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ORIGINAL ARTICLE

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

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ABSTRACT

Purpose: **To report the 4-year outcomes of a consecutive series of anal cancer patients treated with concurrent chemo-radiation delivered with intensity-modulated radiotherapy (IMRT), employing a simultaneous integrated boost (SIB) approach.** ***Methods:*** **A consecutive series of 54 patients was enrolled between 2007 and 2013. Treatment schedule consisted of 50.4 Gy/28 fractions (1.8 Gy daily) to the gross tumor volume, while the elective nodal volumes were prescribed 42 Gy/28 fractions (1.5 Gy/daily) for patients having a cT2N0 disease. Patients with cT3-T4/N0-N3 tumors were prescribed 54 (T3) or 60 (T4) Gy/30 fractions (1.8–2 Gy daily) to the gross tumor volume; gross nodal volumes were prescribed 50.4 Gy/30 fr (1.68 Gy daily) if sized $\leq$ 3 cm or 54 Gy/30 fr (1.8 Gy daily) if > 3 cm; elective nodal regions were given 45 Gy/30 fractions (1.5 Gy daily). Chemotherapy was administered concurrently according to the Nigro's regimen. Primary endpoint was colostomy-free survival (CFS). Secondary endpoints were local control (LC), disease-free survival (DFS), cancer-specific survival (CSS), overall survival (OS), and toxicity profile.** ***Results:*** **Median follow up was 32.6 months (range 12–84). The actuarial probability of being alive at 4 years without a colostomy (CFS) was 68.9% (95% CI: 50.3%–84.7%). Actuarial 4-year OS, CSS, DFS, and LC were 77.7% (95% CI: 60.7–88.1%), 81.5% (95% CI: 64%–91%), 65.5% (95% CI: 47.7%–78.5%), and 84.6% (95% CI: 71.6%–92%). Actuarial 4-year metastasis-free survival was 74.4% (95% CI: 55.5%–86.2%). Maximum detected acute toxicities were as follows: dermatologic – G3: 13%; GI-G3: 8%; GU-G3: 2%; anemia-G3: 2%; neutropenia-G3:11%; G4: 2%; thrombocytopenia- G3:2%. Four-year G2 chronic toxicity rates were 2.5% (95% CI: 3.6–16.4) for GU, 14.4% (95% CI: 7.1–28) for GI, 3.9% (95% CI: 1%–14.5%) for skin, and 4.2% (95% CI: 1.1–15.9) for genitalia.** ***Conclusions:*** **Our study shows the feasibility of IMRT in the combined modality treatment of anal cancer, with comparable results to the literature with respect to LC, sphincter preservation and survival. Acute toxicity is lower if compared to series employing standard techniques. Our results support the use of IMRT on a routine basis for the treatment of anal cancer.**

Keywords: Anal cancer, IMRT, Concomitant radiochemotherapy, Acute toxicity, Late toxicity, Radiotherapy, Radiation

INTRODUCTION

Up to the 80s, squamous cell carcinoma arising from the anal canal has been treated with surgery consisting of abdomino-perineal resection (APR) and permanent colostomy, with 5-year overall survival (OS) rates in the range of 50%–70%, with consistent morbidities (impotence, potential abdominal wall, and perineal fistulae) and eventual psychological and/or social issues associated to colostomy management (1). High-dose external beam radiotherapy (EBRT) has been employed as a sphincter saving alternative to surgery, with 3-years OS rates of 75% as exclusive option (2). The integration of EBRT and endocavitary brachytherapy (BRT) provides 5-year OS rates > 65% with consistent sphincter function preservation (3). BRT alone achieves a 40%–50% local control (LC) rate (3). Actually, combined modality treatment with concurrent chemo-radiation is considered as the standard of

