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ARTICLE

Clinical Studies

Management of non-metastatic anal cancer in the elderly: ancillary study of the French multicenter prospective cohort FFCD-ANABASE

Claire Gouriou[1✉], Claire Lemanski[2], Pascal Pommier[3], Karine Le Malicot[4], Angélique Saint[5], Eleonor Rivin del Campo[6], Cécile Evin[6], Laurent Quero[7], Pauline Regnault[8], Nabil Baba-Hamed[9], Philippe Ronchin[10], Gilles Crehange[11], David Tougeron[12], Elodie Menager-Tabourel[13], Olivia Diaz[14], Michael Hummelsberger[15], Anne de la Rocherfordiere[16], Franck Drouet[17], Véronique Vendrely[18] and Astrid Lièvre[1]

BACKGROUND: Standard care for non-metastatic squamous cell carcinoma of the anus (SCCA) is chemoradiotherapy, data about elderly patients are scarce.

METHODS: All consecutive patients treated for non-metastatic SCCA from the French multicenter FFCD-ANABASE cohort were included. Two groups were defined according to age: elderly (≥75 years) and non-elderly (<75).

RESULTS: Of 1015 patients, 202 (19.9%) were included in the elderly group; median follow-up was 35.5 months. Among the elderly, there were more women ($p = 0.015$); frailer patients ($p < 0.001$), fewer smokers ($p < 0.001$) and fewer HIV-infected ($p < 0.001$) than in the non-elderly group. Concomitant chemotherapy and inguinal irradiation were less frequent ($p < 0.001$ and $p = 0.04$). In the elderly group; 3-year overall survival (OS), recurrence-free survival (RFS) and colostomy-free survival (CFS) were 82.9%, 72.4% and 78.0%, respectively; complete response rate at 4–6 months was 70.3%. There were no differences between groups for all outcomes and toxicity. In multivariate analyses for the elderly, PS ≥ 2 and locally-advanced tumors were significantly associated with poor OS (HR = 3.4 and HR = 2.80), RFS (HR = 2.4 and HR = 3.1) and CFS (HR = 3.8 and HR = 3.0); and treatment interruption with poor RFS (HR = 1.9).

CONCLUSION: In the FFCD-ANABASE cohort, age did not influence tumor and tolerance outcomes of non-metastatic SCCA. Optimal curative treatment should be offered to elderly patients.

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INTRODUCTION

Squamous cell carcinoma of the anal canal (SCCA) is rare and accounts for 2% of gastrointestinal cancers in Europe [1]. Its incidence has increased worldwide [2] and in France it has doubled over the last 30 years [3]. The prevalence is higher in women (sex ratio 1.5), and more than 50% of patients are older than 65 years at diagnosis [4].

The standard of care for patients with non-metastatic SCCA is radiotherapy combined with mitomycin-based chemotherapy [5]. Available data for elderly patients are from retrospective series with small sample sizes [6] because these patients are often excluded from trials. Previous studies have suggested that these frail patients could be less likely to benefit from standard treatment, because of increased hematological toxicity and suboptimal outcomes in terms of local control and survival [7, 8].

To date, there is no specific recommendation for elderly patients, but the latest ESMO guidelines [9] recommend management similar to that in young patients if their general condition is preserved (grade C). It is therefore important to have more "real life" data in these patients in order to better adapt and optimize their management.

The aim of the present study was to describe the characteristics, therapeutic management and outcomes of elderly patients with SCCA included in the nationwide prospective FFCD-ANABASE cohort.

[1]CHU Pontchaillou Rennes, Rennes, France. [2]Institut Régional du Cancer Montpellier, Montpellier, France. [3]Centre Léon Bérard Lyon, Lyon, France. [4]FFCD, Dijon, France. [5]Centre Antoine Lacassagne Nice, Nice, France. [6]CHU Tenon Paris, Paris, France. [7]Hôpital St Louis Paris, Paris, France. [8]Clinique Tivoli Bordeaux, Bordeaux, France. [9]Clinique St Joseph Paris, Paris, France. [10]Centre Azuréen de Cancérologie Mougins, Mougins, France. [11]Centre Georges François Leclerc Dijon, Dijon, France. [12]CHU La Milétrie Poitiers, Poitiers, France. [13]CHD Vendée La Roche-sur-Yon, La Roche-sur-Yon, France. [14]GHM Institut Daniel Hollard Grenoble, Grenoble, France. [15]Centre de Radiothérapie et d'Oncologie Béziers, Béziers, France. [16]Institut Curie Paris, Paris, France. [17]Clinique Mutualiste de l'Estuaire St Nazaire, Saint-Nazaire, France. [18]CHU Haut Lévêque Pessac Bordeaux, Bordeaux, France. ✉email: claire.gouriou@hotmail.fr

