Prognostic Impact of Upfront Surgery for Locally Advanced Upper Rectal Adenocarcinoma

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Abstract. *Background/Aim: Impact of neoadjuvant chemoradiotherapy (CRT) in locally advanced upper rectal adenocarcinoma (LAURC) is debated. The aim of this study was to compare outcomes between LAURC and locally advanced sigmoid and recto-sigmoid junction cancer (LASC). Patients and Methods: This retrospective study included 149 consecutive patients [42 CRT/LAURC, 16 upfront surgery (US/LAURC) and 91 LASC]. Partial mesorectum excision (PME) was performed for all LAURC. Pathology results as well as short-and-long-term outcomes were compared between the three groups. Results: Overall mortality was nil. Morbidity was comparable (CRT/LAURC 23.8% vs. LASC: 20.8% vs. US/LAURC: 37.5%, p=0.2354). CRT was associated with a reduced risk of positive circumferential margin (CRT/LAURC: 9.5% vs. US/LAURC: 18.7%, p<0.0001). Recurrence rate, 5-year disease-free survival and overall survival were similar between the three groups. Conclusion: CRT and PME did not improve LAURC oncological outcomes but were associated with improved margins. CRT for LAURC was not associated with increased morbidity.*

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Neoadjuvant (chemo) radiotherapy (CRT) followed by total mesorectum excision (TME) has been established as the standard treatment for patients with locally advanced rectal cancer (1-5). Although the optimized treatment of locally advanced adenocarcinoma of the lower and mid rectum is now well defined, the optimal treatment of locally advanced adenocarcinoma of upper rectal cancer (LAURC) is still controversial. Indeed, there are only a few studies about the role of neoadjuvant therapy in LAURC, and their conclusions are discordant (3, 6-11). The Dutch TME-trial and the Swedish rectal cancer trial found no statistically significant local control improvement with neoadjuvant radiotherapy (RT) in stage II-III LAURC. In contrast, the MRC-CR7/NCIC-CTG-C016 study (12). found a statistically significant improvement in the 3-year local recurrence rate. Similar, the German CAO/ARO/AIO-94 study found a 10-year local recurrence rate of 4.3% in the preoperative CRT group compared with 10.4% in the surgery alone group (13). However, comparative interpretation of the individual study results and their conclusions is limited because different surgical strategies [partial mesorectum excision (PME) and TME] and definitions of tumour location were applied. Due to study population heterogeneity and conflicting results, the optimal treatment remains controversial and neoadjuvant CRT for LAURC is not recommended by current guidelines namely the National comprehensive Cancer Network (NCCN), the European Society of Medical Oncology (ESMO), and the French thesaurus on gastrointestinal cancers (14-16). However, many authors disagree and consider that patients with cT4 tumours of the upper rectum could potentially benefit from neoadjuvant CRT or chemotherapy (Cx) alone.

Therefore, the aim of this study was to compare the short- and long-term oncologic outcomes between LAURC and

locally advanced sigmoid and recto-sigmoid junction cancer (LASC) treated at a homogeneous consecutive single centre with PME.

Patients and Methods

Study population and oncologic evaluation. The initial oncologic evaluation in all patients was based on a clinical examination, a total colonoscopy with biopsy that showed the adenocarcinomatous nature of the lesion, and a computed tomography (CT) scan of the thorax and abdomen that allowed a morphologic evaluation of the tumour, its lymph node extension, and the exclusion of secondary metastasis. In patients with a tumour in the upper rectum, the examination was completed by rectal echo-endoscopy and/or rectal magnetic resonance imaging (MRI) to determine the size of the tumour, and its local extension in the mesorectum and/or satellite lymph nodes. The distance to the anal verge and the size of the tumour were measured endoscopically (pull back colonoscopy/rigid recto-sigmoidoscopy) and/or morphologically if rectal MRI was performed. A cancer was defined as belonging to the upper rectum if the distance to the anal verge from the inferior margin of the tumour was between 10 to 15 cm, and as belonging to the sigmoid if it was more than 15 cm from the anal verge, according to the European Society for Medical Oncology (ESMO diagnostic guidelines) (15). The indication for neoadjuvant treatment was made after discussion at the interdisciplinary tumour board. All LAURC cases were treated with neoadjuvant therapy at our institution. However, eight patients (n=8) in the LAURC group had medical contraindications. Another eight patients (n=8) declined neoadjuvant treatment for personal reasons.

Between 2004 and 2019, all patients operated on for LAURC, recto-sigmoid or sigmoid colon cancer were retrospectively evaluated at Tours University Hospital. All included patients had clinically or radiologically locally advanced adenocarcinoma (T3-T4) and underwent anterior rectal resection with PME and colorectal anastomosis in the same surgical session. All tumours were located between 10 and 15 cm from the anal verge. LASC was defined when the inferior tumour margin was located more than 15 cm away from the anal verge and CT scan localized the tumour to the left colon. All patients with synchronous distant metastases, a second non-metastatic tumour site, another type of active cancer, TME with coloanal or coloanal anastomosis, or surgery without continuity restoration were excluded from this study.

