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ORIGINAL ARTICLE

Oligo-like liver metastasis: A novel prognostic indicator to improve survival in pancreatic cancer

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Abstract

Purpose: Whether surgical intervention for patients with oligometastatic recurrence can improve their post-recurrent prognosis is unclear. In this study, we introduce a novel concept of oligometastasis in post-surgical pancreatic ductal adenocarcinoma (PDAC) patients with hepatic recurrence, which we call "oligo-like liver metastasis (OLLM)." Patients with OLLM have better post-recurrence prognosis and could therefore be eligible for surgical intervention.

Methods: A total of 121 PDAC patients who underwent radical resection, and who had an initial and single-organ metastasis to the liver, were analyzed. Independent prognostic factors for overall survival after recurrence (OSAR) were examined, and patients with all of these factors were defined as OLLM. The clinicopathological features and post-recurrent prognosis of OLLM patients were evaluated. In addition, a detailed analysis using the oligo-score, which was based on the prognostic factors, was performed.

Results: The prognostic analysis revealed that short recurrence-free interval (RFI) (<6 months), short stable disease interval (SDI) (≤3 months), and four or more recurrent tumors were independent poor prognostic factors. OLLM patients were defined as those with all three conditions: long RFI (≥6 months), long SDI (>3 months), and three or less recurrent tumors. OLLM patients had a significantly better prognosis for OSAR than non-OLLM patients (HR = 0.272, $p < 0.001$). Further analysis demonstrated that the OSAR of patients could be stratified using the oligo-score, which was calculated based on the prognostic factors.

Conclusion: We recommend that OLLM should be used to predict which patients are most likely to experience better post-recurrent prognosis after surgery with curative intent.

KEYWORDS
liver metastasis, oligometastasis, pancreatic cancer, prognosis, recurrence

1 | INTRODUCTION

The prognosis of patients with pancreatic ductal adenocarcinoma (PDAC) is extremely poor.[1,2] Even after radical resection, there is a high rate of postoperative recurrence, highlighting the grim prognosis; indeed, many patients are not eligible for re-resection.[3,4] In fact, the NCCN guidelines recommend systemic chemotherapy as the treatment for metastatic recurrent PDAC and do not recommend surgical intervention.[5] The term "oligometastasis" describes the pathogenic state characterized by a small number of metastases to a few organs.[6-9] Detection of oligometastasis provides an opportunity to surgically intervene and therefore improve prognosis.[6,7] In PDAC, however, recurrent lesions similar to those found in oligometastasis often progress rapidly to multi-organ metastases, and the post-recurrent prognosis is poor.[10-12] Therefore, the concept of oligometastasis has been difficult to apply to PDAC. Recently, there have been several reports of long-term survival in patients who underwent surgical intervention for PDAC lung metastases,[13,14] and a small number of reports for liver metastasis,[15-17] which is also a potential target for resection. Of these two malignancies, patients with lung metastases have a better prognosis after recurrence, with a longer recurrence-free interval (RFI; time from surgery to recurrence).[18,19] This finding suggested to us that there may be a subset of PDAC patients with a long RFI (and with oligometastasis that involved the liver) whose prognosis could be improved by surgical intervention for the liver metastasis.

Regardless of whether a lesion is primary or recurrent, the effect of chemotherapy is limited and/or temporary, and surgical resection is the only option that has the possibility of radical cure for PDAC patients. Thus, this study was designed to identify patients with oligometastasis that were particularly eligible for surgical intervention. For this purpose, the concept of "oligo-like liver metastasis" (OLLM) was proposed in this study. Thus, this study was designed to identify patients with oligometastasis that were particularly eligible for surgical intervention. For this purpose, the concept of "oligo-like liver metastasis" (OLLM) was proposed in this study. The essence of OLLM is that it consists of a limited number of metastatic lesions that remain localized in the liver for a certain period after recurrence (patients with long stable disease interval, SDI). This is in contrast to the general progressive characteristics of liver metastases of PDAC, which tend to grow rapidly, increase in size and number, and spread to other organs. The aim of this study was to select the patients with OLLM, for whom surgical intervention may offer a good long-term prognosis.

