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Research Paper

Predictors of occult metastases in potentially Resectable pancreatic ductal adenocarcinoma

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ABSTRACT

Background: Patients with resectable (R) or borderline resectable (BR) pancreatic ductal adenocarcinoma (PDAC) sometimes show unexpected liver, peritoneal, and para-aortic lymph node metastases intraoperatively. Despite radical pancreatectomy, a nonnegligible number of patients relapse within 6 months after surgery. The aim of this study was to identify the preoperative predictors of occult metastases (OM), defined as intraoperative distant metastases or within 6 months after pancreatectomy.

Materials and methods: This study included patients with R and BR PDAC who underwent curative-intent pancreatectomy or staging laparoscopy between 2006 and 2021. Multivariate logistic regression and Cox hazard analyses were performed to identify the preoperative predictors of OM and to assess the impact of these factors on prognosis after pancreatectomy.

Results: Of the 279 patients, OM was observed intraoperatively in 47 and postoperatively in 34. In the OM group, there were no differences in prognosis between patients who had intraoperative metastases and recurrence within 6 months (median survival time [MST], 18.1 vs. 12.9 months), and between patients who underwent pancreatectomy and those who did not (MST, 13.9 vs. 18.1 months). Preoperative tumor size ≥22 mm (odds ratio [OR], 2.03; 95 % confidence interval [CI], 1.16–3.53; $p = 0.013$) and preoperative CA19–9 level ≥ 118.8 U/mL (OR, 2.64; 95 % CI, 1.22–5.73; $p = 0.014$) were significant predictors of OM. Additionally, positive OM predictors were strong independent prognostic factors for overall survival after pancreatectomy (hazard ratio, 2.47; 95 % CI, 1.54–3.98; $p < 0.001$).

Conclusion: Multidisciplinary treatment strategies should be considered for patients with predictors of OM to avoid inappropriate surgical interventions.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most poorly prognosed cancers, with an overall five-year survival rate of approximately 10 % [1]. It has become the fourth leading cause of cancer-related deaths in Japan [2] and is expected to become the second leading cause of cancer-related deaths in the United States by 2030 [3]. According to the National Comprehensive Cancer Network (NCCN) criteria, resectability status, based on vascular involvement and distant metastases, is classified as resectable (R), borderline resectable (BR), or unresectable (UR) [4]. Early diagnosis of PDAC is difficult, with approximately 80 % of patients diagnosed with UR PDAC due to metastases or locally advanced disease, and only 20 % diagnosed with potentially resectable disease [5].

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Imaging modalities, including multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), endoscopic ultrasonography (EUS), and [18]F fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT are used for the assessment of tumor resectability status. Despite improvements in imaging technology, small liver metastases, peritoneal dissemination, and para-aortic lymph node (PALN) metastases are revealed during surgical exploration in approximately 20 % of patients with R and BR PDAC [6]. Furthermore, in approximately 20 % of patients with PDAC, recurrence occurs within 6 months after radical pancreatectomy [7,8]. Distant metastases within 6 months after surgery is suspected to be a manifestation of micrometastases that could not be detected pre- or intra-operatively. Such early recurrences are associated with a shorter survival than that in cases of late recurrence [8,9]. In addition, pancreatectomy may no longer improve prognosis in these cases of early recurrence [10]. Therefore, distant metastases identified intraoperatively or within 6 months postoperatively are considered similar conditions with less significance for surgical intervention and were defined as occult metastases (OM) in this study.

Multidisciplinary treatment based on resectability status is recommended for the improvement of PDAC prognosis. However, anatomic resectability status is not a sufficient predictor of early recurrence, including OM. In addition, other indicators may be needed for the selection of multidisciplinary treatment. It has been reported that carbohydrate antigen 19–9 (CA19–9) level [8,9] and tumor size measured by CT [7] or EUS [9] are preoperative predictors of early recurrence of PDAC. In addition, previous studies have indicated that in patients with R and BR PDAC, CA19–9 level [6,11,12], tumor size measured by CT [6,11,12], and pancreatic body or tail cancer [11,12] are preoperative predictors of unexpected distant metastases identified during surgery. There is a broad spectrum of cutoff values for CA19–9 levels that predict unexpected distant metastasis or early recurrence, ranging from 150 U/mL to 385 U/mL [6,7,11,12]. Similarly, cutoff values for tumor size range from 30 mm to 50 mm [6,7,9,11,12], with no established consensus on the appropriate value. However, most of these previous studies did not include PALN metastases as distant metastases, which are diagnosed during surgery in approximately 15 % of PDAC cases [13,14]. Furthermore, although the significance of neoadjuvant therapy for R and BR PDAC has become clearer in recent years [15,16], only small proportions of patients who received neoadjuvant therapy were included in these previous studies.

The aim of this study was to identify the preoperative predictors of OM in patients with R and BR PDAC and to evaluate the prognostic impact of the predictors of OM.

