Early-stage Node-negative (T1-T2N0) 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, [3]Medical Sciences, University of Turin, Turin, Italy; [4]Department of Medical Imaging and Radiotherapy–Radiation Oncology, and [5]Oncological Centre for Gastrointestinal Neoplasm, Medical Oncology 1, City of Health and Science Hospital, Turin, Italy

Abstract. *Aim: To report clinical outcomes of a consecutive series of patients with early-stage (T1-T1N0) anal cancer 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 43 patients underwent SIB-IMRT employing a schedule consisting of 50.4 Gy/28 fractions to the gross tumor volume and 42 Gy/28 fractions to the elective nodal volumes for cT1N0 cases, and 54 Gy/30 fractions and 45 Gy/30 fractions to the same volumes for cT2N0 cases. Chemotherapy was administered concurrently following Nigro's regimen. The primary endpoint was colostomy-free survival (CFS). Secondary endpoints were locoregional control (LRC), disease-free (DFS), cancer-specific (CSS) and overall (OS) survival. Results: Median follow-up was 39.7 months. The actuarial 3-year CFS was 79.4% [95% confidence interval (CI)=61.4-89.7%]. Actuarial 3-year OS and CSS were 90.8% (95% CI=74.1-96.9%) and 93.8% (95% CI=77.3-98.4%), while DFS was 75.5% (95% CI=56.4-87.1%). Actuarial 3-year LRC was 86.1% (95% CI=69.6-94%). On multivariate analysis, tumor size >3 cm showed a trend towards significance in predicting CFS [hazard ratio (HR)=8.6, 95% CI=84.7-88.1%; p=0.069]. Maximum detected adverse events included: skin (G3): 18%; gastrointestinal tract (G2): 67%; genitourinary tract (G3): 3%; genitalia (G2): 30%; anemia (G2): 7%; leukopenia (G3): 26%, leukopenia (G4):7%; neutropenia (G3): 15%; neutropenia (G4): 12%; thrombocytopenia (G3): 9%. Conclusion: Our clinical results support the use of SIB-IMRT in the combined modality treatment of patients with anal cancer.*

Anal cancer is considered a rare malignancy, accounting for 6% of cancer of the ano-rectal region and 6% of all gastrointestinal tumors (1). Concurrent radiochemotherapy (CRT) represents a standard treatment option in this setting, and can provide high-rates of locoregional control (LRC) and colostomy-free survival (CFS) (2, 3). Combination therapy is well-established for locally advanced disease, either for T3-T4 tumors or those with nodal involvement, while in early-stage cancer, exclusive radiation is also considered a suitable solution, even if recent data seem to favor CRT (2-7). Intensity-modulated radiotherapy (IMRT) can be performed with a simultaneous integrated boost (SIB) approach, which allows delivery of different daily doses to different target volumes during the same treatment fractions (8, 9). This strategy has also been used to investigate patients with anal cancer (10). In particular, the Radiation Therapy Oncology Group (RTOG) 05-29 phase II trial was designed to investigate the potential of dose-painted IMRT in reducing by at least 15% the grade 2 or more gastrointestinal (GI) and genitourinary (GU) acute toxicity rates compared to the 5-fluorouracil (5-FU)–mytomicin C (MMC) arm of the RTOG 98-11 trial, where radiation was mainly delivered with non-conformal techniques (11, 12). Being designed for study of the toxicity profile, RTOG 05-29 has not yet reported on LRC and survival. Hence, we decided to retrospectively analyze outcomes of a consecutive series of patients with early-stage node-negative anal cancer who were treated at our Institution with IMRT and SIB similarly to the RTOG 05-29 protocol.

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.

Patients and Methods

Eligibility criteria and baseline evaluation. All patients analyzed in the present study were diagnosed with anal cancer of squamous histology and were treated with definitive radiotherapy (RT) at the Department of Radiation Oncology of the University of Turin, Italy. Disease was staged according to the 2002 American Joint Committee on Cancer classification and the focus was directed towards early-stage disease including cT1-T2 N0M0 cases (13). 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 and fluorodeoxyglugose positron-emission tomography or inguinal sentinel lymph node 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 margins, 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*. (11) and was based on an SIB approach. Patients with cT1 or T2 ≤3 cm disease were prescribed 50.4 Gy/28 fractions to the gross tumor PTV and 42 Gy/28 fractions to the elective nodal PTV. Patients staged with disease of cT2 >3 cm were given 54 Gy/30 fractions to the macroscopic anal PTV, while elective nodal PTV was prescribed 45 Gy/30 fractions. Objectives for target volumes were set so that for PTV, V95 would be at least 95%, V110 ≤10% and ≤2% should receive <95% of prescribed dose. Dose constraints for organs at-risk were inspired by Kachnic *et al*. (14).

