Phase II study evaluating conformational radiotherapy with continuous spread intensity modulation (SIB-IMRT) combined with 5-FU and mitomycin-C chemotherapy in patients with locally advanced anal canal cancer

CANAL-IMRT-01

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1 LIST OF PARTICIPATING CENTERS

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2 SYNOPSIS

Title	**Phase II study evaluating conformational radiotherapy with continuous spread intensity modulation (SIB-IMRT) combined with 5-FU and mitomycin-C chemotherapy in patients with locally advanced anal canal cancer**
Acronym	**CANAL-IMRT-01 protocol**
Promoter	**François Baclesse Center**
Coordinator	**Dr Mélanie DOS SANTOS – Professor Marc-André MAHE**
Indication	Locally advanced epidermoid anal canal cancers
Test methodology	Phase II trial, prospective, multicenter, non-randomized
Goals	**Main objective** The primary objective of this study is to evaluate the efficacy and safety profile of a modulated intensity radiotherapy (IMRT) boost in planned uninterrupted tomotherapy in patients with locally advanced anal canal cancer receiving concomitant chemotherapy with 5Fluorouracil and mitomycin C. **Secondary objective** The secondary objectives are to estimate: - Patient quality of life as well as sphincter function - Acute and late skin toxicities, digestive and urinary - The locoregional control rate at 3 months, 6 months and 12 months, with centralized review of scanners - Response time - Colostomy-free (CFS), overall and progression-free survival - Methods of administering radiotherapy (number and duration of breaks, total irradiation dose, duration of treatment)

Inclusion criteria	• ECOG status performance 0-1
	• Age ≥ 18 years old
	• Histologically proven squamous cell carcinoma of the anal canal, locally advanced, with an indication for radiotherapy of the pelvis and inguinal lymph nodes combined with chemotherapy.
	• TNM stage (T corresponds to the large diameter of the clinical tumor by digital rectal examination and N corresponds to lymph node involvement assessed by CT, MRI or echoendoscopy imaging)
	  ○ T2 whose diameter is > 4cm N0 M0
	  ○ T3-T4 N0 M0
	  ○ All T N+ M0
	• Disease measurable according to RECIST 1.1 criteria
	• Leukocytes ≥ 4000/mm^3, Polynuclear neutrophils ≥ 1500/mm^3, Blister ≥ 100 G/l.
	• Total Bilirubin ≤ 1.5 times the upper limit of normal (LNS), Transaminases ≤ 5 times LNS, Alkaline Phosphatases ≤ 2.5 times LNS.
	• Creatinine ≤ 2 times LNS.
	• Patient information and signing of informed consent
	• Affiliation to a social security system.

Non-inclusion criteria	• Metastatic disease • Undifferentiated cell carcinoma or anal canal adenocarcinoma • History of invasive cancer for less than 5 years except previously treated basal cell carcinoma or cervical carcinoma • Tumor with predominant skin invasion without canal invasion. • Severe unbalanced concomitant disease • Symptomatic or grade ≥2 angina, uncompensated heart failure • Severe hepatic or renal failure • Contraindication to carrying out radiotherapy or administering 5 FU and/or Mitomycin-C. • Known DPD deficiency • History of pelvic irradiation or chemotherapy • HIV positive patients • Patient already included in another therapeutic trial with an experimental molecule • Pregnant or breastfeeding woman • Women of childbearing age without contraception • Persons deprived of their liberty or under guardianship.
Therapeutic regimen	Radiotherapy 61.2 Gy in 36 fractions of 1.7 Gy over a spread of 50 days associated with two cycles of 5-FU (1000 mg /m² /d administered IV for 96 h in weeks 1 (days 1 to 4) and 5 (days 29 to 32) of IMRT) and mitomycin-C (10 mg/m², days 1 and 29).
Evaluation criteria	**Main criterion:** The main criterion will be one composite criterion combining both clinical effectiveness and tolerance as proposed by **Bryant & Day** [Bryant J, biometrics, 1995]: L'efficiency is defined by the locoregional control rate 3 months after the end of IMRT by tomotherapy corresponding to the proportion of patients alive without local progression (according to RECIST version criteria??) from the disease 3 months after the end of radiotherapy There tolerance is defined by the proportion of patients without significant toxicities (grade ≥3 according to NCI CTCAE version 4.03) responsible for irradiation breaks. **Secondary criteria:** - quality of life: ➢ EORTC QLQ-C30 questionnaire (version 3.0) and its additional colorectal module QLQ-CR 29 ➢ sphincter function assessed by MSK-AF score and by the Vaizey incontinence questionnaire, the SLOW/SOMA questionnaire for men and women [SLOW/SOMA: Barraclough LH et al. Radiother Oncol; 103:327-32] - Acute and late toxicities assessed according to the NCI CTCAE version 4.03 (Criteria National Cancer Institute Common Terminology Criteria for Adverse Events) - The locoregional control rate at 6 and 12 months defined by the proportion of patients without progression of the local disease (assessed by a centralized CT-scan examination), nor death from any cause (except for distant metastases) at 6 and 12 months after the end of radiotherapy - The duration of the response defined by the time elapsed between the first objective response and progression or death whatever the cause - Colostomy-free survival (CFS) defined as the time interval between the start of treatment and colostomy or death regardless of the cause

	- Progression-free survival defined by the time elapsed between the start of treatment and tumor progression or death whatever the cause, - Overall survival defined by the time elapsed between the start of treatment or death whatever the cause - The number of radiotherapy discontinuations and the total number of days radiotherapy discontinuation, as well as associated reasons, - The total dose of irradiation and the total duration of radiotherapy
Number of patients needed	66 patients in total A two-step phase II design proposed by Bryant and Day (αeff = αtox = 5%, potency (1-β) = 90%) combining both clinical response and toxicity will be used. Considering the following assumptions: • Let p1 = 80%, the theoretical acceptable proportion of patients not experiencing toxicity requiring interruption of irradiation with IMRT, • Let p0 = 60%, the theoretical unacceptable proportion of patients not experiencing toxicity requiring interruption of irradiation, • A loss of effectiveness of 10% (reference value of 90%; response rate of 80% or less, considered unacceptable) is considered unacceptable • The number of patients to be included is increased by 10% to compensate for non-evaluable patients It is planned to include: - 16 patients at the 1st stage (→ 14 evaluable patients) - 50 additional patients at the 2nd stage (→ 46 additional patients evaluable) • Following a national recall of batches of Mitomycin from Kyowa Laboratories there were 5 patients treated with cisplatin. In order to respect the total number of 66 patients treated with the same protocol (Mitomycin), we made the decision to include 5 additional patients for a total of 71 patients.
Number of centers	1st stage: 4 centers 2nd stage: 10-12 centers
Duration of the study	Estimated duration of inclusion at 72 months
Statistical analysis	**Interim analysis after the first step:** It will involve 14 evaluable patients. If fewer than 11 of these 14 patients have a clinical response, the trial will be stopped for futility; If toxicities requiring irradiation breaks are observed in at least 7 of these 14 patients, the trial will be stopped due to an unacceptable safety profile. In other cases, the test will continue with step 2. **Final analysis after the second step:** Final analysis after step 2: 46 additional evaluable patients are required, for a total of 60 evaluable patients. If, among the 60 evaluable patients, at least 57 patients have a clinical response and at most 17 patients present significant toxicities (requiring irradiation breaks), the trial will conclude that the irradiation regimen is tolerable and effective without pause.

