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Comparisons Between Different Procedures of No. 10 Lymphadenectomy for Gastric Cancer Patients With Total Gastrectomy

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Abstract: To compare the effectiveness and safety of in-vivo dissection procedure of No. 10 lymph nodes with those of ex-vivo dissection procedure for gastric cancer patients with total gastrectomy.

Patients were divided into in-vivo group and ex-vivo group according to whether the dissection of No. 10 lymph nodes were performed after the mobilization of the pancreas and spleen, and migration out from peritoneal cavity. Clinicopathologic characteristics, overall survival, morbidity, and mortality were compared between the 2 groups.

There were 148 patients in in-vivo group, while 30 in ex-vivo group. The baselines between the 2 groups were almost comparable. The metastatic ratio of No. 10 lymph nodes were 6.1% and 10.0% ($P = 0.435$) and the metastatic degree were 7.9% and 13.6% ($P = 0.158$) for in-vivo group and ex-vivo group, respectively. There was no difference in morbidity or mortality between the 2 groups. The number of total harvested lymph nodes and No. 10 lymph nodes increased significantly in ex-vivo group at the cost of prolonged operation time. The estimated overall survival rates for patients in in-vivo group and ex-vivo group were (3-year: 52.0% vs 61.8%) and (5-year: 45.3% vs 49.5%), respectively, without statistical significance. Further multivariable analysis had showed that the procedure of No. 10 lymphadenectomy was not a significant independent prognostic factor.

Both in-vivo and ex-vivo dissection of No. 10 lymph nodes could be performed safely. It seems that ex-vivo dissection of No. 10 lymph nodes can result in a higher effective dissection at the cost of the operation time, but the overall survival rates were not statistically significant between the 2 groups, which should be confirmed further in a well-designed randomized controlled trial.

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Abbreviations: IGCC = International Gastric Cancer Congress, JCOG = The Japan Clinical Oncology Group, JGCA = Japanese Gastric Cancer Association, VOLTGA = Volunteer Team of Gastric Cancer Surgery.

INTRODUCTION

The incidence rate of gastric cancer is high worldwide.[1] Surgery is the mainstay of treatment for patients with gastric carcinoma, and D2 lymphadenectomy has also been accepted as the standard surgery in East Asia. There has been a proximal migration of gastric carcinoma in the Western countries.[2–4] The incidence of adenocarcinoma at the upper third of the stomach and esophagogastric junction, as well as the proportion of total gastrectomy, has been increasing in the ensuing years.[2,5]

Splenic hilar lymph nodes (No. 10 lymph nodes) are required to be dissected in D2 lymphadenectomy when total gastrectomy is performed according to the Japanese gastric cancer treatment guideline 2010 (version 3) by the Japanese Gastric Cancer Association (JGCA).[6] Although the survival benefit of No. 10 lymphadenectomy is still controversial, there is a trend that the No. 10 lymphadenectomies might be recommended in total gastrectomy with D2 lymphadenectomy with an acceptable complication rate.[7] Splenectomy was once performed simultaneously for the purpose of effective lymph node dissection at the splenic hilum. However, it was then not recommended as a routine procedure as some reports showed it is not superior to splenic preservation on the survival rate.[8,9] Therefore, spleen-preserved lymphadenectomy is proposed and applied therein.[10]

Nowadays, there are 2 different operative procedures for spleen-preserved No. 10 lymph nodes dissection, which are in-vivo dissection and ex-vivo dissection, according to whether the dissection is performed after the mobilization of the pancreas and spleen, and migration out from peritoneal cavity. The ex-vivo dissection process is completed under direct vision. It creates good exposures for better skeletonization of blood vessels, clearance of tissues locating at the back area of the splenic hilum and easier control of splenic bleeding. However, it needs veteran operative skills and also has potential risk of torsion of the splenic pedicle. Therefore, ex-vivo dissection could lead to a higher dissected effectiveness, but also a theoretically higher mortality. However, no study has compared the effectiveness of dissection and safety of the 2 operative procedures.

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Therefore, this study aimed to compare the effectiveness and safety between the in-vivo and ex-vivo dissection of No. 10 lymph nodes for gastric cancer patients with total gastrectomy.