Material and methods

Patients

This was a single-center retrospective study of 324 consecutive patients with R and BR PDAC who were scheduled for radical pancreatectomy at Sapporo Medical University between January 2006 and December 2021. Patients who underwent staging laparoscopy (SL) because of ascites or nodules suspected to be peritoneal dissemination on MDCT were excluded from this study. In contrast, seven patients diagnosed with R or BR PDAC who underwent SL before curative-intent surgery because of elevated tumor markers, pancreatic body or tail cancer with invasion of other organs, or a large tumor and were found to have distant metastasis were included in the analysis. All the clinical, surgical, and pathological data of the patients were extracted from an institutional database of prospectively acquired data. All the patients were histologically diagnosed with PDAC. Thirty-seven patients with CA19–9 levels <2 U/mL who were deemed likely to be Lewis antigen-negative. This exclusion is because Lewis antigen-negative patients do not produce CA19–9 regardless of tumor burden, which may confound the interpretation of CA19–9 as a biomarker of malignancy. Two patients with 30-day mortality, and six patients with <6 months of follow-up despite the absence of OM were excluded from the analysis. OM was defined as distant metastases that were not detected during preoperative evaluation but were identified intraoperatively or recurrence within 6 months after surgery.

This retrospective study was approved by the Medical Ethics Committee of Sapporo Medical University Hospital (Institutional Review Board approval number: 322–1162) and conducted according to the principles of the Helsinki Declaration. This study was registered at University Hospital Medical Information Network Clinical Trials Registry (date of registration: 05/12/2022, registration number: UMIN000049693). Informed consent was sought from patients using an informed opt-out approach because this was a retrospective study and anonymized clinical data were used in the analysis.

Perioperative treatment strategy

The standard perioperative treatment for R and BR PDAC at our institution was upfront surgery and 6 months of adjuvant therapy until 2013. Neoadjuvant therapy has been used for the treatment of BR PDAC since 2013, and for R PDAC since 2019. Adjuvant therapy was indicated for all postoperative PDAC patients, with gemcitabine being the first choice from 2006 to 2012 and S-1 (tegafur / gimeracil / oteracil potassium) after 2013.

Perioperative evaluation

Tumor resectability status was classified based on both the NCCN and Japanese criteria [4,17]. To assess tumor staging and resectability status, contrast enhanced-MDCT was performed for all patients, unless contraindicated. Tumor diameter was measured using EUS [18]. The diagnosis of PDAC was confirmed using EUS-guided fine needle aspiration (EUS-FNA), brush cytology, or cytological analysis of pancreatic juice. To detect small liver metastases, superparamagnetic iron oxide MRI was performed as a routine preoperative screening until 2012, whereas gadolinium ethoxybenzyl diethylenetriamine penta-acetic acid-enhanced (EOB) MRI was performed after 2013.

Preoperative assessment of PALN was mainly performed using enhanced-MDCT, supplemented by diffusion-weighted MRI and/or PET-CT when necessary. The acquired images were reviewed by a multidisciplinary team (MDT) to determine the appropriate treatment strategy for the patient. PALN were clinically considered to be metastases if CT imaging showed enlargement with a short-axis diameter >8 mm, diffusion-weighted MRI indicated diffusion abnormalities, and PET-CT revealed increased FDG uptake.

Preoperative CA19–9 levels were measured within four weeks before surgery, without elevated total bilirubin levels (< 2 mg/dL). CA19–9 levels before NAT were also measured in the absence of jaundice. Baseline CA19–9 levels were measured before NAT for patients undergoing NAT and before surgery those patients undergoing upfront surgery. MDCT and EOB-MRI were also performed within four weeks before surgery. SL was indicated for some patients with high tumor marker levels and a bulky tumor based on the MDT approach.

A diagnostic frozen section biopsy was performed when nodules suspected to be liver metastases or peritoneal dissemination were found during surgery. In the absence of these metastases, frozen section biopsies of PALN were performed for all patients. Pancreatectomy was generally discontinued when distant metastases were evident, whereas pancreatectomy was performed for some patients with PALN metastases. Based on comprehensive considerations, including oncological factors, the patient's condition, and other clinical considerations, as well as a strong preference for pancreatectomy expressed by some attending physicians or patients themselves, pancreatectomy was selectively indicated in a subset of patients with PALN-positive PDAC. In addition, some PALN metastases were not detected in the intraoperative frozen section but were confirmed postoperatively on final examination after paraffin embedding. Pathological findings were classified using the

Union for International Cancer Control TNM classification [19].

For postoperative surveillance, CA19–9 levels were measured monthly during the first postoperative year and every one to three months thereafter. Contrast-enhanced CT was performed every three months during the first year after surgery and every six months thereafter. When elevated tumor marker levels were observed, CT was promptly performed. Recurrence was diagnosed based on radiological findings and confirmed through biopsy when possible.

Statistical analyses

The $\chi 2$ test, Fisher's exact test, or Mann-Whitney *U* test was used to assess significant differences between two groups. Recurrence-free survival (RFS) and overall survival (OS) were defined as the period from the date of surgery to recurrence, death, or last contact and to death or last contact, respectively. Patients with <3 months of follow-up data were excluded from the OS analysis. Survival curves were calculated using Kaplan–Meier estimation, and the results were compared using the log-rank test. The optimal cut-off points for baseline and preoperative CA19–9 levels and tumor size were identified as the upper left corner of the receiver operating characteristic (ROC) curve. The diagnostic period was divided into two in 2013, a watershed year for perioperative adjuvant therapy and preoperative imaging evaluation. To identify independent factors associated with OM and OS, logistic regression and Cox hazard analysis were performed. Multivariate analysis included variables with $p < 0.1$ in univariate analysis. Statistical significance was set at $p < 0.05$. All analyses were performed using the statistical software package JMP Pro version 16.0.0 (SAS Institute Inc., Tokyo, JAPAN).