3 SUMMARY OF EXAMINATIONS TO BE CARRIED OUT

	Balance sheet inclusion (within 6 weeks)	Follow-up assessments during treatment								Post-therapeutic assessments				
		Chemotherapy/Radiotherapy Association (RTE)												
		J1	J8	D15	D22	D29	J36	J43	J50	1 month	3 months	6 months	Every 4 months up to 2 years	Then every 6 months for 3 years
5fu		**D1 to D4**				**D29 ON D32**								
Mitomycin C		**X**				**X**								
IMRT														
Examinations and Monitoring	→													
Informed consent	•													
Medical history	•													
Complete clinical examination Vital signs: WHO, pulse, blood pressure	•	•	•	•	•	•	•	•	•	•	•	•	•	•
Anorectal touch (1)	•									•	•	•	•	•
-Pelvic abdominosteal thoraco scanner (TAP) (1) **- Endorectal ultrasound and/or mandatory MRI** (1)	**• (3)**										•	•	•	•
Pet scan optional	•													
ECG	•													
NFS-platelets + biochemical (4)	**• (2)**	•							•					
Tumor markers of squamous cell cancers (SCC)	**• (2)**										•	•	•	•
Dosage of DPD or uracilemia	**• (6)**													
HPV serology within 6 months	**• (5)**													
Questionnaires on quality of life and sphincter functions - QLQ-C30 - QLQ-CR29 - MSK-AF - VAIZEY incontinence	•										•	•	•	•[7]
SLOW/SOMA questionnaire (objective and subjective signs)	•										•	•	•	•[7]
Collection of toxicities (NCI CTCAE V4, RTOG EORTC)		•	•	•	•	•	•	•	•	•	•	•	•	•

(1) The tumor evaluation will be done by a clinical examination (rectal examination, palpation of the inguinal and supraclavicular lymph node areas), local extension will be done by a pelvic MRI and/or anorectal echoendoscopy according to the free choice of the investigator, the Remote extension will be done by a TAP scanner. A brain scan and/or bone scan will be performed if there is a warning sign. Intermediate monitoring consultations may be interspersed, and the performance of a PET-Scan is authorized at the discretion of the examiner. Patients with a metastatic course will be monitored according to the habits of the center.

(2) within 2 weeks before starting treatment

(3) in the 4 6 weeks before the start of treatment

(4) The biological assessment before inclusion and weekly during radiotherapy includes: CBC, platelets, blood ionogram, serum creatinine, protein, albumin, complete liver assessment only at inclusion (bilirubin, transaminase, gamma GT and alkaline phosphatases).

(5) optional

(6) prior to inclusion

(7) Performed annually

4 SCIENTIFIC JUSTIFICATION FOR THE STUDY

4.1 Rational

Anal canal cancer represents 1.2% of digestive cancers, with an increasing incidence. In 95% of cases, the histology of anal canal cancer is squamous cell, characterized by high radiosensitivity and chemosensitivity.

❖ Management of anal canal cancer

Radiotherapy (RT) combined with chemotherapy (CT) with 5-fluorouracil and mitomycin-C at weeks 1 and 5 for locally and/or regionally advanced tumors is the treatment of choice for squamous cell carcinomas of the anal canal [1, 2].

In France, conformational radiotherapy, with or without intensity modulation, remains the technique currently used routinely. A first dose of irradiation is delivered in a volume encompassing the tumor, invaded lymph node sites and/or at risk, in concomitant association with chemotherapy at weeks 1 and 5 of treatment. This dose is 45 Gray (Gy) usually delivered in 25 fractions of 1.8 Gy. After a planned break of 1 to 2 weeks, or extended depending on the intensity of local reactions, irradiation is resumed and delivered locally to the tumor and affected lymph nodes, by the same irradiation technique, up to at a variable total dose of up to 54 or 60 Gy, over a spread of more than 9 weeks.

In centers authorized for this approach, the radiotherapy supplement can be delivered by brachytherapy at a dose varying between 15 and 25 Gy, after a break of approximately 6 weeks after the end of the pelvic irradiation. This time is necessary for the clinical evaluation of the tumor response at the end of the first part of treatment.

This combination has proven its effectiveness in terms of locoregional control, sphincter preservation and relapse-free survival [1, 3, 4]. Full response rates are over 80% [3, 4].

However, conventional pelvic radiotherapy for anal canal cancers is frequently accompanied by significant toxicities. Thus, approximately 65% of patients present acute side effects which, in the majority of cases, are diarrhea related to colitis and especially mucositis of the small intestine and radioepithelitis of the perineum, inter-gluteal fold or skin folds. More than 50% of these toxicities require treatment to be interrupted for at least two weeks, this time being necessary for recovery from toxic reactions.

❖ Evolution of radiotherapy techniques

In 4-field conformal radiotherapy (3D-CRT), large volumes of irradiation are required, resulting in significant digestive, urinary, and skin toxicities [5] and responsible for long processing interruptions. Radiotherapy doses with a probability of disease control are thus frequently limited by the tolerance of healthy organs.

Comparison of pelvic irradiation (3D-CRT) and conformal intensity-modulated radiotherapy (IMRT) showed that the dosimetric coverage of the target volume likely to contain microscopic extensions was identical regardless of the technique [6]. On the other hand, IMRT generally makes it possible to deliver the irradiation dose in a manner more consistent with the volume, through spatial and temporal variation of the beams, leading to better sparing of neighboring critical organs. This results in average reductions of 50% in the percentage of small intestine volume receiving more than 30 Gy (small intestine tolerance dose), associated with a significant reduction in digestive toxicity. Likewise, the benefit of IMRT has been shown in the protection of the perineum and genitals [6]. In the study by Milano et al [6], these structures received a dose less than 50 Gy, significantly reduced compared to that of 3D-CRT: none of the 17 patients presented non-hematological toxicities of grade 3 or higher, and no digestive or skin toxicity required interruption of treatment.

Menkarios' team et al in Montpellier compared the dosimetric results of three IMRT protocols with that of conventional 3D-CRT treatment in a total of 10 patients [7]. In two IMRT protocols, irradiation was carried out at a dose of 45 Gy in 25 fractions of 1.8 Gy with a complement of 14.4 Gy in 8 fractions, either by conventional technique or by intensity modulation. The third IMRT protocol with simultaneous integrated boost (SIB) delivered two dose levels: 49.5 and 59.4 Gy out of the 33 fractions. Incorporation of IMRT in the treatment of anal canal tumors reduces the V40 (volume of organ at risk receiving more than 40 Gy) of the perineum to 7% or 3% in case of BIS, *versus* 80% for 3D-CRT treatments. Likewise, IMRT significantly reduces the V30 and V40 of hail compared to 3D-CRT, without additional reduction in case of IMRT with SIB. Concerning the iliac bone, only a reduction of 50% and 32% of V10 and V20 are observed in the event of N2-N3 pelvic lymph node invasion.

Thus, due to the abundance of anatomical structures at risk on contact, such as the small intestine, bladder, genitals, skin, femoral heads and bone marrow, which must be excluded from irradiation, cancer of the anal canal has become a location of interest for the development of IMRT.

The benefit of reducing skin and gastrointestinal toxicities of IMRT associated with chemotherapy, suggested by several retrospective studies [6, 8], lies in the possibility of increasing the total dose delivered to the tumor in advanced stages and demonstrating the anti-tumor impact of dose escalation, through the dose-effect relationship.

The phase II study RTOG 0529 [9] evaluated the benefit of combining dose-painted intensity modulation with 5FU-Mitomycin C chemotherapy to reduce grade 2 gastrointestinal or genitourinary toxicities by at least 15%, by compared to data from the RTOG 9811 trial (conventional radiotherapy and 5FU-Mitomycin C). Preliminary results showed a decrease in the rate of grade dermatological toxicities $\geq$2 to 69% versus 81% (p=0.039) and more grade 3 of 23% versus 49% (p<0.001). Interruption of treatment was necessary in 49% versus 62% in the Mitomycin C-combining arm of the RTOG 9811 study.

IMRT offers the possibility of delivering different doses on several target volumes at the same time thanks to the modification of the fractionation scheme such as SIB-IMRT (simultaneous boost integrated into IMRT). Several SIB-IMRT regimens were evaluated retrospectively [10].

Dynamic intensity modulation by helical tomotherapy was the next step in therapeutic optimization and reduction of radiation-induced morbidity. This technique optimizes the protection of organs at risk (OAR) but increases the treatment time per session [11].

Comparative dosimetric studies have demonstrated that tomotherapy significantly improves the conformity index, the homogeneity of the prescribed dose in the planned volume ensuring better savings of OARs compared to IMRT or 3D-CRT [12-14].

Reducing cumulative toxicity is the major objective of tomotherapy because it would make it possible to shorten, or even eliminate, the therapeutic "pause" of at least two weeks usually observed (for recovery of toxicities) between the end of the irradiation pelvic and the supplement delivered to the tumor and its lymph node extensions.

The feasibility and benefit of tomotherapy in reducing the rate of gastrointestinal and skin toxicities in the treatment of anal canal cancer were the subject of a recent project carried out by INCa [15]. The dose prescribed to the pelvis with inclusion of inguinal lymph nodes was 45 Gy in fractions of 1.8 Gy, with a supplement of 14.40 Gy being administered into the tumor and affected lymph nodes. Gastrointestinal and hematological toxicities of grade $\geq$ 3 were noted for 20.3% and 13% of patients, respectively. If treatment with tomotherapy proved feasible, 45% of patients presented grade skin toxicities $\geq$ 3, responsible for interrupting irradiation.

