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Personalized designs of adjuvant radiotherapy for pancreatic cancer based on molecular profiles

Xiaofei Zhu | Yangsen Cao | Xiaoping Ju | Xianzhi Zhao | Lingong Jiang | Yusheng Ye | Yuxin Shen | Fei Cao | Shuiwang Qing | Huojun Zhang

Departmant of Radiation Oncology, Changhai hospital affiliated to Navy Medical University, Shanghai, China

Correspondence
Huojun Zhang, Department of Radiation Oncology, Changhai Hospital affiliated to Navy Medical University, Shanghai, 168 Changhai Road, Shanghai 200433, China.
Email: chyyzhj@163.com

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Abstract

This study aims to identify postoperative recurrence patterns of pancreatic cancer with different molecular profiles, which provides evidence for personalized target volumes of adjuvant radiotherapy. Patients with pathologically confirmed resectable pancreatic ductal adenocarcinoma were included. Recurrences were treated with stereotactic body radiation therapy. Immunohistochemical staining of Ki-67, P53, and programmed cell death-ligand 1 (PD-L1) was carried out. Both of the intensities of Ki-67 and P53 were classified as 10% or less, 11%-49%, and 50% or more. Eighty-nine patients had PD-L1 tested, stratified as TC0 and IC0, and TC1/2 or IC1/2. Distances with significant differences among different levels or beyond 10 mm were of interest. With the increasing intensity of Ki-67, the distance from the superior and posterior border of 80% recurrences to the celiac axis (CA) ranged from 10.1 to 13.8 mm and 9.2 to 11.0 mm. The distance from the inferior and posterior border of 80% recurrences to the superior mesenteric artery (SMA) ranged from 9.4 to 9.9 mm and 9.4 to 11.0 mm. Similarly, with the increasing intensity of P53, the distance from the superior and posterior border of 80% recurrences to the CA ranged from 9.7 to 13.2 mm and 10.1 to 10.6 mm. The distance from the inferior and anterior border of 80% recurrences to the SMA ranged from 9.5 to 9.9 mm and 8.6 to 9.4 mm. Regarding the increasing level of PD-L1, the distance from the superior border of 80% recurrences to the CA ranged from 10.9 to 13.5 mm. A biologically effective dose of more than 65 Gy to local recurrences was predictive of favorable outcomes in all levels of Ki-67, P53, and PD-L1. Nonuniform expansions of regions of interest based on different levels of molecular profiles to form target volumes could cover most recurrences, which might be feasible for adjuvant radiotherapy.

KEYWORDS

molecular profile, pancreatic cancer, personalized, radiotherapy, target volume delineation

Abbreviations: BED_{10}, biologically effective dose, $\alpha/\beta = 10$; CA, celiac axis; CT, computed tomography; GTV, gross tumor volume; NCCN, National Comprehensive Cancer Network; OS, overall survival; PD-L1, programmed cell death-ligand 1; PFS, progression-free survival; PTV, planning target volume; ROI, region of interest; RTOG, Radiation Therapy Oncology Group; SBRT, stereotactic body radiation therapy; SMA, superior mesenteric artery.

Xiaofei Zhu, Yangsen Cao, and Xiaoping Ju contributed equally to this article.

1 | INTRODUCTION

Despite the controversy of optimal adjuvant therapy, it was recommended that standard treatment included chemotherapy alone or chemoradiation in the case of microscopically margin-positive and/or node-positive disease in the NCCN guideline and American Society of Clinical Oncology clinical practice guideline.[1] Regarding the delineation of clinical target volumes for adjuvant radiotherapy, only the RTOG consensus guideline and later a new approach to radiation field design were proposed.[2,3] However, the contouring of target volumes was identical in all patients based on the atlas. In the case of different molecular profiles, distinct prognosis could be found even if patients with resectable pancreatic cancer were receiving the same treatment, which implied that design of personalized target volumes should be taken into consideration.

As a result, a thorough analysis of patterns of local failure after pancreaticodudenectomy and the correlation between outcomes and doses to recurrent lesions based on molecular profiles could be beneficial for more accurate treatment plan design. This study was designed to investigate the location of radiographic local recurrence in relation to major blood vessels to construct the individualized and reproducible contouring of target volumes and optimal doses to recurrences.

2 | METHODS

2.1 | Patient selection

The study was approved by our institutional review board. Patients with pathologically and radiographically confirmed resectable pancreatic ductal adenocarcinoma receiving pancreaticodudenectomy were included. Written informed consent was required before treatment. A prospective maintained database was used to obtain follow-up information. Patients with neoadjuvant therapy, surgery other than pancreaticodudenectomy, and without completion of adjuvant chemotherapy were excluded. Patients were required to receive imaging examinations, including contrast-enhanced CT and MRI, every 2-3 months after treatment during follow-up.

