Ann Surg Oncol (2019) 26:2587–2594
https://doi.org/10.1245/s10434-019-07471-z

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – PANCREATIC TUMORS

Proton Radiotherapy for Isolated Local Recurrence of Primary Resected Pancreatic Ductal Adenocarcinoma

Takuya Mizumoto, MD, PhD[1,2], Kazuki Terashima, MD, PhD[2], Yoshiro Matsuo, MD, PhD[2], Fumiko Nagano, MD, PhD[2], Yusuke Demizu, MD, PhD[2], Masayuki Mima, MD, PhD[2], Nor Shazrina Sulaiman, MD, PhD[2], Sunao Tokumaru, MD, PhD[2], Tomoaki Okimoto, MD, PhD[2], Hirochika Toyama, MD, PhD[1], and Takumi Fukumoto, MD, PhD[1]

[1]Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Kobe, Hyogo, Japan; [2]Department of Radiology, Hyogo Ion Beam Medical Center, Tatsuno, Hyogo, Japan

ABSTRACT

Background. The optimal treatment for isolated local recurrence (ILR) of pancreatic adenocarcinoma (PDAC) after surgical resection remains unclear. This study aimed to evaluate the safety and efficacy of proton radiotherapy (PRT) for ILR of PDAC after surgery.

Methods. The medical records of patients with ILR of PDAC after surgery who underwent proton beam therapy between 2011 and 2015 at Hyogo Ion Beam Medical Center were retrospectively studied.

Results. The study analyzed 30 patients (14 women and 16 men) with a median age of 65 years (range 38–81 years) who had initially undergone pancreatoduodenectomy ($n = 23$) or distal pancreatectomy ($n = 7$) for their primary tumors. Upon ILR, PRT was administered with a median total cumulative dose of 67.5 gray equivalent (GyE) (range 50–67.5 GyE) using 19 to 25 fractions. For 25 patients, concurrent chemotherapy was administered using gemcitabine ($n = 18$) or S-1 ($n = 7$). Four patients (13.3%) experienced acute grade ≥ 3 gastrointestinal toxicities. After a median follow-up period of 17.6 months (range 2.1–50.4 months), 23 patients had experienced tumor progression and 10 had died. Nine patients (30%) experienced local tumor progression. The median overall, progression-free, and local progression-free survival rates were 26.1, 12.3, and 41.2 months, respectively. Pre-PRT serum levels of cancer antigen 19-9 higher than 100 U/mL and duke pancreatic monoclonal antigen type 2 higher than 150 U/mL were significantly associated with shorter progression-free survival rates.

Conclusions. Proton radiotherapy for ILR of PDAC after surgery is well tolerated and produces good locoregional control and should be considered for eligible patients.

Despite recent advances in diagnostic and therapeutic strategies, the prognosis for patients with pancreatic ductal adenocarcinoma (PDAC) remains dismal.[1] Only surgical resection is a potentially curative treatment. However, approximately 80% of patients with PDAC experience recurrences after surgery with curative intent.[2] Of these patients, 20–30% experience locoregional recurrence without distant metastasis (i.e., isolated local recurrence [ILR]).[3,4] To date, treatment strategies for these patients are not well established. Because up to 30% of patients with PDAC die of local destructive disease, those who experience ILR can achieve extended survival by controlling locoregional recurrence.[5] Moreover, local recurrence may be symptomatic if it involves adjacent structures such as the abdominal nerve plexus or bile duct. Therefore, local treatments such as repeat resection or radiotherapy have been considered as therapeutic options for these patients.[6–12]

Proton radiotherapy (PRT), a type of particle radiotherapy characterized by the Bragg peak phenomenon, enables coverage of the tumor volume with high accuracy while the doses to surrounding normal tissue are reduced much more effectively than with conventional photon radiotherapy.[13] Thus, proton therapy is of particular interest for patients with tumors located close to radiation-sensitive organs such as the gastrointestinal (GI) tract or

First Received: 6 May 2018;
Published Online: 30 May 2019

H. Toyama, MD, PhD
e-mail: tymhr@me.com

spinal cord. As such, the utility of PRT for locally advanced PDAC has been increasingly explored.[14,15] However, the safety and efficacy of this method for patients with ILR of PDAC after surgery is not well reported. Therefore, we performed a retrospective analysis to evaluate PRT for this specific group of patients and investigated their prognoses.

METHODS

Ethics Statement

This study was approved by the institutional review board of the Hyogo Ion Beam Medical Center and performed in accordance with the ethical standards stated in the 1964 Declaration of Helsinki and its later amendments.

