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ORIGINAL SCIENTIFIC REPORT

Oncologic Risk of Rectal Preservation Against Medical Advice After Chemoradiotherapy for Rectal Cancer: A Multicenter Comparative Cross-Sectional Study with Rectal Preservation as Supported by Surgeon

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Abstract

Background Rectal preservation against medical advice after neoadjuvant chemoradiotherapy for rectal cancer may increase oncologic uncertainty. This study aimed to compare the oncologic outcomes of patients undergoing rectal preservation as intended by the surgeon, and the outcomes of patients refusing rectal resection against medical advice.

Methods The study population consisted of patients in whom the rectum was preserved after neoadjuvant chemoradiotherapy for clinical stage I–III mid or low rectal cancer between May 2003 and August 2017 (n = 2883); these patients were divided into those in whom rectal preservation was intended by their surgeon (intended rectal preservation, group A, n = 41) and those in whom the rectum was not resected against medical advice (unintended rectal preservation, group B, n = 101), defined as non-operative management or local excision.

Results The tumor distance, age, and performance status of patients were not significantly different between the groups, while the clinical T stage before chemoradiotherapy was lower in group A than in group B ($P < 0.001$). During the median follow-up period of 34 months (interquartile range 18.0–72.0 months), the 3-year overall survival in group B (59.7%) was worse than that in group A (90.1%; $P < 0.001$), and 80.2% of group B patients had residual or unknown disease status.

Conclusions This study showed that unintended rectal preservation increases oncologic risk after neoadjuvant chemoradiotherapy for rectal cancer regardless of short-term follow-up. Therefore, these findings could be shared with rectal cancer patients who choose to ignore medical advice after chemoradiotherapy to preserve their rectum.

Introduction

Neoadjuvant chemoradiotherapy (nCRT) increases therapeutic compliance and decreases local recurrence in locally advanced rectal cancer [1]. Approximately 11.3–78.4% of patients show a clinical complete response (ycCR) after nCRT [2, 3], and 15–30% of patients experience a pathologic complete response (ypCR) [4, 5]. Previous studies have shown excellent oncologic results after rectal preservation including non-operative management and local excision within these good responders [6, 7]. However, the scientific evidence is limited due to the presence of highly selective or small non-randomized studies as well

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as the uncertainty of long-term oncologic outcomes [4, 6, 7]. In addition, there is no definite diagnostic modality for predicting ypCR after nCRT for rectal cancer [8, 9], and concerns exist that rectal preservation might increase disparities in rectal cancer management [10].

Rectal preservation by avoiding radical resection after nCRT for rectal cancer has increased in clinical practice. Furthermore, refusal of radical surgery against medical advice after nCRT is often happened [11], which is considered 'unintended rectal preservation.' However, little is currently known about the actual oncologic outcome of unintended rectal preservation. This study aimed to compare the oncologic outcomes between rectal preservation as supported by their surgeon (intended rectal preservation) and rectal preservation as chosen by the patients against medical advice (unintended rectal preservation) after nCRT for mid or low rectal cancer.

Materials and methods

This was a multicenter, retrospective, cross-sectional study performed in three referral hospitals (Seoul National University Bundang Hospital, Seoul National University Hospital, and National Cancer Center, Korea). The study included mid or low rectal cancer patients with local excision or non-operative management after nCRT for biopsy proven rectal cancer located lower than 10 cm from the anal verge (AV) from May 2003 to August 2017. We excluded patients who underwent radical resection for rectal cancer and those with a history of previous malignancy, concurrent distant metastasis, or concomitant unrelated malignant disease. This study was approved by the Institutional Review Board of the three included hospitals.

The study population was categorized into two groups: patients undergoing rectal preservation as intended by the surgeon (intended rectal preservation, group A) and patients refusing rectal resection against medical advice (unintended rectal preservation, group B). Unintended rectal preservation included refusal to any type of surgery or local excision instead medical advice of radical surgery. The study period was divided into two periods to identify the proportional change in each group: period I from May 2003 to December 2010 and period II from January 2011 to August 2017.

An initial evaluation of the rectal cancer was performed before nCRT. Colonoscopy with a biopsy was performed to confirm the pathologic diagnosis. Rectal magnetic resonance imaging (MRI) and/or endorectal ultrasonography (US) was used to determine the depth of tumor invasion and lymph node evaluation. Abdominopelvic computed tomography (CT) and chest CT with or without positron emission tomography (PET) were used to identify distant metastasis.