Identification of recurrence was similar to our previous study.[4] Local recurrence was identified as progressive disease inferior to the diaphragm and superior to the bottom of the L3 vertebra excluding hepatic or gastric metastases[3] according to the RECIST criteria,[5] where it was determined as at least a 20% increase in the sum of diameters of the tumor and a minimum of a 5 mm increase. Additionally, a new lesion located in the hepatic hilum was defined as local recurrence.

Data were saved in the database of our center, which would be available with the approval of investigators of this study.

2.1.1 | Immunohistochemical staining of Ki-67, P53, and PD-L1

All surgical specimens underwent immunohistochemical staining of Ki-67 and P53 by the EliVision Plus method. Levels of PD-L1 were evaluated by VENTANA PD-L1 (SP142) Assay in formalin-fixed tumor samples from tumor tissues. The signal intensity of Ki-67 and P53 was categorized into 3 grades: 10% or less, 11%-49%, and 50% or more. As no patient had PD-L1 expression on 50% or more of tumor cells and 10% or more of tumor-infiltrating immune cells, PD-L1 was stratified by TC0 and IC0, and TC1/2 or IC1/2. TC0 and IC0 were defined as PD-L1 expression on less than 1% tumor cells and tumor-infiltrating immune cells, respectively. TC1/2 was defined as PD-L1 expression on 1% or more but less than 50% of tumor cells. IC1/2 was defined as PD-L1 expression on 1% or more but less than 10% of tumor-infiltrating immune cells.[6]

2.2 | Delivery of treatment

The protocol of SBRT was similar to our previous studies.[4,7,8] Stereotactic body radiation therapy was delivered by CyberKnife (Accuray). Three fiducials within or adjacent to the tumor were preferable. Synchrony Respiratory Tracking System (Accuray) was used. The GTV was defined as the gross disease identified in the imaging examinations. The PTV was generated based on 2-5 mm margin expansions from GTV. Doses were prescribed to the 75%-80% isodose covering at least 90% of the PTV. Dose constraints of organs at risk were referred to the American Association of Physicists in Medicine guidelines in TG-101.[9] The delineations of targets and organs at risk were reviewed together by a radiation oncologist and a radiologist. Triphasic CT was used to delineate tumor.

Patients were required to receive gemcitabine as adjuvant chemotherapy based on NCCN guidelines. Gemcitabine (1000 mg/m^2) was given on days 1, 8, and 15 during each 4-week cycle, which repeated for 4-6 cycles. Once local recurrences were confirmed, patients were required to receive SBRT. The same dose that was prescribed to the recurrent lesion at the CA and SMA would also be given to the recurrence at the hepatic hilum in the case of 2 isolated recurrences.

2.3 | Recurrence mapping

The creation of failure mapping had been described in our previous study.[4] Recurrences were plotted on a template CT scan of a patient after pancreaticoduodenectomy, creating a 3-D map of local recurrence that was relative to the CA and SMA, scaling for individual abdominal width. Because the recurrence mapping was based on estimations of the location of each recurrence, there might be uncertainty between the estimation and the origin of each failure. Hence,

TABLE 1 Characteristics of 438 patients with pancreatic ductal adenocarcinoma

Characteristics	
No. of patients	438
Median age (range), y	59.5 (29-84)
Gender, n (%)	
Male	271 (61.9)
Female	167 (38.1)
T stage	
T1	206 (47.0)
T2	232 (33.0)
N stage	
N0	287 (65.5)
N1	151 (24.5)
Margin status	
R0	398 (90.9)
R1	40 (9.1)
Lymphovascular invasion	
Negative	294 (67.1)
Positive	144 (32.9)
Differentiation	
Poor	23 (5.2)
Moderate	253 (57.8)
Well	162 (37.0)
Median tumor diameter before surgical resection (range), cm	2.8 (0.6-4.8)
Median volume of recurrent lesions invading the CA and SMA (range), cm^3 (N = 438)	91.4 (9.7-184.3)
Median volume of recurrent lesions at the hepatic hilum (range), cm^3 (N = 41)	96.1 (15.4-195.5)
Ki-67 signal intensity, n (%)	
≤10%	116 (26.5)
11%-49%	152 (34.7)
≥50%	170 (38.8)
P53 signal intensity, n (%)	
≤10%	261 (59.6)
11%-49%	79 (18.0)
≥50%	98 (22.4)
PD-L1 expression level, n (%) (N = 89)	
TC0 and IC0	68 (76.4)
TC1/2 or IC1/2	21 (23.6)
Median prescription dose (range), Gy	38.4 (30-49.7)/5-8 fractions
Median BED_{10} (range), Gy	64.38 (48-84.987)/5-8 fractions

BED_{10}, biologically effective dose, $\alpha/\beta = 10$; CA, celiac axis; IC0, PD-L1 expression on less than 1% tumor-infiltrating immune cells; IC1/2, PD-L1 expression on 1% or more but less than 10% of tumor-infiltrating immune cells; PD-L1, programmed cell death-ligand 1; SMA, superior mesenteric artery; TC0, PD-L1 expression on less than 1% tumor cells; TC1/2, PD-L1 expression on 1% or more but less than 50% of tumor cells.

