Toxicity of Treatment for Anal Carcinoma: 2D versus 3D Planning

Fadi Atrash MD, Orit Kaidar-Person MD and Salem Billan MD

Division of Oncology, Rambam Health Care Campus, affiliated with Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT: **Background:** Anal cancer is a relatively uncommon disease, accounting for only 4% of cancers of the lower gastrointestinal tract.

Objectives: To summarize a single-center experience in the treatment of anal carcinoma using various radiation techniques.

Methods: We conducted a retrospective chart review of consecutive patients who were treated for anal cancer between the years 2002 and 2011. The data extracted included demographics, type of radiation technique, treatment-associated acute toxicity, and patterns of failure and survival. For statistical analysis purposes, the patients were divided into two groups according to radiotherapy technique: 2D (group A) and 3D (group B).

Results: A total of 42 patients – 25 (59.5%) females and 17 males (40.5%) – underwent definitive chemo-radiation treatment (CRT) for anal cancer. Group A comprised 26 patients and group B 14 patients. Toxicity did not differ significantly between the groups; only in grade 1-2 skin toxicity which was more common in group B. There were significant differences in the unplanned interruptions in treatment, in both the number of patients who needed a treatment break and the number of days needed (more in group A). There were no differences in treatment response and patterns of failure between these two techniques, or in overall survival between the two groups.

Conclusions: Our study results are consistent with reported large randomized trials, indicating that current treatments for anal carcinomas are associated with high grade acute toxicity that may result in significant treatment interruptions. The 2D technique was associated with significantly more treatment interruptions but did not differ from 3D with regard to treatment efficacy.

IMAJ 2015; 17: 414–417

KEY WORDS: anal cancer, carcinoma, toxicity, radiotherapy

Anal cancer is a relatively uncommon disease, accounting for only 4% of cancers of the lower gastrointestinal tract. The treatment of anal carcinoma underwent a paradigm shift in the 1970s from the surgical approach to concurrent chemo-radiation (CRT) with 5-fluorouracil (5-FU) and mitomycin C (MMC), which resulted in high rates of disease-free and colostomy-free survival without the requirement for radical surgery. Since then, trials have been unable to prove superiority of other regimens [1,2], although chemo-radiation for the treatment of anal carcinoma is associated with high rates of acute toxicity. According to our knowledge, there are no reports on treatment outcome and toxicity in the Israeli population. The current study is based on a retrospective cohort of all patients who were treated for anal cancer in the Radiotherapy Unit at Rambam Health Care Campus in Haifa, Israel.

PATIENTS AND METHODS

We conducted a retrospective chart review of all the medical records of consecutive patients who were treated in the Radiotherapy Unit at Rambam for anal cancer during the period 2002–2011. Data extracted from the medical records included demographics, histology, stage of disease at diagnosis, human immunodeficiency virus (HIV) status, type of treatment, radiation dose, type of radiation technique (2D, 3D, IMRT), treatment response and treatment-associated acute toxicity, and patterns of failure and survival. For statistical analysis purposes, the patients were divided into two groups according to radiotherapy technique (which changed over time), department policy and other considerations. Group A represented non-conformal radiation delivery techniques with anteroposterior-posteroanterior (AP/PA) parallel opposed fields (2D technique), and group B represented multi-field arrangements (3D technique). Only two patients were treated with intensity-modulated radiotherapy (IMRT) and thus were not included in the statistical analysis.

