의학석사 학위논문

Spleen-Preserving Lymphadenectomy Versus Splenectomy in Laparoscopic Total Gastrectomy for Advanced Gastric Cancer

진행성 위암에서 복강경 위전절제술 중 비장보존 림프절곽청술과 비장절제술의 비교

2014년 2월

서울대학교 대학원
의학과 임상의과학과
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Master of Science in Clinical Medical Sciences

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Sang-Yong Son
Department of Clinical Medical Sciences
Seoul National University

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지도 교수 이 태 승

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의학과 임상의과학과
손 상 용

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부위원장 이 태 승 (인)
위 원 강 성 범 (인)

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논문제목 : Spleen-Preserving Lymphadenectomy Versus Splenectomy in Laparoscopic Total Gastrectomy for Advanced Gastric Cancer

학위구분 : **석사 □ · 박사 □**
학 과 : 임상의과학과
학 번 : 2012-22701
연 락 처 : spy798@gmail.com
저 작 자 : 손 상 용 (인)

제 출 일 : 2014 년 2 월 5 일

서울대학교총장 귀하

Abstract

Spleen-Preserving Lymphadenectomy Versus Splenectomy in Laparoscopic Total Gastrectomy for Advanced Gastric Cancer

Sang-Yong Son

Department of Clinical Medical Sciences

The Graduate School

Seoul National University

Introduction: To investigate the optimal approach for laparoscopic splenic hilum lymph node dissection in advanced gastric cancer, we compared the operative outcomes between laparoscopic spleen-preserving total gastrectomy (sp-LTG) and laparoscopic total gastrectomy with splenectomy (sr-LTG).

Methods: A retrospective case-control study was conducted between February 2006 and December 2012. The operative outcomes, the number of retrieved splenic hilum lymph node, complication, and patient survival were analyzed.

Results: 112 patients who underwent laparoscopic total gastrectomy with or without splenectomy for advanced gastric cancer were enrolled (68 sp-LTGs and 44 sr-LTGs). The mean operation time (227 min *vs.* 224 min, p=0.762) and estimated blood loss (157 ml *vs.* 164 ml, p=0.817) were not different between two groups. Regarding splenic lymph node dissection, there were significantly differences in the mean number of retrieved lymph nodes between sp-LTG group and sr-LTG group (LN #10; 1.78 *vs.* 3.21, p=0.033, LN #11d; 1.41 vs. 2.76, p=0.004). The complication rate was 17.6% in sp-LTG group and 13.6% in sr-LTG group, respectively (p=0.572). In multivariate analysis, circular lesion and vascular invasion were independent prognostic factors related to overall survival, but splenectomy was not associated with

overall survival (p=0.0.29, p=0.006, and p=0.453, respectively)

Conclusions: sp-LTG may be the treatment of choice for splenic hilum lymph node dissection in advanced gastric cancer.

Keywords: Gastric cancer, Laparoscopy, Total gastrectomy, Splenectomy

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목 차

List of Tables

List of Figures

Introduction

Between 8% and 26% of patients with upper and middle gastric cancer have splenic hilar lymph node metastasis (1-4). For this reason, it is recommended that the D2 lymph node dissection during total gastrectomy in advanced gastric cancer should include the splenic hilar lymph nodes (5). In the past, to dissect the no. 10 and no. 11 lymph nodes completely, it was necessary to perform pancreatosplenectomy. However, this was associated with high rates of morbidity due to complications such as pancreatic fistula, subphrenic abscess, and postoperative diabetes (6, 7). As a result, pancreatosplenectomy in total gastrectomy with D2 lymph node dissection was gradually replaced by pancreas-preserving total gastrectomy. However, this modification did not alter the high rate of morbidity and mortality (8-10). Thereafter, after advances were made in surgical techniques and instruments, some surgeons proposed spleen-preserving no. 10 lymph node dissection. Many studies then showed that this procedure was safe and associated with the same survival rate as pancreas-preserving total gastrectomy (3, 9, 11-13). However, several studies also show that in certain cases, such as bulky lymph node metastasis, Bormann type IV tumor, and tumor located in the greater curvature, splenectomy in total gastrectomy with D2 lymph node dissection associates with survival gains (1, 2). Therefore, role of splenectomy in the treatment of advanced gastric cancer in the upper and middle third of the stomach remains controversial.

