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What is the optimal treatment for T1N0 anal squamous cell carcinoma? Analysis of current practices in the prospective French FFCD ANABASE cohort

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ABSTRACT

Introduction: for localized T1N0 squamous cell carcinoma of the anus (SCCA) standard radiotherapy (RT) may result in overtreatment and alternative strategies are debated.
Methods: T1N0M0 SCCA treated between 2015 and 2020 by local excision (LE) or RT were analyzed from the French prospective FFCD ANABASE cohort. Treatment strategies, recurrence-free and colostomy-free survivals (RFS, CFS) and prognostic factors were reported.
Results: among 1135 SCCA patients, 99 T1N0M0 were treated by LE($n=17$,17.2%), or RT ($n=82$,82.8%) including RT alone ($n=65$,79.2%) or chemo-RT ($n=17$, 20.7%). Median follow-up was 27.2 months [0.03–54.44]. Median tumor size were 11.4 mm [0.9–20] and 15.3 mm [2–20] in the LE and RT groups respectively. Mean RT tumor dose was 59.4 Gy [18–69.4 Gy]. One patient in LE group and 9 in RT group had a pelvic recurrence, either local (60%), nodal (10%) or both (30%). RFS and CFS at 24 months were 92.2%[95%CI,83.4–96.4] and 94.6%[95%CI,86.1–98.0], at 36 months 88.1%[95%CI,77.1–94.2] and 88.5%[95%CI,77.0–94.5], in LE and RT group respectively, without any significative difference (HR = 0.57;[95%CI,0.07–4.45];$p=0.60$). By univariate analysis, male gender was the only prognostic factor(HR = 5.57;95%CI, 1.76–17.63; $p=0.004$).
Conclusion: this cohort confirms the heterogeneity of T1N0M0 SCCA management, questioning the place of RT alone, reduced dose or RT volume, and the safety of LE.

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1. Introduction

Anal squamous cell carcinoma (SCCA) has been considered a rare tumor, accounting for 2.5% of reported gastrointestinal malignancies [1]. Risk factors include human papillomavirus (HPV) infection, high-risk sexual activity or a prior history of sexually transmitted disease, human immunodeficiency virus (HIV) infection-related immunosuppression [2]. During the last decade, the incidence of SCCA has gradually been rising in the Western world and appearing as a public health concern [3].

Since the 1990s, the current standard of care relies on primary chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) and mitomycin C (MMC), resulting in an improvement in locoregional control and reducing the need for colostomy [4–6]. The initial randomized control trials that validated CRT included patients with locally advanced disease and/or tumors with nodal involvement [4–9]. Thereby, early-stage disease, defined as tumors less or equal to 2 cm (T1), were underrepresented with about 10 to 15% of the studied population. For stage I disease, the oncological result of CRT is good with a 5-year relapse-free survival (RFS) of more than 80%. However, considering the substantial toxicity of CRT (skin toxicity, diarrhea and fecal incontinence, myelosuppression) the optimal management of T1 disease is still matter of debate and de-escalation strategies are upon consideration. In France, RT alone represents a suitable front-line treatment for SCCA classified T1N0M0 as it provides a high disease-control rate without jeopardizing anorectal function [1]. However, some oncological teams favor a CRT regimen with a reduced RT dose versus RT alone. To this end, the randomized phase II trial Anal Cancer Trial 4 (ACT4) from PLATO (PersonaLising Anal cancer radioTherapy dOse, ISRCTN88455282) is testing radiation dose de-escalation (41.4 Gy in 23 fractions) compared to standard dose (50.4 Gy in 28 fractions) for patients with T1–T2 (< 4 cm) node-negative anal canal cancer [10]. To date, surgical resection is recommended for anal margin SCCA but limited information is available about surgical options in the management of small SCCA located in the anal canal. However, T1 tumors are sometimes identified on surgical resection from a lesion, initially considered as benign. In such situations, some advocate that adjuvant RT could be omitted in case of small lesions (less than 10 mm) and adequate margins (>1 mm from infiltrating carcinoma) [1]. For such small lesions, the role of local excision (LE) alone is actively debated.

We analyzed the ANABASE cohort in order to evaluate the modalities of treatment and the oncological outcomes of patients with localized T1N0M0 SCCA of the anal canal treated by LE or RT.

2. Methods and materials

The ANABASE cohort is a prospective multicentric observational study conducted in France by the Fédération Francophone de Cancérologie Digestive (FFCD) that aims to collect data on management, oncological outcomes and survival of patients with anal cancer. This study on a subgroup of the ANABASE cohort was designed by the FFCD and the Groupe de Recherche en Proctologie (GREP). It was submitted and approved by the ethics committee and the "Commission National de l'Informatique et des Libertés" (authorization number 915,622). All patients received written information and provided oral informed consent.

The endpoints of our study were to report, treatment strategies for T1N0 SCCA and evaluate recurrence-free survival (RFS), colostomy-free survival (CFS) and prognostic factors depending on treatment.

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2.1. Study population

Data of 1135 patients treated between January 2015 and January 2020 were available in this cohort, with 172 patients of tumor size ≤ 2 cm (T1). Of these patients, 123 presented with anal canal tumors, 39 with anal margin tumors and 10 with other localizations (such as low rectum). Among the 123 patients with anal canal tumors, 22 (17.9%) had lymph node invasion. Finally, 100 patients were treated for T1N0M0 SCCA in 27 French medical centers (Fig. 1). Tumor size was evaluated by physical examination or medical imaging, including magnetic resonance imaging (MRI). Two groups were defined: the local excision (LE) group included patients treated by LE alone ($n = 17$, 17%) and RT group included patients treated by RT or CRT ($n = 82$, 82%) after biopsy or LE.

