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ORIGINAL ARTICLE

Clinical outcome in patients treated with simultaneous integrated boost – intensity modulated radiation therapy (SIB-IMRT) with and without concurrent chemotherapy for squamous cell carcinoma of the anal canal

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ABSTRACT

Background and purpose To retrospectively evaluate locoregional control (LRC), survival and toxicity in anal cancer patients treated with simultaneous integrated boost – intensity modulated radiation therapy (SIB-IMRT) ± concurrent chemotherapy.

Methods and materials Patients with squamous cell anal carcinoma stage T1(≥1 cm)–4, N0–3, M0–1 were included. All patients were treated with SIB-IMRT to a total dose of 59.4 Gy delivered to the primary tumor and macroscopically involved lymph nodes and 49.5 Gy to elective lymph node areas. If macroscopic residual tumor was still present in the fifth week of irradiation, a sequential boost of 5.4 Gy was given. Concurrent chemotherapy was administered in locally advanced cases. Acute and late toxicity were scored.

Results One hundred and six patients treated consecutively between April 2006 and December 2012 were included. Eighty-seven (82.1%) patients received concurrent chemotherapy. The median follow-up was 47 months (range 2–104 months). Ninety-eight patients reached a clinical complete response (92.5%). Four-year actuarial LRC rate, overall survival and colostomy-free survival were 79%, 77% and 77%, respectively. Acute grade ≥3 toxicity occurred in 67.9% of the patients. Late grade 3 toxicity was seen in 16 patients (15.1%).

Conclusions SIB-IMRT ± concurrent chemotherapy for anal cancer was effective with acceptable toxicity.

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Definitive (chemo-)radiation (CRT) is the standard of care for epidermoid cancer of the anus, based on two landmark randomized trials in the UK and Europe [1,2]. However, local recurrence rates still were relatively high (20–30%) and the treatment was quite toxic [1–3]. The former was attributed to, among other factors, the use of a long treatment gap [i.e. a rest period of six weeks between initial CRT and radiotherapy (RT) boost] [4–8], whereas the latter is probably due to the use of two large opposed anterior-posterior fields or a three-field technique [1,2].

Simultaneous integrated boost – intensity modulated radiation therapy (SIB-IMRT) allows for delivering a homogeneous dose distribution to complex-shaped target volumes and effectively sparing nearby normal tissues. This technique has been demonstrated and analyzed for anal carcinoma in a number of retrospective studies and is claimed to be superior to conventional radiation techniques [9–11].

Another way of improving the treatment is to optimize the concurrently given chemotherapy. In a large clinical randomized trial in colorectal cancer, capecitabine has been shown to be at least as effective as intravenous 5-fluorouracil (5-FU) with acceptable toxicity [12]. This was confirmed in a small phase II study in anal cancer patients using a conventional irradiation technique [13]. Capecitabine has some advantages compared to 5-FU: it has a theoretical advantage of more continuous drug concentrations throughout the RT treatment and the administration procedure is less costly and more patient friendly.

SIB-IMRT for anal carcinoma was introduced in our department in March 2006. In February 2008, 5-FU was replaced by capecitabine, first in a pilot study, later on a routine basis. The feasibility and efficacy of capecitabine compared with 5-FU in combination with RT for anal carcinoma was investigated in two other reports [14,15]. Here, we focus on the efficacy and

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toxicity of the SIB-IMRT technique, either with or without the use of concurrent 5-FU or capecitabine.

Material and methods

Patients

All patients with histologically proven invasive squamous cell carcinoma (SCC) of the anal canal or anal margin, stage T1($\geq$1 cm)–4, N0–3, M0–1 treated with SIB-IMRT +/- concurrent chemotherapy between April 2006 and December 2012 were retrospectively reviewed. Pretreatment workup included physical examination including digital rectal examination (DRE), biopsy confirmation, laboratory analysis (including blood count, blood chemistry and the tumor marker SCC), chest radiography, liver ultrasound, ultrasonography of the groin lymph node area, if needed, fine needle aspiration of suspected inguinal lymph nodes, anal endosonography and a magnetic resonance imaging (MRI) of the pelvis. In most cases an ^{18}F-FDG-positron emission tomography (PET) was performed.

