tumors may further improve short-term outcomes such as reduce intraoperative blood loss, the need for postoperative analgesia, the time to first flatus and first oral intake, and support earlier mobilization.⁵⁰ Altogether, these factors may contribute to an improved and shortened recovery for patients after LS compared to OR.

The rate of postoperative chemotherapy after surgery was similar between the open and laparoscopic group with 81 and 82%, respectively ($P = .876$), as indicated by the term “return

to intended oncologic treatment”. For each patient, the course of individual multimodal treatment including chemotherapy and surgery was recommended by a multidisciplinary team of surgeons, radiologists, and gastroenterologists in a preoperatively held consensus-finding conference. The aim to return to the intended oncologic treatment means to continue the perioperative chemotherapy after surgery if this is allowed by the patient’s condition. Currently, we could not show a benefit for LS in this regard. However, LS is only one of the aspects within the framework of the ERAS concept and therefore further reduction of postoperative complications due to the full implementation of ERAS protocol may enable more patients to receive postoperative chemotherapy in the future.

Additional relevant but often under-recognized points are patient satisfaction and quality of life after surgery. Kim et al. evaluated questionnaires of 164 patients with early gastric cancer who underwent laparoscopic or open gastrectomy. After 3 months follow-up, patients following LS expressed higher quality of life. Specifically, symptom scales were significantly higher in patients after LS in regard to fatigue, pain, gastroesophageal reflux, body image, and global health.⁵¹ These data suggest that LS may have also psychological benefits in addition to improved postoperative morbidity. Strikingly, the differences in quality of life aligned in a long-term follow-up. After 5 years, no significant differences in health-related quality of life were found between the two techniques.⁵²

Additionally, LS is associated with higher healthcare-related costs, most likely due to higher costs for specialized instruments.⁵³ However, shorter hospital stays and reduced postoperative morbidity may compensate the cost-effectiveness of LS.

Our study also has some limitations. Firstly, the cohort examined in this analysis remains rather small with 72 patients in each treatment group and patients were included from a single institution. Thus, conclusions should be drawn with caution. Furthermore, our study was retrospective; however, using propensity score matching, we aimed to overcome the treatment-related selection bias for LS and provide a meaningful comparison of surgical techniques.^{54,55} Despite propensity score matching, there may still be unknown confounders influencing our study results. For example, the implementation of LS in the treatment of patients with GI cancer is associated with a possible learning curve.^{36,56–58} Nevertheless, as propensity score matching has only been used in a few studies so far,^{8,12,13} the additional data given by us confirm the previously reported benefits of LS for gastric cancer in a western population. To date, the German guidelines for the treatment of gastric cancer provide only a soft recommendation for the implementation of laparoscopic techniques.¹⁶ In our center, the transition from open to laparoscopic resection has been successfully completed and thus we can provide solid evidence which suggest that patients with gastric cancer should be primarily evaluated for minimally invasive surgery.

Conclusion

LS for adenocarcinoma of the stomach or gastroesophageal junction is feasible and safe and is significantly associated with reduced major postoperative morbidity and reduced length of hospital stay. Our data indicate the advantages of LS over OR and therefore LS should be favored when evaluating patients with cancer of the stomach or gastroesophageal junction for curative resection.

Compliance with Ethical Standards

Conflict of Interest The authors report no conflicts of interest relevant to this article.

