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Original Article

Treatment, outcome, and prognostic factors in non-metastatic anal cancer: The French nationwide cohort study FFCD-ANABASE

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ABSTRACT

Introduction: International guidelines regarding the treatment of squamous cell carcinoma of the anus (SCCA) recommend intensity-modulated radiotherapy (IMRT) combined with mitomycin-based chemotherapy (CT). The French FFCD-ANABASE cohort aimed at evaluating clinical practices, treatment, and outcomes of SCCA patients.

Methods: This prospective multicentric observational cohort included all non-metastatic SCCA patients treated in 60 French centers from January 2015 to April 2020. Patients and treatment characteristics, colostomy-free survival (CFS), disease-free survival (DFS), overall survival (OS), and prognostic factors were analyzed.

Results: Among 1015 patients (male: 24.4 %; female: 75.6 %; median age: 65 years), 43.3 %presented with early-stage (T1-2, N0) and 56.7 % with locally advanced stage (T3-4 or N +) tumors. IMRT was used for 815 patients (80.3 %) and a concurrent CT was administered in 781 patients, consisting of mitomycin-based CT for 80 %. The median follow-up was 35.5 months. DFS, CFS, and OS at 3 years were 84.3 %, 85.6 %, and 91.7 % respectively in the early-stage group compared to 64.4 %, 66.9 %, and 78.2 % in the locally-advanced group ($p < 0.001$). In multivariate analyses, male gender, locally-advanced stage, and ECOG PS ≥ 1 were associated with poorer DFS, CFS, and OS. IMRT was significantly associated with a better CFS in the whole cohort and almost reached significance in the locally-advanced group.

Conclusion: Treatment of SCCA patients showed good respect for current guidelines. Significant differences in outcomes advocate for personalized strategies by either de-escalation for early-stage tumors or treatment intensification for locally-advanced tumors.

Squamous cell carcinoma of the anus (SCCA) is a rare, yet increasing malignancy, mostly associated with infection by human papillomavirus (HPV), with a doubling incidence over the past 20 years, especially in immunosuppressed patients [1,2]. Standard treatment of non-metastatic SCCA is based on definitive chemoradiotherapy with curative intent, whereas abdominoperineal resection is reserved for primary failure of chemoradiotherapy or loco-regional relapses [3,4]. Chemoradiotherapy achieves a good out-

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come for T1-T2 tumors without nodal involvement, but T3-T4 or N1 tumors are associated with a poorer prognosis [5,6]. This therapeutic strategy has remained unchanged since the 1980 s but has benefited from major technical advances in imaging (MRI, endoscopic anal ultrasound, and PET-CT) and radiotherapy, particularly with the development of intensity-modulated radiotherapy (IMRT) [7–11]. By conforming the dose to complex clinical target volumes using multiple beams and varying dose rates, IMRT results in minimizing dose to healthy tissues aiming to reduce toxicity while preserving the dose homogeneity to clinical target volumes. This tolerance improvement was confirmed by the Radiation Therapy Oncology Group (RTOG) 0529 single-arm phase II study when compared with the previous RTOG 9811 trial, where radiotherapy was delivered according to the 3D-conformal technique [12,13]. Therefore, IMRT has been progressively recommended worldwide and in 2015, by the French High Authority of Health (HAS) and the French guidelines for anal cancer treatment were updated subsequently [3,14,15]. The standard treatment of SCCA should combine IMRT and chemotherapy with 5-fluorouracil (or capecitabin) and mitomycin-C [3,4]. However, there is no consensus between countries about the total dose of radiotherapy to achieve, from 50.4 Gy used in the ACT II trial [16], 55–59 Gy for T3-4 or node-positive disease used in the RTOG 98–11 trial [13] and up to 60–65 Gy according to French guidelines, avoiding as much as possible a gap that could be detrimental to efficacy [3,4,17].

Following these guidelines, the "*Fédération Francophone de Cancérologie Digestive*" (FFCD) decided to carry out a French nationwide observational cohort to evaluate clinical practices, treatment, and outcome of SCCA patients. In the present study, we have chosen to focus on patients treated for non-metastatic SCCA using radiotherapy or chemoradiotherapy as first-line treatment, intending to evaluate clinical practices, treatments, patient outcomes, and prognostic factors.