2 radiologists specialized in abdominal imaging and a radiation oncologist identified and plotted all recurrences in order to minimize the impact. Furthermore, the volumes of all recurrent lesions were measured. The distances from the anterior, posterior, superior, inferior, right, and left borders of the recurrence to the origin of the CA and SMA were also recorded.

2.4 | Statistical analysis

Continuous variables are depicted as the median and range, and categorical variables are summarized as number (%). Continuous tumor characteristics of subgroups with different signal intensity (3 subgroups) of each molecular profile were compared with ANOVA (normally distributed continuous covariates) or Kruskal-Wallis test (nonnormally distributed continuous covariates). Regarding only 2 subgroups, Student's *t* test or the Mann-Whitney *U* test was used for analysis in the case of normally or nonnormally distributed continuous covariates. Categorical variables were compared using the χ^2 test. Total OS was defined as the time from the date of surgical resection to death from any cause. The rest OS was determined as the time from the date of SBRT to death from any cause. Disease control was evaluated by PFS, which was defined as the time from the date of surgery to any disease progression before SBRT. Both OS and PFS were assessed using the Kaplan-Meier method. In the case of evaluations of radiation doses, Cox proportional hazards regression was undertaken to calculate hazard ratios (with a hazard ratio less than 1 favoring a biologically effective dose greater than 65 Gy). All tests were 2-sided and *P* values of <.05 were considered significant. Additionally, regarding comparisons between each of the 2 subgroups (within 3 subgroups), *P* values of <.0167 were considered significant. Statistical analyses were undertaken with SPSS version 22.0 (SPSS).

3 | RESULTS

3.1 | Patient characteristics

The baseline clinical characteristics are shown in Table 1. Four hundred and thirty-eight patients with radiographically and pathologically confirmed resectable pancreatic ductal adenocarcinoma were included. The median follow-up was 28.3 months (range, 9.9-49.5 months). There were 116, 152, and 170 patients with the signal intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more, respectively. Furthermore, the signal intensity of P53 of 10% or less, 11%-49%, and 50% or more was found in 261, 79, and 98 patients, respectively. Due to recent clinical practice of immunotherapy, PD-L1 was tested in 89 patients, with 68 and 21 having the expression level of TC0 and IC0, and TC1/2 or IC1/2. The median biologically effective dose (BED_{10}, α/β = 10) was 64.38 (48-84.987)/5-8 fractions.

3.2 | Recurrence patterns

The recurrent lesions of included patients were in the posterior space of the operative beds. Recurrences at the hepatic hilum were simultaneously found in 41 patients. Among them, 4 (3.4%), 10 (6.6%), and 27 patients (15.9%) had the intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more, respectively (*P* = .001). Regarding the intensity of P53 of 10% or less, 11%-49%, and 50% or more, recurrences at the hepatic hilum were found in 16 (6.1%), 11 (13.9%), and 14 patients (14.3%), respectively (*P* = .02). Four (5.9%) and 5 (23.8%) patients with a PD-L1 level of TC0 and IC0, and TC1/2 or IC1/2 experienced recurrences at the hepatic hilum, respectively (*P* = .028).

Moreover, regarding the recurrence at the CA and SMA, the median volume of patients with the intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more was 73.95 cm^3 (range, 10.1-139.2 cm^3), 93.95 cm^3 (range, 9.7-163.2 cm^3), and 105.6 cm^3 (range, 11.4-184.3 cm^3), respectively (*P* < .001; 10% or less vs 11%-49%, *P* = .012; 10% or less vs 50% or more, *P* < .001; 11%-49% vs 50% or more, *P* = .014). The median volume of patients with the intensity of P53 of 10% or less, 11%-49%, and 50% or more was 84.6 cm^3 (range, 9.7-184.3 cm^3), 94.3 cm^3 (range, 12.6-180.1 cm^3), and 101.75 cm^3 (range, 10.1-177.9 cm^3), respectively (*P* = .057). Considering the level of PD-L1 of TC0 and IC0, and TC1/2 or IC1/2, the median volume was 88.85 cm^3 (range, 10.1-180.1 cm^3) and 81.0 cm^3 (range, 23.2-181.4 cm^3), respectively (*P* = .790).

In the case of recurrences at the hepatic hilum, the median volume of patients with the intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more was 38.8 cm^3 (range, 20.5-47.7 cm^3), 72.75 cm^3 (range, 15.4-159.8 cm^3) and 120.8 cm^3 (range, 45.1-195.5 cm^3), respectively (*P* = .001; 10% or less vs 11%-49%, *P* = .109; 10% or less vs 50% or more, *P* = .001; 11%-49% vs 50% or more, *P* = .015). The median volume of patients with the intensity of P53 of 10% or less, 11%-49%, and 50% or more was 34.05 cm^3 (range, 20.6-49.7 cm^3), 54.7 cm^3 (range, 36.8-69.6 cm^3), and 59.55 cm^3 (range, 47.3-84.2 cm^3), respectively (*P* < .001; 10% or less vs 11%-49%, *P* = .001; 10% or less vs 50% or more, *P* < .001; 11%-49% vs 50% or more, *P* = .149). Additionally, the median volume of patients with the level of PD-L1 of TC0 and IC0, and TC1/2 or IC1/2 was 48.6 cm^3 (range, 41.8-62.3 cm^3) and 86.8 cm^3 (range, 60.5-91.9 cm^3), respectively (*P* = .032).