Neoadjuvant therapy. Radiotherapy (RT): All patients received a CT scan for RT planning. In some patients, MRI was fused with the CT scan to facilitate delineation. Patients received either long-duration RT (45 Gy in 25 fractions or 44 Gy in 22 fractions) or short-duration RT (25 Gy in 5 fractions) to the mesorectum and pelvic nodes. In several patients treated with long-term RT, an additional boost of up to 50 Gy or 50.4 Gy was administered to the tumor bed. Both three-dimensional conformal RT (3DCT) and intensity-modulated radiotherapy (IMRT) were used. Three-dimensional conformal RT was generated by opposing anterior-posterior and lateral beams and delivered using the Isogray (Dosisoft®) version 4.2 treatment planning system. IMRT was planned using the Monaco® treatment planning system, version 3.20.02, and delivered using either a TomoTherapy system or an Electa Synergy® linear accelerator. The dose constraint for the bladder was limited to 40% of the bladder volume, which was not to receive more than 50 Gy during standard fractionation. For the femoral heads, it was defined that no more than 10% of the volume would receive 50 Gy, no more than 35% of the volume would receive 40 Gy, and no more than 50% of the volume would receive 30 Gy with standard fractionation. Restrictions for the small intestine were defined as no more than 100 ml receiving 50 Gy, no more than 200 ml receiving 40 Gy, and no more than 350 ml receiving 30 Gy at standard fractionation.

Chemotherapy (Cx): Cx using capecitabin, xeloda Xeloda® (1600 mg/m² per day of RT), was performed during radiotherapy and surgery was performed 7 to 8 weeks after completion of neoadjuvant therapy (17). In patients receiving short-course RT, 25 Gray were delivered in five fractions spanning over 5 to 7 days and surgery was performed a week later (18, 19).

Surgery. Both, laparoscopic and open procedures were included. Surgical procedures consisted of PME [with a constant aim to achieve 5-cm distal margin of mesorectum below the lower edge of the tumour (17)] followed by termino-terminal or latero-terminal stapled anastomosis. Data regarding conversion to open surgery, diverting stoma (placement and time interval before reversal) and pelvic drain use were collected for all patients.

Pathology. All surgical specimens were analysed by an independent expert team of pathologists at the Department of Pathology at Tours University Hospital. Tumour stage was classified according to the 8th edition of the American Joint Committee of Cancer (AJCC). Resection was defined as incomplete (R1) if the circumferential and/or distal resection margin to the tumour borders was ≤1 mm, and complete (R0) if >1 mm. The integrity of the mesorectum, the number of total and affected nodes in the tumour specimen, lymphatic vascular invasion, and the degree of tumour differentiation were also recorded. Data on the administration of adjuvant Cx, which was decided in a multidisciplinary tumour board depending on the patient's condition, as well as the final anatomic-pathologic findings were also recorded.

Post-operative follow-up. All postoperative complications were recorded up to postoperative day 30. A CT scan of the abdomen and pelvis was performed for any clinical or biological suspicion of anastomotic insufficiency. All complications were graded according to the Clavien–Dindo classification and defined as severe if they were > grade II (18).

Long-term oncologic outcomes and survival. Clinical and radiological follow up of all patients was performed every three months for the first three years postoperatively, then every six months until the fifth postoperative year in accordance to the French recommendations (16). Radiological follow up was performed alternately with abdominal ultrasound and CT scan of the thorax, abdomen, and pelvis. Tumor recurrence was defined by the detection of a lesion classified as metastatic on CT and/or MRI and/or positron emission tomography scan, and staged as such after multidisciplinary evaluation at the interdisciplinary tumor board. In case of recurrence, regular follow-up was performed according to the requirements of the treatment and the evolution of the metastatic disease beyond the fifth postoperative year. Follow-up of patients extended from the day of surgery until the day of the patient's last clinical evaluation or the day of death, reported by any physician in our centre or any medical or administrative document related to the patient received at our centre.

Ethical approval. The study complies with the ethical standards of the French national research committee, the 1964 Declaration of Helsinki, and its subsequent amendments or comparable ethical standards. Oral and written informed consent was obtained from all study participants.

Statistical analysis. Qualitative data were expressed as absolute numbers (percentage) whereas continuous data were expressed as mean, median, and range. Statistical analysis was performed using the Graph Pad version 9.1.2 software package. Differences between groups were analysed using the Mann–Whitney *U*-test, chi-square test or Fisher's exact when appropriate. For comparison of more than two groups, one-way analysis of variance or Kruskal–Wallis tests were performed. The Kaplan–Meier method was used to estimate overall survival and relapse-free survival. For all tests, a *p*-value <0.05 was considered significant.

