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의학석사 학위논문

T4a 위암을 대상으로 한 복강경 위절제술과 개복 위절제술의 수술관련 예후 및 종양학적 예후 비교

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이 논문을 의학석사 학위 논문으로 제출함

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정 성 아

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Comparisons of surgical and oncologic outcomes of laparoscopic gastrectomy and open gastrectomy in T4a gastric cancer

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Abstracts

Purpose: Laparoscopic gastrectomy (LG) has gradually increased for treatment of advanced gastric cancer. However, LG for T4a advanced gastric cancer is controversial. The aim of the present study is to evaluate the surgical and oncologic outcomes between laparoscopic and open gastrectomy (OG) for T4a gastric cancer.

Methods: We retrospectively reviewed 711 patients who underwent OG and 94 patients who underwent LG for T4a gastric cancer between August, 2005 and December, 2016. Finally, 86 patients of LG group and 161 patients of OG group were enrolled according to one to two propensity score matching (PSM) analysis. We evaluated surgical and oncological outcomes including overall survival (OS) and recurrence-free survival (RFS).

Results: There were no statistically differences in hospital stay and complication between the two groups. LG group had longer operation time compared to OG group ($p=0.04$). The retrieved lymph nodes of LG group was higher than that of OG (40.45 ± 16.65 vs 33.14 ±

11.39, $p<0.0001$). Also, there was no statistically difference in OS between the two groups. However, RFS of LG group was significantly longer than that of OG group ($p=0.025$).

Conclusion: Laparoscopic gastrectomy could be considered for treatment of T4a gastric cancer.

Contents

Lists of figures, tables & abbreviations

Introduction

Laparoscopic gastrectomy (LG) has been widely used to treat gastric cancer since 1994 after it was first introduced by Kitano et al. [1]. The laparoscopic approach has been shown to have considerable advantages, such as faster recovery, cosmetic gain, less pain, and better short-term postoperative outcomes, over an open approach in diverse operations [2, 3]. However, owing to the concern of tumor spread and the uncertainty of long-term outcomes in LG, laparoscopy has mostly been used for early gastric cancer (EGC). In recent years, the long-term outcomes of advanced gastric cancer (AGC) have been reported in several studies [4, 5]. Nevertheless, some reports suggested the difficulty of safe lymph node (LN) dissection for cancer with serosal invasion [5].

In this study, we aimed to demonstrate the surgical and oncologic outcomes of LG for T4a gastric cancer.

Materials and methods

Patients

We reviewed the data of 805 patients who had T4a gastric cancer after gastrectomy, including LG (n = 94) and open gastrectomy (OG, n = 711), between August 2005 and December 2016 at Asan Medical Center, a tertiary referral center in Seoul, Korea. The patients were selected based on post-surgical pathologic reports of proven T4a disease, in accordance with the American Joint Committee on Cancer (AJCC)-International Union for Cancer Control (UICC) 7th edition [6].

All patients opted for the operation with curative intent. Patients with positive resection margins on pathology were excluded from this study.

Clinical evaluation of outcomes

Data on the following characteristics were collected: age, sex, body mass index (BMI), presence of comorbidity, history of previous abdominal surgery, type of operation (distal gastrectomy or total

gastrectomy), level of LN dissection, combined gall bladder resection, time of starting a liquid diet, postoperative hospital stay, number of harvested LNs, tumor size, node status, and histologic type.

A postoperative complication was defined as any event requiring some treatment, either conservative or surgical, during postoperative hospital stay. These complications were reviewed and classified as anastomosis-associated complications, intraabdominal abscess, and the Clavien-Dindo classification system (CDC) ≥3 complications [7]

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Endpoints

The primary end-point was overall survival (OS), and the secondary outcome was recurrence-free survival (RFS). OS was assessed from the date of operation until the date of the last follow up visit or death. RFS was calculated from the date of surgery until the date of disease recurrence.

