ORIGINAL CONTRIBUTION

Watch and Wait Approach Following Extended Neoadjuvant Chemoradiation for Distal Rectal Cancer: Are We Getting Closer to Anal Cancer Management?

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BACKGROUND: No immediate surgery (Watch and Wait) has been considered in select patients with complete clinical response after neoadjuvant chemoradiation to avoid postoperative morbidity and functional disorders after radical surgery.

OBJECTIVE: The purpose of this study was to demonstrate the long-term results of patients who had a complete clinical response following an alternative chemoradiation regimen and were managed nonoperatively.

DESIGN: This is a prospective study.

SETTINGS: This study was conducted at a single center.

PATIENTS: Seventy consecutive patients with T2-4N0-2M0 distal rectal cancer were studied. Neoadjuvant chemoradiotherapy included 54 Gy and 5-fluorouracil/leucovorin delivered in 6 cycles every 21 days. Patients were assessed for tumor response at 10 weeks from radiation completion. Patients with incomplete clinical response were referred to immediate surgery. Patients with complete clinical response were not immediately operated on and were monitored.

MAIN OUTCOME MEASURES: The primary outcomes measured were the initial complete clinical response rates after 10 weeks and the sustained complete clinical response rates after 12 months from chemoradiotherapy.

RESULTS: One patient died during chemoradiotherapy because of cardiac complications. Forty-seven (68%) patients had initial complete clinical response. Of these, 8 developed local regrowth within the first 12 months of follow-up (17%). Thirty-nine sustained complete clinical response at a median follow-up of 56 months (57%). An additional 4 patients (10%) developed late local recurrences (>12 months of follow-up). Overall, 35 patients never underwent surgery (50%).

LIMITATIONS: This study is limited by the short follow-up and small sample size.

CONCLUSION: Extended chemoradiation therapy with additional chemotherapy cycles and 54 Gy of radiation may result in over 50% of sustained (>12 months) complete clinical response rates that may ultimately avoid radical rectal resection. Local failures occur more frequently during the initial 12 months of follow-up in up to 17% of cases, whereas late recurrences are less

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common but still possible, leading to 50% of patients who never required surgery. Strict follow-up may allow salvage therapy in the majority of these patients (**see Video, Supplemental Digital Content 1**, http://links.lww.com/DCR/A113.)

KEY WORDS: Complete clinical response; Neoadjuvant chemoradiation; Rectal cancer; Watch and wait.

Neoadjuvant chemoradiation therapy (CRT) for rectal cancer may result in significant tumor regression. In fact, the degree of tumor downstaging may lead to clinically relevant consequences in terms of patient outcomes in rectal cancer management. First, survival and local disease control seem to be directly related to tumor regression, and complete pathological response is clearly associated with improved oncological outcomes.[1,2] In addition, tumor downstaging may offer the possibility of sparing patients from the significant postoperative morbidity associated with radical rectal surgery. Tumor downstaging may include the avoidance of a definitive stoma, for the need of total mesorectal excision or even for the need of any surgical resection with an organ-preserving strategy; this is also known as the Watch and Wait strategy.[3]

In this setting, novel neoadjuvant strategies have been considered with the use of different chemotherapy agents and schedules to improve the rates of complete tumor regression without compromising treatment-related toxicity.[4] Even though the addition of a second drug (to 5-fluorouracil-based regimens) was considered a predictive factor for complete tumor regression, studies have failed to demonstrate any increase in complete pathological response with the addition of oxaliplatin or cetuximab.[5,6] On the other hand, extended chemotherapy (using additional 5-fluorouracil (5-FU) cycles during the resting period after radiation therapy (RT) completion) suggested a significant increase in complete tumor regression rates in a preliminary report.[7]

In this setting, we decided to report the outcomes of patients with complete clinical response who were managed without immediate radical surgery following neoadjuvant CRT in a larger series of patients and with longer follow-up.

PATIENTS AND METHODS

Between 2006 and 2010, consecutive patients with nonmetastatic rectal adenocarcinoma treated at the Angelita & Joaquim Gama Institute/ Hospital Alemão Oswaldo Cruz were eligible for this institutional review board-approved study after informed consent. Inclusion criteria included cT2-T4 or cN1-2 rectal cancers located (lower tumor border) no more than 7 cm from the anal verge and accessible to digital rectal examination. Patients with synchronous colorectal cancers, metastatic disease, or refusal to undergo neoadjuvant chemoradiation were excluded from the study.[7]

Initial assessment was performed by 2 experienced colorectal surgeons with the use of rigid proctoscopy (for measurement of distance from anal verge) and digital rectal examination. Patients underwent baseline locoregional staging by the use of high-resolution MRI or 3-dimensional endorectal ultrasound imaging. Systemic staging included abdominal and chest CT scans. Full colonoscopy was attempted in all patients before CRT commencement.

