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RESEARCH ARTICLE

Clinical Outcomes of Salvage Surgery in Locally Advanced Distal Rectal Cancer Patients with Local Regrowth Following Non-operative Management

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ABSTRACT

Aim: Locally advanced distal rectal cancer (LADRC) patients managed with non-operative management (NOM) with complete clinical response following neoadjuvant treatment will experience local regrowth in about 25% of cases. The long-term risks of this strategy or local regrowth treatment have not been well established, and the main concern is the probability of impaired oncological outcomes after salvage surgery. This study aimed to evaluate the feasibility and clinical outcomes of salvage surgery in LADRC patients with local regrowth following NOM.

Method: All locally advanced, distal rectal cancer patients managed with NOM after neoadjuvant therapy with clinical complete response, who developed local regrowth during surveillance, between May 2016 and November 2018, were enrolled in the study. Patients were analyzed for the rate of salvage surgery, disease-free survival and overall survival.

Results: Eleven out of 63 (17.5%) patients developed local regrowth after a mean of 8.4 (3-15) months. The mean surveillance period was 31.8 (14-50) months. Eleven (100%) patients underwent salvage surgery due to the principles of total mesorectal excision. LE was not performed. No patients experienced local recurrence and three out of eleven (27.3%) developed carcinomatosis peritonei and/or distant metastasis after a mean surveillance period of 12.2 (3-26) months. At 30 months, the local and/or systemic recurrence rate, disease-free survival, and overall survival in the patients undergoing surgical treatment were 100%, 73%, 73% and 91%, respectively.

Conclusion: The vast majority of patients with regrowth following NOM were suitable for salvage surgery with curative intent and justifiable pelvic tumor control.

Keywords: Rectal cancer, non-operative management, local regrowth, salvage surgery

Introduction

The introduction and ubiquitous establishment of neoadjuvant treatment strategies, such as the standard trimodal treatment, consolidation, or induction chemotherapy has increased the rate of clinical complete response (cCR) and the rate of the clinically favorable pathologic complete response (pCR). Patients with a pCR have improved oncological outcomes, with local recurrence rates of <1% and a 5-year survival rate of more than 95%.[1,2] Despite dramatic improvements in oncological outcomes in locally advanced distal rectal cancer (LADRC) patients, there has been an increasing interest and focus in organ-preserving approaches, such as local excision (LE) or non-operative management (NOM), which is also known as the "watch and wait" (W&W) strategy. This is mainly because resection surgery based on the principles of total mesorectal excision (TME) is associated with 1-2% preoperative mortality, temporary or permanent colostomy,

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disturbed bowel function and long-term morbidity, such as urinary and sexual dysfunction in more than 60% of patients, which significantly reduces the quality of life.[3,4,5]

Since the pioneering publication reporting W&W among LADRC patients with cCR following neoadjuvant treatment by Habr-Gama et al.[6] in 2004, multiple observational case series have confirmed the feasibility of W&W with nearly equal and acceptable short- and long-term clinical outcomes compared to patients undergoing TME.[7,8,9,10,11] Despite these achievements, there are still concerning and unsolved issues. There is currently no advanced imaging modality, such as magnetic resonance imaging (MRI), capable of detecting small remnants of viable tumor cells in the tumor bed or mesorectal lymph nodes with an accuracy of 100%. That is why 15% to 30% of all LADRC patients managed with NOM will experience local regrowth during frequent surveillance. The only option for treatment with no alternative is salvage surgery.[9,10,11,12]

However, there are risks and concerns related to the deferral of surgery compared to immediate surgery without the delay of NOM. These are: missing the opportunity of "*salvage surgery*" due to increased invasiveness; technical difficulty due to pelvic fibrosis leading to increased intraoperative and postoperative complications; increased postoperative morbidity and mortality; and impaired short- and long-term clinical outcomes in terms of disease-free and overall survival. These issues have not yet been fully clarified and have led to increased and considerable uncertainty regarding NOM.

This study's primary objective was to analyze the clinical and oncological outcomes of "*salvage surgery*" among LADRC patients, who developed local regrowth during follow-up managed with NOM.

Materials and Methods

Study Design

All LADRC patients with a local regrowth, after an initial NOM approach revealing cCR following neoadjuvant treatment, who underwent "*salvage surgery*" between May 2016 and November 2018 in two comprehensive cancer centers, were enrolled in the retrospective observational case series study. Only patients with biopsy-proven distal rectal adenocarcinoma without initial metastasis, neoadjuvant treatment (long-course chemoradiotherapy, consolidation or induction chemoradiotherapy), cCR following neoadjuvant therapy, frequent surveillance according to an adequate predefined and established NOM protocol and radiologically and/or biopsy-proven local intra- or extra-mural regrowth were included.

