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Non-operative Management in Locally Advanced Rectal Cancer Patients with Clinical Complete Response After Chemoradiotherapy Followed by Consolidation Chemotherapy: A Single Center Experience

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Research Article

Keywords: Consolidation chemotherapy, Locally advanced rectal cancer, Non-operative management, Total neoadjuvant therapy

Posted Date: November 19th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11586656/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

This study aims to analyze the long-term clinical outcomes of non-operative management (NOM) in locally advanced mid/distal rectal cancer patients who had a complete clinical response (cCR) following neoadjuvant chemoradiotherapy (nCRT) and consolidation chemotherapy.

Methods

Locally advanced mid/distal rectal cancer patients with stage II/III amenable for surgery who received nCRT followed by consolidation chemotherapy were enrolled into this study. Patients with an incomplete response following nCRT at any stage underwent surgery and patients with a significant clinical response were treated with FOLFOX (5-fluorouracil and oxaliplatin) or CapeOx (capecitabine and oxaliplatin). Patients with a cCR after nCRT followed by consolidation chemotherapy were managed with NOM.

Results

A total of 173 patients treated between January 2014 and March 2025 were enrolled in this observational cohort study. All of these patients were treated with total neoadjuvant treatment and received especially nCRT and consolidation chemotherapy. 83 patients with cCR were followed up with NOM. The rate of local regrowth was 19.3% (n = 16) with all patients having an endoluminal growing pattern confined to the first two years. Distant metastases were diagnosed in 7 (8.4%) out of 83 patients. Disease-free survival and overall survival were 78.3% and 95.2%.

Conclusion

The long-term clinical outcomes of NOM were promising in terms of pelvic tumor control and overall survival in strictly selected patients who had cCR after nCRT followed by consolidation chemotherapy.

Introduction

Over the last decades, the management of locally advanced distal rectal cancer (LADRC) has changed substantially due to the improvement and widely use of advanced imaging modalities, especially of pelvic magnetic resonance imaging (MRI), the innovative implementation of neoadjuvant treatment regimens and increased survival outcomes after pathological complete response (pCR) [1, 2]. The trimodal treatment approach consisting of neoadjuvant long-term chemoradiotherapy (nCRT)/short-term radiotherapy (RT), total mesorectal excision (TME) with/-out sphincter preservation and adjuvant chemotherapy has largely been replaced by a new approach defined as total neoadjuvant treatment

(TNT). The observation of increased pCR rates after TNT compared to neoadjuvant long-term chemoradiotherapy, accelerated the establishment of the widespread use of TNT [3]. TNT is defined as the administration of systemic chemotherapy before (induction) or after (consolidation) nCRT/RT.

The application of TNT has various advantages such as downsizing or downstaging of the primary tumor, improved compliance and completion of adjuvant chemotherapy, treating occult micrometastasis in advance and increasing the pCR rates, which is associated with significantly improved clinical outcomes [1–3]. These findings introduced the non-operative management (NOM) or “Watch and Wait” (W&W) strategy in patients with complete clinical response (cCR) as an alternative treatment option for TME, which is associated with early and long-term morbidity including a permanent stoma, sexual and urinary dysfunction. The NOM or W&W strategy was firstly described by Habr-Gama et al. in 2004 and become a promising treatment option in the management of LADRC patients with cCR following neoadjuvant treatment [4].

Although reporting acceptable short-term and long-term clinical outcomes regarding rates of local regrowth, salvage surgery and distant metastasis with the establishment of NOM among LADRC patients with cCR following neoadjuvant treatment, there are still some uncertainties/ ambiguities. No consensus has been reached especially for the following issues: the appropriate management of near-complete clinical response (nCR) patients after near TNT or after the completion of TNT, the adequate surveillance scheme after cCR, the proper application of chemotherapy regimen and its doses and the histopathological clarification of increased rates of distant metastasis in patients with local regrowth. The aim of this study is to show the long-term results of locally advanced mid/distal rectal cancer patients, managed with NOM after achieving a cCR following consolidation chemotherapy after nCRT.

Material and Method

Patients’ Selection

All locally advanced mid/distal rectal cancer patients, who were treated with TNT with the following sequence, nCRT and consolidation chemotherapy at a comprehensive cancer center between January 2014 and March 2025 were included into this study. In this study the prospectively collected data was retrospectively analyzed. The inclusion and exclusion criteria for the study protocol are detailed shown in Table 1.