All patients underwent neoadjuvant chemoradiation consisting of 54 Gy of radiation and 6 cycles of chemotherapy as described previously.[7] In brief, 45 Gy of radiation was delivered by a 3-field approach with daily doses of 1.8 Gy on weekdays to the pelvis, followed by a 9-Gy boost to the primary tumor and perirectal tissue (54 Gy total). Concomitantly, patients received 3 cycles of bolus 5-FU (450 mg/m^2) and a fixed dose of 50 mg of leucovorin for 3 consecutive days every 3 weeks. After completion of radiation, patients received 3 additional identical cycles of chemotherapy every 3 weeks.

Tumor response assessment was performed after all 6 cycles of chemotherapy, at 10 weeks from radiation completion. The assessment of response included similar clinical (digital rectal examination), endoscopic (proctoscopy), and radiological studies (MRI, endorectal ultrasound imaging, and/or PET/CT).

Patients were considered as having an initial complete clinical response (cCR) in the absence of residual ulceration, mass, or significant rectal wall irregularity as described elsewhere during assessment performed at 10 weeks from RT.[8] Radiological evidence of complete response was also required for inclusion in this Watch and Wait strategy. In brief, radiological features of a complete response included the presence of residual low-signal-intensity areas (MRI), absence of restriction to diffusion (diffusion-weighted MRI), or absence of residual FDG uptake within the rectal wall (PET/CT).[9–11] Patients with radiological evidence of residual cancer (in the mesorectum and/or within the rectal wall) were considered as incomplete responders irrespective of clinical and endoscopic findings. Patients with cCR were offered no immediate surgery and were enrolled in a strict follow-up program, including monthly follow-up visits with reassessment of tumor response without additional chemotherapy (Fig. 1). Patients with any suspicious small residual abnormalities were managed by full-thickness transanal excision for diagnostic purposes. Those with complete primary tumor regression (ypT0) after such excisional biopsy were also considered as complete clinical responders and were offered no additional surgical procedure. Patients were considered as sustained cCRs only when assessment at 12 months from CRT completion maintained a cCR status. Patients who had initial cCR but did not sustain it for 12

