A Possible Definition of Oligometastases in Pancreatic Cancers and Their Survival Outcomes

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Abstract

Background: Among advanced metastatic cancers, oligometastatic cancers (OM) are defined as having limited visible metastases, possibly associated with relatively better survival outcomes. We attempted to identify cases that are in line with the concept of OM among unresectable metastatic pancreatic cancer, using a retrospective cohort.

Methods: A total of 130 cases with unresectable metastatic pancreatic cancer received non-curative surgery (palliative surgery or staging laparotomy) from April 2001 to December 2019. Metastatic sites, clinicopathological information, and surgical outcomes were collected to reveal definition of OM.

Results: Primary tumor sites were pancreatic head in 80 cases and others in 50 cases. Performed operations were gastrointestinal tract bypass in 68 cases and staging laparotomy in 62 cases. Based on the survival outcome differences, OM criteria were defined as single organ metastasis, a few countable lesions (4 or fewer organ metastases or limited peritoneal metastases) and low serum CA19-9 level (< 2000 U/ml). The median overall survival time (MST) after non-curative surgery of OM cases ($n=54$) was 13.0 months and was significantly better than non-OM cases ($n=76$) (MST:8.4months, $P = 0.003$).

Conclusion: We propose single organ metastasis of limited tumor volume (H1 or P1-2 by the Japanese Society of Cancer of the Colon and Rectum classification) and low serum CA19-9 (< 2000 U/ml) as a new criteria for OM.

Synopsis

Oligometastatic cases for pancreatic cancers could be defined by both visible metastatic status and serum CA19-9 level. These cases have greater chances for prolongation of survival through multimodal treatments compared with multiple metastatic cases.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is the fourth reason for estimated cancer deaths in the United States[1]. PDAC remains to be lethal disease in that the majority of patients present with distant metastases at the time of diagnosis[2]. These patients are usually not indicated for surgery and the prognosis is deemed dismal.

In 1995, Hellman et al. proposed the idea of oligometastasis of advanced malignancies, which is defined as a state of limited metastases[3]. The basis of this concept is that a particular group of patients could benefit from long-term survival through surgical resection after precise imaging and appropriate multimodal treatment. For instance, hepatic resection of limited colorectal liver metastases demonstrated 5-year overall survival (OS) of 28-58% [4-6]. Local therapy was also reported to improve the OS of the oligometastatic non-small cell lung cancer patients[7]. Furthermore, Ozawa H et al. reported that the 5-

year OS rate of the patients treated with curative resection of limited peritoneal metastases was significantly higher than patients with diffuse peritoneal metastases[8].

As for the oligometastasis in PDACs, there are no established criteria or consensus of diagnosis and treatment strategy. Damanakis AI et al. proposed a definition of oligometastases in PDACs as the cases with single organ metastases, the presence of ≤ 4 metastases in liver or lung and CA19-9 baseline < 1000 U/ml. These patients survived significantly longer than other metastatic unresectable PDACs[9]. However, they failed to mention peritoneal metastases. The current study attempted to create a new definition of oligometastasis which takes peritoneal metastases into consideration among other types of metastasis, using our metastatic PDAC patients cohort.

Materials And Methods

Patient cohort

To ensure accurate evaluation of peritoneal metastases, we retrieved 140 consecutive cases of unresectable metastatic PDAC patients who received staging laparotomy or gastrointestinal bypass operation at Nagoya University Hospital (Nagoya, Japan) from April 2001 to December 2019. Ten cases with multi-organ metastases were excluded, and the remaining 130 patients with single organ metastasis at the diagnosis were enrolled. Preoperative serum CA19-9 values had been recorded in all patients. The clinical background features were summarized in **Table 1**. Because there were only two metastases to lung cases, we excluded it from the definition of OM.

