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Stereotactic body radiation therapy for the primary tumor and oligometastases versus the primary tumor alone in patients with metastatic pancreatic cancer

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Abstract

Background Local therapies may benefit patients with oligometastatic cancer. However, there were limited data about pancreatic cancer. Here, we compared the efficacy and safety of stereotactic body radiation therapy (SBRT) to the primary tumor and all oligometastases with SBRT to the primary tumor alone in patients with metastatic pancreatic cancer.

Methods A retrospective review of patients with synchronous oligometastatic pancreatic cancer (up to 5 lesions) receiving SBRT to all lesions (including all oligometastases and the primary tumor) were performed. Another comparable group of patients with similar baseline characteristics, including metastatic burden, SBRT doses, and chemotherapy regimens, receiving SBRT to the primary tumor alone were identified. The primary endpoint was overall survival (OS). The secondary endpoints were progression frees survival (PFS), polyprogression free survival (PPFS) and adverse events.

Results There were 59 and 158 patients receiving SBRT to all lesions and to the primary tumor alone. The median OS of patients with SBRT to all lesions and the primary tumor alone was 10.9 months (95% CI 10.2–11.6 months) and 9.3 months (95% CI 8.8–9.8 months) ($P < 0.001$). The median PFS of two groups was 6.5 months (95% CI 5.6–7.4 months) and 4.1 months (95% CI 3.8–4.4 months) ($P < 0.001$). The median PPFS of two groups was 9.8 months (95% CI 8.9–10.7 months) and 7.8 months (95% CI 7.2–8.4 months) ($P < 0.001$). Additionally, 14 (23.7%) and 32 (20.2%) patients in two groups had grade 3 or 4 treatment-related toxicity.

Conclusions SBRT to all oligometastases and the primary tumor in patients with pancreatic cancer may improve survival, which needs prospective verification.

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Keywords Oligometastases, Pancreatic cancer, Local therapy, Stereotactic body radiation therapy

Background

Pancreatic cancer is the fourth and sixth leading cause of cancer-related death in the US and China [1, 2], where the mortality increases slightly. Although surgery is the curative option for pancreatic cancer, only 15–20% patients were eligible for surgical resection at the diagnosis [3–5]. About 50% of patients had metastatic pancreatic cancer at the first presentation, and the current standard of care systemic treatment is chemotherapy alone but with dismal outcomes.

Oligometastases, defined as less than five metastases in an organ, has been considered as a clinically significant condition between local and systemic disease, which has been proposed with potential of curability via local therapy [6]. Though resections of liver or lung oligometastases of pancreatic cancer may contributed to improved survival [7], these patients were highly selective and reports were limited to a small number of patients. Therefore, this option for pancreatic cancer still remains controversial, and when it is applied indiscriminately to any patient with metastatic disease, it may not be beneficial. Additionally, emerging evidence has shown that current treatment paradigm demands alterations due to a unique biologically condition of oligometastatic pancreatic cancer [8].

Recently, studies have shown that stereotactic body radiation therapy to all oligometastases could improve survival compared to standard of care [9, 10], especially in prostate and lung cancer [11, 12]. Additionally, several studies have demonstrated that the delivery of radiation to all involved lesions would most likely better promote antigen presentation, improve immune access, and reduce the immunosuppressive barrier effects of bulky lesions not only in one area, but in all areas of disease. All of these effects cannot be optimally achieved using the current, single-site strategy that is designed to promote abscopal effects. Hence, it was advocated that comprehensive irradiation of multiple/all lesions may enhance the likelihood of obtaining meaningful clinical outcomes, especially when the synergy of radiotherapy and immunotherapy does exist [13]. Therefore, we aim to compare outcomes of stereotactic body radiation therapy to all oligometastases and the primary tumor with the primary tumor alone of pancreatic cancer.

