

# Proton therapy may allow for comprehensive elective nodal coverage for patients receiving neoadjuvant radiotherapy for localized pancreatic head cancers

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**Background:** Neoadjuvant radiotherapy has the potential to improve local disease control for patients with localized pancreatic cancers. Concern about an increased risk of surgical complications due to small bowel and gastric exposure, however, has limited enthusiasm for this approach. Dosimetric studies have demonstrated the potential for proton therapy to reduce intestinal exposure compared with X-ray-based therapy. We sought to determine if neoadjuvant proton therapy allowed for field expansions to cover high-risk nodal stations in addition to the primary tumor.

**Methods:** Twelve consecutive patients with nonmetastatic cancers of the pancreatic head underwent proton-based planning for neoadjuvant radiotherapy. Gross tumor volume was contoured using diagnostic computed tomography (CT) scans with oral and intravenous contrast. Four-dimensional planning scans were utilized to define an internal clinical target volume (ICTV). Five-mm planning target volume (PTV) expansions on the ICTV were generated to establish an initial PTV (PTV1). A second PTV was created using the initial PTV but was expanded to include the high-risk nodal targets as defined by the RTOG contouring atlas (PTV2). Optimized proton plans were generated for both PTVs for each patient. All PTVs received a dose of 50.4 cobalt gray equivalent (CGE). Normal-tissue exposures to the small bowel space, stomach, right kidney, left kidney and liver were recorded. Point spinal cord dose was limited to 45 CGE.

**Results:** Median PTV1 volume was 308.75 cm<sup>3</sup> (range, 133.33–495.61 cm<sup>3</sup>). Median PTV2 volume was 541.75 cm<sup>3</sup> (range, 399.44–691.14 cm<sup>3</sup>). In spite of the substantial enlargement of the PTV when high-risk lymph nodes were included in the treatment volume, normal-tissue exposures (stomach, bowel space, liver, and kidneys) were only minimally increased relative to the exposures seen when only the gross tumor target was treated.

**Conclusions:** Proton therapy appears to allow for field expansions to cover high-risk lymph nodes without significantly increasing critical normal-tissue exposure in the neoadjuvant setting.

**Key Words:** Proton therapy; pancreatic; dosimetry; neoadjuvant radiotherapy



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## Background

Pancreatic cancer is the fifth leading cause of cancer mortality in the United States. In 2011, there were an estimated 44,030 new cases and 37,660 deaths (1). Curative therapy for patients with nonmetastatic disease necessarily includes extirpative surgery. Unfortunately,

the surgical literature suggests a local-regional failure rate ranging from 50% to 80% for patients undergoing pancreaticoduodenectomy (2,3). Recognizing this concern, postoperative radiotherapy has been offered in an effort to increase the likelihood of local disease control. While the shortcomings of these studies have been well-described in

the oncologic literature (4), the results of studies by the European Study Group for Pancreatic Cancer (ESPAC) suggest that postoperative X-ray-based radiotherapy fails to offer an improvement in survival over surgery and chemotherapy alone (5). The problems with postoperative radiation therapy are that (I) radiotherapy cannot be delivered until several weeks after surgery because of postoperative convalescence and (II) postoperative radiotherapy doses are limited by the large volume of transposed small bowel in the radiotherapy target volume.

Preoperative neoadjuvant radiotherapy would potentially avoid these problems. A drawback of preoperative X-ray-based radiotherapy, however, is that small bowel and gastric exposure in the neoadjuvant setting can complicate an already challenging major surgical intervention. Several dosimetric studies suggest that proton therapy has the potential to improve the therapeutic index over X-ray-based radiotherapy by reducing such normal-tissue exposure (6-10). Various clinical outcome studies also suggest low rates of gastrointestinal toxicity when protons are used to treat pancreatic cancers (11,12). Although many published studies on the use of neoadjuvant radiotherapy for patients with pancreatic cancer targeted the primary tumor and *selective* regional nodes (13-15), others only targeted the gross tumor with no specific effort to cover regional lymph nodes (16,17). In this setting, some nodal targets are ostensibly omitted in an effort to limit gastrointestinal toxicity, even though nodal metastases may be identified in 39% to 71% of these patients (3,18,19) at the time of surgery. The current study was undertaken to assess the feasibility of leveraging the improved therapeutic index of protons to deliver comprehensive elective nodal irradiation in the neoadjuvant setting.

