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Scientific Article

# Clinical Implementation of Preoperative Short-Course Pencil Beam Scanning Proton Therapy for Patients With Rectal Cancer

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**Abstract**

**Purpose:** For treatment of rectal cancer, pencil beam scanning proton therapy (PBS-PT) may reduce radiation exposure to normal tissues compared with 3-dimensional conformal photon radiation therapy (3DCRT) or volumetric modulated arc photon radiation therapy (VMAT). The purpose of this study was to report the clinical implementation and dosimetric analysis of preoperative short-course PBS-PT for rectal cancer.

**Methods and Materials:** Eleven patients with stage IIA-IVB rectal cancer received preoperative short-course (25 Gy in 5 fx) PBS-PT between 2018 and 2019 preceding curative-intent total mesorectal excision. PBS-PT plans were generated using single-field optimization with 2 posterior-oblique fields. Verification computed tomography scans were performed on the first 3 days of treatment. Each patient had a backup 3DCRT and VMAT plan.

**Results:** Clinical target volume coverage was similar between PBS-PT, 3DCRT, and VMAT. PBS-PT had statistically significant reductions in dose to the small bowel, large bowel, bladder, and femoral heads across multiple dosimetric parameters. All patients completed PBS-PT as planned without need for replanning. All computed tomography verification scans demonstrated good target coverage with clinical target volume V100 $>$ 95%.

**Conclusions:** Preoperative short-course PBS-PT has been successfully implemented and offers a significant reduction of dose to normal tissues. Prospective studies are warranted to evaluate if dosimetric advantages translate into clinical benefit.



## Introduction

In 2019, an estimated 44,000 patients were diagnosed with rectal cancer in the United States with an increasing incidence among younger generations.[1] Standard of care for patients with T3-4 or node-positive disease is total

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mesorectal excision preceded by either long-course chemoradiotherapy (typically 50.4 Gy in 28 fractions) or short-course radiation therapy (RT) (25 Gy in 5 fractions).[2-5] Preoperative RT is typically delivered using a 3- or 4-field photon 3-dimensional conformal RT (3DCRT) technique. However, patients may experience considerable toxicities of therapy. Retrospective data have suggested low rates of gastrointestinal toxicity with the use of intensity modulated radiation therapy (IMRT)[6-8]; however, a prospective study of IMRT did not demonstrate an improvement compared with 3DCRT historical controls.[9] Studies using short-course RT delivered as 2-dimensional or 3DCRT have reported late toxicity in 25%, including 5% to 10% grade 3 toxicity.[5,10-13] Given the high dose per fraction with this regimen, highly conformal techniques are desired to minimize the risk of late effects, especially in the context of younger patients and improving survival rates.

Recently, proton therapy (PT) has emerged as a potential treatment option for rectal cancer to minimize dose to normal tissues and reduce treatment-related toxicity; however, clinical evidence is lacking.[14-18] The purpose of this study is to report the clinical implementation and dosimetric analysis of preoperative short-course pencil beam scanning PT (PBS-PT) for rectal cancer.

## Methods and Materials

After approval by the institutional review board, we retrospectively identified 11 patients with stage IIA-IVB rectal cancer who received curative-intent preoperative short-course PBS-PT (25 Gy in 5 fractions) between July 2018 and August 2019. Preoperative short-course RT was used for patients with clinical T2-3 disease and non-threatened surgical margins. Patients were treated with PBS-PT (vs photon RT) based on patient preference and insurance coverage. PBS-PT was planned for 5 consecutive weekdays immediately before the planned surgical date. 3DCRT and volumetric modulated arc photon radiation therapy (VMAT) plans were generated for each patient for dosimetric comparison and as backup in the event of proton outage.

Patients underwent computed tomography (CT) simulation in supine position on a foam pad, knee cushion, and vacuum mold immobilization of the legs. Full and empty bladder CT scans were obtained. An Eclipse treatment planning system was used (version 15; Varian Medical System, Palo Alto, CA).

Clinical target volume (CTV) encompassed the primary tumor, involved lymph nodes, mesorectum, and elective regional pelvic lymphatics, specifically the presacral and internal iliac lymph nodes. No patients received external iliac or inguinal lymph node coverage. A 5-mm expansion was added to generate the planning target volume for 3DCRT and VMAT plans. Goal CTV coverage was V100% $\geq$ 98%. The femoral head was defined as the proximal femur inferiorly, from the lowest level of the ischial tuberosity (right and left, respectively) to the top of the femoral head superiorly, including the greater trochanter. The large bowel was defined as individual bowel loops 2 cm superiorly and inferiorly to the most superior and inferior extent of the CTV, respectively. Similarly, the small bowel was contoured as a "bowel bag" to include all loops of small bowel in one encompassing structure 2 cm superiorly and inferiorly to the most superior and inferior extent of the CTV. Additionally, the innominate bones were contoured to represent the pelvic bone marrow and consisted of bilateral ilium, ischium, sacrum, and pubis. Organ-at-risk (OAR) goals were small bowel, V15 Gy $<$ 300 cm$^3$, V20 Gy $<$ 50 cm$^3$, V25 Gy $<$ 2 cm$^3$; bladder, V25 Gy $<$ 45%; femoral head, mean $<$ 18 Gy, V20 Gy $<$ 64%. No specific bone marrow sparing constraints were used. Target coverage was prioritized over OAR constraints.

