



Dosimetric Comparison of Intensity-Modulated Proton Therapy and Volumetric-Modulated Arc Therapy in Anal Cancer Patients and the Ability to Spare Bone Marrow

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Abstract

Purpose: Intensity-modulated radiation therapy (IMRT) has been used to spare organs at risk (OARs) in the definitive treatment of anal cancer. However, treatment continues to result in significant hematologic toxicity. In a cooperative trial assessing IMRT (RTOG 0529), the rate of grade 2+ and grade 3+ hematologic toxicity was 73% and 58%, respectively. Intensity-modulated proton therapy (IMPT) has the potential to decrease the integral bone marrow dose and dose to other OARs compared with photon therapy.

Patients and Methods: Computed tomography datasets of 9 patients with anal cancer previously treated with IMRT, volumetric arc therapy (VMAT), or tomotherapy at our institution were used for comparison. Both VMAT and IMPT plans were created for each patient. The IMPT plans were created using a multi-field optimized, split-target technique. The dose to OARs, including bone marrow, bladder, small bowel, large bowel, femoral heads, and genitalia, were compared using a paired *t* test.

Results: The mean bone marrow dose was 17.42 Gy with IMPT plans and 30.76 Gy with VMAT plans ($P < .0001$). The absolute volume of bone marrow spared 10 and 20 Gy was significantly less with the proton plans. IMPT also showed significant sparing of other OARs, including the small and large bowel, femoral heads, and genitalia. The mean planning target volume receiving at least 95% of the prescribed dose (V95) was similar with IMPT and VMAT plans, 99% and 98%, respectively.

Conclusion: IMPT can decrease the mean bone marrow dose compared with VMAT plans by minimizing the low dose spill associated with standard photon treatment. Prospective studies assessing proton therapy for anal cancer are ongoing to evaluate the potential for improvement in hematologic toxicity and the acute tolerance of therapy.

Keywords: intensity-modulated proton therapy; anal cancer; volumetric arc therapy; hematologic toxicity

Introduction

Although anal cancer is relatively rare, there were an estimated 8080 new cases of anal cancer diagnosed in the United States in 2016 [1]. Definitive radiation with concurrent 5-FU and mitomycin-C has become the standard of care for patients with localized anal cancer. While this treatment results in long-term disease-free survival and anal sphincter preservation, there is often significant acute toxicity associated with the treatment,

Submitted 19 May 2017
Accepted 07 Nov 2017
Published 28 Dec 2017

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Original Article

DOI
10.14338/IJPT-17-00017

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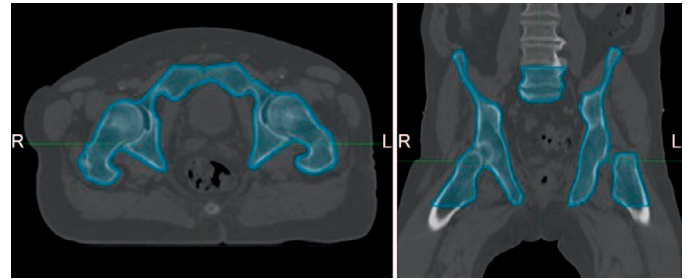
2017 International Journal of
Particle Therapy

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Figure 1. Bone marrow delineation, including iliac bone, lower pelvis, and lumbosacral spine.



particularly dermatologic, gastrointestinal, genitourinary, and hematologic toxicity. Intensity-modulated radiation therapy (IMRT) has been increasingly used over conventional radiation therapy to spare organs at risk (OARs) in the treatment of anal cancer. IMRT has been demonstrated to decrease the risk of gastrointestinal and dermatologic toxicity compared with conventional radiation therapy. However, treatment continues to result in significant hematologic toxicity [2]. In a cooperative trial assessing IMRT (RTOG 0529), the rate of grade 2+ and grade 3+ hematologic toxicity was 73% and 58%, respectively [2]. During IMRT planning, sparing of the bone marrow compartment is often sacrificed in favor of small-bowel sparing or planning target volume (PTV) coverage. Intensity-modulated proton therapy (IMPT) has the potential to decrease integral bone marrow dose and dose to other OARs while still maintaining coverage of the primary tumor.

