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Scientific Article

Initial experience with intensity modulated proton therapy for intact, clinically localized pancreas cancer: Clinical implementation, dosimetric analysis, acute treatment-related adverse events, and patient-reported outcomes

Krishan R. Jethwa MD, Erik J. Tryggestad PhD, Thomas J. Whitaker PhD, Broc T. Giffey CMD, Bret D. Kazemba CMD, Michelle A. Neben-Wittich MD, Kenneth W. Merrell MD, Michael G. Haddock MD, Christopher L. Hallemeier MD *

Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota

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Abstract

Purpose: Pencil-beam scanning intensity modulated proton therapy (IMPT) may allow for an improvement in the therapeutic ratio compared with conventional techniques of radiation therapy delivery for pancreatic cancer. The purpose of this study was to describe the clinical implementation of IMPT for intact and clinically localized pancreatic cancer, perform a matched dosimetric comparison with volumetric modulated arc therapy (VMAT), and report acute adverse event (AE) rates and patient-reported outcomes (PROs) of health-related quality of life.

Methods and materials: Between July 2016 and March 2017, 13 patients with localized pancreatic cancer underwent concurrent capecitabine or 5-fluorouracil-based chemoradiation therapy (CRT) utilizing IMPT to a dose of 50 Gy (radiobiological effectiveness: 1.1). A VMAT plan was generated for each patient to use for dosimetric comparison. Patients were assessed prospectively for AEs and completed PRO questionnaires utilizing the Functional Assessment of Cancer Therapy-Hepatobiliary at baseline and upon completion of CRT.

Results: There was no difference in mean target coverage between IMPT and VMAT ($P > .05$). IMPT offered significant reductions in dose to organs at risk, including the small bowel, duodenum, stomach, large bowel, liver, and kidneys ($P < .05$). All patients completed treatment without radiation therapy breaks. The median weight loss during treatment was 1.6 kg (range, 0.1-5.7 kg). No patients experienced grade ≥3 treatment-related AEs. The median Functional Assessment of Cancer Therapy-Hepatobiliary scores prior to versus at the end of CRT were 142 (range, 113-163) versus 136 (range, 107-173; $P = .18$).

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* Corresponding author. Department of Radiation Oncology, Mayo Clinic, 200 First St SW, Rochester, MN 55905.
E-mail address: hallemeier.christopher@mayo.edu (C.L. Hallemeier).

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Conclusions: Pencil-beam scanning IMPT was feasible and offered significant reductions in radiation exposure to multiple gastrointestinal organs at risk. IMPT was associated with no grade ≥3 gastrointestinal AEs and no change in baseline PROs, but the conclusions are limited due to the patient sample size. Further clinical studies are warranted to evaluate whether these dosimetric advantages translate into clinically meaningful benefits.
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Introduction

Pancreatic cancer is the fourth leading cause of cancer-related deaths in men and women. At the time of diagnosis, approximately 50% will have clinically localized (ie, nonmetastatic) disease. Treatment paradigms continue to evolve, although concurrent chemoradiation therapy (CRT) is considered a reasonable treatment option after potentially curative resection or for patients with intact borderline resectable or locally advanced unresectable pancreatic cancer, typically after initial treatment with combination chemotherapy.[1-8] CRT may improve margin negative resection rates, lymph node downstaging, and locoregional control in patients undergoing subsequent resection while also offering durable local disease control and palliation of local symptoms for those who are unable to undergo curative resection.

Historical trials evaluating the role of CRT in the management of localized pancreatic cancer have reported acute gastrointestinal (GI) grade 3 adverse event (AE) rates of 70% to 90% and grade ≥4 rates of 40%.[2,4,6,9] However, since that time, improvements have been made in techniques of radiation therapy (RT) delivery, understanding of dose-volume relationships for radiation effects on organs at risk (OAR), and the medical management of symptoms.[10-13]

One potential improvement is the advent of proton beam therapy (PBT) because its unique physical properties (ie, lack of exit dose and lower entrance dose compared with photon RT) allows for a more favorable dose distribution compared with photon RT, with relative sparing of radiation dose to normal tissues, thereby allowing for a theoretical improvement in the therapeutic ratio. However, limited data exist on the role of PBT for the treatment of pancreatic cancer.[14-23] Although demonstrating favorably low rates of GI AEs, the previously reported series have limitations with regard to their inclusion of heterogeneous patient cohorts and treatment techniques, lack of technical treatment details, lack of comparative dosimetric data with advanced photon-based techniques, and use of passive scatter PBT as opposed to more advanced pencil-beam scanning (PBS)/intensity modulated proton therapy (IMPT) techniques.