Patients

The medical records of 30 consecutive patients with ILR of PDAC after surgery who subsequently underwent PRT between 2011 and 2015 at Hyogo Ion Beam Medical Center, were retrospectively analyzed. The study defined ILR as recurrence in the remnant pancreas, resection margin of the remnant pancreas, pancreatic bed (i.e., the surrounding locoregional structures such as the nerve plexus), or adjacent lymph nodes in the absence of distant metastasis.

All the patients underwent an abdominal contrast-enhanced computed tomography (CT) scan, chest CT scan, and positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) to rule out distant metastasis. The diagnosis of PDAC was histologically confirmed by examination of the surgical specimens from all the patients.

Prt

The patients were treated with 150- to 210-MeV proton beams using the passive-scattering method during the exhalation phase using a respiratory gating system. This setup was performed daily before irradiation using fiducial markers and bony landmarks. Proton beam treatment plans were developed using a CT-based three-dimensional treatment planning system (Xio-M; Mitsubishi Electric Corporation, Tokyo, Japan) (Fig. 1a, b).

Gross tumor volume (GTV) was defined as the recurrent tumor including the surrounding soft tissue density. Clinical target volume (CTV) comprised the GTV expanded by 5-mm margins in addition to prophylactic irradiation regions such as the para-aortic lymph nodes and nerve plexus surrounding the celiac artery or superior mesenteric artery based on the sites of recurrence. Planning target volume (PTV) was defined as CTV plus a 5-mm setup margin and a 1- to 5-mm respiratory gating margin. The three types of protocols used included the 67.5-gray equivalent (GyE) in 25 daily fractions (determined from the phases 1 and 2 study results for unresectable locally advanced pancreatic cancer). The 50 GyE in 25 daily fractions and the 52 GyE in 26 daily fractions (irradiated in the preliminary study before this phases 1 and 2 study).[14]

In the 67.5-GyE protocol, the field-in-field method was used to irradiate 60 GyE or more while high-dose irradiation to areas such as the GI mucosa was avoided.[14] In general, the dose restrictions to the digestive tract and spinal cord were approximately 48 GyE and 45 GyE, respectively.

Concurrent Chemotherapy

Concurrent chemotherapy was performed using gemcitabine monotherapy or S-1 (tegafur/gimeracil/oteracil) monotherapy, if feasible. In general, gemcitabine (800 mg/m^2) was administered via intravenous infusion for the initial 3 weeks of the 5-week proton therapy period, and S-1 was administered orally at a dose of 80 mg/m^2 twice daily on the day of PRT irradiation.

Follow-Up Evaluation

All the patients were examined every 3 months with repeated measurements of cancer antigen 19-9 (CA19-9), duke pancreatic monoclonal antigen type 2 (DUPAN-2), and contrast-enhanced CT scans and/or FDG-PET. Local progression was defined as tumor progression inside the PTV, and diagnosed comprehensively based on the following findings: radiographic enlargement of the local recurrence site, increased FDG accumulation at the local recurrence site, and sustained increase in tumor markers for at least 3 months with no distant metastases.

The National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.0) were used to define and grade toxicity. All the patients underwent endoscopic examinations from the esophagus to the horizontal part of the duodenum after PRT for investigation of acute radiation-related gastroduodenal complications.

Statistical Analysis

The demographic and treatment characteristics of the patients were summarized using descriptive statistics, and the χ^2 test was used to determine the relationship between categorical variables. Kaplan–Meier curves were used to estimate survival outcomes such as overall survival (OS), progression-free survival (PFS), and local progression-free survival (LPFS). The Cox proportional hazards model was

