Locally Advanced (T3-T4 or N+) Anal Cancer Treated with Simultaneous Integrated Boost Radiotherapy and Concurrent Chemotherapy

PIERFRANCESCO FRANCO[1], FRANCESCA ARCADIPANE[1], RICCARDO RAGONA[1], MASSIMILIANO MISTRANGELO[2], PAOLA CASSONI[3], NADIA RONDI[4], MARIO MORINO[2], PATRIZIA RACCA[5] and UMBERTO RICARDI[1]

Departments of [1]Oncology-Radiation Oncology, [2]Surgical Sciences and [3]Medical Sciences, University of Turin, Turin, Italy;
[4]Department of Medical Imaging and Radiotherapy, Radiation Oncology, AOU Città della Salute e della Scienza, Turin, Italy;
[5]Oncological Centre for Gastrointestinal Neoplasm, Medical Oncology 1, AOU Città della Salute e della Scienza, Turin, Italy

Abstract. *Aim: To report on clinical outcomes of a consecutive series of locally advanced (T3-T4N0-N3) anal cancer patients treated with intensity-modulated radiotherapy (IMRT) and a simultaneous integrated boost (SIB) approach similarly to the RTOG 05-29 trial. Patients and Methods: A cohort of 45 patients underwent SIB-IMRT employing a schedule consisting of 54 Gy/30 fractions to the macroscopic anal planning target volume (PTV), while clinical nodes were prescribed 50.4 Gy/30 fractions if sized ≤3 cm or 54 Gy/30 fractions if >3 cm. Elective nodal PTV was prescribed 45 Gy/30 fractions. Chemotherapy was administered concurrently following the Nigro regimen. Primary end-point was colostomy-free survival (CFS). Secondary end-points were locoregional control (LRC), disease-free survival (DFS), cancer-specific survival (CSS) and overall survival (OS). Results: Median follow-up was 39.7 months. The actuarial 3-year CFS was 63.4 % (95% confidence interval (CI=44.8-77.1%). Actuarial 3-year OS and CSS were 67.7% (95%CI=48.7-80.9%) and 72.9% (95%CI=53.8-85.1%), while DFS was 55.8% (95%CI=37.5.4-70.7%). Actuarial 3-year LRC was 74.1% (95%CI=56.7-85.4%). On multivariate analysis, male sex (hazard ratio (HR)=10.9; p=0.004; 95%CI=2.2-55.5%) had a significant impact on CFS, while higher clinical stage (Stage IIIB vs. others) had borderline significance (HR=2.7; p=0.062; 95%CI=1.8-5.9%). A shorter package time (HR=0.94; p=0.007; 95%CI=0.91-0.98%) predicted for higher CFS. Maximum detected events included: skin (G3): 13%; gastrointestinal (GI) (G3): 13%; genitourinary (GU) (G2): 38%; genitalia (G2): 45%; anemia (G2): 4%; leukopenia (G3): 24%, (G4):7%; neutropenia (G3): 16%; (G4): 11%; thrombocytopenia (G3): 9%, (G4): 2%. Conclusion: Our clinical results support the use of SIB-IMRT in the combined modality treatment of locally advanced anal cancer patients.*

Correspondence to: Pierfrancesco Franco, MD, Department of Oncology-Radiation Oncology, University of Turin School of Medicine, Via Genova 3, 10126, Turin, Italy. Tel: +39 0116705350, Fax: +39 0116638680, e-mail: pierfrancesco.franco@unito.it

Key Words: Anal cancer, IMRT, volumetric modulated arc-therapy, VMAT, concomitant radiochemotherapy, acute toxicity, radiotherapy, radiation.