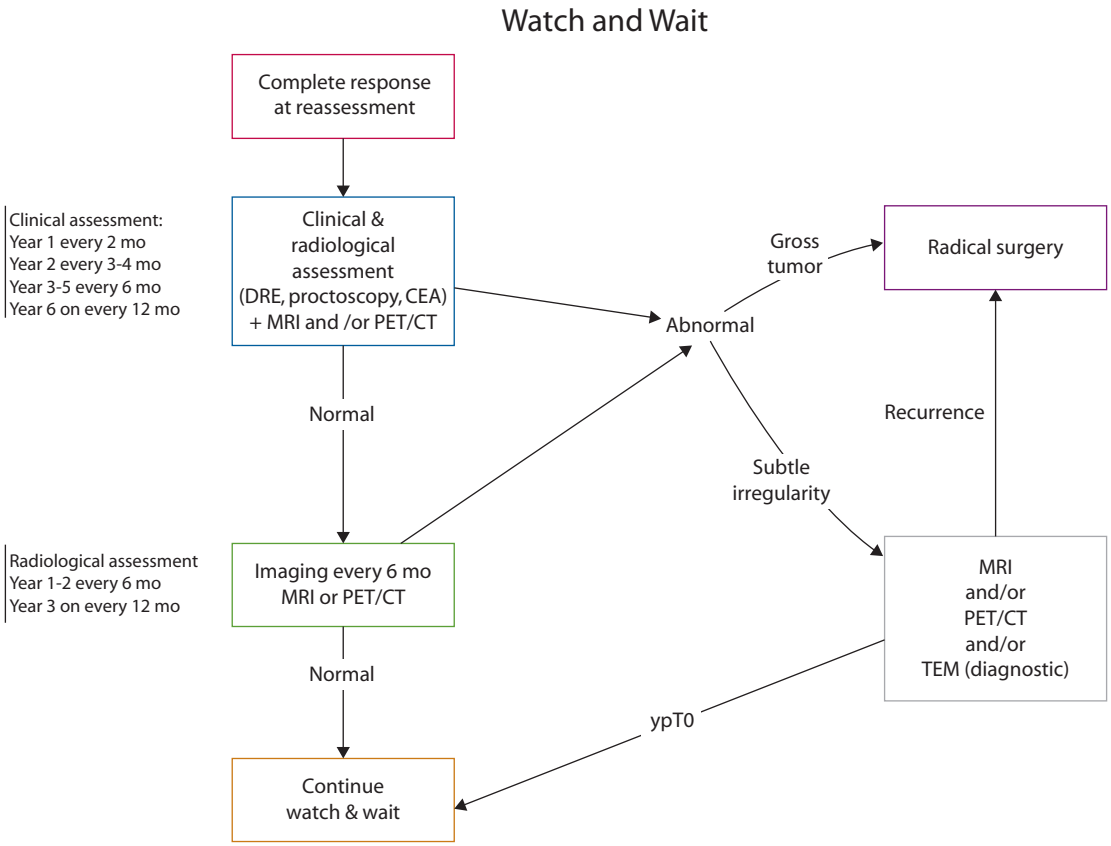

FIGURE 1. Follow-up algorithm. DRE = digital rectal examination; TEM = transanal endoscopic microsurgery.

months were categorized as having early tumor regrowths. Patients who developed local recurrences after having sustained a cCR for 12 months were categorized as having late local recurrences.

Immediate radical resection including total mesorectal excision (TME) was recommended to patients who had an incomplete clinical response at 10 weeks or had a local recurrence. Patients who refused radical resection were offered full-thickness transanal local excision with the use of transanal endoscopic microsurgery primarily as a diagnostic approach. In patients with ypT3, radical surgery was strongly recommended. Patients with residual ypT1/ypT2 were offered radical surgery in the presence of other adverse pathological features (poor differentiation and lymphovascular invasion). Adjuvant chemotherapy was considered individually for these patients based on final pathological findings and performance status. Only patients who had positive lymph node metastases were routinely offered adjuvant chemotherapy. Patients with initial cCR were not offered adjuvant systemic therapy.

Systemic recurrence surveillance was performed by using CT scans (chest and abdominal) every 6 months for the first 2 years and yearly thereafter. Patients undergoing PET/CT for the assessment of response were spared from additional CT imaging during follow-up for at least 6 months.

Statistical Analysis

Patients were compared according to response at 10 weeks from CRT (initial cCR versus incomplete) and at 12 months (sustained cCR) were compared with patients who had incomplete clinical response or early tumor regrowth. Also, among initial complete responders, patients were compared according to the development of local failure (early regrowth or late local recurrence).

Statistical analysis was performed by using the χ^2 test, Fisher exact probability test, and the Student *t* test for comparisons between groups. Results were considered significant for p values ≤ 0.05.

RESULTS

Overall, 70 patients were included in the study. One patient died during CRT after having completed the radiation schedule and received chemotherapy during the resting period. This 88-year-old patient developed a complicated supraventricular arrhythmia that eventually evolved to cardiac arrest and death.

Of the remaining 69 patients, all completed a minimum 12 months of follow-up from CRT completion (Fig. 2). Patients' characteristics and baseline staging information are available Table 1.

