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Scientific Article

Proton Therapy for Unresectable and Medically Inoperable Locally Advanced Pancreatic Cancer: Results From a Multi-Institutional Prospective Registry

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Purpose: Compared with photon-based techniques, proton beam radiation therapy (PBT) may improve the therapeutic ratio of radiation therapy (RT) for locally advanced pancreatic cancer (LAPC), but available data have been limited to single-institutional experiences. This study examined the toxicity, survival, and disease control rates among patients enrolled in a multi-institutional prospective registry study and treated with PBT for LAPC.

Methods and Materials: Between March 2013 and November 2019, 19 patients with inoperable disease across 7 institutions underwent PBT with definitive intent for LAPC. Patients received a median radiation dose/fractionation of 54 Gy/30 fractions (range, 50.4-60.0 Gy/19-33 fractions). Most received prior (68.4%) or concurrent (78.9%) chemotherapy. Patients were assessed prospectively for toxicities using National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. Kaplan-Meier analysis was used to analyze overall survival, locoregional recurrence-free survival, time to locoregional

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recurrence, distant metastasis-free survival, and time to new progression or metastasis for the adenocarcinoma cohort (17 patients).

Results: No patients experienced grade ≥3 acute or chronic treatment-related adverse events. Grade 1 and 2 adverse events occurred in 78.7% and 21.3% of patients, respectively. Median overall survival, locoregional recurrence-free survival, distant metastasis-free survival, and time to new progression or metastasis were 14.6, 11.0, 11.0, and 13.9 months, respectively. Freedom from locoregional recurrence at 2 years was 81.7%. All patients completed treatment with one requiring a RT break for stent placement.

Conclusions: Proton beam RT for LAPC offered excellent tolerability while still maintaining disease control and survival rates comparable with dose-escalated photon-based RT. These findings are consistent with the known physical and dosimetric advantages offered by proton therapy, but the conclusions are limited owing to the patient sample size. Further clinical studies incorporating dose-escalated PBT are warranted to evaluate whether these dosimetric advantages translate into clinically meaningful benefits.

Introduction

Although systemic therapy is commonly administered for inoperable locally advanced pancreatic cancer (LAPC), locoregional control is still imperative for this cohort of patients with pancreatic cancer for symptom control and clinical outcomes. With modern advances in systemic therapy, 44% of pancreatic cancer recurrences have a locoregional component, and 25% have locoregional recurrence alone as a first relapse, even among a population of patients who had their primary tumor resected.[1] This risk is higher (30%-48% as first site of recurrence) in patients with locally advanced unresectable disease, and radiation therapy (RT) is warranted for these patients after initial systemic therapy to improve locoregional control.[2-5] Unfortunately, owing to the close proximity of the pancreas to radiosensitive organs such as the liver, duodenum, and other mucosal gastrointestinal structures, treatment with concurrent chemoradiation for pancreatic cancer can result in high toxicity rates, with more than 23% of patients experiencing grade ≥3 toxicity in the chemoradiation arm of the LAP 07 trial.[3]

Proton RT (PBT) offers a potentially less toxic treatment option relative to photon RT because of the beam's distinct physical characteristics that allow for minimizing dose to the organs at risk (OARs) beyond the target (mainly owing to an absence of exit dose). Dosimetric studies have supported this hypothesis, indicating superior OAR sparing with PBT compared with intensity modulated RT (IMRT) or 3-dimensional conformal RT (3DCRT).[6-9] These dosimetric advantages can be applied with 2 aims: to reduce toxicity and better preserve quality of life while giving the same dose to the target or to dose-escalate and improve local control while keeping toxicity constant.[10] To date, however, the literature on the use of PBT for pancreatic cancer has been limited to single-institution cohorts.[11-18]

To address the paucity of data describing outcomes after PBT, the present study describes the survival, toxicity, and disease control from the multi-institutional prospective registry of patients with LAPC treated with definitive intent PBT at member institutions. To our knowledge, this is the first report of multi-institutional prospective data describing outcomes from PBT for LAPC.

