A phase I dose escalation trial using intensity-modulated radiotherapy with simultaneous integrated boost in pelvic chemoradiotherapy for metastatic rectal cancer

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Research

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Abstract

Background

In unresectable metastatic rectal cancers, the surgery of the primitive tumor remains highly debated. Chemoradiotherapy (CRT) of the primitive could allow sufficient local control in order to avoid major and sometimes mutilating surgery. Dose escalation during CRT could increase this local control. The aim of this study was to evaluate the feasibility and tolerance of a CRT with radiation dose escalation delivered in intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB), in metastatic low and middle rectal cancers.

Methods

This multicenter phase I study included six patients treated for unresectable synchronous metastatic low and middle rectal adenocarcinoma in two dose levels. Radiotherapy was delivered using IMRT with SIB. The dose escalation was 52.5 Gy (level 1) and 56.25 Gy (level 2) in the primary tumor, in 25 fractions of 2.1 Gy and 2.25 Gy, respectively. High-risk clinical target volume (CTV) and low-risk CTV received respectively 50 Gy and 45 Gy in 25 fractions in the two levels. Concomitant chemotherapy was oral capcitabine and CRT was performed after four cycles of mFOLFOX6 chemotherapy. The dose-limiting toxicity (DLT) was defined by a toxicity requiring the interruption of radiotherapy for more than five consecutive fractions.

Results

All six patients received the full course of treatment at scheduled doses. No patients had acute toxicity requiring interruption of radiotherapy therefore no DLT has been reported. No patients had acute toxicity ≥ 3. Concerning late toxicity, three patients experienced grade 3. After CRT, four patients had a partial response and one patient had a complete clinical response. Two patients were considered in local progression at 9.4 months and 20.4 months of inclusion.

Conclusions

Dose escalation at 56.25 Gy in the tumor lesion was possible with good acute tolerance. It needs to be evaluated in a larger study. It could allow sufficient local control in order to avoid mutilating surgery in these metastatic patients.

Trial registration

NCT03634202. Registered 16 August 2018 – retrospectively registered, https://www.clinicaltrials.gov/ct2/show/NCT03634202

Background

The management of metastatic rectal cancer depends on the resectability of the metastases. In cases of resectable metastases, a rectal conventional chemoradiotherapy (CRT) or an exclusive short radiotherapy (5 X 5 grays (Gy)) is proposed, then surgery of the primitive and metastases will be performed according to a strategy discussed in a multidisciplinary team. In case of unresectable metastases, the treatment is based on a systemic treatment by chemotherapy with reassessment of the resectability. The benefits of systematic surgical management of the primitive in terms of overall survival, progression-free survival, local complications, remain highly debated in unresectable synchronous metastatic patients. If the primitive in place becomes or remains symptomatic, a CRT can be proposed. In case of good local response and in order to preserve the quality of life, surgical abstention may be considered, especially in case of mutilating surgery. Indeed, several studies have shown the possibility of a surgical abstention after a complete response after CRT, including in non-metastatic patients. The complete response usually occurs within 10 to 12 weeks after the end of CRT but may sometimes occur after several months. This argument is in favor, particularly in metastatic patients, of a wait-and-see attitude and local monitoring after CRT. A salvage surgery may then be proposed in case of local evolution or symptoms.

However, the rates of complete response and local control remain too low to allow surgical abstention in the majority of patients. Increasing the dose delivered during CRT could increase the overall response rate. In metastatic patients, this dose escalation could provide a local control and avoid major surgery such as abdominoperineal amputation.

The objective of this study was to evaluate the feasibility and tolerance of a CRT with radiation dose escalation delivered by intensity-modulated radiation therapy (IMRT) with simultaneous integrated boost (SIB), in patients with an unresectable synchronous metastatic low or middle rectal cancer.

