The effect of spleen-preserving lymphadenectomy on surgical outcomes of locally advanced proximal gastric cancer

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ABSTRACT

The effect of spleen-preserving lymphadenectomy on surgical outcomes of locally advanced proximal gastric cancer

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Background: The aim of this study was to investigate the effects of D2 lymphadenectomy with spleen preservation on surgical outcomes in locally advanced proximal gastric cancer.

Methods: Between January 2000 and December 2004, a total of 366 patients who underwent curative total gastrectomy were studied retrospectively from a prospectively-designed database.

Results: The spleen-preservation group experienced shorter operation times, a lower incidence of perioperative transfusion, and shorter postoperative hospital stays. Perioperative transfusion and splenectomy were independent risk factors for morbidity. There was no significant difference between the two groups in recurrence or cumulative survival rate when adjusted according to cancer stage. Multivariate analysis showed that tumor size, serosal invasion, and nodal metastasis were independent prognostic factors, while splenectomy was not. The cumulative survival rate in pN0-status patients was significantly higher in the spleen-preservation group, while there was no significant difference in the survival of pN1- or pN2-status patients between the two groups.

Conclusions: Splenectomy for lymph node dissection in proximal gastric cancer patients obviously showed poor short surgical outcomes, but it did not

affect long-term outcomes in terms of recurrence and overall survival rate. Therefore, spleen-preserving lymphadenectomy is a feasible method for radical surgery in locally advanced proximal gastric cancer.

Key words : gastric cancer, spleen-preserving, surgical outcome

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I. INTRODUCTION

Although it is well known that lymph node metastasis is an important factor in the prognosis of gastric cancer, the optimal extent of lymph node dissection is still under debate.[1, 2] Two large prospective randomized trials in Western countries have reported that postoperative morbidity and mortality was higher after D2 than after D1 dissection in gastric cancer surgery, and that splenectomy was a risk factor for morbidity and related to a decreased survival rate.[3, 4] Nevertheless, combined resection of the spleen has been tried completely remove the lymph nodes surrounding the splenic artery and splenic hilum, structures which are included in D2 lymph node dissection in upper-third gastric cancer.[3]

The frequency of lymph node metastasis to the splenic hilum in proximal gastric cancer is 10~25%.[4] Because most metastasis occurs in advanced proximal gastric cancer, extended lymph dissection may be unnecessary for patients without lymph node metastasis to the splenic hilum in the early stages. However, the effect of spleen preservation on lymph node dissection is still under debate due to complicated network of lymphatic drainage of the stomach.[5] Furthermore, it is difficult to compare the previous literature due to different surgical standardizations and quality control among hospitals. For

these reasons, the current study was designed to evaluate postoperative morbidity, lymph node dissection, and long-term surgical outcomes of locally advanced proximal gastric cancer patients undergoing spleen-preserving lymphadenectomy by experienced surgeons in a high-volume hospital.

II. MATERIALS AND METHODS

Patients and surgery

Between January 2000 and December 2004, 3267 patients with gastric adenocarcinoma underwent gastric resection at the Department of Surgery of Yonsei University College of Medicine. Among the 852 patients who underwent total gastrectomy, 486 patients were excluded from the study for the following reasons: 196 patients had stage IV cancers, 153 patients had cancers that were histologically proven to be early-stage, 86 patients underwent combined resection of organs other than the spleen, 33 patients had fewer than 15 lymph nodes retrieved, and 18 patients had a history of malignancies in other organs. The remaining 366 patients who underwent curative total gastrectomy were enrolled for analysis. Among them, 99 patients underwent simultaneous splenectomy either routinely or due to enlarged lymph nodes along the splenic artery or at the splenic hilum. The remaining 267 enrolled patients underwent spleen-preserving lymphadenectomy to remove the lymphatic tissue at the splenic hilum and around the splenic artery. A prospective database was reviewed for the purpose of this study.

All procedures proceeded as follows 1) total gastrectomy with greater than D2 lymphadenectomy was performed according to the rules of the Japanese Research Society for Gastric Cancer.[6] 2) The standard reconstruction method was Roux-en Y esophagojejunostomy. 3) In the spleen-preservation group, lymph nodes around the splenic artery were dissected along the upper border of the pancreas and lymph nodes at the splenic hilum were removed with or without mobilization of the spleen from the retroperitoneum. The dissected lymph nodes were staged by surgeons, and all retrieved lymph nodes were examined for metastasis by specialized pathologists. Cancers were staged according to the tumor node metastasis (TNM) classification system used by the Union Internacional Contra la Cancrum (UICC) [7]; potentially curative resection was defined as R0 resection according to the UICC residual tumor

classification.

