Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer

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**Background:** To assess the potential benefit of proton therapy (PT) over photon therapy, we compared 3-dimensional conformal radiotherapy (3DCRT), intensity-modulated radiotherapy (IMRT), and PT plans in patients undergoing neoadjuvant chemoradiation for resectable rectal cancer at our institution.

**Methods:** Eight consecutive patients with resectable (T2-T3) rectal cancers underwent 3DCRT, IMRT, and 3-dimensional conformal PT treatment planning. Initial target volumes (PTV1) were contoured using the Radiation Therapy Oncology Group anorectal atlas guidelines. Boost target volumes (PTV2) consisted of the gross rectal tumor plus a uniform 2-cm expansion. Plans delivered 45 Gray (Gy) or Cobalt Gray Equivalent (CGE) to the PTV1 and a 5.4-Gy (CGE) boost to the PTV2. Ninety-five percent of the PTVs received 100% of the target dose and 100% of the PTVs received 95% of the target dose. Standard normal-tissue constraints were utilized. Wilcoxon paired t-tests were performed to compare various dosimetric points between the 3 plans for each patient.

**Results:** All plans met all normal-tissue constraints and were isoeffective in terms of PTV coverage. The proton plans offered significantly reduced median normal-tissue exposure over the 3DCRT and IMRT plans with respect to pelvic bone marrow at the V5Gy, V10Gy, V15Gy, and V20Gy levels and the small bowel space at the V10Gy and V20Gy levels. The proton plans also offered significantly reduced median normal-tissue exposure over the 3DCRT plans with respect to the small bowel at the V30Gy and V40Gy levels and the urinary bladder at the V40Gy level.

**Conclusions:** By reducing bone marrow exposure, PT may reduce the acute hematologic toxicity of neoadjuvant chemoradiation and increase the likelihood of uninterrupted chemotherapy delivery. Bone marrow sparing may also facilitate the delivery of salvage chemotherapy for patients who subsequently develop hematogenous metastasis. Reduced small bowel exposure using PT may also reduce toxicity and possibly facilitate the use of more-aggressive chemotherapy with radiotherapy.

**Keywords:** Proton therapy; particle therapy; dosimetry; rectal cancer; gastrointestinal cancer

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Introduction

The introduction of neoadjuvant therapy through short and long courses of radiation therapy for resectable rectal cancer has resulted in reduced relapse rates (1-3). Adding chemotherapy to preoperative long-course radiation has been shown to be superior to radiation alone (2), while preoperative chemoradiation (CRT) results in lower relapse...
rates and better sphincter preservation than postoperative CRT (3). As a result, preoperative CRT is now a standard of care in locally advanced rectal cancer. Nevertheless, despite neoadjuvant CRT, recurrence rates of locally advanced rectal cancer remain high with systemic recurrence in up to 30% to 40% of patients (1,3).

Historically, radiation was delivered using 3-dimensional conformal radiotherapy (3DCRT) techniques in a 3- or 4-field arrangement. The introduction of intensity-modulated radiation therapy (IMRT) has resulted in improved conformality; however, despite this improvement, organs outside of the planning target volume (PTV), including the bladder, small bowel, and pelvic bone marrow, may still receive a significant radiation dose.

Conventional photon radiation uses X-rays to deliver the dose to the target volume. X-ray therapy, however, results in a significant entrance and exit dose along the path of beam delivery in addition to subsequent dose to normal tissue. Compared to X-ray therapy, proton therapy is a form of charged-particle therapy that allows delivery of the equivalent X-ray dose or dose escalation while sparing normal tissue. More specifically, the properties of the spread-out Bragg peak (SOBP) allow improved sparing of non-targeted organs, with proton beams conformed to fit the exact depth and shape of the required target. Reducing the volume and exposure of normal pelvis and bone marrow to radiation will likely reduce long-term toxicity and preserve pelvic bone marrow, which is increasingly important in the setting of systemic recurrences where patients may require multiple lines of myelosuppressive chemotherapy.

In this study, we sought to compare proton therapy plans for patients treated with neoadjuvant CRT to IMRT and 3DCRT plans in an attempt to quantify the dosimetric benefit of proton therapy in a cohort of patients receiving neoadjuvant CRT.

**Materials and methods**

Under an institutional review board-approved study, 8 consecutive patients with resectable rectal cancers underwent treatment planning with 3DCRT, IMRT, and conformal proton therapy. All patients were simulated in the prone position with a full bladder and imaged on a Phillips Brilliance (Phillips Healthcare, Andover, MA) large-bore computed tomography (CT) scanner with a 60-cm field-of-view and 1-mm slices.

