

Original paper

Long-term results of chemoradiation plus pulsed-dose-rate brachytherapy boost in anal canal carcinoma: A mono-institutional retrospective analysis

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Abstract

Purpose: Concurrent chemoradiation (CCRT) is the standard curative treatment of anal canal cancer (ACC). The role of a brachytherapy (BRT) boost in this setting is still debated. Therefore, the aim of this analysis was to retrospectively evaluate the clinical outcomes in a large cohort of ACC patients treated with CCRT plus BRT boost or external beam radiotherapy (EBRT) boost.

Material and methods: Patients with non-metastatic ACC, treated in our department between January 2003 and December 2014 were included in this analysis. The initial treatment was based on EBRT to the pelvis (prescribed dose, 45 Gy/1.8 Gy) plus concurrent chemotherapy (5-fluorouracil and mitomycin-C). Patients received a pulsed-dose-rate BRT boost on the primary tumor (median dose, 20 Gy; range, 13-25 Gy) 2-3 weeks after the end of CCRT. In patients with contraindications to BRT, an EBRT boost (prescribed dose, 16 Gy, 2 Gy/fraction) was delivered immediately after CCRT.

Results: One-hundred-twenty-three patients were included in this analysis (median age, 61 years; range, 36-93 years; squamous-cell carcinoma, 78%; HIV+, 6%; median follow-up, 71 months; range, 2-158 months). The actuarial 5-year local control (LC), distant metastasis-free survival, colostomy-free survival, and overall survival (OS) rates were 81.7%, 92.3%, 62.3%, and 74.0%, respectively. At univariate analysis, patients aged ≤ 65 years ($p < 0.010$), cT1-2 stage ($p = 0.004$), and receiving a BRT boost ($p = 0.015$) showed significantly improved OS. At multivariate analysis, advanced tumor stage cT3-cT4 (HR, 2.12; 95% CI: 1.09-4.14; $p = 0.027$), and age > 65 years (HR, 3.03; 95% CI: 1.54-5.95; $p = 0.001$) significantly predicted increased risk of mortality. The crude rate of toxicity-related colostomies was 4.9%.

Conclusions: The role of BRT boost in ACC remains unclear since the outcomes were not clearly different compared to CCRT alone. However, further improvement of clinical results in ACC treatment is needed, and therefore prospective trials based on advanced (image-guided/adapted) BRT techniques are warranted.

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Key words: anal carcinoma, brachytherapy, colostomy-free survival.

Purpose

Anal canal cancer (ACC) is a relatively rare malignancy representing about 0.4% of all new diagnosed neoplasms [1], with an age-adjusted incidence ratio of 0.32 per 100,000 in the US [2]. Over the past decades, perhaps due to increased transmission of HIV and HPV, the incidence

has increased without clear improvement in survival even if distant metastases occur in only 5-10% of cases [3,4].

Concurrent chemoradiation (CCRT) based on external beam radiation therapy (EBRT) plus concurrent 5-fluorouracil (5-FU) and mitomycin-C (MMC) represents the standard treatment option in non-metastatic ACC

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according to results reported from several randomized trials [5,6,7,8]. However, 20% and 30% 5-year rates of local-regional recurrences and colostomy, respectively, have been reported after CCRT [8,9].

Brachytherapy (BRT) boost has been used to improve these outcomes by delivering a higher and more focused dose to the primary tumor. However, no robust evidence is available on the real advantage produced by a BRT boost after CCRT [10]. Furthermore, most published series were based on the use of low-dose-rate (LDR) BRT and data on the efficacy of pulsed-dose-rate (PDR) are lacking. PDR is a theoretically advantageous BRT technique, since it combines the radiobiological advantages of LDR BRT with the dosimetrical advantages of high-dose-rate BRT.

Therefore, the aim of this study was to contribute to the current evidence on this issue by retrospectively reviewing a large series of patients with prolonged follow-up, treated with CCRT followed by PDR BRT boost.

