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Salvage surgery for local regrowths in Watch & Wait - Are we harming our patients by deferring the surgery?

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ABSTRACT

Background: Rectal cancer surgery conveys significant morbidity/mortality, long-term functional impairment and urinary & sexual dysfunction, especially if associated with neoadjuvant chemo-radiotherapy (ChRT). Watch & Wait (W&W) is gaining momentum as an option for patients with clinical complete response (cCR) after ChRT. Approximately 30% will develop a local regrowth (RG) and need deferred surgery. Our study aimed to assess the short-term clinical outcomes after surgery for regrowths.
Patients and methods: Consecutive rectal cancer patients from a tertiary institution who underwent neoadjuvant ChRT, between January 2013 and October 2018, were identified from a prospectively maintained database. Patients with RG under W&W surveillance were operated - regrowth deferred surgery (RDS) group - and compared to those with persistent disease after ChRT who did undergo surgery - non-deferred surgery (NDS) group.
Results: Total of 124 patients received neoadjuvant treatment: 46 (37%) underwent surgery for persistent disease; 78 (63%) with cCR entered W&W. Twenty three developed RG and underwent surgery, while 55 remain under surveillance. RDS group had lower tumors than NDS group (2.3 cm ± 2 vs 4.5 cm ± 3, $p = 0.002$). All RG underwent minimally invasive surgery (MIS). Anastomotic leaks, 30-day morbidity, reintervention and readmission rates were similar. Pathology features and 3-year oncological outcomes were identical between groups.
Conclusion: Patients with initial cCR and local regrowth may be safely managed by deferred surgery. Short-term outcomes suggest equivalent results to patients with incomplete clinical response and immediate radical surgery. Delayed MIS appears to have no negative impact on oncological outcomes.

Introduction

Currently, most patients with “moderate or high-risk” locally advanced rectal cancer are treated with neoadjuvant short-course radiotherapy (scRT) or chemo-radiotherapy (ChRT) followed by total mesorectal excision (TME) as described by RJ Heald [1,2]. TME is associated with significant peri-operative morbidity and mortality [3]- especially when combined with pre-operative radiotherapy (RT), and particularly in patients that are old and frail [4,5]. Additionally, the introduction of a temporary or permanent stoma and the adverse effects of surgery and radiotherapy may compromise bowel, sexual and urinary functions and can adversely affect quality of life [6]. Therefore, the overall cost of neoadjuvant ChRT as “the standard of care”, submitting most patients to both RT and TME for best local control, can be very high. Most may indeed not benefit from this “one size fits all” strategy. Over the last few

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decades, Habr-Gama has advocated that surgery deferral and Watch & Wait (W&W) might be an important option for patients with an excellent or complete clinical response (cCR) after ChRT [7,8].This form of organ preservation is gaining popularity because W&W can select patients who may avoid the complications of major surgery [9,10] with similar oncological outcomes to patients undergoing both neoadjuvant therapy and radical surgery [11].

After RT, the decision to defer surgery and enter a surveillance program depends on achieving a cCR [12] - no evidence of tumor in clinical and radiological examination on regular re-evaluations [13,14]. As long term oncological outcomes from >1000 rectal cancer patients are being published - from single institutional series [15,16] and from the International Watch and Wait Database (IWWD) [10], the option of organ preservation is gaining momentum and more patients are beginning to ask their physicians about this treatment alternative. In this shared decision-making process they must be informed not only of the self-evident advantages but also of the potential need of a later surgery for local tumor regrowth (RG), and of the risk of a later local recurrence and even distant metastasis.

Currently available data suggest that up to 1/3 of patients chosen for W&W will eventually require surgery for a local regrowth (also referred to as "deferred definitive surgery") at any time during follow-up after an initial "apparent" complete clinical response [17]. Compliance to a strict surveillance protocol ensures early detection of RG, usually amenable to R0 surgery and excellent long-term local disease control [18,19]. However, it is also important to evaluate the peri-operative consequences of having that later surgery for RG, and of whether any harm flows from the deferral.

The aim of our study was to compare peri- and post-operative outcomes between patients that received neoadjuvant RT and underwent surgery with those patients that were included in a W&W program but later experienced a local regrowth and needed deferred surgery.

