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Outcomes after intensity-modulated compared with 3-dimensional conformal radiotherapy with chemotherapy for squamous cell carcinoma of the anal canal

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ABSTRACT

Purpose We report our institution's treatment techniques, disease outcomes, and complication rates after radiotherapy for the management of anal canal carcinoma with intensity-modulated radiotherapy (IMRT) and concurrent chemotherapy relative to prior cases managed with 3-dimensional conformal radiotherapy (3D-CRT).

Methods In a retrospective review of the medical records of 21 patients diagnosed with biopsy-proven stage I (23%), stage II (27%), or stage III (50%) squamous-cell carcinoma of the anal canal treated with curative chemotherapy and IMRT between July 2009 and December 2014, patient outcomes were determined. Results for patients treated with 3D-CRT by the same group were previously reported. The median initial radiation dose to the pelvic and inguinal nodes at risk was 45 Gy (range: 36–50.4 Gy), and the median total dose, including local anal canal primary tumour boost, was 59.4 Gy (range: 41.4–61.2 Gy). Patients received those doses over a median of 32 fractions (range: 23–34 fractions). Chemotherapy consisted of 2 cycles of concurrent fluorouracil–cisplatin (45%) or fluorouracil–mitomycin C (55%).

Results Median follow-up was 3.1 years (range: 0.38–6.4 years). The mean includes a patient who died of septic shock at 38 days. The 3-year rates of overall survival, metastasis-free survival, locoregional control, and colostomy-free survival were 95%, 100%, 100%, and 100% respectively. No patients underwent abdominoperitoneal resection after chemoradiotherapy or required diverting colostomy during or after treatment. Those outcomes compare favourably with the previously published series that used 3D-CRT with or without brachytherapy in treating anal canal cancers. Of the 21 patients in the present series, 10 (48%) experienced acute grade 3, 4, or 5 toxicities related to treatment.

Conclusions The recommended use of IMRT with concurrent chemotherapy as an improvement over 3D-CRT for management of anal canal carcinoma achieves a high probability of local control and colostomy-free survival without excessive risk for acute or late treatment-related toxicities.

Key Words Radiation oncology, anal carcinoma, intensity-modulated radiotherapy, 3-dimensional conformal radiotherapy

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INTRODUCTION

Anal canal cancer is an uncommon malignancy of the gastrointestinal tract, but its incidence in the United States is increasing[1]. The risk factors that are known to drive the development of this disease include an increased number of sexual partners, use of tobacco products, receptive anal intercourse, infection with the human papillomavirus, and immunodeficiency[2]. Squamous cell carcinoma is the most common subtype of anal canal cancer, followed by adenocarcinoma and cloacal cancer.

Historically, the treatment of anal canal cancer consisted primarily of abdominal perineal resection with permanent colostomy bag placement, achieving a 5-year

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overall survival rate of 57.8% for patients with squamous cell carcinoma[3]. That radical surgery was understandably associated with considerable morbidity and mortality. Norman Nigro and colleagues subsequently altered the paradigm for the management of this disease by showing the effectiveness of combined chemotherapy and radiation to avoid the need for abdominal perineal resection[4], allowing for preservation of sphincter function and avoidance of a colostomy.

Because numerous studies have validated the use of chemoradiation for anal canal cancer[5–7], in particular with 5-fluorouracil–mitomycin C (5FU–MCC)[8], the focus on the management of this disease has shifted toward reducing the significant toxicity seen with conventional radiotherapy (RT) techniques[6,7,9]. Intensity-modulated RT (IMRT) has since been shown in several retrospective and prospective studies to reduce grades 3, 4, and 5 toxicities while maintaining excellent overall and colostomy-free survival[10,11].

However, few studies have compared data for the outcomes and toxicities of IMRT with those of 3-dimensional conformal RT (3D-CRT) at a single institution. The aim of the present study was to compare the outcomes and toxicities experienced by a series of patients with anal canal carcinoma treated with IMRT and concurrent chemotherapy with the outcomes and toxicities experienced by patients treated with 3D-CRT as detailed in previously published results from our institution[12].