Methods and Materials

A research consortium of 23 proton centers in the United States created a prospective registry trial for which each institution obtained individual institutional review board approval. The study opened for accrual in 2010 and is currently enrolling patients. The registry was queried for all consecutive patients with unresectable or medically inoperable pancreatic cancer treated with PBT from 2010 to 2019 to allow time for adequate follow-up. Patients with LAPC and adequate performance status were treated with proton therapy based on physician discretion on this registry trial. Indications for treatment varied somewhat based on institution but generally included insurance approval, M0 disease status, absence of gastrointestinal mucosal invasion, and increased risk for significant toxicity with photon-based therapy. Most patients (95%) in this cohort received multidisciplinary review and discussion before undergoing RT. Patient and tumor characteristics, prior and current radiation details, clinical outcomes, and toxicities were extracted and reviewed retrospectively.

Toxicities were prospectively entered using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. Acute toxicities were defined as toxicities noted within 90 days after the last RT fraction. Late toxicities were defined as those that developed more than 90 days after the completion of RT. Additional disease control outcomes were also assessed, including overall survival (OS), locoregional recurrence-free survival (LRFS), time to locoregional recurrence (TTLR), distant metastasis-free survival (DMFS), and time to progression or metastasis (TTPM). OS was defined as months from the beginning of RT to the date of death or last follow-up for patients who remained alive; LRFS as months from the beginning of RT to the date of locoregional recurrence or death or last follow-up for patients who remained alive and did not have a

recurrence; TTLR as months from the beginning of RT to the date of locoregional recurrence or last follow-up for patients who did not have a recurrence; DMFS as months from the beginning of RT to the date of distant recurrence or death or of last follow-up for patients who remained alive and did not have a new progression or metastasis; and TTPM as months from the beginning of RT to the date of distant recurrence or last follow-up for patients who did not have a new progression or metastasis. Disease control outcomes were assessed only for patients with adenocarcinoma histology owing to the rarity of patients with nonadenocarcinoma histology in the registry, precluding meaningful outcome assessments. All outcomes related to disease control were reported only for patients with pancreatic adenocarcinoma. Patients with nonadenocarcinoma histologies (n = 2) were excluded.

Patient selection

All consecutive patients in the registry who received proton therapy for LAPC, defined as patients whose disease was surgically unresectable or who were medically unfit for operation, were identified. Unresectability and inoperability were defined at the discretion of each individual institution. All patients were staged with computed tomography (CT) with pancreas protocol and/or magnetic resonance imaging of the abdomen and biopsy of the primary tumor. Other testing varied based on institution but included chest CT, esophagogastroduodenoscopy with ultrasound, carbohydrate antigen 19-9 (CA 19-9), carcinoembryonic antigen (CEA), positron emission tomography–CT, exploratory laparoscopy, complete blood count, and comprehensive metabolic panel. Patients with distant metastases were excluded, but nodal disease was permitted if patients were treated with definitive intent. Previous and concurrent receipt of systemic therapy were allowed. Patients were staged according to the seventh edition of the American Joint Committee on Cancer's Cancer Staging Manual.

Treatment delivery and follow-up

All patients underwent CT simulation for treatment planning. Clinical target volume (CTV) delineation was at the discretion of the treating institution. All patients were treated using standard fractionation to a dose determined by clinician-assessed risk of local progression balanced with risk of toxicity to OARs. Boosts or cone downs to high-risk volumes were allowed. Proton therapy was delivered using either uniform scanning (11 patients) or pencil beam scanning (8 patients) depending on the institution. Radiation planning approaches varied based upon institutional preference and were not standardized as part of the registry trial. Fourteen patients (73.7%) received elective nodal coverage. Four-dimensional CT simulation and daily on-treatment cone beam CT were used in most patients. For this subset of patients, an internal gross tumor volume was drawn to account for tumor motion, and CTVs were most commonly 5 mm but were modifiable based on physician discretion. Robust planning was used to account for 5 to 10 mm of setup uncertainty.