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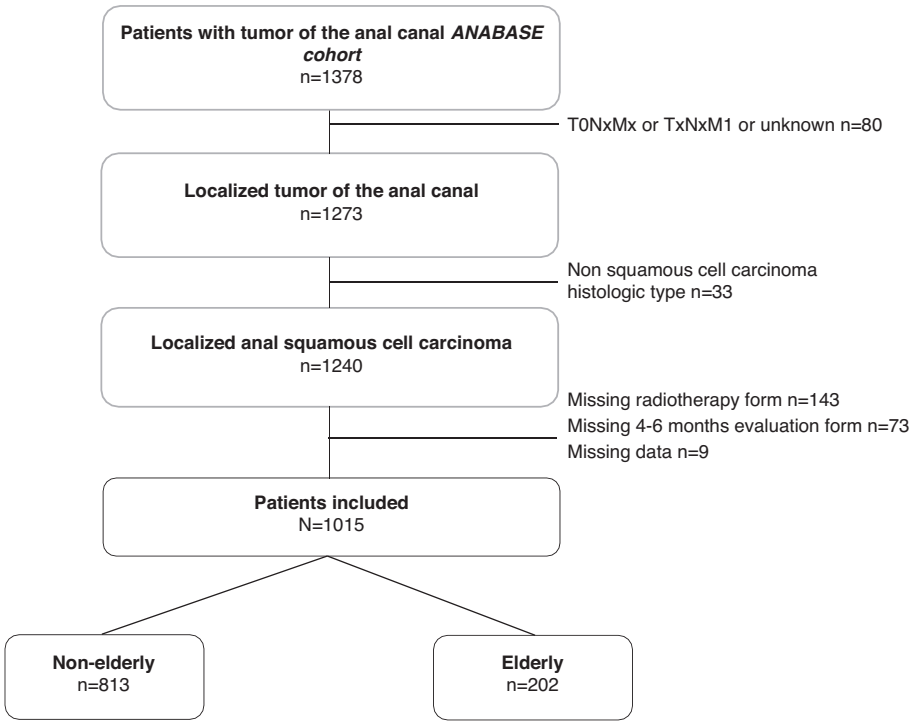

Fig. 1 Patients flowchart.

PATIENTS AND METHODS

Study design

The FFCD-ANABASE cohort is a French observational prospective multicenter cohort conducted by the Fédération Francophone de Cancérologie Digestive (FFCD), with the aim to collect data on the management, oncological outcomes and survival of patients with SCCA, whatever the tumor stage. Patients were assessed and treated according to French guidelines [10]. Assessment recommended is computed tomography of the thorax, abdomen and pelvis (CT-TAP) and pelvic magnetic resonance imaging (MRI); 18F-Fluorodeoxyglucose positron emission computed tomography (18F-FDG-PET/CT)) and transanal ultrasonography (TAUS) are optional. For non-metastatic SCCA, the recommended treatment is exclusive radiotherapy (RT), which must be associated with concomitant chemotherapy in case of locally-advanced stages (T2-T4, N0-N2) [11]. All patients received written information and provided oral informed consent and the study was approved by the ethics committee (CCTIRS-15.698) and the "Commission National de l'Informatique et des Libertés" (authorization number 915,622). Results from all patients with non-metastatic SCCA included in the cohort were previously published [12].

This study focused on elderly patients with non-metastatic SCCA and aimed to (i) compare patient and tumor characteristics, therapeutic management and outcomes of patients aged 75 years and over with those in younger patients from the FFCD-ANABASE cohort and (ii) to analyze prognostic factors in this population.

Patients

All consecutive patients treated by chemoradiotherapy/radiotherapy (CRT/RT) between January 2015 and April 2020 as first-line treatment for a non-metastatic SCCA in 60 French hospitals were prospectively included. Patients that received only chemotherapy or best supportive care were excluded. If data for radiotherapy and follow-up were missing, patients were excluded. Two groups were defined according to the age: non-elderly (<75 years) and elderly (≥75 years).

Data collection

Data were collected in a prospective electronic case report form (eCRF). In each group, clinical parameters included demographic data (age, sex, weight); medical history, such as human Immunodeficiency virus (HIV) infection status and smoking; a baseline physical examination and an evaluation of the performance status (PS). Tumor characteristics were assessed: pathological characteristics including p16 status, tumor size, TNM stage and location. The pre-therapeutic assessment was reported: general staging (CT-TAP and 18F-FDG-PET/CT) and locoregional staging (TAUS and pelvic MRI). T1-2N0 tumors were recorded as "early-stage" tumors and T3-T4 and/or N+ as "locally-advanced" tumors. The treatment strategy was reported: chemotherapy, radiation therapy and surgery. Toxicity was evaluated according to the Common Terminology Criteria of Adverse version 5 (CTCAEv5). In the elderly group, the G8-score could be notified (not mandatory) and frailty was defined as a score <14 that indicates a comprehensive oncogeriatric evaluation [13]. Follow-up was carried out according to the guidelines [11]: every 4 months for 2 years and subsequently every 6 months for 5 years. For each patient, the assessment at 4–6 months and the latest follow-up were collected.