Methods

Study design and participants

It was a retrospective study. Eligible patients were aged 18 years or older with a histopathologic diagnosis of pancreatic ductal adenocarcinoma with oligometastases, which was less than five lesions in an organ or a site. Oligometastases were determined by PET-CT via multidisciplinary approach and assessed by two independent radiologists. Additional inclusion criteria were patients without surgical resection, adequate liver, kidney and bone marrow function. These laboratory tests should be completed within a week of treatment initiation. Exclusion criteria were history of radiotherapy or interventional treatment to the primary tumor and metastatic lesions, and immunotherapy or targeted therapy, multiple-site metastases defined as more than five lesions or confirmed in more than one organ or site, periampullary cancer, neuroendocrine tumors, or cholangiocarcinoma. All patients were presented at a multidisciplinary pancreas board meeting where management decisions were discussed. Independent physicians performed prospective follow-up, and assessed the outcomes and safety of stereotactic body radiation therapy (SBRT) and chemotherapy. All patients provided written informed consents before the study. Outcomes of patients receiving SBRT for the all oligometastases and primary tumor were compared with those receiving SBRT for the primary tumor alone. The study was conducted in accordance with Good Clinical Practice guidelines. And it was approved by the institutional review board of our hospital.

Procedures

SBRT was performed *via* CyberKnife, an image-guided frameless stereotactic robotic radiosurgery system (Accuray Corporation, Sunnyvale CA). Gross tumor volume (GTV) was defined as a radiographically evident gross disease. A 2–5 mm margin expansion on GTV formed planning target volume (PTV). Dose constraints of organs at risk were referred to the American Association of Physicists in Medicine guidelines in TG-101. Target volumes delineations were reviewed and checked by a radiation oncologist and a radiologist for accuracy. 90% of PTV should be covered by the prescription dose. The prescription isodose line was limited to 70–75%, which would restrict the tumor D_{max} [14]. Prescription doses were determined according to the sites of lesions.

Chemotherapy was initiated two to three weeks after SBRT, which included gemcitabine- or 5-FU-based regimen. Most of patients received gemcitabine (1000 mg/m^2) plus nab-paclitaxel (125 mg/m^2) (days 1 and 8, every 14 days for 6–8 cycles) or mFOLFIRINOX (oxaliplatin 85 mg/m^2, leucovorin 400 mg/m^2, irinotecan 150 mg/m^2 at day 1, followed by 46 h continuous infusion of 5-fluorouracil 2400 g/m^2, every 14 days for 6–8 cycles).

The primary tumor and metastatic lesions were evaluated and measured before and after treatment. Imaging examinations were performed every 2 months.

Evaluations were based on RECIST version 1.1 by a blinded independent central imaging vendor. Tumor biomarker (CA19-9) was tested every month. Laboratory evaluations were performed in each cycle of chemotherapy and one week after completion of chemotherapy.

Furthermore, it was clarified that a better response was found in patients with a baseline CA19-9 level of <200U/mL after neoadjuvant therapy [15]. Therefore, baseline CA19-9 level was stratified with <200U/mL and ≥200 U/mL in our study.

Outcomes

The primary endpoint for the study was overall survival (OS), defined as the time from SBRT to death. Progression was defined according to response evaluation criteria in solid tumor (RECIST) as the appearance of one or more new lesions or a 20% increase in the sum of diameters of target lesions with an absolute increase of at least 0.5 cm. [16]. The secondary endpoints were progression free survival (PFS), calculated by the time from SBRT until documentation of any clinical or radiological disease progression or death. Polyprogression was identified when the number of progressing metastatic tumors exceeded 5 lesions and marks the transition from oligometastatic to polymetastatic status. As a result, polyprogression free survival (PPFS) was the time from SBRT to the identification of the number of lesions of more than 5, or death. Furthermore, treatment-related adverse events were determined by Common Terminology Criteria for Adverse Events (version 4.0) throughout the whole treatment.

Statistical analysis

Demographic, disease and treatment characteristics were summarized with frequency and percentage for categorical variables, and median and interquartile range (IQR) for continuous variables. Fischer's exact test or χ^2 test was used for analysis of the categorical binary variables. While normally or non-normally distributed continuous covariates were compared by Student t-test or Mann-Whitney U test. OS and PFS were calculated by Kaplan-Meier methods and compared by Log-rank methods. Factors with a *P*-value<0.05 in the univariate regression analysis were entered as candidate variables into multivariate COX regression analysis. Multivariate Cox proportional hazard regression analysis was used for identification of predictors correlating with OS and PFS. Two-sided *P*-values of less than 0.05 were regarded as statistically significant. Statistical analyses were performed with IBM SPSS version 22.0 (SPSS Inc., Armonk, NY).