References

- Japanese Gastric Cancer A. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011; 14: 113–123.
- Kitano S, Iso Y, Moriyama M, Sugimachi K. Laparoscopy-assisted Billroth I gastrectomy. *Surg Laparosc Endosc* 1994; 4: 146–148.
- Watson DI, Devitt PG, Game PA. Laparoscopic Billroth II gastrectomy for early gastric cancer. *Br J Surg* 1995; 82: 661–662.
- Torre LA, Bray F, Siegel RL et al. Global cancer statistics, 2012. *CA Cancer J Clin* 2015; 65: 87–108.
- Kim W, Kim HH, Han SU et al. Decreased Morbidity of Laparoscopic Distal Gastrectomy Compared With Open Distal Gastrectomy for Stage I Gastric Cancer: Short-term Outcomes From a Multicenter Randomized Controlled Trial (KLASS-01). *Ann Surg* 2016; 263: 28–35.
- Zeng YK, Yang ZL, Peng JS et al. Laparoscopy-assisted versus open distal gastrectomy for early gastric cancer: evidence from randomized and nonrandomized clinical trials. *Ann Surg* 2012; 256: 39–52.
- Hu Y, Huang C, Sun Y et al. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. *J Clin Oncol* 2016; 34: 1350–1357.
- Brenkman HJF, Gisbertz SS, Slaman AE et al. Postoperative Outcomes of Minimally Invasive Gastrectomy Versus Open Gastrectomy During the Early Introduction of Minimally Invasive Gastrectomy in the Netherlands: A Population-based Cohort Study. *Ann Surg* 2017; 266: 831–838.
- Brenkman HJF, Ruurda JP, Verhoeven RHA, van Hillegersberg R. Safety and feasibility of minimally invasive gastrectomy during the early introduction in the Netherlands: short-term oncological outcomes comparable to open gastrectomy. *Gastric Cancer* 2017; 20: 853–860.
- Griffin SM. Gastric cancer in the East: same disease, different patient. *Br J Surg* 2005; 92: 1055–1056.
- Huscher CG, Mingoli A, Sgarzini G et al. Laparoscopic versus open subtotal gastrectomy for distal gastric cancer: five-year results of a randomized prospective trial. *Ann Surg* 2005; 241: 232–237.
- Zhang X, Sun F, Li S et al. A propensity score-matched case-control comparative study of laparoscopic and open gastrectomy for locally advanced gastric carcinoma. *J buon* 2016; 21: 118–124.
- Xu C, Chen T, Hu Y et al. Retrospective study of laparoscopic versus open gastric resection for gastric gastrointestinal stromal tumors based on the propensity score matching method. *Surg Endosc* 2017; 31: 374–381.
- Haverkamp L, Weijs TJ, van der Sluis PC et al. Laparoscopic total gastrectomy versus open total gastrectomy for cancer: a systematic review and meta-analysis. *Surg Endosc* 2013; 27: 1509–1520.
- Jiang L, Yang KH, Guan QL et al. Laparoscopy-assisted gastrectomy versus open gastrectomy for resectable gastric cancer: an update meta-analysis based on randomized controlled trials. *Surg Endosc* 2013; 27: 2466–2480.