Liver metastases

Information of liver metastases was collected from preoperative CT, MR images and operation records. Following the criteria of the Japanese Society of Cancer of the Colon and Rectum (JSCCR)[10], liver metastases were classified into four categories. H0: No liver metastasis, H1: 1-4 metastatic tumors, all of which are 5 cm or less in maximum diameter, H2: Other than H1 or H3, H3: Five or more metastatic tumors, at least one of which is more than 5cm in maximum diameter. We also investigated an association between the number of liver metastasis and survival outcomes. We then tried to find which of the categories can be an ideal threshold of relatively favorable survival outcomes.

Peritoneal metastases

Information of peritoneal metastases was also collected from preoperative CT images and operation records. Peritoneal metastases were also classified into four categories following the criteria of JSCCR[10]. P0: no peritoneal metastasis, P1: metastasis localized to adjacent peritoneum, P2: limited metastasis to distant peritoneum, P3: diffuse metastases to distant peritoneum. We again tried to find which of the categories is most appropriate as a threshold to identify patients with relatively favorable survival outcomes.

Statistics

Continuous variables were analyzed by the Mann-Whitney U test as a non-parametric test and Student's *t*-test (two-tailed) as a parametric test. Categorical variables were analyzed by Fisher's exact test. OS was defined as the time from non-curative surgery to the date of death of PDAC. The association of OM status and clinical factors with OS was evaluated using the log-rank test or Cox proportional hazards model. $P < 0.05$ was considered statistically significant for all statistics. Statistical analyses were carried out using JMP 15 software (SAS Institute, Cary, NC, USA).

Results

Liver metastasis

Among 58 liver-metastatic cases, survival curves of three categories (H1, H2, H3) were compared in **Figure 1**. OS of H1 was significantly longer than others. The median survival time (MST) was 9.8 months (95% CI: 6.8-13 months) in H1 and 4.8 months (95% CI: 3.4-7.3 months) in H2-3 ($P=0.001$). On the other hand, no significant difference was detected between H1-2 (MST: 7.5 months, 95% CI 5.9-9.8 months) and H3 (MST: 4.8 months, 95% CI 1.3-14.4) ($P=0.537$). H1 cases solely seemed to have a potential of relatively favorable prognosis in liver-metastatic cases. Survival curves based on the number of liver metastases were shown in **Figure 2a**. Although the cases with solitary liver metastasis did not show significantly longer OS than others, the cases with two or fewer liver metastases demonstrated significantly longer OS than others (**Figure 2b**, $P=0.001$). The cases with four or fewer liver metastases also showed better OS compared to five or more. (**Figure 2c**, $P=0.001$).

Peritoneal metastasis

Among 70 peritoneum-metastatic cases, survival curves of three categories (P1, P2, P3) were compared in **Figure 3**. No significant difference was found between P1 and P2-3, whereas P1-2 cases tended to have favorable OS than P3 (MST: 14.9 months, 95% CI 8.4-23.4 months in P1-2 vs. 9.7 months, 95%CI 8.4-15.8 months in P3, $P=0.140$).

Tumor markers

As for serum tumor markers, we chose CA19-9 as the most frequently available and reliable tumor marker of PDACs in this study. Hartwig et al. reported CA19-9 predicts resectability, stage of disease, as well as survival in patients with pancreatic adenocarcinoma[11]. To detect an optimal cut-off of preoperative serum CA19-9 value, ROC curve analyses were performed for five months survivors, ten months survivors, or 20 months survivors-specific settings after non-curative operations. We chose 20 months survivors-specific ROC curve because of the most significant area under the curve (0.661) compared with others (0.576 in five months survivors, 0.523 in 10 months survivors). The optimal cut-off value for predicting survival of ≥ 20 months was 2000 U/ml. The sensitivity and specificity of this setting were 100% and 40%, respectively (**Figure 4**).