METHODS

Patient Demographics and Disease Characteristics

With the approval of our institution's institutional review board, we retrospectively reviewed the medical records for 21 patients diagnosed with biopsy-proven stage I (23%), stage II (27%), or stage III (50%) squamous-cell anal canal carcinoma and treated with curative chemotherapy and IMRT between July 2009 and December 2014. Patients who initially received IMRT at another institution, patients with distant metastases at the time of diagnosis, and patients who received a brachytherapy boost were specifically excluded. All patients were staged according to the 2010 guidelines from the American Joint Committee on Cancer[13]. Table I summarizes the characteristics of the patients included in the analysis.

TABLE I Patient demographics and disease characteristics

Characteristic	Value [*n* (%)]
Patients	21
Sex	
Men	9 (43)
Women	12 (57)
Cancer stage	
I	5 (24)
II	6 (29)
III	10 (48)
IV	0 (0)
Recurrent	0 (0)
HIV status	
Positive	1 (5)
Negative	20 (95)
Smoking status	
Smoker	13 (62)
Nonsmoker	8 (38)
Squamous cell histology	21 (100)
Pre-radiation surgery	1 (5)
Chemotherapy	20 (95)
5FU–cisplatin	9 (45)
5FU–mitomycin	11 (55)
Treatment breaks	
Yes	9 (43)
No	12 (57)

HIV = human immunodeficiency virus; 5FU = fluorouracil.

Treatment Characteristics

All analyzed patients underwent computed tomography–based treatment planning. Target volumes for IMRT were identified according to the Radiation Therapy Oncology Group (RTOG) consensus contouring atlas for all identifiable gross disease within the gross tumour volume and the iliac inguinal and iliac nodal regions at risk within the clinical target volume, plus planning target volume expansions consistent with motion management and image-guidance RT capacity at our institution[14]. Approved treatment plans met standard goals for target coverage and dose heterogeneity while minimizing dose to the normal rectum, small bowel, bladder, and femoral heads.

The median initial dose of radiation delivered was 45 Gy (range: 36–50.4 Gy), with the median dose including boost totalling 59.4 Gy (range: 41.4–61.2 Gy). Patients received those doses over a median of 32 fractions (range: 23–34 fractions).

All patients were treated with concurrent chemotherapy at the medical oncologist's discretion after consideration of the patient's comorbidities and goals of care. Chemotherapy consisted of either 2 cycles of concurrent 5FU–cisplatin (45%), or 5FU–MMC (55%). Unplanned treatment breaks occurred in 9 patients (43%), with 6 of the 9 episodes occurring in patients who received MMC chemotherapy. Table I summarizes the information.

Acute skin, hematologic, genitourinary, and gastrointestinal toxicities were assessed by the treating medical oncologist and radiation oncologist, and were scored using the *Common Terminology Criteria for Adverse Events* (version 4.03)[15]. Acute toxicities were defined as toxicities that the patient experienced within 90 days of starting RT, and late toxicities were defined as those that the patient experienced more than 90 days after completing RT. Patients were evaluated weekly by their treating radiation oncologists while they were undergoing RT and were assessed in

follow-up at 1, 3, and 6 months, and then every 6 months unless recurrence was identified.

In addition to blood chemistries and complete blood counts, all patients underwent surveillance positron-emission tomography and computed tomography when indicated. Complete response was defined as no local, regional, or distant disease at the time of follow-up based on physical and radiographic examinations. Partial response was defined as the presence of any remaining tumour burden. Distant failure was defined as tumour progression outside the previously treated pelvic field.

All statistical computations were performed using the SAS (version 9.4) and JMP (version 13) software applications (SAS Institute, Cary, NC, U.S.A.). Estimates of overall survival, metastasis-free survival, locoregional control, and colostomy-free survival were calculated according to the Kaplan–Meier product limit method.

RESULTS

Clinical Outcomes

The 3-year rates of overall survival, metastasis-free survival, locoregional control, and colostomy-free survival were 95%, 100%, 100%, and 100% respectively. At 4 years, the same rates were 83%, 100%, 100%, and 100% respectively. No patient underwent abdominoperineal resection after chemoradiotherapy, and no patient required diverting colostomy during or after treatment as of their last follow-up visit. Figure 1 presents the overall survival and metastasis-free survival curves.