**Target volumes and dose constraints**

Initial target volumes (PTV1) were contoured using the guidelines in the Radiation Therapy Oncology Group (RTOG) anorectal atlas (4). The initial clinical target volume (CTV) consisted of the gross tumor volume (GTV) as determined by a combination of physical examination, colonoscopy, and diagnostic CT and/or magnetic resonance imaging (MRI) scan plus the entire mesorectum, including the perirectal fat and presacral space along with the internal iliac lymph nodes. Boost target volumes (PTV2) consisted of the GTV plus a 2-cm uniform expansion. The dose delivered to the PTV1 was 45 Gray (Gy) or Cobalt Gray Equivalent (CGE) in 25 fractions with a boost of 5.4 CGE in 3 fractions to the PTV2, resulting in a total dose of 50.4 CGE over 28 fractions.

Target goals were similar to those used in the RTOG 0822 protocol for resectable rectal cancer. For each treatment phase, 95% of the PTV received 100% of the target dose and 100% of the PTV received 95% of the target dose. Per the normal-tissue constraints, no more than 180 cm$^3$ of small bowel received greater than 35 Gy, while no more than 40% of the femoral heads received greater than 40 Gy; V40Gy for the bladder was less than 40%.

3DCRT plans delivered the target doses via a standardized 3-field (posterior/anterior, right lateral, and left lateral) approach with a 2-to-1 field weighting by dose contributed to the target volume. IMRT plans delivered the initial 45 Gy following the planning and dose delivery guidelines of the RTOG 0822 protocol and a 5.4-Gy boost by following the same field angles as the initial plan. PT plans utilized a 3-field approach similar to the 3DCRT plans with a heavier weighting of the posterior field relative to the right and left lateral fields (3.1 to 1 to 1). To avoid excess skin toxicity, the maximum dose permitted to 1 cm$^2$ of skin was 35 Gy. To account for air within the rectum when designing the proton plan, the Hounsfield units were overridden for the circumferential air-filled portion of the rectum.

Representative colorwash dose distributions for typical proton therapy, IMRT and 3DCRT plans are shown in Figure 1.

**Statistics**

Descriptive statistics (median and range) were used to characterize the disease-specific and dosimetric points of
interest. A Wilcoxon signed rank sum test for nonparametric paired data was used to compare the 3DCRT and IMRT plans with the proton plans for the various dosimetric points, and to establish statistical significance, $P \leq 0.05$ (WinStat Microsoft Excel, Microsoft, Redmond, WA).

**Results**

*Target volume coverage*

All 3DCRT, IMRT, and proton plans met all normal-tissue constraints and were isoeffective in terms of PTV coverage.

*Pelvic bone marrow dosimetry*

The results for median pelvic bone marrow dosimetry comparing the 3 plans are shown in Table 1. At all dose levels evaluated, proton plans offered significantly reduced pelvic bone marrow exposure over 3DCRT and IMRT.

*Small bowel and bladder dosimetry*

The results for small bowel and bladder dosimetry are shown in Table 2. Proton therapy was statistically superior to 3DCRT with regard to small bowel exposure at all evaluated dose levels and with regard to the urinary bladder at the V40Gy level. The superiority of proton therapy over IMRT with regard to small bowel exposure was limited to the V10Gy and V20Gy levels. There was no significant improvement with protons compared to IMRT with regard to urinary bladder exposure.

**Discussion**

We present the first known dosimetric study comparing 3DCRT, IMRT, and proton therapy plans for neoadjuvant CRT for resectable rectal cancer. The results show superior bone marrow sparing for proton therapy over IMRT and 3DCRT and better sparing of small bowel with proton therapy.
therapy, particularly at low-dose thresholds.

As a result of its dosimetric advantages in certain tumors, such as childhood cancers (5-10) and skull base tumors (11-13), proton therapy is a well-established radiotherapy treatment technique. Furthermore a growing body of evidence is emerging indicating superior dosimetric profiles and sparing of normal tissue over 3DCRT, IMRT, or both in various other tumor sites, including lung tumors (14-16), lymphoma (17,18) and upper gastrointestinal (GI) tumors (19,20).

