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Intensity-modulated Radiation Therapy for Anal Cancer
Results From a Multi-Institutional Retrospective Cohort Study

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Objectives: To assess toxicity and efficacy of intensity-modulated radiation therapy (IMRT) for anal cancer.

Methods: Records of 152 patients were reviewed retrospectively from multiple institutions. Data on disease control and toxicity were collected as well as patient and treatment characteristics. Acute (< 6 mo) and late (≥ 6 mo) severe toxicity (grade ≥ 3) were graded. Four patients were excluded due to the presence of metastatic disease or stage TX. Late toxicity data were available for 120 patients.

Results: Median cumulative IMRT dose was 51.25 Gy (median, 28 fractions). All but 2 patients received chemotherapy. With median follow-up of 26.8 months, local control at 3 years was 87%, worse for patients with T3-T4 than T1-T2 disease on univariate analysis (79% vs. 90%; $P = 0.04$). Regional control, distant control, and overall survival were 97%, 91%, and 87%, respectively, at 3 years. Nodal status was associated with regional control, distant control, and overall survival ($P < 0.01$ for each). Most common severe acute toxicity was hematologic (41%), skin (20%), and gastrointestinal tract (11%). Two grade 5 toxicities occurred (hematologic and gastrointestinal tract). Severe late toxicity affected skin (1%) and gastrointestinal tract (3%).

Conclusions: IMRT with chemotherapy resulted in excellent local control. Although T stage predicted worse local control, most T3-T4 disease was controlled with IMRT. Nodal status predicted regional and distant control and overall survival. Severe toxicity was acceptable.

Key Words: anal cancer, chemoradiotherapy, chemotherapy, combined modality, intensity-modulated radiation therapy, squamous cell carcinoma

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Chemoradiation remains the standard of care for most patients with squamous cell carcinoma of the anal canal.[1–4] Currently, the use of concomitant fluorouracil and mitomycin C along with conventional external-beam radiotherapy can avoid colostomy in the majority of patients, but this approach is not without toxicity.[2] Intensity-modulated radiation therapy (IMRT) has been used to improve the tolerability of this treatment, with most series publishing favorable results.[5–10] One report has raised concern about the use of IMRT for anal cancer.[11] In this publication from a single institution, IMRT seemed to have a lower rate of local control (LC) than 3-dimensional conformal therapy. In this alarming report, the 1-year local recurrence rate was 28.6% for IMRT compared with 15.2% for 3-dimensional conformal therapy. Other institutions have shown excellent control rates with IMRT for anal cancer. To help clarify the role of IMRT for anal cancer, the current study focused on the combined experience of 6 tertiary-care academic medical centers with experience using IMRT to treat anal cancer.

METHODS

After institutional review board approval at each institution, data for patients who received IMRT as a component of treatment were reviewed retrospectively. Deidentified data were then compiled in a single database for analysis. Information included specifics regarding local, regional, and distant failure as well as the rate of colostomy after treatment. A total of 152 patients were identified. Some of these patients were described in an earlier report.[12] Four were excluded due to the presence of either metastatic disease (n = 2) or stage TX (n = 2). There was no standard follow-up procedure in these patients, but the timing and examinations were according to institutional preferences. Acute (< 6 mo) and late (≥ 6 mo) severe (grade ≥ 3) treatment-related toxicity was recorded. On an institutional basis, toxicity was considered severe if it met the criteria for a grade 3 through 5 events using the Radiation Therapy Oncology Group (RTOG) criteria or the Common Terminology Criteria for Adverse Events version 3.0. Data on late toxicity were available for 120 patients.