Details of all distances from different borders of recurrences to the CA and SMA are shown in Table 2 and Figures 1 and 2. In the case of the signal intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more, the mean distance from the superior border to the CA was 8.4 ± 1.6 mm, 9.3 ± 1.0 mm and 11.5 ± 2.2 mm, respectively (*P* < .001; 10% or less vs 11%-49%, *P* < .001; 10% or less vs 50% or more, *P* < .001; 11%-49% vs 50% or more, *P* < .001). Eighty percent of recurrences were within a distance of 10.1 mm, 10.3 mm, and 13.8 mm among the 3 levels. The mean distance from the inferior border to the SMA was 8.2 ± 1.1 mm, 8.5 ± 1.2 mm, and 8.9 ± 1.0 mm, respectively (*P* < .001; 10% or less vs 11%-49%, *P* = .078; 10% or less vs 50% or more, *P* < .001; 11%-49% vs 50% or more, *P* = .006). Eighty percent of recurrences were within a distance of 9.4 mm, 9.7 mm, and 9.9 mm among the 3 levels. The mean distance from the posterior border to the CA was 7.9 ± 1.2 mm, 8.8 ± 1.2 mm, and 9.6 ± 1.3 mm, respectively (*P* < .001; 10% or less vs 11%-49%, *P* < .001; 10% or less vs 50% or more, *P* < .001; 11%-49% vs 50% or more, *P* < .001). Eighty percent of recurrences were within a distance of 9.2 mm, 10.0 mm, and 11.0 mm among

TABLE 2 Mean distances from recurrence to celiac axis (CA) and superior mesenteric artery (SMA) of different molecular profiles

	Ki-67						
	≤10%	11%-49%	≥50%	*P* value	*P* value (≤10% vs 11%-49%)	*P* value (≤10% vs ≥50%)	*P* value (11%-49% vs ≥50%)
Superior border to CA (mm)	8.4 ± 1.6	9.3 ± 1.0	11.5 ± 2.2	<.001	<.001	<.001	<.001
Inferior border to SMA (mm)	8.2 ± 1.1	8.5 ± 1.2	8.9 ± 1.0	<.001	.078	<.001	.006
Anterior border to CA (mm)	7.7 ± 1.6	7.8 ± 1.5	7.6 ± 1.5	.465	—	—	—
Anterior border to SMA (mm)	7.6 ± 1.5	7.6 ± 1.5	7.4 ± 1.4	.372	—	—	—
Posterior border to CA (mm)	7.9 ± 1.2	8.8 ± 1.2	9.6 ± 1.3	<.001	<.001	<.001	<.001
Posterior border to SMA (mm)	8.1 ± 1.2	9.0 ± 1.2	9.6 ± 1.2	<.001	<.001	<.001	<.001
Left border to CA (mm)	8.5 ± 1.3	8.7 ± 1.4	8.5 ± 1.3	.374	—	—	—
Left border to SMA (mm)	8.1 ± 1.4	8.2 ± 1.3	8.1 ± 1.4	.989	—	—	—
Right border to CA (mm)	7.9 ± 1.5	8.1 ± 1.5	8.2 ± 1.5	.267	—	—	—
Right border to SMA (mm)	8.5 ± 1.4	8.2 ± 1.4	8.5 ± 1.5	.157	—	—	—
	P53						
	≤10%	11%-49%	≥50%	*P* value	*P* value (≤10% vs 11%-49%)	*P* value(≤10% vs ≥50%)	*P* value(11%-49% vs ≥50%)
Superior border to CA (mm)	9.6 ± 2.0	10.1 ± 2.1	10.7 ± 2.2	<.001	.095	<.001	.086
Inferior border to SMA (mm)	8.5 ± 1.2	8.4 ± 1.1	8.9 ± 1.0	.012	.686	.006	.013
Anterior border to CA (mm)	7.7 ± 1.6	7.7 ± 1.5	7.7 ± 1.4	.941	—	—	—
Anterior border to SMA (mm)	7.4 ± 1.4	7.9 ± 1.5	7.4 ± 1.4	.013	.006	.771	.010
Posterior border to CA (mm)	8.8 ± 1.4	8.8 ± 1.4	9.2 ± 1.4	.043	.756	.020	.037
Posterior border to SMA (mm)	8.9 ± 1.4	8.9 ± 1.4	9.3 ± 1.4	.149	—	—	—
Left border to CA (mm)	8.7 ± 1.4	8.4 ± 1.3	8.5 ± 1.4	.115	—	—	—
Left border to SMA (mm)	8.1 ± 1.4	8.4 ± 1.4	8.0 ± 1.3	.229	—	—	—
Right border to CA (mm)	8.0 ± 1.6	8.0 ± 1.2	8.2 ± 1.6	.682	—	—	—
Right border to SMA (mm)	8.4 ± 1.4	8.6 ± 1.4	8.3 ± 1.5	.250	—	—	—
	PD-L1						
	TC0 and IC0		TC1/2 or IC1/2			*P* value	
Superior border to CA (mm)	9.6 ± 2.3		10.9 ± 2.2			.011	
Inferior border to SMA (mm)	8.7 ± 1.2		8.5 ± 1.1			.387	
Anterior border to CA (mm)	7.5 ± 1.4		7.7 ± 1.7			.578	
Anterior border to SMA (mm)	7.5 ± 1.4		8.2 ± 1.4			.056	
Posterior border to CA (mm)	8.9 ± 1.3		9.0 ± 1.2			.826	
Posterior border to SMA (mm)	9.1 ± 1.3		8.5 ± 1.5			.095	
Left border to CA (mm)	8.3 ± 1.2		8.4 ± 1.5			.750	
Left border to SMA (mm)	8.3 ± 1.3		8.1 ± 1.2			.721	
Right border to CA (mm)	8.3 ± 1.3		8.0 ± 1.5			.261	
Right border to SMA (mm)	8.3 ± 1.3		8.4 ± 1.4			.721	