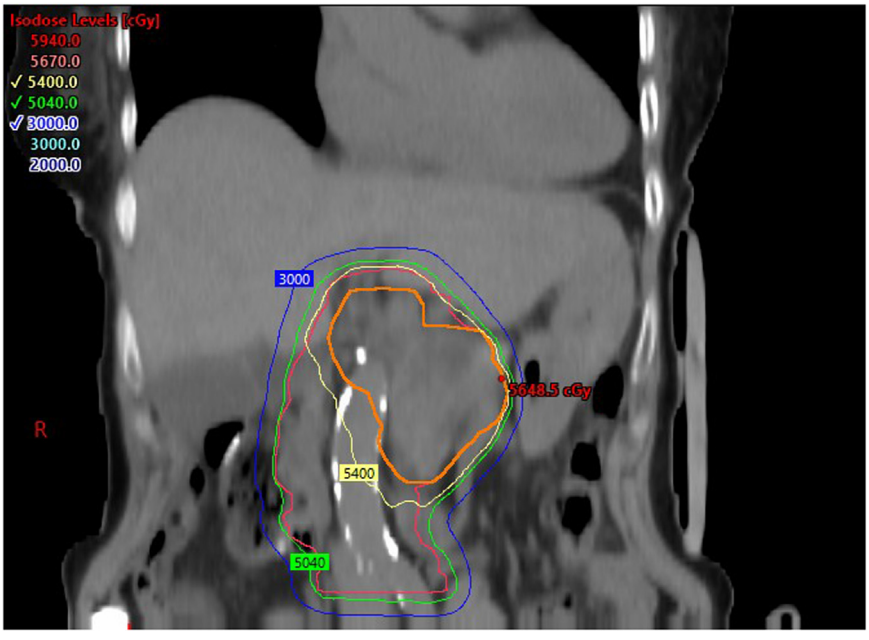

Figure 1 Coronal image of a representative proton therapy plan for a patient in our cohort. The elective nodal treatment volume prescribed 50.4 Gy is shown in red, and the boost treatment volume prescribed 54 Gy is shown in orange.

When 4-dimensional CT was not used (2 patients), CTV margins were larger, measuring up to 1.5 cm radially and 2.5 to 3 cm in the superior-inferior direction depending on the presence of breath hold. Nearly all patients (95%) were reviewed in a multidisciplinary setting before receiving PBT. A table detailing treatment planning with all available information for each patient in the registry is included in the supplementary material (Table E1). A coronal image of a representative patient's treatment plan is shown in Fig. 1. Patients who received neoadjuvant, concurrent, and adjuvant chemotherapy were eligible for inclusion in the analysis. All patients underwent standard-of-care posttreatment follow-up according to National Comprehensive Cancer Network guidelines. Acute and late toxicities were evaluated using CTCAE, version 4.0, as indicated by institutional practices.

Statistical analysis

Descriptive statistics were used to characterize the sample regarding patient demographics as well as tumor and treatment characteristics. Continuous variables, such as age, were described using means, standard deviations, medians, interquartile ranges, and ranges. Categorical variables, including sex, were described using frequencies and percentages. Time-to-event measures (OS, LRFS, TTLR, DFS, and TTPM) were estimated in the overall sample using the Kaplan-Meier method. All statistical analyses were performed using SAS, version 9.4 (SAS Institute Inc, Cary, NC).

Results

Patient characteristics

Nineteen patients (11 women and 8 men) treated at 7 proton therapy institutions met the inclusion criteria for analysis. Most patients (57.9%) were female. The median follow-up for the cohort was 11.5 months. The median age was 70 years (range, 37-88 years). The 14 patients with T staging available were classified as either T2 (1 patient), T3 (3 patients), or T4 (10 patients). Median tumor size was 3.9 cm, and the most common tumor location was within the pancreatic head (63.2%). Five patients had N1 disease, and the remaining patients had N0 disease (14 patients). Thirteen (68.4%) patients received chemotherapy before treatment with RT. Neoadjuvant systemic therapies included FOLFIRINOX (n = 5), gemcitabine/nab-paclitaxel (n = 4), FOLFOX (n = 1), paclitaxel (n = 1), gemcitabine (n = 1), and gemcitabine/oxaliplatin (n = 1). Concurrent chemotherapy was used in 15 patients (78.9%). Concurrent chemotherapy regimens included capecitabine (n = 10), gemcitabine (n = 2), 5-fluorouracil (n = 2), and capecitabine/gemcitabine combination (n = 1). Ten of the patients went on to receive additional systemic therapy after radiation, most commonly gemcitabine/nab-paclitaxel (n = 8). Patient-level details concerning systemic therapy are included in Table E1. The median total radiation dose and fractionation was 54 Gy/30 fractions (range, 50.4-60.0 Gy/19-33 fractions). Seventeen patients (89.5%) had adenocarcinoma, 1 patient had a neuroendocrine tumor, and 1 had cystadenoma. Eastern Cooperative Oncology Group performance status was 0, 1, 2, and not reported in 63.2%, 21.1%, 10.5%, and 5.3% of patients, respectively. A summary of patient characteristics is presented in Table 1.