Material and methods

Study design and objectives

This was a monocentric retrospective analysis of feasibility and clinical outcomes of CCRT followed by BRT boost in ACC. The study was approved by our institutional review board. Patients ≥ 18 years with histologically proven non-metastatic ACC with any tumor (T) and nodal (N) stage, treated with CCRT followed by a BRT boost (or EBRT boost if BRT was contraindicated) were eligible for inclusion. Patients with distant metastases or locally recurrent disease and with tumors of the anal margin were excluded.

From January 2003 to December 2014, 185 patients with ACC were treated in our department. Among them, 123 patients were selected according to our inclusion criteria.

Staging and treatment

Clinical stage was defined according to the American Joint Committee on Cancer criteria [11] by digital rectal examination, anorectal ultrasonography, proctoscopy, computed tomography (CT) scan, and magnetic resonance imaging (MRI). 18F-FDG-PET-CT imaging was used only in a few selected patients with doubtful results after the standard exams.

Patients were first treated with pelvic CCRT. Concurrent continuous infusion of 5-FU (1,000 mg/m²/day continuous intravenous infusion for 4 consecutive days in the first and fourth week of EBRT treatment) and MMC (10 mg/m²/day bolus intravenous infusion on day 1 and 29 of EBRT treatment) were administered. Pelvic EBRT started on the first day of chemotherapy (CHT). The prescribed dose was 45 Gy (1.8 Gy/fraction). EBRT was planned with 3-dimensional conformal technique using 3 or 4 fields and delivered with a linear accelerator (6-18 MV photon energy) with the patient in prone position. The clinical target volume (CTV) was defined as the gross tumor volume (GTV), the anal canal and the whole mesorectum, internal and external iliac nodes, obturator nodes, and presacral nodes. The GTV extension was evaluated in

all patients by transrectal ultrasound. Inguinal nodes were included in the CTV only if metastatic and in patients with cT3-4 ACC or with positive pelvic nodes, according to the Radiation Therapy Oncology Group guidelines. The dose was prescribed and specified according to the International Commission on Radiation Units Measurements report no 50 (ICRU 50) [12].

In 53 patients with positive nodes at clinical staging, a sequential boost was delivered to the involved lymph nodes using multiple fields technique (6-18 MV photons; median dose, 18 Gy; range, 14-20 Gy; 2 Gy/fraction) or with a direct electron beam (20 Gy in 2 Gy/fraction) in case of inguinal nodes.

Clinical response evaluation was performed at the end of CCRT by clinical examination. Patients with cancer involving $> 2/3$ of the anal canal circumference or with > 1 cm involvement of perianal skin before CCRT, or with residual disease > 5 cm in longitudinal or > 1.5 cm in circumferential direction after CCRT, or with medical contraindication to anesthesia were considered not eligible for BRT and were treated with EBRT boost. EBRT boost was delivered immediately after CCRT with multiple fields technique (16 Gy, 1.8 Gy/fraction). The BRT boost was delivered 2-3 weeks after CCRT to allow recovery from acute toxicity using ¹⁹²Ir sources. The needles of an active length varying from 5 to 8 cm depending on the size of the tumor were positioned in parallel, with a distance of 1 cm interval to ensure adequate dosimetry using a perineal template under general anesthesia. To locate the residual tumor or scar, 1-2 landmarks of silver were inserted. At the end of the implantation prior to insertion of the ¹⁹²Ir sources, all patients underwent two orthogonal radiograms in order to verify the correct alignment and position of the hollow needles. In case of deviations detectable with this method, the same needles were repositioned. Dose was prescribed and specified based on the Paris system [13] and delivered with 0.67-0.8 Gy/hour PDR, lasting 24-36 hours. In case of residual disease after CCRT, a BRT boost dose ≥ 20 Gy was prescribed. If complete clinical response was observed after CCRT, the BRT dose was ≤ 16 Gy. Furthermore, for T₁₋₂ and T₃₋₄, the median number of charged loaded needles were 5 and 6-7, respectively.

