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Clean version

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

Short running title: Anal cancer in the French cohort FFCD-ANABASE

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Highlights

- The treatment of patients from the FFCD-ANABASE cohort showed good respect for the current guidelines for anal cancer treatment, and a good implementation of IMRT in France in this indication.
- 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 multivariate analyses, male gender, locally-advanced stage, and ECOG PS \geq 1 were associated with poorer DFS, CFS, and OS.
- Significant differences in DFS, CFS, and OS between early-stage group (T1-2, N0) and locally-advanced group (T3-4, or N+) advocate for personalized strategies by either de-escalation for early-stage tumors or treatment intensification for locally-advanced tumors.

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 \geq 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.

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Keywords : Anal cancer ; Chemoradiotherapy ; IMRT ; observational cohort

Introduction

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 outcome 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 1980s 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 capecitabine) 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 (Figure 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 concurrent 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 ($p < 0.001$, Figure 2A). Similarly, the 3-year OS (78.2 % vs 91.7 %; $p < 0.0001$; Figure 2B) and the 3-year CFS (66.9% vs 85.6%; $p < 0.0001$; Figure 2C) were both significantly lower in the locally-advanced group.

In univariate analysis, male gender, ECOG PS ≥ 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 ≥ 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 ≥ 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 <3cm 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 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 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 practices 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 Interact-ion (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 adherence 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.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2018 Nov;68(6):394–424.
2. Islami F, Ferlay J, Lortet-Tieulent J, Bray F, Jemal A. International trends in anal cancer incidence rates. *Int J Epidemiol* [Internet]. 2016; Available from: <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=27789668&retmode=ref&cmd=prlinks>
3. Moureau-Zabotto L, Vendrely V, Abramowitz L, Borg C, Francois E, Goere D, et al. Anal cancer: French Intergroup Clinical Practice Guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, SNFCP). *Dig Liver Dis*. 2017 Aug;49(8):831–40.
4. Rao S, Guren MG, Khan K, Brown G, Renehan AG, Steigen SE, et al. Anal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up☆. *Ann Oncol*. 2021 Sep;32(9):1087–100.
5. Martin D, Schreckenbach T, Ziegler P, Filmann N, Kalinauskaite G, Tinhofer I, et al. Evaluation of prognostic factors after primary chemoradiotherapy of anal cancer: A multicenter study of the German Cancer Consortium-Radiation Oncology Group (DKTK-ROG). *Radiother Oncol*. 2022 Feb;167:233–8.
6. Gunderson LL, Moughan J, Ajani JA, Pedersen JE, Winter KA, Benson I Al B, et al. Anal Carcinoma: Impact of TN Category of Disease on Survival, Disease Relapse, and Colostomy Failure in US Gastrointestinal Intergroup RTOG 98-11 Phase 3 Trial. *Int J Radiat Oncol*. 2013;87(4):638–45.

7. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Willins J, Esthappan J, et al. RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal. *Int J Radiat Oncol*. 2013 May;86(1):27–33.
8. Franco P, Mistrangelo M, Arcadipane F, Munoz F, Sciacero P, Spadi R, et al. Intensity-Modulated Radiation Therapy with Simultaneous Integrated Boost Combined with Concurrent Chemotherapy for the Treatment of Anal Cancer Patients: 4-Year Results of a Consecutive Case Series. *Cancer Invest [Internet]*. 2015; Available from: <http://eutils.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&id=25950188&retmode=ref&cmd=prlinks>
9. Bazan JG, Hara W, Hsu A, Kunz PA, Ford J, Fisher GA, et al. Intensity-modulated radiation therapy versus conventional radiation therapy for squamous cell carcinoma of the anal canal. *Cancer*. 2011;117(15):3342–51.
10. Saarilahti K, Arponen P, Vaalavirta L, Tenhunen M. The effect of intensity-modulated radiotherapy and high dose rate brachytherapy on acute and late radiotherapy-related adverse events following chemoradiotherapy of anal cancer. *Radiother Oncol*. 2008;87(3):383–90.
11. Vendrely V, Henriques de Figueiredo B, Rio E, Benech J, Belhomme S, Lisbona A, et al. French multicentre clinical evaluation of helical TomoTherapy for anal cancer in a cohort of 64 consecutive patients. *Radiat Oncol Lond Engl*. 2015;10:170.
12. Kachnic LA, Winter K, Myerson RJ, Goodyear MD, Abitbol AA, Koenig JM, et al. NRG Oncology/RTOG 0529: Long-Term Outcomes of Dose-Painted Intensity Modulated Radiation Therapy, 5-Fluorouracil, and Mitomycin-C in Anal Canal Cancer. *Int J Radiat Oncol • Biol • Phys*. 2017 Oct 1;99(2):S64–5.
13. Gunderson LL, Winter KA, Ajani JA, Pedersen JE, Moughan J, Benson AB, et al. Long-Term Update of US GI Intergroup RTOG 98-11 Phase III Trial for Anal Carcinoma: Survival, Relapse, and Colostomy Failure With Concurrent Chemoradiation Involving Fluorouracil/Mitomycin Versus Fluorouracil/Cisplatin. *J Clin Oncol*. 2012 Dec 10;30(35):4344–51.
14. Peiffert D, Huguet F, Vendrely V, Moureau-Zabotto L, Rivin Del Campo E, Créhange G, et al. Radiotherapy of anal canal cancer. *Cancer/Radiothérapie*. 2022 Feb;26(1–2):279–85.
15. National Comprehensive Cancer Network. Anal carcinoma (version 1.2022) [Internet]. [cited 2022 Jul 28]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/anal.pdf
16. James RD, Glynne-Jones R, Meadows HM, Cunningham D, Myint AS, Saunders MP, et al. Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2 × 2 factorial trial. *Lancet Oncol*. 2013 May;14(6):516–24.
17. Peiffert D, Tournier-Rangear L, Gérard JP, Lemanski C, François E, Giovannini M, et al. Induction Chemotherapy and Dose Intensification of the Radiation Boost in Locally Advanced Anal Canal Carcinoma: Final Analysis of the Randomized UNICANCER ACCORD 03 Trial. *J Clin Oncol*. 2012 Jun 1;30(16):1941–8.
18. Goodman KA, Rothenstein D, Lajhem C, Wu A, Cercek A, Saltz LB. Capecitabine Plus Mitomycin in Patients Undergoing Definitive Chemoradiation for Anal Squamous Cell Carcinoma. *Radiat Oncol Biol*. 2014;90(1):S32–3.

