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Original Article

Clinicopathological variables and risk factors for lung recurrence after resection of pancreatic ductal adenocarcinoma

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SUMMARY

Background: Pancreatic ductal adenocarcinoma (PDAC) has a high recurrence rate even after curative resection. Lung recurrence may have better outcomes than other recurrences. However, its detailed clinicopathological features are unclear. We investigated the clinicopathological features and risk factors for lung recurrence after pancreatectomy for PDAC.
Methods: The study included 161 patients with potentially and borderline resectable PDAC who had undergone R0 or R1 pancreatectomy between January 2008 and December 2016. We retrospectively examined the prognosis and predictors for lung recurrence after curative resection.
Results: Seventeen patients (10.6%) had isolated lung recurrence. The median overall and recurrence-free survivals were 38.0 and 16.1 months, respectively. In multivariate analysis, para-aortic lymph node (PALN) metastasis ($p = 0.006$) and female sex ($p = 0.027$) were independent factors for lung recurrence.
Conclusion: Lung recurrence had a better prognosis than other recurrences. PALN metastasis and female sex are independent risk factors for lung recurrence after curative resection for PDAC.

1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy with a five-year survival rate of about 9%.[1] Although the only curative treatment is surgical resection, the recurrence rate after resection is extremely high (up to 80%),[2–4] and the five-year survival rate ranges from 12 to 27%.[5–8] Most post-resection recurrences occur within two years after surgery and often develop in both the distant and local sites.[2] The metastatic pathways of pancreatic cancer are hematogenous, lymphoid, and transperitoneal. Post-resection recurrence can occur in many organs, including the liver, lungs, lymph nodes, and peritoneum. Generally, the primary treatment after recurrence is chemotherapy, but the outcomes are poor despite advances made in the development of chemotherapy regimens.

Some studies[2,3] suggested that the clinical course might differ with the initial recurrence site. Liver and peritoneal recurrences have remarkably poor outcomes.[2,3] Lung recurrence is the third most common following liver and local recurrence, with a recurrence rate of about 3–22%.[2,4,7,9–13] The metastatic route of lung metastasis is thought to be hematogenous, like in liver metastasis. However, it has been reported that the time to recurrence (TTR) was longer in lung recurrence than in other recurrences.[2,14] In addition, there were reports suggesting that isolated lung recurrence had a better prognosis than other recurrences,[3,14] and surgical resection for isolated lung recurrence significantly improves prognosis.[10,15] Hence, the clinicopathological features and mechanism of lung recurrence might differ from other distant metastases. To date, there are few existent reports on lung recurrence, and its

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detailed characteristics are unclear. We aimed to examine the clinicopathological features and risk factors for lung recurrence after pancreatectomy for PDAC.

2. Methods

2.1. Study design

We collected the data of 200 patients who had undergone R0 or R1 pancreatectomy at Kobe University Hospital between January 2008 and December 2016. After excluding 27 patients who had received preoperative chemotherapy or chemoradiotherapy, four patients with residual pancreatic cancer, and eight patients lost to follow-up, we retrospectively reviewed the data of 161 patients. We examined the prognosis and risk factors (age, sex, procedure, curability, tumor diameter, resectability, lymph node metastasis, carbohydrate antigen [CA] 19-9 level, tumor grade, postoperative adjuvant therapy, and para-aortic lymph node [PALN] metastasis) for lung recurrence after pancreatectomy for PDAC. This study was approved by the institutional review board of Kobe University Hospital (No. B190323). The requirement for informed consent was waived based on the retrospective nature of the study.

2.2. Preoperative and postoperative evaluation

According to the National Comprehensive Cancer Network guidelines, we assessed tumor resectability using preoperative multi-detector row computed tomographic imaging and categorized patients into potentially resectable or borderline resectable. We performed fluorodeoxyglucose positron emission tomography for all the patients. The resected pancreatic cancer specimens were assessed pathologically using the 8th edition of the Union for International Cancer Control (UICC) Tumor-Node-Metastasis (TNM) classification.

2.3. Operative technique

Pancreatic resection with regional lymphadenectomy was performed. Patients underwent subtotal stomach-preserving pancreaticoduodenectomy or distal pancreatectomy, depending on the tumor location. Portal vein resection was performed in patients with suspected portal vein invasion. In cases of suspected superior mesenteric artery plexus (plSMA) resection, hemicircumferential plSMA resection was performed. PALN sampling was not routine. It was performed at the discretion of the surgeon. PALN were sampled by harvesting the lymphocellular aortocaval tissue from the celiac artery to the inferior mesenteric artery, between the vena cava and aorta or the left side of the abdominal aorta.