Tumors arising in the anal cancer are thought to be a rare clinicopathological entity, since they account for 6% of all cancers within the anorectal region and for the same percentage of all malignancies of the gastrointestinal tract (1). Concurrent chemoradiation (CT-RT) is considered a standard-of-care in this context as it provides consistent rates of locoregional control (LRC) and colostomy-free survival (CFS) (2, 3). While in early-stage disease, combination therapy is still an option under debate, in locally advanced disease with either T3-T4 tumors or nodal involvement, CT-RT is a well-established solution (2-7). Intensity-modulated radiotherapy (IMRT) is a treatment strategy, that can deliver radiation with robust conformality and modulation, abrupt dose fall-off and reliable consistency and, hence, is a suitable tool in several oncological scenarios (8, 9). IMRT can be performed using a simultaneous integrated boost (SIB) approach, which allows dispensing different daily doses to different target volumes during the same treatment fraction (10). SIB has been demonstrated to consistently spare normal tissues and has been investigated also in anal cancer patients (11, 12). The RTOG

05-29 phase II study investigated the potential of dose-painted IMRT in reducing by at least 15% the ≥G2 gastrointestinal (GI) and genitourinary (GU) acute toxicity rates, compared to the 5-fluorouracil (5FU)-mytomicin C (MMC) arm of the RTOG 98-11 trial where radiotherapy was mainly delivered with non-conformal techniques (13, 14). Having as primary end-point acute toxicity profile, RTOG 05-29 has not yet provided data on LRC and overall survival (OS). Hence, we decided to retrospectively analyze outcomes of a consecutive series of locally advanced anal cancer patients, treated at our Institution with IMRT and SIB according to RTOG 05-29 protocol.

Materials and Methods

Eligibility criteria and baseline evaluation. All patients included in the present analysis presented with squamous cell anal cancer and were submitted to definitive radiotherapy (RT) at the Department of Radiation Oncology of the University of Turin, Italy. Staging was made according to the 2002 American Joint Committee on Cancer classification. Enrolled patients had locally advanced disease (cT3-T4N0M0 or node positive disease). Written informed consent was obtained for all patients. Patients underwent clinical evaluation by the gastrointestinal tumor board of our Institution, including past clinical history, digital rectal examination and anoscopy, complete blood count, thoracic and abdominal computed tomography (CT), pelvic magnetic resonance (MR) and ^{18}FDG-PET and/or inguinal sentinel lymphnode biopsy.

Radiotherapy. Patients underwent a 3-mm slice thickness planning CT scan in supine position with both an indexed shaped knee rest and ankle support (CIVCO Medical Solutions, Kalona, IA, USA). The gross tumor volume (GTV) included all primary and nodal macroscopic disease and was expanded with 2 and 1 cm margin, respectively, to obtain subsequent clinical target volumes (CTVs) and then modified to spare bones and soft tissues. The prophylactic CTV included the mesorectal region and regional groin areas. Nodal regions were outlined with a 1 cm isotropic margin around regional vessels and then corrected to exclude bones and muscles. A 10-mm isotropic margin was added for the corresponding planning target volume (PTV). Dose prescription for target volumes was taken from Kachnic *et al*. and was based on a SIB approach (13). Patients staged as cT3-T4/N0-N3 were given 54 Gy/30 fractions to the macroscopic anal PTV, while clinical nodes were prescribed 50.4 Gy/30 fr if sized ≤3 cm or 54 Gy/30 fr if >3 cm. Elective nodal PTV was prescribed 45 Gy/30 fractions (13). Objectives for target volumes were set so that, for PTV, V_{95} should be at least 95%, V_{110} ≤10% and ≤2% should receive <95% of prescribed dose. Dose constraints for organs at risk (OARs) were inspired by Kachnic *et al*. (15). To compute volumetric modulated arc therapy (VMAT), Elekta Monaco was used as treatment planning system (version 3.2) employing a 360˚ single-arc or the dual-arc approach after system upgrade. For step and shoot IMRT, plans were generated with up to 7 modulated fields, employing 6 MV photons, according to patients' anatomy. RT was performed under daily cone beam CT (CBCT) image guidance.

Chemotherapy. All patients received concurrent chemotherapy (CT), consisting of 5- fluorouracil (1,000 mg/m^2/day) given as continuous infusion along 96 hours (days 1-5 and 29-33) associated with mitomycin C (10 mg/m^2) given as bolus (days 1 and 29). A total of 2 concurrent cycles were planned at baseline for each patient.

Table I. *Patients' and tumor characteristics*.

