Pancreatology 19 (2019) 414–418

Contents lists available at ScienceDirect

Pancreatology

journal homepage: www.elsevier.com/locate/pan

Should a standard lymphadenectomy include the No. 9 lymph nodes for body and tail pancreatic ductal adenocarcinoma?

Yiran Zhou [1], Jiewei Lin [1], Wei Wang [1], Hao Chen, Xiaxing Deng, Chenghong Peng, Dongfeng Cheng[**], Baiyong Shen[*]

Department of General Surgery, Ruijin Hospital Affiliated to Shanghai Jiao Tong University, School of Medicine, 197 Ruijin Er Road, Shanghai, 200025, China

ARTICLE INFO

Article history:
Received 30 January 2019
Received in revised form
10 March 2019
Accepted 12 March 2019
Available online 15 March 2019

Keywords:
Pancreatic ductal adenocarcinoma
Distal pancreatectomy
Lymph nodes involvement
Lymphadenectomy
No. 9 lymph nodes

ABSTRACT

Objectives: This study aimed to use a retrospective data base to investigate whether a standard lymphadenectomy during distal pancreatectomy should include the No. 9 lymph nodes (LNs) for resectable pancreatic ductal adenocarcinoma (PDAC) located in the body and tail of the pancreas.
Methods: Data from 169 patients undergoing curative distal pancreatectomy for PDAC between Jan 1, 2013 and Dec 31, 2016 were collected. According to the tumor location, patients were divided into three groups: pancreatic neck tumor, pancreatic body and tail tumor with margin-to-bifurcation-distance (MTBD) $\leq$ 2.5 cm and pancreatic body and tail tumor with MTBD > 2.5 cm. The metastatic rate of the No. 9 LNs was compared among the 3 groups. The survival outcomes were analyzed.
Results: The involvement rate for No. 9 LNs was 20.7% (6/29) for pancreatic neck tumors, 17.6% (15/85) for body and tail tumors with MTBD $\leq$ 2.5 cm and 1.8% (1/55) for MTBD > 2.5 cm. The No. 9 LNs were significantly more frequently involved in neck or body and tail tumors with MTBD $\leq$2.5 cm than with the cases with MTBD >2.5 cm (OR 0.082, P = 0.016). No. 9 LN involvement was not associated with worse survival compared with survival associated with involvement of other LNs (P = 0.780).
Conclusions: For PDAC located in the neck or in the body and tail of the pancreas with MTBD $\leq$ 2.5 cm, the involvement rate for No. 9 LNs is high. Standard lymphadenectomy should include the No. 9 LNs.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignant tumors, and it carries a dismal prognosis. In contrast to the steady increase in survival of many other cancers, the pancreatic cancer death rate has remained stable over the past 40 years. It is the fourth-leading cause of cancer death in the United States [1] and results in over 432,000 deaths annually worldwide [2]. Surgical resection has been considered the only potential definitive treatment; this combines radical resection of the tumor with standard lymphadenectomy [3,4]. Efforts have been made to clarify to what extent a standard lymphadenectomy should be conducted. Nevertheless, compared with an increasing number of studies focused on lymphadenectomy during pancreaticoduodenectomy [5–8], studies on lymphadenectomy during curative distal pancreatectomy for neck, body and tail PDAC are rare.

The 2014 consensus statement by the International Study Group on Pancreatic Surgery (ISGPS) proposed that lymph nodes (LNs) in stations 10, 11 and 18 should be routinely resected during distal pancreatectomy [9]. However, whether the resection of the No. 9 LNs is necessary remains unclear because of a lack of level I evidence. As a result, only a weak consensus has developed in favor of resection of these lymph nodes when the tumor is located in the pancreatic body. Notably, resection of No. 9 LNs was proposed for all distal pancreatectomies at the consensus meeting in 1999 [10]. Involvement of No. 9 LNs was reported in 6.4%–13.3% of patients undergoing curative distal pancreatectomy for PDAC [11–13]. Recently, it has been believed that No. 9 LNs are more likely to be involved when the tumor is located in the body rather than in the tail of the pancreas because of the different lymphatic drainage pathways [9,14]. However, the definition of the pancreatic body is ambiguous. It is often difficult to definitively conclude whether the tumor is located in the body instead of the tail, especially when the

* Corresponding author.
** Corresponding author.
E-mail addresses: chengdf1059@163.com (D. Cheng), shenby@shsmu.edu.cn (B. Shen).
[1] Yiran Zhou, Jiewei Lin and Wei Wang contributed equally to this work.

https://doi.org/10.1016/j.pan.2019.03.005
1424-3903/

tumor size is large.