Patients and Methods

Study design

The design of this prospective non-randomized, multicenter, phase I study is reported in Fig. 1. It was based on three dose levels. According to the modified Fibonacci method (3 + 3 design), the number of patients required was three to six patients for each dose level (Fig. 2). The escalation of dose at the next level was conditioned by the absence of limiting toxicity. Dose-limiting toxicity (DLT) was defined as the occurrence of toxicity requiring a radiotherapy discontinuation of more than five consecutive fractions. In the absence of DLT observed in the three patients of the current level, three new patients were then included at the next dose level. If one of the three patients in the current stage had a DLT, three additional patients were included at the same level. If no new DLT was observed among these three additional patients (ie one DLT on all six patients), then the dose escalation to the next level was allowed. If two or more DLT were observed among the six patients included in the same level, this dose level was then considered the maximum tolerated dose (MTD) and three new patients were included at the lower dose level.
The maximum recommended dose (MRD) was defined as the level immediately below the level at which two toxic limiting doses (DLTs) occurred or the last level if two DLTs did not occur.

Patients

Patients included in the study had histologically confirmed lower or middle rectum adenocarcinoma, with synchronous metastases deemed unresectable. They must be over 18 years old, have an estimated life expectancy of more than three months, a performance status according to WHO from 0 to 2. They should not have received previous treatment with pelvic radiotherapy or chemotherapy, have a complete deficiency of dihydropyrimidine dehydrogenase (DPD), have a severe or unstable disease, or have diarrhea or neuropathy grade ≥ 2 at baseline.

Intervention

Chemotherapy

Before CRT, patients received four cycles of mFOLFOX6 chemotherapy administered every two weeks. This induction chemotherapy could be combined with targeted therapy (bevacizumab, cetuximab, panitumumab) based on KRAS / NRAS status. CRT started within two to four weeks after these four cycles of mFOLFOX6. Concomitant chemotherapy consisted of capecitabine at a dose of 800 mg / m² twice daily, five days a week. Targeted therapies were not allowed during radiation therapy. First-line metastatic chemotherapy was resumed after the end of CRT.

Radiation therapy

Irradiation was delivered in intensity modulated radiotherapy (IMRT) with simultaneous integrated boost (SIB) (Fig. 3). The treatment was delivered in 25 fractions, five per week, and one per day, over five weeks. The gross tumor volume (GTV) was defined using pre-chemotherapy 18FDG positron emission tomography (PET), ensuring concordance with clinical examination, rectoscopy, endorectal ultrasound, computed tomography (CT) and pelvic magnetic resonance imaging (MRI).

The dose escalation involved increasing the dose in GTV from 52.5 Gy to 60 Gy in fractions of 2.1 to 2.4 Gy, respectively, over the three dose levels (Table 1).

| Level | LR-CTV | HR-CTV | GTV  |
|-------|--------|--------|------|
| 1     | 45 Gy (1.8) | 50 Gy (2) | 52.5 Gy (2.1) |
| 2     | 45 Gy (1.8) | 50 Gy (2) | 56.25 Gy (2.25) |
| 3     | 45 Gy (1.8) | 50 Gy (2) | 60 Gy (2.4) |

The high-risk clinical target volume (CTV-HR) received a dose of 50 Gy (2 Gy per fraction). It corresponded to GTV with a margin of 10 mm excluding unaffected organs (prostate, uterus, vagina, bladder, and sacrum).

The low risk CTV (CTV-LR) received a dose of 45 Gy in 25 fractions (1.8 Gy per fraction). It included mesorectum, internal iliac ganglionic areas and high risk CTV, with the following limitations (Appendix 1): cranial: junction S1 / S2 (possibly S2 / S3 for a lesion of the lower rectum N0); dorsal: concavity of the sacrum (not including foramen); ventral: prostate in men, uterus and rectovaginal septum in women, bladder, ureters; lateral: pelvic wall; caudal: 4 cm under the GTV (pre-chemotherapy). For low-rectal tumors, CTV-LR was extended to ischiorectal fossae (entire anal canal with a margin of at least 10 mm) to the coccyx back. The anal canal was excluded for a lesion of the middle rectum. The anal margin was excluded, except in case of massive invasion of the anal canal.