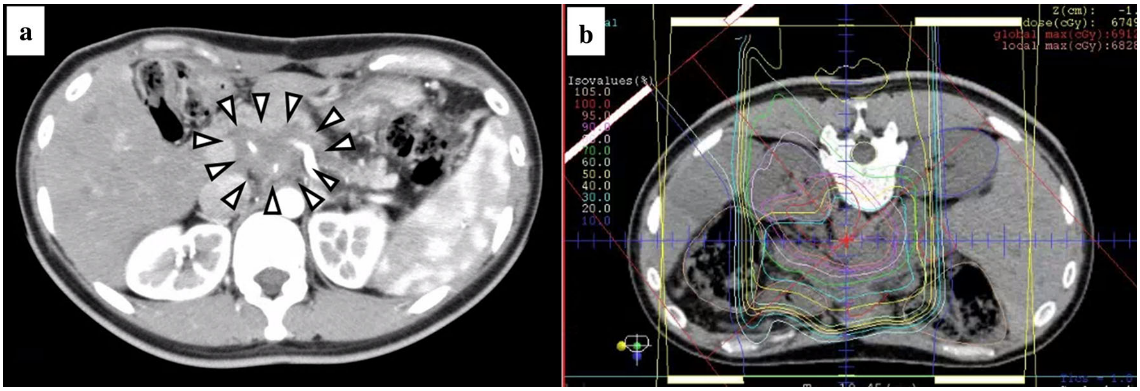

FIG. 1 **a** Contrast-enhanced computed tomography of the isolated local recurrence after pancreatoduodenectomy for pancreatic ductal adenocarcinoma. **b** Proton radiotherapy treatment planning for isolated local recurrence after pancreatoduodenectomy for pancreatic ductal adenocarcinoma

used to assess differences between subgroups. A P value lower than 0.05 was considered statistically significant in all the analyses, which were performed using JMP 12 (SAS Institute Japan, Tokyo, Japan).

RESULTS

Patient Characteristics

Table 1 shows the patient characteristics. The study investigated 30 patients (14 women and 16 men) with a median age of 65 years (range 38–81 years). Of these 30 patients, 23 underwent a pancreatoduodenectomy for their primary tumor, whereas 7 underwent a distal pancreatectomy. All the initial surgeries were curative resections (R0). Adjuvant chemotherapy was administered to 26 (86.7%) of the patients, and 12 (40%) of the patients underwent systemic chemotherapy after local recurrences. No patient was treated with radiation therapy before PRT.

The recurrence sites were the pancreatic bed ($n = 15$), the resection margin of the remnant pancreas ($n = 8$), the adjacent lymph nodes ($n = 1$), and the remnant pancreas ($n = 1$). Five of the patients experienced recurrences at multiple sites.

From the day of surgery, the median time to the first recurrence (i.e., the disease-free interval) was 13 months (range 4–50 months), and the median time to the first day of PRT delivery was 17.8 months (range 6.4–60.7 months).

TABLE 1 Patient characteristics

Variables	Total ($N = 30$)
Patient demographics	
Median age: years (range)	64.5 (38–81)
Sex: n (%)	
Female	14 (46.7)
Male	16 (53.3)
ECOG performance status score: n (%)	
0	21 (70)
1	9 (30)
Median CA19-9: IU/mL (range)	179.6 (0.1–1776)
Median DUPAN-2: U/mL (range)	76 (25–11,000)
Median SUV_{max} on FDG-PET: n (range)[a]	4.4 (1.01–14.7)
Previous treatments	
Initial surgery: n (%)	
Pancreatoduodenectomy	7 (23.3)
Distal pancreatectomy	23 (76.7)
Adjuvant chemotherapy: n (%)	
None	4 (13.3)
Gemcitabine	18 (60)
S-1	6 (20)
Gemcitabine + S-1	2 (6.7)
Median DFI: months (range)	13 (4–50)

ECOG Eastern Cooperative Oncology Group, *CA19-9* cancer antigen 19-9, *DUPAN-2* duke pancreatic monoclonal antigen type 2, SUV_{max} maximum standardized uptake value, *FDG-PET* ^{18}F-2-fluoro-2-deoxyglucose positron-emission tomography, *DFI* disease-free interval

[a]Data were available for 19 patients

Treatment Characteristics

Three protocols were used for treatment: 67.5 GyE in 25 fractions ($n = 23$), 52 GyE in 26 fractions ($n = 4$), and 50 GyE in 25 fractions ($n = 3$). Of the 30 patients, 25 received concurrent chemotherapy with gemcitabine ($n = 18$) or S-1 ($n = 7$), whereas 5 received PRT without concurrent chemotherapy.

Feasibility and Toxicity

Acute and late toxicities of all grades are summarized in Table 2. Acute grade ≥ 3 toxicities experienced by 10 patients (33.3%) were hematologic (leukocytopenia, $n = 7$; thrombocytopenia, $n = 1$) and non-hematologic (radiation-induced GI ulcer/bleeding, $n = 1$; cholangitis, $n = 1$). Of the 23 patients (47.8%) scheduled to receive an integrated dose of 67.5 GyE, 11 experienced GI ulcer/bleeding of all grades. This was more frequent among the patients scheduled to receive 50 or 52 GyE (28.6%). Among the patients who experienced GI bleeding, endoscopic minor cauterization was needed for three patients and total parenteral nutrition for one patient. The remaining patients received medical interventions only. No patient needed transfusion, surgery, major endoscopic hemostasis, or hospitalization for GI ulcer/bleeding.

