Complete Pathological Response Following Radiochemotherapy for Locally Advanced Rectal Cancer: Short and Long-term Outcome

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Abstract. *Background/Aim:* Preoperative radiochemotherapy (RCT) followed by total mesorectum excision has become the gold standard for locally advanced carcinoma of the low and middle rectum. The aim of the study is to evaluate the short and long-term outcomes of patients in complete pathological response (PR) following this treatment sequence. *Patients and Methods:* One hundred and thirty patients were retrospectively included between 2005 and 2017 in an expert centre, with 3 groups formed, according to the PR: i) complete PR (absence of tumour cells on the surgical specimen ypT0N0), ii) partial PR (T or N downsizing) and iii) without PR. *Results:* The complete PR rate was 13.1%. The complete PR group tended to develop less symptomatic fistulas compared to partial PR and without PR groups (5.8% versus 13.5% versus 18.7, respectively; $p=0.607$). The 5-year disease-free survival was increased for complete-PR patients (93% versus 79% versus 47%, respectively; $p=0.0003$) without an improvement in overall survival. *Conclusion:* Complete PR is associated with an improvement

in survival without recurrence and without an improvement in the overall survival at 5 years.

The management of rectal carcinoma has evolved over the last twenty years and is now well standardized (1). Preoperative radiochemotherapy (RCT) followed by proctectomy with total mesorectal excision (TME) is the gold standard for locally advanced rectal carcinoma (2-4). This new management allows a strong decrease of the local recurrence rate (from 16.5% to 8.2%, $p<0.001$) and an improvement of the disease free survival (from 65.8% to 77.3%, $p<0.001$) (3-5). Adding a neoadjuvant treatment by preoperative RCT for locally advanced mid- or low tumour has improved local tumour control. RCT has resulted in a positive response with downstaging in 2/3 of patients and a complete pathological response (cPR) in 1/5 of patients (3, 6, 7). cPR is associated with a decrease in local recurrence, and improvement of disease-free survival (8-10). This breakthrough has not only allowed a decrease in the recurrence rate, but has also offered better outcomes from the anal sphincteric preservation technique (and consequently a decrease in the abdominoperineal resection rate) (11). Some conflicting results have been reported concerning the impact of cPR on the overall survival (9, 12). Similarly, the correlation between cPR and neoadjuvant therapy is still debated, particularly with regard to anastomotic leakage. Maggiori *et al.*, showed that patients without complete cPR have more symptomatic anastomotic fistula while Landi *et al.*, have not found this association (13, 14). To our knowledge, few studies have examined the relationship between cPR and the functional outcomes following

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Key Words: Rectal carcinoma, radiochemotherapy, pathological response.

proctectomy with neoadjuvant RCT. Thus, the impact of the pathological response (PR) on postoperative morbidity and oncological and functional outcomes are yet to be clarified.

The aim of this study is to evaluate short- and long-term outcomes for patients with a complete pathological response following neoadjuvant radiochemotherapy and total mesorectal excision for locally advanced rectal cancer.

Patients and Methods

Population and study design. From January 2005 to December 2017, 600 consecutive patients underwent elective rectal resection for rectal cancer in our department. One hundred and thirty patients (21%) for locally advanced rectal adenocarcinoma biopsy proven with cT3, T4 or TxN+, bulky T2 or anterior T2 by radiologic examination (magnetic resonance imaging and/or endo-ultrasound) of the mid, lower and upper rectum who had received neoadjuvant RCT, were reviewed. All patients were preoperatively treated by neoadjuvant RCT. The exclusion criteria were: i) rectal cancer with synchronous metastasis, ii) previous surgery of the left sided colon and iii) local or abdominoperineal resection or Hartmann's procedure required. Data collection included: i) demographic variables, ii) operative and iii) postoperative features.

Preoperative work-up. Data were retrospectively retrieved from medical records. Demographic features (gender, age at time of surgery, body mass index, comorbidity and ASA score), tumour evaluation before neoadjuvant treatment, pathological and oncological results were collected. Tumour evaluation was based on physical examination using: i) digital rectal exam and anoscopy, ii) total colonoscopy with biopsy, iii) endorectal ultrasound (EUS) and/or iv) pelvic magnetic resonance imaging (MRI), as well as v) computed thoracoabdominal (CT).