Results

Patient characteristics

From 2012 to 2022, there were 59 and 158 patients receiving SBRT to both the primary tumor and all oligometastases and to the primary tumor alone. Among patients with SBRT to all lesions, 49 (83.0%), 3 (5.1%), 3 (5.1%) and 4 (6.8%) patients had metastases in the liver, lung, bone and other sites. While regarding patients receiving SBRT to the primary tumor alone, 121 (76.6%), 9 (5.7%), 5 (3.2%) and 23 (14.6%) patients had metastases in the liver, lung, bone and other sites. The median biologically effective dose (BED_{10}, $\alpha/\beta=10$) to the primary tumor of patients with SBRT to all lesions and the primary tumor alone was 59.5 Gy and 58.0 Gy, respectively. And the radiation dose ranged from 30 to 45 Gy/5-8f and 30–43 Gy/5-8 f. For SBRT to liver oligometastases, the radiation dose ranged from 40 to 64 Gy/5-8f, with a median BED_{10} of 92.625 Gy (interquartile range 85.5–102.6 Gy). There were no statistical differences between two groups regarding baseline characteristics. Details were demonstrated in Table 1.

Survival

The median OS of patients undergoing SBRT to the primary tumor and all oligometastases and the primary tumor alone was 10.9 months (95% CI 10.2–11.6 months) and 9.3 months (95% CI 8.8–9.8 months) ($P<0.001$) (Fig. 1A). One-year OS rate of the two groups was 37.3% (95% CI 31.0%-43.6%) and 2.5% (95% CI 1.3%-3.7%). The median PFS of patients with SBRT to all lesions and the primary tumor alone was 6.5 months (95% CI 5.6–7.4 months) and 4.1 months (95% CI 3.8–4.4 months) ($P<0.001$) (Fig. 1B). Six-month PFS rate of the two groups was 52.5% (95% CI 46.0%-59.0%) and 15.2% (95% CI 12.3%-18.1%), respectively. The median PPFS of patients with SBRT to all lesions and the primary tumor alone was 9.8 months (95% CI 8.9–10.7 months) and 7.8 months (95% CI 7.2–8.4 months) ($P<0.001$) (Fig. 1C). One-year PPFS rate of the two groups was 25.4% (95% CI 19.7%-31.1%) and 1.3% (95% CI 0.4%-2.2%). After multivariate analysis, BED_{10} (<60 Gy as reference; ≥60 Gy HR: 0.52, 95% CI 0.39–0.70, $P<0.001$) and irradiated sites (all lesions as reference; primary tumor alone HR: 3.26, 95% CI 2.26–4.70, $P<0.001$) correlated with OS (Table 2). Similarly, BED_{10} (<60 Gy as reference; ≥60 Gy HR: 0.44, 95% CI 0.32–0.60, $P<0.001$) and irradiated sites (all lesions as reference; primary tumor alone HR: 3.84, 95% CI 2.66–5.54, $P<0.001$) were also predictive of PFS (Table 3).

Adverse events

Among patients receiving SBRT to all lesions and the primary tumor alone (both plus chemotherapy after SBRT), 14 (23.7%) and 32 (20.2%) patients had grade 3 or

Table 1 Patient characteristics

	SBRT to all lesions ($n=59$)	SBRT to the primary tumor alone ($n=158$)	*P* value
Age, years	65 (56–73)	64 (56–69)	0.68
Sex			
Male	39 (66.1%)	104 (65.8%)	0.97
Female	20 (33.9%)	54 (34.2%)	
ECOG			
0 or 1	46 (78.0%)	110 (69.6%)	0.22
2	13 (22.0%)	48 (30.4%)	
Metastatic site			
Liver	49 (83.0%)	121 (76.6%)	0.43
Lung	3 (5.1%)	9 (5.7%)	
Bone	3 (5.1%)	5 (3.2%)	
Other sites	4 (6.8%)	23 (14.6%)	
The number of metastases			
One	43 (72.9%)	122 (77.2%)	0.87
Two	13 (22.0%)	32 (20.2%)	
Three	2 (5.1%)	4 (2.6%)	
GTV volume (cm^3)	31.63 (19.56–40.70)	32.36 (23.54–40.92)	0.15
CA19-9			
Range (U/ml)	1.72-84529.25	1.26-11259.82	
<200U/ml	21 (35.6%)	48 (30.3%)	0.46
≥200U/ml	38 (64.4%)	110 (69.7%)	
Radiation doses to the primary tumor			
BED_{10} (Gy)	59.5 (51.32–64.38)	58.0 (51.15–61.92)	0.36
Chemotherapy			
Gemcitabine-based	35 (59.3%)	96 (60.8%)	0.65
5-FU-based	26 (40.7%)	62 (39.2%)	