19. Glynne-Jones R, Meadows H, Wan S, Gollins S, Leslie M, Levine E, et al. EXTRA—A Multicenter Phase II Study of Chemoradiation Using a 5 Day per Week Oral Regimen of Capecitabine and Intravenous Mitomycin C in Anal Cancer. *Int J Radiat Oncol*. 2008 Sep;72(1):119–26.
20. Jones CM, Adams R, Downing A, Glynne-Jones R, Harrison M, Hawkins M, et al. Toxicity, Tolerability, and Compliance of Concurrent Capecitabine or 5-Fluorouracil in Radical Management of Anal Cancer With Single-dose Mitomycin-C and Intensity Modulated Radiation Therapy: Evaluation of a National Cohort. *Int J Radiat Oncol*. 2018 Aug;101(5):1202–11.
21. Thind G, Johal B, Follwell M, Kennecke HF. Chemoradiation with capecitabine and mitomycin-C for stage I-III anal squamous cell carcinoma. 2014;7.
22. Glynne-Jones R, Sebag-Montefiore D, Adams R, McDonald A, Gollins S, James R, et al. “Mind the gap”--the impact of variations in the duration of the treatment gap and overall treatment time in the first UK Anal Cancer Trial (ACT I). *Int J Radiat Oncol Biol Phys*. 2011;81(5):1488–94.
23. Constantinou EC, Daly W, Fung CY, Willett CG, Kaufman DS, DeLaney TF. Time-dose considerations in the treatment of anal cancer. *Radiat Oncol Biol*. 1997;39(3):651–7.
24. Dewas CV, Maingon P, Dalban C, Petitfils A, Peignaux K, Truc G, et al. Does gap-free intensity modulated chemoradiation therapy provide a greater clinical benefit than 3D conformal chemoradiation in patients with anal cancer? *Radiat Oncol*. 2012;7(1):1–1.
25. Weber DC, Kurtz JM, Allal AS. The impact of gap duration on local control in anal canal carcinoma treated by split-course radiotherapy and concomitant chemotherapy. *Int J Radiat Oncol*. 2001 Jul;50(3):675–80.
26. Elson JK, Kachnic LA, Kharofa JR. Intensity-modulated radiotherapy improves survival and reduces treatment time in squamous cell carcinoma of the anus: A National Cancer Data Base study: IMRT vs 3DCRT in Anal Cancer. *Cancer*. 2018 Nov 15;124(22):4383–92.
27. Bartelink H, Roelofsen F, Eschwege F, Rougier P, Bosset JF, Gonzalez DG, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. *J Clin Oncol Off J Am Soc Clin Oncol*. 1997;15(5):2040–9.
28. Northover J, Glynne-Jones R, Sebag-Montefiore D, James R, Meadows H, Wan S, et al. Chemoradiation for the treatment of epidermoid anal cancer: 13-year follow-up of the first randomised UKCCCR Anal Cancer Trial (ACT I). *Br J Cancer*. 2010 Mar;102(7):1123–8.
29. Bacci M, Quero L, Barbier E, Parrot L, Juguët F, Pommier P, et al. What is the optimal treatment for T1N0 anal squamous cell carcinoma? Analysis of current practices in the prospective French FFCD ANABASE cohort. *Dig Liver Dis Off J Ital Soc Gastroenterol Ital Assoc Study Liver*. 2021 Jun;53(6):776–84.
30. Deutsch E, Lemanski C, Pignon JP, Levy A, Delarochefordiere A, Martel-Lafay I, et al. Unexpected toxicity of cetuximab combined with conventional chemoradiotherapy in patients with locally advanced anal cancer: results of the UNICANCER ACCORD 16 phase II trial. *Ann Oncol*. 2013 Nov;24(11):2834–8.
31. Vendrely V, Lemanski C, Gnep K, Barbier E, Hajbi FE, Lledo G, et al. Anti-epidermal growth factor receptor therapy in combination with chemoradiotherapy for the treatment of locally advanced

