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Optimal extent of lymphadenectomy for radical surgery of pancreatic head adenocarcinoma

2-year survival rate results of single-center, prospective, randomized controlled study

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Abstract

Background: Radical pancreaticoduodenectomy is the only possible cure for pancreatic head adenocarcinoma, and although several RCT studies have suggested the extent of lymph node dissection, this issue remains controversial. This article wanted to evaluate the survival benefit of different lymph node dissection extent for radical surgical treatment of pancreatic head adenocarcinoma.

Methods: A total of 240 patients were assessed for eligibility in the study, 212 of whom were randomly divided into standard lymphadenectomy group (SG) or extended lymphadenectomy group (EG), there were 97 patients in SG and 95 patients in EG receiving the radical pancreaticoduodenectomy.

Result: The demography, histopathology and clinical characteristics were similar between the 2 groups. The 2-year overall survival rate in the SG was higher than the EG (39.5% vs 25.3%; $P = .034$). The 2-year overall survival rate in the SG who received postoperative adjuvant chemotherapy was higher than the EG (60.7% vs 37.1%; $P = .021$). There was no significant difference in the overall incidence of complications between the 2 groups ($P = .502$). The overall recurrence rate in the SG and EG (70.7% vs 77.5%; $P = .349$), and the patterns of recurrence between 2 groups were no significant differences.

Conclusion: In multimodality therapy system, the efficacy of chemotherapy should be based on the appropriate lymphadenectomy extent, and the standard extent of lymphadenectomy is optimal for resectable pancreatic head adenocarcinoma. The postoperative slowing of peripheral blood lymphocyte recovery might be 1 of the reasons why extended lymphadenectomy did not result in survival benefits.

Clinical trial registration: This trial was registered at ClinicalTrials.gov (NCT02928081) in October 7, 2016. https://clinicaltrials.gov/

Abbreviations: EG = extended lymphadenectomy group, EPD = extended lymphadenectomy in pancreatoduodenectomy, OS = overall survival, PD = pancreatoduodenectomy, SG = standard lymphadenectomy group, SPD = standard lymphadenectomy in pancreatoduodenectomy.

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ZW and XW contribute equally to the article.

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Consent for publication was not applicable

The authors have no conflicts of interest to disclose.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Pancreatic cancer is 1 of the most lethal diseases of the digestive system.[1] By 2030, pancreatic cancers are projected to surpass breast, prostate, and colorectal cancers to become the second leading cause of cancer-related death.[2] Presently, surgical resection, in combination with systemic chemotherapy, offers the only hope of cure for patients with pancreatic cancer.[3] Therefore, how to improve surgical outcomes is a crucial aim of current research.

Since the 1980s, Japanese researchers have recommended retroperitoneal lymphadenectomy in pancreatoduodenectomy (PD).[4] Since then, it has become popular to assert that extended lymphadenectomy in pancreatoduodenectomy (EPD) is superior to standard lymphadenectomy in pancreatoduodenectomy (SPD). However, subsequent studies have found that EPD does not result in survival benefits and might increase the incidence of postoperative complications.[5–10] In 2014, the International Pancreatic Surgery Research Group (ISGPS) reached a consensus about SPD that includes the 5, 6, 8a, 12b1, 12b2, 12c, 13a, 13b, 14a, 14b, 17a, and 17b lymph nodes.[11] Furthermore, some researchers reported that lymphadenectomy that includes the 12b,12c, 13, and 17 lymph nodes can be performed safely and efficiently, without negatively affecting oncologic efficacy or long-term survival, only compared with EPD.[9] Therefore, at present, the extent of lymphadenectomy in PD remains controversial.

We designed this randomized controlled study based on the 2014 consensus of the ISGPS. To determine the optimal lymphadenectomy extent for PD in the treatment of pancreatic head adenocarcinoma, we studied the effect of SPD and EPD on the survival time of patients.

2. Materials and methods

2.1. Trial design

This randomized, controlled, single-center, single-blind (subject), parallel-group trial compared standard lymphadenectomy versus extended lymphadenectomy in PD for treatment of pancreatic head adenocarcinoma. It complied with the Declaration of Helsinki, was approved and overseen by the institutional review board of West China Hospital, and is registered at ClinicalTrials.gov (NCT02928081).

2.2. Participants

All patients enrolled in this study were treated in the pancreatic surgery department of West China Hospital from October 2016 to May 2018, and all operations were performed by seven different surgeons who specialize in pancreatic surgery. Inclusion criteria were age below 75, pancreatic head ductal adenocarcinoma, resectable (NCCN Guidelines Pancreatic Adenocarcinoma Version 2.2016),[12] no history of tumor. Exclusion criteria were unresectable or metastasis, with serious diseases of other organs (e.g., coronary heart disease), and other pathology. All patients had to sign informed consent forms before inclusion in the study. Patients selected for analysis from prospective database used the same criteria described above. Data were analyzed in October 2020.