Neoadjuvant treatment: radiochemotherapy. All patients received preoperative external beam megavoltage radiation therapy at a total dose of 45 to 50.4 Gy, delivered in daily 1.8- to 2.1-Gy fractions 5 days per week over a 5-6 week period. Pelvic volume was defined based on tumour characteristics, mesorectum, the ventral side of the sacrum and the hypogastric vessels. L5 and S1 vertebrae determined the upper limit, while the levator ani muscle or the anal verge determined the lower limit. Preoperative chemotherapy was concomitantly administered to all patients (oral 5-FluoroUracil (Capecitabine, Xeloda®, 825 mg/m²/day, twice a day) (15).

Surgical procedure. All patients underwent mechanical bowel preparation before surgery (16). Laparoscopy was the standard approach except for patients presented with T4 tumour or those considered unfit for laparoscopic approach. A medial to lateral approach was performed, with the operative procedure routinely involving high ligation of the inferior mesenteric vessels, complete mobilization of the splenic flexure, and TME (1). Proximal colon was transected by linear stapler, 10 cm above the lesion. The type of anastomosis was left to the discretion of the surgeon. Sphincter preservation was performed when necessary. A temporary loop ileostomy was performed in all cases, and a pelvic single suction drain was placed behind the anastomosis for 48-72 hours in all cases. A protective stoma was closed 6 to 8 weeks postoperatively if CT-scan with water-soluble enema did not show any evidence of anastomotic leakage.

Pathological findings. Surgical specimens were analysed using a standardized protocol (17). Histological evaluation consisted on: i) ypTNM staging, ii) circumferential and longitudinal margins (R0, R1 and R2, for complete, microscopically and macroscopically incomplete resections, respectively), iii) completeness of mesorectum resection, iv) degree of colloid component, v) differentiation grade, vi) presence of vascular, lymphatic or perineural emboli. An involved circumferential resection margin (CRM) was defined as ≤ 1 mm between the deepest tumour invasion and the margin of surgical resection inked previously. This included a tumour within a lymph node, as well as a direct tumour extension. Acellular pools of mucin at the level of the CRM following neoadjuvant radiochemotherapy were considered as a negative CRM (18). PR was obtained by comparing tumour and node staging (cTNM) before RCT to postoperative histological analysis (ypTNM). Three groups were defined as follows: i) complete pathological response (cPR), ii) absence of tumour cell in the surgical specimen (ypT0N0), iii) partial pathological response (pPR) (T or N downstaging) and without pathological response (wPR).

Short-term outcomes. Postoperative morbidity and mortality were defined as events occurring during hospital stay or within 30 postoperative days. Postoperative complications were ranked according to the international Clavien Classification (19). Severe morbidity was defined as Dindo 3 or greater. In-hospital stay was measured from the time of surgery to the date of discharge from the hospital. Post-operative complications have been divided into: i) abdominal complications (*e.g.* fistula, collection, wound abscess, ileus *etc.*) and ii) extra-abdominal complications (*e.g.* urinary tract disease, pulmonary embolism, *etc.*). Anastomotic leakage (AL) was defined according to the International Study Group of Rectal Cancer (20). Symptomatic fistula requiring modification of management (medical, radiological or surgical) have been differentiated from asymptomatic fistula (diagnosed on enema-contrast CT-scan, routinely performed 6 to 8 weeks postoperatively, before considering stoma reversal). Any clinical (sepsis, peritonitis, emission of gas, pus, or faeces from the pelvic drain, purulent discharge per anus, or rectovaginal fistula) and/or biological suspicion of AL led to an early CT-scan assessment. Symptomatic AL management included antibiotics, radiologic or transanal drainage, and/or early abdominal redo surgery (13). In asymptomatic AL, stoma reversal was postponed and enema-contrast CT was repeated until AL tract was no longer seen. If asymptomatic AL persisted >6 months postoperatively, protective stoma reversal was performed, as was described recently (21).

