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Clinical Investigation

Intensity Modulated Radiation Therapy Versus Conventional Radiation for Anal Cancer in the Veterans Affairs System

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Summary

The real-world effectiveness of intensity modulated radiation therapy in reducing acute toxicity during anal cancer treatment remains unclear. In a large sample of patients with anal cancer collected from the Veterans Affairs system, intensity modulated radiation therapy was associated with increased rates of timely and complete treatment delivery and lower rates of ostomy placement related to tumor recurrence or progression. Intensity modulated radiation therapy appears to give substantial short- and

Purpose: Compared with conventional radiation therapy, intensity modulated radiation therapy (IMRT) may reduce acute toxicity from anal cancer treatment, potentially leading to improved long-term outcomes. We analyze the effect of IMRT on short- and long-term outcomes among a large sample of US veterans.

Methods and Materials: From a national Veterans Affairs database, we identified 779 patients (n = 403 conventional radiation therapy, n = 376 IMRT) with locally advanced anal squamous cell carcinoma diagnosed between 2000 and 2015 and treated with concurrent chemoradiation therapy. Radiation treatment planning and dosimetric constraints were not standardized across patients. We analyzed the effect of IMRT on short-term outcomes (acute toxicity, treatment breaks, and incomplete chemotherapy) and long-term outcomes (survival and ostomy placement) in multivariable logistic regression, Fine-Gray, and frailty models, adjusting for potential confounders.

Results: IMRT was associated with decreased radiation treatment breaks ≥5 days (odds ratio [OR] 0.58; 95% confidence interval [CI] 0.37-0.91; $P = .02$), increased rates of receiving 2 cycles of mitomycin C chemotherapy (OR 2.04; 95% CI 1.22-3.45; $P = .007$), increased rates of receiving 2 cycles of any chemotherapy (OR 3.45; 95% CI 1.82-6.25; $P < .001$), and decreased risk of ostomy related to tumor recurrence or progression (subdistribution hazard ratio 0.60; 95% CI 0.37-0.99; $P = .045$). IMRT was not associated with a decrease in grade 3 to 4 hematologic toxicity ($P = .79$), hospitalization for gastrointestinal toxicity ($P = .59$), or cancer-specific survival ($P = 0.18$).

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long-term benefits in a real-world setting.

Conclusions: Among a large sample of US veterans with anal cancer, IMRT was associated with higher rates of receiving 2 chemotherapy cycles, decreased radiation treatment breaks, and decreased rates of ostomy placement. IMRT appears to offer substantial benefits over conventional radiation therapy for patients undergoing concurrent chemoradiation therapy for anal cancer.

Introduction

Intensity modulated radiation therapy (IMRT) has gained popularity among radiation oncologists as a technique for delivering highly conformal radiation doses to treatment volumes while decreasing the dose to normal tissue and lessening the toxicities of radiation (1, 2). In anal cancer, adoption of IMRT has been encouraged by the substantial hematologic, gastrointestinal, and dermatologic toxicities of combined chemotherapy and radiation treatment. Retrospective studies comparing IMRT and conventional conformal radiation therapy (RT) have suggested decreased hospitalization and toxicity benefits (1, 3-7). A phase 2 trial (Radiation Therapy Oncology Group [RTOG] 0529) comparing dose-painted IMRT with a historical conventional radiation arm did not reach its primary endpoint of lower combined gastrointestinal and genitourinary toxicity, although the investigators did find improvements in grade 2+ hematologic toxicity and grade 3+ dermatologic or gastrointestinal toxicity (2).

In RTOG 0529, 81% of IMRT plans had protocol violations on prospective review, suggesting that the real-world toxicity benefits of IMRT may be tempered by errors in the complex treatment planning and delivery process (2). The purpose of this study was to evaluate the real-world comparative effectiveness of IMRT and conventional RT in anal cancer for a range of short- and long-term outcomes.