- anal canal carcinoma: Results of a phase I dose-escalation study with panitumumab (FFCD 0904). *Radiother Oncol.* 2019 Nov;140:84–9.
32. Sparano JA, Lee JY, Palefsky J, Henry DH, Wachsman W, Rajdev L, et al. Cetuximab Plus Chemoradiotherapy for HIV-Associated Anal Carcinoma: A Phase II AIDS Malignancy Consortium Trial. *J Clin Oncol Off J Am Soc Clin Oncol.* 2017 Mar;35(7):727–33.
 33. Garg MK, Zhao F, Sparano JA, Palefsky J, Whittington R, Mitchell EP, et al. Cetuximab Plus Chemoradiotherapy in Immunocompetent Patients With Anal Carcinoma: A Phase II Eastern Cooperative Oncology Group–American College of Radiology Imaging Network Cancer Research Group Trial (E3205). *J Clin Oncol.* 2017 Mar;35(7):718–26.
 34. Ott PA, Piha-Paul SA, Munster P, Pishvaian MJ, van Brummelen EMJ, Cohen RB, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. *Ann Oncol.* 2017 May;28(5):1036–41.
 35. Morris VK, Salem ME, Nimeiri H, Iqbal S, Singh P, Ciombor K, et al. Nivolumab for previously treated unresectable metastatic anal cancer (NCI9673): a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2017 Apr;18(4):446–53.
 36. Marabelle A, Cassier PA, Fakih M, Kao SCH, Nielsen D, Italiano A, et al. Pembrolizumab for previously treated advanced anal squamous cell carcinoma: Pooled results from the KEYNOTE-028 and KEYNOTE-158 studies. *J Clin Oncol.* 2020 May 20;38(15_suppl):4020–4020.
 37. Lièvre A. Anti-PD-1 for pretreated advanced anal carcinoma: which patients will benefit? *Lancet Gastroenterol Hepatol.* 2022 May;7(5):384–6.
 38. Martin D, Balermipas P, Gollrad J, Weiß C, Valentini C, Stuschke M, et al. RADIANCE – Radiochemotherapy with or without Durvalumab in the treatment of anal squamous cell carcinoma: A randomized multicenter phase II trial. *Clin Transl Radiat Oncol.* 2020 Jul;23:43–9.
 39. Rao S, Sclafani F, Eng C, Adams RA, Guren MG, Sebag-Montefiore D, et al. International Rare Cancers Initiative Multicenter Randomized Phase II Trial of Cisplatin and Fluorouracil Versus Carboplatin and Paclitaxel in Advanced Anal Cancer: InterAACT. *J Clin Oncol.* 2020 Aug 1;38(22):2510–8.
 40. Kim S, François E, André T, Samalin E, Jary M, El Hajbi F, et al. Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (Epitopes-HPV02): a multicentre, single-arm, phase 2 study. *Lancet Oncol.* 2018 Aug;19(8):1094–106.
 41. Kim S, Meurisse A, Spehner L, Stouvenot M, François E, Buecher B, et al. Pooled analysis of 115 patients from updated data of Epitopes-HPV01 and Epitopes-HPV02 studies in first-line advanced anal squamous cell carcinoma. *Ther Adv Med Oncol.* 2020 Jan;12:175883592097535.

Figure captions

Figure 1 : Workflow of the study

SCCA : squamous cell carcinoma of the anus ; RT : Radiotherapy ; CRT : Chemoradiotherapy