Statistical analysis

Descriptive statistics were calculated for patient characteristics by operation type. The chi-squared test or Fisher's exact test for categorical variables and the t-test for continuous variables were used to compare the two groups. To reduce the impact of selection bias and potential confounding in an observational study, we performed propensity score matching (PSM). The propensity scores were estimated using multivariate logistic regression models, wherein operative approach was included as the binary dependent variable and age, sex, BMI, history of previous abdominal surgery, type of operation, level of LN dissection, tumor size, node status, and histologic type were included as covariates. PSM was performed with a 1:2 greedy nearest neighbor algorithm within specified caliper widths. The absolute standardized differences were calculated to diagnose balance in covariates between operation types after PSM. All absolute standardized differences in the matched sample were less than 0.1. Generalized linear mixed models were used with identity link function and estimate robust variance to account for clustering by matching. The risks of complication were estimated using logistic regression analysis. Kaplan-Meier curves were used to estimate OS and RFS. P-values <0.05 were considered statistically significant. PSM was performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC USA), and all other analyses were performed using the R version 3.6.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Clinicopathologic characteristics

In this study, we enrolled 94 patients in the LG group and 711 patients in the OG group. Among them, 247 patients were selected for 1:2 PSM between the LG group and OG group (86 patients and 161 patients, respectively) (Table 1).

The mean age in the LG group was 55.0 years and that in the OG group was 57.7 years. In the unmatched analysis, the LG group had a higher proportion of female patients (56.4% vs 37.3%, p<0.001), but no difference was seen in BMI, comorbidity, or previous history of abdominal surgery. The LG group showed a smaller tumor size (<5 cm: 57.4% vs. 30.5%, p<0.001), had a higher proportion of D2 LN dissections (96.8% vs. 79.3%, p<0.001), and a higher node negativity rate (47.9% vs. 18.8%, p<0.001). There were no differences in baseline characteristics in the two groups, as assessed by PSM.

Table 1. Clinical characteristics of patients who underwent the laparoscopic gastrectomy(LG) and open gastrectomy(OG)

	Total group (n=805)		p-value	PSM group (1:2) (n=247)		SMD
	LG (n=94)	OG (n=711)		LG (n=86)	OG (n=161)	
Mean age, years (SD)	55.02 (14.30)	57.65 (12.44)	0.059	55.48 (14.14)	54.89 (11.88)	0.045
Sex, n (%)			<0.001			0.072
Male	41 (43.6)	446 (62.7)		41 (47.7)	71 (44.1)	
Female	53 (56.4)	265 (37.3)		45 (52.3)	90 (55.1)	
Mean BMI, kg/m² (SD)	23.49 (2.64)	23.32 (3.01)	0.615	23.43 (2.66)	23.52 (2.88)	0.034
Cmorbidities (%)			0.068			0.092
No	67 (71.3)	438 (61.6)		60 (69.8)	119 (73.9)	
Yes	27 (28.7)	273 (38.4)		26 (30.2)	42 (26.1)	
Operation history			0.572			0.051
No	61 (64.9)	440 (61.9)		55 (64.0)	99 (61.5)	

Yes	33 (35.1)	271 (38.1)		31 (36.0)	62 (38.5)	
Tumor size, n (%)			<0.001			0.075
<5cm	54 (57.4)	217(30.5)		47 (54.7)	82 (50.9)	
≥5cm	40 (42.6)	494 (69.5)		39 (45.3)	79 (49.1)	
Type of operation, n (%)			<0.001			0.004
DG	68 (72.3)	352 (49.5)		60 (69.8)	112 (69.6)	
TG	26 (27.7)	359 (50.5)		26 (30.2)	49 (30.4)	
Node status, n (%)			<0.001			0.041
Negative	45 (47.9)	134 (18.8)		37 (43.0)	66 (41.0)	
Positive	49 (52.1)	577 (81.2)		49 (57.0)	95 (59.0)	
LN dissection, n (%)			<0.001			0.013
Less than D2	3 (3.2)	147 (20.7)		3 (3.5)	6 (3.7)	
D2	91 (96.8)	564 (79.3)		83 (96.5)	155 (96.3)	
Histology			0.407			0.017
Differectiated	16 (17.0)	147 (20.7)		16 (18.6)	31 (19.3)	
Undifferenciated	78 (83.0)	564 (79.3)		70 (81.4)	130 (80.7)	
GB resection, n (%)			1.000			0.046
No	90 (95.7)	681 (95.8)		82 (95.3)	155 (96.3)	
Yes	4 (4.3)	30 (4.2)		4 (4.7)	6 (3.7)	

Values are expresse as mean(SD) or n (%).

PSM, Propensity score matching; SMD, Standardized difference; BMI, Body mass index; DG, Distal gastrectomy; TG, Total gastrectomy;

SMD < 0.1 is considered as balanced.