Methods and materials

Cohort design

The ANABASE cohort is a prospective multicenter observational study conducted in France by the FFCD including all patients treated for SCCA in all centers willing to participate in France (60 French centers) from January 2015 to April 2020. This study was approved by a French ethics committee (CCTIRS-15.698) and the "*Commission National de l'Informatique et des Libertés*" (authorization number 915622). All patients received written information, and oral information from the investigator and provided oral informed consent.

Population

Patient demographic data included age and gender, neutrophils count, Eastern Cooperative Oncology Group (ECOG) performance status (PS), HIV status, smoking status, and alcohol consumption. Tumor characteristics included pathology, p16 staining, stage, and site of primary and lymph nodes. Patients were classified into 2 groups: early-stage tumors (T1-2, N0), or locally advanced tumors (T3-4 or N + any T) stage according to the UICC TNM classification 8th edition. The type of imaging exams for initial staging as well as characteristics of chemotherapy and radiotherapy treatment were collected. Outcomes included best objective response rate 4 to 6 months following the end of (chemo)radiotherapy, recurrence rates and type of recurrence, disease-free survival (DFS), colostomy-free survival (CFS), and overall survival (OS) rates at 3 years.

Statistical analysis

Results were presented regarding the staging of the tumors defined as early-stage (T1-2 N0) versus locally advanced tumors (T3-4 or N +) and on the overall population. Descriptive analyses were performed for patients' baseline characteristics. Quantitative variables were described with means or medians, standard deviations (SD), or interquartile ranges (IQR) and were compared with the Wilcoxon rank-sum test. Qualitative variables were described as frequencies and percentages and were compared using the chi-square test or Fisher's exact test.

OS, DFS, and CFS were defined as the time between the start of treatment and death (any cause), first recurrence or death, and date of the 1st colostomy or death respectively. Median follow-up was evaluated using the reverse Kaplan-Meier method. OS, DFS, and CFS curves were plotted using the Kaplan-Meier method and described using medians with two-sided 95 % confidence intervals (95 % CI). Log-rank tests were used to compare rates and event-time distributions with a 95 %CI. Univariate and multivariate analyses were made using the Cox model to determine prognostic factors for OS, DFS, and CFS. All statistical analyses were done using SAS software 9.4 (SAS Institute, Cary, NC).

Results

Among the 1378 patients with SCCA included in the whole database, 1096 were treated for a non-metastatic SCCA using radiotherapy or chemoradiotherapy in 60 French centers between January 2015 and April 2020. Eighty-one patients with insufficient data were excluded and 1015 patients were analyzed (Fig. 1). The median age was 65 years [range: 32–94] and 75.6 % were female. A positive HIV serology was found in 17.6 % of the 488 patients with known status. A good ECOG PS of 0 or 1 was reported for 93.2 % of patients (Table 1).

Initial workup included a PET-CT and a pelvic MRI for 73.0 % and 71.2 % of patients respectively. A thoracoabdominal and pelvic CT scan were done in 55.8 % and an anal ultrasound-endoscopy in 30.3 % of patients. Based on this initial workup, tumors were classified as early-stage (T0-1–2, N0, M0) in 440 patients and locally-advanced (T3-4 or N+, M0) in 575 patients (Table 1). The median tumor size was 3.7 cm (range 0.2–15.5). HPV testing was done in tissue tumor samples from 590 patients, 92 % of which were HPV positive.

Radiotherapy consisted of IMRT for 815 patients (80.3 %) either with static fields (n = 177), rotational arc therapy (n = 515), or tomotherapy (n = 123). This proportion of patients treated with IMRT compared to 3D RT remained stable over the period 2015–2020. The median total dose to the primary tumor was 60 Gy (IQ: 50.40; 64.80). The tumor boost was provided by interstitial brachytherapy in 14.8 % of patients. The median overall treatment time (OTT) was 50 days (IQR: 43–61) and there was no difference in OTT regarding IMRT or 3D RT. An interruption of radiation therapy was observed for 32.2 % of patients, with a median duration of 14 days, due to toxicity in 42.5 % but also as a planned gap in 53.8 % of cases. Among patients with treatment interruption for toxicity, 65.4 % were treated by conformal 3D RT compared with 39.6 % by IMRT (p = 0.0006). A concurrent CT was administered in 76.9 % of patients, mainly based on mitomycin (n = 685; 87.7 %) combined with 5FU (n = 482) or capecitabine (n = 203), or by cisplatin-based CT in 24 patients and capecitabine alone in 33 patients. An induction CT before CRT was administered to 58 pts (5.7 %), mainly consisting of cisplatin and 5FU. Treatment characteristics differed significantly according to initial staging: patients with early-stage tumors were more likely to be treated by exclusive radiotherapy or with a brachytherapy boost whereas patients with locally-advanced tumors were more prone to receive concur-