We used the body mass index (BMI) classification by WHO Asia-Pacific guidelines for obesity. BMI was calculated as weight (kg) divided by the square of height (m^2). Perioperative transfusion was defined as either whole blood or packed red blood cells administered during or after surgery within the same hospitalization at the discretion of surgeon and anesthesiologist. Postoperative morbidity was assessed by physical examination, routine laboratory check, and radiologic examination during hospitalization. Hospital mortality was defined as postoperative death within 30 days, or death within the same hospitalization.

Follow-up

The patients were closely followed post-surgery until March 18, 2008 based on institutional follow-up protocol; the median follow-up duration was 52 months (range, 2-100 months). At the time of the last follow-up, 217 patients (59.3%) were still alive and 149 (40.7%) had died from recurrence or other causes. Diagnosis of recurrence was made by clinical and radiological examination or by surgery. The main patterns of recurrence were recorded as the site of detectable failure at the time of diagnosis. We compared the clinicopathological features, perioperative surgical outcomes (operation time, amount of transfusion, time of first flatus, initiation of soft diet, postoperative hospital stay, morbidity, and mortality), recurrence, and cumulative 5-year survival rate between the two groups.

Statistical analysis

Statistical analysis was performed using the software 'Statistical Package for Social Science' (SPSS) version 13.0 for Windows (SPSS, Chicago, Illinois, USA). Clinicopathological variables were analyzed using the chi-square test for discrete variables and Student's *t*-test for continuous variables. The risk factors influencing morbidity were determined using logistic regression analysis. Survival rates were calculated from the day of the operation until death or the last follow-up. Survival curves were calculated using the Kaplan-Meier method

and compared using the log-rank test. Multivariate analysis of patient prognosis was conducted using Cox's proportional hazard model. A P-value < 0.05 was considered statistically significant.

III. RESULTS

Comparison of clinicopathological features

Clinicopathological features of the 267 patients in the (73.0%) spleen-preservation group and the 99 patients (27.0%) in the splenectomy group are shown in TABLE I. Statistically significant differences were found between groups in perioperative transfusion, tumor size, depth of invasion, and status of lymph node metastasis. The frequency of lymph node metastasis around the splenic artery (No.11) and/or splenic hilum (No.10) was 4% in the spleen-preservation group versus 13.3% in the splenectomy group in T2 and 7.7% versus 15.9% in T3, respectively.

TABLE I. Clinicopathological features of patients who underwent curative total gastrectomy

Variable	Spleen-preservation (N = 267)	Splenectomy (N = 99)	*P* value
Age(year)			0.121
< 55	124 (46.4)	37 (37.4)	
≥ 55	143 (53.6)	62 (62.6)	
Gender			0.572
Male	175 (65.5)	68 (68.7)	
Female	92 (34.5)	31 (31.3)	
BMI (kg/m^2)			0.399
< 25	199 (74.5)	78 (78.8)	
≥ 25	68 (25.5)	21 (21.2)	
ASA grade			0.162
1	102 (38.2)	30 (30.3)	
2 or 3	165 (61.8)	69 (69.7)	
Perioperative transfusion			< 0.001

No	222 (83.1)	64 (64.6)	
Yes	45 (16.9)	35 (35.4)	
Tumor size (cm)			0.001
< 5	127 (47.6)	28 (28.3)	
≥ 5	140 (52.4)	71 (71.7)	
Tumor location			0.407
Upper third	68 (25.5)	31 (31.3)	
Middle third	196 (73.4)	66 (66.7)	
Whole	3 (1.1)	2 (2.0)	
Gross type			0.201
Borrmann I	16 (6.0)	9 (9.1)	
Borrmann II	79 (29.7)	24 (24.2)	
Borrmann III	132 (49.6)	44 (44.5)	
Borrmann IV	39 (14.7)	22 (22.2)	
Histologic type			0.174
Differentiated	90 (33.7)	26 (26.3)	
Undifferentiated	177 (66.3)	73 (73.7)	
Depth of invasion			0.005
T2	124 (46.4)	30 (30.3)	
T3	143 (53.6)	69 (69.7)	
Lymph node metastasis			0.004
N0	86 (32.2)	16 (16.2)	
N1	122 (45.7)	49 (49.5)	
N2	59 (22.1)	34 (34.3)	
No. 10 and/or No. 11 lymph node metastasis according to depth of tumor			
T2	5 (4.0)	4 (13.3)	0.073