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care in the management of anal cancer, providing consistent OS rates (50%–78%), higher than with exclusive radiation, and simultaneously sparing the anal sphincter with better colostomy-free survival (CFS) rates (61%–76%) than surgical approaches (4–6). Recently, updated results of the RTOG 98-11 trial confirmed on a long-term basis combined EBRT and concurrent 5-fluorouracil (5-FU) and mitomicin-C (MMC) as the preferred treatment option, with 5-year disease-free survival (DFS) and OS rates of 67.8% and 78.3%, respectively (7). Nevertheless the same trial reported a high rate of major acute toxicities (skin-G3/G4: 48%; gastrointestinal-G3-G4: 35%), mainly due to the use of non-conformal techniques such as AP/PA parallel opposed fields or 4-field conformal approaches, covering a large amount of normal tissues and, consequently, exposing organs at risk (OARs) to undue radiation dose. Intensity-modulated radiotherapy (IMRT) is able to provide robust conformality and modulation, abrupt dose fall-off and reliable accuracy, also in the context of anal cancer, potentially reducing the dose to critical structures such as bowel, bladder, genitalia, perineal skin, and bone marrow (8–11). We herein present a retrospective analysis of patients treated with concurrent IMRT and chemotherapy (CT) within a consecutive case series.

MATERIALS AND METHODS

Eligibility Criteria

All patients accrued had a histologically confirmed diagnosis of anal cancer (anal canal or anal margin) characterized as basaloid, keratinizing, and non-keratinizing and graded according to the degree of differentiation. Patients were enrolled within three different Italian institutional hospitals (University of Torino, Ivrea Community Hospital, and Aosta Community Hospital). Tumor stage was defined according to the 2002 American Joint Committee on Cancer indications and patients with clinical stage T1-T4, N0-N3 were enrolled. Other inclusion criteria included an Eastern Cooperative Oncology Group (ECOG) performance status of 0–1, age between 18 and 80, suitable hematological parameters (neutrophils $\geq 1.5 \times 10^9$/l and platelets $\geq 100 \times 10^9$/l), adequate renal and liver function. Exclusion criteria comprehended systemic disease at diagnosis, prior radiation to the pelvic region, medical contraindications to chemo-radiation, symptoms of bowel occlusion and/or gastro-intestinal bleeding, malabsorption syndrome, peripheral neuropathy, psychiatric disease hampering compliance to treatment, pregnancy, and breast-feeding. Written informed consent was obtained for all patient. The Ethical Review Board of our Institutional Hospitals approved the present study.

Pre-treatment Evaluation

Prior to accrual, all patients were evaluated by the gastrointestinal tumor board of our Institutions, made up of a radiation oncologist, a medical oncologist, and an abdominal surgeon. The clinical evaluation included complete medical history with physical examination, comprising a digital rectal examination and complete laboratory testing. Disease staging included a chest, abdomen, and pelvis computed tomography scan (CT), a magnetic resonance imaging (MRI) of the pelvic region, positron-emission tomography (PET) and/or inguinal sentinel lymphnode biopsy (SLNB), and eventual endoscopic transrectal ultrasounds (EUS) (12,13).

Radiotherapy

Patients underwent virtual simulation in supine position with both an indexed shaped knee rest and ankle support (CIVCO Medical Solutions, Kalona, IO, USA) in order to prevent from hip rotation, but with no custom immobilization. For planning purposes, a CT scan was performed and 3 mm slice thickness axial images were obtained from the top of L1 vertebral body to the mid-femur. An isocenter was found using the CT-simulation software Oncentra Masterplan v. 3.0 (Nucletron, Veendhal, The Netherlands) within the pelvic region and subsequently marked on the patient's skin under laser guidance for daily positioning. For contouring purposes, the gross tumor volume (GTV) consisted of all macroscopic foci of disease with respect to both primary tumor and lymphnodes. GTV was defined taking into account MRI and PET information after performing a non-rigid co-registration within the Velocity software (Varian Medical System, Palo Alto, CA, USA).