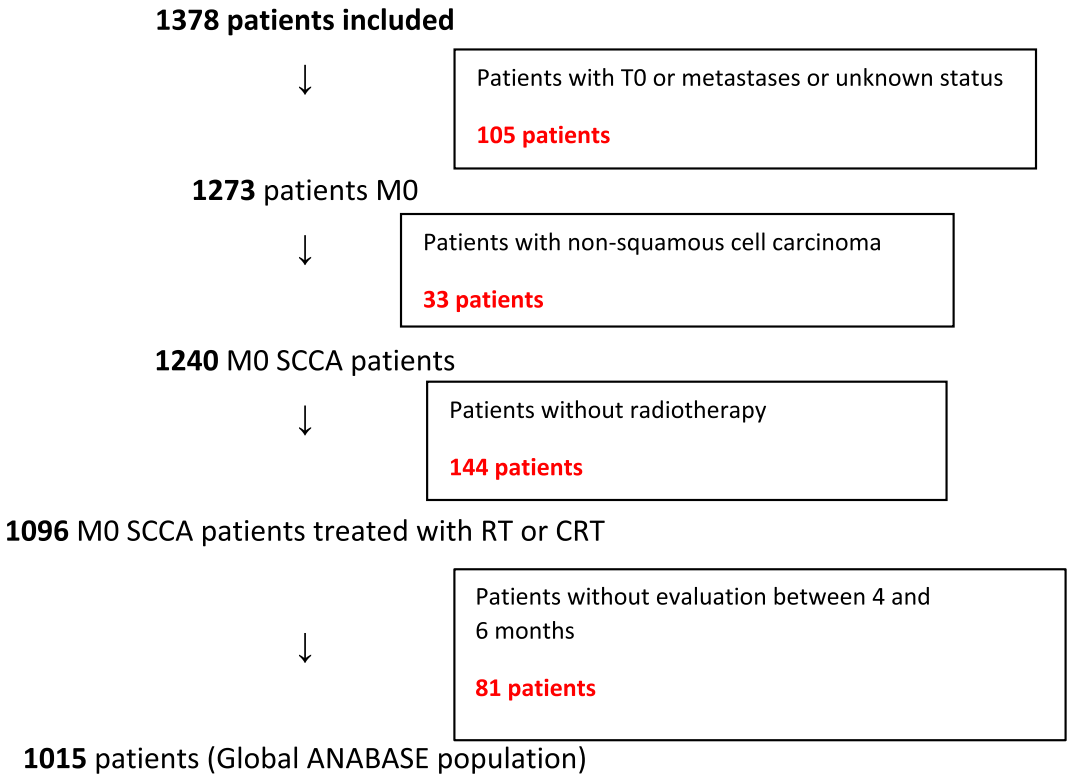

Fig. 1. Workflow of the study: SCCA: squamous cell carcinoma of the anus; RT: Radiotherapy; CRT: Chemoradiotherapy.

Table 1
Patient's characteristics.

		median (range) or n (%)
Gender	Male	248 (24.4)
	Female	767 (75.6)
Age, years		65 (32–94)
HIV status	Positive	86 (8.5)
	Negative	402 (39.6)
	Unknown	527 (51.9)
ECOG PS status	0	665 (65.5 %)
	1	281 (27.7 %)
	2	28 (2.8 %)
	3	9 (0.9 %)
	4	1 (0.1 %)
Tumor size, cm		3.7 [0.2–15]
T-stage	T1	152 (15.0)
	T2	488 (48.1)
	T3	231 (22.8)
	T4	144 (14.2)
N-stage	N0	554 (54.6)
	N1	459 (45.2)
Early stage	T1-2, N0	440 (43.3)
Locally advanced stage	T3-4 or N+	575 (56.6)
P16 staining	Positive	543 (53.5)
	Negative	33 (3.2)
	Unknown	439 (43.3)

rent chemoradiotherapy, induction chemotherapy, and total doses over 60 Gy (Table 2).