Outcomes

The endpoints of our study were (i) to describe baseline characteristics and management of non-metastatic SCCA in elderly patients and compare them with those in non-elderly patients, (ii) to evaluate complete response rates to CRT/RT, overall survival (OS), recurrence-free survival (RFS) and colostomy-free survival (CFS) in elderly compared with non-elderly patients and (iii) to determine prognostic factors in terms of OS, RFS and CFS in elderly patients.

Statistical analysis

A descriptive analysis was conducted to compare patients regarding age (<75 versus ≥75 years). Quantitative variables were expressed as medians [Q1-Q3] and categorical data as numbers and percentages (%). If applicable, a Student or a Wilcoxon test (according to the distribution of the variables) was used to compare the two groups for quantitative variables while a Chi2 test or a Fisher exact test was used for categorical variables.

The Kaplan-Meier method was used to describe censored data. Logrank tests were used to compare rates and time-to-event distributions with a two-sided 95% confidence interval (95% CI), as well as to plot survival curves. OS was defined as the time between the start of treatment and death or last observation if patients were still alive. RFS was defined as the period between the start of treatment and the first recurrence or death (any cause), and CFS was defined as the period between the start of treatment and the first colostomy or death (any cause) without colostomy. Alive patients without recurrence or colostomy were censored at the date

Table 1. Patients characteristics.

	All patients $N = 1015$	Elderly $n = 202$	Non-elderly $n = 813$	*p*-value
Patients characteristics				
Age (years)	65.0 [57.0–73.0]	79.0 [77.0–84.0]	62.0 [55.0–68.0]	–
[75–80]		102 (50.5)		
[80–85]		52 (25.7)		
≥85		48 (23.8)		
Sex: Male/Female	248 (24.4) / 767 (75.6)	36 (17.8) / 166 (82.2)	212 (26.1) / 601 (73.9)	$p = 0.0145$
Body Mass Index (kg/m^2)	*n = 989*	*n = 194*	*n = 795*	$p = 0.31$
	23.9 [20.9–26.9]	24.2 [21.6–26.7]	23.8 [20.7–27.1]	
Performance Status 0–1	*n = 984*	*n = 197*	*n = 787*	$p < 0.001$
	946 (96.1)	173 (87.8)	773 (98.2)	
Smoking	*n = 877*	*n = 171*	*n = 706*	$p < 0.001$
	394 (44.9)	41 (24.0)	353 (50.0)	
HIV positive status	*n = 995*	*n = 196*	*n = 799*	$p < 0.001$
	86 (8.5)	4 (2.0)	82 (10.3)	
Tumor characteristics				
Tumor size (mm)	3.7 [2.5–5.1]	3.5 [2.5–5.0]	3.8 [2.5–5.1]	$p = 0.46$
Clinical T				
T1	152 (15.0)	31 (15.3)	121 (14.9)	$p = 0.69$
T2	488 (48.1)	103 (51.0)	385 (47.4)	
T3	231 (22.8)	40 (19.8)	191 (23.5)	
T4	144 (14.2)	28 (13.9)	116 (14.3)	
Clinical N				
N0	554 (54.6)	106 (52.5)	448 (55.2)	$p = 0.48$
≥N1	459 (45.2)	96 (47.5)	363 (44.8)	
Early-stage tumor (T1–2N0)	440 (43.3)	88 (43.6)	352 (43.3)	$p = 0.94$
Locally-advanced tumor (T3–4 and/or N+)	575 (56.7)	114 (56.4)	461 (56.7)	
p16 immunohistochemistry positive status	*n = 576*	*n = 112*	*n = 464*	$p = 0.72$
	543 (94.3)	103 (92.0)	440 (94.8)	
Location	*n = 981*	*n = 193*	*n = 788*	$p = 0.69$
Anal margin	110 (11.2)	21 (10.9)	89 (11.3)	
Anal canal	790 (80.5)	154 (79.8)	636 (80.7)	
Lower rectum	71 (7.2)	17 (8.8)	54 (6.9)	
Other	10 (1.0)	1 (0.5)	9 (1.1)	
Pre-therapeutic assessment				
MRI	723 (71.2)	135 (66.8)	588 (72.3)	$p = 0.12$
TAUS	308 (30.3)	61 (30.2)	247 (30.4)	$p = 0.96$
CT-TAP	566 (55.8)	125 (61.9)	441 (54.2)	$p = 0.05$
18F-FDG-PET/CT	741 (73.0)	145 (71.8)	596 (73.3)	$p = 0.66$
Locoregional staging (pelvic MRI and/or TAUS)	826 (81.4)	161 (79.7)	665 (81.8)	$p = 0.49$
General staging (CT-TAP and/or 18F-FDG-PET/CT)	887 (87.4)	182 (90.1)	705 (86.7)	$p = 0.19$

For categorical variables, data are given as percentage. For continuous variables, data are given as median [Q1-Q3].
HIV human immunodeficiency virus, *MRI* magnetic resonance imaging, *TAUS* transanal ultrasonography, *CT-TAP* computed tomography of the thorax, abdomen and pelvis, 18F-FDG-PET/CT 18F-Fluorodeoxyglucose positron emission computed tomography.
Statistically significant *p*-values are in bold.

of the last observation. We conducted univariate and multivariate analyses using Cox proportional model reporting hazard ratios (HR) and 95%CI to evaluate prognostic factors associated with RFS for older patients. All statistical analyses were done using SAS software 9.4 (SAS Institute, Cary, NC).