The purpose of this study was to describe the clinical implementation of PBS-IMPT for the treatment of intact, clinically localized pancreatic cancer. We report a detailed description of treatment planning techniques and a matched dosimetric comparison of PBS-IMPT with volumetric modulated arc therapy (VMAT). We also report acute AE rates and patient-reported outcomes (PROs) of health-related quality of life (HRQoL). We hypothesized that IMPT would result in improved OAR-sparing compared with VMAT and would be associated with favorable acute treatment tolerance.

Methods and materials

Patients

This was a retrospective review of the first 13 consecutive patients with intact, clinically localized pancreatic adenocarcinoma who received IMPT with concurrent chemotherapy (capecitabine 825 mg/m^2 twice daily [n = 11] or continuous venous infusion 5-fluorouracil 225 mg/m^2 for 5 days per week during RT [n = 2]) at our institution between July 2016 and March 2017. Patients were chosen for treatment with IMPT on the basis of insurance coverage of IMPT and physician/patient preferences. The institutional review board approved the conduct of this study.

Simulation and treatment setup

Patients were instructed to fast for at least 2 hours prior to simulation and treatment. Oral contrast was not administered. Patients were positioned supine with their arms above their head in a Vac-Lok (CIVCO Radiotherapy, Coralville, IA) or Alpha Cradle (Smithers Medical Products, Inc., North Canton, OH) custom immobilization device on a CIVCO couch (CIVCO Radiotherapy, Coralville, IA). A noncontrast, free-breathing, 4-dimensional computed tomography (CT) scan was obtained. Additionally, an intravenous contrast-enhanced scan was obtained if there were no contraindications.

Intensity modulated proton therapy planning

CT images and structures were imported into the Eclipse Treatment Planning System (Version 13.7, Varian Medical Systems, Inc., Palo Alto, CA) for treatment planning. Plans were generated on the average series of the 4-dimensional CT scans. The amplitude of tumor motion

was assessed on the free-breathing, 4-dimensional CT scan. If the amplitude was ≤1 cm, free-breathing treatment with isolayered repainting, and a maximum monitor-unit (MU) threshold of 0.005 MU was used to reduce dosimetric plan degradation due to motion interplay.[24] For 1 patient with tumor motion of >1 cm, free-breathing treatment with respiratory, phase-based gating was used to reduce tumor motion to <1 cm. The median amplitude of tumor motion was 6 mm (range, 4-10 mm). For the 10 patients with internal stents (8 biliary, 2 duodenal), the Hounsfield units (HU) were overridden to 0 (n = 7), to HU corresponding with adjacent soft tissue (n = 2), or native metal (n = 1). Any air proximal of targets within the stomach/intestine was contoured, and the HU were overridden to 0 for treatment planning. Subsequently, the dose was recalculated without HU corrections for air on the final plan.

The internal gross tumor volume was delineated, which consisted of the postchemotherapy pancreatic primary tumor volume and clinically involved regional lymph nodes accounting for respiratory motion on the 4-dimensional CT scan. The clinical target volume (CTV) that was to receive 50 Gy (CTV50) was a 0.5 to 1 cm geometric expansion of the internal gross tumor volume with the clinically uninvolved bone, muscle, nonduodenum small bowel, and stomach cropped out. The CTV that was to receive 45 Gy (CTV45) included CTV50 and an elective expansion including celiac, superior mesenteric, and adjacent retroperitoneal lymph nodes, with or without porta hepatis, accounting for respiratory motion.

