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Prognostic Impact of Para-aortic Lymph Node Metastasis in Pancreatic Ductal Adenocarcinoma

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Abstract
Background The aim of the present study was to clarify the prognostic impact of para-aortic lymph node metastasis in pancreatic ductal adenocarcinoma.
Methods Medical records of 103 consecutive patients with pancreatic ductal adenocarcinoma, who underwent pancreatic resection with regional and para-aortic lymph node dissection were reviewed retrospectively. Clinicopathological factors and survival were compared between patients with and without para-aortic lymph node metastasis.
Results Tumor size ($p = 0.045$), extrapancreatic nerve plexus invasion ($p = 0.043$), UICC pT factor ($p = 0.026$), and surgical margin status ($p = 0.002$) were associated significantly with para-aortic lymph node metastasis. Postoperative adjuvant chemotherapy ($p < 0.001$) and absence of extrapancreatic nerve plexus invasion ($p = 0.041$) were associated independently with longer survival, but para-aortic lymph node metastasis ($p = 0.078$) was not associated significantly with survival by multivariate analysis. The 2- and 5-year survival rates and median survival time of patients with and without para-aortic lymph node metastasis were 12, 0%, 12.4 months and 49, 23%, 14.5 months, respectively, and there was a significant difference in survival between the two groups by a log-rank test ($p < 0.001$). Postoperative adjuvant chemotherapy significantly improved the survival of patients with para-aortic lymph node metastasis ($p = 0.025$).
Conclusions The prognosis of patients with para-aortic lymph node metastasis is poor in pancreatic ductal adenocarcinoma. However, postoperative adjuvant chemotherapy may improve survival.

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Introduction

The prognosis of patients with pancreatic ductal adenocarcinoma remains extremely dismal, with the overall survival rate being less than 5% [1]. The reason for the poor prognosis of this disease is that candidates for surgical resection represent less than 20% of patients with pancreatic carcinoma, due to locoregional spread or metastatic disease at the time of diagnosis [2, 3]. Surgical resection offers the only chance of cure or long-term survival in the treatment of this disease [4]. Furthermore, the 5-year survival rate of patients with pancreatic ductal adenocarcinoma who undergo surgical resection has been reported recently to be less than 20% [5–14]. To find useful prognostic factors, many investigators have attempted to analyze the clinicopathological features of patients with pancreatic ductal adenocarcinoma after surgical resection with univariate or multivariate analysis. Potential factors include tumor size [6, 7, 9, 13, 14], surgical margin status [6–9, 12–14], and postoperative adjuvant chemotherapy [5–7, 14]. In addition, nodal involvement is one of the most important factors for predicting the long-term survival of patients with pancreatic ductal adenocarcinoma [5–7, 14]. Lymph node metastasis initially occurs in the para-pancreatic nodes and finally spreads to the para-aortic lymph nodes through the nodes along the superior mesenteric artery [15, 16].

However, to our knowledge, there have been few reports concerning the prognostic impact of para-aortic lymph node metastasis, because the para-aortic lymph nodes are not routinely dissected in America and Europe [16–20]. In our institution, dissection of the para-aortic lymph nodes as well as the regional lymph nodes has been performed routinely for patients with pancreatic ductal adenocarcinoma since 1992. The aim of the present study was to evaluate the clinicopathological features of patients with para-aortic lymph node metastasis and to clarify the prognostic impact of para-aortic lymph node metastasis in pancreatic ductal adenocarcinoma. This was achieved by using univariate and multivariate survival analysis to assess patients treated at a single institution.

Methods

Medical records for 103 consecutive patients with pancreatic ductal adenocarcinoma who underwent pancreatic resection with regional and para-aortic lymph node dissection at the Department of Surgery, Hiroshima University Hospital, between January 1992 and December 2008 were reviewed retrospectively. The 103 patients were diagnosed as having no apparent para-aortic lymph node metastasis by preoperative imaging examinations. All patients underwent tumor resection with the aim of achieving cure and had a confirmed pathological diagnosis. Patients with pancreatic ductal adenocarcinoma derived from an intraductal papillary-mucinous neoplasm (16 patients) or a mucinous cystic neoplasm (one patient) were excluded from this analysis [21, 22].