The planning target volume (PTV) was defined by an automatic margin of 5 to 7 mm around previous volumes: PTV 1 = CTV-LR + 5–7 mm; PTV 2 = CTV-HR + 5–7 mm; PTV 3 = GTV + 5–7 mm. PTV 3 was therefore the volume receiving the highest dose by SIB (from 52.5 Gy to 60 Gy at 2.1 to 2.4 Gy per fraction depending on the level).

Dosimetry followed the recommendations of ICRU 83. Image-guided radiation therapy was mandatory with daily image guidance. 3D imaging was recommended, at least for the first fractions.

Evaluation

The primary objective of the study was to determine the maximum recommended dose of radiotherapy delivered in IMRT with SIB during CRT. The primary endpoint was dose-limiting toxicity (DLT), defined as the occurrence of toxicity requiring cessation of radiation therapy for more than five consecutive fractions.

The secondary objectives were: acute (up to 3 months after the end of CRT) and late toxicity according to NCI-CTCAE V4.0; the local response; local progression-free survival at 12 months; 2-year overall survival; local surgery; the quality of life assessed by the QLQ-C30 and QLQ-CR29 questionnaires at inclusion, at the end of treatment and at follow-up.
Patients were followed clinically and biologically every two weeks during induction chemotherapy and weekly during CRT. An interim assessment was performed in the four weeks prior to CRT, including CT and 18FDG PET-CT. An end-of-treatment assessment was made within six weeks of the end of CRT, including clinical and biological evaluation, rectal echo-endoscopy (or rectoscopy), CT, pelvic MRI, 18FDG PET-CT, quality of life questionnaires. Then follow-up was done at 12 weeks and then every eight weeks for two years with at least a TAP CT scan, a biological assessment and quality of life questionnaires.

Ethics

This study received a favorable opinion from the committee for the protection of persons (CPP) (17 February 2014) and was authorized by the national agency for the safety of medicines (ANSM) (first April 2014). An independent committee has been appointed. All patients received from oral and written information, and signed a consent. The study was retrospectively registered on ClinicalTrials.gov (NCT03634202) (https://www.clinicaltrials.gov/ct2/show/NCT03634202) (16 August 2018).

Results

Primary objective

A total of seven patients were included in the trial between May 2015 and February 2017 in our institution. One patient was wrongly included and excluded from the study because he did not meet the inclusion criteria (grade 2 diarrheas at baseline) and was progressing before CRT. Finally, three patients were included in level 1 and three in level 2. No patients were included in level 3. The characteristics of the population and initial disease are detailed in Table 2. The median follow-up was 27.4 months.

Table 2
Characteristics of the population and the initial disease

| Patient | Sex | Age | PS | TNM      | Tumor size (MRI) | Localization          | Localization comment | Metastatic sites                           |
|---------|-----|-----|----|---------|------------------|-----------------------|---------------------|--------------------------------------------|
| 1       | M   | 75  | 1  | T3N0M1  | NA               | Middle and high rectum | 7 to 15 cm from the anal margin (endoscopy) | Liver, lungs                |
| 2       | F   | 62  | 1  | T4N2M1  | 35 mm high + 5 cm lateropelvic mass | Middle rectum | 5 cm from AM (clinical) | Liver, peritoneum             |
| 3       | F   | 66  | 1  | T4N2M1  | 47.5 x 42.5 x 31.5 mm | Low rectum | inf.: AM (endoscopy) (3 cm from AM on RMI) sup.: 15 cm from AM (endoscopy) | Lungs, bilat. pararectal, presacral, mediastinal lymph nodes |
| 4       | F   | 59  | 0  | T3N1M1  | 66 x 35 mm       | Middle and high rectum | Non-passable lesion; MRI: middle and high rectum with wall thickening up to 11 mm | Lungs                        |
| 5       | M   | 61  | 1  | T4N2M1  | 12 cm high       | Low, middle and high rectum | Sup.: 8 cm from the AM to the pectineal line (endoscopy) | Liver, lungs, inguinal lymph nodes |
| 6       | M   | 69  | 1  | T3N2M1  | 8 cm high 36 x 24 mm | Middle and high rectum | 8 to 15 cm from the AM (endo.) | Liver                        |

