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Scientific Article

Multi-institutional Comparison of Intensity Modulated Photon Versus Proton Radiation Therapy in the Management of Squamous Cell Carcinoma of the Anus

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Abstract

Purpose: Concurrent chemoradiation therapy is a curative treatment for squamous cell carcinoma of the anus, but patients can suffer from significant treatment-related toxicities. This study was undertaken to determine whether intensity modulated proton therapy (IMPT) is associated with less acute toxicity than intensity modulated radiation therapy (IMRT) using photons.

Materials and Methods: We performed a multi-institutional retrospective study comparing toxicity and oncologic outcomes of IMRT versus IMPT. Patients with stage I-IV (for positive infrarenal para-aortic or common iliac nodes only) squamous cell carcinoma of the anus, as defined by the American Joint Committee on Cancer's *AJCC Staging Manual*, eighth edition, were included. Patients with nonsquamous histology or mixed IMPT and IMRT treatment courses were excluded. Acute nonhematologic toxicities, per the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4, were recorded prospectively at all sites. Acute and late toxicities, dose metrics, and oncologic outcomes were compared between IMRT and IMPT using univariable and multivariable statistical methods. To improve the robustness of our analysis, we also analyzed the data using propensity score weighting methods.

These data were presented as a mini-oral presentation at the American Society for Radiation Oncology (ASTRO) Annual Meeting in Chicago, Illinois, September 15 to 18, 2019.

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Results: A total of 208 patients were treated with either IMPT (58 patients) or IMRT (150 patients). Of the 208 total patients, 13% had stage I disease, 36% stage II, 50% stage III, and 1% stage IV. IMPT reduced the volume of normal tissue receiving low-dose radiation but not high-dose radiation to bladder and bowel. There was no significant difference between treatment groups in overall grade 3 or greater acute toxicity (IMRT, 68%; IMPT, 67%; $P = .96$) or 2-year overall grade 3 or greater late toxicity (IMRT, 3.5%; IMPT, 1.8%; $P = .88$). There was no significant difference in 2-year progression-free survival (hazard ratio, 0.8; 95% CI, 0.3-2.0).

Conclusions: Despite reducing the volume of normal tissue receiving low-dose radiation, IMPT was not associated with decreased grade 3 or greater acute toxicity as measured by CTCAE. Additional follow-up is needed to assess whether important differences arise in late toxicities and if further prospective evaluation is warranted.

Introduction

The National Cancer Institute's Surveillance, Epidemiology, and End Results Program estimates that 8300 people were diagnosed with anal cancer in 2019, and the incidence is rising.[1] Several randomized trials established radiation therapy with concurrent chemotherapy as the standard of care for patients with squamous cell carcinoma of the anal canal.[2-9] With 5-year survival exceeding 75% for stage I and II disease, as defined by the American Joint Committee on Cancer's *AJCC Staging Manual*, eighth edition, reducing the acute and late toxicities of concurrent chemoradiation therapy has become an important research focus.[10,11]

Clinical trials for anal cancer seek to decrease the toxicity of treatment through radiation therapy dose reduction (ClinicalTrials.gov Identifier: NCT04166318; ISRCTN Registry # 88455282) or technological innovations such as intensity modulated radiation therapy (IMRT) with photons or intensity modulated proton therapy (IMPT).[12,13] In the past, radiation therapy for anal cancer generally used large pelvic fields to encompass all sites at high risk for harboring subclinical disease. The Radiation Therapy Oncology Group (RTOG) 0529 phase 2 trial of IMRT showed decreased hematologic, dermatologic, and gastrointestinal toxicity compared with historical controls treated with 2- or 3-dimensional radiation therapy.[13] On the basis of RTOG 0529, IMRT is the radiation technique standard of care for anal cancer in the United States.

Interest in IMPT for anal cancer has grown with the publication of several dosimetry studies showing that IMPT, compared with IMRT, could reduce the radiation dose to several organ systems.[14-16] Wo et al recently published the results of a feasibility trial of IMPT showing toxicity rates comparable with those of RTOG 0529.[12] Based on its anticipated reduction of radiation dose to normal organs, we hypothesized that IMPT would be associated with less acute toxicity compared with IMRT.