In order to compute VMAT, Elekta Monaco (Elekta, Crawley, Surrey, UK) 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 seven modulated fields, employing 6 MV photons, according to patient's anatomy. Radiotherapy was performed under daily cone-beam CT image guidance.

Chemotherapy. All patients received concurrent chemotherapy consisting of 5-FU (1000 mg/m^2/day) given as continuous infusion over 96 hours (days 1-5 and 29-33) associated with MMC (10 mg/m^2) given as bolus (days 1 and 29). A total of two concurrent cycles were planned at baseline for each patient.

Clinical assessment. Acute toxicity was scored according to the Common Toxicity Criteria for Adverse Events scale v3.0, evaluating GU, GI, hematological, dermatological, 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. Magnetic resonance imaging was performed at 12 weeks and an anal canal bioptic sampling was carried out at 26 weeks. If no residual disease was found on pathological examination, patients were classified as complete responders. Salvage abdomino-perineal resection was offered for persistent disease (pathology) or for locally progressive or recurrent disease (imaging and pathology). Conservative salvage treatment strategies were also considered when appropriate.

Statistical analysis. Disease recurrence was defined as local when occurring in the anal canal or anal margin or mesorectum. Regional relapse comprised disease at draining nodes, while systemic recurrence included distant metastasis. For LRC, we took into account local and regional failures. For cancer-specific survival (CSS), we considered death due to disease. Overall survival (OS) was considered up to death from any cause. Disease-free survival (DFS) included all failures and cancer-related deaths. CFS took into account death from any cause or definitive colostomy. The Kaplan–Meier method was used to calculate survival curves and actuarial rates of relapse. The Wilcoxon signed-rank test was used to perform univariate analysis. Multivariate analysis was performed using stepwise Cox proportional hazard regression models were used to explore potential correlations between clinical prognostic factors and CFS. Covariates included in the analysis were sex, age overall treatment time (OTT), time between biopsy and radiotherapy start, tumor dimension and grading. Stata Statistical Software, version 13.1 (Stata Corporation, TX, USA) was employed for analysis.

Results

A total of 43 patients were treated between July 2007 and June 2015. Patients characteristics are detailed in Table I. Patients had a mean age of 58 (range=45-82) years and were mainly female (68%), HIV-negative (88%), with an anal canal primary tumor (84%), of T2 stage (88%) sized 2.1-4 cm (71%) and G2 (72%).

Patients were mainly treated with the VMAT technique (51%). Most patients received 50.4 Gy/28 fractions to the primary tumor PTV and 42 Gy/28 fractions to the prophylactic nodal PTV (60%). The mean time from biopsy to start of IMRT was 92 days. The mean OTT was 42 days. Patients with breaks of 3 days or more comprised 5% of the population. Details can be seen in Table II.

Toxicity profile. The acute toxicity profile is shown in Table III. The majority of patients experienced grade 2 or more skin toxicity. Moist desquamation (skin), diarrhea with more than seven stools per day and cystitis interfering with activities of daily living were considered as grade 3 events. A total of four out of 43 patients (9%) underwent a single cycle of concurrent 5-FU and MMC due to toxicity.

Clinical outcomes. The median follow-up time was 39.7 (range=7-102) months. Overall, seven treatment failures were observed. A total of five patients experienced exclusive local relapse after CRT. All of them had T2 stage tumor between 3 and 4 cm. One patient showed systemic spread (lung) and another synchronous pelvic nodal and distant (lung) metastases. All patients with local failure were salvaged with abdomino-perineal resection and definitive colostomy. Among

Table I. *Patient and tumor characteristics*.