All patients were prescribed a treatment course of 25 fractions, with 50 Gy (radiobiological effectiveness [RBE]:1.1] administered to CTV50 in 2 Gy per fraction and 45 Gy administered to CTV45 in 1.8 Gy per fraction using multifield optimized PBS-IMPT (Fig 1). All patients were treated with 2 fields, typically posterior and posterior-oblique, to minimize dose to the anterior visceral structures and the kidneys posteriorly. One patient was treated with right lateral and posterior fields. For this process, planning target volumes were not explicitly created; instead, robust optimization was performed with a positional uncertainty of ±5 mm in the x, y, and z directions, range uncertainty of ±5%, and intrafield uncertainty of ±5 mm in the x, y, and z directions.

The goal target coverage for the CTVs were volume of target receiving ≥100% of prescription dose (V100%) >95% and volume of target receiving ≥95% of prescription dose (V95%) >99%. OAR dosimetric constraints included the small bowel (maximum dose: < 52 Gy; volume of organ receiving ≥45 Gy [V45]: <195 cm^3; V30: < 300 cm^3), duodenum (maximum dose: < 54 Gy); liver (mean dose: < 25 Gy; V30: < 60%; volume of organ receiving

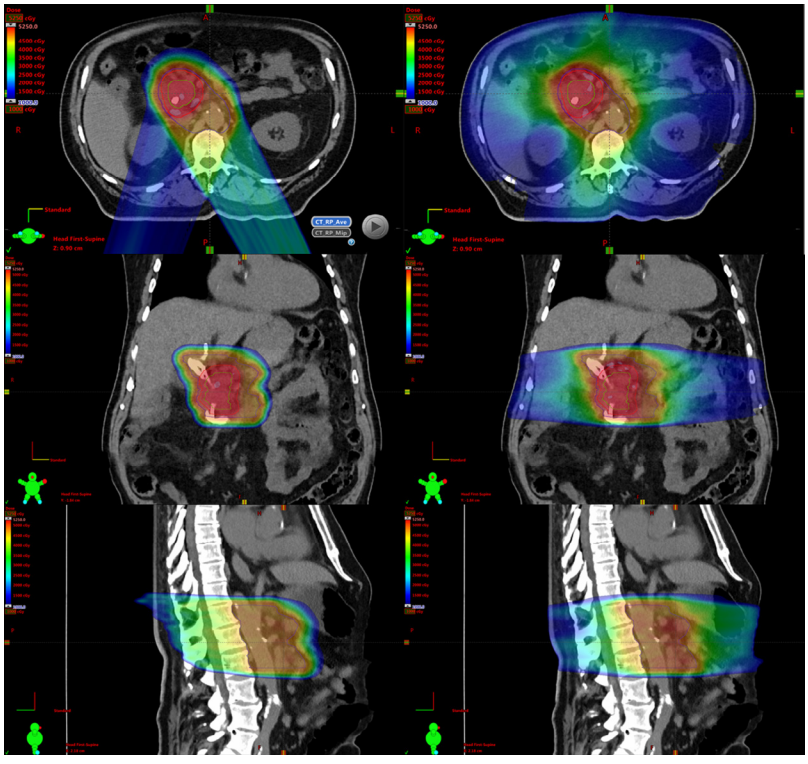

Figure 1 Representative IMPT (left) and VMAT (right) treatment plan for a patient with borderline resectable pancreas cancer receiving neoadjuvant chemoradiation. Prescription dose was 45 Gy (RBE 1.1) to the pancreas tumor and regional lymphatics (CTV45 blue) with a concomitant boost to 50 Gy to the gross pancreas tumor (iGTV green, CTV50 red). IMPT planning used posterior/posterior-oblique treatment fields, which allowed for robust target coverage and excellent sparing of the anterior visceral structures and kidneys.