Methods

Cohort

The study cohort included adults aged 18 years or older with squamous cell carcinoma of the anal canal or perianal skin diagnosed and treated with definitive radiation therapy between October 26, 2012, and March 20, 2018, at University of Pennsylvania (Philadelphia, Pennsylvania), Mayo Clinic in Rochester (Rochester, Minnesota), or Mayo Clinic in Arizona (Scottsdale, Arizona and Phoenix, Arizona) and affiliated network sites. Exclusion criteria included non–squamous cell histology, mixed modality treatment (specifically IMPT with >5 fractions of IMRT), age younger than 18 years, or prior pelvic radiation therapy. Patients with AJCC (eighth edition) M1 stage disease were included if their only site of metastatic disease was in the infrarenal para-aortic or common iliac lymph nodes. Consecutively treated patients meeting these criteria were enrolled on the study. Institutional review board approval was obtained from all participating institutions. Data are not available for reuse.

Treatments

All IMPT patients were treated with pencil beam scanning proton therapy. At PENN, IMPT treatment plans typically consisted of 2 posterior oblique beams with or without an anterior beam for treatment of the inguinal nodes. Patients were typically treated in the supine position with a comfortably full bladder. Robust optimization was not routinely used, and most treatment plans used single-field uniform dose planning. Linear energy transfer (LET) inverse planning was not used. The majority of treatment plans followed simultaneous integrated dose prescriptions according to RTOG 0529. Daily image guidance was routinely used, and verification scans were obtained at least on weeks 1 and 3 of treatment, with more ordered depending on clinical changes.

Similar to PENN, at Mayo Clinic, patients are treated in the supine position using 2 posterior beams and an anterior beam. Robust optimization and multifield optimization are routinely used for planning. LET-based inverse planning is not used, but LET-modeled dose distributions are generated for physician review. If clinically indicated, the physician may request replanning based on the biological dose distribution. The majority of plans follow RTOG 0529

–like dosing. Weekly verification scans are obtained for all patients with anal cancer.

Outcomes

The primary outcome of this study was overall grade 3 or greater acute toxicity, with late grade 3 or greater toxicity and oncologic outcomes as secondary endpoints. Adverse events were defined according to the grading system of the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), version 4. As the standard clinical practice for both photon and proton modalities at all the study institutions and network sites, acute nonhematologic toxicities are recorded prospectively while patients are under treatment. Acute toxicities or hospitalizations in the early posttreatment period were recorded if, after review by a radiation oncology physician, they were deemed to be related to chemoradiation therapy. To decrease the risk of underreporting toxicities owing to patients traveling for IMPT, we did not count acute complications beyond 2 weeks after radiation treatment. Late toxicities were defined as those occurring more than 3 months after completion of radiation therapy and were ascertained from the electronic health record. We recognize that these time window definitions may leave some acute toxicities unaccounted for but believe that this methodology results in a less biased acute toxicity comparison between IMPT and IMRT. Laboratory values, hospitalizations, cases of febrile neutropenia, late grade 3 or greater toxicities, deaths, and progression events were abstracted from electronic health records. Dosimetric data were collected from clinical treatment plans.

Covariates

Demographic, pathologic, clinical, and treatment-related covariates were extracted from the medical and radiation oncology-specific electronic health records. Chemotherapy infusions were verified with institution-specific medication administration records. AJCC (eighth edition) staging was used for recording the cancer stage.

Statistical methods

Multivariable logistic regression was used to compare overall acute toxicity of grade 3 or greater while controlling for relevant confounders. Multivariable Fine-Gray competing risks regression was used to compare the incidence of late grade 3 or greater toxicity with death as a competing risk. Time-to-event survival outcomes were evaluated with the log-rank test and Cox proportional hazards models. Radiation dose metrics were compared using the Kruskal-Wallis test. In addition, patients who underwent IMPT and IMRT were pooled together, and associations of various radiation dose metrics with the maximum acute toxicity grade were determined using logistic regression models.

To increase the robustness of the results, we also analyzed the data using propensity score weighting. Propensity scores were computed for each patient using a logistic regression model incorporating key pretreatment variables: age as a continuous variable, institution, sex, smoking status, HIV status, histologic grade, T stage, N stage, M stage, concurrent chemotherapy use, and dose to primary tumor (categorized as >5400 cGy, <5040 cGy, or 5040-5400 cGy). Inverse probability of treatment weighting was used to create a weighted cohort with balanced measured confounders. Analyses comparing IMPT and IMRT were conducted using the weighted cohort.[17]

