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REVIEW

Proton Beam Therapy for Pancreatic Tumors: A Consensus Statement from the Particle Therapy Cooperative Group Gastrointestinal Subcommittee

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Radiation therapy manages pancreatic cancer in various settings; however, the proximity of gastrointestinal (GI) luminal organs at risk (OARs) poses challenges to conventional radiation therapy. Proton beam therapy (PBT) may reduce toxicities compared to photon therapy. This consensus statement summarizes PBT's safe and optimal delivery for pancreatic tumors. Our group has specific expertise using PBT for GI indications and has developed expert recommendations for treating pancreatic tumors with PBT. Computed tomography (CT) simulation: Patients should be simulated supine (arms above head) with custom upper body immobilization. For stomach/duodenum filling consistency, patients should restrict oral intake within 3 hours before simulation/treatments. Fiducial markers may be implanted for image guidance; however, their design and composition require scrutiny. The reconstruction field-of-view should encompass all immobilization devices at the target level (CT slice thickness 2-3 mm). Four-dimensional CT should quantify respiratory motion and guide motion mitigation. Respiratory gating is recommended when motion affects OAR sparing or reduces target coverage. Treatment planning: Beam-angle selection factors include priority OAR-dose minimization, water-equivalent-

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thickness stability along the beam path, and enhanced relative biological effect consideration due to the increased linear energy transfer at the proton beam end-of-range. Posterior and right-lateral beam angles that avoid traversing GI luminal structures are preferred (minimizing dosimetric impacts of variable anatomies). Pencil beam scanning techniques should use robust optimization. Single-field optimization is preferable to increase robustness, but if OAR constraints cannot be met, multifield optimization may be used. Treatment delivery: Volumetric image guidance should be used daily. CT scans should be acquired ad hoc as necessary (at minimum every other week) to assess the dosimetric impacts of anatomy changes. Adaptive replanning should be performed as required. Our group has developed recommendations for delivering PBT to safely and effectively manage pancreatic tumors.

Introduction

Historically, radiation therapy (RT) has been offered to patients with pancreatic cancer in a variety of settings, including preoperative, postoperative, and definitive. However, due to the proximity of the pancreas to radiosensitive organs such as the liver, duodenum, and other mucosal gastrointestinal (GI) structures, treatment with conventional chemoradiation therapy can result in high toxicity rates, with over 23% of patients experiencing grade ≥ 3 toxicity in the chemoradiation arm of the LAP 07 trial.[1]

Due to its distinct physical properties, proton beam therapy (PBT) has the potential to deliver effective doses to target tissues in the upper abdomen while reducing exposure to surrounding normal tissues. Dosimetric studies have supported this, showing superior organs at risk (OARs) sparing with PBT compared to intensity-modulated RT (IMRT) or 3-dimensional conformal RT (3D-CRT) (Fig. 1).[2-6] This dosimetric advantage can enhance the therapeutic ratio in 2 ways: reducing toxicity (thus better preserving the patient's quality of life) and allowing safer dose escalation to improve oncologic outcomes.

This consensus statement presents expert recommendations from the Particle Therapy Cooperative Group Gastrointestinal Subcommittee discussing the clinical evidence to date, treatment planning considerations, current approaches, and future directions in treating pancreatic tumors with PBT.

Adjuvant Postoperative Therapy

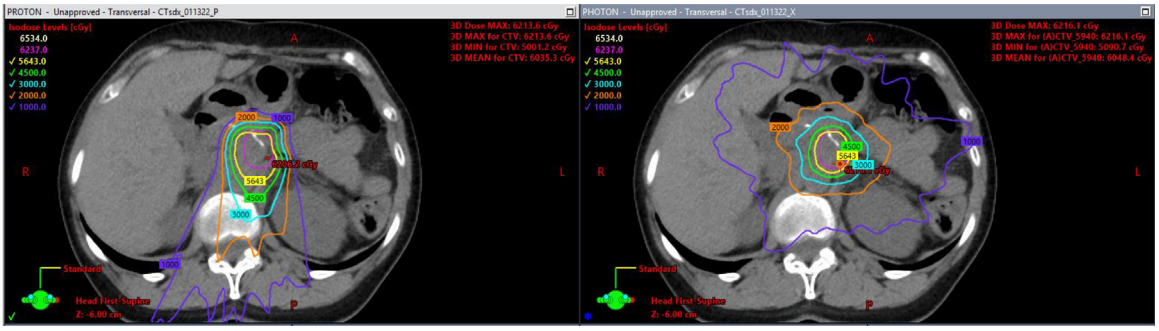
Clinical rationale

Although the European Study Group for Pancreatic Cancer (ESPAC) studies have raised questions about the relevance of postoperative RT in the setting of resected pancreatic cancers,[1,7,8,9] it is recognized that patients undergoing pancreatectomy who receive only adjuvant chemotherapy suffer a high rate of local and regional recurrence. A secondary analysis of the ESPAC-4 adjuvant chemotherapy trial evaluated recurrence patterns and determined that of the patients suffering a recurrence, 60% were local and regional recurrences with or without distant metastases. Results of using adjuvant RT in reducing the risk of local and regional recurrence have been mixed, with studies using conventional RT associated with moderate rates of acute gastrointestinal toxicity, especially in the current era of delivering more aggressive and active systemic treatments. PBT provides an opportunity to reduce toxicity. Nichols et al[10] completed one of the earliest dosimetric studies comparing the dose distributions of optimized IMRT and proton plans for adjuvant treatment of resected pancreatic cancer. Their analysis revealed that while proton plans achieved equivalent planning target volumes (PTV) coverage to IMRT plans, proton therapy allowed greater and statistically significant normal tissue sparing of the small bowel, stomach, and kidneys.

