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par

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TITRE

Résultats et effets secondaires de la radio-chimiothérapie néo adjuvante pour les cancers localement avancés du haut rectum: une étude rétrospective

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

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ABBRÉVIATIONS

- **3DCT: Three Dimension Conformal Radiotherapy**
- **CHU: Centre Hospitalier Universitaire**
- **CRT : Chemoradiotherapy**
- **CT : Computed Tomography**
- **CTCAEv5: Common Terminology Criteria for Adverse Events version 5**
- **D5: Minimal dose received by 5% of an organ at risk**
- **EUS : Endorectal Ultrasound**
- **Gray or Gy: Unit of radiation dose in the International System (SI), expressed in terms of absorbed energy per mass of tissue (Joule/kilogram)**
- **IMRT : Intensity Modulated Radiotherapy**
- **LARC : Locally Advanced Rectal Cancer**
- **MRI : Magnetic Resonnance Imaging**
- **OS: Overall Survival**
- **PFS: Progression Free Survival**
- **RECIST: Response Evaluation Criteria In Solid Tumors**
- **TME : Total Mesorectal Excision**
- **V30: Percentage of volume that receives 30 Grays or more**
- **V40: Percentage of volume that receives 40 Grays or more**

TABLE DES MATIÈRES

I. GÉNÉRALITÉS

Epidémiologie :

Dans une étude internationale s'appuyant sur les données de GLOBOCAN (Global Cancer Observatory) couvrant 185 pays, il a été estimé qu'en 2018 le cancer du rectum était le 8ème cancer dans le monde en terme d'incidence (fréquence des cas dans la population) et le 10ème en terme de mortalité (fréquence de décès causés par la maladie dans la population). En effet, on recense respectivement un nombre de 704 000 nouveaux cas et 310 000 décès par an dans le monde.[1]

Selon une étude de l'American Cancer Society, en 2018 le cancer colorectal a été diagnostiqué aux États –Unis chez 40% des patients à un stade local, chez 35% des patients à un stade loco-régional et chez 19% des patients à un stade métastatique. Dans la même étude, la probabilité de survie à 5 ans pour les stades localisés est de 90%, pour les stades loco régionaux de 71% et chute à 14% pour les stades métastatiques. Le ratio hommes – femmes en terme d'incidence est d'environ 1.3. L'âge au diagnostic est autour de 68 ans pour les hommes et 72 ans pour les femmes.[2]

En France, selon les mêmes données de GLOBOCAN en 2018, le cancer du rectum était (en comparaison) le 7ème cancer en terme d'incidence et le 12ème en terme de mortalité. Ce qui représente respectivement un nombre de 15 441 nouveaux cas et 4 988 décès.[3]

En France également, un dépistage est organisé entre 50 et 74 ans tous les 2 ans pour les patients sans antécédents particuliers et sans facteurs de risques. D'autres modalités de dépistages s'appliquent pour les autres cas.[4]

Au moment du diagnostic, l'adénocarcinome lieberkuhnien est le type histologique le plus fréquent, dérivé des cellules épithéliales de la muqueuse rectale et présente pour plus de 90% des patients. Les autres histologies sont l'adénocarcinome colloïde (mucineux), l'adénocarcinome à cellules en bague à chaton, le carcinome épidermoïde, le carcinome médullaire et le carcinome endocrine.[5]

Facteurs de risque :

Une méta-analyse s'est intéressée aux facteurs de risque du cancer du rectum. Les facteurs modifiables retrouvés dans cette étude étaient l'obésité, la sédentarité, le tabac, la consommation de viande rouge. Le fait de consommer des fruits et légumes est au contraire un facteur protecteur. Les autres facteurs de risque non modifiables étaient un âge supérieur à 50 ans, la présence d'une maladie inflammatoire du côlon, notamment la maladie de Crohn ou la rectocolite hémorragique et enfin un antécédent familial ou personnel. [6]

Par ailleurs, il a été établi dans plusieurs études que la présence d'une mutation génétique, notamment sur l'un des gènes du MMR (mismatch repair) responsable du syndrome de Lynch, ou sur le gène APC responsable de la polypose adénomateuse familiale, augmentait le risque de cancer colorectal. [7-8]

Diagnostic :

Le diagnostic est réalisé par colonoscopie, permettant de visualiser la tumeur et de définir sa localisation, réaliser des biopsies pour un diagnostic histologique et s'assurer de l'absence d'autres lésions.

L'écho-endoscopie rectale et l'IRM pelvienne permettent de préciser l'extension de la tumeur rectale au niveau local et locorégional.

Le bilan d'extension à distance est réalisé par scanner thoraco-abdomino-pelvien.

Prise en charge des cancers rectaux.

La prise en charge des cancers rectaux est réalisée en fonction de leurs stades. (Annexe 1). Notre étude porte sur les cancers rectaux localement avancés, à savoir les stades II et III. Selon les recommandations de la SNFGE, une radio (chimio) thérapie néo adjuvante suivi par une exérèse rectale et une résection totale du mésorectum est le traitement standard pour les cancers du bas et moyen rectum, mais n'est pas recommandé pour les cancers du haut rectum[9]. La place de la radio(chimio)thérapie néo adjuvante pour les cancers du hauts rectum sera détaillée dans notre étude.

Le traitement par radiothérapie se déroule sur 2 semaines ou 5 semaines selon qu'il s'agit d'une radiothérapie courte (25 Gy en 5 fractions) ou longue (50 Gy en 25 fractions). Un délai de 6 à 8 semaines est nécessaire pour la résection totale du mésorectum en cas de radiothérapie longue et de 1 à 2 semaines en cas de radiothérapie courte.

Depuis environ 5 ans, les patients sont traités de manière privilégiée par radiothérapie conformationelle avec modulation d'intensité (RCMI), qui permet une meilleure épargne des organes à risque par rapport à la radiothérapie conformationelle (3DCT) ainsi qu'une diminution des toxicités aigues[10-11-12].

La comparaison des deux modalités de traitement est détaillée ci-dessous.

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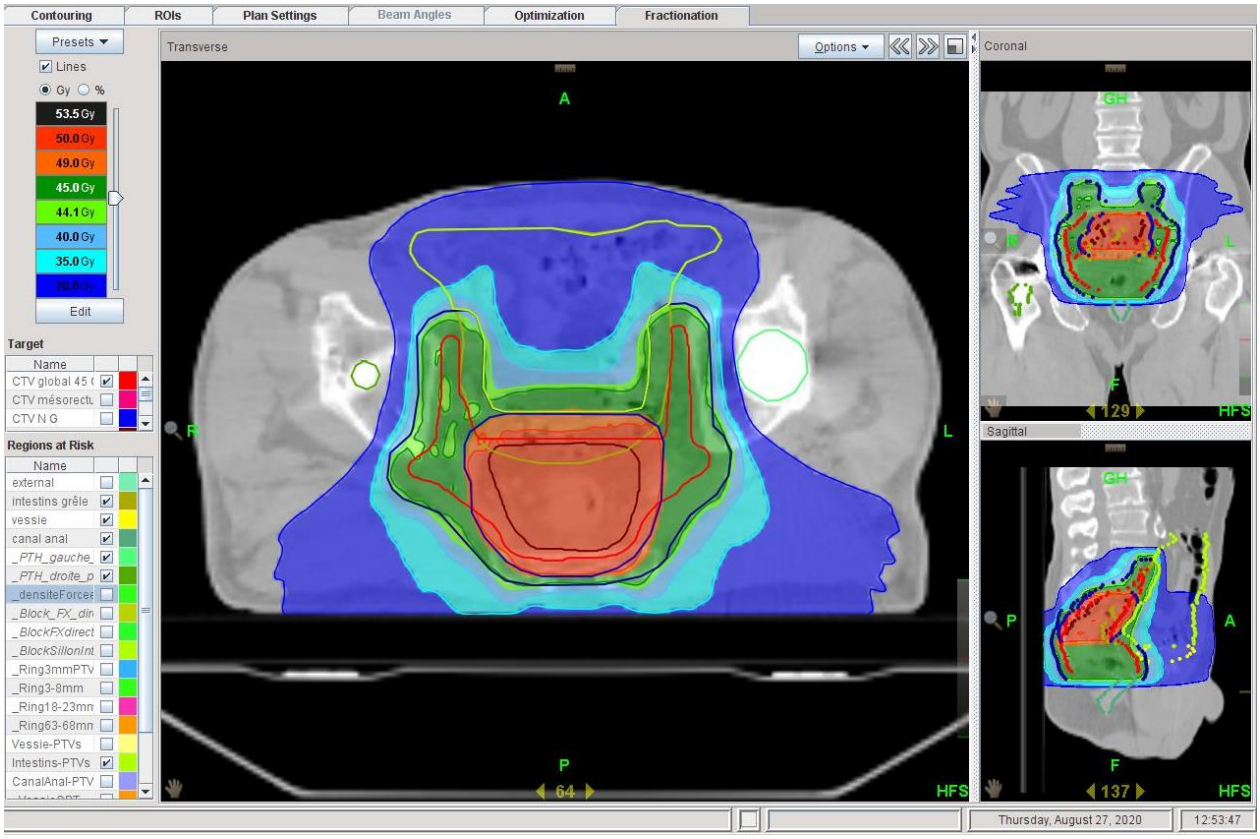
ANNEXES

