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► To cite this version:

Maïlys de Meric de Bellefon, Claire Lemanski, Florence Castan, Emmanuelle Samalin, Thibault Mazard, et al.. Long-term follow-up experience in anal canal cancer treated with Intensity-Modulated Radiation Therapy: Clinical outcomes, patterns of relapse and predictors of failure. *Radiotherapy & Oncology*, 2020, 144, pp.141 - 147. 10.1016/j.radonc.2019.11.016 . hal-03488620

HAL Id: hal-03488620

<https://hal.science/hal-03488620>

Submitted on 21 Jul 2022

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Long-term follow-up experience in anal canal cancer treated with Intensity-Modulated Radiation Therapy: clinical outcomes, patterns of relapse and predictors of failure

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ABSTRACT

Background and purpose: To assess the long-term outcomes of patients with squamous cell carcinoma of the anal canal (SCCAC) treated with Intensity-Modulated Radiation Therapy (IMRT).

Material and Methods: From 2007 to 2015, 193 patients were treated by IMRT for SCCAC. Radiotherapy delivered 45 Gy in 1.8 Gy daily-fractions to the primary tumor and elective nodal areas, immediately followed by a boost of 14.4-20 Gy to the primary tumor and involved nodes. Concurrent chemotherapy with 5-FU-mitomycin (MMC) or cisplatin was added for locally advanced tumors. Survivals were estimated by Kaplan-Meier method. Locoregional (LR) relapses were precisely assessed. Prognostic factors were evaluated by uni- and multivariate analyses. Late toxicity was scored according to the Common Toxicity Criteria for Adverse Events v4.0.

Results: Median follow-up was 70 months (range, 1-131). Forty-nine men (25%) and 144 women (75%) were analyzed. Median age was 62 years. Tumor stages were I, II, III and IV in 7%, 24%, 63% and 6% of cases, respectively. Chemotherapy was delivered in 167 patients (87%), mainly MMC (80%). Five-year OS, DFS, CFS and LR control rates were 74%, 68%, 66% and 85%, respectively. Forty-one patients (21%) had a relapse: 22 were LR, mostly in-field (68%). Predictors for LR failure were exclusive radiotherapy, chemotherapy lacking MMC and treatment breaks >3 days. Overall late toxicity \geq grade 2 occurred in 43% of patients, with 24% grade 3 and one case of grade 4 (hematuria).

Conclusion: CRT with IMRT assures excellent local control in locally advanced SCCAC with manageable long-term toxicity. Multicentric prospective trials are required to reinforce those results.

Keywords: Chemoradiotherapy; Anal canal carcinoma; IMRT; Long-term follow-up; Survival; Patterns of relapse; Prognostic factors

Introduction

Concurrent chemoradiotherapy (CRT) with 5-fluorouracil (FU)-mitomycin (MMC) is the standard of care for anal canal carcinoma, reserving abdominoperineal resection (APR) for salvage therapy [1–5]. Most patients have a favorable prognosis and randomized trials have reported 5-year overall survival and locoregional (LR) failure rates of 58-79% and 16-32%, respectively [1–5]. However, CRT is frequently associated with acute toxicity which can lead to treatment interruptions that might be detrimental for local control by allowing cancer cells repopulation [6].

In the past decade, Intensity-Modulated Radiation Therapy (IMRT) has progressively replaced three-dimensional radiotherapy (3D-RT) in order to decrease CRT morbidity. Indeed, it provides higher conformal doses to the target volumes while sparing organs at risk (OAR) [7–9]. However, this more conformal radiation technique requires an accurate target definition and delineation to prevent the risk of marginal failures [10]. In their phase II trial evaluating IMRT in anal cancer, the RTOG identified inadequate contouring in a high number of cases (81%) which motivated the establishment of contouring guidelines [11,12]. So far, their relevance has only been supported by a retrospective study using 3D-RT which reported that LR relapses were the main pattern of failure, but detailed analysis of recurrences within IMRT fields is lacking in the literature [13]. With the widespread use of IMRT it appears of critical importance that LR control remains ensured but long-term toxicities must also be addressed. So far, they have been sparsely reported and mostly based on small retrospective series with a short-term follow-up.