2.2. Study variables

Collected parameters in each group included demographic data (age, sex, medical history such as superficial lesions or condyloma, HIV infection status, alcohol intake and smoking), baseline physical examination, pathological characteristics of the biopsy or surgery (tumor size, p16 status, margin of resection), baseline digestive endoscopy or initial imaging (echo-endoscopy, computed tomography of the thorax, abdomen and pelvis (CT-TAP), 18F-Fluorodeoxyglucose positron emission tomography/CT (18F-FDG-PET/CT), pelvic MRI), treatment strategy, modalities and toxicity according to the Common Terminology Criteria of Adverse version 5 (CTCAEv5) [11] and latest follow-up of each patient.

2.3. Statistical analysis

A descriptive analysis was performed to evaluate the distribution of variables between LE and RT group, respectively. Quantitative variables have been described with mean (or median), minimum and maximum and were compared with the Wilcoxon rank-sum test. Qualitative variables were compared by the chi-square test or Fisher's exact test. The Kaplan-Meier method was used to describe censored data [12]. Logrank tests were used to compare rate and event time distributions with a 95% confidence interval (95% CI), as well as for comparison curves.

Exploratory analyses included comparisons between LE and RT groups.

Recurrence-free survival (RFS) was defined as the period between the diagnosis and the first recurrence or death (any cause) and colostomy-free survival (CFS) was defined as the period between the diagnosis and the first colostomy or death (any cause) without colostomy. Alive patients without recurrence or colostomy were censored at the date of the latest follow-up.

Univariate analysis with Cox proportional hazards regression reporting hazard ratios (HR) and 95%CI was performed to evaluate prognostic factors associated with RFS.

3. Results

3.1. Patient characteristics

A total of 100 patients with T1N0M0 SCCA were included and one patient treated with primary abdominoperineal resection (APR) due to particular medical history was excluded from comparative analysis because the objective was to assess the factors influencing the treatment choice between RT and LE. Patient characteristics are outlined in Table 1. The cohort was predominantly composed of females ($n = 74$, 74.8%) with significant gender difference between the two groups ($p = 0.011$) and the median age was 64.6 years range 44-89. Median tumor size was 14.6 mm range 0.9-20 with 11.4 mm range 0.9-20 in the LE group and 15.3 mm

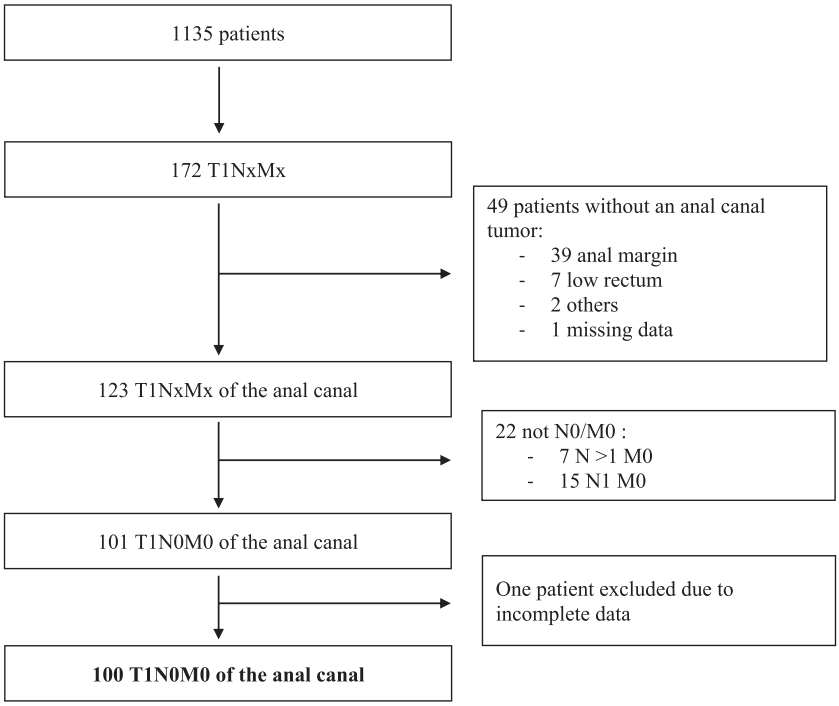

Fig. 1. Patient flowchart.

Table 1
Patients characteristics by treatment group.