Toxicities

Table II summarizes the recorded acute treatment-related toxicities. Most grades 1 and 2 toxicities were gastrointestinal (pain and diarrhea) or cutaneous (pain and desquamation). Of the 21 patients, 10 (48%) experienced grade 3, 4, or 5 toxicities in the acute period secondary to treatment. Of 2 patients (10%) who experienced infection categorized as hematologic toxicities, 1 received 23 fractions of radiation to a dose of 41.4 Gy, and 1 cycle of 5FU–MMC, but was hospitalized because of septic shock secondary to methicillin-resistant *Staphylococcus aureus* bacteremia. That patient died from the infection. Another 3 patients experienced neutropenic fever without a specific infection being identified. Grade 3 diarrhea occurred in 1 patient (5%), and grade 3 colitis, in 1. Neither gastrointestinal toxicity resulted in hospitalization. Grade 3 dehydration, resulting in hospitalization to correct the resulting metabolic derangements, occurred in 1 patient (5%). Grade 3 skin toxicities occurred in 2 patients (10%)—desquamation in both cases. In one of those cases, the patient presented to the hospital for evaluation and treatment. No apparent correlation was observed between the chemotherapy regimen and the rate of toxicity, although the sample size was probably not large enough to reveal such a relationship.

With respect to chronic toxicities, 2 patients (10%) experienced grade 2 gastrointestinal toxicities (diarrhea, abdominal pain). No patient experienced a chronic toxicity greater than grade 2. The most common grade 1 toxicities were diarrhea, abdominal pain, and urinary discomfort.

Treatment Breaks

The median duration of the unplanned treatment breaks that occurred in 8 patients (36%) was 5.5 days. In 3 of the 8 patients (38%), the break was a result of febrile neutropenia, with 1 patient experiencing an 84-day break between the initial RT dose and boost treatment on account of prolonged hospitalization in the intensive care unit. Skin desquamation, pain, and dehydration were all equally frequent causes of treatment breaks (25% each). After a treatment break, 1 patient (13%) discontinued RT and consequently received 55.8 Gy of the prescribed total dose of 59.4 Gy.

DISCUSSION

The aim of the present study was to report our institution's experience treating anal canal carcinoma with IMRT and concurrent chemotherapy and to compare it with our experience treating the same disease with 3D-CRT, as previously published[12]. In both studies, the distribution of patients was similar in terms of cancer stage, with the 3D-CRT study including more patients (69 vs. 21) because of the timespan of the study (1968–2005). Unlike the present investigation, in which 95% of patients underwent concurrent chemotherapy treatment, only 55% of the patients in the 3D-CRT study underwent chemotherapy. In both studies, similar proportions of patients received 5FU–MMC and 5FU–cisplatin. More than half the patients in the 3D-CRT study also received brachytherapy as a part of their treatment

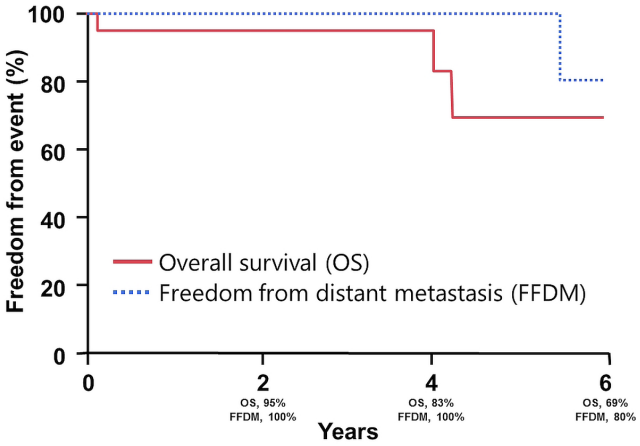

FIGURE 1 Kaplan–Meier curves for overall survival and metastasis-free survival in patients treated with intensity-modulated radiation therapy and chemotherapy for carcinoma of the anal canal at our institution.

TABLE II Acute treatment-related toxicities

Toxicity type	Patients affected [*n* (%)]	
	Grades 1–2	Grades 3–5
Dehydration	0 (0)	1 (5)
Gastrointestinal	5 (24)	2 (10)
Hematologic	0 (0)	5 (23)
Skin and subcutaneous tissue	5 (24)	2 (10)

(57%), but brachytherapy was an exclusion criterion in the present IMRT study. However, on multivariate analysis in the 3D-CRT study, local control, colostomy-free survival, overall survival, and distant metastasis-free survival were found not to be significantly determined by chemotherapy or brachytherapy administration. Thus, although treatment methods in the two investigations had differences, we believe that a useful comparison can still be made between the groups.