METHODS

Patients

From September 2009 to November 2013, a total of 178 gastric cancer patients who underwent total gastrectomy with No. 10 lymphadenectomy by a single surgeon from West China Hospital were retrospectively analyzed. Patients were divided into in-vivo group and ex-vivo group according to whether the dissection of No. 10 lymph nodes were performed after the mobilization of the pancreas and spleen, and migration out from peritoneal cavity. The preoperative diagnosis of gastric carcinoma was confirmed by gastric endoscopy followed by biopsy. Patients diagnosed with other gastric malignances such as lymphoma, gastrointestinal stromal tumor, and any previous malignancy or secondary malignancies other than primary gastric carcinoma were excluded. The West China Hospital research ethics committee approved retrospective analysis of anonymous data. Signed patient informed consent was waived per the committee approval since it was a retrospective analysis.

Surgical Techniques

In this study, all patients underwent open total gastrectomy with D1+ or D2 lymph nodes dissection for gastric cancer defined by Japanese gastric cancer treatment guideline.[6] Roux-en-Y esophagojejunostomy was performed to reconstruct the digestive tract. All the patients underwent spleen-preserved lymphadenectomy to dissect the lymphatic tissue at the splenic hilum without sacrificing the main branches of splenic vessels. The grouping rule of regional lymph nodes was according to the Japanese classification of gastric carcinoma (3rd English version) by JGCA.[11] All the operations were performed by a experienced surgeon specialized in gastrointestinal surgery, at the West China Hospital, Sichuan University.

Initial staging should be performed with multi-detector computed tomography of the thorax, abdomen, and pelvis to screen patients for operation. Those patients without distant disease on imaging were the candidates for operation and can be referred to surgery. After the exploration, operator made the decision whether to perform the ex-vivo dissection according to performance status of patients and potential curative resectability of total gastrectomy.

For in-vivo dissection, the splenic vessels and their branches were exposed at the upper border of the pancreas, and lymph nodes and fatty tissues were dissected along the splenic artery from the distal portion of the splenic vessels to the splenic hilum. Then all the tissues were removed from the splenic lower pole to the upper pole by a combination of blunt and sharp dissections without spleen and pancreatic tail mobilization. Cautious were given to preserve the branches of splenic vessels (Figure 1A).

For ex-vivo dissection, we mobilized spleen and pancreatic tail by dissecting all the ligamentous attachments in a surgical fascial plane firstly. The surgical fascial plane was kept in order to the maximum avoidance of bleeding. When the spleen and pancreatic tail were mobilized to the level where inferior mesenteric vein confluences to splenic vein, they were moved outside from the abdominal cavity. Then all the lymph nodes-bearing tissues at splenic hilum were removed en-bloc under direct vision by a similar aforementioned method. Simultaneously, tissues locating at the back area of splenic hilum were also cleaned by turning the spleen and pancreatic tail to the right side. Sometimes, a few tiny branches of the splenic vessels could be ligated. After the dissection, the spleen and pancreas were fixed to the original position (Figure 1B).

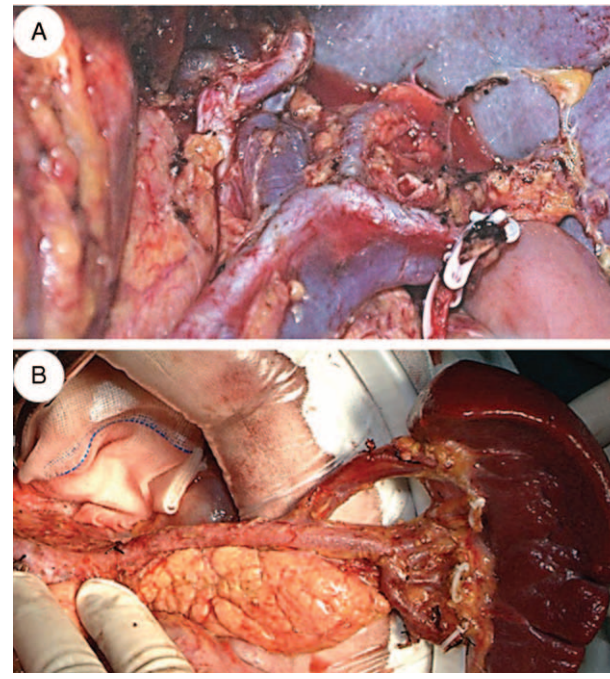

FIGURE 1. Different operative procedures for spleen-preserved No. 10 lymph nodes dissection. A: In-vivo dissection; B: Ex-vivo dissection.

Follow-Up

Patients underwent a follow up which was done by telephone calls, letters, or outpatient visits. Patients who needed postoperative chemotherapy received fluoropyrimidine alone or fluoropyrimidine/platinum regimens. The follow-up information was updated to December 31, 2014. The overall follow-up rate was 94.38% (168/178). Eight patients in in-vivo group and 2 patients in ex-vivo group were lost to follow-up.