Data are median (IQR) or n (%)

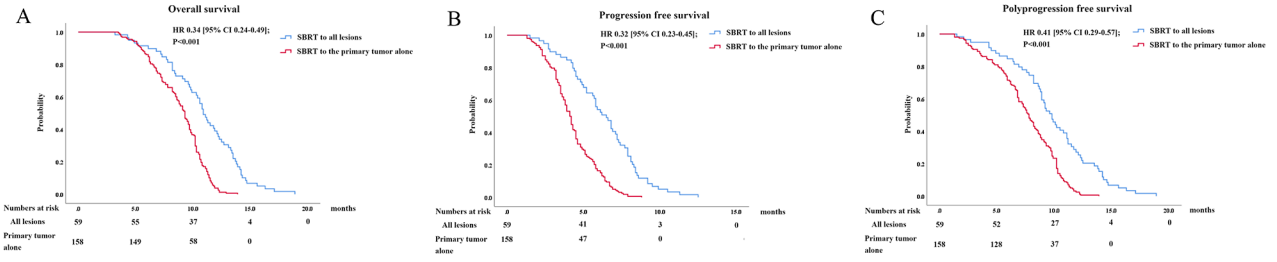

Fig. 1 (**A**) OS, (**B**) PFS and (**C**) Polyprogression of patients receiving SBRT to all lesions and the primary tumor alone

4 treatment-related toxicity. The most common grade 3 or 4 adverse events were neutropenia [12 patients (20.3%) with SBRT to all lesions and 23 (14.6%) with SBRT to the primary tumor alone] and increased ALT or AST [11 (18.6%) with SBRT to all lesions and 32 (20.2%) with SBRT to the primary tumor alone]. Details were shown in Table 4.

Discussion

Metastases were quite common in pancreatic cancer at the initial diagnosis. In this setting, systemic therapy is given the first priority. However, local treatment may synergize with chemotherapy in the case of oligometastases, which may improve survival of patients with oligometastatic pancreatic cancer. This notion has been proved in lung cancer. In this study, it was demonstrated that SBRT to all oligometastases and the primary tumor contributed to favorable outcomes compared with SBRT to the primary tumor alone.

Since the introduction of the concept of the oligometastatic state and advocation of local therapies due to potential survival benefits [17], no widely accepted definitions of oligometastases have been proposed across cancers. In a recent study on investigation of the biology of polymetastases, it was clarified that ten may be cut-off number of the lesions of polymetastases [18]. We chose up to 5 metastases in our study, and most of the patients had one to three lesions. A retrospective study

Table 2 Predictors of OS

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age				
<65 years	1 as reference	0.84	---	---
≥65 years	0.97 (0.74–1.27)		---	---
ECOG				
0 or 1	1 as reference	0.75	---	---
2	1.05 (0.78–1.42)		---	---
Metastases sites				
Liver	1 as reference	0.58	---	---
Other sites	1.10 (0.79–1.52)		---	---
CA19-9				
<200 U/ml	1 as reference	0.73	---	---
≥200 U/ml	0.95 (0.72–1.26)		---	---
Chemotherapy				
Gemcitabine-based	1 as reference	0.75	---	---
5-FU-based	0.96 (0.73–1.26)		---	---
BED_{10}				
<60 Gy	1 as reference	< 0.001	1 as reference	< 0.001
≥60 Gy	0.59 (0.44–0.79)		0.52 (0.39–0.70)	
Irradiated sites				
All lesions	1 as reference	< 0.001	1 as reference	< 0.001
Primary tumor alone	2.91 (2.04–4.14)		3.26 (2.26–4.70)	