In the present IMRT group, the overall survival rate at 5 years was 69% compared with 71% in the 3D-CRT group. The 5-year local control and colostomy-free survival outcomes were, however, superior in the patients treated with IMRT compared with 3D-CRT (local control rate: 100% vs. 86%; colostomy-free survival rate: 100% vs. 74%). With respect to acute toxicities, more patients in the IMRT group than in the 3D-CRT group experienced grades 3–5 gastrointestinal (10% vs. 4%) and hematologic toxicities (23% vs. 13%). It is possible that, in the IMRT group compared with the 3D-CRT group, the acute toxicities were heightened because of greater use of concurrent chemotherapy. No patient treated with IMRT experienced late grades 3–5 toxicities, but 14% of the patients treated with 3D-CRT experienced late grades 3–5 gastrointestinal toxicities. Those data suggest that, compared with use of 3D-CRT, use of IMRT might be associated with a lower rate of late high-grade toxicities, which is particularly relevant to long-term quality of life for the patients. It is important to note that, in the present study, median follow-up is 3 years compared with the 5 years for the 3D-CRT study, and so it will be instructive to continue to watch the present patients for long-term sequelae that might not have yet developed.

To our knowledge, few published studies in anal canal carcinoma have analyzed differences in outcomes and toxicities between IMRT and 3D-CRT treatments performed at the same institution. In 2013, investigators at the H. Lee Moffitt Cancer Center and Research Institute (Tampa, FL, U.S.A.) published a study comparing their experiences with 3D-CRT and IMRT, finding similar clinical outcomes in the two arms, but fewer treatment breaks and cases of grade 3 or greater acute nonhematologic toxicities in the IMRT arm[16]. Similarly, a Finnish study in 2008 compared toxicities for 3D-CRT and IMRT and found significantly fewer toxicities and fewer treatment breaks in the IMRT arm[17]. Such single-institution comparisons are important considering that treatment methods, outcomes tracking, and toxicity reporting would otherwise be uniform for the cohort.

The management of anal canal cancer has evolved from abdominoperineal resection to the current standard of care, which is concurrent chemotherapy and RT. The role of RT has been well-established in the treatment of patients with anal canal carcinoma, although the method of delivery, dose, and utility of planning a treatment break have been the subject of many investigations. As a follow-up to an earlier study (RTOG 87-04, which delivered 45 Gy in 25 fractions), RTOG 92-08 was initiated to analyze the potential benefits of dose escalation and its toxicities[18]. In that study, patients received 5FU–MMC in addition to 59.6 Gy over 8.5 weeks, including a 2-week treatment break. The investigators reported that dose escalation produced no increase in the local control rate when administered with a break, but was associated with an increase in the colostomy rate at 1 and 2 years. Similarly, in the ACCORD 03 trial, a high-dose RT boost did not seem to result in any benefit in colostomy-free survival[19]. Later, RTOG 92-08 was reopened to accrual, with treating physicians delivering the same radiation dose, but without the mandatory treatment break. A later analysis suggested that the treatment break, not the increased total radiation dose, might explain the lack of improvement in outcomes[20]. A pooled analysis later performed for patients enrolled in RTOG 87-04 and RTOG 98-11 found that an increase in total treatment time, rather than actual treatment delivery time, had a negative effect on control rates[21]. That finding gave credence to the results of RTOG 92-08. Further evidence of the importance of expedient completion of therapy came from a retrospective analysis by investigators at Memorial Sloan Kettering Cancer Center in New York, who found higher rates of relapse in patients with prolonged treatment courses or those unable to complete their prescribed RT dose[22].

Considerable attention has been paid to determining the efficacy of chemotherapy, as well as the most optimal regimen, in combination with RT. The normal tissues surrounding the anal canal are sensitive to RT and adding chemotherapy further lowers their radiation tolerance. Patients often experience hematologic toxicities because of the combined effects of chemotherapy and exposure of the pelvic bone marrow to radiation. Skin and gastrointestinal toxicities are also very common. In RTOG 98-11, in which 3D-CRT was used, 65% of patients in the MMC arm experienced grades 3 and 4 bone or bone marrow toxicities, 52% experienced grades 3 and 4 skin toxicities, and 39% experienced grades 3 and 4 gastrointestinal toxicities[23]. Similarly, in the ACT II trial, 48% of patients receiving MMC (including those receiving maintenance chemotherapy) experienced grade 3 or 4 skin toxicities[8].