While radiation therapy for rectal cancer is a long-established practice and neoadjuvant CRT is a standard of care in the management of operable locally advanced rectal cancer (2,3,21,22), preoperative radiation is still delivered in most cancer centers using 3DCRT. Neoadjuvant CRT, however, results in non-trivial rates of acute and late treatment toxicity from treatment as well as significant local and distant recurrence rates. In the German study (3) comparing pre- and postoperative CRT in which preoperative CRT was given to a dose of 50.4 Gy with 5 fluorouracil (5-FU) concurrent chemotherapy, the incidence of acute grade 3+ toxicity was 27% with a late grade 3+ toxicity rate at the 5-year follow-up in the preoperative group of 14%. In an updated report of this study (23), at the 11-year follow-up, the 10-year rate of cumulative local recurrence was 7.1% and the rate of distant metastases 29.8%.

In the Sauer study, 6% of patients in the preoperative group experienced grade 3+ haematological toxicity. In addition, with approximately 30% to 40% of patients recurring at 10 years, a large proportion of patients receiving neoadjuvant CRT will likely require future salvage chemotherapy. Thus, the significant sparing of bone marrow seen in our study with proton therapy over both IMRT and 3DCRT (P<0.05 for V5, V10, V15, and V20 for proton therapy versus IMRT and proton therapy versus 3DCRT) may be of substantial benefit. Indeed, sparing bone marrow through the use of proton therapy may reduce the compromise of delivery of CRT in the acute setting while preserving bone marrow function ahead of several lines of myelosuppressive chemotherapy that are delivered in the salvage setting (3).

Proton therapy offers the potential to reduce acute and late bowel toxicity from CRT compared to IMRT or 3DCRT in the treatment of rectal cancer. In our study, proton therapy plans had statistically significant superior sparing of the small bowel compared to both IMRT and 3DCRT for both V10 and V20. Although the median

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<th>Table 1 Median pelvic bone marrow exposure for 3DCRT versus IMRT versus proton therapy plans (range in parentheses)</th>
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<td>PBM V5Gy [%]</td>
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Abbreviations: 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; PBM, pelvic bone marrow; PT, proton therapy.

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<th>Table 2 Median small bowel and bladder normal-tissue exposures for each planning technique</th>
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<td>Small bowel</td>
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<td>V10Gy (cm³)</td>
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Abbreviations: 3DCRT, 3-dimensional conformal radiation therapy; IMRT, intensity-modulated radiation therapy; NS, not significant; PT, proton therapy.
V30 and V40 for IMRT was slightly less than with proton therapy, this was not statistically significant. In this regard, by reducing the low-dose bowel volume irradiated, proton therapy may better allow for dose escalation or avoidance of treatment interruptions in the acute setting.

Current research in the neoadjuvant setting revolves around adding new chemotherapy agents to radiation: capecitabine has been shown to be equally efficacious as infusional 5-FU in the treatment of colon cancer (24,25) and the effectiveness of agents such as oxaliplatin, irinotecan, and bevacuzimab has led to these agents being piloted in early-phase trials of neoadjuvant rectal cancer.

Nevertheless, bowel toxicity can be a limiting factor in this setting; indeed, the phase II randomized RTOG 0247 trial comparing neoadjuvant radiation combined with capecitabine and oxaliplatin versus capecitabine and irinotecan was temporarily suspended due to excess grade 3+ GI toxicity from both the chemotherapy and the radiation. Several studies have shown a potential benefit with IMRT compared to 3DCRT in rectal cancer with regard to the small bowel dose (26,27). Such studies are the foundation to the hypothesis for the RTOG 0822 study, which involves using IMRT with concurrent multiagent chemotherapy to reduce small bowel exposure and therefore acute GI toxicity, thus enabling better dose delivery and dose escalation of concurrent chemotherapy. Similarly, proton therapy may permit additional small bowel sparing, allow chemotherapy dose escalation, and increased patient compliance.

Proton therapy plans in our study utilized a 3-field approach with uniform scanning. This field arrangement was chosen to avoid the excess skin dose with a single posterior field plan. Furthermore, uniform scanning allowed delivery of the dose to a greater depth in the pelvis than would be possible with double-scattered protons. Advancements in proton therapy, such as the introduction of pencil-beam scanning and with it intensity-modulated proton therapy, may result in proton therapy offering further dosimetric advantages over and above those seen in our study and may merit further investigation as intensity-modulated proton therapy becomes increasingly available.

Conclusions

In this small series of patients with rectal cancer undergoing neoadjuvant CRT for rectal cancer, proton therapy plans offered superior sparing of bone marrow and the small bowel compared to both IMRT and 3DCRT. The dosimetric advantages seen with proton therapy may therefore merit further investigation as a means of limiting the acute toxicity of neoadjuvant CRT and preserving both bone marrow and bowel function in advance of future myelosuppressive chemotherapy in the relapse setting.

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References