Methods and Materials

Data source

We identified patients with anal cancer from the Veterans Affairs (VA) Informatics and Computing Infrastructure (VINCI). VINCI is a comprehensive informatics platform that allows researchers access to patient-level electronic health record information and administrative data for all veterans within the VA health care system. VINCI incorporates tumor registry data uploaded from individual VA sites; these data are gathered at individual VA medical centers by trained registrars according to standard protocols issued by the American College of Surgeons (8). Although some VA sites have maintained tumor registry operations since the 1990s, all VA sites began collecting registry data after a VA-wide directive in 1999. These data include veterans who are treated at non-VA facilities if they received any care at a VA facility over the course of their illness. This study was approved by the VA San Diego Institutional Review Board.

Patient cohort and treatment variables

We included patients with nonmetastatic, American Joint Committee on Cancer stage I to III (9) anal squamous cell carcinoma who received diagnoses between 2000 and 2015 and were treated with chemoradiation. Patients were categorized as having received chemoradiation if chemotherapy was initiated within 2 weeks of the radiation start date. We obtained chemotherapy information via VA pharmacy records, bar code administration records, intravenous infusion records, and clinical orders.

Radiation dose and fractionation were obtained via manual review of tumor registry data and clinical notes. Radiation treatment planning and dosimetric constraints were not standardized across patients because of local practice patterns; dosimetric data were not available for review. The delivery of IMRT was identified with Common Procedural Terminology (CPT) codes for either IMRT planning or treatment delivery during the course of radiation. Patients without IMRT were assumed to have received 2-dimensional or 3-dimensional conformal RT and were combined into the conventional RT study group. Radiation modality for those with missing CPT codes (15% of the study cohort) was determined with chart review.

Covariates

Variables obtained through VA tumor registry data included tumor stage, nodal stage, age at diagnosis, race, year of diagnosis, history of malignancy, employment, and body mass index (BMI). Pretreatment positron emission tomography scan was determined through inpatient and outpatient CPT codes. Comorbidities were ascertained through inpatient and outpatient International Classification of Diseases (ICD)-9/10 diagnosis codes; comorbidities were included in the calculation of the Charlson Comorbidity Index if the diagnosis code was associated with at least 1 inpatient admission or 2 outpatient visits within 1 year before the date of diagnosis (10-12). For HIV status, patients were defined as HIV-positive if they had an ICD-9/10 diagnosis code for AIDS or HIV infection any time before the date of cancer diagnosis plus 6 months, to include HIV workup started at the time of cancer diagnosis. ICD-9 codes included

042.X-044.X and V08.X; ICD-10 codes included B20.X-B24.X and Z21.X (10, 13). ZIP code–level median income and education were obtained through the American Community Survey 5-year estimates.

Outcomes

Short-term outcomes included receipt of 2 cycles of chemotherapy, radiation treatment breaks, grade 3 to 4 hematologic toxicity, and hospitalization for gastrointestinal toxicity. The standard course of chemotherapy for anal cancer includes 2 cycles of chemotherapy delivered concurrently with radiation (14). Patients were defined as having completed 2 chemotherapy cycles if they received a second chemotherapy infusion within 3 to 6 weeks of the first cycle. Missed radiation treatment days were calculated by subtracting the number of radiation fractions from the number of weekdays (minus federal holidays) throughout the radiation course. Acute hematologic toxicities (leukopenia, neutropenia, thrombocytopenia, or anemia within 90 days of treatment start) were assessed through VA laboratory data using Common Terminology Criteria for Adverse Events (v. 4.0) criteria. Hospitalization within 90 days of treatment at VA and non-VA hospitals was obtained through inpatient admission records. Reason for admission was determined by manual review of the admitting diagnosis or, if this was not available, review of ICD-9/10 diagnosis codes associated with the admission.

Long-term outcomes included survival and ostomy placement. Survival outcomes included anal cancer–specific mortality, non–anal cancer mortality, and all-cause mortality. Cause of death was obtained through the National Death Index (98% of death data), and missing values were supplemented with tumor registry data (2%). Ostomy placement (colostomy or ileostomy) and reason for placement (related to treatment toxicity or tumor recurrence or progression [15]) were determined through manual chart review. Patients with ostomies before treatment were excluded from the ostomy analysis.