Therefore, in this study, we attempted to use a quantitative value—the distance from the right margin of the tumor to the celiac bifurcation—to evaluate the likelihood of No. 9 LN involvement. From this point of view, we aimed to investigate whether a standard lymphadenectomy during distal pancreatectomy should include No. 9 LNs.

Methods

Between January 2013 and December 2016, a total of 428 patients underwent distal pancreatectomy by laparotomy or robotic surgery in the Department of General Surgery of Ruijin Hospital Affiliated to Shanghai Jiao Tong University, School of Medicine, China. A total of 169 patients were finally diagnosed with R0 resectable PDAC confirmed by pathology ($T_{1\text{-}3}N_{0\text{-}2}M_0$). Patients with other malignant pancreatic tumors, PDACs with major artery involvement (staged T_4), R1 resectable PDACs confirmed by pathology and R2 resectable PDACs were excluded from this study. All 169 patients had preoperative abdominal CTA or contrast CT scan and none of them had neoadjuvant treatment. The surgical procedures included standard distal pancreatectomy along with the removal of the peripancreatic LNs (No. 11 and No. 18), the LNs at the splenic hilum (No. 10) and the LNs around the celiac axis (No. 9). The LNs along the superior mesenteric artery (No. 14), along the common hepatic artery (No. 8a) and the para-aortic LNs (No. 16a) were only resected at the surgeons' discretion when potential LN involvement was suspected during surgery.

Patients were divided into groups according to tumor location. The pancreatic neck tumor group was defined as a tumor with a right margin to the right of the celiac bifurcation between the common hepatic artery and the splenic artery, and pancreatic body and tail tumors were defined as having a right margin to the left of the bifurcation. All of the 169 patients were found to have the bifurcation without variated common hepatic artery originated from the superior mesenteric artery. For patients with pancreatic body and tail tumors, the distance from the right margin of the tumor to the celiac bifurcation was measured on preoperative CT images. Receiver operating characteristic (ROC) curve was applied to examine the predictive value of the margin-to-bifurcation-distance (MTBD) for No. 9 LN involvement. Youden's index indicated that 2.5 cm was the proper cut-off. Thus, patients were finally divided into 3 groups: pancreatic neck tumor, pancreatic body and tail tumor with MTBD from 0 cm to 2.5 cm and pancreatic body and tail tumor with MTBD more than 2.5 cm. The metastatic rates of No. 9 LNs were compared among the 3 groups, and the survival outcomes were analyzed. The study was approved by the ethics committee of Ruijin Hospital Affiliated to Shanghai Jiao Tong University, School of Medicine.

SPSS 22.0 was used to perform statistical analysis. Data were presented as medians (range) or numbers (percentage). The Chi-square test of Fisher's exact test was used to compare differences between groups. The Kaplan-Meier method was used for overall survival and Cox regression for multivariate survival analysis. A two-sided P value < 0.05 was considered statistically significant.