Two patients failed to complete the prescribed protocol of 67.5 GyE in 25 fractions because of GI toxicities. For the first patient, the daily fractional dose was reduced to 1.8 GyE after the 16th fraction because of radiation-induced gastroduodenal ulcer development (total of 58.5 GyE in 25 fractions). The second patient ceased treatment after receiving a total of 51.3 GyE in 19 fractions due to radiation-induced colitis.

All toxicities were treated adequately with conservative therapy, and none of the patients died of treatment-related adverse events. Concerning late toxicity, three patients experienced a grade 3 spinal fracture 12, 13, and 36 months after the first day of PRT, respectively.

Patient Survival and Prognostic Factors

After a median follow-up time of 17.6 months (range 2.1–50.4 months), 10 patients (33.3%) died, and 23 (76.7%) experienced tumor progression. Local tumor progression occurred for 9 patients (30%). Of the remaining 20 patients, 17 experienced distant metastasis in the lung ($n = 6$), liver ($n = 5$), peritoneum ($n = 3$), and other sites ($n = 3$), and 3 experienced both local and distant tumor progression. From the first day of PRT, the patients showed a median OS of 26.1 months, a median PFS of 12.3 months, and a median LPFS of 41.2 months (Fig. 2a–c). The 1-year OS and PFS rates were respectively 91.7% and 51.7%.

In the univariate analyses of patient survival, a pre-PRT serum CA 19-9 level higher than 100 U/mL was associated with a shorter PFS, but not with a shorter OS (Table 3; Fig. 2d, e). Concerning recurrence patterns, the patients with a higher pre-PRT serum CA19-9 level (> 100 U/mL) experienced significantly more distant metastases than those with a pre-PRT serum CA19-9 level of 100 U/mL or lower (64.7% vs 23.1%, respectively; $P = 0.021$). A similar correlation, although not significant, was observed regarding pre-PRT DUPAN-2 (> 150 vs $\leq$ 100 U/mL; 70% vs 35%, respectively; $P = 0.068$). In contrast, higher pre-PRT serum CA19-9 and DUPAN-2 levels were not associated with local progression ($P = 0.466$ and 0.388, respectively).

TABLE 2 Acute and late toxicities in all grades for the patient who underwent proton radiotherapy

Toxicity	$n = 30$ n (%)
Acute toxicities	
Hematologic	
Leukocytopenia	
Grade 1/2	12 (40.0)
Grade 3	7 (23.3)
Thrombocytopenia	
Grade 1/2	12 (40.0)
Grade 3	1 (3.3)
Gastrointestinal	
Gastrointestinal bleeding/ulcer	
Grade 1/2	12 (40.0)
Grade 3	1 (3.3)
Nausea/vomiting	
Grade 1/2	6 (20.0)
Diarrhea	
Grade 1/2	4 (13.3)
Constipation	
Grade 1/2	6 (20.0)
Anorexia	
Grade 1/2	8 (26.7)
Epigastric pain	
Grade 1/2	5 (16.7)
Others	
Dermatitis	
Grade 1/2	24 (80.0)
Cholangitis	
Grade 2	4 (13.3)
Grade 3	1 (3.3)
Fatigue	
Grade 1/2	5 (16.7)
Late toxicities	
Spinal fracture	
Grade 3	3 (10.0)
Dermatitis	
Grade 2	1 (3.3)
Intestinal pneumonia	
Grade 2	1 (3.3)
Liver abscess	
Grade 2	1 (3.3)