Following a previous study conducted in our institution [14], we present our experience after a long-term follow-up on a large cohort with locally advanced squamous cell carcinoma of the anal canal (SCCAC) treated with IMRT. Clinical outcomes, prognostic factors and patterns of relapse are reported.

Materials and Methods

Patients

Records of consecutive patients with pathologically confirmed SCCAC treated in our Cancer Center between 2007 and 2015 were reviewed. Patients treated in a curative intent with IMRT for the whole treatment were eligible. Initial work-up consisted in physical examination, routine blood tests, chest and abdominal Computed Tomography (CT) scan, Positron Emission Tomography (PET)-CT, pelvic Magnetic Resonance Imaging (MRI) and endoscopic ultrasound. Tumors were staged according to the American Joint Committee on Cancer 7th edition and retrospectively restaged with the 8th edition [15]. The study was approved by our institutional ethics committee. All patients alive at the time of the analysis were seen in our department or contacted by phone for follow-up.

Target contouring and treatment planning

Simulation process has been previously described [14]. Targets and OAR were contoured according to the International Commission on Radiation Units and Measurements (ICRU) 50 and published guidelines [12,16]. Gross Tumor Volume (GTV) comprised primary macroscopic disease and nodes suspected of involvement on MRI and/or PET-CT, and was delineated after fusion of both imaging modalities with the planning CT-scan. Clinical Target Volume (CTV) included the GTV and anal canal expanded by 1 cm margin and draining lymphatic areas (perirectal, external and internal iliacs, obturator, inguinal), defined by a 0.7-1 cm expansion around vessels. Presacral nodes were included in case of N2-3 and/or T3-T4 tumors. Planning Target Volume 1 (PTV1) was created by adding 0.7-1 cm to the CTV, and the boost volume (PTV2) comprised the initial GTV uniformly expanded by 1 to 1.5 cm for involved nodes and primary tumor, respectively.

Patients were treated with 7-fields static IMRT until 2010 and with RapidArc® (RA) thereafter (Varian, Palo Alto, CA), based on a study conducted in our center [17]. Prescribed doses were 45 Gy to PTV1 in 1.8 Gy/fraction, immediately followed by a boost delivering 14.4-20 Gy to PTV2 (1.8-2Gy/fraction). Treatment plans were considered acceptable if 95% of the PTV received $\geq 95\%$ of the prescribed dose, and $< 2\%$ of the PTV received $> 107\%$ of the prescribed dose. Set-up accuracy was assured by daily kV/kV electronic portal images and by weekly kV-cone-beam CT (CBCT).

Chemotherapy

Concurrent chemotherapy was delivered in case of tumors ≥ 30 mm and/or any N+, and Karnofsky performance status ≥ 70 . It consisted in a continuous infusion of 5-FU along 96 hours (800-1000 mg/m²/day, days 1-4 and 29-32) combined with either MMC (10-12 mg/m²) or cisplatin (80-100 mg/m²) on days 1 and 29, at the discretion of the physician.

Outcomes assessment and statistical analyses

Response to treatment was assessed 3 months after completion of CRT by digital rectal examination and endoscopic ultrasound. PET-CT was also recommended. Post-treatment biopsies were not performed and were kept for suspect lesions. A clinically complete tumor response (CCR) was defined as the absence of any sign of residual disease. Patients were followed every 3 months the first year, and every 4-6 months thereafter. Local or regional recurrences were defined as any sign of disease in the anorectal or pelvic/inguinal areas, respectively, after a patient reached a CCR. We assessed their precised location within the radiation fields by fusion of the planning CT-scan and the imaging on which the relapse appeared. They were defined as in-field, marginal or out-of-field whether they occurred within, on the verge or outside the PTVs. Recurrences occurring within the PTV but extending beyond it were classified as marginal. Late toxicities (i.e. occurring >90 days after treatment completion) were scored according to the Common Toxicity Criteria for Adverse Events v4.0 (CTCAE v4.0) [18].