Results

Patient cohort

A total of 279 patients with R and BR PDAC who underwent curative-intent surgery or SL during the study period were included in the analysis. The median age of the patients was 70 years (range, 29–87 years), and 143 (51.3 %) and 136 (48.7 %) patients were female and male, respectively. Regarding tumor location, 198 patients (71.0 %) had PDAC located in the pancreatic head, whereas 81 (29.0 %) had PDAC in the pancreatic body and tail. Regarding tumor resectability status, 209 patients (74.9 %) had R PDAC, whereas 70 (25.1 %) had BR PDAC. Neoadjuvant therapy was administered to a total of 114 patients (40.9 %) (Table 1), 73 patients (34.9 %) with R PDAC and 41 (58.6 %) with BR PDAC. Intraoperatively, 47 (16.8 %) patients had unexpected distant metastases, including 23 PALN metastases, 17 peritoneal dissemination, 6 liver metastases and 1 peritoneal and liver metastasis. Adjuvant therapy after pancreatectomy was administered to 223 patients (89.6 %) (Table S1). The median follow-up period for the censored cases was 24.9 months (3.5–170.8 months). Until the last follow-up in July 2022, 133 patients (57.3 %) had recurrence. Of these, 34 (14.7 %) had recurrence within 6 months after surgery (Fig. 1), and 118 (42.3 %) died.

Differences in patient characteristics between the non-OM and OM groups

The characteristics of the 198 (71.0 %) and 81 (29.0 %) patients in the non-OM and OM groups are shown in Table 1. Preoperative tumor size on EUS was significantly larger in the OM group than in the non-OM group (2.5 [1.0–5.9] vs. 2.0 [0.6–5.0] mm; $p = 0.011$). Baseline CA19–9 levels (156.3 [2.2–35,033] vs. 78.1 [2.5–10,317] U/mL; $p = 0.010$) and preoperative CA19–9 levels (87.4 [2.4–12,199] vs. 41.7 [3.2–8373] U/mL; $p = 0.0006$) were also significantly higher in the OM group than in the non-OM group. There were no significant differences in age, sex, tumor location, resectability status, or receipt of neoadjuvant therapy between the two groups. The frequency of OM before 2012 was comparable with the frequency after 2013 (31.6 % [31/98] vs. 27.6 % [50/181], respectively; $p = 0.481$), which was when EOB-MRI was introduced as part of preoperative evaluation in our institution.

Table 1
Patient characteristics.

Variables	Non-occult metastases	Occult metastases	*P*-value
	N = 198	*N* = 81	
Age (years)	71 [44–86]	70 [29–87]	0.267
Sex			
Male	96 (48)	40 (49)	0.892
Female	102 (42)	41 (51)	
Tumor location			
Head	137 (69)	61 (75)	0.307
Body or tail	61 (31)	20 (25)	
Tumor size on EUS (mm)	2.0 [0.6–5.0]	2.5 [1.0–5.9]	0.011
Resectability status †			
Resectable	151 (76)	58 (72)	0.415
Borderline resectable	47 (24)	23 (28)	
Baseline CA19–9 (U/mL)	78.1 [2.5–10,317]	156.3 [2.2–35,033]	0.010
Preoperative CA19–9 (U/mL)	41.7 [3.2–8373]	87.4 [2.4–12,199]	<0.001
Baseline CEA (ng/mL)	3.0 [0.5–37.2]	3.2 [0.6–458.8]	0.281
Neoadjuvant therapy			
Yes	80 (40)	34 (42)	0.809
No	118 (60)	47 (58)	
Diagnostic period			
2006–2012	67 (34)	31 (38)	0.481
2013–2021	131 (56)	50 (62)	

Categorial data are expressed as n (%). Continuous variables are presented as the median [range].
Abbreviations: CA19–9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; EUS, endoscopic ultrasonography.
† According to the National Comprehensive Cancer Network criteria.

Postoperative outcomes

Table 2 shows the comparison of surgical and postoperative factors between the two groups. In the OM group, 47 patients had distant metastases, 17 completed pancreatectomy, and 30 underwent palliative surgery. The rate of adjuvant therapy after pancreatectomy in the OM group was significantly lower than that in the non-OM group (78.4 % [40/51] vs. 92.4 % [183/192], respectively; $p = 0.004$). Recurrence prior to adjuvant therapy was the most common reason for failure to initiate adjuvant therapy in the OM group. The metastatic sites were the liver, lung, peritoneum, lymph node, and others, in 31, 10, 8, 5, and 3 patients in the OM group and in 28, 25, 17, 10 and 27 patients in the non-OM group, respectively. Liver metastases were significantly frequent in the OM group ($p < 0.001$). Median RFS after pancreatectomy was 3.6 months in the OM group, significantly worse than 29.7 months in the non-OM group ($p < 0.001$). The median survival time (MST) in the OM group was significantly poorer than that in the non-OM group (15.0 vs. 54.1 months, respectively; $p < 0.001$; Fig. 2a). In the OM group, there was no difference in OS between patients who showed recurrence within 6 months after surgery and those who had metastases detected during surgery (12.9 vs. 18.1 months; $p = 0.239$; Fig. 2b), those who had PALN metastases and those who had other occult metastases (18.1 vs. 13.1 months; $p = 0.119$; Fig. 2c), and those who underwent pancreatectomy and those who did not (13.9 vs. 18.1 months; $p = 0.908$; Fig. 2d).