2 | PATIENTS AND METHODS

2.1 | Patients and ethical concerns

We began with 815 PDAC patients who underwent curative resection at National Cancer Center Hospital between January 2003 and December 2020. Patients who underwent surgical resection with macroscopical residual tumors or palliative surgery, or who already had metastasis to other organs, were excluded. Of the initial 815 patients, 576 had postoperative recurrence, and 132 of them initially had a recurrence in the liver. Excluding 11 of 132 patients with insufficient clinical data on the post-relapse course due to follow-up at other institutions or for other reasons, 121 patients were finally included in the analyses. The study was approved by the Ethics Committee of the National Cancer Center Hospital (Approval Number 2018-299) and was performed in accordance with the ethical standards of the Declaration of Helsinki and its later amendments.[20] There was no requirement for obtaining additional statements of informed consent from each patient in this current study.[21]

2.2 | Clinical data collection and patient follow-up

Clinical data including findings at perioperative and recurrent periods, as well as prognostic information, were collected from the database of the Department of Hepatobiliary and Pancreatic Surgery, National Cancer Center Hospital, in which clinical findings and short- and long-term outcomes were prospectively recorded. Preoperative evaluation for resectability status was performed anatomically, based on the current NCCN criteria,[5] according to imaging examination. Postoperative follow-up was based on the evaluation of tumor markers and imaging examination by contrast computed tomography every 3–6 months. Liver metastatic recurrence of PDAC was determined by detection of new tumors at the liver based on imaging examination. If the liver metastatic recurrence was detected, the disease was evaluated by imaging examinations every 2–3 months with or without chemotherapy. Assessment of disease status, including changes in the number and size of tumors, was performed based on RECIST criteria.[22] Postoperative patients were basically eligible for adjuvant chemotherapy (Most patients received S1, and some received gemcitabine.). Contrastingly, preoperative chemotherapy was administered for some patients only in recent years, in this cohort (gemcitabine and S1 were administered basically; some patients received gemcitabine and nab-paclitaxel.). Many patients were treated with systemic chemotherapy after relapse (FOLFORINOX, gemcitabine and nab-paclitaxel, and other agents).

2.3 | Definition of prognostic indicators

Four different prognostic indicators were evaluated in this study. Recurrence-free interval (RFI) was defined as the period from surgery to recurrence. Stable disease interval (SDI) was determined as the period during which the recurrent tumor remained stable disease (SD) on imaging examinations, following RECIST criteria. Specifically, SD was defined as lesions that fluctuated within 20% of baseline and in the absence of new lesions, while progressive disease (PD) was defined as lesions that increased by more than 20% or the development of new intra/extrahepatic metastatic lesions revealed by imaging studies. The time of overall survival (OS) was defined as the

period from surgery until death or from any cause or the last follow-up, and the time of overall survival after recurrence (OSAR) was that from recurrence to those, respectively. The relationship between each clinical indicator is summarized in Figure 1.

2.4 | Definition of oligo-like liver metastasis

Patient benefit from surgical intervention for recurrent liver metastases was defined as limited progression of the recurrent lesion accompanied by an improved prognosis after recurrence. To identify these conditions, we analyzed the post-relapse prognosis. The prognostic factors included histopathological tumor parameters associated with the primary PDAC such as tumor size and presence of lymph node metastasis, surgery-related factors such as the operation time, intraoperative blood loss, the microscopic residual tumor, and recurrence-related factors. Specifically, recurrence-related factors included RFI, SDI, and the number of recurrent tumors, in addition to tumor markers at the recurrence and whether patients received adjuvant chemotherapy or not.

