Pathogen infection and drug resistance in laparoscopy-assisted total gastrectomy for upper gastric cancer

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Abstract: With the abuse of antibiotics, pathogenic bacteria more resistant to infection, prevention and control of postoperative, we conducted a systematic analysis of the pathogenic bacteria and drug resistance in patients with infection after surgery. At the same time, we evaluate long-term outcomes between laparoscopy-assisted and open approaches to total gastrectomy for upper gastric cancer. Overall survival (OS) and disease-free survival (DFS) was evaluated using the Kaplan-Meier method. We matched all 246 laparoscopic cases 1:1 with open cases according to age, sex, body mass index and clinical TNM stage. The laparoscopy-assisted approach was associated with a significant decrease in surgical blood loss, number of analgesic injections, time to first flatus and length of hospital stay relative to the open approach. The postoperative morbidity did not differ between the two groups. There were no significant differences between the two groups in OS and DFS. The laparoscopy-assisted approach to total gastrectomy for upper gastric cancer results in comparable long-term survival compared with laparotomy.

Keywords: Gastric carcinoma, laparoscopy-assisted total gastrectomy, minimally invasive surgery, survival.

INTRODUCTION

The infection after gastrectomy has a great impact on the success rate of gastric resection, and also poses a threat to the quality of life and health and safety of patients. With the abuse of antibiotics, more and more pathogens are resistant to the drug, which brings a lot of problems to the medical staff. In order to prevent and control infections after gastrectomy, we conducted a systematic analysis of the pathogenic bacteria and drug resistance in patients with infectious diseases room after surgery, and the risk factors of infection after gastrectomy were analyzed for better prevention of infection after gastrectomy. Total gastrectomy with D2 lymphadenectomy performed by laparotomy is the standard of care for otherwise healthy patients with upper gastric cancer (Imada *et al*. 2016; Japanese Gastric Cancer Associatio 2010; Sandri *et al*., 2015; Yamada *et al*., 2016; Zheng *et al*., 2015). However, surgeons have increasingly adopted laparoscopy-assisted total gastrectomy with D2 lymphadenectomy over the last two decades (Kitano *et al*., 1994; Lee and Kim 2013; Liu *et al*., 2016; Mellotte *et al*., 2015; Phillips *et al*., 2013; Shinohara *et al*., 2013; Zeng *et al*., 2012). This technique has the advantages of reducing trauma and facilitating a more rapid postsurgical recovery. Despite the increasing adoption, there are no large prospective studies comparing the efficacy of this technique with that of open surgery (Chang *et al*., 2016; Chen *et al*., 2015; Kalanovic *et al*., 2016; Morise *et al*., 2016; Parikh *et al*., 2016; Rha *et al*., 2016; Ueda *et al*., 2016). Most comparative studies have focused on short-term rather than on long-term outcomes The present study evaluated long-term outcomes for a homogenous group of patients with upper gastric cancer who underwent total gastrectomy by either laparoscopy-assisted or open surgery.

Several institutional series have shown that long-term survival after laparoscopy to achieve total gastrectomy for upper gastric cancer is equivalent and perhaps better than that after laparotomy, although many of these studies were limited by small sample sizes and the potential bias of selecting laparoscopy when treating earlier TNM stage tumors (Bo *et al*., 2013; Cai *et al*., 2013; Lin *et al*., 2014). Several studies have shown that fewer lymph nodes were harvested after laparoscopy-assisted total gastrectomy in comparison with those harvested after open total gastrectomy (Bo *et al*., 2013; Cai *et al*., 2013; Lin *et al*., 2014). Although the results of our study provide further evidence that laparoscopy does not compromise patient prognosis, it must be emphasized that surgeons performing laparoscopy-assisted total gastrectomy for upper gastric cancer must achieve D2 lymphadenectomy that is equivalent to laparotomy. Patient outcomes are likely more dependent on whether a surgeon performs a good oncologic procedure and not on the use of laparoscopy or laparotomy.