Survival endpoints were estimated by Kaplan-Meier method, calculated starting from the first day of radiotherapy and defined as follows: death from any cause for overall survival (OS), death from SCCAC for cancer specific survival (CSS), death from any cause or recurrence for disease-free survival (DFS), death or definitive colostomy for colostomy-free survival (CFS), death or distant relapse for metastasis-free survival (MFS), and residual disease, local and/or regional recurrences for locoregional failure (LRF) (STATA v13.0). A colostomy performed before radiotherapy was considered as a failure on the first day of treatment as long as it was not reversed later on. In patients with unknown cause of death and still presenting evidence of disease at last follow-up, death was attributed to SCCAC. Prognostic factors were assessed by univariate and multivariate analyses (Cox proportional hazard's regression model, threshold for statistical significance was $p < 0.05$).

Results

Among 233 consecutive SCCAC patients treated between July 2007 and December 2015 in our institution, 193 met the eligibility criteria. Patients, tumors and treatment characteristics are displayed in Table 1. Ten patients initially presented as hemorrhoids, condylomas or anal fissure undergone a local excision prior to radiotherapy, one of them microscopically incomplete. Six patients were on remission from a previous malignancy and three patients were treated for a synchronous malignancy such as breast, lung cancer and colon with peritoneal carcinomatosis. Thirteen patients (7%) received a neoadjuvant chemotherapy, 5 for initial metastases and 8 for voluminous tumors. Treatment breaks >3 days occurred in 45 patients (23%) for a median duration of 11 days (range, 3-35). Reasons were acute toxicity (n=28), planned gap (n=5), intercurrent medical conditions (n=4) and logistical issues (n=8). Four patients interrupted their treatment prematurely because of grade 3 dermatitis (n=2) or diarrhea (n=1), and one died from a heart attack during the second course of chemotherapy.

Median follow-up was 70 months (range, 1-131). Median survival time was not reached. At the time of the analysis, 146 patients (76%) were alive and 143 (74%) were free of disease. Five-year OS, CSS, DFS, CFS and MFS rates were 74% (95% confidence interval (CI): 67-80), 82% (95% CI: 75-87), 68% (95% CI: 61-75), 66% (95% CI: 59-73) and 71% (95% CI: 64-77), respectively (see Supplementary material). Five-year locoregional control (LRC) rate was 85% (95% CI: 78-89). Ninety-five percent of patients achieved a CCR, after a median time of 5 months (range, 2-15). Seven patients with residual disease underwent a salvage APR and two received palliative chemotherapy or best supportive care (BSC) for metastatic progression. All patients initially stage IV presented a CCR and four also achieved a complete distant response.

Forty-one patients experienced a relapse (21%); 22 patients (11%) had a LR relapse (LRR) among whom 7 had synchronous metastases and 19 patients (10%) relapsed distantly only. Fourteen patients had an anorectal relapse; ten were treated by APR, two received palliative chemotherapy and two had BSC. Seven are still alive at the time of the analysis. Eight patients with a first LRR developed a second LRR.

Cumulative sites of LRR are listed in Table 2 (patients may have one or more sites of LRR). Most relapses occurred in-field (68%). All anal margin relapses occurred in patients with no initial margin involvement. One patient with no initial inguinal involvement experienced an inguinal failure within PTV1. All marginal nodal relapses occurred in locally advanced stages along with synchronous metastases. A marginal miss occurred in the right part of a vulva on the

verge of PTV1, whilst the left part was initially involved. Two patients T4N0-1 experienced presacral failure after an APR, classified as marginal as their voluminous size extended outside the PTV1, although presacral space was covered initially. All out-of-field recurrences occurred in common iliac nodes along with metastases in patients with T3 or N+ disease (see Supplementary material). Examples of LRR are illustrated in Figure 1.