## Methods

Twelve consecutive patients with nonmetastatic cancers of the pancreatic head underwent treatment planning for neoadjuvant chemoradiation at our institution. Patients were immobilized using a standard wing-board and a lower extremity stabilizer. Four-dimensional computed tomography (CT) without contrast and three-dimensional CT with oral and intravenous contrast was performed. Patients were imaged on a Philips Brilliance large-bore CT scanner with a 60-cm field of view and 1-mm slices (Philips Healthcare, Amsterdam, the Netherlands). Gross tumor volume was contoured and guided by diagnostic CT scans with contrast, magnetic resonance imaging (MRI), and positron emission tomography (PET)-CT. Four-dimensional planning scans were utilized to define an internal clinical target volume (ICTV). Five-mm planning

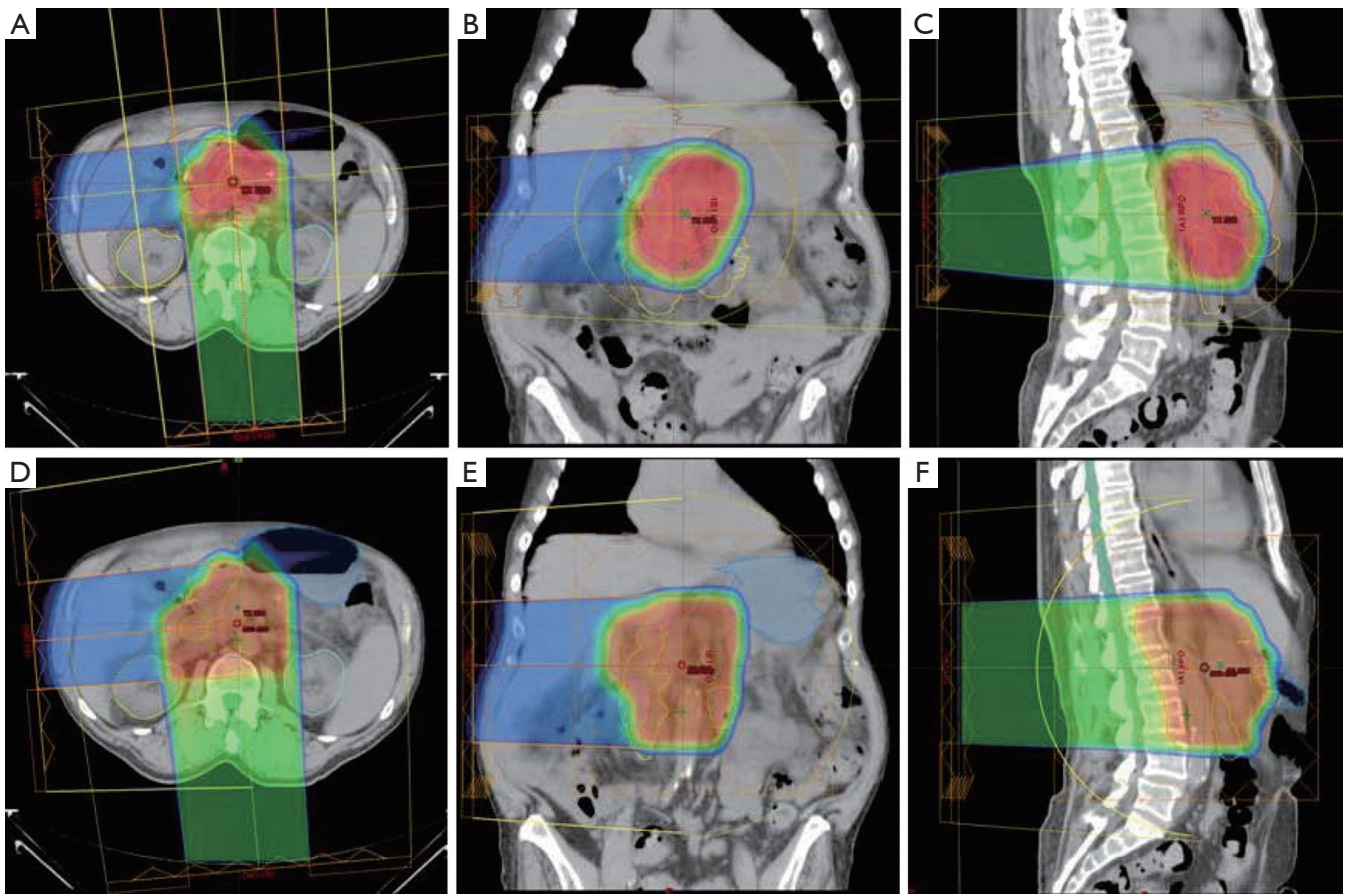
target volume (PTV) expansions were generated to establish the final PTV (labeled the PTV1) for the gross disease.