The patients received a long-course nCRT regimen as described in our previous paper [12]. A dose of 50.4 Gy was provided over 5.5 weeks as long-course radiation therapy. The common chemotherapy regimens were 5-fluorouracil or capecitabine-based. Two cycles of an intravenous 5-fluorouracil bolus with leucovorin were administered in weeks 1 and 5 of radiotherapy, or oral capecitabine was administered continuously during radiotherapy. Short-course radiotherapy using an institutionally approved protocol with 25 Gy or 33 Gy in 5 or 10 fractions with concurrent chemotherapy was performed in some patients as part of an experimental study [13, 14].

The tumor response was assessed 6–8 weeks after nCRT completion. The protocol was similar to the baseline work-up. Local excision or non-operative management was offered as an alternative treatment for some patients with a ycCR or near ycCR at the surgeon's discretion [15, 16]. The criteria used to determine a ycCR were 1) no residual tumor, including a scar or small ulcer on digital rectal examination (DRE) or colonoscopy and 2) a subtle or small hypointense wall thickening without isointense signal on T2-weighted MRI [8, 17]. Local excision included the excision of a full thickness mesorectum and an adequate safety margin distance using direct vision or transanal minimally invasive surgery [15]. For poor responders, curative surgery was recommended if they were fit for radical surgery. Radiotherapy with an escalated radiation dose or adjuvant chemotherapy was also recommended depending on the patient's condition. For poor responders, the choice between rectal preservation or extraction was at the surgeon's discretion or patient's preference.

The follow-up surveillance protocols were generally similar in all three hospitals. The patients visited the hospital every 3 or 6 months for the first 2 years and every 6 months thereafter. DRE and laboratory tests including carcinoembryonic antigen (CEA) were performed at every visit. An abdominopelvic CT scan with or without chest CT was performed every 6 months. A colonoscopy was performed 1 year after treatment and then biennially. A group of patients undergoing non-operative management were under close follow-up surveillance at the discretion of the surgeon using sigmoidoscopy and rectal MRI in addition to the routine protocol.

The survival status of all eligible patients was confirmed based on the extinction of a resident registration number from Statistics Korea (*KOSTAT, mdis.kostat.go.kr*). The time interval for overall survival was determined from the final day of nCRT to death from any cause.

Mann–Whitney *U* test was used to compare continuous variables. Fisher's exact test was used to compare categorical variables. Two-sample *z* test was used to compare

Table 1 Percentage of patients in each group based on study period

	Period I (n = 1450)	Period II (n = 1433)	P value*
Radical surgery	1397 (96.3%)	1344 (93.8%)	0.002
Non-radical management			
Intended rectal preservation	13 (0.9%)	28 (2.0%)	0.025
Unintended rectal preservation	40 (2.8%)	61 (4.3%)	0.037

Period I, May 2003–December 2010; Period II, January 2011–August 2017

*Two-sample z test

proportions. The survival outcome was assessed using the Kaplan–Meier curve and a log-rank test. A P value < 0.05 was considered statistically significant. Statistical analyses were performed using the R program for Statistical Computing Version 3.2.3 software (R Development Core Team, Vienna, Austria).

Results

Patient selection and clinicopathologic characteristics

Among 2883 patients who received nCRT for mid or low rectal cancer during the study period, 142 patients were identified as eligible for this study. Group A included local excision (n = 28) and non-operative management (n = 13). Group B consisted of five patients with unintended local excision and 96 patients with unintended non-operative management. The reasons for unintended rectal preservation were avoidance of radical surgery including permanent colostomy (n = 69), poor physical condition (n = 8), old age (n = 4), personal problems (n = 4) and unknown reasons (n = 16). Both groups showed significant proportional changes from period I to period II: from 0.9% (13 of 1450) to 2.0% (28 of 1433) in group A (P = 0.025) and from 2.8% (40 of 1450) to 4.3% (61 of 1433) in group B (P = 0.037) (Table 1).

nCRT was administered to all patients except for six who received radiotherapy alone because of reluctance to receive chemotherapy. Total radiation doses ranging from 34.2 to 66.0 Gy were administered due to an incomplete radiotherapy course or radiotherapy without surgery. Three patients received short-course radiotherapy, but neither underwent local excision.