Long-term outcomes. Long-term functional and oncological outcomes were recorded for all patients. Patient follow-up was performed every 3 months for the first 2 postoperative years, every 6 months for the next 3 years, and annually thereafter. Follow-up was updated until December 2018 and consisted of clinical examination, CT-scan and blood samples with colonoscopy performed 1 year following surgery and then every 3 years. Follow-up data was obtained from medical records of the outpatient clinic or through phone interviews. Local recurrence was defined as tumour recurrence at the anastomotic site or in the pelvic cavity, while distant recurrence was defined as tumour recurrence beyond the loco-regional area, including liver, lung and other extrapelvic sites. Surviving patients were assessed for disease recurrence and site of recurrence. Long-term functional genito-urinary and digestive

Table I. Study population (n=130) demographic data.

	Without PR n (%)	Partial PR n (%)	Complete PR n (%)	Overall n (%)	p-Value
Patient features	32 (24.6)	81 (62.3)	17 (13.1)	130 (100)	
Gender (Male/Female)	12/20	26/55	6/11	44/86	0.853
Median age (years)*	63.5 (39-83)	66 (37-84)	64 (42-81)	65.5 (37-84)	0.533
Median BMI (kg/m ²)*	24.5 (18-39)	24 (19-60)	24 (18-39)	24 (18-60)	0.961
Diabetes mellitus	5 (15.6)	6 (7.4)	2 (11.7)	13 (10)	0.409
Arteriopathy	4 (12.5)	6 (7.4)	2 (11.7)	12 (9.2)	0.651
ASA Score					
1	17 (53.1)	43 (53)	12 (70.5)	72 (55.4)	0.646
2	13 (40.6)	32 (39.5)	5 (29.4)	50 (38.5)	
3	2 (6.2)	6 (7.4)	0	8 (6.1)	
Tumor location					
Upper (10-15 cm)	6 (18.7)	18 (22.2)	3 (17.6)	27 (20.7)	0.014
Mid (5-10 cm)	21 (65.6)	44 (54.3)	4 (23.5)	69 (53.1)	
Low (2-5 cm)	5 (15.6)	19 (23.4)	10 (58.8)	34 (26.1)	
Preoperative EUS, MRI, CT, TNM evaluation					
Tumor staging					
T1	0	0	0	0	0.029
T2	3 (9.3)	2 (2.4)	4 (23.5)	9 (6.9)	
T3	28 (87.5)	75 (92.6)	13 (76.5)	116 (89.2)	
T4	1 (3.1)	4 (4.9)	0	5 (3.8)	
Node staging					
N0	12 (37.5)	11 (13.5)	6 (35.3)	29 (22.3)	0.004
N1	20 (62.5)	70 (86.4)	11 (64.7)	101 (77.7)	

PR: Pathological response; ASA: American society of anesthesiologists; EUS: endorectal ultrasound; MRI: magnetic resonance imaging; CT: computed tomography; TNM preoperative evaluation. *Values presented median (range).

outcomes, as well as quality of life assessments were recorded using a French translation of the low anterior resection score (LARS) and the Wexner continence grading scale (22, 23). Overall, 8 (6.2%) patients had a follow-up of less than 6 months and 18 (13.8%) a follow-up of less than 12 months.

Statistical analysis. Statistical analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). All tests were two-sided and statistical significance was accepted at the 0.05 level. Continuous variables are expressed as their medians and ranges (min, max) and were compared using ANOVA or nonparametric ANOVA tests, accordingly. Categorical variables are reported as numbers and percentages and were compared using the χ^2 test with Bonferroni correction whenever necessary. The Kaplan-Meier method was used to estimate recurrence-free survivals (RFS) and overall survivals (OS), which were compared using the Log-rank test. This study was conducted according to the ethical standards of the Committee on Human Experimentation of our institution and were reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines (24).

Results

One hundred and thirty patients with locally advanced rectal carcinoma who underwent curative intent neoadjuvant RCT and rectal resection with total or partial mesorectum excision

were included. According to the aim of the study, three groups of patients were identified: i) wPR group 24.6% (n=32), ii) pPR group 62.3% (n=81) and iii) cPR group 13.1% (n=17).