Methods

Consecutive rectal cancer patients from a single tertiary institution who underwent neoadjuvant ChRT for rectal cancer between January 2013 and May 2018 were identified from a prospectively maintained database. Rectal cancer was defined as a biopsy-proven adenocarcinoma present within 15 cm from the anal verge, determined by endoscopy and confirmed by MRI.

This study was approved by the institutional Ethics Committee and informed consent for research was obtained from all patients.

Staging, neoadjuvant radiotherapy and consolidation chemotherapy

Oncological staging was performed by colonoscopy, computed tomography (CT) of the chest/abdomen and specialised magnetic resonance imaging (MRI) of the abdomen/pelvis. All cases were discussed in a multidisciplinary team (MDT) meeting before treatment was started. Neoadjuvant RT was offered to patients with MRI moderate or high risk features for local recurrence (usually with threatened or invaded circumferential resection margin (CRM), positive Extramural Venous Invasion (EMVI) or "high risk" mrLR3-4 lower tumors, as advocated by Brown G. [2,20]

RT was delivered with Volumetric Modulated Arc Therapy technique (VMAT) in two different protocols; Long-course (LC-RT) during a period of 25 consecutive treatment days or Short-course (scRT) during a period of 5 consecutive days. An elective dose to the potential pelvic areas at risk of 45–50.4 Gy and 25 Gy was prescribed for the LC-RT and scRT respectively. Most patients of the LC-RT protocol received a simultaneous integrated boost (SIB) up to 54–56 Gy to involved areas (tumor±lymph nodes) defined by planning pelvic T2-sequence MRI and FDG PET/CT. A photon beam energy with flattering filter-free (10X-FFF) was used. Image guided radiotherapy (IGRT) was implemented with daily cone-beam CT in order to correct inter-fraction variability of patient and/or tumor position. Long course RT was delivered with concomitant oral capecitabine.

Patients were proposed to neoadjuvant - consolidation - chemotherapy if they were medically fit and considered to have tumors with higher risk for distant disease (particularly positive EMVI, mrT4, mrLR3 & mrLR4 and mrN positive) [20]. Consolidation usually started between 4 and 6 weeks after the last dose of RT and consisted of capecitabine 1000 mg/m^2 twice daily, day 1–14 combined with oxaliplatin 130 mg/m^2 once every 3 weeks with a planned total of six cicles.

Assessment of response and patient selection

All patients were restaged 8–10 weeks after the last dose of RT by digital rectal examination (DRE), rectoscopy, CEA levels and pelvic MRI. cCR was defined as: 1) no residual tumor felt on DRE, 2) white scar and/or telangiectasia of the mucosa, and 3) low signal intensity at the area of the original tumor on MRI-T2W (mrTRG 1) and absence of restriction to diffusion on MRI-DW. Near complete response (nCR) was defined as: 1) minor mucosa abnormality/irregularity felt on DRE, 2) superficial/shallow ulceration and/or mild persisting erythema of the scar and, 3) intermediate/low residual signal on MRI-T2W (mrTRG 2) and minimal areas of restriction to diffusion on MRI-DW were also included [21].

No biopsies were performed during assessment of response. Patients with cCR/nCR were offered an organ-preserving strategy pathway without immediate surgery (W&W). Patients in W&W that presented with a clinical evidence/radiologic suspicion of regrowth were offered radical surgery – regrowth deferred surgery (RDS) group Those with persistent disease (visible tumor or deep ulceration or mrTRG 3–4) were referred to radical surgery - non-deferred surgery (NDS) group …

Surgery

Surgery was performed open, laparoscopic, or robotic. Surgical modality was based on surgeon and patient's discretion. Minimally invasive TME was performed in a standardized fashion as described previously [22,23]. Decision on the timing to operate was based on a shared-decision making process, including patient's preferences and MDT meeting recommendations.

Post-operative care followed a routine enhanced recovery programme based on the method described by Kehlet and Wilmore [24]. Patients were discharged home per set criteria for discharge.

Follow-up

Follow-up of patients under our W&W protocol was performed with DRE, rectal endoscopy, pelvic MRI and CEA level every 3 months for the first year, every 4 months the second year and every 6 months thereafter. Abdominal and thoracic CT scans were performed every 6 months for the first 2 years and yearly thereafter.