All analyses were conducted with SAS, version 9.4 (SAS Institute, Cary, North Carolina), using 2-sided statistical tests, and $P < .05$ was considered statistically significant. Adjustments for multiple comparisons were not performed. Figures were generated using the *ggplot2* package of R, version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 208 patients were included and received either IMRT (150 patients) or IMPT (58 patients). As shown in Table 1, the distribution of AJCC (eighth edition) clinical stage groups was stage I (13%), IIA (30%), IIB (6%), IIIA (25%), IIIB (1%), IIIC (23%), and IV (1%). Lymph node–positive disease was more common in the IMRT cohort (57%) than the IMPT cohort (31%; $P = .003$). A larger proportion of IMRT patients were treated with prescribed doses greater than 5400 cGy (IMRT cohort, 20%, vs IMPT, 3%; $P = .002$). There was no difference in the number of intravenous chemotherapy cycles between patients receiving IMRT versus IMPT (median, 2 [interquartile range, 2-2] for both groups). After weighting for inverse probability of treatment, all baseline characteristics were balanced between the IMRT and IMPT groups except for smoking status, although this was considered acceptable because smoking status would be included as a covariate in the primary multivariable analysis (Table E1). Median follow-up of the entire cohort, the IMRT group, and the IMPT group was 30 months, 34 months, and 26 months, respectively.

Radiation dose metric correlations

There were several differences between the IMPT and IMRT groups in various radiation dose metrics (Fig 1).

Table 1 Baseline characteristics for patients receiving IMPT (proton) versus IMRT (photon)

	All patients, No. (%) (N = 208)	Patients receiving IMPT, No. (%) (n = 58)	Patients receiving IMRT, No. (%) (n = 150)	*P* value
Age, mean (range), y	62 (23-88)	63 (23-88)	61 (28-86)	.17
Institution				
PENN	111 (53)	36 (62)	75 (50)	.0003
Mayo Clinic Rochester	90 (43)	16 (28)	74 (49)	
Mayo Clinic Arizona	7 (4)	6 (10)	1 (1)	
Sex				
Female	152 (73)	44 (76)	108 (72)	.61
Male	56 (27)	14 (24)	42 (28)	
Smoking status				
Never	78 (37)	24 (42)	54 (36)	.01
Current	49 (24)	6 (10)	43 (29)	
Former	81 (39)	28 (48)	53 (35)	
HIV status				
Negative	150 (72)	43 (74)	107 (71)	.91
Positive	25 (12)	6 (10)	19 (13)	
Unknown	33 (16)	9 (16)	24 (16)	
Histologic grade				
1	15 (7)	3 (5)	12 (8)	.35
2	89 (43)	28 (48)	61 (41)	
3	55 (26)	17 (30)	38 (25)	
4	8 (4)	0 (0)	8 (5)	
Unknown	41 (20)	10 (17)	31 (21)	
T stage*				
c0	2 (1)	0 (0)	2 (1)	.60
c1	34 (16)	11 (19)	23 (16)	
c2	108 (52)	30 (52)	78 (52)	
c3	49 (24)	11 (19)	38 (25)	
c4	15 (7)	6 (10)	9 (6)	
N stage*				
c0	104 (50)	40 (69)	64 (43)	.003
c1a	88 (42)	16 (28)	72 (48)	
c1b	0 (0)	0 (0)	0 (0)	
c1c	16 (8)	2 (3)	14 (9)	
M stage*				
c0	205 (98)	56 (97)	149 (99)	.19
c1	3 (2)	2 (3)	1 (1)	
Stage group*				
I	27 (13)	10 (17)	17 (11)	.004
IIA	62 (30)	24 (41)	38 (25)	
IIB	12 (6)	4 (7)	8 (5)	
IIIA	52 (25)	7 (12)	47 (31)	
IIIB	3 (1)	2 (3)	1 (1)	
IIIC	47 (23)	9 (16)	38 (25)	
IV (RP node only)	3 (1)	2 (3)	1 (1)	
Concurrent chemotherapy				
Yes	205 (98)	57 (98)	148 (99)	1
No	3 (2)	1 (2)	2 (2)	
Chemotherapy regimen				
5-FU/MMC	180 (87)	50 (86)	130 (87)	.49
Cape/MMC	16 (8)	3 (5)	13 (9)	
5-FU/Cisplatin	6 (3)	3 (5)	3 (2)	
Cape alone	2 (1)	1 (2)	1 (<1)	
No chemotherapy	3 (1)	1 (2)	2 (1)	
Unknown regimen	1 (<1)	0 (0)	1 (<1)	
Boost technique				
Sequential	49 (24)	14 (24)	35 (23)	1
Integrated	159 (76)	44 (76)	114 (77)	
Primary tumor dose				
>5400 cGy	32 (15)	2 (3)	30 (20)	.002
5040-5400 cGy	158 (76)	47 (81)	111 (74)	
<5040 cGy	18 (9)	9 (16)	9 (6)	

Abbreviations: 5-FU = 5-fluorouracil; cape = capecitabine; HIV = human immunodeficiency virus; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; MMC = mitomycin-C; RP = retroperitoneal.