In addition to its short-term benefits, laparoscopy for total gastrectomy to treat upper gastric cancer has other advantages over laparotomy. Several studies have shown that the benefits of laparoscopy are most pronounced in higher risk patients who are not suitable for open resection (Bo *et al*., 2013; Cai *et al*., 2013; Lin *et al*., 2014). Therefore, laparoscopy may allow safe surgical

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resection with patients who may have been traditionally regarded to be poor candidates for resection based on laparotomy (Abu 2017; Fang and Ruan 2017; Liu *et al*., 2017; Takahashi 2017). In this study, we have found several limitations about our research. The main study limitation which influenced the whole result was its retrospective nature. An imbalance between groups pertaining to patient characteristics that were not evaluated may have biased the study results. In addition, despite the relatively large number of patients, the study may have been underpowered to detect small group differences according to the overall and disease-free survivals. So that, we found out the result as add to the growing amount of published evidence demonstrating that the use of laparoscopy-assisted total gastrectomy for upper gastric cancer does not compromise patient long-term outcomes or survival.

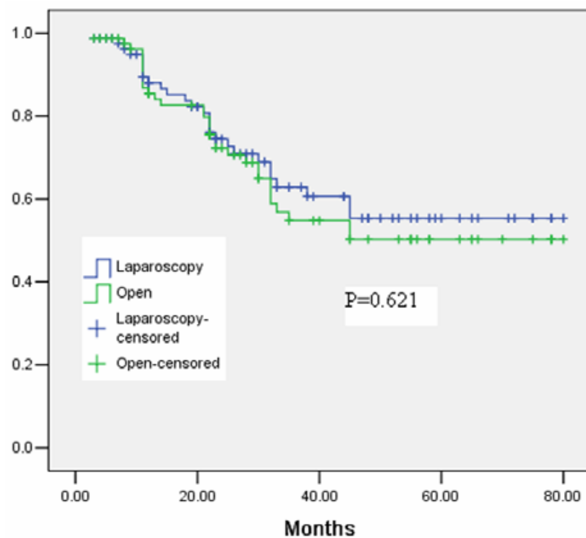

Fig. 1: Overall survival of all patients by operative approach (P = 0.621).

MATERIALS AND METHODS

We retrospectively evaluated the medical records by using statistical methods, totally 1,456 consecutive patients with gastric cancer who underwent gastrectomy between April 2008 and December 2014. All clinical and follow-up data in the records were verified and updated through May 2015 using a central database. Based on these criteria, 246 patients who had undergone laparoscopy-assisted total gastrectomy were enrolled and compared with 246 patients who had undergone open total gastrectomy. Between groups (laparoscopic versus open), patients were matched for age, gender, body mass index (BMI) and clinical tumor node metastasis (TNM) stage. Gastric cancer clinical staging was performed based on the 7th edition of the TNM classification of gastric cancer .All patients were managed according to the same standardized postoperative gastrectomy protocol (Altorki *et al*., 2016; August *et al*., 2016; Bergmann *et al*., 2016; Breitenbuecher *et al*., 2015; Cahill *et al*., 2015; Dobson *et al*., 2015; Dagher *et al*., 2016; Gao *et al*., 2016; Ghoneum *et al*., 2015; Hase *et al*., 2016; Jin *et al*., 2016; Lee *et al*., 2015; Othman *et al*., 2015; Smithers *et al*., 2015; Spiliotis *et al*., 2016; Sterling *et al*., 2015; Tsiaras *et al*., 2016; Wang 2016; Yung *et al*., 2015). Perioperative mortality was defined as patient death within 30 days of gastrectomy or during initial hospitalization. Postoperative complications were defined as morbidity occurring within the first 30 days of gastrectomy or during hospital stay and were graded according to the Clavien–Dindo classification (Aldea *et al*., 2016; Apostolakis *et al*., 2015; Bruera *et al*., 2015; Chen *et al*., 2015; Freeman and Terracin 2016; Guo *et al*., 2015; Horgan *et al*., 2016; Hou *et al*., 2015; Jesche *et al*., 2016; Kowgier *et al*., 2015; Liu *et al*., 2015; Liu *et al*., 2016; Luo *et al*., 2015; Powles *et al*., 2016; Qian *et al*., 2016; Ramirez *et al*., 2016; Sheng *et al*., 2015; Tannir *et al*., 2016; Toyozumi *et al*., 2016; Wang 2015; Wang *et al*., 2015; Wu 2016; Zhu and Chen 2015). Patient follow-up data were obtained through office visits and telephonic interviews. Disease recurrence was defined as locoregional or distant metastasis with radiologic or pathologic validation (Cao *et al*., 2015; Chen *et al*., 2016; Zhou *et al*., 2016).

