

The optional extent of lymph node dissection for pancreatic head cancer*

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Abstract

Objective The extent of lymph node dissection for pancreatic head cancer (PHC) is uncertain and controversial; therefore, this study evaluated whether PHC patients can benefit from different extents of lymph node dissection.

Methods A total of 106 PHC patients underwent standard regional lymphadenectomy (SRLN; $n = 56$, 52.8%) and extended regional lymphadenectomy (ERLN; $n = 50$, 47.2%) between September 2015 and September 2019. None of the study participants had distant metastases. The median survival time and complications were compared between the two groups.

Results The median survival time in the SRLN and ERLN groups was 27.01 months and 21.17 months, respectively ($P = 0.30$). The postoperative major morbidity and mortality rates were 37.50% and 1.79% in the SRLN group, and 46.00% and 2.00% in the ERLN group, respectively. Moreover, the tumor differentiation, tumor diameter, lymph node involvement, perineural invasion, vascular invasion, and margin status all correlated with survival ($P < 0.05$).

Conclusion For PHC patients, ERLN cannot provide a significant survival benefit over SRLN. Moreover, ERLN increased morbidity and mortality, although without statistical significance. This indicates that ERLN should not be considered in PHC patients.

Key words: pancreatic head cancer (PHC); standard regional lymphadenectomy (SRLN); extended regional lymphadenectomy (ERLN); survival; complication

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Pancreatic cancer is one of the most fatal tumors for which the poor survival rate is often attributable to inefficient therapy. According to some reports, patients with pancreatic head cancer (PHC) who underwent pancreaticoduodenectomy had a median overall survival of only 13 months, and a 5-year survival rate of only 7%–8% [1–3]. Lymph node metastasis is very high among PHC patients and is one of the adverse prognostic factors that indicate progressively decreased survival [4]. To date, radical surgery is the only option to increase survival in PHC patients; therefore, there is a need for studies evaluating whether PHC patients can benefit from different extents of lymph node dissection.

Extended regional lymphadenectomy (ERLN) was originally intended to remove the entire pancreas as well as the adjacent tissues (nervous, adipose, and lymphatic tissues, among others). In Japan, radical pancreaticoduodenectomy has been used most extensively

and has been thought to guarantee a better survival [5–6]. Nevertheless, as per some reports, it did not prolong the survival time, but increased postoperative complications [7–8]. Our paper aimed to evaluate the benefits of different extents of lymphadenectomy in PHC patients.

Patients and methods

A total of 166 PHC patients were admitted to the Xuzhou Central Hospital (Xuzhou, China) from September 2015 and September 2019. Of them, 60 patients were excluded because of preoperative chemoradiation therapy, the presence of tumors other than adenocarcinoma, and the absence of informed consent. In total, 106 patients were eligible for the study, and all patients received ethical and written consent.

Standard regional lymphadenectomy (SRLN) included the removal of the following lymphatic fat tissue: No.

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5/6/8a/12b1/12b2/12c/13a/13b/14a/14b/17a/17b. By contrast, ERLN included the additional removal of all lymphatic, connective, and neural tissue No. 8p/9/16^[9].

The 106 patients were divided between the SRLN and ERLN groups according to the lymphadenectomy extent. The SRLN group included 56 patients (27 males and 29 females). The ERLN group included 50 patients (29 males and 21 females). No patient with macroscopically positive resection margins was included in the study. Matched-pair analysis was performed to assess the impact of the different extents of lymphadenectomy in PHC patients. Patients in both groups were matched for the gender, performance status, tumor differentiation, tumor diameter, lymph node involvement, surgery type, perineural invasion, vascular invasion, and margin status.

Statistical analyses were performed using SPSS 13.0 software (SPSS Inc., Chicago, Illinois). Data were presented as mean \pm standard deviation or median (range). Chi-square test or Fisher's exact test was used for categorical variables. The Kaplan-Meier method was used to calculate overall survival rates. A P value < 0.05 was considered statistically significant.

Results

The mean age of the all patients was 49 years (range: 30–70 years), and there were 56 males and 50 females. In the SRLN group, 48% of the patients were male, compared to 58% in the ERLN group ($P = 0.314$). As for the surgery type, the patients underwent traditional pancreaticoduodenectomy (PD) (SRLN: 36; ERLN: 26; $P = 0.20$). Tumor differentiation was also comparable between the two groups ($P = 0.677$). In the SRLN and ERLN groups, 32 and 24 patients had tumors with a diameter of > 2 cm, respectively. The SRLN group had microscopic carcinoma at a surgical margin in 27% of patients; by contrast, this was in 14% of patients in the ERLN group. Perineural invasion was identified in the majority of patients, but no difference was observed between the two groups. For both groups, 34% of patients had histologically positive lymph node metastases in the resection specimen (Table 1).

Univariate analysis showed that the tumor differentiation, diameter, lymph node involvement, perineural invasion, vascular invasion, and margin status was closely related to survival (Table 2). However, there was no difference in the median survival time between the two groups (27.01 vs. 21.17 months, $P = 0.30$). Fig. 1 shows the survival curves for all PHC patients.