Variable	N (%)
Age, years	
Mean	58
Range	45-82
Gender	
Female	29 (68)
Male	13 (32)
HIV status	
Positive	5 (12)
Negative	38 (88)
Primary tumor site	
Anal canal	36 (84)
Anal margin	7 (16)
T-Stage	
T1	5 (12)
T2	38 (88)
Tumor size, cm	
0.1-1	2 (4)
1.1-2	3 (7)
2.1-3	17 (39)
3.1-4	13 (32)
4.1-5	8 (18)
Grading	
1	4 (9)
2	31 (72)
3	8 (19)
Prophylactic colostomy	
Yes	0 (0)
No	43 (100)

Table II. *Treatment characteristics*.

Variable	N (%)
IMRT approach	
Step-and-shoot	21 (49)
VMAT	22 (51)
PTV dose to tumor (Gy)	
54 Gy/30 fractions	17 (40)
50.4 Gy/28 fractions	27 (60)
PTV dose to negative nodes (Gy)	
45 Gy/30 fractions	28 (40)
42 Gy/28 fractions	11 (60)
Chemotherapy	
None	3 (7)
5-FU	1 (2)
5-FU + MMC	39 (91)
5-FU + MMC cycles (39 pts)	
1	4 (10)
2	35 (90)
Chemotherapy dose reduction (40 pts)	
Yes	1 (3)
No	39 (97)
Biopsy-RT interval (days)	
Mean	92
Range	30-193
RT duration (days)	
Mean	42
Range	37-48
RT breaks ≥3 days	
Yes	2 (5)
No	41 (95)

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

them, one patient underwent interstitial brachytherapy as first salvage option and subsequent salvage surgery because of persistent disease. All patients with metastases received chemotherapy as part of their salvage treatment.

Overall, four patients died. Two events were cancer-related, while the other two were due to other causes. Actuarial 3-year LRC was 86.1% (95% CI=69.6-94%) (Figure 1A). Actuarial 3-year OS and CSS were 90.8% (95% CI=74.1-96.9%) and 93.8% (95% CI=77.3-98.4%), respectively (Figure 1B and C). Actuarial 3-year DFS was 75.5% (95% CI=56.4-87.1%) (Figure 1D). The actuarial probability of being alive at 3 years without a colostomy (CFS) was 79.4% (95% CI=61.4-89.7%) (Figure 2). On multivariate analysis, tumor size greater than 3 cm exhibited a trend towards significance in predicting poorer CFS (HR=8.6, 95% CI=84.7-88.1%; p=0.069).

Table III. *Acute toxicity*.

	Grade, N(%)				
Acute toxicity	0	1	2	3	4
Skin	0	8 (18)	27 (64)	8 (18)	0
Gastrointestinal	1 (3)	13 (30)	29 (67)	0	0
Genitourinary	10 (23)	22 (51)	10 (23)	1 (3)	0
Genitalia	3 (7)	27 (63)	13 (30)	0	0
Anemia	26 (60)	14 (33)	3 (7)	0	0
Leukopenia	7 (15)	11 (26)	11 (26)	11 (26)	3 (7)
Neutropenia	14 (34)	10 (24)	7 (15)	7 (15)	5 (12)
Thrombocytopenia	25 (57)	10 (24)	3 (7)	4 (9)	1 (3)

Discussion

CRT is considered a standard of care in patients with anal cancer (2). Recent multidisciplinary guidelines indicate this approach as a current treatment option in all settings except T1 tumors of the anal margin (15). Nevertheless, the use of combination therapy is largely established for locally advanced disease (T3-T4, N+), while the addition of chemotherapy remains debatable for early-stage disease (T1-T2) (6). The randomized phase III trials that provided