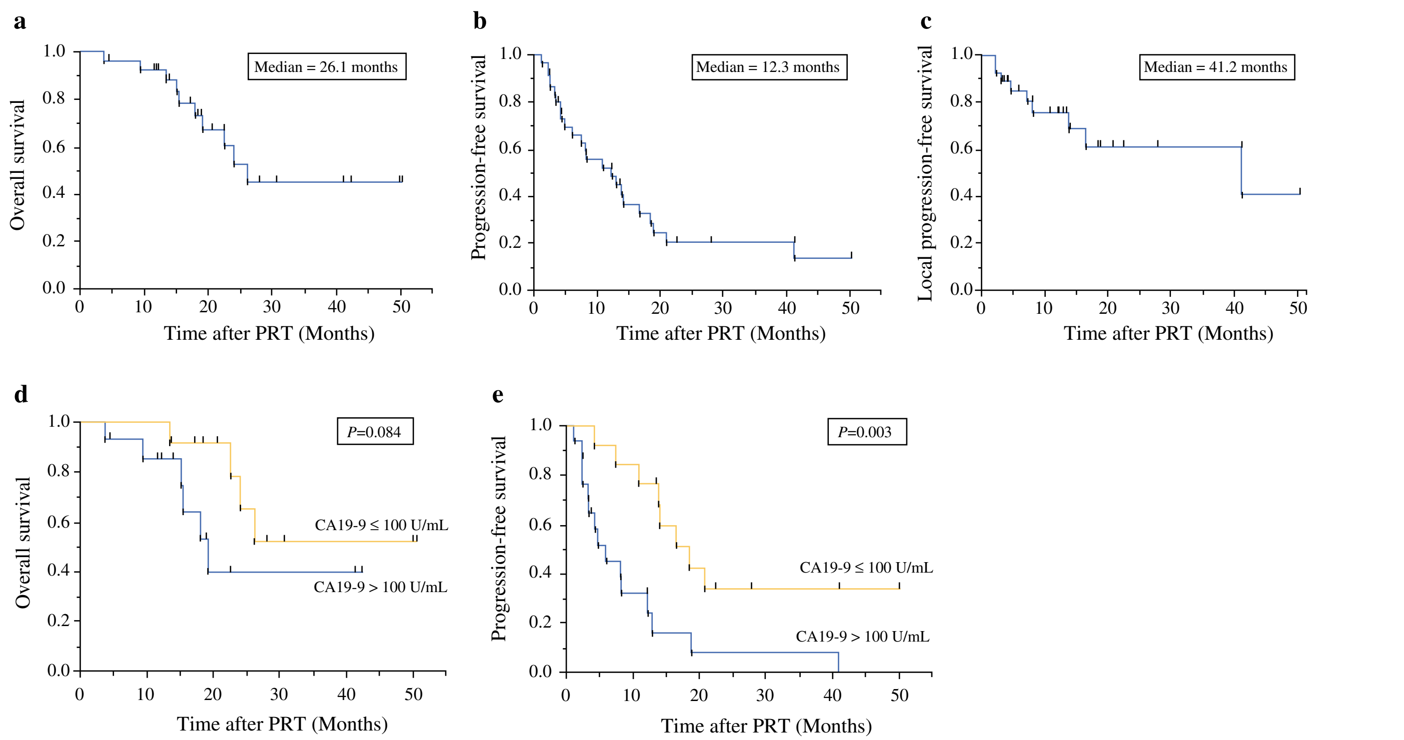

FIG. 2 Kaplan–Meier curves showing **a** overall survival, **b** progression-free survival, and **c** local progression-free survival calculated from the first day of proton radiotherapy (PRT). **d** Overall-survival and **e** progression-free survival were stratified by pre-proton radiotherapy (PRT) cancer antigen 19-9 (CA19-9). Differences in survival rates were compared using the Wilcoxon test

DISCUSSION

We found that PRT is a potentially safe and effective treatment for patients with ILR of PDAC after surgical resection. The study identified pre-PRT levels of serum CA19-9 higher than 100 U/mL as a predictor of distant metastasis after PRT in this group of patients.

The optimal therapeutic strategies for patients with ILR of PDAC after primary resection are not well established. Several previous studies showed that repeat resection is beneficial for selected patients with ILR of PDAC[6–10]. The median OS rate ranged from 16 to 44 months for the resected patients (from the day of repeat surgery) and from 9.4 to 10.8 months for the non-resected patients. However, most patients with locally recurrent PDAC cannot undergo repeat resection because of tumor invasion into the major adjacent vessels. Even with repeat resection, considerable risk exists for incomplete excision.[16] Moreover, repeat resection for locally recurrent PDAC carries technical difficulties due to intra-abdominal adhesions, often leading to total pancreatectomy, which may significantly impair a patient's quality of life.[17]

As a less invasive therapy, conventional photon-based radiotherapy is an alternative option for these patients. Two previous studies showed that conventional radiotherapy appeared to be effective for patients with ILR after initial resection, with a median OS of 16 months in both studies.[11,12] Stereotactic body radiation therapy (SBRT), which delivers more conformal radiation doses than conventional radiation therapy, enabled reduction of acute and late toxicities, but the studies found no survival benefit for SBRT over conventional radiation therapy.[18–20]