Similarly, Ding et al[11] performed a dosimetric comparison of a postoperative pancreatic treatment to a dose of 50.4 Gy delivered with the following techniques: 3D-CRT, 5-field IMRT, 2-arc volumetric modulated arc therapy, 2-field passive-scattering PBT, and 2-field pencil beam PBT. Target volume included the tumor bed and elective nodal coverage and was adequately covered with all techniques. Comparison of normal tissue doses showed that all proton plans resulted in significantly lower doses to the left kidney (mean and V18Gy) and stomach (mean and V20Gy) compared to all photon plans. Additionally, the pencil beam PBT plans resulted in better right kidney (mean and V18Gy), liver (mean dose), total bowel (mean and V20Gy), and small bowel sparing compared to all photons plans and the passive-scattering PBT plans.

However, the study to which the dosimetric benefits of adjuvant proton therapy translate into clinical benefits remains limited. Nichols et al[12] reported the outcomes and toxicity data on 18 patients who received postoperative proton therapy to a median dose of 50.5 Gy on the Proton Collaborative Group (PCG) multicenter registry trial. Of note, only 6 patients had negative surgical margins. Treatment was well tolerated, with only 1 patient demonstrating grade 3 GI toxicity. The 2-year survival rate was 37%.

Additionally, in 2016, Woodhouse et al[13] performed a comparative analysis of 105 pancreatic cancer patients treated with adjuvant chemoradiation therapy with either photon (n = 67) or proton (n = 38) therapy. The median dose was 50.4 Gy and 54 Gy for photons and PBT, respectively. The primary analysis compared maximum acute GI toxicity during adjuvant chemoradiation therapy. Median follow-up was 24 and 20 months for patients receiving photon and proton therapy, respectively. Grade 3 toxicity rates were 18% for photons and 5% for proton therapy, respectively (P = .079). Additionally, it was noted that more photon patients required multiple (≥3) hospitalizations



Left plan is Proton Plan to 59.4Gy/33 fx'x
Right is a Comparison VMAT Plan to 59.4Gy/33 fx's
CTV is in Pink. Isodose Lines with Associated Dose Shown

Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
	Duodenum	Approved	PROTON	COMPARISON	200.0	100.0	100.0	0.0	4646.3	91.6
	Duodenum	Unapproved	PHOTON	COMPARISON	200.0	100.0	100.0	14.8	4527.3	538.3
	Esophagus	Approved	PROTON	COMPARISON	12.4	100.0	99.9	0.0	1290.8	90.0
	Esophagus	Unapproved	PHOTON	COMPARISON	12.4	100.0	100.0	31.5	288.4	103.8
	LargeBowel	Approved	PROTON	COMPARISON	232.5	100.0	100.0	0.0	257.7	1.4
	LargeBowel	Unapproved	PHOTON	COMPARISON	232.5	100.0	100.0	27.3	1400.9	444.9
	Liver	Approved	PROTON	COMPARISON	918.1	100.0	100.0	0.0	1488.4	7.8
	Liver	Unapproved	PHOTON	COMPARISON	918.1	100.0	100.0	17.9	1952.9	327.0
	SmallBowel	Approved	PROTON	COMPARISON	126.7	100.0	100.0	0.0	4900.7	116.0
	SmallBowel	Unapproved	PHOTON	COMPARISON	126.7	100.0	100.0	29.2	4778.4	606.9
	SpinalCord	Approved	PROTON	COMPARISON	87.5	100.0	100.1	0.0	2281.1	177.0
	SpinalCord	Unapproved	PHOTON	COMPARISON	87.5	100.0	100.1	0.0	1082.8	85.7
	Stomach	Approved	PROTON	COMPARISON	214.4	100.0	100.0	0.0	5031.3	250.5
	Stomach	Unapproved	PHOTON	COMPARISON	214.4	100.0	100.0	42.5	4946.4	798.3

• Max and Mean Doses for Respective Organs at Risk Between Proton vs VMAT Plans

Fig. 1. Comparison of treatment plans for locally recurrent pancreatic adenocarcinoma. (A) Proton PBS plan versus (B) VMAT treatment plan to 59.4 Gy in 33 treatments. Clinical treatment volume dose (pink) with associated isodose lines show. (C) Table displays maximum and mean doses for respective organs at risk between plans.
Abbreviations: PBS = pencil beam scanning; VMAT = volumetric modulated arc therapy.

(P = .001). There was no difference in overall survival rates as a function of RT modality.

Based on the promising dosimetric and clinical data previously mentioned, adjuvant proton therapy for pancreatic patients can potentially reduce the toxicity profile compared to photons while maintaining equivalent control rates. Therefore, although the upfront cost of proton therapy may be higher globally, this enhancement in the therapeutic ratio makes protons potentially more cost-effective if multiple hospitalizations can be avoided or the cost of side effects can be mitigated. As such, further investigation of adjuvant proton therapy is warranted.[13]

Preoperative Proton Therapy: Resectable Pancreatic Cancer

Clinical rationale

Early investigations of neoadjuvant proton therapy for resectable pancreatic cancer helped establish the feasibility and safety of this approach. After completing a dosimetric analysis showing reduced normal tissue doses with protons compared to photon therapy,[14] researchers from Boston conducted a phase 1 dose-escalation study using proton therapy to doses of 30 Gy in 5 fractions with concurrent capecitabine.[15] The regimen was well tolerated at the highest doses and prompted further examination in a phase 2 study.[16] The dose was set at 25 Gy in 5 fractions for the phase 2 trial, and postoperative chemotherapy was advised.[14-16] A total of 50 patients were enrolled in the phase 1 and 2 cohorts, with 37 patients completing surgical resection. The primary endpoint was grade 3+ toxicity of < 20%. Study results showed that only 4% of patients experienced grade 3 toxicity and no grade 4 or 5 events. Local recurrence occurred in 16% of resected patients, with distant spread in 73%. Median progression-free and overall survival rates were 10 and 17 months, respectively.