RESULTS

From 2002 to 2011, 42 patients were treated with definitive CRT for anal cancer; 25 (59.5%) were female and 17 were male (40.5%). Mean age at diagnosis was 64 years (median 65 years). Three patients were positive for hepatitis C virus (HCV) and one patient for HIV. Four patients had a secondary malignancy. Mean tumor size (clinically estimated at patient's first visit) was 3.9 cm (median 3.1 cm). Involvement of inguinal lymph nodes was suspected in seven patients and pelvic

Table 1. Acute treatment-associated toxicity according to Common Toxicity Criteria version 2.0

Radiation technique		Toxicity, Grade							
		No toxicity	Mucositis G1-2	Mucositis G3-4	Proctitis G3-4	Skin toxicity G1-2	Skin toxicity G3-4	Diarrhea G3-4	Leukopenia
Group A	No. of patients	3	1	7	1	1	9	4	6
	% patients	11.5%	3.8%	26.9%	3.8%	3.8%	34.6%	15.4%	
Group B	No. of patients	2	2	0	0	8	1	1	0
	% patients	14.3%	14.3%	.0%	.0%	57.1%	7.1%	7.1%	
	P value	NS	NS	0.076	NS	0.0003	0.0696	NS	NS
Total	No. of patients	5	3	7	1	9	10	5	6
	% patients	12.5%	7.5%	17.5%	2.5%	22.5%	25.0%	12.5%	

NS = non-significant

lymph nodes in eight. Most patients (40/42) had squamous cell carcinoma histology, and 2 had adenocarcinoma. Twenty-five had grade 2-3 tumors, while the grade was undefined in 14.

The irradiation field included the pelvis and inguinal area to a usually planned total dose of 45 Gy (1.8 Gy daily dose for 5 weeks), after which a boost was given to the tumor and involved lymph node up to 54–60 Gy. Some patients were treated with a planned interruption and were evaluated 7 days after the completion of 45 Gy; those who did not progress received a boost up to 60 Gy. The 2D technique consisted of AP/AP pelvic field up to 45 Gy, with a boost to the inguinal lymph nodes given by electron fields. The 3D field arrangement was used according to the RTOG 98-11 protocol.

The median total dose (for all techniques) was 56.7 Gy (range 14.4–66 Gy). The planned chemotherapy regimen given concurrently with the radiotherapy treatment included two cycles of 5-FU (1000 mg/m^2/day) continuous infusion on days 1–4 and 22–25 of radiation and MMC (10 mg/m^2) IV bolus on days 1 and 43 of radiation. One patient received only concomitant radiation with cisplatin; this patient had ulcerative colitis and it was decided not to use the 5-FU-MMC protocol which was assumed to be more toxic to the gastrointestinal tract. One patient did not receive any chemotherapy due to acquired immunodeficiency syndrome and a low CD4 count. Salvage surgery was reserved for patients with less than a partial response.

The median total dose (for all techniques) was 56.7 Gy (range 14.4–66 Gy). The planned chemotherapy regimen given concurrently with the radiotherapy treatment included two cycles of 5-FU (1000 mg/m^2/day) continuous infusion on days 1–4 and 22–25 of radiation and MMC (10 mg/m^2) IV bolus on days 1 and 43 of radiation. One patient received only concomitant radiation with cisplatin; this patient had ulcerative colitis and it was decided not to use the 5-FU-MMC protocol which was assumed to be more toxic to the gastrointestinal tract. One patient did not receive any chemotherapy due to acquired immunodeficiency syndrome and a low CD4 count. Salvage surgery was reserved for patients with less than a partial response.

Group A included 26 patients and group B 14 patients. Toxicity was documented according to Common Toxicity Criteria (CTC) version 2.0 [Table 1]. There were significant differences in the unplanned interruptions in treatment, both in the number of patients who needed a treatment break and in the number of days required [Table 2]. Unplanned interruption of the irradiation treatment occurred in 19 patients (73%) in group A as compared to 3 (21.4%) in group B ($P = 0.003$). Unplanned treatment interruptions occurred in our study after a median dose of 38.7 Gy (range 12.6–46.8 Gy). There were no differences with regard to treatment response and patterns of failure between these two techniques [Tables 3 and 4]. Two patients from group B died at the time of data collection; however, no statistical differences in overall survival were found between the two groups. Two patients who were treated with IMRT (and not included in the data analysis) were alive at the time of data

Table 2. Unplanned treatment interruptions (days)

