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### ► To cite this version:

Maxime Collard, Eric Rullier, Yves Panis, Gilles Manceau, Stéphane Benoist, et al.. Non-metastatic ypT0 rectal cancer after neoadjuvant treatment and total mesorectal excision: Lessons from a retrospective multicentric cohort of 383 patients. *Surgery*, 2022, 171 (5), pp.1193-1199. 10.1016/j.surg.2021.10.003 . hal-04522381

**HAL Id: hal-04522381**

**<https://hal.science/hal-04522381>**

Submitted on 22 Jul 2024

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**Non-metastatic ypT0 rectal cancer after neoadjuvant treatment and total mesorectal excision: lessons from a retrospective multicentric cohort of 383 patients.**

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## **Abstract**

**Background.** A better understanding of pathological features and oncological survival in ypT0 rectal cancer after neoadjuvant chemoradiotherapy (CRT) is required to improve patient selection criteria for rectal-preserving approach by local excision. Our aim was to define risk of lymph node metastasis and oncological outcomes in ypT0 rectal cancer after CRT and total mesorectal excision (TME).

**Methods.** All consecutive patients who underwent TME for a non-metastatic rectal adenocarcinoma classified ypT0 after neoadjuvant CRT, with or without locoregional lymph node involvement (ypN+ or ypN-) in 14 French academic centers between 2002 and 2015 were included. Data were collected retrospectively. Overall and disease-free survival (OS and DFS) were explored.

**Results.** Among the 383 ypT0 patients, 6% were ypN+ (23/283). Before CRT, 86% (327/380) were staged cT3-T4 and 41% (156/378) were staged cN+. The risk of ypN+ did not differ between cT3-T4 and cT1-T2 patients ( $p=0.345$ ) and between cN+ and cN- patients ( $p=0.384$ ). After a median follow-up of 61.1 months, we observed 95% 95CI[92%-97%] of 5-year OS and 93% 95CI[91%-96%] of 5-year DFS. In Cox-multivariate analysis, OS was altered by intra-abdominal septic complications (HR=2.53 CI[1.11-5.78],  $p=0.028$ ). Regarding DFS, ypN+ status and administration of adjuvant chemotherapy were associated with a reduced DFS ( $p=0.001$  for both). cT3/T4 staging and cN+ staging did not modify OS ( $p$ -value=0.332 and  $p=0.450$ ) nor DFS ( $p$ -value= 0.862 and  $p=0.124$ ).

**Conclusions.** The risk of LN metastasis and the oncological survival do not depend on the initial cT or cN staging in cases of ypT0 complete rectal tumor regression.

## **Introduction**

For decades, definitive curative management of rectal cancer consisted of radical surgery requiring total mesorectal excision (TME), with or without neoadjuvant radiotherapy or chemoradiotherapy (CRT).<sup>1,2</sup> For all patients, including those with a complete response as assessed clinically, radiologically and at endoscopy, radical surgery was recommended in order to ensure complete resection of the residual tumor and to remove all potential metastatic lymph nodes (LN) located in the mesorectum.<sup>3</sup> However, around 15% of patients undergo TME despite a pathological complete response (ypT0N0) after conventional CRT<sup>4,5</sup> and this percentage might be increased by more intensive neoadjuvant therapies.<sup>6</sup> For these patients, different strategies, such as Watch & Wait and local excision, are currently under evaluation in order to allow these patients to avoid the functional consequences of TME and concomitant quality of life impairment without affecting the oncological prognosis.<sup>7</sup> The main difficulty concerns the appropriate selection of patients, as TME is required to provide a definitive pathological diagnosis of a true ypT0N0. The Watch & Wait strategy after a complete clinical response relies on an active follow-up after CRT to detect local regrowth, which occurred in 28% of patients during the first 5 years in the International Watch & Wait Database.<sup>8</sup> Local excision after CRT is an alternative strategy that allows the pathological analysis of ypT status. In a randomized control trial conducted by our group specialized in surgical rectal cancer research (GRECCAR-2), the oncological safety of this strategy has been validated for small T2-T3 low rectal cancer with good clinical response after CRT.<sup>9</sup> To progress in the optimization of patient selection for local excision, a better understanding of non-metastatic ypT0 rectal cancer is required as many questions persist.

Our aim was to explore LN metastasis risk and oncological features of ypT0 rectal cancer after CRT followed by TME and to assess the impact of cT and cN staging on the risk of

ypN+ and on the oncological survival in a large retrospective multicentre cohort of the GRECCAR group.

## **Methods**

### *Population*

From January 1, 2002 to December 31, 2015, all patients who underwent TME for a non-metastatic rectal adenocarcinoma classified ypT0 after neoadjuvant CRT, with or without locoregional LN involvement (ypN+ or ypN-), in 14 French academic centers of the GRECCAR, were retrospectively included. We excluded patients classified ypT0 after local excision and patients with synchronous distant metastasis. Patients with a tumor located in the upper rectum (above 10 cm from the anal verge on pre-therapeutic MRI) were also excluded. Thus, theoretically, all included patients would have been technically eligible for rectal sparing management after the neoadjuvant treatment. Data regarding pre-operative staging, neoadjuvant treatment, TME, pathological analysis and post-operative morbidity were retrospectively collected. This study was conducted according to the ethical standards of the Committee on Human Experimentation of each institution, and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

10

### *Pre-therapeutic staging*

Rectal tumors were initially assessed by digital rectal examination, colonoscopy with biopsy, pelvic MRI, and thoraco-abdomino-pelvic computed tomography (CT) scan. Endorectal ultrasound was performed only for cT1 lesions at the discretion of surgeons and of physicians in each expert center. Pre-therapeutic staging (cTNM) relied on pelvic MRI for cT and cN classification and on thoraco-abdomino-pelvic CT-scan for cM classification. We used the 8<sup>th</sup> edition of TNM classification from AJCC.<sup>11</sup>