Predictive factors for OM

The optimal cut-off tumor size, baseline CA19–9 level, and preoperative CA19–9 level for predicting OM were assessed using ROC curve analysis. The areas under the curves for tumor size, baseline CA19–9 level, and preoperative CA19–9 level were 0.597, 0.598, and 0.631, respectively. The optimal cut-off tumor size, baseline CA19–9 level, and preoperative CA19–9 level for the prediction of OM were 22 mm (sensitivity: 0.642; specificity: 0.556), 87.0 U/mL (sensitivity: 0.630;

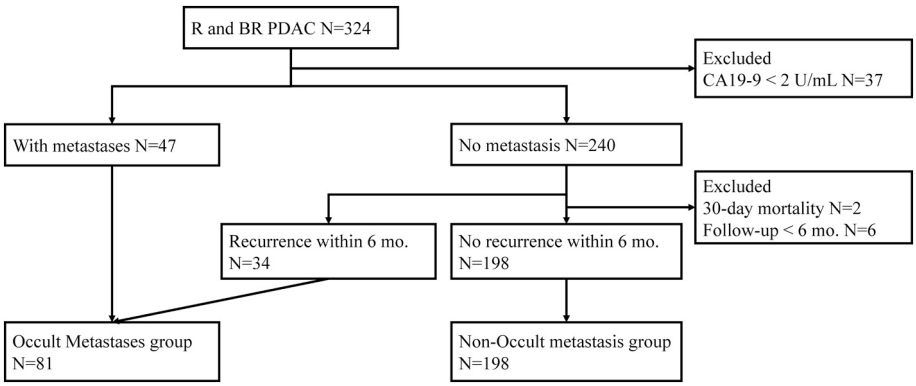

Fig. 1. Patient enrollment flowchart and postoperative outcomes
BR, Borderline resectable; R, Resectable.

Table 2
Postoperative outcomes.

Variables	Non-occult metastases	Occult metastases	Metastases	Recurrence within 6 months	*P*-value [††]
	N = 198	N = 81	*N* = 47	*N* = 34	
Surgical procedure					<0.001
PD	134 (67)	36 (44)	14 (30)	22 (65)	
DP	63 (32)	11 (14)	1 (2)	10 (29)	
TP	1 (1)	4 (5)	2 (4)	2 (6)	
Other procedures [†]	0 (0)	30 (37)	30 (64)	0	
Pathological stage [‡]					<0.001
CR	3 (2)	0 (0)	0 (0)	0 (0)	
IA	36 (18)	3 (4)	0 (0)	3 (9)	
IB	47 (24)	2 (2)	0 (0)	2 (6)	
IIA	4 (2)	0 (0)	0 (0)	0 (0)	
IIB	72 (36)	17 (21)	0 (0)	17 (50)	
III	36 (18)	12 (15)	0 (0)	12 (35)	
IV	0 (0)	47 (58)	47 (100)	0 (0)	
Residual tumor					<0.001
R0	188 (95)	44 (54)	14 (30)	30 (88)	
R1	10 (5)	7 (9)	3 (6)	4 (12)	
R2	0 (0)	30 (37)	30 (64)	0 (0)	
Adjuvant therapy [§]					0.004
Yes	183 (92)	40 (78)	14 (82)	26 (76)	
No	15 (8)	11 (22)	3 (18)	8 (24)	
Recurrence after pancreatectomy [¶]					
No. of patients	99	49	15	34	
Total	105	59	17	42	
Liver	28 (27)	31 (53)	7 (41)	24 (57)	<0.001
Lung	25 (24)	10 (17)	4 (24)	6 (14)	0.303
Peritoneum	17 (16)	8 (14)	3 (18)	5 (12)	0.653
Lymph node	10 (10)	5 (8)	1 (6)	4 (10)	0.823
Local recurrence	13 (12)	3 (5)	0 (0)	3 (7)	0.216
Remnant pancreas	6 (6)	2 (3)	2 (12)	0 (0)	0.775
Bone	4 (4)	0 (0)	0 (0)	0 (0)	0.322
Gastric wall	2 (2)	0 (0)	0 (0)	0 (0)	0.745

Categorial data are expressed as n (%).
Abbreviations: CR, complete response; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; TP, total pancreatectomy
[†] Other procedures included laparotomy (n = 8), choledochojejunostomy (*n* = 7), staging laparoscopy (n = 7), cholecystectomy (*n* = 6), and gastrojejunostomy (*n* = 2).
[‡] According to the Union for International Cancer Control TNM classification 8th edition.
[§] Patients who did not undergo pancreatectomy were excluded from adjuvant therapy. [¶] Recurrences were observed in multiple sites in 17 patients.
[††] Comparison between the non-occult metastasis group (n = 198) and occult metastases group (*n* = 81).

specificity: 0.546), and 118.8 U/mL (sensitivity: 0.482; specificity: 0.738), respectively. In the univariate analysis, tumor size (≥ 22 mm vs. < 22 mm), baseline CA19–9 level (≥ 87.0 U/mL vs. < 87.0 U/mL), and preoperative CA19–9 level (≥ 118.8 U/mL vs. < 118.8 U/mL) were identified as predictors of OM. In the multivariate analysis, tumor size ≥22 mm (odds ratio [OR] = 2.03; 95 % confidence interval [CI]: 1.16–3.53; $p = 0.013$) and preoperative CA19–9 level ≥ 118.8 U/mL (OR = 2.64; 95 % CI: 1.22–5.73; $p = 0.014$) were significant predictors of OM (Table 3).