Results

Demographics and preoperative characteristics. One hundred and forty-nine patients (n=149) were included in this study. Of these patients, 42 underwent surgery for LAURC with neoadjuvant CRT, 91 underwent surgery for LASC or locally advanced recto-sigmoid junction cancer, and 16 underwent upfront surgery (US) for adenocarcinoma of the upper rectum without neoadjuvant treatment. Table I shows the demographic and preoperative characteristics of the total population and the three groups. Overall, the median age was 70 years (range=37-103 years) and was significantly different between the groups (Group LAURC, LASC, US: 65 *vs.* 76 *vs.* 71; *p*=0.004). Patients were significantly younger in the LAURC group than in the LASC group (65 *vs.* 71; *p*=0.0015). The sex ratio was 2.10 and significantly different between groups (LAURC, LASC, US: 1.1 *vs.* 2.37 *vs.* 15; *p*=0.0075), and particularly between groups LAURC and US (1.1 *vs.* 15; *p*=0.0048). Thirteen patients (8.73%) had an ASA score >2, with a significant difference between the three groups (LAURS, LASC, US; 2.4% *vs.* 8.8% *vs.* 25%; *p*=0.0242). LAURC group was significantly less comorbid than the US group with less patients with ASA score <2 (8.8% *vs.* 25%; *p*=0.0176). Preoperatively, there were 117 patients (77.37%) with a tumour classified as T3, and 32 patients (22.63%) with a tumour classified as T4, with a significant difference between the groups. The stage was significantly less advanced in the LAURC group compared to the other groups (T3: LAURC 95.24% *vs.* LASC 69.23% *vs.* US 87.5%; *p*=0.020). This difference was significantly different between the LAURC group and LASC group (*p*=0.006). This difference between groups persisted for the preoperative lymph node stage, with 82 patients (57.72%) classified as Nodal (N) positive (+) and 67 patients (42.28%) classified as N negative (–). (*p*=0.0105 between groups), with a significantly higher rate of lymph node extension in the LAURC group compared to the LASC group (73.8% *vs.* 49.4%; *p*=0.0001) and significantly higher in the LASC

group compared to the US group (49.4% *vs.* 37.5%; *p*=0.0001). The median distance of the tumour to the anal margin was 15 cm (range=6-60 cm) and was significantly lower in the LAURC group than in the LASC group (11 *vs.* 25 cm; *p*=0.0001), and lower in the US group than in the LASC group (12 *vs.* 25 cm; *p*=0.0001). Thirty-six patients (n=36; 85.71%) in the LAURC group had neo-adjuvant RCT and 6 patients (14.29%) only neo-adjuvant RT. No patient in groups LASC and US had neoadjuvant treatment.

Intraoperative characteristics and postoperative morbidity and mortality. Intraoperative characteristics and postoperative results at 30 days are presented in Table II. One hundred and five (n=105) patients underwent laparoscopic surgery, significantly more in the LAURC group than in the LASC group (85.7% *vs.* 60.4%; *p*=0.0046) and significantly more in the US group than in the LASC group (87.5% *vs.* 60.4%; *p*=0.0473). Twenty-two patients (21.27%) were converted to laparotomy after an initial laparoscopic approach, with a significantly higher conversion rate in the LAURC group compared to the LASC group (30.5% *vs.* 14.5%; *p*=0.0143). All patients had a PME, and there was no significant difference between the groups regarding the type of colorectal anastomosis performed. Diverting stoma rates were significantly more frequent in the LAURC group than in the LASC group (90.5% *vs.* 3.3%; *p*<0.0001) and more frequent in the US group than in the LASC group (56.3% *vs.* 3.3%; *p*<0.0001) and in the LAURC group than in the US group (90.5% *vs.* 56.25%; *p*<0.0063).

Concerning postoperative outcomes, mortality rate was nil. Twenty patients presented postoperative sepsis, without significant difference between the groups. Anastomotic leakage was diagnosed in 18 patients, with no difference between the groups (LAURC, LASC, US: 9.5% *vs.* 12.08% *vs.* 18.7%; *p*=0.6286). Thirty-eight patients (25.5%) presented a postoperative complication, with no difference between the groups. However, there was a significant difference between the groups regarding non-severe complications (Clavien–Dindo I and II), which were more frequent in the LAURC group than in the LASC group (26.2% *vs.* 9.9%; *p*=0.0196). This significant difference disappeared when looking at severe complications (Clavien–Dindo >II) with a complication rate of 4.7%, 10.9% and 18.75% in the LAURC, LASC, and US group, respectively (*p*=0.2562). Twelve patients required revision surgery, with no significant difference between groups. Sixteen patients required intensive care hospitalization, and the median total hospital stay was 10 days (median 5-52 days), with no significant difference between groups. The rate of diverting stoma closure was significantly different between the groups (LAUR, LASC, US: 89.5% *vs.* 40% *vs.* 88.88%, *p*=0.0145), and between LAURC and LASC groups (89.5% *vs.* 40%; *p*=0.042). There was no difference between the groups