Results

Clinical data for the 169 study patients

The clinical data for the study population are listed in Table 1. Among the study patients, 91 were male and 78 were female. Sixty-nine (40.8%) were aged 65 or older. The tumor was located in the neck of the pancreas in 29 patients (17.2%) and in the body and tail of the pancreas in 140 patients (82.8%). As no patients with T_4 tumor were included, the number of patients at stages T_1, T_2 and T_3 were 24 (14.2%), 86 (50.9%) and 59 (34.9%), respectively. Sixty-two of 169 patients (36.7%) had LN involvement. According to the 8th AJCC staging system, 14 patients were staged IA (8.3%), 57 patients were staged IB (33.7%), 36 patients were staged IIA (21.3%), 55 patients were staged IIB (32.5%), and 7 patients were staged III (4.2%, $T_{any}N_2M_0$ only, and no $T_4N_0M_0$). To properly distinguish the tumor stage, a median of 9 LNs were found and examined by a pathologist (range, 2–37). The median numbers of examined No. 9 LNs, peripancreatic LNs (No. 11 and No. 18) and LNs at the splenic hilum (No. 10) were 2 (range, 0–11), 4 (range, 1–25) and 3 (range, 0–7), respectively. No. 9 LN involvement was found in 22 out of 169 patients (13.0%). The metastatic rate was 23.7% for No. 11/No. 18 LNs and 4.7% for No. 10 LNs. The median lymph node ratio (LNR) was 0.20 in N1/N2 patients. A total of 54.4% of patients had poorly–differentiated tumors and 90 patients (53.3%) received postoperative adjuvant chemotherapy.

Table 1
Data of the 169 patients undergoing surgery between Jan 1, 2013 and Dec 31, 2016.

Variables	Number of patients (%)
Gender	
Male	91 (53.8%)
Female	78 (46.2%)
Age	
$\geq$ 65y	69 (40.8%)
$\leq$ 64y	100 (59.2%)
Tumor location	
Pancreatic neck	29 (17.2%)
Pancreatic body/tail	140 (82.8%)
T status	
T_1	24 (14.2%)
T_2	86 (50.9%)
T_3	59 (34.9%)
T_4	0
N status	
N_0	107 (63.3%)
N_1	55 (32.6%)
N_2	7 (4.1%)
AJCC stage (The 8th edition)	
IA	14 (8.3%)
IB	57 (33.7%)
IIA	36 (21.3%)
IIB	55 (32.5%)
III ($T_{any}N_2M_0$)	7 (4.2%)
Examined LNs (median, range)	
Total	9 (2–37)
No. 9	2 (0–11)
No. 11/No. 18	4 (1–25)
No. 10	3 (0–7)
Patients with metastatic LNs	
No. 9	22 (13.0%)
No. 11/No. 18	40 (23.7%)
No. 10	8 (4.7%)
LNR in N1/N2 patients (median, range)	0.20 (0.06–1.00)
Differentiation	
High	3 (1.8%)
Moderate	74 (43.8%)
Poor	92 (54.4%)
Adjuvant chemotherapy	90 (53.3%)

Metastatic rate of the No. 9 LNs and associated risk factors

The overall metastatic rate of the No. 9 LNs was 13.0%. This was found in 6 out of 29 patients (20.7%) with pancreatic neck tumors but only in 16 out of 140 patients (11.4%) with pancreatic body and tail tumor. To further investigate the potential relationship between the MTBD and involvement of No. 9 LNs, the ROC curve based on MTBD was applied in 140 patients with pancreatic body and tail tumors to evaluate its influence on the No. 9 LN involvement.

Finally, Youden's index showed that 2.5 cm was the proper cut-off with an area under the ROC curve (AUC) of 0.786. The ROC curve is shown in Supplementary Fig. 1.

The 169 patients were then divided into 3 groups: pancreatic neck tumor, pancreatic body and tail tumor with MTBD ≤2.5 cm and pancreatic body and tail tumor with MTBD >2.5 cm. When the MTBD was more than 2.5 cm, only 1.8% of patients (1 out of 55) were found to have No. 9 LN involvement, while 17.6% of patients (15 out of 85) had positive No. 9 LNs when the MTBD was from 0 cm to 2.5 cm. Compared with the former group, the metastatic rate of the No. 9 LNs was significantly higher in the latter group (17.6% vs 1.8%, P = 0.004) and in the pancreatic neck group (20.7% vs 1.8%, P = 0.006) (Table 2).