Definition of oligometastatic cases

As a result, we defined OM cases as single organ metastasis (H1 or P1-2) and low serum CA19-9 (< 2000 U/ml). All cases were classified according to the number of metastatic organs, metastatic sites and serum CA19-9 (**Figure 5**). Finally, 130 patients with single organ metastasis were divided into OM cases (n=54) and non-OM cases (n=76). The survival curves according to the OM criteria were shown in **Figure 6**. OM cases had significantly longer OS than non-OM cases (MST: 13.0 months, 95% CI 8.8-18.4 months vs. 8.4 months, 95% CI 6.3-9.7 months, $P=0.003$). Clinical characteristics of both groups were compared in **Table 2**. No difference was found in age, gender, operation procedure, serum CEA and tumor location, while significantly greater proportion of OM patients underwent chemotherapy ($P=0.015$). Thus, we compared OM cases with non-OM cases in the cohort that underwent chemotherapy and found that the OM cases showed significantly better OS outcomes (**Figure 7**). On the contrary, there was no difference in survival between the two groups in the cohort that received no chemotherapy.

Discussion

In some malignancies, such as colorectal, kidney and lung cancers, there is growing body of evidence that a metastasectomy can improve survival outcomes of selected patients[4-7, 12-14]. For colorectal cancers and kidney cancers, surgical metastasectomy is the treatment of choice in the National Comprehensive Cancer Network (NCCN) guidelines. In non-small-cell lung cancer, Gomez et al. showed local consolidative therapy with radiotherapy or surgery improved both PFS and OS of OM cases[7]. In colorectal cancer, Kobayashi et al. proposed synchronous resection of localized peritoneal metastasis improved survival outcomes[13].

In PDAC with distant metastases, Tachezy M et al. suggested a survival benefit for undergoing simultaneous pancreas and liver resection[15]. Several prior studies have revealed that the resection of lung and liver metastases prolong prognosis in PDAC[15-17]. Kandel et al. considered oligometastasis can be defined as the status of two or fewer metastatic tumors[18]. Demanakis et al. reported that oligometastasis could be defined as four or fewer metastatic tumors[9]. They insist that patients with limited metastatic status have a chance to get a good prognosis by metastasectomy, even for PDACs.

Another standard requirement of oligometastases is a low level of serum tumor markers. Although we defined the optimal cut-off value of preoperative serum CA19-9 as 2000 U/ml, it does not appropriately work for Lewis antigen-negative patients. Luo et al. proposed that CEA and CA125 can be applied as biomarkers in patients with no CA19-9 secretion from PDACs[19]. Wei et al. proposed that tumor makers' criteria was at least a 50% reduction of serum CA125 or CEA levels if the patient had a normal CA19-9 level before conversion chemotherapy[16]. Basically, we need other rules for these patients.

Our analyses revealed that four or fewer liver metastases have a good prognosis. This is the same cut-off number as previous retrospective reports[9, 15, 20]. As for peritoneal metastases, some studies mentioned that only localized peritoneal metastasis can be included in oligometastases and can be treated[21, 22]. It implies that peritoneal metastasis basically has a poor prognosis, and incomplete metastasectomy does not affect the survival outcomes. In colorectal cancers, synchronous resection of

localized peritoneal metastasis improved survival outcomes, while the diffuse or larger size (> 20 mm) peritoneal metastases were independent poor prognostic factors[13]. Staging laparoscopy of PDAC cases sometimes reveals unsuspected peritoneal dissemination, as Karabicak et al. reported (19%)[23]. At that time, it is still unknown peritoneum metastases removal affects the patient's survival or not.

The period when we examined it is long, and there is the change of the standard treatment, too, and chemotherapy varies in this examination. With evolution of the chemotherapy, a recent case tends to have a good prognosis. However, as for the prognostic difference by OM, the developing front of the chemotherapy is more remarkable. It may be said that the situation of tumor determines OM than contents of the treatment intervention.