2.3. Interventions

According to the 2014 ISGPS consensus statement, in SPD, the resected lymph nodes included 5, 6, 8a, 12b, 12c, 13, 14a, 14b, and 17. In EPD, in addition to those lymph nodes removed in SPD, the following nodes were resected as well: 9, 12p, 14c, 14d, 16a2, and 16b1, and all soft tissues surrounding the hepatoduodenal ligament were dissected and skeletonized, and the right celiac plexus and superior mesenteric artery right plexus were resected. The differences in specific resection extent are shown in Supplement Table 1, http://links.lww.com/MD/G379. We recommended postoperative chemotherapy to all patients, except for patients with poor physical condition or organ insufficiency, or those who refused adjuvant chemotherapy. All patients underwent surgical field photographs to verify that the required surgical extent was achieved. All photos and data are monitored and stored by the clinical trial center of West China Hospital of Sichuan University. The chemotherapy regimen included gemcitabine (1000 mg per square meter on days 1, 8, and 15 every 4 weeks) for 24 weeks.

2.4. Outcomes

The primary endpoint of this study was 2-year overall survival (OS), which was defined as the time from randomization to death. The secondary endpoints were morbidity and postoperative mortality which means death due to any cause at postoperative day 30.

2.5. Sample size

Our trial was powered for superiority of survival data at 2 years according to the previous trial, assuming that the 2-year survival rate (38%) of patients who underwent extended pancreatectomy was 18% higher than that of the standard group (20%).[13–15] With alpha = 0.05, beta = 0.20, and the power of 90%, assuming a drop-out rate of 20%, a total sample size of n = 200 patients would be allocated to this trial and a sample size of 100 per group is necessary to detect a difference between the intervention groups, because of the high dropout rate (>20%), we added an additional 30 patients during the recruitment, using PASS 11.0 software (NCSS, LLC, Kaysville, Utah).

2.6. Randomization

After confirming patient eligibility and determining that the tumor could be removed, patients were randomly assigned 1:1 using the Multi Random Data Generator. Sealed and numbered envelopes that contained the allocated group were prepared and opened before surgery.

2.7. Statistical analysis

Patient eligibility for follow-up and analysis was determined by evaluating the photographs taken during the operation. The

results are presented as mean ± standard error or median with interquartile range. Nominal data were compared using the Chi-squared test, and continuous variables were analyzed with Student *t*-test. The Kruskal–Wallis test was used for data that did not conform to the normal distribution. Survival data were calculated using the Kaplan–Meier method and compared using the log-rank test. A Cox proportional hazards regression model was used to calculate the effect of multiple factors on survival time, and variables that presented significant differences in univariate analysis were included in the final analysis. All statistical analyses were performed using SPSS 23.0 software (SPSS Inc, Chicago, Illinois), and 2-sided *P* values less than .05 were considered statistically significant.

3. Results

3.1. Demographics

A total of 240 patients were assessed for eligibility in this randomized controlled study, and the 212 patients were randomly divided 1:1 into the SPD group (SG) or EPD extended lymphadenectomy group (EG) (Fig. 1). In total, we analyzed 153 patients, including 79 who underwent SPD and 74 who underwent EPD. The inclusion and exclusion criteria for this group of patients were consistent with the aforementioned criteria. Therefore, the patients in 2 groups matched well in terms of age, gender, nutritional status, preoperative conditions, portal vein resection rate, tumor staging, and follow-up time (Table 1). The number of patients who received postoperative adjuvant chemotherapy was 32 in SG, and 29 in EG.

3.2. Pathologic differences

Table 1 shows the pathologic differences among the 2 groups. No significant differences were observed in the R1 resection rate among the 2 group ($P = .768$), and no significant differences were observed among the 2 groups in tumor size ($P = .870$) and T stage ($P = .790$), or American Joint Committee on Cancer (8th edition) stage ($P = .733$). In terms of retrieving the number of lymph nodes, the EG was significantly higher than the SG (24 [range, 22–26] vs 18 [range, 16–19]; $P < .001$).

3.3. Morbidity and mortality

No significant differences were observed in morbidity and mortality between the SG and EG (39.2% vs 44.6%, $P = .502$) (Table 2). Because 2 patients in the SG had long postoperative hospital stays (>60 days), the average postoperative hospital stay in this group was slightly longer than the average postoperative hospital stay in the EG, but the difference was not significant (mean [SD] days 14.66 [10.32] vs 12.65 [4.93], $P = 0.131$). Three patients in the SG (3.8%) died, one of postoperative intra-abdominal bleeding, the others of respiratory failure due to sepsis and pulmonary infection. Two patients in the EG (2.7%) died, both of intraabdominal bleeding.

