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ORIGINAL RESEARCH

Stereotactic body radiation therapy plus induction or adjuvant chemotherapy for early stage but medically inoperable pancreatic cancer: A propensity score-matched analysis of a prospectively collected database

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Background: To evaluate and compare the efficacy and safety of stereotactic body radiation therapy (SBRT) plus induction chemotherapy and SBRT plus adjuvant therapy.

Methods: Patients with radiographically resectable, biopsy-proven pancreatic cancer were enrolled. Data were prospectively collected from 2012 to 2016. Cox proportional hazards regression was used to identify factors predictive of survival. Propensity score matching analysis was performed to assess the efficacy of SBRT combined with different timing of chemotherapy.

Results: One hundred patients were enrolled with 48 receiving induction chemotherapy and 52 undergoing adjuvant chemotherapy. The median overall survival (OS) and progression-free survival (PFS) were 17.5 months (95% CI: 15.8–19.2 months) and 13.7 months (95% CI: 12.3–15.1 months), respectively. Patients with adjuvant chemotherapy (P <0.001), CA19-9 response (P <0.001) and BED_{10} (biological effective dose, $\alpha/\beta = 10$) ≥ 60 Gy (P = 0.024) had a longer OS, while the former two correlated with PFS. Patients with more positive factors had a superior OS and PFS. After propensity score matching analysis, there were 23 patients from each group included in the analysis. Longer OS (23.1 months versus 15.6, P <0.001) and PFS (18.0 months versus 11.6 months, P <0.001) were found in patients with adjuvant chemotherapy compared with those with induction chemotherapy.

Conclusion: SBRT was safe and effective in early stage pancreatic cancer. Combined with adjuvant chemotherapy, SBRT could be an alternative for patients with resectable pancreatic cancer but not eligible for surgical resection.

Keywords: stereotactic body radiation therapy, early stage pancreatic cancer, resectable pancreatic cancer, medically inoperable, chemotherapy

Introduction

Pancreatic cancer has been the fourth leading cause of cancer mortality in the United States with a dismal 5-year survival rate of 7%.[1] The latest findings also showed that in contrast to the declining trends for the four major cancers, the mortality of pancreatic cancer continues to increase slightly (by 0.3% per year) in men but has leveled off in women.[2] Similar trends were found in China with increasing incidences and cancer deaths.[3]

Although surgical resection has been confirmed as the only strategy for cure, especially for resectable pancreatic cancer, only 15–20% of the patients were amenable

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to this curative-intent treatment at the initial diagnosis.[4,5] The overall 5-year survival rate of those patients even with R0 resection with or without adjuvant therapy is less than 20%.[6–10]

However, there was no consensus or clinical trials about optimal multimodality treatment for patients with resectable but medically inoperable pancreatic cancer. Due to the limited employment of targeted therapy and immunotherapy for pancreatic cancer, radiotherapy and chemotherapy may be the alternatives if patients are not candidates for surgery. Given the shortcomings of conventional radiotherapy, stereotactic body radiation therapy (SBRT) has become a promising option due to its precise treatment delivery with sharp dose fall-off within adjacent organs at risk, acceptable toxicity and online image verifications. Also the shorter duration of SBRT compared with conventional radiotherapy could avoid delaying delivery of chemotherapy. Therefore, a complete understanding of the feasibility and tolerability of SBRT for early stage, resectable pancreatic cancer would have profound clinical importance. Furthermore, the factors associated with prognosis might suggest the underlying mechanism by which treatment effects occur.

In this study, we sought to compare the efficacy and safety of SBRT plus induction chemotherapy and SBRT plus adjuvant chemotherapy and identify clinical factors associated with survival in a large cohort of patients with early stage, resectable but medically inoperable pancreatic cancer.

Methods

The institutional review board of Changhai Hospital has approved this study. Individual written informed consent was mandatory before treatment. Data were prospectively collected from 2012–2016. A prospective maintained pancreatic cancer database was used to identify all patients who were not amenable to surgery and received SBRT between January 2012 and December 2016. Treatment decisions were made at the discretion of the institutional multidisciplinary pancreatic cancer board, which generally followed National Comprehensive Cancer Network guidelines. Typically, induction chemotherapy plus SBRT was performed for patients without severe local symptoms. SBRT with adjuvant chemotherapy might be given priority for amelioration of local symptoms.

Eligibility

All patients included in this study had resectable pancreatic cancer. Patients' medical records were firstly reviewed by surgeons for evaluation of the feasibility of surgical resection. Only when they were medically inoperable or declined operations, subsequent radiotherapy and chemotherapy was taken into consideration.

Patients who had completed induction chemotherapy would receive positron emission tomography-computed tomography (PET-CT) to preclude metastasis. Those with metastasis were excluded from the study and received other treatment based on the multidisciplinary approach. Those without metastasis would receive SBRT thereafter.