AM: anal margin; bilat.: bilateral; F: female; inf.: inferior; M: male; PS: performance status; sup.: superior

All six patients enrolled received four cycles of chemotherapy mFOLFOX6 and the entire CRT at the recommended doses (Table 3). Doses to organs at risk have been respected, except for two patients where the dose to the peritoneal cavity was slightly exceeded with for the first patient a V50Gy at 23 cubic centimeter (cc) (vs ≤ 15 cc) and V40Gy at 287 cc (vs ≤ 150 cc), and for the second patient a V50Gy at 92 cc and V40Gy at 175 cc. The duration of radiation therapy was 35 to 39 days. No patient had acute toxicity requiring interruption of radiotherapy for more than five consecutive fractions. No DLT was therefore reported. In the absence of inclusion in level 3 and in the absence of DLT, the maximum recommended dose was therefore level 2, ie a dose escalation of 56.25 Gy in 25 fractions of 2.25 Gy in SIB in GTV, 50 Gy in 25 fractions of 2 Gy in CTV-HR and 45 Gy in 25 fractions of 1.8 Gy in the CTV-LR.
Table 3
Treatments and patient follow-up

| Patient | Chemotherapy | Radiotherapy | Evaluation | Objectives |
|---------|--------------|--------------|------------|------------|
|         | Number of Folfox cycles before CRT | Associated targeted therapy | Dose level | Technique | Duration of radiotherapy (Days) | Report for toxicity | After CRT (endoscopy) | Weeks since the end of the CRT | Dose-limiting toxicity | Local progression | Months since inclusion |
| 1       | 4             | Non          | 1          | Tomotherapy | 36         | No | Partial response | 6,8 | No | No | - | - |
| 2       | 4             | Non          | 1          | Static IMRT | 39         | No | Complete response | 5,6 | No | No | - | - |
| 3       | 4             | bevacizumab (C3 and C4) | 1          | Tomotherapy | 37         | No | Partial response | 4,7 | No | Yes | 20,4 | I
| 4       | 4             | bevacizumab (C1 to C4) | 2          | Tomotherapy | 38         | No | Partial response | 0,6 | No | Yes | 9,8 | I
| 5       | 4             | panitumumab (C1 to C4) | 2          | Tomotherapy | 35         | No | NA | - | No | No | - | - |
| 6       | 4             | Non          | 2          | Tomotherapy | 38         | No | Partial response | 5,7 | No | No | - | - |

NA: non available

Secondary objectives

Acute tolerance of treatment was good with no acute toxicity ≥ 3 (Table 4). Of the six patients, four showed an acute gastrointestinal toxicity grade 1, and one patient a grade 2. On the urinary side, two patients had acute grade 1 toxicity and one patient grade 2. Note also grade 1 hematological toxicities in five patients and grade 2 in one patient, and also grade 1 neurotoxicity in two patients, to be related to chemotherapy prior to CRT.