Radiation technique	Mean	N	SD	Median	Minimum	Maximum
Group A	16.79	19	10.097	15.00	2	40
Group B	4.00	3	2.646	3.00	2	7
Total	15.05	22	10.404	14.00	2	40

$P = 0.027$

Table 3. Treatment response according to radiation technique

Radiation technique		Response to treatment				
		CR	PR	SD	PD	Total
Group A	No. of patients	20	5	0	1	26
	% patients	76.9%	19.2%	0%	3.8%	100.0%
Group B	No. of patients	6	3	1	3	13
	% patients	46.2%	23.1%	7.7%	23.1%	100.0%
Total	No. of patients	26	8	1	4	39
	% patients	66.7%	20.5%	2.6%	10.3%	100.0%

CR = complete response, PR = partial response, SD = standard deviation, PD = progressive disease, NS = non-significant

Table 4. Patterns of failure

Radiation technique		Recurrence		
		No	Local	Distant
Group A	No. of patients	20	5	1
Group B	No. of patients	9	3	2
Total	No. of patients	29	8	3
	% patients			

P = non-significant

collection (median follow-up 12 months), with no evidence of recurrence. Both had complete response at the end of the treatment. One patient suffered from grade 2 mucositis and the other from grade 1-2 skin toxicity.

DISCUSSION

The histology of invasive carcinomas of the anal region can vary. Squamous cell carcinomas (Sqcc) are the most prevalent and account for approximately 95% of the tumors. Other histology subtypes previously described in the anal region are adenocarcinoma, mucinous adenocarcinoma, small cell carcinoma, and undifferentiated carcinoma. Of the 42 patients in our study, 40 had Sqcc histology. Two patients had adenocarcinoma, which is extremely rare and is considered to arise from the anal glands and ducts. These patients were treated with CRT. Due to the rarity of anal canal adenocarcinoma the literature regarding treatment is sparse. Nonetheless, most authors advocate abdominoperinal resection (APR) for early-stage disease and suggest that these tumors be treated similar to adenocarcinoma of the rectum [3,4]. On the other hand, a retrospective report on 84 cases from the Rare Cancer Network concluded that combined modality (CRT) has a better outcome and recommended keeping APR as salvage treatment [5].

According to previous reports, stage distribution shows that 50% of anal cancers are diagnosed as localized, 29% as regional, and the corresponding 5 year relative survival rates according to stage: 80.1% for localized disease, 60.7% for regional lymph nodes [2,6]. In our study, although not evaluated by statistical analysis due to the paucity of patients, it seems that recurrence and survival were in accordance with the stage at diagnosis.

The concept of CRT as definitive treatment for anal carcinoma first evolved from the 1974 report by Nigro et al. of neoadjuvant CRT that resulted in complete pathological response [1]. Years later, as data accumulated, CRT has become the definitive standard of anal carcinoma. However, this treatment imposes a considerable challenge. Acute treatment toxicity is a huge concern as radiation total dose and treatment interruptions were found to be important clinical prognostic factors. A total dose of at least 54 Gy within 60 days of starting treatment has demonstrated significant improvement in local control of anal cancer [2,7-9].