2.5 | Statistics

Comparative analyses between two groups were performed using the chi-square test for nominal variables and Student's *t*-test for continuous variables. Prognostic analyses were performed for OSAR. Survival curves were obtained using the Kaplan–Meier method, and statistically analyzed using the log-rank test in the present series. Cox proportional hazard model was used to determine hazard ratios of each indicator, and to perform multivariate prognostic analyses using variables with *p*-values <0.05 in a univariate analysis. $p<0.05$ was considered as statistically significant in this study. All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria).[23]

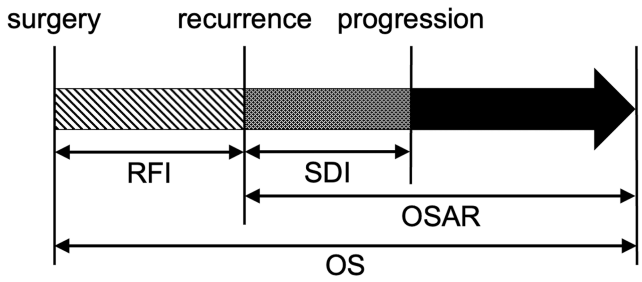

FIGURE 1 Summary of temporal clinical indices. RFI is the time from surgery to recurrence, SDI is the time from recurrence to tumor progression, and OSAR is time from the recurrence to the survival event. OS, overall survival; OSAR, overall survival after recurrence, RFI, recurrence-free interval; SDI, stable disease interval.

3 | RESULTS

3.1 | Patients' characteristics

The characteristics of patients included in this study are shown in Table 1. The histopathological features were consistent with those of primary PDAC; almost all patients had extra-pancreatic invasions (93.4%) and lympho-vascular invasions (98.3%), and 68.6% of patients had pathological lymph node metastasis. Regarding surgery-related issues, 88.4% of patients were preoperatively diagnosed with resectable tumors, and postoperative pathology revealed that 11 patients (9.1%) had microscopic residual tumors. In this cohort, neoadjuvant chemotherapy (NAC) was performed only for specific patients (9.1%) such as those with borderline resectable or unresectable PDAC; this contrasted with adjuvant chemotherapy (AC), which was performed for 39.7% of patients. Forty-one patients had a single recurrent tumor, while 52 were found with four or more recurrent tumors. Most of the patients with relapses had mainly been treated with systemic chemotherapy.

3.2 | Recurrence-free interval, stable disease interval, and recurrent tumor numbers are independent prognostic factors for overall survival after recurrence

To identify the post-recurrent prognostic factors for PDAC patients with liver metastatic recurrence, a prognostic analysis for OSAR was performed using various clinicopathological factors including RFI, SDI, and recurrent tumor numbers. We found that short RFI (less than 6 months; $p<0.001$, HR = 2.788), short SDI (3 months or less; $p<0.001$, HR = 4.953), and four or more recurrent tumors ($p<0.001$, HR = 2.259) were significant adverse prognostic factors, as were the presence of microscopic residual tumor ($p=0.048$, HR = 1.842) and LN metastasis ($p=0.032$, HR = 1.596) (Table 2). After multivariate prognostic analysis using these factors, short RFI ($p=0.008$, HR = 1.851), short SDI ($p<0.001$, HR = 4.149), and four or more recurrent tumors ($p=0.036$, HR = 1.597) were identified as independent adverse prognostic factors of OSAR.

3.3 | Clinicopathological features of patients with oligo-like liver metastasis

Based on the results of the prognostic analyses above, we used the following three criteria to define OLLM patients, who had a relatively better prognosis. First, a long RFI (6 months or more). Second a long SDI (more than 3 months). Third, a low number of recurrent tumors (three or less). Each factor was assigned a score of 1 point, and the total score was set as an oligo-score of 0 to 3 points (Figure 2). In other words, OLLM patients would have an oligo-score of 3 points, whereas non-OLLM patients would have between 0 and 2 points.

TABLE 1 Clinicopathological features of patients.