Clinicopathologic Analysis

The clinicopathologic features, such as gender, age, tumor size, tumor differentiation, tumor location, depth of tumor invasion, lymph node metastasis, staging, morbidity, mortality, and survival outcome were collected from the database and compared between the in-vivo group and the ex-vivo group. Metastatic ratio of lymph nodes was defined as the ratio of the number of patients with metastatic lymph nodes over the total number of patients; whereas metastatic degree of lymph nodes was defined as the ratio of the number of metastatic lymph nodes over the number of harvested lymph nodes.[7] In addition, metastatic ratio and metastatic degree of lymph nodes locating at the back area of splenic hilum were analyzed separately. Clinicopathologic terminology was based on the Japanese Classification of Gastric Carcinoma (3rd English version).[11]

Statistical Analysis

SPSS 19.0 software (SPSS, Chicago, IL) was used for statistical analyses. Variables of normality were tested, and if

TABLE 1. General Clinicopathologic Characteristics of the Patients

	In-Vivo Group (N = 148), %	Ex-Vivo Group (N = 30), %	*P* Value
Gender			0.623
Female	41 (27.7)	7 (23.3)	
Male	107 (72.3)	23 (76.7)	
Age, yr			0.541
<60	65 (43.9)	15 (50.0)	
≥60	83 (56.1)	15 (50.0)	
Comorbidity	75 (50.7)	15 (50.0)	0.946
Tumor location			0.033
Upper third	65 (43.9)	20 (66.7)	
Middle third	37 (25.0)	8 (26.7)	
Lower third	39 (26.4)	1 (3.3)	
Linitis plastica	7 (4.7)	1 (3.3)	
Lymphadenectomy			0.385
D1+	18 (12.2)	2 (6.7)	
D2	130 (87.8)	28 (93.3)	
Curative degree			0.883
R0	137 (92.6)	28 (93.3)	
R1/R2	11 (7.4)	2 (6.7)	
Differentiation			0.139
Well	0 (0)	0 (0)	
Moderate	19 (12.8)	7 (23.3)	
Poor	129 (87.2)	23 (76.7)	
Lauren type			0.587
Intestinal	54 (36.5)	13 (43.3)	
Diffused	69 (46.6)	14 (46.7)	
Mixed	25 (16.9)	3 (10.0)	
Lymphovascular infiltration			0.976
No	123 (83.1)	25 (83.3)	
Yes	25 (16.9)	5 (16.7)	
Tumor size, cm			0.585
≤2	6 (4.1)	0 (0)	
~5.0	44 (29.7)	12 (40.0)	
~8.0	62 (41.9)	12 (40.0)	
>8.0	36 (24.3)	6 (20.0)	
Depth of infiltration (T)			0.969
T1	6 (4.1)	2 (6.7)	
T2	20 (13.5)	3 (10.0)	
T3	20 (13.5)	4 (13.3)	
T4a	82 (55.4)	17 (56.7)	
T4b	20 (13.5)	4 (13.3)	
Nodal status (N)			0.758
N0	26 (17.6)	3 (10.0)	
N1	23 (15.5)	4 (13.3)	
N2	27 (18.2)	11 (36.7)	
N3a	35 (23.6)	8 (26.7)	
N3b	37 (25.0)	4 (13.3)	
Distant metastasis (M)			0.437
M0	131 (88.5)	28 (93.3)	
M1	17 (11.5)	2 (6.7)	
Stage			0.532
Ia	4 (2.7)	2 (6.7)	
Ib	7 (4.7)	1 (3.3)	
IIa	13 (8.8)	3 (10.0)	
IIb	16 (10.8)	3 (10.0)	
IIIa	18 (12.2)	3 (10.0)	
IIIb	23 (15.5)	6 (20.0)	
IIIc	50 (33.8)	10 (33.3)	
IV	17 (11.5)	2 (6.7)	
Adjuvant chemotherapy			0.846
No	81 (54.7)	17 (56.7)	
Yes	67 (45.3)	13 (43.3)	

conforming to the normal distribution, data were expressed as means ± standard deviation. Two independent *t* tests for quantitative data and Chi-squared test or Fisher's exact test for categorical data were performed. Otherwise, data were expressed as medians with a range taking the Spearman test into consideration. Survival was calculated by Kaplan–Meier estimation and the log-rank test. Independent prognostic factors were identified by Cox proportional hazards regression model. Two-sided *P* value <0.05 was considered as statistical significance.