The rate of grades 3–5 hematologic toxicity observed in the present work is within the range observed at other institutions as outlined in Table III, and it compares favourably with the MMC arm in RTOG 98-11. In our investigation, 45% of patients received 5FU–cisplatin chemotherapy, which, compared with 5FU–MMC in the ACT II trial, was shown to be associated with fewer hematologic toxicities and no significant differences in several important clinical outcomes[8]. Authors of a 2014 investigation at the MD Anderson Cancer Center in Houston, Texas, hypothesized that using 5FU–cisplatin in most of their patients resulted in a very low rate of acute high-grade hematologic toxicities (3%)[28]. Acute gastrointestinal toxicities in patients treated at our institution were similarly within the range of those from other institutions and compared favourably with the MMC arm in RTOG 98-11. The reduced gastrointestinal toxicity associated with IMRT is likely explained by a reduction in bowel dose. In a study conducted by Hodges *et al.* in 2009[32], IMRT was used to treat anal cancer with para-aortic lymph node involvement; in that study, 66% of patients experienced grade 3 acute gastrointestinal toxicities, which is likely explained by the larger treatment fields required to treat the affected lymph nodes. Chronic toxicities at our institution were minimal and considered tolerable by most patients, with no patients experiencing greater than grade 2 chronic toxicities.

TABLE III Literature review of outcomes

Reference (institution)	Treatment	Pts (*n*)	Median follow-up (months)	Grades 3–5 toxicities (%)		Outcome (%)
				GI	Hematologic	
Milano *et al.*, 2005[11] (University of Chicago)	IMRT with concurrent CTx	17	20.3	0	53	2-Year DFS: 65 2-Year OS: 91 2-Year CFS: 82
Salama *et al.*, 2007[10] (University of Chicago)	IMRT with concurrent CTx	53	14.5	15	59	18-Month LC: 83.9 18-Month OS: 93.4 18-Month CFS: 83.7 18-Month MFS: 92.9
Pepek *et al.*, 2010[9] (Duke University)	IMRT with concurrent CTx	47	14	13	24	2-year LC: 90 2-Year OS: 85 2-Year CFS: 91 2-Year MFS: 100
Call *et al.*, 2012[24] (Mayo Clinic)	IMRT with concurrent CTx	34	22	9	58	2-Year LC: 91 2-Year OS: 93 2-Year CFS: 91
DeFoe *et al.*, 2012[25] (University of Pittsburgh)	IMRT with concurrent CTx	78	16	27.7	42.9	2-Year LC: 83.6 2-Year OS: 86.9 2-Year CFS: 81.2 2-Year MFS: 81.8
Kachnic *et al.*, 2012[26] (Massachusetts General Hospital)	Dose-painted IMRT with concurrent CTx	43	12	7	61	2-Year LC: 95 2-Year OS: 94 2-Year CFS: 90 2-Year MFS: 92
Han *et al.*, 2014[27] (Princess Margaret Cancer Centre)	IMRT with concurrent CTx	58	34	9	41	2-Year LC: 84 2-Year OS: 90 2-Year CFS: 84 2-Year DFS: 77
Mitchell *et al.*, 2014[28] (MD Anderson Cancer Center)	IMRT with simultaneous integrated boost and concurrent CTx	65	19	9	3	2-Year LC: 93 2-Year OS: 96 2-Year DC: 93 2-Year DFS: 86
Franco *et al.*, 2015[29] (University of Turin)	IMRT with simultaneous integrated boost and concurrent CTx	54	32.6	8	17	4-Year LC: 84.6 4-Year OS: 77.7 4-Year CFS: 68 4-Year MFS: 74.4
Yates *et al.*, 2015[30] (The Chris O'Brien Lifehouse)	IMRT with simultaneous integrated boost and concurrent CTx	42	43	19	14	3-Year LC: 94 3-Year OS: 92 3-Year CFS: 89 3-Year MFS: 89
Julie *et al.*, 2016[31] (Memorial Sloan Kettering Cancer Center)	IMRT with concurrent CTx	108	29.4	Grade 2 or greater: 25	anemia, 62 thrombocytopenia, 19	3-Year LC: 90 3-Year OS: 91.5 3-Year MFS: 85
Present series, 2017 (University of Florida)	IMRT with simultaneous or sequential boost and concurrent CTx	21	28.8	10	23	2-Year LC: 100 2-Year OS: 95 2-Year CFS: 100 2-Year MFS: 100

Pts = patients; GI = gastrointestinal; IMRT = intensity-modulated radiation therapy; CTx = chemotherapy; DFS = disease-free survival; OS = overall survival; CFS = colostomy-free survival; LC = local control; MFS = metastasis-free survival; DC = distant control.