	LE $n=17$	RT $n=82$	p-value	Total $n=99$[1]
Age (years) Mean (min-max)	61.3 (45–81)	65.2 (44–89)	0.197	64.6 (44–89)
Gender n (%)				
Male	9 (52.9%)	16 (19.5%)	0.011	25 (25.2%)
Female	8 (47.1%)	66 (80.5%)		74 (74.8%)
Medical history n (%)				
Condyloma	8 (47.1%)	12 (14.6%)	0.013	20 (20.2%)
AIN 1–2–3	8 (47.1%)	19 (23.2%)	0.092	27 (27.3%)
Cervico-uterine conization	2 (11.8%)	1 (1.2%)	0.045	3 (3.0%)
Smoking	8 (47.1%)	22 (26.8%)	0.007	30 (30.3%)
Alcohol intake	2 (11.8%)	13 (15.9%)	0.671	15 (15.2%)
HIV status				
Positive	5 (29.4%)	6 (7.3%)	0.006	11 (23.4%)
Negative	8 (47.1%)	28 (34.2%)		36 (76.6%)
Unknown	4 (23.5%)	48 (58.5%)		50 (50.5%)
P16 immunohisto-chemistry n (%)				
no	5 (29.4%)	27 (32.9%)	0.778	32 (32.3%)
yes	12 (70.6%)	55 (67.1%)		67 (67.7%)
Positive	12 (100%)	51 (92.7%)	1.00	63 (94.0%)
Negative	0 (0.0%)	4 (7.3%)		4 (6.0%)
Tumor size (mm) Mean (min-max)	11.4 (0.9–20)	15.3 (2–20)	0.026	14.6 (0.9–20)

RT : RadioTherapy ; AIN : Anal Intra-épithélial Neoplasy ; HIV : Human Immunodeficiency Virus.
[1] Total number of patients is 99 because the patient treated by abdomino-perineal resection was excluded from the analysis.

range 2-20 in the RT group ($p=0.026$). Medical history of condyloma ($p=0.013$), cervico-uterine conization ($p=0.045$), smoking ($p=0.007$) and HIV infection ($p=0.006$) were significantly more frequent in the LE group. Baseline imaging evaluation was performed with pelvic MRI for 81 patients (81.8%), 18F-FDG-PET/CT for 70 patients (70.7%), CT-TAP for 54 patients (54.5%), with no difference between the two groups and digestive endoscopy for 51 patients (51.5%, 17.7% in LE group and 58.5% in RT group, $p=0.002$) (Supplementary Table A1).

In the complete population, 58 patients had an initial biopsy followed by RT ($n=45$, 77.6%) or CRT ($n=13$, 22.4%) and 42 patients had initial surgery, 41 LE with 28 (68.3%) free margins (defined as >1 mm to infiltrating SCCA) and 13 (31.7%) positive margins. Regarding patients with free margins, 13 (46.4%) had no ad-