### *Therapeutic sequence*

Neoadjuvant treatment modalities were decided during a multidisciplinary cancer conference in each center. All patients received long-course neoadjuvant CRT (45-50 Gy with intravenous 5-fluorouracil or capecitabine). The radiation fields and the doses administered were standardized among all participating centers and were in accordance with French guidelines.<sup>12</sup> The interval between the end of the neoadjuvant treatment and the TME was appreciated at the discretion of the surgeon. No specific imaging was required after the end of the neoadjuvant CRT and the surgery. Through an open or laparoscopic approach, the surgery consisted of TME with either a sphincter-saving procedure or abdominoperineal resection, depending on the height of the tumor and on the surgeon's decision. All LN in the mesorectum and along the inferior mesenteric artery were harvested, whereas no other LN such as lateral pelvic LN were dissected, as recommended in the French guidelines.<sup>3, 12</sup> A coloanal anastomosis or a definitive colostomy (abdominoperineal resection or low Hartmann) was performed at the end of the procedure. Thirty-day postoperative morbidity and mortality were recorded. Postoperative morbidity was defined as any deviation from the normal postoperative course, graded according to the Dindo–Clavien classification.<sup>13</sup> A complication classified Dindo-Clavien III or higher was considered as major. Intra-abdominal septic morbidity included anastomotic leakage and intra-abdominal abscess.

The final pathology of the resected specimen was analyzed. Data collected included the ypT0 status of the resected rectal tumor, the total number of LN harvested and the number of metastatic LN found in each surgical specimen.

Adjuvant chemotherapy was given according to the multidisciplinary cancer conference in each participating center, primarily but not exclusively for patients with nodal metastasis on definitive pathological analysis (ypN+).

### *Local/distant recurrence and survival*

Follow-up was planned in accordance with the French Guidelines<sup>3, 12</sup> and consisted of clinical examination, thoraco-abdomino-pelvic CT-scan (or abdominal ultrasound with chest radiography) and serum CEA analysis every 3 to 4 months for the first 3 years, and subsequently every 6 months for 2 years. Follow-up data regarding oncological recurrence and survival were completed with medical consultation reports or by contacting the patients, the general practitioners, the surgeon or the oncologist. Any recurrence in the liver, lung, distant nodes, or carcinomatosis were considered as distant recurrences. Any pelvic or anastomotic recurrence were classified as local recurrences. We assessed overall survival (OS) (delay between surgery and death whatever the cause) and disease-free survival (DFS) (delay between the surgery and first recurrence of the rectal cancer). Time was censored at the date of the last follow-up for patients who were still alive.

### *Statistical analysis*

Qualitative data was reported as frequencies and percentages and compared with the  $\chi^2$  test if expected cell count  $\geq 5$  and with Fisher's exact test if not. Quantitative data were expressed as medians and interquartile range (IQR) and compared using the Mann-Whitney U test. Survival curves were plotted using the Kaplan–Meier method. Log-rank test was used to compare survival curves regarding OS and DFS. Multivariate Cox proportional hazards regression was conducted to explore the potential prognostic factors influencing survival. All factors achieving a p-value  $<0.05$  in the univariate analysis with log-rank test were included in the multivariate model with backward stepwise selection defined by successive eliminations of the variable with the highest p-value of the model and with a threshold of p-value  $>0.5$ . Hazard ratios (HR) were presented with their 95% confidence interval (95CI). In



an intention-to-treat analysis, postoperative deaths were not excluded from the survival analysis. Follow-up time was estimated using the reverse Kaplan-Meier method. All tests were two-sided. A  $p$ -value of  $<0.05$  was considered statistically significant. All analyses were performed using the R 4.0.2 Software (R Core Team, Austria).

## Results

### *Population*

Between January 1, 2002 and December 31, 2015, in 14 French academic centers participating in GRECCAR, 383 patients underwent TME after neoadjuvant CRT for a non-metastatic rectal adenocarcinoma classified ypT0 on the surgical specimen. Characteristics of this cohort are reported in **Table 1**. Briefly, the median age was 63.2 (IQR 56.0-69.2) years and 40% of the patients were female (154/383). Before starting neoadjuvant treatment, the majority of tumors were classified cT3 (79%, 301/380), 13% were cT2 (49/380), 7% were cT4 (26/380). Before CRT, 59% of the tumors were considered cN+ (222/378). The median delay between CRT and TME was 56.0 (IQR 49.0-65.0) days. Surgery consisted of a Hartmann procedure or abdominoperineal resection for 11% of the cohort (42/383), whereas a coloanal anastomosis was performed in 89% (341/383).

Overall postoperative morbidity occurred in 34% of the cases (129/378). Morbidity due to intra-abdominal sepsis occurred in 15% (62/373). The post-operative mortality rate was 0.8% (3/378).

On final pathological analysis, 6% of ypT0 patients were ypN+ (23/383), including 5.5% (21/383) ypT0N1 and 0.5% (2/383) ypT0N2. Among the ypT0N+ patients, the median LN ratio was 0.1 (IQR 0.1-0.1) and the median number of metastatic LN was 1 (IQR 1-1). More than 2 metastatic LN were found in 13% of ypT0N+ patients (3/23). Adjuvant chemotherapy was administered to 8% of the cohort (30/364), mainly influenced by the ypT0N+ status since

73% of ypT0N+ (16/22) received adjuvant chemotherapy versus 4% (14/342) of ypT0N- patients ( $p < 0.001$ ).