Table 4
Acute and late toxicity

| Patient | Acute toxicity (all grades) | Late toxicity (G ≥ 3) |
|---------|-----------------------------|----------------------|
|         | GI | GU | Abdo-pelv. pain | Hematologic | Neurotoxicity | GI | GU | Other | Time from end of CRT (months) |
| 1       | 1  | 0  | 1               | 0           | -         | -   | -   | - | - |
| 2       | 1  | 1  | 1               | 0           | -         | -   | -   | - | - |
| 3       | 2  | 2  | 2               | 1           | G3 Pre-occlusive syndrome | - | G3 Pelvic pain | 3,9 |
|         |    |    |                 |             |           |     | G3 Neurotoxicity |   |
| 4       | 0  | 1  | 1               | 0           | -         | -   | -   | G3 Pelvic pain | 4,1 |
| 5       | 1  | 1  | 1               | 0           | -         | G3 recto-vesical fistula (suprapubic catheter) | - | 12,9 |
| 6       | 1  | 0  | 1               | 1           | -         | -   | -   | - | - |

Toxicities graded according to NCI-CTCAE V4.0.

abdo-pelv.: abdominopelvic; GI: gastrointestinal; GU: genitourinary.

Regarding the late toxicity, 3 patients presented a grade 3. The first patient, included in level 1, developed pelvic pain and pre-occlusive syndrome 3.9 months after the end of CRT, requiring a colostomy. The second patient, included in level 2, presented pelvic pain 4.1 months after the end of RT-CT, management resulted in a colostomy and later posterior pelvectomy. The third patient, enrolled in level 2, presented a recto-vesical fistula 12.9 months after the end of CRT, requiring a suprapubic catheter. Note also grade 3 neurotoxicity in one patient to relate to oxaliplatin.

On the endoscopic evaluation after CRT, four patients had a partial response, one patient had a complete response, and one patient was not evaluable.
Of the six patients, two patients were classified in local progression. The first, included in level 1, has been classified as progressive on PET-CT at 20.4 months of inclusion. However, the biopsies did not show any carcinomatous proliferation but only fibrous and cicatricial changes. During the follow-up, he had no local complications and no need for surgical management. The second patient, included in level 2 and considered in local progression at 9.8 months of inclusion on PET-CT, was finally operated by posterior pelvectomy. It was probably a false positive because the surgical specimen did not show any tumor infiltration but only cicatricial changes. The other four patients did not show any local progression during their follow-up. For the two patients classified in local progression, CRT allowed to increase local control compared with metastatic disease. Indeed, local progression-free survival was increased to 20.4 and 9.8 months compared with distant progression-free survival at 14.1 and 4.3 months, respectively.

Regarding overall survival, five out of six patients were alive at 2 years of inclusion. At the time of the analysis, three patients had died with an overall survival ranging from 14.6 to 32.8 months.

Quality of life scores provided a qualitative assessment of several dimensions. The functional score for physical activity was improved between inclusion and the end of CRT for four out of six patients, a patient was stable, and one patient had a decrease just after CRT before increasing to a higher level than baseline. Pain appeared to decrease after CRT compared to baseline (Fig. 4). Patients with digestive symptoms at inclusion such as diarrhea, flatulence, faecal incontinence, were improved at the end of CRT (Fig. 5). Two patients with no diarrhea at baseline experienced this symptom increase at the end of CRT before normalizing at the next assessment.

**Discussion**

This trial showed that a dose escalation with a SIB-IMRT technique for CRT of rectal cancer is possible at a dose of 56.25 Gy in the tumor lesion with good acute tolerance. Indeed, no interruption of radiotherapy and no grade ≥ 3 of acute toxicity was reported. The SIB technique made it possible to increase the dose without increasing the duration of the CRT. The good tolerability and the conserved duration of CRT allowed early resumption of first-line metastatic chemotherapy after CRT. Nevertheless, three patients had late Grade 3 toxicity. Of these three patients, two had received anti-angiogenic treatment (bevacizumab) and one anti-EGFR treatment (panitumumab) with chemotherapy prior to CRT. The other three patients without reported late toxicity, had received chemotherapy by mFOLOX without targeted therapy associated before CRT. The other three patients without reported late toxicity had received chemotherapy by mFOLOX without targeted therapy associated before CRT. The involvement of these targeted therapies, administered just prior to CRT, needs to be assessed in terms of toxicity. The patient with recto-vesical fistula had undergone colostomy surgery before inclusion in the trial. It should also be remembered that the included population is that of metastatic patients, with heavy treatments, and are potentially more fragile and prone to complications. Patients in the study also had advanced tumors (T3 or T4) with large volumes to irradiate. Patients with a less advanced disease could potentially benefit from higher dose escalation in a smaller volume, with good acute and late tolerance.