Variable	N (%)
Age	
Mean	62
Range	34-79
Gender	
Female	35 (78)
Male	10 (22)
HIV status	
Positive	3 (7)
Negative	42 (93)
Primary tumor site	
Anal canal	38 (84)
Anal margin	7 (16)
T stage	
T2	17 (38)
T3	24 (53)
T4	4 (9)
N stage	
N0	15 (33)
N1	5 (11)
N2	21 (47)
N3	4 (9)
Global stage	
II	13 (29)
IIIA	8 (18)
IIIB	24 (53)
Grading	
G1	3 (7)
G2	29 (64)
G3	13 (29)
Prophylactic colostomy	
Yes	0 (0)
No	45 (100)

Clinical assessment. Acute toxicity was scored according to the Common Toxicity Criteria for Adverse Events scale v3.0, evaluating GU, GI, hematologic, dermatologic, genital and osseous events. The worst toxicity for each category was considered. Follow-up included digital rectal examination and anoscopy at 4, 8, 12 and 26 weeks. MRI was performed at 12 weeks and an anal canal bioptic sampling was done at 26. If no residual disease was found at pathology, patients were classified as complete responders. Salvage abdomino-perineal resection was offered for persistent disease (at pathology) or for locally progressive or recurrent disease (at imaging and pathology). Conservative salvage treatment strategies were also considered if appropriate.

Statistical analysis. Disease recurrence was defined as local when detected in the anal canal and/or anal margin and/or mesorectum. Regional relapse included evidence of disease at draining nodes, while systemic recurrence comprised distant metastasis. For LRC, we took into account local and regional failures. Metastasis-free survival (MFS) included failures other than those occurring in the

Table II. *Treatment characteristics*.

Variable	N (%)
IMRT approach	
Step and shoot	19 (42)
VMAT	26 (58)
PTV dose-tumor (Gy)	
54 Gy/30 fractions	38 (84)
50.4 Gy/28 fractions	7 (16)
PTV dose-positive nodes (Gy)	
54 Gy/30 fractions	2 (5)
50.4 Gy/30 fractions	19 (42)
PTV dose-negative nodes (Gy)	
45 Gy/30 fractions	41 (91)
42 Gy/28 fractions	4 (9)
Chemotherapy	
5-FU + MMC	41 (91)
5-FU	1 (2)
MMC	1 (2)
None	2 (5)
Cycles	
1	2 (5)
2	41 (95)
Chemotherapy dose reduction	
Yes	4 (9)
No	39 (91)
Biopsy-RT interval (days)	
Mean	68
Range	25-159
RT duration (days)	
Mean	44
Range	37-59
Package time	
Mean	112
Range	68-211
RT breaks ≥3 days	
Yes	2 (5)
No	43 (95)

IMRT: Intensity-modulated radiotherapy; PTV: planning target volume; RT: radiotherapy; 5-FU: 5-fluorouracil; MMC: mytomicin C.

anal region and regional nodes. For cancer-specific survival (CSS), we took into account death due to disease. OS considered death of any cause. Disease-free survival (DFS) included all failures and cancer-related deaths. CFS accounted for death of any cause or definitive colostomy. Kaplan-Meier method was used to calculate survival curves and actuarial rates of relapse. Wilcoxon signed-rank test was used to perform univariate analysis. Multivariate analysis was performed using stepwise Cox proportional hazard regression models and related. Eventual correlation between clinical prognostic factors and CFS was tested. Covariates included in the analysis were sex, age, stage, grading overall treatment time (OTT) (days), time between biopsy and radiotherapy start (days) and between biopsy and radiotherapy end (days), called 'package time'. Stata Statistical Software, version 13.1 (Stata Corporation, College Station, TX, USA) was employed for analysis.

Table III. *Acute toxicity profile*.