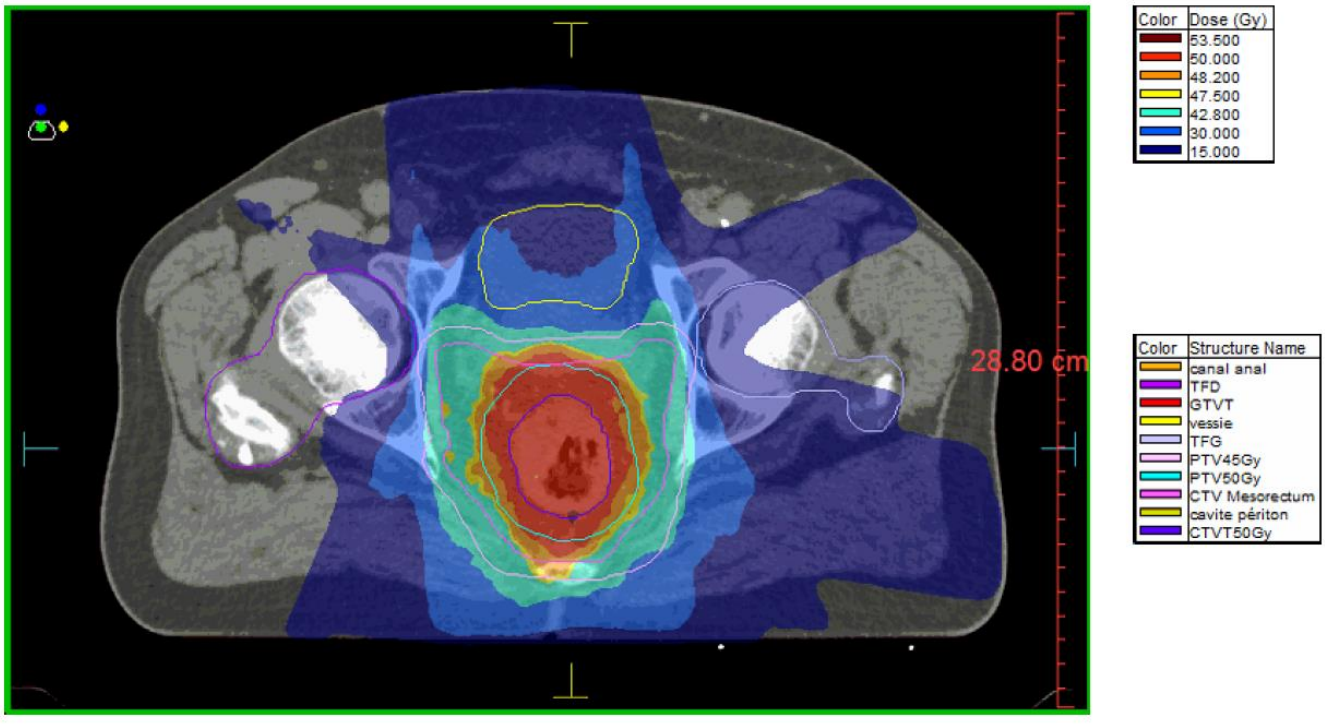
a) Stades des cancers rectaux

Stade	T	N	M
I	T1-2	N0	M0
IIa	T3	N0	M0
IIb	T4a	N0	M0
IIc	T4b	N0	M0
IIIa	T1-2 T1	N1 N2a	M0
IIIb	T3-4a T2-3 T1-2	N1 N2a N2b	M0
IIIc	T3-4a T4b	N2b N1-2	M0
Iva	Tout T	Tout N	M1a
IVb	Tout T	Tout N	M1b
IVc	Tout T	Tout N	M1c

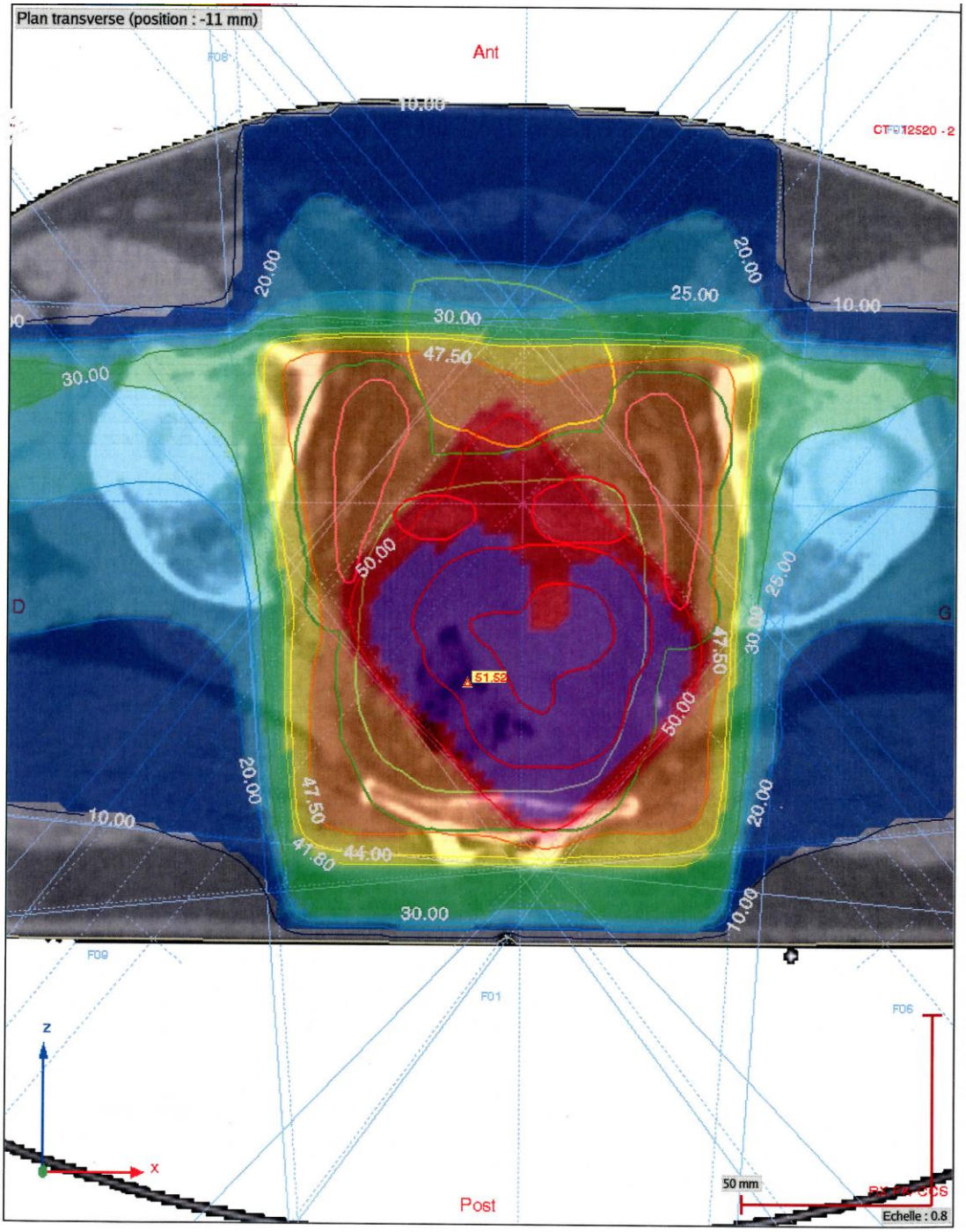
b) Plan de traitement avec RCMI – Accélérateur Tomothérapy