Staging

Before treatment, comprehensive clinical and radiographic staging, including abdominal computed tomography (CT) or magnetic resonance imaging (MRI) scan, chest CT, and laboratory studies were required. Additionally, histopathological diagnosis with fine-needle aspiration guided by endoscopic ultrasound was required for all patients before treatment. The most recent results of laboratory studies before initiation of treatment were utilized for analysis. The definition of resectable pancreatic cancer was referred to NCCN guidelines.[11]

Chemotherapy

Chemotherapy regimens were based on NCCN guidelines and determined by a multidisciplinary program. Due to the high incidence of neurological toxicity of nab-paclitaxel and low tolerance of FOLFIRINOX in Chinese patients, the chemotherapy regimen was gemcitabine plus S-1. Additionally, S-1, the prodrug of 5-fluorouracil comprising of tegafur, gimeracil and oteracil, was an option as the regimen. Previous studies have proven that S-1 was not inferior to gemcitabine in terms of overall survival (OS) rates and progression-free survival (PFS) rates with tolerable effects.[12–15] Patients were recommended to receive chemotherapy for 6 months and SBRT was initialized with an interval of 2 to 3 weeks before or after chemotherapy. Intravenous administration of gemcitabine (1000 mg/m^2) was initiated on days 1, 8, and 15 during each 4-week cycle, which repeated for 6 cycles. S-1 was orally administered at a dose of 80 mg/m^2 for 28 days followed by a 14-day rest, which also continued for 6 cycles.

Follow-up

Patients were evaluated initially every 2 to 3 months within one year after treatment and later every 4 to 6 months with CT or MRI scans, physical examinations and CA19-9 for a planned follow-up of 5 years. Any other examinations prompted by new-onset symptoms or at the physician's discretions were also used to record events.

Definitions and collection of data

The definition of disease recurrence was based on review of the medical records and imaging studies. A new low density mass or growth of the tumor on CT or MRI consistent with recurrent local, regional, or metastatic disease was considered as such and tumor biopsy was rarely performed.[16] Differential diagnosis of tumor necrosis induced by SBRT, which may be mistaken for progression, would be performed by three radiologists based on MRI scan. OS was defined from the initial date of treatment to death. PFS was determined from the initial date of treatment to the date of the first recurrence or death. Adverse effects induced by chemotherapy were evaluated by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Radiation-induced acute toxicities were determined by "Acute radiation morbidity scoring criteria" from Radiation Therapy Oncology Group. While late toxicities were evaluated by "Late radiation morbidity scoring schema" from Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer.[17]

A systemic inflammation response index (SIRI) might correlate with survival of patients with pancreatic cancer.[18] The value was calculated as:

$$\text{SIRI} = \frac{\text{total neutrophil count}(/mm^3) \times \text{total monocyte count}(/mm^3)}{\text{total lymphocyte count}(/mm^3)}.$$

The prognostic nutritional index (PNI) represented patient's nutritional status, which might also associate with survival of pancreatic cancer.[19,20] The formula was as follows:

PNI = 10 × serum albumin (g/dl) + 0.005 × total lymphocyte count (/mm^3). Charlson age-comorbidity index (CACI) was originally designed to classify prognostic comorbidity.[21] It was identified that CACI was associated with prognosis of patients with pancreatic cancer.[22] Pain was quantified by visual analogue scale (VAS).

The recommended upper limit of normal for CA19-9 is 37 U/mL.[23] Additionally, a phase I/II study of *nab*-paclitaxel + gemcitabine that preceded advanced pancreatic cancer reported a significant correlation between decreases in CA19-9 levels of ≥50% versus <50% from baseline and improved survival.[24] Therefore, CA19-9 response was defined as the level of CA19-9 decreased by 50% from baseline levels of ≥74 U/mL. Hence, three CA19-9 groups were formed for univariate analysis: CA19-9 levels ≥74 U/mL with response versus CA19-9 levels ≥74 U/mL with no response (including CA19-9 levels within the normal range before SBRT while increased after SBRT) versus CA19-9 levels <74 U/mL (before SBRT and during follow-up). The nadir value of CA19-9 level during the follow-up was utilized for the estimation of CA19-9 decrease. Additionally, it was demonstrated that CA19-9 level less than 200 U/mL was associated with major response for localized pancreatic cancer treated with preoperative therapy.[25] Therefore, the serum level of CA19-9 before SBRT was stratified as: <200 U/mL and ≥200 U/mL.

SBRT technique

The protocol was based on our previous studies.[26,27] SBRT was delivered via CyberKnife® (Accuray Incorporated, Sunnyvale, CA, USA), an image-guided frameless stereotactic robotic radiosurgery system. A plain CT and a contrast-enhanced pancreatic parenchymal CT were performed and co-registered for treatment planning and target delineations. Before CT simulations, at least three fiducials were implanted using endoscopic ultrasound or CT guidance. Gross tumor volume (GTV) was delineated as a radiographically evident gross disease by contrast CT. Clinical target volume (CTV) encompassing areas of the potential subclinical disease spread was also designated. In most cases, the CTV equaled GTV. A 2–5 mm expansion margin was included to determine the planning target volume (PTV). When the tumor was adjacent to critical organs, the expansion of PTV outside of CTV in this direction should be avoided. Therefore, the margin expansion was allowed to be non-uniform. At least 90% of PTV should be covered by the prescription dose. Normal tissue constraints were according to the American Association of Physicists in Medicine guidelines in TG-101.[28]

Propensity score matching

To correct for potential imbalances in treatment assignments, we performed propensity score matching, which decreased the differences between SBRT plus induction chemotherapy and SBRT plus adjuvant chemotherapy. We first built a logistic regression model with treatment modality as the dependent variable and all other variables that could potentially influence its prognostic impact as independent variables.