Significantly, more patients had elevated initial CEA levels in group B than in group A (P = 0.002). The initial clinical T stage and post-nCRT T stage were lower in group A patients than in groups B ($P < 0.001$). The P value did not reach statistical significance in the analysis of the initial clinical N stage (P = 0.059). Age, performance status, and tumor height were not significantly different between groups (Table 2).

Clinical course

Among patients who underwent local excision in group A, five patients had recurrence. Among them, four patients received a salvage operation, and one patient was treated with palliative chemotherapy due to distant bone metastasis. Of the four patients who received a salvage operation, only one patient exhibited no evidence of disease (NED) at the end of hospital follow-up. Two patients undergoing non-operative management in group A experienced tumor regrowth. One patient showed regrowth 28 months after the end of neoadjuvant therapy and NED status after abdominoperineal resection (APR), but the other patient was recommended for palliative chemotherapy because of multiple lung metastases (Fig. 1a). Among five patients who underwent unintended local excision in group B, three patients developed recurrence, one of whom underwent a salvage operation because of lung metastasis. The two other recurrent patients refused a salvage operation. The majority of group B refused surgery after neoadjuvant therapy (n = 96). Seven patients maintained ycCR status over a median hospital follow-up period of 66 months. Eighteen patients later decided to undergo a salvage operation. Salvage operations included one pelvic exenteration, one Hartmann's operation and nine APRs. Of the 18 patients who underwent a salvage operation, ten patients were NED status at the end of hospital follow-up. The remaining 71 patients discontinued their regular visits, and 43 patients were confirmed to have died at the end of this study (Fig. 1b).

Survival outcome

The median follow-up period was 34 months (interquartile range 18.0–72.0). The 3-year overall survival rate of 59.7% (95% CI 50.1–71.1%) in group B was worse than the rate of 90.1% (95% CI 79.8–100%) in group A ($P < 0.001$) (Fig. 2). In group B, 80.2% (81 of 101) of patients had

Table 2 Patient characteristics

Characteristic	Group A (n = 41) n (%)	Group B (n = 101) n (%)	P value
Age (IQR) (years)	66 (55–77)	72 (62–78)	0.130*
Gender			0.712†
Male	21 (51.2)	56 (55.4)	
Female	20 (48.8)	45 (44.6)	
Performance status			0.496†
ECOG 0–1	30 (93.8)	63 (87.5)	
ECOG 2–3	2 (6.2)	9 (12.5)	
Missing	9	29	
Tumor height (IQR) (cm)	3 (1–4)	3 (2–5)	0.112*
Initial CEA (ng/ml)			0.002†
<5	37 (90.2)	65 (65.0)	
≥5	4 (9.8)	35 (35.0)	
Missing	0	1	
Differentiation			0.724†
WD	12 (30.0)	22 (22.9)	
MD	26 (65.0)	68 (70.8)	
PD/SRC	2 (5.0)	6 (6.2)	
Missing	1	5	
Initial clinical T stage			<0.001†
T1–2	16 (40.0)	14 (13.9)	
T3	24 (60.0)	72 (71.3)	
T4	0 (0.0)	15 (14.9)	
Missing	1	0	
Initial clinical N stage			0.059†
Negative	23 (57.5)	39 (38.6)	
Positive	17 (42.5)	62 (61.4)	
Missing	1	0	
Post-nCRT T stage			<0.001†
T0–2	30 (79.5)	14 (40.0)	
T3	7 (20.5)	18 (51.4)	
T4	0 (0.0)	3 (8.6)	
Missing/no imaging study	4§	66	
Post-nCRT N stage			0.509†
Negative	33 (89.2)	29 (82.9)	
Positive	4 (10.8)	6 (17.1)	
Missing/no imaging study	4	66	
Chemotherapy agent			0.110†
FL	9 (23.1)	40 (41.7)	
X	26 (66.7)	49 (51.0)	
Other agents‡	4 (10.3)	7 (7.3)	
RT alone/missing	2	5	
Type of radiotherapy¥			0.558†
Long course	40 (100.0)	98 (97.0)	
Short course	0 (0.0)	3 (3.0)	
Missing	1	0	