As indicated in our results, most of the patients suffered from significant toxicity that resulted in treatment interruptions. Treatment breaks induced by or used to mitigate these morbidities are not uncommon and may compromise efficacy. In the RTOG 87-04 study, 12% of patients had an unplanned treatment break of at least 2 weeks. The possibility of planned treatment breaks to reduce radiation-related toxicity was addressed in the RTOG 92-08 split-course study [10]. The study attempted to decrease radiation-related toxicity associated with dose escalation to a total dose of 59.4 Gy. The study was a phase 2 trial that included 46 patients with anal carcinoma ($T \geq 2$ cm) who received 5-FU (1000 mg/m^2 over 24 hours for 4 days) during weeks 1 and 7 of radiation and MMC (10 mg/m^2 bolus) on day 1 of each course of 5-FU. The radiation dose was 59.4 Gy for 9 weeks with a 2 week mandatory rest. The investigators indicated that skin toxicity predominated during treatment or in early follow-up. These findings are similar to our study, where 10 patients suffered from grade 3-4 perineal skin toxicity (in both techniques). The 2D technique was associated with more grade 3-4 toxicity than the 3D technique. Unplanned treatment interruptions occurred in our study after a median dose of 38.7 Gy (range 12.6–46.8 Gy). In the RTOG 92-08 trial, one patient developed septicemia and died of multiple gastrointestinal toxicities, emphasizing that this protocol, even with the use of a planned break, is highly toxic. The investigators indicated that 12 patients (26%) had grade 4 toxicity and, of these, 9 (20%) had hematologic side effects alone. Similar to the RTOG 92-08 study and common toxicity of MMC, we encountered early hematological toxicity (leukopenia, thrombocytopenia); however, all were grade 1-2 toxicity (data not shown).

A later publication of the study results reported a comparative analysis with 147 patients treated with the RTOG 87-04 protocol [10,11]. Patients treated on the RTOG 92-08 had a lower incidence of grade 3 dermal toxicity (34% vs. 55%) but a higher colostomy rate at 1 year (23% vs. 6%) and at 2 years (30% vs. 7%) compared with RTOG 87-04. Unexpectedly, the increase in the total dose in the RTOG 92-08 split-course study compared to that used in the RTOG 87-04 study (total of 45 Gy) did not increase local control when given in a split-course fashion. The investigators noted that radiation may have to be given in a continuous fashion for higher radiotherapy doses (> 50 Gy) to increase local control. Our results are consistent with reported large randomized trials, demonstrating that the current treatments for anal carcinomas are associated with high grade acute toxicity that may result in significant treatment interruptions and lower compliance which cannot be compensated by dose escalation [10,11]. Despite a significant difference in the number of patients who required treatment interruptions between the groups, there was no difference with regard to treatment response or recurrence.

One patient in our study was HIV-positive with acquired immunodeficiency syndrome (AIDS). It was decided to treat this patient with radiation alone, although current recommendations suggest that it is not necessary to alter standard management recommendations for HIV-infected patients with AIDS (CD4 count < 200/μl). These patients should be monitored for increased risk of toxicity when treated with CRT [12].

Our report is a retrospective study of a small number of patients from a single institution. The study included the 2D technique, which is currently not used in most institutions. This may be considered a major flaw of the study. However, this research is consistent with the results of large-scale studies and raises once again the important issue of toxicity and treatment interruption. Although our study did not show statistically significant differences in treatment efficacy and toxicity between the two radiotherapy techniques, it seems that the 2D group suffered from more toxicity, such as leukopenia and grade 3 mucositis, and had two cases of mortality compared to none in the 3D group. Hematological toxicity is often encountered in patients treated with CRT for anal carcinoma. Current reports compare the dosimetric advantage of IMRT [13] to 3D conventional radiation treatment with regard to organs-at-risk avoidance, including iliac bone marrow to allow better sparing of bone marrow and to lower the risk of leukopenia and subsequent treatment interruptions. At the time of data collection, only two of our patients were treated with IMRT. None of the patients who were treated with 3D or IMRT suffered from leukopenia, compared to six who were treated with the 2D technique.

Locally advanced-disease anal carcinomas are highly curable using CRT, with preservation of sphincter function. Toxicity and treatment interruption have been proven harmful. Often, the clinical target volume for the nodes is extended to include the inguinal nodes, and anal margins (and perineal skin) are included in the irradiated field along with exposure of pelvic organs. These volumes combined with a chemotherapy protocol of two drugs account for the acute toxic effects (mostly hematologic, gastrointestinal and skin). The patients in the present study were treated mostly with 2D or 3D treatment planning. The new era of IMRT that allows sparing of normal tissue with maintaining maximal doses to the target might be associated with less toxicity and hopefully better outcome. However, early reports still indicate widespread toxicity [14]. Intensity-modulated irradiation allows optimization of the dose distribution in this "complex U-shaped" volume, while maintaining the dose distribution for the target volumes and sparing of organs at risk [15,16]. Due to the rarity of the disease, we were unable to draw conclusions regarding the use of IMRT for anal carcinoma in our institution, and we call for collaboration with other institutions in Israel to perform a multicenter study of IMRT with regard to toxicity and treatment outcome.