	N(%)				
Acute toxicity	G0	G1	G2	G3	G4
Skin 1 (2)	4 (9)	34 (76)	6 (13)	0	
Gastrointestinal	0	11 (25)	28 (62)	6 (13)	0
Genitourinary	6 (13)	22 (49)	17 (38)	0	0
Genitalia 2 (4)	23 (51)	20 (45)	0	0	
Anemia 23 (51)	20 (45)	2 (4)	0	0	
Leukopenia	7 (16)	11 (24)	13 (29)	11 (24)	3 (7)
Neutropenia	14 (31)	10 (22)	9 (20)	7 (16)	5 (11)
Thrombocytopenia	25 (56)	10 (22)	5 (11)	4 (9)	1 (2)

Results

A total of 45 patients were treated between June 2007 and June 2015. Details of patients' characteristics can be found in Table I. Mean age was 62 (range=34-79). They were mainly female (78%), HIV-negative (93%), with an anal canal primary (84%), T2-T3 (91%) and N1-N2 (58%) stage and G2 (64%) grading. Patients were mainly treated with VMAT technique (58%). Most of the patients received 54 Gy/30 fractions on the primary tumor-PTV (84%), 50.4 Gy/30 fractions on the macroscopic nodes (42%) and 45 Gy/30 fractions on the prophylactic nodal PTV (91%). Most patients received 5-FU/MMC- based CT (91%) for a total of 2 cycles (95%). The mean time from biopsy to start of IMRT was 68 days. Mean OTT was 44 days. Mean package time was 112 days. Patients with breaks ≥3 days were 5%. Details are given in Table II.

Toxicity profile. Acute toxicity profile is shown in Table III. Maximum detected events included: skin (G3): 13%; GI (G3): 13%; GU (G2): 38%; genitalia (G2): 45%; anemia (G2): 4%; leukopenia (G3): 24%, (G4):7%; neutropenia (G3): 16%; (G4): 11%; thrombocytopenia (G3): 9%; (G4): 2%. Moist desquamation (skin), diarrhea with more than 7 stools per day (GI) and cystitis interfering with activities of daily living (GU) were considered as G3 events.

Clinical outcomes. Median follow-up time was 36 months (range=6-105). Globally, 15 treatment failures were observed. A total of 4 patients experienced locoregional relapse only after combined CT-RT, while 5 had distant spread as an exclusive pattern of failure (liver and lung). Up to 6 patients had both locoregional and metastatic failure. A total of 6 patients were salvaged with abdomino-perineal resection and definitive colostomy. One patient relapsing within the anal margin underwent local excision and subsequent adjuvant interstitial brachytherapy. All metastatic patients received chemotherapy as part of their salvage

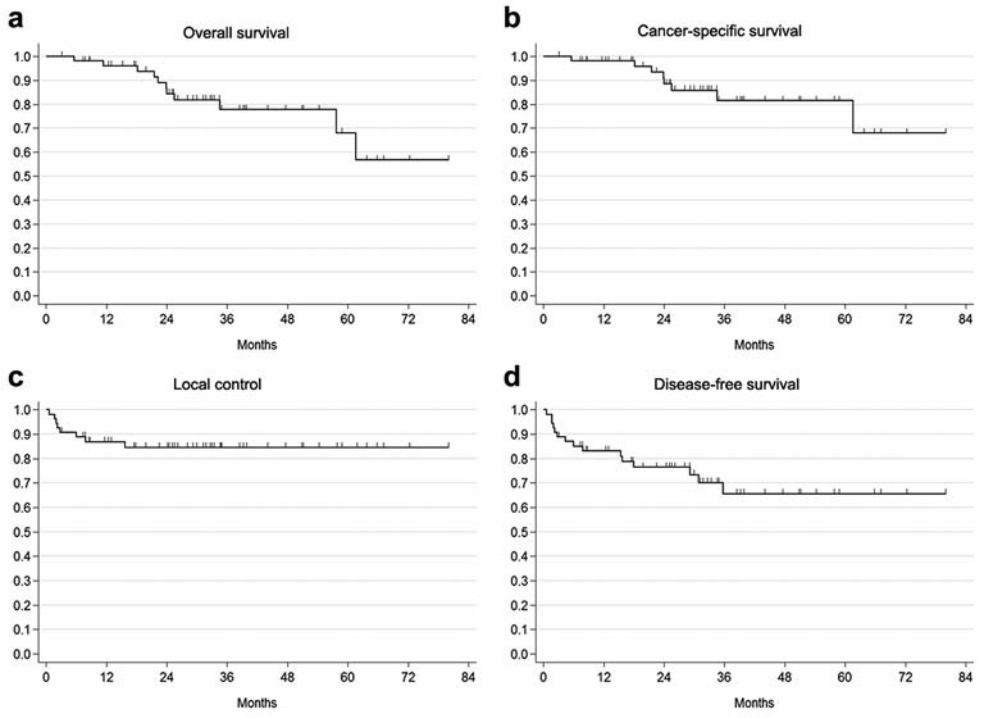

Figure 1. *Overall survival (a), cancer-specific survival (b), local control (c), disease-free survival (d).*