Preoperative Proton Therapy: Borderline Resectable Pancreatic Cancer

Clinical rationale

The probability of complete resection with negative surgical margins decreases in pancreatic cancers with vascular invasion. Since residual tumor after surgery is associated with a poor prognosis,[17] preoperative therapy is often considered in patients with borderline resectable disease. In 2013, researchers from University of Florida reported on 5 preoperatively treated patients as part of a toxicity analysis concerning patients receiving proton therapy for both operable and inoperable pancreatic or ampullary tumors.[18] Doses of

50.4 to 59.4 cobalt Gy equivalent with concomitant capecitabine were used. No grade 3+ toxicities were reported at a median follow-up of 11 months.

Clinicians from Mayo Clinic reported their initial experience with proton therapy for pancreatic cancer in 2018.[2] They reviewed the outcomes and acute toxicity profile for 13 patients, 10 of whom had borderline resectable disease, receiving pencil beam PBT concurrent with 5-fluorouracil-based chemotherapy. They treated 2 clinical target volumes (CTVs): CTV50Gy relative biological effectiveness (RBE), a 0.5- to 1-cm expansion of the gross tumor volume, and CTV45Gy RBE, which was CTV50Gy RBE plus elective nodal regions. All patients received multiagent induction chemotherapy for a median of 4 months before PBT. With a median follow-up of 16 months, the estimated 1-year local control, freedom from distant metastases, and overall survival rates were 66%, 53%, and 62%, respectively. No patient experienced a grade $\geq$ 3 adverse event, and the rate of grade 2 GI toxicity was only 15%. The FACT-Hep and FACT-Gen questionnaires further evaluated these low toxicity rates with a patient-reported quality-of-life (QOL) assessment. QOL comparison pre- and post-PBT showed no change in baseline patient-reported health-related QOL outcomes.

In 2018, Murphy et al[19] reported the results of a prospective phase 2 trial examining PBT following FOLFIRINOX chemotherapy (4-8 cycles) for borderline resectable pancreatic cancer.[2] The primary outcome was the R0 resection rate, and the study was powered to detect a 20% improvement in the historical R0 rate of 20%. Fifty patients were enrolled. Of the eligible patients, 27 completed short-course radiation, with 15 receiving 25 Gy in 5 fractions using protons and the remainder receiving 30 Gy in 10 fractions with photons. Seventeen patients showed persistent vascular involvement after FOLFIRINOX and were treated with long-course RT to 50.4 Gy, with the vascular margin treated to 58.8 Gy using IMRT. All patients received daily capecitabine or 5-fluorouracil. Among the 48 evaluable patients, 32 underwent surgery, with 31 achieving R0 resection. No patients achieved a pathological complete response. Median progression-free and overall survival rates were 14.7 and 37.7 months, respectively. The 2-year overall survival rate was 72% among the patients who underwent surgery, with the median not being reached.

The benefits of proton therapy for borderline resectable pancreatic cancer warrant further examination. Ongoing clinical trials in Austria (NCT04894643), the University of Florida (NCT02598349), and the Mayo Clinic (NCT03902600) may help to clarify the full potential of this modality.

Proton Therapy for Locally Advanced Pancreatic Cancer

Clinical rationale

Clinical outcomes data evaluating proton therapy for managing locally advanced unresectable and inoperable pancreatic cancer (LAPC) arise primarily from single-institution experiences. One of the earliest reports utilizing PBT for managing LAPC comes from the Hyogo Ion Beam Medical Center (Japan).[20] This group assessed the feasibility and efficacy of gemcitabine-based concurrent PBT regimens for LAPC, which they defined as both borderline resectable and unresectable cases. Two PBT regimens were evaluated in the early phase of the study: (a) P1: 50 Gray equivalents (GyE) in 25 fractions for GI-adjacent LAPC; and (b) P2: 70.2 GyE in 26 fractions for non−GI-adjacent LAPC. After the early phase, all patients were treated with a P3 regimen of 67.5 GyE in 25 fractions. All PBT regimens were delivered concurrently with gemcitabine (800 mg/m^2) on days 1, 8, and 15, with 90% of patients also receiving adjuvant gemcitabine. Fifty patients were studied, with 5 enrolled on P1, 5 on P2, and 40 on P3. Results revealed 1-year freedom from local progression, progression-free survival, and overall survival rates of 81.7%, 64.3%, and 76.8%, respectively. Toxicities were limited except for a 12% risk of acute hematologic or GI toxicity and a 10% risk of grade $\geq$ 3 late gastric ulcer and hemorrhage. Local control and survival rates of this study compared favorably to modern photon therapy results,[1] with acceptable toxicity rates despite dose escalation.