≤30 Gy [CV30]: >700 cm^3), kidney (V18: < 10%), and spinal cord (maximum dose: < 45 Gy). The dose distribution and target coverage were evaluated on the extreme respiratory phases (0 and 50). In addition, plan evaluation, as per institutional quality assurance standards, utilized commercially available Eclipse (Varian Medical Systems, Inc., Palo Alto, CA) treatment planning system (RBE: 1.1), in-house graphics processing unit–based Monte Carlo physical dose simulation (RBE: 1.1), and in-house Monte Carlo biologic dose simulation, which assumes a linear relationship between RBE and linear energy transfer.[25]

IMPT was delivered via PBS using a Hitachi Probeat-V system (Hitachi, Ltd., Tokyo, Japan) that was incorporated into a compact, half-gantry system, which provides a native pencil-beam spot size effectively ranging from approximately 4 to 7 mm (σ), depending on energy and residual range.[26] Daily image guidance involved stereoscopic (oblique pair) kilovoltage imaging and 6-degree of freedom based (2-/3-dimensional) matching to the spine with a 3-mm tolerance. A fully robotic patient positioning system (couch) was used to achieve this match. All patients underwent weekly verification 4-dimensional CT scans performed to assess for target volume coverage, dose to OAR, and the need for adaptive replanning. Four of 13 patients had a single replan performed due to changes in internal anatomy affecting target coverage.

Intensity modulated radiation therapy planning

All patients had a VMAT photon plan created for dose comparison purposes and as a backup in case of proton center outage. The same CTVs and dose/fractionation were utilized. A planning target volume margin of 5 mm was added to the respective CTVs. Plans were generated using RapidArc (Varian Medical Systems, Inc., Palo Alto, CA) VMAT. VMAT plan optimization utilized the same target volume coverage and OAR planning dose constraints as used for IMPT planning.

Outcomes assessment and statistical analysis

Patients were assessed prospectively for AEs by the treating physician before and at the end of CRT for changes in weight and AEs per the Common Terminology Criteria for Adverse Events version 4.0. Patient-reported HRQoL questionnaires were collected prior to initiation and at the end of CRT utilizing the Functional Assessment of Cancer Therapy-Hepatobiliary (FACT-Hep) questionnaire, which is a 45-item questionnaire designed to assess HRQoL in patients with hepatobiliary cancer.[27] The FACT-Hep questionnaire consists of the 27-item FACT-General to assess patient symptoms and concerns within 4 dimensions (physical, social/family, emotional, and functional well-being) and the 18-item hepatobiliary cancer subscale (HCS) to assess back/stomach pain, GI symptoms, anorexia, weight loss, and jaundice. Respondents rate each item using a 5-point Likert-type scale that ranges from 0 (not at all) to 4 (very much) whereby 5 subscale scores and an overall HRQoL score can be derived,[27] with higher scores reflecting better HRQoL.

Although data are limited, an increase of 7.77 in FACT-Hep total score has been demonstrated to correlate with a 1-point improvement in Eastern Cooperative Oncology Group performance status (ECOG PS), and a reduction of 13.5 correlates with a 1-point decrement in ECOG PS.[28] Similarly, an increase of 3.61 of the HCS correlates with a 1-point improvement in ECOG PS, and a reduction of 3.80 correlates with a 1-point decrement in ECOG PS.

Survival, local control, and freedom from distant metastasis were estimated using Kaplan-Meier methods. Descriptive statistics for continuous variables were reported as mean ± standard deviation or median (range), and categorical variables were reported as number (percentage). Dosimetric comparisons were made by performing matched analyses among individual patients. Mean dosimetric parameter comparisons were made using a matched-pair Student *t* test. All statistical tests were two-sided, and $P < .05$ was considered statistically significant. The statistical analysis was performed using JMP v10.0.

Results

Patients

The patient characteristics are shown in Table 1. The median patient age was 70 years (range, 67-80 years). Most patients had National Comprehensive Cancer

Table 1 Patient characteristics

Variable (n = 13)	Value*
Age (years)	70 (67-80)
Sex	
Male	5 (38%)
Female	8 (62%)
T stage	
T3	9 (69%)
T4	4 (31%)
Nodal status	
cN0	9 (69%)
cN+	4 (31%)
NCCN Classification	
Borderline resectable	10 (77%)
Unresectable	3 (23%)

NCCN, National Comprehensive Cancer Network.

* Values are reported as median (range); other values are number of n (%).

Network–defined borderline resectable disease (77%) at the pancreatic head (77%) with no clinically apparent nodal involvement (cN0: 69%). All patients received multi-agent chemotherapy prior to CRT administration for a median of 4 months (range, 1-7 months) with modified 5-fluorouracil, leucovorin, irinotecan, and oxaliplatin (46%), gemcitabine and nab-paclitaxel (31%), or both regimens (23%). After chemotherapy and before CRT, all patients had restaging studies demonstrating stable or responsive local-regional disease without evidence of distant metastases.