After a median follow-up of 61.1 (IQR 36.5-84.2) months, we observed 95% 95CI [92%-97%] of 5-year OS and 93% 95CI [91%-96%] of 5-year DFS. During the follow-up, 25 recurrences were diagnosed after a median follow up interval of 23.3 (IQR 12.2–31.0) months, including 19 distant recurrences (76%), 5 local recurrences (20%) and 1 recurrence with missing data for the site of recurrence (4%).

#### *Risk factors for LN involvement*

We searched for factors that could predict ypN+ status among ypT0 patients through univariate analysis. As reported in **Table 2**, none of the tested variables were statistically associated with LN involvement in ypT0 patients after CRT and TME. Interestingly, the risk of nodal involvement did not differ between cT3/T4 (6%, 18/327) patients and cT1/T2 (9%, 5/53) ( $p = 0.345$ ). In detail, cT1, cT2, cT3 and cT4 were ypT0N+ in 0% (0/4), 10% (5/49), 5% (15/301) and 10% (3/26) of the cases respectively ( $p = 0.239$ ).

Similarly, cN+ patients did not have a higher rate of ypT0N+ in comparison with cN- patients ( $p = 0.384$ ): among the 222 patients classified cN+, 7% were ypT0N+ ( $n = 16$ ) whereas 93% were ypT0N- ( $n = 206$ ). Of the ypN+ patients, 30% were initially staged cN- (7/23). In the subgroup of the cT3 patients, 7% ( $n = 12$ ) of the 178 patients classified cN+ were ypT0N+ and 20% of ypN+ patients were initially staged cN- (3/15).

#### *Overall and disease-free survival analysis*

We explored factors that may influence OS and DFS in ypT0 patients through univariate and multivariate analysis. Results of this analysis are presented in **Table 3**. OS was significantly altered by patient characteristics (age  $\geq 60$  years, male sex and ASA3-4), by the occurrence of

major post-operative complications and by intra-abdominal septic complications in univariate analysis. In multivariate analysis, only the occurrence of intra-abdominal septic complications significantly reduced OS (HR=2.53 95CI[1.11-5.78], p=0.028). Regarding DFS, only ypN+ status and administration of adjuvant chemotherapy were associated with a reduced DFS in univariate analysis (p=0.001 for both). Three-year DFS was 96% IC95[94%-98%] in ypN- patients and 77% CI95[61%-97%] in ypN+ patients. In total 73% of ypT0N+ (16/22) received adjuvant chemotherapy versus 4% (14/342) of ypT0N- patients (p<0.001). Thus, we did not conduct a multivariate Cox proportional hazard regression for the DFS because these two variables were strongly correlated.

We focused our analysis on the potential impact of the clinical staging before CRT+TME on OS and DFS. cT3/T4 patients were not observed to have a poorer OS or DFS than cT1/T2 patients (p-value=0.332 and 0.862 respectively, see **figures 1A and 1B**). Regarding pretherapeutic LN staging, here again, OS and DFS did not differ between cN+ and cN- patients (p-value=0.450 and 0.124 respectively, see **figures 2-A and 2-B**).

## **Discussion**

Among 383 patients with rectal cancer treated by TME after neoadjuvant CRT and classified ypT0, 94% of them did not have LN metastasis on the surgical specimen. The risk of LN metastasis was not higher in tumors initially staged cT3-T4 versus cT1-2 or cN+ versus cN-. The oncological prognosis of the cohort was excellent with 93% 5-year DFS. OS and DFS were not lower for patients with a rectal cancer classified cT3-T4 or cN+. Intra-abdominal septic complications, which were a frequent event occurring in 15% of patients after TME, was the only factor that compromised OS in multivariate analysis.

In a recent meta-analysis exploring ypT0 patients treated for a rectal cancer, the rate of ypT0N+ was 4.6% 95CI[2.4-7.3].<sup>14</sup> This result is comparable with the rate of 6% we found in our study. However, a higher risk of ypN+ for male was also reported in this meta-analysis.<sup>14</sup> We did not confirm this result since we observed 6.0% (13/216) of ypT0N+ in male versus 6.9% (10/144) in female (p=0.912). Moreover, none of the variables we evaluated including cN staging were predictive of LN metastasis in ypT0 lesions (**table 2**). Some relevant variables, such as the pretherapeutic CEA level were not collected in our database and so were not included in the statistical analysis. This is a limitation of our work, as we cannot conclude that ypN staging is absolutely impossible to predict. However, our analysis mainly indicates that the currently recommended pre-therapeutic imaging assessment is a poor indicator of the pathological LN involvement for rectal cancers after CRT. Given the existence of current organ-sparing approaches for rectal cancer patients with a complete pathological response to CRT, the ability to predict LN involvement is of great relevance in order to enhance patient selection, e.g. TME only for those with persistent LN metastasis. However, the accuracy of pre-operative imaging in diagnosis of LN metastasis is low, as has already been reported in the literature.<sup>15</sup> In our study, 30% of ypN+ patients were initially staged cN- and 93% of patients initially staged cN+ were ypN-. Since systematic restaging by MRI or endorectal ultrasound (ERUS) after CRT and prior to surgery was not routinely conducted, we are not able to report the performance of these imaging modalities to assess the clinical response after neoadjuvant CRT. However, in a meta-analysis evaluating the performance of MRI and ERUS for the restaging of LN involvement, the average accuracy reported was only 72% for MRI and 73% for ERUS.<sup>16</sup> The rate of under-staging, which is the most unfavorable situation when a strategy of organ preservation is being considered, was 16% for MRI and 14% for ERUS in this same meta-analysis.<sup>16</sup> Different strategies have been attempted to increase the performance of LN staging after neoadjuvant CRT, such as

comparing MRI before and after the CRT<sup>17, 18</sup> or proposing a nomogram that aggregates clinical, pathological and imaging data<sup>19</sup>, but the performances obtained are still sub-optimal.