In 2022, the Hyogo Ion Medical Center group updated their toxicity report for 123 patients with LAPC treated on the P3 regimen (67.5 GyE in 25 fractions with concurrent 800 mg/m^2 gemcitabine).[21] The target volume included the primary tumor, gross involved nodes, and elective nodal coverage of the celiac artery, superior mesenteric artery, and para-aortic regions. All patients received upper endoscopic examinations before and after completion of PBT to investigate the development of any PBT-related acute gastroduodenal changes. With a median follow-up of 15.2 months, the median overall survival rate was 18.7 months. The 1- and 2-year overall survival rates were 70.4% and 35.7%, respectively. The poor prognostic factors for overall survival were shown to be anterior invasion and pancreatic head cancer. The 1- and 2-year local progression-free survival rates were 78.2% and 59.0%, respectively. Grade 3 and 4 acute toxicities, all of which were hematologic, were observed in 42% and 2% of patients, respectively. There were no grade 5 acute toxicities or treatment-related deaths. Regarding late toxicities, grade 3, 4, and 5 toxicities occurred in 5%, 2%, and 2% of patients, respectively. Notably, late toxicities of grade $\geq$ 3 were more likely to occur for tumors of the pancreatic head that were in proximity to the bile duct and GI tract. Given the acceptable rates of late moderate and severe toxicity, this update further supported the safety of dose-escalated PBT regimens in managing LAPC.[22]

In 2014, the University of Florida reported outcomes and toxicity for 11 patients treated on an institutional protocol (PC01) of patients with unresectable pancreatic cancer who received definitive passive-scattering proton therapy to 59.4 Gy RBE at 1.8 Gy RBE per fraction targeting only gross disease with concurrent oral capecitabine.[23] Eight patients (73%) received induction chemotherapy. With a median follow-up of 14 months, 1- and 2-year local control rates were

86% and 69%, respectively. The rate of 1- and 2-year freedom from distant metastases was 68% and 27%, respectively. One- and 2-year overall survival rates were 61% and 31%, respectively. No patient experienced a grade $\geq$ 3 acute or late toxicity; only 1 experienced grade 2 fatigue.

More recently, the University of Tsukuba compared longer-term outcomes and treatment tolerance for patients with LAPC undergoing both conventionally fractionated and dose-escalated hypofractionated PBT regimens.[24] Forty-two patients underwent passive-scattering PBT with concurrent chemotherapy (Gemcitabine [Gem]: 38, S-1, an oral fluoropyrimidine: 4). Of note, 76% of patients received induction chemotherapy, whereas 81% received adjuvant post-PBT chemotherapy. Additionally, 55% received concurrent hyperthermia with their PBT course. Dose fractionation was conventionally fractionated in 25 patients ranging from 50 GyE to 60 GyE in 1.8 to 2 Gy per fraction, whereas 17 patients received dose-escalated therapy to 67.5 GyE in 25 fractions. Despite the escalation of therapeutic modalities used in this experience, there was no grade $\geq$ 3 GI-related acute toxicity (all were hematologic) and no grade $\geq$ 3 late toxicities. The 1- and 2-year local control rates were 83% and 79%, respectively, with higher doses trending for longer local control (median time of local recurrence: 11 months for 50 GyE and >36 months for 54-60 GyE and 67.5 GyE). One- and 2-year overall survival rates were 78% and 51%, respectively, with an association between longer median survival rates and higher doses: 13.1, 28.4, and 42.5 months for 50 GyE, 54 to 60 GyE, and 67.5 GyE, respectively. This study showed that despite the delivery of multimodality therapy, dose-escalated PBT could achieve higher local control rates with low toxicity rates.

Further ultrahypofractionated dose-escalated strategies with PBT for the management of LAPC were assessed by the Korean National Cancer Center,[25] which reported the efficacy and feasibility of PBT using a simultaneous integrated boost technique. Of the 81 patients, 18 (22.2%) patients received PBT without upfront and maintenance chemotherapy (group 1), 44 (54.3%) patients received PBT followed by maintenance chemotherapy (group 2), and 19 (23.5%) patients received PBT after upfront chemotherapy (group 3). Concurrent chemotherapy was delivered to 72.2%, 95.5%, and 89.5% of patients in groups 1, 2, and 3, respectively. The PTVs consisted of PTV1, defined as internal target volume (ITV) plus a 3- to 5-mm margin while excluding a 5-mm expanded volume of GI organs, and PTV2, defined as ITV plus 7 to 12 mm in all directions. PTV1 received 45 to 50 Gy in 10 fractions, whereas PTV2 received 30 Gy in 10 fractions. Median and 1-year locoregional control was 19.2 months, and 79.4%, respectively, with a trend for improved locoregional control for group 3, followed by group 2 and group 1. Median overall survival was 19.3 months and was also longer for group 3, followed by group 2 and then group 1. Despite the escalated dose per fraction utilized in this study, there were no grade $\geq$ 3 acute or late toxicities. The survival and control outcomes achieved by the Korean National Cancer Center group were also similar to those of modern photon series.[26]

In addition to the aforementioned single-institution experiences, which reveal that PBT can achieve comparable outcomes to photon therapy with a lower incidence of toxicity for the management of LAPC, Am Chhabra et al[27] recently published a multi-institutional report of outcomes and toxicity of patients treated on the PCG prospective registry. Nineteen consecutive patients with primarily T3 to 4 (68.4%) LAPC were identified who underwent definitive PBT between 2013 and 2020. Patients either had adenocarcinoma (n = 17), neuroendocrine tumor (n = 1), or cystadenoma (n = 1) histology. Median definitive PBT dose was 54 Gy (interquartile range: 50.5-59.4). Of patients with adenocarcinoma histology, 76.4% received induction chemotherapy prior to definitive PBT, and 82% received concurrent chemotherapy, primarily with Xeloda (Genentech). With a follow-up time of 10.0 months, median and 1-year overall survival rates were 13.0 months and 50.8%. The 1-year freedom from locoregional recurrence and freedom from distant metastases rates were 81.3%, and 58.0%, respectively. Toxicities were mild and predominantly related to anorexia (21% grade 2) or fatigue (21% grade 2), with no patient developing any grade $\geq$ 3 acute or late toxicity.