Statistical analysis

Descriptive statistics of patient, tumor, and treatment characteristics were stratified by whether patients received IMRT or conventional radiation. Differences in patient characteristics between the IMRT and conventional radiation groups were determined with χ^2 tests for categorical variables and Student t tests for continuous variables. We used both unadjusted and multivariable adjusted analyses when assessing the impact of IMRT on short- and long-term outcomes. Logistic regression models were used to determine the impact of IMRT on short-term outcomes, including treatment-related outcomes and acute toxicity. The impact of IMRT on long-term ostomy placement was assessed with Fine-Gray competing risk analyses to account for the competing risk of mortality. Each analysis was performed on the subset of patients for whom outcome data were available, ranging from 82% to 100% of the overall sample.

With the cause-specific survival analysis, we hypothesized that selection bias resulting from unmeasured variables could influence the impact of IMRT on survival. To address this issue, we used an individual frailty model to help account for unmeasured covariates in our cause-specific survival analysis (16). The individual frailty model posits a patient-specific random effect (frailty) in the Cox model that acts multiplicatively on the baseline hazard. Frailty is related to the patient's underlying predilection to experience the event, and accounting for this underlying predilection has been proposed to help account for the effects of unobserved covariates (16-18). We assumed a log-normal distribution for the random frailty variable (19). To test the robustness of our survival analysis, we conducted a secondary instrumental variable (IV) analysis (20, 21), which represents an additional technique to address the issue of unmeasured covariates. Methodological details and results of the IV analysis are shown in the supplementary materials (available online at www.redjournal.org).

All variables in the multivariable models were chosen a priori and included radiation modality, pretreatment positron emission tomography scan, tumor stage, nodal stage, Charlson Comorbidity Index (10, 11), age at diagnosis, race, year of diagnosis, mitomycin C chemotherapy, history of malignancy, ZIP code median income, ZIP code education, BMI, sex, and employment status. Because of a low number of events in the cause-specific ostomy regressions, to prevent overfitting we included only radiation modality, tumor stage, nodal stage, Charlson Comorbidity Index, and BMI in the models. All P values were 2-sided. Statistical analyses were performed with SAS (v. 9.4) (SAS Institute, Cary, NC).

Results

Patient characteristics

The overall sample included 779 patients, including 403 treated with conventional RT and 376 treated with IMRT (Table 1). IMRT patients tended to have higher stage disease at presentation (40% stage 3 vs 27% for conventional RT, $P < .001$), with the largest differences in nodal stage (28% N2 or N3 in IMRT vs 18% in conventional RT, $P = .001$). Both groups received similar cumulative radiation doses, although the IMRT group was more likely to receive a chemotherapy regimen that included mitomycin C chemotherapy (88% vs 72%, $P < .001$). IMRT use increased steadily over the study period, with no patients receiving IMRT before 2004 and up to 89% receiving IMRT in 2012 to 2015. Median follow-up for the sample was 5.9 years.

Table 1 Characteristics of the sample

Covariate	Conventional RT	IMRT	*P*
Sample size (n [%])	403 (52)	376 (48)	-
Age at diagnosis, y (mean, SD)	60 (10)	62 (9)	.008
Race (n [%])			
White	333 (83)	315 (84)	.52
Black	60 (15)	48 (13)	
Other	10 (2)	13 (3)	
Male (n [%])	377 (94)	340 (90)	.11
ZIP code percent with high school diploma (mean [SD])	85 (8.5)	85 (7.8)	.33
ZIP code median income, in $1000 (mean [SD])	49 (19)	49 (16)	.92
Unemployed (n [%])	221 (55)	188 (50)	.18
Body mass index (mean [SD])	25 (5)	26 (6)	<.001
HIV positive (n [%])	83 (21)	76 (20)	.89
Charlson comorbidity index (n [%])			
0	223 (55)	198 (53)	.19
1	62 (15)	56 (15)	
2	28 (7)	43 (11)	
≥ 3	90 (22)	79 (21)	
Clinical stage (n [%])			
I	65 (16)	51 (14)	<.001
II	229 (57)	173 (46)	
III	109 (27)	152 (40)	
Tumor stage (n [%])			
1	73 (18)	63 (17)	.75
2	202 (50)	180 (48)	
3	107 (27)	110 (29)	
4	21 (5)	23 (6)	
Nodal stage (n [%])			
0	302 (75)	234 (62)	.001
1	28 (7)	35 (9)	
2	41 (10)	53 (14)	
3	32 (8)	54 (14)	
History of prior malignancy (n [%])	58 (14)	69 (18)	.13
Mitomycin C chemotherapy (n [%])	291 (72)	330 (88)	<.001
Year of diagnosis (n [%])			
2000-2003	121 (30)	0 (0)	<.001
2004-2007	169 (42)	40 (11)	
2008-2011	88 (22)	143 (38)	
2012-2015	25 (6)	193 (51)	
Cumulative radiation dose, Gy (mean [SD])	53.1 (8.3)	53.5 (6.9)	.47
PET scan (n [%])	66 (16)	186 (49)	<.001