Follow-up

Follow-up visits were performed by a multidisciplinary team including clinical examination and anorectal ultrasonography every 4 months in the first two years after treatment, every 6 months in the following 3 years, and then yearly. Biopsies under anesthesia were used for differential diagnosis between recurrence and radiation-induced complications, but never before 6 months from the end of the treatment due to the risk of complications and the low probability of early local relapse.

Statistical analysis

Local control (LC), colostomy-free survival (CFS), distant metastatic-free survival (DMFS), and overall survival (OS) were calculated from the date the treatment started. LC was evaluated considering events clinical-

ly evident for local-regional (T and N) disease relapse, persistence, or progression, positive biopsy, and salvage surgery. DMFS was evaluated taking into consideration any treatment failure outside the pelvis. OS was defined as death resulting from any cause. Colostomy-free survival was measured from the day of treatment initiation to colostomy, death, or last follow-up evaluation if the patient was alive with no surgery. Descriptive statistics was used to report patient, tumor, and treatment characteristics. Survival functions were described using the Kaplan-Meier method [14] and compared with log-rank test [15] to investigate differences in OS, LC, CFS, and DMFS between groups defined, based on clinical and pathological factors. Multivariable analysis was performed using Cox's proportional hazard model [16]. Covariates to be introduced in the multivariable models were selected based on backward stepwise strategy (p inclusion < 0.1 ; p exclusion ≥ 0.1). All tests were two-sided and p value < 0.05 was considered statistically significant. Statistical analysis was performed with SPSS version 22.0 (IBM Corp., Armonk, NY, USA).

Table 1. Patient characteristics of the analyzed cohort with the number of patients' and percentage of the total number of patients [%]

Variable	Median (range)	No. of patients (%)
Age (years)	61 (36-93)	
Follow-up (months)	71 (2-158)	
Gender		
Male		30 (24.4)
Female		93 (75.6)
Age (years)		
≤ 65		71 (57.7)
> 65		52 (42.3)
Histology		
Squamous		96 (78.0)
Cloacogenic		8 (6.5)
Basaloid		14 (11.4)
Other		5 (4.1)
cT-stage		
1		18 (14.6)
2		45 (36.6)
3		41 (33.3)
4		19 (15.4)
cN-stage		
N0		70 (56.9)
N1		28 (22.8)
N2		13 (10.5)
N3		12 (9.8)
HIV		
Positive		7 (5.7)
Negative		116 (94.3)

BRT – brachytherapy, EBRT – radiotherapy, HIV – human immunodeficiency virus, No – number

Results

From 123 ACC patients included in this analysis, 116 were treated with CCRT followed by a sequential boost of BRT (102 patients) or EBRT (21 patients), while 7 patients did not receive CT because of advanced age (> 85 years, 3 patients), cardiovascular comorbidities (3 patients), and severe herpes zoster infection (1 patient). The median prescribed BRT boost dose was 20 Gy (range, 13-25 Gy). Median follow-up was 71 months (range, 2-158 months). Patients characteristic are summarized in Table 1.