Statistical analysis

Patient characteristics and demographic data were summarized by descriptive statistics. Quantitative outcomes were compared by chi-square test (Fisher's exact tests). Next, demographic and clinical factors were investigated for their association with OS and PFS using univariate log-rank comparisons and then multivariate proportional hazards regression model. OS and PFS curves were calculated by the Kaplan–Meier method. Median OS and PFS and 95% CIs were reported. Long-term survival of patients with different treatment options was assessed with propensity score

matched analysis. Two-sided *P* values <0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 22.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics

A total of 100 patients were identified including 48 patients with induction chemotherapy and 52 receiving adjuvant chemotherapy. The median prescription dose of patients with induction chemotherapy and adjuvant chemotherapy was 35 Gy (range: 30–43 Gy/5–8 f) and 39 Gy (range: 30–45 Gy/5–8 f), respectively. Patients treated with adjuvant chemotherapy had higher BED_{10} (biological effective dose, $\alpha/\beta = 10$) than those treated with induction chemotherapy (69.1 Gy versus 59.5 Gy, $P < 0.001$), as well as longer follow-up (21 versus 15 months, $P = 0.001$). All radiation doses were delivered in 5–8 fractions. Tumors were similarly sized and T1 or T2 in both induction and adjuvant chemotherapy group (2.8 versus 3.0 cm median maximum diameter, $P = 0.37$). Patients were treated with SBRT plus induction chemotherapy or adjuvant chemotherapy contemporaneously throughout the time range studied (Table 1).

Association of clinical factors with OS

Seventy patients (70.0%) died during the observation period and 30 patients (30.0%) were still alive at their last follow-up. The median OS was 17.5 months (95% CI: 15.8–19.2 months). Moreover, 1-year and 2-year OS rate was 87.0% and 38.0%, respectively. Before treatment, a level of CA19-9 less than 200 U/mL was found in 57 patients while 43 patients had a level more than 200 U/mL. Among patients with the level of CA19-9 ≥2 upper limit of normal, significant decrease was found in 42 patients while 33 patients had no response or even elevated levels during follow-up. On univariate log-rank comparisons, CA19-9 response, chemotherapy strategies,

Table 1 Baseline patient characteristics

Characteristics	SBRT + induction chemotherapy	SBRT + adjuvant chemotherapy	*P*-value
No. of patients	48	52	
Sex			0.36
Male	29 (54.2)	36 (69.2)	
Female	19 (39.6)	16 (30.8)	
Age, years			0.89
Median	67.5	66	
Range	39–88	32–87	
ECOG			0.85
1	24 (50.0)	27 (51.9)	
2	24 (50.0)	25 (48.1)	
Stage			0.32
$T_1N_0M_0$	5 (10.4)	9 (17.3)	
$T_2N_0M_0$	43 (89.6)	43 (82.7)	
Tumor diameter, maximum, cm			0.37
Median	3.0	2.8	
Range	0.6–5.1	1.0–4.4	
Tumor diameter, maximum, cm			0.46
≤3cm	26 (54.2)	32 (61.5)	
>3cm	22 (45.8)	20 (30.5)	
Baseline CA19-9 (U/mL)			0.17
≤200	24 (50.0)	33 (63.5)	
>200	24 (50.0)	19 (36.5)	
BED_{10}			0.001
≥60 Gy	20 (41.7)	38 (73.1)	
<60 Gy	28 (58.3)	14 (26.9)	
BED_{10}			
Median (Gy)	59.5/5–8f	69.1/5–8f	<0.001
Range (Gy)	48–79.98	48–88.32	
Follow-up for all patients, months			
Median	15.0	21.0	0.001
Range	6.0–25.6	13.0–46.9	

Note: Data presented as n (%) unless otherwise noted.
Abbreviations: SBRT, stereotactic body radiation therapy; ECOG, Eastern Cooperative Oncology Group; BED_{10}, biological effective dose ($\alpha/\beta = 10$); f, fractions

and BED_{10} ≥ 60 Gy were predictive factors of OS (Table 2). On multivariate regression, patients with CA19-9 response after treatment, adjuvant chemotherapy and BED_{10} ≥60 Gy had a longer OS (Table 2). The number of predictive factors was associated with OS: (0) 12.2 months (95% CI: 11.1–13.3 months); (1) 14.7 months (95% CI: 13.0–16.4 months); (2) 19.7 months (95% CI: 17.3–22.1 months); (3) 23.5 months (95% CI: 21.7–25.3 months); P <0.001 (Figure 1A). Furthermore, patients receiving adjuvant chemotherapy had a longer OS than those with induction chemotherapy: adjuvant chemotherapy: 23.1 months (95% CI: 21.7–24.5 months); induction chemotherapy: 13.9 months (95% CI: 12.7–15.1 months); P <0.001 (Figure 2A).

Association of clinical factors with PFS

The median PFS was 13.7 months (95% CI: 12.3–15.1 months), while 1-year and 2-year PFS rate was 65% and 16%, respectively. On univariate log-rank comparisons, CA19-9 response, chemotherapy strategies and BED_{10} ≥60 Gy were also associated with PFS (Table 3). On multivariate regression, longer PFS was found in patients with CA19-9 response after treatment and adjuvant chemotherapy (Table 3). The number of predictive factors was associated with PFS: (0) 10.1 months (95% CI: 9.0–11.2 months); (1) 16.2 months (95% CI: 13.3–19.1 months); (2) 20.8 months (95% CI: 18.7–22.9 months) P <0.001 (Figure 1B). Additionally, adjuvant chemotherapy correlated with longer PFS compared with induction chemotherapy: adjuvant chemotherapy: 18.8 months (95% CI: 16.7–20.9 months); induction chemotherapy: 10.5 months (95% CI: 9.9–11.1 months); P <0.001 (Figure 2B).