Dosimetric comparison between intensity modulated proton and volumetric modulated arc therapy

Dosimetric comparisons between the 2 planning techniques are presented in Table 2. Target coverage was comparable between IMPT and VMAT plans with CTV45 and CTV50 volume of target receiving ≥95% of prescription dose (V95%) of 100% versus 100% versus 100% ($P = 1.0$) and 99.9% versus 99.9% ($P = 1.0$), respectively. IMPT resulted in significant reductions ($P < .05$) in mean, intermediate, and low doses to the small bowel, duodenum, stomach, large bowel, liver, and kidneys. Additionally, V45 Gy to the small bowel, duodenum, and stomach was significantly lower with IMPT compared with VMAT.

Treatment-related adverse events and patient-reported outcomes

All patients completed treatment as planned without breaks due to AEs. Median weight loss during treatment was 1.6 kg (range, 0.1-5.7 kg). Treatment-related AEs are shown in Table 3.

All 13 patients completed PRO questionnaires at initiation and immediately after CRT. The median (range) FACT-Hep scores prior to CRT versus at the end of CRT were 142 (113-163) versus 136 (107-173) with a mean difference of −7.5 ($P = .18$). The median (range) FACT-General scores were 89 (70-106) versus 83 (55-108) (mean difference: −6.3; $P = .09$), and the FACT-HCS scores were 55 versus 54 (mean difference: −1.2; $P = .63$).

Early oncologic outcomes

Median patient follow-up was 16 months (range, 9-24 months). The estimated 1- and 2-year survival rates were 62% (95% confidence interval [CI], 23%-90%) and 40% (95% CI, 9%-82%). Four patients (31%) experienced locoregional progression, which occurred concurrently with distant metastases for all 4 patients. Sites of locoregional progression were in the pancreas primary in a patient who did not undergo surgery, pancreas bed adjacent to the superior mesenteric artery, pancreas bed and retroperitoneal

Table 2 Dosimetric comparison of pencil-beam scanning IMPT and VMAT for localized pancreatic cancer

CTV/OAR	DVH parameter (unit)	IMPT Mean (SD)	VMAT Mean (SD)	*P*-value
CTV	CTV45 V95% (%)	100.0 (0.12)	100.0 (0.12)	1.0
	CTV50 V95% (%)	99.9 (0.3)	99.9 (0.3)	1.0
Small bowel	Mean (Gy)	3.7 (3.7)	17.4 (5.6)	< .0001*
	V15 (cc)	55 (75)	292 (311)	.008*
	V30 (cc)	26 (49)	84 (109)	.02*
	V45 (cc)	6 (12)	18 (31)	.05
Duodenum	Mean (Gy)	30.5 (12.0)	38.3 (9.0)	.0005*
	V30 (cc)	41 (20)	51 (25)	.0003*
	V45 (cc)	27 (16)	35 (21)	.0019*
Stomach	Mean (Gy)	5.9 (2.8)	18.9 (3.5)	< .0001*
	V30 (cc)	29 (25)	86 (38)	< .0001*
	V45 (cc)	5 (7)	17 (11)	< .0001*
Large bowel	Mean (Gy)	1.7 (1.3)	15.9 (4.2)	< .0001*
	V30 (cc)	10 (12)	70 (90)	.02*
	V45 (cc)	98 (303)	663 (1125)	.09
Liver	Mean (Gy)	3.6 (2.2)	11.6 (3.2)	< .0001*
	V30 (%)	4.3 (2.9)	8.2 (4.2)	.001*
Kidney	Mean (Gy)	4.1 (1.9)	10.1 (1.6)	< .0001*
	V12 (%)	15.9 (7.5)	36.4 (12.8)	.0001*
	V18 (%)	6.8 (2.9)	7.5 (3.3)	.5
Spinal cord	Maximum (Gy)	39.0 (7.1)	37.4 (4.6)	.54

CTV, clinical target volume; CTV45, CTV to receive 45 Gy; CTV50, CTV to receive 50 Gy; DVH, dose-volume histogram; IMPT, intensity modulated proton therapy; OAR, organ at risk; SD, standard deviation; Vn, volume of organ receiving n Gy; V95%, volume of target receiving ≥95% of prescription dose; VMAT, volumetric modulated arc therapy.