In our study, the median OS for the patients who received PRT for ILR of PDAC was 26.1 months, which compared well with that for the patients who underwent repeat resection and appeared to have yielded more favorable results than conventional radiation therapy. These results might have been partly due to the higher radiation dose (median, 67.5 GyE) delivered to the tumors with the aid of the high conformality of PRT compared with conventional radiation therapy (45–60 Gy). Moreover, the improved local control (median LPFS, 41.2 months) also may have contributed to the prolonged survival.[11–13]

Previous studies evaluated local tumor control by measuring tumor diameters.[11–13] However, because of the poorly defined edges of PDACs and post-radiotherapy inflammation, it may be difficult to assess local progression solely using this parameter.[21] Therefore, we also considered FDG accumulation at the local recurrence site as well as the sustained increase in tumor marker levels when assessing local tumor progression.

TABLE 3 Subgroup analysis of the overall and progression-free survival

Variables	n (%)	Overall survival		Progression-free survival	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* value
Age (years)			0.491		0.559
< 65	15 (50.0)	1 (reference)		1 (reference)	
≥ 65	15 (50.0)	1.56 (0.44–6.11)		0.78 (0.33–1.79)	
Sex			0.341		0.184
Female	14 (46.7)	1 (reference)		1 (reference)	
Male	16 (53.3)	0.54 (0.14–1.91)		0.57 (0.24–1.30)	
ECOG performance status			0.278		0.850
0	21 (70%)	1 (reference)		1 (reference)	
1	9 (30%)	2.07 (0.53–7.33)		1.1 (0.42–2.57)	
CA19-9 (IU/mL)			0.167		0.004[a]
< 100	13 (43.3)	1 (reference)		1 (reference)	
≥ 100	17 (56.7)	2.45 (0.69–9.75)		3.52 (1.48–8.98)	
DUPAN-2 (U/mL)			0.081		0.102
< 150	20 (66.6)	1 (reference)		1 (reference)	
≥ 150	10 (33.3)	3.60 (0.85–15.4)		2.15 (0.26–5.09)	
SUV_{max} on FDG-PET			0.901		0.271
< T4	7 (36.8)	1 (reference)		1 (reference)	
≥ 4	12 (63.2)	1.11 (0.19–6.68)		1.93 (0.61–7.38)	
Initial surgery			0.421		0.621
Pancreatoduodenectomy	7 (23.3)	1 (reference)		1 (reference)	
Distal pancreatectomy	23 (76.7)	1.79 (0.38–6.51)		1.30 (0.42–3.30)	
Adjuvant chemotherapy			0.720		0.845
Yes	26 (86.7)	1 (reference)		1 (reference)	
No	4 (13.3)	0.67 (0.04–3.74)		1.1 (0.26–3.37)	
DFI, months			0.238		0.757
< 12	8 (26.7)	1 (reference)		1 (reference)	
≥ 12	22 (73.3)	0.45 (0.13–1.78)		1.16 (0.46–3.56)	
Scheduled irradiation protocol			0.083		0.538
67.5 GyE/25 fractions	23 (76.7)	1 (reference)		1 (reference)	
52 GyE/26 fractions	4 (13.3)	2.01 (0.29–8.80)		0.51 (0.08–1.77)	
50 GyE/25 fractions	3 (10.0)	11.2 (1.29–98.8)		1.26 (0.29–3.89)	
Concurrent chemotherapy			0.135		0.500
Yes	25 (83.3)	1 (reference)		1 (reference)	
No	5 (16.7)	3.10 (0.67–11.2)		1.48 (0.42–4.06)	

HR hazard ratio, *95% CI* 95% confidence interval, *ECOG* Eastern Cooperative Oncology Group, *CA19-9* cancer antigen 19-9, *DUPAN-2* duke pancreatic monoclonal antigen type 2, SUV_{max} maximum standardized uptake value, *FDG-PET* ^{18}F-2-fluoro-2-deoxyglucose positron-emission tomography, *DFI* disease-free interval

[a]Statistically significant ($P < 0.05$). The *P* values were calculated using the Cox proportional hazard model

Because no well-accepted criteria exist for diagnosing local PDAC progression after radiotherapy, it is difficult simply to compare the local progression rates between studies. Standardized, well-designed criteria are required to compare local control rates between different treatment strategies.