RESULTS

Patient Characteristics

There were 148 patients undergoing No. 10 lymph nodes dissection in-vivo (in-vivo group) and 30 patients with No. 10 lymphadenectomy ex-vivo (ex-vivo group). Although the tumor locations between the 2 groups were slightly significantly different ($P = 0.033$), other parameters including the age, gender, comorbidity, the degree of lymph node resection, curative degree, tumor differentiation, tumor size, depth of invasion, lymph node metastasis status, and Tumor Node Metastasis staging were comparable between the 2 groups (Table 1). The general clinicopathologic characteristics are summarized in Table 1.

Metastatic Ratio and Degree of Lymph Nodes

The dissected No. 10 lymph nodes of 60 patients were proved to be fatty tissues by histological examination in-vivo group, and there were 5 patients whose No. 10 lymph nodes were proved to be fatty tissues in ex-vivo group. The metastatic ratio of No. 10 lymph nodes were 6.1% (9/148) and 10.0% (3/30) for in-vivo group and ex-vivo group, respectively ($P = 0.435$). A total of 140 splenic hilar lymph nodes were harvested in in-vivo group with 88 in ex-vivo group. There were 11 and 12 positive No. 10 lymph nodes for in-vivo group and ex-vivo group, respectively. Hence, the metastatic degree of No. 10 lymph nodes were 7.9% (11/140) and 13.6% (12/88) ($P = 0.158$). In our study, there were 4 patients with lymph nodes locating at the back area of pancreatic tail and splenic pedicle identified by the pathologic examinations. Totally 6 lymph nodes locating at the back area of pancreatic tail and splenic pedicle were retrieved without metastasis.

Operative Variables

Actually, the numbers of total harvested lymph nodes and No. 10 lymph nodes increased significantly in ex-vivo group at the cost of prolonged operation time, compared to the in-vivo group ($P < 0.05$). However, there were no significant differences

TABLE 2. Operative Variables, Morbidity, and Mortality of the Patients

	In-Vivo Group (N = 148)	Ex-Vivo Group (N = 30)	*P* Value
No. of total harvested lymph nodes, medians (range)	34 (11–93)	44 (18–142)	0.041
No. of harvested No. 10 lymph nodes, medians (range)	1 (1–4)	3 (1–9)	0.000
Postoperative hospital stays, d	11.24 ± 3.77	11.59 ± 4.63	0.696
Blood lost volume, mL	111.82 ± 57.47	111.00 ± 42.54	0.886
Operation time, min	259.01 ± 40.87	282.50 ± 27.72	0.010
No. of patients with reoperation	1	1	0.309
Morbidity	30 (20.27%)	6 (20.00%)	0.973
Mortality	0	0	1.000
Clavien–Dindo classification			0.634
I	3	1	
II	23	3	
IIIa	3	1	
IIIb	1	1	
IVa	0	0	
IVb	0	0	
V	0	0	
Surgical-related complications			
Anastomotic fistula	1	0	
Wound infections	3	1	
Intraperitoneal infection	4	1	
Intraperitoneal hemorrhage	0	1	
Nonsurgical-related complications			
Pulmonary infections	17	3	
Diarrhea	2	0	
Urinary infections	2	0	
Arrhythmia	1	0	

in terms of intraoperative estimated blood loss ($P = 0.886$), postoperative hospital stays ($P = 0.696$) and reoperation rates ($P = 0.309$) between the 2 groups. The details can be seen in Table 2.

Morbidity and Mortality

The overall postoperative morbidity rates were 20.27% in the in-vivo group and 20.00% in the ex-vivo group ($P = 0.973$), respectively (Table 2). The postoperative complications as well as the Clavien–Dindo classifications are summarized in Table 2.[12] No. 10 lymphadenectomy-related complications, such as pancreatic fistula, pancreatitis, whole splenic infarction, iatrogenic spleen injury, or delayed aneurysm of splenic artery, had not been observed in the 2 groups. However, 1 patient who experienced postoperative intraperitoneal hemorrhage in the ex-vivo group received reoperation and was cured. There was no death in each group (Table 2).

Long-Term Survival

As of December 31, 2014, 58 patients in the in-vivo group and 10 in the ex-vivo group died. Although the 3-year overall survival rate for patients in the ex-vivo group was slightly better than that of in-vivo group (61.8% vs 52.0%), the estimated 5-year survival rates of in-vivo group and ex-vivo group were 45.3% and 49.5%, respectively, without statistical significance ($P = 0.302$) (Figure 2).