treatment. Overall, 16 patients died. Twelve events were cancer-related, while other 4 were due to other causes. Actuarial 3-year OS and CSS were 67.7% (95% confidence interval (CI)=48.7-80.9%) and 72.9% (95%CI=53.8-85.1%) (Figure 1a and 1b). Actuarial 3-year LRC was 74.1% (95%CI=56.7-85.4%) (Figure 1c). Actuarial 3-year DFS was 55.8% (95%CI=37.5.4-70.7%) (Figure 1d). Three-year MFS was 76.2% (95%CI=56.1-87.9%) (Figure 2). The actuarial probability of being alive at 3 years without a colostomy (CFS) was 63.4 % (95%CI=44.8-77.1%) (Figure 3). On multivariate analysis, male sex (hazard ratio (HR)=10.9; p=0.004; 95%CI=2.2-55.5%) had a significant impact on CFS, while higher clinical stage (Stage IIIB *vs.* others) had borderline significance (HR=2.7; p=0.062; 95%CI=1.8-5.9%). A shorter package time (HR=0.94; p=0.007; 95%CI=0.91-0.98%) has been shown to be a protective factor towards the occurrence of death and definitive colostomy.

Discussion

Concomitant RT-CT is presently pointed out as a standard therapeutic option in patients affected with anal cancer (2). Recent multidisciplinary guidelines indicate this treatment option as appropriate in all clinical stages, excluding T1-tumors arising from the anal margin (16). For instance, most of the data coming from prospective randomized phase III trial can be extrapolated from the context of locally advanced disease (T3-T4, N^+), where combination therapy is widely established, while CT addition still remains under debate in early-stage disease (T1-T2) (6). For example, the European Organization for Research and Treatment of Cancer (EORTC) trial included only locally advanced disease, excluding from accrual T1-T2 node negative patients (3). More than a half of patients enrolled in the ACT I study were staged as T3-T4 and up to 20% of them had palpable nodal disease, while cases staged as T1N0 were excluded (2). In the ACT II trial, 46% of patients had T3-T4 tumors and 32% had positive regional lymphnodes (15). In the RTOG 98-11 study, 35% of patients had T3-T4 disease and 26% presented with clinically positive lymphnodes (14). The EORTC is the most comparable study to our consecutive case series. It compared exclusive radiotherapy to combination therapy (with 5-FU and MMC) in locally advanced disease on 110 patients affected with cT3-T4/N0-N3 or cT1-T2/N1-N3 anal cancer (3). Radiotherapy was given up to a total dose of 45 Gy over 5 weeks using conventional fractionation to the whole pelvis followed, after a 6-week interval, by a boost dose modulated according to treatment response (20 Gy to partial and 15 Gy to complete responders). Salvage surgery was reserved to non-responders 6 weeks after the first 45 Gy delivered or to patients with residual palpable disease after

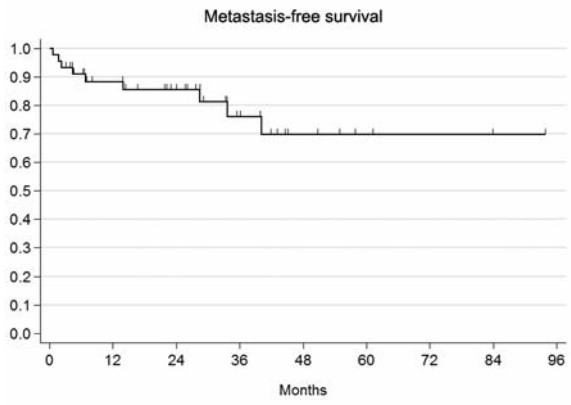

Figure 2. *Metastasis-free survival*.