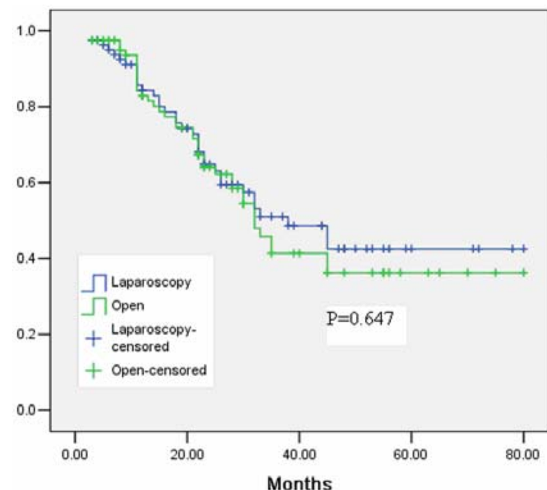

Fig. 2: Disease-free survival of all patients by operative approach (P = 0.647).

STATISTICAL ANALYSIS

All statistical analyses were performed using SPSS for Microsoft windows version 14.0 software (SPSS Inc., Chicago, IL, USA). Patient survival was analyzed using the Kaplan–Meier method, with group differences analyzed using the log-rank test. P<0.05 was considered statistically significant.

RESULTS

The incidence of infection was 112 in the patients with gastric resection, and the infection rate was 45.5%. A total

Table 1: The kinds of pathogenic bacteria distribution and constituent ratio

Pathogenic bacteria	Number	Constituent ratio
Gram positive bacteria	*48*	*38.71*
Enterococcus faecalis	19	15.32
Staphylococcus aureus	14	11.29
Staphylococcus haemolyticus	9	7.25
Staphylococcus epidermidis	3	2.40
Other	3	2.40
Gram negative bacteria	*76*	*61.21*
Escherichia coli	27	21.74
Pseudomonas aeruginosa	22	17.75
klebsiella pneumoniae	17	13.70
Acinetobacter baumannii	7	5.61
Other	3	2.45

Table 2: Antimicrobial resistance rate of main gram positive bacteria

Antibacterial drugs	*Enterococcus faecalis*		*Staphylococcus aureus*	
	number	Resistance rate	number	Resistance rate
Penicillin G	18	94.71	12	84.64
Ampicillin	15	77.15	10	76.59
Erythromycin	12	65.18	8	56.48
Amoxicillin	11	52.34	7	50.13

Table 3: Antibiotic resistance rate of main gram negative bacteria

Antibacterial drugs	*Escherichia coli*		*Pseudomonas aeruginosa*	
	Number	Resistance rate	Number	Resistance rate
Cefixime	11	40.49	10	44.56
ciprofloxacin	9	33.26	9	41.13
norfloxacin	8	30.07	8	37.37
Amikacin	2	5.13	1	4.45

Table 4: Clinical characteristics of the patients

	Laparoscopy (n=82)	Open (n=82)	*P* value
Age (years)	58 (43-76)	55 (39-79)	0.984
Sex			0.427
Male	51	46	
Female	31	36	
Comorbidity			0.845
Liver cirrhosis	2	3	
Hypertension	5	3	
Diabetes Mellitus	3	5	
Arrhythmia (orla take aspirin or warfarin)	1	2	
Hyperthyroidism	1	1	
BMI (kg/m2)	22 (17-27)	24 (18-32)	0.231
Clinical TNM stage (7th UICC)			0.485
IB	33	29	
IIA	39	41	
IIB	10	12	
Operative time (min)	275 (225-310)	230 (180-260)	0.000
Estimated blood loss (ml)	230 (200-255)	280 (255-405)	0.000
Number of analgesic injections	6.5 (2-10)	12 (5-18)	0.000
Time to first flatus (days)	3 (1-5)	4 (2-5)	0.000
Length of hospital stay (days)	16.5 (13-19)	19 (13-27)	0.000