Variable		All patients ($n = 121$) (%)
Sex	Male	71 (58.7)
Age [range]		68.0 [33.0–83.0]
CA19-9 at surgery (U/mL) [range]		197.0 [0.0–11 420.0]
CEA at surgery (ng/mL) [range]		3.0 [0.6–54.7]
Tumor size (cm) [range]		3.2 [0.0–12.5]
Intraoperative blood loss (mL) [range]		727.0 [20.0–5467.0]
Operation time (min) [range]		440.0 [136.0–850.0]
Surgical procedure	PD	73 (60.3)
	DP	40 (33.1)
	TP	8 (6.6)
Microscopic residual tumor	Present	11 (9.1)
Extra-pancreatic invasion	Present	113 (93.4)
Lympho-vascular invasion	Present	119 (98.3)
Lymph node metastasis	Present	83 (68.6)
Artery invasion	Present	21 (17.4)
Portal vein invasion	Present	43 (35.5)
Resectability	Resectable	107 (88.4)
Neoadjuvant chemotherapy	Performed	11 (9.1)
Adjuvant chemotherapy	Performed	48 (39.7)
CA19-9 at recurrence (U/mL) [range]		271.5 [0.0–91 000.0]
CEA at recurrence (ng/mL) [range]		4.4 [1.0–118.0]
Recurrent tumor number	1	41 (33.9)
	2	20 (16.5)
	3	8 (6.6)
	≥4	52 (43.0)
Recurrent location in the liver	Hemilobe	65 (53.7)
	Bilobe	56 (46.3)
Treatment for recurrence	Chemotherapy	97 (80.2)
	Chemotherapy + Surgery/RFA	3 (2.5)
	Radiation ± Chemotherapy	2 (1.7)
	Non	19 (15.7)

Abbreviations: CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; DP, distal pancreatectomy; PD, pancreaticoduodenectomy; RFA, radiofrequency ablation; TP, total pancreatectomy.

The characteristics of OLLM and non-OLLM patients are summarized in Table 3. Of the 121 patients included in this study, 57 (47.1%) had long RFI, 53 (43.8%) had long SDI, and 69 (57.0%) had three or less tumors. Thirty patients (24.8%) who met all three of these criteria were defined as those with OLLM, and the other 91 were placed in the non-OLLM category. Compared to non-OLLM patients, those with OLLM had higher CA19-9 levels before surgery and at recurrence, a relatively low LN metastatic rate and a high rate of AC.

3.4 | Post-recurrent prognosis was better in OLLM patients, and definitively stratified by oligo-score

We next compared post-recurrent prognosis based on OLLM status. This revealed that OLLM patients had a significantly better prognosis than non-OLLM patients (median survival time (MST) 23.6 months vs. 8.0 months, respectively, HR = 0.272, $p < 0.001$, Figure 3A). Detailed prognostic analysis revealed that survival could be stratified according to the oligo-score (Figure 3B). The post-recurrence

TABLE 2 Prognostic analysis of overall survival after recurrence.

			Univariate			Multivariate		
Variable		*n*	HR	95% C.I.	*p*-value	HR	95% C.I.	*p*-value
Sex	Male	71	1.168	0.789–1.729	0.420			
Age	≥70	46	1.392	0.936–2.069	0.089			
CA19-9 at surgery (U/mL)	≥37	92	1.353	0.857–2.135	0.177			
CEA at surgery (ng/mL)	≥5.0	28	1.253	0.813–1.930	0.289			
Tumor size (cm)	≥3.0	84	1.384	0.914–2.097	0.110			
Intraoperative blood loss (mL)	≥727	61	1.022	0.695–1.503	0.910			
Operation time (min)	≥440	61	1.003	0.686–1.468	0.986			
Surgical procedure	PD	73	1.103	0.728–1.670	0.768			
	DP	40	1.000	–				
	TP	8	1.313	0.579–2.974				
Resectability	BR/UR	14	1.134	0.634–2.030	0.659			
Microscopic residual tumor	Present	11	1.842	0.971–3.495	**0.048**	1.756	0.912–3.382	0.092
Extra-pancreatic invasion	Present	113	1.239	0.574–2.677	0.569			
Lymph node metastasis	Present	83	1.596	1.040–2.449	**0.032**	1.159	0.748–1.797	0.509
Artery invasion	Present	21	1.18	0.716–1.944	0.499			
Portal vein invasion	Present	43	1.251	0.840–1.863	0.253			
Adjuvant chemotherapy	Not performed	73	1.444	0.936–2.069	0.058			
CA19-9 at recurrence (U/mL)	≥37	92	1.421	0.844–2.393	0.169			
CEA at recurrence (ng/mL)	≥5.0	41	0.943	0.600–1.481	0.791			
RFI (month)	<6	64	2.788	1.861–4.176	**<0.001**	1.851	1.171–2.923	**0.008**
SDI (month)	≤3	68	4.953	3.158–7.768	**<0.001**	4.149	2.597–6.629	**<0.001**
Recurrent tumor number	≥4	52	2.259	1.520–3.358	**<0.001**	1.597	1.026–2.459	**0.036**