RESULTS

Patients' characteristics

Of the 1378 patients included in the FFCD-ANABASE cohort, 1015 were treated for a non-metastatic SCCA by RT or CRT and included in the present analysis: 202 (19.9%) in the elderly group and 813

Table 2. Treatment characteristics.

	All patients $N = 1015$	Elderly $n = 202$	Non-elderly $n = 813$	*p*-value
Induction chemotherapy[a]	58 (5.7)	9 (4.5)	49 (6.0)	$p = 0.39$
Colostomy before radiotherapy	45 (4.4)	11 (5.4)	34 (4.2)	$p = 0.44$
Radiotherapy				
Total radiotherapy dose (Gy)	60.0 [50.4–64.8]	60.0 [50.4–64.8]	60.0 [50.4–64.8]	$p = 0.33$
Duration (days)	50.0 [43.0–61.0]	50.0 [42.0–64.0]	50.0 [43.0–60.0]	$p = 0.99$
Prophylactic pelvic irradiation dose (Gy)	45.0 [45.0–46.0]	45.0 [45.0–48.0]	45.0 [45.0–45.0]	$p = 0.71$
Inguinal areas irradiation	$n = 961$	$n = 191$	$n = 770$	$\mathbf{p = 0.04}$
Yes	748 (77.8)	138 (72.3)	610 (79.2)	
Treatment interruption	$n = 996$	$n = 199$	$n = 797$	$p = 0.54$
Yes	327 (32.8)	69 (34.7)	258 (32.4)	
Concomitant chemotherapy	*n = 781 (76.9)*	*n = 131 (64.9)*	*n = 650 (80.0)*	$\mathbf{p < 0.001}$
Type				
CDDP + 5Fu	24 (3.0)	2 (1.5)	22 (3.3)	
Mitomycin-C + 5Fu	482 (61.1)	73 (55.7)	409 (62.3)	
Mitomycin-C + Capecitabine	203 (25.7)	32 (24.4)	171 (26.0)	
Capecitabine/5Fu	37 (4.7)	20 (15.3)	17 (2.6)	
Other[b]	35 (3.4)	4 (3.1)	31 (4.7)	
Tumor stage				
Early-stage	261 (33.4)	39 (44.3)	222 (63.1)	
Locally-advanced	520 (66.6)	92 (80.7)	428 (92.8)	

For categorical variables, data are given as percentages. For continuous variables, data are given as medians [Q1–Q3].
Gy Grays.
Statistically significant *p*-values are in bold.
[a]Mainly consisting of CDDP + 5Fu.
[b]Other regimens included association of mitomycin, 5FU and panitumumab for 20 patients included in the FFCD0904 trial or Mitomycin-C + 5FU followed by CDDP + 5FU when mitomycin was out of stock in France.

(80.1%) in the non-elderly group. Among the excluded patients, the median age was 66 years [56–74] and the distribution between elderly and non-elderly patients was comparable (22.6% and 77.4%). The recruitment flowchart is presented in Fig. 1 and the baseline characteristics of the study population are provided in Table 1.

Among the elderly, the median age was 79 years: 52 patients were ≥80 years and 48 were ≥85 years. There were more women (82.2% vs. 73.9%, $p = 0.015$) and fewer patients with a PS of 0–1 (87.8% vs. 98.2%, $p < 0.001$)) in the elderly group than in the younger group. The proportions of smokers and HIV-infected patients were significantly lower in the elderly group ($p < 0.001$). The G8-score was available in only 47 patients, among whom 30 had a score ≤14.

Regarding tumor characteristics, the initial stage was similar between elderly and non-elderly patients, with a predominance of locally-advanced tumors (T3-T4 and/or N+ tumors: 56.4% and 56.7% respectively, $p = 0.94$). More than 90% of tumors were human papillomavirus (HPV) positive as based on p16 immunohistochemistry status. Initial tumor assessment modalities were similar in both groups: 18F-FDG-PET/CT in 71.8% and 73.3% of elderly and non-elderly patients, respectively ($p = 0.66$), except for the CT-TAP, which was more frequently performed in the elderly group ($p = 0.05$).