Two-, 5-, and 10-year OS rates were 88.6%, 74.0%, and 64.3%, respectively (Figure 1). At univariate analysis, age ≤ 65 years ($p < 0.010$), initial tumor stage T_{1-2} ($p = 0.004$), and sequential boost delivered with BRT ($p = 0.015$) were significantly correlated with improved OS (Table 2). At multivariable analysis, patients with cT_{3-4} stage (HR, 2.12; 95% CI: 1.09-4.14; $p = 0.027$) and aged > 65 years (HR, 3.03; 95% CI: 1.54-5.95; $p = 0.001$) showed a significantly higher risk of mortality. Table 3 shows LC, CFS, and DMFS stratified for clinical-pathological factor at univariate analysis. Twenty-two patients had local recurrence, more frequently in male patients ($p < 0.001$). Two-, 5-, and 10-year LC was 84.2%, 81.7%, and 81.7%, respectively (Figure 2). Considering the large and statistically significant difference in terms of LC between gender, a detailed analysis of this difference in various tumor stage subgroups was performed (Table 4). Our analysis showed that a statistically higher LC rate in female patients was recorded in $T_{1-2}N_0$ subjects ($p < 0.001$) with a trend in the $T_{1-2}N_+$ and in the $T_{3-4}N_+$ groups ($p = 0.085$ and $p = 0.082$, respectively). Ten patients developed metastases, and 2-, 5-, and 10-year DMFS was 93.3%, 92.3%, and 92.3%, respectively (Figure 3). DMFS rate was higher in patients treated with BRT boost ($p < 0.001$). Two-, 5-, and 10-year CFS was 74.8%, 62.3%, and 55.2%, respectively (Figure 4). CFS was significantly worse in male patients ($p < 0.001$) and in patients > 65 years old ($p = 0.002$). Overall, 26 patients underwent colostomy during follow-up (21.1%). In 20 patients, colostomy was performed because of local recurrence (16.3%) and in 6 cases because of treatment-related toxicity (4.9%). Colostomy due to treatment-related toxicity was recorded in 5 patients treated with BRT boost (4.9%) and in 1 patient treated with EBRT boost (4.8%).

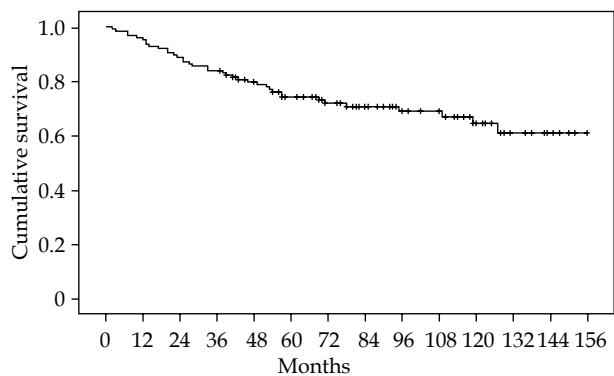


Fig. 1. Overall survival

Table 2. Univariate analysis including 2- and 5-year overall survival, median survival time, and log-rank *p*-value

Variable	No. of patients	2-year OS (%)	5-year OS (%)	Median OS (months)	<i>p</i> value
Gender					
Male	30	86.7	62.2	NR	0.096
Female	93	89.2	79.0	158	
Age (years)					
≤ 65	71	93.0	84.1	NR	< 0.001
> 65	52	82.7	62.3	119	
Histology					
Squamous	96	87.5	74.4	158	0.556
Cloacogenic	8	87.5	46.7	57	
Basaloid	14	92.9	85.7	NR	
Other	5	100.0	80.0	NR	
HIV					
Positive	7	85.7	85.7	NR	0.489
Negative	116	88.8	74.4	158	
cT-stage					
T1	18	100.0	88.2	NR	0.020
T2	45	95.6	81.8	NR	
T3	41	75.6	63.1	158	
T4	19	89.5	66.3	NR	
cT-stage					
T1-2	63	96.8	83.6	NR	0.004
T3-4	60	80.0	63.9	158	
cN-stage					
N0	70	90.0	79.5	NR	0.235
N1	28	96.4	73.1	78	
N2	13	69.2	61.5	158	
N3	12	83.3	66.7	95	
cN-stage					
N0	70	90.0	77.9	NR	0.058
N1-N2-N3	53	86.8	68.9	109	
Boost					
Brachytherapy	102	91.2	78.7	158	0.015
External beam RT	21	76.2	51.6	NR	
BRT boost dose (Gy)					
≤ 18	38	97.4	84.0	158	0.284
> 18	64	87.5	75.8	NR	
Chemotherapy					
No	7	85.7	42.9	43	0.059
Yes	116	88.8	75.9	158	