Materials and Methods

Computed tomography datasets of 9 patients with anal cancer who were previously treated with IMRT, volumetric arc therapy (VMAT), or tomotherapy at our institution were identified and used for comparison after obtaining institutional review board approval. Pelvic bone marrow was delineated using the external surface of bone as described by Mell et al [3] and included (1) iliac bone extending from the iliac crests to the superior border of the femoral head; (2) lower pelvis, including the pubes, ischia, acetabula, and proximal femora extending from the superior border of the femoral heads to the inferior border of the ischial tuberosities; and (3) lumbosacral spine extending from the superior border of the L5 vertebral body to the coccyx but not extending below the superior border of the femoral head. The 3 subsites were included in 1 contour (**Figure 1**). The bony contour was used as a surrogate for bone marrow. Our patient population consisted of 5 females and 4 males with clinical stages ranging stage II to IIIB disease, based on the American Joint Committee on Cancer's *AJCC Cancer Staging Manual* (7th edition) [4] (**Table 1**). Dose prescriptions were the same as those used in Radiation Therapy Oncology Group (RTOG) 0529 [2], except patient No. 1 who was cT2N0 and received 45 Gy to elective lymph nodes based on the guidelines of the Australian Gastrointestinal Trials Group [5].

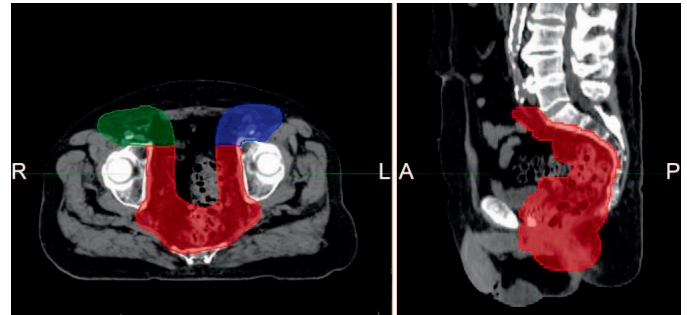
Both VMAT and IMPT plans were created for each patient using the Eclipse treatment planning system (Varian Medical Systems, Inc., North Charleston, SC). The IMPT plans were created using a 3-field multi-field optimized split target technique [6]. A posterior field was used to cover the primary tumor and pelvic lymph nodes and a right and left anterior oblique field was used to cover the right and left inguinal lymph nodes (**Figures 2 and 3B**). All VMAT plans were accomplished using a 2-arc

Table 1. Patient characteristics.

Patient	Age (y)	Sex	Stage	Elective			No. of fractions	PTV V95 IMPT (%)	PTV V95 VMAT (%)
				Primary dose (Gy)	intermediate dose (Gy)	Elective low dose (Gy)			
1	76	M	T2N0	50.4	-	45	28	99.96	99.14
2	48	F	T3N3	54	50.4	45	30	95.26	91.95
3	84	F	T3N2	54	50.4	45	30	97.97	98.59
4	62	M	T2N0	50.4	-	42	28	99.58	99.01
5	50	F	T3N0	54	-	45	30	100	100
6	57	M	T4N1	54	-	45	30	99.45	98.24
7	56	M	T3N2	54	50.4	45	30	99.6	97.29
8	60	F	T3N1	54	50.4	45	30	100	99.24
9	70	F	T2N0	50.4	-	42	28	100	99.53

Abbreviations: PTV, planning target volume; IMPT, intensity-modulated proton therapy; VMAT, volumetric arc therapy; M, male; F, female.

Figure 2. The 3-field, split-target multi-field optimization (MFO) and intensity-modulated proton therapy (IMPT) beam arrangement. One posterior field covers the primary tumor and pelvic lymph nodes (MFO_PA, red) and 2 anterior oblique fields cover the inguinal lymph nodes (MFO_LAO, blue; MFO_RAO, green).



technique (716 total arc degrees) with complementary collimator angles of 30° and 330° and a 6-MV energy photon mode (**Figure 3A**). During VMAT optimization, dose conformity and fall-off were controlled using dose-limiting structures (ring) and Eclipse’s Normal Tissue Objective. The OAR constraints, per RTOG 0529, and the bone marrow constraints, including mean bone marrow < 22.5 Gy, V10 < 90%, and V40 < 37%, were used for treatment planning (**Table 2**). The dose to OARs, including bone marrow, bladder, small bowel, large bowel, femoral heads, and genitalia, were compared with a paired *t* test.