c) Plan de traitement avec RCMI – Accélérateur Synergy



d) Plan de traitement avec 3DCT



II. ÉTUDE

Résultats et effets secondaires de la radio chimiothérapie néo adjuvante dans les cancers localement avancés du haut rectum : une étude rétrospective

RÉSUMÉ

Introduction:
La radio(chimio)thérapie néo adjuvante suivie de l'excision totale du mésorectum est le traitement standard des cancers localement avancés du bas et moyen rectum. Toutefois, ce traitement reste débattu pour les cancers du haut rectum. Notre objectif a été d'évaluer les résultats et les effets secondaires des patients traités par cette séquence pour les cancers de stade II-III du haut rectum au CHU de Tours.

Méthodes:
D'Avril 2004 à octobre 2019, tous les patients avec un cancer du haut rectum de stade II –III traités par radio(chimio)thérapie suivie d'une résection rectale et une excision totale du mésorectum ont été inclus. La survie globale, la survie sans progression et la probabilité de développer une récidive locale ont été analysées par la méthode de Kaplan-Meier. Les toxicités aigues et tardives ont été gradées selon la classification CTCAEv5.

Résultats:
Dans cette cohorte de 106 patients, l'âge moyen était de 67.3 ans. La population était constituée de 40% de stades II et 60% de stades III après bilan par scanner thoraco-abdomino-pelvien, IRM rectale et écho-endoscopie rectale. La médiane de suivi était de 4 ans et 5 mois (écart-type +/-3.43). À 5ans, la survie globale et sans progression étaient respectivement de 78% [69.2-88] et 81% [73.3-90]. Le taux de récidive locale à 5 ans était de 3.78% [0-7.98]. Quarante-deux % des patients ont eu des toxicités aigues majoritairement de grade 1. Une toxicité tardive de grade 1-2 a été observée chez 27.4% des patients.

Conclusion:
Dans cette étude, nous avons observé un bon contrôle local et un profil de toxicité acceptable chez les patients traités par radio(chimio)thérapie préopératoire. De futures études comparatives sont nécessaires pour préciser les bénéfices de ce traitement.

Mots clés : Cancer du haut rectum, radiothérapie néo adjuvante, contrôle local, toxicité

Outcomes and side effects of preoperative radio chemotherapy for locally advanced upper rectal cancer: a retrospective analysis

ABSTRACT

Introduction:
While neoadjuvant (chemo) radiotherapy followed by total mesorectal excision is the standard of care for lower and middle locally advanced rectal cancer, such management for upper rectal cancer remains controversial. We aimed to evaluate the outcome of patients with stage II-III upper rectal cancer undergoing this treatment modality in our institution.

Methods:
From April 2004 to October 2019, all patients with stage II to III upper rectal cancer treated with neoadjuvant (chemo) radiotherapy followed by total mesorectal excision were included. Overall survival, progression free survival and local recurrence were assessed the Kaplan-Meier method. Acute and late treatment-related toxicities were recorded using the CTCAE.5 version.

Results:
A total of 106 patients were retrieved from our database. Mean age was 67.3 years. Our population was composed of respectively 40% and 60% patients with stage II and III upper rectal cancer after assessment for locoregional and metastatic spread with chest, abdominal and pelvic computed tomography (CT), magnetic resonance imaging (MRI) and endorectal ultrasound. The median follow-up period was 4 years and 5 months (standard deviation, +/- 3.43 years). Five-year overall survival and progression free survival were respectively 78% [69.2-88] and 76.8% [68.4-86.2]. The rate of local recurrence at 5 years was 3.78% [0-7.98]. Forty-two % of patients experienced early toxicities with a predominance of grade 1. Late toxicities limited to grade 2 occurred in 27.4% patients.

Conclusion:
In our study, neoadjuvant (chemo) radiotherapy followed by total mesorectal excision in stage II-III upper rectal cancer patients was associated with effective local control and an acceptable toxicity profile. Comparative studies are needed to address further results of this treatment.

Key words: Upper rectal cancer, neoadjuvant radiotherapy, local control, side effects

Introduction

Rectal cancer is the 8th most common cancer worldwide with 704, 000 new cases and the 10th most deadly with 310,000 deaths expected in 2018[1]. In the United States, rectal cancer is diagnosed for 40% of patients at a localized stage while 35% of patients present with locally advanced rectal cancer (LARC) and 19% at a metastatic stage[2]. For patients with locally advanced rectal cancer, defined as stage II-III disease, neoadjuvant (chemo) radiotherapy followed by total mesorectum excision (TME) has been established as the standard treatment by randomized trials[3–7].

Yet, whether it applies to all tumor location is still debated. In several randomized trials, the addition of neoadjuvant (chemo) radiotherapy to surgery was associated with improved local control in low and middle locally advanced rectal cancer and lead to higher sphincter preservation[5]. However, these randomized studies have yielded heterogeneous results on the outcomes of neoadjuvant (chemo) radiotherapy in locally advanced upper rectal cancer. The Dutch TME-trial found no statistically significant local control improvement with neoadjuvant radiotherapy in stage II-III upper rectal cancer, a result that was also supported by the Swedish rectal cancer trial. Contrarily, the MRC-CR7/NCIC-CTG-C016 study[8] found a statistically significant improvement on 3-year local recurrence and the German CAO/ARO/AIO-94 study[9] found a 10-year local recurrence of 4.3% in the preoperative chemo radiotherapy group compared with 10.4% in the TME only group.

With several conflicting outcomes, neoadjuvant (chemo) radiotherapy for locally advanced upper rectal cancer is subsequently not recommended by current guidelines namely the National comprehensive Cancer Network[10], the European Society of Medical Oncology[11] and the French thesaurus on gastrointestinal cancers[12]. Nonetheless, neoadjuvant (chemo) radiotherapy for locally advanced rectal cancer remains a controversial topic and is used heterogeneously worldwide depending cancer centers' practice.

Hence we aimed in this study to retrospectively review the efficacy and toxicity of patients treated with preoperative radiotherapy for locally advanced rectal cancer.