In univariate analysis, advanced T-stage (T3-T4) and stage IV were significantly associated to poorer OS, DFS, CFS and MFS, and high lymph nodes involvement (N2-N3) was associated to poorer OS and DFS ($p < 0.05$). In multivariate analysis, advanced T-stage remained an independent prognostic factor for all survival rates (Table 3). Five-year OS rate for Tis-T1-T2 vs. T3-T4 was 87% vs. 60% ($p < 0.001$). Similarly, 5-year DFS and CFS rates were 78% vs. 58% ($p < 0.001$) and 80% vs. 51% ($p < 0.001$), respectively (see Supplementary material). Table 4 summarizes outcomes data by TNM stages. The prognostic factors for LRF in univariate and multivariate analyses were exclusive radiotherapy, chemotherapy regimens lacking MMC and radiotherapy breaks > 3 days (Table 3). Five-year risk of LRF for patients lacking MMC was 28% vs. 10% with MMC ($p = 0.01$). Similarly, patients with radiotherapy breaks > 3 days had a 5-year LRF risk of 27% vs. 11% with no break ($p = 0.02$).

Late toxicity was assessed in patients presenting at least 6 months of follow-up (190 patients). Eighty-two patients (43%) experienced late adverse effects \geq grade 2; 37 patients (19%) with grade 2 worst overall late toxicity and 47 (24%) with at least one grade 3 (Table 5). There was one case of grade 4 hematuria in a patient with multiple recurrent LRR treated by APR, systemic chemotherapy and melphalan pelvic perfusion. A definitive colostomy was performed in 38 patients (20%), either done prior to radiotherapy ($n = 7$) or because of a residual disease ($n = 7$), a local relapse ($n = 12$) or a treatment-related toxicity ($n = 12$).

Discussion

Our results further support the implementation of IMRT on a routine basis for the treatment of SCCAC. Our long-term survival rates compared favorably with historical trials using 3D-RT and concurrent 5FU-MMC, which reported 5-year OS, DFS CFS and LRC rates of 58-79%, 50-68%, 47-75% and 68-84%, respectively, even though we included metastatic patients (6%) [1–5]. They

were also similar to the RTOG 0529 IMRT trial which reported 5-year OS, DFS, CFS and LRC rates of 76%, 68%, 74% and 84%, respectively [19].

Prognostic factors were concordant with previous reports, confirming the beneficial impact of MMC-based regimens on survival and LRC [3–5]. Before the publication of the RTOG 9811 long-term outcomes, we used to deliver cisplatin as in the ACCORD 03 trial; MMC has now become our standard regimen [3,20]. Our results also encourage minimizing extended treatment breaks or planned gaps whose negative impact on LRC is well recognized [21,22]. The use of IMRT has not compromised LRC as we achieved high rates independently of T and N-stages, whereas advanced stages predict for lower LRC rates in the literature [23]. An adequate GTV definition with the performance of a PET-CT and an MRI in 89% and 77% of patients, respectively, might have contributed to those results. The increased sensitivity of ¹⁸FDG-PET-CT over conventional imaging for staging nodal disease is well known and can lead to a change in treatment planning in a significant number of cases [24,25].

Target delineation is also a major issue for LRC with discrepancies remaining among guidelines [12,26]. Our analysis provides consistent data in terms of target contouring. Most LRR occurred in-field (68%), in favor of radioresistance rather than in a miss in tumor targeting. The anorectal area was the most frequent location of LRR (64% of cases), concordant with previous series reporting primary site involvement in 60-78% of cases [1,13,20,27–30]. Anal margin relapses were common and a marginal miss happened in the vulva, suggesting that genital dose constraints set as per RTOG should not be prioritized above CTV coverage [11,31]. Common iliac failures were marginal or out-of-field as those nodes were not systematically delineated according to guidelines and occurred with synchronous metastases. The inclusion of those nodal areas in the CTV could be considered in advanced stages although its impact on distant spread is uncertain while increasing doses to bowel. Finally, encompassing systematically the entire IRF in the CTV is controversial [26]. None of our perineal failures occurred in the lateral edges of the IRF, suggesting that a more conformal coverage of the low anorectum as per RTOG is likely to be adequate [12].