BRT – brachytherapy, HIV – human immunodeficiency virus, No – number, NR – not reached, OS – overall survival, RT – radiotherapy

Table 3. Univariate analysis including 2- and 5-year colostomy-free survival, local control, metastasis-free survival, and log-rank *p*-value

Variable	No. of patients	2-year CFS (%)	5-year CFS (%)	<i>p</i> value	2-year LC (%)	5-year LC (%)	<i>p</i> value	2-year DMFS (%)	5-year DMFS (%)	<i>p</i> value
Gender										
Male	30	56.7	32.7	< 0.001	69.0	56.4	< 0.001	96.2	96.2	0.361
Female	93	80.6	71.8		91.0	89.8		92.4	91.1	
Age (years)										
≤ 65	71	81.7	71.8	0.002	86.8	83.7	0.400	94.3	92.7	0.779
> 65	52	63.5	48.9		81.9	78.8		91.9	91.9	
Histology										
Squamous	96	76.0	62.1	0.532	85.9	82.2	0.832	92.5	91.2	0.782
Cloacogenic	8	50.0	50.0		71.4	71.4		100.0	100.0	
Basaloid	14	78.6	78.6		84.6	84.6		92.9	92.9	
Other	5	80.0	60.0		80.0	80.0		100.0	100.0	
HIV										
Positive	7	75.0	62.6	0.717	71.4	57.1	0.078	100.0	100.0	0.453
Negative	116	71.4	57.1		85.5	83.4		92.0	91.8	
cT-stage										
T1-2	63	81.0	64.0	0.006	85.7	84.0	0.445	95.2	93.4	0.564
T3-4	60	68.3	49.2		83.2	78.9		91.3	91.3	
cN-stage										
N0	70	72.9	67.1	0.189	84.2	84.2	0.830	94.2	94.2	0.387
N1-2-3	53	77.4	55.9		85.4	78.4		92.1	89.6	
Boost										
BRT	102	77.5	65.4	0.198	86.1	83.9	0.215	95.0	95.0	0.015
EBRT	21	61.9	47.6		75.6	68.0		81.7	77.0	
BRT boost dosage (Gy)										
≤ 18	38	86.8	73.5	0.335	92.1	92.1	0.233	100.0	100.0	0.050
> 18	64				82.3	80.5		91.9	91.9	
Chemotherapy										
No	7	71.9	60.7	0.186	100.0	100.0	0.242	100.0	100.0	0.443
Yes	116	85.7	42.9		83.7	80.7		92.9	91.8	

BRT – brachytherapy, CFS – colostomy-free survival, DMFS – distant metastatic-free survival, EBRT – external beam radiotherapy, HIV – human immunodeficiency virus, LC – local control, No – number, NR – not reached

Discussion

In this retrospective analysis on 123 patients with ACC treated with CCRT followed by PDR BRT boost, the 5-year rates of LC, CFS, and OS were 81.7%, 62.3%, and 74.0%, respectively. Furthermore, the 10-year rates of LC, CFS, and OS were 81.7%, 55.2%, and 64.3%, respectively. Moreover, we recorded a crude rate of 4.9% of patients receiving colostomy due to treatment-related toxicity.

The study suffers from several limitations: retrospective design, no available data on acute toxicity, no separate analysis of local and regional relapses, lack of

description of late toxicity apart from those requiring colostomy, and lack of information about number and site of metastatic nodes.

However, this analysis presents one of the largest available series and the longest follow-up period. Furthermore, to the best of our knowledge, it is the largest series on PDR-based BRT boost in ACC.