Multivariable Analysis for Overall Survival

The results of univariate analysis and multivariate analysis are showed in Table 3. Results of multivariable analysis have showed that only adjuvant chemotherapy was an independent prognostic factor for overall survival ($P = 0.009$), after adjusting other factors (tumor location, Lauren type, lymphovascular infiltration, lymphadenectomy degree, curative degree, adjuvant chemotherapy, tumor size, histological differentiation, T stage, N stage, M stage, and procedure of No. 10

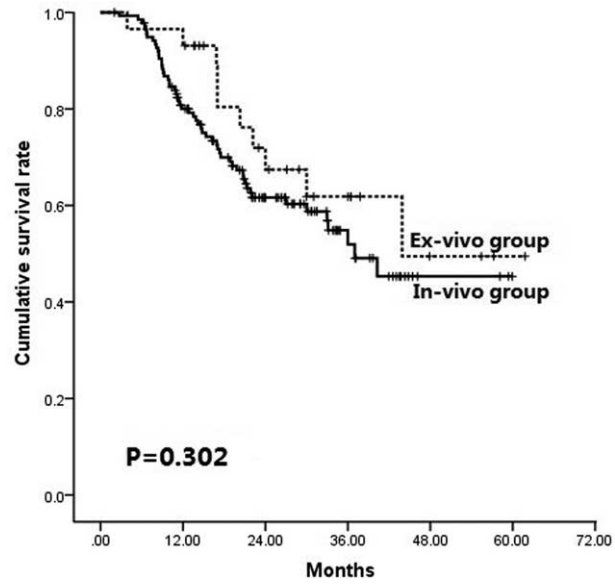

FIGURE 2. Survival curves of the 2 groups ($P = 0.302$).

TABLE 3. Prognostic Factors on the Univariate and Multivariate Analysis

	Univariate HR (95% CI)	*P* Value	Multivariate HR (95% CI)	*P* Value
Gender		0.458		
Male	1			
Female	1.227 (0.714, 2.108)	0.458		
Age, yr		0.399		
<60	1			
≥60	0.807 (0.490, 1.329)	0.399		
Tumor location		0.001		0.402
Upper third	1		1	
Middle third	1.296 (0.676, 2.486)	0.434	1.797 (0.827, 3.902)	0.139
Lower third	2.768 (1.482, 5.170)	0.001	1.602 (0.745, 3.443)	0.228
Linitis plastica	4.562 (1.818, 11.449)	0.001	2.032 (0.663, 6.221)	0.215
Differentiation		0.025		0.570
Moderate	1		1	
Poor	2.851 (1.141, 7.122)	0.025	1.422 (0.422, 4.793)	0.570
Lauren type		0.001		0.644
Intestinal	1		1	
Diffused	3.480 (1.819, 6.656)	0.000	1.392 (0.544, 3.559)	0.490
Mixed	3.516 (1.543, 8.016)	0.003	1.674 (0.571, 4.913)	0.348
Lymphovascular infiltration		0.089		0.881
No	1		1	
Yes	1.640 (0.928, 2.899)	0.089	1.052 (0.541, 2.045)	0.881
Tumor size, cm		0.000		0.877
0–5.0	1		1	
~8.0	2.887 (1.506, 5.929)	0.004	1.246 (0.538, 2.886)	0.609
>8.0	4.408 (2.095, 9.274)	0.000	1.204 (0.477, 3.042)	0.695
Depth of infiltration (T)		0.000		0.395
Serosa negative	1		1	
T4a	3.002 (1.450, 6.215)	0.003	1.652 (0.712, 3.834)	0.242
T4b	6.135 (2.667, 14.114)	0.000	2.028 (0.705, 5.831)	0.189
Nodal status (N)		0.000		0.144
N0	1		1	
N1	1.907 (0.455, 7.989)	0.377	1.883 (0.427, 8.308)	0.403
N2	3.759 (1.060, 13.330)	0.040	3.970 (0.995, 15.832)	0.051
N3a	6.040 (1.776, 20.539)	0.004	3.626 (0.943, 13.946)	0.061
N3b	11.479 (3.428, 38.433)	0.000	5.538 (1.330, 23.051)	0.019
Distal metastasis (M)		0.000		0.110
M0	1		1	
M1	3.529 (1.894, 6.576)	0.000	1.825 (0.873, 3.817)	0.110
Lymphadenectomy		0.047		0.785
D1+	1		1	
D2	0.527 (0.280, 0.993)	0.047	1.107 (0.534, 2.296)	0.785
Curative degree		0.000		0.083
R0	1		1	
R1/R2	4.872 (2.252, 10.536)	0.000	2.262 (0.898, 5.696)	0.083
Adjuvant chemotherapy		0.015		0.009
No	1		1	
Yes	0.514 (0.301, 0.877)	0.000	0.434 (0.232, 0.811)	0.009
No. 10 lymphadenectomy		0.331		0.605
In-vivo dissection	1		1	
Ex-vivo dissection	0.674 (0.305, 1.492)	0.331	0.794 (0.331, 1.905)	0.605