A second planning target volume (PTV2) was created using the initial PTV expanded to include the high-risk nodal targets as defined by the Radiation Therapy Oncology Group (RTOG) contouring atlas (20). Elective nodal expansions were based on either (I) the most proximal 1.0 to 1.5 cm of the celiac artery (CA); (II) the most proximal 2.5 to 3.0 cm of the superior mesenteric artery (SMA); (III) the portal vein segment extending from the bifurcation to the confluence with either the superior mesenteric vein (SMV) or splenic vein (SV); and (IV) the aorta from the most cephalad contour of either the celiac axis or portal vein to the bottom of the L2 vertebral body. If the gross tumor volume (GTV) contour extended to or below the bottom of L2, the aorta contour was extended towards the bottom of L3. To achieve elective nodal expansions on the CTV, the CA, SMA, and portal vein were expanded by 1.0 to 1.5 cm in all directions and the aortic region of interest was expanded 2.5 to 3.0 cm to the right, 1.0 cm to the left, 2.0 to 2.5 cm anteriorly, and 0.2 cm posteriorly towards the anterior edge of the vertebral body. The goal of the asymmetric expansion was to include the prevertebral nodal regions (retroperitoneal space) from the top of the portal vein or celiac axis (whichever was most superior) to the bottom of L2 (or L3 if the GTV location was too low).

Proton plans were generated on a Varian Eclipse 8.9 planning system (Varian Medical Systems Inc., Palo Alto, CA).

The proton treatment table top was inserted into the CT images manually and aligned with the CT table top so that the proton range and skin dose could be correctly calculated. A CT-Hounsfield unit to proton relative stopping-power conversion curve was used for proton range calculations. An effort was made to account for patient setup variability, respiratory motion, and delivery uncertainties, both by using appropriate distal and proximal margins to account for uncertainties in stopping-power conversion and by evaluating the presence of bowel and stomach contents in beam paths. The distal and proximal margins for each treatment field were estimated to be 2.5% of the beam range to the distal/proximal PTV plus 1.5 mm. Distal and proximal median spread-out Bragg peak (SOBP) expansions of 8 mm (range, 6-9 mm) and 10 mm (range, 8-12 mm) smearing margins were utilized for each beam.