RT planning

All patients underwent a computed tomography (CT)-based treatment planning. CT of the pelvis was obtained in supine position with standard immobilization of the feet to avoid hip rotation (Figure 1). In male patients, a custom-made supportive device was used to lift the penis and scrotal sac outside the high dose area of the anus (Figure 1). CT images were fused with T2-weighted MRI images and with ^{18}F-FDG-PET and used for delineation. The gross tumor volume (GTV) included the primary tumor and macroscopically involved lymph nodes. The clinical target volume (CTV) was drawn as contiguous areas to encompass the elective lymph nodes and lymphatic pathways draining from the anus with a 5–7 mm margin [16]. For most cases the CTV encompassed the superficial and deep inguinal lymph node areas, the external and internal iliac, as well as the pudendal, obturator and presacral lymph node regions. The upper border of the RT field was located at the bifurcation of the internal and external iliac vessels. The inguinal lymph node areas were always included in the CTV, except for T1N0 tumors of the proximal anal canal. GTV and CTV were expanded with a 10 mm margin, to planning target volume $(PTV)_1$ and PTV_2, respectively, except in the vicinity of the external genitals, where a 5-mm margin was used.

SIB-IMRT plans typically consisted of seven coplanar fields using 6-, or 18-MV photons. Plans were optimized to achieve 59.4 Gy in PTV_1 and 49.5 Gy in PTV_2 in 33 fractions in an overall treatment time (OTT) of 6.5 weeks. The total dose to the lymph nodes of 49.5 Gy was calculated based on the old fractionation schedule of 45 Gy in 25 fractions of 1.8 Gy, previously used with the conventional irradiation technique and taken into account the difference in biological effect of 1.5 Gy relative to 1.8 Gy, using the linear quadratic formalism of iso-effective dose calculations for late responding tissues with a α/β ratio of 3 [17]. Inherently, this results in a somewhat higher biological dose to (eventual) microscopic tumor deposits in the lymph nodes as compared with conventional fractionated RT. If residual tumor was still present in Week 5, a boost of 5.4 Gy in 3 fractions was given sequentially to macroscopically involved tumor localizations without a treatment gap.

Planning constraints to the PTVs were according to ICRU 62. Planning constraints to normal tissue were: bladder $D_{mean} \leq 46$ Gy, $D_{1\%} \leq 52$ Gy; vulva $D_{mean} \leq 44$ Gy, $D_{1\%} \leq 57$ Gy; external genitals $D_{mean} \leq 27$ Gy, $D_{1\%} \leq 50$ Gy; femoral heads $D_{1\%} \leq 52$ Gy; bowel area $D_{mean} \leq 30$ Gy, $D_{1\%} \leq 52$ Gy. The entire bowel area in the lower abdomen is delineated on the plannings CT up to 2 cm above the CTV; no individual loops are delineated. For patient-specific quality assurance, in vivo

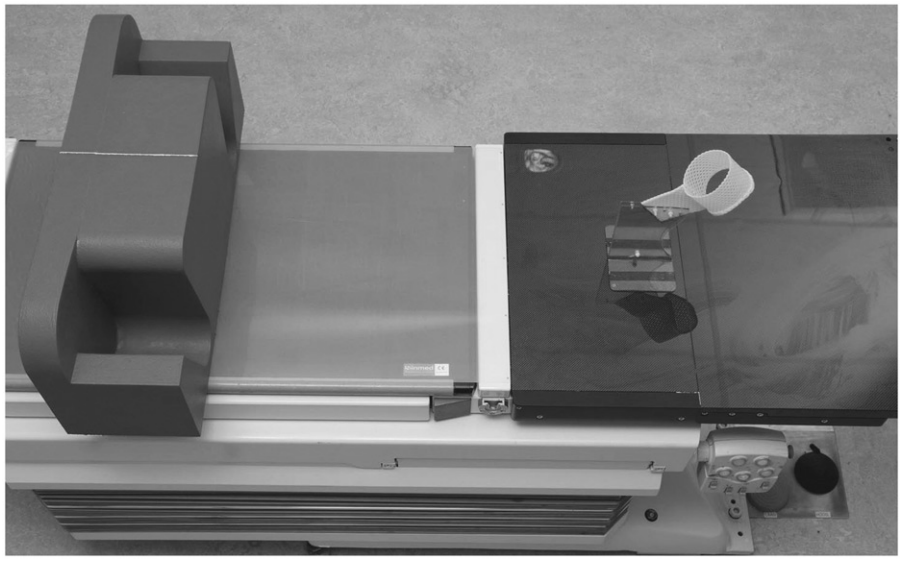

Figure 1. Custom immobilization of the feet to avoid hip rotation and supportive device for male patients to lift the penis and scrotal sac outside the high dose area of the anus.

dosimetry was performed using EPID dosimetry or megavoltage cone-beam CT imaging.