❖ Radiotherapy parameters associated with tumor control

Furthermore, if the stage, size and lymph node status of the tumor are recognized as prognostic factors, the total dose radiotherapy as well as duration of spreading irradiation also determines disease control.

There total irradiation dose is in fact a factor independent of the risk of late toxicities and colostomies carried out outside of relapse. The dose per fraction is associated with the risk of late toxicities of healthy tissues.

Concerning the escalation of the irradiation dose, no interest has been found and the dose of 60 Gy therefore remains the standard [16].

More specifically, the Accord 3 study [16] evaluated the benefit of an irradiation supplement of 15 Gy or 20 to 25 Gy depending on the tumor response carried out after a 3-week break at the end of radiochemotherapy with 5-FU and cisplatin up to a dose of 45 Gy in five weeks. No significant impact of dose escalation beyond 60 Gy was found on local control, relapse-free survival (RFS) or colostomy-free survival.

On the other hand, in some retrospective studies, the concomitant radiochemotherapy combination does not allow reducing the total irradiation dose below 55 Gy, nor extending the rest interval between the first series of irradiation and the supplement irradiation beyond 35 days, without risk of significantly reducing the local tumor control rate [17-20].

Phase II study RTOG 92-08 examined the role of dose escalation in improving local control. In this study, a total dose of 59.40 Gy was delivered over a period of 8.5 weeks, including 2-week breaks necessary for improvement in treatment-induced toxicities. Local control was lower than that found in previous studies with lower doses (between 40 and 50.4 Gy) of radiotherapy carried out continuously, with a higher rate of colostomy, despite a higher total dose of radiotherapy. The authors assumed the negative effect of irradiation pauses that counteract the presumed benefits of dose escalation and thus explain the high rates of local relapses [4, 21].

In the RTOG 9811 study, if a break was necessary, it did not exceed 10 days for a total treatment duration of 49 days and delivered doses of 55-59 Gy [2].

Concerning irradiation spreading, this is a fundamental principle in oncological radiotherapy: once irradiation has been initiated, treatment interruptions must be minimized to avoid the phenomenon of accelerated tumor repopulation [22]. As previously specified, conventional 4-beam irradiation was inevitably accompanied by significant toxicities, requiring therapeutic pauses. For this reason, treatment regimens immediately provided for interruptions in order to reduce toxicities and improve tolerance to treatment.

Likewise, several retrospective studies have shown the determining role of total processing time for local control and SSR. These findings are similar to observations made in other types of squamous cell carcinomas, VADS sphere or cervical carcinoma with similar proliferation parameters. Thus, in the treatment of ENT squamous cell cancers, a one-week break reduces local control by 12%-14%, and a 15-day break reduces it approximately twice as much. Regarding the cervix, local control decreases by 1% if the total treatment duration exceeds 52 days. The time factor is therefore essential for tumor control. Prolonged irradiation spreading stimulates repopulation of clonogenic cells, explaining the reduction in local control [22, 23].

To illustrate the importance of total duration of anal canal cancer treatment, Ben-Josef et al [24] performed a combined analysis of data from study RTOG 87-04 and RTOG 98-11. Multivariate analysis demonstrated a statistically significant relationship between total irradiation duration and tumor control: each increase in treatment duration beyond 14 days is accompanied by a 9.4% increase in the risk of colostomy for relapse.

Meyer et al [25] were retrospectively interested in the feasibility and effectiveness of concomitant radiochemotherapy according to a conformational modality and without planned pause. Short interruptions of treatment were accepted if they did not exceed 8 days in a row. For the 68 patients evaluated, the median treatment duration was 53 days. An interruption of 8 days or more was necessary for 49% of patients.

Published results from non-randomized retrospective series show that the impact of treatment duration on local control is greater for tumors classified T3 or T4 than for small tumors (T1-T2), for which responses complete are found at a dose of 30 Gy. The benefit of a higher dose in advanced tumors is blurred by extending the treatment duration. In a retrospective series of 28 patients studied by the UCSF [26]2-year progression-free survival was significantly higher for patients who received more than 54 Gy over a spread of less than 60 days than for those who received less than 54 Gy over 60 days (89% versus 42%, p< 0.01).

In a retrospective study, Graf et al [27] compared a split-course irradiation regimen at a total dose of 45 Gy, with planned interruption of two weeks after the 30 Gy dose, to continuous treatment of 45 Gy in 25 fractions. A total treatment duration (DT) > 41 days was associated with a significant reduction in local control at 5 years (58% versus 79% for DT ≤ 41 days, p=0.04). No relationship was found with the radiotherapy regimen used.

Finally, the feasibility and effectiveness of doses in fractions of 1.5 to 1.8 Gy in intensity modulation, in non-invaded, or low-risk, lymph node sites, have been proven in mainly retrospective studies, without compromising loco-regional control [9].

4.2 Research hypothesis and expected results

We propose a phase II study aimed at evaluating the feasibility of chemotherapy concomitant with radiotherapy **IMRT without planned breaks** to improve the treatment of locally advanced anal canal cancer (ACC) by reducing the proportion of patients requiring toxicity-induced irradiation breaks with similar effectiveness.

4.3 Benefit/risk ratio

As observed in head and neck cancers, IMRT represents a promising strategy to improve the treatment of squamous cell anal canal cancers.

The radiotherapy regimen currently used achieves complete response rates greater than 80%. Acute toxicities of grade 3 and above (digestive, urinary and skin) occurring during treatment frequently result in suspensions of radiotherapy for more than a week, which can have an impact on local control and survival.

Compared to the conformal radiotherapy regimen (with or without intensity modulation), delivering 25 fractions of 1.8 Gy concomitantly with chemotherapy at weeks 1 and 5, then, after a planned break (1 to 2 weeks), a boost for total irradiation of 54 to 60 Gy over 9 weeks, we hypothesize that IMRT without planned pause with modified splitting pattern represents a promising strategy for the treatment of anal canal cancer. We hope that IMRT with integrated boost without planned pause reduces acute severe toxicities (requiring irradiation suspension) while also being effective in terms of locoregional control.

This IMRT scheme could therefore make it possible to eliminate the irradiation pause and thus reduce the spread of irradiation.

Given the complexity of IMRT and the high variability in terms of margins used, doses delivered and IMRT techniques, prospective validation of a standardized SIB-IMRT regimen for the treatment of anal canal cancer (CCA) is essential. In addition, there is very little therapeutic innovation in CCA and a clinical trial evaluating the interest of SIB-IMRT represents an opportunity for patients, but also for doctors to correctly "contour" the tumor volume and the organs at risk.

If our results show that SIB-IMRT (without planned interruption) allows a locally advanced locoregional control rate of CCA identical to that obtained with the classic radiotherapy regimen (including a planned break) with fewer acute digestive, urinary and skin toxicities, and therefore a shorter duration of irradiation, it will thus be possible to offer this radiotherapy treatment regimen to these patients with a good prognosis.

The main challenge in improving the management of patients with locally advanced ACC is to reduce severe toxicities that can compromise treatment and its effectiveness.

In addition, toxicities that occur during radiotherapy can persist over time and become chronic, impacting patients' quality of life, with possible repercussions on healthcare consumption.

These considerations are all the more important given the good prognosis of these patients and the increasing incidence of CCA.

5 OBJECTIVES OF THE STUDY

5.1 Main objective

The primary objective of this study is to evaluate the efficacy and safety profile of an integrated boost by modulated intensity radiotherapy (IMRT) in tomotherapy without planned interruption in patients with locally advanced anal canal cancer receiving concomitant chemotherapy with 5-Fluorouracil and mitomycin C.

5.2 Secondary objectives

The secondary objectives are to evaluate:
- Quality of life and sphincter function of patients
- Acute and late skin, digestive and urinary toxicities,
- The locoregional control rate at 3 months, 6 months and 12 months, with centralized review of scanners and according to RECIST 1.1 criteria
- The duration of tumor response
- Colostomy-free survival (CFS), overall and progression-free survival
- Methods of administering radiotherapy (number and duration of breaks, total irradiation dose, duration of treatment)

6 PRACTICAL REALIZATION OF THE STUDY and FEASIBILITY

We propose a multicenter phase II, prospective, non-randomized trial.