lymphadenectomy). However, the procedure of No. 10 lymphadenectomy was not a significant independent prognostic factor (hazard ratio: 0.794 [0.331–1.905], $P = 0.605$).

DISCUSSION

The incidence of lymph node metastasis has been reported to be 9.8% to 20.9% at the splenic hilum.[13–15] Due to the high metastatic frequency of No. 10 lymph nodes, No. 10 lymphadenectomy for gastric cancer patients with total gastrectomy has attracted many attentions worldwide. Although No. 10 lymph nodes have to be dissected for a curative total gastrectomy as defined by the Japanese gastric cancer treatment guideline,[6] the survival benefit of No. 10 lymphadenectomy is still controversial and the related data or evidence is rare.[7] A randomized controlled trial (The Japan Clinical Oncology Group study

0110, JCOG 0110 study) was conducted in Japan to evaluate the role of splenectomy for gastric cancer patients with total gastrectomy in 2002.[16] In this trial, patients were randomly divided into splenectomy group or spleen preservation group. Recently, the preliminary results of this trial showed the overall survival rate of spleen preservation group in which the No. 10 lymphadenectomy was optional was not inferior to that of splenectomy group (the No. 10 lymph nodes were completely cleared).[17] Although the results could provide the strong evidence for the rationality of spleen preservation and may evoke our concern whether it is really necessary to perform the No. 10 lymphadenectomy, the trial does not answer the question directly. Furthermore, regarding to the previous reported high metastatic frequency of No. 10 lymph nodes,[13–15] No. 10 lymphadenectomy should be considered to be beneficial and necessary for some patients with positive No. 10 lymph nodes or patients with high metastatic risk of No. 10 lymph nodes.[18] This is also the reason why the Japanese gastric cancer treatment guideline does not abolish the No. 10 lymph nodes dissection in total gastrectomy.[6] Therefore before stronger evidence being available, the necessity of No. 10 lymph nodes dissection in total gastrectomy with D2 lymphadenectomy should be recommended, which has been proved in our previous research.[7] And, the optimal candidates for No. 10 lymphadenectomy should also be confirmed in the future clinical trials. As results in previous studies did not support the performance of prophylactic splenectomy to remove macroscopically negative lymph nodes at the splenic hilum in patients undergoing total gastrectomy for proximal gastric cancer.[8,9,19] So, spleen-preserved lymphadenectomy has been proposed. Nowadays, in-vivo or ex-vivo dissection for No. 10 lymph nodes has been classified by whether the dissection is performed after the mobilization of the pancreas and spleen, and migration out from peritoneal cavity. However, to our limited knowledge, no research has compared the dissected effectiveness and safety between the 2 operative procedures.

Because the ex-vivo dissection process is done after the mobilization of the spleen and migration out from peritoneal cavity, the difficult of operating in a narrow and deep space at the splenic hilum is overcome. In addition, the ex-vivo dissection could be completed under direct vision, achieving a better exposures, higher skeletonization of blood vessels, complete clearance of tissues locating at the back area of splenic hilum simultaneously and easier control of splenic bleeding. Therefore, it could lead to a higher dissected effectiveness compared with in-vivo dissection theoretically. That the results of metastatic ratio and the metastatic degree in our study were similar to those of other studies.[19–21] However, we should notice that the metastatic ratio and metastatic degree of ex-vivo group were higher than those of in-vivo group although the difference was not significantly different. Actually, the number of total harvested lymph nodes and No. 10 lymph nodes increased significantly in the ex-vivo group, lymph nodes locating at the back area of pancreatic tail and splenic pedicle were indeed identified by the pathologic examinations as well. Our results seemed to demonstrate the higher dissected effectiveness of ex-vivo dissection at the cost of operation time. The relative higher metastatic ratio and metastatic degree in the ex-vivo group indicated that the ex-vivo dissection may lead to a stage migration, but it still needs to be confirmed in further research. According to the Kaplan–Meier and log-rank analysis, we found that there was no statistical significance on overall survivals between the 2 groups. And referring to the results of Cox regression model of proportional hazards, the procedure of No. 10 lymphadenectomy was not a significant independent prognostic factor. Therefore, we could not consider that the ex-vivo dissection of No. 10 lymph nodes is a positive prognostic factor and could improve survival, which still needs to be researched further in a large-scale well-designed randomized controlled trials.