Abbreviations: IMRT = intensity modulated radiation therapy; PET = positron emission tomography; RT = radiation therapy.

Short-term outcomes

Eight percent of patients in the IMRT group did not receive a second cycle of any chemotherapy, compared with 21% in the conventional RT group (Table 2). Among patients receiving mitomycin C, 20% of IMRT patients did not receive 2 cycles of mitomycin C chemotherapy versus 49% of conventional RT patients. Overall, 19% of IMRT patients and 43% of conventional RT patients did not complete 2 full cycles of chemotherapy. The association between IMRT and receipt of 2 chemotherapy cycles persisted on multivariable analysis (Table 2). We found that IMRT patients had a decreased likelihood of requiring a radiation treatment break of greater than 5 days (hazard ratio [HR] 0.58; 95% confidence interval [CI] 0.37-0.91; $P = .02$) and at trend level for breaks greater than 10 days (HR 0.56; 95% CI 0.32-1.00; $P = .05$). IMRT was not associated with acute grade 3 to 4 hematologic toxicity or hospitalization for gastrointestinal toxicity. In further analyses, we did not find an association between IMRT and acute grade 3 to 4 hematologic toxicity within 3 weeks of the first chemotherapy cycle (HR 0.84; 95% CI 0.53-1.32; $P = .44$) in the subset of patients who received 2 cycles of mitomycin C (HR 0.93; 95% CI 0.51-1.73; $P = .83$) or after controlling

Table 2 Results of univariable and multivariable models for short-term outcomes and ostomy placement

	Events N (%)		Unadjusted analysis		Adjusted analysis	
Short-term outcome	Conventional RT	IMRT	Odds ratio for IMRT (95% CI)	*P* value	Odds ratio for IMRT (95% CI)	*P* value
Radiation treatment interruption						
≥5 days	128 (41)	94 (29)	0.57 (0.41-0.80)	.001	0.58 (0.37-0.91)	.02
≥10 days	62 (20)	45 (14)	0.64 (0.42-0.97)	.04	0.56 (0.32-1.00)	.05
Failure to complete second cycle of chemotherapy						
Mitomycin C	136 (49)	53 (20)	0.25 (0.17-0.37)	<.001	0.49 (0.29-0.82)	.007
Any chemotherapy	73 (21)	25 (8)	0.32 (0.20-0.52)	<.001	0.29 (0.16-0.55)	<.001
Hospitalization for GI toxicity	51 (13)	45 (12)	0.90 (0.58-1.38)	.62	0.85 (0.47-1.54)	.59
Acute grade 3-4 hematologic toxicity	150 (40)	162 (47)	1.35 (1.00-1.81)	.048	1.06 (0.70-1.61)	.79
Long-term outcome			SDHR (95% CI)	*P* value	SDHR (95% CI)	*P* value
Ostomy placement						
Treatment related	14 (3)	10 (3)	0.95 (0.42-2.18)	.91	1.03 (0.44-2.39)	.95
Tumor related	50 (12)	26 (7)	0.62 (0.39-1.01)	.05	0.60 (0.37-0.99)	.045

Abbreviations: CI = confidence interval; GI = gastrointestinal; IMRT = intensity modulated radiation therapy; SDHR = subdistribution hazard ratio; RT = radiation therapy.

Multivariable models adjusted for IMRT, HIV status, pretreatment positron emission tomography, tumor stage, nodal stage, Charlson Comorbidity Index, age at diagnosis, race, year of diagnosis, mitomycin C chemotherapy, history of malignancy, ZIP code median income, ZIP code education, body mass index, sex, and employment status. The ostomy analyses adjusted for tumor stage, nodal stage, Charlson Comorbidity Index, and body mass index.

for receipt of 2 chemotherapy cycles (HR 1.08; 95% CI 0.69-1.67; $P = .74$).