2.4. Postoperative treatment and follow-up

After surgery, patients with an Eastern Cooperative Oncology Group performance status of 0 or 1 at baseline were administered adjuvant chemotherapy with gemcitabine or S-1 for six months. Follow-up was scheduled every three months during which computed tomography (CT) and measurement of tumor markers were performed for every patient. Magnetic resonance imaging and fluorodeoxyglucose positron emission tomography were additionally performed when needed for diagnosis.

2.5. Definitions of recurrence

According to the initial relapse site, all patients were categorized into six mutually exclusive categories: local-only, liver-only, lung-only, peritoneum-only, multiple sites, and others, according to the involvement of metastatic organs. Patients with simultaneous recurrences in two or more sites were classified as “multi.” Radiological or histological evidence was necessary to diagnose recurrent disease, but biopsy was rarely performed. The occurrence of lung metastasis was confirmed by reviewing the CT findings, i.e., enlargement of lung nodules over time.

2.6. Statistical analysis

Statistical analyses were performed using JMP® software 14.0 (SAS Institute Inc., Cary, NC, USA). Continuous variables are expressed as median (range). Overall survival (OS) was calculated from the date of surgery to death or to the date the patient was last known to be alive, if death had not been reported. Recurrence-free survival (RFS) was calculated from the date of surgery to the date of recurrence. Kaplan–Meier curves were used to estimate OS and RFS distributions. Univariate and multivariate logistic regressions were performed to identify possible clinical variables associated with lung recurrences. All the variables in the univariate analysis with a p value ≤ 0.05 were further analyzed in the multivariate analysis. A p value ≤ 0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and recurrence type

The patient characteristics are summarized in Table 1. The median follow-up length for all patients was 24.9 months. This study included 100 (62.1%) males and 61 (37.9%) females. The median age was 69 (40–86) years. R0 resection was performed in 111 (69.0%) patients. One hundred and nine (67.7%) patients were diagnosed with regional lymph node metastasis. In 90 patients who underwent PALN sampling, 11 (12.2%) patients were diagnosed with PALN metastasis. Postoperative recurrence occurred in 113 (70.2%) patients. The initial recurrence type in 33 (20.5%) patients was local, 28 (17.4%) in the liver, 17 (10.6%) in the lungs, 10 (6.2%) in the peritoneum, 5 (3.1%) in the others, and 20 (12.4%) in multiple sites. Out of 20 patients with multiple site recurrences, five patients developed lung recurrence. In total, 22 patients (13.7%) developed lung recurrence. The clinical details of 17 patients (10.6%) with isolated lung recurrence are shown in Supplementary Table 1.

3.2. Overall survival and recurrence-free survival

The OS according to individual pattern of initial recurrence are shown in Fig. 1.

The median OS of patients with isolated lung recurrence was 38.0 (95% confidence interval [CI], 28.8–49.9) months and 22.2 (95% CI, 18.4–24.9) months (stratified log-rank $p = 0.001$; Fig. 2a) in the patients with other recurrence. The median RFS of patients with isolated lung recurrence was 16.1 (95% CI: 7.8–26.9) months and was 9.8 (95% CI: 8.1–11.4) months (stratified log-rank $p = 0.008$; Fig. 2b) in the patients with other recurrence.

The median OS of patients with oligopulmonary recurrence was 75.9 months. The median OS of patients with multiple pulmonary recurrence 36.8 months. (stratified log-rank $p = 0.055$; Supplementary Fig. 1). The prognosis of patients with oligopulmonary recurrence tends to be longer than that of patients with multiple pulmonary recurrence.

3.3. Univariate and multivariate analysis of clinicopathological variables in relation to lung recurrence after curative resection

The multivariate and univariate analysis results are shown in

Table 1
Patient characteristics and recurrence type.