the 3 levels. The mean distance from the posterior border to the SMA was 8.1 ± 1.2 mm, 9.0 ± 1.2 mm, and 9.6 ± 1.2 mm, respectively ($P < .001$; 10% or less vs 11%-49%, $P < .001$; 10% or less vs 50% or more, $P < .001$; 11%-49% vs 50% or more, $P < .001$). Eighty percent of recurrences were within a distance of 9.4 mm, 10.3 mm, and 11.0 mm among the 3 levels.

Regarding the intensity of P53 of 10% or less, 11%-49%, and 50% or more, the mean distance from the superior border to the CA was 9.6 ± 2.0 mm, 10.1 ± 2.1 mm, and 10.7 ± 2.2 mm, respectively ($P < .001$; 10% or less vs 11%-49%, $P = .095$; 10% or less vs 50% or more, $P < .001$; 11%-49% vs 50% or more, $P = .086$). Eighty percent of recurrences were within a distance

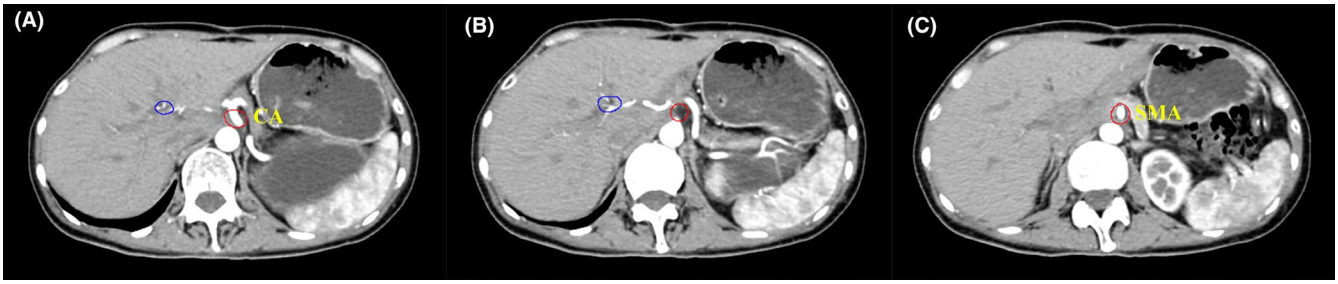

FIGURE 1 Transverse plane of local recurrence plots in relation to the celiac axis (CA), superior mesenteric artery (SMA), and the hepatic hilum in patients with pancreatic ductal adenocarcinoma. A, B, The areas encompassed by the red and blue lines indicated the gross tumor volume of recurrences at the CA and hepatic hilum, respectively. C, The area in the red line indicates the gross tumor volume of recurrences at the SMA