T3	11 (7.7)	11 (15.9)	0.091

Values in parentheses are percentages

Comparison of perioperative surgical outcomes, morbidity, and mortality

Perioperative surgical outcomes of patients in spleen-preservation and splenectomy groups are listed in TABLE II. The spleen-preservation group had a shorter operation time, lower incidence of perioperative transfusion, and a shorter hospital stay. The mean total number of retrieved lymph node was 46.5 in the spleen-preservation group and 50.3 in the splenectomy group ($P = 0.058$). There was no significant difference between groups in the time of first flatus or the initiation of a soft diet.

TABLE II. Perioperative surgical outcomes between spleen-preservation and splenectomy patients

Variable	Spleen-preservation (N = 267)	Splenectomy (N = 99)	*P* value
Operation time (min)	171.8 ± 48.2	184.0 ± 47.0	0.029
Perioperative transfusion (unit)	0.5 ± 1.4	0.8 ± 1.4	0.028
Number of total retrieved LN	46.5 ± 16.2	50.3 ± 17.2	0.058
Time of first flatus (day)	3.8 ± 0.9	4.0 ± 1.0	0.076
Initiation of soft diet (day)	6.8 ± 4.8	7.4 ± 2.4	0.248
Postoperative stay (day)	11.1 ± 6.9	13.4 ± 7.9	0.008

LN: lymph node

Values are mean ± standard deviation

Postoperative complications in the spleen-preservation and splenectomy group were 31 (11.6%) and 29 (29.3%), respectively; this difference was statistically significant. Higher frequency rates of pleural effusion, intra-abdominal abscess,

and pancreatitis were apparent in splenectomy patients. One case of a complication requiring reoperation occurred in the spleen-preservation group. The incidence of hospital mortality was 0.7% in the spleen-preservation group and 1.0% in the splenectomy group (TABLE III). Logistic regression analysis showed that perioperative transfusion (P = 0.008, odds ratio, 2.354; 95% confidence interval, 1.256 – 4.412) and splenectomy (P = 0.001, odds ratio, 2.721; 95% confidence interval, 1.490 – 4.971) were independent risk factors for morbidity.

TABLE III. Postoperative morbidity and mortality between spleen-preservation and splenectomy patients

Variable	Spleen-preservation (N = 267)	Splenectomy (N = 99)	*P* value
Morbidity	31 (11.6)	29 (29.3)	< 0.001
Nonsurgical complication			
Atelectasis	1 (0.4)	1 (1.0)	0.468
Pneumonia	2 (0.7)	0	1.000
Pleural effusion	10 (3.7)	11 (11.1)	0.007
Pulmonary embolism	0	1 (1.0)	0.270
Surgical complication			
Wound infection	7 (2.6)	2 (2.0)	1.000
Intra-abdominal abscess	1 (0.4)	5 (5.1)	0.006
Intra-abdominal bleeding	1 (0.4)	0	1.000
Postoperative ileus	5 (1.9)	4 (4.0)	0.260
Anastomotic leakage	2 (0.7)	0	1.000
Anastomitic stricture	0	1 (1.0)	0.270
Pancreatitis	0	3 (3.0)	0.019
Acalculous cholecystitis	2 (0.7)	0	1.000

Hepatic ischemia	0	1 (1.0)	0.270
Reoperation	1 (0.4)	0	1.000
Hospital mortality	2 (0.7)	1 (1.0)	1.000

Values in parentheses are percentages

Comparison of recurrence and prognosis

A higher recurrence rate was observed in the splenectomy group (40.4%) compared to the spleen-preservation group (25.1%) (P = 0.011). However, no significant difference was shown in recurrence rates between groups after adjusting for TNM stage (TABLE IV).