Preoperative workup included ultrasonography, computed tomography, endoscopic sonography, endoscopic retrograde pancreatocholangiography, and percutaneous transhepatic cholangiography to evaluate the local or distant extension of the tumors. Tumor resection was abandoned if distant metastasis, invasion to the celiac or superior mesenteric artery, and apparent para-aortic lymph node metastasis were found by these preoperative examinations.

Patients with carcinoma in the pancreatic head usually underwent pylorus-preserving pancreatoduodenectomy. If the tumor was close to the duodenal bulb in the superior pancreatic head, conventional pancreatoduodenectomy was performed. All patients with carcinoma in the pancreatic body or tail underwent distal pancreatectomy with splenectomy. Total pancreatectomy was performed when the tumor invaded the whole pancreas. All 103 patients underwent regional and para-aortic lymph node dissection. The para-aortic lymph nodes were dissected from the upper part of the celiac trunk to the upper part of the origin of the inferior mesenteric artery. Intraoperative pathological assessment of the proximal or distal pancreatic margins was performed on frozen tissue sections. If the pancreatic margin was positive for cancerous cells, further resection of the pancreas was performed to the maximum extent possible.

After tumor resection, hematoxylin and eosin staining was performed. All specimens were examined pathologically, and each tumor was classified as well-differentiated, moderately differentiated, or poorly differentiated adenocarcinoma according to the predominant pathological grading of differentiation. Anterior serosal invasion, retropancreatic tissue invasion, choledochal invasion, duodenal invasion, portal vein invasion, lymph node metastasis, and extrapancreatic nerve plexus invasion were all examined pathologically. Surgical margins were considered positive if infiltrating adenocarcinoma was present at the proximal or distal pancreatic transection line or in the dissected peripancreatic soft tissue margins. The final stage of pancreatic carcinoma was examined pathologically according to the TNM classification system of malignant tumors published by the International Union Against Cancer (UICC), 6th edition [23].

Postoperative adjuvant chemotherapy was administered beginning in 1999. Patients who were offered postoperative adjuvant chemotherapy had three options after surgical resection: intra-arterial chemotherapy alone, intravenous chemotherapy alone, or intravenous and oral chemotherapy. Intra-arterial chemotherapy was performed with Seldinger's method. Briefly, a catheter was placed into the common hepatic artery with a reservoir in the lower abdomen. An intra-arterial bolus injection of 5-fluorouracil (5-Fu) 160 mg/m^2 was administered bi-weekly. Intravenous chemotherapy consisted of gemcitabine 700 mg/m^2 administered bi-weekly for 30 min by intravenous drip infusion. Patients who received intravenous and oral chemotherapy were given intravenous gemcitabine 700 mg/m^2 on day 1 and orally administered S-1 50 mg/m^2 for 7 consecutive days; this cycle was repeated every 14 days [24]. No patient received radiation therapy during the study periods.

Patients were followed regularly in outpatient clinics by undergoing computed tomography twice a year for 5 years after surgery. Information on outcomes beyond 5 years after surgery was collected by telephone or personal interview. For patients who died, survival time after surgery and cause of death were recorded. For surviving patients, postoperative survival time and status of recurrence were recorded.

Survival analyses on four clinical factors (gender, age, tumor location, and use of adjuvant chemotherapy) and 13 pathological factors (tumor size, tumor differentiation, anterior serosal invasion, retropancreatic tissue invasion, choledochal invasion, duodenal invasion, portal vein

invasion, lymph node metastasis, para-aortic lymph node metastasis, extrapancreatic nerve plexus invasion, surgical margin status, UICC pT factor, and UICC stage) were performed with univariate and multivariate methods. Clinicopathological factors and survival were compared between patients with and without para-aortic lymph node metastasis.

The χ^2 test or Fisher's exact test was used for comparison among the two groups. Survival curves were constructed based on the Kaplan–Meier method, and differences in survival curves were compared with a univariate log-rank (Mantel-Cox) test. Factors found to be significant on univariate analysis were subjected to multivariate analysis with a Cox proportional hazards model. A value of $p < 0.05$ was considered statistically significant. Statistical analysis was performed using the Macintosh version of StatView version 5.0 (SAS Institute, Cary, NC).