Treatment of OM cases of PDAC is still controversial. The current study suggests that patients with OM status could benefit from systematic chemotherapy. This may be an important finding that should however be verified with a larger cohort of patients. Non-OM patients with sufficient performance status should not be denied the opportunity to receive chemotherapy at this time. Since the study population does not include patients who underwent metastasectomy, we could not make any recommendation on whether or not to consider metastasectomy for PDAC. This issue could be solved from the viewpoint of conversion surgery, for which only responders to the chemotherapy are usually considered eligible.

Our study has some limitations. First, patient selection bias can exist because of the retrospective nature of the study. Most of subjects in this cohort had relatively good performance status enough to receive palliative or probe laparotomy without postoperative complications. Secondly, we did not evaluate metastases outside of the liver and peritoneal surface because of the small number of such cases. Thirdly, we did not evaluate the case that a bypass does not need with distant metastasis diagnosed without laparotomy. Fourthly, considerations for Lewis antigen-negative patients have not been made at this time. Unlike the case with other types of cancer, we have not discussed on relevance of metastasectomy. This is in part attributable to the particular poor prognosis of PDAC, but metastasectomy could still be an issue for future debate, pending improvements in systemic treatment.

In conclusion, PDAC OM cases can be identified by limited visible metastatic sites with moderately low serum CA19-9.

Declarations

Ethics approval and consent to participate

All methods were carried out in accordance with relevant guidelines and regulations. The institutional review board of the Nagoya University Graduate School of Medicine approved (registration no. 2020-0344) in Oct 2020. By opt-out, informed consent was obtained from all subjects, or from parents and / or legal guardians if subjects were under the age of 18.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patients' privacy policy but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

M.Y., M.H. and S.Y. designed the project. M.Y. and M.H. collected clinical data and analyzed them. M.H., S.Y., F.S., H.T. and Y.I. followed up the patients. D.S., N.H., M.K., C.T., G.N, M.K. and Y.K. reviewed the manuscript. S.Y. and Y.K. prepared the materials and analytic tools. M.Y. and M.H. wrote the manuscript.

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Authors' information (optional)

Not applicable.

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Tables

Due to technical limitations, table 1-2 is only available as a download in the Supplemental Files section.

Figures

Figure 1

Figure 1

Survival curves of liver metastatic cases were shown. a: Survival curves of three categories (H1, H2, H3) were drawn (H1 vs. H2 ($P < 0.001$), H2 vs. H3 ($P = 0.261$), H1 vs. H3 ($P = 0.229$)). b: Survival curves of H1 cases and H2-3 cases were compared. c: Survival curves of H1-2 cases and H3 were compared.

Figure 2

Figure 2

a: Survival curves of the liver metastatic cases were compared depending on the number of tumors. b: The survival curve of the cases with two or fewer liver metastases was compared with others. c: The survival curve of the cases with four or fewer liver metastases was compared with others.

Figure 3

Figure 3

Survival curves of peritoneal metastatic cases were shown. a: Survival curves of three categories (P1, P2, P3) were drawn(P1 vs. P2 (P=0.844), P2 vs. P3 (P=0.188), P1 vs. P3 (P=0.251)).. b: Survival curves of P1 cases and P2-3 cases were compared. c: Survival curves of P1-2 cases and P3 cases were compared.

Figure 4

Figure 4

a: ROC curve analyses were performed for 20 months survivors-specific setting after non-curative operations. The optimal cut-off of CA19-9 was 2000 U/ml. b: Survival curves of the cases with CA19-9 ≥ 2000 U/ml and CA19-9 < 2000 were compared.

Figure 5

Figure 5

All cases were classified according to the number of metastatic organs, metastatic sites and CA19-9.

Figure 6

Figure 6

Survival curves of the OM group and the non-OM group were shown.

Figure 7

OM vs non-OM
OM(H1,P1,P2,CA19-9<2000)

Figure 7

Survival curves of the OM group and the non-OM group chemotherapy-treated were compared in both chemotherapy-treated and non-treated cases.

Supplementary Files

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