Adjusted survival of induction chemotherapy and adjuvant chemotherapy

Baseline ECOG (Eastern Cooperative Oncology Group), CA19-9 response and BED_{10} were as independent variables

Table 2 Univariate and multivariate analysis of clinical factors associated with OS

Variable		n = 100	Univariate, overall survival (months)		P-value (log-rank)	Multivariate, hazard ratio			P-value (Cox regression)
			Median	95% CI		HR	95% CI	B	
Age	<65	40	19.5	14.3–24.7	0.293	NS	NS	NS	NS
	≥65	60	16.7	17.1–19.2		NS	NS	NS	
Smoking	Absent	70	17.1	15.4–18.8	0.086	NS	NS	NS	NS
	Present	30	19.7	13.8–25.6		NS	NS	NS	
Diabetes mellitus	Absent	73	16.7	14.9–18.5	0.157	NS	NS	NS	NS
	Present	27	19.5	13.8–25.2		NS	NS	NS	
VAS	<3	61	20.2	15.7–24.7	0.168	NS	NS	NS	NS
	≥3	39	16.3	14.0–18.5		NS	NS	NS	
Weight loss	<5kg	72	18.3	14.6–22.0	0.227	NS	NS	NS	NS
	≥5kg	28	16.3	14.7–17.8		NS	NS	NS	
Tumor diameter	≤3cm	58	17.7	14.3–21.1	0.966	NS	NS	NS	NS
	>3	42	16.9	14.3–19.4		NS	NS	NS	
ECOG	1	41	19.2	16.4–22.0	0.441	NS	NS	NS	NS
	2	59	15.7	12.4–19.0		NS	NS	NS	
Chemotherapy strategies	Induction chemotherapy	48	13.9	12.7–15.1	<0.001	1			<0.001
	Adjuvant chemotherapy	52	23.1	21.7–24.5		0.14	0.06–0.3	–2.0	
SIRI	≤0.8	52	17.1	15.3–18.9	0.306	NS	NS	NS	NS
	>0.8	48	19.7	13.0–26.3		NS	NS	NS	
PNI	<48.5	49	16.9	11.0–22.8	0.768	NS	NS	NS	NS
	≥48.5	51	17.5	15.4–19.6		NS	NS	NS	
CACI	≤5	79	17.5	15.7–19.3	0.878	NS	NS	NS	NS
	>5	21	17.7	12.6–22.8		NS	NS	NS	
CA19-9	<200 U/mL	57	19.5	17.0–22.0	0.107	NS	NS	NS	NS
	≥200 U/mL	43	15.8	14.1–17.5		NS	NS	NS	
CA19-9 response	≥74 U/mL with response	42	22.8	20.7–24.9	<0.001	1			<0.001
	Remain <74 U/mL	25	21.7	16.4–27.0		1.2	0.6–2.4	0.2	
BED_{10}	≥74 U/mL with no response	33	13.2	12.0–14.4		6.8	3.4–13.7	1.9	
	≥60	58	19.7	16.3–23.1	<0.001	1			0.024
	<60	42	13.1	12.0–14.2		1.8	1.1–3.2	0.6	

Abbreviations: OS, overall survival; NS, not significant; VAS, visual analogue scale; ECOG, Eastern Cooperative Oncology Group; SIRI, systemic inflammation response index; PNI, prognostic nutritional index; CACI, Charlson age-comorbidity index; BED_{10}, biological effective dose (α/β = 10)