Table 2. Surgical outcomes in patients undergoing the LG and OG

	Total groups (n=805)		p-value	PSM groups (1:2) (n=247)		p-value
	LG (n=94)	OG (n=711)		LG (n=86)	OG (n=161)	
Operative time, min (SD)	154 (41.31)	148 (33.87)	0.152	156 (41.5)	146 (33.60)	0.041
Time to liquid diet, Median, days (IQR)	3 (3.00, 4.00)	4 (3.00, 5.00)	0.001	3 (3.00, 4.00)	4 (3.00, 4.00)	
Time to liquid diet, Log (SD)	1.25 (0.35)	1.38 (0.37)	0.002	1.26 (0.36)	1.30 (0.35)	0.398
Hospital day after surgery, median, days (IQR)	7 (6.00, 8.00)	8 (7.00, 10.00)	<0.001	7 (6.00, 8.00)	7 (7.00, 9.00)	
Hospital day after surgery, Log (SD)	2.04 (0.40)	2.17 (0.35)	<0.01	2.05 (0.41)	2.07 (0.21)	0.679
Retrieved LN, n (SD)	41 (16.59)	36 (13.65)	0.01	40 (16.65)	33 (11.39)	<0.0001

Values are expressed as mean(SD) or median (range).

PSM, Propensity score matching; LN, Lymph node

Postoperative outcomes

After surgery, the time to starting a liquid diet and length of hospital stay were the same in both groups (Table 2). The operation time was longer in the LG group (156 mins) than in the OG group (146 mins, p=0.04). According to pathologic review, the number of harvested abdominal LNs was higher in the LG group than in the OG group (40.5 vs. 33.1; p<0.0001).

Comparison of postoperative complication rates are given in Table 3. The overall complication rate was similar in both groups (p=0.41). The overall complications were classified into subgroups: Clavien-Dindo classification ≥3 complications, anastomosis-related complications, and intraabdominal abscess. Comparing the hazard ratios (HRs), we found that the types of complication were not affected by the operation type.

Table 3. Postoperative Complications in PSM patients

	LG (n=86)	OG (n=161)	HR (59% CI)	p-value
Overall complication, n (%)	30 (34.9)	48 (29.8)	0.79 (0.46, 1.38)	0.409
CDC ≥3 complications, n (%)	4 (4.7)	2 (1.2)	0.26 (0.04, 1.47)	0.127
Anastomosis complication, n (%)	3 (3.5)	4 (2.5)	0.70 (0.15, 3.29)	0.651
Intraabdominal abscess, n (%)	5 (5.8)	7 (4.34)	0.74 (0.22, 2.48)	0.629

Values are expressed number (%)., CDC, Clavien-dindo classification

Higher age (HR 1.62, p<0.001), presence of comorbidity (HR 1.91, p<0.001), and a longer operation time (HR 1.82, p<0.001) were associated with adverse effects in univariate analysis. In multivariate analysis, only the operation time was associated with complications (HR 1.81, p<0.001). Although the OG group showed a more frequent occurrence of overall complications, the difference did not reach statistical significance (HR 1.16, p=0.53).

Table 4. Analysis of risk factors for overall complications

	Univariate analysis			Multivariate analysis		
	p-value	HR	(95% CI)	p-value	HR	(95% CI)
Op. approach						
LG		1			1	
OG	0.537	1.15	0.73-1.81	0.525	1.16	0.73-1.86
Age						
< 60		1			1	
≥ 60	0.001	1.62	1.21-2.15	0.034	1.39	1.02-1.89
BMI						
< 25		1			1	
≥ 25	0.515	0.90	066-1.24	0.187	0.80	0.57-1.11
Comorbidities						
No		1			1	
Yes	< 0.001	2.42	1.21-4.87	0.001	1.69	1.23-2.31
Operation history						
No		1				
Yes	0.506	1.10	0.82-1.48			
Tumor size						
< 5cm		1				
≥ 5cm	0.124	1.27	0.94-1.72			
Operation time						
< 150min		1			1	

≥ 150min	< 0.001	1.82	1.37-2.43	< 0.001	1.81	1.34-2.44
Retrieved LN						
< 30		1			1	
≥ 30	0.327	1.16	0.86-1.56	0.374	1.15	0.84-1.57
Histology						
Differenctiated		1				
Undifferenciated	0.204	0.80	0.56-1.13			

Oncologic outcomes

The 5-year OS rates were 64.9% and 55.4% in the LG and OG groups, respectively. This rate was similar between the two groups (p=0.054). However, the 5-year RFS rate was 58.8% in the LG group and 47.7% in the OG group, showing a significant difference (p=0.025).