Comparing our results with the ones of other series using LDR BRT boost after CCRT [10], the clinical results seem to be quite similar. In particular, in this current study and the series analyzed by Frakulli *et al.*, 5-year LC was 81.7% vs. 78.6%, CFS was 62.3% vs. 76.1%, and OS

Table 4. Univariate analysis comparing local control in male and female patients in different tumor stage subgroups

Stage	Number of patients		2-year local control		5-year local control		p value
	Male	Female	Male	Female	Male	Female	
T1-2 N0	12	35	58.3	97.1	58.3	97.1	< 0.001
T1-2 N1-2-3	3	13	66.7	84.6	33.3	84.6	0.085
T3-4 N0	7	16	71.4	80.8	71.4	80.8	0.649
T3-4 N1-2-3	8	29	71.4	92.3	57.1	88.1	0.082

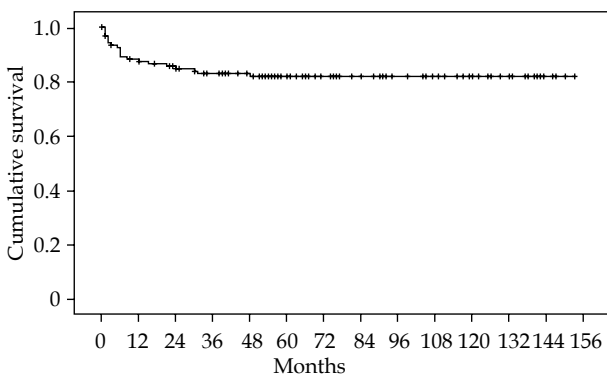


Fig. 2. Local control

was 74.0% vs. 69.4%. However, it should be noted that our patients had a more unfavorable prognostic profile compared to those included in the review by Frakulli *et al.* (cT₁₋₂: 51.2% vs. 61.0%; cN₀: 56.9% vs. 72.3%, SCC histology: 78.0% vs. 94.2%). Our crude rate of toxicity-related colostomies was similar to the one presented in the above-mentioned review (4.9% vs. 3.7%). In conclusion, based on this data, we cannot draw definitive conclusions about the PDR BRT advantage as boost technique after CCRT.

We also tried to compare our results with those of 5-FU plus MMC arm of the RTOG-9811 randomized trial, where a CCRT dose of 45-59 Gy without BRT boost was prescribed [8,9]. Again, the clinical results of our series are similar to those reported in that trial. In particular, in our analysis and in the RTOG-9811 study, 5-year LC was 81.7% vs. 80.0%, CFS was 62.3% vs. 71.9%, and OS was 74.0% vs. 78.3%. Even

in this case, the comparison is complicated by the different prognostic profile of our series and that of the RTOG trial (cT₁₋₂: 51.2% vs. 63.0%; cN₀: 56.9% vs. 70.0%, SCC histology: 78.0% vs. 86.0%). However, the finding of similar results in an unfavorable prognostic population would lead to the hypothesis of some benefit in patients undergoing BRT boost. A comparison of our treatment-related colostomy rate (4.9%) with that of the RTOG trial is complicated because this data was not clearly reported in the two publications [8,9]. The authors only stated that the rate of late grade 4 gastrointestinal complications was 3% without describing the side effects types. However, if we compare the 5-year LC (80.0%) with the 5-year CFS (71.9%) recorded in the RTOG trial [8,9], we can hypothesize that the rate of colostomies due to toxicity was not negligible and probably almost similar to the one recorded in our series.

In the last 5 years, some studies on the use of IMRT-SIB in this setting have been published [17,18,19,20,21]. The use of IMRT is promising, since a reduction in acute toxicity has been demonstrated with the use of this technique. Furthermore, the use of IMRT-SIB allows the delivery of an increased total dose and dose per fraction on the macroscopic tumor. Therefore, this technique is potentially useful to intensify the effect of CCRT as an alternative to BRT boost. However, the efficacy of IMRT-SIB is hardly comparable with our case series, since all publications reported results with a shorter timing (< 5 years). The only data that can be observed even with this modern technique is the reported rate of around 4% of treatment-related colostomies due to toxic effects [20,21].