The median follow-up of patients was 35.5 months [95 %CI: 34.4;36.0]. The objective response rate at 4–6 months following the end of treatment was 87.3 % in the overall population. A complete response was observed in 741 patients (74.2 %) More precisely, 386 patients (68.1 %) in the locally advanced group compared to 355 patients (82.4 %) in the early-stage group were complete responders (OR: 2.2; 95 % CI: 1.6–2.97) ($p < 0.0001$). At the time of analysis, 120 patients had died, including a cancer-related death in 77 patients (64.2 %). In the entire cohort, the 3-year DFS, CFS, and OS rates were 73.2 % [95 %CI 69.9;76.1], 75.3 % [95 %CI:72.0;78.7], and 84.3 % [95 %CI: 81.4;86.8], respectively. The 3-year DFS was 64.4 % [95 %CI: 59.7;68.7] in the locally advanced group and 84.3 % [95 %CI: 80.1;87.8] in the early-stage group ($p < 0.001$, Fig. 2A). Similarly, the 3-year OS (78.2 % vs 91.7 %; $p < 0.0001$; Fig. 2B) and the 3-year CFS (66.9 % vs 85.6 %; $p < 0.0001$; Fig. 2C) were both significantly lower in the locally-advanced group.

In univariate analysis, male gender, ECOG PS $\geq$ 1, locally advanced tumors, neutrophils count $\geq$ 5G/l, and induction chemotherapy were significantly associated with poor DFS (Table 3), whereas a brachytherapy boost was associated with a good prognosis. In addition to these factors, HIV positive status was also significantly associated with CFS and OS in univariate analysis but not in multivariate analysis. Moreover, IMRT technique was significantly associated with CFS in univariate analysis (supplementary Table 2). In multivariate analysis, only male gender, ECOG PS $\geq$ 1, and locally-advanced tumors were associated with poorer DFS, CFS and OS (Table 3, supplementary Tables 2 and 1), whereas IMRT technique was significantly associated with a better CFS (supplementary Table 2).

We looked further at prognostic factors in each subgroup. In the early-stage tumors group, male gender, tumor size > 3 cm, ECOG PS $\geq$ 1 were associated with poorer CFS in multivariate analysis (Table 4). In the locally-advanced tumors group, in addition to ECOG PS < 1 and tumor size < 3 cm was a trend for a better CFS with IMRT and with a brachytherapy boost (Table 4).

A recurrence occurred in 202 patients: local and/or lymph nodes in the pelvis for 115 patients (56.9 %), metastatic for 72 patients (35.6 %), or both for 12 patients (5.9 %). Salvage surgery (abdominoperineal resection) was done in 90 patients, because of recurrence or residual tumor after CRT for 79 patients and because

Table 2
Treatment characteristics.

		T1-2/N0 (n = 440) N (% or median)	T3-4 or N+ (n = 575) N (% or median)	All (n = 1015)	*p value*[#]
Exclusive RT		**179 (40.7)**	**55 (9.6)**	**234 (23.1)**	*< 0.0001*
Chemoradiotherapy		**261 (59.3)**	**520 (90.4)**	**781 (76.9)**	*< 0.0001*
CT-regimen	5FU-MMC	167 (63.0)	315 (60.1)	482 (61.1)	
	Capecitabine MMC	72 (27.2)	131 (25.0)	203 (25.7)	
	5FU Cisplatine	2 (0.8)	22 (4.2)	24 (3.0)	
	Capecitabine	15 (5.7)	18 (3.4)	33 (4.2)	
	Other*	9 (3.4)	38 (7.3)	47 (6.0)	
Induction CT		13 (3.0)	45 (7.8)	58 (5.7)	*0.0009*
RT technique	3D	83 (18.9)	84 (14.6)	167 (16.5)	
	Static IMRT	71 (16.1)	106 (18.4)	177 (17.4)	
	Rotational IMRT	227 (51.6)	288 (50.1)	515 (50.7)	
	Tomotherapy	52 (11.8)	71 (12.3)	123 (12.1)	
	unknown	7 (1.6)	26 (4.5)	33 (3.3)	
Total RT dose (gy)	**Median [IQR]**	**59.4 [45;63]**	**60.0 [59.4;65]**	**60.0[50.4;64.8]**	
	< 50 Gy	129 (29.3)	93 (16.2)		*< 0.001*
	[50–60] Gy	148 (33.6)	190 (33.0)		
	> 60 Gy	160 (36.4)	266 (46.3)		
RT interruption		**133 (30.2)**	**194 (33.7)**	**327 (32.2)**	
	planned	71 (53.4)	101 (52.1)	172 (52.6)	
	for toxicity	59 (44.4)	80 (41.2)	139 (42.5)	
Interruption (days)	**Median [IQR]**	**15 [7;17]**	**14 [7;19]**	**14 [7;19]**	
OTT	Median [IQR]	47 [38; 59]	51 [45; 64]	50 [43;61]	
Brachytherapy boost		106 (24.1)	44 (7.7)	150 (14.8)	*< 0.001*