Table 5: Pathological data of the patients

	Laparoscopy (*n*=82)	Open (*n*=82)	*P* value
Histological type			0.639
Differentiated	37	40	
Undifferentiated	45	42	
Retrieved lymph nodes	19 (16-21)	20 (16-25)	0.207
Pathological TNM stage (7th UICC)			0.904
IB	24	23	
IIA	23	25	
IIB	25	24	
IIIA	5	6	
IIIB	4	3	
IIIC	1	2	
Residual tumor (R0/R1/R2)	82/0/0	82/0/0	1.000

Table 6: Postoperative complications of the patients

	Laparoscopy (n=82)	Open (n=82)	P value
Overall complications n (%)	16 (19.5)	19 (23.1)	0.567
Major complications n (%)	5 (6.1)	7 (8.5)	0.951
Pulmonary embolism	1	2	
Anastomosis leakage	2	2	
Intra-abdominal bleeding	1	2	
Intra-abdominal abscess	1	1	
Minor complications n (%)	11 (13.4)	12 (14.6)	0.704
Wound infection	2	4	
Ileus	5	6	
Urinary tract infection	2	1	
Atelectasis	2	1	

Table 7: Prognostic factors for overall survival

Factors	Univariate P value	Multivariate P value
Age	0.023	
Sex	0.302	
BMI	0.099	
Operation time	0.020	
Tumor size	0.038	
Histological type	0.980	
Pathological T state	0.000	0.002
Pathological N stage	0.000	0.009
Adjuvant therapy	0.209	

Table 8: Recurrences after surgery

	Laparoscopy (n=82)	Open (n=82)	P value
Overall recurrence n (%)	14 (17.1)	17 (20.7)	0.550
Locoregional n (%)	8 (9.8)	9 (13.4)	0.954
Peritoneal seeding	3	4	
Anastomosis	2	3	
Lymph nodes	2	2	
Distant n (%)	6 (7.3)	8 (9.7)	0.739
Brain	1	2	
Liver	2	3	
Lung	1	1	
Bone	1	2	
Ovary	1	0	
Recurrence-free interval (median)	19 months	16 months	0.583

of 124 strains of pathogenic bacteria were detected. The distribution of the pathogens was shown in table 1. The main gram positive bacteria were resistant to penicillin was higher than 85%; of linezolid and teicoplanin

resistance rate is low, less than 12%; gram negative bacteria were resistant to imipenem and Amikacin low rate < 6%; separated from the main gram positive bacteria and gram negative bacteria resistance rate is shown in table 2 and 3. Patient demographics, including comorbidities, BMI, clinical disease stage, were similar between groups. Positron emission tomography-computerized tomography was performed for disease staging in 10% of patients belonging to the laparoscopy-assisted surgery group and 12% of those belonging to the open surgery group. No patients in this study had early stage disease (cT1). Patients in the laparoscopy-assisted surgery group had a longer total operative time (P= 0.000), underwent less blood loss (P=0.000), received fewer analgesic injections (P=0.000), and required a shorter hospital stay (P=0.000).

There was no significant difference between groups pertaining to the disease pathological stage (P = 0.904) or tumor subtype (P = 0.639). The number of harvested lymph nodes was also similar between the groups (P = 0.207), with more than 15 lymph nodes harvested during each resection. There were no instances of perioperative mortality. Postoperative complications occurred in 19.5% of patients in the laparoscopy-assisted surgery group and 23.1% of patients in the open surgery group. The overall frequency of complications was similar in both groups (P =0.951). The rate of major complications determined to be grade 3b or higher according to the Clavien–Dindo classification was also similar between the groups (P= 0.704).

The last follow-up was conducted in May 2014. After a median follow-up period of 42 months, the 5-year overall survival was 56% in the laparoscopy-assisted surgery group and 52% in the open surgery group (fig. 1, P = 0.621). The disease-free 5-year survival rate was 42% in the laparoscopy-assisted surgery group and 38% in the open surgery group, with no significant differences between the 2 groups (fig. 2, P=0.647). The recurrence location and recurrence-free interval were not significantly different between the 2 groups. There was no port-site recurrence in patients who underwent laparoscopy-assisted total gastrectomy.