Patients were primarily analyzed for local recurrence-free rate, distant metastasis-free rate, disease-free survival, and overall survival. The second aim was assessment of the feasibility of "*salvage surgery*" and associated morbidity and mortality. Every patient signed an infomred consent previous to NOM or surgery. They also allowed us to use their information for research.

cCR Assessment and Surveillance

Neoadjuvant treatment response was evaluated with the combination of the digital rectal examination (DRE), sigmoidoscopy and pelvic MRI with the addition of contrast and advanced functional sequences such as diffusion-weighted MRI (DW-MRI) and dynamic contrast-enhanced MRI. The response was defined as: the absence of the primary tumor on DRE; replacement flat white scar tissue and/or telangiectasia without nodularity and ulcer of the mucosa on sigmoidoscopy; and complete normalization of the rectal wall or dense fibrotic lesion with low signal intensity without intermediate tumor signal intensity and no evidence of diffusion restriction within the tumor or lymph nodes on MRI.[13,14]

After confirming a cCR and approving NOM by the institutional tumor board, all patients were followed-up with carcinoembryonic antigen measurements, DRE, sigmoidoscopy, and pelvic MRI in the first three years at an interval of three months and then every six months up to five years. Additional standard rectal cancer surveillance according to international guidelines, was performed, including annual colonoscopy and imaging of the thorax and abdomen with computer tomography (CT) or MRI every six or twelve months for five years.

Local Regrowth and Treatment

Local regrowth was defined as any sign of tumor regrowth in the rectal wall on DRE, new mucosal abnormalities on sigmoidoscopy or concerning imaging findings on MRI, such as an isointense mass or wall thickening of the fibrotic scar on T2W-MRI, new focal high signal intensity on DW-MRI or an enlarging mass in the mesorectum. In some instances, there were no endoscopy changes suggesting endoluminal local regrowth due to an intramural regrowth pattern defined as a new mass with intermediate signal intensity or wall thickening of the fibrotic scar on T2W-MRI first without initial changes on endoscopy. Patients suspected of endoluminal or intramural regrowth patterns were histologically confirmed with an endoscopic biopsy.

Regardless of the growing pattern, endoluminal or extraluminal regrowth was an indication for "*salvage surgery*" based on the principles of TME, which is the only proven rationale and curative treatment option. As part of clinical staging, thorax and abdomen CT was performed

for all patients with local regrowth to determine the local extent of the tumor and to exclude the presence of distant metastasis prior to radical resection surgery. In both centers, LE was not performed due to the potential risk of recurrence compared to TME.

Statistical Analysis

All statistical analyses were performed with SPSS, version 26.0 (IBM Corp., Armonk, NY, USA) and only descriptive statistics were calculated for the entire case series without comparisons. Categorical data were calculated using the number (n) and percentage (%), while continuous variables were analyzed using mean, standard deviation, median and minimum-maximum. We considered the date of diagnosis as the baseline starting point for survival analysis. We calculated the time to diagnosis of local recurrence after salvage surgery from the date of surgery. Local recurrence-free rate, disease-free survival, distant metastasis-free rate, and overall survival were estimated with Kaplan-Meier.

Results

Baseline Characteristics

Eleven of the 63 (17.5%) LARC patients, initially managed with a NOM strategy after cCR following neoadjuvant treatment, who developed local regrowth between May 2016 and November 2018, were included in the study. Mean age, gender distribution and mean tumor distance from the dentate line at initial diagnosis was 60.2 (43-71) years, 81% male and 2.9 (0-5) cm, respectively. At initial diagnosis, all patients were staged as LADRC (T3≤, any N or any T, N+) with pelvic MRI and all patients received long-course chemoradiotherapy (100%). The mean follow-up was 31.8 (14-50) months. Median time from the end of neoadjuvant radiotherapy to local regrowth diagnosis was 15.2 (9-26) months. Further baseline characteristics are depicted in Table 1.

Salvage Surgery and Pathologic Assessment

All patients with local regrowth underwent salvage surgery based on the principles of TME, of which eight (73%) patients underwent low anterior resection (LAR), two (18%) patients underwent abdominoperineal resection (APR), and one (9%) underwent intersphincteric resection (ISR). Minimal invasive surgery, either laparoscopic or robotic surgery, was performed in all (100%) regrowth patients with only rare and minor complications (see below). LE was not performed as a treatment option for local regrowth.