Demographic and tumour characteristics. Demographic data and carcinoma features and comparison between the three groups are summarized in Table I. There were 44 males (33.8%) with a median age of 65.5 years (37-84). According to the ASA score, patients' comorbidities were comparable between the three groups ($p=0.646$). One hundred and thirty patients who underwent sphincter-preserving resection with curative intent for upper 20.7% (n=27), mid 53.1% (n=69) and low 26.1% (n=34) rectal adenocarcinoma were included. The rate of low rectal tumour was higher in the cPR group (58.8% *versus* 23.4% *versus* 15.6% for cPR, pPR, wPR, respectively; $p=0.014$). Concerning tumour staging in the whole cohort the rates were: 6.9% uT2, 89.2% uT3, 3.8% uT4. Nevertheless, there a higher rate of uT3 in the pPR group compare to wPR and cPR group (92.6% *versus* 87.5% *versus* 76.5%; $p=0.029$). The rate of nodes invaded was 77.7% (n=101), and the group with pPR had a higher rate of nodes invaded compared to the other two groups (86.4% *versus* 62.5% *versus* 64.7% for pPR, wPR, cPR, respectively; $p=0.004$).

Table II. *Surgical procedure and short-term outcomes.*

	Without PR N (%)	Partial PR N (%)	Complete PR N (%)	Overall N (%)	<i>p</i> -Value
Surgical procedure	32 (24.6)	81 (62.3)	17 (13.1)	130 (100)	
Laparoscopic approach	29 (90.6)	75 (92.6)	16 (94.11)	120 (92.3)	0.898
Conversion	10 (31.2)	19 (23.4)	1 (5.8)	30 (23.1)	0.132
Complete TME	27 (84.3)	55 (67.9)	15 (88.2)	97 (74.6)	0.074
Anastomosis type					
Latero-terminal rectal anastomosis	18 (56.3)	39 (48.2)	10 (58.8)	67 (51.5)	0.601
Termo-terminal rectal anastomosis	14 (43.7)	42 (51.8)	7 (41.2)	63 (48.5)	
Colo-anal manual anastomosis	6 (18.7)	10 (12.3)	3 (17.6)	19 (14.6)	0.638
Sphincter preservation	30 (93.8)	79 (95.1)	15 (88.2)	124 (95.4)	0.224
Short-term outcomes					
Overall	12 (37.5)	31 (38.3)	7 (41.2)	50 (38.5)	0.967
Clavien-Dindo					
I-II	9 (28.1)	21 (25.9)	5 (29.4)	35 (26.9)	0.942
III-IV	3 (9.3)	10 (12.3)	2 (11.8)	16 (12.3)	0.905
Abdominal complication					
Anastomotic leak	7 (21.8)	16 (19.7)	3 (17.6)	26 (20)	0.936
Symptomatic Leak	6 (18.7)	11 (13.5)	1 (5.8)	18 (13.8)	0.607
Asymptomatic leak	1 (3.1)	5 (6.1)	2 (11.8)	8 (6.1)	
Pelvic collection	5 (15.6)	7 (8.6)	1 (5.8)	13 (10)	0.446
Wound infection	1 (3.1)	0	1 (5.9)	2 (1.5)	0.141
Abdominal complication management					
Surgical drainage	2 (6.2)	8 (9.8)	2 (11.7)	12 (9.2)	0.966
Hartman	1 (3.1)	3 (3.7)	1 (5.8)	5 (3.8)	0.889
Transanal drainage	0	3 (3.7)	0	3 (2.3)	0.395
Antibiotics only	7 (21.9)	9 (11.1)	4 (23.5)	20 (15.4)	0.218
Extra abdominal complication	5 (15.6)	12 (14.8)	4 (23.5)	19 (14.6)	0.292
Permanent stoma	7 (21.8)	11 (13.6)	1 (5.8)	19 (14.6)	0.292
Hospital stay*	11 (6-51)	11 (6-77)	14 (7-28)	12 (6-77)	0.947

PR: Pathological response. *Values presented as median (range).