Materials and Methods

e) Patients

All patients, with pathologically proven rectal carcinoma and locally advanced upper rectal cancer (stage II-III) treated with radiotherapy followed by total mesorectal excision were identified from our radiotherapy database. All patients included in our study were treated in our institution. Tumor height was measured either through rigid rectoscopy, colonoscopy, MRI, echo endoscopy or a combination of these modalities. Patients with tumors' caudal margin located between 10 cm and 15 cm from the anal verge were included. Local staging

was assessed with magnetic resonance imaging (MRI) in 38 (35.8%) patients and with endorectal ultrasound (EUS) in 29 (27.4%) patients. Thirty-one (29.2%) patients had both MRI and EUS staging. In total, 98 (92.5%) patients had local staging prior to treatment. A hundred and two (96.2%) patients were staged for distant metastasis, with 93 (87.7%) patients assessed with a chest-abdomen-pelvic computed tomography (CT), 6 (5.7%) patients assessed with a chest CT or X-ray and abdominal ultrasound and 3 (2.8%) patients assessed with abdominal ultrasound only. Staging was determined according to the seventh edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual[13]. Gender, age at the time of treatment, staging, modality of radiation therapy (IMRT/3DCT) and concurrent chemotherapy regimen were recorded. The study was approved by the institutional review board.

f) Radiotherapy

All patients underwent CT planning for radiotherapy delineation. A few patients had a MRI fused with their planning computed tomography (CT) to help delineation. Radiotherapy was given on weekdays and exceptionally on saturdays. Long-course radiotherapy delivered 45 Gy in 25 fractions or 44 Gy in 22 fractions to the mesorectum and pelvic nodes (internal iliac, pre-sacral and peri-rectal). An additional boost up to 50 or 50.4 Gy could be delivered to the gross tumor. Short-course radiotherapy delivered 25Gy in 5 fractions to the mesorectum and pelvic nodes.

Both three dimensional conventional radiotherapy (3DCT) and intensity modulated radiation therapy (IMRT) were used. 3DCT was generated through opposed anterior – posterior and lateral beams, and delivered through the Isogray (Dosisoft®) treatment planning system version 4.2. IMRT was designed with the Monaco® treatment planning system version 3.20.02 and delivered either through a TomoTherapy system or an Electa Synergy® linear accelerator. The bladder dose constraint was limited to 40% of the bladder volume receiving no more than 50 Gy in standard fractionation. Femoral heads' constrains were defined as no more than 10% of the volume receiving 50 Gy, no more than 35% of the volume receiving 40 Gy and no more than 50% of the volume receiving 30 Gy in standard fractionation. Constraints for the Small bowel were defined as no more than 100ml receiving 50 Gy, no more than 200 ml receiving 40 Gy and no more than 350 ml receiving 30Gy in standard fractionation.

g) Chemotherapy

Neoadjuvant chemotherapy was delivered concurrently with long course radiotherapy. CAPECITABIN, TEGAFUR, FOLFOX 6, LV5FU2 and FUFOL were among the regimen used.

Adjuvant chemotherapy was indicated for (y)pT4 tumors or in case of pathological lymph node involvement. In this setting, patients were administered either the FOLFOX or LV5FU2 regimen.

h) Surgery

All patients underwent total mesorectum excision (TME) after (chemo) radiotherapy. The majority of patients were treated in our institution. Surgery was performed one to two weeks after short course radiotherapy and six to eight weeks after long course (chemo) radiotherapy. The rate of early and late surgical effects was retrieved. Negative surgical margins notified as R0 were defined as a circumferential resection margin >1mm.

i) Treatment and secondary effects evaluation

Per our institution, patients were first assessed after treatment at 3 months, with a CT followed by clinical review. They were usually further followed-up every 3 months for the first two years and every 6 months the 3rd year and after. A chest, abdominal and pelvic CT in rotation with a Chest X-ray and abdominal ultrasound were performed each time prior to clinical review up to the first 2 years, and then CT was the only modality used prior to clinical review. Colonoscopy was performed every three years. If clinical suspicion of metastasis or deterioration was present, the appropriate imaging was additionally performed. Radiological progression was assessed according to RECIST criteria. Acute toxicity was evaluated and recorded weekly during treatment according to the CTCAE-5 criteria. Late toxicities were defined as the persistence of side effects at least 6 months after treatment. Their presence was assessed using the last clinical report available and graded according to the CTCAE-5 criteria. Survival data analysis included progression free survival (PFS) and overall survival (OS); recurrence was identified either as regional, metastatic, or both.

j) Statistical analysis

- Data collection

The 1st radiotherapy day was collected for each patient and served as the start date for survival analyses. Additionally, progression, local or distant recurrence and death were retrieved from our database. We encountered 3 cases of incomplete data with accessible months and years but missing days, and decided to convert the date to the middle of the month. One patient had accessible year but missing month and day, we choose to convert the date to the middle of the year and month.

- Data analysis

All calculations were made using R[14] and more specifically the survival package (https://cran.r-project.org/web/packages/survival/index.html). Every survival analysis was done using Kaplan-Meier method. Briefly survival analysis aims at the prediction of survival rate over time among a population sample. Kaplan-Meier method allows the modelling of a specific event as the occurrence rate by taking into account right censoring which is essential in clinical research when a patient is lost to follow-up, or is alive without event occurrence at last follow-up. For overall survival analysis the event of interest is death of any kind.

Alternatively we used different definitions of this event that are regularly used for clinical study in cancerology: (i) the cancer-related survival where the event of interest is only death caused by cancer or its treatment, (ii) the overall and progression free survival analysis where the event of interest is death of any kind or cancer progression, (iii) the cancer-related and progression free survival analysis where the event of interest is cancer progression or death caused by cancer or its treatment and (iv) the local recurrence analysis where the event of interest is the local cancer progression. In case or missing type of death, patients with missing info (n=3 out of 106) relative to the cause of death were not considered for cancer-specific survival analyses. Finally, predicted survival rates are given with a 95% confidence interval.

Results

From April 2004 to October 2019, 106 patients have been treated with neoadjuvant (chemo) radiotherapy followed by total mesorectum excision for stage II-III rectal cancer. Mean age was 67.3 years, with rectal cases higher in men (62.3%) than women (37.7%). Thirty-height (35.8%) patients were diagnosed with stage II rectal cancer, 65 (61.3%) patients were diagnosed with stage III and 4 (3.8%) patients had incomplete staging. Sixty-four (60.4%) patients received neoadjuvant concurrent chemoradiotherapy with the remainder receiving short-course radiotherapy (18.9%) or long-course radiotherapy without chemotherapy (20.8%). Out of 86 (81.1%) patients who received long-course radiotherapy, 53 (50.0%) patients received a tumor boost and 33 (31.1%) didn't. 3DCT the most used planning technique with 94 (88.7%) patients treated as such. The most common protocol was CAPECITABIN 825 mg/m2 twice a day on radiotherapy days, given to 35 patients. Twenty-three patients received 300 mg/m2/day tegafur plus 90 mg/day calcium folinate (30 mg/dose) administered in three divided doses (every 8 hours) orally on radiotherapy days. Two patients received the modified FOLOX 6 regimen, which consisted in fortnightly OXALIPLATIN 85mg/m2 given concurrently with LEUCOVORIN, 400 mg/m2, followed by a bolus 5-FU, 400 mg/m^2, and a 22-hour continuous infusion of 5-FU, 2400 mg/m2 administered during 46 hours. Two patients received the LV5FU2 regimen, consisting in fortnightly LEUCOVORIN, 200 mg/m2, followed by a bolus 5-FU, 400 mg/m^2, and a 22-hour continuous infusion of 5-FU, 2400 mg/m2 administered during 46 hours. One patient received the FUFOL regimen which consisted in LEUCOVORIN, 20mg/m2/day followed by a bolus of LV5FU, 350 mg/m2/day during 5 days on week 1 and 5. The concurrent chemotherapy regimen was not specified in one patient. Patients' and treatment characteristics are described in Table 1 and 2.

Twenty-six (24.5%) patients received adjuvant chemotherapy, with 22 (20.8%) treated with the modified FOLFOX 6 regimen and 3 (2.8%) with the LV5FU2 regimen. One patient was intended to receive adjuvant chemotherapy but was lost to follow up priorly. Five (4.7%) patients did not receive adjuvant chemotherapy while eligible as a result of surgical complications in three patients and cardiac side effects experienced during concurrent

chemo radiotherapy in two patients. Postoperative patient and tumor characteristics are detailed in Table 2.