Outcome assessment

The baseline characteristics and surgical outcomes of NDS and RDS groups were analyzed. Data was collected prospectively. Baseline characteristics analyzed were sex, age, body mass index (BMI), American Society of Anesthesiologists Physical Status Classification (ASA) and T stage. Peri-operative data collected included operative time, estimated blood loss, surgical approach (open vs

laparoscopic vs robotic), operation performed and conversion to open for laparoscopic and robotic procedures (defined as any incision needed to either mobilize the colon or rectum or ligate the vessels). Post-operative clinical and pathological data examined included length of stay, 30-day postoperative complications [25], 30-day readmission, 30-day reoperation, 30-day mortality, anastomotic leak, lymph node yield, ypT0 rate and circumferential resection margin (CRM) clearance.

Oncological outcomes included: Local Recurrence (LR) rates - LR was defined as any form of pelvic relapse after effective surgery for the primary tumor; Distant Disease (DD) rates - DD was established as any form of distant disease dissemination); and Overall Survival (OS) - was defined as death from any cause). Local Regrowth was considered in patients with cCR having tumor reappearance at the primary disease site and was not considered local recurrence.

Statistical analysis

Mann-Whitney *U* test was used for continuous variables. For categorical variables, differences between groups were analyzed using Fisher's exact test or Chi-square test of independence. LR, DD and OS rates were compared using Kaplan-Meier method with a log rank test. Statistical significance was set at a P value of <0.05. Analyses performed using SPSS® statistical software (ver. 22 SPSS Inc., Chicago, IL, USA).

Results

A total of one hundred and twenty four patients received neoadjuvant RT and all were included in the study. 46 patients with persistent disease (37%) were allocated in NDS group and 78 (63%) entered W&W. Out of the 78 patients in W&W, 23 had a regrowth for which they received deferred surgery - RDS and the remaining 55 patients are still under surveillance - Fig. 1.

Clinical characteristics and RT regimen

The baseline characteristics of the two groups are summarised in Table 1. With the exception of the distance from the anorectal ring, which was shorter in the RDS arm (2.3 cm ± 2 vs 4.5 cm ± 3, $p = 0.002$), the co-morbidities and clinical stage of the two groups were broadly comparable. Most patients in RDS group were treated by long-course RT (87% vs 67%, $p = 0.032$) and received a significantly higher dose on the gross tumor bed (54Gy vs 52Gy, $p = 0.042$).

Operative procedures and pathology features

The peri-operative characteristics of the two groups are summarised in Table 2. Time to operation after ChRT was prolonged in RDS group (16 vs 6 months, $p < 0.001$), with an increased number of abdomino-perineal (APE) procedures (39% vs 30%, $p = 0.014$). There were no exenterative procedures in the RDS group and all patients were managed by minimally invasive surgery (MIS). Pathological characteristics were similar between groups. In our cohort of RDS, we had 14 male patients, of which 6 had tumors with anteriorly located component. From these 6 patients we observed one R1 resection that was clinically addressed with subsequent re-irradiation. Patient has currently 11 months of follow-up with no radiological evidence of local and distant recurrence.

Table 3 demonstrates specific characteristics and outcomes of patients submitted to local excision.

Post-operative clinical outcomes

The post-operative characteristics of the two groups are summarised in Table 4. There were no differences in anastomotic leak, 30-day morbidity, 30-day readmission and 30-day reoperation rates between the two cohorts. Hospital and ICU length of stay were longer in NDS group (8 vs 5 days, $p = 0.013$ and 1 vs 0 days, $p = 0.015$ respectively).

There was no 30-day mortality in either group.