Results

The 103 eligible patients included 50 men and 53 women (median age: 67 years; range: 31–83 years), and 47 patients (46%) were more than 70 years old. No 30-day postoperative deaths occurred among the 103 patients. Tumors were located mainly in the pancreatic head in 73 patients and in the body or tail in 30 patients. Pylorus-preserving pancreatoduodenectomy, conventional pancreatoduodenectomy, distal pancreatectomy with splenectomy, and total pancreatectomy were performed for 65, 4, 30, and four patients, respectively. Postoperative chemotherapy was performed for 71 patients: intra-arterial chemotherapy alone in 3 patients, intravenous chemotherapy alone in seven patients, and intravenous and oral chemotherapy in 61 patients. Overall survival rates for the 103 patients were 74% at 1 year, 41% at 2 years, and 19% at 5 years (median survival, 14.0 months; range: 1–122 months).

The mean number of dissected lymph nodes was 29 (range: 2–75), and the mean number of dissected para-aortic lymph nodes was 5 (range: 1–26). There were 72 tumors (70%) with lymph node metastasis and 31 (30%) without lymph node metastasis. The number of involved lymph nodes ranged from 1 to 40 (median 3). Para-aortic lymph node metastasis was found in 18 patients (17%). The number of involved para-aortic lymph nodes ranged from 1 to 16 (median 2).

Table 1 indicates a comparison of clinicopathological factors between patients with and without para-aortic lymph node metastasis. Extrapancreatic nerve plexus invasion ($p = 0.043$), surgical margin status ($p = 0.002$), and UICC pT factor ($p = 0.039$) were associated significantly with para-aortic lymph node metastasis.

Table 1 Comparison of clinicopathological factors of patients with pancreatic ductal adenocarcinoma who did or did not have para-aortic nodal involvement

Factors	Para-aortic nodal involvement		*p* Value
	Absent ($n = 85$)	Present ($n = 18$)	
Clinical factors			
Gender			
Male	46	7	0.240
Female	39	11	
Age, years			
<70	47	9	0.682
≥70	38	9	
Location of the tumor			
Head	59	14	0.478
Body or tail	26	4	
Adjuvant chemotherapy			
Yes	62	9	0.056
No	23	9	
Pathological factors			
Tumor size, cm			
<2	16	0	0.068
≥2	69	18	
Tumor differentiation			
Well	28	2	0.064
Moderate, poor	57	16	
Anterior serosal invasion			
Yes	49	11	0.787
No	36	7	
Retroperitoneal tissue invasion			
Yes	59	15	0.233
No	26	3	
Choledochal invasion			
Yes	36	11	0.147
No	49	7	
Duodenal invasion			
Yes	32	6	0.730
No	53	12	
Portal or splenic vein invasion			
Yes	24	9	0.072
No	61	9	
Extrapancreatic nerve plexus invasion			
Yes	22	9	0.043
No	63	9	
Surgical margin			
Positive	24	12	0.002
Negative	61	6	
UICC pT factor			
pT 1,2	19	0	0.039
pT 3	66	18	

The *p* value is the result of a χ^2 test or Fisher exact test

Seventeen clinicopathological factors were investigated to determine their prognostic significance. The results of the log-rank test are shown in Table 2. Gender, age, tumor location, tumor size, anterior serosal invasion, choledochal invasion, and duodenal invasion did not influence postoperative survival. Univariate analysis revealed that postoperative adjuvant chemotherapy ($p < 0.001$), tumor differentiation ($p = 0.037$), retroperitoneal tissue invasion ($p = 0.040$), portal or splenic vein invasion ($p = 0.002$), extrapancreatic nerve plexus invasion ($p < 0.001$), lymph node metastasis ($p < 0.001$), para-aortic lymph node metastasis ($p < 0.001$), surgical margin status ($p < 0.001$), UICC pT factor ($p = 0.003$), and UICC stage ($p < 0.001$) were associated significantly with increased survival. These factors were entered into multivariate analysis with a Cox proportional hazards model, and use of postoperative adjuvant chemotherapy ($p < 0.001$) and absence of extrapancreatic nerve plexus invasion ($p = 0.041$) remained associated independently with longer survival (Table 3). In contrast, para-aortic lymph node metastasis ($p = 0.078$) was not associated significantly with survival in the final multivariate model. To avoid confounding due to nodal status and other pathological factors, neither UICC pT factor nor UICC stage were used as dependent variables in the multivariate survival analysis.