* As defined in the American Joint Committee on Cancer's *AJCC Staging Manual*, eighth edition.

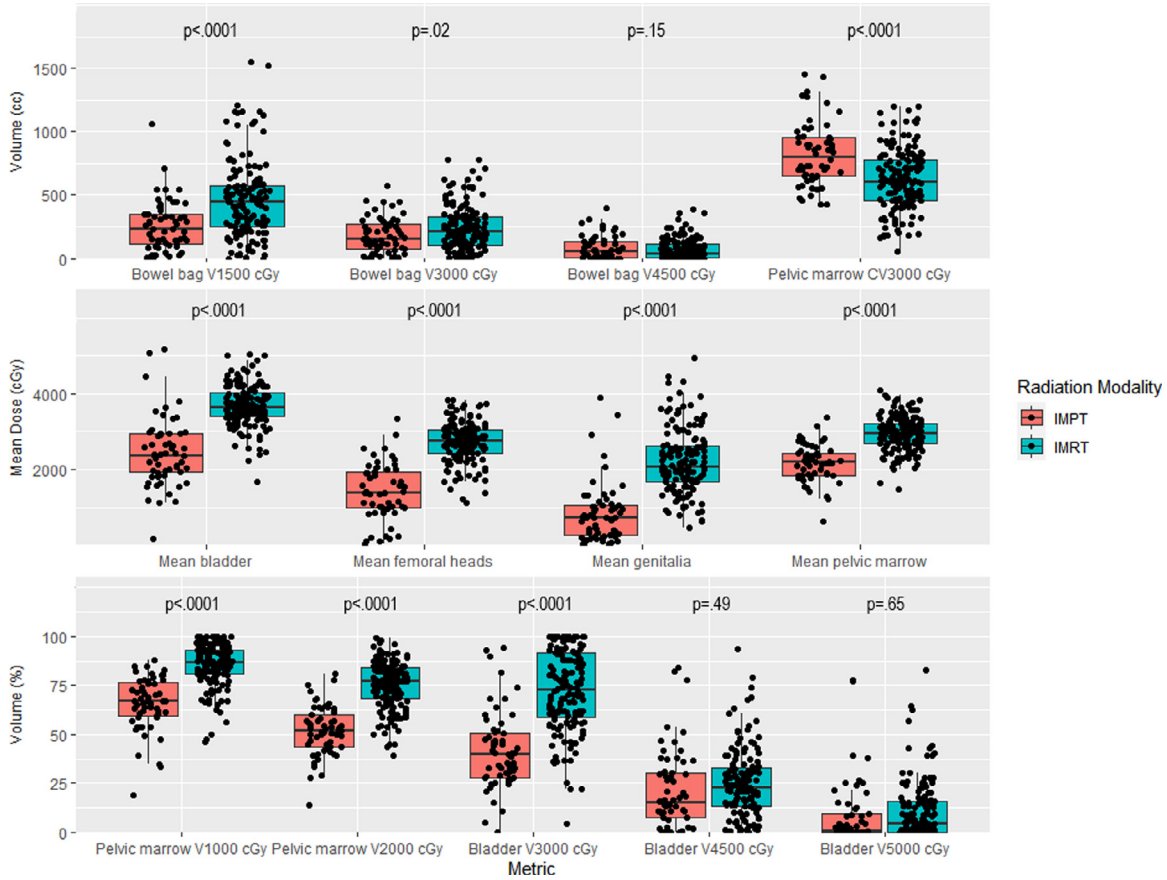

Fig. 1 Box plots of dose metrics.

When controlling for T and N stage among patients, IMPT was associated with significant reductions in the volume of bowel bag receiving at least 1500 cGy ($P < .0001$), the volume of bowel bag receiving at least 3000 cGy ($P = .02$), the volume of bladder receiving at least 3000 cGy ($P < .0001$), and mean dose to bladder, femoral heads, and genitalia (all $P < .0001$). IMPT reduced the dose to pelvic bone marrow across all dose metrics, including the volume of pelvic marrow receiving at least 1000 cGy, the volume receiving at least 2000 cGy, the mean dose to the pelvic marrow, and the volume of pelvic marrow spared from 3000 cGy or more (all $P < .0001$). Pelvic bone marrow was segmented according to previously described methods.[18] There were no significant differences between treatment modalities in the organ volumes receiving higher doses of radiation.