Long-term outcomes

In the unadjusted analyses, IMRT was associated with lower overall, anal cancer, and non−anal cancer mortality (Table 3), although after adjustment in the frailty model, the associations between IMRT and mortality were nonsignificant (all $P > 0.05$). Similar results were found in the instrumental variable analysis (Table E1; available online at www.redjournal.org). The 5-year tumor-related ostomy rate was 7.5% in the IMRT group and 11% in the conformal radiation group. After adjustment, IMRT was associated with 40% reduced hazard of tumor-related ostomy placement (HR 0.60; 95% CI 0.37-0.99; $P = .045$) (Table 2; Fig. 1). We found no difference in treatment-related ostomy placement between IMRT and conformal radiation.

Discussion

In this study of 779 US veterans with anal cancer, we found that IMRT was associated with fewer radiation treatment breaks, increased rates of receiving 2 cycles of chemotherapy, and a lower risk of tumor-related ostomy placement, although there was no difference in acute hematologic and gastrointestinal toxicity or long-term survival outcomes. These results suggest that, in a real-world sample of patients with anal cancer, IMRT improves

Table 3 Results for survival outcomes

	5-year cumulative incidence (%)		Unadjusted analysis		Adjusted analysis	
Outcome	Conventional RT	IMRT	Hazard ratio for IMRT (95% CI)	*P* value	Hazard ratio for IMRT (95% CI)	*P* value
Anal cancer mortality	21.4%	12.7%	0.55 (0.38-0.79)	.001	0.72 (0.45-1.17)	.18
Overall mortality	45.3%	25.5%	0.56 (0.44-0.71)	<.001	0.89 (0.66-1.21)	.46
Non−anal cancer mortality	23.9%	12.8%	0.44 (0.31-0.62)	<.001	0.97 (0.62-1.52)	.90

Abbreviations: CI = confidence interval; GI = gastrointestinal; IMRT = intensity modulated radiation therapy; RT = radiation therapy.

Multivariable models adjusted for IMRT, HIV status, pretreatment positron emission tomography, tumor stage, nodal stage, Charlson Comorbidity Index, age at diagnosis, race, year of diagnosis, mitomycin C chemotherapy, history of malignancy, ZIP code median income, ZIP code education, body mass index, sex, and employment status.

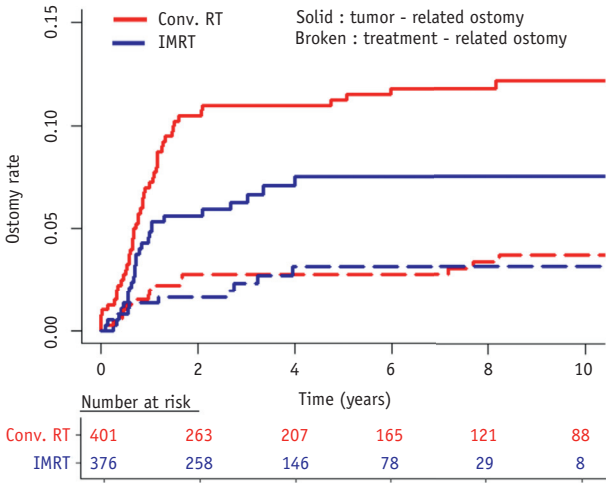

Fig. 1. Rates of tumor- and treatment-related ostomy by radiation group. *Abbreviations*: conv. RT = conventional radiation therapy; IMRT = intensity modulated radiation therapy.

the ability of patients to receive timely and complete chemoradiation therapy and may reduce the need for ostomy placement.