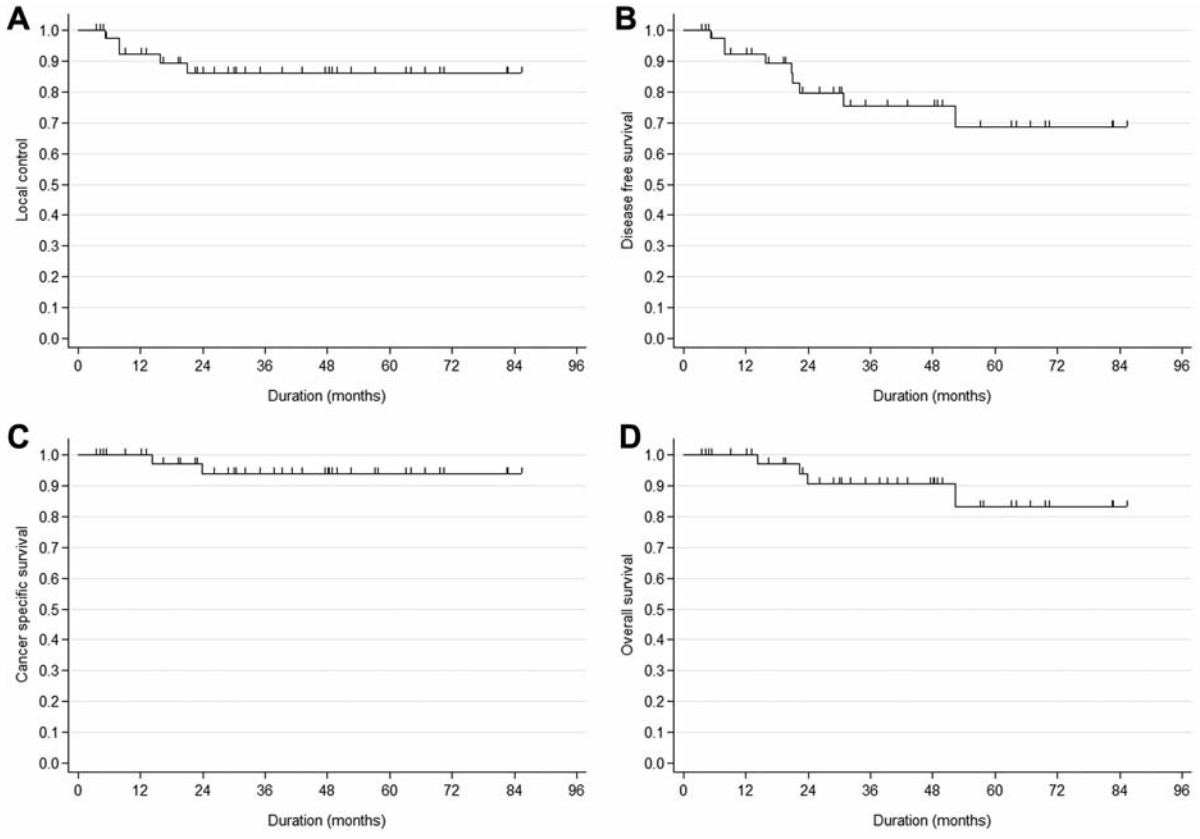

Figure 1. *Local control (A), and overall (B), cancer-specific (C) and disease-free (B) survival.*

clinical evidence on the role of CRT were unable to solve this issue. The European Organisation for Research and Treatment of Cancer trial was only targeted to locally advanced disease and excluded patients with T1-T2 node-negative disease from accrual (3). In the ACT I study, disease in more than half of the patients was staged as T3-T4 and up to 20% of enrolled cases had palpable nodal disease. Patients with T1N0 stage disease were excluded (2). In the ACT II trial, 46% of patients had T3-T4 tumors and 32% had positive regional lymph nodes (16). Targeted analysis of patients with early-stage disease has not been performed, thus the benefit of concurrent chemotherapy in this setting needs further investigation.

Some interesting data can be derived from robust and retrospective analyses. Zilli *et al*. provided clinical data on a cohort of 146 patients affected with early-stage node-negative T1-T2 anal cancer (6). Results in terms of LRC and CSS were similar to historical series. The outcome in the cohort was excellent for patients with tumors of 3 cm or less, with a 5-year LRC in excess of 85%, regardless of treatment modality. Interestingly, patients treated with exclusive RT had a lower 5-year LRC rate compared to those treated with CRT (75.5% *vs*. 86.8%), even if the difference was not statistically significant (p=0.065). This finding was also confirmed after stratification according to different clinical- and treatment-related factors (6). Another interesting study was reported by De Bari *et al*. (7). Their retrospective analysis on 122 patients with anal cancer found a benefit at univariate analysis in terms of LRC (+9.8%; p=0.03), DFS