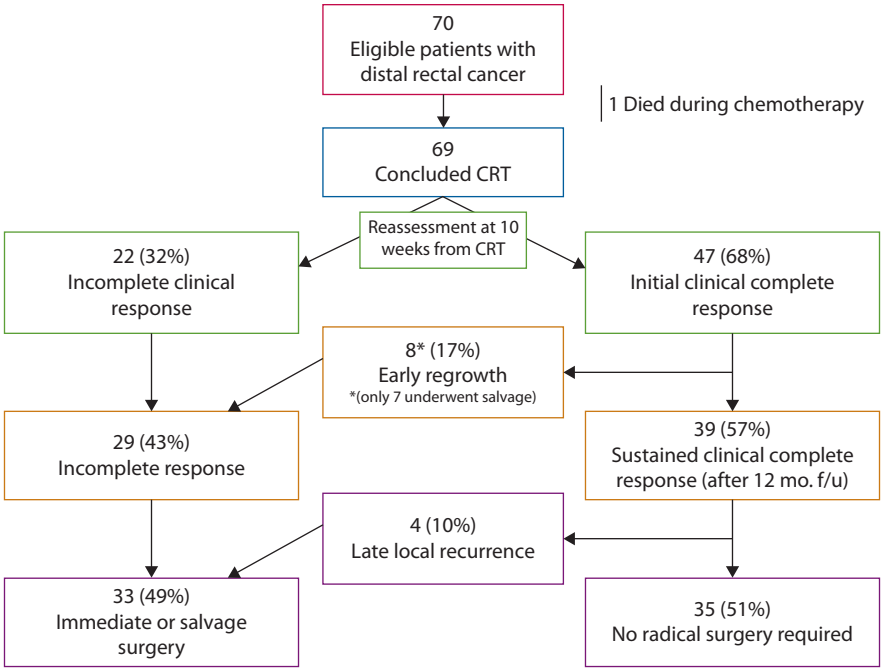

FIGURE 2. Study design and outcomes. CRT = chemoradiation therapy; f/u = follow-up.

Early Tumor Regrowths

Complete clinical response at 10 weeks from RT completion (initial cCR) was observed in 47 patients (68%). However, during strict follow-up, early tumor regrowth was detected in 8 patients (17%). Seven of these patients were amenable for salvage resection. One elderly woman was medically unfit for surgery and died of disease progression. Intervals for tumor regrowth and procedures performed for salvage are available in Table 2. In brief, 4 patients underwent radical TME (anterior resection in 2 and abdominoperineal resection in 2), and 3 underwent local excision. One of the patients undergoing radical TME (ypT3N2) developed systemic recurrent disease and died of disease progression. Two patients who underwent full-thickness local excision developed systemic recurrences: 1 died of disease progression and the other patient is undergoing neoadjuvant chemotherapy preceding a possible liver resection. The remaining 4 patients currently have no evidence of disease and are being followed after a median follow-up of 26 months.

Three-year overall and disease-free survival for patients with initial cCR was 90% and 72% (Fig. 3).

TABLE 1. Patient demographics

	N = 70
Sex M:F	39: 31 (55.7:44.3)
Age, y	60.2 ± 12.9
Baseline tumor size, cm	4.3 ± 1.5
Distance from anal verge, cm	3.6 ± 1.7
Initial radiological staging	
cT	
2	20 (28.6)
3	47 (67.1)
4	3 (4.3)
cN	
0	43 (61.4)
1–2	27 (38.6)
UICC	
I	17 (24.3)
II	26 (37.1)
III	27 (38.6)

UICC = Union for International Cancer Control.

Late Recurrences

Thirty-nine patients (56%) sustained a cCR for at least 12 months of follow-up (sustained cCR). Four of these patients (5%) underwent full-thickness local excision for confirmation of a complete response (ypT0) owing to subtle suspicious mucosal irregularities. Thirty-five (51%) of these patients did not undergo any type of resection and were closely followed.

Four of these 39 patients with sustained cCR (10%) developed late local recurrent disease between 13 and 35 months from CRT completion (none of these patients had undergone previous full-thickness transanal local excision for confirmation of ypT0). All of them were managed by R0 salvage resections. Features of patients with late recurrences are available in Table 3. All patients undergoing salvage resection for late local recurrences are being followed with no evidence of recurrent (local or systemic) disease at a median follow-up of 25.5 months.

Five patients with sustained cCR developed exclusive systemic recurrence leading to 1 death due to central

TABLE 2. "Early regrowths" (developing within first 12 months following CRT completion and initial cCR)

No.	Initial staging	Interval from CRT to regrowth, wk	Salvage	Pathology	Local re-recurrence	Systemic recurrence	Interval to re-recurrence, mo	F/U, mo
1	cT3N0	50	AR	ypT3N2	Yes	Yes	10	16
7	cT3N1	37	AR	ypT2N0	No	No	NA	11
5	cT2N0	35	APR	ypT3N0	No	No	NA	55
8	cT3N0	27	Brachytherapy + APR	ypT3N0	No	No	NA	27
2	cT3N0	38	FTLE	ypT3	No	Yes	6	17
6	cT3N1	45	FTLE	ypT3	No	Yes	4	14
4	cT3N1	45	FTLE	ypT1	No	No	NA	26
3	cT3N0	16	Medically unfit for surgery		NA	No	NA	16

APR = abdominoperineal resection; AR = anterior resection; FTLE = full-thickness local excision; CRT = chemoradiation therapy; cCR = complete clinical response; F/U = follow-up; NA = not applicable.

nervous system metastases. Overall, 35 patients of the 69 patients having completed CRT (51%) had a sustained cCR that never required surgery for locally recurrent cancer after a median follow-up of 56 months.