In contrast to the low risk of LN metastasis of 6%, 34% of the patients developed postoperative complications. Of the cohort, 15% developed an intra-abdominal septic complication and 12% a major postoperative complication after TME. In previous randomized controlled trials conducted by our group with a prospective collection of the outcomes, the postoperative morbidity reported was close to our results collected retrospectively, with postoperative complication and intra-abdominal septic complication rates of 48% and 17% in the GRECCAR-5 trial and of 38% and 15% in the GRECCAR-6 trial.<sup>20, 21</sup> Interestingly, a recent meta-analysis found a higher risk of anastomotic leakage after TME for rectal cancer in patients with a complete pathological response than in patients without.<sup>22</sup> In addition to this risk of anastomotic leakage, 11% of the patients in our series did not have coloanal anastomosis after the TME, which is also consistent with previous data on this topic.<sup>21</sup>

We found that the occurrence of an intra-abdominal septic complication was the only factor that significantly impaired the OS in multivariate analysis. Hain et al. reported a negative oncological impact of anastomotic leakage after TME.<sup>23</sup> All in all, the negative impact of intra-abdominal septic complications on survival, the low rate of LN metastasis in ypT0 tumors and the high rate of post-operative complications related to radical surgery are all arguments in favor of rectal preservation strategies. During the inclusion period of our study, local excision or watch and wait procedures were rarely performed because guidelines did not recommend them at this time.<sup>12, 24</sup> Recent advances in the treatment of rectal cancer led to new recommendations considering rectal preservation strategies.<sup>3</sup> However, rectal

preservation for locally advanced tumors classified cT3 or cT4 is a challenging situation. Regarding the watch and wait strategy, the study from the International Watch & Wait Database published in 2021 and based on 793 patients treated by active surveillance after clinical complete response reported a significant higher rate of local recurrence in patients with cT3-T4 tumor versus those with a cT1-T2 tumor ( $p=0.0083$ ).<sup>8</sup> In addition, the risk of LN metastasis increases as cT and ypT stages increase.<sup>25, 26</sup> For this reason, prospective trials assessing local excision after neoadjuvant treatment often considered only early-stage rectal cancer classified cT1 or cT2.<sup>27-29</sup> Lesions staged cT3 were included in three prospective studies.<sup>9, 30, 31</sup> In the CARTS-study, cT1-T3 lesions were considered but always with a cN0 stage.<sup>31</sup> The GRECCAR-2 trial included patients with a higher clinical staging than assessed up to now, considering up to cT3 and cN1 lesions with a maximum size of 4 cm. cT3 tumors larger than 4 cm, cT4 and cN2 were excluded.<sup>9</sup> Our results indicate that patients with cT3/T4 lesions are not more at risk than cT1/T2 lesions with LN involvement in case of ypT0 tumor after CRT (respectively 6% and 9% of ypN+,  $p=0.345$ ). Nevertheless, our work provides only pathological arguments and does not directly evaluate local excision. Therefore, only a prospective study comparing the oncological survival after local excision versus TME in cT4 or cT3 patients with a large rectal tumor in case of a complete histological response (ypT0) after CRT could validate the oncological safety of this therapeutic strategy. To go further, two recent trials have asserted the oncological benefit of intensifying the neoadjuvant treatment by chemotherapy in addition to (chemo)-radiotherapy.<sup>32, 33</sup> In the RAPIDO-trial, the rate of ypT0 after TME was significantly increased by the intensified protocol (short-course radiotherapy followed by chemotherapy) in comparison to the conventional neoadjuvant CRT from 17% to 30%.<sup>32</sup> The rate of LN involvement among ypT0 patients after this intensified protocol was of 7.5%. In the PRODIGE-23 trial, the rate of ypT0 after TME was also significantly increased by the intensified protocol (neoadjuvant chemotherapy followed by preoperative

chemoradiotherapy) from 13% to 28%, and only 2% of ypT0 had a concomitant LN involvement.<sup>33</sup> Interestingly, in the intensified groups, 32% and 18% of the tumors were cT4 in the RAPIDO and PRODIGE-23 trials respectively and 91% and 90% were cN+, strengthening our results. The ongoing NORAD-01 trial assessing the oncological safety of preoperative chemotherapy alone by FOLFIRINOX without radiotherapy in locally advanced rectal cancer will continue to hone the ongoing optimization of neoadjuvant treatments before surgery.<sup>34</sup>

This study has some limitations due to the retrospective nature of the collected data. Some variables were missing, and the interpretation of conclusions are based only on the pathological findings. However, the large number of included patients, the multicenter collection and the long follow-up should counter-balance these limitations.

In conclusion, the risk of LN metastasis in ypT0 rectal cancer after neoadjuvant CRT and TME is about 6%, and this risk cannot be safely predicted by the cT or the cN stage. The oncological survival in this situation is excellent with a 95% 5-year OS and 93% 5-year DFS and does not depend on the cT or cN stage.