With respect to the safety, our previous results have showed that the complication rate of No. 10 lymphadenectomy was acceptable,[7] compared to the group without No. 10 lymph nodes dissection. Other studies also reported spleen-preserved splenic hilum lymph nodes dissection could be performed safely, even in the laparoscopic gastrectomy.[10,21–24] However, the fragile texture of the spleen, the presence of intricate and complex vessels, the narrow and deep space at the splenic hilum and the complicated mobilization process of pancreatic tail and spleen make No. 10 lymphadenectomy always be a technically difficult procedure and may increase the morbidity of patients, particular for ex-vivo dissection since higher skeletonization of blood vessels is needed. Even so, our results failed to show that it was significantly different in morbidity or mortality between the in-vivo group and ex-vivo group. Most of the postoperative complications in each group were pulmonary infections. Only 1 patient suffering from postoperative intraperitoneal hemorrhage in the ex-vivo group was cured by reoperation. Other No. 10 lymphadenectomy-related complications had not been observed in the 2 groups. At the same time, with regard to the operation-related variables, there were no significant differences in terms of intraoperative estimated blood loss, postoperative hospital stays, and reoperation rate between the 2 groups. So, both of the 2 procedures for No. 10 lymph nodes dissection could be performed safely. But what more important is that the procedure should be performed only by experienced surgeons in high-volume hospitals because postoperative splenic bleeding may be potential fatal, especially for ex-vivo dissection procedure.[20]

There are also some limitations of this study. First, possible selection bias, detection bias, and performance of analysis bias might exist in a retrospective study.[7,25] The ex-vivo dissection procedure would not be performed for too obese patients or patients with adhesions surrounding the spleen. And the frequency of ex-vivo dissection was significantly higher in proximal tumors. That because the metastatic risk of No. 10 lymph nodes in the patients with upper third tumor is higher and the No. 10 lymphadenectomy in these patients would attract more attentions, compared with middle or lower third tumors.[26] Therefore, ex-vivo dissection which has a theoretical higher dissection effectiveness was mostly selected for patients with upper third tumors. Although the tumor location was not balanced, other important prognostic clinicopathological factors, such as T, N, M stage, were well balanced. Therefore, our results still make sense. Second, maybe the follow-up time for some patients was not long enough. However, our results still remains meaningful on the survival to some extent because most of patients would recur and die within 3 years,[27,28] and the analysis of safety between the 2 procedures would not be compromised. In addition, type II error probably exists in our results, because the sample size in the ex-vivo group is relatively small. So, large-scale randomized controlled trials are needed to explore the effectiveness and safety of ex-vivo dissection for No. 10 lymph nodes. Furthermore, the results of metastatic ratio and metastatic degree may be biased since No. 10 lymph nodes may be veiled to be checked out by the presence of fatty tissues in the patients whose dissected No. 10 lymph nodes were microscopically proved to be fatty tissues. Anyway, this research could give some clues for the further researches.

CONCLUSION

In conclusion, both in-vivo and ex-vivo dissection of No. 10 lymph nodes could be performed safely. It seems that ex-vivo dissection of No. 10 lymph nodes can result in a higher effective dissection at the cost of the operation time, but the overall survival rates were not statistically significant between the 2 groups, which should be confirmed further in a well-designed randomized controlled trial.