Table I. *Clinical demographic presentation and radiological investigation.*

	LAURC	LASC	LAURC Without NT (US)	Overall population	*p*-Value
N (%)	42 (28.18)	91 (61.07)	16 (10.75)	149 (100)	-
Age* (years), median (range)	65 (37-88)	76 (42-103)	71 (47-85)	70 (37-103)	**0.0040**
Gender ratio (Female/Male)	20/22 (47.6%)	27/64 (29%)	1/15 (6.6%)	48/101 (32.2%)	**0.0075**
BMI * (kg/m^2), median (range)	24.41(19.59-59.86)	26.51 (12.45-58.13)	25,47(16-34,01)	25.51 (12.45-58.86)	0.6478
ASA Score, n (%)					**0.0242**
1-2	41 (97.62)	83 (91.20)	12 (75)	136 (91.27)	
3-4	1 (2.38)	8 (8.80)	4 (25)	13 (8.73)	
Arteriopathy, n (%)	2 (4.76)	4 (4.39)	2 (12,5)	8 (5.37)	0.4063
Diabetes, n (%)	4 (9.52)	17 (18.68)	4 (25)	25 (16.77)	0.2734
Tumor diagnosis, n (%)					
Screening test	9 (21.43)	15 (16.48)	2 (12,5)	26 (17.45)	0.6728
Symptoms	33 (78.57)	76 (85.52)	14 (87,5)	123 (82.49)	
Clinical T stage, n (%)					**0.0020**
T3	40 (95.24)	63 (69.23)	14 (87,5)	117 (77.37)	
T4	2 (4.76)	28 (30.77)	2 (12,5)	32 (22.63)	
Clinical N stage, n (%)					**0.0105**
N+	31 (73.8)	45 (49.45)	6 (37,5)	82 (57.72)	
N–	11 (26.2)	46 (50.55)	10 (62,5)	67 (42.28)	
Distance from anal verge median * (cm), median (range)	11 (10-15)	25 (15-60)	12 (10-18)	15 (6-60)	**<0.0001**
Neoadjuvant radiation therapy, n (%)					
Long-course radiotherapy (with chemotherapy)	36 (85.71)	-	-	36 (24.16)	-
Short-course radiotherapy (without chemotherapy)	6 (14.29)	-	-	6 (4.02)	-

LAURC: Locally advanced upper rectal cancer; LASC: locally advanced sigmoid or recto-sigmoid cancer; NT: neoadjuvant treatment; US: upfront surgery; BMI: body mass index; ASA: American Society of Anaesthesiologists. *p*-Values in bold indicate statistical significance.

Table II. *Intraoperative parameters and postoperative outcomes.*

	LAURC	LASC	LAURC Without NT (US)	Overall population	*p*-Value
N (%)	42 (28.18)	91 (61.07)	16 (10.75)	149 (100)	
Laparoscopic, n (%)	36 (85.7)	55 (60.4)	14 (87.5)	105 (68.6)	**0.0035**
Conversion to laparotomy (% of laparoscopy)	11 (30.5)	8 (14.5)	3 (21.4)	22 (21.27)	**0.0282**
PME, n (%)	42 (100)	91 (100)	16 (100)	149 (100)	-
Rectal anastomosis technique, n (%)					
Latero terminal	10 (23.8)	11 (12.1)	2 (12.5)	23 (16.1)	0.2077
Termino terminal	32 (76.2)	80 (87.9)	14 (87.5)	126 (83.9)	
Diverting stoma, n (%)	38 (90.5)	5 (3.35)	9 (56.25)	52 (31.4)	**<0.0001**
Postoperative sepsis, n (%)	3 (7.14)	14 (15.38)	3 (18.7)	20 (14.6)	0.3053
Anastomotic fistula, n (%)	4 (9.5)	11 (12.08)	3 (18.7)	18 (10.9)	0.6286
Postoperative complications, n (%)	13 (23.8)	19 (20.87)	6 (37.5)	38 (25.5)	0.2354
Clavien–Dindo, n (%)					
I-II	11 (26.2)	9 (9.89)	3 (18.75)	23 (15.43)	**0.0498**
III-IV	2 (4,7)	10 (10.99)	3 (18.75)	15 (10.06)	0.2562
Redo surgery, n (%)	2 (4.76)	8 (8.79)	2 (12.50)	12 (8.05)	0.5772
ICU stay requirement, n (%)	2 (4.76)	14 (15.38)	0	16 (10.74)	0.0541
Hospital stay (days), median (range)	11 (6-36)	10 (5-52)	11 (5-30)	10 (5-52)	0.9288
Stoma reversal, n (%)	34/38 (89.5)	2/5 (40)	8/9 (88.88)	44/52 (84.61)	**0.0145**
Days before stoma reversal, median (range)	91 (20-336)	57 (48-66)	119 (64-438)	91 (20-438)	0.0898

PME: Partial mesorectal excision; ICU: intensive care unit; NT: neoadjuvant treatment; LAURC: locally advanced upper rectal cancer; LASC: locally advanced sigmoid cancer; NT: neoadjuvant treatment; US: upfront surgery. *p*-Values in bold indicate statistical significance.

Table III. *Pathological findings of 149 patients who underwent resection for locally advanced rectal and recto-sigmoid carcinoma.*