Previously published Lyman-Kutcher-Burman normal tissue complication probability modeling suggests that the mean bone marrow dose can predict for grade 3+ hematologic toxicity in patients with anal cancer treated with definitive chemoradiation. Bazan et al [7] found that a mean pelvic bone marrow dose < 22.5 Gy was associated with a 5% risk of hematologic toxicity. Normal tissue complication probability modeling for patients with cervical cancer has also demonstrated an association between the volume of pelvic bone marrow receiving low-dose radiation and acute hematologic toxicity. These patients were similarly treated with concurrent chemotherapy with pelvic radiation. If the volume of bone marrow receiving 10 Gy (V10) was kept less than 90%, there was decreased rate of grade 2 leukopenia [8, 9]. RTOG 0418, a phase II study evaluating the use of IMRT for postoperative gynecologic cancers, also found that the volume of bone marrow receiving 40 Gy was predictive for hematologic toxicity. Among patients with cervical cancer with V40 > 37%, 75% had grade 2 or higher hematologic toxicity compared with 40% of patients with V40 < 37% [10]. As a result of these previously published studies, we selected mean bone marrow dose < 22.5 Gy, V10 < 90%, and V40 < 37% as bone marrow constraints for our comparative plans. In addition, recent data suggest that bone marrow toxicity may be more accurately measured as a volume-based parameter [11]. The absolute volume of bone marrow spared 10, 20, and 40 Gy was therefore also assessed for IMPT and VMAT plans.

For IMPT and VMAT plans, coverage was assessed to confirm that at least 95% of the PTV was receiving at least 95% of the prescribed dose. PTV expansions were the same for both the IMPT and VMAT plans. Additionally, coverage for the IMPT plans was evaluated using a ±3% range uncertainty criteria.

Figure 3. (A) Volumetric arc therapy versus (B) intensity-modulated proton therapy plans for a patient with cT3N0 anal cancer. Isodose lines are displayed in color wash and represent the following doses: 56.7 Gy (pink), 54 Gy (red), 51.3 Gy (light blue), 43.2 Gy (yellow), 35.2 Gy (green), 27 Gy (teal), 10.8 Gy (dark blue).

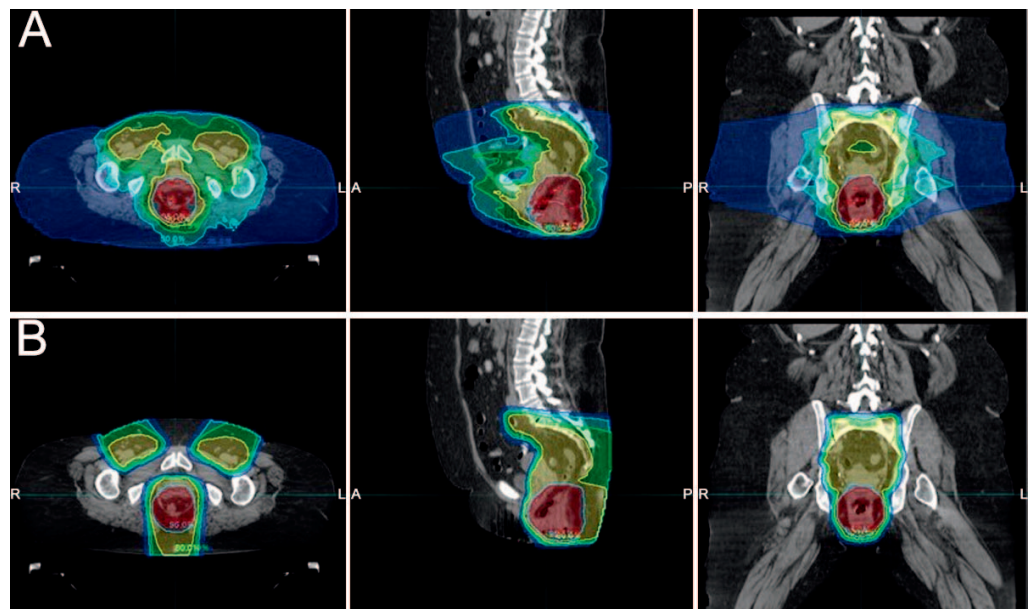


Table 2. Organ at risk constraints.