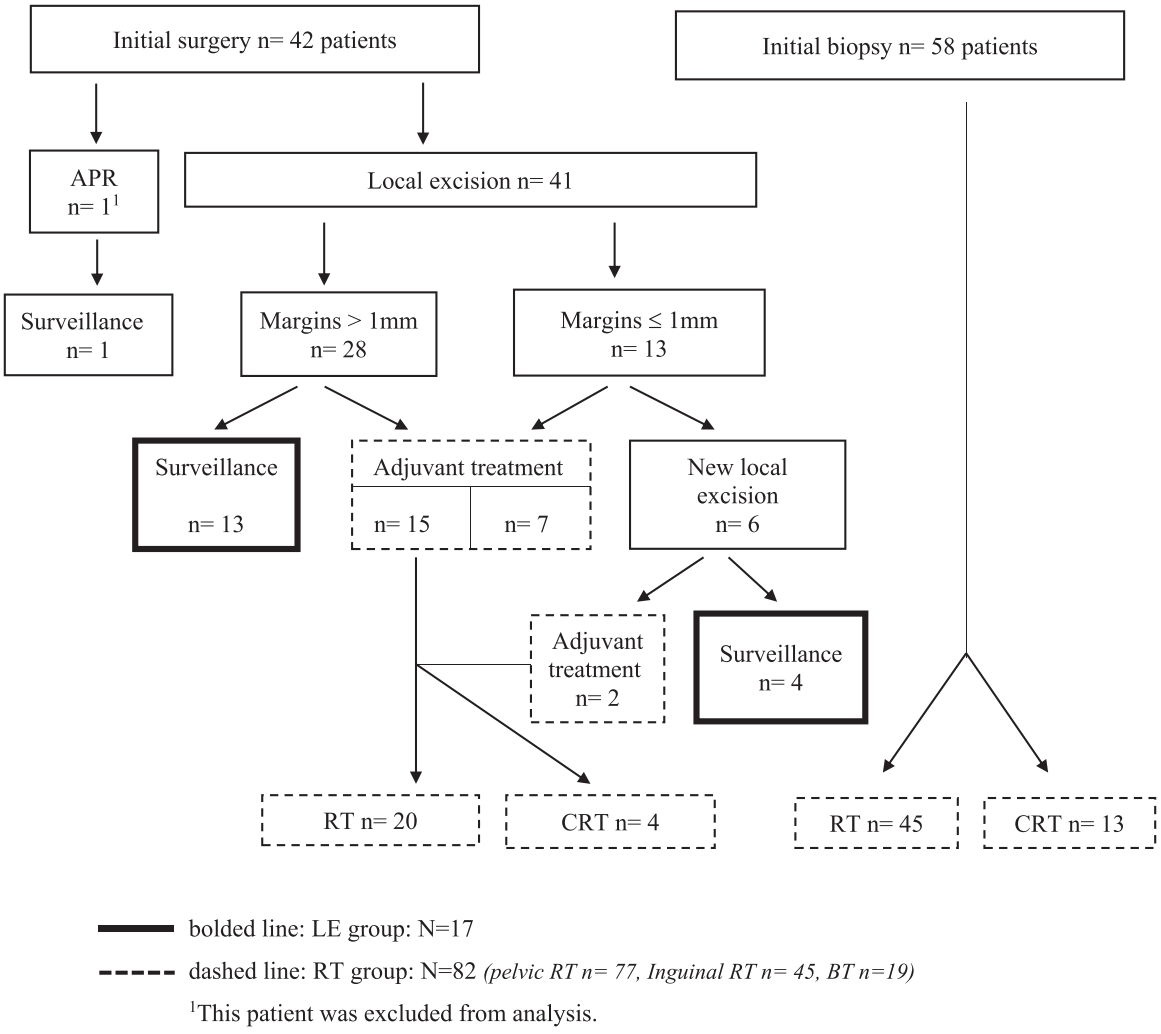

Fig. 2. Distribution of patients T1N0M0 according to treatment groups.

juvant treatment and 15 (53.6%) had one. Regarding patients with positive margins, 6 (46.2%) had further surgery. Finally, 4 (30.8%) had surveillance and 9 (69.2%) had adjuvant treatment (Fig. 2).

Median follow-up of the T1N0M0 population was 27.2 months [0.03–54.44] with 20.9 months [0.03–52.5] in the LE group and 31.0 months [6.6–54.4] in the RT group. The follow-up was superior to 36 months for 37 patients (37.3%) and to 24 months for 55 patients (55.6%). Ten patients (10.1%) were lost to follow-up. Three patients died, one with cancer-associated death.

3.2. Descriptive analysis of treatment strategies

In the LE group, resection margins were free for 13 patients (76.5%) and positive for 4 patients (23.5%) who had additional surgical resection that led to negative margins (Fig. 2). For the patients treated by LE, the lesion was diagnosed as malignant upon histological analysis of the surgical specimen. Therefore, baseline imaging evaluation (MRI and/or PET-CT) was done after the LE.

In the RT group, 45 patients (54.9%) were treated by RT alone, 13 patients (15.9%) by CRT, 20 patients (24.4%) by LE followed by RT and 4 patients (4.9%) by LE followed by CRT (Fig. 2). Among 24 patients treated by primary LE, tumor size was ≥ 10 mm for 23 patients (96%) and 9 had positive resection margins (37.5%) (Table 1 and Supplementary Table A2). The median age was not significantly different between these patients and LE groups (64.3 vs 61.3 years, $p = 0.55$), neither was median tumor size (14.2 vs 11.4 mm, $p = 0.18$).

Treatment modalities and protocols, including intensity-modulated radiotherapy (IMRT) and 3D conformal radiotherapy (3DCRT), were heterogeneous and are detailed in Supplementary Table A3. The median total dose delivered to the tumor was 59.4 Gy [18–69.4]. Prophylactic pelvic irradiation was performed in 77 patients (93.9%) with a median dose of 45 Gy range 36-50.4 Prophylactic inguinal irradiation was performed in 45 patients (54.9%) with a median dose of 44.8 Gy range 30.6-50.4. Treatment interruption occurred in 19 patients (23.2%), due to preplanned protocol interruption ($n = 9$, 47.4%) or to treatment-related toxicity ($n = 10$, 52.6%). An additional dose of interstitial brachytherapy was received by 19 patients (23.2%) with a total median dose of 16.6 Gy range 9-20 (Fig. 2 and Supplementary Table A3). In RT group, radiotherapy characteristics based to tumor size are detailed in Supplementary Table A4. There was no difference in terms of total dose or volumes according to tumor size within this group of patients treated for tumor staged T1. There was no significant difference between patients treated by RT or LE followed by RT in terms of pelvic and inguinal irradiation, respectively 87.5% vs 96.6% ($p = 0.3$) and 50% vs 56.9% ($p = 0.7$) (Supplementary Table A5)

Acute radiotherapy-induced toxicities of grade 3 or more were reported in 14 patients (17.1%), 4 (16.7%) treated by primary LE fol-