		Total ($n = 161$)	Isolated lung recurrence ($n = 17$)	Without isolated lung recurrence ($n = 144$)
Age, years	Median (range)	69 (40–86)	65 (46–74)	70 (40–86)
Sex, n (%)	Male	100 (62.1)	6 (35.3)	94 (65.3)
	Female	61 (37.9)	11 (64.7)	50 (34.7)
Tumor diameter, mm	Median (range)	30 (6–97)	33 (15–62)	30 (6–97)
Location, n (%)	Head	111 (69.0)	11 (64.7)	100 (69.4)
	Body, Tail	50 (31.0)	6 (35.3)	44 (30.6)
Resectability status, n (%)	PR	119 (73.9)	14 (82.4)	105 (72.9)
	BR	42 (26.1)	3 (17.7)	39 (27.1)
Lymph node metastasis, n (%)	Yes	109 (67.7)	13 (76.5)	96 (66.7)
Residual tumor status, n (%)	R0	111 (69.0)	10 (58.8)	101 (70.1)
	R1	50 (31.0)	7 (41.2)	43 (29.9)
pStage, UICC[a] ver.8.0, n (%)	IA	21 (13.0)	1 (5.9)	20 (13.9)
	IB	25 (15.5)	1 (5.9)	24 (16.7)
	IIA	6 (3.7)	2 (11.8)	3 (2.1)
	IIB	75 (46.6)	8 (47.1)	68 (47.2)
	III	23 (14.3)	1 (5.9)	22 (15.3)
	IV	11 (6.8)	4 (23.5)	7 (4.9)
PALN metastasis, n (%)	yes	11/90(12.2)	5/12(41.7)	6/78(7.7)
Recurrence, n (%)	No	48 (29.8)	17 (100)	48 (33.3)
	Yes	113 (70.2)	0 (0)	96 (66.7)
Recurrence type, n (%)	Local only	33 (20.5)		
	Liver only	28 (17.4)		
	Lung only	17 (10.6)		
	Peritoneal only	10 (6.2)		
	Other	5 (3.1)		
	Multiple	20 (12.4)		
	Lung: No lung	22 (13.7): 139 (86.3)		

PR: potentially resectable.
BR: borderline resectable.
PALN: Para-aortic lymph node.
[a] Union for International Cancer Control (UICC) tumor-node-metastasis (TNM) classification 8th edition.

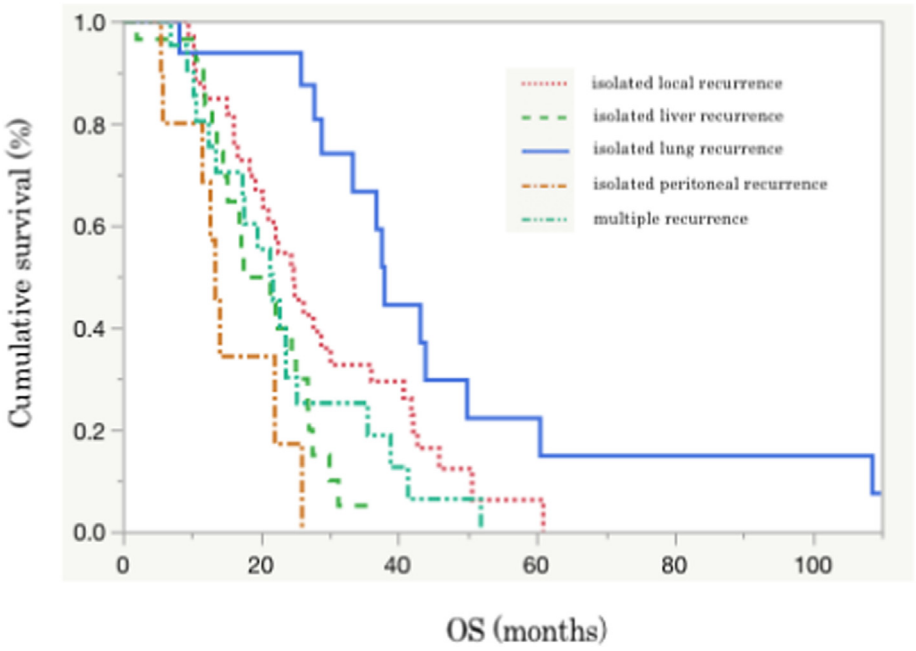

Fig. 1. · The median OS of patients with isolated local recurrence was 24.7 (95% confidence interval [CI], 19.3–30.1) months.
· The median OS of patients with isolated liver recurrence was 17.5 (95% confidence interval [CI], 14.5–25.1) months.
· The median OS of patients with isolated lung recurrence was 38.0 (95% confidence interval [CI], 28.8–49.9).
· The median OS of patients with isolated peritoneal recurrence was 13.4 (95% confidence interval [CI], 5.6–26.0) months.
· The median OS of patients with multiple recurrence was 21.4 (95% confidence interval [CI], 12.5–25.2) months.