As seen in Table 3, the morbidity and mortality rates of patients in the ERLN group were higher than those in the SRLN group. Postoperative major morbidity and mortality rates were 37.50% and 1.79% in the SRLN group, and 46.00% and 2.00% in the ERLN group, respectively.

Table 1 Comparison of PHC patients between SRLN and ERLN groups (n)

	SRLN group	ERLN group	P
Gender			0.314
Male	27	29	
Female	29	21	
Performance status			0.713
Score 90–100	26	25	
Score 70–80	30	25	
Differentiation			0.677
Well	10	6	
Moderately	28	28	
Poorly	18	16	
Tumor diameter (cm)			0.347
≤ 2	24	26	
> 2	32	24	
Lymph node metastasis (N)			0.994
Yes	19	17	
No	37	33	
Surgery type			0.200
PD	36	26	
PPPD	20	24	
Perineural invasion			0.872
Yes	40	35	
No	16	15	
Vascular invasion			0.727
Yes	14	14	
No	42	36	
Margin status			0.411
R0	51	43	
R1	5	7	

Note: PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy

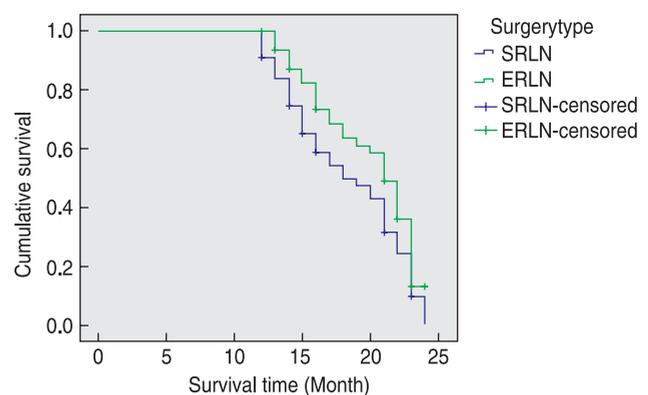


Fig. 1 The survival curves for all PHC patients

The most common postoperative complication was delayed gastric emptying and pancreatic fistula, which were observed in 8 patients. Other complications, such as wound infection, intraabdominal abscess, intraperitoneal hemorrhage, cholangitis, bile leak,

Table 2 Univariate analysis and Cox multivariate analysis to identify independent prognostic factors

	Median Survival	Univariate P	Multivariate P
Gender		0.102	
Male	27.65		
Female	19.05		
Performance status		0.935	
Score 90–100	24.31		
Score 70–80	23.82		
Differentiation		0.000	0.000
Well	34.91		
Moderately	28.50		
Poorly	12.08		
Tumor diameter (cm)		0.006	0.128
≤ 2	30.39		
> 2	18.16		
Lymph node metastasis (N)		0.033	0.033
Yes	15.03		
No	27.48		
Surgery type		0.100	
PD	23.35		
PPPD	12.00		
Extent of lymph node dissection		0.300	
SRLN	27.01		
ERLN	21.17		
Perineural invasion		0.008	0.040
Yes	19.97		
No	30.77		
Vascular invasion		0.000	0.005
Yes	10.85		
No	30.26		
Margin status		0.008	0.048
R0	25.73		
R1	8.13		

Note: PD, pancreaticoduodenectomy; PPPD, pylorus-preserving pancreaticoduodenectomy

Table 3 The morbidity and mortality of PHC patients between SRLN and ERLN groups (n)

	SRLN group	ERLN group	P
Morbidity	21 (37.50%)	23 (46.00%)	0.375
Delayed gastric emptying	3	5	
Pancreatic fistula	4	4	
Wound abscess	3	3	
Intraabdominal abscess	3	2	
Intraperitoneal hemorrhage	1	2	
Cholangitis	2	2	
Bile leak	2	2	
Lymphocele dysfunction	1	1	
Diarrhea	2	2	
Mortality	1 (1.79%)	1 (2.00%)	0.935
Cardiac & Respiratory failure	1	0	
Bleeding	0	1	

lymphocele dysfunction, and diarrhea occurred with similar frequency between the two groups. In the SRLN group, 1 death was directly related to respiratory failure resulting in multi-organ failure. There was also 1 death in the ERLN group, due to acute abdominal bleeding. Postoperative complications were graded according to the Clavien-Dindo classification^[10].

Discussion

Despite improvements in techniques associated with extended regional lymph nodes, we have not established the appropriate extent of lymphadenectomy. More radical surgical strategies have been developed to improve the survival of PHC patients, with extensive lymph node dissection being the most important aspect. Nevertheless, extended radical surgery remains controversial because of the high rates of complications.