The majority of LRR (77%) occurred within the first 3 years of follow-up, as previously reported [2,13,28]. Locoregional relapses are reported to be the main pattern of recurrences, representing 67-86% of all failures in the literature [1,13,20,27–30]. In our series, isolated distant spread appeared almost as frequent as LRR (46% vs. 54%), whereas the overall incidence of

distant relapses (13%) remained similar to the 6-18% previously reported [1,2,13,20,27–30]. Arcadipane et al. postulated that a long interval (>60 days) between initial diagnosis and CRT in a high proportion of their cohort (30%) might have influenced systemic spread, similar to 28% in our cohort [30]. Overall distant spread was the most frequent cause of death from disease (81%) compared to LRR (19%); research on factors implicated in metastases development is warranted to improve systemic strategies to ultimately impact long-term survival.

Whether dose escalation contributes to improve LRC remains controversial. Seventy-nine percent of our patients received >59.4 Gy to the primary tumor. Several retrospective series reported improved LRC with doses ≥ 52 -54 Gy [32–36]. Recently, a post-hoc pooled analysis of two prospective trials assessed that doses ≥ 60 Gy (between 60 and 65 Gy (HR=0.37, $p < 0.001$) and ≥ 65 Gy (HR=0.61, $p = 0.028$)) were associated with an improved CFS [37]. These results should be interpreted with caution, as the original report failed to demonstrate any significant benefit in CFS with increased boost dose of 20-25 Gy vs. 15 Gy ($p = 0.067$) [20]. In the RTOG 9208 phase II trial, increasing the total dose to 59.4 Gy did not appear to improve local control when given in split-course [38]. Similarly, higher 5-year LRF rates of 30% were found in randomized trials that delivered doses up to 60-70 Gy with a mandatory 6 week-gap [1,2]. Conversely, phase II and III trials using lower doses of 50.4-59 Gy reported favorable 5-year LRF rates of 16-20%, similar to 15% rate [3,4,11]. Nevertheless, those studies still supported the administration of higher radiation doses for advanced stages and adopted risk-adapted doses strategies depending on initial T and N stages. The question of optimal dose is currently being addressed by the multicentric PLATO trial (Personalizing Anal cancer radioTherapy dOse) funded by Cancer Research UK. This integrated protocol comprises three trials (ACT3, ACT4 and ACT5) aiming to optimize radiotherapy dose to gross tumor and elective nodal areas across different LR risk strata. Personalizing radiation regimens might help to ensure LRC whilst limiting treatment-related late toxicities that may affect quality of life [39].

Late complications have been poorly reported so far and assessment tools vary among studies [18,40]. Historical trials reported overall late toxicity \geq grade 3 of 13-43% with 3D-RT, which should be reduced with a more conformal radiation technique [1–3]. Most data with IMRT are based on small retrospective series with a short follow-up [14]. Chuong et al. observed an improvement in late \geq grade 3 gastrointestinal (GI) toxicity with IMRT compared to 3D-RT ($p = 0.012$) [41]. The long-term RT0G 0529 update published in abstract form reported 55% grade

2, 16% grade 3 and 2% grade 5 overall late toxicities, similar to our findings [19]. In our study, treatment-related toxicities required a definitive colostomy in 12 patients (6%) compared to 3% of patients in the ACCORD 03 trial; the earlier tumor stage (T1-T2) in their patients might have contributed to diminish the risk of post-treatment complications [20]. Gastrointestinal late adverse effects are varied with severe toxicity seen in one-third of patients [42]. Vaginal adverse effects are also common [43]. Some studies investigated the use of a vaginal dilator during radiation which seemed to lower the rates of late dyspareunia and the mean dose to the vagina [44,45]. Allal et al. reported that late morbidity correlated significantly with anatomic tumor extent and prescribed external beam dose [46]. Younger age, higher tumor dose, and earlier year of treatment were associated with a higher grade of vaginal stenosis [47]. Further investigations are needed to better understand the complexity of the effects of CRT on anal canal functions and sexual morbidity in order to develop adequate therapies. Future studies should include accurate and symptom-specific assessment tools to standardize measurements.