Those volumes were then isotropically expanded, adding 20 mm and 10 mm, respectively, to generate the corresponding clinical target volumes (CTVs), but properly modified in order to exclude surrounding osseous and muscular tissues. The elective CTV encompassed the mesorectum and appropriate draining lymphatic regions such as inguinal, external iliac, internal iliac, obturator, and perirectal nodes. For locally advanced cases (cT4 and/or N2/N3), presacral nodes were also included in the CTV. In general, lymphatic areas were contoured as a 10 mm isotropic expansion around regional vessels, with a subsequent modification to exclude bones and muscles. A subsequent 10 mm isotropic margin was added to generate the consequential planning target volume (PTV), accounting for organ motion and set up errors (14,15). This margin remained the same throughout the years in this cohort of patients for homogeneity, even if different strategies of image-guidance were employed during those years (weekly portal imaging for early and daily KvCT/MvCT for late patients). Dose prescription for target volumes was inspired by Kachnic et al, being congruent to the clinical stage at presentation (16). Basically, patients having a cT2N0 disease were prescribed 50.4 Gy/28 fractions (1.8 Gy daily) to the gross tumor PTV, while the elective nodal PTV was prescribed 42 Gy/28 fractions (1.5 Gy/daily). Patients with a cT3-T4/N0-N3 disease were prescribed 54 (T3) or 60 (T4) Gy/30 fractions (1.8–2 Gy daily) to the anal gross tumor PTV, while gross nodal PTVs were prescribed 50.4 Gy/30 fr (1.68 Gy daily) if sized ≤ 3 cm or 54 Gy/30 fr (1.8 Gy daily) if > 3 cm; elective nodal PTV was prescribed 45 Gy/30 fractions (1.5 Gy daily) (16). For inverse planning, target volumes objectives were driven to obtain at least 95% of the prescribed dose to 95% of the PTV, 110% of prescription dose to $\leq 10\%$ of the PTV and $\leq 2\%$ of PTV receiving $< 95\%$ of prescribed dose. OARs dose constraints were adapted from Kachnic et al. (14). Three different treatment modalities were available for

patients: step and shoot (S&S) IMRT, volumetric arc-therapy (VMAT), and helical tomotherapy (HT). For S&S IMRT, plans were generated with up to seven modulated fields, employing 6 MV photons, depending on patients' anatomy. For VMAT, all plans were computed on Elekta Monaco treatment planning system (version 3.2), allowing for optimization with biological cost-functions for both PTV and OARs with hree main functions (Poisson statistics cell-kill model, serial and parallel complication models) and employing a single-arc of 360° (starting from 180°) or, more recently, the dual-arc approach. Both S&S and VMAT plans were planned for Elekta Synergy or Varian DHX-S LINACs. The XVMC/VEF Monte Carlo algorithm with a 3% variance was used for all cases. HT plans were generated using Tomotherapy Hi-Art version 4.1 (Accuray Inc, Sunnyvale, CA), choosing the appropriate field width, pitch, and modulation factor and calculating the dose distribution of each beamlet with the convolution/superposition algorithm. Generally, HT plans had a modulation factor of 2.5–3.7, a pitch of 0.287 and a 2.5 cm field width.

Chemotherapy

Patients received concomitant CT, consisting of 5-FU (1,000 mg/m^2/day) given as continuous infusion for 96 hr (days 1–5 and 29–33) combined with MMC (10 mg/m^2) given as bolus (days 1 and 29). A total of two concurrent cycles were planned for each patients. CT schedule adaptation (for example mono-chemotherapy) was allowed based on baseline patient's characteristics. Blood cell counts were routinely performed prior to each CT administration. Prophylactic antiemetic medications consisted of intravenous granisetron 3 mg and dexamethasone 8 mg. CT discontinuation or drugs modification were planned whenever G3-G4 toxicities according to NCI-CTC v3.0 occurred. Continuation at reduced dose could be undertaken in case of toxicity profile reduction down to G1. Patients were taken off the study in case of persistence of toxicity $\geq$ G3 over 2 weeks or repeated episodes of toxicity $\geq$ G3 occurring despite dose reduction.

Clinical Assessment

Acute gastro-intestinal (GI), genitourinary (GU), dermatologic, hematologic, genital, and osseous toxicities were assessed during treatment and scored according to the Common Toxicity Criteria for Adverse Events scale v3.0. The worst grade toxicity for each category observed within 90 days from treatment end was recorded as an acute toxicity event. All toxicities occurring $>$ 90 days from RT discontinuation were classified as late toxicity. During follow-up patients had a clinical examination with digital rectal exam and anoscope observation at 4, 8, and 12 weeks. At 12 weeks, an MRI was performed and bioptic sampling of the anal canal was performed. A complete response was defined with respect to the negativity of the pathology examination at biopsy. A salvage APR was recommended for persistent disease (at pathology) or for locally progressive or recurrent disease (at imaging and pathology).

