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Article

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Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer

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Abstract

Background: The aim of this study was to establish the oncological and functional results of organ preservation with a watch-and-wait approach (W&W) and selective transanal endoscopic microsurgery (TEM) in patients with a clinical complete or near-complete response (cCR) after neoadjuvant chemoradiation for rectal cancer.

Methods: Between 2004 and 2014, organ preservation was offered if response assessment with digital rectal examination, endoscopy, and MRI showed (near) cCR. Watch-and-wait was offered for cCR, and two options were offered for near cCR: TEM or reassessment after three months. Follow-up included endoscopy and MRIs every three months during the first year, and every six months thereafter. Long-term outcome was assessed with Kaplan-Meier curves. Functional outcome was assessed with colostomy-free survival and Vaizey incontinence score (0 = perfect continence, 24 = totally incontinent).

Results: One hundred patients were included, with median follow-up of 41.1 months. Sixty-one had cCR at initial response assessment. Thirty-nine had near cCR, of whom 24 developed cCR at the second assessment and 15 patients underwent TEM (9 ypT0, 1 ypT1, 5 ypT2). Fifteen patients developed a local regrowth (12 luminal, 3 nodal), all salvageable and within 25 months. Five patients developed metastases, and five patients died. Three-year overall survival was 96.6% (95% confidence interval [CI] = 89.9% to 98.9%), distant metastasis–free survival was 96.8% (95% CI = 90.4% to 99.0%), local regrowth–free survival was 84.6% (95% CI = 75.8% to 90.5%), and disease-free survival was 80.6% (95% CI = 70.9% to 87.4%). Colostomy-free survival was 94.8% (95% CI = 88.0% to 97.8%), with a good continence after watch-and-wait (Vaizey = 3.4, SD = 3.9) and moderate after TEM (Vaizey = 9.7, SD = 5.1).

Conclusions: Organ preservation appears oncologically safe for selected rectal cancer patients with a cCR or near cCR after neoadjuvant chemoradiation when applying strict selection criteria and frequent follow-up, including endoscopy and MRI. The low colostomy rate and the good long-term functional outcome warrant discussing this option with the patient as an alternative to major surgery.

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The standard treatment for patients with a locally advanced rectal cancer is neoadjuvant chemoradiation followed by total mesorectal excision (TME) after a six- to 10-week interval. In up to 15% to 20% of the patients, no residual tumor is found at histopathology (1). In 2004, Habr-Gama et al. suggested that surgery may be omitted in a selected patient group with a clinical complete response (cCR) (2). Although initially this concept resulted in considerable scepticism, there is now an increasing interest in organ preservation in patients with a clinical complete response. Both omission of surgery with a watch-and-wait regimen (3–7) and transanal endoscopic microsurgery (TEM) of the residual scar (8–11) have shown promising outcomes in relatively small series.

In 2011, we reported a pilot study on watch-and-wait (W&W) policy in 21 patients with a clinical complete response after neoadjuvant chemoradiation, with an important role for MRI in the selection and follow-up of patients (4). In this pilot study, the two-year disease-free survival was 89%, and the overall survival 100%. As expected, the functional outcome was also better when compared with complete responders who underwent TME. However, the number of patients was limited, and the mean follow-up was relatively short. Since then, we have experienced a high interest of both clinicians and patients, and we have continued to offer organ-preserving treatment as an alternative to a major resection of the rectum in patients with a very good response.

The aim of this study was to establish the long-term oncological and functional results of organ preservation with a W&W approach and selective TEM in patients with a clinical complete or near-complete response after neoadjuvant chemoradiation for rectal cancer.

Methods

Patient Selection

Between 2004 and 2014, patients who were treated with neoadjuvant chemoradiotherapy in standard patient care and who presented with a clinical complete response at restaging were offered an organ-preserving treatment. Organ preservation was offered in a prospective cohort study, approved by the local institutional review board and registered in clinicaltrials.gov since 2009 (NCT00939666 and NCT02278653). All patients provided informed consent. Inclusion criteria were 1) rectal cancer without distant metastasis, 2) neoadjuvant treatment (standard chemoradiation of 28x1.8Gy combined with 2x825mg/m^2 capecitabine or 5x5Gy with a long interval to surgery), and 3) a clinical complete or near-complete response. The response was evaluated approximately eight weeks after completion of neoadjuvant treatment with digital rectal examination (DRE), MRI, and endoscopy. Criteria for a clinical complete response were described previously (Table 1) (4). Eligible patients with a clinical complete response were offered the watch-and-wait policy as an alternative to standard TME. Patients were specifically informed of the experimental nature and the potentially increased risk of this alternative treatment in a shared-decision process. Figure 1 represents a typical example of the MRI and endoscopic images of a patient with a clinical complete response. Some patients had a near-complete response at initial response assessment, defined as a very good response that did not meet all criteria for a clinical complete response, for example, a small red lesion at endoscopy or equivocal lymph nodes on MRI (see Table 1). Figure 2 shows an example of the MRI and endoscopic images of a patient with a near-complete response. These patients were offered, in addition to the standard TME, the option of transanal endoscopic microsurgery (TEM) when the tumor was not involving the sphincter complex or the option of postponing the decision between W&W and TME until a second assessment three months later. Patients who met all the criteria for cCR at this second assessment were offered watch-and-wait. All other patients were referred for TME.