Treatment Details

All patients received IMRT-based treatment, with a median dose of 51.25 Gy (range, 4.32 to 61.20 Gy) in a median of 28 fractions (range, 2 to 34 fractions). The median elapsed treatment time for radiation was 40 days. All but 2 patients received chemotherapy. The most common chemotherapy regimen was fluorouracil plus mitomycin C (n = 113), followed by fluorouracil and cisplatin (n = 17), fluorouracil, cisplatin, and mitomycin C (n = 6), fluorouracil, cisplatin, and cetuximab (n = 5), fluorouracil alone (n = 3), capecitabine and mitomycin C (n = 1), and capecitabine and cisplatin (n = 1). One patient received only a dose of 432 cGy in 2 fractions because of grade 5 hematologic toxicity. Another patient only received 900 cGy in 5 fractions because of grade 5 gastrointestinal toxicity.

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There was no uniform technique for IMRT, and no standard dose constraints were used, across the centers included here. In general, organs at risk included small bowel, large bowel, femurs, external genitalia, and bladder. Bone marrow constraints were used at the discretion of the treating physician. At Mayo Clinic, all patients were treated with a single IMRT plan using a simultaneous integrated boost. The usual field arrangement consisted of 9 static 6 MV IMRT beams. There was no standard for defining target volumes, although generally the gross disease (with a minimum margin ranging from 1 to 2 cm for the high-dose planning target volume [PTV]) and the elective areas (anal canal, perirectal, presacral, external iliac, internal iliac, and inguinal nodal regions) were covered for all stages of disease. The majority of patients were treated in the supine position, and daily imaging with an on-board kV imaging device was used in 50% of cases.

At the University of Alabama at Birmingham, patients were treated with both simultaneous integrated boost (n = 13) and sequential boost (n = 16) composed of 7 to 9 fields of intensity-modulated 6 MV photons. The high-dose target volume included gross tumor and involved lymph nodes; the low-dose volume included clinically or radiographically uninvolved nodal volumes (perirectal, presacral, external iliac, internal iliac, and inguinal nodal basins) at presumed risk for subclinical involvement. All patients were treated in the supine position.

At the University of California, San Diego, patients were treated with intensity-modulated pelvic-inguinal radiation therapy followed by a sequential IMRT boost. The prescription dose for the pelvic-inguinal plan was 30.6 to 45.0 Gy in 1.8 Gy daily fractions. The true pelvis was treated with 45.0 Gy in 1.8 Gy daily fractions. Gross tumor plus margin was treated with 50.4 to 54.0 Gy total in 1.8 Gy daily fractions. The usual field arrangement consisted of 7 to 9 static 6 MV and/or 15 MV fields. The nodal clinical target volume (CTV) was defined as the gross tumor, anal canal, perirectal, presacral, inguinal, external iliac, and internal iliac nodes. Nodal regions were contoured as the fatty or perivascular region plus a 3 to 5 mm margin. Gross tumor volume was contoured and expanded by 1 cm, excluding muscle and bone and areas extending outside the skin, to create the boost CTV. The CTV was expanded by 7 mm to generate the PTV, excluding extension outside the skin. All patients were simulated and treated in the supine position using custom immobilization. All patients underwent daily setup verification with gantry-mounted kV imaging.

At Memorial Sloan-Kettering Cancer Center, all patients were treated with a single IMRT plan using a simultaneous integrated boost. The usual field arrangement consisted of 7 static mixed energy 6 and 15 MV beams. The gross tumor volume included the primary tumor and involved nodes identified on physical examination, endorectal ultrasound, computed tomography, and positron-emission tomography. The elective nodal regions were defined on the basis of the RTOG anorectal atlas and were covered for all stages of disease. The majority of patients were treated in the prone position with a full bladder.

At the Cancer Institute of New Jersey, patients were treated with a single IMRT plan using the RTOG protocol 0529 paradigm, doses, and CTV/PTV volumes and expansions, with a simultaneous integrated boost. A total of 7 to 9 coplanar beams of mixed 6 and 15 MV energies were used. Patients were all treated in the supine position with daily on-board kV imaging.