3.4. Survival data and recurrence patterns

After excluding deaths in the hospital, survival analysis was performed on 75 patients in the SG, on 71 patients in the EG. There were 32 patients and 29 patients received postoperative

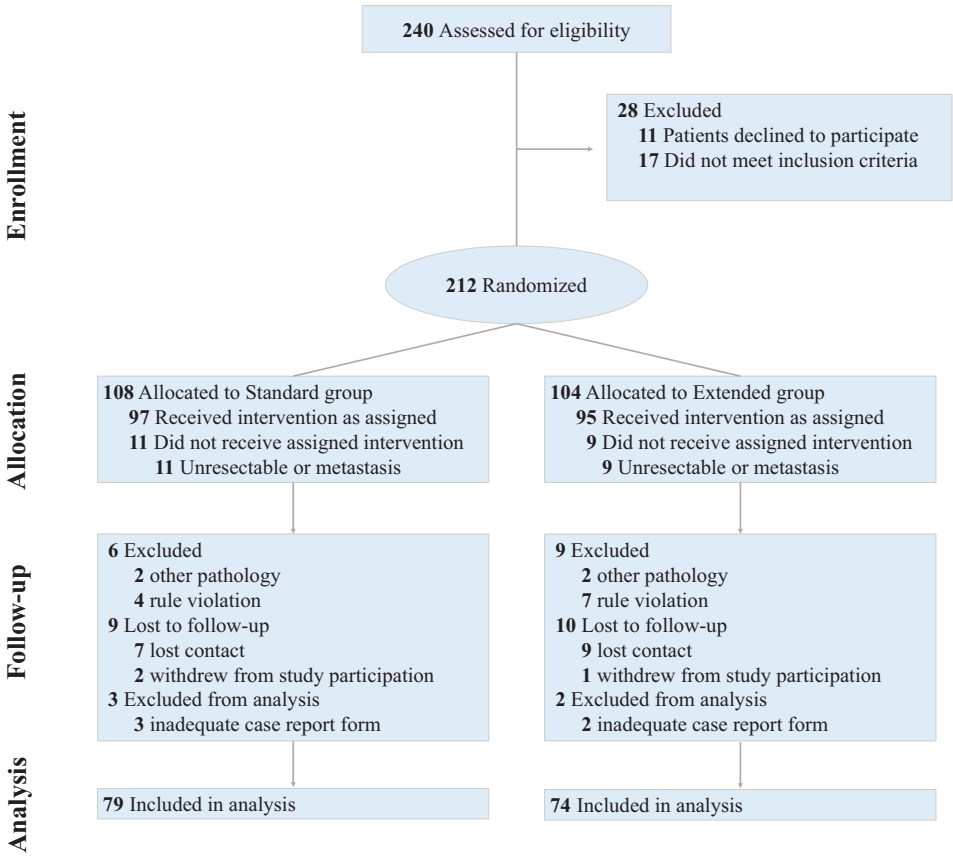

Figure 1. consort diagram.

Table 1

Demographic and pathologic findings between 2 groups.

	Standard (n = 79)	Extended (74)	*P*
Clinical variables			
Age, mean (SD), yr	59.48 (10.55)	57.20 (9.91)	.172
Sex, M:F	1.55:1	1.55:1	.995
Initial CEA, median (IQR), ng/ml	3.79 (2.06–6.46)	3.36 (1.98–5.16)	.537
Initial CA125, median (IQR), U/ml	17.74 (13.45–25.39)	18.00 (12.73–38.18)	.774
Initial CA19–9, median (IQR), U/ml	198.60 (49.22–582.20)	170.35 (45.56–833.50)	.923
Initial albumin, median (IQR), g/L	39.40 (36.9–41.8)	39.65 (36.18–43.05)	.638
Operation time, median (IQR), min	324 (270–390)	350 (295–430)	.038
Transfusion (RBC+FFP), quantity (%)			.289
0 ml	58 (73.43)	48 (64.87)	
0–400 ml	6 (7.59)	9 (12.16)	
400–800 ml	6 (7.59)	10 (13.51)	
>800 ml	9 (11.39)	7 (9.46)	
Infusion, median (IQR), ml	3700 (3000–4400)	4100 (3375–4725)	.047
EBL, median (IQR), ml	300 (200–600)	425 (300–725)	.064
Follow-up, median, m	30.27	27.55	
Portal vein resection, quantity (%)	27 (34.17)	22 (29.72)	.556
Pathologic variables			
R1 resection, quantity (%)	12 (15.19)	10 (13.51)	.768
Tumor size, median (IQR), cm	3.1 (2.5–4.0)	3.0 (2.5–4.0)	.870
T stage, quantity (%)			.790
T1	6 (7.6)	5 (6.8)	
T2	58 (73.4)	57 (77.0)	
T3	15 (19.0)	12 (16.2)	
Total retrieved lymph nodes, median (IQR)	18 (16–19)	24 (22–26)	<.001
Positive lymph nodes, quantity (%)			.209
0	36 (45.57)	32 (43.24)	
0–3	16 (20.25)	8 (10.81)	
3–6	25 (31.65)	30 (40.54)	
>6	2 (2.53)	4 (5.41)	
AJCC stage (8th edition)			.733
IA	3 (3.8)	3 (4.1)	
IB	29 (36.7)	23 (31.1)	
IIA	4 (5.1)	6 (8.1)	
IIB	29 (36.7)	30 (40.5)	
III	14 (17.7)	12 (16.2)	

AJCC, American Joint Committee on Cancer; CEA, carcinoembryonic antigen; CA125, cancer antigen 125; CA19–9, cancer antigen 19–9; RBC, red blood cell; FFP, fresh frozen plasma; EBL, estimated blood loss.