Forty-four (41.5%) patients had early (chemo) radiotherapy-related side effects. Grade 1 early side effects were predominant occurring in 58% of patient. No patient experienced grade 4 side effects. Four patients experienced grade 3 side effects, in the form of diarrhea, bowel obstruction, and myocardial infarction. Gastro-intestinal side effects were most the common, occurring in 31 (29.2%) patients, yet they were largely limited to stage 1 (20.8%). Fourteen patients (13.2%) experienced urinary toxicities with one patient (0.9%) only experiencing grade 2 side effects. Three (2.8%) patients had perineal dermatitis limited to grade 2. Chemotherapy-related side effects included grade 1 leukopenia and thrombocytopenia in respectively 1 (0.9%) and 2 (1.9%) patients, grade 2 and 3 myocardial infarction in 2 (1.9%) patients and grade 1 and 2 fatigue in respectively 5 (4.7%) and 2 (1.9%) patients. Early radio(chemo)therapy effects are presented in Table 3.

Twenty-nine (27.4%) patients experienced early surgical complications. In 18 (17.0%) patients, surgical complications were limited to grade 1 and 2 according to the Clavien-Dindo classification[15]. Seven (6.6%) patients had grade 3 complications and one (0.9%) patient had grade 4b complications. Two patients died following postoperative stroke and muti-organ dysfunction. Among patients with early surgical complications, 10 experienced fistulae and 7 experienced abscesses. Anastomotic leakages, bowel obstructions, peritonitis and sepsis all occurred in respectively 2 patients. One patient experienced wound healing disorders.

Late surgical complications occurred in 3 (2.8%) patients. Seven (6.6%) patients had both early and late surgical complications. Anastomotic stenosis and fistula occurred both in 4 patients and anastomotic leakage and abscess both occurred in one patient. Early and late surgical complications are presented in Table 3 and 4.

Late side effects occurred in 29 (27.4%) with a predominance of grade 1 (57% of patients). One patient only had persistent grade 3 diarrhea. Respectively 17 (16%) and 8 (7.5%) patients had grade 1 and 2 digestive late side effects. No patients experienced late genitourinary side effects. Late incontinence was present in 10 patients, including 7 patients with grade 1 and 2 with grade 2. Of note, 24 (22.6%) patients could not be analyzed for late side effects as they didn't undergo rectal reconstruction or were lacking (accurate) assessed following reconstruction. Precisely, six (5.7%) patients didn't have restoration of gastrointestinal continuity as a result of postoperative complication including fistulae in 3 (2.8%) patients, anastomotic leakage in 2 (1.9%) patients and incontinence in 1 (0.9%) patients. Another 10 patients were not reconstructed following tumor progression in four (3.8%) patients, second cancer in 2 (1.9%) patients, perioperative death in two (1.9%) patients, and respectively a grade 2 performance status and history of peripheral artery disease in two octogenarian patients. Late secondary effects are presented in Table 4.

Postoperatively, histopathological analyses found that 33.0% of patients benefited from tumor downstaging and that 67.2% of patients who initially had positive lymph node experienced downstaging. Of note, lymph node downstaging was defined as the reduction in nodal stage between radiological assessment (which might carry a potentional bias for its lack of accuracy) and pathological assessment. Both tumor and lymph node downstaging occurred in 13.2% patients. Pathological complete response was found in 7.5% of patients. Three (2.8%) patients had positive surgical margins and 39 (36.8%) had lymphovascular or/and perineural invasion. Downstaging characteristics are detailed in Table 2.

At the time of analysis, 19 patients experienced recurrence, locally in 2 (1.9%) patients, distantly in 15 (14.2%) patients and both in 2 (1.9%) patients. Out of 19 recurrences, 17 patients were initially diagnosed with stage III. Twenty-seven (25.5%) patients had died. Thirteen (12.3%) deaths were cancer-related or treatment-related, 11 (10.4%) deaths were associated with other causes, and 3 (2.8%) deaths were not specified. Survival curves have been computed as specified in methods (see Figures 1-4). Five-year overall survival and progression free survival were respectively 78% [69.2-88] (Figure 1) and 76.8% [68.4-86.2] (Figure 2) with a median follow-up time of respectively 4.47 (+/-3.43) and 3.92 (+/- 3.2) years. Removing unknown cause of deaths, five-year cancer-specific survival was 85.5% [77.2-94.6] (Figure 3) with a median follow-up time of 4.51 (+/- 3.41) years. Local recurrence at 5 years was 3.82% [0-7.98] and 7.67% [0-15.7] at 10 years (Figure 4). Population analyzed was N=106 except for the study of cancer-specific survival (N=103) due to missing data.

Discussion

Our study retrospectively evaluated neoadjuvant (chemo) radiotherapy for stage II-III upper rectal cancer. Our patients' population was composed with a substantial proportion of patients with high risk factors, with 60% of them diagnosed with stage III and 38% of patients with perineural and/or perivascular invasion. In comparison, the Swedish rectal cancer trial and the Dutch TME-trial included respectively 31% and 35% of patients with stage III rectal cancer. The presence of perineural or perivascular invasion was not specified in these studies. In the MRC-CR7/NCIC-CTG-C016 trial[8], patients with stage III rectal cancer accounted for 40% preoperatively and 43% postoperatively. The presence of perineural or perivascular invasion was as well not specified. A majority of patients in our study were treated with concurrent chemoradiotherapy (59.8%). A total of 7.5% achieved complete pathological response, a result similar to the German CAO/ARO/AIO-94 study (9%)[9].

Our survival analysis showed effective local control with a five-year local recurrence of 3.78% [0-7.98]. This rate is overall similar to the MRC-CR7/NCIC-CTG-C016 and the CAO/ARO/AIO-94 trial, which respectively reported a five-year upper rectal cancer local recurrence of 4.7% and 2.5%. Recently, Huang et al[16] compared retrospectively the outcome of neoadjuvant (chemo) radiotherapy for locally advanced upper rectal cancer to the one of middle and

lower rectal cancer. They found a five-year upper rectal cancer local recurrence rate of 8.6%, distant recurrence rate of 6.9%, overall survival of 88% and progression free survival of 84%. Except for some moderate difference, these results are overall in line with ours. Park et al[17] conducted a retrospective study on the outcome of stage II- III rectal cancer and sigmoid cancer treated with surgery only, without specifying whether total mesorectal excision was used. Five-year upper rectal cancer local recurrence was 3.5%, however a majority of patients had stage II rectal cancer (58.8%). When considering patients with stage III only, local recurrence rate increased to 5.9%.

Interesting, our study found that a considerable amount of patients that progressed were initially diagnosed with stage III. In the TME trial with a 12-year follow –up[18], as opposed to patients with stage II rectal cancer, those with stage III experienced a significant improvement in local recurrence with preoperative radiotherapy. In addition, when these patients had a negative circumferential resection margin, 10-year survival was significantly higher in the preoperative group. The RAPIDO trial[19] evaluated the role of neoadjuvant chemotherapy in patients with high-risk features (cT4a/b, extramural vascular invasion, cN2, involved mesorectal fascia or enlarged lateral lymph nodes considered to be metastatic) treated in the experimental arm with of short course radiotherapy with subsequent six cycles of CAPOX or nine cycles of FOLFOX4 followed by total mesorectal excision. Patients in the standard arm were treated with concurrent chemotherapy followed by total mesorectal excision. A significantly higher pathological complete response (27.7%) and 3-year disease-related treatment failure (23.7) was found in the experimental arm compared to the standard arm. Correspondingly, the PRODIGE trial[20] investigated the results of neoadjuvant chemotherapy and included a majority of stage III rectal cancer patients treated in the experimental arm with 6 cycles of mFOLFIRINOX regimen every 14 days, followed with preoperative chemo radiotherapy, surgery and 3 months of adjuvant chemotherapy. Patients in the standard arm were treated with preoperative chemo radiotherapy, surgery followed by 6 months of adjuvant therapy. A significant higher pathological response (27.5%) and 3-year disease-free survival (75.7%) was observed in the experimental arm.