Chemotherapy

Chemotherapy was indicated for T2(>4 cm)–4N0 and T1–4N1–3 tumors. Patients were treated with concurrent 5-FU/MMC or capecitabine/MMC. MMC (10 mg/m^2) was administered intravenously on Day 1 and 5-FU (750 mg/m^2) on Days 1–5 and Days 29–33. Capecitabine (850 mg/m^2 BID) was taken orally on RT days, but not during the sequential boost irradiation.

Follow-up

Patients were monitored weekly during treatment. Follow-up took place at four weeks, every three months up to two years and every six months for at least five years after the end of treatment. Evaluation during follow-up included physical examination and laboratory analysis. Additional imaging and biopsies were performed if a recurrence was suspected. Toxicity was retrospectively assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0. The highest grade of toxicity was reported for each patient.

Tumor response was evaluated by DRE and palpation of the groins. A clinical complete response (CCR) was defined as the absence of any sign of residual disease within three months after the end of treatment. If after three months, or earlier (from six to eight weeks after the end of radiation treatment) a suspicious mass was still palpable, a DRE under anesthesia was performed in the operating theater, with multiple biopsies for pathological examination. Those cases, even if the pathology did not show tumor activity, were not scored as CCR. A recurrence was defined as any sign of disease after a patient reached a complete response.

Statistics

The primary endpoint of this study was locoregional control (LRC). Secondary endpoints were CCR, overall survival (OS), colostomy-free survival (CFS) and toxicity. LRC, OS and CFS were estimated from the end date of treatment using the Kaplan-Meier method. LRC was defined as the time to first clinical and/or pathological evidence of residual tumor or locoregional recurrence. CFS was defined as the time to definitive colostomy or death. Pretreatment colostomies were defined at $t = 1$. Colostomies that were reversed during follow-up were not considered as an event. OS was defined as the time to death from any cause. Comparisons of these outcomes between groups were made using log-rank tests. To determine to what extent acute toxicity was associated with the type of treatment the Mann-Whitney U-test was used. All statistical analyses were performed using the SPSS 23 statistical package.

Results

Patients and treatment characteristics

Patient charts of a total of 106 cases, treated between April 2006 and December 2012, were retrieved (Table I). All patients had histologically proven SCC. Small cell carcinoma, adenocarcinoma or melanoma were excluded. Most patients had locally advanced disease. Nine of the included patients had metastatic disease and were not treated with a curative intent. One patient was treated concurrently for lung carcinoma with cisplatin instead of MMC. Six patients (5.7%) had a microscopically incomplete local excision prior to RT. Fifty-six patients (52.8%) received a sequential boost of three times 1.8 Gy.

Eighty-seven patients (82.1%) received concurrent chemotherapy: 29 (27.4%) 5-FU/MMC, 57 (53.8%) capecitabine/MMC and one cisplatin.

Clinical outcomes

With a median follow-up of 47 months (range 2–104 months), the four-year actuarial LRC rate was 79% [95% confidence interval (CI): 69.6–86.4; Figure 2A] and the four-year actuarial OS rate 77% (95% CI: 67.3–84.3; Figure 2C). For patients who received concurrent CRT, the four-year actuarial LRC rate, CFS and OS were 75%, 74% and 76%, respectively. Excluding patients with stage IV disease, the numbers were 78%, 75% and 82%, respectively. There was no significant difference in outcome between the 5-FU- and capecitabine-treated cases (data not shown).

Ninety-eight patients (92.5%) reached a CCR. CCR rates in the RT- and CRT group were 94.7% and 92.0%, respectively.

Eight patients (7.5%) had locoregional residual disease. Two had already metastasized but received the same radiation schedule. Of these eight patients, three underwent a salvage abdominoperineal resection, two patients received palliative chemotherapy and three had best supportive care. Twenty-two patients (20.8%) developed a recurrence within a time interval of 2–71 months (median 15 months). Of these, 12 were local, five regional and two local and regional (Figure 3). Three patients developed distant metastases as a first recurrence.

Seventeen patients (16%) had a pretreatment colostomy of which six were reversed. Twenty-eight patients (26.4%) received a permanent colostomy for various reasons within a

Table I. Patient and tumor characteristics ($n = 106$).