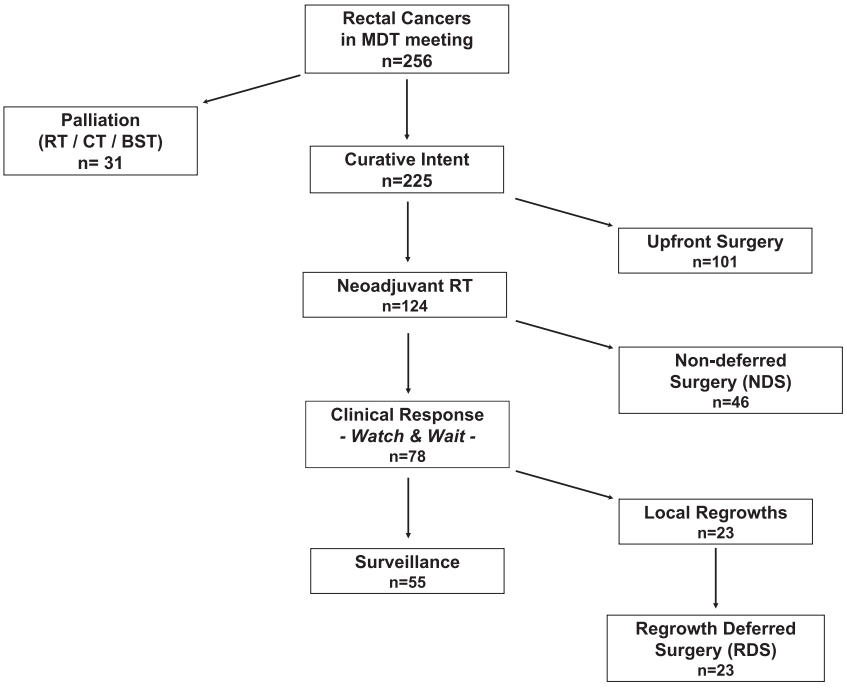

Fig. 1. Flowchart of rectal cancer patients discussed in multidisciplinary team (MDT) meetings. RT - Radiotherapy; CT - Chemotherapy; BST - Best supportive treatment

Table 1
Patient's clinical characteristics and radiotherapy regimens.

	Non-deferred Surgery (n = 46)	Regrowth Deferred Surgery (n = 23)	*p* value
Age (Mean ± SD)	63 ± 10	65 ± 9	.619[m]
Gender			.793[f]
male	30 (65.22%)	14 (60.87%)	
female	16 (34.78%)	9 (39.13%)	
Body Mass Index (Mean ± SD)	26 ± 5	27 ± 6	.976[m]
Co-Morbidity			.752[c]
Cardio-Vascular	29 (63.0%)	22 (95.6%)	
Diabetes	9 (19.5%)	6 (26.1%)	
Pulmonary	9 (19.5%)	8 (34.8%)	
Renal & Urological	8 (17.3%)	6 (26.1%)	
Other neoplasia	11 (23.9%)	3 (13.4%)	
Other	27 (58.7%)	17 (73.9%)	
Previous Abdominal Surgery			.286[c]
Intestinal	10 (21.7%)	4 (17.4%)	
With Stoma	3 (6.5%)	0	
Urological	8 (17.3%)	6 (17.4%)	
Other	11 (23.9%)	2 (8.7%)	
Distance to ARR (cm)	4.5 ± 3	2.3 ± 2	.002[m]
Tumor with anteriorly located component	26 (56.5%)	9 (39.1%)	.208[f]
T stage			.118[c]
1	0	0	
2	3 (6.5%)	2 (8.7%)	
3	26 (56.5%)	18 (78.2%)	
4	17 (36.9%)	3 (13.0%)	
N stage			.222[c]
0	4 (8.7%)	1 (4.3%)	
1	19 (41.3%)	15 (65.2%)	
2	15 (32.6%)	6 (17.4%)	
X	8 (17.3%)	1 (4.3%)	
M stage			.254[f]
0	38 (82.6%)	22 (95.65%)	
1	8 (17.4%)	1 (4.35%)	
MRF involvement			.085[c]
clear	16 (34.78%)	13 (56.52%)	
threatened/invaded	30 (65.22%)	10 (43.48%)	
Radiotherapy			.032[c]
LC-RT	5 (10.8%)	0 (0)	
LC-ChemoRT	26 (56.5%)	20 (86.9%)	
scRT	15 (32.6%)	3 (13.1%)	
Elective Dose Pelvis (Gy)			
LC-(Chemo)RT	45 [45–56.2]	45 [45–50.4]	.606[m]
scRT	25 [25]	25 [25]	.999[m]
Selective Dose Tumor (Gy)			
LC-(Chemo)RT	52 [45–64]	54 [54–56]	.042[m]
scRT	30 [25–35]	30 [25–35]	.699[m]
Consolidation Chemotherapy			.085[c]
yes	16 (34.78%)	13 (56.52%)	
no	30 (65.22%)	10 (43.48%)	

MRF - mesorectal fascia; EMVI - extramural venous invasion; ARR - ano-rectal ring, measured on MRI from the tumor to the top of the internal sphincter; LC-RT - long-course radiotherapy; LC-ChemoRT - long-course chemo-radiotherapy; scRT - short-course radiotherapy; c - Chi-square test; f - Fisher's exact test; m - Mann Whitney test.