Abbreviations: BR, borderline resectable; CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; C.I., confidence interval; DP, distal pancreatectomy; HR, hazard ratio; PD, pancreaticoduodenectomy; RFI, recurrence-free interval; SDI, stable disease interval; TP, total pancreatectomy; UR, unresectable.

Statistically significant differences are shown as bold values.

Factor	Indicator	Point
Recurrence-free interval (RFI)	≥ 6 months	1
Stable disease interval (SDI)	> 3 months	1
Recurrent tumor number	≤ 3	1
Total (oligo-score)		**0-3**

FIGURE 2 Calculation of oligo-score. Oligo-score is simply calculated as a total score by the RFI, SDI, and number of recurrent tumors. RFI, recurrence-free interval; SDI, stable disease interval.

MSTs were 5.9, 7.8, 14.1, and 23.6 months for oligo-scores of 0, 1, 2, and 3, respectively; the differences between each of the survival curves were significant ($p < 0.05$). Hence, our definition of OLLM is an effective approach for identifying a patient group that is likely to have good prognosis after recurrence.

4 | DISCUSSION

This study was conducted to identify PDAC patients with recurrent liver metastasis who have a good prognosis after recurrence, and who could therefore be expected to benefit from surgical intervention. For this purpose, we first evaluated the prognostic indicators for overall survival after recurrence. This revealed that short RFI, short SDI, and four or more recurrent tumors were independent adverse prognostic factors. We therefore based the oligo score opposite these adverse prognostic factors (longer RFI and SDI, and ≤3 recurrent tumors). We designated OLLM patients as those meeting all three criteria (oligo-score of 3) and non-OLLM patients as those with oligo-scores of 0–2. Further analyses revealed that OLLM patients had a significantly better prognosis than non-OLLM patients, and that prognoses were obviously stratified by oligo-score.

TABLE 3 Characteristics of OLLM and non-OLLM.

Variable		OLLM ($n=30$) (oligo-score: 3)	Non OLLM ($n=91$) (oligo-score: 0–2)	p-value
Sex	Male	17 (56.7)	54 (59.3)	0.833
Age [range]		68.0 [45.0–82.0]	68.0 [33.0–83.0]	0.900
CA19-9 at surgery (U/mL) [range]		54.5 [0.0–2887.0]	238.0 [0.0–11420.0]	**0.012**
CEA at surgery (ng/mL) [range]		2.9 [0.6–54.7]	3.3 [0.8–43.8]	0.532
Tumor size (cm) [range]		3.0 [1.0–8.5]	3.5 [0.0–12.5]	0.119
Intraoperative blood loss (mL) [range]		560.0 [101.0–2470.0]	763.0 [20.0–5467.0]	0.411
Operation time (min) [range]		443.0 [210.0–654.0]	438.0 [136.0–850.0]	0.909
Surgical procedure	PD	19 (63.3)	54 (59.3)	0.942
	DP	9 (30.0)	31 (34.1)	
	TP	2 (6.7)	6 (6.6)	
Microscopic residual tumor	Present	1 (3.3)	10 (11.0)	0.289
Extra-pancreatic invasion	Present	27 (90.0)	86 (94.5)	0.408
Lympho-vascular invasion	Present	30 (100.0)	89 (97.8)	>0.999
Lymph node metastasis	Present	15 (50.0)	68 (74.7)	**0.022**
Artery invasion	Present	4 (13.3)	17 (18.7)	0.590
Portal vein invasion	Present	9 (30.0)	34 (37.4)	0.516
Resectability	Resectable	27 (90.0)	80 (87.9)	>0.999
Neoadjuvant chemotherapy	Performed	4 (13.3)	7 (7.7)	0.463
Adjuvant chemotherapy	Performed	18 (60.0)	30 (33.0)	**0.011**
CA19-9 at recurrence (U/mL) [range]		72.0 [0.0–4276.0]	407.0 [0.0–91000.0]	**0.010**
CEA at recurrence (ng/mL) [range]		4.6 [1.5–13.7]	4.3 [1.0–118.0]	0.947
RFI (month)	≥6	30 (100.0)	27 (29.7)	**<0.001**
SDI (month)	>3	30 (100.0)	23 (25.3)	**<0.001**
Recurrent tumor number	1	20 (66.7)	21 (23.1)	**<0.001**
	2	5 (16.7)	15 (16.5)	
	3	5 (16.7)	3 (3.3)	
	≥4	0 (0.0)	52 (57.1)	
Recurrent location in the liver	Hemilobe	28 (93.3)	37 (40.7)	**<0.001**
	Bilobe	2 (6.7)	54 (59.3)	
Treatment for recurrence	Performed	29 (96.7)	73 (80.2)	**0.041**

