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

Xiaofei Zhu1,1,*
Fuqi Li1,1,*
Wenyu Liu2,2,*
Dongchen Shi1,1,*
Xiaoping Ju1
Yangsen Cao1
Yuxin Shen1
Fei Cao1
Shuiwang Qing1
Fang Fang1
Zhen Jia1
Huojun Zhang1

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 $\text{BED}_{10}$ (biological effective dose, $\alpha/\beta = 10$) $\geq 60$ 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...
to this curative-intent treatment at the initial diagnosis.\textsuperscript{4,5} The overall 5-year survival rate of those patients even with R0 resection with or without adjuvant therapy is less than 20%.\textsuperscript{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 Shanghai 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.\textsuperscript{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.\textsuperscript{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\textsuperscript{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\textsuperscript{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.\textsuperscript{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.\textsuperscript{17}

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

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

The prognostic nutritional index (PNI) represented patient’s nutritional status, which might also associate with survival of pancreatic cancer.\textsuperscript{19,20} The formula was as follows:

\[
\text{PNI} = 10 \times \text{serum albumin (g/dl)} + 0.005 \times \text{total lymphocyte count} (/mm}^3\text{)}.
\]

Charlson age-comorbidity index (CACI) was originally designed to classify prognostic comorbidity.\textsuperscript{21} It was identified that CACI was associated with prognosis of patients with pancreatic cancer.\textsuperscript{22} Pain was quantified by visual analogue scale (VAS).

The recommended upper limit of normal for CA19-9 is 37 U/mL.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{26,27} SBRT was delivered via CyberKnife\textsuperscript{®} (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.\textsuperscript{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 \( \text{BED}_{10} \) (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 \( \geq 2 \) 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       |
| \( T_{1}N_{0}M_{0} \)            | 5 (10.4)                    | 9 (17.3)                      |            |
| \( T_{2}N_{0}M_{0} \)            | 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       |
| \( \leq 3 \text{ cm} \)          | 26 (54.2)                   | 32 (61.5)                     |            |
| \( >3 \text{ cm} \)             | 22 (45.8)                   | 20 (30.5)                     |            |
| **Baseline CA19-9 (U/mL)**       |                             |                               | 0.17       |
| \( \leq 200 \)                   | 24 (50.0)                   | 33 (63.5)                     |            |
| \( >200 \)                       | 24 (50.0)                   | 19 (36.5)                     |            |
| **\( \text{BED}_{10} \)**        |                             |                               | 0.001      |
| \( \geq 60 \text{ Gy} \)         | 20 (41.7)                   | 38 (73.1)                     |            |
| \( <60 \text{ Gy} \)            | 28 (58.3)                   | 14 (26.9)                     |            |
| **\( \text{BED}_{10} \)**        |                             |                               |            |
| 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** |                       |                               | 0.001      |
| Median                           | 15.0                        | 21.0                          |            |
| 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; \( \text{BED}_{10} \), biological effective dose (\( \alpha/\beta = 10 \)); f, fractions
SBRT in early stage pancreatic cancer

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

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

| Variable                  | n = 100 | Univariate, overall survival (months) | Median | 95% CI | P-value (log-rank) | Multivariate, hazard ratio | P-value (Cox regression) |
|---------------------------|---------|---------------------------------------|--------|--------|--------------------|---------------------------|-------------------------|
| Age                       |         |                                       |        |        |                    |                           |                         |
| <65                       | 40      | 19.5                                 | 14.3–24.7 | 0.293 | NS                 | NS                        | NS                      |
| ≥65                       | 60      | 16.7                                 | 17.1–19.2 | NS    | NS                 | NS                        | NS                      |
| Smoking                   |         |                                       |        |        |                    |                           |                         |
| Absent                    | 70      | 17.1                                 | 15.4–18.8 | 0.086 | NS                 | NS                        | NS                      |
| Present                   | 30      | 19.7                                 | 13.8–25.6 | NS    | NS                 | NS                        | NS                      |
| Diabetes mellitus         |         |                                       |        |        |                    |                           |                         |
| Absent                    | 73      | 16.7                                 | 14.9–18.5 | 0.157 | NS                 | NS                        | NS                      |
| Present                   | 27      | 19.5                                 | 13.8–25.2 | NS    | NS                 | NS                        | NS                      |
| VAS                       |         |                                       |        |        |                    |                           |                         |
| <3                        | 61      | 20.2                                 | 15.7–24.7 | 0.168 | NS                 | NS                        | NS                      |
| ≥3                        | 39      | 16.3                                 | 14.0–18.5 | NS    | NS                 | NS                        | NS                      |
| Weight loss               |         |                                       |        |        |                    |                           |                         |
| <5kg                      | 72      | 18.3                                 | 14.6–22.0 | 0.227 | NS                 | NS                        | NS                      |
| ≥5kg                      | 28      | 16.3                                 | 14.7–17.8 | NS    | NS                 | NS                        | NS                      |
| Tumor diameter            |         |                                       |        |        |                    |                           |                         |
| ≤3cm                      | 58      | 17.7                                 | 14.3–21.1 | 0.966 | NS                 | NS                        | NS                      |
| >3cm                      | 42      | 16.9                                 | 14.3–19.4 | NS    | NS                 | NS                        | NS                      |
| ECOG                      |         |                                       |        |        |                    |                           |                         |
| 1                         | 41      | 19.2                                 | 16.4–22.0 | 0.441 | NS                 | NS                        | NS                      |
| 2                         | 59      | 15.7                                 | 12.4–19.0 | NS    | 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                      |
| >0.8                      | 48      | 19.7                                 | 13.0–26.3 | NS    | NS                 | NS                        | NS                      |
| PNI                       |         |                                       |        |        |                    |                           |                         |
| <48.5                     | 49      | 16.9                                 | 11.0–22.8 | 0.768 | NS                 | NS                        | NS                      |
| ≥48.5                     | 51      | 17.5                                 | 15.4–19.6 | NS    | NS                 | NS                        | NS                      |
| CACI                      |         |                                       |        |        |                    |                           |                         |
| ≤5                        | 79      | 17.5                                 | 15.7–19.3 | 0.878 | NS                 | NS                        | NS                      |
| >5                        | 21      | 17.7                                 | 12.6–22.8 | NS    | NS                 | NS                        | NS                      |
| CA19-9                    |         |                                       |        |        |                    |                           |                         |
| <200 U/mL                 | 57      | 19.5                                 | 17.0–22.0 | 0.107 | NS                 | NS                        | NS                      |
| ≥200 U/mL                 | 43      | 15.8                                 | 14.1–17.5 | NS    | 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 ($\alpha/\beta = 10$)
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