Missing information was excluded from data analysis

IQR interquartile range, *ECOG* Eastern Cooperative Oncology Group, *CEA* carcinoembryonic antigen, *WD* well differentiated, *MD* moderately differentiated, *PD* poorly differentiated, *SRC* signet ring cell *carcinoma*, *nCRT* neoadjuvant chemoradiotherapy, *FL* 5-fluorouracil with leucovorin, *X* xeloda, *RT* radiotherapy, *Gy* gray

*Mann–Whitney *U* test

†Fisher's exact test

§In these patients, cCR or near cCR was determined with endoscopic finding

‡Other agents included tegafur/uracil with leucovorin and xeloda with irinotecan

¥Among group A and B patients, 3 and 4 patients did not complete radiotherapy due to complication, respectively

remaining disease or an unknown disease status at the last hospital visit.

Discussion

This study showed that unintended rectal preservation as chosen by the patients against medical advice increased oncologic risk compared to intended rectal preservation as supported by their surgeon after nCRT despite short-term follow-up, even after a salvage operation. Therefore, we suggest that these findings should be shared with rectal cancer patients who act against medical advice after nCRT.

To the best of our knowledge, no report has addressed oncologic outcomes in a group with unintended rectal preservation. In this study, we assessed the possible harm of rectal preservation against medical advice after nCRT. Although rectal preservation after nCRT is a promising treatment for rectal cancer, clinicians should be cautious and estimate the potential negative effect to prevent patient harm as this option is increasingly used clinically. Recent surveys revealed that surgeons favor non-operative management and wish to discuss options with patients when a ycCR is suspected [18, 19]. In addition, one prospective study showed that patients are also more likely to accept local excision than radical surgery and a considerable number of patients refused completion total mesorectal excision [7]. Further investigation is warranted to determine whether inappropriate rectal preservation is increasing as shown in this study.

According to previous studies, the potential reasons for refusing surgery or standard treatment included the avoidance of radical surgery [20], older and sicker