Table 1
Inclusion and exclusion criteria for patients selection

Inclusion Criteria	Exclusion Criteria
> 18 years old	< 18 years old
Biopsy confirmed adenocarcinoma	Presence of distant metastasis
≥T3, any N, M0 or any T, N+, M0	Underlying inflammatory bowel disease
Amenable for surgery	Underlying hereditary colorectal cancer
Amenable for chemoradiotherapy	Recurrent rectal cancer patients
Amenable for chemotherapy	Previous history of malignancy
	Previous application of chemoradiotherapy
	Contraindication for chemotherapy

The study protocol was approved by the Institutional Ethics Committee (No: 2025/479), and the study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

All patients, who were enrolled in this study had a biopsy proven tumor in the mid/distal part of the rectum within 6–8 cm from the dentate line accessible for digital rectal examination (DRE) by the surgeon at the time of initial total colonoscopy. The endoscopic procedure was performed under sedation for the detailed documentation of the tumor's features such as density, mobility, size and localization. After endoscopic evaluation of the tumor, local staging was performed with pelvic MRI and systemic staging was performed with intravenous contrast media used computer tomography of the chest and abdomen. Patients with a locally advanced mid/distal rectal cancer (≥ T3, N0 or any T, N+) received nCRT with subsequent consolidation chemotherapy. Long-term neoadjuvant chemoradiotherapy was delivered with doses of 50.4 or 54 Gy and with simultaneous integrated boost to the primary tumor and involved lymph nodes. As chemotherapy capecitabine (825 mg/m^2 orally twice daily) or continuous infusion fluorouracil (5-FU) (5-FU; 225 mg/m^2/day) was administered. Consolidation chemotherapy was administered as six cycles of CapeOx (capecitabine and oxaliplatin) every three weeks or as 8 cycles of FOLFOX (Folinic acid, 5-FU and oxaliplatin) every two weeks.

The first tumor response assessment was performed at the 12th week beginning from the end of nCRT and administration of **partial consolidation chemotherapy**. This treatment method is defined as near TNT. Tumor restaging was done by tumor markers, DRE (preferably by the same surgeon at the initial evaluation), flexible sigmoidoscopy, pelvic MRI and CT of the chest and abdomen. Clinical tumor response was stratified according to the three-tier grading schema defined as incomplete clinical response (iCR), nCR and cCR [5]. A cCR was defined as normal rectum wall on DRE, flat white scar, telangiectasia and no ulceration or nodularity on endoscopy and replacement of the initial tumor area

with fibrotic tissue and the absence of lymph nodes in T2-weighted sequences on MRI. nCR is defined as minor mucosal abnormality and smooth induration on DRE, irregular mucosa, small nodules, minor mucosal abnormality, superficial ulceration and mild persisting erythema on endoscopy and partial replacement of the initial tumor area with fibrotic tissue and partial regression of lymph nodes in T2-weighted sequences on MRI. A palpable tumor and a visible tumor with/-out progression on all three modalities is defined as iCR.

Patients who achieved nCR or cCR were referred to complete TNT. After completion of TNT all patients were restaged with the three baseline modalities (DRE, endoscopic and radiological) and were classified as cCR or nCR. Patients with iCR after the first response assessment and patients with nCR after TNT were suggested to undergo a minimally invasive TME with/without permanent stoma. Patients with a clinical, endoscopic and radiological complete response following TNT were also suggested to be managed with NOM.

NOM patients were intensively followed up at frequent intervals, especially for the next three years. The surveillance schedule consisted of tumor markers, DRE, flexible sigmoidoscopy, and pelvic MRI every three months for the first two years, then every six months for the third year, and annually for the next two years. For the detection of distant metastasis CT-scan of the chest and abdomen was performed every six months in the first three years and then annually for the next two years.

In any patient the reappearance of malignant lesions at the initial tumor site in the rectal lumen, rectal wall, mesorectum or lateral side wall lymph nodes are considered as local regrowth. Patients endoscopically or radiologically diagnosed for local regrowth warranted a prompt salvage surgery on the principles of TME with/-out permanent stoma.