Abbreviations: CT = chemotherapy; RT = radiotherapy; IQR = Inter-Quartile Range.
*Other chemotherapy consisted of 5FU-MitoC associated with panitumumab for 20 pts included in FFCD0904 trial; 5FU alone, or 5FU-MitoC followed by CDDP for the second cycle when mitomycin was out of stock in France.
[#] X^2 test.

of functional reasons (vaginal fistula, pain, or fecal incontinence) for 10 patients (reason unknown for 1 patient).

Discussion

This nationwide observational cohort is the largest study conducted in SCCA to date and the first one to give a comprehensive representation of current (chemo)radiotherapy practice and patient outcomes with long-term results. Following the modification of the national and international guidelines[3,4], our first goal was to evaluate the implementation of IMRT as well as the type of concurrent chemotherapy prescribed in France. Indeed, twenty years ago, concurrent chemotherapy associated with radiotherapy consisted of MMC and FU or cisplatin and 5FU. In France, cisplatin and 5FU remained mainly used and were chosen for the standard arm of the ACCORD03 trial [17]. Since ACT2 [16] and RTOG 98–11 [13] trials results have been published, cisplatin and 5FU have been progressively discontinued in favor of mitomycin and 5FU. More recently, capecitabine has been considered as efficient as 5FU in continuous infusion and has been increasingly used in combination with mitomycin [18–21].

Interestingly, our study shows good accordance with current guidelines with almost 80 % of patients treated with IMRT and concomitant chemotherapy with mitomycin and 5FU or capecitabine. In addition, more than 70 % of patients underwent a PET-CT and a pelvic MRI in their initial workup.

In contrast, one-third of patients still experienced an interruption of treatment with a median duration of 14 days, because of toxicity but also as a planned gap for 16.9 % of patients, while the reduction in gap duration was associated with an improved prognosis [22–25]. Therefore, such a planned gap should be restricted to patients treated with brachytherapy where the gap is supposed to let the tumor shrink to reduce the brachytherapy volume. Interestingly, two-thirds of patients with treatment interruption for toxicity were not treated with IMRT but 3D conformal RT. Conversely, IMRT was significantly associated with a better CFS. In the UK observational cohort, including 242 cases in 40 centers over 6 months in 2015, 78 % of patients were treated with IMRT resulting in reduced toxicity with only 4 % of treatment interruptions versus 11 % in patients treated with conformal 3D RT [26]. The development of new techniques with better tolerance, such as IMRT has led to the reduction of interruptions, which probably explains why that IMRT was associated with both reduced overall treatment time and improved survival [26].

Surprisingly, induction chemotherapy was still prescribed in 5.7 % of patients, whereas randomized trials ACT2 and ACCORD03 did not show any benefit for either neoadjuvant or adjuvant chemotherapy [16,17]. This could be due to the physician's choice especially for locally advanced tumors that could be close to metastatic disease, or to poor accessibility to radiotherapy in a few centers. Interestingly, in our study, induction chemotherapy was associated with a poorer prognosis whereas a brachytherapy boost was associated with a good prognosis in univariate analysis but not in multivariate analysis for the whole population. As a matter of fact, induction chemotherapy was more frequently prescribed in locally advanced tumors whereas brachytherapy boost was more frequently prescribed in early-stage tumors. HIV status was also found as a poor prognostic factor in univariate analysis but not in multivariate analysis where only gender, ECOG PS, and initial tumor stage were associated with prognosis.

Male gender was strongly associated with poor overall survival in our study (p = 0.003) as already found in the EORTC 22861, RTOG 9811, and ACT I/II studies [16,27,28]. Performance status and tumor stage (tumor size or T-stage and N-stage) are also prognostic factors reported in previous studies and notably in a large recent German cohort dedicated to patients treated with chemoradiotherapy [5]. The authors of this study also found that HIV status was correlated with worse DFS in the subgroup of patients with early-stage (cT1-T2N0) tumors.