Laparoscopic distal gastrectomy has rapidly become popular for the treatment of early stage gastric cancer. Indeed, as laparoscopic surgery experience has grown, some institutions have extended the indications for laparoscopic distal gastrectomy to include locally advanced gastric cancer. However, laparoscopic total gastrectomy, with or without splenectomy is not popular: only a few studies have described cases of laparoscopic total with D2 lymph node dissection (14-16). This is because

laparoscopic esophagojejunostomy is associated with a very steep learning curve; moreover laparoscopic splenic hilar and paracardial nodal dissection is a technically demanding procedure. Splenic hilar node dissection is particularly difficult when splenectomy is not performed. In open surgery, to remove the lymph nodes along the splenic vessels without splenectomy, the distal pancreas and spleen are mobilized from the retroperitoneum. This maneuver allows surgeons to easily dissect the lymph nodes under direct view and palpitation. However, in laparoscopic surgery, this approach cannot be used because of the space limitations and the limited tactile sensation of the instrument. Although several spleen-preserving approaches to laparoscopic total gastrectomy with D2 lymph node dissection have been introduced (15, 17-19), laparoscopic splenic hilar node dissection remains a time-consuming procedure that requires meticulous surgical technique to avoid unexpected injury to a splenic vessel or the pancreas. Furthermore, a recent retrospective study showed that, on average, fewer splenic hilar lymph nodes are retrieved in laparoscopic surgery than in open surgery (20).

The present retrospective case-control study of patients with advanced gastric cancer who underwent laparoscopic total gastrectomy with splenic hilum lymph node dissection was performed to assess the outcomes of splenectomy versus spleen-preserving approaches.

Materials and methods

This case-control retrospective was based on a prospectively collected gastric cancer database. Some clinical information was taken retrospectively from electric medical records of the hospital. The Institutional Review Board at our institution approved for this research on human subjects (protocol registration number B1310-222-107).

Patients

Between February 2006 and December 2012, 164 patients with clinically advanced gastric cancer underwent laparoscopic total gastrectomy with D2 lymph node dissection with or without splenectomy at Seoul National University Bundang Hospital. All patients were preoperatively diagnosed with advanced gastric cancer by routinely performed computed tomography and endoscopic ultrasonography. Of the 164 patients, 52 were excluded because they underwent open conversion (n=19), were diagnosed with early gastric cancer at the final pathological examination (n=17), underwent distal pancreatectomy (n=8), underwent completion total gastrectomy for remnant gastric cancer (n=1), or underwent a palliative operation (n=7). The remaining 112 patients were enrolled into the study and divided into two groups depending on whether splenectomy had been performed. The institutional indication for splenectomy was clinical suspicion of serosa exposure of the tumor. The spleen-preserved and spleen-resected groups were denoted as the sp-LTG and sr-LTG groups, respectively.

Operative technique of spleen-preserving lymphadenectomy and splenectomy

Laparoscopic surgery was conducted with the patient in the supine position. A five-port system (two 5 mm ports and three 12 mm ports) was used for the laparoscopic