Statistical Analysis

Data were collected prospectively and analyzed retrospectively. Continuous variables were tested for normality with the Shapiro–Wilk test. They are presented as mean ± standard deviation (range) when normally distributed and as median (interquartile range) otherwise. Categorical variables are presented as numbers and percentages. Categorical variables were compared with the chi-square test or Fisher's exact test, as appropriate. Survival was estimated with the Kaplan–Meier method and is reported with 95% confidence intervals. Median follow-up was calculated with the reverse Kaplan–Meier method. The rate of distant metastasis in patients with and without local regrowth was compared with Fisher's exact test. A two-sided p value below 0.05 was considered statistically significant.

Results

Out of 173 patients 83 (48.0%) patients developed a cCR following consolidation chemotherapy including nCRT and were enrolled into the study. 53 (63.9%) patients were male and 30 (36.1%) were female with a mean age of 60.1411 (35–83) years. According to the American Society of Anesthesiologists (ASA) physical status classification system 16 (19.3%) patients were graded as ASA

score I, 59 (71.1%) patients as ASA score II and as 8 (9.6%) patients as ASA score III. The mean distance of the primary tumor from the dentate line at initial diagnosis or staging was measured as 1.972 (0–8) cm. Baseline patients' characteristics are summarized in Table 2.

Table 2
Patients' baseline characteristics

Age, mean (range) years	**n = 83**
	60.14±11 (35–83)
Gender, n (%)	
Female	30 (36.1)
Male	53 (63.9)
Tumor distance from dentate line, mean (range) cm	1.97 ± 2 (0–8)
Body mass index, mean (range), kg/m²	27.71 ±4.18(18.1–38.2)
ASA physical status classification score, n (%)	
1	16 (19.3)
2	59 (71.1)
3	8 (9.6)

After the initial staging at the 12th week starting from the end of nCRT, nCR was observed in 108 (62.4%) patients, cCR in 40 (23.1%) and iCR in 25 (14.5%). After the completion of TNT cCR was observed in 43 (39.8%) out of 108 nCR patients and cCR sustained in all 40 (100%) cCR patients at the initial evaluation. The compliance to consolidation chemotherapy was very high with a completion rate of 92.8% (64/69). Five patients were not able to complete all consolidation chemotherapy cycles due to febrile neutropenia (n = 2), severe diarrhea (n = 1), allergic reactions (n = 1), and bone marrow suppression (n = 1) (Table 3). Fourteen (16.9%) of the 83 patients did not receive consolidation chemotherapy due to refusal and this decision was primarily made because of the side effects of chemotherapy.

Table 3
Compliance to TNT

Treatment response evaluation (12th week), n (%)	
iCR	25 (14.5)
nCR	108 (62.4)
cCR	40 (23.1)
Treatment response evaluation (20th week), n (%)	
nCR ◊ cCR	43 (39.8)
cCR ◊ cCR	40 (100)
Completion of TNT, n (%)	
Yes	64 (92.8)
No	5 (7.2)
Reasons for discontinuing TNT, n (%)	
Febrile neutropenia	2 (40)
Severe diarrhea	1 (20)
Allergic reaction	1 (20)
Bone marrow suppression	1 (20)

During follow-up 16 (19.3%) patients developed local regrowth with a solely endoluminal growth pattern, who were diagnosed by DRE and endoscopic evaluation with pathological confirmation. In the current study, all local regrowths occurred in the first two years with the vast majority detected in the first year and a percentage of 68.8% (n = 11). Salvage surgery based on the principles of TME due to local regrowth was suitable and was immediately performed in 13 of the 16 patients with local regrowth (81.25%). Of the three remaining patients diagnosed with local regrowth, two (12.5%) patients refused salvage surgery despite a detailed explanation of the potential risks in near time future, while one (6.25%) patient underwent endoscopic submucosal dissection (ESD). Sphincter preserving procedures were performed in 8 (8/13; 61.5%) patients such as low anterior resection (n = 6) or intersphincteric resection (n = 2) and abdominoperineal resection was performed in five (5/13; 38.5%) patients. The evaluation of the salvage surgery specimen revealed a complete mesorectal excision in 4 patients, near complete mesorectal excision in 5 patients and incomplete mesorectal excision in 4 patients (Table 4).