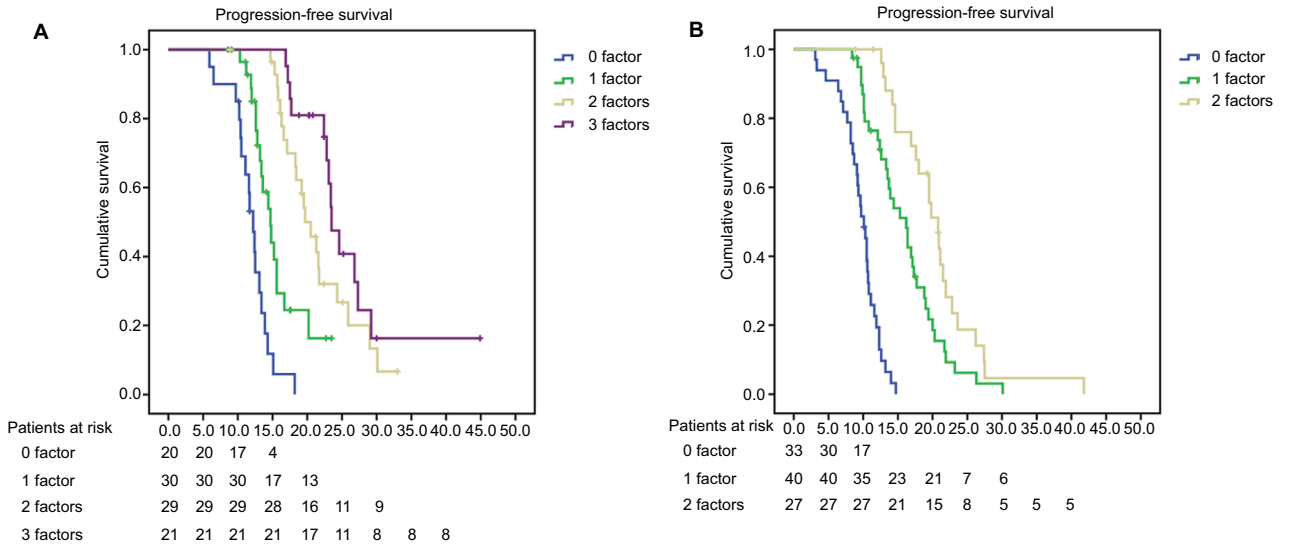

Figure 1 Association with number of positive predictive factors and (**A**) overall survival and (**B**) progression-free survival.

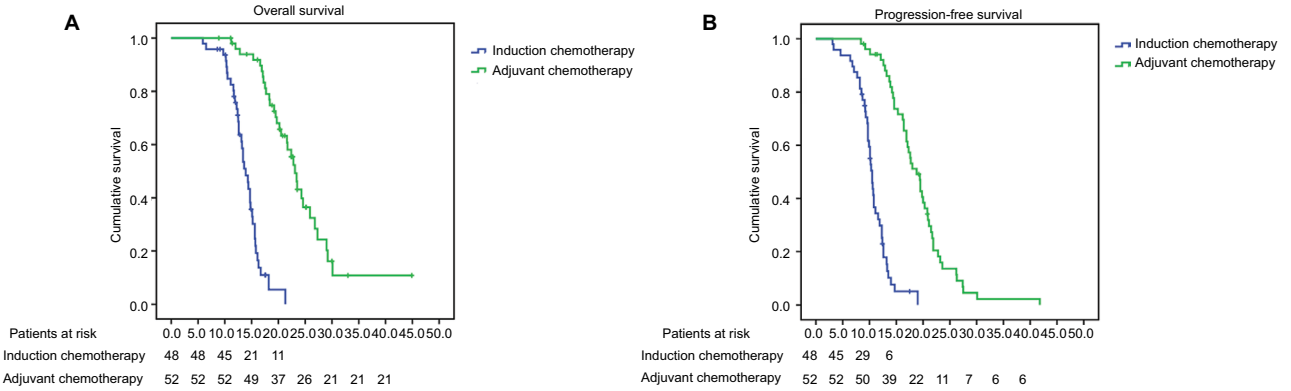

Figure 2 (**A**) Overall survival and (**B**) progression-free survival of patients with induction chemotherapy and adjuvant chemotherapy.

for propensity score matched analysis (Supplementary Table 1). After propensity matching, there were 23 patients of each group included in the analysis. Both an overall survival and a progression survival benefit were found in patients with adjuvant chemotherapy: OS: induction chemotherapy: 15.6 months (95% CI: 14.4–16.8 months), adjuvant chemotherapy: 23.1 months (95% CI: 18.1–28.1 months); P <0.001. PFS: induction chemotherapy: 11.6 months (95% CI: 9.8–13.4 months), adjuvant chemotherapy: 18.0 months (95% CI: 14.5–21.5 months); P <0.001.

Adverse effects of SBRT and chemotherapy

Regarding acute radiation-induced toxicities, only 16 patients had grade 1 to 2 abdominal pain. There were no grade 3 or more acute or late radiation-induced adverse effects. With regard to induction chemotherapy, 11 (22.9%) and 15 patients (31.2%) experienced grade 3 neutropenia and gastrointestinal toxicity, including nausea, vomiting and abdominal pain, respectively. Furthermore, grade 3 neutropenia and gastrointestinal toxicity was found in 13 (25.0%) and 16 (30.8%) patients, respectively. There was no difference of incidences of hematological toxicity between induction chemotherapy group and adjuvant chemotherapy group (P = 0.81) and nor was the incidence of gastrointestinal toxicity (P = 0.96).

Discussion

Although surgical resection was given the first priority for resectable pancreatic cancer, there was no consensus or even reference guides for clinicians on treatment for patients with medically inoperable resectable pancreatic cancer. Therefore, these patients may be amenable to radiotherapy and chemotherapy. This pilot study sought to address the efficacy and

Table 3 Univariate and multivariate analysis of clinical factors associated with PFS