The dose escalation presented in the study provided good local control of the disease. Indeed, four out of six patients did not show any local progression and for the two patients classified in local progression, the histology was negative and the local progression was later than the distant progression. This dose-escalation CRT strategy could provide sufficient local control in metastatic patients to avoid heavy and mutilating surgery throughout their management.

This study has several limitations. First, it was a phase I feasibility study, the size of the population was therefore reduced. It is necessary to evaluate the dose escalation retained in a phase II study with a larger population. Then there was no inclusion in level 3. The trial was prematurely closed due to the difficulty of including the target population, which can be explained by competitiveness with other clinical trials, and acceptable follow-up in included patients who had good tolerance and control in level 2. Regarding local control, the lines of chemotherapy can also participate, with a possible bias on the evaluation of control provided by the CRT. However, local control was superior to distant control, and the two treatment modalities are involved in the objective of surgical abstention in this population. Another limitation is the assessment of patients. The original schedule has not been applied in full. Indeed, an amendment has been made to lighten the monitoring schedule which was heavy in these metastatic patients treated by chemotherapy. Similarly, not all quality of life questionnaires were completed during the entire follow-up.

In the literature, the principle of increasing the radiation dose in rectal cancer was already discussed in three-dimensional conformal radiotherapy (3D-CRT)\(^{12}\). The development of IMRT in recent years has facilitated its development through the SIB\(^{14}\). An additional dose delivered by SIB-IMRT, for an equivalent total dose, appears less toxic than a complement by 3D-CRT, but without increasing the local response rate\(^{15}\).

Dose escalation appears to increase local response rate and pathologic complete response\(^{11}\). The dose escalation with a SIB-IMRT technique therefore seems promising on local control, while maintaining a good tolerance\(^{16}\). However, its benefit on the increase of the pathologic complete response is not yet provided. The retrospective study of Yamashita et al. showed a nonsignificant increase at 17% (vs. 11%, p = 0.39) of pathologic complete response rates in non-metastatic patients who received 55 Gy in SIB-IMRT, compared to 50.4 Gy in 3D-CRT\(^{17}\).

Delivering chemotherapy before the CRT has several interests. In our population of metastatic patients, it provides a global and rapid control of metastatic disease. It also has an effect on the local disease with a partial local response on the assessment before CRT in our population. Neo-adjuvant chemotherapy combined with CRT may increase the local response, also in non-metastatic patients. The study by Garcia-Aguilar et al. found an increase in the rate of pathologic complete response in locally advanced tumors to 18%, 25%, 30% and 38% by completing the CRT with zero, two, four, and six cycles of mFOLFOX6, respectively\(^{18}\).

In some patients, the tumor response may be longer after the CRT\(^{10}\). The study by Sloothaak et al. showed that out of 1,593 patients managed by preoperative CRT, the pathological complete response rate was maximal when surgery was performed at 14 weeks from the start of CRT, with a maximum plateau appearing to be reached at 17 weeks\(^{19}\). Shift surgery at 15 or 16 weeks after the start of the CRT (ie 10–11 weeks after the end of CRT) could increase the
pathologic complete response rate. In a perspective of preservation, also in non-metastatic patients, this is an argument to wait for a complete clinical response up to 17 weeks from the beginning of the CRT before considering mutilating surgery. Indeed, studies of Habr-Gama et al. and Maas et al. have shown the possibility of preservation in non-metastatic patients\(^1,^2\). Patients with low rectal cancer presenting a complete clinical response after CRT were not operated and were closely monitored. Comparison of these monitored patients with operated patients with a complete histological response found no significant difference in progression-free survival and overall survival.