**Funding/support:** None

**COI/Disclosure:** The authors have no related conflicts of interest to declare.

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**Table 1.** Population description

Variables	N = 383
<b>Baseline characteristics</b>	
Age (years) (n=377)	63.2 (56.0-69.2)*
Sex : Female/Male (n=383)	154 (40) <sup>#</sup> / 229 (60)
ASA score <sup>+</sup> (n=371)	
1	130 (35)
2	187 (50)
3	51 (14)
4	3 (0.8)
cT stage (n=380)	
1	4 (1.1)
2	49 (13)
3	301 (79)
4	26 (6.8)
cT stage: cT1-2 / cT3-4 (n=380)	53 (14) / 327 (86)
cN stage : positive / negative (n=378)	222 (59) / 156 (41)
<b>Surgery</b>	
Delay between the end of CRT <sup>§</sup> and surgery (days) (n=271)	56.0 (49.0-65.0)
Surgical approach (n=280)	
<i>Laparotomy</i>	152 (40)
<i>Laparoscopy</i>	201 (53)
<i>Conversion to laparotomy</i>	27 (7.1)
Coloanal anastomosis / No anastomosis (n=383)	341 (89) / 42 (11)
Post-operative overall morbidity (n=378)	129 (34)
Major post-operative morbidity (n=378)	46 (12)
Surgical morbidity (n=365)	93 (25)
Intra-abdominal septic morbidity (n=377)	56 (15)
Medical morbidity (n=373)	62 (17)
Length of hospital stay (days) (n=378)	10.0 (8.0-13.0)
<b>Pathology</b>	
Number of metastatic LN <sup>†</sup> harvested	12.0 (8.0-18.0)
ypN positive / negative (n=383)	23 (6.0) / 360 (94)
ypN classification (n=383)	
<i>N0 (0 metastatic LN)</i>	359 (94)
<i>N1 (1 to 3 metastatic LN)</i>	22 (5.5)
<i>N2 (≥4 metastatic LN)</i>	2 (0.5)
<b>Adjuvant chemotherapy (n=364)</b>	30 (8.2)

\* Median (Interquartile 25%-75%); # Number (percentage); + American Society of Anesthesiologists; § Chemoradiotherapy; † Lymph nodes.

**Table 2.** Baseline characteristics, surgery, pathology and adjuvant treatment between patients with pathological LN metastasis (ypN+) and patients without (ypN-)

Variables	ypN- N=360	ypN+ N=23	p-value
<b>Baseline characteristics</b>			
Age (years) (n=377)	63.4 (56.1-69.5) *	60.8 (52.5-66.0)	0.196
Sex: Female/Male	144 (40) #/216 (60)	10 (43)/13 (57)	0.912
ASA score <sup>+</sup> (n=371)			>0.999
1	123 (35)	7 (33)	
2	176 (50)	11 (52)	
3	48 (14)	3 (14)	
4	3 (0.9)	0 (0)	
cT stage: cT1-2 /cT3-4 (n=380)	48 (13)/309 (87)	5 (22)/18 (78)	0.345
cN stage: positive / negative (n=378)	206 (58)/149 (42)	16 (70)/7 (30)	0.384
<b>Surgery</b>			
Delay between the end of CRT <sup>§</sup> and surgery (days) (n=271)	56.0 (49.0-65.0)	60.0 (55.5-69.5)	0.131
Surgical approach (n=380)			>0.999
Laparotomy	143 (40)	9 (39)	
Laparoscopy	188 (53)	13 (57)	
Conversion to laparotomy	26 (7)	1 (4)	
Anastomosis / No anastomosis	323 (90)/37 (10)	18 (78)/5 (22)	0.157
Post-operative overall morbidity (n=378)	121 (34)	8 (35)	>0.999
Major post-operative morbidity (n=378)	43 (12)	3 (13)	0.751
Surgical morbidity (n=365)	87 (25)	6 (29)	0.939
Intra-abdominal septic morbidity (n=377)	52 (15)	4 (17)	0.761
Medical morbidity (n=373)	57 (16)	5 (22)	0.561
Length of hospital stay (days) (n=378)	10.0 (8.0-13.0)	11.0 (8.5-13.5)	0.528
<b>Pathology</b>			
Number of metastatic LN <sup>†</sup> harvested	12.0 (8.0-18.0)	14.0 (11.0-21.5)	0.071

\* Median (Interquartile 25%-75%); # Number (percentage) ; <sup>+</sup> American Society of Anesthesiologists; <sup>§</sup> Chemoradiotherapy; <sup>†</sup>Lymph nodes.

**Table 3.** Univariate (log-rank) and multivariate (Cox regression) analysis of factors that may be associated with an altered OS or DFS in ypT0 patients after CRT and TME.