In summary, the studies above provide evidence that PBT in LAPC can achieve control rates equivalent to those achieved with photon therapy but with a reduced toxicity rate. Additional clinical trials are encouraged to utilize this favorable therapeutic ratio, given the potential for dose-escalated strategies to improve outcomes in LAPC.

Reirradiation

Clinical rationale

Local recurrences are common after definitive or adjuvant RT for pancreatic cancer. In RTOG 9704, 28% of patients treated with surgery and adjuvant chemoradiotherapy developed local recurrences without distant metastases.[28] As such, reirradiation may be considered a salvage treatment option.[29] PBT may be particularly well suited to allow for safer reirradiation and dose escalation in the recurrent setting by achieving reduced doses to adjacent normal tissues that may have previously received significant radiation doses from an initial course of RT.[30] To date, however, data for pancreatic reirradiation are limited.

In a single-institution report of patients enrolled in a prospective registry study, investigators from the University of Pennsylvania reported their experiences using PBT in 15 patients with local-only recurrent pancreatic cancer.[31] All but 1 patient had recurrences directly in the prior radiation field, with recurrences most commonly in the surgical bed and associated regional areas. The median follow-up was 15.7 months, with a median time from the prior course of

treatment of 26.7 months. In the setting of a median prior RT radiation dose of 50.4 Gy, the median PBT reirradiation dose was 59.4 Gy RBE, most commonly with concurrent chemotherapy (67%). The 1-year local in-field control, locoregional progression-free survival, distant metastasis-free survival, and overall survival rates were 87%, 72%, 64%, and 67%, respectively. Of those patients that initially reported pain prior to reirradiation, nearly all (86%) reported palliation of their pain. The rate of severe acute toxicities (≥ grade 3) was 13%. Notably, both patients with grade 4 and 5 adverse events had prior stent placement. Although both patients also had disease progression that may have contributed to the adverse events, caution should be taken when considering stenting just prior to proton reirradiation, especially in the presence of metallic stents. With limited follow-up, however, these data suggest that PBT in the reirradiation setting for isolated, locally recurrent pancreatic cancer is reasonable to consider, given the encouraging local control rates, palliative benefit, and acceptable acute toxicity. Although many of these patients may have limited survival, data on the late toxicities of PBT reirradiation would still be useful since long-term survivorship can still be observed (ranging up to 36 months in this study).

Technical Considerations for Simulation, Treatment Planning, and Treatment Delivery

Simulation

The patient should be simulated in the supine position with arms above the head on a wing board. Custom upper body immobilization, such as an Alpha Cradle (Smithers Medical Products, Inc) or a vacuum bag, should be used to ensure body and arm positioning reproducibility.[32-34] A knee cushion may be used for patient comfort. To ensure consistency of stomach and duodenum filling, patients should restrict oral intake for at least 3 hours prior to simulation and treatments.[35,36] Fiducial markers may be implanted to aid image guidance; however, fiducial design and material composition require careful consideration. Although gold markers are easy to visualize by most onboard imaging systems, they cast a dosimetric shadow along the proton beam path. Such effects are minimized with helical coil or carbon composite fiducials; however, they may be harder to see with some kV systems.[37-45]

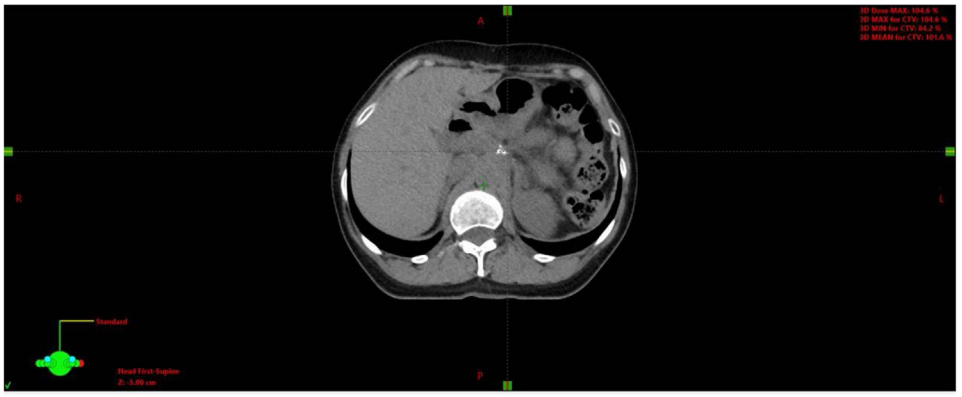
The computed tomography (CT) slice thickness should be 2 to 3 mm, and the reconstruction field-of-view should be large enough to encompass all immobilization devices used at the target level. A digital couch should be added to the CT data set before the planning stage if the Hounsfield units (HUs) of the simulation couch do not accurately translate into proton range calculations through the treatment couch. Contrast CT is recommended; however, intravenous iodine contrast does affect the correct determination of proton-stopping power ratios of the patient's anatomy. Therefore, if used in the simulation, it should be done after the planning images are acquired to avoid the need to override HU. Dual-energy CTs (DECTs) can accurately subtract the iodine contrast and may be an option to correct planning images acquired with contrast. However, abdominal motion should be factored in when the DECT is acquired depending on the DECT technology, ie, sequentially acquired scans versus fast switching source, as respiratory motion may not allow accurate iodine subtraction.[46-48] Additionally, DECT is known to improve the overall proton range calculation uncertainty to about 2.2% when used to determine the tissue stopping power,[49] though the same limitations related to respiratory breathing remain valid. Additional imaging, such as positron emission tomography, CT, and/or magnetic resonance imaging should also be considered for target delineation.