Follow-up

Follow-up included the standard follow-up according to national guidelines, with imaging of the chest and liver, CEA, and out-patient clinic visits for a period of five years. For the organ preservation–specific follow-up, patients additionally underwent MRI and sigmoidoscopy every three months during the first year and every six months until five years after inclusion (Supplementary Table 1, available online) (4).

Functional Outcome

Patients with a follow-up of at least three years were approached to participate in a questionnaire to assess the presence of fecal

Table 1. Criteria for a clinical complete response after neoadjuvant therapy

Modality	Criteria for clinical complete response	Criteria for clinical near-complete response*
DRE	No palpable tumor, when initially palpable with DRE	Small superficial soft irregularity
Endoscopy	No residual tumor and white scar	Small residual erythematous ulcer or irregular wall thickening
MRI	Standard T2-weighted MRI	Standard T2-weighted MRI
	Substantial downsizing with no residual tumor or	Obvious downstaging with residual fibrosis but heterogeneous
	Residual fibrosis or	or irregular aspect and signal or
	Residual wall thickening because of edema	Obvious downstaging of lymph nodes but remaining node(s) ≥5 mm
	And no suspicious lymph nodes	
	Diffusion-weighted MRI†	Diffusion-weighted MRI†
	Low signal on high b-value	Small focal area of high signal on high b-value
	Gadofosveset-enhanced MRI†	Gadofosveset-enhanced MRI†
	No suspicious lymph nodes	Obvious downstaging of lymph nodes but remaining node(s) ≥5 mm without malignant enhancement pattern
Histopathology	Negative biopsies from scar (biopsy not mandatory)	Dysplastic changes

*Patients had a clinical near-complete response if they missed only one or two criteria of a clinical complete response but matched the other criteria for a clinical near-complete response. DRE = digital rectal exam; MRI = magnetic resonance imaging.
†Available since 2006.

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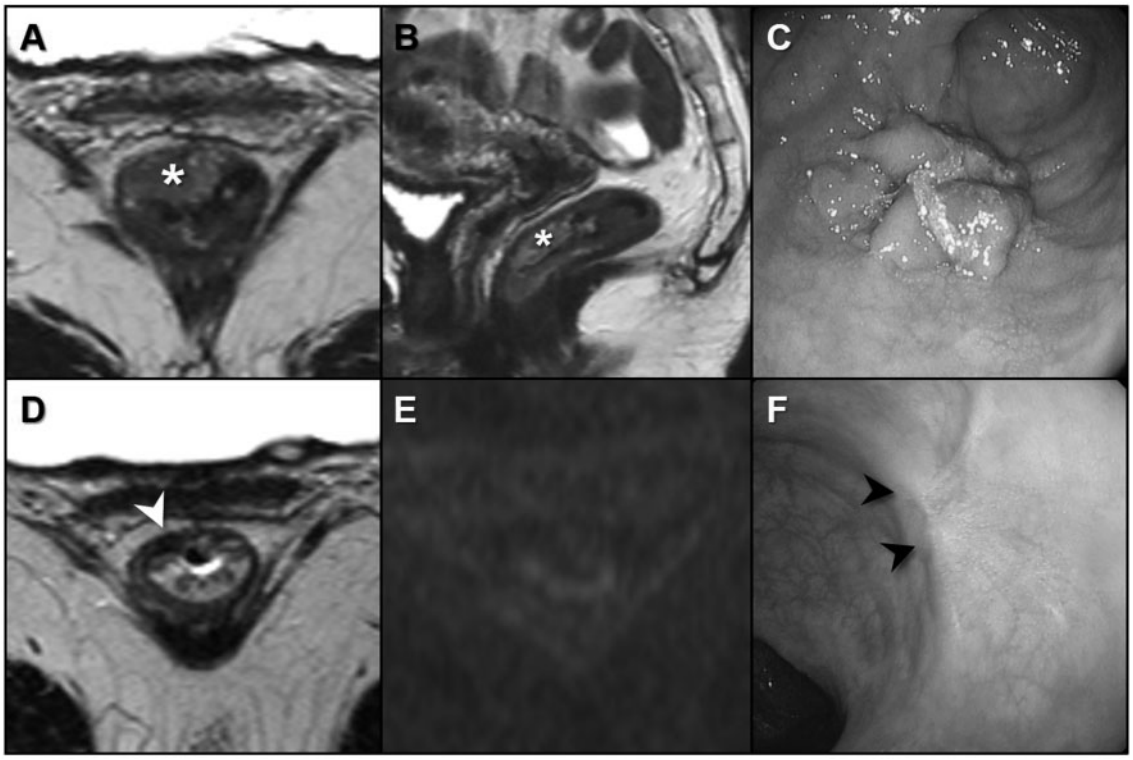