In our series, we observed (as expected in a tumor with relatively favorable prognosis) a worse OS in older

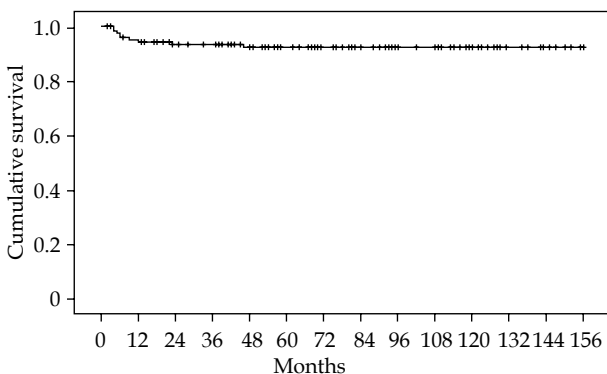


Fig. 3. Distant metastasis-free survival

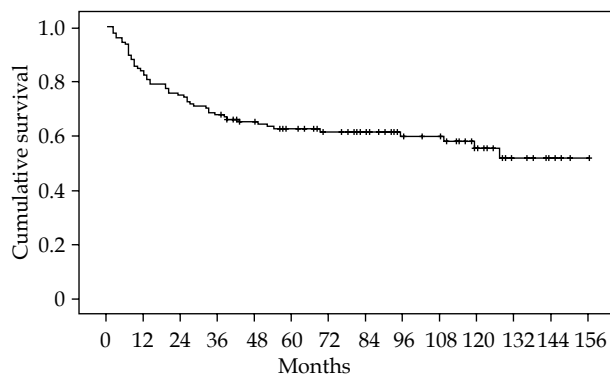


Fig. 4. Colostomy-free survival

patients. Furthermore, significantly higher DMFS and OS rates were recorded at univariate analysis in patients undergoing BRT boost compared to EBRT boost. This result could be attributed to a probably larger tumor volume in patients treated with EBRT technique, even if we cannot confirm this hypothesis due to lack of data on tumor volume or simply tumor diameter. We also observed significantly lower CFS rate in male patients as described by Franco *et al.* [17] and significantly lower LC in the same patients. A negative prognostic effect of male gender was previously reported also in the RTOG 9811 trial [9].

Another interesting result of our analysis is that 5-year and 10-year rates of LC and DMFS were identical. This data would suggest that late ACC relapses are very rare.

Two groups reported the results of small series, presenting very preliminary data on IGBT/IABT-based BRT boost in ACC [22,23]. In the first study, 11 patients underwent CCRT followed by BRT boost (total EQD₂, 60 Gy) that was planned with multi-parametric MRI. With 25 months median follow-up, Tagliaferri *et al.* reported 91% LC (crude rate), without cases of grade > 2 late toxicity [22]. Similarly, Kapoor *et al.* treated 16 patients with CT-based IGBT boost and reported 87.5% 2-year LC rate and no cases of grade > 2 late toxicity (median follow-up, 41 months) [23].

In conclusion, based on the retrospective design and other limitations of our analysis, we cannot recommend the routine prescription of a BRT boost in clinical practices. However, there is a need for further improvement of the results of ACC treatment, where clinical outcomes did not change significantly in the last decades. Therefore, further evaluation of this technique, with the aim to improve its efficacy and safety, is warranted. The use of IGBT techniques in combination with IMRT-based irradiation of the pelvic and inguinal volumes should be tested in well-designed prospective trials. In order to favor treatment modulation with tailored techniques and doses, it is necessary that future studies will describe in detail the results stratifying them based on the characteristics of the neoplasm and particularly, in terms of stage and histology.

Disclosure

Authors report no conflict of interest.

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