total gastrectomy. A 10 mm flexible laparoscope was used and the CO_2 pressure was maintained at 12–14 mmHg. An ultrasonically activated coagulating scalpel (Harmonic Scalpel, Ethicon EndoSurgery Inc., Cincinnati, OH, USA) and LigaSure (Valleylab, Boulder, CO, USA) were used for radical lymphadenectomy, which was conducted from the perigastric lymph nodes to the no. 7, 8, 9, 11p and 12a lymph nodes. In spleen-preserving lymphadenectomy, no. 11d and splenic hilum dissection proceeded without spleen mobilization after lower esophageal transection. In the case of splenectomy, the spleen was fully mobilized, after which the caudal splenic artery and vein were ligated with the Hem-o-Lok clip (Weck Closure System, Research Triangle Park, USA) or linear stapler at the point of the pancreas tail. Almost esophagostomy was performed by using a laparoscopic purse-string clamp (Lap-Jack, Eterne, Kyeonggi-do, South Korea) and, in most cases, end-to-side esophagojejunostomy was performed intracorporeally by using a circular stapler. However, in five cases, side-to-side esophagojejunostomy was performed by using linear staplers. The Roux-en-Y construction was completed by performing jejunojejunal anastomosis *via* mini-laparotomy. After retrieving the specimen from the abdomen, all dissected lymph nodes were classified according to the Japanese Classification of Gastric Carcinoma.

Statistical Analysis

All statistical analyses were performed by using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The χ^2 test, Fisher's exact test, and Student's *t*-test were used to compare the two groups in terms of demographic, clinical and operative variables. For univariate and multivariate analysis for overall survival, Kaplan–Meier curves and

cox proportional hazard method were used. A p-value of < 0.05 was considered to indicate statistical significance

Results

Patient characteristics

The patient characteristics are summarized in Table 1. In the sp-LTG and sr-LTG groups, the mean ages were 60.2 and 54.6 years, respectively (p=0.034), and the mean body mass indices were 23.87 and 22.56, respectively (p=0.041). The sp-LTG group patients were more likely to have T3 and N0 stage cancer, while the sr-LTG group patients were more likely to have T4a and N3 stage cancer. The two groups did not differ significantly in terms of sex, ASA class, and tumor location (horizontal). Regarding splenic hilum metastasis, six (8.8%) sp-LTG group patients and four (9.1%) sr-LTG group patients had no. 10 metastasis, while six (8.8%) sp-LTG group patients and seven (15.9%) sr-LTG group patients had no. 11d metastasis.

Table 1. Patient's characteristics

Variables	sp-LTG (n=68)	sr-LTG (n=44)	*p*-value
Age (years)	60.28 ± 14.03	54.66 ± 12.75	0.034
Sex (male:female)	50:18	28:16	0.266
Body Mass Index (kg/m^2)	23.87 ± 3.33	22.56 ± 3.13	0.041
ASA class			0.878
1	33 (48.5%)	23 (53.5%)	
2	28 (41.2%)	16 (37.2%)	
3	7 (10.3%)	4 (9.3%)	
Tumor location (vertical)			0.030
Upper	54 (79.4%)	33 (75.0%)	
Middle	10 (14.7%)	5 (11.4%)	
Whole	4 (5.9%)	6 (13.6%)	
Tumor location (horizontal)			0.570
Anterior	12 (17.6%)	9 (20.5%)	
Posterior	21 (30.9%)	10 (22.7%)	
Lesser curvature	27 (39.7%)	17 (38.6%)	
Greater curvature	3 (4.4%)	1 (2.3%)	
Circular	5 (7.4%)	7 (15.9%)	
Histology			0.046
Intestinal	25 (37.3%)	7 (15.9%)	
Diffuse	36 (53.7%)	33 (75.0%)	
Mixed	6 (9.0%)	4 (9.1%)	
T-stage			<0.001
T2	23 (33.8%)	6 (13.7%)	
T3	31 (45.6%)	13 (29.5%)	
T4a	14 (20.6%)	25 (56.8%)	
N-stage			0.003
N0	28 (41.2%)	8 (18.2%)	
N1	17 (25.0%)	7 (15.9%)	
N2	10 (14.7%)	10 (22.7%)	
N3	13 (19.1%)	19 (43.2%)	
Stage			0.001
IB	16 (23.5%)	4 (9.3%)	
IIA	23 (33.8%)	6 (14.0%)	