Figure 1. Images of a patient with a clinical complete response at the initial response assessment. Axial **(A)** and saggital **(B)** T2-weighted MRI of a distal cT2N0 tumor before treatment (indicated with *) and **(C)** endoscopic image of primary tumor. **D)** Axial T2-weighted MRI eight weeks postchemoradiation, with the **white arrowhead** indicating residual fibrosis. **E)** Diffusion-weighted MRI without any high signal, suggesting a complete response. **F)** Endoscopy with a typical white scar (**black arrowheads**) consistent with complete response.

incontinence. Functional outcome was measured with the Vaizey score (12), consisting of seven questions with a total score ranging between 0 (no incontinence) and 24 (major incontinence). All scores of 12 or higher are considered major incontinence.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 20.0, Inc., Chicago, IL) and Stata (Stata/SE version 11.2, Stata Corp. LP, College Station, TX). Functional outcome scores were compared between W&W and TEM patients with a Mann-Whitney U test. Local regrowth–free survival (LRFS), distant metastasis–free survival (DMFS), disease-free survival (DFS), and overall survival (OS) were estimated with Kaplan-Meier curves and were compared between different groups using the log-rank test, and 95% confidence intervals (CIs) were calculated.

Local regrowth was defined as tumor regrowth in the lumen or in a regional lymph node, DMFS as the absence of distant metastases, DFS as the absence of local regrowth, distant metastasis, and death from any cause, and OS as the absence of death from any cause. Duration of follow-up was calculated from the start of treatment (first day of radiotherapy) to the event of interest or the last follow-up date. A *P* value of .05 or less was considered statistically significant. All statistical tests were two-sided.

Results

A total of 100 patients entered the organ preservation program between 2004 and 2014, including the previously reported 21 patients (4). Sixty-one patients had a cCR at the first assessment and were immediately included in a watch-and-wait policy (W&W). Thirty-nine patients had a "near cCR," most commonly based on an inconclusive endoscopy such as a small red lesion or ulcer, or equivocal findings on MRI (see Table 1). Fifteen of the patients with a near cCR underwent a TEM, which showed a ypT0 in nine of 15 patients (60.0%), ypT1 in one patient (6.7%), and ypT2 in and five of 15 patients (33.3%). The patients with a residual tumor after TEM opted for continued follow-up rather than completion surgery. The remaining 24 patients with a near cCR at the first assessment were included when the second assessment after three months showed a typical complete response on both MRI and endoscopy. Figure 3 shows a flowchart with the detailed selection and inclusion process.

Patient Characteristics

Sixty-seven patients were male (67.0%), and the mean age was 63.2 years (SD = 10.5 years). Median follow-up was 41.1 months (range = 12–120 months), and 60 patients (60.0%) had a follow-up of at least three years. Detailed patient and treatment characteristics are given in Table 2. Of the included 100 patients, 24 were diagnosed and treated in our center, constituting 17.0% (24/141) of all patients treated with chemoradiation in our center during the study period. The remaining 76 included patients were primarily treated in another center according to national guidelines and referred to our center specifically for response assessment and organ preservation.