Patients with stage III upper rectal cancer are likely to benefit more from preoperative (chemo) radiotherapy than patients with stage II. For this reason, consideration of patient subgroups with moderate or high-risk features should be considered in future studies to identify patients that take most advantage of neoadjuvant radio(chemo)therapy. Additionally, regardless of tumor location, total neoadjuvant therapy will likely be the future paradigm for locally advanced rectal cancer with high-risk features, yet patients and treatment modality remains to be defined.

A few studies evaluated the rate of acute toxicities in stage II-III upper rectal cancer treated with preoperative radiotherapy. Out of 58 patients with locally advanced upper rectal cancer treated with preoperative chemo radiotherapy in Huang's study[16], respectively 4.5% and 1.6% of patients experienced grade 3 toxicities with 3DCT and IMRT. Grade 1-2 early digestive toxicities occurred in 28.3% while no genitourinary toxicities were present. These results are overall consistent with ours, except for the genitourinary ones. In our study,

patients were majorly treated with 3DCT, while it has been demonstrated that IMRT allows better dose conformation of the target volume. In addition, IMRT planning produced significantly lower D5 and V40 values for the bladder and the small bowel compared to 3DCT in a study of 15 patients with locally advanced rectal cancer[21]. Huang et al[22] compared potential dosimetric advantages and toxicities in 144 patients treated with 3DCT and IMRT. They found a significant lower mean dose to the bladder and significantly lower V40 and V30 values to the small bowel with IMRT. These results clinically manifested in less acute digestive toxicity, yet no difference was observed as for genitourinary toxicities. Similar clinical outcomes are found in several additional studies.[23–25] In terms of early postoperative complications, the Dutch TME-trial found a significant increase in blood loss and perineal complications in the preoperative radiotherapy group. We observed in our study a similar early perineal complication rate with preoperative treatment (26%). This trial also found no difference in terms of mortality between the two groups but didn't mention the number or rate of postoperative deaths.

To our knowledge, no studies specifically assessed late toxicities in locally advanced upper rectal cancer. A number of trials have focused on this problematic, yet irrespectively of tumor location. Birgisson et al[26] evaluated late side effects of preoperative radiation therapy for rectal cancer using the study population of the Swedish rectal cancer trial. They found no difference between the two groups. By constrast, Peeters et al[27] evaluated late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer, in a population that was composed or 30% of upper rectal cancers. They reported a significantly higher fecal incontinence in the irradiated group (62% vs 38%), which compared to our results, is nearly 5 times higher. This difference might be explained by the inherent bias when collecting data but arguably, the evolution of radiotherapy over the last two decade played with no doubt a role in our result. Finally, Azria et al reported on the late toxicities of the ACCORD 12/0405-PRODIGE 02[28] trial, and found that respectively 39.5% of patients treated with the CAP45 regimen experienced late gastrointestinal side effects, a result just slightly above ours.

Overall, our study shows effective local control associated with favorable survival outcomes and acceptable side effects. There is some limitation to our work, including the retrospective aspect, associated with inherent bias, as well as the 15-year inclusion period, which is associated with lower treatment homogeneity. In addition, although our survival results compare to the benchmark trials' ones, we lack a comparative, surgery only group in order to confirm the role played by preoperative (chemo)radiotherapy. In this regard, a number of recent retrospective studies analyzed the results of lower, middle, upper rectal cancers and sigmoid cancers in order to identify whether upper rectal cancer survival outcomes compared to low and middle cancer or to sigmoid cancer[29]. Depending on the result, authors concluded that preoperative (chemo) radiotherapy should or should not be performed; however none of these studies had a comparative, surgery only group. Recently, total neoadjuvant therapy showed promising results and could be recommended for high-

risk, locally advanced rectal cancers, regardless of tumor location given the good results of PRODIGE 23 and RAPIDO trials.

Conclusion

In our study, neoadjuvant (chemo) radiotherapy followed by total mesorectal excision in stage II-III upper rectal cancer patients was associated with effective local control and favorable survival outcomes as well as an acceptable toxicity profile. Comparative studies are needed to address further results of this treatment, and in this regard, we are aiming to further collect and work on data in order to generate a larger-size study with a control group.

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Tables and figures

Table 1: Patient and tumor characteristics

Characteristics	N°	%
Age (Years)	67.3 (40-88)	
Male	66	62.3%
Female	40	37.7%
Local staging		
Magnetic resonance imaging (MRI)	38	35.8%
Endorectal ultrasound (EUS)	29	27.4%
Both MRI and EUS	31	28.2%
Staging for distant metastasis		
Thoracic abdominal and pelvic CT scan	93	87.7%
Thoracic CT scan/Chest X-ray and abdominal ultrasound	6	5.7%
Abdominal ultrasound only	3	2.8%
Clinical tumor extension		
T2	5	4.7%
T3	98	92.5%
T4	2	1.9%
Unknown	1	0.9%
Clinical lymph node metastasis		
N0	38	35.8%
N1a	21	19.8%
N1b	22	20.8%
N1x	3	2.8%
N2a	2	1.9%
N2b	1	0.9%
N2x	15	14.2%
Unknown	4	3.8%
Stage II	38	35.8%
Stage III	64	61.3%
Pathological tumor extension		
(y)pT0	9	8.5%
(y)pT1	6	5.7%
(y)pT2	20	18.9%
(y)pT3	57	53.8%
(y)pT4a	3	2.8%
(y)pT4b	1	0.9%
Unknown	10	9.4%
Pathological lymph node staging		
(y)pN0	65	61.3%
(y)pN1a	14	13.2%
(y)pN1b	11	10.4%
(y)pN2a	1	0.9%
(y)pN2b	6	5.7%
Unknown	9	8.5%
R0	85	80.2%
R1	3	2.8%
Unknown	18	16.9%
Histopathological risk factors		
Absent	46	43.4%
Present	39	36.8%
Unknown	21	19.8%

Table 2: Treatment and post treatment characteristics

Characteristics	N°	%
Radiotherapy technique		
3DCT	95	89.6%
IMRT	11	10.4%
Concurrent chemotherapy regimen		
Xeloda	35	33.0%
UFT	23	21.7%
Folfox	2	1.9%
LV5FU2	2	1.9%
FUFOL	1	0.9%
Unknown	1	0.9%
Downstaging		
Tumor downstaging	**35**	**33.0%**
Absence of tumor downstaging	60	56.6%
Unknown	11	10.4%
Lymph node downstaging in cN+ patients (64)	**43**	**67.2%**
Unchanged lymph node staging in N+ patients	14	21.9%
Upstaged lymph node status in N+ patients	4	6.3%
Unknown pathological status in N+ patients	3	4.7%
Tumor and lymph node downstaging	**14**	**13.2%**
Absence of tumor and node downstaging	82	77.4%
Unknown	10	9.4%
Pathological complete response	**8**	**7.5%**
Absence of pathological complete response	89	84.0%
Unknown	9	8.5%
Histopathological risk factors (lymphovascular/perineural invasion)		
Absent	46	43.4%
Present	39	36.8%
Unknown	21	19.8%
Adjuvant chemotherapy		
No	65	61.3%
Including patients eligible to adjuvant chemotherapy	*5*	*4.7%*
Yes	26	24.5%
Unknown	8	7.5%
Progression prior to adjuvant chemotherapy	2	1.9%
Type of adjuvant chemotherapy		
Folfox	22	20.8%
LV5FU2	3	2.8%
Unknown	1	0.9%
Cancer-related gene mutation in patients scheduled to receive adjuvant chemotherapy (33 patients)		
Absent	11	33.3%
KRAS	5	15.2%
NRAS	1	3.0%
BRAF	0	
FGFR3	1	3.0%
Unknown	15	45.5%