Table 4
Local regrowth and salvage surgery features

Local regrowth, n (%)	
Absent	67 (80.7)
Present	16 (19.3)
Local regrowth pattern, n (%)	
Intraluminal	16 (100)
Extraluminal	0
Salvage Surgery, n (%)	
LAR	6 (37.5)
ISR	2 (12.5)
APR	5 (31.25)
ESD	1 (6.25)
Denied salvage surgery	2 (12.5)
Grading of TME specimen, n (%)	
Complete	4 (30.8)
Near complete	5 (38.4)
Incomplete	4 (30.8)
(LAR: low anterior resection, ISR: intersphincteric resection, APR: abdominoperineal resection), TME: total mesorectal excision, ESD: endoscopic submucosal dissection)	

Distant metastasis was detected in seven (8.4%) patients. Two patients (3%) with distant metastasis had no local regrowth and the remaining five (31.25%) patients had a local regrowth (2/67 vs. 5/16; *p = 0.002*) (Table 5). During surveillance four patients died due to disease related reasons such as disease progression, while three patients died due to causes unrelated to this disease, such as car accident and pneumonia during Covid-19 pandemic. The local disease-free survival (DFS), distant metastasis without local regrowth DFS, local regrowth and distant metastasis DFS and overall survival was 80.7% (67/83), 97% (65/67), 78.3% (65/83) and 95.2% (79/83), respectively with mean follow-up of 61 (16–144) months (Figs. 1 and 2).

Table 5
Local regrowth and distant metastasis features

Local regrowth, n (%)	
Absent	67 (80.7)
Present	16 (19.3)
Distant metastasis, n (%)	
Absent	76(91.6)
Present	7 (8.4)
Distant metastasis after local regrowth, n (%)	
Local regrowth absent (n = 67)	2 (3)
Local regrowth present (n = 16)	5 (31.25)

Discussion

The results of this study support non-operative management as a safe option for locally advanced mid/distal rectal cancer patients who achieve a cCR following with/-out TNT, with favorable clinical outcomes. After a waiting period of approximately 18–20 weeks with the concomitant administration of consolidation chemotherapy, the patients showed an increased treatment compliance with 92.8% completion of TNT, a local regrowth rate of 19.3% and a distant metastasis rate of 8.4%. On the other hand, all patients diagnosed with local regrowth considered resectable based on the principles of TME with a total sphincter-preservation rate of 94% (78/83).

In recent decades, considerable effort has been directed towards improving tumor response rates and increase sphincter preservation rates while improving clinical outcomes. Although previous studies have shown a direct proportional correlation between waiting time and tumor response, there is still a dilemma regarding the exact time of the waiting period following neoadjuvant nCRT and the application of chemotherapy. Although, the randomized GRECCAR-6 trial comparing rectal cancer patients with a waiting period of seven weeks versus eleven weeks after nCRT showed similar pCR rates in TME specimen among the two groups (15% vs 17.4%, p = 0.6), another randomized study comparing waiting periods of shorter and longer than eight weeks reported a significantly higher pCR rate in patients with longer waiting periods (10% versus 18.6%, p = 0.03) [6, 7]. The Timing of Rectal Cancer Response to Chemoradiation trial, which compared none, two, four and six cycles of mFOLFOX6 during the waiting period of 6, 12, 18 and 24 weeks, respectively after nCRT showed an increased pCR rate with up to 38% in locally advanced rectal cancer patients following a waiting period of 24 weeks [3]. These findings led to the widespread adoption of TNT either as systemic chemotherapy followed by RT/nCRT or upfront nCRT followed by systemic chemotherapy in locally advanced rectal cancer patients.