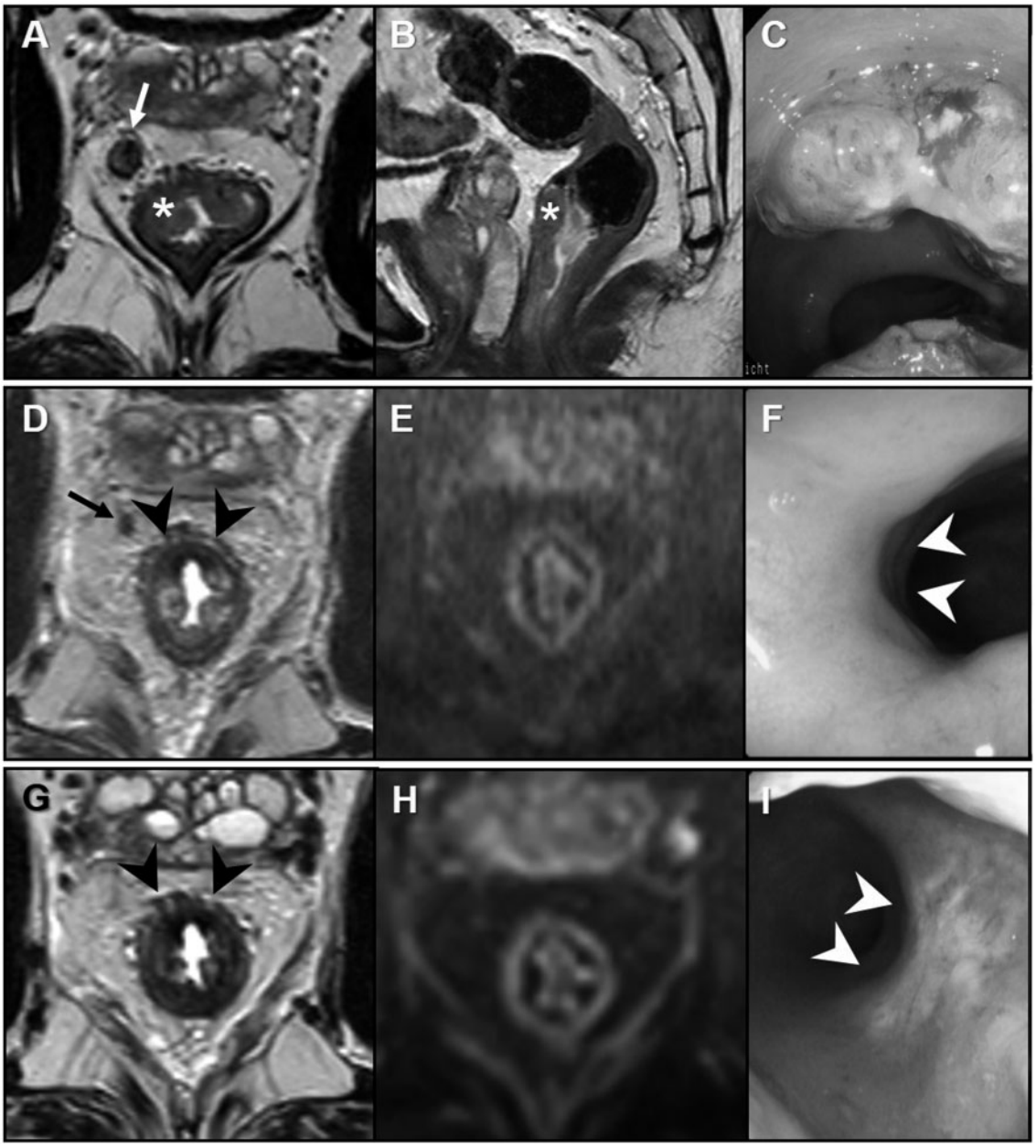

Figure 2. Images of a patient with a near-complete response at initial assessment and clinical complete response after a reassessment three months. Axial **(A)** and saggital **(B)** T2-weighted MRI of distal cT3 tumor (indicated with *) with evident malignant lymph node (**white arrow**) before treatment and **(C)** endoscopic image of primary tumor. **D)** Axial T2-weighted MRI at initial response assessment 16 weeks postchemoradiation, with the **black arrow** indicating a residual lymph node, potentially malignant. **Black arrowheads** indicate residual fibrosis. **E)** Diffusion-weighted MRI without any high signal, suggesting complete response. **F)** Endoscopy with a small superficial erythematous ulcer (**white arrowheads**). **G)** Axial T2-weighted MRI three months later: the lymph node has disappeared. **Black arrowheads** indicate residual fibrosis. **H)** Diffusion-weighted MRI without high signal. **I)** Typical white scar (**white arrowheads**) visible on endoscopy.

Oncological Outcome

Fifteen of the 100 patients treated with an organ-preserving treatment developed a local regrowth within the lumen (n = 12) or in a lymph node (n = 3). All luminal regrowths were primarily detected with endoscopy and occurred within 25 months of follow-up. Four of these regrowths were also visible on MRI (3 on both T2W and DWI, and 1 only on DWI). All lymph node regrowths were detected with MRI. See Supplementary Figure 1 (available online) for MRI and endoscopy images of a luminal regrowth and Supplementary Figure 2 (available online) for a nodal regrowth. Of the 15 patients with a local regrowth, three occurred in the TEM group, all in patients with ypT2 residual tumor in the TEM specimen. Two of the fifteen patients with a local regrowth presented with simultaneous distant metastases, and the treatment was primarily aimed at the metastases with a continued control of the local situation. All but one of 13 isolated local regrowths without synchronous metastasis were detected when small and were easily amenable to salvage therapy with a surgical procedure that was not more extensive than it would have been originally. One patient required a pelvic exenteration for a regrowth after a TEM (histopathology of the TEM specimen ypT2). At present, all 13 patients remain free of

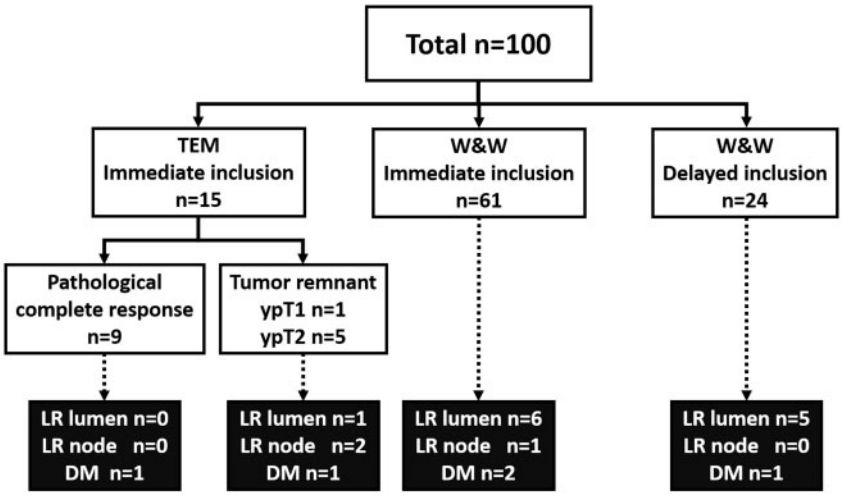

Figure 3. Flowchart of patient selection and inclusion. DM = distant metastasis; LR = local regrowth; TEM = transanal endoscopic microsurgery; TME = total mesorectal excision; W&W = watch-and-wait.