Our study has several limitations, including its retrospective design, patients treated in a single institution and some remaining heterogeneity between physicians' practices. However, it remains the largest series so far among retrospective studies on IMRT for SCCAC and has the longest median follow-up. As the majority of events happen within two years after treatment completion, most of them were captured in our series, which allows these results to be generalized to patients treated outside of a clinical trial context.

In conclusion, our study confirmed the efficiency of IMRT in the treatment of SCCAC with excellent LRC and survival despite advanced disease, with manageable late toxicity. Radioresistance and distant failures remain, emphasizing the need for prospective multicentric trials to investigate biologic and prognostic factors to improve patients management.

Conflict of interest

None.

Acknowledgement

A grateful acknowledgement to Dr Dominique Mathieu for his advices in editing the manuscript.

Appendix A. Supplementary data

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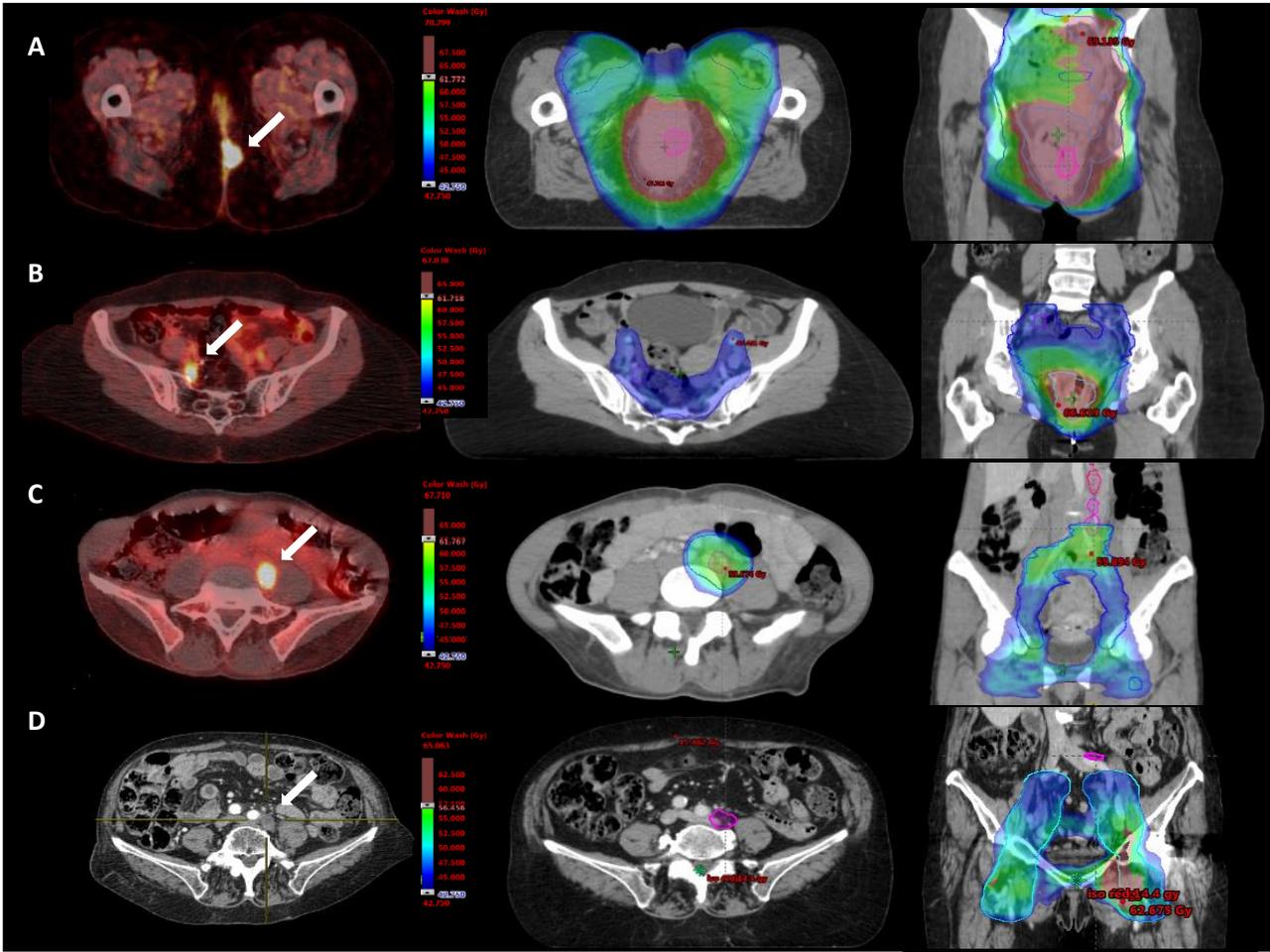