* Denotes statistical significance.

Table 3 Provider-assessed adverse event rates (Common Terminology Criteria for Adverse Events version 4.0)

Endpoint	Pre-CRT			Post-CRT		
	Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
Maximum gastrointestinal	31%	8%	8%	46%	15%	—
Anorexia	8%	—	8%	46%	8%	—
Nausea	15%	8%	—	23%	15%	—
Vomiting	—	—	—	8%	—	—
Diarrhea	8%	—	—	15%	8%	—
Pain	15%	—	—	31%	—	—
Fatigue	54%	—	8%	69%	8%	—
Dermatitis	—	—	—	46%	—	—

CRT, chemoradiation therapy.

lymph node, and retroperitoneal lymph node alone. The estimated 1-year local control rate was 66% (95% CI, 26%-91%). The estimated 1- and 2-year freedom from distant metastasis rates were 53% (95% CI, 17%-86%) and 28% (95% CI, 4%-40%).

Discussion

In the present study, we report our initial experience with IMPT and concurrent chemotherapy for intact, localized pancreatic cancer. Clinical implementation was feasible, and IMPT demonstrated significant dosimetric reductions to multiple relevant OARs compared with VMAT. Treatment was well tolerated in this initial cohort of patients, with low rates of acute GI AEs and no change in baseline PROs as assessed by the FACT-Hep questionnaire. These data support the feasibility of using IMPT for pancreatic cancer and provide a rationale for further exploration in a larger patient cohort.

There are several novel aspects to this series. We report use of PBT in a homogeneous cohort of patients with localized, intact pancreatic cancer treated with consistent target volumes and RT dose, use of posterior/posterior-oblique field design to maximally spare OARs, the use of advanced PBT planning and delivery techniques with robustly optimized PBS-IMPT using a small effective spot size (4-7 mm), and comparison with state of the art photon treatment techniques (ie, VMAT). Additionally, we report prospectively collected provider and patient-reported acute AEs.

The limitations of the study include its retrospective study design, small sample size, and lack of long-term clinical follow-up, which currently prevents us from performing an adequately powered clinical comparison study with patients treated with other RT techniques including intensity modulated radiation therapy (IMRT). Furthermore, oncologic outcomes should be interpreted descriptively given the limitations of a small patient cohort. Nonetheless, these results provide proof of the principal that PBS-IMPT reduces doses to OARs and could potentially reduce clinical AE rates.

Previous studies have compared dosimetry of PBT relative to photon IMRT for intact or resected pancreatic cancer.[14,15,20-23] Studies examining passive scatter PBT (vs. photon IMRT)[14,15,20-23] have demonstrated a reduction in low-dose dose-volume histogram parameters for some OARs; however, some dose-volume histogram parameters such as V45 Gy of the duodenum, small bowel, and stomach were higher with passive scatter PBT versus photon IMRT[14,15,22] due to the inferior conformality index with passive scatter techniques.[21,23]

Two studies (both from the University of Pennsylvania) have compared the dosimetry of a single-field optimized (ie, single-field uniform dose) PBS PBT versus IMRT for postoperative[21] or intact[22] pancreatic cancer. Our study is the most similar to that of Thompson et al.,[22] who observed that PBS reduced dose to the duodenum, small bowel, stomach, liver, kidneys, and total body for doses <30 Gy but noted no significant difference for any of these organs for doses >30 Gy. In contrast, we noted significant reductions in V45 Gy to the duodenum, small bowel, and stomach, in addition to reductions in doses <30 Gy. This difference is likely explained by the use of multifield, optimized IMPT in our study (vs. single-field optimization used by Thompson et al.) and the use of a small PBS spot size, reducing the effective beam penumbra.