Table 2. Patient characteristics

Parameter	Total (n = 100)	W&W (n = 85)	TEM (n = 15)
Age, mean (±SD), y	63.2 (±10.5)	62.7 (±10.6)	65.8 (±9.8)
Sex, No. (%)			
Male	67 (67.0)	56 (65.9)	11 (73.3)
Female	33 (33.0)	29 (34.1)	4 (26.7)
Clinical T-stage, No. (%)			
cT1-2	25 (25.0)	22 (25.9)	3 (20.0)
cT3	67 (67.0)	55 (64.7)	12 (80.0)
cT4	8 (8.0)	8 (9.4)	–
Distance from anorectal verge, No. (%)			
0–5 cm	79 (79.0)	70 (82.4)	9 (60.0)
5–10 cm	18 (18.0)	12 (14.1)	6 (40.0)
10–15 cm	3 (3.0)	3 (3.5)	–
Clinical N-stage, No. (%)			
cN0	26 (26.0)	20 (23.5)	6 (40.0)
cN1	41 (41.0)	36 (42.4)	5 (33.3)
cN2	33 (33.0)	29 (34.1)	4 (26.7)
Neoadjuvant treatment, No. (%)			
50.4Gy + capecitabine	95 (95.0)	83 (97.6)	12 (80.0)
5x5Gy + CAPOX	2 (2.0)	2 (2.4)	–
5x5Gy + interval	3 (3.0)	–	3 (20.0)
"Adjuvant" chemotherapy (CAPOX), No. (%)*			
Yes	34 (34.0)	32 (37.6)	2 (13.3)
No	60 (60.0)	48 (56.5)	12 (80.0)
Incomplete	6 (6.0)	5 (5.9)	1 (6.7)
Interval between last RTx and assessment post-CRT, median (IQR), wk	10.0 (3.3–16.7)	10.0 (3.1–16.9)	10.7 (5.8–16.6)
Pathology, No. (%)†			
ypT0	N/A	N/A	9 (60.0)
ypT1			1 (6.7)
ypT2			5 (33.3)

*Adjuvant chemotherapy was offered according to our national guidelines. CAPOX = capecitabine and oxaliplatin; CRT = chemoradiation; Gy = Gray; IQR = interquartile range; RTx = radiation therapy; TEM = transanal endoscopic microsurgery; W&W = watch-and-wait.
†Pathology after TEM.

further local recurrence. Three patients developed distant metastases without local regrowth, one of whom died of metastatic disease. One patient died of postoperative complications, and three other patients of unrelated causes. Table 3 gives a complete overview of all regrowths, distant metastases, and causes of death. The cumulative three-year local regrowth–free survival was 84.6% (95% CI = 75.8% to 90.5%), distant metastasis–free survival was 96.8% (95% CI = 90.4% to 99.0%), disease-free survival was 80.6% (95% CI = 70.9% to 87.4%), and overall survival was 96.6% (95% CI = 89.8% to 98.9%) (Figure 4).

The three-year LRFS for the TEM group vs the W&W group was 80.0% (95% CI = 50.0% to 93.1%) vs 85.8% (95% CI = 75.7% to

Table 3. Overview of patients with local regrowth, distant metastasis, and/or cause of death*

Patient	Age, y	Sex	cT stage	cN stage	Distance from ARJ, cm	Neoadjuvant treatment	Histology (TEM)	Adjuvant CTx	Time to event, mo	Local regrowth	Distant metastasis	Treatment	Total follow-up, mo
Local regrowth without evidence of distant metastasis													
1	70	Male	3	1	0.0	CRT	–	1 cycle	7	Lumen	–	APR (ypT3N0)	54, NED
2	72	Male	3	1	1.0	CRT	–	No	9	Lumen	–	APR (ypT2N0)	13, NED
3	81	Female	3	0	0.0	CRT	–	No	11	Lumen	–	APR (ypT2N0)	13, NED
4	55	Male	2	0	0.5	CRT	TEM: ypT2	No	13	Lumen	–	CRT + pelvic exenteration (ypT3N0)	56, NED
5	69	Male	3	1	5.0	CRT	–	No	13	Lumen	–	TEM (ypT2) followed by LAR (ypT0N0)	17, NED
6	60	Male	3	0	3.7	CRT	–	No	14	Lumen	–	APR (ypT2N0)	17, NED
7	76	Male	2	1	4.0	CRT	–	No	15	Lumen	–	Endoscopic resection followed by LAR (ypT2N0)	35, NED
8	84	Male	4	2	0.0	CRT	–	No	15	Lumen	–	APR (ypT3N0)	21, DOD (postoperative complications)
9	55	Male	4	2	4.0	CRT	–	Yes	15	Lymph node	–	LAR (ypT0N1)	50, NED
10	61	Male	2	0	2.0	5x5+long interval	TEM: ypT2	No	15	Lymph node	–	CRT + APR (ypT0N1)	54, NED
11	57	Female	2	2	8.0	CRT	–	Yes	22	Lumen	–	LAR (ypT2N0)	39, NED
12	63	Female	3	2	0.0	CRT	–	No	18	Lumen	–	APR (ypT2N0)	20, NED
13	63	Male	3	0	5.5	CRT	–	Yes	25	Lumen	–	TEM (ypT2), reregrowth LAR (ypT2N0)	82, NED
Local regrowth with synchronous distant metastasis													
14	55	Male	3	1	2.0	CRT	–	No	11	Lumen	Lung	Stereotactic radiation lung, brachytherapy rectum	30, AWD
15	55	Female	3	2	1.5	CRT	TEM: ypT2	No	12	Lymph node	Lung	Palliative CAPOX (multiple bilateral lungmetastases)	13, AWD
Distant metastasis without evidence of local regrowth													
16	57	Male	3	0	0.0	CRT	–	No	22	–	Lung+liver	Resection liver metastasis and stereotactic radiation lung; second resection repeated liver metastasis	37, AWD
17	78	Female	3	2	6.5	CRT	TEM: ypT0	Yes	37	–	Lung	Stereotactic radiation	59, NED