Thus, body and tail PDAC with MTBD greater than 2.5 cm negatively correlated with No. 9 LN involvement. Other potential risk factors for No. 9 LN involvement were then investigated, including age, tumor size >4 cm, tumor differentiation, high CA 19–9 and CA 125 level. The results of the univariate analysis are shown in Table 3. Only MTBD >2.5 cm was associated with a lower metastatic rate in No. 9 LNs (4.5% vs 36.7%, P = 0.016). Age ≥65 years old (P = 0.471), tumor size > 4 cm (P = 0.423), poorly–differentiated tumor (P = 0.171), CA 19–9 > 35 U/ml (P = 0.205) and CA 125 > 35 U/ml (P = 0.974) failed to significantly correlate with No. 9 LN involvement. As a result, a multivariate analysis was not conducted.

Influence of No. 9 LN involvement on survival outcomes

At a median follow-up time of 20.5 months (range, 1.3–63.9 months), the median overall survival (OS) time was 24.0 months. The median OS time for each stage was 27.3 months for stage I PDAC, 22.5 months for stage II PDAC and 13.8 months for stage III PDAC ($T_{any}N_2M_0$ only). No patients were lost from the study population, and a total of 112 patients died during the follow-up period. The Kaplan-Meier analysis of OS according to the 8th AJCC stage is shown in Supplementary Fig. 2.

As shown in Fig. 1(a), patients without LNs involvement (stage IA, IB and IIA) had a better median OS of 27.3 months (95% CI 25.0–29.6 months) than did LN-positive patients (stage IIB and III) whose median OS was 16.5 months (95% CI 9.6–23.4 months), and this difference was statistically significant (P = 0.017). We then investigated whether No. 9 LN involvement was a worse predictor than were other LN involvements. As is shown in Fig. 1(b), the OS in LN-involved patients (stage IIB and III) was comparable between those with and without No. 9 LN involvement (18.6 months vs 14.2 months, P = 0.780), which indicating that No. 9 LN involvement should not be considered a contraindication to curative surgery.

Analysis of the prognostic factors for body and tail PDAC

The results of Cox multivariate survival analysis of the prognostic factors for curative body and tail PDAC are shown in Table 4. In the univariate analysis, LN involvement (P = 0.019) instead of No. 9 LN involvement (P = 0.277) was associated with worse survival. Adjuvant chemotherapy was associated with better survival (P = 0.005), while LNR > 0.2 (P < 0.001), poor tumor differentiation (P < 0.001) and CA 19–9 > 35 U/ml (P = 0.002) were predictors of poor outcome. Tumor location was not a significant prognostic factor (P = 0.071). In the multivariate analysis, LN involvement was insignificant (P = 0.863), while LNR > 0.2 (P = 0.004), poor tumor differentiation (P = 0.011), adjuvant chemotherapy (P = 0.009) and CA 19–9 > 35 U/ml (P = 0.005) remained significant.

Discussion

LN involvement occurs frequently in PDAC patients [15]. In body and tail PDAC patients undergoing curative resection, No. 9 LNs were thought to be both N1 and N2 node groups because they may receive lymph not only from the N1 nodes but also pancreatic lymph directly [16,17]. After curative surgery, No. 9 LN involvement has been reported in 6.4%–13.3% of cases [11–13]. In this study, all patients underwent resection of No. 9 LNs and the metastatic rate was 13.0% (22 out of 169 patients), indicating that No. 9 LN involvement might be underestimated if these nodes are not routinely resected and examined.

To our knowledge, this was the first study to use the distance from the right margin of the tumor to the celiac bifurcation to evaluate the potential for No. 9 LN involvement. With a median of 9 LNs examined, ranging from 2 to 37, the ROC curve and the Youden's index demonstrated that MTBD = 2.5 cm was a proper cut-off to distinguish high from low involvement potential, and the metastatic rate of No. 9 LNs reached as high as 18.4% (21 out of 114 patients) when the tumor was located in the neck or in the body and tail of the pancreas with MTBD ≤ 2.5 cm. The median number of the examined No. 9 LNs was 2 ranging from 0 to 11 and only a total of 6 patients were found to have no No.9 LNs harvested which was because that no LNs were found in the connective and adipose tissue around the celiac axis in these patients. Briefly, No. 9 LN involvement is more likely to be found when the tumor is located close to the celiac bifurcation. This increase in involvement is likely because the lymphatic drainage pathways are not exactly the same between the body and the tail of pancreas. Although the lymphatic vasculature of the pancreas is quite complex [18], it is thought that the lymphatic drainage of the pancreatic tail distant from the celiac axis is primarily towards the LNs at the splenic hilum [16,17,19,20]. By contrast, the lymphatic drainage of the median part of the pancreas close to the celiac bifurcation is towards the No. 9 LNs. The data obtained above suggested that tumors located in the neck or in the body and tail of the pancreas with MTBD ≤2.5 cm should be considered as close to the celiac bifurcation with high metastatic rates of the No. 9 LNs.