6.1 Patient selection

6.1.1 Inclusion criteria

- ECOG status performance 0-1
- Age ≥ 18 years old
- Histologically proven squamous cell carcinoma of the anal canal, locally advanced with an indication for radiotherapy of the pelvis and inguinal lymph nodes combined with chemotherapy.
- TNM stage (T corresponds to the large diameter of the clinical tumor by digital rectal examination and N corresponds to lymph node involvement assessed by CT, MRI or echoendoscopy imaging)
  - T2 whose diameter is > 4 cm N0 M0
  - T3-T4 N0 M0
  - All T N+ M0
- Disease measurable according to RECIST 1.1 criteria
- Leukocytes ≥ 4000/mm^3, Polynuclear neutrophils ≥ 1500/mm^3, Blister ≥ 100 G/l.
- Total Bilirubin ≤ 1.5 times the upper limit of normal, Transaminases ≤ 5 times the upper limit of normal, Alkaline Phosphatases ≤ 2.5 times the upper limit of normal.
- Creatinine ≤ 2 times the upper limit of normal.

- Patient information and signing of informed consent
- Affiliation to a social security system.

6.1.2 Non-inclusion criteria

- Metastatic disease
- Undifferentiated cell carcinoma or anal canal adenocarcinoma
- History of invasive cancer for less than 5 years except previously treated basal cell carcinoma or cervical carcinoma
- Tumor with predominant skin invasion
- Severe unbalanced concomitant disease without invading the canal
- Symptomatic or grade ≥2 angina, uncompensated heart failure
- Severe hepatic or renal failure
- Contraindication to carrying out radiotherapy or administering 5 FU and/or Mitomycin-C.
- Known DPD deficiency
- History of pelvic irradiation or chemotherapy
- HIV positive patients
- Patient already included in another therapeutic trial with an experimental molecule
- Pregnant or breastfeeding woman
- Women of childbearing age without contraception
- Persons deprived of their liberty or under guardianship.

6.1.3 Registration procedure in the study

After obtaining signed informed consent, verifying all selection criteria and before starting treatment, an inclusion request form will be faxed to the Study Coordination Center:

Clinical Research Department of the François Baclesse Center

Fax: 02 31 45 51 58

After verification of all the selection criteria, the inclusion form will be returned by fax with the identification number specific to each patient which will be used throughout the trial.

If there is a problem, please contact the responsible persons:

Doctor Project Manager:

François Baclesse Center
E-mail: m.dossantos@baclesse.unicancer.fr
Tel.: 02 31 45 50 02 – Fax: 02 31 45 51 58

Project manager:

Jean-Michel GRELLARD
François Baclesse Center
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6.1.4 Criteria for premature exit from study

- General condition not allowing continuation of treatment
- Refusal to continue the study
- Withdrawal of consent
- Investigator's decision
- Patient lost to follow-up
- Major protocol violation

6.2 Feasibility

All participating centers have IRMT, IMAT technology (V-MAT, arc therapy) and tomotherapy.

Each investigative center has an annual active queue of approximately 8-10 patients with locally advanced anal canal cancer.

The main challenge for radiotherapists and oncologists is to manage severe acute toxicities, which remain frequent and compromise the optimal course of treatment for these patients. They can only be very involved in offering this trial to their patients.

6.3 Assessments before, during and after treatment

6.3.1 Inclusion report

Patients eligible for the trial and having signed their consent to participate will have to carry out an initial assessment in the weeks preceding the start of treatment.

- Clinical examination
  - Clinical examination with determination of weight, height, body surface area, anorectal touch
  - Vital signs (pulse, blood pressure) and WHO performance index
  - Description of the lesion and lymphadenopathy

- ECG

- Biological examinations (completed within 15 days)
  - Hematology
  - Blood ionogram (calcium, potassium, sodium, bicarbonate, protein, albumin)
  - Liver assessment (bilirubin, AST/ALT, PAL, γGT)
  - Kidney assessment (creatinine, urea)
  - Tumor markers of squamous cell cancers (SCC)
  - Pregnancy test (if applicable)
  - Optional: HPV research and HIV serology less than 6 months old
  - Dosage of DPD or uracilemia (pre-inclusion)

- Tumor evaluation (performed in the 4 6 weeks)
  - Pelvic abdominos thoraco scan
  - Endorectal ultrasound and/or mandatory MRI
  - Pet scan optional

- Quality of life and sphincter function questionnaires
  - MSK-AF
  - QLQ-C30
  - QLQ-CR29
  - Vaizey Incontinence
  - SLOW/SOMA

6.3.2 Weekly follow-up assessment during radiochemotherapy treatment

- Clinical examination
  - Clinical examination with determination of weight, height, body surface area
  - WHO Performance Index
  - Assessment of toxicities

- Biological examinations before chemotherapy (D1 and D29)

- Hematology
- Blood ionogram (calcium, potassium, sodium, bicarbonate, protein, albumin)
- Kidney assessment (creatinine, urea)

6.3.3 End of treatment assessment at 1 month post-radiotherapy

➢ Clinical examination

- Clinical examination with determination of weight, height, body surface area, anorectal touch
- WHO Performance Index
- Assessment of toxicities

6.3.4 Monitoring report

Examinations to be carried out at 3 months, 6 months, then every 4 months up to 2 years and every 6 months over the following 3 years (in accordance with the monitoring methods for patients treated for anal canal cancer)

➢ Clinical examination

- Clinical examination with determination of weight, height, body surface area, anorectal touch
- WHO Performance Index
- Assessment of late toxicities

➢ Biological examinations

- Tumor markers of squamous cell cancers (SCC)

➢ Tumor evaluation

- Pelvic abdominos thoraco scan
- Endorectal ultrasound and/or mandatory MRI (use the same examination as at inclusion)

➢ Quality of life and sphincter function questionnaires to be carried out once a year

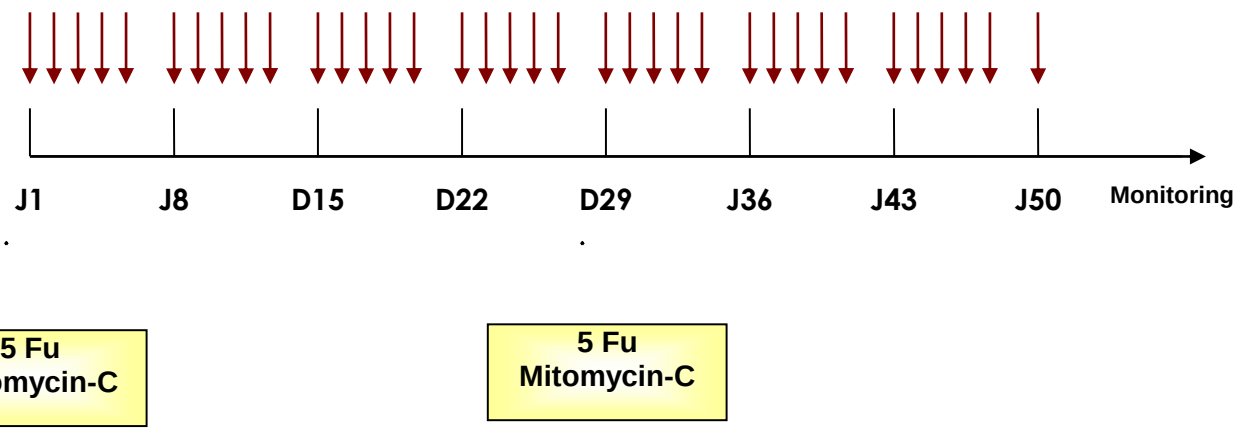
- MSK-AF
- QLQ-C30
- QLQ-CR29
- Vaizey Incontinence
- SLOW/SOMA

Patients with a metastatic course will be monitored according to the habits of the center.

6.4 Treatment by radiothemotherapy

Treatment will begin within 4 weeks of inclusion.

6.4.1 Chemotherapy



The patient will receive concomitant chemotherapy **starting MONDAY** of the **1era** and there **5th radiotherapy week** in IV hospitalization (central venous route not obligatory). It will contain mitomycin-C on D1 and D29, at a dose of 10 mg/m² as an IV infusion (15 to 30 min) with the presence of the nurse the passage time of mitomycin-C if a venous route peripheral is used. Mitomycin-C will preferably be delivered before radiotherapy. 5 FU will be administered after mitomycin-C, in continuous infusion over 24 hours, at a dose of 1000 mg/m² from D1 to D4 and from D29 to D32. Antiemetic preventive treatment is not imposed and will be carried out according to service habits.

DCI	Specialty name	Pharmaceutical form	Route of administration	Dosage
Mitomycin-C	Ametycin®	Powder for solution for injection	IV	10 mg/m² D1 and D29
5 FU		Concentrate for solution for infusion	IV	1000 mg/m² D1 to D4 and D29 to D32

6.4.2 Conformational radiotherapy with intensity modulation (IMRT)

❖ **Medical radiotherapy devices and radiotherapy modalities**

Eligible patients must receive radiotherapy treatment using the technique of helical tomotherapy.