Table 1. Patients' characteristics

Variable	*N* (%)
Age	
Mean	62
Range	39–78
Sex	
Female	43(80)
Male	11(20)
HIV status	
Positive	3(6)
Negative	51(94)
Primary tumor site	
Anal canal	46(85)
Anal margin	7(13)
Both	1(2)
T stage	
T1	1(2)
T2	33(62)
T3	17(31)
T4	3(5)
N stage	
N0	30(55)
N1	7(13)
N2	14(26)
N3	3(6)
Global stage	
II	29(54)
IIIA	8(15)
IIIB	17(31)
Grading	
G1	17(31)
G2	18(33)
G3	19(36)
Preventive colostomy	
Yes	5(10)
No	49(90)

Statistical Analysis

Disease recurrence was defined as local if occurring within the anal canal and/or anal margin and/or mesorectum, regional if involving draining lymphnodes (inguinal, external iliac, internal iliac, obturator, perirectal, and presacral nodes) and systemic if arising elsewhere. Local and regional failures were taken into account for loco-regional control. Death of disease was defined as death due to disease and taken into account for cancer-specific survival (CSS). Death of any cause was considered for OS. All failures and cancer-related deaths were considered for DFS. Death of any cause or submission to definitive colostomy (excluding preventive colostomies) were considered events for CFS. Failures in sites other than anal region and draining lymphnodes were taken into account for distant metastasis-free survival (DMFS). Survival curves and actuarial rates of relapse were calculated using Kaplan–Meier method. Multivariate analysis was performed using stepwise Cox proportional hazard regression models and related to OS, CSS, and DFS. A p value < 0.05 was considered significant. Variables considered as continuous for the analysis were: age, treatment breaks (days), overall treatment time (OTT) (days), time between biopsy and radiotherapy start (days). Variable considered as categorical were: sex, tumor location (anal canal vs anal margin), stage, inguinal lymphnode involvement, staging procedure (PET vs inguinal SLNB),

Table 2. Treatment characteristics

Variable	*N* (%)
IMRT approach	
S&S	40 (74)
VMAT	7 (13)
Tomotherapy	7 (13)
PTV dose-tumor (Gy)	
Mean	54
Range	50.4–60
PTV dose-positive nodes (Gy)	
Mean	51.7
Range	50.4–54
PTV dose-negative nodes (Gy)	
Mean	44
Range	42–45
Chemotherapy	
5-FU + MMC	52 (96)
5-FU	1 (2)
MMC	1 (2)
Biopsy-RT interval (days)	
Mean	72
Range	25–193
Chemotherapy dose reduction	
Yes	14 (26)
No	40 (74)
RT duration (days)	
Mean	44
Range	37–55
RT breaks ≥ 3 days	
Yes	5 (9)
No	49 (91)

tumor grading, eventual CT dose reduction. Stata Statistical Software, version 13.1 (Stata Corporation, Texas) was employed for analysis.

RESULTS

A total of 54 patients were enrolled from June 2007 to June 2013. For detailed patients characteristics see Table 1. Generally, patients had a mean age of 62 (range 39–78) and were mainly female (80%), HIV-negative (94%), with an anal canal primary (85%), T2-T3 stage (93%), N0-N2 (94%), G2-G3 (69%), and without a preventive colostomy (90%). Patients were mainly treated with a S&S IMRT approach (74%). Mean doses to the PTVs volumes were 54 Gy, 51.7 Gy, and 44 Gy for the gross tumor, gross nodal, and elective nodal volumes, respectively. The mean interval between biopsy and EBRT initiation was 72 days. Mean EBRT duration was 44 days. Patients undergoing a treatment break were 9 (17%) with a mean duration of 3.9 days (considering also machine breakdown-related ones). Those having breaks ≥ 3 days were 9%. See Table 2 for details.

Toxicity Profile

Acute toxicity for the whole cohort is presented in Table 3. Maximum detected acute toxicities were as follows: dermatologic – G3: 13%; GI-G3: 8%; GU-G3: 2%; anemia-G3: 2%; neutropenia-G3:11%; G4: 2%; thrombocytopenia- G3:2%. Grade 3 events comprehended moist desquamation for skin toxicity, diarrhea with more than 7 stools per day for GI, and cystitis interfering with activities of daily living for GU. Actuarial rates of main chronic toxicities may be seen in Figure 1; in particular 4-year G2 chronic toxicity rates were 2.5% (95% CI: 3.6–16.4) for GU, 14.4% (95% CI: 7.1–28) for GI, 3.9% (95% CI: 1–14.5%) for skin, and 4.2% (95% CI: 1.1–15.9) for genitalia. Grade 2 events consisted of colic pain and intermittent intestinal bleeding, frequency and sporadic hematuria, moderate atrophy to both perineal skin and external genitalia. A total of 14 out of 54 patients (26%) underwent a CT dose reduction during treatment due to hematologic toxicity.