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REFERENCES

1. Jemal A, Bray F, Center MM, et al. Global cancer statistics. *CA Cancer J Clin.* 2011;61:69–90.
2. Blot WJ, Devesa SS, Kneller RW, et al. Rising incidence of adenocarcinoma of the esophagus and gastric cardia. *JAMA.* 1991;265:1287–1289.
3. Powell J, McConkey CC. Increasing incidence of adenocarcinoma of the gastric cardia and adjacent sites. *Br J Cancer.* 1990;62:440–443.
4. Falk J, Carstens H, Lundell L, et al. Incidence of carcinoma of the oesophagus and gastric cardia. Changes over time and geographical differences. *Acta Oncol.* 2007;46:1070–1074.
5. Hasegawa S, Yoshikawa T. Adenocarcinoma of the esophagogastric junction: incidence, characteristics, and treatment strategies. *Gastric Cancer.* 2010;13:63–73.
6. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer.* 2011;14:113–123.
7. Yang K, Zhang WH, Chen XZ, et al. Survival benefit and safety of No. 10 lymphadenectomy for gastric cancer patients with total gastrectomy. *Medicine (Baltimore).* 2014;93:e158.
8. Yang K, Chen XZ, Hu JK, et al. Effectiveness and safety of splenectomy for gastric carcinoma: a meta-analysis. *World J Gastroenterol.* 2009;15:5352–5359.
9. Yu W, Choi GS, Chung HY. Randomized clinical trial of splenectomy versus splenic preservation in patients with proximal gastric cancer. *Br J Surg.* 2006;93:559–563.
10. Li C, Kim S, Lai JF, et al. Lymph node dissection around the splenic artery and hilum in advanced middle third gastric carcinoma. *Eur J Surg Oncol.* 2009;35:709–714.
11. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English version. *Gastric Cancer.* 2011;14:101–112.
12. 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.
13. Ikeguchi M, Kaibara N. Lymph node metastasis at the splenic hilum in proximal gastric cancer. *Am Surg.* 2004;70:645–648.
14. Mönig SP, Collet PH, Baldus SE, et al. Splenectomy in proximal gastric cancer: frequency of lymph node metastasis to the splenic hilus. *J Surg Oncol.* 2001;76:89–92.
15. Sasada S, Ninomiya M, Nishizaki M, et al. Frequency of lymph node metastasis to the splenic hilus and effect of splenectomy in proximal gastric cancer. *Anticancer Res.* 2009;29:3347–3351.
16. Sano T, Yamamoto S, Sasako M, et al. Randomized controlled trial to evaluate splenectomy in total gastrectomy for proximal gastric carcinoma: Japan Clinical Oncology Group Study JCOG 0110-MF. *Jpn J Clin Oncol.* 2002;32:363–364.
17. Sano T. Role of splenectomy in total gastrectomy for proximal gastric cancer. In: Presented in Korea International Gastric Cancer Week 2015 (KINGCA Week 2015) on April 2, 2015.
18. Chen XL, Yang K, Zhang WH, et al. Metastasis, risk factors and prognostic significance of splenic hilar lymph nodes in gastric adenocarcinoma. *PLoS ONE.* 2014;9:e99650.
19. Oh SJ, Hyung WJ, Li C, et al. The effect of spleen-preserving lymphadenectomy on surgical outcomes of locally advanced proximal gastric cancer. *J Surg Oncol.* 2009;99:275–280.
20. Lee KY, Noh SH, Hyung WJ, et al. Impact of splenectomy for lymph node dissection on long-term surgical outcome in gastric cancer. *Ann Surg Oncol.* 2001;8:402–406.
21. Li P, Huang CM, Zheng CH, et al. Laparoscopic spleen-preserving splenic hilar lymphadenectomy in 108 consecutive patients with upper gastric cancer. *World J Gastroenterol.* 2014;20:11376–11383.
22. Hyung WJ, Lim JS, Song J, et al. Laparoscopic spleen-preserving splenic hilar lymph node dissection during total gastrectomy for gastric cancer. *J Am Coll Surg.* 2008;207:e6–e11.
23. Zhang CH, Zhan WH, He YL, et al. Spleen preservation in radical surgery for gastric cardia cancer. *Ann Surg Oncol.* 2007;14:1312–1319.
24. Schwarz RE. Spleen-preserving splenic hilar lymphadenectomy at the time of gastrectomy for cancer: technical feasibility and early results. *J Surg Oncol.* 2002;79:73–76.
25. Eom BW, Joo J, Kim YW, et al. Improved survival after adding dissection of the superior mesenteric vein lymph node (14 v) to standard D2 gastrectomy for advanced distal gastric cancer. *Surgery.* 2014;155:408–416.
26. Sasako M, McCulloch P, Kinoshita T, et al. New method to evaluate the therapeutic value of lymph node dissection for gastric cancer. *Br J Surg.* 1995;82:346–351.
27. Sasako M, Sano T, Yamamoto S, et al. D2 lymphadenectomy alone or with para-aortic nodal dissection for gastric cancer. *N Engl J Med.* 2008;359:453–462.
28. Noh SH, Park SR, Yang HK, et al. Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): 5-year follow-up of an open-label, randomised phase 3 trial. *Lancet Oncol.* 2014;15:1389–1396.