(continued)

Table 3. (continued)

Patient	Age, y	Sex	cT stage	cN stage	Distance from ARJ, cm	Neoadjuvant treatment	Histology (TEM)	Adjuvant CTx	Time to event, mo	Local regrowth	Distant metastasis	Treatment	Total follow-up, mo
18	79	Female	3	0	8.0	CRT	–	No	38	–	Peritoneum	No treatment	39, DOD (progression of metastases)
Death unrelated to disease													
19	74	Male	3	1	0.0	CRT	–	No	13	–	–	–	13, DOC (cerebral infarction)
20	79	Male	3	1	15.0	CRT	–	No	30	–	–	–	30, DOC (ruptured abdominal aortic aneurism)
21	66	Male	3	2	5.5	CRT	–	Yes	73	–	–	–	73, DOC (metastasized melanoma)

*APR = abdominoperineal resection; ARJ = anorectal junction; AWD = alive with disease; CAPOX = capecitabine and oxaliplatin; CRT = chemoradiotherapy; CTx = chemotherapy; DOC = death of other cause; DOD = death of disease; FU = follow-up; LAR = low anterior resection; NED = no evidence of disease; TEM = transanal endoscopic microsurgery.

91.5%, $P = .57$), DMFS was 93% (95% CI = 61.3% to 99.0%) vs 97.4% (95% CI = 90.0% to 99.4%), and OS was 100% vs 96.0% (95% CI = 87.9% to 98.7%); these were not statistically different between the two groups. There were no statistically significant differences between primarily more advanced tumors (cT4 and/or cN2) vs less advanced tumors: three-year LRFS was 86.7% (95% CI = 70.9% to 94.2%) vs 83.4% (95% CI = 71.3% to 90.7%, $P = .63$), DMFS was 97.4% (95% CI = 82.8% to 99.6%) vs 96.5% (95% CI = 86.7% to 99.1%, $P = .98$), and OS was 97.1% (95% CI = 81.4% to 99.6%) vs 96.4% (95% CI = 86.1% to 99.1%, $P = .87$).

Functional Outcome

Eight patients had a definitive colostomy, all after salvage resection for a local regrowth (8 APR, 1 exenteration), resulting in a three-year colostomy-free survival of 94.8% (95% CI = 88.0% to 97.8%). Forty-five patients were at least three years in follow-up and sustained a complete response without regrowth. Twenty-nine of these patients completed the questionnaire (22 W&W, 7 TEM, response rate 64.4%). The mean total Vaizey score of W&W patients was 3.4 (SD = 3.9), indicating a good continence. This was statistically significantly better than the 9.7 (SD = 5.1) in TEM patients ($P = .003$). See Figure 5 for detailed results. Only one W&W patient (1/22, 4.5%) suffered from major incontinence (score $\geq$ 12) compared with three patients in the TEM group (3/7, 42.8%).

Discussion

The main conclusion is that organ-preserving treatment for complete responders and near-complete responders after CRT for locally advanced rectal cancer is feasible and results in a high three-year overall survival of 97% with a local regrowth rate of 15%. Long-term functional outcome was promising, with only 8% of patients with a colostomy and very few incontinence problems after W&W. This study suggests that in a careful program of organ preservation there is little or no oncological disadvantage for selected patients with a clinical complete or near-complete response.