Radiotherapy will be carried out in intensity modulation using the technique of helical tomotherapy using photons of 6 MV energy. It will be administered according to the principle of concomitant "boost", i.e. SIB-IMRT (simultaneous-integrated boost intensity modulated radiation therapy) to reach the doses planned on the PTV *(Planned Target Volume)*, in 36 fractions and 50 days of spreading.

The following recommendations apply to all investigators participating in the study.

❖ **Immobilization**

The patient will be treated in the supine position. A restraint system is desirable to ensure better reproducibility of patient positioning.

❖ **Dosimetric scanner**

It will be carried out with injection of contrast product, and in the treatment position, with a full bladder in contiguous sections of 3 to 5 mm maximum. The acquisition volume will begin at the level of the iliac ridges and end under the small trochanters. Identifying the anal margin by lead wire or ball can be useful, as can in the event of skin extension of the tumor beyond the anal margin.

❖ **Contouring target volumes and organs at risk (OAR) according to ICRU (International Commission for Radiation units)**

It will be carried out taking into account data from the clinical examination and paraclinical examinations (echoendoscopy, pelvic MRI, PET scan). A pelvic fusion MRI with centering scanner is recommended.

♦ The GTV (*Gross Tumor Volume or Macroscopic Tumor Volume) corresponds to the tumor, its local macroscopic extensions and lymphadenopathy visualized on scannographic imaging, MRI, Echoendoscopy, PET scan: GTV T and GTV N*

♦ The CTV 1 (Clinical Target Volume or *Anatomo-clinical Target Volume*) represents the anal canal and the lower rectum (if invasion). It is created from the GTV T with an expansion of 1.5 cm cranio-caudal and 1 cm in other directions. In the case of lower tumors with invasion of the anal margin, the expansion will be 2 cm at the level of the perianal skin.
Lymphadenopathy larger than 3 cm in size will be included in CTV1 with an expansion of 1 cm in all directions and treated at the same dose as the primary tumor.

♦ The CTV 2 represents macroscopically invaded pelvic and/or inguinal lymph nodes (documented by imaging examinations). It is created from the GTV N with an expansion of 1 cm in all directions.

♦ The CTV 3 includes lymph node areas at risk of microscopic invasion:
- bilateral inguinal chains
- external iliac ganglion chains
- obturator chains and internal iliacs
- ischio-rectal fossae
- mesorectum and presacral space

Contouring is carried out 7 mm around the lymphatic drainage pathways of the anal canal [28] with exclusion of bone or muscular structures.

♦ THE PTV includes CTV with an expansion of 1 cm, except 0.5 cm towards external genitalia.

From the corresponding CTVs, PTV 1, PTV 2 and PTV 3 will be created.

Delineation of organs at risk (OAR) will be carried out according to Recorad recommendations (Cancer Radiotherapy 2016 S36-S60).

The SROs are as follows:
- Bladder
- Right and left femoral heads
- External genitalia
- Iliacal ridges
- Lumbosacral plexus
- Small and sigmoid intestines will be bypassed in the same block called the peritoneal cavity

❖ **Dose prescription** for each PTV.

There dose prescription will be done in accordance with ICRU criteria 62 and 83 (international standards for radiation units & measurement-Volumes for Prescribing, recording, and Reporting Photon-Beam Intensity-modulated Radiation Therapy -IMRT)
- The dose is prescribed at the median PTV
- 95% of the volume should receive 95% of the dose
- 98% of the volume should receive at least 90% of the dose

- 3% of the volume should not receive more than 107% of the dose.

The dose prescription will be validated by carrying out dose-volume histograms.

- **For tumors stage T2 of more than 4 cm, T3, T4 N0**
  - The primary tumor, i.e **PTV 1** will receive the dose of 61.20 Gy in 36 fractions of 1.7 Gy (BED of 59.70 Gy for alpha/beta 10) over a spread of 50 days
  - The N0 lymph node sites, i.e. the **PTV 3** will receive the dose of 54 Gy in 36 fractions of 1.5 Gy (BED of 51.80 Gy for alpha/beta 10) over a spread of 50 Days

- **For a tumor with T1-4 N+ lymph node involvement (pelvic and/or inguinal)**
  - The primary tumor, i.e **PTV 1** will receive the dose of 61.20 Gy in 36 fractions of 1.7 Gy over a spread of 50 days (as previously specified).
  - The lymph nodes considered invaded on the imagery, i.e. the **PTV 2** will receive the dose of 57.60 Gy in 36 fractions of 1.60Gy (BED of 55.70 Gy alpha/beta 10) on the spread studied.

The dose delivered will be established according to the PTV:

Volumes	**Dose**	**Number of fractions**	**Dose/fraction**
PTV1	61.20 Gy	36	1.7 Gy
PTV2	57.60 Gy	36	1.6 Gy
PTV3	54 Gy	36	1.5 Gy

❖ **Dose constraints - Doses reported to SROs**

The proposed dose constraints serve as a basis for optimization in IMRT. The priority remains PTV coverage and the most optimal protection of SROs.
With this in mind, the creation of "ARO – PTV" type structures is permitted to assist in optimization; similarly, ghost structures (or dummies) can be drawn with the aim of conforming the dose to the volume of the PTV.

Dose constraints : ANAL CANAL –IMRT – 01 (RECORAD Usual) C

	α/β	**Dmedian**	**D95%**	**D98%**	**D2%**
PTVs		= Dp	≥ 95% of the	≥ 95% of the Dp	≤ 107% of the Dp
PTV 1		**61.2 Gy**			
PTV 2		**57.6 Gy**			
PTV 3		**54 Gy (1.5Gy/fr)**			

		Dmoy		VXGy < Y% (or cc)	D2%
External Genital Organs	**1**			V30 (< 35%)	
Bladder (Wall)	**2**			V60 = (< 50%) V40 (< 35%)	
Small Intestine	**2**			SCART CAVITY: V15 = (< 830cc) V45 = (< 150cc)	Surround the entire peritoneal cavity
Iliac bone	**3**			V40 = (< 37%)	
Femoral Heads	**3**			V50 = (< 10%)	
Lumbosacral Plexus	**3**				(D2% < 50Gy)
Colon				V30= (<200cc) V35 = (<150cc) V45 = (<20cc)	

Definitions ICRU 83	
PTV	Dp: Prescription dose at the median (Dmedian = D50%) D95% ≥ 95% of the Dp: 95% of the volume of the PTV should receive more than 95% of the prescribed dose **OR** D98% ≥ 95% of the Dp: 98% of the volume of PTV should receive more than 95% of the prescribed dose 2% of the volume should not receive more than 107% of the dose
OAR	Dmoy: Average dose VXGy < Y%: The X Gy dose should not be delivered in more than Y% of the volume of the OAR **OR** DY% < XGy: Y% of the OAR volume should not receive more than X Gy Dmax or Dnear-max = D2% or the dose in 2% of the volume

❖ **Calculation of the treatment plan and optimization**

It will be realized by the TPS (Treatment Planning System) helical tomotherapy.

❖ **Validation from the treatment plan**

It will be based on the analysis of dosimetry, dose-volume histograms of each PTV and organs at risk**.** The priority remains dose homogeneity in the PTV while respecting the rules of ICRU 62, while approaching the dose constraint objectives proposed above for critical organs.

❖ **Daily repositioning check**

Daily monitoring of the patient's repositioning will be carried out by superimposing the scanner carried out under the treatment machine (MVCT) with the reference scanner carried out during the simulation step.

❖ **Observation clinic and follow-up**

The patient will be seen in a monitoring consultation by the radiotherapist doctor on a weekly basis to assess the tolerance of the treatment (NCI-CTC-AE toxicity scale version 4.03).

6.4.3 Procedure and adaptations of radio-chemotherapy treatment

If chemotherapy is stopped for toxicity, radiotherapy will be continued.