Four-dimensional CT (4DCT) should be used to quantify respiratory motion and guide motion mitigation strategies. Breath-hold is recommended when motion is known to affect OAR sparing or reduce target coverage.[50] Other methods for respiratory management include gating and compression belt. Our recommendation for users of gating is to fully characterize their system with respect to gating latency, as this has been shown to interfere with the dose coverage.[51] As for abdominal compression, we recommend using a flexible pneumatic system with no hard components in the path of the proton beams to avoid increased range uncertainties. The users of abdominal compression are advised that image guidance should aim at target alignment rather than bony anatomy.[52,53]

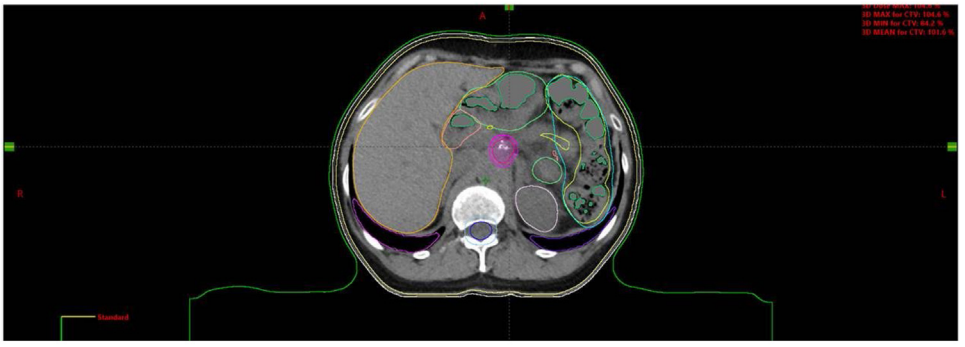
Treatment planning

Consistent with proton treatment planning considerations for other sites, the primary factors for beam-angle selection for pancreas plans include minimization of priority OAR doses, stability of the water equivalent thickness (WET) along the beam path, and consideration of the enhanced RBE due to the increased linear energy transfer (LET) at the end of the proton beam range. Many modern pencil beam scanning approaches utilize 2 posterior-oblique beams. Variations include a posterior/posterior-oblique geometry as well as the inclusion of a right-lateral beam entering through the liver. Posteriorly oriented beams have the advantage of traversing through anatomy, which generally presents a more reproducible WET, as opposed to the more anteriorly oriented beams passing through GI structures. These structures, including the stomach and bowels, are susceptible to daily variations in the contents of the digestive tract (Fig. 2).

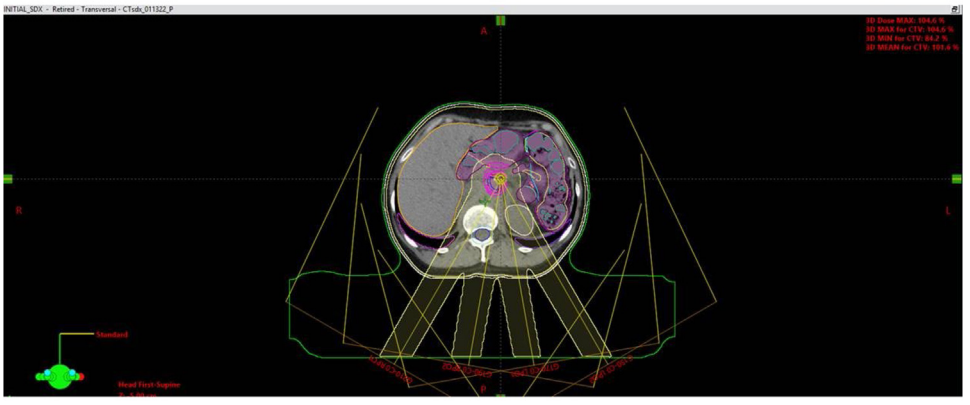
Moreover, the dosimetric advantages of minimizing dose (particularly in the mid-to-low ranges) and corresponding side effects to the GI structures are preserved by eliminating anterior beams.[2,4,10,11,14,15,54] When it is not possible to avoid beams passing through bowel gas, applying an HU override between −1000 HU and 0 HU to these volumes for



Original CT Simulation



CT SIM Scan with Overides



Associated Beam Arrangement

Fig. 2. Representative proton PBS. (A) Original CT simulation scan. (B) CT simulation scan with overrides. (C) Associated beam arrangements.
Abbreviations: CT = computed tomography; PBS = pencil beam scanning.

optimization can be considered. The plan can then be cast back on the nonoverridden scan for evaluation and approval. These overrides will tend to compensate on the side of ensuring target coverage (as the HU override value increases toward 0 HU) at the possible expense of increased OAR doses. Other heterogeneous anatomy should also be considered when choosing beam angles. For plans with beams passing through the spine, good alignment with the spine should be achieved during localization to avoid deleterious range-difference effects due to displacements of large volumes of bony anatomy. When possible, minimizing the use of beams that pass through the lung/diaphragm interface is also desirable, as respiratory motion can induce large variations in WET. Careful consideration is also required

when stents are present along the beam path, especially when traversing metal stents.