Some East Asian surgeons have advocated for aggressive radical lymph node dissection, with PHC patients gaining long-term survival time through ERLN. For example, Ishikawa *et al*^[11] reported a significantly different ($P < 0.05$) 3-year survival rate between patients receiving SRLN (13%) and ERLN (38%). Moreover, Manabe *et al*^[12] showed that for pancreatic cancer without lymph node metastasis, the 2-year survival rate was 22% and 48% in the standard and radical groups, respectively ($P < 0.05$). By contrast, two randomized controlled trials (RCTs) have not found better outcomes in PHC patients who underwent extended lymph node dissection versus standard lymphadenectomy^[13–14]. However, these RCT studies were of low quality, having numerous confusing factors that made it less convincing to compare the results between the two groups and determine the preferred lymphadenectomy method. In our study, we also found no significant difference in the survival rates between the two groups; the median survival time was 27.01 months and 21.17 months for the SRLN and ERLN groups, respectively ($P = 0.30$; Fig. 1). Therefore, ERLN serves no benefit for PHC patients.

In addition to the tumor diameter, our study showed that tumor grade was a significant prognostic factor when tumor differentiations were compared. The tumors of patients under the T3 and T4 stages extend out of the capsule of the pancreas; therefore, the risk of direct perineural invasion is probably very high. Moreover, perineural invasion was identified in the majority of the patients, and was also an important survival predictor.

In other reports, lymph node metastasis represents a strong negative prognostic factor. Hellan *et al*^[15] found that the number of lymph node dissections directly affects prognosis. The median survival for patients with < 11 lymph nodes and > 11 lymph nodes was 20 months and 15 months, respectively. Riediger *et al*^[16] also reported

the relationship between lymph nodes ratio (LNR) and 5-year survival rate after surgery: when $LNR > 0.2$, the 5-year survival rate was 6%, whereas when $LNR \leq 0.2$, the 5-year survival rate was 19%. In our study, patients with positive lymph nodes had a median survival time of 15.03 months, whereas that of the patients with negative lymph nodes was 27.48 months ($P = 0.033$).

In most series, the portal or mesenteric vein infiltration is correlated with poor prognosis and a very low 5-year survival rate. Our current study showed that the portal involvement was significantly associated with the worst prognosis. The median overall survival was 10.85 months and 30.26 months for patients with and without the portal vein involvement, respectively ($P < 0.001$). Nevertheless, because these operations could guarantee a better survival, and morbidity and mortality rates did not increase, we can proceed intraoperatively with segmental resection if there is a possibility to achieve an R0 resection.

With improvements in surgical techniques, some surgeons have sought to perform more radical surgeries. However, it was shown in our study that R0 resection rates were similar in patients between the two groups (91.07% and 86.00% in the SRLN and ERLN groups, respectively). Even if the surgery was performed to cure, pancreatic cancer recurrence rates were as high as that of classical R0 resection. Thus, controlling the local tumor recurrence through extended lymphadenectomy cannot overcome the lymph node metastasis after surgery.

Some studies have reported that the most important factor for improved overall survival of PHC patients following pancreatoduodenectomy is proper systemic chemoradiotherapy rather than extensive surgery. According to some research, chemoradiotherapy and targeted therapy may improve survival outcomes after curative resection [14, 17–18]. A large multicenter RCT suggested that aggressive systemic treatment could lead to long-term survival [19–20]. With emerging chemotherapeutic agents and targeted medicines, we must pay more attention to the benefits of adjuvant treatment and not focus only on pure resection. In our study, the patients did not receive any postoperative adjuvant therapy, which could explain their low survival time. Nevertheless, by eliminating adjuvant therapy in our study, we were able to judge if there were any benefits derived exclusively from the extended lymphadenectomy.

There are 2 surgical techniques performed in the treatment of pancreatic head surgery. Several RCTs have compared these 2 techniques in terms of postoperative complications and survival; there was no evidence of superiority for one procedure over the other in terms of overall survival, and the differences in mortality and morbidity were not statistically significant [21–22]. Similar to the findings of our study, the type of surgery did not have an influence on survival or postoperative morbidity.

The mortality and morbidity rates in the two groups are summarized in Table 3. The results in our study were similar to those previously reported. The overall postoperative morbidity and mortality in the ERLN group was higher, but the difference was not statistically significant. Postoperative major morbidity and mortality rates were 37.50% and 1.79% in the SRLN group, and 46.00% and 2.00% in the ERLN group, respectively, which were similar to the previous reports of 40% to 50%, respectively [23–24]. Pancreatic fistula and delayed gastric emptying were the most frequent complications, which tended to be higher in patients who underwent ERLN, but no statistically significant differences were observed. Some studies reported that the rates of postoperative diarrhea tended to be higher in patients who underwent ERLN, mainly due to extended excision of the retroperitoneal and pancreatic head plexus. In our paper, 2 out of 56 patients and 2 out of 50 patients in the SRLN and ERLN groups, respectively, had diarrhea, which differed from the conclusion of other studies. Finally, 2 studies have also reported that postoperative quality of life was poorer among patients in the extended lymphadenectomy group [13, 25].

Since ERLN increases morbidity and does not appear to improve survival, it should be noted that extended lymphadenectomy does not provide a better survival rate. Therefore, PHC patients should be treated with caution. Surgery combined with comprehensive treatments should be considered for PHC patients.

Conflict of interest

The authors indicated no potential conflicts of interest.

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