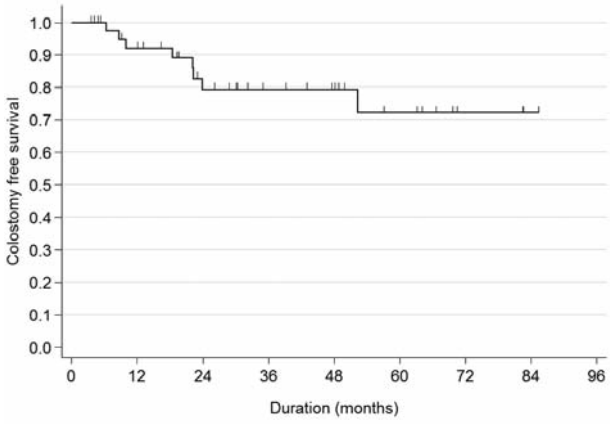

Figure 2. *Colostomy-free survival.*

(+8.5%; p=0.04), CFS (+21.2%; p=0.001) and OS (+18.5%; p=0.03) for the addition of chemotherapy. The advantage of CRT was also confirmed by multivariate analysis (7). In this series, the impact of chemotherapy was detected only for those with T2 tumors.

Our patient cohort was treated according to RTOG 05-29 indications, employing IMRT and different daily doses to different treatment sites following an SIB approach (11,17). The RTOG 05-29 phase II trial was designed to investigate whether dose-painted IMRT would reduce by at least 15% the grade 2 or more GI and GU toxicity rates compared to conventional radiation and concurrent 5-FU/MMC, as delivered in the standard arm of the RTOG 98-11 trial, which employed non-conformal techniques (namely anterior-posterior parallel-opposed fields or 4-field conformal beam arrangements) (11, 12). In that trial, the primary endpoint was not reached, but the study showed a significant reduction in acute G2 hematological (73% *vs*. 85% for RTOG 98-11), G3 GI (21% *vs*. 36% for RTOG 98-11) and G3 dermatological acute adverse events (23% *vs*. 49% for RTOG 98-11) compared to standard RT (11). However, no results in terms of local control and survival have been reported so far. Our patients were treated similarly to RTOG 05-29. Actuarial 3-year LRC, DFS, CSS and OS were 86.1% (95% CI=69.6-94%), 75.5% (95% CI=56.4-87.1%), 93.8% (95% CI=77.3-98.4%) and 90.8% (95% CI=74.1-96.9%). Actuarial 3-year CFS was 79.4% (95% CI=61.4-89.7%). These results compare favorably with the available literature, especially considering that our cohort included patients mainly with T2 tumors (88%) sized greater than 3 cm (50%). Five local relapses were recorded, all salvaged with abdomino-perineal resection according to Miles (18). All patients had T2 stage and maximal tumor dimension ranging between 3 and 4 cm. Notably, on multivariate analysis, tumor size in excess of 3 cm tended to predict poorer CFS (HR=8.6; 95% CI=84.7-88.1%; p=0.069).

An advantage in delivering RT employing an SIB approach is the contraction of the OTT. The 5-FU/MMC arm of the RTOG 98-11 trial had a mean OTT of 49 days (12). In the RTOG 05-29 trial, the mean OTT was 43 days, comparably to our series (42 days) (11). The cohort reported by Zilli *et al*. had a mean OTT of 62 days (6), while that described by De Bari *et al*. was 52 days (7). As pointed out by De Bari *et al*., concomitant chemotherapy may provide a benefit in terms of clinical outcomes, especially when RT is delivered optimally, with an acceptable toxicity profile able to avoid treatment breaks and consequently shorten the overall duration of CRT. Our results show that SIB-IMRT delivered with concurrent chemotherapy similarly to the RTOG 05-29 protocol has consistent clinical outcomes and a mild toxicity profile. Treatment intensification for T2 tumors larger than 3 cm may be a hypothesis-generating investigational field.

Financial Support

None to declare.

Conflicts of Interest

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

Acknowledgements

None.

References

1 Siegel R, Ma J, Zou Z and Jemal A: Cancer statistics 2014. CA Cancer J Clin *64*: 9-29, 2014.

2 UKCCCR Anal cancer Trial Working Party. UK Co-ordination Committee on Cancer Research: Epidermoid anal cancer: results from the UKCCCR randomized trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet *348*: 1049-1054, 1996.

3 Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, Peiffert D, van Glabbeke M and Pierart M: 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 Group. J Clin Oncol *15*: 2040-2049, 1997.