Table 2. There were significant differences in sex ($p = 0.018$) and PALN metastasis ($p = 0.003$). There was no difference in procedures, residual tumor status, tumor diameter, resectability status, lymph node metastasis, CA 19-9 level, tumor differentiation, and adjuvant therapy. In the multivariate analysis, female sex (odds ratio [OR] = 5.26, 95% CI: 1.21–22.8, $p = 0.027$) and PALN metastasis positivity(OR = 8.40, 95% CI: 1.83–38.5, $p = 0.006$) were independent factors for lung recurrence. Also, the similar results were

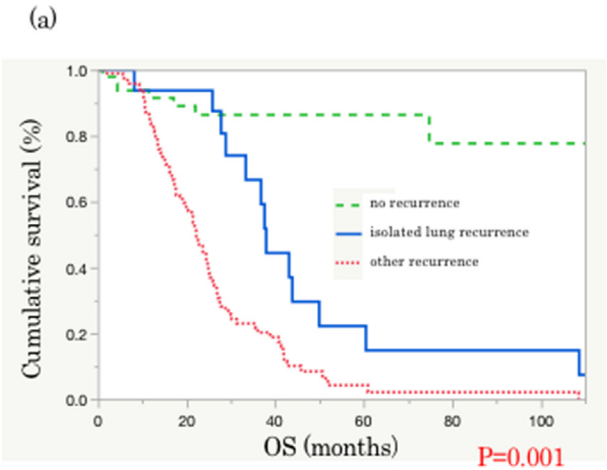

Fig. 2,a. Over survival in patients with isolated lung recurrence, patients with other recurrence, and patients without recurrence.

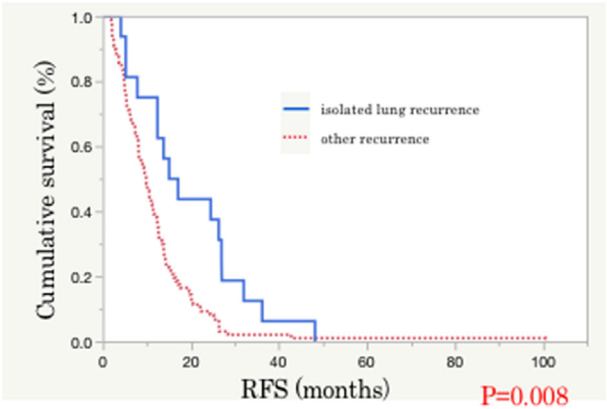

Fig. 2,b. Recurrence free survival in patients with isolated lung recurrence and patients with other recurrence.

obtained in an analysis limited to patients with PALN resection (Supplementary Table 2).

Similar results were obtained in an analysis of patients with recurrence (Table 3). In multivariate analysis, female sex (OR = 4.47, 95% CI: 1.00–19.9, $p = 0.049$) and PALN metastasis positivity (OR = 5.88, 95% CI: 1.23–28.0, $p = 0.026$) were independent lung recurrence factors.

3.4. Recurrence types in patients with PALN metastasis

The recurrence types in patients with PALN metastasis are shown in Table 4.

Lung-only recurrence was highest (45.5%) in the patients who had PALN metastasis. Multiple site recurrences were found in two patients; one of them had lung recurrence. In total, six patients among the patients with PALN metastasis developed lung recurrence.

4. Discussion

This study demonstrates that female sex and PALN metastasis were independent risk factors for lung recurrence after pancreatectomy for PDAC. This study is the first study to identify PALN metastasis as a risk factor for lung recurrence.

To date, initial lung recurrences are reported to account for about 3%–22% of recurrences.[2,4,9–13] Patients with lung recurrence after curative resection have a better prognosis than patients with recurrence in other sites.[2,3,9,14] Vincent et al.[2,3] reported that patients with isolated lung recurrence after curative resection for PDAC had an RFS and OS of 18.4 and 39.6 months, respectively, which were significantly better than the survival associated with recurrence in the liver (RFS and OS of 7.3 and 15.4 months, respectively) and peritoneum. Our study also showed a similar trend. The patients with isolated lung recurrence after curative surgery for PDAC had an RFS and OS of 16.1 and 38.0 months, respectively. The mechanism for lung metastasis is hematogenous, like liver metastasis; however, they differ in prognosis and TTR. Therefore, the mechanisms of lung recurrence might be different from other distant metastases mechanisms.