Therapeutic management

Treatment characteristics are detailed in Table 2. All patients underwent radiotherapy. Overall, there were no differences between elderly and non-elderly patients for therapeutic management except for two modalities: concomitant chemotherapy and inguinal-area irradiation, which were less frequently performed in the elderly group ($p < 0.001$ and $p = 0.04$, respectively). In the elderly group, 64.9% of patients received concomitant chemotherapy, but the proportion decreased with increasing age: 80.4% for [75–80] years, 65.4% for [80–85] years and 31.3% for ≥85 years. Elderly patients were more likely to receive concomitant 5FU or Capecitabine monotherapy (15.3% vs. 2.6%). This likelihood tended to increase with age: 9/82 (10.9%) for [75–80] years, 5/34 (14.7%) for [80–85] years and 6/15 (40.0%) for ≥85 years. Concerning tumor stage, patients were less likely to receive concomitant chemotherapy for early-stage tumors, and this difference was more pronounced in older patients (44.3% vs 63.1%). The median treatment interruption was 14 days [7–19], with no difference between groups ($p = 0.11$) and 15% of elderly patients had a brachytherapy boost. Treatment interruption was initially planned in 62% and due to toxicity in 38% in the elderly group. Before CRT, 45 (4.4%) patients underwent colostomy (11/202 vs. 34/813, $p = 0.44$) and two patients, both in the non-elderly group, had an abdominoperineal resection. Regarding surgery, after treatment, 149 (14.7%) patients of the whole cohort underwent surgery, of whom 90 (8.9%) underwent abdominoperineal resection. This was less frequent in the elderly group (5.0% vs. 9.8%, $p = 0.03$). The indication for surgery before CRT was mainly functional (73.3%) whereas after CRT, surgery was principally for recurrence (62.7%).

Response rate, survival and prognostic factors

Overall, the median follow-up was 35.5 months [34.4–36.0]. The complete response rate at 4–6 months was 70.3% ($n = 137$) in elderly and 75.3% in non-elderly patients ($n = 604$); $p = 0.30$.

Survival data are presented in Fig. 2 and the results of the uni and multivariate analysis in Table 3. In the elderly, 3-year overall

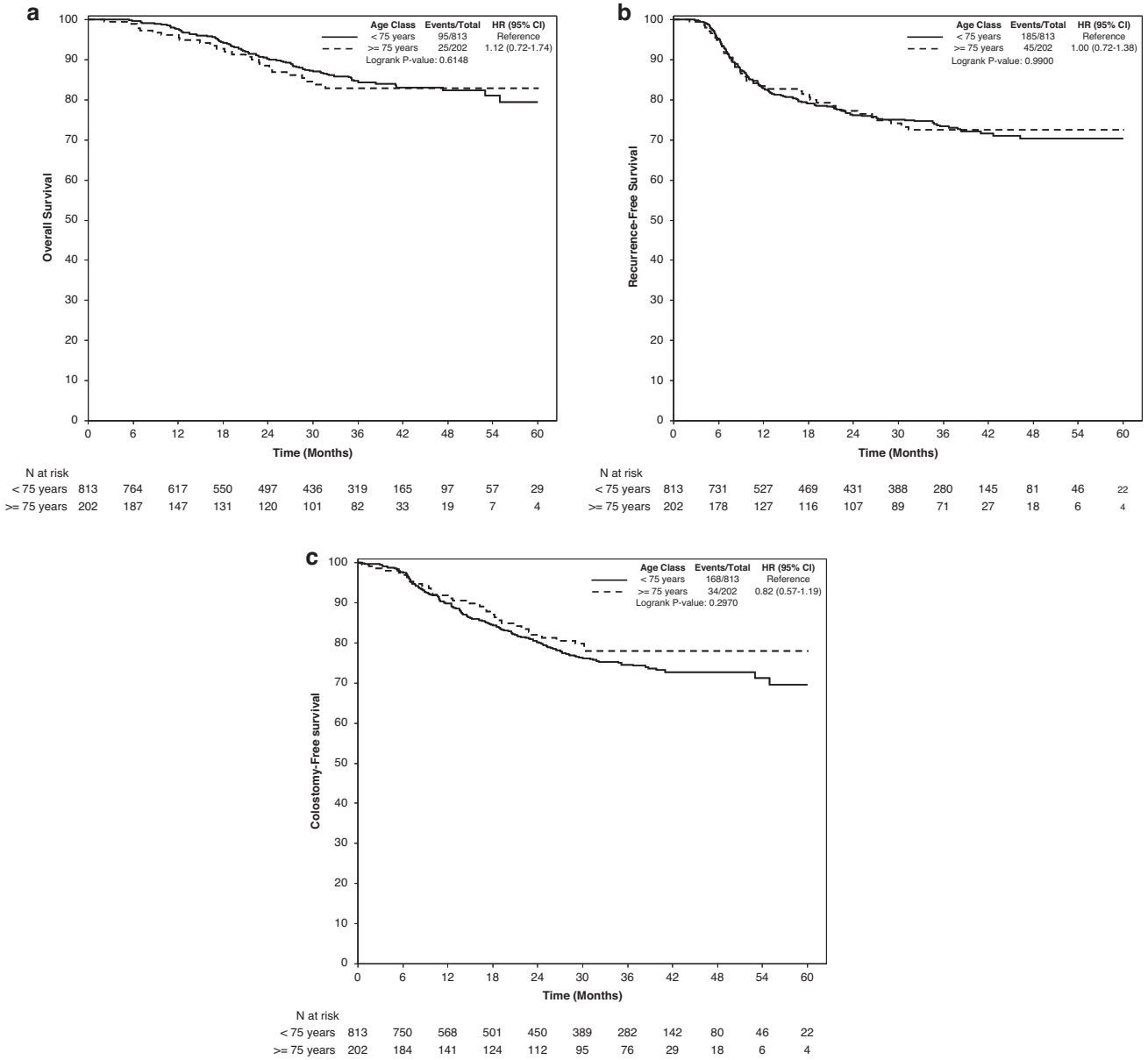

Fig. 2 Overall survival (**a**) Recurrence-free survival (**b**) and Colostomy-free survival (**c**).