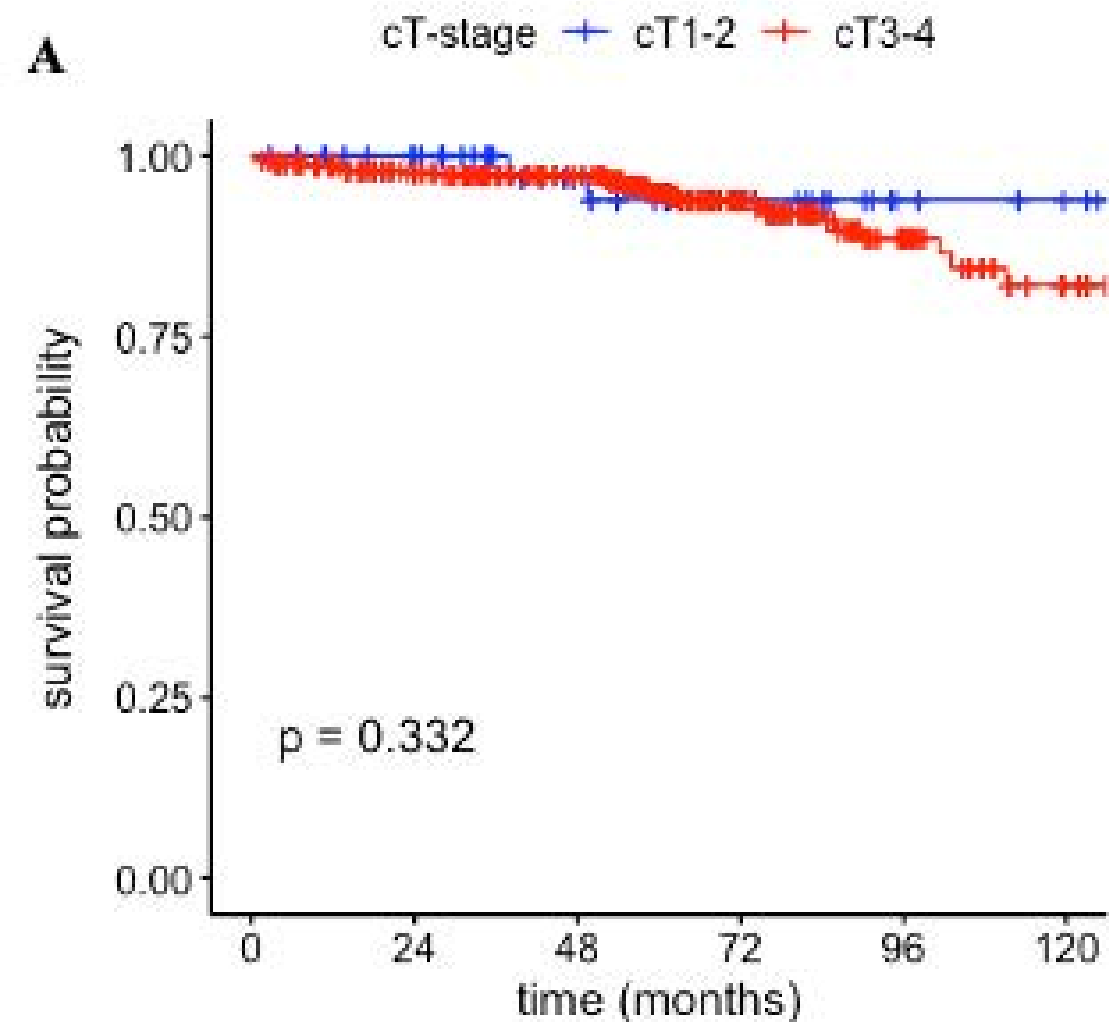
Variables	Univariate	Multivariate		
	log-rank	HR <sup>§</sup>	95% CI <sup>†</sup>	P-value
<u>OVERALL SURVIVAL</u>				
Age ≥ <b>60y</b> <sup>*</sup> / < 60y	<b>0.014</b>	2.45	[0.90-6.6]	0.078
Sex: <b>Male</b> <sup>*</sup> / Female	<b>0.043</b>	2.14	[0.89-5.14]	0.088
ASA score <sup>+</sup> : 1-2 / <b>3-4</b> <sup>*</sup>	<b>0.019</b>	2.19	[0.89-5.3]	0.086
cT: cT1-2 / cT3-4	0.332	-	-	-
cN: positive / negative	0.450	-	-	-
Delay between the end of CRT <sup>§§</sup> and surgery: ≤ 7 weeks / > 7 weeks	0.777	-	-	-
Post-operative overall morbidity: Yes/No	0.119	-	-	-
Major post-operative morbidity: <b>Yes</b> <sup>*</sup> /No	<b>0.001</b>	-	-	NS <sup>‡</sup>
Intra-abdominal septic morbidity <b>Yes</b> <sup>*</sup> /No	<b>0.001</b>	<b>2.53</b>	<b>[1.11-5.78]</b>	<b>0.028</b>
ypN : Positive / Negative	0.543	-	-	-
Adjuvant chemotherapy Yes/No	0.179	-	-	-
<u>DISEASE-FREE SURVIVAL</u>				
Age ≥ 60y / < 60y	0.888	-	-	-
Sex: Female / Male	1.000	-	-	-
ASA score <sup>+</sup> : 1-2 / 3-4	0.647	-	-	-
cT: cT1-2 / cT3-4	0.862	-	-	-
cN: positive / negative	0.124	-	-	-
Delay between the end of CRT <sup>§</sup> and surgery: ≤ 7 weeks / > 7 weeks	0.227	-	-	-
Post-operative overall morbidity: Yes/No	0.431	-	-	-
Major post-operative morbidity: Yes/No	0.084	-	-	-
Intra-abdominal septic morbidity Yes/No	0.084	-	-	-
ypN : Positive / Negative	<b>0.001</b>	NI <sup>¶</sup>	-	-
Adjuvant chemotherapy Yes/No	<b>0.001</b>	NI <sup>¶</sup>	-	-

<sup>§</sup> Hazard ratio; <sup>†</sup> Confidence interval 95%; <sup>\*</sup> Bold text indicates the variable's reference used for the multivariate analysis with the Hazard ratio calculation; <sup>+</sup> American Society of Anesthesiologists; <sup>§§</sup> Chemoradiotherapy, <sup>‡</sup> Backward elimination of this variable from the multivariable Cox proportional hazard model (p-value > 0.5). <sup>¶</sup> NI: not included, we did not perform Cox regression on these two variables as they reflected the same patient profile in the cohort. OS, overall survival; DFS, disease free survival; CRT, chemoradiotherapy; TME, total mesorectal excision