Toxicity

A total of 75 adverse treatment-related events spanning 19 categories were reported, including 59 (78.7%) grade 1 adverse events and 16 (21.3%) grade 2 adverse events, with no adverse events reaching grade ≥3 in either the acute or late setting. Grade 1 and 2 adverse events were present in 10 patients (52.6%) and 18 patients (94.7%), respectively. Most patients (94.7%) experienced at least 1 acute adverse event (median events per patient, 3; range, 0-13). Only 26.3% of patients experienced late adverse events, with no grade ≥3 late events observed. The most frequently reported grade 1 to 2 adverse events were anorexia (n = 12), fatigue (n = 11), radiation dermatitis (n = 9), and nausea (n = 9). No patients experienced treatment termination due to toxicity. Focusing on only grade ≥2 adverse events, the most common were anorexia (n = 5) and fatigue (n = 4). One out of 19 patients required a treatment break for stent placement. A table detailing all adverse events at the patient level and event level is included in the supplementary material (Table E2).

OS and disease control

After assessing all patients with available data for OS, median OS was 14.6 months (95% confidence interval [CI], 6.3-22.9 months). The OS rates at 12 months and 24 months were 58.0% and 18.1%, respectively (Fig. 2).

Locoregional recurrence-free survival

After assessing all patients with available data for LRFS analysis, median LRFS was 11.0 months (95% CI, 5.1-14.6 months). The LRFS rates at 12 months and 24 months were 39.1% and 15.7%, respectively.

Locoregional control and TTLR

After assessing all patients with available data for locoregional recurrence, the locoregional control rate at 12 months and 24 months was 81.7% at both time

Table 1 Patient characteristics

Characteristic	Overall sample (N = 19)*
Sex	
Female	11 (57.9)
Male	8 (42.1)
Age, y	
Mean (SD)	68.0 (12.4)
Median (IQR)	70.0 (63.0-77.0)
Range	37.0-88.0
Location of tumor	
Body of pancreas	3 (15.8)
Head of pancreas	12 (63.2)
Tail of pancreas	2 (10.5)
Head and body of pancreas	1 (5.3)
Pancreas, NOS	1 (5.3)
Tumor size, cm (n = 7)	
Mean (SD)	3.8 (1.0)
Median (IQR)	3.9 (3.3-4.4)
Range	2.3-5.5
Clinical T stage	
T2	1 (5.3)
T3	3 (15.8)
T4	10 (52.6)
Not reported	5 (26.3)
Clinical N stage	
N0	14 (73.7)
N1	5 (26.3)
Clinical M stage	
M0	19 (100)
ECOG performance status	
0	12 (63.2)
1	4 (21.1)
2	2 (10.5)
Not reported	1 (5.3)
Prior chemotherapy	
Yes	13 (68.4)
No	1 (5.3)
Not reported	5 (26.3)
Concurrent chemotherapy	
Yes	15 (78.9)
No	4 (21.1)
Total cumulative dose, raw value/BED α/β = 10, Gy	
Mean (SD)	54.5 (3.7) / 64.5 (4.7)
Median (IQR)	54.0 (50.5-59.4) / 63.7 (59.5-70.1)
Range	50.4-60.0 / 59.5-72.0

(*continued on next page*)

Table 1 (*Continued*)

Abbreviations: BED = biologic equivalent dose; ECOG = Eastern Cooperative Oncology Group, NOS = not otherwise specified.
* Data are presented as the number (percentage) of patients unless otherwise noted.

points (Fig. 3). Two patients with pancreas adenocarcinoma experienced a local recurrence. One recurred in the pancreas within the radiation field, and the other patient did not have further recurrence details available for analysis within the registry. Only one patient had a locoregional recurrence as a first site of recurrence. Among patients who did experience recurrence, mean TTLR was 7.2 months (SE, 0.47). Table 2 details the sites of first recurrence among all patients in our cohort with data available.