Table 1
Patients, tumors and treatment characteristics
(N=193).

Characteristic	No. of patients (%)
Age (years), Median (range)	62 (35–92)
Gender	
Male	49 (25)
Female	144 (75)
Immunosuppression	
HIV positive	10 (5)
Prior transplant	3 (1.5)
Tobacco exposure	
Yes	82 (42)
No	96 (50)
Unknown	15 (8)
HPV tumor status	
Positive	90 (47)
Negative	5 (2)
Unknown	98 (51)
Tumor size (mm), Median (range)	44 (2–150)
T stage	
Tis	1 (0.5)
T1	19 (10)
T2	81 (42)
T3	58 (30)
T4	34 (18)
N stage (AJCC 7 th ed.)	
N0	67 (35)
N1	54 (28)
N2	36 (19)
N3	36 (19)
N stage (AJCC 8 th ed.)	
N0	67 (35)
N1a	101 (52)
N1b	5 (3)
N1c	20 (10)
AJCC stage (7 th and 8 th ed.)*	
0-I	14 (7)
II	46 (24)
III	122 (63)
IV	11 (6)
Concurrent chemotherapy	
Yes	167 (87)
No	26 (13)
Type of chemotherapy	
5-FU/MMC	134 (80)
5-FU/Cisplatin	25 (15)
Capecitabine alone	5 (2)
Other	3 (3)
RT technique	
Static IMRT	42 (22)
RapidArc [®]	151 (78)
Radiation duration (days)	
Median (range)	51 (28–92)
Prescribed RT dose (Gy)	
PTV1, Median (range)	45 (45–50)
PTV2, Median (range)	65 (50–69)

*Details on stages according to both AJCC editions are provided in Supplementary material.

Table 2

Cumulative sites of all locoregional relapses within the Planning Target Volumes (N=35).

Localization	No. (%)
In-field PTV2	18 (51)
Anal canal	5 (14)
Anal margin	6 (17)
Affixed to anal canal	2 (6)
Recto-vaginal	1 (3)
Inguinal	3 (8)
Mesorectal	1 (3)
In-field PTV1	6 (17)
Inguinal	1 (3)
External iliac	1 (3)
Internal iliac	1 (3)
Low pelvis post-APR	3 (8)
Marginal	6 (17)
Common iliac	1 (3)
Internal iliac	2 (6)
Vulva	1 (3)
Presacral post-APR	2 (6)
Out-of-field	5 (14)
Common iliac	5 (14)

PTV: Planning target volume; APR: Abdominoperineal resection.

Table 3

Prognostic factors of 5-year locoregional failure and survivals in multivariate analysis.