In our study, in all patients (100%) local regrowth was confined to the bowel wall and were classified as endoluminal local regrowth. None of the patients had an extraluminal growing pattern of the primary tumor. Most of the patients (73%) had a local regrowth at an early stage and in three (27%) patients diagnosed for local regrowth, no viable malignant tumor cells were detected on histopathological examination of the TME specimen. These patients were staged as ypT0N0. The R0 rate after TME was 100% and the TME specimen was also inspected and graded as complete, nearly complete, or incomplete mesorectum. Nine out of eleven (82%) TME revealed a complete mesorectum, one patient (9%) had a nearly complete mesorectum and one patient (9%) had an incomplete mesorectum. All patients' histopathological findings are outlined in Table 2.

Intraoperative and Postoperative Outcomes

The mean hospital stay was 7 (4-20) days, the operating time for salvage surgery was 180 (155-212) minutes and the amount of intraoperative blood loss was 90 (30-200) milliliters (Table 3). Intraoperative and postoperative complications were observed at about 9% and were not related to pelvic fibrosis or local regrowth. One (9%) patient received a grade I laceration of the spleen that was managed

Table 1. Baseline features of patients after salvage surgery for local regrowth after initial NOM

	n=11
Age, mean (range), years	60.2 (43-71)
Gender	
Female, n (%)	2 (19)
Male, n (%)	9 (81)
Body mass index, median (range), kg/m^2	29.5 (22.3-43.8)
ASA score	
I, n (%)	4 (36)
II, n (%)	6 (55)
III, n (%)	1 (9)
Height from dentate line, median (range), cm	2.9 (0-5)
Clinical tumor (T) stage	
cT2, n (%)	1 (9)
cT3, n (%)	9 (82)
cT4, n (%)	1 (9)
Clinical nodal (N) stage	
Negative, n (%)	0
Positive, n (%)	11 (100)
Neoadjuvant treatment	
Induction chemotherapy, n (%)	2 (18)
Consolidation chemotherapy, n (%)	9 (82)

NOM: Non-operative management, ASA: American Society of Anesthesiologists

Table 2. Salvage surgery and histopathologic results

	(n=11)
Type of regrowth	
Extraluminal, n (%)	0
Endoluminal, n (%)	11 (100)
Type of salvage surgery	
Low anterior resection, n (%)	8 (73)
Interspincteric resectio, n (%)	1 (9)
Abdominoperineal resection, n (%)	2 (18)
Type of TME approach	
Open surgery, n (%)	0
Minimal invasive, n (%)	11 (100)
Conversion, n (%)	0
ypT-stage	
T0, n (%)	3 (27)
T1, n (%)	3 (27)
T2, n (%)	4 (36)
T3, n (%)	1 (9)
T4, n (%)	0
ypN-stage	
N0, n (%)	7 (64)
N1, n (%)	3 (27)
N2, n (%)	0
Nx, n (%)	1 (9)
Type of salvage surgery resection margin	
R0, n (%)	11 (100)
R1, n (%)	0
TME specimen grading	
Complete, n (%)	9 (82)
Near complete, n (%)	1 (9)
Incomplete, n (%)	1 (9)

TME: Total mesorectal excision

with laparoscopic electrocauterization and concomitant serosal injury of the small bowel managed with laparoscopic primary repair suture. After salvaging, another patient (9%) had an endoscopic decompression due to pseudo-obstruction and underwent an exploration because of bleeding (Table 3).

Clinical Outcome

After salvage surgery, the local recurrence-free rate and pelvic tumor control was 100% and no patient developed local recurrence. However, during surveillance three

Table 3. Perioperative outcomes

	(n=11)
Length of hospital stay, mean (range), days	7 (4-20)
Postoperative complication (Clavien-Dindo grade), n of patients	
II	0
IIIa	0
IIIb	2
IV	0
V	0
Operating time, mean (range), minutes	180 (155-212)
Intraoperative blood loss, mean (range), milliliters	90 (30-200)
Intraoperative complication	
Yes, n (%)	0
No, n (%)	11 (100)

out of eleven (27%) developed distant metastases with dissemination predominantly to the lung. Two patients underwent video-assisted thoracic surgery for pulmonary metastasis, but one of these patients passed away due to disease progression after surgery while under chemotherapy treatment. The third patient with distant metastasis after surgery was advised to receive third-line chemotherapy because of widespread metastatic disease.