TABLE IV. Comparison of recurrence rate between spleen-preservation and splenectomy patients

Stage	Spleen-preservation	Splenectomy	*P* value
Ib	2/51 (3.9)	1/6 (16.7)	0.367
II	15/91 (16.5)	8/24 (33.3)	0.086
III a	29/80 (36.3)	17/44 (38.6)	0.902
III b	21/45 (46.7)	14/25 (56.0)	0.261

Values are numbers of recurrence/total numbers of patients

Values in parentheses are percentages

The most common pattern of recurrence in both groups was peritoneal recurrence (spleen preservation, 38.8% vs. splenectomy, 52.5%). Locoregional recurrence was 20.9% in spleen-preservation patients and 10.0% in splenectomy patients (P = 0.690) (TABLE V).

TABLE V. Patterns of recurrence

Pattern	Spleen-preservation (N = 67)	Splenectomy (N = 40)	P value
Locoregional	14 (20.9)	4 (10.0)	0.789
Peritoneal recurrence	26 (38.8)	21 (52.5)	0.003
Hematogenous	16 (23.9)	6 (15.0)	0.965
Extra-abdominal nodes*	2 (3.0)	1 (2.5)	0.466
Combined recurrence	9 (13.4)	8 (20.0)	0.054

Values in parentheses are percentages

∗ Paratracheal, mediastinal lymph nodes

The mean survival time was 72.0 months in the spleen-preservation group compared with 56.7 months in the splenectomy group ($P < 0.001$). There was no significant difference in the cumulative 5-year survival rates between groups in patients with cancers of the same stage (TABLE VI).

TABLE VI. Comparison of cumulative 5 year survival rates according to the each stage

Stage	Spleen-preservation (N = 267)	Splenectomy (N = 99)	*P* value
Ib	84.4	83.3	0.815
II	75.8	62.5	0.221
III a	56.6	46.1	0.224
III b	36.4	20.0	0.131

Multivariate analysis showed that tumor size ($P = 0.013$, odds ratio, 1.591; 95% confidence interval, 1.105 – 2.290), serosal invasion ($P < 0.001$, odds ratio, 2.338; 95% confidence interval, 1.598 – 3.420), and nodal metastasis ($P < 0.001$,

odds ratio, 2.355; 95% confidence interval, 1.282 – 3.125) were independent prognostic factors, while splenectomy was not (*P* = 0.148, odds ratio, 1.297; 95% confidence interval, 0.912 – 1.846). Moreover, in patients with pN0 status, the cumulative 5-year survival rate of the spleen-preservation group was significantly higher than that of the splenectomy group, while there was no significant difference in survival rates in patients with pN1 or pN2 status between groups (Figure 1).

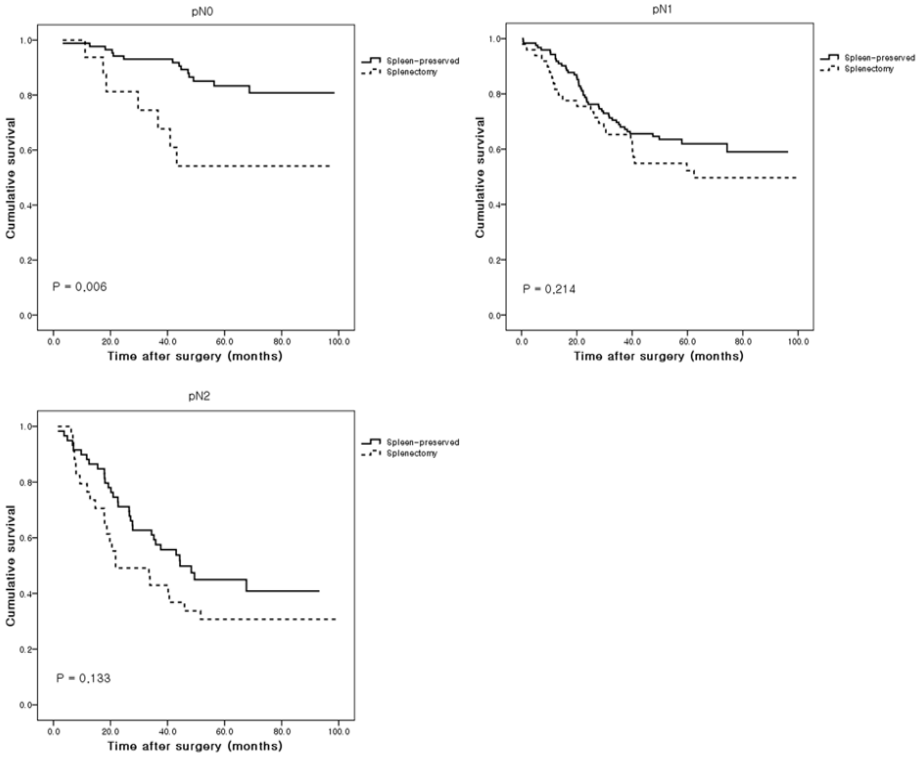

Fig.1. Cumulative survival rates stratified by nodal status (pN) for patients undergoing curative total gastrectomy.