Reductions in the stomach and bowel dose in the 30 to 45 Gy range are likely clinically meaningful because previous clinical studies have demonstrated a correlation of these parameters with acute GI AEs in patients with pancreatic cancer.[13,29] A major limitation of these previously published dosimetric studies[14,15,20-23] is that they involved in silico proton plans that were generated in a treatment planning system but not actually delivered to a patient. It is unknown whether such plans would be technically deliverable when considering particle-accelerator, beamline, and gantry characteristics as well as robustness to inter- and intrafraction uncertainties related to patient setup, internal organ motion, and anatomic changes. Therefore, a major strength of our dosimetric study compared with previous studies is that all patients were actually treated with the robustly optimized IMPT plans.

To date, there is limited published clinical experience using PBT for pancreatic cancer. Limitations of the published series include the retrospective study design, small sample size, heterogeneous patient cohorts, and heterogeneous RT dose/fractionation regimens. Nichols et al. reported clinical outcomes of a group of 22 patients with nonmetastatic pancreatic or ampullary cancer treated with passive scatter PBT.[15] Treatment tolerance was favorable and no patients experienced grade ≥3 acute AEs.

Lukens et al. reported clinical outcomes of 13 patients with pancreatic cancer (1 intact, 12 postoperative) treated with passive scatter PBT and concurrent chemotherapy.[19] Acute grade ≥3 GI AEs occurred in 1 patient (8%), which compared favorably with a rate of 24% in a contemporaneous cohort of 17 patients treated with photon RT and concurrent chemotherapy. Additionally, a prospective phase 1/2 trial examining a preoperative passive scatter PBT regimen of 25 Gy in 5 fractions found a 4.1% rate of grade 3 acute AEs.[17] Our data further corroborate the favorable toxicity profile of PBT for pancreatic cancer, and this observation was supported by prospectively obtained PROs using a validated assessment tool for pancreatic cancer.

The available literature suggests that advanced RT technologies have improved the tolerance of CRT for pancreatic cancer, namely by reducing severe acute GI AEs. In prospective studies of patients with pancreatic cancer treated with CRT using 2- or 3-dimensional conformal techniques, the reported AE rates were 70% to 80% for grade 3 AEs and 40% for grade 4.[2,4,5,9] In a recent systematic review of contemporary series of CRT for pancreatic cancer, Bittner et al. found that IMRT (vs. 3-dimensional conformal RT) was associated with lower rates of grade ≥3 acute nausea ± vomiting (8 vs. 13%), diarrhea (2 vs. 12%), and late GI AEs (5% vs. 11%).[10] Notably, the rates of grade >3 toxicity with 3-dimensional CRT in this analysis were lower than those reported with 3-dimensional CRT in previous trials, suggesting that improvements in chemotherapy delivery, supportive care, and other components of RT planning (eg, target volume delineation, OAR constraints, and image guidance) also likely contributed to better tolerance of CRT for pancreas cancer. Nonetheless, the low rates of acute grade 3 + GI toxicity (0-8%) reported in the limited series of PBT for pancreatic cancer compare favorably with those reported in a contemporary series using modern, advanced photon RT techniques including IMRT, although further comparative clinical data are needed.

Our clinical data are hypothesis generating but support the continued evaluation of PBT for pancreatic cancer. Additional research is needed to optimize IMPT planning and delivery for pancreatic cancer. Further clinical studies are needed to evaluate whether these dosimetric advantages translate into improvements in clinical outcomes relative to those of advanced photon techniques such as IMRT. Ideally this would be evaluated in prospective trial designs, although well-conducted retrospective studies utilizing an appropriate photon comparison cohort are needed as well. Additionally, the reduction in dose to OARs associated with IMPT may allow for the opportunity to explore RT dose escalation, hypofractionation, and/or intensification of concurrent systemic therapies with the goal of improving oncologic outcomes for patients with localized pancreatic cancer.[20,30]

Conclusions

For patients with clinically localized, intact pancreatic cancer, IMPT offers significant reductions in radiation dose to OARs relative to VMAT. In our initial experience, IMPT was associated with a low rate of acute GI AEs and favorable PROs. Further clinical studies are needed to evaluate whether these dosimetric advantages translate into clinically meaningful benefits and to evaluate the possibility of treatment intensification.

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