The 30-month local recurrence-free rate, distant metastasis-free rate, disease-free survival and overall survival were 100%, 73%, 73% and 91%. The reason why distant metastasis-free rate and disease-free survival have the same value is that the patients in the study only developed distant metastasis and died as a result of this disease state. The oncological outcomes of patients undergoing salvage surgery due to local regrowth are given in Table 4.

Discussion

Before approving and enrolling a patient in a NOM protocol, deteriorating outcomes and impacts during surveillance, such as local regrowth or distant metastasis, most probably associated with the deferral of surgery, must be discussed in detail with the patient. This is because approximately 25% of LADRC patients initially managed with NOM, with cCR following neoadjuvant treatment, will experience local regrowth.[9,10,11,12] In our study 17.5% of NOM patients developed local regrowth and all (100%) patients were suitable for "salvage surgery" based on the principles of TME. Compared to other studies, our "salvage surgery" rate was similar to previously reported large scale NOM case-series by Habr-Gama et al.[7] (93%), Dossa et al.[11] (95%), van der Sande et al.[15] (97%) and Smith et al.[13] (100%). Despite

Table 4. Clinical characteristics of NOM patients with local regrowth

Patient	Local regrowth	Salvage surgery	Mesorectum	CRM	Pathologicstaging	Time to local regrowth (months)	Distant metastasis	Surgery for distant metastasis	Survival
1	Endoluminal	LAR	Complete	Negative	ypT1N0	5	None	None	Alive
2	Endoluminal	LAR	Complete	Negative	ypT0N0	13	None	None	Alive
3	Endoluminal	LAR	Complete	Negative	ypT2N1c	5	None	None	Alive
4	Endoluminal	LAR	Complete	Negative	ypT2N0	10	Lung	Metastasectomy	Alive
5	Endoluminal	LAR	Complete	Negative	ypT1N0	5	None	None	Alive
6	Endoluminal	APR	Near complete	Negative	ypT0N0	10	None	None	Alive
7	Endoluminal	LAR	Complete	Negative	ypT2N0	15	None	None	Alive
8	Endoluminal	ISR	Complete	Negative	ypT1N1c	14	None	None	Alive
9	Endoluminal	LAR	Complete	Negative	ypT3N1b	6	Lung	Metastasectomy	Died
10	Endoluminal	APR	Complete	Negative	ypT2N0	6	None	None	Alive
11	Endoluminal	LAR	Incomplete	Negative	ypT2Nx	3	Lung, CP	None	Alive

NOM: Non-operative management, CRM: Circumferential resection margin, APR: Abdominoperineal resection, ISR: Intersphincteric resection, LAR: Low anterior resection

these promising findings, there is still growing concern and uncertainty regarding perioperative complications or quality of the completeness of the TME specimen related to pelvic fibrosis and the oncological outcomes.

As discussed with the patients from the initiation of the NOM protocol, every local regrowth is an indication for "salvage surgery" such as LAR, APR or ISR. In this study, nine (82%) patients underwent sphincter preserving surgery (LAR or ISR), and only two patients (18%) had rectal amputation (APR). These results show a very high sphincter-preservation and organ-preservation rate among the whole cohort with 96% and 82%, respectively. Our rate of organ preservation (82%) is similar or even higher than other reported case series from previous studies.[7,8,9,10,11,12,13] One of the troublesome dilemmas surgeons often face is that patients with local recurrence in the distal part of the rectum commonly seek alternative treatment options, such as brachytherapy or LE, to avoid a permanent colostomy. Although some studies have reported promising clinical outcomes with LE as an alternative treatment option for salvage surgery, we did not perform LE. The reasons for this were patients undergoing LE have an increased risk of both, the need for completion TME because of underprivileged pathology greater than ypT1 and local recurrence. LE, in the form of transanal endoscopic microsurgery (TEM), is associated with partial removal of the perirectal fat, which in turn causes technical difficulties during the completion of the TEM or treatment of potential local recurrence during follow-up.[7] The final reason for avoiding LE was that postoperative scarring of the locally excised area leads to confusion and difficulty in distinguishing local recurrence from scar tissue during surveillance.