Table 3. Acute toxicity

	N (%)				
Acute toxicity	*G0*	*G1*	*G2*	*G3*	*G4*
Skin	1(2)	9(16)	37(69)	7(13)	0
Gastrointestinal	10(18)	13(24)	27(50)	4(8)	0
Genitourinary	24(44)	12(22)	17(32)	1(2)	0
Anemia	50(93)	3(6)	1(2)	1(2)	0
Neutropenia	36(67)	2(4)	9(16)	6(11)	1(2)
Thrombocytopenia	48(88)	1(2)	4(8)	1(2)	0

Clinical Outcomes

Median observation time was 32.6 months (range 12–84). A total of 8 patients presented with a loco-regional failure. Three patients had persistent anal disease after combined chemo-radiation; 4 patients experienced a local relapse within the anal canal after treatment: among them 1 patient had a synchronous occurrence of both hepatic and lung metastases and 1 a concomitant pelvic lymphnode failure. The remaining patient had a loco-regional failure within pelvic nodes (with concurrent liver metastases). Six patients received salvage APR; three patients had further CT and 1 patient underwent liver metastasis resection. A total of 10 patients developed distant metastases: 4 within the liver, 5 within the lungs, and 1 within both liver and lungs. Among those, 3 patients had also loco-regional failure. All metastatic patients received CT as part of their salvage treatment. Overall, 11 patients died; 8 of them were cancer-related deaths, while 3 were due to other causes. Actuarial 4-year OS, CSS, DFS, and LC were 77.7% (95% CI: 60.7%–88.1%), 81.5% (95% CI: 64%–91%), 65.5% (95% CI: 47.7%–78.5%), and 84.6% (95% CI: 71.6%–92%) (see Figure 2). The actuarial probability of being alive at 4 years without a colostomy (CFS) was 68.9% (95% CI: 50.3%–84.7%). Actuarial 4-year MFS was 74.4% (95% CI: 55.5%–86.2%) (Figure 3).On multivariate analysis, independent variables related to a worse OS were male sex (HR: 10.3; 95% CI: 1.2–89.6; $p = 0.034$), advanced clinical stage (HR: 7.1; 95% CI: 1.3–39.7; $p = 0.025$), and treatment breaks (HR: 1.5; 95% CI: 1.1–2.2). Inguinal node involvement (HR: 28.6; 95% CI: 1.1–813; $p = 0.05$), clinical stage (HR: 13.7; 95% CI: 1.6–116.1; $p = 0.016$), and treatment breaks (HR: 2.2; 95% CI: 1.1–4.6; $p = 0.023$) also influenced CSS in a statistically significant manner. Clinical stage (HR: 3.1; 95% CI: 1.2–8.5; $p = 0.024$) and treatment breaks (HR: 1.4; 95% CI: 1.04–1.75; $p = 0.023$) influenced also DFS.