The MTBD is a quantitative value that can be measured on preoperative CT images. As shown in Tables 2 and 3, for tumors necessitating a distal pancreatectomy, the No. 9 LN involvement rate was low in those with MTBD >2.5 cm (1.8%) and that pancreatic neck tumor or pancreatic body and tail tumor with MTBD ≤ 2.5 cm is a risk factor for No. 9 LN involvement. In the literature, the risk factors for No. 9 LN involvement have rarely been discussed. With a

Table 2
The metastatic rate of No. 9 LNs.

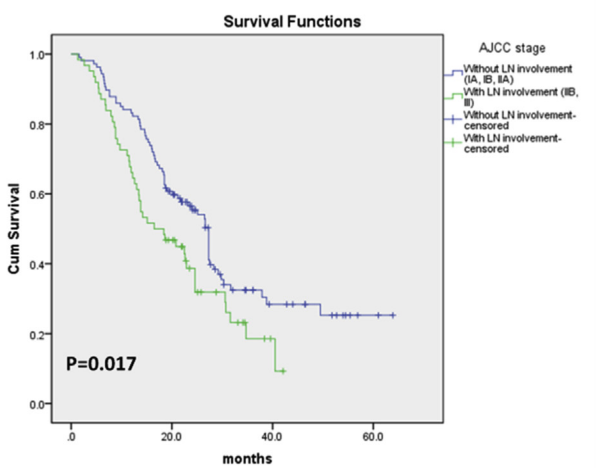
Tumor location	Metastatic No. 9 LNs (%)	P
Pancreatic body/tail with MTBD more than 2.5 cm	1/55 (1.8%)	1
Pancreatic body/tail with MTBD from 0 cm to 2.5 cm	15/85 (17.6%)	0.004*
Pancreatic neck	6/29 (20.7%)	0.006†
Total	22/169 (13.0%)	

*Chi-squared test; †Fisher exact test.

Table 3
Univariate analysis of risk factors for No. 9 LN involvement.

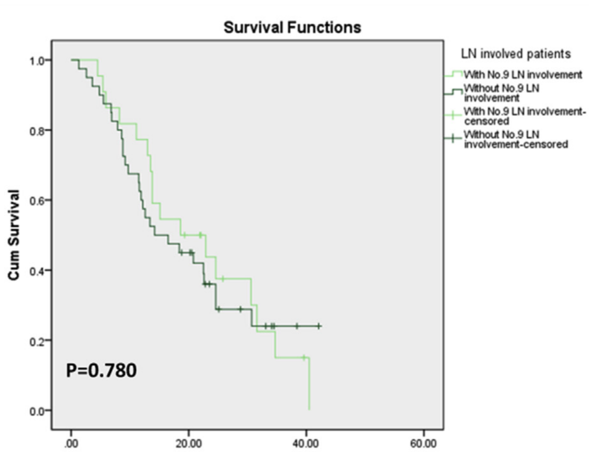
Variables	LN9+ (n = 22)	LN9-(n = 147)	OR (95% CI)	P
Age ≥ 65y	10 (45.5%)	55 (37.4%)	1.394 (0.565–3.440)	0.471
MTBD > 2.5 cm	1 (4.5%)	54 (36.7%)	0.082 (0.011–0.627)	0.016
Tumor size > 4 cm	6 (27.3%)	53 (36.1%)	0.665 (0.245–1.802)	0.423
Poorly differentiated	15 (68.2%)	77 (52.4%)	1.948 (0.751–5.056)	0.171
CA 19–9 > 35 U/ml	14 (63.6%)	114 (77.6%)	0.526 (0.195–1.420)	0.205
CA 125 > 35 U/ml	4 (18.2%)	27 (18.4%)	1.020 (0.317–3.275)	0.974

lack of level I evidence, No. 9 LNs were recommended by experts to be resected when the tumor was located in the body instead of in the tail [9]. Nevertheless, without a quantitative value such as