survival, recurrence-free survival and colostomy-free survival were 82.9% (75.6–88.2), 72.4% (64.7–78.8) and 78.0 (70.5–83.9), respectively. These survival rates were not significantly different from those in younger patients, which were respectively 84.7% (HR = 1.1 (0.7–1.7), $p = 0.61$), 73.3% (HR = 1.0 (0.7–1.4), $p = 0.99$) and 74.6% (HR = 0.8 (0.6–1.2), $p = 0.30$). For elderly patients, the only parameters that remained significant in multivariate analysis for a worse prognosis were a performance status ≥2 (HR = 3.4 [1.4;8.3], $p = 0.008$; HR = 2.4 [1.2;4.9], $p = 0.02$; HR = 3.8 [1.8;8.1], $p = 0.001$ for OS, RFS and CFS respectively) and a locally-advanced tumor (HR = 2.8 [1.2;7.1], $p = 0.03$; HR = 3.1 [1.5;6.4], $p = 0.002$; HR = 3.0 [1.4;6.7], $p = 0.007$) for the three endpoints and a treatment interruption for RFS (HR = 1.9 [1.1;3.5], $p = 0.03$).

Among patients with a complete response, 14/137 (10.2%) in the elderly group and 67/604 (11.1%) in the non-elderly group experienced disease recurrence during the follow-up ($p = 0.77$). Recurrence occurred after a median of 17.0 [8.9; 21.6] and 14.2 [10.1; 22.2] months in the elderly and non-elderly groups, respectively ($p = 0.45$). Recurrence was more frequently metastatic in the elderly group (6/14 (42.9%) vs. 24/67 (35.8%)) and less frequently local or locoregional (3/14 (21.4%) vs. 29/67 (43.3%)). Death occurred in 5/14 patients in the elderly group and 14/67 in the non-elderly group.

Toxicity

CRT-related adverse events of grade 3 or greater happened in 90 (44.6%) and 316 (38.9%) patients in the elderly and non-elderly groups, respectively ($p = 0.14$). These were predominantly cutaneous and/or mucosal (29.7% vs. 27.3%) followed by digestive (10.9% vs. 9.0%) and hematological (6.4% vs. 7.6%). Grade 3 toxicity was more frequent in patients who had concomitant chemotherapy: 71 elderly (54.2%) and 288 non-elderly (44.3%) patients; versus 19 elderly (26.8%) and 28 non-elderly (17.2%) patients without concomitant chemotherapy ($p < 0.0001$). The rate of radiotherapy interruption for toxicity was no different between the groups ($p = 0.33$). Radiotherapy-induced grade 3 late toxicity was described in 1.5% of patients in the elderly group and 2.7% in the non-elderly group ($p = 0.32$).

Table 3. Uni and Multivariate analysis of elderly patients.