Overall survival rates for patients without para-aortic lymph node metastasis were 79% at 1 year, 49% at 2 years, 29% at 3 years, and 23% at 5 years, whereas those for patients with para-aortic lymph node metastasis were 53% at 1 year, 12% at 2 years, and 0% at 3 years. All patients who exhibited para-aortic lymph node metastasis except for one died of recurrence within 2 years after surgery (Fig. 1). The 5-year survival rate of patients with para-aortic lymph node metastasis was significantly lower than that of patients without nodal involvement ($p < 0.001$). In addition, a significant difference in the survival rates of patients with or without para-aortic lymph node metastasis was found among patients who had nodal involvement ($p = 0.012$, Fig. 2). Figure 3 indicates survival curves of patients with para-aortic lymph node metastasis who did or did not receive postoperative adjuvant chemotherapy. Survival time of patients who received postoperative adjuvant chemotherapy was significantly longer than that of patients who did not (median survival time, 14.1 months versus 10.1 months; $p = 0.025$).

Table 2 Univariate survival analysis of prognostic factors for patients with pancreatic ductal adenocarcinoma

Factors	No. of patients	5-Year survival rate (%)	*p* Value
Clinical factors			
Gender			
Male	50	14	0.360
Female	53	27	
Age, years			
<70	56	23	0.906
≥70	47	16	
Location of the tumor			
Head	73	14	0.110
Body or tail	30	37	
Adjuvant chemotherapy			
Yes	71	33	< 0.001
No	32	0	
Pathological factors			
Tumor size			
<2 cm	16	53	0.089
≥2 cm	87	14	
Tumor differentiation			
Well	30	32	0.037
Moderate, poor	73	15	
Anterior serosal invasion			
Yes	60	8	0.236
No	43	27	
Retroperitoneal tissue invasion			
Yes	74	0	0.040
No	29	41	
Choledochal invasion			
Yes	47	0	0.075
No	56	29	
Duodenal invasion			
Yes	38	12	0.504
No	65	25	
Portal or splenic vein invasion			
Yes	33	0	0.002
No	70	27	
Extrapancreatic nerve plexus invasion			
Yes	31	0	< 0.001
No	72	28	
Lymph node metastasis			
Yes	72	5	< 0.001
No	31	42	
Para-aortic lymph node metastasis			
Yes	18	0	< 0.001
No	85	23	
Surgical margin			
Positive	36	8	< 0.001
Negative	67	27	

Discussion

Lymph node involvement has been reported to range from 50 to 78% in cases of resected pancreatic ductal adenocarcinoma [5–14]. However, reports concerning para-aortic lymph node metastasis rates are few, because para-aortic

Table 2 continued

Factors	No. of patients	5-Year survival rate (%)	*p* Value
UICC pT factor			
pT 1,2	19	59	0.003
pT 3	84	0	
UICC stage			
IA, IB	11	72	< 0.001
IIA, IIB, III, IV	92	0	

The *p* value is the result of a log-rank (Mantel-Cox) test

Table 3 Multivariate survival analysis of prognostic factors for patients with pancreatic ductal adenocarcinoma

Factors	Hazard ratio	95% Confidence interval	*p* Value
Adjuvant chemotherapy			
Yes	1.00	1.91–5.76	<0.001
No	3.32		
Extrapancreatic nerve plexus invasion			
Yes	1.93	1.03–3.62	0.041
No	1.00		
Para-aortic lymph node metastasis			
Yes	1.84	0.28–1.07	0.078
No	1.00		
Tumor differentiation			
Well	1.00	0.27–1.01	0.091
Moderate, poor	1.82		
Portal or splenic vein invasion			
Yes	1.37	0.40–1.32	0.299
No	1.00		
Retroperitoneal tissue invasion			
Yes	1.22	0.45–1.50	0.520
No	1.00		
Surgical margin			
Positive	1.03	0.52–1.81	0.925
Negative	1.00		