Organ at risk	Constraint
Bone marrow	Mean < 22.5 Gy
	V10 < 90%
	V40 < 37%
Bladder	V35 < 50%
	V40 < 35%
	V50 < 5%
Small and large bowel	V30 < 200 cm ³
	V35 < 150 cm ³
	V45 < 20 cm ³
Femoral heads	V40 < 35%
	V44 < 5%
Genitalia	V20 < 50%
	V30 < 35%
	V40 < 5%

Results

The mean bone marrow dose with IMPT and VMAT plans was 17.42 and 30.76 Gy, respectively ($P < .0001$). The mean volume of bone marrow receiving 10 Gy (V10) was significantly less with the IMPT plans, 48.97% compared with 92.56% for the VMAT plans ($P < .0001$). In addition, the absolute volume of bone marrow spared 10 and 20 Gy was higher in the IMPT plans compared with the VMAT plans (10 Gy, 814 cm³ versus 111 cm³ $P < .0001$; 20 Gy, 932 cm³ versus 246 cm³ $P < .0001$). There was no significant difference in the volume of bone marrow receiving 40 Gy in the IMPT plans compared with the VMAT plans (23.67% and 20.82%, respectively; $P = .346$) and the absolute volume of bone marrow spared 40 Gy (1254 cm³ versus 1194 cm³, $P = .379$).

The IMPT plans provided similar PTV coverage as the VMAT plans (primary PTV V95 was 99% versus 98%). The PTV coverage for each individual computed tomography dataset is listed in **Table 1**. IMPT also showed significant sparing of the OARs, including the small and large bowel, femoral heads, and genitalia (**Table 3**). This was more apparent for the lower isodose levels. For example, the mean volume of bladder receiving 35 Gy was 44.2% for IMPT compared with 72.96% for VMAT ($P = .0122$). In contrast, the mean volume of bladder receiving 50 Gy was not statistically significant (6.69% IMPT versus 7.02% VMAT; $P = .8856$).

Discussion

Treatment for anal cancer has evolved from abdominoperineal resection to organ preservation with concurrent chemoradiation [12]. While chemoradiation has resulted in long-term disease-free survival and sphincter preservation, acute toxicity remains high and can result in treatment breaks. RTOG 0529 demonstrated that IMRT for localized anal cancer can decrease gastrointestinal and dermatologic acute toxicity compared with historical controls treated with 3-dimensional conformal radiation therapy enrolled on RTOG 9811 [2]. However, the rate of grade 3 or higher toxicity events remain high, even with IMRT. In RTOG 0529, 37% of patients had grade 3 or higher gastrointestinal or genitourinary toxicity, and 49% of patients required a treatment break. In addition, grade 3 or higher hematologic toxicity was observed in 58% of patients [2].

The use of mitomycin-C–based chemotherapy has often been implicated in the high rates of hematologic toxicity in the definitive treatment of patients with anal cancer. However, concomitant radiation therapy to the pelvic bones can further increase the risk of hematologic toxicity due to the high radiosensitivity of hematopoietic stem cells in the active bone marrow [13], and pelvic bones may contain up to 40% of the total functional bone marrow. A dose-response relationship of radiation dose to the pelvic bone marrow and rates of grade 3 or higher toxicity have been demonstrated by Bazan et al [7], even in the setting of all patients receiving mitomycin and 5-FU based chemotherapy. This suggests that radiation to the pelvic bone marrow contributes to hematologic toxicity and indicates that, with more conformal avoidance of the bone marrow as an OAR, a reduction in hematologic toxicity may be possible.

Integral bone marrow dose can increase due to the low-dose bath effect associated with IMRT [14]. Historically, pelvic bone marrow has not been considered an avoidance structure in treatment planning. Therefore, low dose received by the bone

Table 3. Mean results of organs at risk.

Constraint	Intensity-modulated proton therapy	Volumetric arc therapy	P value
Bone marrow			
Mean dose	17.42 Gy	30.76 Gy	<.0001
V10	48.97%	92.56%	<.0001
V40	23.67%	20.82%	.3460
Bladder			
V35	44.20%	72.96%	.0122
V40	38.94%	52.35%	.1243
V50	6.69%	7.02%	.8856
Small bowel			
V30	176.64 cc	400 cc	.0009
V35	151.12 cc	291.91 cc	.0051
V45	50.93 cc	48.8 cc	.8076
Large bowel			
V30	79.10 cc	131.68 cc	.0071
V35	70.37 cc	114.23 cc	.0136
V45	27.18 cc	24.95 cc	.7926
Femoral heads			
V40	2.80%	21.94%	.0160
V44	1.30%	4.24%	.2982
Genitalia			
V20	2.55%	63.68%	.0006
V30	1.24%	41.67%	.0164
V40	0.53%	20.47%	.1210