Toxicity and oncologic outcomes

There were no statistically significant differences between the treatment groups in unadjusted rates of acute toxicities of grade 2 or greater or toxicity of grade 3 or greater for all domains (Table 2). The rates of overall acute toxicity of grade 2 or greater for the IMPT and IMRT groups were 98% and 95%, respectively ($P = .34$). The rates of overall grade 3 or greater toxicity for the IMPT and IMRT groups were 67% and 68%, respectively ($P = .96$). There was 1 grade-5 hematologic toxicity, owing to septic shock, and 1 grade-5 gastrointestinal toxicity, owing to severe diarrhea (Table E2). Specific hematologic toxicity was similar between groups except for neutropenia—IMPT was associated with higher grade neutropenia (Table E2; Fisher test $P = .01$). Similar proportions of patients in both groups were hospitalized during radiation therapy (IMPT, 40%; IMRT, 33%; $P = .34$), and median treatment times were also similar (IMPT, 41 days; IMRT, 42 days; $P = .33$). Although acute hematologic toxicity of grade 3 or greater was not significantly different between the 2 groups, there was significantly more febrile neutropenia in the IMPT group (28%) versus the IMRT group (15%; $P = .03$). There was no significant difference between the treatment groups in unadjusted 2-year late toxicity of grade 3 or greater (cumulative incidence: IMPT, 1.8%; IMRT, 3.5%; $P = .88$) (Table E3). There were no late dermatologic toxicities of grade 3 or greater in either group.

In the primary analysis, overall grade 3 or greater acute toxicity was not significantly different between patients who received IMPT versus IMRT in a multivariable logistic regression model (odds ratio [OR], 0.7; 95% CI, 0.3-1.5) (Table 3). Node positivity was associated

Table 2 Unadjusted rates of acute toxicity

	Patients receiving IMPT, No. (%)	Patients receiving IMRT, No. (%)	*P* value
Hospitalized during radiation therapy	23 (40)	49 (33)	.34
Febrile neutropenia	16 (28)	22 (15)	.03
Median treatment time, d	41	42	.33
	Grade 2 or greater acute toxicity		
GI or GU	39 (67)	91 (61)	.38
GI	38 (65)	88 (59)	.37
GU	4 (7)	14 (9)	.58
Skin	50 (86)	117 (78)	.19
Pain	31 (53)	80 (53)	.99
Hematologic	40 (69)	87 (69)	.99
Overall	57 (98)	141 (95)	.34
	Grade 3 or greater acute toxicity		
GI or GU	14 (24)	31 (21)	.59
GI	13 (22)	30 (20)	.70
GU	1 (2)	1 (1)	.50
Skin	12 (21)	43 (29)	.24
Pain	7 (12)	20 (13)	.81
Hematologic	32 (55)	59 (47)	.29
Overall	39 (67)	92 (68)	.96

Abbreviations: GI = gastrointestinal; GU = genitourinary; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy.

with less acute toxicity (OR, 0.3; 95% CI, 0.2-0.7), whereas having a stage T3 or T4 tumor was associated with more acute toxicity (OR, 2.9; 95% CI, 1.2-6.5). We also found a significant difference in acute toxicity by institution (OR, 0.3; 95% CI, 0.1-0.7). Toxicity outcomes were collected similarly between institutions. There were notable differences in patient populations between urban Philadelphia and primarily nonurban Mayo Clinic, as reflected by the fact that the HIV positivity rate among patients at PENN was 20% versus 1% at Mayo Clinic institutions. The propensity score–weighted analysis also showed that IMPT was not associated with decreased acute grade 3 or greater toxicity (OR, 0.7; 95% CI, 0.4-1.1) (Table E4).

In univariable logistic regression models, only the bowel bag doses of V1500 cGy (P = .007), V3000 cGy (P = .0009), and V4500 cGy (P = .0004) were associated with greater toxicity (Table E5). This relationship is shown graphically in Figure E1, where it appears that the V1500 and V3000 were associated specifically with the 3 patients who experienced a grade 4 acute gastrointestinal (GI) toxicity. In contrast, the V4500 cGy increased as the grade of GI toxicity increased.

In a multivariable Fine-Gray competing risks regression model, IMPT was not associated with late toxicity of grade 3 or greater (hazard ratio [HR], 0.8; 95% CI, 0.2-3.4) (Table 3). Patients who were currently smokers or were node-negative at the time of radiation therapy were more likely to experience a late toxicity. The propensity score–weighted analysis also showed that IMPT was not associated with late toxicity of grade 3 or greater (HR, 0.7; 95% CI, 0.3-1.6) (Table E4).