P value is the result of a Cox proportional hazards model

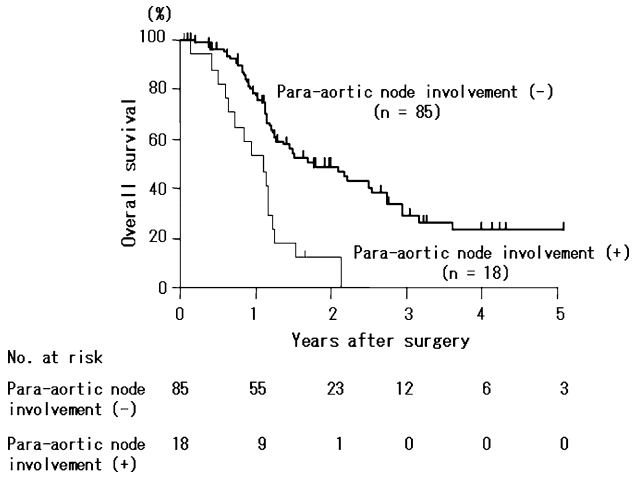

Fig. 1 Comparison of postoperative survival in patients with or without para-aortic lymph node involvement following resection for pancreatic ductal adenocarcinoma ($p < 0.001$)

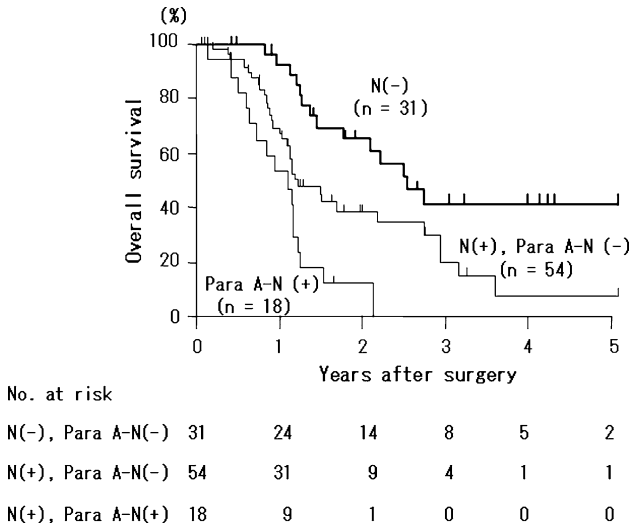

Fig. 2 Comparison of postoperative survival in patients who had no lymph node involvement, lymph node involvement without para-aortic involvement, and para-aortic lymph node involvement after resection for pancreatic ductal adenocarcinoma. N(−) versus N(+), para-A N (−) $p = 0.006$; N(−) versus para-A N (+), $p < 0.001$; N(+), para-A N (−) versus para-A N (+) $p = 0.012$. *N* lymph node involvement, *Para-A N* para-aortic lymph node involvement

lymph node dissection is performed routinely only in Japanese institutions. According to these reports, the rate of para-aortic lymph node metastasis ranged from 13 to 26% (Table 4) [16–20]. In the present study the rates of nodal involvement and para-aortic lymph node involvement were 70 and 17%, respectively. These rates were similar to those in previous reports.