Field apertures were designed to conform to the PTV in the beam's-eye view, with an aperture margin adequate to account for the beam penumbrae (typically 10 mm uniformly around the PTV) depending on the beam range, except for edits that may have been necessary to avoid critical organs such as the kidneys. Range compensators



**Figure 1** Typical field configurations used to treat pancreatic cancers with protons. A heavily weighted (75% of the target dose) posterior or posterior-oblique field is combined with a more lightly weighted (25% of target dose) right lateral-oblique field. Since the posterior beam is unlikely to pass through an air-filled space on its way to the retroperitoneal target, there is very little uncertainty in its range. Although the treatment plans that include the elective nodes irradiate a larger volume, because of the conformality of the proton dose distribution and posterior location of the target relative to the small bowel space, the elective plans were not associated with meaningfully increased small bowel or gastric exposure compared to the plans treating the gross disease alone. A. Axial (Gross tumor only); B. Coronal (Gross tumor only); C. Sagittal (Gross tumor only); D. Axial (Elective nodes included); E. Coronal (Elective nodes included); F. Sagittal (Elective nodes included)

were constructed with Lucite using median parameters for smearing margins and border smoothing of 6 and 8 mm, respectively.

A 2-field approach was utilized on all patients (posterior oblique: right lateral oblique) with a 3-to-1 weighting to the posterior field while limiting the spinal cord dose to less than 46 CGE. The heavy weighting of the posterior field allowed for coverage of the retroperitoneal region with minimal dose to the small bowel space anteriorly and to the body of the stomach left of the midline. Since no air-filled space (i.e., small bowel) would be situated in the beam path between the posterior proton source and the targeted tissues, there would be very little range uncertainty for the dose delivered from this field. The more lightly weighted right lateral-oblique field allowed for the degree of spinal cord sparing described above without delivering excessive

dose to the liver. Since the lateral field had the potential to pass through a possibly air-filled small bowel space, however, the SOBP was generously expanded proximally and distally to compensate for the associated range uncertainty. This expansion did not result in meaningfully increased normal-tissue exposure due to the low dose delivered (approximately 12.6 Gy at 0.45 Gy per fraction).

Both PTV1 and PTV2 were prescribed to a total dose of 50.4 CGE; 95% of all PTVs received 100% of the target dose and 100% of the PTVs received at least 95% of the target dose. Normal tissue goals of particular interest were as follows: right kidney V18 to <70%; left kidney V18 Gy to <30%; small bowel/stomach V20 Gy to <50%, V45 Gy to <15%, V50 Gy to <10%, and V54 Gy to <5%; liver V30 Gy to <60%; and spinal cord maximum to <46 Gy. Typical proton plans are illustrated in *Figure 1*.

## Results

The median PTV1 volume was 270.7 cm<sup>3</sup> (range, 133.33-495.61 cm<sup>3</sup>). Median PTV2 volume was 541.75 cm<sup>3</sup> (range, 399.44-691.14 cm<sup>3</sup>). All proton plans achieved the assigned PTV coverage. The median and range of normal-tissue exposures for each set of treatment plans are shown in *Table 1*.

All 12 plans that treated the PTV1 volumes (gross tumor only) met all of the previously described normal tissue goals. Eight of the 12 plans that targeted the PTV2 volumes (gross tumor plus high-risk nodes) met all constraints. Of the 4 PTV2 plans that did not meet constraints, one failed to meet the bowel space constraint (V54, 9.6%; V50, 10.6%) constraint, one failed to meet the right kidney (V18, 85.5%) and bowel space constraints (V54, 17.1%; V50, 20.2%; V45, 23.8%), one failed to meet the gastric constraint (V50, 15.5%; V45, 23.9%), and one failed to meet the right kidney (V18, 75.8%) and gastric constraints (V50, 10.6%; V45, 19.0%).

## Discussion

Various reports in the contemporary literature describe the use of neoadjuvant radiotherapy with or without chemotherapy for nonmetastatic resectable or marginally resectable pancreatic cancers (13-17). *Table 2* presents a review of this literature. Neoadjuvant therapies provide numerous theoretical and practical advantages over postoperative treatment:

- (I) Malignant cells are more likely to oxygenate preoperatively, allowing radiation to be more effective through the production of radicals causing DNA damage;
- (II) Preoperative treatment may reduce the likelihood of tumor spillage, dissemination, or implantation at the time of surgery;
- (III) Since the irradiated bowel is likely to be resected at the time of pancreaticoduodenectomy, patients treated with preoperative radiotherapy may experience less long-term nutritional problems compared to patients irradiated postoperatively;
- (IV) With neoadjuvant therapy, there is no delay between systemic therapy and surgery, as opposed to adjuvant therapy where the delay is caused by postoperative recovery, possibly reducing the control of distant metastases;
- (V) Neoadjuvant therapies may effectively downstage marginally resectable tumors and render them resectable.