Three-year overall and disease-free survival for patients with sustained cCR was 94% and 75% with a median follow-up of 53 months (Fig. 4).

Incomplete Clinical Responses

All patients who had an incomplete clinical response at 10 weeks from RT completion were referred to radical surgery. Two patients were considered medically unfit for radical surgery and were exclusively managed by diverting colostomy. After a median follow-up of 53 months, 3-year overall and disease-free survival among these patients was 90% and 58% (Fig. 5). Procedures and final pathological features of these patients are listed in Table 4.

Predictors of Complete Response

Baseline tumor characteristics, tumor radiological stage, and patients' demographics were all not associated with the development of either initial (Table 5) or sustained cCR following neoadjuvant CRT (Table 6). Even though there was a trend between earlier baseline staging (T2N0) and the likelihood of sustained cCR, this difference was not statistically significant ($p = 0.059$).

Three-year overall survival according to baseline staging was 100%, 88%, and 80% for stages I, II, and III ($p = 0.2$). Three-year disease-free survival according to baseline staging was 54%, 64%, and 69% for stages I, II, and III ($p = 0.9$).

DISCUSSION

The significant postoperative morbidity associated with radical total mesorectal excision has increased the interest in organ-preserving strategies among patients with rectal cancer.[12] Despite inherent difficulties in the accurate diagnosis of complete pathological response by clinical and radiological means, patients with cCR have been enrolled in a strict follow-up program without immediate radical surgery with acceptable long-term overall and disease-free survival.[3] Relapses after this nonoperative management of patients with rectal cancer and cCR after neoadjuvant CRT are frequently (if not always) amenable to salvage surgical resection and without oncological compromise.[13] Interestingly, one of the most frequently used arguments against this approach with no immediate surgery has been that it

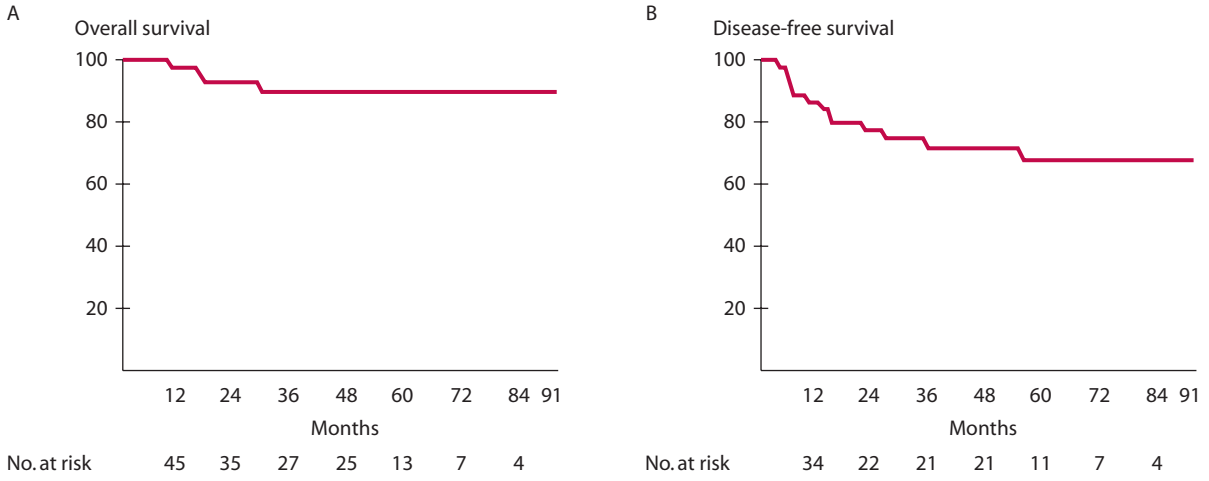

FIGURE 3. Three-year overall (A) and disease-free (B) survival for patients with initial complete clinical response.