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**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.
SBRT in early stage pancreatic cancer

The 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 and steep dose gradients through multiple beam directions, 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 $\text{BED}_{10} \geq 60$ Gy achieved better tumor response 6 months after SBRT than those who received $\text{BED}_{10} < 60$ Gy, though no correlation was found between the radiation

| 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 |
| ≥65                   | 60      | 13.7   | 11.6–15.8       | NS                | NS | NS     | NS |
| Smoking               |         |        |                 |                   |    |        |   |
| Absent                | 70      | 13.2   | 11.7–14.6       | 0.185             | NS | NS     | NS |
| Present               | 30      | 16.4   | 12.0–20.8       | NS                | NS | NS     | NS |
| Diabetes mellitus     |         |        |                 |                   |    |        |   |
| Absent                | 73      | 13.2   | 11.9–14.5       | 0.062             | NS | NS     | NS |
| Present               | 27      | 16.4   | 12.3–20.5       | NS                | NS | NS     | NS |
| VAS                   |         |        |                 |                   |    |        |   |
| <3                    | 61      | 14.6   | 11.6–17.6       | 0.242             | NS | NS     | NS |
| ≥3                    | 39      | 13.2   | 12.2–14.1       | NS                | NS | NS     | NS |
| Weight loss           |         |        |                 |                   |    |        |   |
| <5kg                  | 72      | 13.7   | 12.1–15.3       | 0.964             | NS | NS     | NS |
| ≥5kg                  | 28      | 14.4   | 11.3–17.5       | NS                | NS | NS     | NS |
| Tumor diameter        |         |        |                 |                   |    |        |   |
| ≤3cm                  | 58      | 13.7   | 11.3–16.1       | 0.601             | NS | NS     | NS |
| >3cm                  | 42      | 13.5   | 11.6–15.4       | NS                | NS | NS     | NS |
| ECOG                  |         |        |                 |                   |    |        |   |
| 1                     | 41      | 14.6   | 12.0–17.2       | 0.565             | NS | NS     | NS |
| 2                     | 59      | 12.3   | 9.9–14.7        | NS                | 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 |
| >0.8                  | 48      | 14.0   | 11.7–16.3       | NS                | NS | NS     | NS |
| PNI                   |         |        |                 |                   |    |        |   |
| ≤48.5                 | 49      | 14.2   | 12.4–16.0       | 0.485             | NS | NS     | NS |
| >48.5                 | 51      | 13.2   | 11.7–14.7       | NS                | NS | NS     | NS |
| CACI                  |         |        |                 |                   |    |        |   |
| ≤5                    | 79      | 13.9   | 12.6–15.2       | 0.908             | NS | NS     | NS |
| >5                    | 21      | 12.6   | 6.8–18.4        | NS                | NS | NS     | NS |
| CA19-9                |         |        |                 |                   |    |        |   |
| <200 U/mL             | 57      | 14.7   | 11.9–17.5       | 0.520             | NS | NS     | NS |
| ≥200 U/mL             | 43      | 12.9   | 11.5–14.3       | NS                | 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 |
| <60                   | 42      | 10.5   | 9.9–11.1        | NS                | 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 ($\alpha/\beta = 10$).
dose and survival. However, it was shown in this study that BED$_{10}$ $\geq$ 60 Gy associated with OS and PFS. Likewise, Krishnan et al 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$_{10}$ $\geq$ 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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The authors report no conflict of interest in this work.

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Supplementary material

Table S1 PSM-adjusted patient characteristics

| Variables                  | Unadjusted SBRT + induction chemotherapy (n = 48) | SBRT + adjuvant chemotherapy (n = 52) | Post-PSM 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 ($\alpha/\beta = 10$).