Contemporary scanned beam deliveries allow for either single-field optimization, where each beam is optimized independently, or multifield optimization (MFO), where all the treatment fields are optimized together. The usual tradeoffs associated with this choice also apply to pancreas treatment planning. Single-field optimization plans are preferred when all dosimetric constraints can be met, as they are more robust to dose degradation due to respiratory motion effects, interfield patient movement, and daily anatomical differences affecting the beam range. MFO should be considered for cases when reducing OAR doses takes priority over plan robustness. These plans allow the high-dose irradiated volumes to be shaped more precisely around high-priority OARs such as the duodenum, the large and small bowels, and the stomach. Furthermore, the reduction of mid-to-low doses in upstream structures, such as the spinal cord and kidneys in the posterior beam geometry, is facilitated.

Modern spot scanning treatment planning techniques typically utilize robust optimization and evaluation, in which the planning system considers various perturbations of isocentric displacements in multiple directions along with systematic range uncertainties in its optimization cost function.[55] Typically, the setup uncertainty specific to the treatment site (approximately 5 mm), as well as a range uncertainty of approximately 3% to 3.5% inherent to the HU to stopping power ratio calibration curve, are used. This theoretically obviates the need for an explicit PTV expansion, which also does not appropriately account for potential dose degradation due to mobile heterogeneities and range uncertainties in proton plans. Robust optimization is performed on the ITV, which accounts for respiratory target motion based on an analysis of the CTV structures drawn on each of the respiratory motion phases acquired during a 4DCT-based simulation. Planning based on 4DCT imaging can either be performed on the intensity-weighted average projection (average CT) data set and verified on at least the 3DCT data sets for both the end-inhalation and end-exhalation phases of the respiratory cycle or by multiphase optimization. Studies of proton scanning treatment planning for lung and liver have shown that breath-hold combined with volumetric rescanning performs best for mitigating the dosimetric impact of respiratory motion, although at the expense of delivery times.[56,57] In addition to target considerations, robust optimization objectives must be applied to OARs to help ensure that these structures are sufficiently protected.

Passively scattered beam delivery techniques are inherently less sensitive to anatomical motion, although designing highly conformal dose distributions that adequately meet constraints for proximity OAR is more difficult than with scanned beams. Positional and systematic beam range uncertainties still need to be accounted for when planning passive-scattered proton beams. Distal and proximal margins should be expanded from the CTV (or ITV) along each individual beam path to account for the range uncertainty of 3% to 3.5%. Aperture margins expended from the CTV (or ITV) in the beam's-eye-view should account for both the positional uncertainty of the target and the lateral penumbrae of each beam. As distal and proximal margins are beam-direction specific, the concept of the beam-specific PTV should be used for designing adequate spread-out Bragg peak widths and for assessment of plan robustness. Beam-specific range compensators should be used for conforming the dose from each beam to the distal edge of the target. Range compensators should be designed with appropriate smearing to account for lateral setup uncertainty and internal anatomical motion. A concise overview of passive-scattered treatment planning techniques is provided by Zeng et al.[58]

End-of-range LET enhancement is an important factor in evaluating proton pancreas plans. For posterior beam geometries, high RBE will generally be present at the anterior edge of the target, which commonly abuts GI structure OARs. Several strategies can be used to mitigate the potential for excessive biological dose enhancement in these structures. A larger separation between beam angles allows for high-LET protons to be spread out over a larger volume. This is one potential justification for the inclusion of a right-lateral beam, in addition to the extra degrees of freedom it provides to the optimizer in tailoring the target coverage/OAR tradeoffs in regions of high dose. Another commonly used technique is undercovering the target in the region of the distal OAR/target interface with a lower yet still clinically acceptable physical dose. The end-of-range biological enhancement and the associated "biological push" of approximately 2 to 3 mm help compensate for the reduced physical dose.

Fractionation and respiratory motion may also play a role in mitigating the effects of high LET, as day-to-day differences in the relative location of GI structures can smooth the aggregate sum of high-RBE regions. Finally, there is immense value in utilizing Monte Carlo dose calculation engines, which can provide information on LET distributions and incorporate biological dose models in evaluating pancreas protons plans.[59,60] Particularly with respect to MFO plans, in which there can be significant dose modulation between fields and unpredictable LET distributions.

Treatment delivery

Volumetric image guidance should be used daily where available. Verification CT scans should be acquired ad hoc as deemed necessary, or at least every week, to assess the dosimetric impact of changes in anatomy, such as weight loss and variation in bowel and gastric filling. Adaptive replanning should be performed as required. For institutions treating with only orthogonal kV imaging, careful adherence to oral intake restrictions pretreatment should be followed, and at least weekly verification CT scans are highly advised.

Patient selection

Per the consensus of this panel of experts and in concordance with the above-discussed clinical and treatment planning considerations, a subset of patients with pancreatic tumors may benefit from proton therapy. No phase 3 randomized trials for proton therapy in pancreatic cancer are currently underway. Therefore, these recommendations are based on level 2 or 3 evidence and experts' consensus. As more clinical data are available, these recommendations will be modified as such.