	HR (95% CI)	<i>P</i> value
Locoregional failure		
T-stage ^a	2.00 (0.89-4.51)	0.10
RT breaks ^b	2.47 (1.15-5.30)	0.02
Exclusive RT ^c	3.41 (1.21-9.57)	0.005
Lack of MMC ^d	3.11 (1.28-7.56)	0.01
Overall survival		
T-stage	4.91 (2.25-10.72)	<0.001
Stage IV ^e	2.82 (1.22-6.53)	0.02
Exclusive RT	3.38 (1.29-10.72)	0.01
Lack of MMC	1.88 (0.92-3.85)	0.09
Colostomy-free survival		
T-stage	4.10 (2.23-7.52)	<0.001
Male vs. female	1.9 (1.10-3.10)	0.02
Residual disease ^f	7.78 (3.41-17.77)	<0.001
Exclusive RT	3.03 (1.39-6.57)	0.005
Lack of MMC	1.71 (0.90-3.26)	0.10
Disease-free survival		
T-stage	2.57 (1.42-4.66)	0.002
Stage IV	2.23 (0.99-5.01)	0.05
Exclusive RT	1.77 (0.77-4.06)	0.18
Lack of MMC	1.86 (0.99-3.49)	0.06
Metastasis-free survival		
T-stage	2.61 (1.45-4.70)	0.001
Stage IV	3.05 (1.41-6.62)	0.005

CI: Confidence interval; HR: Hazard ratio; RT: Radiotherapy; MMC: Mitomycin; CT: Chemotherapy; ^aT1-T2 vs. T3-T4; ^bRT breaks >3 days vs. no break; ^cExclusive RT vs. chemoradiotherapy; ^dLack of MMC vs. chemotherapy comprising MMC; ^eStage IV at diagnosis vs. non metastatic stages; ^fResidual disease vs. complete tumor response.

Table 4

Locoregional control and survival rates at 5 years by T, N and AJCC stages.

	5-y OS (CI) %	5-y DFS (CI) %	5-y CFS (CI) %	5-y LRC (CI) %
T and N stages				
Tis-T1	90 (66-97)	80 (55-92)	85 (60-95)	85 (60-95)
T2	86 (75-93)	78 (66-86)	79 (68-87)	87 (76-93)
T3	69 (54-80)	65 (50-76)	58 (43-70)	87 (75-94)
T4	46 (28-63)	45 (28-62)	38 (22-55)	75 (57-87)
N0	79 (66-88)	76 (63-85)	68 (54-78)	86 (75-93)
N+*	72 (62-79)	64 (55-72)	65 (56-73)	84(75-90)
AJCC stages				
0-I	93 (59-99)	86 (54-96)	86 (54-96)	86 (54-96)
II	77 (59-88)	75 (58-86)	63 (46-77)	87 (73-94)
III	75 (66-82)	68 (58-75)	69 (59-76)	84 (76-90)
IV	18 (1-51)	18 (1-51)	18 (1-51)	79 (39-94)

CI: 95% confidence interval; OS: overall survival; DFS: disease-free survival; CFS: colostomy-free survival; LRC: locoregional control; AJCC: American Joint Committee on Cancer; *Detailed N stages according to both 7th and 8th AJCC editions are provided in Supplementary material.

Table 5

Late toxicity (N=190).

	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Diarrhea	13 (7)	12 (6)	0
Rectal ^a	16 (8)	14 (7)	0
Anal sphincter dysfunction ^b	12 (6)	3 (2)	0
Urinary disorders ^c	8 (4)	0	1 (0.5)
Skin ^d	14 (7)	4 (2)	0
Vaginal ^e	25 (18)	27 (19)	0
Bone ^f	3 (1)	0	0
Hematologic ^g	0	0	0

^aProctitis or rectal ulcer; ^bFecal incontinence; ^cCystitis or urethra stenosis; ^dFibrosis or chronic ulcer; ^eVaginal stricture, dyspareunia, discharge, or rectovaginal fistula; ^fPainful sacral fracture; ^gHemoglobin, neutrophils, platelets.