Abbreviations: CA19-9, carbohydrate antigen 19–9; CEA, carcinoembryonic antigen; DP, distal pancreatectomy; OLLM, oligo-like liver metastasis; OS, overall survival; OSAR, overall survival after recurrence; PD, pancreaticoduodenectomy; RFA, radiofrequency ablation; RFI, recurrence-free interval; SDI, stable disease interval; TP, total pancreatectomy.

Statistically significant differences are shown as bold values.

Prior to the prognostic analysis, we had to determine the cut-off values for RFI and SDI. To achieve this, we divided patients into groups with RFI or SDI cutoff values of 3, 6, and 12 months, and compared the OSAR curves for each of these values. The difference in OSAR for RFI was greatest with the cutoff value of 6 months (Figure S1), while for SDI, the difference was most pronounced with the cutoff value of 3 months (Figure 4). We performed a similar analysis to determine the cutoff value for the number of recurrent tumors. We divided patients into groups with one, two, three, and four or more recurrent tumors and compared OSAR curves. There was a significant difference in survival between patients with three or fewer tumors and those with four or more tumors; four or more was therefore set as the cutoff value (Figure S2). Since three or fewer tumors has been used to define oligometastasis for several cancer types, we think it is reasonable to consider surgical resection for patients with three or less liver metastases.[7]

We believe that further consideration is needed regarding the significance of SDI, as shown in Figure 4, where cases with SDI > 12 months have a particularly favorable prognosis. In the context of conversion surgery for unresectable pancreatic cancer patients, it is generally accepted that the longer the duration of chemotherapy, the better the prognosis after surgery.[24] Similarly, the longer the SDI, the better the prognosis, i.e., the more strictly we narrow down the conditions, the more we can narrow down