Chemoradiation with IMRT and concurrent chemotherapy regimen associating mitomycin and 5FU has remained the standard treatment for 40 years regardless of initial staging like a « one size

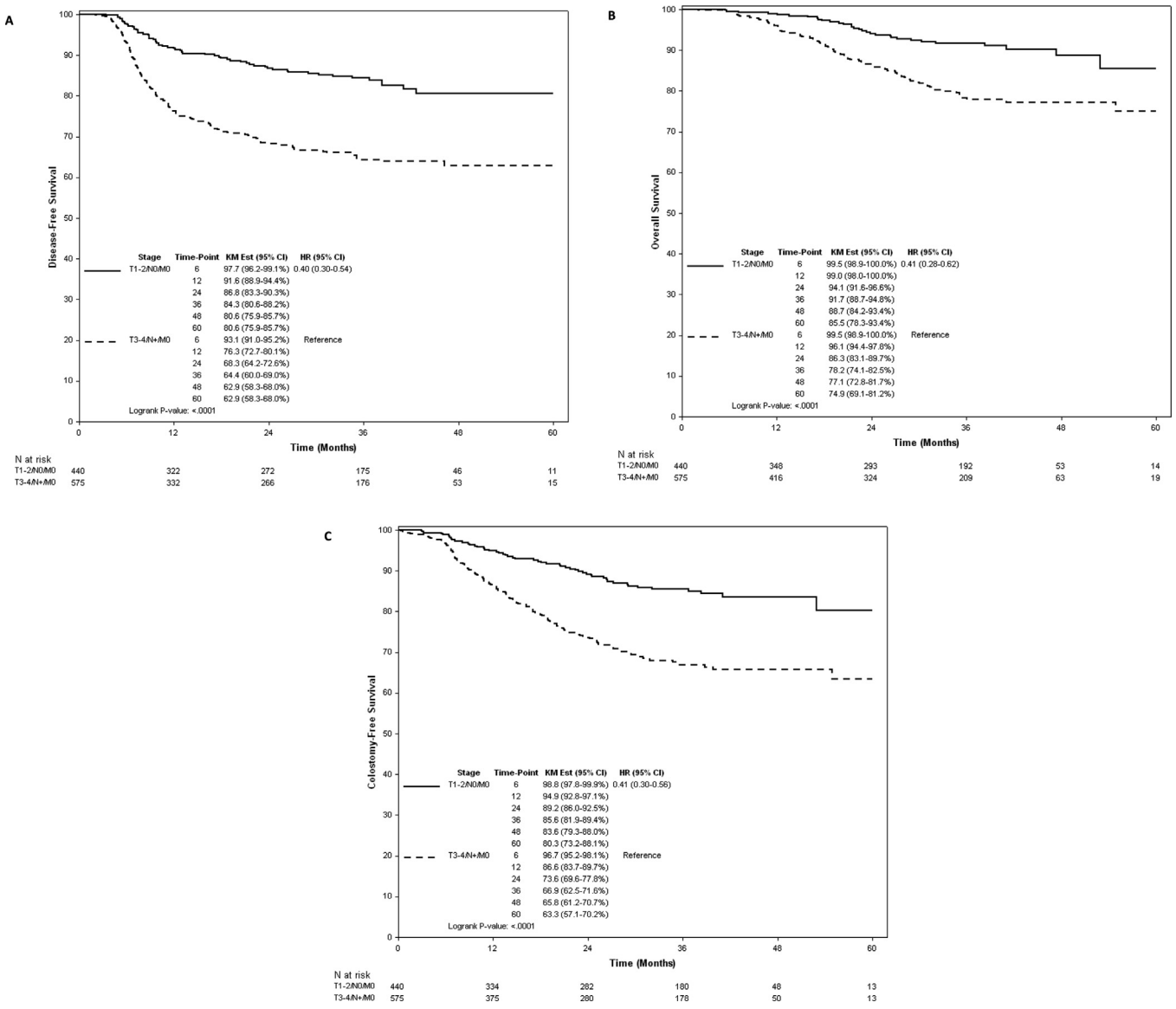

Fig. 2. Kaplan Meier Plots grouped according to early-stage SCCA (T1-2, N0) and locally-advanced SCCA (T3-4 or N +) for disease-free survival (A), overall survival (B), and colostomy-free survival (C).

Table 3
Uni- and multivariate cox regression for disease free survival (DFS) in the whole population (n = 1015).