There was no statistically significant difference in unadjusted 2-year locoregional recurrence-free survival (IMPT, 91%; IMRT, 88%; P = .49) (Fig 2) or adjusted progression-free survival between IMPT and IMRT (HR, 0.8; 95% CI, 0.3-2.0) (Table E6). Progression-free survival also was not significantly different in the propensity score–weighted cohort (HR, 0.6; 95% CI, 0.4-1.1).

Discussion

Technological innovation in radiation therapy is prompted by the well-recognized relationship between the risk of toxicity and the radiation dose delivered to a volume of normal organ.[19-21] One such technology is proton beam therapy (IMPT), which, owing to the particle's physical properties, delivers a markedly decreased radiation dose beyond the target along its beam path. IMPT undoubtedly decreases the integral radiation dose to the body, but it is unknown if these dose advantages translate to clinical improvements for patients with anal cancer.

This multi-institutional study was designed to test the hypothesis that IMPT is associated with less overall acute toxicity of grade 3 or greater compared with photon radiation (IMRT). The results suggest that IMPT in this cohort of patients was not associated with decreased

Table 3 Multivariable regression models for overall acute and late toxicity of grade 3 or greater

	Odds ratio (95% CI)	*P* value
Acute toxicity of grade 3 or greater (logistic regression)		
IMPT vs IMRT	0.7 (0.3-1.5)	.39
≤5400 cGy vs >5400 cGy	0.8 (0.3-2.1)	.60
N+ vs N0	0.3 (0.2-0.7)	.004
T3/4 vs T1/2	2.9 (1.2-6.5)	.01
No chemotherapy vs chemotherapy	1.1 (0.1-17.9)	.97
HIV positive vs negative	1.1 (0.3-4.1)	.85
HIV unknown vs negative	0.8 (0.3-2.4)	.66
Age (per year of age)	1.0 (0.96-1.03)	.91
Current vs never smoker	1.2 (0.5-2.9)	.74
Former vs never smoker	0.7 (0.3-1.4)	.32
Female vs male	1.7 (0.7-3.9)	.22
Institution* Mayo Clinic vs PENN	0.3 (0.1-0.7)	.004
	Hazard ratio (95% CI)	***P* value**
Late toxicity of grade 3 or greater (Fine-Gray regression)		
IMPT vs IMRT	0.8 (0.2-3.4)	.79
≤5400 cGy vs >5400 cGy	0.6 (0.1-4.9)	.64
N+ vs N0	0.3 (0.1-1.0)	.047
T3/4 vs T1/2	1.0 (0.3-3.6)	.94
HIV positive vs negative	7.4 (0.7-76.7)	.10
HIV unknown vs negative	3.4 (0.5-21.3)	.20
Age (per year of age)	1.0 (0.9-1.03)	.44
Current vs never smoker	6.3 (1.2-32.4)	.03
Former vs never smoker	0.8 (0.2-3.7)	.81
Female vs male	8.1 (0.8-83.6)	.08
Institution* Mayo Clinic vs PENN	0.3 (0.1-1.2)	.08

Abbreviations: N+ = node-positive; HIV = human immunodeficiency virus; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy.

* Mayo Clinic Rochester and Mayo Clinic Arizona were combined owing to low numbers of patients treated with IMRT at Mayo Clinic Arizona.

overall grade 3 or greater acute toxicity compared with IMRT, despite our finding that IMPT reduced the volume of normal organs that received incidental low-dose radiation. As expected, given the dose deposition properties of protons and photons, we did not observe a difference in the volume of normal organ tissue receiving high-dose radiation. We observed similar oncologic outcomes between IMPT and IMRT.

A recently published prospective feasibility study of proton chemoradiation therapy for anal cancer showed IMPT acute toxicity rates similar to those seen in RTOG 0529, a prospective phase 2 trial evaluating intensity modulated photon chemoradiation therapy for anal cancer.[12] We included patients treated at any of 3 tertiary care centers offering IMPT or IMRT as well as affiliated network sites that offered only IMRT—all of which were spread across 3 different regions of the United States with unique patient populations (urban Northeast, Midwest, and urban Southwest). Although this was a retrospective study, CTCAE acute nonhematologic toxicity grades were collected prospectively while patients were receiving treatment as part of standard clinical practice for patients receiving IMRT or IMPT. Given the low incidence of anal cancer and the difficulty of completing IMPT versus IMRT trials, a multi-institutional observational study provides important comparative evidence regarding this disease site.[22,23]