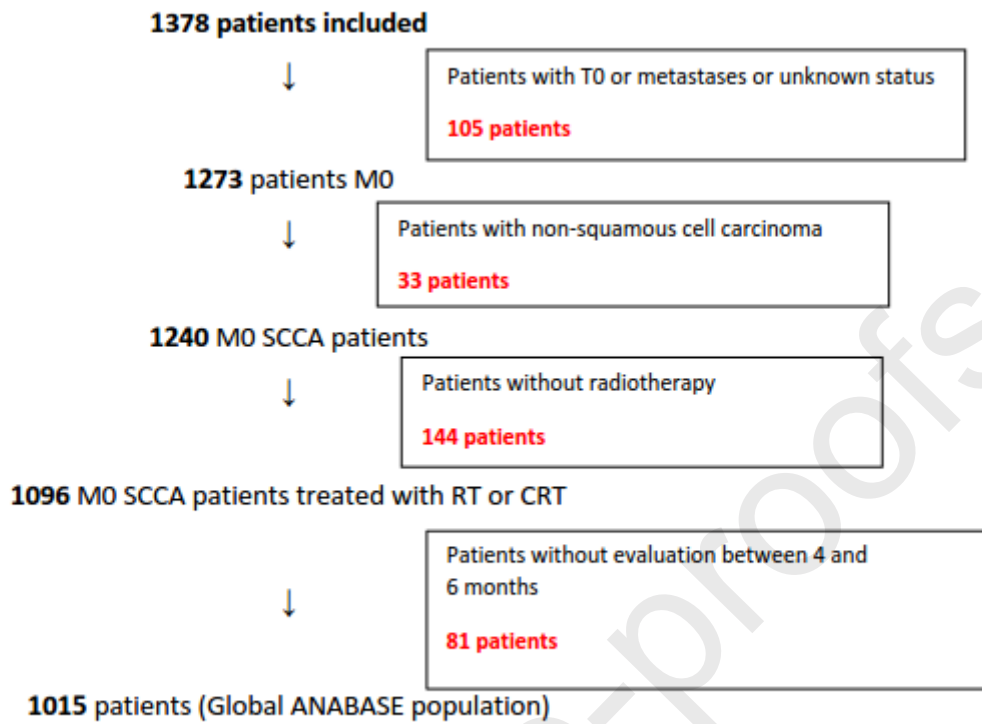
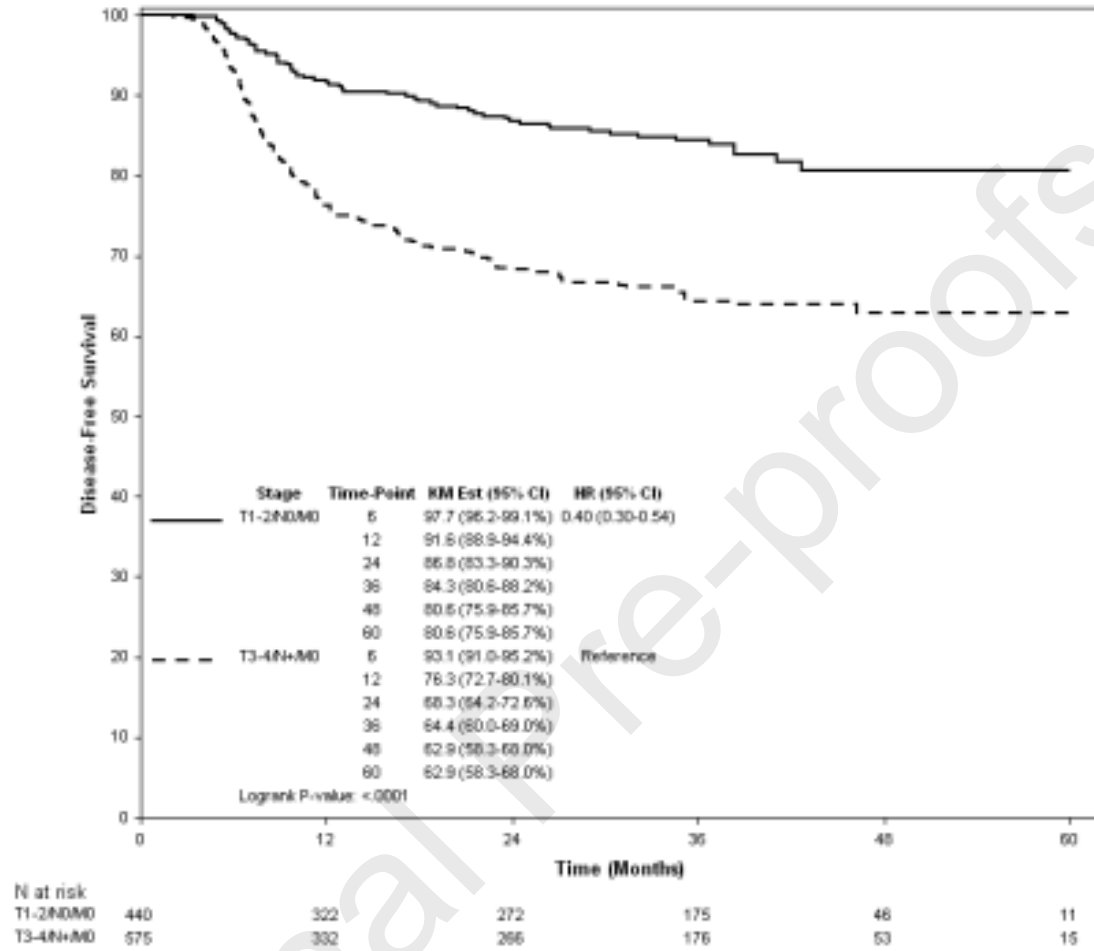