Variable		n = 100	Overall survival (months)		*P*-value (log-rank)	Multivariate, hazard ratio			*P*-value (Cox regression)
			Median	95% CI		HR	95% CI	B	
Age	<65	40	13.9	11.9–15.9	0.908	NS	NS	NS	NS
	≥65	60	13.7	11.6–15.8		NS	NS	NS	
Smoking	Absent	70	13.2	11.7–14.6	0.185	NS	NS	NS	NS
	Present	30	16.4	12.0–20.8		NS	NS	NS	
Diabetes mellitus	Absent	73	13.2	11.9–14.5	0.062	NS	NS	NS	NS
	Present	27	16.4	12.3–20.5		NS	NS	NS	
VAS	<3	61	14.6	11.6–17.6	0.242	NS	NS	NS	NS
	≥3	39	13.2	12.2–14.1		NS	NS	NS	
Weight loss	<5kg	72	13.7	12.1–15.3	0.964	NS	NS	NS	NS
	≥5kg	28	14.4	11.3–17.5		NS	NS	NS	
Tumor diameter	≤3cm	58	13.7	11.3–16.1	0.601	NS	NS	NS	NS
	>3cm	42	13.5	11.6–15.4		NS	NS	NS	
ECOG	1	41	14.6	12.0–17.2	0.565	NS	NS	NS	NS
	2	59	12.3	9.9–14.7		NS	NS	NS	
Chemotherapy strategies	Induction chemotherapy	48	10.5	9.9–11.1	<0.001	1			<0.001
	Adjuvant chemotherapy	52	18.8	16.7–20.9		0.2	0.08–0.3	–1.9	
SIRI	≤0.8	52	13.2	11.3–15.1	0.640	NS	NS	NS	NS
	>0.8	48	14.0	11.7–16.3		NS	NS	NS	
PNI	<48.5	49	14.2	12.4–16.0	0.485	NS	NS	NS	NS
	≥48.5	51	13.2	11.7–14.7		NS	NS	NS	
CACI	≤5	79	13.9	12.6–15.2	0.908	NS	NS	NS	NS
	>5	21	12.6	6.8–18.4		NS	NS	NS	
CA19-9	<200 U/mL	57	14.7	11.9–17.5	0.520	NS	NS	NS	NS
	≥200 U/mL	43	12.9	11.5–14.3		NS	NS	NS	
CA19-9 response	≥74 U/mL with response	42	18.0	13.5–22.5	<0.001	1			<0.001
	Remain <74 U/mL	25	16.4	13.3–19.5		1.4	0.8–2.5	0.4	
	≥74 U/mL with no response	33	10.1	9.1–11.1		4.0	2.2–7.3	1.4	
BED_{10}	≥60	58	16.2	13.9–18.5	0.002	NS	NS	NS	NS
	<60	42	10.5	9.9–11.1		NS	NS	NS	

Abbreviations: PFS, progression-free survival; NS, not significant; VAS, visual analogue scale; ECOG, Eastern Cooperative Oncology Group; SIRI, systemic inflammation response index; PNI, prognostic nutritional index; CACI, Charlson age-comorbidity index; BED_{10}, biological effective dose ($\alpha/\beta = 10$).

tolerability of SBRT with chemotherapy for early stage but medically inoperable pancreatic cancer.

Hallmarks of SBRT include accurate, conformal delivery of high-dose radiation to targets while minimizing doses to organs at risk via precise target localization[29] and steep dose gradients through multiple beam directions,[30] rendering SBRT as a potential curative modality for cancer.

Given the growing body of literature of prospective studies evaluating the efficacy of that modality, the median OS in the surgery-only arms ranged between 11 and 20.2 months, while it was 12.5–29.8 months and 9.9–19.4 months in the adjuvant treatment arms and in the neoadjuvant setting, respectively.[6,31–39] The median PFS was 5–10.2 months and 8.6–15.2 months in the surgery alone and neoadjuvant or adjuvant group.[6,31–39] In addition to conventional radiotherapy, preoperative short-course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic cancer was investigated.[40] The median OS and PFS for the entire group were 17 months and 10 months.[40] In our study, the median OS and PFS were 17.5 months and 13.7 months. Therefore, it was identified that SBRT with chemotherapy may not be inferior to surgery with chemotherapy for early stage pancreatic cancer.

The treatment strategy in our study showed that adjuvant chemotherapy was beneficial for OS. After adjustment for dose, patients with adjuvant chemotherapy still had longer OS and PFS than those with induction chemotherapy. The potential mechanism of this correlation might be speculated stimulation of anti-tumor immunity by SBRT, rendering a synergic effect of SBRT and chemotherapy.[41,42]

In our previous study, it was elucidated that patients receiving BED_{10} ≥60 Gy achieved better tumor response 6 months after SBRT than those who received BED_{10} <60 Gy, though no correlation was found between the radiation

dose and survival.[27] However, it was shown in this study that BED_{10} ≥60 Gy associated with OS and PFS. Likewise, Krishnan et al[43] also reported that BED_{10} >70 Gy was the predictor of OS. The potential reason may be the difference in patient selection. In the previous study, patients were elderly with advanced or medically inoperable pancreatic cancer with high tumor burdens or large tumor volumes. Hence, SBRT was majorly delivered as the palliative setting, while all patients in this study had resectable pancreatic cancer, indicating that curative radiotherapy should be administered. Nevertheless, patients with better performance status had higher doses, which may result in over-interpretation of prognostic impact of high doses. The limitation of this study was non-randomization. Therefore, the results might be influenced by potential factors though with stringent criteria, which required prospective and randomized studies. Another limitation was the small sample size of the two groups.

Conclusion

In conclusion, SBRT was safe and effective in resectable pancreatic cancer. Adjuvant chemotherapy, CA19-9 response and BED_{10} ≥60 Gy correlated with OS and the former two were predictive of PFS. We believe that SBRT, due to its short duration and excellent tolerability, combined with adjuvant chemotherapy may be an alternative for patients with early stage and resectable but medically inoperable pancreatic cancer.