Intensity-modulated RT has been used to treat various cancers in different anatomic regions of the body, notably head-and-neck cancers and prostate cancer, for which maximizing dose to the treatment site while minimizing dose to normal tissues is of particular importance. Dosimetric studies comparing IMRT with 3D-CRT plans for the pelvis specifically have shown decreased radiation doses to organs of interest such as the bladder, small bowel, genitalia, iliac crests, and femoral heads, with adequate coverage of the tumour volume[33]. Use of IMRT in the treatment of anal cancer began to increase in the 2000s, with a 2007 investigation led by Salama and colleagues[10] showing that, compared with conventional RT, IMRT yields similar clinical outcomes with a more favourable toxicity profile. Most cases of acute grades 3–5 toxicity that have been reported in the literature in association with IMRT have been gastrointestinal and hematologic, which is understandable given the exposure to 5FU–MMC, and the volume of bowel and bone marrow irradiated in any sufficiently thorough plan[9–11,24–31].

The RTOG 05-29 trial was one of the first prospective multi-institutional studies to compare toxicities experienced with dose-painted IMRT to those experienced with 3D-CRT in the 5FU–MMC arm of RTOG 98-11[34]. Unfortunately, the study did not reach its primary endpoint, given that grade 2 and greater gastrointestinal and genitourinary toxicities did not decline by at least 15% compared with the 5FU–MMC treatment arm in RTOG 98-11. Additionally, one-to-one comparisons between RTOG 98-11 and RTOG 05-29 are difficult to make because of differences in dosing and fractionation.

As previously mentioned, treatment breaks and longer overall duration of treatment have been associated with poorer outcomes. Nevertheless, the 8 patients in the present study who experienced toxicities resulting in unplanned breaks did not experience inferior outcomes compared with the outcomes reviewed here or those in the prior 3D-CRT study conducted at our institution. As with any analysis describing physician-reported toxicities and treatment breaks, ours is subject to bias. For example, one patient's hospitalization that resulted in a treatment break was attributable to skin desquamation that was unchanged and not worsened from earlier in the treatment course. Pain is similarly difficult to objectively quantify and was a factor in the treatment breaks in 2 patients. Those observations underscore the need for further resources devoted to objective identification and exploration of treatment-related toxicity. Patient-reported symptom assessments and quality of life measurements are needed to help guide discussions of goals of care and assessment of improved treatment methods. An example of such work in a different disease site is seen in RTOG 12-03, which investigated the benefits of using IMRT for postoperative endometrial and cervical cancer by measuring patient-reported quality-of-life metrics[35].

The clinical outcomes at our institution compared favourably with those seen in RTOG 98-11 in terms of overall survival, local control, distant failure, and colostomy-free survival[23]. The outcomes observed in our study are in line with the existing body of literature (Table III), with an acceptable median follow-up[9–11,24–31].

Concerns have been raised about the cost-effectiveness of IMRT for anal canal cancer[36]. In the setting of limitations in the measurement of important variables such as willingness-to-pay thresholds, and given the lack of randomized studies comparing IMRT with less-expensive 3D-CRT, further analysis will be needed to ensure the economic appropriateness of using IMRT technology. Similar questions will likely be raised with regard to proton therapy for anal canal cancer, for which a dosimetric study from the University of Pennsylvania showed a reduction in radiation dose to organs of interest without compromising the dose to target[37].

Our report is limited by being a retrospective analysis and thus exposed to the same potential biases as other similarly designed trials. We also acknowledge having a relatively limited sample size in our IMRT group. And we understand the inherent subjectivity in grading patient toxicities. However, because this IMRT investigation and the previous 3D-CRT study were both conducted at the same institution and within the same prospectively annotated database, we feel that the interrater reliability was relatively high. In the absence of phase III trials comparing IMRT and 3D-CRT, our study summarizes data for anal canal squamous cell carcinoma that we hope will be useful in guiding clinicians and patients as they determine the best course of treatment. Although most toxicities in our investigation resolved within the follow-up window that our study entailed, longer follow-up is needed to ensure that no later relapses or chronic toxicities go undescribed.