Characteristic	*n*	%
Gender		
Female	56	52.8
Male	50	47.2
Chemotherapy	87	82.1
5FU/MMC	29	27.4
capecitabine/MMC	57	53.8
cisplatin	1	0.9
T stage		
T1	4	3.8
T2	47	44.3
T3	40	37.7
T4	14	13.2
Tx	1	0.9
N stage		
N0	45	42.5
N1	30	28.3
N2	14	13.2
N3	17	16.0
Stage		
I	4	3.8
II	35	33.0
III	58	54.7
IV	9	8.5

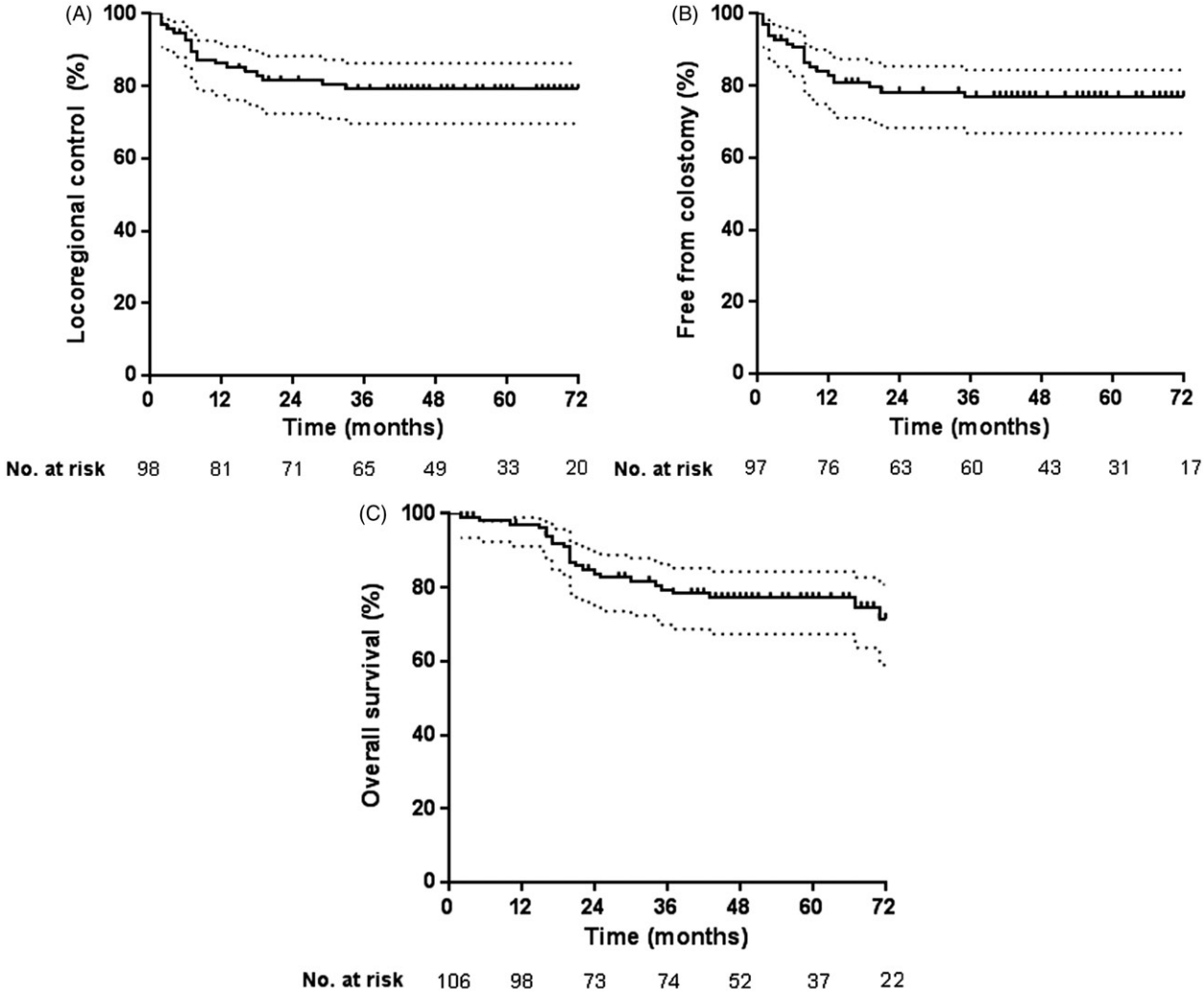

Figure 2. Locoregional control (A), colostomy-free survival (B) and overall survival (C) for the entire cohort. Dotted line represents the 95% confidence intervals.

time interval of 0–35 months (Table II). The most important reason for a permanent colostomy was residual or recurrent disease ($n = 23$). The four-year actuarial CFS rate was 77% (95% CI 66.9–84.4; Figure 2B).