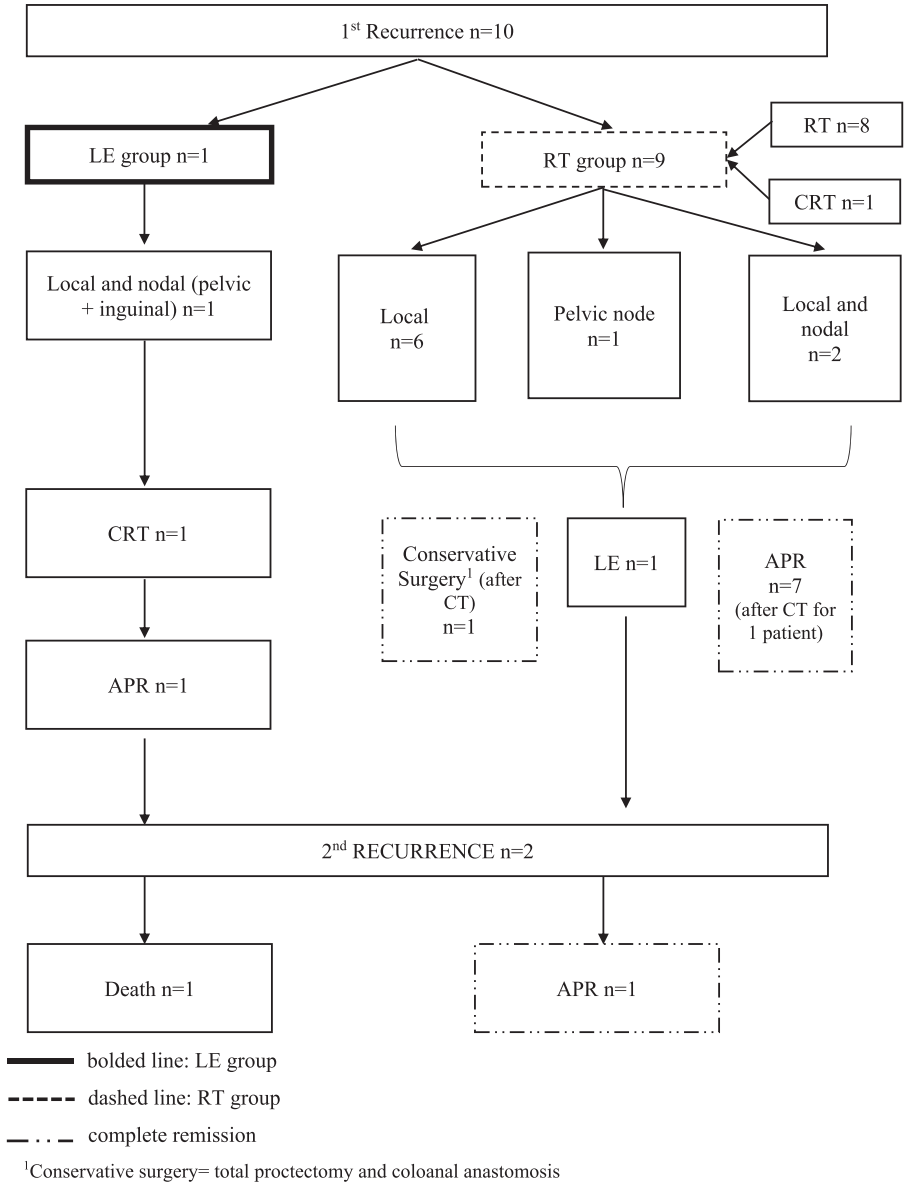

Fig. 3. Description of recurrences and specific management according to the treatment group.

lowed by RT and 10 (17.2%) by RT . The most common adverse events were radiation dermatitis (78.6%) and diarrhea (14.3%).

Concurrent CRT was performed in 17 patients (21%); 9 patients (52.3%) received 5-FU+MMC administered at week 1 and 5 of RT, 6 patients (35.3%) received capecitabine +MMC, 1 patient (5.9%) capecitabine alone and 1 patient (5.9%) received 1 cycle of 5-FU +MMC followed by weekly cisplatin owing to grade 3 multi-organ adverse events. The common chemotherapy-related adverse events of grade 3 or greater were mucositis (11.8%), one patient (5.9%) presented cytolytic hepatitis on capecitabine and one patient (5.9%) presented coronary spasm on capecitabine.

3.3. Descriptive analysis of recurrence

In the total population, 10 patients (10.1%) relapsed without statistical difference between the two groups, with 1 relapse (5.9%) in the LE group and 9 (11.0%) in the RT group. Five patients (50%) had negative HPV status and 2 (20%) were positive for HIV.

The description of recurrences and their specific management according to treatment group was shown in Fig. 3**.** There were local ($n = 6$, 60%), nodal ($n = 1$, 10%) or both ($n = 3$, 30%). All local recurrences were in the irradiated volume with a mean total dose to the tumor of 54.9 Gy range 45-65 Nodal recurrences were inguinal in 2 patients, none of whom received inguinal prophylactic irradiation, and pelvic in 3 patients prophylactically irradiated at 45 Gy. Of 4 patients with nodal recurrence, 3 patients (75%) had received primary LE. These 3 patients had no 18F-FDG-PET/CT at baseline extension workup.

In the LE group, recurrence was local and nodal (pelvic and inguinal). The patient was treated by CRT followed by APR owing to incomplete response after CRT. He presented an early second inguinal recurrence, then further metastatic recurrence and died for disease progression. This patient didn't have an 18-FDG-PET/CT during the initial extension workup.

In the RT group, the recurrence was local (66.7%), nodal (11.1%) or both (22.2%). Among these 9 patients, 8 had been treated by RT alone and one by CRT. One patient refused APR and was treated with chemotherapy (3 cycles of 5-FU and cisplatin) followed by conservative surgery (total proctectomy and coloanal anastomosis). The others were treated with APR, 1 after chemotherapy (4 cycles