There is a legitimate concern that organ preservation in rectal cancer could negate the improvements in oncological outcome that have been achieved by optimal use of a good surgical TME technique and (neo)adjuvant treatment. The concern is that the increased number of local recurrences will lead to a decreased survival because some may not be amenable to salvage therapy and because some may cause metastases later. In the present study, only one of the hundred patients was disadvantaged by the organ preservation approach because a pelvic exenteration was required to control the local regrowth. This occurred after a TEM for a ypT2 tumor, where immediate completion surgery is now recommended. We have not yet seen an unresectable local regrowth and have not encountered a local recurrence after salvage TME surgery. In two patients with a local regrowth, systemic disease was diagnosed simultaneously, and there were no patients with systemic disease diagnosed after the local regrowth. Given this timeframe, it is unlikely that the regrowth was the source of the metastases. The recent report of Habr-Gama et al. (13) on watch-and-wait in 90 patients with a median follow-up of 60 months showed a local regrowth in 31%, higher than the 15% in the present study. In that study, the majority were easily amenable to salvage treatment, but regrettably four patients experienced a further unresectable local recurrence that could only be treated palliatively. Two of the 28 patients with a local regrowth developed late metastases after

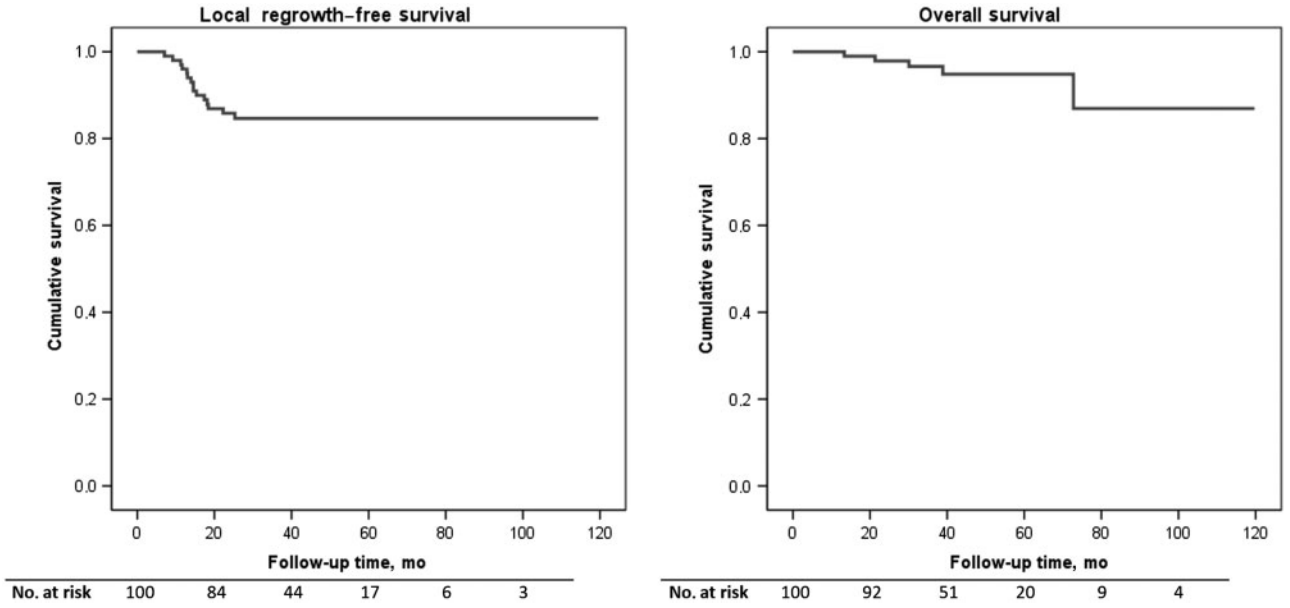

Figure 4. Local regrowth–free survival and overall survival for the total of 100 patients in an organ-preserving treatment. The numbers of patients at risk at various timepoints are **below each curve.**

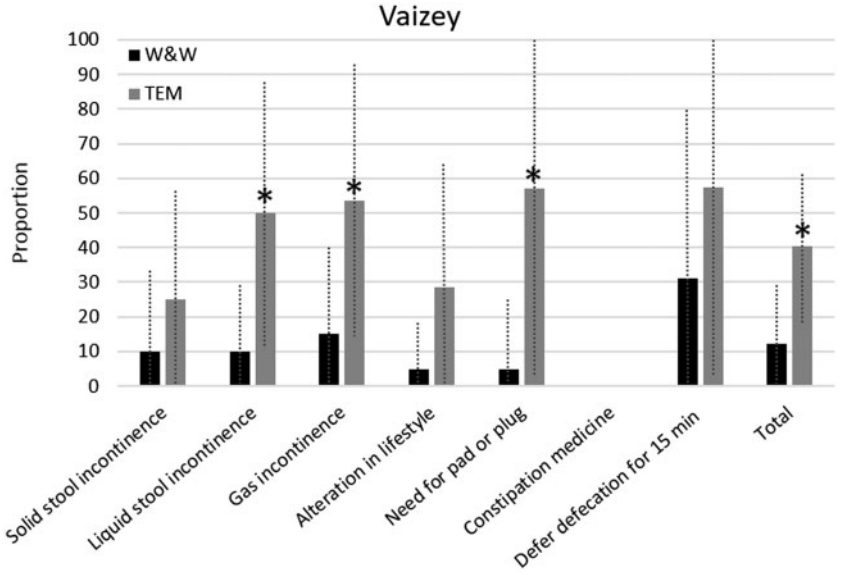

Figure 5. Functional outcome based on Vaizey score. A higher score indicates a poorer result. * indicates that the difference was statistically significant with a two-sided Mann-Whitney U test. TEM = transanal endoscopic microsurgery; W&W = watch-and-wait.