The typical regimen at Oregon Health & Science University was a 30-fraction regimen treating gross disease and elective volumes at different doses per fraction in a simultaneous integrated boost. The primary tumor and nodes >3 cm were treated at 1.8 Gy per day, whereas nodes <3 cm received 1.68 Gy per day and elective volumes received 1.5 Gy per day. Dose limitations to the femurs, large bowel, small bowel, and external genitalia were similar to those specified in the RTOG 0529 protocol.

TABLE 1. Patient Characteristics (N = 148)

Characteristics	Value*
Age, median (range) (y)	56 (32-86)
IMRT dose, median (range) (Gy)	51.25 (4.32-61.20)
TNM category (N)	
T1	28 (19)
T2	79 (53)
T3	29 (20)
T4	12 (8)
N0	77 (52)
N1	40 (27)
N2	19 (13)
N3	12 (8)

*Values are number (percentage) unless indicated otherwise.
IMRT indicates intensity-modulated radiation therapy.

Statistical Analysis

The Kaplan-Meier method was used to estimate overall survival (OS), LC, regional control, distant control, and colostomy-free survival (CFS). LC, regional control, and distant control were defined as the time to local, regional, or distant relapse, respectively. CFS was defined as the time to the date of a colostomy procedure. The association of different patient, disease, and treatment details on disease outcomes was tested using log-rank analysis. Cox regression analysis was used to perform a multivariate analysis. Significance was declared at $P < 0.05$. Calculations were performed using JMP software (version 8.0 statistical package; SAS Institute Inc.).

RESULTS

Patient Characteristics

The median age was 56 years (range, 32 to 86 y). Staging is shown in Table 1. Median follow-up was 26.8 months (range, 0 to 74 mo) for all patients and 27.9 months (range, 1 to 70.1 mo) for living patients.

OS

The Kaplan-Meier estimate of OS is shown in Figure 1. For all 148 patients, the 3-year OS was 87% (95% CI, 79%-92%). Higher nodal stage significantly predicted worse OS ($P < 0.01$). The 3-year OS was 90% (95% CI, 79%-96%) for

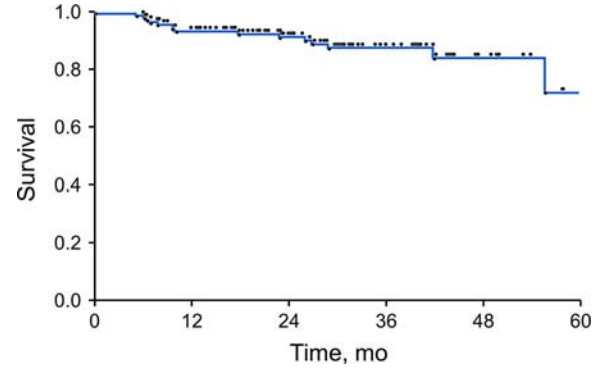

FIGURE 1. Overall survival. The 3-year overall survival was 87%.

TABLE 2. Multivariate Analysis of Patient Outcomes

Variables	RR for Death (95% CI)	*P*	RR for LF (95% CI)	*P*	RR for Colostomy (95% CI)	*P*
Dose*	1.51 (0.41-3.28)	0.79	1.11 (0.37-3.27)	0.85	1.27 (0.33-5.53)	0.73
N stage†	1.88 (1.16-3.10)	0.01	1.24 (0.72-2.06)	0.42	0.88 (0.41-1.68)	0.71
T stage‡	0.98 (0.33-2.81)	0.97	2.39 (0.81-7.08)	0.11	4.00 (1.03-17.09)	0.04
RT duration§	0.60 (0.21-1.71)	0.34	0.36 (0.10-1.08)	0.07	0.62 (0.15-2.35)	0.48

*RR calculated as a risk of dose $\geq$51.25 versus <51.25 Gy.
†RR calculated as risk of increasing by an N stage.
‡RR calculated as a risk of T3-T4 versus T1-T2.
§RR calculated as a risk of RT duration >40 versus $\leq$40 days.
CI indicates confidence interval; LF local failure; RR, relative risk; RT, radiation therapy.

patients with N0 status; 91% (95% CI, 77%-97%) for N1; 92% (95% CI, 60%-99%) for N2; and 48% (95% CI, 19%-79%) for N3. On multivariate analysis, N stage was found to be associated with a higher risk of death (Table 2; $P=0.01$).