	LAURC	LASC	US	Overall population	*p*-Value
N (%)	42 (28.18)	91 (61.07)	16 (10.75)	149 (100)	-
Preoperative tumour diameter* (mm), median (range)	42 (10-90)	53 (20-110)	42,5 (30-60)	50 (10-110)	
Pathology T stage, n (%)					**<0.0001**
T0	2 (4.8)	0	0	2 (1.3)	
T1	1 (2.4)	0	0	1 (0.7)	
T2	15 (35.7)	0	0 (0)	17 (11.4)	
T3	21 (5)	63 (69.2)	14 (87.5)	98 (65.8)	
T4	3 (7.15)	28 (30.8)	2 (12.5)	33 (22.1)	
T3-4 stages, n (%)	24 (57.14)	91 (100.0)	16 (100)	131 (87.9)	**<0.0001**
Pathology N stage, n (%)					**0.0087**
N+	10 (23.8)	45 (49.4)	4 (25)	59 (39.6)	
N–	32 (76.2)	46 (50.5)	12 (75)	80 (60.4)	
Lymphovascular invasion, n (%)	7 (16.7)	35 (38.5)	6 (37.5)	48 (32.21)	
Lymph nodes sample, median (range)	17 (6-34)	24.5 (11-103)	25.5 (10-62)	23 (6-103)	**0.0002**
Pathology tumour diameter (mm), median (range)	25 (0-65)	52,5 (22-110)	50 (20-90)	42 (0-110)	**<0.0001**
Tumour differentiation, n (%)					0.1527
Well/moderate	35 (83.3)	79 (86.8)	14 (87.5)	128 (85.9)	
Mucinous/poor5	7 (16.8)	5 (5.5)	2 (12.5)	14 (9.4)	
Overall positive margin, n (%)	4 (9.5)	2 (2.1)	3 (18.7)	9 (6)	**0.0200**
Positive lateral margin, n (%)	4 (9.5)	2 (2.1)	3 (18.7)	9 (6)	**0.0200**
Positive distal margin, n (%)	0 (0)	0 (0)	0 (0)	0 (0)	-

NT: Neoadjuvant treatment; LAURC: locally advanced upper rectal cancer; LASC: locally advanced recto-sigmoid cancer; US: upfront surgery. *p*-Values in bold indicate statistical significance.

regarding the median time to stoma closure (91 days *vs*. 57 days *vs*. 119 days; *p*=0.0898).

Pathological findings. The pathological results are presented in Table III. The pT stage was significantly different between the three groups (*p*<0.0001), and between LAURC and LASC groups (*p*<0.0001) and LAURC and US groups (*p*=0.0414). There were significantly fewer tumours classified as pT3 or pT4 in the LAURC group than in the other two groups (LAURC: 57.1% *vs*. LASC: 100%; *p*<0.0001 and LAURC: 57.1% *vs*. US: 100%; *p*=0.011). The lymph node extension was significantly different between the groups, with particularly significantly less pN pos (+) stages in the LAURC group than in the LASC and US groups (LAURC, LASC, US: 23.8% *vs*. 49.4% *vs*. 25%; *p*=0.0087), but these patients also had fewer nodes examined on the surgical specimen (LAURC, LASC, US median: 17 *vs*. 24.5 *vs*. 25.5; *p*<0.0001). Tumour size on the surgical specimen was significantly different between groups, with a significantly smaller median size in the LAURC group compared to the LASC group (25 cm *vs*. 52.50 cm; *p*<0.001) and US group (25 cm *vs*. 50 cm; *p*<0.0001). The rate of invaded circumferential margin on the surgical specimen was higher in the LAURC group than in the LASC group but

without statistical difference (9.5% *vs*. 2.1%; *p*=0.5395). The rate of invaded circumferential margin was significantly higher in the US group compared to LASC group (18.7% *vs*. 2.1%; *p*=0.0232) and compared to LAURC group (18.7% *vs*. 9.5%, *p*<0.001). No patient had an invaded distal margin on the surgical specimen.

Oncologic follow-up and survival. Data regarding oncologic follow up and survival are presented in Table IV. The median total follow up was 52 months and was comparable between the groups. Sixty-six (44.3%) patients received adjuvant Cx, the majority in the LASC group compared to the other two groups (23.8% *vs*. 57.1% *vs*. 25%; *p*=0.0004). Local recurrence after completed follow-up was observed in 13 patients (8.7%), distant recurrence was observed in 27 patients (18.1%), and overall recurrence was observed in 31 patients (20.8%). These recurrence rates were statistically comparable between the groups. The overall survival rates were 91% at 3 years and 84% at 5 years of postoperative follow up with no statistically significant difference between the three groups (*p*=0.2989) (Figure 1). Overall disease-free survival was 80% at 3 years and 77% at 5 years (Figure 2). It did not differ significantly between the groups, although it appeared to be higher at 3 and 5 in the LASC group compared to the other

Table IV. *Overall and disease-free survival of 149 patients with upper rectal and recto-sigmoid cancer.*

	LAURC	LASC	LAURC Without NT (US)	Overall population	*p*-Value
N (%)	42 (28.18)	91 (61.07)	16 (10.75)	149 (100)	-
Follow-up (months), median (range)	51 (0-153)	59 (0-184)	33.5 (1-103)	52 (0-184)	0.0523
Adjuvant chemotherapy, n (%)	10 (23.8)	52 (57.1)	4 (25)	66 (44.3)	**0.0004**
Recurrence, n (%)					
Local	5 (11.9)	7 (7.7)	1 (6.2)	13 (8.7)	0.6777
Distant	8 (19)	16 (17.6)	3 (18.7)	27 (18.1)	0.9771
Overall	10 (23.8)	18 (19.8)	3 (18.7)	31 (20.8)	0.8483
Time to recurrence (months), median (range)	21 (1-42)	12 (0-123)	10 (8-26)	13.5 (0-123)	0.8094
Overall survival					0.2989
At 3 years	90%	93%	83%	91%	
At 5 years	83%	86%	83%	84%	
Disease free survival					0.8281
At 3 years	76%	85%	72%	80%	
At 5 years	70%	81%	72%	77%	
Permanent stoma, n (%)	2 (2.1)	5 (5.5)	3 (18.7)	10 (6.7)	0.1241
Ileostomy	2 (2.1)	2 (2.2)	2 (12.5)	6 (4)	0.3292
Colostomy	0	3 (3.3)	1 (6.25)	4 (2.7)	