	Univariate Analysis		Multivariate Analysis	
	HR (95 % CI)	*p value*	HR (95 % CI)	*p value*
Gender (Male vs Female)	**1.57 [1.19;2.07]**	***0.001***	**1.65 [1.14;2.38]**	***0.008***
ECOG PS (≥1 vs 0)	**2.32 [1.78;3.03]**	***< 0.0001***	**1.78 [1.28;2.50]**	***0.001***
T3-4 or N + vs T1-2/N0	**2.50 [1.86;3.34]**	***< 0.0001***	**1.72 [1.19;2.47]**	***0.004***
HIV status (+vs -)	1.52 [0.99;2.34]	*0.057*	0.96 [0.57;1.63]	*0.882*
Induction CT (yes vs no)	**2.30 [1.55;3.42]**	***< 0.0001***	1.45 [0.88;2.38]	*0.148*
Neutrophils (≥5G/l vs < 5G/l)	**1.40 [1.02;1.93]**	***0.04***	1.08 [0.77;1.53]	*0.648*
Brachytherapy Boost (yes vs no)	**0.47 [0.29;0.75]**	***0.001***	1.05 [0.59;1.87]	*0.858*
RT interruption (yes vs no)	1.26 [0.96;1.66]	*0.091*	1.20 [0.86;1.67]	*0.292*
OTT	1 [0.99; 1.01]	*0.97*		
RT technique (3D vs IMRT)	1.17 [0.82;1.66]	*0.385*		
Concomitant CT (yes vs no)	1.13 [0.82;1.55]	*0.458*		
Tobacco (yes vs no)	1.13 [0.86;1.49]	*0.391*		
Age (<75 vs ≥ 75)	1.00 [0.72;1.39]	*0.99*		

fits all » strategy. Excellent results are observed for small T1-T2, N0 tumors, with a 3-year OS of 91.7 %, and a 3-year DFS of 84.3 %, making it possible to consider therapeutic de-escalation strategies in early-stage tumors. In the French guidelines, exclusive radiotherapy is considered an option for T1 and T2 less than 3 cm without nodal involvement. Regarding T1 tumors, however, clinical prac-

Table 4
Final multivariate cox regression for colostomy-free survival (CFS) in the early-stage subgroup (T1-2, N0) and the locally-advanced subgroup (T3-4 or N +).

	Early-stage subgroup		Locally-advanced subgroup	
	HR (95 % CI)	*p-value*	HR (95 % CI)	*p-value*
Gender (Male vs Female)	**2.47 [1.37;4.47]**	***0.03***	**1.39 [0.93;2.08]**	***0.108***
ECOG PS (≥1 vs 0)	**0.47 [0.27;0.84]**	***0.01***	**0.59 [0.41;0.85]**	***0.005***
Tumor size (<3 vs ≥ 3)	**0.53 [0.3;0.95]**	***0.033***	**0.28 [0.1;0.75]**	***0.012***
RT technique (3D vs IMRT)	1.54 [0.8;2.97]	*0.2*	1.53 [0.97;2.41]	*0.066*
Brachytherapy Boost (yes vs no)			0.32 [0.1;1.02]	*0.054*