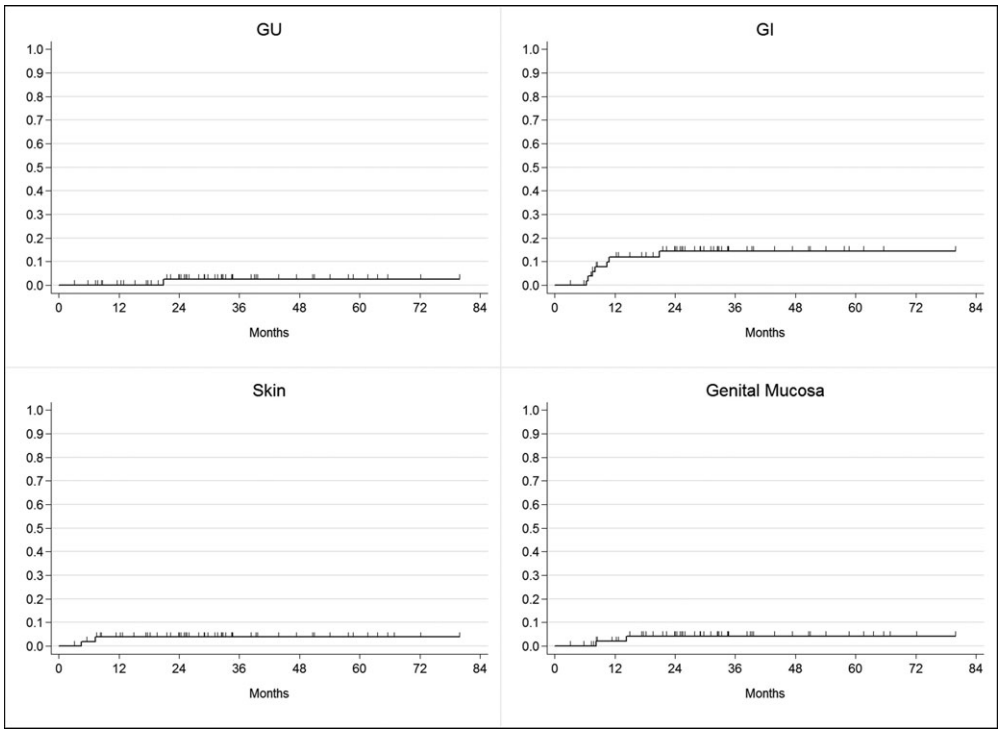

Figure 1. Chronic toxicity.

DISCUSSION

EBRT to the pelvic region for the treatment of anal cancer has been traditionally delivered with 2-dimensional or 3-dimensional approaches. Hence, a large amount of normal tissues was generally included within treatment fields, leading to consistent unintended dose to critical structures such as bladder, bowel, perineal region, and bone marrow and consequently to high rates of acute toxicities and consequential late effects (17). IMRT has been demonstrated to

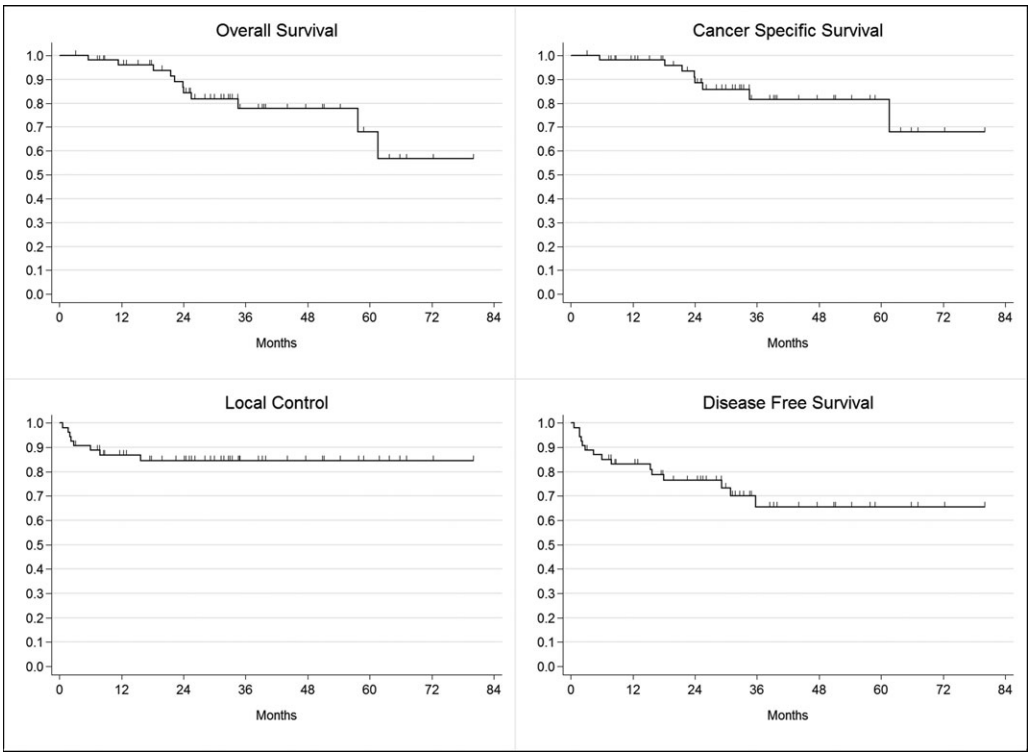

Figure 2. Local control and survival.