Oncological outcomes

At a median follow-up of 36 months in both groups, there was no difference in Local Recurrence and Distant Disease rates, or in Overall Survival - Fig. 2.

Discussion

Long-term survivors of rectal cancer are increasingly focused on functional outcomes and quality of life. As such, W&W is an attractive treatment option for selected patients with cCR. However, the problem of early detection and management of local regrowths remains a challenge. Some data has already been published by the group from Sao Paulo [18], but there is still little evidence in the literature on how to treat these regrowths or on the outcomes of this deferred surgery. In many institutions with active W&W programs rectal preservation is still considered as a limited or “occasional” decision that is not even considered for the majority of patients. Therefore it is difficult to estimate how many of their rectal cancer patients might have benefited from a W&W protocol. In our center, we have incorporated W&W as one of our primary treatment options, with a strong multidisciplinary commitment to discuss it with all our patients that were potential candidates. This gives us the opportunity to estimate how many W&W patients

Table 2
Operative procedures and pathology features.

	Non-deferred Surgery (n = 46)	Regrowth Deferred Surgery (n = 23)	*p* value
ASA grade			.798[c]
I	7 (15.2%)	2 (8.7%)	
II	22 (47.8%)	13 (56.5%)	
III	11 (23.9%)	7 (30.4%)	
IV	3 (6.52%)	1 (4.3%)	
Time from RT —> Surgery (months)	6 [0–18]	16 [5–32]	**.001[m]**
Surgical approach			**.001**
Open	18 (39.1%)	0 (0%)	
LE	0 (0%)	4 (17.4%)	
Laparoscopic	16 (34.7%)	6 (26.1%)	
Robotic	12 (26.1%)	13 (56.5%)	
Conversion			.312[f]
Lap to Open	2	0	
to Lap/Open	0	0	
Resection			**.014[c]**
LAR	30 (65.2%)	10 (43.5%)	
APE	14 (30.4%)	9 (39.1%)	
LE	0 (0%)	4 (17.4%)	
Exenterations	2 (4.3%)	0	
Quality of TME Specimen (*)			.109[f]
Mesorectal	42 (91.3%)	14 (73.7%)	
Intra-mesorectal	4 (8.7%)	5 (26.3%)	
Muscular	0	0	
ypT stage			.162[c]
0	8 (17.4%)	2 (10.5%)	
1	1 (2.2%)	2 (10.5%)	
2	9 (19.5%)	8 (42.1%)	
3	25 (54.3%)	6 (31.6%)	
4	3 (6.5%)	1 (5.3%)	
Lymph nodes harvested (mean ± SD)	16 ± 7	16 ± 11	.856[m]
ypN stage			.489[c]
0	36 (78.2%)	13 (68.4%)	
1	6 (13.4%)	5 (26.3%)	
2	2 (4.3%)	1 (5.3%)	
x	2 (4.3%)	0	
Closest CRM (mm)	6 [0–30]	7.5 [2–30]	.982[f]
R0 clearance (*)	42 (91.3%)	18 (94.7%)	.637[f]

ASA - American Society of Anesthesiologists Physical Status Classification System; APE - Abdominoperineal excision; CRM circumferential resection margin; LAR - Low anterior resection; LE - Local Excision; RT - Radiotherapy; c - chi-square; f - Fisher's exact test; m - Mann Whitney test; (*) - 4 local excisions in RG group.

Table 3
Overview of patient's characteristics treated with local excision for regrowth.

Gender	Age	Clinical Staging (mr)	Distance to ARR (cm)	Neoadjuvant Treatment	Time to Regrowth (months)	Type of Regrowth	Pathologic Staging	R0/R1	Completion TME	Recurrence	Follow Up after Local Excision (months)
M	79	T3N1	3	ChRT	5	Luminal	ypT2	R0	Not fit for surgery	No	61
M	60	T3N1	4	ChRT + CAPOX	14	Luminal	ypT0	R0	No	No	33
M	68	T3N1	4	ChRT + CAPOX	10	Luminal	ypT2	R1	Refused	No	34
M	76	T2N1	2	ChRT	8	Luminal	ypT2	R1	Refused	No	16

mr - clinical staging by MRI; ARR - ano-rectal ring, measured in MRI from the tumor to the top of the internal sphincter; RT - radiotherapy; ChRT - chemoradiotherapy; CAPOX - capecitabine/oxaliplatin; TME - total mesorectal excision.

could be “selected” from the total of patients with rectal cancer that are seen in a single tertiary referral center.