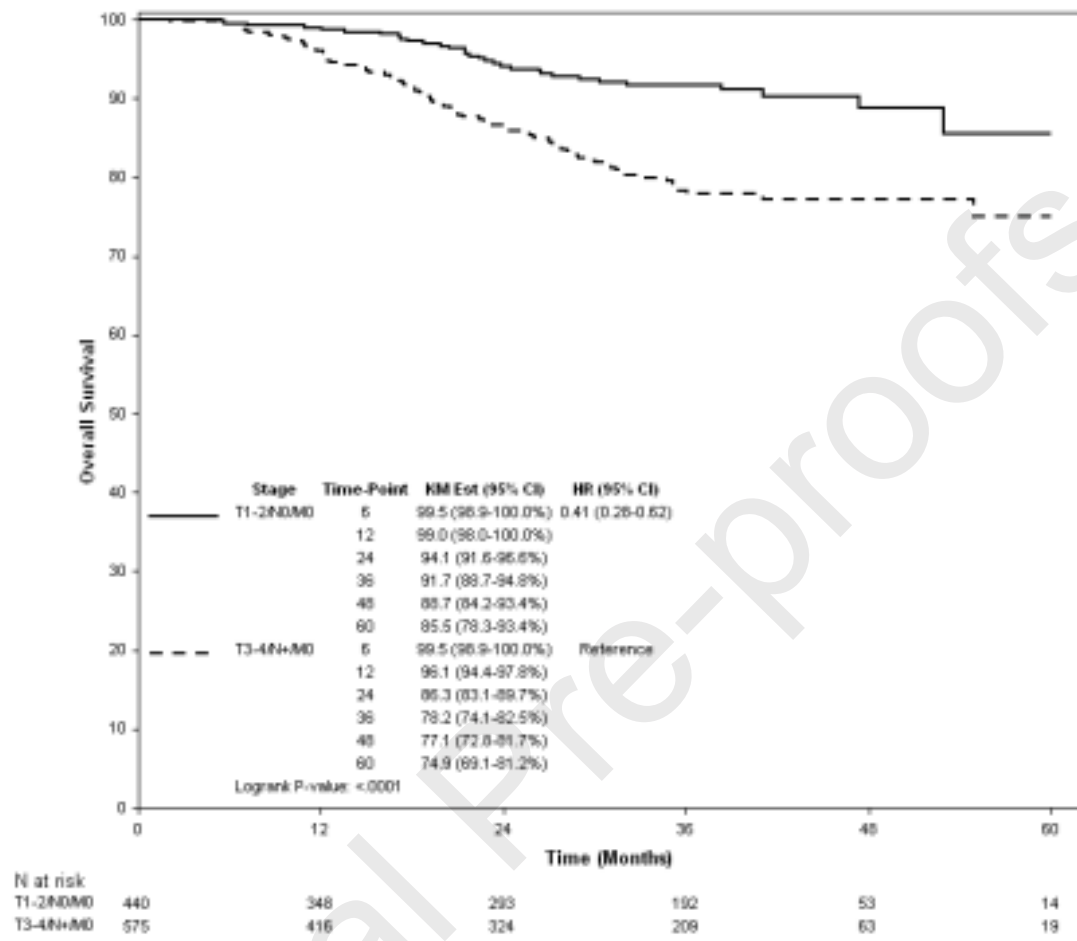
Figure 2 : Kaplan Meier Plots grouped according to early-stage SCCA (T1-2, N0) and locally-advanced SCCA (T3-4 or N+) for disease-free survival (A), overall survival (B), and colostomy-free survival (C)