Disease Control

At 3 years, LC was estimated at 87% (95% CI, 80%-92%) (Fig. 2). Higher doses (>51.25 Gy) did not correlate with improved LC ($P=0.89$). Similarly, no significant difference was seen for patients with median radiation therapy duration >40 days compared with those who had radiation therapy lasting $\leq$40 days ($P=0.10$). However, T stage was found to be significantly associated with LC on univariate analysis (Fig. 3). For patients with T1-T2 lesions, 3-year LC was 90% (95% CI, 82%-95%) compared with 79% (95% CI, 63%-89%) for patients with T3-T4 disease ($P=0.04$). We were not able to show a significant association of T stage and local failure on multivariate analysis (Table 2; $P=0.11$).

Regional control for the entire group at 3 years was 97%. Nodal stage predicted nodal failure (Fig. 4; $P<0.01$), but there was no significant relationship with radiation dose or duration or type of chemotherapy. Similarly, distant control was 91% at 3 years and correlated with nodal stage ($P<0.01$). At 3 years, distant control was 97% (95% CI, 89%-99%) for patients with N0 disease, 97% (95% CI, 82%-100%) for N1, 87% (95% CI, 59%-97%) for N2, and 44% (95% CI, 18%-73%) for N3.

Toxicity

The most common acute severe toxicity was hematologic, found in 41% of patients (29 patients with grade 3, 1 with grade 4, and 1 with grade 5 toxicity). Severe acute gastrointestinal tract toxicity was 11% (15 with grade 3, 1 with grade 4, and 1 with grade 5), and severe acute skin toxicity was 20% (29 with grade 3 and 1 with grade 4). Severe late toxicity was uncommonly reported, with 3% gastrointestinal tract (2 with grade 3 and 1 with grade 4) and 1% skin (1 patient with grade 3 toxicity). There was no severe genitourinary toxicity in these patients.

CFS

The estimated CFS was 92% at 3 years (95% CI, 86%-96%). Patients with T3-T4 tumors had significantly worse 3-year CFS (84%; 95% CI, 68%-93%) than those with T1-T2 disease (96%; 95% CI, 90%-98%; $P=0.02$). In addition, the risk of colostomy was significantly worse for patients with higher T stage on multivariate analysis (Table 2; $P=0.04$). Even for patients with T4 tumors, the majority avoided colostomy at 3 years (74%; 95% CI, 43%-91%). There was no significant relationship between CFS and nodal status, duration of radiation, or radiation dose.

DISCUSSION

Chemoradiation is the most common initial treatment for patients with squamous cell carcinoma of the anal canal. IMRT represents an attractive means of delivering radiation to the tumor while decreasing dose to surrounding normal structures.

Long-term results using conventional radiotherapy with mitomycin C in the RTOG 9811 study showed a locoregional failure rate of 25% at 5 years.[2] There is now a growing body of literature on the use of IMRT for anal cancer.[5–11] IMRT may be a means to decrease toxicity while obtaining disease control. However, 1 report has raised concern about LC with use of this technique.[11] In this report by Vuong et al,[11] LC at 1 year was 71.4%, which contrasts with other data in the literature, noting an LC rate of 80% to 95% (estimated at 18 to 24 mo). The RTOG has completed a phase 2 trial of chemoradiation using IMRT, accruing 63 patients with anal cancer.[5,6] These