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Disclosure

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Reference

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin.* 2016;66(1):7–30.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7–30.
3. Chen W, Zheng R, Baade PD, et al. Cancer statistics in China, 2015. *CA Cancer J Clin.* 2016;66(2):115–132.
4. Sener SF, Fremgen A, Menck HR, Winchester DP. Pancreatic cancer: A report of treatment and survival trends for 100313 patients diagnosed from 1985–1995 using the National Cancer Database. *J Am Coll Surg.* 1999; 189(1):1–7.
5. Myrehaug S, Sahgal A, Russo SM, et al. Stereotactic body radiotherapy for pancreatic cancer: Recent progress and future directions. *Expert Rev Anticancer Ther.* 2016;16(5):523–530.
6. Regine WF, Winter KA, Abrams R, et al. Fluorouracil-based chemoradiation with either gemcitabine or fluorouracil chemotherapy after resection of pancreatic adenocarcinoma: 5-year analysis of the U.S. Intergroup/RTOG 9704 phase III trial. *Ann Surg Oncol.* 2011;18(5): 1319–1326.
7. Herman JM, Swartz MJ, Hsu CC, et al. Analysis of fluorouracil-based adjuvant chemotherapy and radiation after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreas: Results of a large, prospectively collected database at the Johns Hopkins Hospital. *J Clin Oncol.* 2008;26(21):3503–3510.
8. Oettle H, Neuhaus P, Hochhaus A, et al. Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: The CONKO-001 randomized trial. *JAMA.* 2013;310(14):1473–1481.
9. Tseng JF, Raut CP, Lee JE, et al. Pancreaticoduodenectomy with vascular resection: margin status and survival duration. *J Gastrointest Surg.* 2004;8(8):935–949.
10. Hoyer M, Roed H, Sengelov L, et al. Phase-II study on stereotactic radiotherapy of locally advanced pancreatic carcinoma. *Radiother Oncol.* 2005;76(1):48–53.
11. Tempero MA, Malafa MP, Al-Hawary M, et al. Pancreatic adenocarcinoma. Version 2. 2017, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2017;15(8):1028–1061
12. Ueno H, Okusaka T, Ikeda M, Takezako Y, Morizane C. An early phase II study of S-1 in patients with metastatic pancreatic cancer. *Oncology.* 2005;68(2–3):171–178.
13. Ueno H, Ioka T, Ikeda M, et al. Randomized phase III study of gemcitabine plus S-1, S-1 alone, or gemcitabine alone in patients with locally advanced and metastatic pancreatic cancer in Japan and Taiwan: GEST study. *J Clin Oncol.* 2013;31(13):1640–1648.
14. Morizane C, Okusaka T, Furuse J, et al. A phase II study of S-1 in gemcitabine-refractory metastatic pancreatic cancer. *Cancer Chemother Pharmacol.* 2009;63(2):313–319.
15. Sudo K, Yamaguchi T, Nakamura K, Denda T, Hara T, Ishihara T, Yokosuka O. Phase II study of S-1 in patients with gemcitabine-resistant advanced pancreatic cancer. *Cancer Chemother Pharmacol.* 2011;67(2): 249–254.
16. Kharofa J, Tsai S, Kelly T, et al. Neoadjuvant chemoradiation with IMRT in resectable and borderline resectable pancreatic cancer. *Radiother Oncol.* 2014;113(1):41–46.
17. Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys.* 1995;31(5):1341–1346.
18. Qi Q, Zhuang L, Shen Y, et al. A novel systemic inflammation response index (SIRI) for predicting the survival of patients with pancreatic cancer after chemotherapy. *Cancer.* 2016; 122(14): 2158-2167.
19. Lee SH, Chung MJ, Kim B, et al. The significance of the prognostic nutritional index for all stages of pancreatic cancer. *Nutr Cancer.* 2017;69(3): 512–519.
20. Geng Y, Qi Q, Sun M, Chen H, Wang P, Chen Z. Prognostic nutritional index predicts survival and correlates with systemic inflammatory response in advanced pancreatic cancer. *Eur J Surg Oncol.* 2015;41(11):1508–1514.
21. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* 1994;47(11):1245–1251.
22. Dias-Santos D, Ferrone CR, Zheng H, Lillemoe KD, Fernández-Del Castillo C. The Charlson age comorbidity index predicts early mortality after surgery for pancreatic cancer. *Surgery.* 2015;157(5):881–887.