A total of 174 patients had positive predictors of OM, and 62 (35.6 %) of them had OM. In comparison, 105 patients had negative predictors, and 19 (18.1 %) of them had OM. The combination of tumor size ≥22 mm and/or CA19–9 level ≥ 118.8 U/mL predicted OM with a sensitivity of 76.5 % and a specificity of 43.4 %.

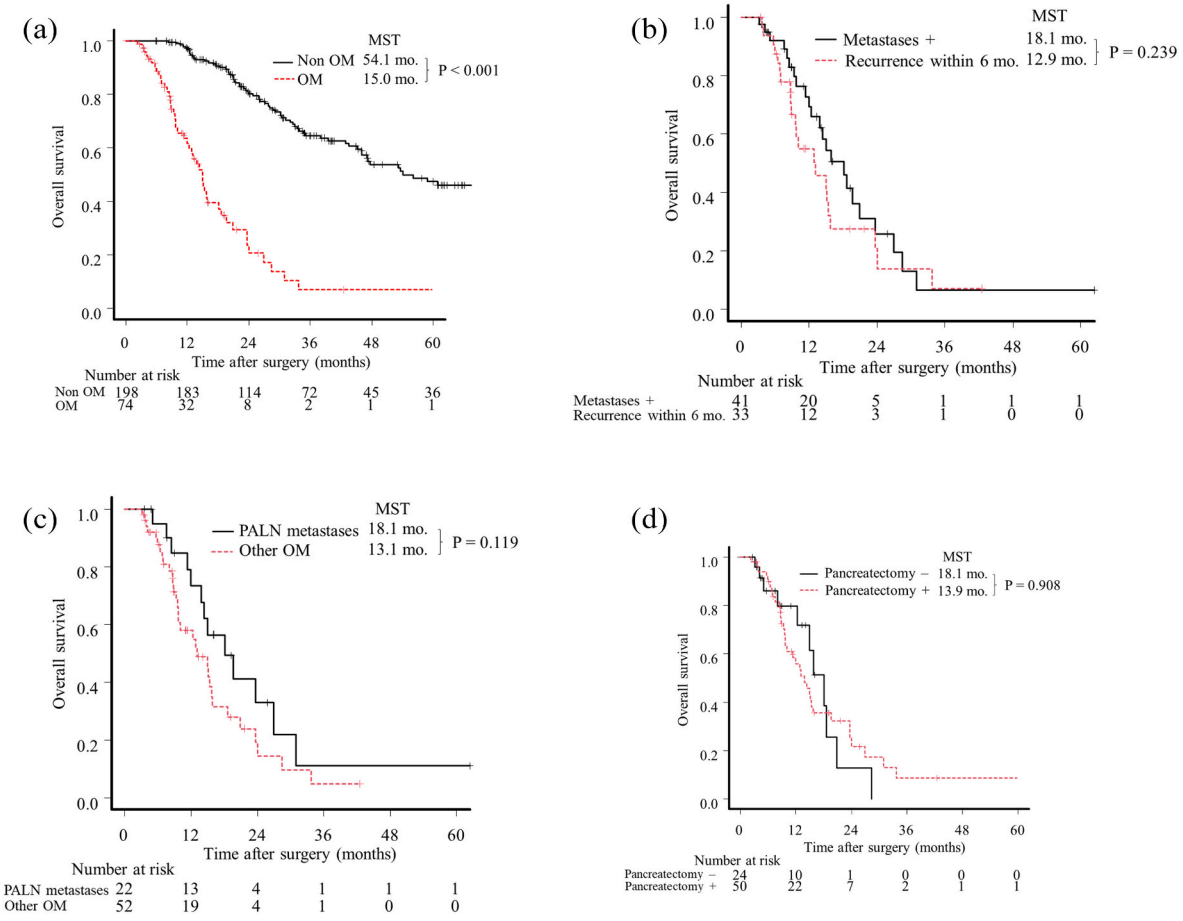

Fig. 2. Kaplan–Meier survival curves in overall survival for patients with pancreatic ductal adenocarcinoma
a. patients with occult metastases (OM) and without OM.
b.patients with metastases detected during surgery and recurrence within 6 months after surgery
c. patients with PALN metastases and other OM
d. patients with OM who underwent pancreatectomy and those who did not
MST, median survival time; Other OM, liver metastases, peritoneal dissemination, and recurrence within 6 months; PALN, para-aortic lymph node.

Table 3
Univariate and multivariate analyses of predictive factors for occult metastases.