In our study, the waiting period from the end of nCRT to the final decision for NOM was between 18–20 weeks. During the waiting period consolidation chemotherapy was applied in two steps, first as partial consolidation chemotherapy after nCRT, defined as near TNT until the first evaluation for treatment response approximately at the 12th week. Second, only patients revealing an endoscopic and radiologic nCR or cCR after restaging completed TNT. Our approach consisting of near-TNT and subsequent completion of consolidation chemotherapy in selected patients had several advantages including high cCR rates of 48.0%, identifying good responders and referring them to complete TNT with the aim of achieving a cCR and a subsequent NOM and suggesting patients with an iCR to undergo TME without wasting time. Identifying the good responders is of essential importance. Prolonging the waiting period is associated with impaired long-term clinical outcomes, especially in LARC patients, who have a poor pathological treatment response such as partial or incomplete response pattern. Patients with poor responses and longer waiting periods than eight weeks had significantly worse 5-years DFS compared to patients with shorter waiting periods before surgery (59% vs. 72%, p< .001) [8]. In our study completion of TNT within 18–20 weeks is only approved in patients with a nCR or cCR during the first treatment response evaluation at the 12th week. Patients with a partial or incomplete response, defined as non-responders are recommended for surgery to prevent detrimental clinical outcomes.

The selection of appropriate and most effective neoadjuvant treatment regimen that will increase the chances of the patients achieving a cCR with a subsequent NOM is also essential. To the best of our knowledge, the standard trimodal neoadjuvant treatment approach (nCRT/RT, surgery and adjuvant chemotherapy) has shown pCR or cCR rates of approximately 25% [2, 5]. But with the incorporation of induction or consolidation chemotherapy as TNT in locally advanced rectal cancer patients, the cCR rates increased nearly up to 50% [9–11]. Both the German trial showing higher rates of pCR with consolidation chemotherapy compared to induction chemotherapy (25% vs. 17%) and the OPRA study showing higher rates of sustained organ preservation with consolidation chemotherapy compared to induction chemotherapy (53% vs. 41%), demonstrated the superiority of consolidation chemotherapy in terms of pCR and/or cCR [10, 11]. It is important to mention that in the German study systemic chemotherapy consisted of three cycles of FOLFOX, whereas in the OPRA study systemic chemotherapy consisted of eight cycles of FOLFOX or five cycles of CapeOx. The differences in systemic chemotherapy cycles consequently resulted in longer waiting periods, which could have affected the doubling of cCR rates in the OPRA study. In the current study, nCRT followed by consolidation chemotherapy either with FOLFOX or CapeOX was preferred in all locally advanced rectal cancer patients received, according to the current data in several studies. We performed a restaging at the 12th week after the administration of partial consolidation chemotherapy (near-TNT) to identify the good responders and sort them from the non-responders. In this setting, the identification of good responders and the completion of consolidation chemotherapy after nCRT in this group of locally advanced rectal cancer patients allowed to achieve a relatively high cCR rate of 48.0%, which is in line with several other studies with rates between 25% and 53% [9–11].

Despite the application of TNT and a sufficient waiting period following nCRT some patients with initially locally advanced rectal cancer do not develop a cCR and end up with nCR. Although nCR is a quite novel

entity without a standardized definition, the term “nCR” is frequently used for lesions with significant regression of the primary tumor that do not fulfill endoscopic or radiological cCR criteria [12, 13]. In addition the management of patients with nCR after neoadjuvant treatment is rather quite controversial. In the current study, patients with a nCR after the first response assessment at the approximately 12th week were suggested to complete consolidation chemotherapy, and more than one-third of these patients showed a transition to cCR after completion of TNT with a rate of 39.8% (43/108). In contrast to the OPRA study, we excluded patients with a nCR after completion of TNT from the NOM approach and recommended a definitive surgery for these patients. In the OPRA study patients with a nCR were managed with a NOM strategy requiring salvage surgery with a rate of 50% during intensive and frequent surveillance [11].

Most of the important concerns regarding the NOM strategy are the potentially detrimental clinical outcomes in terms of local regrowth and increased distant metastasis with deferral and/or prolonging the index surgery. We have reported a local regrowth of 19.3%, which is in consistent with previously published studies reporting rates varying from 16% to 31% [11, 14–22]. In our study, the local regrowth pattern in all NOM patients was intraluminal confined to the rectal wall and detected during the first two years of intensive surveillance. The local regrowth risk after an initial cCR in the first three years is reported as approximately 95% and subsequently decreases dramatically to less than 5% after three years. All of these patients were amenable for salvage surgery based on the principles of TME with similar reports ranging from 83%-100% [11, 14, 15, 19–21]. According to these results the organ- and sphincter preserving rate was relatively high with 84% (salvage surgery n = 13) and 94%, respectively.