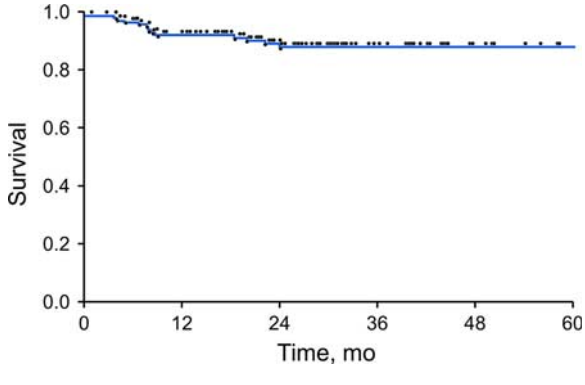

FIGURE 2. Local control. For all patients, the 3-year local control was 87%.

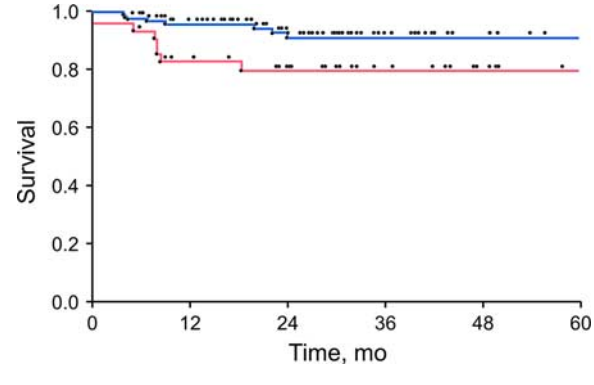

FIGURE 3. Local control according to T stage. Higher T stage predicted worse local control (79% vs. 90% at 3 y). T1-T2 is shown in blue and T3-T4 is shown in red.

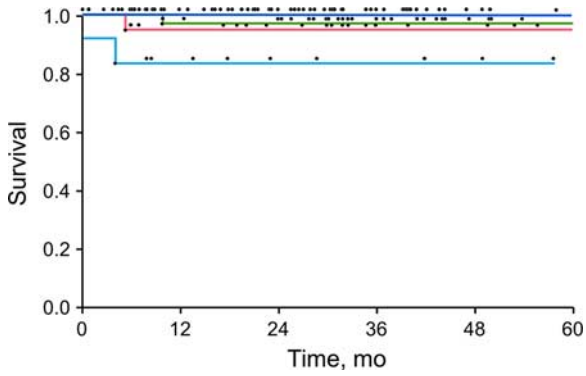

FIGURE 4. Regional control according to nodal stage ($P < 0.01$). Higher N stage predicted worse regional control. N0 is shown in dark blue, N1 in green, N2 in red, and N3 in light blue.

prospectively acquired data have been reported in an abstract form and have shown a 2-year LC rate of 80%. In addition, acute severe toxicity was 22% for gastrointestinal tract and 20% for skin. These findings seem to be an improvement from prior data using conventional techniques. Our data add to the current data by showing the efficacy of IMRT in a large patient sample. To our knowledge, this report represents the largest group of patients who received IMRT for squamous cell carcinoma of the anus.

In this report, LC for anal cancer was excellent using IMRT, with a control rate of 87% at 3 years. Thus, IMRT seems capable of achieving a high rate of control despite the concerning report by Vuong et al[11] and seems to maintain the results achieved with conventional therapy.[2] Although radiation dose did not predict LC, T stage did seem to have an impact on LC when comparing patients with T1-T2 disease (90%) and those with T3-T4 disease (79%) on univariate analysis. Although the risk of local failure with higher T stage was not statistically significant on multivariate analysis, this may have been due to the low number of events in our patients. Although there seemed to be a lower rate of control for patients with higher T stage, IMRT seemed to result in a high rate of control at 3 years, even for locally advanced disease. Bazan et al[13] also found a higher rate of local failure for patients with higher T stage. In addition, CFS was excellent at 92% at 3 years. Although patients with higher T stage had worse CFS, the majority of patients were able to avoid a colostomy.