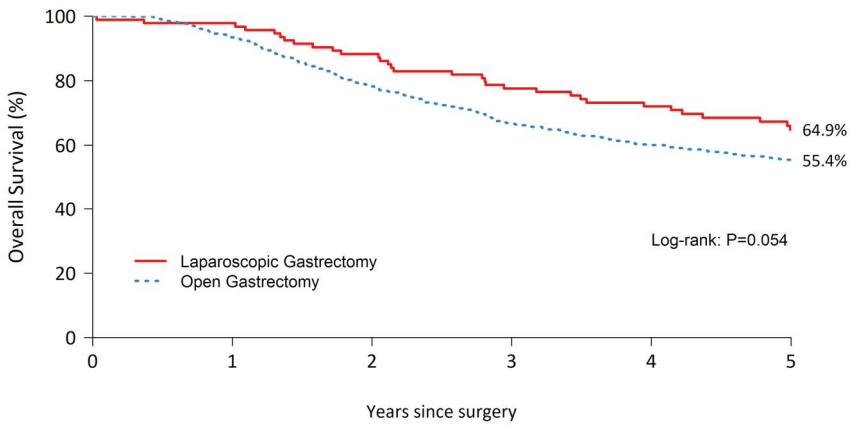

Figure 1. overall survival

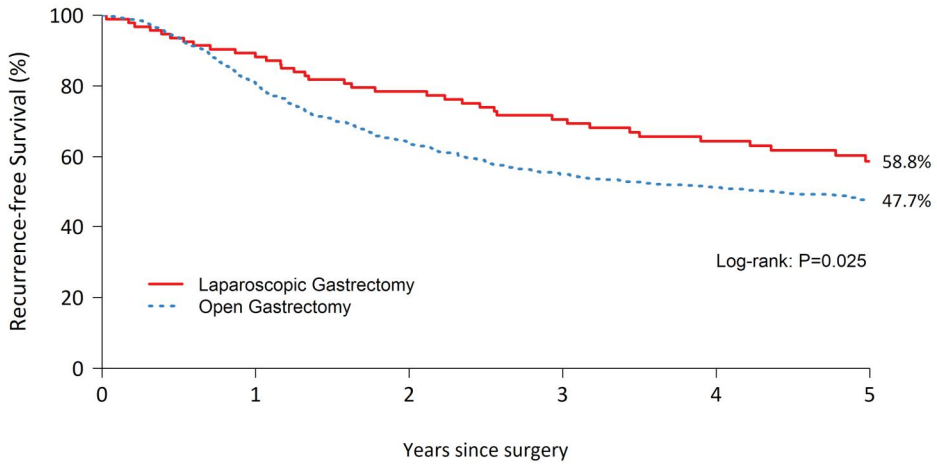

Figure 2. Recurrence-free survival

Discussion

In this study, we observed similar surgical outcomes between LG and OG for T4a gastric cancer; however, the 5-year RFS was superior in the former group. Although LG showed a longer operation time than OG, it did not lead to more postoperative complications or a longer hospital stay.

Several studies have demonstrated that LG is an effective alternative to OG for EGC [8]. Kim et al. proved the short-term superiority of LG and its long-term oncologic safety [9]. These superior or similar outcomes of minimally invasive surgery over the open approach have made LG the standard treatment for clinical stage I gastric cancer.

Lee et al. found short-term benefits of LG in terms of a lower complication rate, faster recovery, and less pain in AGC [10]. Recently, a randomized controlled trial was performed to investigate the long-term outcomes of LG for AGC and showed that LG was comparable to OG in terms of 3-year RFS [11]. Although many researchers have conducted studies on the safety of LG for AGC, many guidelines recommend OG as the standard treatment for AGC due to the lack of evidence for LG from long-term randomized controlled trials [12, 13].

Many studies have reported that laparoscopic surgery shows superior outcomes, such as a lower postoperative pain score, shorter hospital stay, early recovery of bowel movement, and a good cosmetic effect[3,14]. Another study showed a longer operation time for LG, similar to our study, but it also reported lower estimated blood loss, fewer postoperative complications, and a shorter hospital stay [8]. Our analysis showed similar outcomes in terms of postoperative recovery and all types of postoperative complications.