PBS-PT plans consisted of 2 beams: left and right posterior oblique beams, with an 80° hinge angle (Fig 1). Single-field optimization with equal beam weights was used. The dose distribution was calculated using the Eclipse proton convolution superposition algorithm and verified using Monte Carlo.[19-21] All doses were prescribed in Gy relative biological effectiveness (1.1 $\times$ physical dose).

Rectal and bowel gas was contoured and assigned Hounsfield units of −450 for optimization. Field-specific target volumes were created using the CTV and a 0.9- to 1.2-cm margin for spot placement and 5% for range uncertainties. The CTVs were robustly optimized using an Eclipse Nonlinear Universal Proton Optimizer. Systematic plan uncertainty parameters were generated by shifting isocenter 5 mm in x, y, and z directions and applying a calibration curve error of 5%. Additional plan robustness was evaluated on the nonoverridden structure set and the empty bladder CT scan.

Patients were treated with a full bladder. Daily image guidance consisted of orthogonal kilovoltage radiographs with a 6 degree of freedom robotic couch, with matching performed to the bony pelvis. For the first 3 fractions of treatment, in-room CT on rails scan was acquired for plan verification.

3DCRT plans were generated using 6 to 18 MV photons with 3 to 4 fields (opposed laterals, posterior, with or without anterior), using field-in-field techniques. VMAT plans were generated using 6 MV photon 360° arcs.

A one-way analysis of variance was used to assess for a difference among the 3 treatments. A nonparametric test was used for assessment of significance among the treatments. Threshold for statistical significance was $P <$ .05. The protected least significant difference method was used to account for the point that 3 pairwise comparisons were examined, but only those comparisons, for variables where the overall tests of difference among the 3 groups

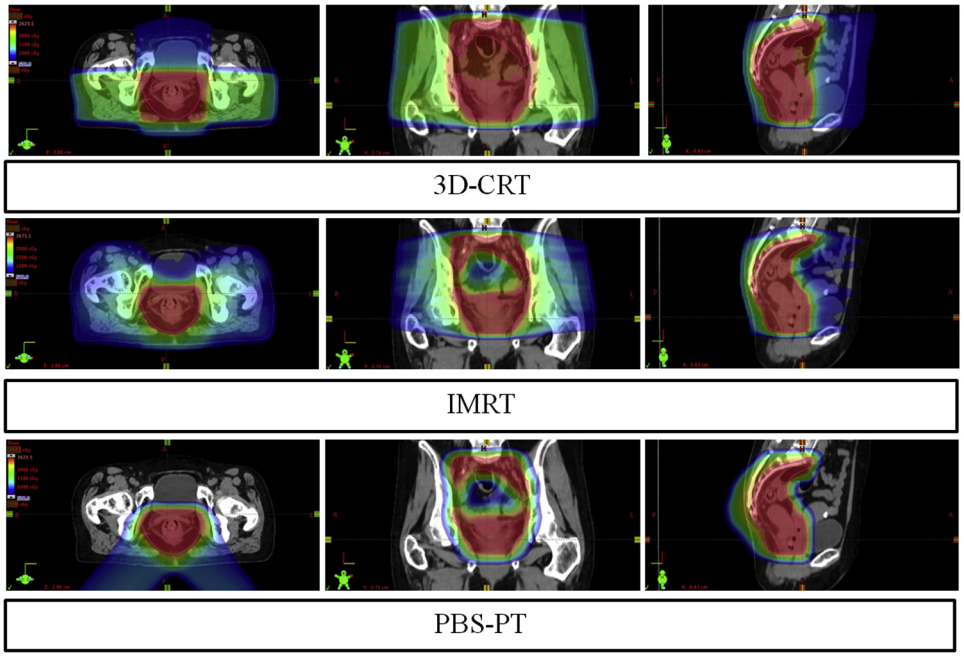


**Figure 1** Comparative plans for a single patient.

were statistically significant ($P < .05$), were further analyzed.