(a)

Numbers at risk vs. time				
Months	0	20	40	60
IA/IB/IIA	107	62	13	2
IIB/III	62	27	2	0



(b)

Numbers at risk vs. time				
Months	0	20	40	60
LN9+	22	10	1	0
LN9-	40	17	1	0

Fig. 1. Kaplan-Meier curves for overall survival (OS) differences (a) between patients with (n = 62) and without (n = 107) LN involvement and (b) between LN-involved patients with (n = 22) and without (n = 40) No. 9 LN involvement.

Table 4
Cox multivariate survival analysis of the prognostic factors.

Factors	Patients (%)	Univariate	Multivariate	
		P	HR (95% CI)	P
MTBD > 2.5 cm	55 (32.5%)	0.071		
N_1 - N_2	62 (36.7%)	0.019	0.955 (0.564–1.617)	0.863
No. 9 LNs involvement	22 (13.0%)	0.277		
LNR > 0.2	26 (15.4%)	<0.001	0.404 (0.218–0.751)	0.004
Poorly differentiated	92 (54.4%)	<0.001	0.599 (0.403–0.891)	0.011
Adjuvant chemo	90 (53.3%)	0.005	1.688 (1.143–2.494)	0.009
CA 19–9 > 35 U/ml	128 (75.7%)	0.002	0.453 (0.261–0.787)	0.005

MTBD, the definition of the pancreatic body tumor or the pancreatic tail tumor can be rather subjective and ambiguous, especially when the tumor size is large. Thus, it is more accurate and clearer to use MTBD to predict No. 9 LN involvement. Furthermore, no other risk factors were found for No. 9 LN involvement; older age, tumor size, tumor differentiation and level of tumor markers were not significantly associated with it. As a result, we suggest that No. 9 LN involvement is primarily affected by the lymphatic drainage pathway, which is in turn affected by the tumor location rather than factors such as age, tumor size, tumor differentiation and level of tumor markers.

Survival analysis was used to evaluate whether or not No. 9 LN involvement in the pancreatic body and tail PDAC should be considered as distant lymphatic involvement. Unlike the para-aortic LN (No. 16a) involvement in pancreatic head PDAC that has been frequently discussed recently [21–24], the role of No. 9 LN involvement in body and tail PDAC remains unclear. As shown in Fig. 1, LN involvement was associated with decreased survival compared with patients without LN involvement (16.5 vs 27.3 months, P = 0.017), consistent with findings in the literature [25,26]. However, when concerning LN-involved patients, the survival outcomes were not significantly different between patients with or without No. 9 LN involvement. This indicated that No. 9 LN involvement was not associated with decreased survival compared with other LN involvements; concerning the postoperative prognosis, No. 9 LNs gave similar predictions to those of other LNs that are included in the standard lymphadenectomy. Thus, No. 9 LN involvement should be considered as a regional lymphatic invasion instead of a distal metastasis. The resection of No. 9 LNs should be included in the standard lymphadenectomy in neck PDAC or body and tail PDAC with MTBD ≤2.5 cm when it is potentially positive. Moreover, No. 9 LN involvement should not be considered a contraindication to curative distal pancreatectomy. Similarly, in the survival analysis, No. 9 LN involvement was not associated with overall survival. In the multivariate analysis, LNR >0.2, poor differentiation and high CA 19-9 level were associated with worse survival and adjuvant chemotherapy was associated with better survival that was the contemporary accepted fact. LN involvement was revealed to be significant in univariate analysis but insignificant in multivariate analysis. This was probably because that body and tail PDAC was associated with poor prognosis [19,27] weakening the influence of LN involvement.