	Overall survival		Recurrence-free survival		Colostomy-free survival	
	Univariate OR [95% CI], *p*	Multivariate OR [95% CI], *p*	Univariate OR [95% CI], *p*	Multivariate OR [95% CI], *p*	Univariate OR [95% CI], *p*	Multivariate OR [95% CI], *p*
Sex						
Female	1 (ref)	1 (ref)	1 (ref)		1 (ref)	1 (ref)
Male	2.1 [0.9;5.0], $p = 0.10$	2.0 [0.8;4.9], $p = 0.11$	1.6 [0.8;3.2], $p = 0.15$		1.9 [0.9;4.0], $p = 0.11$	2.0 [0.9;4.3], $p = 0.08$
Performance status						
0–1	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
≥2	4.2 [1.8;10.2], $p = 0.001$	3.4 [1.4;8.3], $\mathbf{p = 0.008}$	2.9 [1.4;5.9], $p = 0.003$	2.4 [1.2;4.9], $\mathbf{p = 0.02}$	4.4 [2.1;9.3], $p < 0.001$	3.8 [1.8;8.1], $\mathbf{p = 0.001}$
HIV status						
Negative	1 (ref)		1 (ref)		1 (ref)	
Positive	2.6 [0.3;21.0], $p = 0.36$		1.0 [0.1;7.7], $p = 0.98$		1.4 [0.2;10.4], $p = 0.76$	
Tumor staging						
Early-stage	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Locally-advanced	3.2 [1.3;8.1], $p = 0.01$	2.8 [1.2;7.1], $\mathbf{p = 0.03}$	3.7 [1.8;7.5], $p < 0.001$	3.1 [1.5;6.4], $\mathbf{p = 0.002}$	3.4 [1.5;7.5], $p = 0.03$	3.0 [1.4;6.7], $\mathbf{p = 0.007}$
Treatment interruption						
No	1 (ref)		1 (ref)	1 (ref)	1 (ref)	
Yes	1.3 [0.6;3.0], $p = 0.48$		2.1 [1.1;3.7], $p = 0.02$	1.9 [1.1;3.5], $\mathbf{p = 0.03}$	1.2 [0.6;2.5], $p = 0.54$	
Radiotherapy dose						
≥60 Gy	1 (ref)		1 (ref)		1 (ref)	
<60 Gy	1.5 [0.7;3.5], $p = 0.33$		1.1 [0.6;1.9], $p = 0.87$		1.4 [0.7;2.7], $p = 0.38$	
Brachytherapy boost						
Yes	1 (ref)		1 (ref)	1 (ref)	1 (ref)	
No	3.6 [0.5;26.9], $p = 0.20$		2.4 [0.7;7.6], $p = 0.15$	1.6 [0.5;5.0], $p = 0.15$	2.5 [0.6;10.5], $p = 0.21$	
Induction chemotherapy						
No	1 (ref)		1 (ref)		1 (ref)	
Yes	1.1 [0.15;8.3], $p = 0.91$		0.5 [0.1;3.4], $p = 0.45$		0.7 [0.1;5.2], $p = 0.74$	
Concomitant chemotherapy						
Yes	1 (ref)		1 (ref)		1 (ref)	
No	1.1 [0.5;2.3], $p = 0.89$		0.6 [0.3;1.2], $p = 0.18$		0.7 [0.4;1.5], $p = 0.42$	

OR Odds ratio, *CI* confidence interval, *HIV* Human immunodeficiency virus, *Gy* Grays.
Statistically significant *p*-values are in bold.

DISCUSSION

Our study, based on one of the largest prospective cohorts of SCCA patients conducted to date, showed that the complete response rate, overall survival, recurrence-free survival and colostomy-free survival in elderly patients treated with (chemo) radiotherapy for non-metastatic SCCA were no different from those in younger patients.

In the FFCD-ANABASE cohort, the median age was 65, similar to the registry data available in France in which the mean age was 67 with 33% of patients aged over 70 and 13.2% aged over 80 [14]. The cut-off age chosen to define elderly patients varies from one study to another (60, 65, 70 years). We chose an age 10 years higher than the median in order to specifically study old and very old patients. This is already the case for other digestive cancers [15]. In colorectal cancer, the French authorities have chosen a threshold of 75 years to define oncogeriatry as frailty and comorbidities are more frequent than in patients aged 70–75. Elderly patients were frailer, less likely to be HIV-infected and less likely to smoke, but with similar tumor characteristics, which is consistent with published data [7].

Standard of care for non-metastatic SCCA is CRT but elderly patients are often excluded from phase III trials. For example, in the RTOG trial, median age was around 60 [5] while another trial included only patients under 76 years [16]. Thus, current recommendations on their therapeutic management are based on extrapolations of data from younger patients included in clinical trials and from retrospective studies conducted mostly on small numbers of patients. The feasibility of CRT in the elderly has already been shown [6, 17–21]. Nevertheless, according to registry data [14], patients aged over 70 had a lower probability to receive CRT compared to younger patients. In our study, the prescription of concomitant chemotherapy was different between elderly and

non-elderly subjects. First, elderly subjects, especially very old patients aged 80 or 85 years and more, were less likely than non-elderly subjects to be given concomitant chemotherapy, particularly in cases of early-stage (T1-T2N0) tumor. However, the benefit of concomitant chemotherapy in early-stage tumors remains a question of debate, which could explain that despite less use of concomitant chemotherapy, there were no differences in terms of oncological outcomes. Second, when concomitant chemotherapy was prescribed, a single agent regimen was preferred. This is consistent with the results of a recent large retrospective study [8] performed on more than 7000 patients over 70 that also reported a higher proportion of patients treated with single agent chemotherapy among patients aged ≥65 years compared to younger patients (16.9% vs. 11.8%; $p < 0.0001$).

Regarding the prognosis, the complete response rate was 70% and 3-year overall survival and disease-free survival were respectively 82.9% and 72.4%, with no statistically significant difference between the two groups. Our results are comparable with the results of a recent German real-life cohort [22]. Few studies have compared the prognosis of elderly subjects with that of younger subjects, and their results are divergent. Saarilahti et al. showed a similar 5-year RFS among patients over and under 70 years of age, while Claren et al. found a poorer prognosis in elderly patients (≥70 years) [7, 23]. Overall comparison with previous studies that included elderly subjects is difficult since the cohorts are very heterogeneous with variable cut-off ages and small sample sizes. Prognostic factors in this cohort are those already described in previous studies: performance status, tumor staging and treatment interruption during CRT, with no specificity for elderly patients. Age was not associated with a poorer prognosis. In contrast to published data, the type of chemotherapy had no impact on oncological prognosis. Indeed, Miller et al. showed that three-year OS was significantly lower when single agent chemotherapy was used as compared with multi-agent chemotherapy (67.5% vs. 77.1%, $p < 0.0002$). Outcomes were unchanged with a cut-off age of 65 or 70 years. In our study, results are reassuring as they suggest that the standard of care protocol can be adjusted for our most fragile patients without impacting the prognosis or the time to recurrence. Ideally, prospective studies should be carried out, but in the case of a rare cancer and in a specific sub-population, such studies seem difficult to carry out.