We found that laparoscopy resulted in a long-term survival comparable with that achieved by laparotomy. Several studies have shown that fewer lymph nodes were harvested after laparoscopy-assisted total gastrectomy in comparison with those harvested after open total gastrectomy (Bo *et al*. 2013; Cai *et al*. 2013; Lin *et al*. 2014). Although the results of our study provide further evidence that laparoscopy does not compromise patient prognosis, it must be emphasized that surgeons performing laparoscopy-assisted total gastrectomy for upper gastric cancer must achieve D2 lymphadenectomy that is equivalent to laparotomy. Patient outcomes are likely more dependent on whether a surgeon performs a good oncologic procedure and not on the use of laparoscopy or laparotomy.

DISCUSSION

The gastric resection patients, the infections occurred in 112 patients, 12 patients with more than 2 kinds of pathogenic bacteria infection. 124 strains of pathogens, including 48 strains of gram positive bacteria accounted for 38.71%, mainly for 19 strains of Enterococcus faecalis accounted for 15.32%, 14 strains of Staphylococcus aureus accounted for 11.29%, 9 strains of Staphylococcus haemolyticus accounted for 7.26% and 3 strains of Staphylococcus epidermidis accounted for 2.42%; 76 strains of gram negative bacteria accounted for 61.29%, mainly Escherichia coli 27 21.77% strains, 22 strains of Pseudomonas aeruginosa accounted for 17.74%, 17 strains of Klebsiella pneumoniae accounted for 13.71% and 7 strains of A.baumannii were accounted for 5.65%. The main gram positive bacteria were resistant to teicoplanin and linezolid was low; gram negative bacteria were resistant to imipenem and Amikacin's low rate.

Previous studies have demonstrated the short-term superiority of laparoscopy over laparotomy for total gastrectomy, with benefits that include fewer complications and shorter hospital stays (Bo *et al*. 2013; Cai *et al*. 2013; Lin *et al*. 2014). Several institutional series have shown that long-term survival after laparoscopy to achieve total gastrectomy for upper gastric cancer is equivalent and perhaps better than that after laparotomy, although many of these studies were limited by small sample sizes and the potential bias of selecting laparoscopy when treating earlier TNM stage tumors (Bo *et al*. 2013; Cai *et al*. 2013; Lin *et al*. 2014). We found that laparoscopy resulted in a long-term survival comparable with that achieved by laparotomy. Several studies have shown that fewer lymph nodes were harvested after laparoscopy-assisted total gastrectomy in comparison with those harvested after open total gastrectomy (Bo *et al*. 2013; Cai *et al*. 2013; Lin *et al*. 2014). Although the results of our study provide further evidence that laparoscopy does not compromise patient prognosis, it must be emphasized that surgeons performing laparoscopy-assisted total gastrectomy for upper gastric cancer must achieve D2 lymphadenectomy that is equivalent to laparotomy. Patient outcomes are likely more dependent on whether a surgeon performs a good oncologic procedure and not on the use of laparoscopy or laparotomy.

In addition to its short-term benefits, laparoscopy for total gastrectomy to treat upper gastric cancer has other advantages over laparotomy. Several studies have shown that the benefits of laparoscopy are most pronounced in higher risk patients who are not suitable for open resection (Bo *et al*. 2013; Cai *et al*., 2013; Lin *et al*. 2014).

CONCLUSION

Laparoscopy may allow safe surgical resection with patients who may have been traditionally regarded to be poor candidates for resection based on laparotomy (Abu 2017; Fang and Ruan 2017; Liu *et al*. 2017; Takahashi 2017).

In this study, we has find several limitations about our research. The main study limitation which will influence the whole result is its retrospective nature. An imbalance between groups pertaining to patient characteristics that were not evaluated may have biased the study results. In addition, despite the relatively large number of patients, the study may have been underpowered to detect small group differences according to the overall and disease-free survivals. So that, we find out the result as add to the growing amount of published evidence demonstrating that the use of laparoscopy-assisted total gastrectomy for upper gastric cancer does not compromise patient long-term outcomes or survival.

ACKNOWLEDGEMENTS

Zheng Wang and Lian Liu contributed equally to this article and both should be considered first author.This work was supported by grants from the National Natural Science Foundation of China (No. 81100663) and Chinese postdoctoral Science Foundation (No. 2014M562136).

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