Table 3 Predictors of PFS

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	***P* value**	**HR (95% CI)**	***P* value**
Age				
<65 years	1 as reference	0.69	---	---
≥65 years	0.95 (0.72–1.24)		---	---
ECOG				
0 or 1	1 as reference	0.93	---	---
2	0.99 (0.73–1.33)		---	---
Metastases sites				
Liver	1 as reference	0.38	---	---
Other sites	1.16 (0.83–1.60)		---	---
CA19-9				
<200 U/ml	1 as reference	0.36	---	---
≥200 U/ml	0.88 (0.66–1.16)		---	---
Chemotherapy				
Gemcitabine-based	1 as reference	0.77	---	---
5-FU-based	0.96 (0.73–1.26)		---	---
BED_{10}				
<60 Gy	1 as reference	< 0.001	1 as reference	< 0.001
≥60 Gy	0.56 (0.42–0.75)		0.44 (0.32–0.60)	
Irradiated sites				
All lesions	1 as reference	< 0.001	1 as reference	< 0.001
Primary tumor alone	3.11 (2.21–4.37)		3.84 (2.66–5.54)	

has compared survival of patients receiving SBRT to all oligometastases and chemotherapy with those receiving chemotherapy alone. The median OS was 42 months and 18 months, which was much longer than ours [19]. The reason contributed to the difference may be ascribed to the included patients. First, in their study, 20 patients received SBRT to all lesions, of whom 14 had history of surgical resections of primary tumors and 3 received surgery after SBRT and chemotherapy. In our study, no patients had surgical resections. Secondly, patients with

Table 4 Treatment-related adverse events

	SBRT to all lesions ($n=59$)			SBRT to the primary tumor alone ($n=158$)		
	Grade 1 or 2	Grade 3	Grade 4	Grade 1 or 2	Grade 3	Grade 4
Pyrexia	12 (20.3%)	0	0	41 (25.9%)	0	0
Fatigue	43 (72.9%)	4 (6.8%)	0	111 (70.2%)	16 (10.1%)	0
Nausea	33 (56.0%)	6 (10.2%)	0	76 (48.1%)	14 (8.9%)	0
Vomiting	16 (27.1%)	5 (8.5%)	0	53 (33.5%)	10 (6.3%)	0
Diarrhea	14 (23.7%)	0	0	22 (13.9%)	3 (1.9%)	0
Decreased appetite	39 (66.1%)	0	0	123 (77.8%)	0	0
Increased ALT or AST	36 (61.0%)	11 (18.6%)	2 (3.4%)	106 (67.1%)	32 (20.2%)	0
Stomatitis	7 (11.9%)	0	0	13 (8.2%)	0	0
Constipation	6 (10.2%)	0	0	9 (5.7%)	0	0
Rash	9 (15.2%)	0	0	12 (7.6%)	0	0
Arthralgia	5 (8.5%)	0	0	8 (5.1%)	0	0
Palmar-plantar erythrodysesthesia	3 (5.1%)	0	0	4 (2.5%)	0	0
Anemia	13 (22.0%)	0	0	41 (25.9%)	0	0
Neutropenia	40 (67.8%)	12 (20.3%)	3 (5.1%)	120 (75.9%)	23 (14.6%)	0
Thrombocytopenia	38 (64.4%)	9 (15.2%)	0	103 (65.2%)	18 (11.4%)	3 (1.9%)
Headache	7 (11.9%)	0	0	12 (7.6%)	0	0
Abdominal pain	11 (18.6%)	0	0	9 (5.7%)	0	0
Proteinuria	4 (6.8%)	0	0	2 (1.3%)	0	0
Increased blood bilirubin	16 (27.1%)	0	0	29 (18.4%)	0	0
Increased blood creatinine	2 (3.4%)	0	0	7 (4.4%)	0	0
Gastrointestinal hemorrhage	1 (1.7%)	0	0	0	0	0