In No. 10 and No.11 lymph node-negative patients, spleen-preservation patients showed significantly better survival than splenectomy patients (P = 0.005), whereas there was no significant difference between groups in the No. 10 and/or No.11 lymph node-positive patients (P = 0.076) (Figure 2).

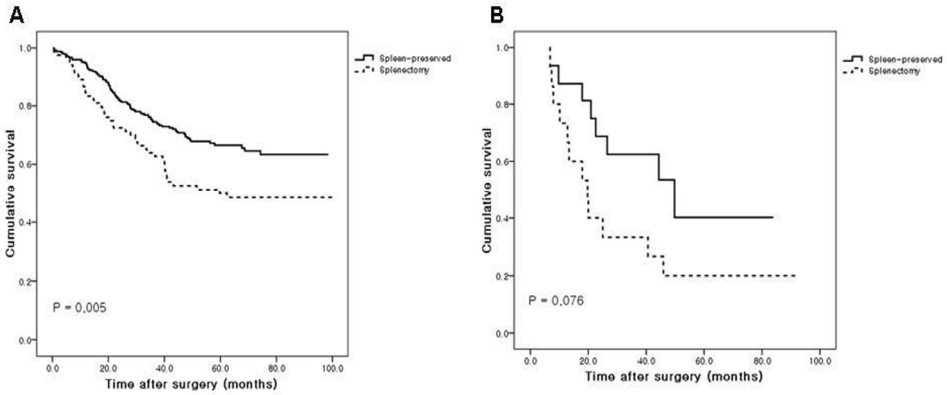

Fig. 2. Cumulative survival curves for patients undergoing curative total gastrectomy with and without splenectomy.

IV. DISCUSSION

In recent years, the incidence of proximal gastric cancer has increased, most likely due to Barrett's esophagus and distal esophagus adenocarcinoma caused by increased BMI and modern eating habits. The current standard treatment of proximal gastric cancer in Korea is total gastrectomy with D2 lymph node dissection. Although Dutch and MRC trials reported poor outcomes of D2 dissection with combined resection of the spleen and/or tail of the pancreas compared to D1 dissection,[8, 9] splenectomy had been justified to completely remove the lymph nodes around the splenic artery and hilum for extended radical surgery.[10, 11]

Unfortunately, it has been shown that splenectomy for complete lymph node removal not only causes high morbidity and mortality, but also lacks survival benefit.[12-15] For example, Otsuji *et al*. reported that splenectomy was an independent risk factor for morbidity and mortality that resulted in severe postoperative complications.[12] In this study, we also found that splenectomy patients had a higher incidence of postoperative complications such as pleural effusion, intra-abdominal abscess, and pancreatitis than spleen-preservation patients. Splenectomy may be associated with longer operation time as well as increased blood loss, requiring transfusion. Logistic regression analysis revealed that splenectomy was the most important risk factor for morbidity (P = 0.001, odds ratio, 2.721; 95% CI, 1.490 - 4.971). However, these complications were well-managed with antibiotics and ultrasound-guided aspiration drainage without reoperation, and thus did not result in increased mortality. Another risk factor for postoperative complications was the increased blood loss and thus need for transfusion with splenectomy. Although perioperative transfusion was not an independent risk factor for prognosis in multivariate analysis, it was marginally significant (P = 0.054, odds ratio, 1.427; 95% CI, 0.993 – 2.051). In other studies, perioperative transfusion in a patient undergoing an operation for a malignancy was associated with high tumor recurrence and poor survival.[16-18]

This may be due to the immunosuppressive findings after transfusion, which are as follows: decreased helper/suppressor T-cell ratio, decreased natural killer cells, decreased macrophage antigen presentation, and suppression of lymphocyte blastogenesis.[19]