The Appelt et al study combines the different principles mentioned above, ie a multimodality radiation dose escalation associated with a desire for preservation through a wait and see attitude in patients with complete clinical response\(^2\). It proposed a dose escalation with SIB-IMRT at 60 Gy, with an additional 5 Gy in brachytherapy in patients with T2-T3, N0-N1 of the lower rectum. Of the 55 patients included, 40 patients had a complete clinical response and were actively monitored. The local recurrence rate at 1 year was 15.5%. The treatment was generally well tolerated with the preservation of a good sphincter function in the monitored patients. The combination of different strategies to increase the complete response rate (radiation dose escalation by SIB-IMRT, brachytherapy, neoadjuvant chemotherapy, repeated evaluation of the response over time) could potentially increase the number of patients eligible for sphincter preservation and surgical abstention.

**Conclusion**

Radiation dose escalation in the CRT of low and middle rectal cancer was possible with good acute tolerance at a dose of 56.25 Gy in the tumor lesion using SIB-IMRT. It allows a good local control on the studied follow-up. Future studies with larger populations are needed to assess this dose escalation with the aim of avoiding major surgery in these metastatic patients. In future trials, this dose escalation could also be evaluated in order to increase the clinical complete response and avoid mutilating surgery in non-metastatic patients.

**Abbreviations**

- CRT: chemoradiotherapy
- CT: computed tomography
- CTV-HR: high-risk clinical target volume
- CTV-LR: low risk clinical target volume
- DLT: Dose-limiting toxicity
- DPD: dihydropyrimidine dehydrogenase
- IMRT: intensity-modulated radiation therapy
- GTV: gross tumor volume
- Gy: grays
- 18-FDG PET: 18 fluoro-deoxy-glucose positron emission tomography
- MRI: magnetic resonance imaging
- MTD: maximum tolerated dose
- PTV: planning target volume
- SIB: simultaneous integrated boost
- 3D-CRT: three-dimensional conformal radiotherapy

**Declarations**

**Ethical Approval and Consent to participate:**

This study received a favorable opinion from the committee for the protection of persons (CPP) (17 February 2014) and was authorized by the national agency for the safety of medicines (ANSM) (first April 2014). An independent committee has been appointed. All patients received from oral and written...
information, and signed a consent. The study was retrospectively registered on ClinicalTrials.gov (NCT03634202) (https://www.clinicaltrials.gov/ct2/show/NCT03634202) (16 August 2018).

Consent for publication:
All authors read and approved the final manuscript

Availability of supporting data:
The datasets during and/or analysed during the current study are available from the corresponding author on reasonable request.

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Author's contributions:
Amaury Paumier and Valérie Seegers: protocol redaction and methodology
Thibaut Lizée and Amaury Paumier: results analyses and writing the article
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Damien Autret: dosimetry

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Figures

Figure 1

Study design
Figure 2

Dose escalation methodology according to the modified Fibonacci method called "3 + 3". DLT: Dose-limiting toxicity
Figure 3

Dose distribution in IMRT with SIB-IMRT Treatment plan with visualization of the dose distribution in color wash from 42.75 Gy (95% of the prescribed dose at PTV 1) to 58.09 Gy (maximum dose) with dark blue, sky blue and orange outline, respectively PTV 1, PTV2 and PTV 3. A: Axial section B: Dose-volume histogram of PTV 1 (sky blue), PTV 2 (dark blue), PTV 3 (purple) used to report the dose received (abscissa) by a percentage of PTV volume (ordinate) C: Coronal section D: Sagittal section
Figure 4
Symptoms according to QLQ-C30 The first assessment was performed at inclusion, the second after RT-CT.
Figure 5

Symptoms according to QLQ-CR29 The first assessment was performed at inclusion, the second after chemoradiotherapy.