In our study, the patients scheduled to receive an integrated dose of 67.5 GyE experienced GI ulcer/bleeding more frequently than those scheduled to receive 50 or 52 GyE. Moreover, non-completion of the prescribed protocol occurred only among the patients scheduled to receive 67.5 GyE. This may have been due to the higher dose per irradiation session in the 67.5-GyE protocol (2.7 GyE) than in the other protocols (2 GyE). The postoperative administration of PRT may have made it more difficult to take precautions in terms of the target volume's proximity to the GI tract. However, GI toxicities (including grade 3) were successfully managed by conservative treatments. We performed routine upper GI endoscopy during PRT, and colonoscopy was performed when radiation-induced colitis was suspected. Therefore, we successfully diagnosed and treated GI ulcers and bleeding before they became life-threatening. Whereas routine upper GI endoscopy and coloscopy for selected patients should be recommended, routine balloon-assisted endoscopy should not be recommended because symptomatic small bowel ulcer bleeding is rare.

For late toxicities, three patients experienced spinal fracture, which was scarcely reported in previous studies of radiotherapy for ILR after pancreatic resection. One reason might have been that unlike conventional radiotherapy, the proton beam was regularly delivered from the patient's dorsal side as part of multiple-field irradiation. Another reason may have been the longer follow-up time. All three patients experienced spinal fracture during the 12 months after their first day of PRT. Because such fractures may greatly impair a patient's quality of life, efforts to reduce spinal exposure to PRT should be made, particularly when longer survival is expected.

In our analysis of prognostic factors, higher levels of pretreatment CA19-9 were associated with lower PFS rates in our cohort. In particular, higher pre-PRT serum tumor markers appeared to be associated with distant metastasis. Considering that elevated serum tumor markers are associated with hematogenous metastasis and peritoneal dissemination, it is possible that our cohort included patients who had sub-radiographic metastases when they began PRT.[22,23] In addition to concurrent/sequential systemic chemotherapy, staging laparoscopy (a minimally invasive technique to detect sub-radiographic peritoneal dissemination or small liver metastases on the surface of the liver) is an option for patients who show higher levels of pretreatment tumor markers.[24]

Our study had some limitations. First, it was a retrospective investigation performed at a single center and included a relatively small number of patients with highly heterogeneous backgrounds. Second, therapeutic approaches might have changed since the time when our patients were treated. New multi-agent therapies such as FOLFIRINOX and GEM + nab-PTX are increasingly administered to patients with unresectable or recurrent PDAC.[25,26] The impact of PRT on locally recurrent PDAC should be reevaluated in conjunction with these more potent therapeutic agents.

In conclusion, PRT should be considered a therapeutic option for patients with ILR of PDAC as part of a multidisciplinary approach. Thanks to the Bragg peak phenomenon, PRT can target the tumor with high accuracy while reducing the doses to the surrounding normal tissue. This allows for dose escalation (in contrast to conventional RT) with production of manageable toxicities, even in the postoperative setting. Patients who show high pretreatment levels of serum tumor markers should be managed with the possible existence of subradiographic micrometastases taken into account.

DISCLOSURE There are no conflicts of interest.