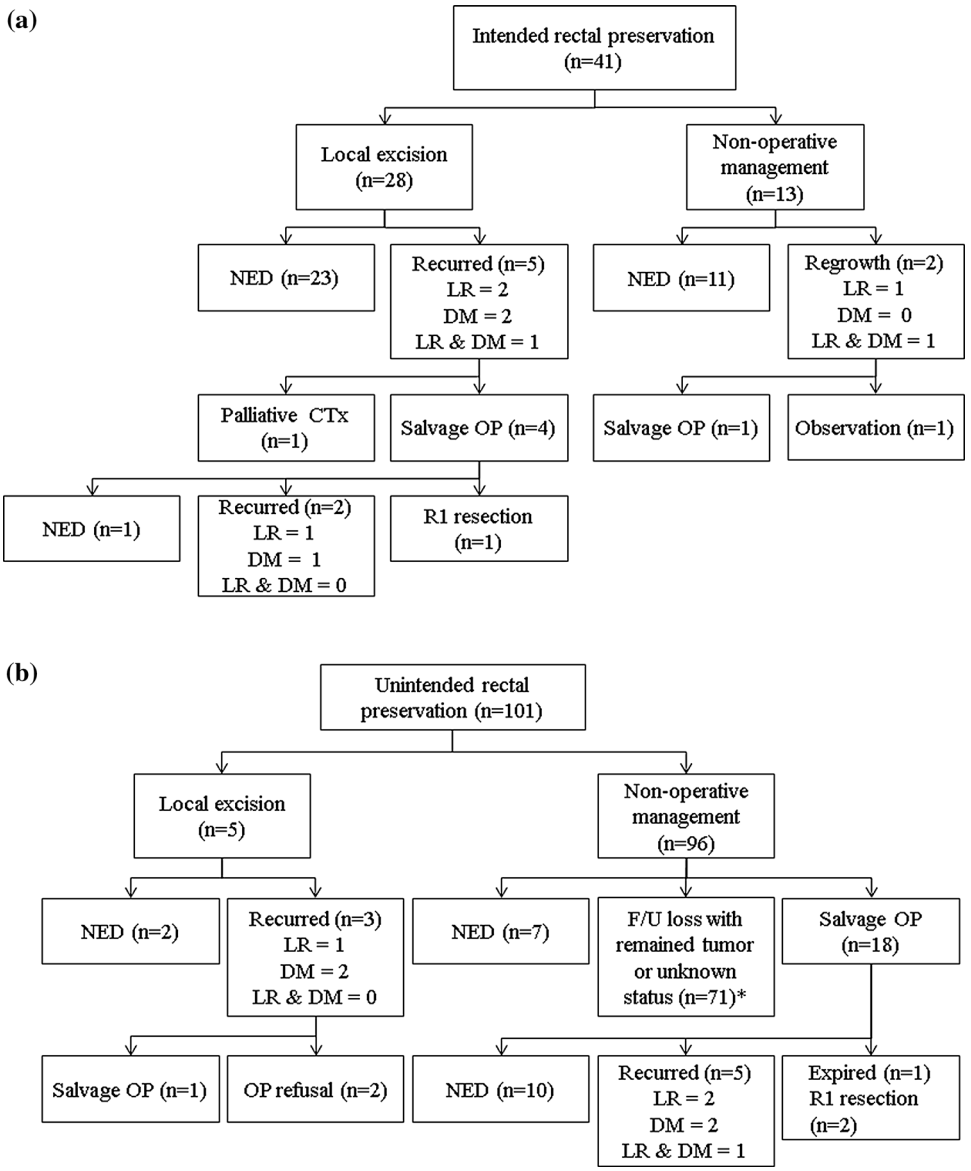

Fig. 1 Clinical course of **a** group A and **b** group B. *Of the 71 patients lost to follow-up, 43 patients had died by the end of the study. NED: no evidence of disease, LR: local recurrence, DM: distant metastasis, OP: operation, CTx: chemotherapy, F/U: follow-up

populations [21, 22], patient preferences [23], and communication problems between patients and their physicians [24, 25]. In our study, the main reason for unintended rectal preservation was the avoidance of radical surgery, including permanent colostomy. Although the unintended rectal preservation group showed a more advanced disease status, their age and general performance were not different from the intended rectal preservation group, and many of them could have been cured if they had received radical surgery. We considered that losing an rectum and requiring a permanent stoma are overestimated by patients as important reasons to avoid radical surgery. However, there is no clear evidence comparing quality of life after APR with permanent stoma placement to inter-sphincteric resection with low anterior resection syndrome. Therefore, future studies should compare the quality of life and functional outcome between APR and sphincter preservation surgery in low rectal cancer patients.

In some cases, radical surgery is not possible, and an alternative treatment method is needed. Among older or morbid patients, radical surgery-related risks may outweigh the oncologic risks [26]. Additionally, some patients refuse radical surgery even if they understand that their survival outcome will be poor [27]. Local excision may be a possible alternative treatment instead of radical surgery if the patient's condition and disease status are acceptable. One notable finding of our study was the considerable number of unintended non-operative management cases and the few unintended local excisions during the study period, which was much lower than expected. We believe that

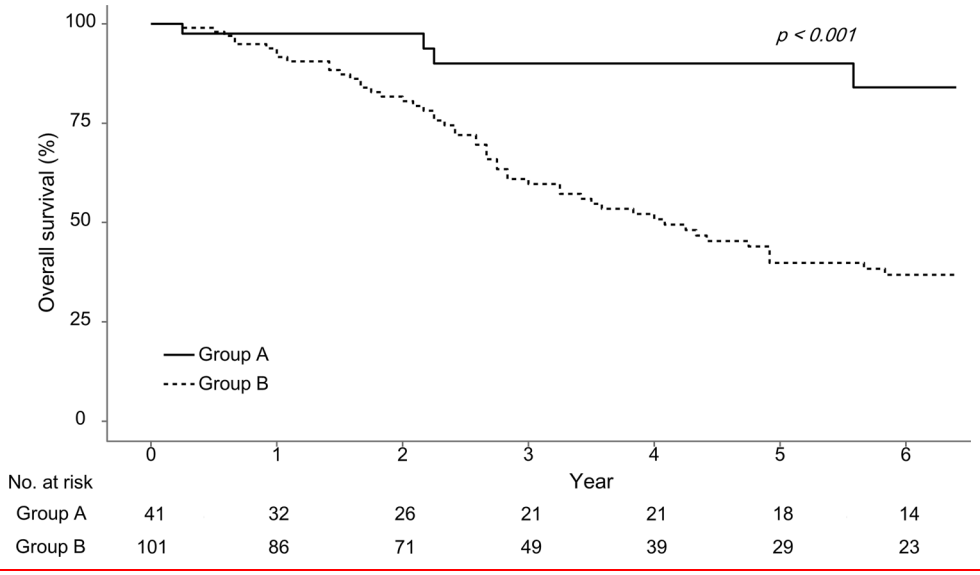

Fig. 2 Kaplan–Meier curve for overall survival of each group

local excision may be considered more often as an alternative treatment to non-operative management. However, the knowledge that no solid evidence exists regarding the safety of local excision after nCRT for rectal cancer should be shared with patients.