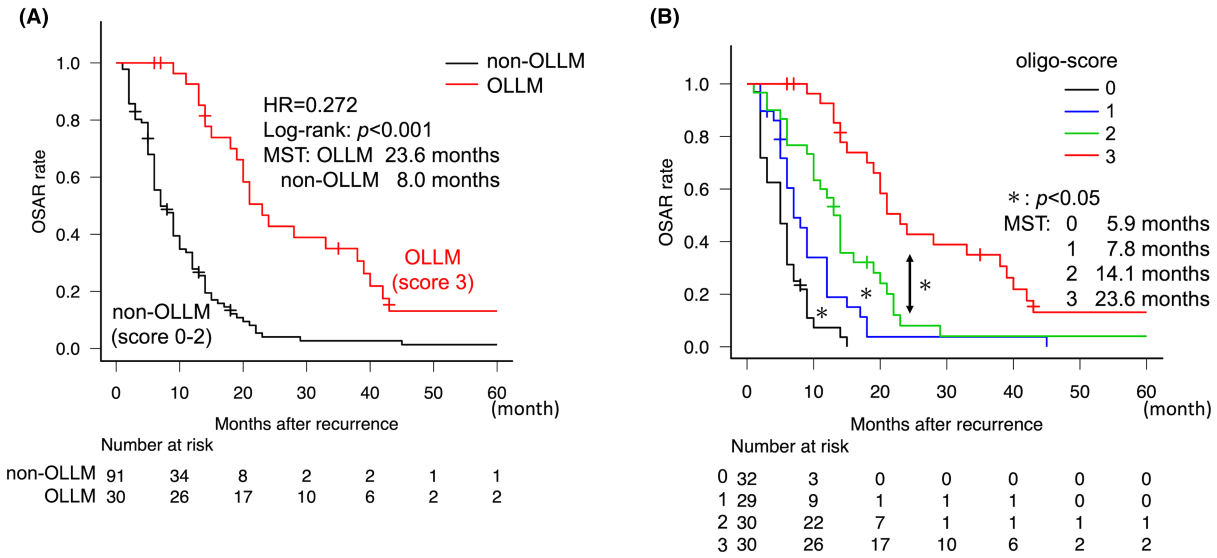

FIGURE 3 Prognostic analysis of overall survival after recurrence based on oligo-like liver metastasis status. (A) The post-recurrent prognosis of patients in the OLLM (oligo-score: 3) group was significantly better than that of patients in the non-OLLM (oligo-score: 0–2) group (HR = 0.272, $p < 0.001$). (B) The survival curves for each group were clearly stratified by oligo-score ($p < 0.05$). MST, median survival time; OLLM, oligo-like liver metastasis; OSAR, overall survival after recurrence.

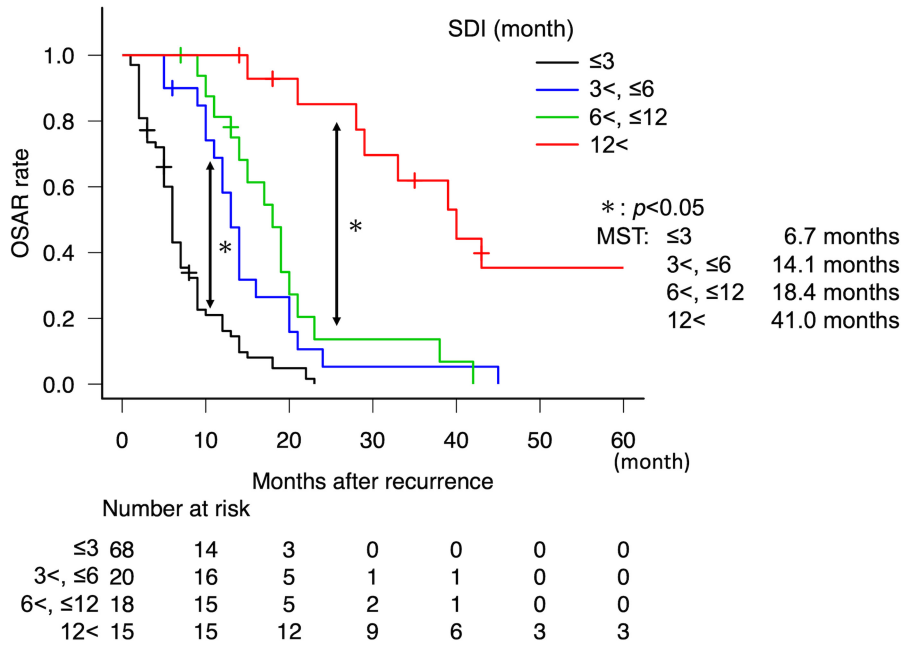

FIGURE 4 Preliminary analysis of stable disease interval and post-recurrent prognosis. The post-recurrent prognoses were compared in each patient group divided based on the range of SDI. The difference in survival curves for OSAR was most pronounced with an SDI cutoff value of 3 months (HR = 4.953, $p < 0.001$). MST; median survival time; OSAR, overall survival after recurrence; SDI, stable disease interval.