Table 2

Morbidity and mortality between standard group and extended group.

	Standard (n = 79)	Extended (n = 74)	*P*
Postoperative hospital stay, mean (SD), d	14.66 (10.32)	12.65 (4.93)	.131[e]
In-hospital death, quantity (%)	3 (3.8)	2 (2.7)	NS
Complications, quantity (%)	31 (39.24)	33 (44.59)	.502[f]
Pancreatic fistula[a]	8 (10.12)	12 (16.21)	
Delayed gastric emptying (DGE)[b]	8 (10.12)	9 (12.16)	
Diarrhea[c]	7 (8.86)	9 (12.16)	
Intra-abdominal bleeding	6 (7.59)	4 (5.40)	
Gastrointestinal bleeding	4 (5.06)	3 (4.05)	
Severe sepsis	3 (3.80)	2 (2.70)	
Pulmonary infection	9 (11.39)	8 (10.81)	
Re-operation	6 (7.59)	4 (5.40)	
Others[d]	7 (8.86)	10 (13.51)	

[a] Only grade B and C pancreatic fistula was counted.
[b] Only grade B and C DGE was counted.
[c] Postoperative day 3 mouths.
[d] Including chylous fistula, wound infection, adhesive intestinal obstruction.
[e] Student *t* test.
[f] Chi-squared test, NS indicates not significant.

chemotherapy in SG and EG respectively, and 43 patients and 42 patients did not receive postoperative chemotherapy in SG and EG respectively. The median survival time of the enrolled patients was 22 months (SG), and 15 months (EG). The 2-year OS rate were 39.5% (SG), and 25.3% (EG). The 2-year OS rate of patients in the SG was higher than that of patients in the EG ($P = .034$) (Fig. 2A). The 2-year DFS rate of patients in the SG was higher than that of patients in the EG (28.25% vs 19.32%; $P = .046$) (Fig. 2B). For intention-to-treat analysis, which included all patients who finally received the radical pancreaticoduodenectomy randomly assigned to the standard (n = 97) and extended (n = 95) groups, the 2-year OS rate was 41.0% and 26.2% ($P = .023$), respectively (Fig. 2C).

The 2-year OS rate of patients who received postoperative chemotherapy in 2 groups was higher than that of patients who did not receive chemotherapy respectively (SG:60.7% vs 24.3%, $P < .001$; EG: 37.1% vs 17.7%, $P = .009$) (Supplement Figure 1, http://links.lww.com/MD/G379). The 2-year OS rate of patients in the SG who received postoperative chemotherapy was higher than that of patients in the EG (60.7% vs 37.1%; $P = .021$) (Fig. 3A). Patients who did not receive chemotherapy showed no difference in 2-year OS rate between the SG and EG (31.6% vs 20.2%; $P = .366$) (Fig. 3B). No differences were observed in the survival rate of lymph node-positive patients between the SG and EG (28.6% vs 18.1%; $P = .065$) (Fig. 3C). Although the 2-year OS rate of lymph node-negative patients in the SG was higher than that of lymph node-negative patients in the EG, no significant differences were observed between 2 groups (55.3% vs 35.2%; $P = .182$) (Fig. 3D).

For patients with positive lymph nodes who received postoperative chemotherapy, no differences were observed in the 2-year OS rate between the SG and EG (37.5% vs 49.0%; $P = .698$) (Fig. 3E). However, for patients with negative lymph nodes who received postoperative chemotherapy, the 2-year OS rate of patients in the SG was higher than that of patients in the EG (87.5% vs 30%; $P = .004$) (Fig. 3F).

In addition, for patients with negative lymph nodes who did not receive postoperative chemotherapy, no differences were observed in the 2-year OS rate between the SG and EG (26.5% vs 40.8%; $P = .491$) (Fig. 3H). However, for patients with positive lymph nodes who did not receive postoperative chemotherapy, the 2-year OS rate of patients in the SG was higher than that of patients in the EG (23.0% vs 7.1%; $P = .036$) (Fig. 3G).