LAURC: Locally advanced upper rectal cancer; LASC: locally advanced recto-sigmoid cancer; NT: neoadjuvant treatment; US: upfront surgery. *p*-Values in bold indicate statistical significance.

two groups. The definitive stoma rate was 6.7%, and was statistically comparable between the groups, even after analysis according to the type of definitive stoma.

Discussion

The need for neoadjuvant therapy in the treatment of LAURC is largely controversial, as heterogeneous patient populations have been studied to date in the various trials that have included middle and lower rectal cancer in addition to upper rectal cancer (1, 19, 20). In a recent study published by Tabchouri *et al.*, it was reported that the disease-free survival of LAURC was not improved by neoadjuvant therapy compared to patients without neoadjuvant therapy. However, this study was multicentric and patients were managed with PME or TME for LAURC. Furthermore, the study was designed to compare only upper rectal cancer with or without neoadjuvant therapy (21), whereas this study only compared the outcome of advanced adenocarcinoma of upper rectal cancer with or without neoadjuvant therapy with rectosigmoid junction cancer with only PME. Indeed, the need of a TME for LAURC remains unclear and the impact of performing PME instead of TME on postoperative and oncological outcomes is not well defined. Whereas some authors note a "sigmoid-like" URC behaviour, making PME sufficient from an oncologic point of view and leading to lower morbidity, other authors consider TME mandatory due to the higher local recurrence rate when only PME is performed (10, 17, 21-23). Therefore, the goal of our study

was to evaluate the impact of neoadjuvant CRT and PME in LAURC regarding post-operative and oncological outcomes.

Our study demonstrated that when PME was performed, there was no significant difference in terms of severe post-operative outcomes between a rectal resection after neoadjuvant therapy for LAURC, US for LAURC, and rectosigmoid resection for LASC. Recurrence rates, 5-year disease-free survival and 5-year overall survival were also similar between these three groups. Patients with LAURC who received CRT presented with a similar postoperative sepsis rate as LASC and US (7.14% *vs.* 15.38% *vs.* 18.7%), a similar severe post-operative complication rate (4.7% *vs.* 10.99% *vs.* 18.75%), and a similar anastomotic fistula rate (9.5% *vs.* 12.08% *vs.* 18.7%). These results suggest that severe post-operative complications in rectal resection with PME is not increased by the administration of neoadjuvant CRT. This finding is consistent with the results of several studies showing an absence of impact of neoadjuvant CRT on severe post-operative outcomes (1, 24). A possible explanation for this might be explained by a significantly higher rate of diverting stoma in the CRT group (90.5% *vs.* 3.35% *vs.* 56.25%), which led to fewer septic complications in our study. This finding is a further reaffirmance to the importance of a diverting stoma for rectal resection, even when only PME is performed (25). However, the presence of an ileostomy could be the reason for a higher rate of non-severe postoperative complications (Clavien–Dindo <II), which were more frequent in the CRT group (26.2% *vs.* 9.89% *vs.* 18.75%; *p*=0.0498).