CA19-9 level of more than 1000U/ml were excluded. However, 21 (35.6%) and 70 (44.3%) patients having SBRT to all lesions and the primary tumor alone had CA19-9 levels of more than 1000U/ml. Therefore, it was indicated that tumor burden of patients in our study was much higher than that in their study, which may result in worse prognosis. Thirdly, patients who had the initial diagnosis of oligometastatic pancreatic cancer and did not have any progressions after 5 months of mutiagent chemotherapy could be included in their study. While no matter whether patients had progressions within 5 months of chemotherapy before SBRT, they were all included in the study. Another study also reported SBRT to oligometastases of 41 stage IV pancreatic cancer patients with up to 5 metastatic lesions, and the median survival was 23 months. Similarly, most of the patients included in the study had a history of surgical resection [20]. Therefore, our study was the first study about the efficacy of SBRT to all oligometastases and the primary tumor for patients without surgery and with a high tumor burden, which showed a larger cohort of patients may benefit from this approach. For radiotherapy to the primary tumor alone, previous studies have shown that the median OS was 6 months and 11.6 months, while the median PFS was 2.4 months and 4 months [21, 22]. The outcomes were similar to those of patients having SBRT to the primary tumor alone in our study.

Regarding therapeutic options, the clinical introduction of online adaptive magnetic resonance (MR) guided systems has allowed dose escalation towards an effective BED, such as SBRT, for pancreatic cancer, theoretically improving clinical efficacy while minimizing the risk of serious toxicity, which may be a promising role in SBRT for pancreatic cancer. According to the previous studies about MR-guided SBRT for pancreatic cancer, the median PFS after treatment ranged from 7.0 to 21.0 months, and 1- and 2-year PFS ranged between 32 and 52% and between 21 and 25% [23–30]. Median OS from treatment ranged from 9.8 to 18.0 months, and 1-year OS ranged between 54% and 80%, and 2-year OS between 28% and 57% [31–33]. Hence, these results indicate further investigation of the effectiveness of ablative MR-guided SBRT as a well-tolerated and minimally-invasive therapy for pancreatic cancer in prospective clinical trials.

Disease progression of tumors is classically defined with RECIST criteria. However, it may not be clinically meaningful for patients with all lesions irradiated. In this study, we proposed two categories of progressions: disease progression as the radiological progression of any lesions, polyprogression involving the number of metastases that exceeded 5. We speculated that polyprogression was the biologically, clinically relevant outcome that influenced survival, predictive of poor prognosis. There was a paucity of effects of SBRT to all metastatic lesions on survival. Our study was exploratory due to the small number of patients and should be the evidence for

prospective studies. Nevertheless, it was possible that SBRT to all sites of pancreatic cancer would improve survival.

In the case of priming of tumor microenvironment induced by SBRT, radiomics may be a potential option to visualize the changes, predict outcomes and correlate the molecular findings and gene expressions in tumors with image phenotypes. Previous studies have investigated the role of CT- and MR-based radiomics and PET-CT texture for evaluations of outcomes [34–38]. Additionally, two studies have distinguished quasi-mesenchymal subtype from non quasi-mesenchymal subtype of pancreatic cancer and performed survival predictions with machine learning algorithms [39, 40]. While another study has clarified that genetic alterations of KRAS and SMAD4 had significant associations with FDG PET-based radiomic features in pancreatic cancer [41]. An important role to improve prognosis of pancreatic cancer is represented by the innovative approach of personalization through tailored treatment based on stratifications of patients into different groups, and early prediction or simulation of potential treatment response with radiomics, which helps physicians to choose therapeutic patterns accordingly.