Patients were assessed prospectively for acute toxicities using Common Terminology Criteria for Adverse Events version 5.0 during a single on-treatment visit at the end of a 5-day treatment course. Additionally, charts were retrospectively reviewed for additional toxicity assessed during preoperative visits with the colorectal surgery team. Local control (defined as no presence of disease recurrence within the CTV) was retrospectively assessed at last clinical follow-up and reported descriptively.

## Results

Patient characteristics are in Table 1. Five patients received neoadjuvant chemotherapy before PBS-PT.

The CTV coverage goals were met for all plans (Table 2) for all modalities. The mean CTV and planning target volume (3D-CRT and VMAT) were 635.9 $cm^3$ (154.6) and 933.9 $cm^3$ (175.0), respectively. All patients completed PBS-PT as planned without treatment break or need for replanning. All CT verification scans demonstrated CTV V100 > 95%.

**Table 1** Patient characteristics

| Patient number | Sex | Age | Clinical TNM stage | Pathologic TN stage | Tumor location (cm from anorectal junction) etermined by MRI | Type of surgery |
|---|---|---|---|---|---|---|
| 1 | M | 74 | T3N0M0 | T2N0 | 0.0 | APR |
| 2 | M | 58 | T3N2M1a | T3N1b* | 6.0 | LAR |
| 3 | F | 68 | T3N2aM0 | T2N0* | 10.0 | LAR |
| 4 | M | 57 | T2N1aM0 | T2N0 | 6.0 | LAR |
| 5 | F | 59 | T3N2M1b | T3N1a* | 5.5 | LAR |
| 6 | F | 55 | T3N0M0 | T2N1b | 6.0 | LAR |
| 7 | M | 55 | T3N1bM1a | T3N0* | 5.8 | LAR |
| 8 | M | 46 | T3N0M0 | T2N0 | 5.5 | LAR |
| 9 | M | 78 | T3N2M1a | T0N0* | 4.2 | LAR |
| 10 | M | 56 | T3N0M0 | T0N0 | 6.2 | LAR |
| 11 | F | 54 | T2N1M0 | T2N0 | 4.2 | LAR |

*Abbreviations:* APR = abdominal perineal resection; LAR = low anterior resection; M = metastasis; MRI = magnetic resonance imaging; N = regional lymph nodes; T = tumor.

* Receipt of neoadjuvant chemotherapy

**Table 2** Comparative dosimetric analysis

| Dose parameter | 3DCRT mean (SD) | VMAT mean (SD) | PBS-PT mean (SD) | ANOVA *P* value | 3D vs proton *P* value | 3D vs VMAT *P* value | Proton vs VMAT *P* value |
|---|---|---|---|---|---|---|---|
| CTV2500 V100 (%) | 99.3 (1.1) | 99.9 (0.1) | 99.4 (0.3) | .11 | – | – | – |
| Bowel large V15 (cc) | 32.1 (30.0) | 59.9 (37.4) | 17.4 (13.9) | <.01 | <.01 | <.01 | <.01 |
| Bowel large V20 (cc) | 21.6 (21.2) | 27.3 (19.7) | 12.9 (12.4) | <.01 | <.01 | .02 | <.01 |
| Bowel large V25 (cc) | 13.4 (16.0) | 11.1 (12.0) | 6.5 (9.7) | <.01 | <.01 | .68 | <.01 |
| Bowel small V15 (cc) | 78.3 (138.5) | 140.0 (241.1) | 41.8 (73.9) | <.01 | <.01 | .01 | <.01 |
| Bowel small V20 (cc) | 66.7 (123.5) | 78.4 (148.5) | 32.0 (62.2) | <.01 | .01 | .05 | <.01 |
| Bowel small V25 (cc) | 50.4 (107.1) | 25.5 (52.1) | 17.3 (40.1) | .01 | .02 | .22 | .03 |
| Bladder mean (Gy) | 14.9 (2.3) | 14.0 (3.0) | 6.2 (3.4) | <.01 | <.01 | .14 | <.01 |
| Bladder V15 (%) | 32.8 (17.6) | 40.2 (23.8) | 19.9 (11.9) | <.01 | <.01 | .36 | <.01 |
| Bladder V25 (%) | 14.8 (10.2) | 10.8 (9.8) | 6.5 (7.4) | <.01 | <.01 | .02 | <.01 |
| Innominate bones V10 (%) | 53.9 (7.7) | 54.7 (7.8) | 30.3 (5.4) | <.01 | <.01 | .44 | <.01 |
| Innominate bones V15 (%) | 43.3 (9.1) | 35.6 (6.3) | 21.0 (4.7) | <.01 | <.01 | <.01 | <.01 |
| Innominate bones V20 (%) | 22.4 (4.8) | 19.3 (3.7) | 15.1 (3.6) | <.01 | <.01 | <.01 | <.01 |
| Left femoral head mean (Gy) | 8.6 (3.3) | 7.4 (1.9) | 0.3 (0.3) | <.01 | <.01 | .02 | <.01 |
| Left femoral head V10 (%) | 40.4 (19.1) | 30.9 (9.8) | 0.1 (0.3) | <.01 | <.01 | .06 | <.01 |
| Left femoral head V15 (%) | 29.5 (19.7) | 9.3 (10.8) | 0.0 (0.0) | <.01 | <.01 | .01 | <.01 |
| Left femoral head V20 (%) | 1.8 (2.6) | 0.9 (2.6) | 0.0 (0.0) | <.01 | <.01 | .18 | .04 |
| Right femoral head (Gy) | 8.0 (3.7) | 7.1 (1.6) | 0.3 (0.3) | <.01 | <.01 | .64 | <.01 |
| Right femoral head V10 (%) | 36.8 (22.7) | 29.4 (8.3) | 0.3 (0.7) | <.01 | <.01 | .74 | <.01 |
| Right femoral head V15 (%) | 28.0 (22.1) | 9.0 (7.4) | 0.0 (0.1) | <.01 | <.01 | .01 | <.01 |
| Right femoral head V20 (%) | 1.1 (1.9) | 0.3 (0.5) | 0.0 (0.0) | .03 | .02 | .40 | .04 |