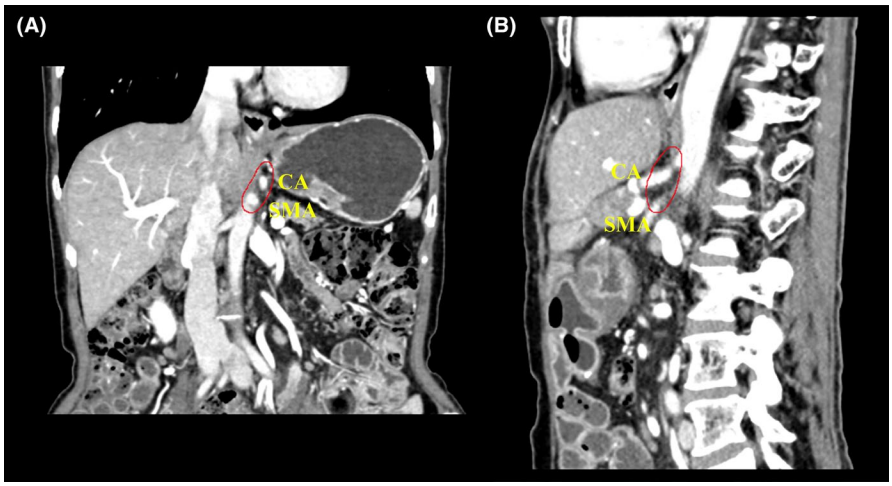

FIGURE 2 Coronal (A) and sagittal plane (B) of local recurrence plots of pancreatic ductal adenocarcinoma in relation to the celiac axis (CA) and superior mesenteric artery (SMA). The areas encompassed by the red line indicate the gross tumor volume of recurrences at the CA and SMA

of 9.7 mm, 11.8 mm, and 13.2 mm among the 3 levels. The mean distance from the inferior border to the SMA was 8.5 ± 1.2 mm, 8.4 ± 1.1 mm, and 8.9 ± 1.0 mm, respectively (P = .012; 10% or less vs 11%-49%, P = .686; 10% or less vs 50% or more, P = .006; 11%-49% vs 50% or more, P = .013). Eighty percent of recurrences were within a distance of 9.7 mm, 9.5 mm, and 9.9 mm among the 3 levels. The mean distance from the anterior border to the SMA was 7.4 ± 1.4 mm, 7.9 ± 1.5 mm, and 7.4 ± 1.4 mm, respectively (P = .013; 10% or less vs 11%-49%, P = .006; 10% or less vs 50% or more, P = .771; 11%-49% vs 50% or more, P = .010). Eighty percent of recurrences were within a distance of 8.9 mm, 9.4 mm, and 8.6 mm among the 3 levels. The mean distance from the posterior border to the CA was 8.8 ± 1.4 mm, 8.8 ± 1.4 mm, and 9.2 ± 1.4 mm, respectively (P = .043; 10% or less vs 11%-49%, P = .756; 10% or less vs 50% or more, P = .020; 11%-49% vs 50% or more, P = .037). Eighty percent of recurrences were within a distance of 10.1 mm, 10.2 mm, and 10.6 mm among the 3 levels.

For the level of PD-L1 of TC0 and IC0, and TC1/2 or IC1/2, the mean distance from the superior border to the CA was 9.6 ± 2.3 mm and 10.9 ± 2.2 mm, respectively (P = .011). Eighty percent of recurrences were within a distance of 10.9 mm and 13.5 mm among the 2 levels.

3.3 | Outcomes of patients with different molecular profiles

The total OS of patients with the signal intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more was 34.5 months (95% CI, 32.5-36.5 months), 30.1 months (95% CI, 29.0-31.2 months), and 23.2 months (95% CI, 21.8-24.6 months), respectively (P < .001; 10% or less vs 11%-49%, P < .001; 10% or less vs 50% or more, P < .001; 11%-49% vs 50% or more, P < .001). The total OS of patients with the signal intensity of P53 of 10% or less, 11%-49%, and 50% or more was 29.2 months (95% CI, 27.8-30.6 months), 32.3 months (95% CI, 28.3-36.3 months) and 24.7 months (95% CI, 23.0-26.4 months), respectively (P < .001; 10% or less vs 11%-49%, P = .123; 10% or less vs 50% or more, P < .001; 11%-49% vs 50% or more, P < .001). Additionally, the total OS of patients with the level of PD-L1 of TC0 and IC0, and TC1/2 or IC1/2 was 34.3 months (95% CI, 32.1-36.5 months) and 25.4 months (95% CI, 20.9-30.0 months) (P = .010).

The PFS of patients with the signal intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more was 19.2 months (95% CI, 18.1-20.2 months), 18.6 months (95% CI, 17.7-19.5 months), and 14.9 months (95% CI, 13.7-16.1 months), respectively (P < .001; 10% or less vs 11%-49%, P = .132; 10% or less vs 50% or more, P < .001; 11%-49% vs 50% or more, P < .001). The PFS of patients with the

signal intensity of P53 of 10% or less, 11%-49%, and 50% or more was 18.3 months (95% CI, 17.8-18.8 months), 18.6 months (95% CI, 17.6-19.6 months), and 14.4 months (95% CI, 13.4-15.4 months), respectively (P = .001; 10% or less vs 11%-49%, P = .913; 10% or less vs 50% or more, P < .001; 11%-49% vs 50% or more, P = .004). Additionally, the PFS of patients with the level of PD-L1 of TC0 and IC0, and TC1/2 or IC1/2 was 20.0 months (95% CI, 17.7-22.3 months) and 17.4 months (95% CI, 14.0-20.8 months) (P = .008).