TABLE 3. Late local recurrence after Watch and Wait (developing after the first 12 months following CRT completion)

No.	Initial staging	Interval from CRT to local recurrence, mo	Salvage	Pathology	Local re-recurrence	Systemic recurrence	F/U
1	cT2N0	22	FTLE	ypT2	No	No	41
2	cT2N0	35	AR	ypT3N1	No	No	67
3	cT2N0	13	FTLE	ypT3	No	No	53
4	cT3N0	15	APR	ypT4Nx	No	No	30

APR = abdominoperineal resection; AR = anterior resection; FTLE = full-thickness local excision; CRT = chemoradiation therapy; cCR = complete clinical response; F/U = follow-up.

was restricted to a single center and therefore lacked replication of the observed results. This skepticism from the oncological community was reflected in the resistance to implement this treatment alternative in the armamentarium of rectal cancer management.[14] However, the recent reports of this "Watch and Wait" experience with nearly identical results by different European institutions dedicated to the management of rectal cancer has brought the issue back to center stage.[15,16] In fact, not only better characterization of clinical findings of cCR have been reported, but also an increasing number of studies are now available describing radiological findings consistent with complete clinical or pathological response by using different imaging modalities such as MRI, diffusion-weighted MRI, and PET/CT.[9–11] In the present series, 17% of patients with initial cCR developed early tumor regrowth. This percentage is consistent with our 17% previously reported rate of early tumor regrowth with the standard CRT regimen.[17] In the present series, all patients with early recurrences or regrowth were amenable to salvage resection with R0 resections. The presence of baseline cT3 disease in all of these patients is indeed quite concerning. However, one could expect that residual deep (between muscular and fat layers) foci of residual cancer cells are probably the reason for the early regrowth among these patients. In addition, considering that all patients underwent R0 resections, negative circumferential resection margin and node-negative disease may suggest no oncological compromise to these patients even though longer follow-up and a larger sample size is needed to appropriately address this issue.

An additional 10% of patients developed late recurrences after sustaining a cCR for at least 12 months. This result is also consistent with our previously reported rate of 5% to 10%. These patients were also amenable to salvage therapy with R0 resection including radical surgery and local excision alone in selected patients. Patients who develop late recurrent disease after initial cCR probably reflect low-grade and "slow-growing" tumors and therefore are intrinsically associated with improved outcomes. In fact, systemic recurrences were observed exclusively among early tumor regrowths, further reinforcing this hypothesis. Also, a larger sample size and longer follow-up are needed before reaching definitive conclusions.

The excellent outcomes of patients who have complete tumor response (clinical and pathological) have prompted the search for alternative CRT regimens that could potentially increase these rates. Several studies using alternative chemotherapy agents including oxaliplatin, capecitabine, and even monoclonal antibodies have been reported. In fact, none of these strategies have been successful in increasing the rates of complete pathological response and occasionally even at the cost of an increase in treatment-related toxicity.[5,6] Even though a review of phase II and III studies of neoadjuvant CRT for rectal cancer has reported a complete pathological

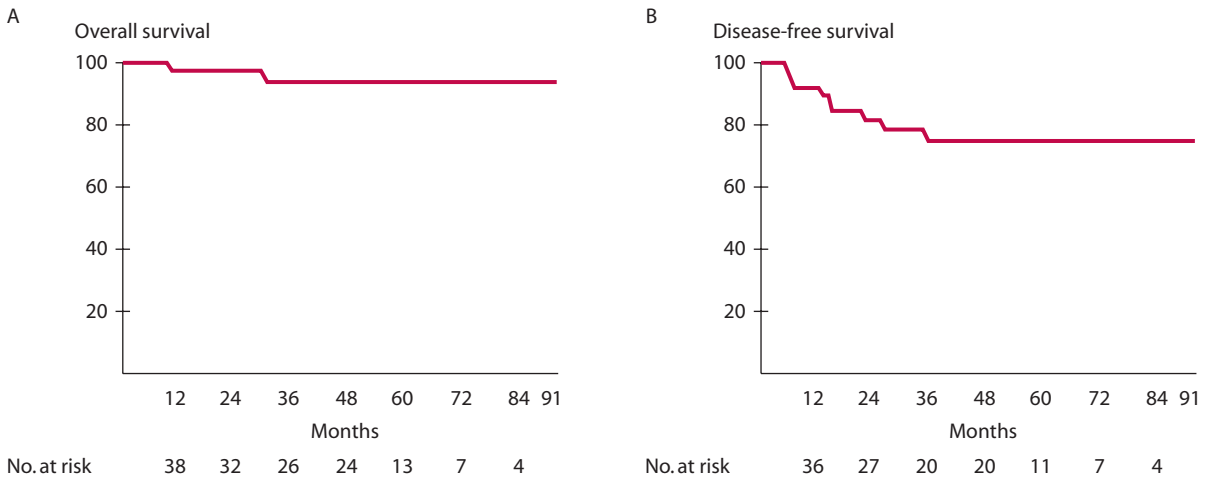

FIGURE 4. Three-year overall (A) and disease-free (B) survival for patients with sustained complete clinical response.