To date, there are few reports on risk factors for lung metastasis from PDAC. Vincent et al.[2] conducted a study involving 692 patients who underwent pancreatectomy for PDAC and reported that a lymph node ratio >0.2 and perivascular invasion were lung recurrence predictors. Lovecek et al.[14] reported that the proportion of females was significantly higher in patients with metachronous pulmonary metastasis than in those with non-pulmonary metastases after pancreatectomy for PDAC. Liu et al.[16] reported that female sex, poorly differentiated or undifferentiated tumor, and tumor size ≥80 mm were risk factors for lung metastasis in patients with stage IV pancreatic cancer. In our study, PALN metastasis and female sex were risk factors for lung recurrence.

PALN metastasis of pancreatic cancer is classified as distant metastasis with poor prognosis in the 8th edition of the UICC/TNM classification. Pancreatic resection is generally contraindicated if PALN metastasis is diagnosed.[17–19] However, PALN metastasis is difficult to diagnose preoperatively and is often diagnosed pathologically after resection. In addition, pancreatic resection may provide survival benefits to patients with PALN metastasis in some cases.[20,21] A recent study demonstrated that patients with PALN metastasis who received adjuvant chemotherapy had a similar prognosis to those with regional lymph node metastasis.[22] In our study, the recurrence rate after resection of pancreatic cancer with PALN metastasis was very high (10/11, 91%). Interestingly, a high proportion of 6 out of 10 (60%) patients with both recurrence and PALN metastasis had an initial lung recurrence. Lung metastasis is generally thought to be via hematogenous spread. Anatomically, all veins draining the pancreas flow into the portal system, and thus, the liver is thought to be the first organ to provide filtration.[23] However, some patients develop lung metastasis without liver metastasis first. Moreover, patients with lung recurrence have a significantly longer TTR. Anatomically, lymphatic fluid in the peritoneal cavity flows into the thoracic duct via the PALNs and enters the superior vena cava via the left venous angle. It finally reaches the lungs via the pulmonary artery, which might explain the association between PALN metastasis and lung recurrence. Our study suggests that the mechanism of lung metastasis is also due to lymphatic flow, apart from blood flow.

Our study also demonstrates that female sex is a risk factor for lung recurrence, in line with previous reports.[14,16] Lovecek et al.[14] reported that female sex was a risk factor for lung metastasis after pancreatectomy for PDAC. Liu et al.[16] reported that female sex was a risk factor for lung metastasis in patients with stage IV pancreatic cancer. It has also been reported that the female sex is associated with a better OS in patients with stage IV PDAC.[24] Female patients with unresectable PDAC have a better treatment response to chemotherapy than male patients.[25] These reports suggest that the intrinsic pathogenesis differences of sex in pancreatic cancer

Table 2
Factors influencing isolated lung recurrence: Univariate and multivariate analysis.

	Isolated Lung recurrence (n = 17)	Without isolated lung recurrence (n = 144)	*Univariate Analysis*		*Multivariate Analysis*	
			OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age, (65yr≦), n (%)	9 (52.9)	102 (70.8)	0.46 (0.17−1.28)	0.138		
Sex (Female), n (%)	11 (64.7)	50 (34.7)	3.45 (1.20−9.87)	0.018	5.26 (1.21−22.8)	0.027
Location, n (%)				0.690		
Head	11 (64.7)	100 (69.4)	0.81 (0.28−2.32)			
Body, Tail	6 (35.3)	44 (30.6)				
Residual tumor status (R1), n (%)	7 (41.2)	43 (29.9)	1.64 (0.59−4.60)	0.434		
Tumor diameter (40 mm≦), n (%)	4 (23.5)	27 (19.0)	1.31 (0.40−4.34)	0.658		
Resectability status, n (%)				0.407		
PR	14 (82.4)	105 (72.9)	1.73 (0.47−6.36)			
BR	3 (17.7)	39 (27.1)				
Lymph node metastasis (yes), n (%)	13 (76.5)	96 (66.7)	1.63 (0.50−5.25)	0.417		
CA19-9 (37≦), n (%)	13 (76.5)	108 (75.0)	1.08 (0.33−3.53)	0.894		
Poorly differentiated, n (%)	1 (5.9)	15 (10.4)	0.54 (0.07−4.34)	0.560		
Postoperative adjuvant therapy (no), n (%)	4 (23.5)	32 (22.2)	1.08 (0.33−3.53)	0.903		
PALN metastasis (yes)	5/12 (41.7)	6/78 (7.7)	8.57 (2.08−35.4)	0.003	8.40 (1.83−38.5)	0.006