IIB	8 (11.8%)	6 (14.0%)	
IIIA	6 (8.8%)	9 (20.9%)	
IIIB	11 (16.2%)	5 (11.6%)	
IIIC	4 (5.9%)	13 (30.2%)	
Splenic hilum metastasis			
No. 10	2 (8.7%)	3 (9.1%)	1.000
No. 11d	6 (9.7%)	7 (17.1%)	0.269

sp-LTG spleen-preserving laparoscopic total gastrectomy; *sr-LTG* laparoscopic total gastrectomy with splenectomy; *ASA* American Society of Anesthesiologist

Perioperative outcomes

The perioperative outcomes are summarized in Table 2. The sp-LTG and sr-LTG groups did not differ significantly in terms of operation time (227.6 *vs*. 224.9 min; p = 0.762) or estimated blood loss (157.8 *vs*. 164.2 ml; p = 0.518). However, compared to the sr-LTG group, the sp-LTG group had significantly smaller tumors (5.39 *vs.* 7.40 cm; p = 0.004) and fewer lymph nodes were retrieved (59.3 *vs.* 68.0; p=0.033), especially from the no. 10 and 11d lymph node stations (no. 10: 1.78 *vs.* 3.21, p = 0.033; no. 11d: 1.41 *vs*. 2.76, p = 0.004).

Regarding the postoperative course, the two groups did not differ significantly in terms of time to flatus passage or postoperative hospital stay. The sp-LTG and sr-LTG groups also had similar rates of >grade II complications (*Clavien-Dindo* classification) (17.6% *vs.* 13.6%; p = 0.572). Four sp-LTG group patients and one sr-LTG group patient exhibited anastomotic leakage: all of these cases underwent side-to-side anastomosis by using linear staplers. None of the patients died after laparoscopic total gastrectomy.

Table 2. Postoperative outcomes

Variables	sp-LTG (n=68)	sr-LTG (n=44)	*p*-value
Operation time (min)	227.6 ± 59.9	224.9 ± 35.5	0.762
Estimated blood loss (mL)	157.8 ± 124.5	164.2 ± 160.26	0.817
Tumor size (cm)	5.39 ± 3.39	7.40 ± 3.64	0.004
Resection margin (cm)			
Proximal	3.39 ± 1.75	3.31 ± 3.15	0.860
Distal	13.89 ± 5.22	11.44 ± 3.95	0.009
Retrieved LNs	59.35 ± 19.89	68.00 ± 20.21	0.033
No. 10	1.78 ± 2.09	3.21 ± 2.79	0.042
No. 11p	2.69 ± 2.19	3.32 ± 2.72	0.208
No. 11d	1.41 ± 1.55	2.76 ± 2.29	0.004
Flatus passage (day)	4.0 ± 1.0	4.2 ± 1.10	0.360
Hospital stay (day)	9.3 ± 6.3	8.6 ± 5.0	0.557
Complications	12 (17.6%)	6 (13.6%)	0.572
Wound	1 (1.5)	1 (2.3%)	
Anastomotic leakage	4 (5.9%)	1 (2.3%)	
Passage disturbance	3 (4.4%)		
Pulmonary problem	1 (1.5%)		
Pancreatic fistula†		2 (4.5%)	
Others	3 (4.4%)	2 (4.5%)	

sp-LTG spleen-preserving laparoscopic total gastrectomy; *sr-LTG* laparoscopic total gastrectomy with splenectomy; *LNs* lymph nodes

†Grade B and C which was defined by the international Study Group on Pancreatic Fistula (ISGPF).

Survival and recurrence after laparoscopic total gastrectomy: spleen-preserving vs. splenectomy

The mean durations of follow-up were 35.7 months in the sp-LTG group and 29.3 months in the sr-LTG group (p=0.069). Since the two groups were heterogenous in terms of TNM stage and the sample size on each stage was small, univariate and multivariate analysis were performed for survival analysis. By univariate analysis, ASA score 2-3, circular lesion, lymphatic invasion, vascular invasion, T4a stage, N2-3 stage, lymph node #10, 11p metastasis, and postoperative complication were associated with poor overall survival (Table 3). Otherwise, splenic hilar dissection (spleen-preserving or splenectomy) had no marked impact on patient survival: the overall survival of durations of the sp-LTG and sr-LTG were 82.3 and 69.9 months, respectively (p= 0.453) (Figure 1). Multivariate analysis revealed that circular lesion and vascular invasion were independent prognostic factor of poor overall survival of patients with upper and middle advanced gastric cancer.