The prognosis of patients with para-aortic lymph node involvement has been reported to be extremely poor. The reported 2-year survival rates of patients with para-aortic lymph node involvement ranged from 0 to 18%, with few 3-year survivors (Table 4) [16–20]. Doi et al. [20] reported that metastasis to the para-aortic lymph nodes was the single independent factor associated with a shorter survival time by multivariate analysis (median survival time, 5.1 months), and they concluded that surgical resection should be abandoned and alternative treatment strategies including chemotherapy or radiotherapy should be considered if para-aortic lymph node metastasis is detected. Shimada et al. [19] reported that the median survival time in 26 patients with para-aortic lymph node involvement

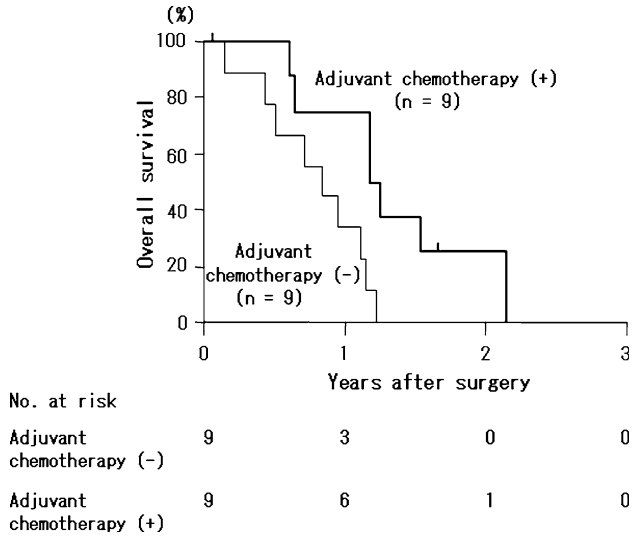

Fig. 3 Comparison of postoperative survival in patients with para-aortic lymph node involvement who did or did not receive postoperative adjuvant chemotherapy following resection for pancreatic ductal adenocarcinoma ($p = 0.025$)

was 13 months versus 30 months in 106 patients without para-aortic lymph node involvement ($p < 0.001$), and they concluded that radical pancreatectomy including extended lymphadenectomy should not be recommended when para-aortic lymph node involvement is confirmed by intraoperative frozen diagnosis. In our study, the survival time of patients with para-aortic lymph node involvement was significantly shorter than that of patients without para-aortic lymph node involvement by univariate analysis, but para-aortic lymph node involvement was not found to be an independent prognostic factor by multivariate analysis. Moreover, adjuvant chemotherapy with new anticancer drugs significantly improved the survival of patients with para-aortic lymph node involvement. Further studies on larger numbers of patients are needed to determine whether surgical resection should be abandoned for patients who are found to have para-aortic lymph node involvement by pathological examination despite no apparent para-aortic lymph node metastasis by preoperative imaging examinations.

Reports concerning the survival benefits of postoperative adjuvant chemotherapy for patients with para-aortic lymph node metastasis in pancreatic ductal adenocarcinoma are scarce. It was reported that application of adjuvant systemic chemotherapy rather than radiotherapy might be suitable in para-aortic node-positive patients, because the major cause of failure in these patients was distant metastases [19]. Recently, postoperative gemcitabine chemotherapy, compared with surgery alone, significantly delayed the development of recurrent disease after complete resection of pancreatic ductal adenocarcinoma in a multi-center randomized controlled phase III trial (CONKO-001) [25]. Moreover, gemcitabine plus S-1 therapy has been associated with an excellent survival benefit in patients with unresectable [26] or resected [24, 27] pancreatic ductal adenocarcinoma. In the present series, we selected mainly new anticancer drugs including gemcitabine or S-1, as an adjuvant chemotherapy regimen. As a result, adjuvant chemotherapy significantly improved the survival of patients with para-aortic node involvement compared with surgery alone. We believe that adjuvant chemotherapy with new anticancer drugs may provide a survival benefit for para-aortic lymph node-positive patients in pancreatic ducta adenocarcinoma, although our result is based on a small number of patients.