Distant metastasis-free survival

After assessing all patients with available data for DMFS, median DMFS was 11.0 months (95% CI, 2.56-15.55 months). The DMFS rates at 12 months and 24 months were 38% and 0%, respectively.

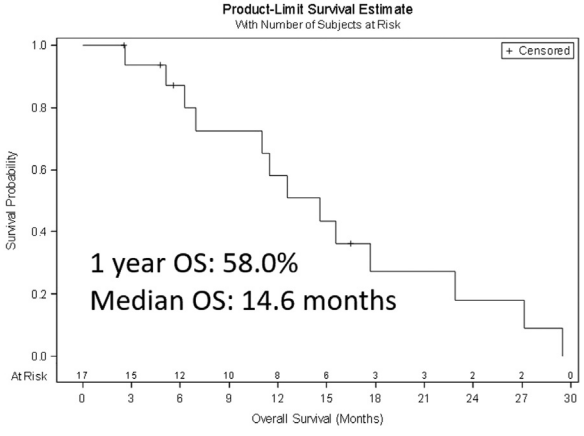

Figure 2 Kaplan-Meier analysis of overall survival (OS) for patients treated with proton radiation therapy for locally advanced pancreatic cancer.

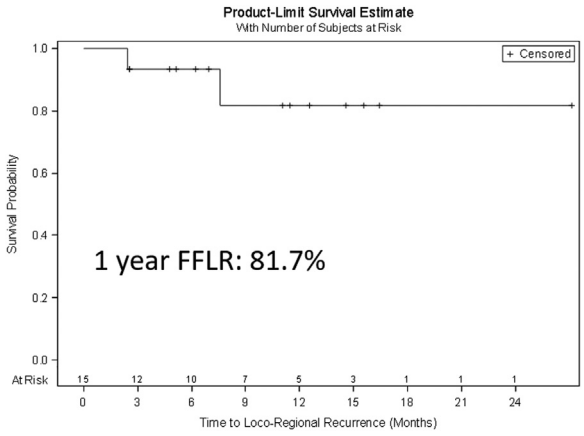

Figure 3 Kaplan-Meier analysis of time to locoregional recurrence for patients treated with proton radiation therapy for locally advanced pancreatic cancer. *Abbreviation:* FFLR = freedom from locoregional recurrence.

Table 2 Anatomic site of first recurrence for patients with pancreatic adenocarcinoma

Site	Patients, no.*
Locoregional	1
Distant	8
Synchronous locoregional and distant	1
No recurrence	6

* Patients with nonadenocarcinoma histologies (n = 2) or incomplete data available (n = 1) were not included.

Time to new progression or metastasis

After assessing all patients with available data for TTPM, median time to new progression or metastasis was 13.9 months (95% CI, 2.4-13.9 months). The rates of no progression or metastasis at 12 months and 24 months were 58% and 0%, respectively (Fig. 4).

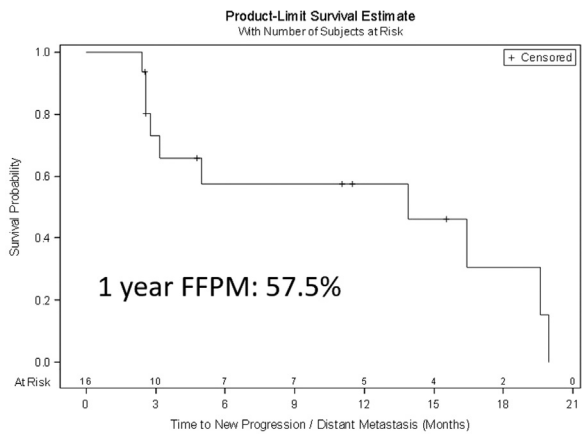

Figure 4 Kaplan-Meier analysis of time to new progression or distant metastasis for patients treated with proton radiation therapy for locally advanced pancreatic cancer. *Abbreviation:* FFPM = freedom from progression or distant metastasis.