Table 3: Early secondary effects

Characteristics	N°	%
Early toxicities		
Absent	47	44.3%
Present	44	41.5%
Unknown	15	14.2%
Early Gastrointestinal toxicities		
Absent	60	5.6%
grade 1	22	20.8%
grade 2	6	5.7%
grade 3	3	2.8%
Unknown	15	14.2%
Early Urinary toxicities		
Absent	77	72.6%
grade 1	13	12.3%
grade 2	1	0.9%
Unknown	15	14.2%
Early Perineal dermatitis		
Absent	88	83.0%
grade 1	1	0.9%
grade 2	2	1.9%
Unknown	15	14.2%
Early chemotherapy -related side effects		
Absent	88	83.0%
Thrombocytopenia		
grade 1	2	1.9%
Leukopenia		
grade 1	1	0.9%
Unknown	15	14.2%
Early myocardial infarction		
Absent	89	84.0%
grade 2	1	0.9%
grade 3	1	0.9%
Unknown	15	14.2%
Fatigue		
Absent	84	79.2%
grade 1	5	4.7%
grade 2	2	1.9%
Unknown	15	14.2%
Early surgical complications		
Absent	**58**	54.7%
Present	**29**	27.4%
grade 1	6	5.7%
grade 2	12	11.3%
grade 3a	1	0.9%
grade 3b	7	6.6%
grade 4a	0	
grade 4b	1	0.9%
grade 5	2	1.9%
Unknown	19	17.9%

Table 4: Late secondary effect

Characteristics	N°	%
Late toxicities		
Absent	48	45.3%
Present	29	27.4%
Unknown	6	5.7%
No assessment of late toxicities as a result of:	**8**	**7.5%**
- No follow-up/assessment after reconstruction	4	3.8%
- Follow up after reconstruction < 6 months	4	3.8%
No restoration of GI continuity as a result of:	**16**	**15.1%**
- Tumor Progression	4	3.8%
- Second cancer	2	1.9%
- Perioperative death	2	1.9%
- Poor performance status	1	0.9%
- History of peripheral artery disease	1	0.9%
- Fistula	3	2.8%
- Anastomotic leakage	2	1.9%
- Incontinence	1	0.9%
Late gastrointestinal toxicities		
Absent	51	48.1%
grade 1	17	16.0%
grade 2	8	7.5%
grade 3	1	0.9%
Unknown	6	5.7%
Patients without assessment or restoration of GI continuity	24	22.6%
Late incontinence		
Absent	68	64.2%
grade 1	7	6.6%
grade 2	2	1.9%
grade 3	0	
Unknown	6	5.7%
Patients without assessment or restoration of GI continuity	24	22.6%
Late surgical complications		
Absent	**77**	72.6%
Present	**3**	2.8%
Associated with early surgical complications	***7***	*6.6%*
Unknown	**19**	17.9%