Seven patients (four sp-LTG group and three sr-LTG group patients) were lost to follow-up. In the remaining patients, the recurrence rate was 15.6% (10/64) and 31.7% (13/41) in the sp-LTG and sr-LTG group, respectively (p=0.251). One, four and one of the sp-LTG group patients developed locoregional, hematogenous and peritoneal metastases, respectively, while one, five, and seven of the sr-LTG group patients developed locoregional, hematogenous and peritoneal metastases, respectively.

Table 3. Prognostic factors related to overall survival of advanced gastric cancer patients underwent laparoscopic total gastrectomy with D2 lymphadenectomy

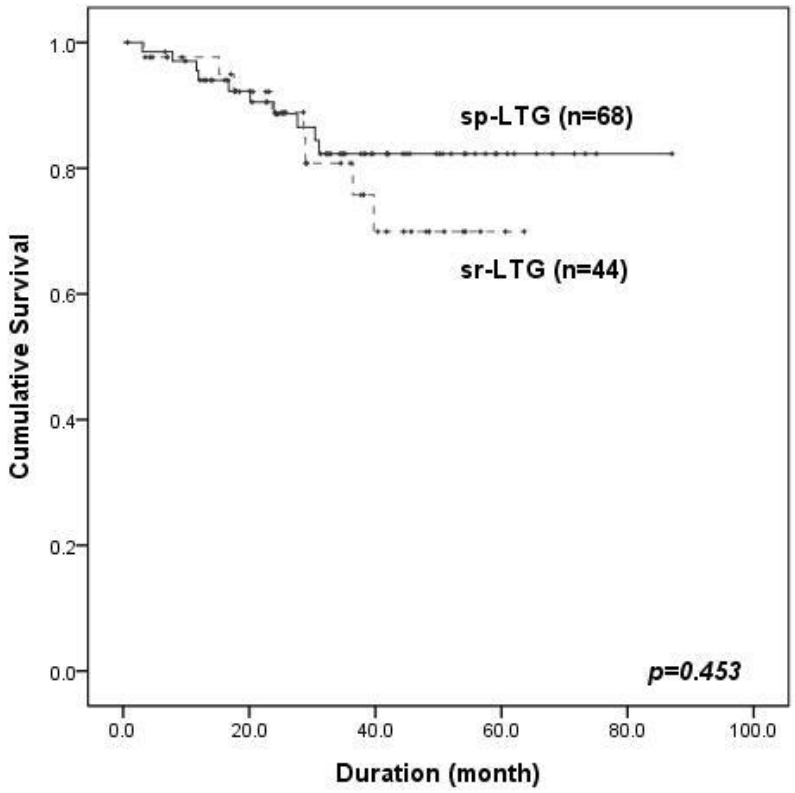
Variables	Univariate analysis		Multivariate analysis		
	5-year overall survival, %	*p*-value*	Hazard ratio	95% confidence interval	*p*-value†
Age (years)		0.186			
< 60	83.1				
≥ 60	72.3				
Sex		0.101			
Male	71.3				
Female	89.5				
Body Mass Index (kg/m^2)		0.799			
< 23	74.9				
≥ 23	80.2				
ASA class		0.005			0.066
1	91.7		1		
2-3	62.3		3.386	0.922-12.441	
Comorbidity		0.614			
No	77.6				
Yes	77.7				
Tumor location (horizontal)		0.001			0.029
Anterior/Posterior/Lesser/Greater	83.4		1		
Circular	39.0		5.397	1.186-24.565	
Splenic hilar dissection		0.453			
Spleen-preserving	82.3				
Splenectomy	69.9				
Tumor size		0.035			0.826
< 5cm	88.4		1		
≥ 5cm	66.6		1.196	0.242-5.926	
Histology		0.906			
Intestinal	79.9				
Diffuse	79.0				
Mixed	65.6				
Lymphatic invasion		0.049			0.901