We have not irradiated early “low-risk” rectal cancers for the benefit of a potential cCR. Indeed we have not changed our criteria for neoadjuvant treatment. Nevertheless, we have observed a cCR in 63% of all patients undergoing ChRT. Our results thus repeat the reported 68% cCR from the second phase of the Habr-Gama results [7]. This is probably due to applying less strict criteria for cCR and because we have intensified our RT regimens and administered simultaneous integrated boosts (SIB) (54Gy in RGS vs 52Gy in NDS group, $p = 0.042$). These might also explain our relatively high RG rate of 29%, which also repeats the 17% of early plus 10% of late RG reported by Sao Paulo.

As expected, the time to surgery was significantly higher in the RDS group as compared to the NDS group (16 months vs 6 months respectively, $p < 0.001$). The relatively longer waiting time to surgery in the NDS group is explained by the fact that almost 35% received consolidation chemotherapy.

In our center, minimally invasive surgery has been implemented from 2013, initially standardized laparoscopic TME and later robotic TME. Although the time from the last dose of RT was well over the usual 10–12weeks, all RDS patients underwent MIS – 83%

Table 4
Post-operative clinical outcomes.

	Non-deferred Surgery (n = 46)	Regrowth Deferred Surgery (n = 23)	*p* value
Length of hospital stay (days)	8 [2–67]	5 [1–19]	**.013[m]**
30-day Morbidity			
Number of patients	24 (52.2%)	9 (39.1%)	.443[f]
Surgical	17 (36.9%)	3 (13.0%)	
Pulmonary	0	1 (4,3%)	.236[c]
Infectious	11 (23.9%)	4 (17.4%)	
Other	10 (21.7%)	3 (13.0%)	
Anastomotic leak	3 (6.5%)	1 (4.3%)	.999[f]
CTCAE			
1	13 (28.3%)	7 (30.4%)	.646[c]
2	5 (10.8%)	1 (4.3%)	
3	5 (10.8%)	1 (4.3%)	
4	1 (2.2%)	0	
5	0	0	
Clavien-Dindo Classification			
I	4 (13%)	2 (8.7%)	.799[c]
II	14 (30.4%)	5 (21.7%)	
IIIa	2 (4.3%)	0	
IIIb	3 (6.5%)	2 (8.7%)	
IVa	1 (2.2%)	0	
IVb	0	0	
	0	0	
30-day reintervention	6 (8.7%)	2 (8.7%)	0.709[f]
Reintervention			
Radiology	1 (2.2%)	1 (4.3%)	.446[c]
Endoscopy	1 (2.2%)	0	
Laparoscopy	1 (2.2%)	1 (4.3%)	
Laparotomy	3 (6.5%)	0	
ICU Length of Stay (days)*	1 [1–3]	0 [0–2]	**.015[m]**
30-day readmission	1 (2.2%)	1 (4.3%)	.999[f]
30-day mortality	0	0	

CTCAE - Common Terminology Criteria for Adverse Events; ICU - Intensive Care Unit; * - only in patients with complications; c - chi-square test; f - Fisher's exact test; m - Mann Whitney test.

laparoscopically or robotically; the remaining 4 patients received transanal minimally invasive local excision (TAMIS). We had no conversions from laparoscopic to open approach, nor from robotic to laparoscopic or open, in the RDS group.

The increased APE rates in the RDS population is because these tumors were initially located significantly lower in the rectum, and needed an APE from the outset. There was no need for pelvic exenterations in the RDS group (opposed to 4% in NDS group) and it was still possible to offer organ preservation in 17% of the RDS cases – Table 2. These 4 patients (described in detail in Table 3) had regrowths between 8 and 14 months after the completion of RT and all had luminal regrowths identified clinically and confirmed by MRI.