1. The following patients should be ***strongly considered*** for proton therapy:
   a. Patients who had prior radiation in the abdomen, including those with locoregional recurrence after radiation.
   b. Patients in whom critical structure dose constraints cannot be met with other radiation modalities. Table 1 presents the dose constraints agreed upon by our group for different fractionation schemes.
   c. Patients with unusual anatomy, such as transplanted kidneys or liver within or nearby the target volume or a solitary kidney adjacent to the treatment volume.
   d. Patients at high risk for radiation-induced secondary malignancy: adolescents and young adults /young patients and patients with genetic syndromes that make them high risk for radiation-induced secondary malignancy.
   e. Patients at high risk for bowel complications, such as those with multiple prior abdominal surgeries or active inflammatory bowel disease (eg, Crohn's, ulcerative colitis).
   f. Any patient enrolled in a prospective clinical trial.
2. The following scenarios should be considered for proton therapy due to the putative clinical significance and/or dosimetric benefit as evaluated by the treating physician on a case-by-case basis:
   a. Patients with advanced locoregional disease, particularly with gross lymph nodes, and/or intent for dose-escalated definitive treatment.
   b. Preoperative patients.
   c. Postoperative patients.
   d. Patients with active connective tissue disorder (eg, scleroderma, lupus).
3. The following diagnoses should not be considered for proton therapy:
   a. For palliative intent treatment in patients with a life expectancy < 3 months.

Table 1 Dose constraints for PTCOG pancreas

	5 fractions			15 fractions			28-30 fractions		
	Volume (cm^3)	Volume max (Gy)	D0.035cc (Gy)	Volume (cm^3)	Volume max (Gy)	D0.035cc (Gy)	Volume (cm^3)	Volume max (Gy)	D0.035cc (Gy)
Stomach	<5	25-26.5	30-35	<50	39	45-51	<50	45	54-60
Duodenum	<5	25-26.5	30-35	<5	39	45-51	<5	45	54-60
Small bowel	<30	24	30-35	<120	39	45-46.5	<120	45	54
Large bowel	<20	32.5	33-40	<20	47	50-55	<20	54	60-62
Spinal cord	<0.35	22	25-28	<5	39	35-42	<5	47.4	50.4-54
Kidneys	200 cm^3 or one-third of organ	17.5	–	200 cm^3 or one-third of organ	24	–	200 cm^3 or one-third of organ	27	–
Liver	700	<15-21.5	–	700	<24-30	–	700	<28-36	–

Future Directions

Ongoing clinical trials

Several institutions are currently investigating the efficacy and toxicity of proton therapy for treating pancreatic cancer.

The University of Maryland and Georgetown University are enrolling patients in a phase 1 study to determine the maximally tolerated dose of a 15-fraction course of intensity-modulated proton therapy (up to 67.5 Gy) with nab-paclitaxel and gemcitabine (NCT03652428). Georgetown University is also investigating the safety of a five-fraction course of intensity-modulated proton therapy to 25 Gy delivered between cycles of FOLFIRINOX for adjuvant therapy of resected pancreatic cancer (NCT03885284). The PCG, a consortium of over a dozen proton centers in the United States, is enrolling patients with unresectable, borderline resectable, or medically inoperable pancreatic cancer in a phase 2 trial investigating dose-escalated proton therapy to 63 Gy in 28 fractions with concurrent capecitabine (NCT02598349). The National Cancer Center of Korea is enrolling patients in a prospective cohort study of proton therapy for pancreatic cancer (NCT0466189). Additionally, the Hyogo Ion Beam Medical Center is enrolling patients in a prospective interventional study to evaluate the efficacy and safety of radical resection and postoperative PBT (67.5 Gy in 25 fractions) for resectable borderline or unresectable locally advanced pancreatic cancer (UMIN-R58073), as well as a dose-escalation study (up to 82.5 Gy in 25 fractions) of proton therapy in combination with absorbable spacer implantation for unresectable locally advanced pancreatic body/tail cancers (UMIN-R58074). The results of these trials will add to the growing body of evidence investigating the safety of efficacy of proton therapy when combined with chemotherapy for treating pancreatic cancer.

Proton therapy in the era of dose-escalated RT

Radiation dose escalation for initially unresectable pancreatic cancer has also been attempted using photon therapy. Early outcomes of 5-fraction stereotactic magnetic resonance imaging-guided online adaptive radiation therapy (SMART) prescribed to 50 Gy have been encouraging, and in the multicenter phase 2 SMART trial for borderline resectable and locally advanced pancreatic cancer included 2-year overall survival > 50% from diagnosis with no acute grade 3+ GI toxicity definitely attributed to SMART. Another promising approach is moderately hypofractionated CT-guided RT on a standard linear accelerator either prescribed to 67.5 Gy in 15 fractions or 75 Gy in 25 fractions; clinical outcomes appear similar to those achieved in the phase 2 SMART trial.[26] Although these results are encouraging, it is uncertain whether they are superior to those achieved with particle therapy that may have advantages including enhanced LET/RBE possibly leading to improved tumor control, reduced effects on circulating lymphocytes leading to a more robust immune response, and lower dose to critical organs such as the stomach, bowel, and liver that may achieved a more favorable toxicity profile.[61,62] However, there are limited comparative data in this regard and future studies should explore differences between ablative proton and photon therapies to guide treatment decision making.[63]

Conclusion

With the increasing utilization of more aggressive and modern forms of systemic therapy for pancreatic malignancies, the benefit and role of RT in managing local and regional disease extent in the neoadjuvant, adjuvant, and definitive settings have become more critical. Given its unique normal tissue-sparing properties, PBT provides an opportunity in these settings to allow safer dose escalation and/or mitigation of side effects. This consensus statement provides recommendations concerning clinical rationale, specific treatment planning considerations, and current approaches to proton delivery to ensure the safe and effective management of pancreatic tumors. The utilization of PBT in the treatment of pancreatic malignancies also represents an evolving field, with a growing number of clinical trials underway that will further help to define the appropriate use criteria for proton therapy for this disease.

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