Discussion

To our knowledge, this is the first study examining a prospective multi-institutional registry of patients receiving PBT for LAPC. In this study, we have found that proton therapy for LAPC was well tolerated and efficacious. Specifically, patients in our cohort did not experience any grade 3 CTCAE toxicities despite their receiving a median dose of 54 Gy (biologic equivalent dose, 63.72 Gy) and 78.9% also receiving concurrent chemotherapy. Disease control was excellent in the context of LAPC, with a rate of freedom from local recurrence of 81.7% at 1 year after RT, which was associated with a median OS of 14.6 months. These results add to the pool of clinical data to support the notion that PBT may improve the therapeutic ratio for patients receiving RT for pancreatic cancer.

The lack of grade 3 toxicities in our cohort compares favorably with patient series of concurrent chemoRT using photons and is consistent with other proton therapy series (Table 3). For example, Loehrer et al[19] found that 79% of patients who received concurrent chemoRT using 3DCRT and gemcitabine experienced grade 3 or 4 toxicities, including 41% of patients with grade 4 toxicities. Of note, this rate includes hematologic toxicities from induction systemic therapy, which likely accounts for a significant portion of the toxicities.[19] Mukherjee et al[20] analyzed toxicity results from induction chemotherapy and concurrent chemoRT separately and showed lower but still significant rates of grade ≥3 toxicities for the chemoRT phase of therapy. Rates were 12% to 37%, depending on the systemic therapy of choice.[20] IMRT and moderately hypofractionated RT resulted in similar rates of toxicity to those for 3DCRT, ranging from 13.4% to 35.7%.[21-23] Of note, Lee et al[24] reported 0% grade ≥3 toxicities for a mixed cohort of 3DCRT and IMRT, but the only toxicities being tracked in that cohort were gastrointestinal-related, which underestimates the total rate of grade ≥3 toxicities. Publications using stereotactic body RT (SBRT) for LAPC have shown potentially lower rates of toxicity, with reported rates of grade ≥3 toxicities ranging from 0% to 25%.[25-27] Patient series assessing PBT generally observe lower rates of grade ≥3 toxicities,[28] with 4 of 6 studies identified showing a rate of 0%.[11,13,14,16,17,29] Two other publications displayed slightly higher rates of grade ≥3 toxicities.[11,16] Both studies treated the majority of their patients with dose escalated and/or hypofractionated RT regimens and incorporated concurrent gemcitabine with proton RT; despite this aggressive approach, these experiences demonstrated acute and late grade ≥3 gastrointestinal toxicity rates of <17% and 11%, respectively.[11,16]

Table 3 Studies reporting with toxicity and survival outcomes for chemoradiation in LAPC

Modality	Authors	Year	Study design	No.	Concurrent therapy	Dose, Gy/fx	Grade ≥3 toxicity rate, %	Median OS, mo
3DCRT	Loehrer et al[19]	2011	Trial	74	Gem 1000 mg/m^2 × 3	50.4/28	79	11.1
3DCRT	Mukherjee et al[20]	2013	Trial	38	Gem 300 mg/m^2 × 6	50.4/28	37	13.4
3DCRT	Mukherjee et al[20]	2013	Trial	36	Cap 830 mg/m^2 bid 5 d/wk	50.4/28	12	15.2
3DCRT	Lee et al[24]	2016	RR	40	Gem 1000 mg/m^2 × 3 or 5FU 1000 mg/m^2 × 3	45/25 or 50.4/28	0 (only GI toxicities documented)	15.8
IMRT	Lee[24]	2016	RR	44	Gem 1000 mg/m^2 × 3 or 5FU 1000 mg/m^2 × 3	45/25 or 50.4/28	0 (only GI toxicities documented)	22.6
IMRT and 3DCRT	Chung et al[21]	2017	RR	497	Mixed regimens	58.42/23 or 57/20	>21.3*	15.7
IMRT	Zschaeck et al[22]	2017	RR	28	Cap 825 mg/m^2 bid or Gem 600 mg weekly	60-66/ 30-33	35.7	19.0
Hypofractionated photon RT	Reyngold et al[23]	2021	Prospective cohort	119	Fluoropyrimidine (107/119 patients)	75/25	13.4	18.2
SBRT	Herman et al[25]	2015	Trial	49	None	33/5	12.2 acute/10.6 late	13.9
SBRT	Chuong et al[26]	2013	RR	16	Gem, Taxotere, Cap	35-50/5	25	15.0
SBRT	Polistina et al[27]	2010	Trial	23	Gem 1000 mg/m^2 × 6	30/3	0	10.6
PBT	Terashima et al[16]	2012	Trial	50	Gem 800 mg/m^2 × 3	50-70.2/ 25-26	>38*	NR, 1-y OS 76.8%
PBT	Sachsman et al[17]	2014	Trial	11	Cap 1000 mg/m^2 bid 5d/wk	59.4/33	0	18.4
PBT	Jethwa et al[14]	2018	RR	13	Cap 825 mg/m^2 bid or CVI 5FU 225 mg/m^2 daily	50/25	0	NR, 1-y OS 62%
PBT	Nichols et al[13]	2012	RR	10	Cap 1000 mg/m^2 bid 5d/wk	59.4/33	0	8.4
PBT	Hiroshima et al[11]	2019	RR	42	Gem or S-1	50-67.5/ 25-33	45	25.6
PBT	Kim et al[29]	2020	RR	81	Cap or 5FU	45-50/10	0	18.0
PBT	Present study	2022	Prospective multi-institutional cohort	19	Cap, Gem, or 5FU	50.4-60/ 19-33	0	13.0