A

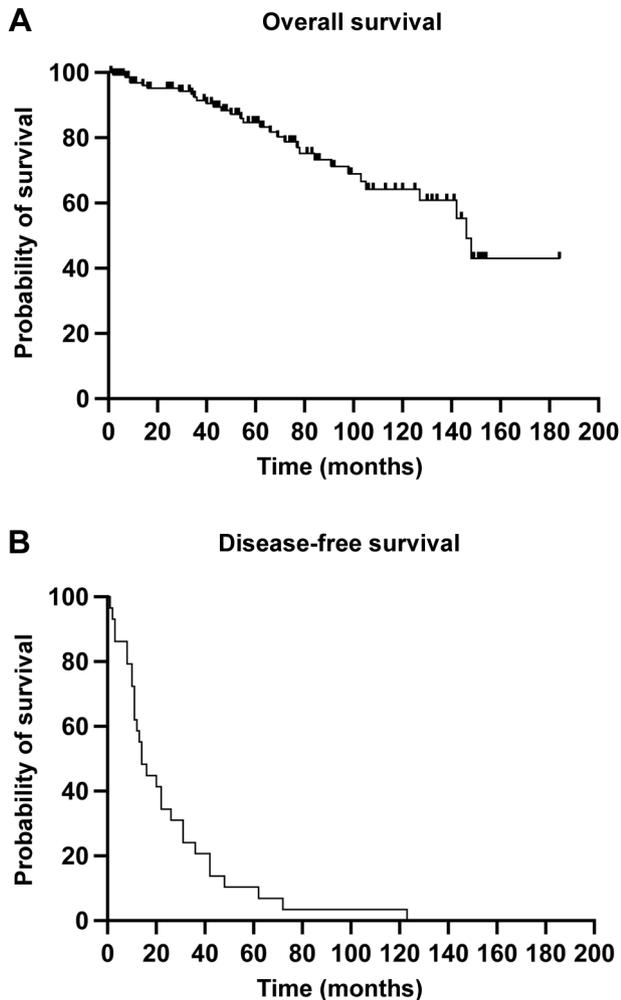### Overall survival

B

Disease-free survival

Figure 1. *Overall Kaplan--Meier survival curves of total LAURC and LASC populations. (A) Overall survival. (B) Disease-free survival. LAURC: Locally advanced cancer of the upper rectum; LASC: Locally advanced sigmoid and recto-sigmoid junction cancer. X axis: months; Y axis: percentage survival.*

Despite not being statistically different, the higher rate of global complications, anastomotic fistula, and post-operative sepsis in the US group might be explained by the monocentric bias. CRT for LAURC is often proposed in our centre, and patients who are excluded from neoadjuvant treatment are mainly suffering from severe medical comorbidities, which are a counter-indication to neoadjuvant CRT. Hence, a significantly higher ASA 3/4 score among the US group (2.38% *vs*. 8.8% *vs*. 25%; *p*=0.0242) was observed.

Regarding oncological outcomes, as expected, the rate of complete resection was significantly higher in the CRT group *versus* US group (9.5% *vs*. 2% *vs*. 18.7%; *p*<0.0001), which confirms the impact of neoadjuvant CRT on locally advanced tumours without predictive resection margin (1, 24).

However, performing PME did not impair the number of complete distal resections, as no distal margin was involved in any of the groups.

pTN staging, while similar on preoperative evaluation between the groups, was significantly lower in the CRT group, with 44.7% of patients being pT2 or lower and 76.2% being pN0.

However, despite these results confirming the efficiency of neoadjuvant CRT on pathology outcomes, no significant difference was found between the groups in terms of global, local or distal recurrence. This is consistent with other studies showing that, while being efficient on achieving complete resection and tumour downstaging, neoadjuvant CRT fails to improve the local and distant recurrence rate, particularly in LAURC, which seems to have a lower local recurrence rate than other rectal tumours (6, 9, 26). In our study, administration of adjuvant chemotherapy was significantly lower in the CRT group than in the LASC group (23.8% *vs*. 57.1%, *p*=0.004), probably due to the tumour downstaging allowing to exonerate patients of an adjuvant treatment. As recent studies have shown that total neoadjuvant treatment (TNT) followed by a mandatory adjuvant chemotherapy was effective on the global recurrence rate in locally advanced rectal cancer (27, 28), we speculate whether the avoidance of adjuvant treatment, which is made possible by tumour downstaging after neoadjuvant CRT, may be the reason for the lack of improvement in recurrence rate in LAURC compared with US, in which there is no preoperative tumour downstaging by neoadjuvant therapy and thus, adjuvant treatment is often indicated according to pathology results (29).

In our study, overall survival and disease-free survival at 3 and 5 years were similar between the three groups. In a recent study, Falch *et al*. showed that the oncological profile of rectosigmoid junction cancer seemed to be worse than that of upper rectal cancer (5y overall survival rate 44.8% *vs*. 70.2%), mainly due to a higher rate of synchronous liver metastasis, although the rate of metachronous hepatic recurrence rate seemed to be higher but not significant (20% *vs*. 8.7%) (30). In fact, several studies have shown upper rectal cancer behaving more like a sigmoid cancer (6, 22, 31), which may explain the absence of difference in disease-free survival, as we did not separate rectosigmoid cancer from sigmoid cancer. Most upper rectal cancers in these studies did not receive neoadjuvant treatment, leading to difficulties to evaluate its impact.