Pathology results from radical resections were comparable in both groups. R0 resection was accomplished in 91.3% (NDS group) vs 94.7% (RDS group) and both had an average of 16 lymph nodes harvested (p-values of 0.99 and 0.856 respectively). The NDS arm had 91% optimal mesorectal specimens compared with 74% in the RG arm ($p = 0.1$). Although not significant, this could reflect increased surgical difficulty in some patients from the established fibrosis and pelvic oedema. This would support the findings of GRECCAR-6 although the reported increased morbidity of their 11 weeks group is due to medical complications, not surgical morbidity. Anastomotic leak, transfused units of packed blood, perineal complications after APE and postoperative ileus were not different between their 2 groups [26], This is in line with our own findings where overall 30-day morbidity (including stage by stage Clavien-Dindo) was not different between RDS and NDS.

Except for the TME quality, we have not found any other indirect sign of surgical difficulty in our RDS cohort. RDS patients actually had a lower hospital stay compared to NDS patients (mean 5 vs 8 days respectively, $p = 0.013$), with similar anastomotic leak rates, 30-day morbidity rate, Clavien-Dindo classification of complication rates, and 30-day re-admission rates. Our overall morbidity rates of 39–52% are comparable with the 37–58% reported in COLOR II and ACOSOG Z6051 [27,28]. In the same way, in this study we report a 4.3% leak rate and 8,7% of re-interventions for the RDS group, similar to the published 13% and 16% for COLOR II and 2,1% and 5% of ACOSOG Z6051 respectively.

All regrowths in this small series were salvaged by effective local excision (n = 4) or radical surgery (n = 19). We acknowledge that a potential 2–3% of RG might not be salvageable, as reported by Habr-Gama [18] due to: a) unresectable local invasion; b) concomitant non-curative systemic recurrence; or c) significant medical comorbidities.

Non-operative treatment and deferred surgery for regrowths has shown promising results in the form of comparable short-term surgical and oncological outcomes. Nevertheless, there is a potential undefined risk of distant metastasis within the W&W follow-up, which still needs to be addressed by carefully constructed randomized controlled trials.

In a recent study published by Smith et al., the authors analyzed the outcomes after W&W, when compared to a cohort of patients who underwent radical operation and had a pathological complete