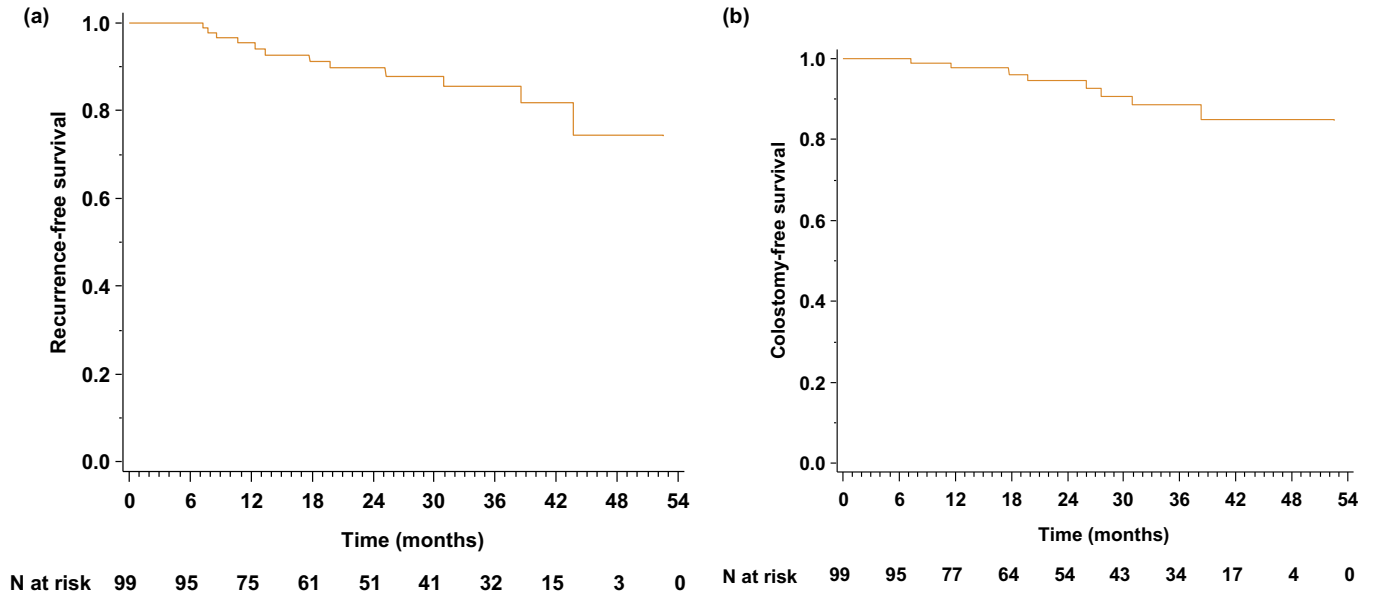

Fig. 4a. (a) Recurrence Free Survival and Colostomy Free Survival in overall population.
Fig. 4a. Recurrence-Free Survival in overall population.
[1]RFS was 95.4% [88.3–98.3] at 12 months, 89.7% [80.2–94.7] at 24 months and 85.7% [74.5–92.2] at 36 months.
(b) Recurrence Free Survival and Colostomy Free Survival in overall population.
Fig. 4b. Colostomy-Free Survival in overall population.
[1]CFS was 97.6% [90.9–99.4] at 12 months, 94.6% [86.1–98.0] at 24 months and 88.5% [77.0–94.5]at 36 months.

of 5-FU, leucovorin, oxaliplatin and docetaxel) and 1 after LE followed by a second recurrence. All patients were in complete response after APR or conservative surgery at the time of analysis.

The RFS at 12, 24 and 36 months were 95.4% [IC95%, 88.3–98.3], 89.7% [IC 95%, 80.2–94.7], 85.7% [IC 95%, 74.5–92.2], respectively. The CFS at 12, 24 and 36 months were 97.6% [95%CI, 90.9–99.4], 94.6% [95%CI, 86.1–98.0] and 88.5% [95%CI, 77.0–94.5], respectively (Fig. 4a and b).

3.4. Univariate analysis of recurrence-free-survival

In univariate analysis, the only factor significantly associated with an increased risk of recurrence or death was male gender (HR 5.57; 95%CI, 1.76 −17.63; $p = 0.004$). There was a trend regarding the total dose delivered to the tumor (HR 0.96; 95%CI 0.92–1.00; $p = 0.06$). Regarding disease management, here was no significant difference between the LE and RT groups (HR 0.57; 95%CI 0.07–4.45; $p = 0.59$). Other factors such as concomitant CT (HR 2.31; 95%CI 0.70–7.70; $p = 0.17$) or the interruption during irradiation period (HR 0.40; 95%CI 0.08–1.90, $p = 0.25$) had no significant impact (Table 2).

4. Discussion

Our study highlights the good prognosis for small anal canal tumors described in the literature [13,14] with an 85.7% RFS and 88.5% CFS at 3 years, regardless of the treatment group. Tumors less than 2 cm are usually associated with a low risk, about 12%, of lymph node involvement (1), however, in the ANABASE cohort, a rate of 17.9% was observed, underlining the lymphophile feature and the importance of a complete initial extension assessment. Currently, 18F-FDG-PET/CT with pelvic MRI are recommended for the initial staging [1,15]. Initial 18F-FDG-PET/CT leading to 28% stage change following changes in therapeutic strategies (target volumes, dose levels) [16]. In our study, among the 4 patients who relapsed at the lymph node level, only one was evaluated with 18F-FDG-PET/CT at the initial diagnosis.

CRT is the recommended first-line treatment for the management of non-metastatic anal canal tumors. Surgery is recommended only for anal margin tumors (LE) or as salvage treatment (APR) in case of local recurrence after CRT [15]. In France, incidental diagnosis of T1 lesions located in the anal canal after surgery for another reason, may lead to surveillance provided small size (less than 10 mm) and negative margins. The possibility to offer primary LE for T1 of the anal canal is still a matter of debate. In our study, there was no difference in terms of RFS between LE and RT groups (HR 0.57; 95% CI 0.07–4.45; $p = 0.59$). However, the only patient who died because of disease progression was in the LE group and had no 18-FDG-PET/CT during initial extension workup.