In this study, para-aortic lymph node metastasis was associated significantly with extrapancreatic nerve plexus invasion, UICC pT factor, and surgical margin status. No patients who had pT1 or pT2 tumors exhibited para-aortic lymph node involvement. Sakai et al. [18] reported that no patients with a tumor diameter of less than 2 cm had para-aortic lymph node involvement, and Shimada et al. [19] reported that para-aortic lymph node involvement was associated with elevated CA19-9 a month after operation, larger tumor size, and a positive surgical margin. In addition, Connor et al. [28] described that para-aortic lymph node metastasis was found to be associated with a positive

Table 4 Reports on survival of patients with para-aortic lymph node metastasis in pancreatic ductal adenocarcinoma

Author	Year	No. of patients	No. of patients with PALN metastasis (%)	Survival of patients with PALN metastasis			
				1 Year (%)	2 Year (%)	3 Year (%)	MST (months)
Our series	2009	103	18 (17)	53	12	0	12.4
Doi et al. [20]	2007	133	19 (14)	16	NR	NR	5.1
Shimada et al. [19]	2006	133	26 (20)	65	5	0	13.0
Sakai et al. [18]	2005	178	34 (19)	30	7	3	NR
Yoshida et al. [17]	2004	34	9 (26)	22	0	0	NR
Kayahara et al. [16]	1999	99	18 (18)	38	18	11	NR

PALN para-aortic lymph node, *MST* median survival time, *NR* not reported

resection margin. Based on our results and these reports, patients with para-aortic lymph node involvement tend to exhibit extensive locoregional invasion of the tumor. For this reason, margin-negative resection cannot be performed for most patients with para-aortic lymph node involvement.

In the present study, several node-positive patients without para-aortic lymph node metastasis had longer survival and one patient who has survived for more than 5 years had only one involved node in the regional lymph nodes. There have been several previous reports concerning relationship between the number of involved lymph nodes and survival in pancreatic ductal adenocarcinoma. Riediger et al. [29] reported that patients with a single metastatic node had the same survival as node-negative patients and that survival of patients with no more than one metastatic node was significantly better than that of patients with two or more involved nodes. Another group of investigators reported that more than three lymph nodes positive for metastasis was an independent predictor of survival in a consecutive series of 77 patients: they established that the cutoff of three nodes was useful in identifying subsets of patients with worst prognosis among those with positive nodes [30]. We routinely performed dissection of the regional lymph nodes in our series. We believe that lymph node dissection may contribute to longer survival for patients with pancreatic ductal adenocarcinoma, especially for node-positive patients without para-aortic lymph node metastasis.

In conclusion, the prognosis of patients with para-aortic lymph node involvement is extremely poor compared with that of patients without para-aortic lymph node involvement. However, postoperative adjuvant chemotherapy with new anticancer drugs may improve the survival of patients with para-aortic lymph node involvement. Further studies are needed to clarify the effectiveness of surgical resection for patients with para-aortic lymph node involvement.