the cases with a good prognosis. However, this approach would result in a small number of special cases (SDI > 12 months in only 15 cases out of the total number of cases) being included in the target group, which would limit the versatility of this approach in actual clinical practice. Therefore, in this study, we set 3 months of SDI as the cutoff to include as many cases as possible. The factors influencing the treatment indications for OLLM are multifaceted. They encompass not only the biological behavior of the tumor but also the efficacy of anticancer therapies. There is no universally accepted definition for OLLM or a specific cutoff value to identify it. In this study, we proposed a scoring system for OLLM that is not simply defined by a single parameter, but rather by multiple parameters to assess the degree of progression of OLLM. The proposal was presented to allow for future considerations. The setting of each cutoff

and the weighting assigned to each parameter are not conclusively addressed by this study alone. These are important issues to be considered in the future.

We also found that OS was significantly improved in the OLLM group (MST 45.2 months) compared to the non-OLLM group (MST 13.6 months, Figure S3A). Furthermore, comparison of the survival curves by oligo-score showed a notable stratification with a remarkable difference ($p < 0.001$) for each (Figure S3B). This effect was even pronounced than OLLM-associated improvement in OSAR discussed above. Thus, we believe that our OLLM classification (which can identify recurrent PDAC patients likely to have an improved prognosis in terms of both OS and OSAR) will have significant utility in clinical practice.

This study also compared tumor status at recurrence in OLLM and non-OLLM patients. Two-thirds of patients who fulfilled the OLLM criteria had a single recurrent tumor, and 28 of 30 (93.3%) patients had tumors localized in the hemilobe of the liver. Comparing the status at the time of tumor progression after recurrence ("PD" in RECIST criteria), we found significantly more patients with three or fewer tumors that were localized in the liver in the OLLM group (47.4%) compared the non-OLLM group (16.1%, $p = 0.011$, detailed data not shown). These observations might reflect the less malignant nature of OLLM tumors, and there is no clinical conflict in considering surgical intervention for such localized tumors. Although surgical resection is expected to further improve the long-term outcome for the good prognosis group defined by OLLM, there is currently no sufficient evidence to support this hypothesis.[16,25,26] Prospective and large-cohort validation will be required to resolve this question. In any case, clarification of these issues is urgently needed for pancreatic cancer patients, as the deployment of aggressive recurrence therapy (including surgical intervention with curative intent) is already being discussed by physicians. We believe that the novel OLLM criteria and oligo-score proposed in this study will help identify patients that may benefit from recurrence therapy.

There are several limitations to acknowledge in this study. First, it was retrospective, and the requirement for patients with postoperative recurrence in a single organ (i.e., the liver) limited the number of enrolled individuals. Second, preoperative chemotherapy had rarely been performed during this study period. This is due to the fact that most of the patients included in the study had resectable PDAC, which reflects the historical background. A relatively small number of patients also received postoperative adjuvant chemotherapy. This is because the study focused on patients with liver metastatic recurrence, many of the liver metastases recurred early after surgery (≤6 months) as shown in the results, and many of the patients had recurred before the introduction of chemotherapy. In addition, SDI is included as part of OSAR; this might lead to a potential confounding bias when SDI is used as a prognostic factor for OSAR. Nevertheless, in practical decision-making, it is useful to look for opportunities for surgical intervention while monitoring the post-recurrent course, such as SDI. In conclusion, we have proposed the novel concept of OLLM in patients with PDAC. Although the results of this study should be validated prospectively, we think they represent a significant step towards improving the current poor outcomes for PDAC patients with recurrent liver metastasis.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest for this article.

ETHICS STATEMENT

Approval of the research protocol: The study was approved by the Ethics Committee of the National Cancer Center Hospital (2018-299).

Informed consent: The requirement for informed consent was waived owing to the anonymous nature of the data.

Registry and the registration no. of the study/trial: N/A.

Animal studies: N/A.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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