Surgery and short-term outcomes. Intraoperative parameters are reported in Table II. Laparoscopic resection was performed in 92.3% (n=120) of patients with comparable rates between the three groups ($p=0.898$). The total mesorectal excision was complete in 74.6% (n=97) of patients with no difference found between both groups ($p=0.132$). Overall, conversion was required in 23.1% (n=30) of patients and there was no difference between the three groups. Latero-terminal anastomosis was performed in 51.5% (n=67) of patients and manual colo-anal anastomosis was performed in 14.6% (n=19) of patients with no statistical difference found between the three groups ($p=0.601$, and $p=0.638$, respectively). Postoperative details are also reported in Table II. Thirty-day mortality rate was nil. Overall complication rate was 38.5% (n=50) for the whole

series without difference between the three groups. A fraction of patients 12.3% (n=16) experienced severe postoperative complications (grade III-IV). AL occurred in 20% (n=26) of patients, including 13.8% of patients (n=18) with a symptomatic leak. AL was more frequent, although statistically not significant, in the wPR group (21.8%).

Redo abdominal surgery was performed after an average of 7 (3-22) days in 15.4% (n=20) of patients (anastomosis resection and/or colostomy placement, n=5 and peritoneal lavage or transanal drainage, n=15). Trans-anal drainage under general anesthesia was performed in 2.3% (n=3) of patients. Overall, 15.4% (n=20) of patients were managed with antibiotics only.

Pelvic collections were present in 10% (n=13) of patients, 15.6% (n=5) of which belonged in the wPR group while

Figure 1. Overall survival in the three groups: i) without pathological response (wPR; black line), ii) group with partial pathological response (pPR; red), and iii) group with complete pathological response (cPR; blue).

Figure 2. Disease free survival in the three groups: i) without pathological response (wPR; black line), ii) group with partial pathological response (pPR; red), and iii) group with complete pathological response (cPR; blue).

8.6% (n=7) were in the pPR and 5.8% (n=1) in the cPR group ($p=0.446$). The overall rate of permanent stoma was 14.6% with no difference found between wPR, pPR and cPR groups ($p=0.292$). The hospital average length of stay was 12 (6-77) days and there was no difference between the three groups.

Long-term outcomes. The median follow up was about 45.3 (4.4-151) months. Three and five-year overall and disease-free survivals were 95:83% and 75.7:72.5%, respectively. Three- and five-year overall survival was not different between the three groups (96:89% wPR, 95:86% pPR, 100:100% cPR; $p=0.392$), as shown in Figure 1. Three- and five-year disease-free survival was statistically different between the three groups (51:47% wPR, 82:79% pPR, 93:93% cPR, $p=0.0003$). There were 19 (14.6%) patients requiring permanent stoma without any difference in the three groups. Analysis of long-term functional results was available in 20 patients. Excluding deceased patients (n=16) and patients with a permanent stoma placement (n=19), this represented a 21.05% response rate for functional assessment scores. Only the Wexner continence and LARS grading scales were not different between the groups. Overall, the functional results were disappointing. The results are not significant but some trends may be noted. Over the entire series, 65% (n=13) of patients had a major LARS, all patients (n=4) with complete PR had a major LARS unlike

the 2 patients without PR who had a minor LARS. Concerning faecal incontinence, 55% (11) of patients had minimal to moderate incontinence, 45% (9) had important to severe incontinence and no patient reported normal continence (Table III).

Discussion

It is now established that neoadjuvant radio chemotherapy combined with proctectomy and TME is the standard treatment for cancer of the low and mid rectum. This therapeutic strategy demonstrates a clear anti-tumoral benefit. However, the impact of the pathological response on post-operative morbidity remains debated.