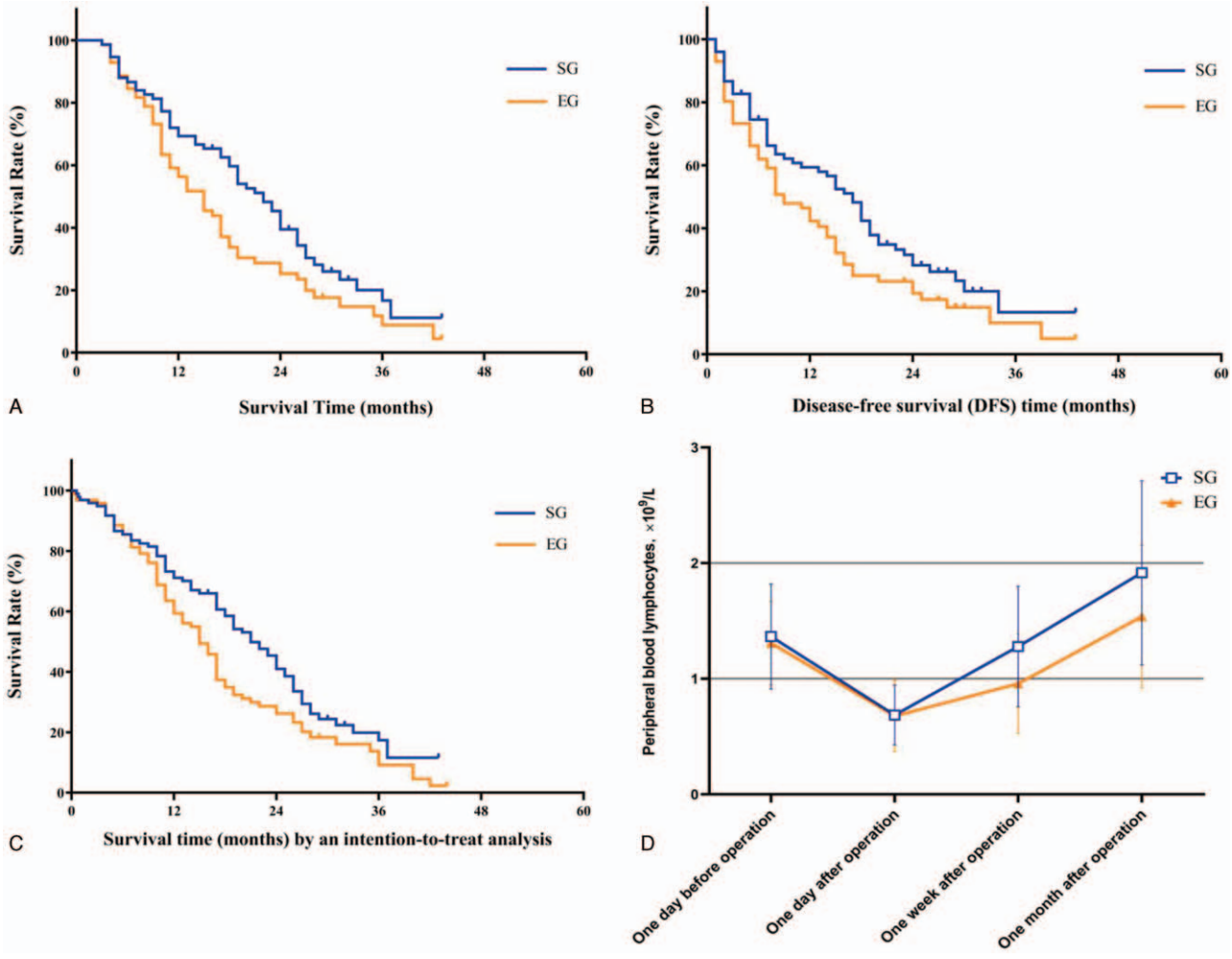

Figure 2. Survival curves between 2 groups. A: Overall survival in 2 groups, B: Disease-free survival (DFS) in 2 groups, C: Overall survival by an intention-to-treat analysis, D: The trend of peripheral blood lymphocytes between 2 groups in different time. SG: standard lymphadenectomy group, EG: extended lymphadenectomy group.