Another important, sensitive issue is whether pelvic fibrosis associated with delayed "salvage surgery" after deferral of initial surgery leads to increased perioperative complications and decreased quality of the completeness of the TME specimen. The completeness of the mesorectum and tumor-free circumferential resection margin (CRM) is associated with favorable oncological outcomes, such as decreased local recurrence and increased overall survival and are important prognostic factors.[16,17] Prolonged waiting interval after neoadjuvant treatment causes pelvic fibrosis, which is measured by subjective intraoperative scales, but it has no effect on technical difficulties or intraoperative complications.[18] Only the French GRECCAR 6 study showed a higher morbidity rate in patients with delayed surgery (11 weeks vs 7 weeks), mostly due to an increased risk of medical complications.[19] Discussion of pelvic fibrosis is beyond the scope of this study, but we had a complete TME specimen of (82%) and tumor-free CRM in all (100%) patients, mean operating time of 180 minutes and intraoperative blood loss of 90 milliliters, which is similar to other case series.[15] One patient's pathology report revealed ypT2Nx with an incomplete mesorectum and negative CRM and developed carcinomatosis peritonei and distant metastasis after "salvage surgery". In this study consisting of LARDC patients initially managed with NOM, two patients developed carcinomatosis peritonei and distant metastasis after "salvage surgery", which accounts for 3.2% of the whole NOM cohort. When enrolling patients in a NOM protocol,

we do expect some degree of increased risk in terms of distant metastasis but we should always keep in mind that even initial surgery revealing a pCR bears the risk of local recurrence of up to 2.8% and is not a definitive solution.[1]

To our knowledge, "salvage surgery" is the only and most effective choice of treatment for local regrowth, but its effectiveness in preventing distant metastasis is open to question. In our cohort, none of the patients who underwent "salvage surgery" experienced local recurrence during follow-up and pelvic tumor control was achieved in all patients (100%). However, three (27%) patients developed distant metastasis localized exclusively in the lung. Thus there was an increased rate of systemic dissemination to the lung in patients undergoing "salvage surgery" due to local regrowth compared to patients with sustained cCR (27% vs 0). In addition to our results, several other pioneering studies have shown that NOM patients with local regrowth have a higher predisposition to distant metastases than those patients with sustained cCR: 18% vs 5% and 36% vs 1%. Although our 30-month distant metastasis-free rate (73%) after salvage surgery was lower compared to the study conducted by van der Sande et al.[15] with a 24-month metastatic disease rate of 91.8%, our 30-month overall survival rate was 91% among patients undergoing "salvage surgery" and 98.4% in the entire NOM cohort, which is promising. All these findings show that local regrowth is a risk in terms of short- and long-term clinical outcomes, which cannot be overcome with frequent surveillance or "*salvage surgery*". Currently, it is still unclear whether the risk of disease progression is related to the deferral of surgery, local recurrence of tumor cells with a high metastatic progression potential, or inherited aggressive tumor biology associated with incomplete response to neoadjuvant therapy.

Study Limitations

The major limitation of the study was the small sample size and intermediate surveillance period. As we expect some degree of change in the long-term interval, another weakness was that associated with the nature of retrospective studies, including selection bias and recall bias. However, in contrast to large-scale international databases with heterogeneity in neoadjuvant treatment, interpretation of cCR, surveillance protocols, diagnosis of local regrowth, and salvage surgery approaches, our cohort consisted of two comprehensive cancers institutions collaborating for many years with precisely the same clinical approach in terms of LADRC patients NOM.

Conclusion

This study showed that a NOM protocol for LADR patients with cCR following neoadjuvant treatment was a safe and promising treatment option with a "salvage surgery" rate of 100% after local regrowth. Uncontrolled disease progression after salvage surgery among local regrowth patients was observed in 81%, and in 96.8% in the entire NOM cohort. Overall survival was 91% among local regrowth patients and 97.9% in the whole cohort. These findings suggest NOM in LADRC patients in comprehensive cancer centers with experienced multidisciplinary teams consisting of surgeons, medical and radiation oncologists, pathologists and radiologists can be effective. It is important to keep in mind that a reliable and frequent NOM surveillance protocol is the key to success.

Ethics

Ethics Committee Approval: Retrospective study.

Informed Consent: Every patient signed an infomred consent previous to NOM or surgery. They also allowed us to use their information for research.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: C.B.K., M.K., H.A.B., Concept: İ.Ö., E.B., C.B.K., Y.K., Design: İ.Ö., C.B.K., M.K., Data Collection or Processing: Analysis or Interpretation: B.G., B.A., M.T.B., D.B., E.B., Literature Search: M.B., Y.K., B.G., Writing: İ.Ö., C.B.K., M.K.

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