Factor		Univariate analysis			Multivariate analysis		
		Odds ratio	95 % CI	*P*-value	Odds ratio	95 % CI	*P*-value
Age	≥70 (years)	0.86	0.51–1.45	0.573			
Sex	Male	1.03	0.62–1.74	0.892			
Tumor location	Pbt	0.74	0.41–1.33	0.308			
Tumor size on EUS	≥22 (mm)	2.24	1.31–3.82	0.003	2.03	1.19–3.53	0.013
Resectability status †	BR	1.27	0.71–2.28	0.416			
Baseline CA19–9	≥87.0 (U/mL)	1.90	1.12–3.22	0.018	0.85	0.39–1.84	0.674
Preoperative CA19–9	≥118.8 (U/mL)	2.67	1.52–4.47	<0.001	2.64	1.22–5.73	0.014
Neoadjuvant therapy	Yes	1.07	0.63–1.80	0.809			

Abbreviations: BR, borderline resectable; CA19–9, EUS, endoscopic ultrasonography; carbohydrate antigen 19–9; 95 % CI, 95 % confidence interval.
† According to the National Comprehensive Cancer Network criteria.

Prognostic impact of predictive factors for OM after pancreatectomy

Table 4 shows the univariate and multivariate Cox hazard analyses for OS according to clinicopathological factors for patients who underwent pancreatectomy. In the univariate analysis, resectability status, neoadjuvant therapy, presence of predictors, T category, and N category were significant prognostic factors. In the multivariate analysis including these factors, BR (hazard ratio [HR] = 1.63; 95 % CI: 1.06–2.50; $p = 0.026$), N1 (HR = 2.19; 95 % CI: 1.38–3.48; $p = 0.001$), and positive OM predictors (HR = 2.47; 95 % CI: 1.54–3.98; $p < 0.001$) were independent prognostic factors for PDAC. Of the 198 patients without OM, 86 had no predictors and 112 had predictors. Fig. 3a and b show the Kaplan–Meier curves for RFS and OS with or without OM predictors. Patients with OM predictors had significantly shorter RFS (median RFS; 21.5 vs. 67.2 months, respectively; $p < 0.001$) and OS (40.1 vs. 112.8 months, respectively; $p < 0.001$) than patients without OM predictors.

Table 4
Univariate and multivariate analyses for overall survival after pancreatectomy.

Factor		Univariate analysis			Multivariate analysis		
		Hazard Ratio	95 % CI	*P*-value	Hazard Ratio	95 % CI	*P*-value
Age	≥ 70 (years)	0.98	0.67–1.44	0.923			
Sex	Male	1.22	0.84–1.80	0.299			
Tumor location	Ph	1.09	0.61–1.39	0.686			
Resectability status †	BR	1.44	0.96–2.17	0.082	1.63	1.06–2.50	0.026
Neoadjuvant therapy	Yes	0.65	0.41–1.02	0.062	0.68	0.41–1.10	0.117
Predictors	≥ 1	2.94	1.88–4.59	<0.001	2.47	1.54–3.98	<0.001
	≥ 2	2.62	1.74–3.97	<0.001			
T category ‡	≥ T2	1.8	1.11–2.93	0.018	0.97	0.58–1.63	0.901
	≥ T3	1.77	1.08–2.90	0.025			
N category ‡	≥ N1	2.76	1.77–4.30	<0.001	2.19	1.38–3.48	0.001
Residual tumor	R1	1.6	0.77–3.29	0.207			
Adjuvant therapy	Yes	0.84	0.46–1.53	0.562			

Abbreviations: BR, borderline resectable; CA19–9, carbohydrate antigen 19–9; 95 % CI, 95 % confidence interval.
† According to the National Comprehensive Cancer Network criteria.
‡ According to the Union for International Cancer Control TNM classification, 8th edition.

Discussion

Modern chemotherapy regimens [20,21] and neoadjuvant therapy [15,16] have improved the prognosis of PDAC. Initiating neoadjuvant therapy for patients with R or BR PDAC who show OM may be disadvantage for the patients due to inappropriate treatment intensity and the withdrawal period before and after surgery. Therefore, predicting OM and refining a multidisciplinary treatment strategy is essential. Several studies have indicated that conversion surgery with appropriate multidisciplinary treatment may improve prognosis, even in patients with PDAC with oligometastasis [22,23]. Consequently, accurate diagnosis of OM and early introduction of potent chemotherapy may increase the number of patients indicated for conversion surgery.

In the present study, we retrospectively analyzed 279 consecutive patients with R and BR PDAC who underwent surgical exploration to identify predictors of OM. Preoperative tumor size (≥ 22 mm) and preoperative CA 19–9 level (≥ 118.8 U/mL) were identified as independent preoperative predictors of OM. These factors were not only predictors of OM but were independent prognostic factors for OS as well, with a very favorable prognosis observed when these factors were not present. Therefore, patients with predictors of OM require comprehensive clinical investigation for the detection of distant metastases. Even in the absence of distant metastases, the timing of pancreatectomy should be carefully selected because of the high possibility of early recurrence. The OS of patients who show recurrence within 6 months after pancreatectomy did not differ from that of those who had distant metastases detected during surgery. Pancreatectomy is invasive, leading to difficulties in the early introduction of postoperative interventions such as intensified chemotherapy. Therefore, identifying the preoperative predictors of OM may be useful for making multidisciplinary treatment decisions.

In the context of delineating tumors using EUS, where tumor size measurement is commonly performed using CT, this study opted for EUS. This is because, in measuring the tumor size of PDAC, especially for those 30 mm or smaller, EUS is superior to CT [24,25]. Consequently, we reported the usefulness of tumor size measured by EUS as a predictor of early recurrence within the first postoperative year [9]. In this study, the identification of tumor size by EUS as a risk factor for OM represents a highly distinctive feature when compared to studies utilizing tumor size measured through conventional CT methods.