23. Ferrone CR, Finkelstein DM, Thayer SP, Muzikansky A, Fernandez-delCastillo C, Warshaw AL. Perioperative CA19-9 levels can predict stage and survival in patients with resectable pancreatic adenocarcinoma. *J Clin Oncol.* 2006;24(18):2897–2902.
24. Von Hoff DD, Ramanathan RK, Borad MJ, et al. Gemcitabine plus nab-paclitaxel is an active regimen in patients with advanced pancreatic cancer: A phase I/II trial. *J Clin Oncol.* 2011;29(34):4548–4554.
25. Cloyd JM, Wang H, Egger ME, et al. Association of clinical factors with a major pathologic response following preoperative therapy for pancreatic ductal adenocarcinoma. *JAMA Surg.* 2017;152(11):1048–1056.
26. Zhu X, Ju X, Cao F, et al. Safety and efficacy of stereotactic body radiation therapy combined with S-1 simultaneously followed by sequential S-1 as an initial treatment for locally advanced pancreatic cancer (SILAPANC) trial: study design and rationale of a phase II clinical trial. *BMJ Open*. 2016;6(12):e013220.
27. Zhu X, Li F, Ju X, et al. Prognostic role of stereotactic body radiation therapy for elderly patients with advanced and medically inoperable pancreatic cancer. *Cancer Med.* 2017;6(10):2263–2270.
28. Benedict SH, Yenice KM, Followill D, et al. Stereotactic body radiation therapy: the report of AAPM Task Group 101. *Med Phys.* 2010;37(8):4078–4101.
29. Leksell L. The stereotaxic method and radiosurgery of the brain. *Acta Chir Scand.* 1951;102(4):316–319.
30. Hartmann GH, Schlegel W, Sturm V, Kober B, Pastyr O, Lorenz WJ. Cerebral radiation surgery using moving field irradiation at a linear accelerator facility. *Int J Radiat Oncol Biol Phys.* 1985;11(6):1185–1192.
31. Neoptolemos JP, Stocken DD, Friess H, European Study Group for Pancreatic Cancer, et al. A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer. *N Engl J Med.* 2004;350(12):1200–1210.
32. Van Laethem JL, Hammel P, Mornex F, et al. Adjuvant gemcitabine alone versus gemcitabine-based chemoradiotherapy after curative resection for pancreatic cancer: A randomized EORTC-40013-22012/FFCD-9203/GERCOR phase II study. *J Clin Oncol.* 2010;28(29):4450–4456.
33. Neoptolemos JP, Stocken DD, Bassi C, European Study Group for Pancreatic Cancer, et al. Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial. *JAMA.* 2010;304(10):1073–1081.
34. Ueno H, Kosuge T, Matsuyama Y, et al. A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. *Br J Cancer.* 2009;101(6):908–915.
35. Yoshitomi H, Togawa A, Kimura F, Pancreatic Cancer Chemotherapy Program of the Chiba University Department of General Surgery Affiliated Hospital Group, et al. A randomized phase II trial of adjuvant chemotherapy with uracil/tegafur and gemcitabine versus gemcitabine alone in patients with resected pancreatic cancer. *Cancer.* 2008; 113(9): 2448-2456.
36. Palmer DH, Stocken DD, Hewitt H, et al. A randomized phase 2 trial of neoadjuvant chemotherapy in resectable pancreatic cancer: Gemcitabine alone versus gemcitabine combined with cisplatin. *Ann Surg Oncol.* 2007;14(7):2088–2096.
37. Schmidt J, Abel U, Debus J, et al. Open-label, multicenter, randomized phase III trial of adjuvant chemoradiation plus interferon Alfa-2b versus fluorouracil and folinic acid for patients with resected pancreatic adenocarcinoma. *J Clin Oncol.* 2012;30(33):4077–4083.
38. Golcher H, Brunner TB, Witzigmann H, et al. Neoadjuvant chemoradiation therapy with gemcitabine/cisplatin and surgery versus immediate surgery in resectable pancreatic cancer. Results of the first prospective randomized phase II trial. *Strahlenther Onkol.* 2015;191(1):7–16.
39. Reni M, Balzano G, Aprile G, et al. Adjuvant PEFG (cisplatin, epirubicin, 5-fluorouracil, gemcitabine) or gemcitabine followed by chemoradiation in pancreatic cancer: A randomized phase II trial. *Ann Surg Oncol.* 2012;19(7):2256–2263.
40. Hong TS, Ryan DP, Borger DR, et al. A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. *Int J Radiat Oncol Biol Phys.* 2014;89(4):830–838.
41. Demaria S, Formenti SC. Radiation as an immunological adjuvant: Current evidence on dose and fractionation. *Front Oncol.* 2012;2:153.
42. Popp I, Grosu AL, Niedermann G, Duda DG. Immune modulation by hypofractionated stereotactic radiation therapy: Therapeutic implications. *Radiother Oncol.* 2016;120(2):185–194.
43. Krishnan S, Chadha AS, Suh Y, et al. Focal radiation therapy dose escalation improves overall survival in locally advanced pancreatic cancer patients receiving induction chemotherapy and consolidative chemoradiation. *Int J Radiat Oncol Biol Phys.* 2016;94(4):755–765.

Supplementary material

Table S1 PSM-adjusted patient characteristics

Variables	Unadjusted		Post-PSM	
	SBRT + induction chemotherapy (n = 48)	SBRT + adjuvant chemotherapy (n = 52)	SBRT + induction chemotherapy (n = 26)	SBRT + adjuvant chemotherapy (n = 26)
ECOG				
1	24 (50.0)	27 (51.9)	17 (65.4)	18 (69.2)
2	24 (50.0)	25 (48.1)	9 (34.6)	8 (30.8)
BED_{10}				
≥60 Gy	20 (41.7)	38 (73.1)	16 (61.5)	15 (57.7)
<60 Gy	28 (58.3)	14 (26.9)	10 (38.5)	11 (42.3)
BED_{10}				
Median (Gy)	59.5	69.1	61.92	61.92
Range (Gy)	48–79.98	48–88.32	48–79.98	48–85.5
CA19-9 response				
≥74 U/mL with response	15 (31.3)	27 (51.9)	12 (46.2)	13 (50.0)
Remain <74 U/mL	8 (16.7)	17 (32.7)	5 (19.2)	5 (19.2)
≥74 U/mL with no response	25 (52.0)	8 (15.4)	9 (34.6)	8 (30.8)

Note: Data presented as n (%) unless otherwise noted.
Abbreviations: PSM, propensity score matching; SBRT, stereotactic body radiation therapy; ECOG, Eastern Cooperative Oncology Group; BED_{10}, biological effective dose ($\alpha/\beta = 10$).