In our cohort of 130 patients, the complete pathological response rate is 13.1%, which is consistent with previous series where the response rate varies from 11.4% to 27% (25, 26). In a recent meta-analysis, the mean rate of pCR after RCT for rectal cancer was found to be about 24.4% (5). The variability between studies is explained by the heterogeneity in defining cPR, stages from ypT0 to ypT0N0 and ypT0N0M0, and the lack of standardised methodology to evaluate the pathological assessment of the tumour response, despite of different grading systems available (27, 28). Moreover, several studies are limited by their small size sample and a short follow-up period, which does not allow analysing the impact of PR on survival.

Table III. Pathological findings, oncological and functional results.

	Without PR n (%)	Partial PR n (%)	Complete PR n (%)	Overall n (%)	p-Value
Pathological findings	32 (24.6)	81 (62.3)	17 (13.1)	130 (100)	
Median tumour diameter (mm)	25 (12-50)	25 (1-55)	11 (0-40)	22.5 (0-55)	0.007
Positive margins	5 (15.6)	0	0	5 (3.8)	0.001
T stage					
No residual tumour	0	0	17 (100)	17 (13.1)	
T1	0	14 (17.3)	0	14 (10.8)	
T2	0	41 (50.6)	0	41 (31.5)	0.001
T3	29 (90.6)	26 (32.1)	0	55 (42.3)	
T4	3 (9.4)	0	0	3 (2.3)	
N stage					
N0	8 (25)	71 (87.6)	17 (100)	96	0.001
N1	24 (75)	10 (12.4)	0	34	
Adjuvant therapy	23 (71.8)	12 (14.8%)	0	35	0.001
Oncological results					
Median of follow up (months)	47.7 (6-151)	43.5 (4.4-134)	49.4 (5.3-105)	45.3 (4.4-151)	0.718
3-year OS (%)	96%	95%	100%	95%	0.392
5-year OS (%)	89%	86%	100%	83%	
Median of overall survival (months)	-	-	-	-	
3-year RFS (%)	51%	82%	93%	75.7%	0.0003
5-year RFS (%)	47%	79%	93%	72.5%	
Median of recurrence free survival (months)	42.5	-	-	-	
Recurrence site					
Local recurrence	4 (12.5)	4 (4.9)	0	8 (6.1)	0.169
Distant metastasis	13 (40.6)	12 (14.8)	1 (5.9)	26 (20)	0.002
Functional results					
Definitive stoma	7 (21.8)	11 (13.6)	1 (5.8)	19 (14.6)	0.292
n	2 (6.3)	14 (17.3)	4 (23.5)	20 (15.4)	-
Wexner score median	6.5 (1-15)	8 (1-13)	11.5 (4-15)	8 (1-15)	0.491
Normal	0	0	0	0	
Minimal-moderate	2 (100)	7(50)	2 (50)	11 (55)	
Important-severe	0	7(50)	2 (50)	9 (45)	
LARS score	24 (14-35)	32 (0-42)	32 (5-37)	31 (5-42)	0.825
No LARS	0	4 (28.6)	0	4 (20)	
Minor LARS	2 (100)	1 (7.1)	0	3 (15)	
Major LARS	0	9 (64.3)	4 (100)	13 (65)	

PR: Pathological response; OS: overall survival; RFS: recurrence-free survival; LARS: low anterior resection syndrome.

In our study, we found that cPR was associated with an improvement in recurrence-free survival, but without an improvement in overall survival. Recurrence-free survival increased due to a significant reduction in the occurrence of distant metastasis and a not very significant trend towards a decrease in the number of local recurrences. These results are variably reported in literature. Theodoropoulos *et al.*, have observed that disease-free survival improved significantly in cases of cPR and T-downstaging (10). For others, the only complete pathological response was significantly associated with improved disease-free survival, with 5-year disease-free survival rates ranging from 83.4% to 89% for a complete response, compared to 38.6% to

73.4% for a residual tumour (14, 29). Nevertheless, the association between a complete pathological response and overall survival remains unclear. Landi *et al.*, have shown that the 5-year overall survival of patients with complete PR was better compared to those of the non-PR (92.7% versus 75.3%) (14). On the other hand, some authors have not identified any significant association between PR and improved survival (12, 30, 31).