Toxicity

The predominant acute grade 3/4 toxicity was skin (Table III). There was no statistically significant difference in grade 3/4 acute dermatologic toxicity between the RT- and CRT group: 42.1% for the RT group and 66.6% in the CRT group, respectively. Nor was there a difference between patients who received 5-FU/MMC and capecitabine/MMC (data not shown).

One hundred patients (94.3%) completed the planned RT. Treatment interruption was necessary in six patients: one case due to internal herniation of the small bowel, which required surgery at two weeks, one with a presumably radiation-induced ileus in the first week of irradiation, one with an ileus due to pretreatment surgery, one with grade 3 gastrointestinal complaints, one with grade 3 radiation enteritis and a psychiatric patient with non-compliance to treatment after 17 days.

One patient in the 5-FU/MMC group developed a grade 3 hemorrhage (transfusion necessary). Eleven patients developed grade 3 anal ulcera (at least one of them received a colostomy). Grade 3 telangiectasia was observed in 13 patients. Grade 3 anal stenosis was seen in two patients (at least one of them received a colostomy). One patient received a colostomy due to a grade 3 fistula. Another patient received a colostomy because of grade 3 proctitis. One patient was treated with hyperbaric oxygen because of perineal pain. No patients developed grade 4 late toxicity.

Discussion

This report on the use of SIB-IMRT with capecitabine and MMC for anal carcinoma shows that the efficacy is similar as in recent larger series using conventional radiation techniques [18–20]. This is also in accordance with a recently published smaller retrospective series, using SIB-IMRT with 5-FU instead of capecitabine [21]. Our data also appear better than the two randomized trials of the 1990s, in which a long treatment gap was used [1,2]. The omission of a treatment gap in our series is probably the most important factor responsible for the better LRC and CCR compared with these two older trials.

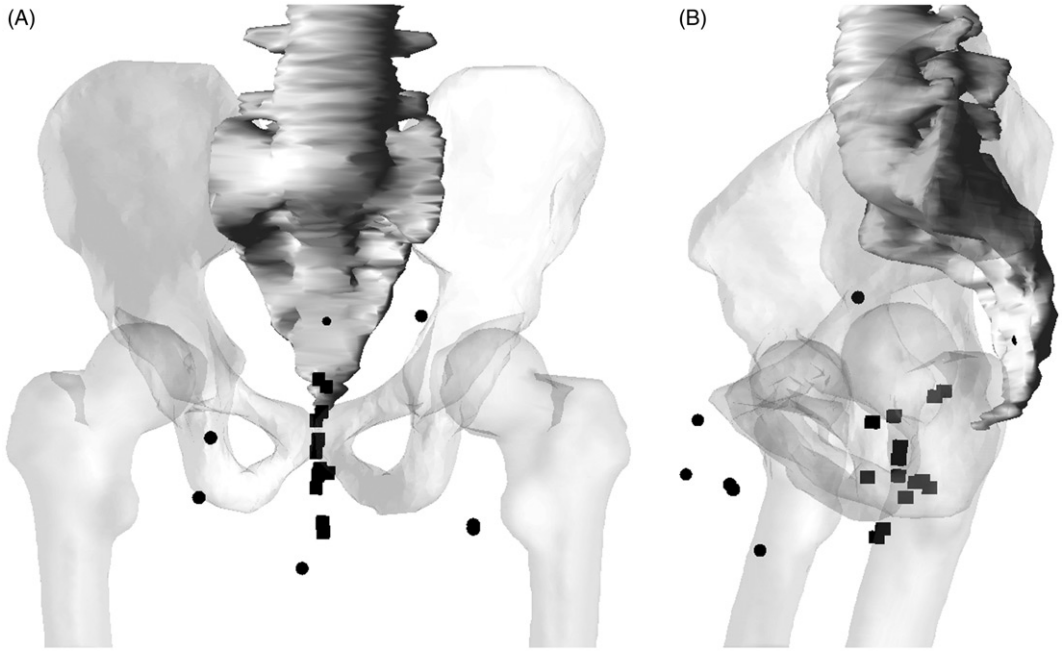

Figure 3. Sites of locoregional recurrence ($n = 18$); in one patient imaging was not performed): anal/rectal (local; sphere), inguinal/sacral/scrotal (regional; square).

Table II. Colostomy ($n = 28$).