Figure 2

A



B



c

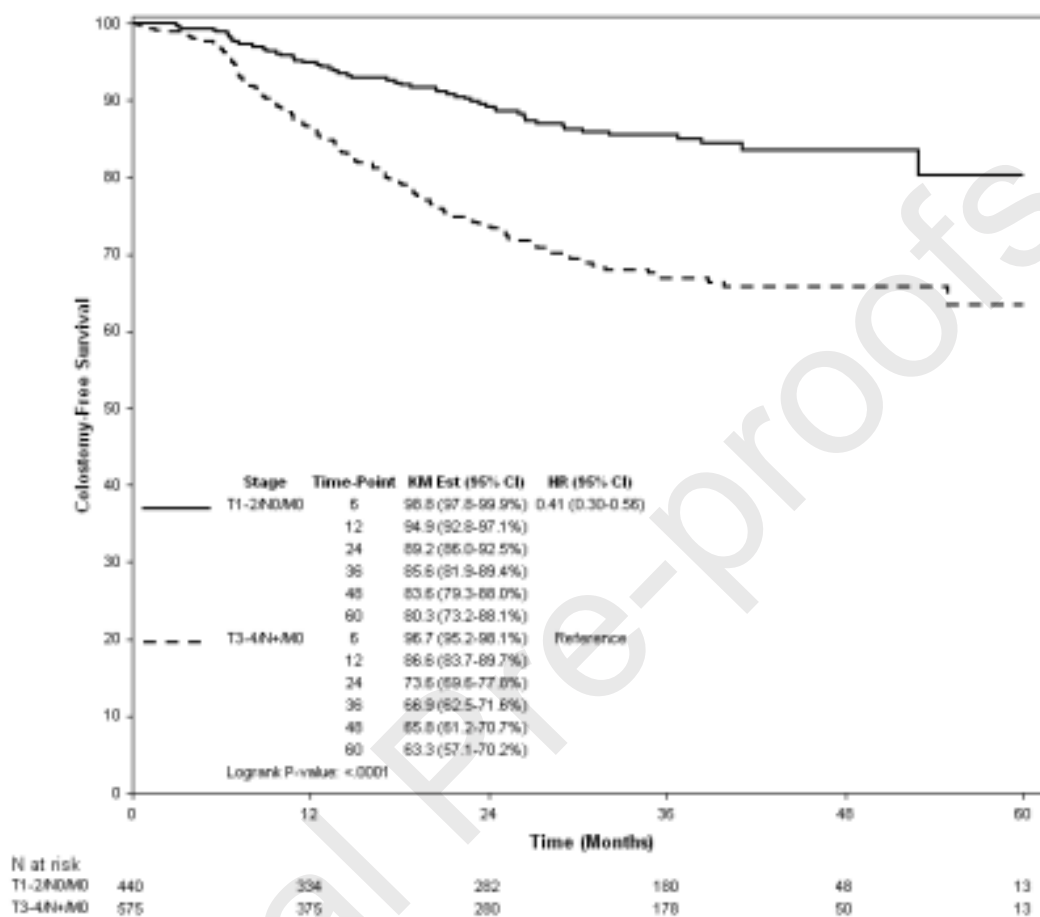


Table 1: Patient's characteristics

		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)

Table 2: Treatment characteristics

Abbreviations: CT= chemotherapy; RT= radiotherapy; IQR=Inter-Quartile Range

X² test

		T1-2/N0 (n= 440) N (% or median)	T3-4 or N+ (n=575) N (% or median)	All (n=1015)	<i>p value</i> [#]
Exclusive RT		179 (40.7)	55 (9.6)	234 (23.1)	<i><0.0001</i>
Chemoradiotherapy		261 (59.3)	520 (90.4)	781 (76.9)	<i><0.0001</i>
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)	<i>0.0009</i>
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)		<i><0.001</i>
	[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)	<i><0.001</i>

*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.

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)	<i>p value</i>	HR (95% CI)	<i>p value</i>
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		

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)	<i>p-value</i>	HR (95% CI)	<i>p-value</i>
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

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 interpretation, revision ; E.Menager-tabourel : data collection ; O.Diaz : data collection, M.Hummelsberger : data collection, M.Minsat : data collection ; F.Drouet : data collection ; A.Larrouy : data collection ; D.Peiffert : data collection and revision ; X.Zasadny : data collection ; V.Hautefeuille : data collection ; F.Mornex : data collection ; N.Barbier : data collection ; C.Lepage : supervising ; L.Quero : study design, data collection, Data analysis and interpretation, revision

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 Viatrix.

Pr Côme Lepage declare consulting fees from Amgen, AAA, Pierre Fabre and Ipsen.

The others authors declare no competing interests.

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