4 Flam M, John M, Pajak TF, Petrelli N, Myerson R, Doggett S, Quivey J, Rotman M, Kerman H, Coia L and Murray K: Role of mytomicin 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 *14*: 2527-2539, 1996.

5 Deniaud-Alexandre E, Touboul E, Tiret E, Sezeur A, Houry S, Gallot D, Parc R, Huang R, Qu SH, Huart J, Pene F and Schlienger M: Results of definitive irradiation in a series of 305 epidermoid carcinomas of the anal canal. Int J Radiat Oncol Biol Phys *56*: 1259-1273, 2003.

6 Zilli T, Schick U, Ozsahin M, Gervaz P, Roth AD and Allal AS: Node-negative T1-T2 anal cancer: Radiotherapy alone or concomitant chemoradiotherapy? Radiother Oncol *102*: 62-67, 2012.

7 De Bari B, Lestrade L, Pommier P, Maddalo M, Buglione M, Magrini SM and Carrie C: Could concomitant radiochemotherapy improve the outcomes of early-stage node negative anal canal cancer patients? A retrospective analysis of 122 patients. Cancer Invest *33*: 114-120, 2015.

8 Franco P, Zeverino M, Migliaccio F, Cante D, Sciacero P, Casanova Borca V, Torielli P, Arrichiello C, Girelli G, La Porta MR, Tofani S, Numico G and Ricardi U: Intensity-modulated and hypofractionated simultaneous integrated boost adjuvant breast radiation employing static ports of tomotherapy (TomoDirect): a prospective phase II trial. J Cancer Res Clin Oncol *140*: 167-177, 2014.

9 Ricardi U, Franco P, Munoz F, Levis M, Fiandra C, Guarneri A, Moretto F, Bartoncini S, Arcadipane F, Badellino S, Piva C, Trino E, Ruggieri A, Filippi AR and Ragona R: Three-dimensional ultrasound-based image-guided hypofractionated radiotherapy for intermediate-risk prostate cancer: results of a consecutive case series. Cancer Invest *33*: 23-28, 2015.

10 Franco P, Mistrangelo M, Arcadipane F, Munoz F, Sciacero P, Spadi R, Migliaccio F, Angelini V, Bombaci S, Rondi N, Numico G, Ragona R, Cassoni P, Morino M, Racca P and Ricardi U: 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 33: 259-266, 2015.

11 Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, Haddock MG, Rotman M, Parikh PJ, Safran H and Willett CG: RTOG 0529: a phase II evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mytomycin C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys 86: 27-33, 2013.

12 Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB 3rd, Thomas CR Jr., Mayer RJ, Haddock MG, Rich TA and Willett C: Fluorouracil, mitomycin, and radiotherapy *vs*. fluorouracil, cisplatin, and radiotherapy for carcinoma of the anal canal: a randomized controlled trial. JAMA 299: 1914-1921, 2008.

13 AJCC Cancer Staging Manual – 6th Edition, 2002. Springer, Berlin, Germany.

14 Kachnic LA, Tsai HK, Coen JJ, Blaszkowsky LS, Hartshorn K, Kwak EL, Willins JD, Ryan DP and Hong TS: 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 82: 153-158, 2012.

15 Glynne-Jones R, Nilsson PJ, Aschele C, Goh V, Peiffert D, Cervantes A and Arnold D: Anal cancer: ESMO-ESSO-ESTRO clinical practice guidelines for diagnosis, treatment and follow up. Radiother Oncol *111*: 330-339, 2014.

16 James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, Maughan T, McDonald A, Essapen S, Leslie M, Falk S, Wilson C, Gollins S, Begum R, Ledermann J, Kadalayil L and Sebag-Montefiore D: 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 *14*: 516-524, 2013.

17 Franco P, Arcadipane F, Ragona R, Mistrangelo M, Cassoni P, Munoz F, Rondi N, Morino M, Racca P and Ricardi U: Volumetric modulated arc therapy (VMAT) in the combined modality treatment of anal cancer patients. Brit J Radiol 2016 http://www.birpublications.org/doi/abs/10.1259/bjr.20150832

18 Miles WE: A method of performing abdominoperineal excision for carcinoma of the rectum and the terminal portion of pelvic colon. Lancet *2*: 1812-1813, 1908.

Received January 22, 2016
Revised March 5, 2016
Accepted March 16, 2016