This study contains several biases. First, the monocentric design of the study leads to CRT and US group being not similar, most patients being proposed a neoadjuvant CRT at our centre, leading to an US group too comorbid and not big enough to be statistically relevant. Moreover, our choice of not separating rectosigmoid and sigmoid junction cancer might have led to a bias in terms of oncologic outcomes, as their
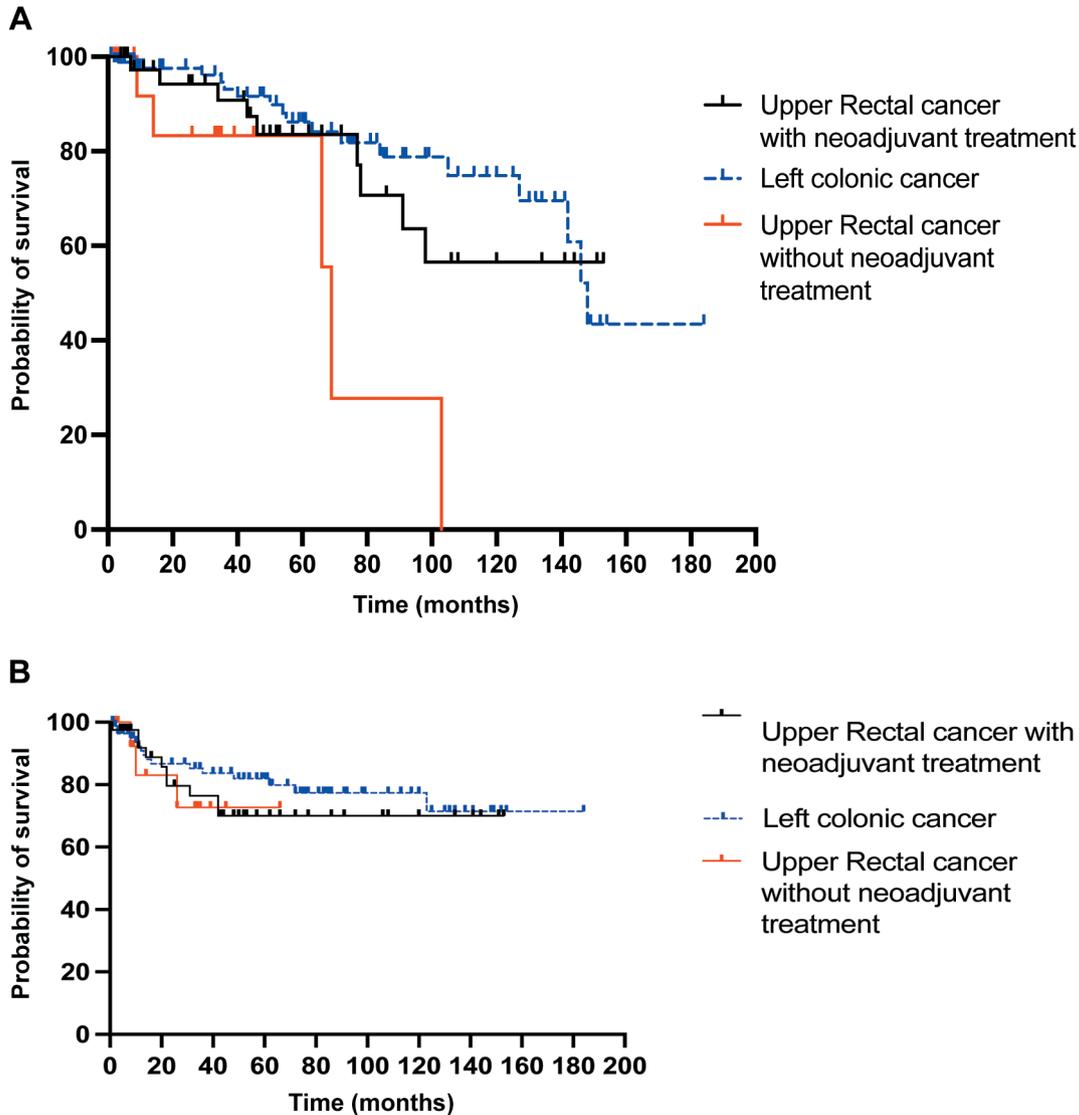
Figure 2. *Overall survival comparison differences between patients presenting with LAURC treated with or without neoadjuvant treatment and patients presenting with LASC. (A) Overall survival. (B) Disease-free survival. LAURC: Locally advanced upper rectal cancer; LASC: Locally advanced sigmoid and recto-sigmoid junction cancer.*

oncologic pattern seem to be different. Finally, no quality of life (QoL) evaluation was performed, and this can be a strong choice factor leading to avoidance of neoadjuvant CRT, as several studies have shown an impaired QoL after CRT (30).

However, our study showed that for non-metastatic locally advanced upper rectal cancer, when PME is performed, neoadjuvant CRT administration did not impair severe post-operative outcomes compared to a left colectomy with colorectal anastomosis for locally advanced recto-sigmoid or sigmoid cancer. Finally, it allowed to achieve a higher complete resection rate compared to patients treated with upfront surgery for locally advanced

upper rectal cancer. These results should be taken into consideration, as some patients with LAURC may benefit from CRT by downstaging the tumour and achieving a complete resection, which are known to be independent protective factors regarding local recurrence, and as total neoadjuvant treatment including CRT might be the key in the next coming years for improving global oncological outcomes in LAURC.

The main focus should be drawn towards selection of patients with LAURC who may actually benefit form neoadjuvant CRT, particularly for patients with an invaded resection margin on pre-operative screening, and those for

whom it seems to be an unnecessary overtreatment (32). Rethinking upper rectal cancer classification in preoperative screening might also be the key, and new radiologic classifications might help in identifying tumour heights in upper rectum, which may be at higher risk of recurrence (33).

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Concept/design of the work: M. Ouaissi, O. Muller, S. Chockry. Data acquisition: O. Muller, N. Tabchouri, R. Sindayigaya, E. Karam. Data analysis and interpretation: R. Sindayigaya, N. Tabchouri, M. Ouaissi, Y. Drafting: R. Sindayigaya, N. Tabchouri, M. Ouaissi. Critical revision: O. Muller, E. Karam, N. Tabchouri, E. Salamé, D. Moussata, T. Lecomte, S. Chapet, G. Calais, M. Ouaissi, U. Pabst-Giger. Final approval: M. Ouaissi.

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