marrow can increase in an attempt to cover the PTV while decreasing dose to other surrounding bowel and other OARs. Leukopenia and neutropenia can put patients at increased risk for infection and hospitalization, which can compromise treatment efficacy by prolonging the overall treatment time. Multiple institutions have demonstrated that the volume of bone marrow receiving a low dose of radiation, V10 and V20, strongly correlates with cytopenias [8, 9, 15, 16]. In our study, we found that the mean absolute volume of bone marrow spared 10 Gy was significantly higher with IMPT plans, 814 cm³ compared with VMAT plans, 111 cm³ ($P < .0001$); and the volume of bone marrow spared 20 Gy was also significantly higher (932 cm³ versus 246 cm³, $P < .0001$).

Since bone marrow is considered a parallel organ, the mean bone marrow dose is a good predictor for hematologic toxicity. In our study, the mean bone marrow dose was significantly lower with IMPT plans compared with VMAT plans, 17.42 and 30.76 Gy, respectively. Based on the Lyman-Kutcher-Burman normal tissue complication probability model developed by Bazan et al [7], the expected rate of grade 3+ hematologic events would be 40% for VMAT plans and <10% for IMPT plans. Despite the heterogeneity of dosimetric parameters assessed for hematologic toxicity in prior studies, there appears to be a consistent association with volume of bone marrow receiving low doses of radiation. Radiation planning and delivery using scanning proton beam therapy offers a reduction in dose to the bone marrow space compared with VMAT. This is similar to the finding by Anand et al, who also demonstrated that scanning proton beam therapy can reduce to dose to bone marrow by >50% compared with IMRT [6].

Given the large volume of the total pelvic bone marrow, investigators have attempted to identify which subsites may contribute most to the hematologic toxicity and therefore allow physicians to spare certain subsites instead of the total pelvic bone marrow. The lumbosacral spine has been found to have the highest region of active bone marrow within the pelvis [17], and the V40 of the lumbosacral spine has been shown to be strong predictor of grade 3+ hematologic toxicity [15]. However, Rose et al [18] has demonstrated that radiation doses to the total pelvic bone marrow, lumbosacral bone marrow, and iliac bone marrow are all individually associated with hematologic toxicity and therefore sparing just a portion of the pelvic bone marrow may be insufficient to decrease bone marrow suppression. Due to this finding, we did not find it necessary to evaluate the dose to each of the 3 subsites of the pelvic bone marrow and instead focused on dose to the total pelvic bone marrow.

One limitation of our study was the use of total bone volume as a surrogate for the bone marrow contour. There is increasing interest in sparing the metabolically active subset of the bone marrow given the inherent difficulty of maintaining adequate tumor coverage while simultaneously sparing pelvic OARs and bone marrow. Computed tomography lacks the ability to delineate active bone marrow composed of hematopoietic cells and inactive bone marrow composed primarily of fat cells. ^{18}F -FDG-PET has been used to identify areas of metabolically active bone marrow. Franco et al [17] demonstrated that areas of active bone marrow significantly correlate with white blood cell count, absolute neutrophil count, and platelet nadirs. Further work is needed to define the optimal SUV parameters to segregate an active marrow subsite and it is uncertain whether this is a better dosimetric predictor of hematologic toxicity compared with total bone. Several investigators have concluded that dose to the total bone contour is still a good surrogate for determining hematologic toxicity. Rose et al [19] demonstrated that FDG-based active bone marrow models failed to improve the ability to predict hematologic toxicity compared with total bone marrow models in patients with anal cancer who were undergoing chemoradiation. For the purposes of this study, the total bone was used as a surrogate for bone marrow in comparing the different modalities.

Conclusion

We created IMPT plans using a multi-field optimized, split-target technique and demonstrated that IMPT can decrease the mean dose to the bone marrow in addition to other OARs, including the small and large bowel, femoral heads, and genitalia. IMPT can minimize low dose spill to the bone marrow compared with VMAT plans using standard photon therapy. Prospective studies assessing proton therapy for anal cancer are ongoing to evaluate the potential for improvement in hematologic toxicity and the acute tolerance of therapy.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: The authors have no conflicts to disclose.

Acknowledgments: The abstract of this article was presented as a poster at the 58th Annual Meeting of the American Society for Radiation Oncology in Boston, Massachusetts, during September 25-28, 2016.

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