Salvage surgery with frequent and intensive surveillance ensures desirable pelvic disease control in local regrowth patients achieving a cCR following neoadjuvant treatment, on the other hand it brings concerns towards the potential of developing distant metastasis. In the last decade, the increased risk of distant metastasis, especially in patients with local tumor growth, has raised concerns among surgeons. Previously published studies reported a relatively low rate of distant metastasis of up to 6.5% in patients with a sustained cCR, compared with 17.8%-36.4% in patients with local regrowth [22–24]. These findings are consistent with our current study, reporting increased distant metastasis rates of 31.25% in local regrowth patients compared with 3% in patients without local regrowth. The reason for the increased distant metastasis rates in patients with local regrowth has not been elucidated so far. It is not known whether the increased proportion of distant metastasis is caused by local regrowth, or the primary tumor causing initial occult metastasis or caused by the worse tumor biology of local regrowth patients leading to an increased risk of developing distant metastasis [24]. However, the question “Could we have prevented the development of distant metastasis after local regrowth if we have performed a TME procedure for patients with cCR?” still remains.

Conclusion

The NOM strategy is a safe and feasible treatment option for locally advanced mid/distal rectal cancer patients achieving a cCR following total neoadjuvant treatment and should be considered in the

management of rectal cancer. An adequate initial and post-treatment evaluation of the primary is important to define or determine neoadjuvant treatment response in terms of cCR, nCR or iCR. Surgery was recommended for all patients with iCR after initial treatment response assessment and for all patients with nCR after completion of TNT. Once a cCR following neoadjuvant treatment is achieved, frequent and intensive surveillance is essential to detect local regrowth as early as possible to perform salvage surgery for pelvic disease control.

Declarations

Competing interests

The authors have no relevant financial or non-financial interests to disclose.

Ethics approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Institutional Ethics Committee (No: 2025/479).

Consent to participate:

Written informed consent was obtained from all individual participants included in the study.

Consent to publish:

Not applicable; no identifiable individual data are included.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

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Not applicable; the manuscript contains no identifiable individual data.

Funding:

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

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Acknowledgments

None

Data Availability

The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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Figures