RTOG 05292 was a single-arm phase 2 trial comparing toxicity outcomes between dose-painted IMRT and a historical comparator arm of conventional RT; this trial represents the most well-powered prospective data on IMRT in anal cancer to date. In RTOG 0529, there was a trend toward decreased radiation treatment breaks and a significant difference in overall duration of treatment; similarly, we found that IMRT patients had fewer ≥5-day treatment breaks than patients receiving conventional RT (29% vs 41%). Reducing treatment breaks appears to be important for improving local control (22, 23), although the long-term results of RTOG 92-08 suggested a more ambiguous effect on survival (24). Our finding is also consistent with a number of primarily retrospective studies that showed a low frequency of treatment breaks with IMRT (3-5) and with a recent report suggesting a trend toward shorter and fewer treatment breaks with IMRT (25). Compared with the findings of RTOG 0529, we observed a slightly higher rate of incomplete chemotherapy courses among IMRT patients (19% in our study vs 16% in RTOG 0529), likely reflecting differences in practice and patient characteristics between a clinical trial setting and real-world practice. We found that IMRT was associated with a higher proportion of patients receiving 2 cycles of chemotherapy, a finding with important prognostic implications, given the proven benefit of concurrent chemotherapy (26, 27). We found a lower risk of tumor-related ostomy placement among IMRT patients, which might be attributable in part to higher chemotherapy completion rates, given randomized data showing an improvement in colostomy-free survival with concurrent chemotherapy (27). Finally, we found no difference in survival outcomes after multivariable adjustment, consistent with prior data that have not demonstrated a large survival improvement for IMRT (6, 7, 25).

We found no difference in hematologic or gastrointestinal toxicity between IMRT and conventional RT groups. This stands in contrast to the results from RTOG 0529, which found lower grade 2+ hematologic and grade 3+ gastrointestinal toxicity for IMRT, along with other retrospective studies that have shown similarly low rates of acute toxicity with IMRT (1-7). There are multiple potential explanations for this discrepancy. Chemotherapy is a primary contributor to treatment toxicity, so the increased rate of receiving 2 chemotherapy cycles among IMRT patients may have obscured the effect of IMRT in our analysis. However, in sensitivity analyses, we did not find that IMRT reduced toxicity immediately after the first chemotherapy cycle among the subset of patients who received 2 cycles and when controlling for receipt of 2 chemotherapy cycles. Another potential explanation is that the toxicity benefit of IMRT might be dependent on technically correct planning and delivery, which could be questionable in a real-world cohort, given the complexities of IMRT planning. As evidence of this complexity, 81% of submitted IMRT plans needed revision in RTOG 0529. Unlike in RTOG 0529, in this observational study, there was no standardized set of dosimetric guidelines limiting dose to the gastrointestinal tract or bone marrow, and dosimetric data were not available for review. The resulting variability in treatment planning may help explain the lack of observed toxicity benefit with IMRT.

Our study is subject to several important limitations. As a retrospective analysis, our conclusions are likely subject to selection bias and confounding by indication; although we attempted to address this limitation by including a wide range of measured covariates and using analytic techniques, such as the frailty model and instrumental variable analysis to account for unmeasured covariates, the potential for residual confounding remains. We were unable to review IMRT plans to assess quality, although our study included more granular and extensive radiation data than other comparable retrospective analyses (7). As IMRT use increased over the study period, our analyses may be subject to confounding by changing practice patterns or standards of care over time, although we controlled for year of diagnosis in the analysis. A subset of patients may have been planned for only 1 cycle of 5-fluorouracil/mitomycin C, and we were unable to account for these patients in our analysis; similarly, we were unable to account for planned versus unplanned radiation treatment breaks, and we could not differentiate treatment noncompliance from treatment breaks. Because of the VA setting, our study population was 92% male and thus may not generalize to the broader population of patients of both sexes with anal cancer. The VA also provides social and supportive benefits to veterans that may be less readily available to patients outside the VA; our results regarding treatment adherence and completion must therefore be generalized with caution to non-VA populations. Finally, we had no data on grade 1 to

2 toxicities or dermatologic toxicity, which may differ between IMRT and conventional RT.

Conclusions

In summary, we show that, compared with conventional RT, IMRT is associated with decreased radiation treatment breaks, increased receipt of 2 chemotherapy cycles, and decreased ostomies resulting from tumor recurrence or progression, although its effect on acute toxicity and survival outcomes is unclear. These data support the short-term and potentially long-term benefit of IMRT, although additional data are needed regarding real-world quality assurance of IMRT planning and delivery.

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