tices are heterogenous between local resection, exclusive radiotherapy, inguinal irradiation omission, or chemoradiation with reduced radiotherapy doses as we showed in our previous analysis of this subgroup from the ANABASE cohort [29]. In the UK, the ongoing trials ACT3 and ACT 4 investigate different radiotherapy doses for early-stage SCCA in the single-protocol « umbrella platform » PLATO (PersonaLising Anal cancer radioTherapy dOse, ISRCTN88455282). These good results for early-stage are in contrast with those obtained for more advanced stages (T3-T4 or N +), with a 3-year DFS of 65 %. These results are in line with the recently published German cohort where 3-year DFS for patients with early-stage ASCC was 84.9 %, and 67.1 % for patients with locally-advanced disease (HR 2.4, p < 0.001) [5]. For such tumors, treatment intensification is needed and different strategies are being tested. First radiotherapy dose-escalation is being tested in trials such as ACT5 where different total doses with simultaneous integrated boost are evaluated. Interestingly, in our locally-advanced subgroup, there was a trend towards a better CFS with a brachytherapy boost, suggesting dose escalation allowed by brachytherapy achieving a high dose gradient within the residual tumor could be of interest. Other ways to intensify treatment include new therapies such as targeted therapies. Epidermal Growth Factor Receptor (EGFR) is overexpressed in squamous cell carcinomas of the anal canal and is co-expressed with c-Met and VEGFR1 in anal cancers, especially in HIV-positive individuals. Moreover, EGFR overexpression was identified in human HPV-16-immortalized anal epithelial cell line. Based on these observations, combinations of standard CRT and anti-EGFR agents, like Panitumumab (Pmab) or Cetuximab, have been theorized to be clinically helpful in locally advanced SCCA. Despite a strong rationale, the association between radiotherapy and anti-EGFR therapies has been disappointing, resulting in poor tolerance without improving outcomes [30–33]. New hopes are rising with immunotherapy development. Immunotherapy trials in patients with recurrence after CRT or metastatic disease have shown objective response rates ranging from 14 to 24 %, durable anti-tumor activity, and median OS between 9 and 12 months [34–37]. Immunotherapy is currently under evaluation in combination with radiotherapy or/ and as adjuvant treatment in several trials such as Interaction (NCT04719988), Corinth (NCT NCT04046133), or Radiance (NCT04230759) [38]. Neoadjuvant chemotherapy with CDDP-5FU has failed to improve outcomes [16,17]. However, in the ACCORD03 trial, the best 3-year DFS (78.8 %) was seen for the induction chemotherapy CDDP-5FU and high dose RT 66 Gy arm [17]. Recently, chemotherapy regimens adding docetaxel to platinum have shown striking results in patients with recurrent or metastatic anal cancer [39–41]. In the InterAACT phase 2 trial, paclitaxel associated with carboplatin (CP) was compared to CDDP-5FU in 91 patients treated for metastatic or recurrent anal cancer. Median OS was 12.3 months in the CDDP-5FU group compared to 20 months for the CP group (HR 2,00; p = 0,014)[39]. Similarly, in the final updated pooled analysis of Epitopes-HPV01 and Epitopes-HPV02 trials, including 115 advanced SCCA patients treated with Docetaxel, Cisplatinum, and 5FU (mDCF) at first-line, median OS was 39.2 months (26.0–109.1) [40,41]. The objective response rate was 87.7 % with 40.3 % of complete response. Fifty-seven patients (49.6 %) underwent complementary treatment after DCF [41]. Among these patients, 16 patients received chemoradiotherapy after DCF. Importantly, no radiotherapy dose reduction was observed. In addition, no unexpected local toxicity was reported [41].

Our study presents several limitations. HIV status was known only in 488 patients. Data monitoring was not funded at the conception of the study and could be done only in the biggest recruiting centers. Moreover, we could not check if each center included all patients treated for anal cancer over the inclusion period. However, this cohort included more than 1300 patients treated over 5 years in 60 French centers disseminated over the country and we believe that it is strongly representative of the current practice in France. These results allow us to evaluate the respect of the current guidelines and to identify ways of improvement and points to highlight in our continuing medical education as well as build a network of practitioners involved in anal cancer treatment.

Conclusion

The treatment of patients from the ANABASE cohort showed good adhesion to the current guidelines for anal cancer treatment, and a good implementation of IMRT over the country in this indication. Of note, whereas guidelines are shared regardless of disease staging, differences in outcomes require personalized strategies by either de-escalation for early-stage tumors and/or treatment intensification for locally-advanced tumors in clinical trials.

Conflict of interest

Pr Véronique Vendrely declare consulting fees and lectures honorarias from BMS, Servier and AMGEN. Pr Astrid Lièvre declare consulting fees and honorarias from AAA, Astellas, BMS, Incyte, Pierre Fabre, Servier, Amgen, Bayer, Leo-Pharma, Novartis, Mylan, Sandoz, Sanofi and Viatris.

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Credit author statement

V.Vendrely :Study design, Data collection, Data analysis and interpretation, writing, supervising; A.Lièvre : Data collection, Data analysis and interpretation, revision ; K.Le Malicot : study design, data analysis and interpretation, revision ; C.Lemanski : data collection, data analysis and interpretation, ; P. Pommier : data collection and revision ; A.Saint : data collection ; E.Rivin Del Campo : Data collection, Data analysis and interpretation, writing ; P. Regnault : data collection ; N.Baba-hamed : data collection, P. Ronchin : data collection and revision ; G.Crehange : data collection ; D.Tougeron : Data collection, Data analysis and interpreta-

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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