The limitation of this study was that the sample size was relatively small because this was a retrospective single-center study. Nevertheless, considering that all patients enrolled in the study underwent systematic resection of No. 9 LNs, its metastatic rate was theoretically not affected by the study type. Another limitation was that for pancreatic neck tumor or body and tail tumor with MTBD $\leq$2.5 cm, whether a standard lymphadenectomy including No. 9 LNs would provide a better overall survival or not remained unstudied. Prospective studies can be designed to compare lymphadenectomy in such cases with and without the No. 9 LN resection to further clarify the necessity of its resection.

Conclusions

For patients undergoing curative distal pancreatectomy for body and tail PDAC, the No. 9 LN involvement rate is high when the tumor is located in the neck or in the body and tail of the pancreas with MTBD $\leq$2.5 cm, and a standard lymphadenectomy should include No. 9 LNs in such cases. When the tumor is located in the body and tail of the pancreas with MTBD >2.5 cm, the No. 9 LN involvement rate is low, and whether a systematic resection of No. 9 LNs is necessary remains to be further investigated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.pan.2019.03.005.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics. CA A Cancer J Clin 2018;68(1):7–30. 2018.

[2] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018 Nov;68(6):394–424. https://doi.org/10.3322/caac.21492. Epub 2018 Sep 12.

[3] Nitecki SS, Sarr MG, Colby TV, van Heerden JA. Long-term survival after resection for ductal adenocarcinoma of the pancreas. Is it really improving? Ann Surg 1995;221(1):59–66.

[4] Yamamoto T, Satoi S, Kawai M, Motoi F, Sho M, Uemura KI, et al. Is distal pancreatectomy with en-bloc celiac axis resection effective for patients with locally advanced pancreatic ductal adenocarcinoma? -Multicenter surgical group study. Pancreatology 2018;18(1):106–13.

[5] Jang JY, Kang MJ, Heo JS, Choi SH, Choi DW, Park SJ, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. Ann Surg 2014;259(4):656–64.

[6] Nimura Y, Nagino M, Takao S, Takada T, Miyazaki K, Kawarada Y, et al. Standard versus extended lymphadenectomy in radical pancreatoduodenectomy for ductal adenocarcinoma of the head of the pancreas: long-term results of a Japanese multicenter randomized controlled trial. J Hepato-Biliary-Pancreatic Sci 2012;19(3):230–41.

[7] Farnell MB, Pearson RK, Sarr MG, DiMagno EP, Burgart LJ, Dahl TR, et al. A prospective randomized trial comparing standard pancreatoduodenectomy with pancreatoduodenectomy with extended lymphadenectomy in resectable pancreatic head adenocarcinoma. Surgery 2005;138(4):618–28. discussion 28-30.

[8] Pedrazzoli S, DiCarlo V, Dionigi R, Mosca F, Pederzoli P, Pasquali C, et al. Standard versus extended lymphadenectomy associated with pancreatoduodenectomy in the surgical treatment of adenocarcinoma of the head of the pancreas: a multicenter, prospective, randomized study. Lymphadenectomy Study Group. Ann Surg 1998;228(4):508–17.

[9] Tol JA, Gouma DJ, Bassi C, Dervenis C, Montorsi M, Adham M, et al. Definition of a standard lymphadenectomy in surgery for pancreatic ductal adenocarcinoma: a consensus statement by the International Study Group on Pancreatic Surgery (ISGPS). Surgery 2014;156(3):591–600.

[10] Pedrazzoli S, Beger HG, Obertop H, Andren-Sandberg A, Fernandez-Cruz L, Henne-Bruns D, et al. A surgical and pathological based classification of resective treatment of pancreatic cancer. Summary of an international workshop on surgical procedures in pancreatic cancer. Dig Surg 1999;16(4):337–45.

[11] Kanda M, Fujii T, Nagai S, Kodera Y, Kanzaki A, Sahin TT, et al. Pattern of lymph node metastasis spread in pancreatic cancer. Pancreas 2011;40(6):951–5.