For decades, IMPT has been considered a promising means to reduce the toxicity of pelvic radiation therapy, but clinical data showing this have been lacking.[24,25] Multiple dosimetric studies comparing IMPT and IMRT radiation plans for anal cancer show that IMPT reduces low-dose radiation to the bone marrow, bowel, femoral heads, and genitalia, with the authors concluding that this had the potential to reduce gastrointestinal and hematologic toxicities of chemoradiation therapy for anal cancer.[14-16] These are not unreasonable predictions, because the Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) group summarized prior model-based and clinical data suggesting that greater doses to and volumes of irradiated bowel are associated with more grade 3 or greater gastrointestinal toxicities.[21] Multiple clinical studies have also found that greater doses to and volumes of irradiated bone marrow are associated with hematologic toxicity.[18,26,27] The findings of the current study are consistent with those of prior studies

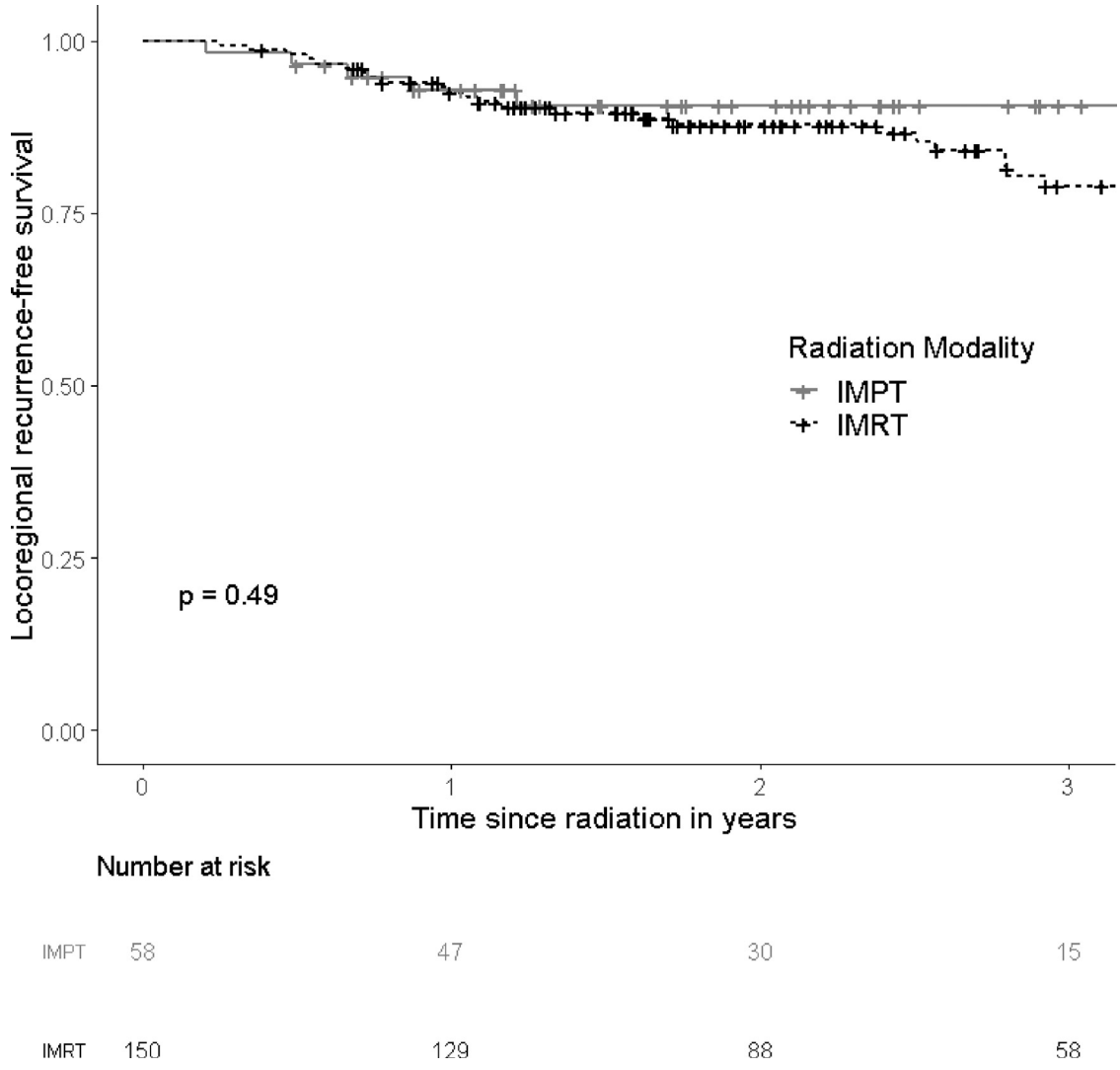

Fig. 2 Locoregional recurrence-free survival.