The main expected or possible side effects are:

- Affection of the 3 hematological lines
- Nausea, vomiting, anorexia, diarrhea, stomatitis
- Skin toxicity: hand-foot syndrome, alopecia, scaling, pruritus, rash, photosensitization, mucositis
- Rare cases of diffuse interstitial lung disease with mitomycin, to be systematically mentioned in the face of dyspnea, dry cough, hypoxia, and which can progress to fibrosis
- Cardiac toxicity: coronary spasms, rare cases of myocardial infarction or heart failure
- Renal toxicity: moderate renal insufficiency or in the context of hemolytic uremic syndrome (renal insufficiency, hemolytic anemia, thrombocytopenia, micro-angiopathy...)
- Cerebellar ataxia at 5 FU
- Tear hypersecretion

Dose adjustments:

Toxicities will be evaluated and graded according to NCI-CTC v4 criteria.
Dose reductions are planned in the event of toxicities, depending on the grades. If a patient has several types of toxicity, the dose that puts the patient at the least risk will be used. Doses that have been reduced for toxicity should not be increased thereafter. In the event of grade 4 toxicity, the investigator and the patient can discuss stopping chemotherapy together.

Hematological toxicity:

- Use of growth factors and adaptation of doses according to the usual center procedures.
- Transfusion if Hg < 8g/dl and/or poor tolerance
- Delay treatment if PNN< 1500/mm^3 and blister <100G/l, until complete recovery; If there is no recovery within 15 days, definitive cessation of chemotherapy.

Digestive toxicity :

- In case of grade ≥ 2 nausea or vomiting: reinforcement of antiemetic treatment (setron, corticosteroids and/or aprepitant in the next cycle)
- In case of nausea or vomiting grade ≥ 3: reinforcement of antiemetic treatment and reduction of the dose by 25% of the 2 drugs
- In case of grade ≥ 2 diarrhea: symptomatic treatment
- In case of diarrhea grade ≥ 3: symptomatic treatment and dose reduction of 25% of the 2 drugs

- In case of grade 4 toxicity: permanent cessation of chemotherapy

Cutaneous-mucosal toxicity:

- In case of epidermitis and/or mucositis grade ≥ 2: local treatment according to the usual procedures of the centers.
- In case of grade 4 epidermitis and/or mucositis: local treatment, suspension of radiotherapy until return to grade 2 toxicity.

6.4.4 Associated treatments

All symptomatic treatments (antiemetics, anti-diarrheals, local topicals) are authorized and at the discretion of the investigator. Growth factors are not shown in 1^{era} intention but can be administered as secondary prevention.

No other anti-tumor treatments will be used other than those in the study.

The yellow fever vaccine is contraindicated during chemotherapy.

Cimetidine may increase the blood concentration of 5 fluorouracil and its use should be avoided. Phenytoin introduced as prophylaxis of the convulsant effect of certain anticancer drugs should be avoided.

7 JUDGMENT CRITERIA

7.1 Main criterion

The main criterion retained is a composite criterion combining both clinical effectiveness and tolerance as proposed by Bryant & Day [29]:

Efficacy is defined by the locoregional control rate 3 months after the end of IMRT by tomotherapy corresponding to the proportion of patients alive without local progression (according to RECIST 1.1 criteria) of the disease 3 months after the end of the radiotherapy.

Tolerance is defined by the proportion of patients without significant toxicities (grade ≥3 according to NCI CTCAE version 4.03) responsible for irradiation breaks.

7.2 Secondary criteria

- Criteria for quality of life and sphincter function
  - Health-related quality of life scores from the EORTC QLQ-C30 questionnaire (version 3.0) and its additional colorectal module QLQ-CR 29
  - Sphincter function assessed by MSK-AF score and by the Vaizey incontinence questionnaire, and the SLOW/SOMA questionnaire for men and women [SLOW/SOMA: Barraclough LH et al. Radiother Oncol; 103:327-32]
- Acute and late toxicities assessed during and after treatment according to the NCI CTCAE version 4.03 (Criteria National Cancer Institute Common Terminology Criteria for Adverse Events)
- Locoregional control rate at 6 and 12 months defined by the proportion of patients without progression of the local disease (assessed by a centralized CT-scan examination and according to RECIST 1.1 criteria),), nor death from any cause (except for metastases at a distance) at 6 and 12 months after the end of radiotherapy
- Duration of tumor response defined by the time elapsed between the first objective response and progression or death whatever the cause

- Colostomy-free survival (CFS) defined as the time interval between the start of treatment and colostomy or death regardless of the cause
- Progression-free survival defined by the time elapsed between the start of IMRT and tumor progression or death whatever the cause,
- Overall survival defined by the time elapsed between the start of IMRT or death regardless of the cause
- Number of radiotherapy discontinuations and total number of days radiotherapy discontinuation, as well as associated reasons,
- Total dose of irradiation and total duration of radiotherapy

8 ASSESSMENT OF VIGILANCE

Vigilance will be conducted in accordance with current regulations. European Regulation No. 2017/745 relating to medical devices entered into force on 05/26/2021 and requires the implementation of new measures concerning test vigilance, including for tests authorized before this date. It introduces new definitions
/

8.1 Definitions

Adverse events

Any harmful manifestation, unintentional illness or injury, or unfortunate clinical sign, including an abnormal laboratory result, in participants, users, or others, in the course of a clinical investigation, whether or not related to the device medical subject to clinical investigation

The nature of each adverse event, the date of occurrence, duration, severity, relationship to treatment, associated treatments and progression will be established. The intensity of adverse events will be rated according to the criteria depending on the pathology studied (CTC-NCIAE rating).

The investigator will need to clarify whether the events are related to research, the products being tested, associated medications, an underlying pathology or another cause.

Serious Adverse Events
Is considered a *serious adverse event (SAE)* any adverse event that caused
a) death;
b) a serious deterioration in the participant's state of health, which is the cause:
- an illness or injury endangering the patient's life;
- a permanent deficiency of an anatomical structure or function;
- hospitalization or extension of the patient's hospitalization;
- a medical or surgical intervention aimed at preventing any illness or injury endangering the patient's life or any permanent deficiency of an anatomical structure or function;
- from a chronic illness;

c) fetal distress, fetal death, congenital physical or mental deficiencies, or congenital malformation.

Some "hospitalization/extension of hospitalization" are not considered serious adverse events:
- **admission for social or administrative reasons**
- **hospitalization predefined by the protocol**
- **hospitalization for medical or surgical treatment scheduled before research**

- **passage to day hospital**
- **hospitalizations for pre-existing, non-aggravated signs and symptoms**

It is therefore not necessary to notify them as SAEs

Medical device (DD) defect:
any defect in the identity, quality, durability, reliability, safety or performance of a medical device under investigation, including any malfunction, error in use or defect in the information provided by the manufacturer

New security development
Any new data that may lead to a reassessment of the benefit and risk ratio of the research or the MD studied, to modifications in the use of this MD, including the investigation procedure, in the conduct of the research, or documents relating to research, or to suspend or interrupt or modify the research protocol or similar research.

8.2 Responsibilities of the investigator

8.2.1 Methods for detecting and collecting adverse events

All adverse events should be investigated, reported and recorded, treated and evaluated.

Adverse events **occurring from the signing of consent will be collected in the CRF, up to 30 days after the last radiotherapy session**

Skin, digestive and urinary toxicities as well as adverse events of other natures considered to be related to radiotherapy must be collected throughout the duration of participation in the study.

Each adverse event observed will be the subject of an individual collection. The intensity of adverse events will be estimated according to the NCI-CTCAE version 4.0 classification (toxicity grades 1 to 5). The intensity of adverse events not listed in this classification will be assessed according to the following qualifiers:

Mild (grade 1): does not affect the patient's usual daily activity
Moderate (grade 2): disrupts the patient's usual daily activity
Severe (grade 3): prevents the patient's usual daily activity
Very Severe (grade 4): imposes resuscitation measures/threatens the vital prognosis
Death (grade 5): Death

The nature of each adverse event and the severity will be established *(see paragraph "SERIOUS adverse event or effect"),* date of onset/end, duration, severity, relationship to treatment and course.

The investigator will need to clarify whether the events are related to research, the products being tested, associated medications, an underlying pathology, disease progression or another cause.

If an adverse event meets the definition of serious adverse event, it must also be notified to the promoter without delay on the dedicated form according to the procedures described in paragraph*Notification of Serious Adverse Events* ".

8.2.2 Notification of Serious Adverse Events and Medical Device Defects

The investigator informs the Clinical Research Unit of all serious adverse events and defects in the medical device **which occur during the study or within 30 days of the last administration of the product.**

All Serious Adverse Events Delayed (**occurring after this 30 day period)** considered reasonably **related** protocol processing(s) or research must be declared without time limit.

The investigator must **notify the promoter without delay (immediately) and no later than 3 calendar days from the moment he becomes aware of it**, all serious adverse events and medical device defects that occurred in the trial, except those identified in the protocol as not requiring immediate notification.
This notification is the subject of a written report and must be followed if necessary by one or more detailed written report(s)).