## **Figures titles and legends**

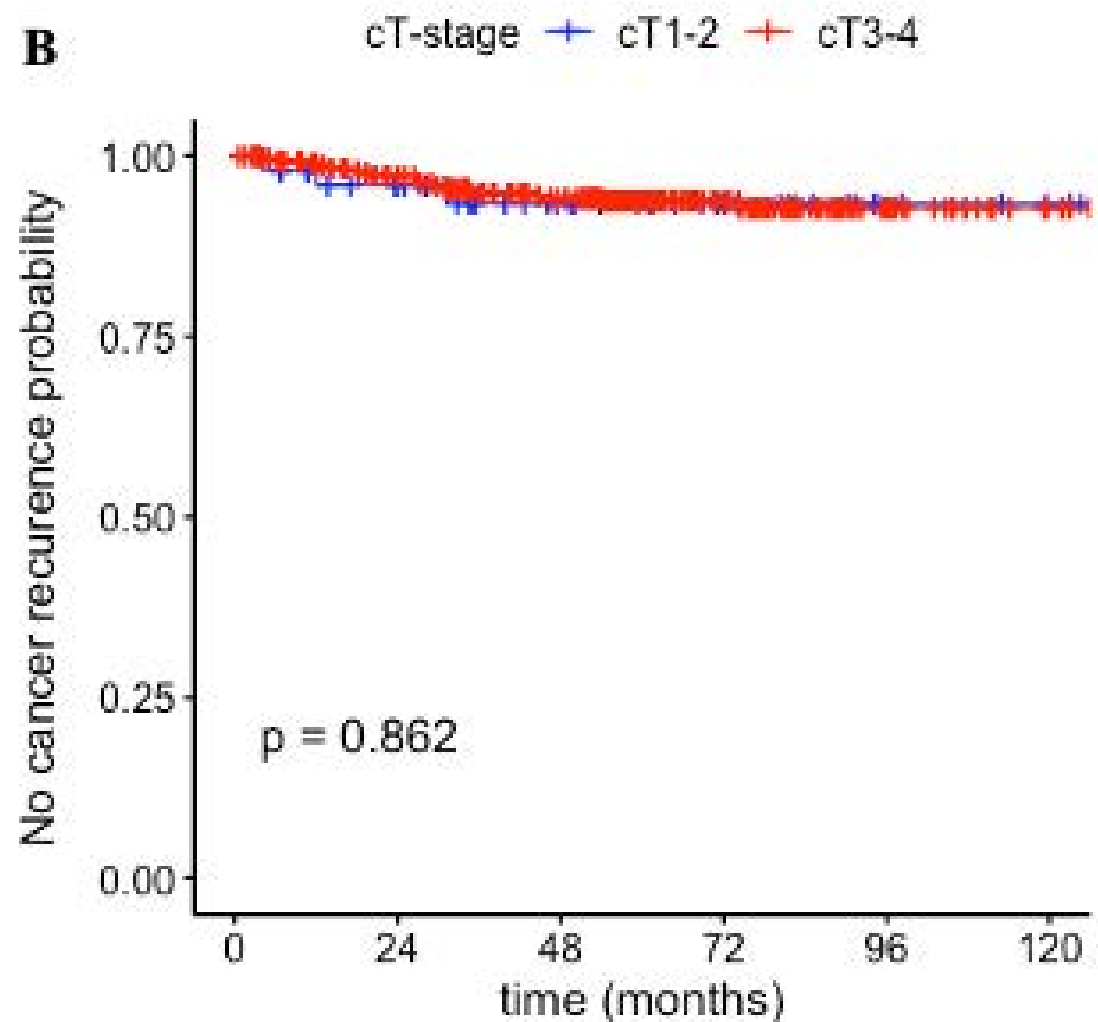
**Figure 1:** Overall survival (1-A) and disease-free survival (1-B) curves according to the cT staging (cT1-2 versus cT3-4) before neoadjuvant CRT and surgery.

**Figure 2:** Overall survival (2-A) and disease-free survival (2-B) curves according to the cN staging (cN positive versus cN negative) before neoadjuvant CRT and surgery.