3.4 | Correlation between survival and dose escalation in different molecular profiles

The rest OS of patients with the signal intensity of Ki-67 of 10% or less, 11%-49%, and 50% or more was 13.1 months (95% CI, 11.5-14.7 months), 10.8 months (95% CI, 10.1-11.5 months), and 7.3 months (95% CI, 6.5-8.1 months), respectively (P < .001; 10% or less vs 11%-49%, P < .001; 10% or less vs 50% or more, P < .001; 11%-49% vs 50% or more, P < .001). The rest OS of patients with the signal intensity of P53 of 10% or less, 11%-49%, and 50% or more was 10.5 months (95% CI, 9.6-11.4 months), 10.9 months (95% CI, 9.8-12.0 months), and 8.4 months (95% CI, 7.4-9.4 months), respectively (P < .001; 10% or less vs 11%-49%, P = .215; 10% or less vs 50% or more, P < .001; 11%-49% vs 50% or more, P < .001). Additionally, the rest OS of patients with the level of PD-L1 of TC0 and IC0, and TC1/2 or IC1/2 was 11.9 months (95% CI, 9.7-14.1 months) and 10.1 months (95% CI, 7.0-13.2 months) (P = .034) (Figure 3).

The median BED_{10} of the whole cohort was 64.38 Gy, therefore, BED_{10} of 65 Gy was taken as the cut-off. Associations between survival benefits and doses are provided in detail in Table 3. It was clarified that higher doses could provide survival benefits for patients with all expression levels of Ki-67, P53, and PD-L1.

4 | DISCUSSION

Local recurrence still remains a major cause of mortality and morbidity in resectable pancreatic cancer after surgical resection. Therefore, precise adjuvant radiotherapy could be pivotal for improvement of survival. However, the RTOG consensus and modifications[3] of contouring of target volumes were identical in all patients. Due to outcomes probably dependent on molecular profiles of tumors, delineations based on molecular profiles of pancreatic adenocarcinoma could favor personalized treatment. Hence, to the best of our knowledge, this is the first study to clarify patterns of local failure of different molecular profiles.

The study showed that more patients with a higher level of Ki-67, P53, and PD-L1 experienced recurrences both at the CA and SMA and the hepatic hilum. This implied a correlation between higher expression levels of Ki-67, P53, and PD-L1 and higher tumor burden after recurrence, which corresponded with the larger volumes of recurrent lesions at the CA and SMA and hepatic hilum. Therefore, it might indicate a poorer prognosis in those patients. This was confirmed in the study, which showed that superior survival was found in patients with weaker signal intensities of Ki-67 and P53 and lower levels of PD-L1. This was consistent with previous studies showing the negative impacts of high levels of Ki-67, P53, and PD-L1 on outcomes.[10,11]

In RTOG consensus, 10 mm uniform expansions on the CA and SMA were required to form clinical target volume. It might result in inadequate radiation due to nonuniform involvement of the CA and SMA by the tumor. Thus, a deeper understanding about the association between molecular profiles of tumors and patterns of failure was necessary. In this study, it was clarified that the distance from the superior and inferior border of the recurrence to the CA and SMA, and the posterior border of the recurrence to the CA and SMA increased significantly in the case of a stronger intensity of Ki-67. In addition to the former 3 distances, a longer distance from the anterior border of the recurrence to the SMA was found in patients with a stronger intensity of P53. With the increasing level of PD-L1, only the distance from the superior border of the recurrence to the CA distinctly increased. Moreover, it was found that the distances from the superior border of the 80% recurrences to the CA were more than 10 mm regarding stronger intensities of Ki-67, P53, and higher levels of PD-L1, which indicated that the 10 mm expansion of ROI recommended by RTOG might not be adequate. Hence, a 14-15 mm