The investigator will note for each event/defect

- ✓ Its description as clearly as possible according to medical terminology.
- ✓ Intensity,
- ✓ The start and end date of the event,
- ✓ The consequences of possibly stopping the use of the medical device and, if necessary, resuming its use.
- ✓ The measures taken and the need or not for corrective treatment,
- ✓ Its evolution. In the event of a non-fatal event, the progress must be followed until recovery or return to the previous state or stabilization of possible after-effects
- ✓ There **causal relationship** between this event and **the medical device** on trial,
- ✓ There **causal relationship** between this event and the **procedure for implementing the DM, and also the research procedures,**
- ✓ Relevant elements facilitating the evaluation of the case such as: associated pathologies (which may have a causal link with the SAE), medical and family history, results obtained after specific investigations.

To do this, he uses the dedicated study form made available in the Investigator binder, which he completes, dates and signs. He must also attach laboratory results or examination or hospitalization reports providing information on the serious event, including relevant negative results without failing to report these ***anonymous documents,*** so that it does not appear that the patient's initials (1st letter of the last name and 1st letter of the first name), their gender and their date of birth (month/year)***.*** If necessary, he may also send the promoter a copy of the autopsy report.
All these documents will be sent to the vigilance service, mandated by the promoter, according to the procedures listed on the dedicated research form.

Clinical Research Unit, pharmacovigilance unit
pv-cfb@baclesse.unicancer.fr

Additional information may be requested (by email, by telephone or during a visit) by the instructor or the vigilante.

The investigator must document the event as best as possible, if possible give it **medical diagnosis** and establish one causal link between the serious adverse event and research, the products under test, associated medications, underlying pathology, disease progression or other cause.

The investigator immediately communicates to the sponsor additional information concerning serious adverse events as he becomes aware of them.

The investigator must monitor the patient who has experienced a serious adverse event **until resolved**, stabilization at a level deemed acceptable by the investigator or return to the previous state, **even if the patient has exited the trial and inform the sponsor of the progress of the serious adverse event**.

8.2.3 Special cases

8.2.3.1 Adverse Event of Special Interest (AESI)

Any serious or non-serious adverse event that requires special attention and will be specifically investigated. These AESIs must be notified and monitored in the same way as serious adverse events.

There is no AESI for this research

8.2.3.2 Serious adverse event not to be reported immediately

Any event that is part of the natural history of the disease (progression of the disease or hospitalization for progression of the disease) should not be notified to pharmacovigilance on the SAE form but should be reported in the research CRF.

Certain "hospitalization/extension of hospitalization" are not considered serious adverse events and do not require notification to pharmacovigilance (see last paragraph *"SERIOUS Adverse Event or Effect").*

8.2.3.3 Pregnancy case

If a woman begins a pregnancy as part of research or in certain cases if it is her partner who participates in research (medication that can reach the man's seminal lineage), the pregnancy must be declared to the sponsor.
The investigator informs the sponsor (by telephone, fax or email) who will send him a "collection of initial pregnancy data" form. This form must contain the expected date of delivery, contact details of the obstetrician and the maternity ward planned for delivery if the pregnancy continues.
The investigator must follow the patient until the end of the pregnancy or its termination and notify the outcome to the sponsor.
If the outcome of pregnancy falls within the scope of the definition of serious adverse events (spontaneous abortion with hospitalization, fetal death, congenital anomaly, ...) the investigator must follow the IGE reporting procedure.
If it is a paternal exposure, the investigator must obtain the consent of the parturient to collect information about the pregnancy.

8.3 Responsibility of the promoter

8.3.1 Vigilance reference document for determining expected/unexpected nature

It is the promoter who determines the expected/unexpected nature of an event with regard to the reference document

The following adverse effects with regard to radiotherapy will be considered expected by the sponsor:

- Skin toxicity: perineal, inguinal and gluteal radiorepithelitis (radiodermatitis, ulceration)
- Gastrointestinal toxicity: spasms, diarrhea, tenesmus, anal incontinence, bleeding,
- Genitourinary toxicity: dysuria, pollakiuria, hematuria, urinary incontinence, vaginitis, pruritus, impotence

With regard to research procedures and more particularly associated chemotherapies, all adverse effects described in the SPCs of Mytomycin C and 5 Fluorouracil will be considered expected by the sponsor.

8.3.2 Reporting of serious adverse events and device defects by the sponsor to the authorities

The promoter declares:
a) any serious adverse event maintaining, with the MD under investigation, the comparator MD or the investigation procedure, a proven or reasonably conceivable causal link;
b) any defect in a MD that could have resulted in a serious adverse event in the absence of appropriate action or intervention, or if circumstances had been less favorable;
c) any new element concerning an event referred to in points a) and b).

8.3.3 Annual safety report

An annual safety report will be sent to the CPP and the competent authority, taking into account all available safety information. The sponsor will also transmit to the study investigators any information likely to affect personal safety.

8.3.4 New fact

Any new development of interest to research (or the product used) and likely to harm the safety of persons carrying out research will be subject to appropriate urgent security measures and information without delay by the Promoter to the competent authority and the Personal Protection Committee.

9 STATISTICAL CONSIDERATIONS

9.1 Number of topics needed

A two-step Phase II methodology proposed by Bryant and Day will be used, combining both clinical response and toxicity.

With risks αeff = αtox = 5% and a power of 90%, and under the following assumptions:

- Let p1 = 80%, the theoretical acceptable proportion of patients not experiencing toxicity requiring interruption of irradiation with IMRT,
- Let p0 = 60%, the theoretical unacceptable proportion of patients not experiencing toxicity requiring interruption of irradiation,
- A loss of effectiveness of 10% (reference value of 90%; response rate of 80% or less considered unacceptable) is considered unacceptable

14 evaluable patients are needed in the first stage, 60 in total.

To anticipate 10% of non-evaluable patients, we plan to include **66 patients in total** :

- 1^{era} step: 16 patients

- 2th step: 50 additional patients

Following the recent national recall of batches of Mitomycin from Kyowa Laboratories, there were 5 patients who were treated with cisplatin instead of Mitomycin. For the few patients currently undergoing treatment (n=5), we made the decision to **replace Mitomycin with Cisplatin** according to a administration schedule defined above, in order to guarantee optimal care of these patients.

The study population being defined by patients receiving conformational radiotherapy with continuous spreading intensity modulation (SIB-IMRT) combined with chemotherapy with 5-FU and mitomycin-C for the treatment of locally anal canal cancer advanced, we propose to "replace" the 5 patients who received cisplatin. As a result, the number of patients to be included would be increased to **71 patients** instead of 66 patients initially planned.

9.2 Statistical analysis

- **Study populations**

Per protocol: excluded from the per protocol analysis i) are all patients who have stopped, modified or changed their treatment (chemotherapy or radiotherapy) for any reason other than toxicity, ii) as well as patients with missing data for the (s) judgment criterion(s) studied).

Intention to treat (ITT): only patients with missing data for the outcome(s) studied are excluded from the ITT analysis.

- ***Primary endpoint***

Interim analysis after the first step:

It will involve 14 evaluable patients (per protocol analysis). If fewer than 11 of these 14 patients have a clinical response, the trial will be stopped for futility; If toxicities requiring irradiation breaks are observed in at least 7 of these 14 patients, the trial will be stopped due to an unacceptable safety profile. In other cases, the test will continue with step 2.

Final analysis after the second step:

Final analysis after stage 2 (per protocol analysis): 46 additional evaluable patients are required, for a total of 60 evaluable patients. If, among the 60 evaluable patients, at least 57 patients have a clinical response and at most 17 patients present significant toxicities (requiring irradiation breaks), the trial will conclude that the irradiation regimen is tolerable and effective without pause.

- **Secondary endpoints**

General considerations

Qualitative variables will be described using numbers and percentages, quantitative variables using mean (+/- standard deviation) or median and extent if the assumption of normality is not not verified.

The statistical significance threshold is set at 5% for each statistical analysis and confidence interval.

The various analyzes will be conducted per protocol and ITT.

Quality of life and sphincter functions

Given that symptoms and toxicities will be assessed over time and classified according to the NCI CTCAE v4.0, the targeted dimensions of the QLQC30 questionnaire will be the overall quality of life, the 5 functional dimensions as well as the dimension of financial problems, not assessed Moreover.

All dimensions of the questionnaires will be described using descriptive analyses.