- Moehler M, Baltin CT, Ebert M et al. International comparison of the German evidence-based S3-guidelines on the diagnosis and multimodal treatment of early and locally advanced gastric cancer, including adenocarcinoma of the lower esophagus. *Gastric Cancer* 2015; 18: 550–563.
- Cunningham D, Allum WH, Stenning SP et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. *N Engl J Med* 2006; 355: 11–20.
- Al-Batran SE, Hofheinz RD, Pauligk C et al. Histopathological regression after neoadjuvant docetaxel, oxaliplatin, fluorouracil, and leucovorin versus epirubicin, cisplatin, and fluorouracil or capecitabine in patients with resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4-AIO): results from the phase 2 part of a multicentre, open-label, randomised phase 2/3 trial. *Lancet Oncol* 2016; 17: 1697–1708.
- Andreou A, Biebl M, Dadras M et al. Anastomotic leak predicts diminished long-term survival after resection for gastric and esophageal cancer. *Surgery* 2016; 160: 191–203.
- Struecker B, Chopra S, Heilmann AC et al. Routine Radiologic Contrast Agent Examination After Gastrectomy for Gastric Cancer Is Not Useful. *J Gastrointest Surg* 2017; 21: 801–806.
- Mortensen K, Nilsson M, Slim K et al. Consensus guidelines for enhanced recovery after gastrectomy. *British Journal of Surgery* 2014; 101: 1209–1229.
- Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004; 240: 205–213.
- Clavien PA, Barkun J, de Oliveira ML et al. The Clavien-Dindo classification of surgical complications: five-year experience. *Ann Surg* 2009; 250: 187–196.
- Biondi A, Persiani R, Cananzi F et al. R0 resection in the treatment of gastric cancer: room for improvement. *World J Gastroenterol* 2010; 16: 3358–3370.
- Xiong JJ, Nunes QM, Huang W et al. Laparoscopic vs open total gastrectomy for gastric cancer: a meta-analysis. *World J Gastroenterol* 2013; 19: 8114–8132.
- Gurusamy KS, Pallari E, Midya S, Mughal M. Laparoscopic versus open transhiatal oesophagectomy for oesophageal cancer. *Cochrane Database Syst Rev* 2016; 3: Cd011390.
- Seesing MFJ, Gisbertz SS, Goense L et al. A Propensity Score Matched Analysis of Open Versus Minimally Invasive Transthoracic Esophagectomy in the Netherlands. *Ann Surg* 2017; 266: 839–846.
- van Hagen P, Hulshof MC, van Lanschot JJ et al. Preoperative chemoradiotherapy for esophageal or junctional cancer. *N Engl J Med* 2012; 366: 2074–2084.
- Chen XZ, Wen L, Rui YY et al. Long-term survival outcomes of laparoscopic versus open gastrectomy for gastric cancer: a systematic review and meta-analysis. *Medicine (Baltimore)* 2015; 94: e454.
- Wei HB, Wei B, Qi CL et al. Laparoscopic versus open gastrectomy with D2 lymph node dissection for gastric cancer: a meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2011; 21: 383–390.
- Vinuela EF, Gonen M, Brennan MF et al. Laparoscopic versus open distal gastrectomy for gastric cancer: a meta-analysis of randomized controlled trials and high-quality nonrandomized studies. *Ann Surg* 2012; 255: 446–456.