PDAC tends to exhibit infiltrative growth, often resulting in an unclear gross appearance of tumor boundaries. Therefore, measuring tumor size by CT, especially for non-nodular type tumors, might lack fairness [24]. In this regard, EUS offers a better alternative with higher resolution, particularly when diagnosing pancreatic malignancies in patients suspected of cancer but with non-diagnostic MDCT. Contrast-Enhanced EUS (CE-EUS) and EUS elastography enhance the characterization of pancreatic lesions initially identified by EUS [25]. CE-EUS and EUS elastography complement each other, aiding in the identification of target lesions for subsequent EUS-FNA. Importantly, a considerable portion of lesions missed on CT are associated with PDAC [26].

MDCT is the standard imaging modality for diagnosis of the local extension and resectability status of PDAC [4]. However, the accuracy of MDCT in diagnosing small peritoneal dissemination, small liver, or PALN metastases is limited. It has been reported that EOB-MRI can detect small liver metastases, which are difficult to differentiate using CT [27]. Our institution introduced EOB-MRI as a preoperative imaging procedure in 2013. This may be why the frequency of unexpected intraoperative liver metastases in the present study is lower than previously reported values [6,12,28].

Preoperative diagnosis of small peritoneal dissemination remains difficult despite advances in diagnostic modalities. SL is a minimally invasive procedure that can detect small liver metastases and peritoneal dissemination, contributing to the accurate assessment of resectability status [29]. In a meta-analysis, SL for R and BR PDAC identified unresectable disease in 20 % of patients with false negative rates as low as 4–7 %, reducing the frequency of nontherapeutic laparotomy [30]. SL is effective in detecting unexpected metastases and should be performed for selected patients with a high risk for metastases, not in all R and BR PDAC cases. However, although SL is effective in detecting metastases on the liver surface and peritoneal dissemination, evaluating deep liver and PALN status using SL is challenging.

PALN metastases of PDAC are defined as distant metastases [17,19] similar to liver metastases and peritoneal dissemination. Pancreatectomy is generally not recommended for PALN metastases of PDAC [17,19]. However, intraoperative PALN sampling is not a standard procedure worldwide. In addition, PALN was not included as a metastatic site in most previous studies. PALN metastases accounted for more than half of the distant metastases identified during surgery in our study cohort. In addition, the MST for the PALN metastases group was 18.1 months, with no significant difference in OS between the PALN metastases group and the other OM group. The implications of resecting PDAC with unexpected PALN metastases remain unclear [13,14]; thus, perioperative evaluation of PALN status is warranted. Kurita et al. [31] reported that EUS-FNA can diagnose PALN metastases of ≥5 mm with a sensitivity of 96.7 % and specificity of 100 %. SL and EUS-FNA might be promising tools for detecting OM in high-risk patients to help minimize the number of unnecessary laparotomies performed or inappropriate administration of preoperative adjuvant treatment.

In the present study, CA19–9 level and tumor size predicted OM with relatively high sensitivity (76.5 %); however, the specificity was 43.4 %. Diagnosing OM with a high specificity and sensitivity using only preoperative clinicopathologic factors is limited; thus, a novel biomarker

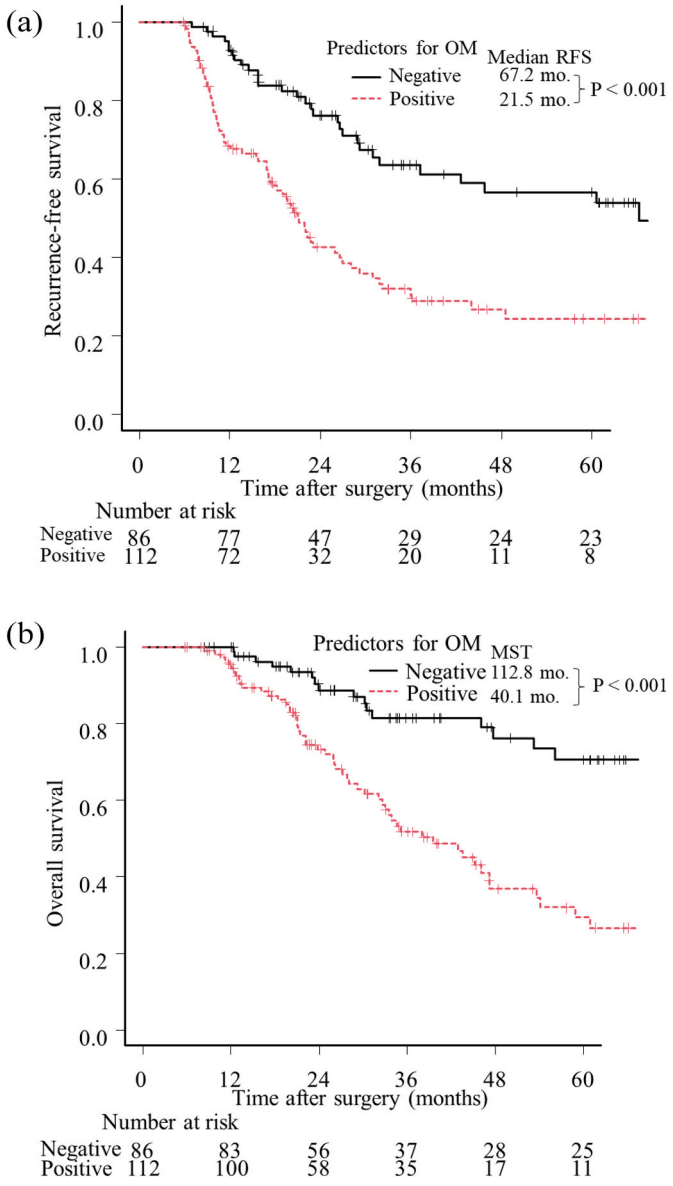

Fig. 3. Kaplan–Meier survival curves for patients without occult metastases (OM) after pancreatectomy

a. Recurrence-free survival for patients with positive and negative predictors of OM.