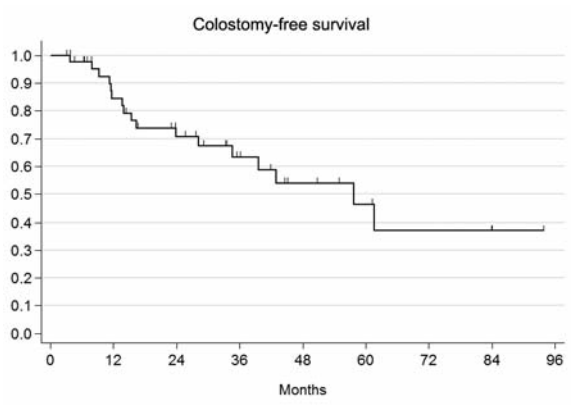

Figure 3. *Colostomy-free survival*.

the whole treatment course. In the CT-RT arm of the study, progression-free survival (PFS) was around 48% at 3 years. Actuarial 3-year OS was around 68%, while 3-year CFS was around 73%. Among treatment outcomes, authors reported also on event-free survival (EFS) defined as being free from local progression, colostomy, death and severe late complications (stenosis, severe rectal bleeding, skin or anal canal ulceration, fistula, perforation and severe fibrosis), which in the combined modality treatment arm was around 30% (3). In our series, actuarial rates of OS, DFS and CFS were 67.7%, 55.8% and 63.4%, respectively. Those results compare similarly to EORTC data, except for CFS, which was found to be lower in our series whose case mix was rather unfavorable with more than half of the patients staged as IIIB. The end-point described by the EORTC trial, namely EFS, takes into account both tumor control at any site and long-term toxicity profile. Reported rates in that study were extremely poor, in particular around 30% at 3 years. That means, in practice, that patients either developed treatment failure, eventually dying of that, or experienced RT-CT induced long-term sequelae. This consideration points out the importance of both OTT contraction and optimal radiation delivery in order to decrease acute and chronic toxicity profile. The EORTC trial delivered radiation with a 6-week interval between the whole-pelvis and the boost phase, leading to a consistent OTT with a potential detrimental effect on treatment outcomes. In fact, PFS was as low as 48% in this study. For a rapidly repopulating tumor, such as squamous cell anal cancer, the reduction of treatment delivery time is crucial. The 5FU/MMC arm of the RTOG 98-11 trial had a mean OTT of 49 days (14). In the RTOG 05-29, mean OTT was 43 days, comparably to our series (44 days) (13). This contraction in OTT is made possible by the use of SIB-based IMRT, which is able to deliver different daily doses to different treatment volumes within the same fraction (12). The effective time of radiation delivery is important, but also the global duration of diagnostic procedures and staging work-up is focal. In our series, a shorter package time was found to be predictive of a lower likelihood to experience death or definitive colostomy (HR=0.94; p=0.007; 95%CI=0.91-0.98%). The other key point is toxicity profile as it affects both patient's quality of life and treatment global intensity. Our patient cohort underwent a treatment strategy similar to the RTOG 05-29 trial using IMRT and SIB (13). The RTOG 05-29 phase II study was designed to assess whether dose-painted IMRT could reduce by at least 15% the ≥G2 GI and GU toxicity rates, compared to conventional radiation and concurrent 5-FU/MMC as delivered in the standard arm of RTOG 98-11 trial, which employed non-conformal techniques, namely anterior-posterior parallel-opposed fields or 4-field conformal beam arrangements (13, 14). In the aforementioned trial, the primary end-point was not reached, but the study demonstrated a significant decrease 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) compared to standard radiation (13, 14). Similarly, our results showed a reasonable toxicity profile with a mild rate of major events. Our data support the use of SIB-IMRT delivered with concurrent 5FU/MMC-based CT similarly to the RTOG 05-29 protocol with consistent clinical outcomes and acceptable side effects in locally advanced anal cancer patients. Treatment intensification either with dose-escalation or with other adjunctive drugs, such as targeted therapies, may be suggested for patients having high-risk features, such as male sex and advanced nodal stage. However, a focused attention should be paid to avoid treatment breaks and unintended delays in the diagnostic and therapeutic process (18).

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Conflicts of Interest

The Authors declare that we do not have any conflict of interest

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