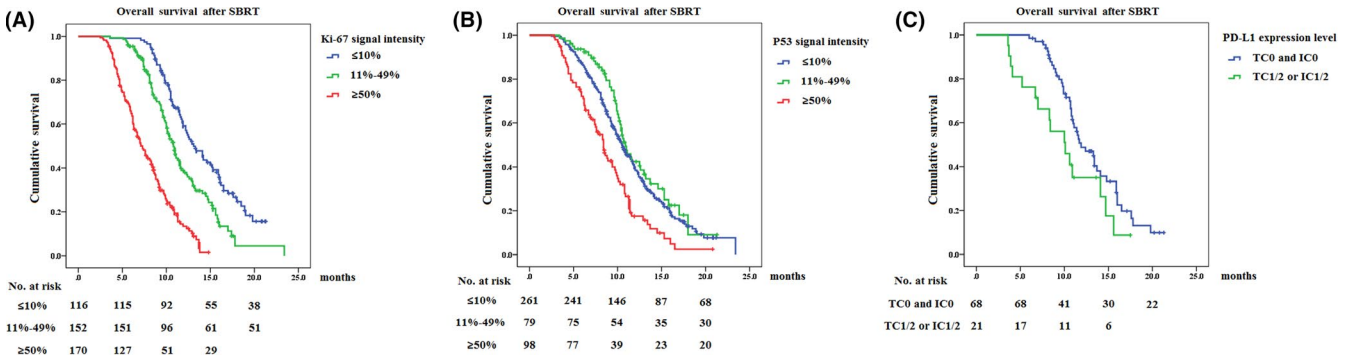

FIGURE 3 Overall survival after stereotactic body radiation therapy (SBRT) of patients with pancreatic ductal adenocarcinoma with different levels of (A) Ki-67, (B) P53, and (C) programmed cell death-ligand 1 (PD-L1). IC0, PD-L1 expression on less than 1% tumor-infiltrating immune cells; IC1/2, PD-L1 expression on 1% or more but less than 10% of tumor-infiltrating immune cells; TC0, PD-L1 expression on less than 1% tumor cells; TC1/2, PD-L1 expression on 1% or more but less than 50% of tumor cells

TABLE 3 Relationship between dose escalation and outcomes in different molecular profiles of patients with pancreatic ductal adenocarcinoma

		Cox regression model	
Ki-67	BED_{10}	HR (95% CI)	*P* value
≤10%	≤65 Gy	1.000 (reference)	<.001
	>65 Gy	0.086 (0.047-0.158)	
11%-49%	≤65 Gy	1.000 (reference)	<.001
	>65 Gy	0.088 (0.050-0.156)	
≥50%	≤65 Gy	1.000 (reference)	<.001
	>65 Gy	0.216 (0.145-0.321)	
P53			
≤10%	≤65 Gy	1.000 (reference)	<.001
	>65 Gy	0.196 (0.139-0.276)	
11%-49%	≤65 Gy	1.000 (reference)	<.001
	>65 Gy	0.163 (0.080-0.335)	
≥50%	≤65 Gy	1.000 (reference)	<.001
	>65 Gy	0.279 (0.169-0.461)	
PD-L1			
TC0 and IC0	≤65 Gy	1.000 (reference)	<.001
	>65 Gy	0.081 (0.034-0.196)	
TC1/2 or IC1/2	≤65 Gy	1.000 (reference)	.036
	>65 Gy	0.286 (0.089-0.921)	

BED_{10}, biologically effective dose, $\alpha/\beta = 10$; CI, confidence interval; HR, hazard ratio; IC0, PD-L1 expression on less than 1% tumor-infiltrating immune cells; IC1/2, PD-L1 expression on 1% or more but less than 10% of tumor-infiltrating immune cells; PD-L1, programmed cell death-ligand 1; TC0, PD-L1 expression on less than 1% tumor cells; TC1/2, PD-L1 expression on 1% or more but less than 50% of tumor cells.

expansion superiorly on the CA could probably cover at least 80% of recurrences. With the increasing intensity of Ki-67 and P53, 80% recurrent lesions were within a distance of 9.9 mm from the inferior border to the SMA. Therefore, a slight larger expansion, at least 10-11 mm inferiorly on the SMA, could be required. Although it was shown that recurrences were inclined to involve posterior space of the CA and SMA with a distance beyond 10 mm, there was 20 mm posterior expansion on the aorta in the consensus, which could cover most recurrences.

Furthermore, it was elucidated that survival benefits were provided by a higher radiation dose in all subgroups. In our previous studies, superior survival was found in patients receiving BED_{10} of 60 Gy or more.[4,8,9,12] Similar results also showed that higher BED_{10} was the predictor of improved OS, PFS, and local control.[13-15] However, a metaanalysis clarified that BED_{10} beyond 70 Gy did not improve local control.[16] Nevertheless, this study included some patients with local disease progression after failure of initial treatment, which could negatively impact the efficacy due to aggressiveness. Moreover, chemotherapy regimens varied between studies, which also resulted in differing effects on survival. Additionally, OS was not included in the analysis. Hence, dose escalation radiotherapy may provide survival benefits but need to be further validated.

Due to the retrospective analysis, there are some limitations in our study. First, due to the small number of patients with PD-L1 tested, patterns of local failure and the correlation between radiation doses to recurrences and outcomes should be further verified. Second, distances from the different borders of 95% recurrences to the CA and SMA were not measured. Although expansions of ROI based on these distances could greatly improve local control, it would also lead to the increasing risk of radiation-induced toxicity, contributing to counteracting the efficacy of radiotherapy. Finally, a large range of dose fractionations of SBRT was used in the study. This was attributable to mitigating against gastrointestinal toxicity. Patients with tumor abutting to the stomach or duodenum could receive protracted courses of SBRT.

Our data suggest that nonuniform expansions of the CA and SMA based on molecular profiling after pancreaticodudenectomy of each patient were feasible. Additionally, higher doses could be beneficial in patients with recurrence after surgical resection.

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DISCLOSURE

The authors declare no potential conflicts of interest.

ORCID

Xiaofei Zhu https://orcid.org/0000-0001-5769-9308

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