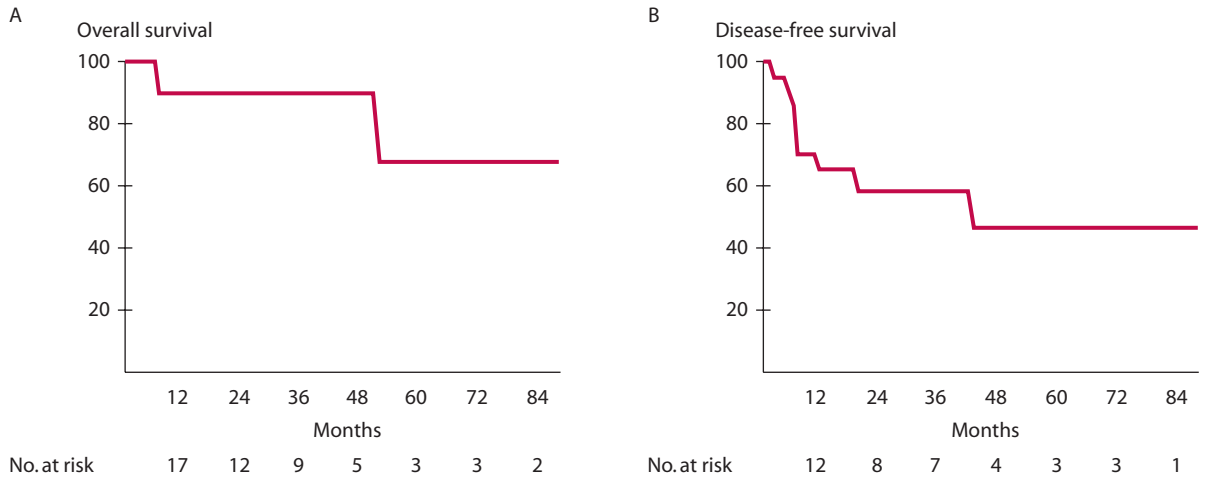

FIGURE 5. Three-year overall (A) and disease-free (B) survival for patients with incomplete response following surgical resection.

TABLE 4. Features of patients with incomplete clinical response

	n = 23[a]
Initial radiological staging	
cT	
2	5 (21.7)
3	16 (69.6)
4	2 (8.7)
cN	
0	10 (43.5)
1–2	13 (56.5)
UICC	
I	3 (13.0)
II	7 (30.4)
III	13 (56.5)
Surgery	
FTLE	
ypT1	4 (19.0)
ypT2	3 (14.3)
ypT3	2 (9.5)
AR	10 (47.7)
APR	2 (9.5)
Tumor size, cm	1.9 ± 1.2
ypT	
0	1 (4.8)
1	5 (23.8)
2	7 (33.3)
3	8 (38.1)
4	0 (0.0)
ypN	
0	9 (81.8)
1 + 2	4 (30.8)
Stage	
pCR	1 (4.5)
I	10 (45.5)
II	6 (27.3)
III	4 (18.2)

UICC = Union for International Cancer Control; FTLE = full-thickness local excision; AR = anterior resection; APR = abdominoperineal resection; pCR = complete pathological response.
[a] Two patients were medically unfit for surgery and were managed by palliative loop colostomy.

response rate as high as 42%, our series of patients with an initial and sustained cCR rate of 68% and 57% is still somewhat surprising.[4] First, these rates are due to the exclusive use of 5-FU without additional agents and, therefore, a low added chemo-related toxicity and also a reduced treatment cost. Still, it is worthwhile mentioning that 1 patient died owing to cardiac complications during CRT (1.5%). Second, because this 57% of sustained cCR compares significantly favorably to the historical control of 25% to 27% of cCR obtained with a standard CRT regimen with only 2 cycles of chemotherapy and 50.4 Gy of radiation.[18]

Curiously, none of the pretreatment characteristics (including baseline locoregional staging) were predictors