b. Overall survival for patients with positive and negative predictors of OM

MST, median survival time; OM, occult metastases; RFS, recurrence-free survival.

needs to be identified. Liquid biopsy is an emerging biomarker for cancer management and therapeutics. Hata et al. [32] reported that circulating tumor DNA (ctDNA) might be a predictor of radiologically invisible metastases and undetectable metastatic PDAC. We have already initiated ctDNA research on perioperative PDAC and reported its preliminary findings, which indicate that preoperative ctDNA is a potential prognostic factor after pancreatectomy [33]. The identification of new biomarkers for the highly accurate prediction of OM will facilitate the exploration of optimal multidisciplinary treatment of high-risk patients who have PDAC with OM.

Multidisciplinary treatment is selected according to resectability status as defined by the NCCN, which is an anatomical classification of whether negative margin resection (R0) is technically possible [4,17]. Achieving R0 status is essential for improving oncological outcomes. Anatomical factors alone are not adequate for stratifying prognosis and may not be sufficient for selecting multidisciplinary treatment. Notably, BR PDAC was not an independent predictor of OM in the present study, although biases, such as differences in the proportion of neoadjuvant therapy, treatment regimens, and duration of treatment, existed between R and BR PDAC. The International Association of Pancreatology (IAP) proposed a new definition of BR PDAC [34] that combines biological (CA 19–9 level and lymph node metastases) and conditional (performance status) factors with anatomical factors. These IAP criteria have been reported to be superior to NCCN criteria for stratifying OS [35,36]. The present study showed that CA19–9 level and tumor size, which are preoperative biological factors, are not only predictive factors for OM but are prognostic factors for OS as well. These results indicate the importance of focusing on these biological factors for determining multidisciplinary treatment, the same concept shared by the IAP, even in a cohort that includes patients with PALN metastases as distant metastases and a relatively high proportion of patients receiving neoadjuvant therapy.

This study has several limitations. First, as this was a long-term, single-center, retrospective study with a relatively small sample size, biases such as heterogeneity, lack of standardization of preoperative imaging modalities, and perioperative treatment strategies are present despite using the MDT approach. Second, we did not include baseline diagnosis of lymph node metastases as a predictor of OM based on preoperative factors. The preoperative diagnostic efficiency of lymph node metastases in PDAC is limited even with the current diagnostic imaging modalities; therefore, we considered it unsuitable as a predictor of OM.

Conclusion

This study showed that preoperative CA19–9 level $\geq$ 118.8 U/mL and tumor size $\geq$22 mm are predictors of OM and significant prognostic factors for OS. PDAC with OM has a poor prognosis and may not be eligible for pancreatectomy. Therefore, perioperative evaluation for OM, including PALN metastases, is important. Although neoadjuvant therapy is mandatory for patients with PDAC who have poor prognoses and predictors of OM, the significance of extending the duration of neoadjuvant therapy or switching to another chemotherapy regimen for patients who still have predictors of OM after undergoing the prescribed neoadjuvant therapy needs to be clarified in well-designed future trials.

Authors contributions

T.M. and Y.K. designed the study. T.M., Y.K., M.I., M.N., K.K., T.K., M.Y., Y.M., and H.N. collected and assessed clinical data. T.M. wrote the first draft of the manuscript. Y.K., M.I., and I.T. revised the manuscript. I. T. supervised the study. All the authors approved the final version of the manuscript.

CRediT authorship contribution statement

Takeshi Murakami: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Yasutoshi Kimura:** Writing – review & editing, Project administration, Funding acquisition, Data curation, Conceptualization. **Masafumi Imamura:** Writing – review & editing, Data curation. **Minoru Nagayama:** Writing – review & editing, Data curation. **Toru Kato:** Writing – review & editing, Data curation. **Kazuharu Kukita:** Writing – review & editing, Data curation. **Makoto Yoshida:** Writing – review & editing, Data curation. **Yoshiharu Masaki:** Writing – review & editing, Data curation. **Hiroshi Nakase:** Writing – review & editing, Data curation. **Ichiro Takemasa:** Writing – review & editing, Supervision, Conceptualization.

Declaration of competing interest

We declare that the authors have no conflicts of interest.

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Ethics approval and consent to participate

The protocol for this research project has been approved by the Medical Ethics Committee of Sapporo Medical University Hospital (Institutional Review Board approval number:322–1162) and it conforms to the provisions of the Declaration of Helsinki. This study was registered at University Hospital Medical Information Network Clinical Trials Registry as UMIN000049693. Informed consent was sought from patients using an informed opt-out approach because this was a retrospective study and anonymized clinical data were used in the analysis.

Consent for publication

Not applicable.

Availability of data and materials

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

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.sopen.2024.07.010.

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