Reason	*n*	%
Locoregional recurrence/residue (APR/posterior exenteration performed)	17	60.7
Locoregional recurrence (no APR/posterior exenteration performed)	6	21.4
Inadequate sphincter function	3	10.7
Fistula	1	3.6
Preoperative colostomy not reversed (reason unknown)	1	3.6

Table III. Acute grade $\geq$3 toxicity.

Toxicity	RT group (%)	CRT group (%)
Skin	42	67
Gastrointestinal	5	16
Hematological		8

The negative impact of increased gap duration is well recognized [4–8]. The SIB-IMRT technique used in our series allows an even shorter treatment gap and further reduces the OTT, which has the theoretical advantage of improving local control. Nevertheless, a locoregional recurrence was still observed in 19 of the 106 patients (18%).

Fourteen patients developed a local recurrence in the anus or rectum (Figure 3). This pattern is strikingly similar to the one found by Wright and colleagues using a conventional radiation technique [22]. We re-analyzed the site of local recurrence in each of these 14 patients and found that all recurrences were at the primary tumor location, i.e. within the GTV.

We did not observe a relationship with the initial tumor stage: seven patients had a T2-, five patients a T3- and one patient a T4-tumor. This is in contrast with the observations of Das et al., who clearly found a higher locoregional recurrence rate with higher T and N stage [23]. Inguinal failure occurred in four of our patients, despite inguinal irradiation. Three of these patients had initially macroscopic inguinal lymph node involvement and one was clinically node negative. This is in the same order of magnitude as in the series of Wright and coworkers, using conventional three-field radiation technique giving only 30.6 Gy electively to the groins and 45 Gy with additional electron beams to macroscopic inguinal lymph nodes [22]. It therefore seems that the more conformal IMRT technique and the higher total dose did not result in a reduction in inguinal recurrence as compared with conventional irradiation. Some recent retrospective studies do suggest, however, that IMRT is potentially more effective than conventional irradiation [9–11,24]. Two-year LRC, OS and CFS vary from 83.6% to 95.0%, 86.9% to 100% and 81.2% to 91.0%, respectively. Although these data seem to be more favorable than ours, most of these studies had a relatively short follow-up. The most important reason for a permanent colostomy was residual or recurrent disease ($n = 22$), but in some cases patients received a colostomy because of chronic radiation toxicity ($n = 4$).

A potential hazard of utilizing a shorter OTT is increased acute toxicity. The acute skin toxicity grade 3 or more in our series was considerably higher than in the previously mentioned IMRT studies and in the same range as reported in the older large randomized trials using conventional radiation techniques with a treatment gap [1,2,9–11,24]. However, it should be noted that in our series this is the worst grade toxicity reported during the irradiation, with no treatment interruption, most likely due to the small volume of acute grade 3 or more skin toxicity. Typically, this volume is much smaller than the conventional irradiation. In addition, in the study of Milano et al. a different toxicity system (i.e. RTOG morbidity scoring criteria) was used. Comparison between these studies remains difficult, due to heterogeneity in patient

and treatment characteristics and the retrospective nature of the analyses.

In contrast to acute skin toxicity, gastrointestinal toxicity seems to be very low. This may be due to the low dose per fraction (i.e. 1.5 Gy) and/or the use of IMRT. Hematological toxicity was also low, probably because of the omission of MMC in cycle 2.

Most of our patients were treated with capecitabine/MMC. There was no significant difference in clinical outcome and toxicity compared to the 5-FU/MMC group. This issue has been analyzed earlier by our group in a set of patients with locally advanced anal carcinoma [15]. LRC, CCR and OS were similar between the two groups, but acute skin toxicity was more prominent in the capecitabine group. Possible explanations for this observation were the omission of a treatment gap in the capecitabine group and the longer exposure time of capecitabine during the radiation treatment, as this was given on all irradiation days, as opposed to 5-FU, which was only administered in Week 1 and 5.

This study has, admittedly, several limitations. First, it is a retrospective study of patients treated in a single institution. Second, our toxicity data are based on clinical notes instead of patient-reported outcomes or quality of life questionnaires, so toxicity may have been underestimated. However, nearly all patients were seen during follow-up by one of the coauthors (LD).

In summary, this study demonstrates that patients with anal cancer can be safely and effectively treated with SIB-IMRT ± concurrent chemotherapy. Although acute skin toxicity was significant, it was manageable without treatment interruptions. CFS needs to be improved and despite our slightly better LRC compared to historical data, there is still room for improvement. These findings indicate that there is need for exploration of novel treatment strategies in patients with anal carcinoma.

Declaration of interest

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

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