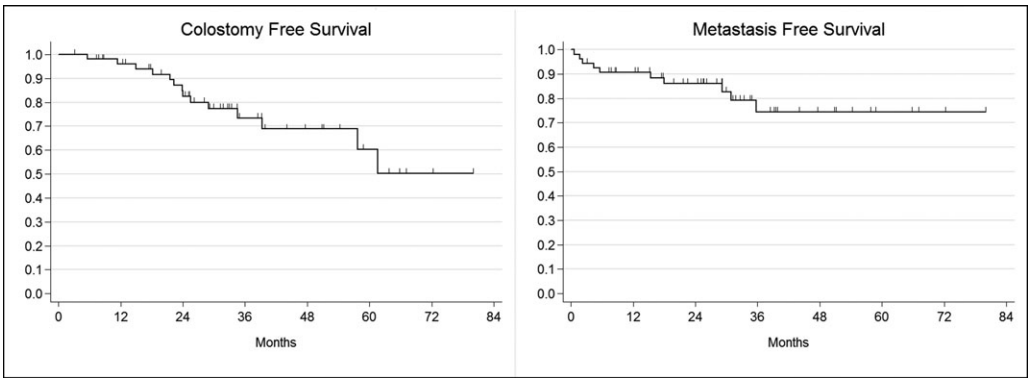

Figure 3. Sphincter preservation and systemic spread results.

provide a dosimetric advantage in terms of both target coverage and OARs avoidance compared to 3D-conformal EBRT (18,19). Combined chemo-radiation in anal cancer patients without the use of IMRT has been reported to have high rate of GI (G3-G4: 35%, mainly diarrhea) and hematologic (G3-G4: 61%) side effects, as shown in the RTOG 98-11 trial (20). IMRT is able to provide a more favorable toxicity profile. Salama et al. reported the use of intensity-modulated EBRT as part of combined modality therapy within a multi-institutional retrospective study, demonstrating a 15.1% rate of G3 acute GI, 37% skin toxicities, and a 58.5% of G3-G4 hematologic side effects at 3 tertiary-care academic medical centers(9). Interestingly, in this study all the Grade 4 events were hematologic (leukopenia: 30.2%; neutropenia: 34%). Treatment breaks occurred in 41.5% of patients, with a median duration time of 4 days (9). Kachnic et al. employed a dose-painted IMRT approach, observing on a retrospective multi-institutional framework, a G3 acute toxicity rate of 7% for GI, 5% for GU, 5% for dermatologic, and 49% for hematologic toxicities (13). In this series, G4 events were observed not only for hematologic toxicity (12%), but also for GU (2%) and dermatologic (5%). No G4 events were detected for GI. Treatment breaks occurred in 40% of patients, with a median duration time of 2 days. Among them, patients with a $>$ 3 days break were 35% (16). Our results compared favorably with reported series. In particular, G3 acute events were 13% for dermatologic toxicity, 8% for GI, 2% for GU, and 15% for hematologic. Grade 4 events were seen only for neutropenia (2%). Those rates are similar to those reported, excluding for hematologic which was lower in our series, maybe due to the fact that up to 26% of patients underwent a CT dose reduction during combined modality treatment. Generally, findings on early side effects were confirmed on a long-term basis with a favorable chronic toxicity profile. In our cohort, patients experiencing a treatment break were 9 (17%) with a mean duration of 3.9 days. Those with a break $\geq$ 3 days were 9%. The lower rate of acute toxicity in our study, with a consequent acceptable rate and duration of treatment breaks is notable, since overall treatment time is of paramount importance in anal cancer. Patients enrolled in the RTOG 92-08 trial, which included a mandatory 2-week break during treatment, had a 30% 2-year colostomy rate, compared with a 10% 5-year colostomy rate in the RTOG 98-11 trial with patients treated with 5-FU/MMC concurrent to EBRT with no breaks required (7, 21). In our series, all patients were treated with an unconstrained IMRT approach towards pelvic bone marrow. Thus osseous structures were not included within the optimization process as structures to be selectively avoided. It has been demonstrated, in the context of both cervical and anal cancer treated concomitantly to CT, that specific volumes of pelvic bones receiving a certain dose have a significant correlation with acute hematologic toxicity (10,22). On multiple regression analysis, an increasing level of pelvic and lumbosacral bone marrow receiving 5,10,15,20 Gy was significantly associated with decreased white blood cell count and absolute neutrophil count nadirs (10). Hence, a reduction in the rate, intensity, and duration of hematologic toxicity may be hypothesized employing intentional sparing techniques avoiding osseous structures with IMRT. In order to prospectively test the hypothesis that intensity modulation may potentially enlarge the therapeutic window, the RTOG 05-29 phase II trial investigated whether dose-painted IMRT might be able to reduce by at least 15% the $\geq$ G2 GI and GU toxicity rates, compared to conventional EBRT concurrent to 5-FU/MMC as in the RTOG 98-11 trial (23). Although the primary endpoint of the study was not reached, a significant reduction in acute G2 hematologic (73% vs 85% for RTOG 98-11), G3 GI (21% vs 36% for RTOG 98-11), and G3 dermatologic acute adverse events (23% vs 49% for RTOG 98-11) was observed (24). In the RTOG 05-29 study, overall treatment time was 43 days (range 32-59), comparably to our cohort (44 days; range 37–55) and shorter than RTOG 98-11 (49 days; range 4–100). Treatment breaks were seen in 49% of patients, higher than in our dataset (17%), but lower than RTOG 98-11. Conversely, median interruption time was lower than ours (median 0 days vs 3.9 days) and RTOG 98-11 (3 days). Actuarial 4-year rates of OS, CSS, DFS, LC were 77.7%, 81.5%, 65.5%, and 84.6%, respectively. Moreover, the actuarial probability of being alive at 4 years without a colostomy (CFS) was 68.9%. Actuarial 4-year DMFS was 74.4%. These results are similar to 5-year outcomes of the EBRT/5-FU/MMC arm of RTOG 98-11 (OS: 78.3%; DFS:

67.8%; LC: 80%; CFS: 68.9%; DMFS: 86.9%), except for a higher rate of distant metastases. Our findings support the feasibility of IMRT in the combined modality treatment of anal cancer. Clinical outcomes were comparable to those reported in the literature, providing a proof of principle that, generally speaking, IMRT might not be detrimental in terms of tumor control, anal sphincter preservation rate, and survival if compared to standard techniques. Acute skin toxicity profile and consequently patient's compliance seems improved compared to historical data employing conventional approaches (25). This may be due to the use of IMRT, but also a role may be played by patients' characteristics in our cohort with the majority of patients having early tumors (T1-T2: 64%; N0-N1: 68%), leading to the delivery of lower doses to target volumes according to protocol strategy. In our series, several IMRT techniques have been used, including both static (S&S) and volumetric/rotational (VMAT or tomotherapy) approaches. This might be a potential selection bias, given the different dosimetric outcomes which may influence toxicity profile. Since our series was not balanced in terms of treatment techniques, with the majority of patients treated with fixed gantry IMRT, and given that toxic event rate was low, we were not able to perform a subset analysis accounting for technical aspects as variable. As a consequence, no dosimetric factors could be investigated as predictors of toxicity. However, IMRT in our series seems to be reasonably safe regardless of the approach employed. Treatment breaks are decreased with respect to frequency and duration, compared to historical series. This is important considering that in our series, as in others, treatment breaks significantly worsened DFS. In adjunct, we employed a SIB approach as in the RTOG 0529 trial, allowing for the delivery of a different daily dose to selected treatment volumes during the same treatment fraction. SIB has been demonstrated to provide dosimetric benefits in terms of target volume dose conformity and homogeneity and normal tissue sparing in the setting of both head and neck and breast cancer (26–28). This advantage may be postulated also for anal cancer. This is of particular importance as the SIB approach is able to shorten the overall treatment time with a consequent potential benefit on treatment outcomes. With the treatment schedule we employed, SIB leads us to deliver daily doses as low as 1.5 Gy to prophylactic volumes. Given that only one local-regional relapse occurred in negative-node regions irradiated with low daily dose, our data seem to support the use of low dose per fraction for clinically uninvolved regions as in RTOG 0529 trial and other retrospective reports (23, 29). In general, our finding further support the implementation and use of IMRT on a routine basis for the treatment of cancer of the anal canal in combination with concurrent CT.

DECLARATION OF INTEREST

The authors report no declaration of interest. The authors alone are responsible for the content and writing of this paper.

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