References

1. Jemal A, Siegel R, Ward E et al (2008) Cancer statistics, 2008. CA Cancer J Clin 58:71–96
2. Tan HP, Smith J, Garberoglio CA (1996) Pancreatic adenocarcinoma: an update. J Am Coll Surg 183:164–184
3. Sener SF, Fremgen A, Menck HR et al (1999) Pancreatic cancer: a report of treatment and survival trends for 100, 313 patients diagnosed from 1985–1995, using the National Cancer Database. J Am Coll Surg 189:1–7
4. Murakami Y, Uemura K, Sasaki T et al (2005) Long-term survival of pancreatic cancer patient diagnosed by positive telomerase activity of pancreatic juice. Surgery 138:962–963
5. Murakami Y, Uemura K, Sudo T et al (2008) Postoperative adjuvant chemotherapy improves survival after surgical resection for pancreatic carcinoma. J Gastrointest Surg 12:534–541
6. Winter JM, Cameron JL, Campbell KA et al (2006) 1423 Pancreaticoduodenectomies for pancreatic cancer: a single-institution experience. J Gastrointest Surg 10:1199–1211
7. Moon HJ, An JY, Heo JS et al (2006) Predicting survival after surgical resection for pancreatic ductal adenocarcinoma. Pancreas 32:37–43
8. Wagner M, Redaelli C, Lietz M et al (2004) Curative resection is the single most important factor determining outcome in patients with pancreatic adenocarcinoma. Br J Surg 91:586–594
9. Kuhlmann KF, de Castro SM, Wesseling JG et al (2004) Surgical treatment of pancreatic adenocarcinoma; actual survival and prognostic factors in 343 patients. Eur J Cancer 40:549–558
10. Matsuno S, Egawa S, Fukuyama S et al (2004) Pancreatic Cancer Registry in Japan: 20 years of experience. Pancreas 28:219–230
11. Berger AC, Meszoely IM, Ross EA et al (2004) Undetectable preoperative levels of serum CA 19–9 correlate with improved survival for patients with resectable pancreatic adenocarcinoma. Ann Surg Oncol 11:644–649
12. Richter A, Niedergethmann M, Sturm JW et al (2003) Long-term results of partial pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head: 25-year experience. World J Surg 27:324–329
13. Wenger FA, Peter F, Zieren J et al (2000) Prognosis factors in carcinoma of the head of the pancreas. Dig Surg 17:29–35
14. Sohn TA, Yeo CJ, Cameron JL et al (2000) Resected adenocarcinoma of the pancreas-616 patients: results, outcomes, and prognostic indicators. J Gastrointest Surg 4:567–579
15. Nagakawa T, Kobayashi H, Ueno K et al (1994) Clinical study of lymphatic flow to the paraaortic lymph nodes in carcinoma of the head of the pancreas. Cancer 73:1155–1162
16. Kayahara M, Nagakawa T, Ohta T et al (1999) Analysis of paraaortic lymph node involvement in pancreatic carcinoma: a significant indication for surgery? Cancer 85:583–590
17. Yoshida T, Matsumoto T, Sasaki A et al (2004) Outcome of paraaortic node-positive pancreatic head and bile duct adenocarcinoma. Am J Surg 187:736–740
18. Sakai M, Nakao A, Kaneko T et al (2005) Para-aortic lymph node metastasis in carcinoma of the head of the pancreas. Surgery 137:606–611
19. Shimada K, Sakamoto Y, Sano T et al (2006) The role of para-aortic lymph node involvement on early recurrence and survival after macroscopic curative resection with extended lymphadenectomy for pancreatic carcinoma. J Am Coll Surg 203:345–352
20. Doi R, Kami K, Ito D et al (2007) Prognostic implication of para-aortic lymph node metastasis in resectable pancreatic cancer. World J Surg 31:147–154
21. Murakami Y, Uemura K, Ohge H et al (2006) Intraductal papillary-mucinous neoplasms and mucinous cystic neoplasms of the pancreas differentiated by ovarian-type stroma. Surgery 140:448–453
22. Murakami Y, Uemura K, Hayashidani Y et al (2007) Predictive factors of malignant or invasive intraductal papillary-mucinous neoplasms of the pancreas. J Gastrointest Surg 11:338–344
23. International Union Against Cancer (UICC) (2002) TNM classification of malignant tumors, vol 6. Wiley-Liss, New York
24. Murakami Y, Uemura K, Sudo T et al (2008) Adjuvant gemcitabine plus S-1 chemotherapy after surgical resection for pancreatic adenocarcinoma. Am J Surg 195:757–762
25. Oettle H, Post S, Neuhaus P et al (2007) Adjuvant chemotherapy with gemcitabine vs. observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial. JAMA 297:267–277
26. Nakamura K, Yamaguchi T, Ishihara T et al (2006) Phase II trial of oral S-1 combined with gemcitabine in metastatic pancreatic cancer. Br J Cancer 94:1575–1579

27. Murakami Y, Uemura K, Sudo T et al (2009) Impact of adjuvant gemcitabine plus S-1 chemotherapy after surgical resection for adenocarcinoma of the body or tail of the pancreas. J Gastrointest Surg 13:85–92
28. Connor S, Bosonnet L, Ghaneh P et al (2004) Survival of patients with periampullary carcinoma is predicted by lymph node 8a but not by lymph node 16b1 status. Br J Surg 91:1592–1599
29. Riediger H, Keck T, Wellner U et al (2004) The lymph node ratio is the strongest prognostic factor after resection of pancreatic cancer. J Gastrointest Surg 13:1337–1344
30. Massucco P, Ribero D, Sgotto E et al (2009) Prognostic significance of lymph node metastases in pancreatic head cancer treated with extended lymphadenectomy: not just a matter of numbers. Ann Surg Oncol 16:3323–3332