Abbreviations: 3DCRT = 3-dimensional conformal radiation therapy; 5FU = 5-fluorouracil; bid = twice daily; Cap = capecitabine; CVI = continuous venous infusion; fx = fractions; Gem = gemcitabine; GI = gastrointestinal; IMRT = intensity modulated radiation therapy; LAPC = locally advanced pancreatic cancer; OS = overall survival; PBT = proton radiation therapy; RR = retrospective review; RT = radiation therapy; SBRT = stereotactic body radiation therapy, NR = not reported, S-1 = S-1 chemotherapy.

* The study did not report the overall toxicity rate but did report rates of each type of grade ≥3 toxicity. The most common toxicity type is reported, but the total grade ≥3 rate is likely higher.

Disease control and survival endpoints in our cohort were similar to those of other studies investigating chemoradiation for LAPC. Our median OS of 14.6 months falls within the range of other survival intervals reported from PBT series (8.4-25.6 months).[11,13,17,29] The locoregional control in our study was 81.7% at 1 and 2 years, which is similar to locoregional control rates of other cohorts receiving PBT for pancreatic cancer (1-year range, 66%-86%).[11,14,16,17,29] This range is also consistent with the 1-year locoregional control reported after moderately hypofractionated photon chemoradiation (82.4%) and SBRT (69.6%-86.4%).[23,25,26,30] Similarly, our cohort had high rates of metastatic disease progression, which is uniform among patients with LAPC, regardless of the modality used for local control. Although the size of our cohort limited our ability to stratify for disease control based on radiation dose, other studies have found that increased RT dose is associated with better local control and OS for both proton and photon modalities.[11,31] Unfortunately, the NRG Oncology randomized phase 2 investigation studying dose escalation for inoperable pancreatic cancer was terminated owing to poor enrollment.[32]

Although it has, to our knowledge, the largest multi-institutional cohort reported to date, our study was still limited by the size of our cohort and availability of specific data input across institutions, which reduced the ability to detect treatment or patient characteristics significantly associated with prognosis or treatment toxicity. Additionally, all of the patients in this study were seen at tertiary medical centers with access to PBT, which may have resulted in patient selection bias. Finally, although we report numerically better toxicity rates than those reported from photon-based RT cohorts and trials, we do not have access to a matched cohort of IMRT-SBRT patients for comparison.

Conclusion

This study, describing results of the first multi-institutional prospective cohort treated with PBT for LAPC, indicates that standard-fractionation PBT is well tolerated and results in rates of local control and survival consistent with those reported by studies using photon-based modalities. Given the increasing data supporting a potential benefit of RT dose escalation and the favorable toxicity profile of this modality underpinned by well-documented theoretical and dosimetric advantages, dose escalation with PBT and incorporation of hypofractionation hold promise for the future treatment of LAPC and warrant further study.

Disclosures

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.adro.2023.101250.

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