In terms of toxicity, IMRT seems to have an acceptable rate of acute nonhematologic toxicity. Similar to the findings of RTOG protocol 0529, we found a relative low rate of acute severe nonhematologic toxicity. Acute severe gastrointestinal tract toxicity was only 12% and acute severe skin toxicity was 20% in our patients. In addition, the rate of severe late toxicity was low, with only 1% having severe skin toxicity and 3% having severe gastrointestinal tract toxicity. Others have found a low rate of acute nonhematologic toxicity using IMRT. In the report by Milano et al,[8] no acute grade 3+ nonhematologic toxicity was observed. In the multicenter experience of Salama et al,[10] the acute grade 3+ gastrointestinal tract and skin toxicities were 15.1% and 37.7%, respectively. Pepek et al[9] found an acceptable level of nonhematologic toxicity, with the most common acute severe event being diarrhea (9%). This finding was similar for the subset with squamous histologic characteristics (severe diarrhea in 10%, hematologic toxicity in 24%). Pepek et al[9] did not observe any severe acute dermatologic toxicity. The multicenter experience of Kachnic et al[7] similarly found IMRT to be well tolerated in terms of severe nonhematologic toxicity. Bazan et al[13] retrospectively compared a group of patients who received IMRT with a similar cohort of patients who received conventional radiotherapy. In that report, IMRT had a low rate of severe nonhematologic toxicity (21%) compared with conventional radiotherapy (65%).

In contrast to the reported literature on IMRT, conventional radiation has been associated with a high rate of toxicity. For example, the RTOG protocol 9811 had an acute nonhematologic toxicity rate of 61% for grade 3 and 13% for grade 4.[2] Late toxicities also continued to be a problem, at a rate of 11% for all grade 3 and grade 4 toxicities. In addition, grade 4 toxicity (any acute or late) was 23% in the mitomycin C arm of the RTOG protocol 8704/Eastern Cooperative Oncology Group protocol 1289, and the grade 5 toxicity was 3%.[4] In the recently reported preliminary results of the Cancer Research United Kingdom Anal Cancer Trial II, 61% nonhematologic toxicity was reported in the mitomycin C arm.[14]

The most common acute severe toxicity with IMRT in this report was hematologic (41%), and this is consistent with other reports using IMRT.[7–11] Mitomycin-based chemoradiation for anal cancer has been associated with high rates of hematologic toxicity. For example, RTOG 9811 reported a 61% rate of grade 3 to 4 toxicity in the mitomycin arm, and this was more common than in the nonmitomycin arm.[2] Thus, chemoradiation using either IMRT or conventional techniques can result in high rates of such toxicity. It may be possible in the future to improve the rate of severe hematologic toxicity using IMRT if attention is given to the bone marrow during radiation planning.[15–17]

The current study has several limitations. One of these limitations is the lack of specific details regarding radiation design and treatment. Thus, conclusions cannot be drawn from these data on the appropriate setup for patients, target volume delineation, boost technique, specific dose constraints for normal tissues, or other specifics of treatment with IMRT. In addition, the reasons for undergoing colostomy were not likely to be uniform. In addition, the choice of substituting potentially less myelosuppressive chemotherapy in place of mitomycin C was not based on uniform criteria. Although this is a large study of IMRT for anal cancer, it still has the weaknesses common to all retrospective reports. In addition, follow-up was short, at a median of 26.8 months. Despite these limitations, this study is one of the largest series of patients treated with IMRT for anal cancer. In addition, a factor common in the treatment of these patients is that they were all treated at large centers with experience in contouring and planning IMRT treatments and in managing hematologic toxicity. Nevertheless, there was no uniform approach to IMRT. Such heterogeneity may represent a more realistic estimate of what occurs in actual clinical practice.

In conclusion, IMRT seems to be safe and effective in the treatment of squamous cell carcinoma of the anal canal. T stage predicts LC, although the majority of patients had disease control with IMRT. Nodal status is a predictor of regional and distant control as well as OS in these patients.

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