CONCLUSIONS

The findings of this small series, which exhibits highly consistent treatment management, support the use of IMRT in conjunction with chemotherapy for squamous cell anal canal carcinoma based on the ability of that regimen to control disease and minimize acute and chronic toxicities. We advocate for the use, when possible, of IMRT, on the basis of disease control, favourable toxicity rates, and the associated improvement in quality of life that results.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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REFERENCES

1. Nelson VM, Benson AB 3rd. Epidemiology of anal canal cancer. *Surg Oncol Clin N Am* 2017;26:9–15.
2. Palefsky JM. Anal human papillomavirus infection and anal cancer in HIV-positive individuals: an emerging problem. *AIDS* 1994;8:283–95.
3. Beahrs O. Janeway Lecture. Management of cancer of the anus. *AJR Am J Roentgenol* 1979;133:790–5.
4. Nigro ND, Vaitkevicius VK, Buroker T, Bradley GT, Considine B. Combined therapy for cancer of the anal canal. *Dis Colon Rectum* 1981;24:73–5.
5. Flam M, John M, Pajak TF, *et al.* Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized Intergroup study. *J Clin Oncol* 1996;14:2527–39.

6. Bartelink H, Roelofsen F, Eschwege F, *et al.* Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol* 1997;15:2040–9.
7. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. UKCCCR Anal Cancer Trial Working Party. UK Co-ordinating Committee on Cancer Research. *Lancet* 1996;348:1049–54.
8. James RD, Glynne-Jones R, Meadows HM, *et al.* Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol* 2013;14:516–24.
9. Pepek JM, Willett CG, Wu QJ, Yoo S, Clough RW, Czito BG. Intensity-modulated radiation therapy for anal malignancies: a preliminary toxicity and disease outcomes analysis. *Int J Radiat Oncol Biol Phys* 2010;78:1413–19.
10. Salama JK, Mell LK, Schomas DA, *et al.* Concurrent chemotherapy and intensity-modulated radiation therapy for anal canal cancer patients: a multicenter experience. *J Clin Oncol* 2007;25:4581–6.
11. Milano MT, Jani AB, Farrey KJ, Rash C, Heimann R, Chmura SJ. Intensity-modulated radiation therapy (IMRT) in the treatment of anal cancer: toxicity and clinical outcome. *Int J Radiat Oncol Biol Phys* 2005;63:354–61.
12. Rabbani AN, Zlotecki RA, Kirwan J, *et al.* Definitive radiotherapy for squamous cell carcinoma of the anal canal. *Am J Clin Oncol* 2010;33:47–51.
13. Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL, Trotti A, eds. *AJCC Cancer Staging Manual.* 7th ed. New York, NY: Springer–Verlag; 2009.
14. Myerson RJ, Garofalo MC, El Naqa I, *et al.* Elective clinical target volumes for conformal therapy in anorectal cancer: a Radiation Therapy Oncology Group consensus panel contouring atlas. *Int J Radiat Oncol Biol Phys* 2009;74:824–30.
15. United States, Department of Health and Human Services, National Institutes of Health, National Cancer Institute (NCI). *Common Terminology Criteria for Adverse Events (CTCAE).* Ver. 4.03. Bethesda, MD: NCI; 2010.
16. Chuong MD, Freilich JM, Hoffe SE, *et al.* Intensity-modulated radiation therapy vs. 3D conformal radiation therapy for squamous cell carcinoma of the anal canal. *Gastrointest Cancer Res* 2013;6:39–45.
17. Saarilahti K, Arponen P, Vaalavirta L, Tenhunen M. The effect of intensity-modulated radiotherapy and high dose rate brachytherapy on acute and late radiotherapy-related adverse events following chemoradiotherapy of anal cancer. *Radiother Oncol* 2008;87:383–90.
18. John M, Pajak T, Flam M, *et al.* Dose escalation in chemoradiation for anal cancer: preliminary results of RTOG 92-08. *Cancer J Sci Am* 1996;2:205–11.
19. Peiffert D, Tournier-Rangeard L, Gerard JP, *et al.* Induction chemotherapy and dose intensification of the radiation boost in locally advanced anal canal carcinoma: final analysis of the randomized UNICANCER ACCORD 03 trial. *J Clin Oncol* 2012;30:1941–8.