REFERENCES

1. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. *N Engl J Med.* 2014;371:1039–49.
2. Ferrone CR, Brennan MF, Gonen M, et al. Pancreatic adenocarcinoma: the actual 5-year survivors. *J Gastrointest Surg.* 2008;12:701–6.
3. Groot VP, Rezaee N, Wu W, et al. (2017) Patterns, timing, and predictors of recurrence following pancreatectomy for pancreatic ductal adenocarcinoma. *Ann Surg.* 2018;267:936–45.
4. Hishinuma S, Ogata Y, Tomikawa M, Ozawa I, Hirabayashi K, Igarashi S. Patterns of recurrence after curative resection of pancreatic cancer, based on autopsy findings. *J Gastrointest Surg.* 2006;10:511–8.
5. Iacobuzio-Donahue CA, Fu B, Yachida S, et al. DPC4 gene status of the primary carcinoma correlates with patterns of failure in patients with pancreatic cancer. *J Clin Oncol.* 2009;27:1806–13.
6. Nakayama Y, Sugimoto M, Gotohda N, Konishi M, Takahashi S. Efficacy of completion pancreatectomy for recurrence of adenocarcinoma in the remnant pancreas. *J Surg Res.* 2018;221:15–23.
7. Miyazaki M, Yoshitomi H, Shimizu H, et al. Repeat pancreatectomy for pancreatic ductal cancer recurrence in the remnant pancreas after initial pancreatectomy: is it worthwhile? *Surgery.* 2014;155:58–66.
8. Strobel O, Hartwig W, Hackert T, et al. Re-resection for isolated local recurrence of pancreatic cancer is feasible, safe, and associated with encouraging survival. *Ann Surg Oncol.* 2013;20:964–72.
9. Kleeff J, Reiser C, Hinz U, et al. Surgery for recurrent pancreatic ductal adenocarcinoma. *Ann Surg.* 2007;245:566–72.
10. Miura F, Takada T, Amano H, et al. Repeated pancreatectomy after pancreatoduodenectomy. *J Gastrointest Surg.* 2007;11:179–86.
11. Nakamura A, Itasaka S, Takaori K, et al. Radiotherapy for patients with isolated local recurrence of primary resected pancreatic cancer: prolonged disease-free interval associated with favorable prognosis. *Strahlenther Onkol.* 2014;190:485–90.
12. Habermehl D, Brecht IC, Bergmann F, et al. Chemoradiation in patients with isolated recurrent pancreatic cancer: therapeutical efficacy and probability of re-resection. *Radiat Oncol.* 2013;8:27.
13. Greco C, Wolden S. Current status of radiotherapy with proton and light ion beams. *Cancer.* 2007;109:1227–38.
14. Terashima K, Demizu Y, Hashimoto N, et al. A phase I/II study of gemcitabine-concurrent proton radiotherapy for locally advanced pancreatic cancer without distant metastasis. *Radiother Oncol.* 2012;103:25–31.
15. Nishioka K, Prayongrat A, Ono K, et al. Prospective study to evaluate the safety of the world-first spot-scanning dedicated, small 360-degree gantry, synchrotron-based proton beam therapy system. *J Radiat Res.* 2018;59(Supp 1):i63–i71.
16. Ishida J, Toyama H, Matsumoto I, et al. Second primary pancreatic ductal carcinoma in the remnant pancreas after

pancreatectomy for pancreatic ductal carcinoma: high cumulative incidence rates at 5 years after pancreatectomy. *Pancreatology.* 2016;16:615–20.

17. Groot VP, van Santvoort HC, Rombouts SJ, et al. Systematic review on the treatment of isolated local recurrence of pancreatic cancer after surgery: re-resection, chemoradiotherapy, and SBRT. *HPB Oxford.* 2017;19:83–92.
18. Ryan JF, Groot VP, Rosati LM, et al. Stereotactic body radiation therapy for isolated local recurrence after surgical resection of pancreatic ductal adenocarcinoma appears to be safe and effective. *Ann Surg Oncol.* 2018;25:280–9.
19. Wild AT, Hiniker SM, Chang DT, et al. Re-irradiation with stereotactic body radiation therapy as a novel treatment option for isolated local recurrence of pancreatic cancer after multimodality therapy: experience from two institutions. *J Gastrointest Oncol.* 2013;4:343–51.
20. Gkika E, Adebahr S, Kirste S, et al. Stereotactic body radiotherapy (SBRT) in recurrent or oligometastatic pancreatic cancer: a toxicity review of simultaneous integrated protection (SIP) versus conventional SBRT. *Strahlenther Onkol.* 2017;193:433–43.
21. Toesca DA, Pollom EL, Poullos PD, et al. Assessing local progression after stereotactic body radiation therapy for unresectable pancreatic adenocarcinoma: CT versus PET. *Pract Radiat Oncol.* 2017;7:120–5.
22. Kurahara H, Maemura K, Mataki Y, et al. Clinical significance of serum carbohydrate antigen 19.9 and duke pancreatic monoclonal antigen type 2 for the prediction of hematogenous metastases in patients with pancreatic ducal adenocarcinoma. *Pancreatology.* 2016;16:1051–6.
23. Fujioka S, Misawa T, Okamoto T, Gocho T, Futagawa Y, Ishida Y, Yanaga K. Preoperative serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels for the evaluation of curability and resectability in patients with pancreatic adenocarcinoma. *J Hepatobiliary Pancreat Surg.* 2007;14:539–44.
24. Fong ZV, Alvino DML, Fernández-Del Castillo C, et al. Reappraisal of staging laparoscopy for patients with pancreatic adenocarcinoma: a contemporary analysis of 1001 patients. *Ann Surg Oncol.* 2017;24:3203–11.
25. Conroy T, Desseigne F, Ychou M, et al. FOLFIRINOX versus gemcitabine for metastatic pancreatic cancer. *N Engl J Med.* 2011;364:1817–25.
26. Von Hoff DD, Ervin T, Arena FP, et al. Increased survival in pancreatic cancer with nab-paclitaxel plus gemcitabine. *N Engl J Med.* 2013;369:1691–703.