[12] Nakao A, Harada A, Nonami T, Kaneko T, Nomoto S, Koyama H, et al. Lymph node metastasis in carcinoma of the body and tail of the pancreas. Br J Surg 1997;84(8):1090–2.

[13] Kayahara M, Nagakawa T, Futagami F, Kitagawa H, Ohta T, Miyazaki I. Lymphatic flow and neural plexus invasion associated with carcinoma of the body and tail of the pancreas. Cancer 1996;78(12):2485–91.

[14] Lee H, Heo JS, Choi SH, Choi DW. Extended versus peripancreatic lymph node dissection for the treatment of left-sided pancreatic cancer. Annal. Surg. Treat. Res. 2017;92(6):411–8.

[15] Fink DM, Steele MM, Hollingsworth MA. The lymphatic system and pancreatic cancer. Cancer Lett 2016;381(1):217–36.

[16] O'Morchoe CC. Lymphatic system of the pancreas. Microsc Res Tech 1997;37(5–6):456–77.

[17] Strasberg SM, Drebin JA, Linehan D. Radical antegrade modular pancreatosplenectomy. Surgery 2003;133(5):521–7.

[18] Cesmebasi A, Malefant J, Patel SD, Du Plessis M, Renna S, Tubbs RS, et al. The surgical anatomy of the lymphatic system of the pancreas. Clin Anat 2015;28(4):527–37.

[19] Strasberg SM, Linehan DC, Hawkins WG. Radical antegrade modular pancreatosplenectomy procedure for adenocarcinoma of the body and tail of the pancreas: ability to obtain negative tangential margins. J Am Coll Surg 2007;204(2):244–9.

[20] Strasberg SM, Fields R. Left-sided pancreatic cancer: distal pancreatectomy and its variants: radical antegrade modular pancreatosplenectomy and distal pancreatectomy with celiac axis resection. Cancer J 2012;18(6):562–70.

[21] Schwarz L, Lupinacci RM, Svrcek M, Lesurtel M, Bubenheim M, Vuarnesson H, et al. Para-aortic lymph node sampling in pancreatic head adenocarcinoma. Br J Surg 2014;101(5):530–8.

[22] Nappo G, Borzomati D, Perrone G, Valeri S, Amato M, Petitti T, et al. Incidence and prognostic impact of para-aortic lymph nodes metastases during pancreaticoduodenectomy for peri-ampullary cancer. HPB : Off. J. Int. Hepato Pancreato Biliary Assoc. 2015;17(11):1001–8.

[23] Liu C, Chen R, Chen Y, Fu D, Hong D, Hao J, et al. Should a standard lymphadenectomy during pancreatoduodenectomy exclude para-aortic lymph nodes for all cases of resectable pancreatic head cancer? A consensus statement by the Chinese Study Group for Pancreatic Cancer (CSPAC). Int J Oncol 2015;47(4):1512–6.

[24] Paiella S, Malleo G, Maggino L, Bassi C, Salvia R, Butturini G. Pancreatectomy with para-aortic lymph node dissection for pancreatic head adenocarcinoma: pattern of nodal metastasis spread and analysis of prognostic factors. J Gastrointest Surg : Off. J. Soc. Surg. Alimentary Tract 2015;19(9):1610–20.

[25] Fujita T, Nakagohri T, Gotohda N, Takahashi S, Konishi M, Kojima M, et al. Evaluation of the prognostic factors and significance of lymph node status in invasive ductal carcinoma of the body or tail of the pancreas. Pancreas 2010;39(1):e48–54.

[26] Shimada K, Sakamoto Y, Sano T, Kosuge T. Prognostic factors after distal pancreatectomy with extended lymphadenectomy for invasive pancreatic adenocarcinoma of the body and tail. Surgery 2006;139(3):288–95.

[27] Abe T, Ohuchida K, Miyasaka Y, Ohtsuka T, Oda Y, Nakamura M. Comparison of surgical outcomes between radical antegrade modular pancreatosplenectomy (RAMPS) and standard retrograde pancreatosplenectomy (SPRS) for left-sided pancreatic cancer. World J Surg 2016;40(9):2267–75.