two and four years, and it cannot be ruled out that in that study the regrowth was the source of the metastases. Smith et al. reported a retrospective series on watch-and-wait in 32 patients with a median follow-up of 28 months and six patients developing a local regrowth (19%). All six regrowths could be salvaged by standard TME and remained locally controlled. Two of the six patients developed late metastatic disease about a year later, and again it cannot be ruled out that the regrowth was the source of the late metastases (5). In the prospective trial of Appelt et al. with a median follow-up of 24 months, nine of 40 patients who entered the watch-and-wait program developed a local regrowth (23%). All regrowths were detected within two years of follow-up and underwent salvage surgery. One patient with a regrowth developed distant metastases before the local regrowth (6). Renehan and colleagues reported a local regrowth rate of 34% after 33 months of follow-up in 129 patients (44/129), including three patients with synchronous distant metastasis. Salvage surgery was performed in 32 of 44 (73%), Papillon contact radiotherapy in five of 44 (11%), and palliative therapy in the remaining seven patients, of whom two patients had synchronous distant metastasis. Four other patients developed distant metastasis without evidence for local regrowth (7).

The regrowth rate in the present series is lower than in the other reported series, and there was no evident oncological risk. Although this could be because of chance or a relatively short follow-up, it could also be related to a strict selection process with clinical examination, endoscopy, and MRI, including diffusion-weighted MRI (14), and a careful follow-up program

that also includes state-of-the-art MRI techniques (15). Only an estimated 17% of the patients treated primarily in our center with chemoradiation were considered cCR, compared with 49% in the Habr-Gama series. This suggests inclusions of larger tumors in our series and possibly also a stricter selection. In the first phase of the present study (4), we adhered strictly to the predefined selection criteria of a completely normalized rectum on DRE, endoscopy, and MRI. There was only one local regrowth of 21 patients, but one-third of complete responders were missed and underwent TME. Following this observation, it was decided to include TEM or a second assessment after three months for patients now considered "near-complete responders."

In the absence of randomized data and very large series, it is difficult to calculate an exact oncological risk, but based on our study and the series described above we estimate the excess oncological risk of dying with a watch-and-wait policy in the order of 2% to 3% or less. In the shared decision process with the patient, this needs to be carefully balanced against the operative risk and loss of function of major rectal surgery. We experienced that patients are often willing to take this small potential risk in order to avoid major surgery, potentially poor functional outcome, or a colostomy. Despite the limitations of decision-analytic modeling, it is reassuring that a recent study showed a calculated operative risk in elderly and comorbid patients that was higher than the oncological risk, and in younger patients the risk was equal (16).

An alternative to repeated assessment in patients with a "near-complete response" is a local excision, preferably TEM, providing histological proof of a ypT0. The risk of residual lymph node metastasis in ypT0 is 5%, as shown in a meta-analysis (1). In the current study, a ypT1-2 tumor that was completely resected by TEM and without evidence of lymph node metastases on MRI was considered a candidate for organ preservation. However, three of five patients with ypT2 residual tumors developed local regrowths, confirming other reports, and we now recommend immediate completion surgery (17–19). Some of the disadvantages of a TEM are postoperative complications (10,17), a more difficult follow-up because of fibrotic changes, and more difficult salvage TME (17,20). Additionally, in our series, the functional outcome after TEM was not as good as after W&W. On the other hand, it is likely that TEM can prevent a number of local regrowths in small ypT1 remnants. The exact roles of W&W and TEM in organ preservation of rectal cancer are not yet clearly defined.

In the present study, the majority of patients received chemoradiation with the goal to improve local control after TME surgery for more advanced and distal tumors, not with a deliberate goal to preserve the rectum. The incidence of cCR is only 15% to 20%. A number of trials with the explicit goal of rectal preservation in relatively small tumors have shown a success rate of over 50% (21,22). The downside is that the patients who still need major surgery may end up with a worse function than they would have had with TME surgery without neoadjuvant therapy. Better prediction methods for response to radiotherapy at initial diagnosis would allow a better treatment choice that minimizes toxicity of futile neoadjuvant radiotherapy.

There are some limitations to this study. First, a median follow-up of 41 months is generally considered short for good estimates for DMFS and OS. Because most regrowths in both our series and other series have occurred within the first 18 to 24 months and 60% of patients in our series had a follow-up of more than three years, we believe that the results will not change much with a longer follow-up. Second, the number of patients is relatively small for analyses of differences between subgroups.

Organ-preserving treatment appears to be an oncologically safe option for selected rectal cancer patients with a clinical complete or near-complete response after neoadjuvant chemoradiation when applying strict criteria and frequent follow-up, including endoscopy and MRI. The low colostomy rate and the good long-term functional outcome warrant discussing this option with the patient as an alternative to major TME surgery.

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