While others reported higher hematologic and digestive toxicity rates in aged patients than in younger ones [7, 23], in our study, overall or grade 3 toxicity in the elderly was comparable to that in the non-elderly. Indeed, toxicity was increased in patients with concomitant chemotherapy, but by the same proportion in the two groups. This confirms the feasibility of curative treatment in elderly patients, in whom physicians are always cautious about side-effects that could decompensate for possible co-morbidities.

With 202 patients aged over 75 years, of whom 100 were aged over 80 years, this is a large prospective cohort of elderly patients with non-metastatic SCCA managed in real life. Data collection was made by clinicians themselves, which limits potential bias and ensures their veracity. The median follow-up of 35 months is the longest in the literature for a prospective cohort focusing on SCCA in elderly patients. We studied colostomy-free survival, which, as yet, has never been reported in the literature. Nevertheless, our study has several limitations. First, the FFCD-ANABASE cohort included all patients that received a treatment for a SSCA, whatever the tumor stage, which implies a certain degree of "patients' selection". Regarding non-metastatic tumor patients, all were treated with a curative intent but the treatment could be non-optimal (exclusive radiotherapy or single agent chemotherapy), according to the clinician assessment (frailty, comorbidities). Palliative treatment concerned only metastatic patients that were therefore excluded from the present analysis. Second, regarding completion of treatment data, the study eCRF did not specifically include this item, but included the total dose of radiotherapy, which indirectly give information about treatment compliance and we found no difference between elderly and non-elderly groups regarding this parameter. In our study, radiotherapy dose was not associated with oncological outcomes, which could be partly explained by the fact that the total radiotherapy dose received was relatively homogeneous among patients as to be included in our cohort they had to be treated in a curative intent. Concerning concomitant chemotherapy, the eCRF did include the dose-intensity or reductions/modifications but only toxicity, so that we could not analyze the completion of this part of treatment.

Finally, this cohort was not restricted to the elderly, and therefore specific geriatric data, such as the G8 frailty score, were not collected systematically. Although recommended for elderly subjects, this score was not mandatory in the eCRF, and it was available in only 47 patients, underlining its under-utilization in clinical practice. G8 score has been developed in older patients with cancer, and is one of the most sensitive screening tools for detecting frail patients requiring a complete geriatric assessment [24]. In the field of gastrointestinal cancers, its prognostic value and usefulness in therapeutic decision-making have been particularly well demonstrated in colorectal cancer [25]. The systematic use of the G8 score in routine clinical practice could lead to significant improvements in the management of elderly patients. In the same way, information on comorbidities (Charlson index) and patients' level of autonomy (Instrumental Activities of Daily Living score) are missing in our study while they are known to influence therapeutic decisions in elderly patients in whom age should not be the only parameter to take into account.

CONCLUSION

In the FFCD-ANABASE cohort, age on its own does not seem to influence the prognosis and treatment tolerance of non-metastatic SCCA. Concomitant chemotherapy in elderly patients is less frequently prescribed, especially for early-stage tumors and in older elderly patients. When it is used, monotherapy is more frequent than doublet chemotherapy. In practice, curative treatment should be systematically proposed to elderly patients with SCCA, and should be based on the oncologist's clinical evaluation. Specific studies on this population are needed.

DATA AVAILABILITY

Researchers with appropriate proposals can request deidentified individual participant data. Data collected for the cohort, including participant data with identifiers and a data dictionary defining each field in the set, are not available. Requests should be sent to the corresponding author. The data will be shared after approval of a proposal, with a signed data access agreement.

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AUTHOR CONTRIBUTIONS

All authors participated in the cohort. CG wrote the first draft of the manuscript and all authors participated in reviewing, correcting, and editing the manuscript. VV and KLM also participated in conceptualization of the cohort. KLM had access to the raw data and was involved in the formal analysis of the data. CG, VV, AL and KLM accessed and verified all the data. All authors had full access to the data in the cohort and had final responsibility for the decision to submit the publication. All authors approved the manuscript for submission and vouch for the accuracy and completeness of the data.

COMPETING INTERESTS

The authors declare no competing interests.

ETHICS APROVAL AND CONSENT TO PARTICIPATE

All patients received written information and provided oral informed consent and the cohort was approved by the ethics committee (CCTIRS-15.698) and the "Commission Nationale de l'Informatique et des Libertés" (authorization number 915,622).

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Claire Gouriou.