Excisional surgery has historically been described for selected lesions of the anal canal (< 1 cm, no muscle invasion), with excellent local control rates and survival in retrospective observational studies [17,18]. However, more recent retrospective studies comparing surgery and RT showed controversial results. For example, a study of 190 patients with T1N0 anal canal tumors found no significant difference in OS between the surgery, RT and RCT groups ($p = 0.32$) [19]. Moreover, a cohort study has included 2243 patients from the National Cancer DataBase (NCDB) treated by RCT (77.6%) or LE alone (22.4%) between 2004 and 2012. A significant increase in the use of excision over time ($p<0.001$) was observed, with a greater absolute increase in patients with tumors ≤ 1 cm ($p = 0.04$) but no significant difference in 5-year OS between the two groups ($p = 0.93$). However, no locoregional control and pathology data were described [20]. On the other hand, the Nordic Anal Cancer Database study with 93 patients treated between 2000 and 2007 by primary surgery (LE or APR) alone or combined with CRT (63.4% surgery vs. 36.6% RT+/-CT) for anal canal/margin tumors Tx-T1-T2N0 obtained opposite results. The locoregional recurrence rate was significantly higher in the surgery alone group ($p = 0.006$) and all the more so for anal canal (43%) than for anal margin tumors (30%). Additionally, RFS and OS were also signif-

Table 2
Uni-variate analysis of factors influencing recurrence-free-survival in overall population.

	n	Events number/ *n*	HR	95%CI	*p* (logrank)
Demographic characteristics					
Gender Male vs Female	99	7/25 vs 5/74	5.57	[1.76–17.63]	0.004
Age	99	–	0.97	[0.91–1.02]	0.21
Tumor characteristics					
Tumor size	98	–	0.62	[0.22–1.76]	0.37
HPV status Positive vs Negative	66	7/63 vs 1/3	0.43	[0.05–3.53]	0.43
Medical history					
Condyloma Yes vs No	94	4/20 vs 8/74	2.02	[0.60–6.78]	0.26
HIV status Positive vs Negative	47	2/11 vs 5/36	2.70	[0.52–14.07]	0.24
Treatment					
LE vs RT	99	1/17 vs 11/82	0.57	[0.07–4.45]	0.59
Concurrent CT Yes vs No	99	4/18 vs 8/81	2.31	[0.70–7.70]	0.17
Total dose to the tumor	82	–	0.96	[0.92–1.00]	0.06
Treatment interruption Yes vs No	82	2/20 vs 9/62	0.40	[0.08–1.90]	0.25
Additional dose of interstitial BT Yes vs No	99	4/20 vs 8/79	2.18	[0.65–7.29]	0.20
Baseline imaging evaluation					
Digestive endoscopy Yes vs No	99	6/51 vs 6/48	0.92	[0.29–2.86]	0.88
Pelvic MRI Yes vs No	99	11/81 vs 1/18	3.46	[0.44–26.94]	0.24
18-FDG-PET/CT Yes vs No	99	6/70 vs 6/29	0.43	[0.14–1.32]	0.14
CT-TAP Yes vs No	99	9/54 vs 3/45	1.92	[0.52–7.12]	0.33

HR: Hazard Ratio; CI: Confident Interval; HPV: Human PapillomaVirus; AIN: Anal squamous Intra-épithélial Neoplasy ; HIV : Human Immonodeficiency Virus ; LE : Local Excision ; RT : RadioTherapy ; CT : Chemotherapy ; BT: Brachytherapy; MRI: magnetic resonance imaging; 18-FDG-PET/CT: 18F-Fluorodeoxyglucose positron emission tomography/CT; CT-TAP: computed tomography of the thorax, abdomen and pelvis;.

icantly lower in the surgery group (52.7% and 70%, respectively) compared to CRT (84.2% and 87.2%, respectively). In this study, the addition of CRT was the only factor influencing the RFS in multivariate analysis ($p = 0.02$). Patients in the surgery group were significantly older ($p = 0.026$), had a smaller tumor ($p = 0.026$) and a higher percentage of radical resection [21]. In our study, among 24 patients treated by initial LE, median age and tumor size were not statistically different from the LE group ($p = 0.55$ and $p = 0.18$, respectively) and 37.5% of these patients had positive resection margins. On the other hand, among 28 patients treated by initial LE with free margins, 15 (53.6%) received an adjuvant treatment although there was no clear recommendation in such a situation. Therefore, many questions remain unanswered regarding the management of these small tumors by surgery alone, particularly regarding the tumor size or resection margins. In our study, tumor size had no significant impact on RFS (HR 0.62; 95% CI 0.22–1.76; $p = 0.37$). However, numerous data in the literature reported a prognosis directly correlated to tumor size, with an increasing risk of lymph node invasion according to the size of the primary lesion [1,13,14].

Although RCT remains the standard treatment for anal canal tumors, the addition of CT to RT is still controversial for tumors less than 4 cm, because of the lack of disease-free survival benefit and the cost of increased toxicity [22,23]. Given the absence of a firm consensus, several therapeutic de-escalation strategies are currently being debated (RT alone, reduction of the RT dose or volumes) and the management of these tumors is disparate. Our study reports on the heterogeneity of therapeutic practices, whether concomitant CT was performed or not (18% of patients received concomitant chemotherapy with no significant impact on the risk on the RFS (HR 2.31; 95% CI 0.70–7.70; $p = 0.17$), the type of associated chemotherapy, the modalities, the doses and the volumes irradiated.