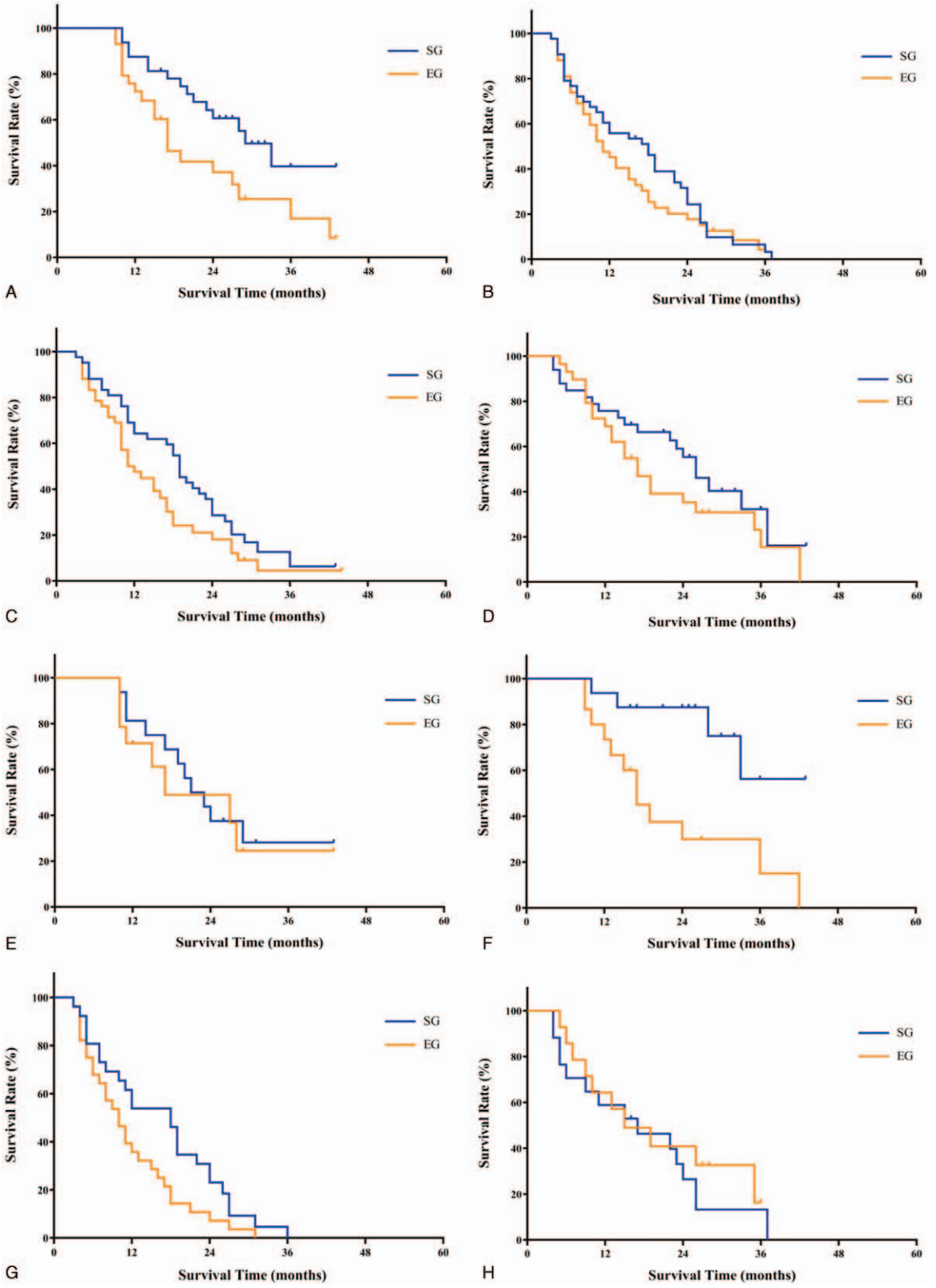

Figure 3. A: Survival curves for patients receiving chemotherapy in 2 groups, B: Survival curves for patients not receiving chemotherapy in 2 groups, C: Survival curves for patients with positive lymph nodes in 2 groups, D: Survival curves for patients with negative lymph nodes in 2 groups, E: Survival curves for patients with positive lymph nodes and receiving chemotherapy in 2 groups, F: Survival curves for patients with negative lymph nodes and receiving chemotherapy in 2 groups, G: Survival curves for patients with positive lymph nodes and not receiving chemotherapy in 2 groups, H: Survival curves for patients with negative lymph nodes and not receiving chemotherapy in 2 groups.SG: standard lymphadenectomy group, EG: extended lymphadenectomy group.

Table 3

Univariate and multivariate analyses of survival.

			Univariate	Multivariate		
	N	2YSR, %	P	HR	95% CI	P
Sex, M/F	88/58	37.5/25.8	.076			
Age, ⩾65/<65	43/103	38.8/30.1	.918			
Initial CEA, ⩾5.0/<5.0	49/97	37.1/30.6	.610			
Initial CA-199, ⩾37.0/<37.0	114/32	36.7/19.9	.258			
OP extent, standard/extended	75/71	39.5/25.3	.034	1.67	1.130–2.254	.010
Portal vein resection, Yes/No	44/102	29.7/34.2	.749			
R state R0/R1	125/21	35.3/17	.428			
T stage T1/T2/T3	8/112/26	37.5/32.4/32.7	.937			
N stage N0/N+	62/84	39.5/28	.044	1.254	0.823–1.910	.292
Stage I/II/III	53/68/25	44.6/34/8	.001	1.338	0.992–1.804	.056
Histology, WD/MD/PD	5/116/25	75/36.6/5	.002	2.190	1.370–3.502	.001
Adjuvant treatment, +/-	61/85	50.3/21.1	<.001	2.226	1.464–3.384	<.001
Perineural invasion, +/-	120/26	32.3/35.2	.678			
Endolymphatic tumor emboli, +/-	32/114	16.4/37.8	.154			

M: male, F: female, OP: operation, WD: well differentiated, MD: moderately differentiated, PD: poor differentiated.