Number at risk

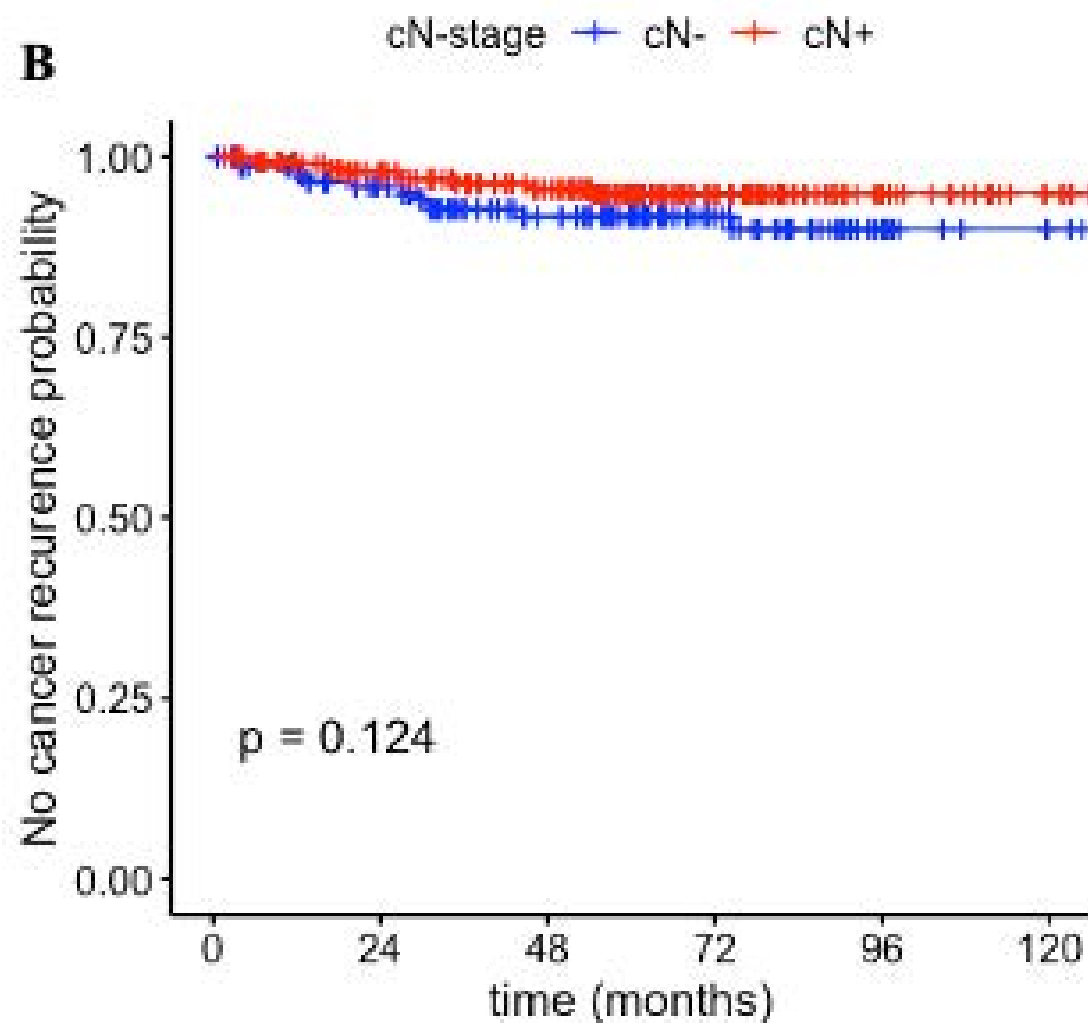
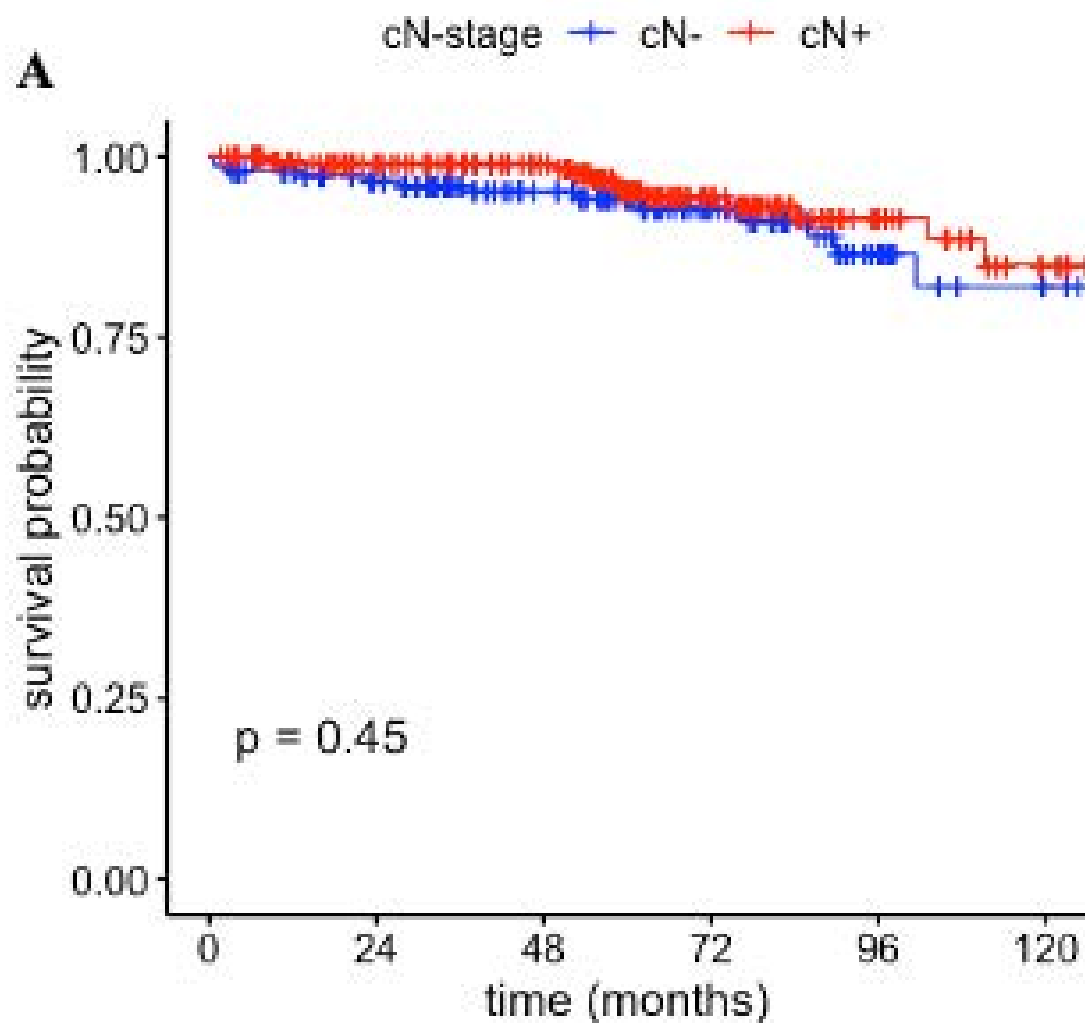
	0	24	48	72	96	120
cT1-2	53	45	30	18	7	4
cT3-4	327	279	226	120	55	28



Number at risk

	0	24	48	72	96	120
cT1-2	53	43	28	16	6	3
cT3-4	323	270	213	111	49	26





Number at risk						
	0	24	48	72	96	120
cN-	156	135	101	58	26	14
cN+	222	187	153	80	36	18

Number at risk						
	0	24	48	72	96	120
cN-	154	127	93	53	23	13
cN+	220	184	146	74	32	16