In the absence of distant metastasis, prognosis of locally advanced rectal cancer depends mainly on rectal wall invasion and spread to the mesorectal lymph nodes. The Korean Radiation Oncology Group (KROG) 09-01(KONCLUDE) trial concluded that rectal cancer patients

achieving cPR following preoperative RCT had favourable long-term outcomes, whereas a positive ypN status had a poor prognosis, even after the complete regression of the tumour. Five-year disease free and overall survival were about 88.5% *versus* 45.2% and 94.8% *versus* 72.8% in case of ypT0N0 or ypT0N+, respectively ($p < 0.001$) (32). Moreover, despite complete regression of the primary rectal wall tumour, residual disease in the mesorectal lymph nodes has been reported to occur in up to 17% of patients (10). The accuracy of lymph node staging is thereby essential, although the performance of current imaging procedures seems to be limited, accuracy rates with EUS, MRI and CT scan have been about 61%, 65%, 62%, respectively (33).

All of our patients were systematically operated five to six weeks following RCT. For this reason we did not analyse the impact of the interval between completion of neoadjuvant RCT and surgery. The time interval between these two procedures is frequently debated. Kalady *et al.*, have reported that an interval greater than or equal to 8 weeks following completion of RCT was the only predictive factor of pCR in their study (34). Tulchinsky *et al.*, have shown that waiting 8 to 24 weeks resulted in higher rates of cPR, whereas Stein *et al.*, have not shown any difference between 4 to 8 and 10 to 14 weeks (35, 36). The recent multicentre French randomized trial (Greccar-6 trial), comparing the periods of 7 *versus* 11 weeks between the end of RCT and surgery and demonstrated there was no difference (16).

Recently, the notion of organ preservation for locally advanced rectal cancers has emerged. Habr-Gama *et al.*, have shown that pre-operative radiochemotherapy provides a 27% complete clinical response allowing for a "watch and wait" observational strategy (37). Nevertheless, the local recidivism rate is not negligible (17% in the first year), these recurrences are probably initial responses that are ultimately incomplete and are subject to transanal resection. Thus, for locally advanced rectal cancers, the aggressive strategy remains in line with the current state of the literature. Locally advanced cancer must be the subject of further prospective studies.

Regarding post-operative outcomes, there was no difference between the groups for overall complication rate, minor complications and severe complications. This is consistent with previous studies that have not shown that patients in complete response have the same overall complication rate, although Maggiori *et al.*, have shown that they have more severe complications (22% *versus* 6%, $p = 0.04$) (12, 13). Concerning anastomotic fistulas feared following proctectomy, there was again no difference between our groups. However, there is a trend towards a decrease in symptomatic fistula rates in patients with cPR compared to those with pPR and wPR. This could have been consolidated by a larger population. Indeed, Maggiori *et al.*, were the first to report an association between a complete response to neo-adjuvant therapy and a decrease in the

occurrence of symptomatic anastomotic fistula (13). In our work, the weakness of our population size did not allow us to draw conclusions about functional results; however, to our knowledge no other study has so far compared functional results according to the pathological response.

This study is limited by its retrospective nature and the size of its population size, which may explain its statistical weakness. On the other hand, patients with upper rectal cancer were included in the same way as patients with cancer in other locations because they receive the same treatment by neoadjuvant radiochemotherapy in our centre upon expert agreement.

We demonstrated that for locally advanced rectal adenocarcinoma patients treated with RCT followed by total mesorectum excision with cPR presented an increased disease-free survival compared to those with pPR or wPR. There was no impact on the overall survival. The post-operative complication rate appeared to be reduced following surgery for patients with cPR.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

Study concept and design was performed by MO, LC, OI and NT, acquisition of data by AA, OI, NM and OM, analysis and interpretation by MO and LC.. Administrative, technical, and material support as well as supervision was done by MO. MO, LC, OI and NT drafted the manuscript, and PB, UGP, AKB, TL, SG, SC, GC, ES and MO critically reviewed the manuscript.

Acknowledgements

The Authors are deeply grateful to Katarzyna GAJ and Guillaume Prouthau for their invaluable secretarial assistance.

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Received July 10, 2019

Revised July 19, 2019

Accepted July 22, 2019