For each dimension (quality of life or sphincter function):

- the population analyzed will be all patients for whom at least the inclusion score of the dimension considered is available
- a time to deterioration analysis will be performed considering a clinically important difference of 10 points /100 [30]

- a linear mixed effects model will be used to model the average value of the dimension over time while considering intra-individual correlations
- missing data will be described and a sensitivity analysis will be performed to compare different methods of handling missing data.

Tolerance profile

All toxicities noted between treatment and the end of follow-up will be described in terms i) of type, ii) frequency, iii) delay, iv) relationship to the treatment studied, and v) grade (according to the NCI CTCAE v.4.0 classification)

The cumulative toxicity risk will be analyzed using the Nelson-Aalen estimator over time. An estimate can be made for each minimum grade considered in the analysis (grade 1 or +, grade 2 or +, etc.)

Efficiency and survival

Disease response to treatment will be assessed over time using RECIST 1.1 criteria. At each evaluation time, the proportions of patients in objective response (complete or partial), in stability or in progression will be described.

The locoregional control rate at time t is defined by the proportion of patients without progression of the local disease (at the level of the anus and/or inguinal or pelvic lymph nodes) nor death from any cause (except for distant metastasis) at this time t. [Olivatto, Cancer, 2013]

The different survivals and censored data will be estimated using the Kaplan-Meier method.

Survival without toxicity, without complications or progression (Q-TWIST method)

The Q-TWIST method (*Quality-adjusted Time Without Symptoms and Toxicity*) breaks down survival into three states: uncomplicated time (TWIST, *time without symptoms or toxicity*), time with complications (TOX, *toxicity*) and time in progress until death (REL, *relapse*) and is represented using 3 superimposed survival curves.

Grade 2 toxicities as well as a drop of 10 points /100 to at least one dimension of quality of life or sphincter function will be considered complications.

Prevalence of complications

The wPreval method (*weighted prevalence function*) makes it possible to estimate, over time, the prevalence of complications among living patients who have not relapsed, while considering that complications can be "cured" and then had again [30, 31].

Toxicities of grade 2 or higher as well as a reduction of 10 points /100 to at least one dimension of quality of life or sphincter function will be considered complications and a weighting will be defined for each complication.

10 QUALITY CONTROL

10.1 Independent supervisory committee

The creation of a trial monitoring committee (IDMC = Independent Data Monitoring Committee) will be set up to guarantee the protection of patients, to ensure that the trial is conducted ethically, to assess the benefit/risk ratio of the trial and to ensure independent review of scientific results during or at the end of the trial. The role of this committee is advisory to the Promoter who is responsible for making the final decision to implement the recommendations proposed by this committee

The committee will include a biostatistician, a radiotherapist and an oncologist.

This committee will be consulted:

- Before the start of inclusions;
- To the intermediate analysis after the end of 1^{era} step
- To the final analysis.

For safety reasons, the committee will be informed by the sponsor of all observed toxicities (EI, EIG) for advice. In the event of unacceptable toxicities (in terms of severity and/or frequency), he may propose stopping the inclusions.

10.2 Quality Assurance

10.2.1 Data collection

All information required by the protocol must be recorded in the observation notebooks under the responsibility of the principal investigator and an explanation must be provided for each missing data. The data must be collected as it is obtained, and transcribed into these notebooks in a clear and readable manner.

10.2.2 Monitoring

11 RIGHT OF ACCESS TO SOURCE DATA and DOCUMENTS

11.1 Source data

Source documents being defined as any original document or object making it possible to prove the existence or accuracy of data or a fact recorded during research, will be kept for 15 years by the investigator or by the hospital if it is a hospital medical file.

11.2 Data confidentiality

In accordance with the provisions concerning the confidentiality of data to which persons responsible for quality control of biomedical research have access (article L.1121-3 of the public health code), in accordance with the provisions relating to the confidentiality of information concerning in particular the people who take part in the research and the results obtained (article R. 5121-13 of the Public Health Code), persons with direct access will take all necessary precautions to ensure the confidentiality of information relating to persons who are involved in the research and in particular with regard to their identity as well as 'to the results obtained.

These people, like the investigators themselves, are subject to professional secrecy (according to the conditions defined by articles 226-13 and 226-14 of the penal code).

During the research or at its conclusion, the data collected on the people who are involved in it and transmitted to the promoter by the investigators (or any other specialized stakeholders) will be made anonymous.

The promoter will ensure that each person who takes part in the research has given their written consent for access to individual data concerning them and strictly necessary for quality control of the research.

12 ETHICAL AND REGULATORY CONSIDERATIONS

The study will be conducted in accordance with:

- to Law n° 2004-801 of August 6, 2004 relating to the protection of individuals with regard to the processing of personal data and amending Law n° 78-17 of January 6, 1978 relating to data processing, files and freedoms;
- the provisions of article L1121-1, second paragraph of the public health code relating to research aimed at evaluating routine care.

The research protocol will be submitted for opinion to the North-West III Personal Protection Committee.

Patients will be informed completely and fairly, in understandable terms, of the objectives and constraints of the research, the possible risks involved, the necessary surveillance and security measures, their rights to refuse to participate in the research or the possibility of withdrawing at any time.

All this information appears on an information and consent form given to the patient. The patient's free, informed and written consent will be obtained by the investigator, or a doctor representing him, before final inclusion in the study. A copy of the information and consent form signed by both parties will be given to the patient, the other copy will be kept by the investigator. For any substantial modification of the protocol, concerning the objectives of the research, its plan, population, examinations or significant administrative aspects, new consent from the persons participating in the research will be obtained if necessary.

13 DATA PROCESSING AND RETENTION OF DOCUMENTS AND DATA

13.1 Data entry and processing

Data entry and management will be carried out by the Data Processing Center (CTD) of the Cancéropôle Nord-Ouest. The CTD provides a database management software package dedicated to clinical research: *Capturesystem™* (version 5.05.4005, CLINSIGHT company, France).Access to the application is via a VPN link (*Virtual Personal Network*) secure.

This software package, which is based on a database architecture *Oracle™*, is designed for the overall management of clinical and epidemiological studies, meets the regulatory requirements related to this type of study. A data validation plan will be developed and will describe in detail the checks to be performed for each variable as well as the list of obvious corrections allowed.

A study-specific database will be created, tested and validated before entry begins.

The questionnaires will be completed in the form of an electronic questionnaire (decentralized entry possible). The data will then be checked by the management team using error messages from validation programs. Obvious errors will be corrected. Other errors, omissions or inconsistencies will be noted on correction request forms which will be sent to the investigator for resolution. As soon as the response is received, the corrections will be included in the database.

The database will be frozen after final quality control and then exported to the statistical software *Stata™* (StataCorporation, College Station, USA) according to an automated and validated procedure.

13.2 Committee for the Protection of Persons (CPP)

The protocol, the information and consent form will be submitted by the promoter for opinion to the Personal Protection Committee.

13.3 Competent authority

An authorization request will be sent by the Promoter to the Competent Authority (ANSM) before the start of the study.

13.4 Archiving

The promoter will ensure the archiving of essential documents on the conduct of the study under conditions ensuring their safety, for the minimum period provided for by Good Clinical Practices, i.e. 15 years after the end of the research.

These documents are: the protocol and its annexes, including possible amendments; signed original information forms and consents; questionnaires; monitoring documents; statistical analysis reports.

14 PUBLICATION RULES

The results of this study, owned by the promoter (Centre François Baclesse), will be published in the form of scientific articles. Publications concerning or resulting from this research will be communicated and submitted for rereading by the study coordinators to all investigators.

The authors will include the investigators who included the most patients, the biostatistician who carried out the data analysis, the project manager as well as the participants who made a substantial contribution to the development of the study, the analysis and the interpretation of the results and/or the writing of the manuscript.

Publication rank will be defined based on the investment provided in developing and conducting the study.

This work will be the property of all authors and will be made available to them for the production of communications and transversal publications.

Publications relating to the results of possible additional studies will be subject to the prior agreement of the coordinating investigator and the methodologist; they will be subsequent to the publication of the main study, which must be cited as a reference.

15 FINANCING AND INSURANCE

Any additional costs referred to in the Public Health Code are the subject of an agreement negotiated between the François Baclesse Center and the representative of the establishment, taking into account the financial means available to the François Baclesse Center as part of its activity public promotion.

However, the François Baclesse Center ensures the organization of the study and takes charge of providing the following equipment (protocol, observation notebook, investigator file) necessary for conducting the study.

In the event that materials or treatments are provided by other partners, the conditions must be specified in the study agreement.

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