*Abbreviations:* 3DCRT = 3-dimensional conformal photon radiation therapy; ANOVA = 1-way analysis of variance; PBS-PT = pencil beam scanning proton therapy; SD = standard deviation; VMAT = volumetric modulated arc photon radiation therapy.

PBS-PT offered a significant reduction in multiple OAR dosimetric parameters (Table 2). The dose to small bowel, large bowel, bladder, innominate bones, and femoral heads was significantly lower with PBS-PT versus IMRT or 3DCRT.

The majority of patients (n = 7) experienced grade 1 fatigue and grade 1 diarrhea. There were no acute grade 2 or higher skin, gastrointestinal, or genitourinary toxicities. Patients underwent surgery a median of 3 days (range, 1-3) after completion of RT. At a median follow-up of 10.5 months (range, 3.4-17.8) after surgery, no patient had experienced a local failure.

## Discussion

PBS-PT offered excellent target coverage, plan robustness, and a reduction in radiation exposure to all

normal tissues compared with 3DCRT and VMAT in the delivery of short-course preoperative RT for rectal cancer. Our planning technique allows for the safe, effective, and robust delivery of PBS-PT, with the ultimate goal of offering convenient care while minimizing treatment-related toxicities.

Published dosimetric studies have demonstrated that PT may reduce dose to OARs in delivery of long-course RT for rectal cancer.[15,17,18] Our study is unique in that it demonstrates dosimetric benefit of PBS-PT specifically for short-course preoperative RT, which could be of greater importance when considering the higher doses per fraction and potential increase in late treatment-related effects. A strength is that all plans were robustly optimized, clinically deliverable, and robust to inter- and intrafractional uncertainties. Purely "in silico" planning comparisons suffer from limitations of unknown plan deliverability when considering accelerator, beam line, gantry, and couch characteristics and unknown plan robustness to inter- and intrafractional uncertainties.

In recent years, there has been increased emphasis on providing efficient and cost-effective cancer care to reduce financial burdens on the patient and payers. Using 2019 United States Centers for Medicare and Medicaid Services fee schedules,[21] the approximate reimbursement for 5 fractions of PT is $8782, representing a significant cost reduction compared with 28 fractions of 3DCRT ($13,204) or IMRT ($21,405). However, the reimbursement rate for 5 fractions of PT remains higher than 5 fractions of 3DCRT ($4432) or IMRT ($5838). In the proposed 2020 Centers for Medicare and Medicaid Services radiation oncology alternative payment model, the base reimbursement rate for colorectal cancer is approximately $14,000, thus it is anticipated that there will be a significant increase in utilization of short-course RT for rectal cancer in the United States.[20,21]

Limitations include the retrospective nature and small patient sample size. Patients were treated supine to improve setup reproducibility and patient comfort, whereas prone treatment with a belly board may reduce bowel dose for all 3 modalities. Additionally, there is a lack of data defining the clinically relevant dosimetric parameters to normal tissues with this regimen. Longer follow-up is needed to assess clinical outcomes such as efficacy, long-term adverse effects, quality of life, and cost effectiveness.

## Conclusions

Preoperative short-course PBS-PT is feasible and offers a significant reduction of radiation dose to normal tissues compared with 3D-CRT and VMAT. Prospective studies are warranted to evaluate if dosimetric advantages translate into clinical benefits.

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