It is difficult to detect lymph node metastasis around the splenic artery and hilum through preoperative imaging or intra-operative gross findings. Mönig *et al.* reported that lymph node metastasis to the splenic hilum was observed only in advanced-stage cancer (UICC IIIb/IV), particularly in tumors located in the greater curvature and Borrmann type IV tumors.[4] In another report, splenic hilar node metastasis was identified in only 3% of patients with T2 proximal gastric cancer and 13% of patients with T3 tumors.[20] In our study, although the frequency of lymph node metastasis to the splenic artery and/or splenic hilum according to tumor depth was higher in the splenectomy group, it was not statistically significant in patients with T2 or T3 tumors. Furthermore, the frequency of involvement of No.10 and No.11 lymph nodes was lower than expected in the spleen-preservation group, because spleen-preserving lymphadenectomy in proximal gastric cancer maybe performed in a less advanced stage.

The effect of splenectomy in proximal gastric cancer patients on prognosis is still controversial. Some authors have reported that spleen preservation resulted in a better surgical outcome than splenectomy.[21, 22] In contrast, some reports show a higher survival rate after splenectomy compared to spleen preservation.[23, 24] Our current study showed that splenectomy adversely affected survival in pN0-status patients, while there was no significant difference in survival rates between groups in patients with pN1 and pN2 status. Splenectomy was clearly an independent risk factor for poor prognosis on multivariate analysis for node-negative patients (data not shown).

Spleen-preserving D2 lymphadenectomy requiring anatomical lymph node dissection is technically difficult. For this reason, unintentional splenectomy

sometimes occurs due to injury of the splenic vessels or tearing of the splenic capsule during lymphadenectomy around the splenic artery and hilum. In the early 2000s, some experienced surgeons in our institute preferred to perform a splenectomy in advanced proximal gastric cancer. Today we have a policy of spleen-preserving lymphadenectomy for proximal gastric cancer based on previous results, [25] except in cases with definite lymph node enlargement in the splenic hilum or direct tumor invasion of the gastrosplenic ligament. Even though the limitations of our study include the fact that it was conducted in a single institute, was not applicable to non-specialists, and there have been still selection bias, we have confirmed the benefit of spleen preservation on postoperative morbidity and long-term surgical outcomes.

V. Conclusion

Splenectomy for lymph node dissection in proximal gastric cancer patietns was the most important risk factor for postoperative morbidity and was not effective in long-term surgical outcomes in terms of recurrence and prognosis. Therefore, spleen-preserving lymphadenectomy is a more feasible method to achieve better short-term outcomes and to accomplish radical surgery in locally advanced proximal gastric cancer.

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ABSTRACT

국소적 진행성 상부위암에서 비장보존 림프절 절제술이 수술결과에 미치는 영향

< 지도교수 노 성 훈 >

연세대학교 대학원 의학과

오 성 진

배경: 본 연구의 목적은 국소적 진행성 상부위암에서 비장보존 D2 림프절 절제술이 수술결과에 미치는 영향에 대해 알아보고자 하였다.
방법: 2000년 1월부터 2004년 12월까지 근치적 위전절제술을 시행받은 총 366명의 환자를 후향적으로 분석하였다.
결과: 비장 보존군에서 짧은 수술시간, 적은 수혈빈도, 짧은 술 후 재원기간을 보였다. 수술 직후 수혈과 비장절제술은 합병증에 위험인자였다. 각 병기에 따른 재발률 혹은 누적 생존율은 비장 보존군과 절제군간에 의미 있는 차이를 보이지 않았다. 다변량 분석에서 종양의 크기, 장막침범, 림프절 전이는 독립적인 예후 인자였지만 비장절제는 아니었다. p N0환자들에서 누적생존율은 비장 보존군에서 의미 있게 더 높았지만 p N1과 p N2 환자들에서 누적생존율은 두군간에 차이가 없었다.
결론: 림프절 절제를 위한 비장절제는 상부위암환자에서 분명히 나쁜 단기 수술결과를 보였다. 하지만 재발률이나 전체 생존율 측면에서는 영향을 주지 못했다. 그러므로 비장보존 림프절절제술은 국소적으로 진행된 상부위암에서 근치적 수술의 적합한 방법이라 생각한다.

핵심되는 말 : 위암, 비장보존, 수술 결과