There were no differences of overall recurrence rate in the SG and EG (70.7% vs 77.5%; $P=.349$), and there were no differences in the patterns of recurrence between 2 groups (Table 4). Indeed, the most important metastasis patterns of the 2 groups was the liver (Table 4).

3.5. Prognostic factors

Univariate analysis showed that the insufficient extent of surgical dissection, regional lymph node metastasis, later stage, poor histologic differentiation, and absence of postoperative adjuvant chemotherapy were associated with adverse outcomes (Table 3). In the multivariate Cox proportional hazards model, lymphadenectomy extent (hazard ratio [HR] = 1.67; 95% confidence interval [CI], 1.130–2.254; $P=.010$), Stage (HR = 1.338; 95% CI, 0.992–1.804; $P=.056$), histologic differentiation (HR = 2.190; 95% CI, 1.370–3.502; $P=.001$), and postoperative adjuvant chemotherapy (HR = 2.226; 95% CI, 1.464–3.384; $P<.001$) remained statistically significant.

The peripheral blood lymphocyte levels of all patients who underwent PD experienced a process of declining and then slowly rising during the perioperative period. However, the lymphocyte count of patients in the EG was significantly lower than the lymphocyte counts of patients in the SG (mean [SD] $\times 10^9$, 0.957 [0.429] vs 1.278 [0.521]; $P=.001$) at 1 week, and the lymphocyte count of patients in the EG was significantly lower than the lymphocyte count of patients in the SG (mean [SD] $\times 10^9$, 1.538 [0.618] vs 1.917 [0.796]; $P=.009$) at 1 month (Fig. 2D).

4. Discussion

Previously, Pedrazzoli et al suggested that extended lymphadenectomy can be performed in some patients, and patients with positive lymph nodes seem to benefit from extended dissection.[5] However, a subsequent randomized controlled study by Yeo et al showed that the 5-year OS rate and median survival time of patients with negative lymph nodes were significantly higher than patients with positive lymph nodes, this conclusions possibly because approximately 78% of the patients in this study received different types of postoperative adjuvant treatment.[6] An additional study by Farnell et al included only patients with adenocarcinoma of the pancreatic head. Their results showed that extended lymphadenectomy did not improve survival time regardless of lymph node status.[7] Although there was some ethical controversy, none of the patients enrolled in a Japanese randomized controlled study received postoperative adjuvant treatment, and the final results were similar to Farnell et al's report.[8] Interestingly, patients who received extended lymphadenectomy had a higher local recurrence rate, which, it is speculated, might have been influenced by increased immunologic suppression associated with the more extensive resection.[8] However, this explanation is not supported by relevant data.

Table 4

Recurrence rate and patterns between 2 groups.

	Overall	Standard (n = 75)	Extended (n = 71)	P
Recurrence	108/146 (74.0%)	53/75 (70.7%)	55/71 (77.5%)	.349
Locoregional	28/108 (25.93%)	12/53 (22.64%)	16/55 (29.09%)	.445
Systemic	92/108 (85.19%)	44/53 (83.02%)	48/55 (87.27%)	.534
Liver	70/108 (64.81%)	33/53 (64.0%)	37/55 (67.3%)	.586
Peritoneal seeding	13/108 (12.04%)	5/53 (9.43%)	8/55 (14.55%)	.414
Lung	10/108 (9.26%)	6/53 (11.32%)	4/55 (7.27%)	.468
LN	25/108 (23.15%)	15/53 (28.30%)	10/55 (18.18%)	.213
Others	3/108 (2.78%)	1/53 (1.98%)	2/55 (3.63%)	.580

LN = lymph node.

Subsequently, Korean researchers further confirmed that extended lymphadenectomy did not improve patient survival time compared to standard lymphadenectomy, whether the lymph nodes were positive or negative, and lacking of postoperative adjuvant treatment may be the primary factor influencing prognosis.[9,10]

The past five randomized controlled studies had different definitions of standard lymphadenectomy. Because the most commonly metastatic lymph nodes of pancreatic head cancer were No. 14, which have an important effect on the prognosis,[16] standard lymphadenectomy that includes No. 14 lymphadenectomy has gradually become an international consensus.[11] Therefore, the Japanese and Korean studies might have ignored the potential survival benefits of No.14 lymphadenectomy.