Concerns related to recurrence, such as increased risk of locoregional and peritoneal recurrence, have been reported earlier. Memon et al. reported a technical difficulty regarding LG in manipulating the cancerous tissue, leading to inadequate LN dissection [5]. In contrast, in our study, we harvested more LNs using the laparoscopic procedure. As laparoscopic operation involves a more detailed surgical view, especially for patients with a deep abdominal cavity or high BMI, it might lead to an easier lymphadenectomy for an experienced surgeon. To address the questions regarding peritoneal recurrence caused by CO2 pneumoperitoneum [15,16], further investigation is needed to analyze the recurrence pattern.

The number of metastatic LNs had a significant impact on oncologic outcomes [17, 18]. The number of metastatic LNs might be affected by the total number of retrieved LNs. Thus,

the metastatic lymph node ratio (MLR) is a more precise indicator of OS and RFS [19,20]. Luyang et al. showed that the MLR is a valuable indicator for the prognosis of gastric cancer with serosal invasion [21]. In this study, the laparoscopic approach helped in harvesting a higher number of LNs, but there was no difference in node status between the two groups. Moreover, further evaluation to classify the patients in the present study by N stage revealed that the LG group had a higher number of metastatic LNs (LG vs. OG; N0: 43.0% vs. 41.0%, N1: 15.1% vs. 14.9%, N2: 10.5% vs. 20.5%, N3: 23.3% vs. 18.0%, N4: 8.1% vs. 5.6%, SMD, Standardized difference = 0.30).

A few limitations should be taken into consideration for this study. We performed a retrospective single-center database study, which might have introduced an inherent bias. The number of patients undergoing LG was considerably low since an open approach was more acceptable for AGC during the study period. This made it difficult to analyze the recurrence pattern or other surgical outcomes because the LG group had a smaller sample size, which was inadequate to obtain significantly reliable results by statistical analysis. Furthermore, there was bias associated recurrence due to follow-up loss.

Conclusion

In conclusion, LG could be considered for the standard treatment of T4a gastric cancer; it showed postoperative outcomes comparable to those of OG. Moreover, laparoscopic surgery allows the harvesting of a higher number of LNs, thus improving RFS. To ensure an oncologically safe laparoscopic approach for gastric cancer with serosal invasion, operators

must have sufficient laparoscopy-related skills. Additional large-scale investigations are needed to compare peritoneal recurrence or port-site recurrence between the two groups.

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국문 요약

연구목적

진행 위암에서 복강경 위절제술은 점차 활발하게 시행되고 있다. 하지만 T4a 위암에서 복강경 수술을 적용하는 것은 아직 논란이 있는 상태이다. 따라서 본 연구에서는 T4a 위암을 대상으로 복강경 위절제술과 개복 위절제술의 수술 후 예후와 종양학적 예후를 비교하는 것을 목표로 하였다.

연구방법

2005 년 8 월부터 2016 년 12 월까지 위절제술을 시행 받은 후 T4a 위암을 진단받은 환자들을 대상으로 후향적 연구를 진행하였다. 전체 환자군 805 명 중에서 복강경 수술군은 71 명이었고 개복 수술군은 711 명이었다. 이를 대상으로 1:2 성향 점수 매칭을 시행하여 86 명의 복강경 수술군과 161 명의 개복 수술군을 분류하였다. 본 연구에서는 두 군 간의 수술 후 회복 및 합병증의 발생 정도를 비교하였으며 종양학적 예후 예측을 위해 전체 생존률과 재발 생존률을 비교하였다.

연구결과

복강경 수술군과 개복 수술군에서 수술 후 회복과 합병증 발생률에서는 차이가 확인되지 않았다. 복강경 수술은 개복수술보다 더 긴 수술시간이

확인되었다(p=0.04). 복강경 수술군에서는 개복 수술군보다 더 많은 림프절을 박리할 수 있음이 확인되었다(41 ± 16.65 vs 33 ± 11.39, p<0.0001). 두 환자군을 5 년간 추적 관찰 하였을 때 전체 생존률에서는 차이가 나지 않았으나, 재발 생존률에서 복강경 수술군이 더 좋은 결과를 보였다(p=0.025).

결론 및 제언

본 연구의 결과를 통해 복강경 위절제술을 T4a 위암의 치료로 고려할 수 있다는 결론을 내릴 수 있었다.