No	89.4		1		
Yes	68.8		1.106	0.225-5.444	
Vascular invasion		<0.001			0.006
No	92.5		1		
Yes	32.2		6.940	1.754-27.462	
T-stage		0.005			0.262
T2-3	88.9		1		
T4a	55.1		2.621	0.87-14.113	
N-stage		0.001			0.660
N0-1	90.6		1		
N2-3	51.5		1.500	0.246-9.146	
Lymph node #10 metastasis		0.042			0.777
No	79.8		1		
Yes	50.0		1.292	0.219-7.639	
Lymph node #11p metastasis		0.004			0.132
No	80.6		1		
Yes	40.6		3.741	0.671-20.862	
Lymph node #11d metastasis		0.641			
No	78.0				
Yes	75.0				
Postoperative complication		0.003			0.258
No	84.7		1		
Yes	43.7		2.398	0.528-10.898	
Adjuvant chemotherapy		0.237			
No	88.0				
Yes	73.2				

ASA American Society of Anesthesiologist

*Log-rank test; †Cox proportional hazard model.

Figure 1. Overall survival according to spleen-preserving lymphadenectomy or splenectomy during laparoscopic total gastrectomy with D2 lymphadenectomy



Discussion

Since Kitano performed 1st laparoscopy-assisted distal gastrectomy for gastric cancer (21), many studies have shown that laparoscopic gastric surgery has many benefits over open gastric surgery (22-25). Recent advances in laparoscopic devices and techniques have led several surgeons to extend the indications of this procedure to include locally advanced cancer. Several ongoing clinical studies are presently evaluating the feasibility of laparoscopic extended lymph node dissection for advanced gastric cancer (26, 27). However, laparoscopic total gastrectomy for proximal advanced cancer is not popular because complete D2 lymphadenectomy and esophagojejunostomy after gastrectomy are technically difficult procedures.

Regarding complete radical lymphadenectomy during total gastrectomy, Japanese Gastric Cancer guidelines (3rd edition) recommend that D2 lymph node dissection should include the splenic hilar nodes (5). However, the intricacy and variability of the splenic vessels in the splenic hilum makes it very difficult for surgeons to dissect the splenic hilar nodes laparoscopically without performing a splenectomy. Spleen-preserving laparoscopic splenic hilar dissection may thus increase the risk of unintended injury to the splenic vessels or pancreas, which could result in dreadful complications such as splenic arterial pseudoaneurysm. However, several skillful surgeons have suggested technical solutions for laparoscopic splenic hilar dissection. Shinohara *et al.* (14) reported that meticulous dissection of suprapancreatic nodes can be performed after the initial mobilization of the pancreas body and downward retraction of the caudal gland of the pancreas by gauze traction. Hur *et al*. (15) reported that taping of the splenic artery is helpful when dissecting the lymph nodes during spleen- and pancreas-preserving laparoscopic total gastrectomy. Okabe *et al.* (19) described a medial approach in which the pancreas is mobilized from the cranial

side, while Jia-Bin *et al*. (18) suggested a left-sided approach for laparoscopic splenic hilar lymphadenectomy. However, while these studies showed that these procedures are associated with acceptable operation times (range: 206−406 minutes) and mean retrieved lymph node numbers (range: 23−60), only a few studies have reported the mean retrieved splenic hilar node numbers associated with these spleen-preserving procedures (range: 2.6−2.8) (18, 19, 28).

Whether splenectomy should be performed during laparoscopic lymphadenectomy for upper and middle advanced gastric cancer remains controversial. While many reports showed that splenectomy did not offer any survival benefit and was associated with high morbidity and mortality, these studies were limited by their inclusion of early gastric cancers and palliative operations (3, 11). However, some studies have shown that splenectomy can improve survival in some cases, such as Bormann type IV gastric cancer or cancer in the greater curvature (29, 30). A well-designed randomized controlled trial that resolves this controversy is needed. For this reason, we are awaiting the results of the JCOG 0110-MF trial.