These theoretical advantages are promising, but, to date, there are no randomized trials that directly compare neoadjuvant and adjuvant therapies.

In a phase 1 clinical trial, Hong *et al.* demonstrated the feasibility of hypofractionated neoadjuvant proton therapy with concomitant capecitabine for patients with resectable adenocarcinoma of the pancreatic head (11). Fifteen patients received doses ranging from 30 GyE in 10 fractions over 2 weeks to 25 GyE in 5 fractions over 1 week. Chemotherapy consisted of capecitabine at 825 mg/m<sup>2</sup> twice daily. No dose-limiting toxicities were observed. Evaluation of 30-day postoperative mortality and morbidity showed no deaths or anastomotic leaks. Limited elective nodal irradiation was offered. Of note, 10 of 11 patients undergoing surgery had positive lymph nodes in the operative specimen.

Nichols *et al.* reported negligible weight loss and gastrointestinal toxicity in a group of 20 patients treated with conventionally fractionated protons and concomitant capecitabine (1,000 mg orally twice-daily) (12). Patients had marginally resectable (N=5), resected (N=5), or unresectable (N=10) disease and received planning target volume (PTV) proton doses ranging from 50.40 to 59.40 CGE. No elective nodal irradiation was offered to the patients with measurable gross disease. The median PTV volume was 406 cm<sup>3</sup> (range, 244 to 1,811 cm<sup>3</sup>). For the 17 patients treated with a 2-field plan (posterior oblique and right lateral oblique) which minimized gastric and small bowel exposure, the median weight loss was only 1.11 lbs (range, gain of 10.4 lbs to loss of 14.1 lbs) over the course of treatment. No patient experienced grade 2 or greater GI toxicity.

## Conclusions

Protons allow for substantial gastric and small bowel sparing compared with X-rays in the setting of neoadjuvant radiotherapy for pancreatic cancer. This normal-tissue sparing offers the potential to reduce the risk of perioperative complications. As such, surgeons evaluating patients with resectable disease may ultimately be more willing to accept neoadjuvant radiotherapy if protons are to be used.

Additionally, in the majority of the cases we evaluated, we were able to expand the neoadjuvant radiotherapy field to safely cover both the gross tumor and the high-risk regional lymph nodes without significantly increasing the volume of critical normal tissues irradiated.

In light of this dosimetric data, as well as our clinical data showing a virtual absence of gastrointestinal toxicity when protons are used to treat pancreatic cancer, our current trial in development for neoadjuvant radiotherapy for patients with resectable and marginally resectable disease offers 50.40 CGE over 28 fractions to the above-described PTV2 volume with concomitant capecitabine (1,000 mg orally

**Table 1** Median and range of normal-tissue exposures for each set of treatment plans

	Right kidney		Left kidney		Stomach			Bowel space			Liver		
	V18	n=53	V18	n=53	V45	V20	V54	V45	V20	V54	V59	V54	V30
Gross tumor only	22.7% (0-68%)	3.9% (0-28%)	5.0% (0-33%)	1.1% (0-25%)	0.2% (0-18%)	0% (0-0.1%)	12.7% (4-26%)	4.7% (1-16%)	2.3% (0-12%)	0% (0-0.1%)	4.3% (1-14%)	0% (0-0.1%)	4.3% (1-14%)
Elective nodes included	34.6% (13-86%)	11.4% (1-31%)	7.5% (0-40%)	2.4% (0-24%)	1.3% (0-15%)	0% (0-0.9%)	17.5% (7-38%)	10% (3-24%)	7.2% (0-17%)	0.3% (0-17%)	8.3% (3-22%)	0.3% (0-17%)	8.3% (3-22%)