Figure 1: Overall Survival

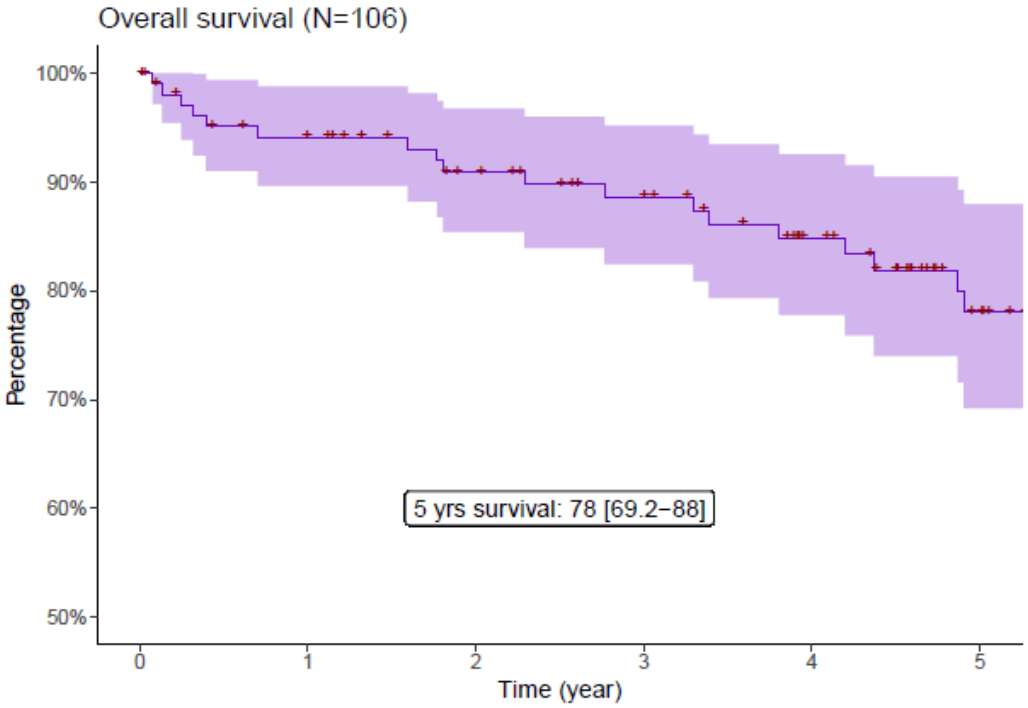


Figure 2: Progression-free survival

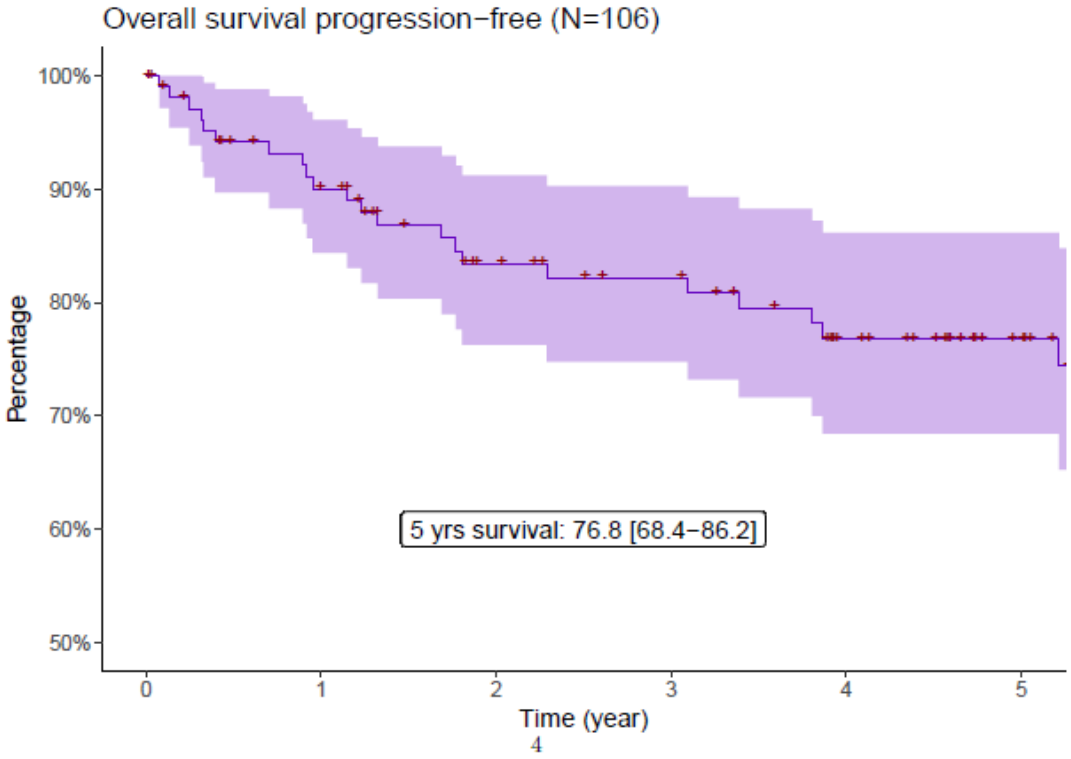


Figure 3: Cancer -specific survival

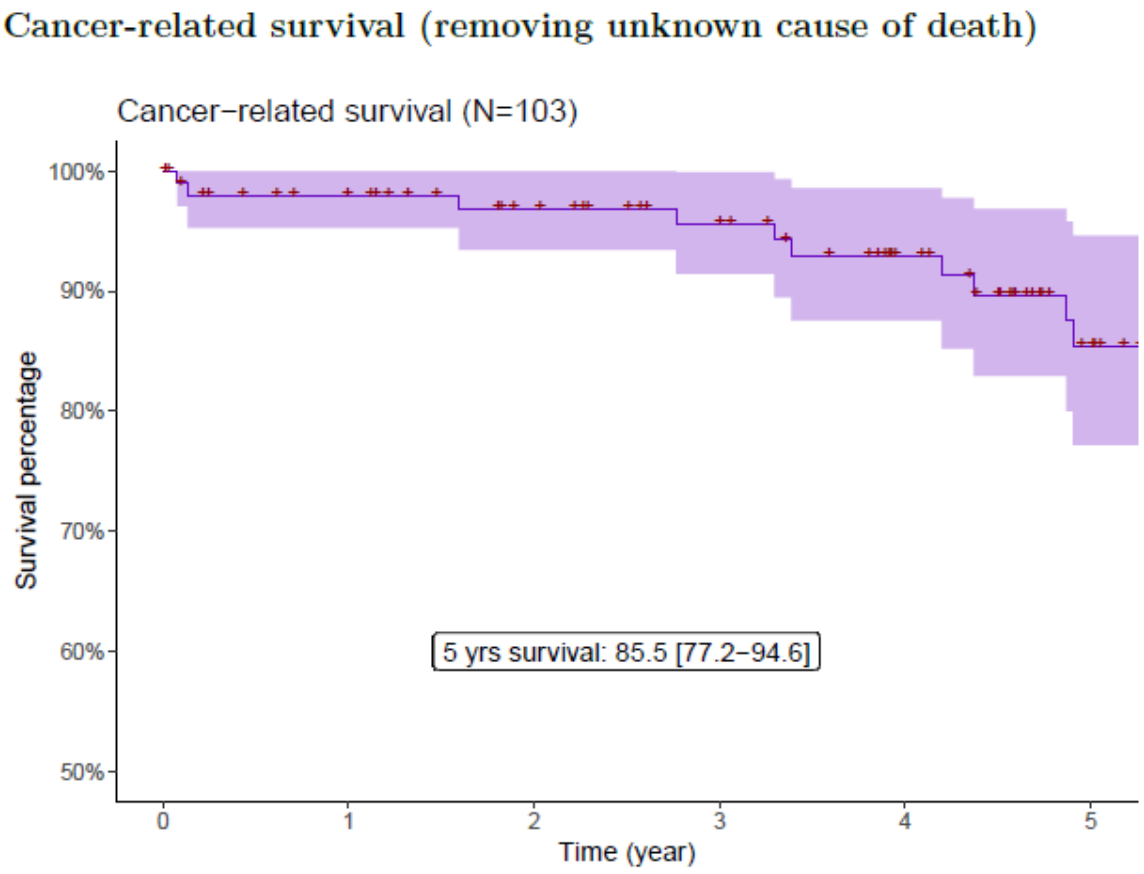
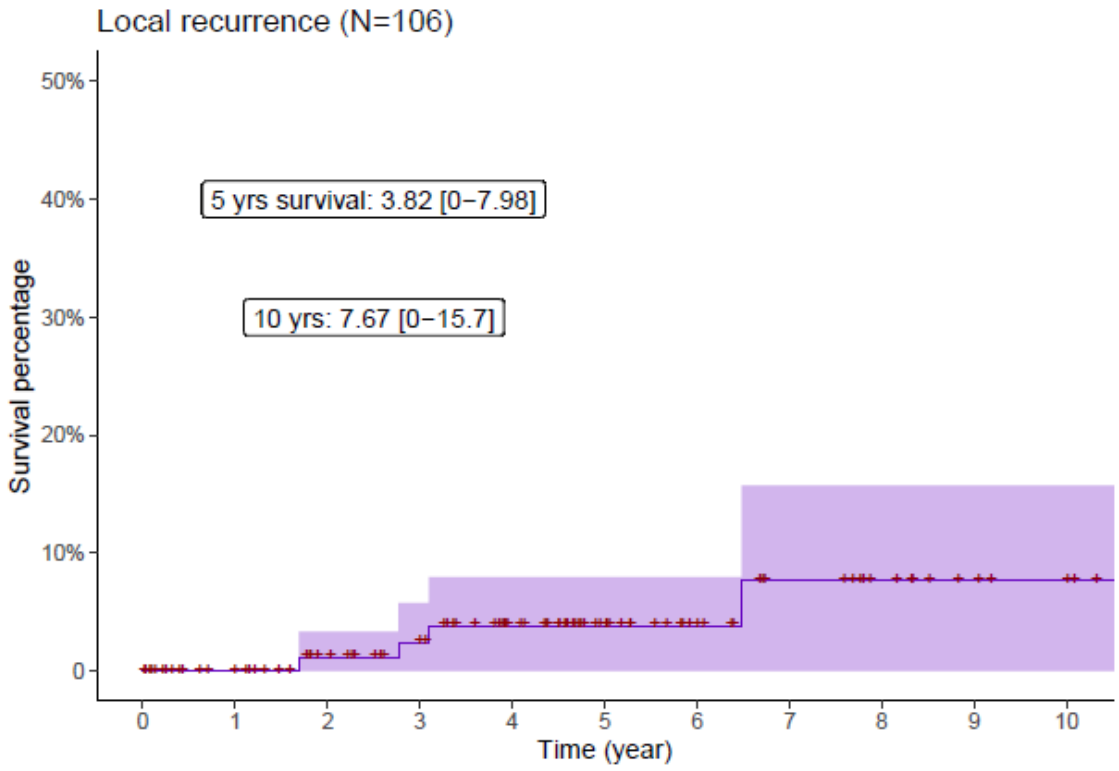


Figure 4: Local recurrence



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Résumé :

Introduction: La radio(chimio)thérapie néo adjuvante suivie de l'excision totale du mésorectum est le traitement standard des cancers localement avancés du bas et moyen rectum. Toutefois, ce traitement reste débattu pour les cancers du haut rectum. Notre objectif a été d'évaluer les résultats et les effets secondaires des patients traités par cette séquence pour les cancers de stade II-III du haut rectum au CHU de Tours.

Méthodes: D'Avril 2004 à octobre 2019, tous les patients avec un cancer du haut rectum de stade II –III traités par radio(chimio)thérapie suivie d'une résection rectale et une excision totale du mésorectum ont été inclus. La survie globale, la survie sans progression et la probabilité de développer une récidive locale ont été analysées par la méthode de Kaplan-Meier. Les toxicités aigues et tardives ont été gradées selon la classification CTCAEv5.

Résultats: Dans cette cohorte de 106 patients, l'âge moyen était de 67.3 ans. La population était constituée de 40% de stades II et 60% de stades III après bilan par scanner thoraco-abdomino-pelvien, IRM rectale et écho-endoscopie rectale. La médiane de suivi était de 4 ans et 5 mois (écart-type +/- 3.43). À 5ans, la survie globale et sans progression étaient respectivement de 78% [69.2-88] et 81% [73.3-90]. Le taux de récidive locale à 5 ans était de 3.78% [0-7.98]. Quarante-deux % des patients ont eu des toxicités aigues majoritairement de grade 1. Une toxicité tardive de grade 1-2 a été observée chez 27.4% des patients.

Conclusion: Dans cette étude, nous avons observé un bon contrôle local et un profil de toxicité acceptable chez les patients traités par radio(chimio)thérapie préopératoire. De futures études comparatives sont nécessaires pour préciser les bénéfices de ce traitement.

Mots clés : Cancer du haut rectum, radiothérapie néo adjuvante, contrôle local, toxicité

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