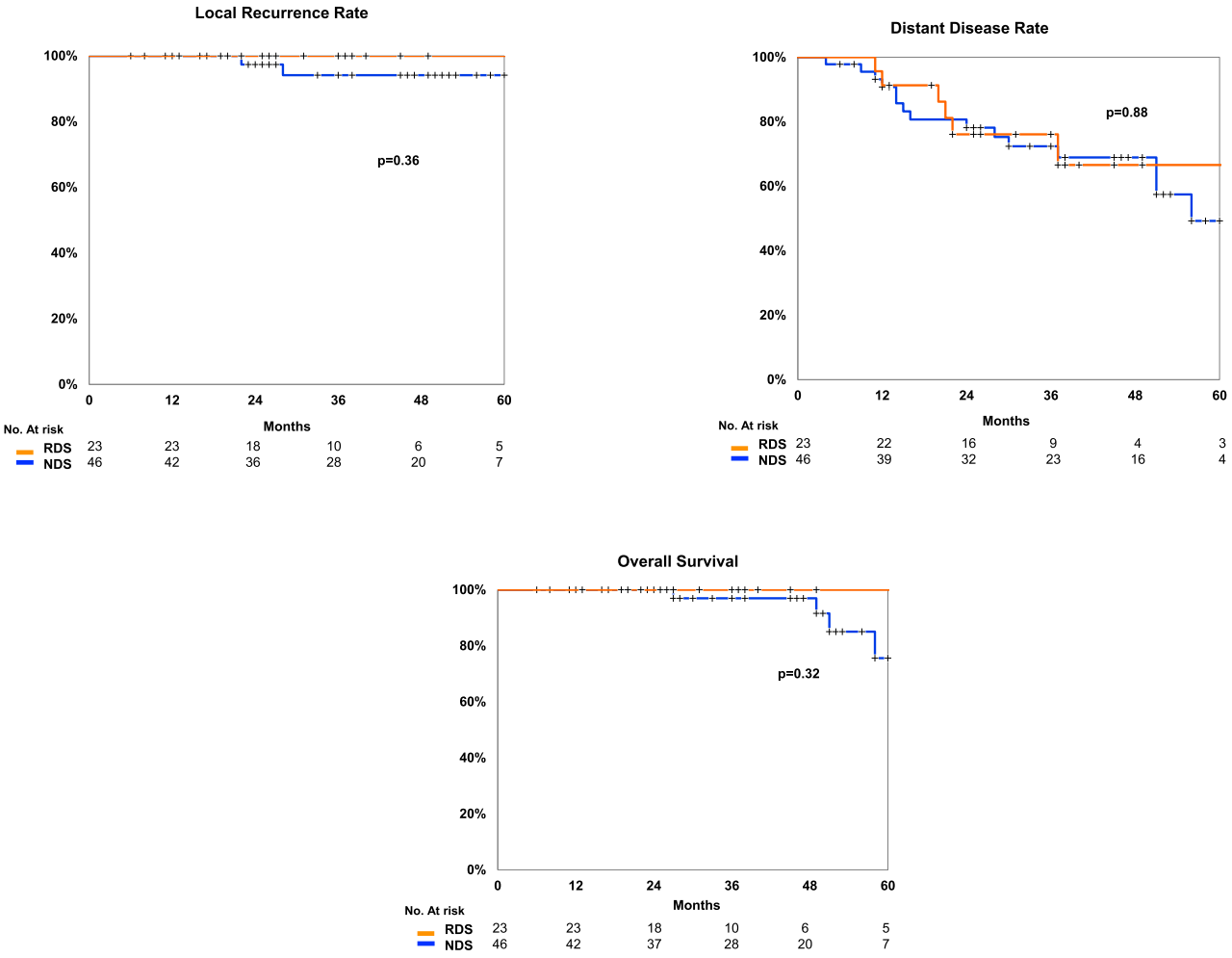

Fig. 2. A) 3-year local recurrence rate between groups was not statistically different (p=0.36); B) 3-year distant disease rate between groups was not statistically different (p=0.88); C) Overall survival was similar between groups at 3 years (p=0.32). NDS - non-deferred surgery group; RDS - regrowth deferred surgery

response. They concluded that the subgroup of patients with local regrowth presented worse overall survival and a higher incidence of distant progression when compared to those with sustained cCR (that never developed local regrowth) [29]. In our study, we compared the outcomes of patients with local regrowth to patients with incomplete clinical response managed by immediate radical surgery. These two comparable subgroups, that ultimately have not responded completely to ChRT, showed no differences in oncological outcomes - Fig. 2.

Interestingly, the systematic review by Dattani [17] reports only 7% metastases for cancers selected for W & W in the published literature, and the IWWD consortium reported 8% [10]. This may suggest that this risk is much smaller than in rectal cancer cases undergoing routine surgical management.

Our study was not designed to answer these very important questions but our results do show no difference in local recurrence, distant disease or overall survival at 3 years between the NDS and RDS groups - i.e. no apparent penalty for the delay involved in trying to maximise the number of patients who may safely avoid surgery.

We acknowledge several limitations of our study: retrospective analysis, single-center data and small cohort of patients. Despite the retrospective nature of the study, data was collected through a prospectively maintained database and all consecutive patients who received neoadjuvant RT were included, minimizing observer bias. By separating all the treated patients with neoadjuvant RT followed by surgery in one group, and all the W&W patients with RG in the second arm, we have tried to minimize selection bias.

To our knowledge, this is the first attempt in literature to compare short-term clinical outcomes between: a) patients with locally advanced rectal cancer submitted to neoadjuvant treatment who fail to achieve a cCR and are operated, and; b) patients who achieve an initial cCR, enter a W&W protocol, but fail to have a sustained complete response and eventually develop a primary tumor regrowth that needs deferred surgery.

Conclusion

Patients with an initial cCR who develop a local regrowth may be safely managed by deferring the surgery. These short-term outcomes suggest equivalent results to patients with an incomplete clinical response who undergo immediate radical surgery. Delayed minimally invasive surgery appears to have no negative impact on oncological outcomes.

Authors contributions

Nuno Figueiredo, Amjad Parvaiz, Irfan Nasir, Laura Fernandez and Pedro Vieira designed the study, performed data analysis and drafted the manuscript. Carlos Carvalho, Richard J. Heald and

Geerard L. Beets revised the manuscript critically for important intellectual content. Oriol Parés, Inês Santiago, Mireia Castillo-Martin, José F. Cunha and Hugo Domingos performed data collection and collaborated in study design. All authors read and approved the final manuscript.

Conflicts of interest

The authors have no conflicts of interest to declare.

Declarations of interest

None.

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