The present study was performed to investigate the optimal approach for D2 lymphadenectomy during laparoscopic total gastrectomy for advanced gastric cancer. Comparison of the sp-LTG and sr-LTG groups revealed that they did not differ in terms of operation time, estimated blood loss, or postoperative course. Their rates of >grade II complications (according to the Clavien-Dindo system) also did not differ. In the present study, sr-LTG was associated with higher rates of no. 10 and 11d lymph node retrieval, and this suggests that sr-LTG may be superior to sp-LTG in terms of complete D2 lymph node dissection for upper and middle advanced gastric cancer. However, univariate and multivariate analysis showed that splenic hilar dissection

with or without splenectomy was not associated with overall survivals, this result means that splenectomy for complete D2 lymph node dissection during laparoscopic total gastrectomy does not guarantee survival improvement. Thus, spleen-preserving lymphadenectomy is recommended during laparoscopic total gastrectomy for advanced gastric cancer if there is no direct invasion or metastasis to splenic hilum, according to the current Japanese gastric cancer guidelines. However, it should be noted that our study is limited by its small sample size and retrospective design. More robust and large-scale phase III studies are warranted.

Conclusion

In conclusion, sr-LTG could be a way for confidential splenic hilum lymph node dissection in advanced gastric cancer in terms of retrieved number of splenic hilar nodes. However, sr-LTG and sp-LTG did not differ in terms of overall survival, complication rates or short-term postoperative outcomes, which suggest that sp-LTG may be the treatment of choice for splenic hilum lymph node dissection in advanced gastric cancer.

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초 록

서론: 진행성 위암에서 복강경 위전절제술시 비문부 림프절 곽청을 위해 최적의 방법을 찾기 위하여 비장보존 비문부 림프절 곽청술과 비장절제술의 결과를 비교하고자 한다.

방법: 2006 년 2 월 2012 년 12 월까지 기간을 대상으로 후향적 환자군-대조군 연구를 진행하였으며, 두 군의 임상결과를 비교하기 위하여 수술 단기 결과, 수술결과 얻어진 림프절 수, 수술 후 합병증, 그리고 수술 후생존률 등을 비교 분석하였다.

결과: 연구대상 환자는 총 112명으로 비장보존 복강경 위전절제술을 시행받은 68명과 비장절제 위전절제술을 시행 받은 44명이 포함되었다. 각 군에서 평균 수술시간은 227분과 224분(p=0.762), 평균 출혈량은 157ml와 164ml로 두 군간 통계학적 차이는 없었다. (p=0.817). 그러나 수술 후 얻어진 비문부 림프절 수에 있어서는 유의한 차이가 있었는데, 비장절제 복강경 위전절제술에서 10번과 11d 림프절 수가 더 많았다. (LN #10; 1.78 *vs.* 3.21, p=0.033, LN #11d; 1.41 vs. 2.76, p=0.004). 합병증은 비장보존 복강경 위전절제술의 경우 17.6% 비장절제 복강경 위전절제술의 경우 3.6%로 두 군간 통계학적으로 유의한 차이는 없었다 (p=0.572). 일변량 및 다변량 분석 결과 위를 둘러싸는 형태의 종양과 혈관 침범 여부가 생존과 관련된 예측 인자였지만, 비문부 림프절 곽청을 위한 비장절제 여부는 생존율과 연관이 없었다 (p=0.453)

결론: 복강경 위전절제술시 비장절제술은 수술 후 얻어진 림프절 수 측면에서 좀더 확실한 비문부 림프절 곽청 방법이다. 하지만, 복강경 비장보존 림프절 곽청술과 비교하여 생존률, 합병증, 그리고 단기 수술 결과 등에서 차이가 없으므로, 비장보존 복강경 위전절제술이 진행성 위암에서 비문부 곽청에 가장 적합한 방법이다.

주요어: 위암, 복강경 수술, 위전절제술, 비장절제술

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