Non-operative management has increased, especially among certain races and populations with poor medical insurance backgrounds [10, 28]. Previous studies revealed that the decision making of rectal cancer patients is affected by their socioeconomic and educational status [29, 30]. Taken together, the process of adopting non-operative management in clinical practice might aggravate the disparity in rectal cancer management. There is little information about the survival outcome of unintended non-operative management in rectal cancer patients [11, 27], and one recent study reported a poor 5-year overall survival rate of 58.3% in rectal cancer patients who refused any surgery after nCRT, which is similar to the results of our study [27]. Therefore, non-operative management should be employed cautiously with consideration of patient compliance.

Although this study was limited to three large volume centers, our data showed a gradual but distinct trend of increasing intended rectal preservation in rectal cancer management [31, 32]. This change might reflect surgeon preference, but there is no standardized indication for each rectal preservation method to date [17]. Additional collaborative work is required to form a consensus or standardized criteria for rectal preservations.

Our study has several limitations. First, inevitable selection bias was present due to the retrospective nature of the study. Clinical data were also limited, especially for post-nCRT evaluation and follow-up surveillance, due to the lack of compliance in the unintended rectal preservation group. However, this study adds clinical value because it is not feasible for a comparative prospective study to identify clinical outcomes for unintended rectal preservation. Second, the sample size was insufficient to draw firm conclusions, even though we collected study populations from three referral centers. This was based on practical constraints due to the uncertainty of current diagnostic modalities for predicting ypCR after nCRT for rectal cancer. Third, the disease-free survival in the unintended rectal preservation group could not be estimated because most of the patients still had disease despite the short follow-up period. However, we confirmed their survival status at the end of the study period using the national registration system.

Our study shows the poor oncologic outcomes of unintended rectal preservation compared to the acceptable results of intended rectal preservation. Therefore, this finding could be shared with rectal cancer patients who desire inappropriate rectal preservation against a doctor's recommendation of radical surgery. In addition, well-designed studies are necessary to confirm the oncologic safety of intended rectal preservation compared with that of radical management after nCRT for rectal cancer.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights and informed consent Institutional review boards of the three included hospitals reviewed this study and waived the requirement for informed consent on the basis of its retrospective design and minimal risk to the participants. However, method was conducted in accordance with the committee's approved guidelines to protect patients' health information.