Our survival data showed that the 2-year OS and DFS rate of patients in the SG were better than the 2-year OS and DFS rate of patients in the EG. This is different from the results of previous randomized controlled studies, and the most important reason is the different definition of the standard. The standard extent of lymphadenectomy performed by Farnell et al was similar to ours,[7] but their results did not indicate that the survival time of the standard group was superior to the survival time of the extended group. We speculate that the primary reason for this discrepancy is their small sample size.[7] Through the analyze of recurrence data, the systemic recurrence rate of the 2 groups was significantly higher than the local recurrence rate, which means that pancreatic cancer is a systemic disease when it occurs. Comprehensive control using postoperative chemotherapy is more important than expanding the extend of surgery to reduce recurrence rate. Moreover, whether the regional lymph nodes are positive has no effect on the survival of the 2 groups of patients, which also shows that trying to reduce the recurrence rate of patients by resecting more lymph nodes has no expected effect. Some studies found that the postoperative peripheral blood lymphocytes of patients who underwent PD experienced a polyline change (sharp decline, slow rise, and gradual recovery).[17,18] Patients who do not fully and rapidly recover the level of lymphocytes after the operation are considered to be prone to recurrence and have a poor prognosis.[17] We measured the trend of lymphocytes after operation in 2 groups of patients, the slowdown of lymphocyte recovery of patients in the extended resection group may be the reason why extended lymphadenectomy will contrarily bring higher local recurrence rate and worse survival time. This suggests that the impact of surgical stress on the immune system is likely to affect the recurrence rate and survival rate. In this study, the local recurrence rate of the EG group was indeed higher than that of the SG, but no statistical difference was observed (Table 4). This may need to be determined by a larger sample size and longer follow-up time.

Even though chemotherapy after radical resection can significantly improve survival rate, and modified FOLFIRINOX regimen led to significantly longer disease-free survival and overall survival than adjuvant chemotherapy with gemcitabine, but most our patients cannot tolerate the modified FOLFIRINOX regimen, Which led to the lower overall survival rate we reported to compare with that reported by Conroy et al.[19] Subgroup analysis revealed that postoperative chemotherapy could significantly improve the survival time of patients regardless of extent of lymphadenectomy, and the 2-year OS rate of patients in the SG who received postoperative chemotherapy was significantly higher than the 2-year OS of patients in the EG (60.7% vs 37.1%; $P=.021$), which might be related to the recovery of patients' immune systems. The above analysis suggests that the efficacy of chemotherapy should be based on the appropriate extent of lymphadenectomy, while extended lymphadenectomy (including 16a2 and 16b1) is likely to lead to higher local recurrence rate and poor efficacy of chemotherapy. Further analysis showed that the patients in the SG with negative lymph nodes who received postoperative chemotherapy had the highest survival rate because of the effective local radical lymphadenectomy and reasonable systemic therapy. However, this advantage did not exist in patients in the SG with positive lymph nodes who received postoperative chemotherapy compared with that of patients from EG, which supporting an approach that minimizes the extent of lymphadenectomy to lymph nodes which have a clear histologic metastasis to avoid the excessive surgical trauma and ensuring the effect of chemotherapy. Thus, the studies of Nimura et al and Jang et al adopted a limited "standard" lymphadenectomy.[8–10] Some of our patients also received the "standard" extent of lymphadenectomy (only No.12b,12c,13 and 17) reported by Jang et al, survival analysis of this part of patients showed that their 2-year survival rate was not statistically different from the EG group (26.1% vs 25.3%; $P=.484$) (Supplement Figure 2B, http://links.lww.com/MD/G379), but was lower than the SG group (26.1% vs 39.5; $P=.047$) (Supplement Figure 2A, http://links.lww.com/MD/G379), which means that although a limited extent of lymphadenectomy (only No.12b,12c,13 and 17) can obtain a similar survival time as the EG group, it may also lose the survival benefits of dissection of the NO.14 lymph nodes. Of course, this result was only based on the analysis of current survival data and has not been confirmed by RCT trials.

Early pancreatic cancer is considered a systemic disease because the formation of local and regional micrometastases is inevitable.[20] Through a reasonable lymphadenectomy (No. 14), patients with a relatively normal immune system who receive postoperative chemotherapy can survive and benefit. According to the Cox proportional hazards model, the most important factors affecting prognosis were the extent of lymphadenectomy, chemotherapy, staging, and differentiation. More extensive lymphadenectomy is not suitable to improve the survival rate in all cases; rather, to increase the survival of patients with pancreatic head cancer, it is reasonable to propose that proper systemic treatment after surgery is better than extended lymphadenectomy. Pancreas includes the fusion of the ventral pancreas and dorsal pancreas. Therefore, some studies have pointed out that, when the tumor is located in the ventral pancreas, lymph node metastasis and nerve invasion often occur around the superior mesenteric artery and pancreatic head nerve plexus.[21,22] However, if the tumor is located in the dorsal pancreas, lymph node metastasis and nerve invasion often present in the common hepatic artery and hepatoduodenal ligament region.[21,22] This means that although extended lymphadenectomy is not recommended in all studies, there might be more individualized options for standard or limited lymph node dissection that could be identified through future randomized controlled studies grouped by different tumor sites.

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