32. Ding J, Liao GQ, Liu HL et al. Meta-analysis of laparoscopy-assisted distal gastrectomy with D2 lymph node dissection for gastric cancer. *J Surg Oncol* 2012; 105: 297–303.
33. Qiu J, Pankaj P, Jiang H et al. Laparoscopy versus open distal gastrectomy for advanced gastric cancer: a systematic review and meta-analysis. *Surg Laparosc Endosc Percutan Tech* 2013; 23: 1–7.
34. Chen K, Xu XW, Zhang RC et al. Systematic review and meta-analysis of laparoscopy-assisted and open total gastrectomy for gastric cancer. *World J Gastroenterol* 2013; 19: 5365–5376.
35. Lin JX, Huang CM, Zheng CH et al. Surgical outcomes of 2041 consecutive laparoscopic gastrectomy procedures for gastric cancer: a large-scale case control study. *PLoS One* 2015; 10: e0114948.
36. Jeong O, Ryu SY, Choi WY et al. Risk factors and learning curve associated with postoperative morbidity of laparoscopic total gastrectomy for gastric carcinoma. *Ann Surg Oncol* 2014; 21: 2994–3001.
37. Karpeh MS, Leon L, Klimstra D, Brennan MF. Lymph node staging in gastric cancer: is location more important than Number? An analysis of 1,038 patients. *Ann Surg* 2000; 232: 362–371.
38. Park YK, Yoon HM, Kim YW et al. Laparoscopy-Assisted versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: Results from a Randomized Phase II Multicenter Clinical Trial (COACT 1001). *Ann Surg* 2017.
39. Kim YD, Kim MC, Kim KH et al. Readmissions following elective radical total gastrectomy for early gastric cancer: a case-controlled study. *Int J Surg* 2014; 12: 200–204.
40. Kohlnhofer BM, Tevis SE, Weber SM, Kennedy GD. Multiple complications and short length of stay are associated with postoperative readmissions. *Am J Surg* 2014; 207: 449–456.
41. Kim JW, Kim WS, Cheong JH et al. Safety and efficacy of fast-track surgery in laparoscopic distal gastrectomy for gastric cancer: a randomized clinical trial. *World J Surg* 2012; 36: 2879–2887.
42. Mortensen K, Nilsson M, Slim K et al. Consensus guidelines for enhanced recovery after gastrectomy: Enhanced Recovery After Surgery (ERAS(R)) Society recommendations. *Br J Surg* 2014; 101: 1209–1229.
43. Ljungqvist O, Scott M, Fearon KC. Enhanced recovery after surgery: A review. *JAMA Surgery* 2017.
44. Abdikarim I, Cao XY, Li SZ et al. Enhanced recovery after surgery with laparoscopic radical gastrectomy for stomach carcinomas. *World J Gastroenterol* 2015; 21: 13339–13344.
45. Shida D, Tagawa K, Inada K et al. Modified enhanced recovery after surgery (ERAS) protocols for patients with obstructive colorectal cancer. *BMC Surg* 2017; 17: 18.
46. Xiong J, Szatmary P, Huang W et al. Enhanced Recovery After Surgery Program in Patients Undergoing Pancreaticoduodenectomy: A PRISMA-Compliant Systematic Review and Meta-Analysis. *Medicine (Baltimore)* 2016; 95: e3497.
47. Zhao Y, Qin H, Wu Y, Xiang B. Enhanced recovery after surgery program reduces length of hospital stay and complications in liver resection: A PRISMA-compliant systematic review and meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2017; 96: e7628.
48. Wang C, Zheng G, Zhang W et al. Enhanced Recovery after Surgery Programs for Liver Resection: a Meta-analysis. *J Gastrointest Surg* 2017; 21: 472–486.
49. Gustafsson UO, Oppedstrup H, Thorell A et al. Adherence to the ERAS protocol is Associated with 5-Year Survival After Colorectal Cancer Surgery: A Retrospective Cohort Study. *World J Surg* 2016; 40: 1741–1747.
50. Li HZ, Chen JX, Zheng Y, Zhu XN. Laparoscopic-assisted versus open radical gastrectomy for resectable gastric cancer: Systematic review, meta-analysis, and trial sequential analysis of randomized controlled trials. *J Surg Oncol* 2016; 113: 756–767.
51. Kim YW, Baik YH, Yun YH et al. Improved quality of life outcomes after laparoscopy-assisted distal gastrectomy for early gastric cancer: results of a prospective randomized clinical trial. *Ann Surg* 2008; 248: 721–727.
52. Kim YW, Yoon HM, Yun YH et al. Long-term outcomes of laparoscopy-assisted distal gastrectomy for early gastric cancer: result of a randomized controlled trial (COACT 0301). *Surg Endosc* 2013; 27: 4267–4276.
53. Hoya Y, Taki T, Tanaka Y et al. Disadvantage of operation cost in laparoscopy-assisted distal gastrectomy under the national health insurance system in Japan. *Dig Surg* 2010; 27: 343–346.
54. Austin PC. An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies. *Multivariate Behav Res* 2011; 46: 399–424.
55. Lonjon G, Boutron I, Trinquart L et al. Comparison of treatment effect estimates from prospective nonrandomized studies with propensity score analysis and randomized controlled trials of surgical procedures. *Ann Surg* 2014; 259: 18–25.
56. Jung DH, Son SY, Park YS et al. The learning curve associated with laparoscopic total gastrectomy. *Gastric Cancer* 2016; 19: 264–272.
57. Kim HG, Park JH, Jeong SH et al. Totally laparoscopic distal gastrectomy after learning curve completion: comparison with laparoscopy-assisted distal gastrectomy. *J Gastric Cancer* 2013; 13: 26–33.
58. Moon JS, Park MS, Kim JH et al. Lessons learned from a comparative analysis of surgical outcomes of and learning curves for laparoscopy-assisted distal gastrectomy. *J Gastric Cancer* 2015; 15: 29–38.