TABLE 5. Predictive factors for initial complete clinical response

	Initial complete response	*Incomplete response*	*p*
n	47	23	
Sex M: F	27:20 (57.4:42.6)	12:11 (52.2:47.8)	0.43
Age, y	60.2 ± 12.7	60.2 ± 13.6	0.99
Tumor size, cm	4.1 ± 1.5	4.5 ± 1.6	0.34
Distance from anal verge, cm	3.7 ± 1.7	3.5 ± 1.7	0.66
Initial CEA serum level	8.1 ± 22.2	15.7 ± 38.4	0.53
Initial staging			
cT			
2	15 (31.9)	5 (21.7)	
3	31 (66.0)	16 (69.6)	
4	1 (2.1)	2 (8.7)	0.32
cN			
0	33 (70.2)	10 (43.5)	
1 + 2	14 (29.8)	13 (56.5)	0.12
UICC			
I	14 (29.8)	3 (13.0)	
II	16 (34.0)	7 (30.4)	
III	14 (29.8)	13 (56.5)	0.10

UICC = Union for International Cancer Control.

TABLE 6. Predictive factors for sustained complete response

	Sustained complete response	*Incomplete response*	*p*
n	39	31	
Sex M: F	24:15 (61.5: 38.5)	15:16 (48.4: 51.6)	0.19
Age, y	59.5 ± 12.9	61.1 ± 13.0	0.61
Tumor size, cm	4.1 ± 1.6	4.4 ± 1.5	0.49
Distance from anal verge, cm	3.4 ± 1.6	3.9 ± 1.9	0.28
Initial CEA serum level	8.3 ± 24.8	12.9 ± 31.6	0.62
Initial staging			
cT			
2	14 (35.9)	6 (19.4)	
3	24 (61.5)	23 (74.2)	
4	1 (2.6)	2 (6.5)	0.29
cN			
0	28 (71.8)	15 (48.4)	
1 + 2	11 (28.2)	16 (51.6)	0.06
UICC			
I	13 (33.3)	4 (12.9)	
II	15 (38.5)	11 (35.5)	
III	11 (28.2)	16 (51.6)	0.059

UICC = Union for International Cancer Control.

of initial or sustained cCR among the present series. Still, however intuitive the association between earlier cT classification and better response to CRT is, such an association has been observed by few of the previous studies.[9,19–21]

The limitations of our study include the rather small number of patients and the relatively short follow-up. Patients who have rectal cancer treated by neoadjuvant CRT are expected to develop local failures at longer intervals than those usually observed for patients undergoing surgical resection alone.[13] Also, one may raise the question of whether the improved rates of cCR in comparison with historical controls is a consequence of the "modest" increase in radiation therapy (from 50.4 to 54 Gy) or the increased number of cycles of chemotherapy (2–6 cycles). In fact, even though the credit for this significant increase in cCR rates may be quickly attributed to the increase in the number of 5-FU cycles, the radiation therapy dose escalation may have played a significant role. In fact, improved pathological response rates in the setting of radiation dose escalation have been observed in the Lyon 96-02 trial. In addition, sphincter preservation was more frequently possible among patients undergoing increased RT doses.[22] It is indeed possible that the increment in chemotherapy doses could have resulted in higher radiosensitivity of the primary tumor and therefore actively participated in the increased rates of cCR. However, the results of the ACCORD 12/0405-Prodige 2 that also implemented modifications in both RT and chemotherapy regimens also seem to support the idea of improved tumor response secondary to RT dose escalation. In that study, the slightly improved complete pathological response rates undergoing Capox-50 regimen have been attributed to the increase in RT dose with oxaliplatin offering no advantage over capecitabine alone acting as radiosensitizer.[5] Still, one could argue that the increased number of overall cycles of chemotherapy would also have a potential benefit in long-term survival and perhaps decrease the risk of late systemic relapses. Longer follow-up and perhaps a randomized trial will be required to properly address this issue.

CONCLUSION

Neoadjuvant CRT using 54 Gy of radiation and 3 cycles of chemotherapy concomitant to RT and 3 additional cycles during the interval period before reassessment may lead to significantly high rates of sustained cCR avoiding immediate radical surgery in a substantial proportion of patients with nonmetastatic rectal cancer. A significant proportion of patients with initial cCR may still develop local failure during the first 12 months of follow-up meaning that significant improvements in appropriate identification of cCR are warranted. Early recognition may allow appropriate salvage therapy; however, these patients are at considerable risk for further systemic relapse. Long-term failures may also develop (>12 months), even though less frequently. Even though we are still far away from anal canal cancer treatment outcomes with a nearly 80% cCR rate, the fact that more than half of the patients ultimately are spared from radical resection is quite significant.

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