Correspondence
Dr. S. Billan
Division of Oncology, Rambam Health Care Campus, P.O. Box 9602, Haifa 31096, Israel
Phone: (972-4) 854-3284
Fax: (972-4) 854-2929
email: s_billan@rambam.health.gov.il

References

1. Nigro ND, Vaitkevicius VK, Considine B Jr. Combined therapy for cancer of the anal canal: a preliminary report. *Dis Colon Rectum* 1974; 17(3): 354–6.
2. Glynne-Jones R, Nilsson PJ, Aschele C, et al. Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow-up. *Eur J Surg Oncol* 2014; 40 (10): 1165-76.
3. Kounalakis N, Artinyan A, Smith D, Mojica-Manoso P, Paz B, Lai LL. Abdominal perineal resection improves survival for nonmetastatic adenocarcinoma of the anal canal. *Ann Surg Oncol* 2009; 16 (5): 1310-15.
4. Nudelman IL, Fuko V, Geller A, Fenig E, Lelchuk S. Treatment of rectal cancer by chemoradiation followed by surgery: analysis and early clinical outcome in 66 patients. *IMAJ* 2005; 7 (6): 377-80.
5. Belkacémi Y, Berger C, Poortmans P, et al; Rare Cancer Network. Management of primary anal canal adenocarcinoma: a large retrospective study from the Rare Cancer Network. *Int J Radiat Oncol Biol Phys* 2003; 56 (5): 1274-83.
6. Bilimoria KY, Bentrem DJ, Rock CE, Stewart AK, Ko CY, Halverson A. Outcomes and prognostic factors for squamous-cell carcinoma of the anal canal: analysis of patients from the National Cancer Data Base. *Dis Colon Rectum* 2009; 52 (4): 624-31.
7. Huang K, Haas-Kogan D, Weinberg V, Krieg R. Higher radiation dose with a shorter treatment duration improves outcome for locally advanced carcinoma of anal canal. *World J Gastroenterol* 2007; 13 (6): 895-900.
8. Constantinou EC, Daly W, Fung CY, Willett CG, Kaufman DS, DeLaney TF. Time-dose considerations in the treatment of anal cancer. *Int J Radiat Oncol Biol Phys* 1997; 39 (3): 651-7.
9. Hughes LL, Rich TA, Delclos L, Ajani JA, Martin RG. Radiotherapy for anal cancer: experience from 1979–1987. *Int J Radiat Oncol Biol Phys* 1989; 17 (6): 1153-60.
10. 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 (4): 205-11.
11. 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 (1): 114-18.
12. Wexler A, Berson AM, Goldstone SE, et al. Invasive anal squamous-cell carcinoma in the HIV-positive patient: outcome in the era of highly active antiretroviral therapy. *Dis Colon Rectum* 2008; 51 (1): 73-81.
13. Janssen S, Glanzmann C, Bauerfeind P, et al. Clinical experience of SIB-IMRT in anal cancer and selective literature review. *Radiat Oncol* 2014 8;9:199. doi: 10.1186/1748-717X-9-199.
14. 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 (1): 27-33.
15. Ng M, Leong T, Chander S, et al. Australasian Gastrointestinal Trials Group (AGITG) contouring atlas and planning guidelines for intensity-modulated radiotherapy in anal cancer. *Int J Radiat Oncol Biol Phys* 2012; 83 (5): 1455-62.
16. 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 (29): 4581-6.

"No one has ever become poor by giving"

Anne Frank (1929-1945), Holocaust diarist