RT alone is the first alternative for these small tumors, as evaluated in several retrospective studies [13,24]. The combination with CT did not result in a significant increase in locoregional control and specific survival in the management of T1-T2N0 tumors [22]. To date, no prospective randomized study has validated RT alone treatment, but is considered as an option for T1N0M0 in France [1,25].

Interestingly, all local recurrences occurred in the radiation field despite a total dose of 59.4 Gy, but without concurrent CT. There is no international consensus on the optimal doses to be delivered to the tumor and lymph node drainage areas. For locally advanced tumors, national guidelines recommend a total dose of 36 to 45 Gy with conventional fractionation on a first volume corre-

sponding to the tumor and pelvic lymph node areas (internal and external iliac, ilio-obturator, mesorectum, ischiorectal fossae, inguinal pre-sacral), followed by a boost of 15 to 20 Gy to the tumor [25]. These recommendations relate to all locally advanced anal tumors, but several studies suggest that small tumors could be sterilized by lower doses. For example, the Radiation Therapy Oncology Group (RTOG)- 8314 study found an 84% local and nodal control rate more than 8 months after treatment in 26 patients (33%) treated for small tumors ($<$ 3 cm) by RCT with a total dose of 40.8 Gy [26]. Total dose as low as 30 Gy could be sufficient with chemotherapy as suggested by the high control rate (only one local recurrence and no distance recurrence) in a descriptive study conducted on 21 patients with localized tumors (T *in situ*, T1-T2 N0) [27]. Considering pelvic prophylactic irradiation, 36 Gy may be sufficient to sterilize subclinical lymph node disease [28].

The target volumes for these small tumors are also discussed. For example, in a multicenter retrospective study of 69 patients treated for $\leq$ 10 mm tumors, the probability of perirectal lymph node invasion was as low as 2% and no inguinal recurrence was found. Thus, the authors suggested that a restricted volume of irradiation, encompassing the tumor of the anal canal, the first 2–3 cm of the lower rectum and the perirectal lymph node areas up to the 3rd sacral vertebra, would be sufficient [29]. Similarly for T1N0, the need for prophylactic irradiation of the inguinal lymph node areas remains debated, as recommended by the RTOG [30], in contrast to the Australian GastroIntestinal Trials Group (AGTG) [31]. However, in our study, inguinal recurrences occurred only in patients for whom inguinal irradiation was omitted. Likewise a other retrospective study found a 12% cumulative inguinal recurrence rate at 5 years in the T1–T2 group without inguinal irradiation as compared to 3% in the inguinal irradiated group ($p = 0.17$) [32]. In addition, all the current recommendations relate to the management of invasive tumors and diagnosed by biopsy, but no specific data exist concerning the dose to be delivered after a surgical resection. In a retrospective study conducted at the Memorial Sloan Kettering Cancer Center on 149 patients, a total pelvic dose of 30 Gy was considered as sufficient after excisional surgery, with local control and overall progression-free survival being equivalent to patients receiving a total dose of 45 Gy [33].

Our study is descriptive and retrospective with several limitations related to the scarcity of patients treated with LE (17 patients), the low number of events (10 recurrences) and the percentage of patients lost to follow-up (10.1%). Some patients characteristics were significantly different between the two groups. For example, there are more patients with HIV infection in the LE group ($p = 0.006$), probably because these patients are followed regularly by proctologists who perform LE more easily. However, anal canal cancer is a rare disease and our study remains one of the largest conducted to date in France with 100 patients treated for a T1N0M0 tumor. The median follow-up of 27 months is sufficient for the analysis, but prolonged surveillance is necessary with an average of 1% of recurrences occurring after 3 years [15,34]. The inconsistent care and monitoring practices, due to the lack of national and international consensus, also represent a limit to the interpretation of our results. In addition, a possible recruitment bias exists with potential underreporting of patients treated with LE alone.

In conclusion, this study reflects the current heterogeneity in the management of T1N0M0 SCCA of the anal canal. For these tumors with a good prognosis, standard CRT treatment may result in over-treatment and therapeutic de-escalation strategies emerge, particularly in terms of dose, irradiated volume or concurrent CT.

Local resection resulted in similar local recurrence rates compared with radiotherapy but remains debated. Our small number of patients and events can't allow a recommendation to be made.

Moreover, the lymph node invasion found in 18% of patients with T1 tumor included in the ANABASE cohort underlines the importance of the initial extension assessment even in case of small tumors.

Although the ANABASE cohort remains open to the inclusion of patients with a T1 anal canal tumor, prospective collection or Europe-wide clinical trials would be required to achieve valid endpoints.

Declaration of Competing Interest

Astrid Lievre reports conflicts of interest with AAA, Amgen, Bayer, BMS, Incyte, Ipsen, Lilly, Merck, Novartis, Pierre Fabre, Pfizer, Roche, Sandoz, Sanofi, Servier, Integragen, HalioDx. Laurent Quero reports personal fees from IPSEN, from Astellas Pharma, outside the submitted work. The others authors declare non conflicts of interest. Come Lepage reports conflicts of interest with Board AA, Novartis, Educational Symposia Amgen, Bayer.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2021.03.015.

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