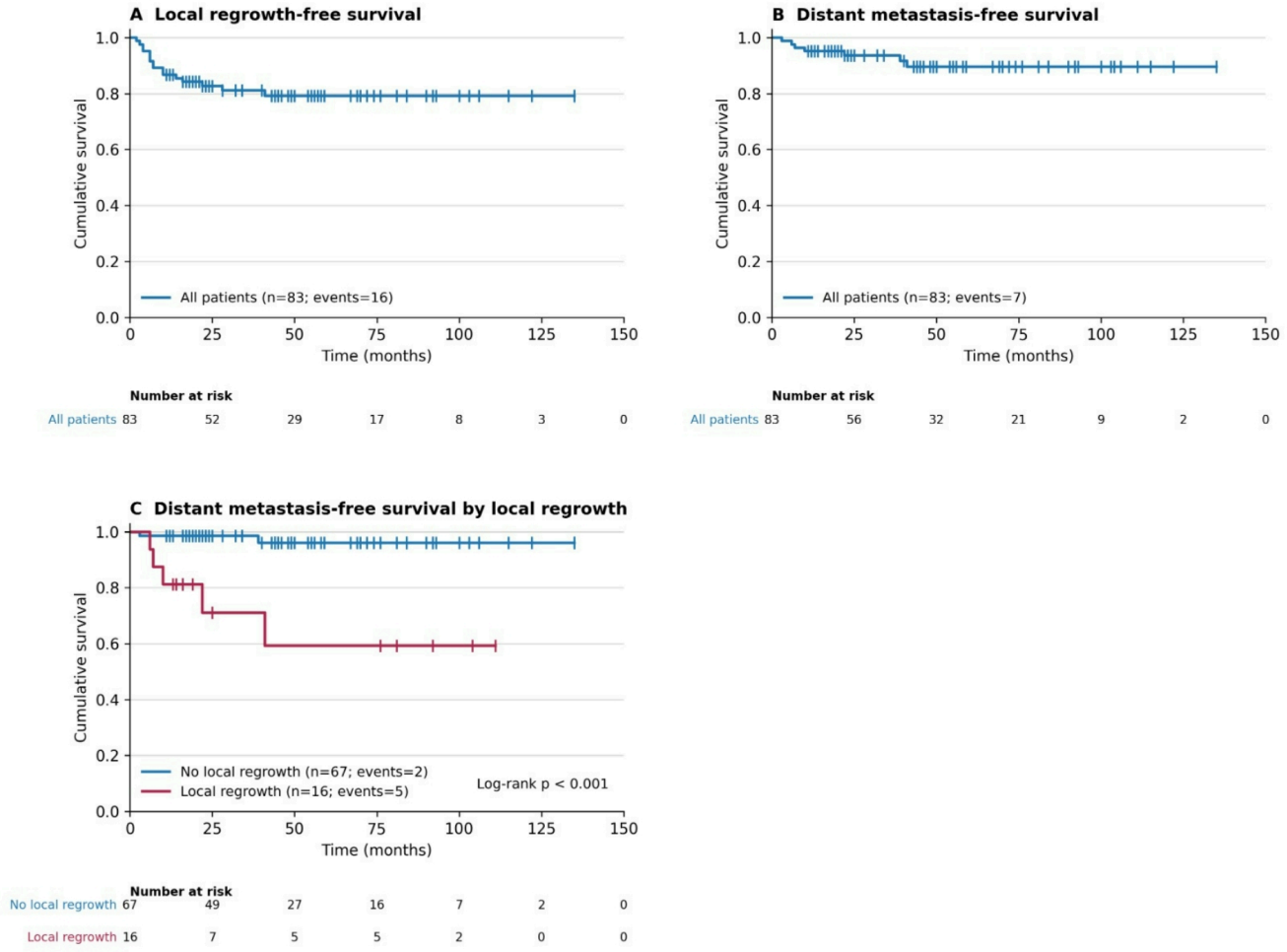


Figure 1

Kaplan–Meier curves of patients managed with non-operative management (n=83): (a) local regrowth-free survival, (b) distant metastasis-free survival and (c) distant metastasis-free survival according to local regrowth status, with numbers at risk

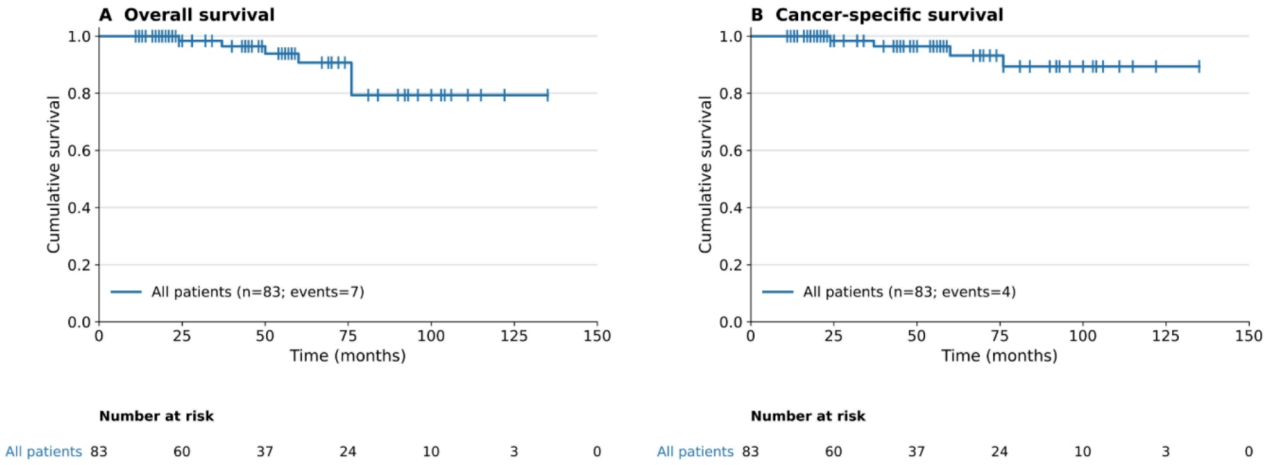


Figure 2

Kaplan–Meier curves of patients managed with non-operative management (n=83): (a) overall survival and (b) cancer-specific survival, with numbers at risk