20. Konski A, Garcia M Jr, John M, *et al.* Evaluation of planned treatment breaks during radiation therapy for anal cancer: update of RTOG 92-08. *Int J Radiat Oncol Biol Phys* 2008;72:114–18.
21. Ben-Josef E, Moughan J, Ajani JA, *et al.* Impact of overall treatment time on survival and local control in patients with anal cancer: a pooled data analysis of Radiation Therapy Oncology Group trials 87-04 and 98-11. *J Clin Oncol* 2010;28:5061–6.
22. Roohipour R, Patil S, Goodman KA, *et al.* Squamous-cell carcinoma of the anal canal: predictors of treatment outcome. *Dis Colon Rectum* 2008;51:147–53.
23. Ajani JA, Winter KA, Gunderson LL, *et al.* Fluorouracil, mitomycin, and radiotherapy vs fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. *JAMA* 2008;299:1914–21.
24. Call JA, Haddock MG, Quevedo JF, Larson DW, Miller RC. Concurrent chemotherapy and intensity modulated radiation therapy in the treatment of anal cancer: a retrospective review from a large academic center. *Pract Radiat Oncol* 2013;3:26–31.
25. DeFoe SG, Beriwal S, Jones H, *et al.* Concurrent chemotherapy and intensity-modulated radiation therapy for anal carcinoma—clinical outcomes in a large National Cancer Institute–designated integrated cancer centre network. *Clin Oncol (R Coll Radiol)* 2012;24:424–31.
26. Kachnic LA, Tsai HK, Coen JJ, *et al.* Dose-painted intensity-modulated radiation therapy for anal cancer: a multi-institutional report of acute toxicity and response to therapy. *Int J Radiat Oncol Biol Phys* 2012;82:153–8.
27. Han K, Cummings BJ, Lindsay P, *et al.* Prospective evaluation of acute toxicity and quality of life after IMRT and concurrent chemotherapy for anal canal and perianal cancer. *Int J Radiat Oncol Biol Phys* 2014;90:587–94.
28. Mitchell MP, Abboud M, Eng C, *et al.* Intensity-modulated radiation therapy with concurrent chemotherapy for anal cancer: outcomes and toxicity. *Am J Clin Oncol* 2014;37:461–6.
29. Franco P, Mistrangelo M, Arcadipane F, *et al.* Intensity-modulated radiation therapy with simultaneous integrated boost combined with concurrent chemotherapy for the treatment of anal cancer patients: 4-year results of a consecutive case series. *Cancer Invest* 2015;33:259–66.
30. Yates A, Carroll S, Kneebone A, *et al.* Implementing intensity-modulated radiotherapy with simultaneous integrated boost for anal cancer: 3 year outcomes at two Sydney institutions. *Clin Oncol (R Coll Radiol)* 2015;27:700–7.
31. Julie DA, Oh JH, Apte AP, *et al.* Predictors of acute toxicities during definitive chemoradiation using intensity-modulated radiotherapy for anal squamous cell carcinoma. *Acta Oncol* 2016;55:208–16.
32. Hodges JC, Das P, Eng C, *et al.* Intensity-modulated radiation therapy for the treatment of squamous cell anal cancer with para-aortic nodal involvement. *Int J Radiat Oncol Biol Phys* 2009;75:791–4.
33. Menkarios C, Azria D, Laliberte B, *et al.* Optimal organ-sparing intensity-modulated radiation therapy (IMRT) regimen for the treatment of locally advanced anal canal carcinoma: a comparison of conventional and IMRT plans. *Radiat Oncol* 2007;2:41.
34. Kachnic LA, Winter K, Myerson RJ, *et al.* RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. *Int J Radiat Oncol Biol Phys* 2013;86:27–33.
35. NRG Oncology. *RTOG 1203: A Randomized Phase III Study of Standard vs. IMRT Pelvic Radiation for Post-operative Treatment of Endometrial and Cervical Cancer (TIME-C)* [trial protocol]. Philadelphia, PA: NRG Oncology; 2015.
36. Hodges JC, Beg MS, Das P, Meyer J. Cost-effectiveness analysis of intensity modulated radiation therapy versus 3-dimensional conformal radiation therapy for anal cancer. *Int J Radiat Oncol Biol Phys* 2014;89:773–83.
37. Ojerholm E, Kirk ML, Thompson RF, *et al.* Pencil-beam scanning proton therapy for anal cancer: a dosimetric comparison with intensity-modulated radiotherapy. *Acta Oncol* 2015;54:1209–17.