**Table 2** Neoadjuvant trials for borderline resectable pancreatic cancers

	RT prescription	Target coverage	Chtx	OS	DFS	LR	DM
ECOG (12 institutions) (13)	39.6 Gy/22 fx; 10.8 Gy/ 6 fx	GTV + [2-3] cm; Porta hepatis\Celiac; GTV + [1-2] cm	96 h iv 5-FU, 1,000 mg/m <sup>2</sup> days 2-5 & 29-32 and mitC 10 mg/m <sup>2</sup> (IV) bolus day 2	2 y OS: 27%	MDFS: 8.5 m	17%	79%
Duke (16)	45 Gy/25 fx; Boost 540 cGy to the tumor bed	NR	5-5FU alone; --bolus mitC; --iv cisplatin; 5-FU, mitC, and CDDP	2 y OS: 32%; MS not reached @ F/U of 16 m	NR	18%	>20%
Fox chase (U Penn) (14)	39.6 Gy/22 fx; Resectable; 10.8 Gy/6 fx (n=40)	GTV + [2-3] cm; Porta hepatis\Celiac; GTV + [1-2] cm	On day 2 RT, bolus mitC cont iv 5-FU (1,000 mg/m <sup>2</sup> /day); On day 28 96 h course 5-FU	MS: 20 m	MDFS: 20 m	16%	84%
Harvard (15)	50.4 Gy/28 fx	The primary tumor plus regional lymph nodes were targeted in all patient	--Gem: 1,000 mg/m <sup>2</sup> /iv for 3 w, then 1 w off followed by CRT: cont iv 5-FU or Xeloda; --CRT alone	MS, NC-CRT: 18.7 m; CRT: 12.4 m (P=0.02)	MPFS, NC-CRT: 11.4 m; MP: 6.7 m (P=0.02)	LR, NC-CRT: 23%; MP: 4.1 m; CRT: 25%; MP: 6.4 m	DM, NC-CRT: 77%; MP: 5.4 m; CRT: 65%; MP: 2.7 m
MD Anderson (17)	30 Gy/10 fx	The primary tumor and gross adenopathy were treated with a 3-cm block margin cranially and caudally and a 2-cm block; margin radially	--Gem (750 mg/m <sup>2</sup> ) & CDDP (30 mg/m <sup>2</sup> ) q2w for 4 doses; --CRT: 4 qw iv Gem (400 mg/m <sup>2</sup> ) combined w\RT;	Overall: 5 y OS, 18%; MS, 17.4 m. Resected: 5 y OS, 30%; MS, 31 m; Unresected: 5 y OS, 18%; MS, 10.5 m	Overall: MPFS, 13.2 m	LR: 65%; MP: 8.9 m	50%

RT, radiotherapy; Chtx, chemotherapy; OS, overall survival; DFS, disease-free survival; LR, local recurrence; DM, distant metastasis; Gy, Grey; fx, fractions; LN, lymph node; FU, fluorouracil; iv, intravenous; MS, median survival; NR, not reported; ECOG, Eastern Cooperative Oncology Group; GTV, gross target volume; h, hours; mitC, mitomycin C; y, years; MDFS, median disease-free survival; CDDP, cisplatin; CT, computed tomography; lat, lateral; ant, anterior; CTV, clinical target volume; PTV, planning target volume; CRT, chemo-radiation therapy; NC-CRT, Neoadjuvant chemotherapy followed by chemo-radiation; MPFS, median progression-free survival; q2w, every 2 weeks; qw, weekly; w, week; d, day; m, month; F/U, follow-up; MP, median time to progression; GEM, Gemcitabine; NR, not reported; NC-CRT, neoadjuvant chemotherapy followed by chemoradiation

twice daily). If normal-tissue constraints cannot be met, a reduction in volume (to PTV1) will be made after 45.00 CGE (or as low as 39.60 CGE, if necessary).

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