indicating that IMPT reduces the volume of normal organs receiving low-dose radiation. The current study also builds on the prior literature by showing that the dosimetric advantages of IMPT did not translate to reductions in measured grade 3 or higher acute toxicities. On ordinal logistic regression, we found associations between the grade of GI toxicity and bowel bag receiving V1500 cGy, V3000 cGy, and V4500 cGy. However, on inspection of the box plots in Figure E1, the regression association seen for V1500 cGy and V3000 cGy is entirely affiliated with a small number of patients with grade 4 GI toxicity. In contrast, the box plot data show that patients with a higher grade of GI toxicity clearly had greater volumes of bowel bag receiving 4500 cGy or more. The similar observed toxicity of IMPT and IMRT is not surprising, then, because we did not find that IMPT reduced bowel bag V4500 cGy compared with IMRT.

Notably, IMPT significantly reduced the dose to bone marrow, but we did not detect a decrease in acute hematologic toxicity despite the association of these bone marrow metrics with toxicity in prior literature.[18,28,29] In fact, the IMPT group had significantly more febrile neutropenia. This is a novel finding that requires further investigation. Given that the majority of infections causing febrile neutropenia are owed to gut translocation of commensal bacteria, the study's finding could potentially be a result of greater intestinal wall damage at the distal edge of the proton beam resulting from higher LET as protons lose energy.[30,31]

This study's results are not consistent with those of a recent publication by Baumann et al of 391 patients receiving IMPT and 1092 receiving IMRT chemoradiation therapy for head and neck, lung, brain, esophagus, pancreas, rectal, anal, or gynecologic malignancies.[32] Baumann et al found that IMPT was associated with significantly less acute toxicity leading to unplanned hospitalizations among all disease sites combined. They did not report results for the subgroup of patients with anal cancer, although the number of patients in

that subgroup would be small (18 IMPT and 62 IMRT). The discordance of their results with those of the current study could be owed to several factors, the most likely being that the acute toxicity reductions they reported may have been associated with disease sites other than anal cancer. Baumann et al also used an endpoint of acute toxicities leading to hospitalization up to 90 days after the completion of chemoradiation therapy, whereas we recorded acute toxicities and hospitalizations during treatment and in the first 2 weeks after the completion of treatment. The current study's results could be biased in favor of IMRT if patients receiving IMPT were less likely to have late hospitalizations. We chose not to count acute complications or hospitalizations beyond 2 weeks posttreatment because IMPT patients frequently travel from farther away for treatment—sometimes internationally. We were concerned that this would potentially cause a measurement bias by underascertaining toxicities in the IMPT group. These methodological choices could explain the discordance between this study's findings and those of Baumann et al.

This study's results are concordant with the early pilot results presented by the group led by Wo et al, who found that toxicity from IMPT in patients with anal cancer was similar to that reported in prior RTOG studies.[7,12,13] The current study builds on the Wo trial, whose primary objective was to demonstrate feasibility of IMPT, by comparing IMPT to IMRT within a single study using a consistently applied set of metrics to assess outcomes. The similarity of findings from the current study and the trial by Wo et al lends credence to the argument that in anal cancer, toxicity is mainly the result of the radiation therapy dose to the target volume and the use of concurrent systemic therapy. Greater therapeutic gains and toxicity reduction may result from a tailored radiation therapy dose and systemic therapy regimens. These concepts are actively being tested in Eastern Cooperative Oncology Group (ClinicalTrials.gov Identifier: NCT04166318) and UK (ISRCTN88455282) trials.

Because the current study was retrospective, we were unable to control for unmeasured confounding variables. It was challenging to adjust for the fact that at the main centers, both IMRT and IMPT were offered, whereas at the community sites, only IMRT was offered. In addition, we did not collect patient-reported health-related quality-of-life data, which may detect adverse effects not adequately characterized by the physician-assessed CTCAE. Given the relatively short follow-up in a curative treatment paradigm with excellent long-term survival potential, late effect differences may not appear until after many more years of follow-up. Another limitation of this study is the heterogeneity of planning techniques between institutions, specifically with regard to robust optimization and multifield optimization.

Conclusions

In this multi-institutional cohort of patients with anal cancer, IMPT was not associated with decreased acute toxicity of grade 3 or greater compared with IMRT.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.adro.2021.100744.

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