PR: potentially resectable.
BR: borderline resectable.
CA19-9: carbohydrate antigen 19-9.
PALN: Para-aortic lymph node.
OR: Odds ratio.
CI: confidence interval.

Table 3
Factors influencing isolated lung recurrence: Univariate and multivariate analysis (analysis for recurrence patients).

	Isolated lung recurrence (n = 17)	Without isolated lung recurrence (n = 96)	*Univariate Analysis*		*Multivariate Analysis*	
			OR (95% CI)	p-Value	OR (95% CI)	p-Value
Age, (65yr≦), n (%)	9 (52.9)	70 (72.9)	0.42 (0.15−1.20)	0.105		
Sex (Female), n (%)	11 (64.7)	35 (36.5)	3.20 (1.09−9.39)	0.035	4.47 (1.00−19.9)	0.049
Location, n (%)				0.875		
Head	11 (64.7)	64 (66.7)	0.92 (0.31−2.70)			
Body, Tail	6 (35.3)	32 (33.3)				
Residual tumor status (R1), n (%)	7 (41.2)	35 (36.5)	1.22 (0.43−3.49)	0.711		
Tumor diameter (40 mm≦), n (%)	4 (23.5)	21 (22.1)	1.08 (0.32−3.68)	0.897		
Resectability status, n (%)				0.333		
PR	14 (82.4)	68 (70.8)	1.92 (0.51−7.21)			
BR	3 (17.7)	28 (29.2)				
Lymph node metastasis (yes), n (%)	13 (76.5)	76 (79.2)	0.86 (0.25−2.91)	0.802		
CA19-9 (37≦), n (%)	13 (76.5)	81 (84.4)	0.60 (0.17−2.10)	0.426		
Poorly differentiated, n (%)	1 (5.9)	12 (12.5)	0.44 (0.05−3.60)	0.442		
Postoperative adjuvant therapy (no), n (%)	4 (23.5)	19 (19.8)	1.25 (0.37−4.26)	0.725		
PALN metastasis (yes)	5/12 (41.7)	5/49 (10.2)	6.29 (1.44−27.4)	0.015	5.88 (1.23−28.0)	0.026

PR: potentially resectable.
BR: borderline resectable.
CA19-9: carbohydrate antigen 19-9.
PALN: Para-aortic lymph node.
OR: Odds ratio.
CI: confidence interval.

Table 4
Recurrence types in patients with PALN metastasis.

		Total ($n = 11$)
Recurrence type, n (%)	Local only	0 (0)
	Liver only	1 (9.1)
	Lung only	5 (45.5)
	Peritoneal only	2 (18.2)
	Other	0 (0)
	Multi	
	Local + Lung	1 (9.1)
	Lymph node + peritoneal	1 (9.1)
	No recurrence	1 (9.1)

PALN: Para-aortic lymph node.
Case of No recurrence; Early death from other diseases.

are related to clinical presentation and outcome. In animal models, it has been reported that estrogen acts as an inhibitor and androgen as a promoter during the process of pancreatic carcinogenesis.[26,27] Sex hormones might influence the clinical course. Detailed studies are needed for further clarification.

There are some limitations to this study. First, this is a single-center retrospective study analyzing only 161 patients with resected PDAC. Second, because sampling of PALN was performed at the discretion of the surgeon, we had data of PALN metastasis in only 90 patients. It seems to exist as biased. However, the similar results were obtained in an analysis limited to patients with PALN resection. Further verification in a larger study is necessary.

In conclusion, lung recurrence had a better prognosis than other recurrences. Female sex and PALN metastasis were independent risk factors for lung recurrence after curative resection in PDAC. The mechanism of lung metastasis may be different from that of other distant metastases. Since lung recurrence can occur even a long time after surgery, patients at risk of lung recurrence should be followed up for a long period of time.

Declaration of competing interest

The Authors declare no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2022.03.043.

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