Regarding the oligometastases, surgical resection has been performed in highly selected patients in addition to radiotherapy. However, metastasectomy in the management of metastatic pancreas cancer still remains controversial. Previous studies have evaluated the efficacy of surgical resection of patients with both synchronous and metachronous oligometastatic disease. The median OS from the diagnosis and surgery to death was 14.5 months and 12.3 months [42]. The outcomes were similar to those in our study. Nevertheless, only a small number of patients may be eligible for surgery. Some studies have identified several potential criteria of resection, which included major biochemical response (significant decrease of CA19-9) after neoadjuvant therapy, complete or major radiological response with single remaining metastasis or small, few lesions after chemotherapy. Regarding safety of metastasectomy, the reported complication rates of the resection of pancreatic cancer with simultaneous hepatic metastasectomy were 18–68%, with a median complication rate of 45% [42], which was comparable to that of pancreaticoduodenectomy alone [43]. One of the studies reported that 30-day morbidity and mortality of synchronous liver metastases resection was 45.0% and 2.9%, respectively. While after metachronous resection, the 30-day morbidity and mortality was 21.7% and 4.3% [44]. Therefore, in the case of efficacy, outcomes of SBRT to all oligometastases and the primary tumor were comparable with those of surgical resection. While risk of adverse events of SBRT to all lesions were much lower than those of metastasectomy, which may even result in mortality.

Regarding prognosis of the metastatic sites, it had been demonstrated that lung metastases showed favorable outcomes compared with liver metastases [45–47]. A median OS of lung-only recurrence was 18.1 to 37.1 months [46, 48–51], which was longer than that in our study. It had been clarified that patients with lung primary metastasis had lower T stage and less vascular invasion. The possible mechanism of lung metastasis that bypass the portal vein system may be ascribed to lymphatic invasion or lymph node metastases [47]. Other studies have proposed several possible lymphatic spreads from pancreatic cancer: (1) pleural lymphatics along connective tissue septa and into the alveolar spaces and bronchial walls; (2) retrograde lymphatic invasion of the lung from the tracheobronchial or mediastinal glands; and (3) via the systemic circulation with involvement of metastatic lymph nodes in the venous angle [52, 53]. However, this may be one possible pathway for the development of primary lung metastasis, bypassing the liver. Additionally, tumor biology is also vital in the metastasis sites, including organ-specific metastases.

Additionally, though upfront chemotherapy was usually given followed by radiotherapy, SBRT was delivered before administration of chemotherapy in our study. The rationale was due to the shorter duration of SBRT compared with conventional radiotherapy, usually about 5 days, which may not delay the initiation of chemotherapy. Furthermore, some of Chinese patients are not tolerant of mFOLFIRINOX/NALIRIFOX. And for patients with metastatic pancreatic cancer, even though the scores of performance status was 0 to 2 before treatment, most of them were vulnerable to aggressive regimens, which may result in deteriorations of performance status and quality of life. Hence, upfront gemcitabine and nab-paclitaxel was offered to 60% of patients in both two groups. Nevertheless, for the rest patients, mFOLFIRINOX was still given as the first-line therapy.

The results of the study should be interpreted with cautions given the limitations. The small number of patients included in the study and retrospective design limit the robustness of results. However, patients in our study had synchronous metastases without surgical resection of the primary tumor and a higher tumor burden compared with those in aforementioned studies, which implied that patients in our study were less selective. Also, there was no statistical difference between characteristics of two groups. However, potential bias still could not be eliminated without prospective selection. Additionally, the statistical methods in the study had the inherent statistical limitations. The Kaplan-Meier method provides unadjusted survival probabilities. The results of the study did not provide definitive evidence, suggesting larger

cohort of confirmative studies should be needed. However, the study may be an initial step to shed light on the benefits of SBRT to all lesions for an appropriate cohort of patients with oligometastatic pancreatic cancer, which may be a distinct disease condition with clinically favorable outcomes.

Our study showed that patients with oligometastatic pancreatic cancer may benefit from SBRT to all lesions with improved survival and slowing polyprogression. Nevertheless, the perception should be verified prospectively in the robust design trials.

Abbreviations

SBRT	Stereotactic body radiation therapy
GTV	Gross tumor volume
PTV	Palnning target volume
OS	Overall survival
PFS	Progression free survival
PPFS	Polyprogression free survival
IQR	Interquartile range
BED10, $\alpha/\beta = 10$	Biologically effective dose

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Author contributions
ZHJ designed the study. ZXF, JLG and FZR were responsible for the treatment. ZXF, JLG, ZXZ and LWY performed the follow-up. FZR and YYS were responsible for data curation. ZXF, YYS and CYS analyzed the data. ZXF and JLG wrote the manuscript. ZHJ revised the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The study was approved by the institutial review board of Changhai Hospital.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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