References

1. Song JH, Jeong JU, Lee JH et al (2017) Preoperative chemoradiotherapy versus postoperative chemoradiotherapy for stage II-III resectable rectal cancer: a meta-analysis of randomized controlled trials. Radiat Oncol J. https://doi.org/10.3857/roj.2017.00059
2. Seshadri RA, Kondaveeti SS, Jayanand SB et al (2013) Complete clinical response to neoadjuvant chemoradiation in rectal cancers: can surgery be avoided? Hepatogastroenterology. https://doi.org/10.5754/hge12354
3. Appelt AL, Pløen J, Harling H et al (2015) High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol 16:919–927. https://doi.org/10.1016/S1470-2045(15)00120-5
4. Garcia-Aguilar J, Renfro LA, Chow OS et al (2015) Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol. https://doi.org/10.1016/S1470-2045(15)00215-6
5. Silberfein EJ, Kattepogu KM, Hu CY et al (2010) Long-term survival and recurrence outcomes following surgery for distal rectal cancer. Ann Surg Oncol. https://doi.org/10.1245/s10434-010-1119-8
6. Renehan AG, Malcomson L, Emsley R et al (2016) Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. Lancet Oncol. https://doi.org/10.1016/S1470-2045(15)00467-2
7. Rullier E, Rouanet P, Tuech JJ et al (2017) Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. Lancet. https://doi.org/10.1016/S0140-6736(17)31056-5
8. Maas M, Lambregts DMJ, Nelemans PJ et al (2015) Assessment of clinical complete response after chemoradiation for rectal cancer with digital rectal examination, endoscopy, and MRI: selection for organ-saving treatment. Ann Surg Oncol. https://doi.org/10.1245/s10434-015-4687-9
9. Perez RO, Habr-Gama A, Pereira GV et al (2012) Role of biopsies in patients with residual rectal cancer following neoadjuvant chemoradiation after downsizing: can they rule out persisting cancer? Color Disease. https://doi.org/10.1111/j.1463-1318.2011.02761.x
10. Ellis CT, Samuel CA, Stitzenberg KB (2017) Innovation or disparity? National trends in nonoperative management of rectal adenocarcinoma. J Clin Oncol. https://doi.org/10.1200/jco.2016.34.4_suppl.688
11. Wang Y, Cummings B, Catton P et al (2005) Primary radical external beam radiotherapy of rectal adenocarcinoma: long term outcome of 271 patients. Radiother Oncol. https://doi.org/10.1016/j.radonc.2005.09.001
12. Kang SB, Park JW, Jeong SY et al (2010) Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy (COREAN trial): Short-term outcomes of an open-label randomised controlled trial. Lancet Oncol. https://doi.org/10.1016/S1470-2045(10)70131-5
13. Yoo S-G, Oh JH, Kim DY et al (2013) Preoperative short-course concurrent chemoradiation therapy followed by delayed surgery for locally advanced rectal cancer: a phase 2 multicenter study (KROG 10-01). Int J Radiat Oncol Biol Phys 86:34–39
14. Lee JH, Kim JG, Oh ST et al (2014) Two-week course of preoperative chemoradiotherapy followed by delayed surgery for rectal cancer: a phase II multi-institutional clinical trial (KROG 11-02). Radiother Oncol 110:150–154. https://doi.org/10.1016/j.radonc.2013.11.013
15. Yeo SG, Kim DY, Kim TH et al (2010) Local excision following pre-operative chemoradiotherapy-induced downstaging for selected cT3 distal rectal cancer. Jpn J Clin Oncol. https://doi.org/10.1093/jjco/hyq062
16. Habr-Gama A, Perez RO, Nadalin W et al (2004) Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 240:711
17. Han KS, Sohn DK, Kim DY et al (2016) Endoscopic criteria for evaluating tumor stage after preoperative chemoradiation therapy in locally advanced rectal cancer. Cancer Res Treat. https://doi.org/10.4143/crt.2015.195
18. Habr-Gama A, Perez RO, São Julião GP et al (2011) Factors affecting management decisions in rectal cancer in clinical practice: results from a national survey. Tech Coloproctol. https://doi.org/10.1007/s10151-010-0655-3
19. São Julião GP, Smith FM, Macklin CP et al (2014) Opinions have changed on the management of rectal cancer with a complete clinical response to neoadjuvant chemoradiotherapy. Color Disease. https://doi.org/10.1111/codi.12599
20. Landrum MB, Keating NL, Lamont EB et al (2012) Reasons for underuse of recommended therapies for colorectal and lung cancer in the veterans health administration. Cancer. https://doi.org/10.1002/cncr.26628
21. Keating NL, Landrum MB, Klabunde CN et al (2008) Adjuvant chemotherapy for stage III colon cancer: do physicians agree about the importance of patient age and comorbidity? J Clin Oncol. https://doi.org/10.1200/JCO.2007.15.9434
22. Rogers SO, Gray SW, Landrum MB et al (2010) Variations in surgeon treatment recommendations for lobectomy in early-stage non-small-cell lung cancer by patient age and comorbidity. Ann Surg Oncol. https://doi.org/10.1245/s10434-010-0946-y
23. Margolis ML, Christie JD, Silvestri GA et al (2003) Racial differences pertaining to a belief about lung cancer surgery: results of a multicenter survey. Ann Intern Med. https://doi.org/10.7326/0003-4819-139-7-200310070-00007
24. Gordon HS, Street RL, Sharf BF et al (2006) Racial differences in trust and lung cancer patients' perceptions of physician communication. J Clin Oncol. https://doi.org/10.1200/JCO.2005.03.1955
25. Cykert S, Dilworth-Anderson P, Monroe MH et al (2010) Factors associated with decisions to undergo surgery among patients with newly diagnosed early-stage lung cancer. J Am Med Assoc. https://doi.org/10.1001/jama.2010.793
26. Habr-Gama A, Smith FM, Oliva Perez R et al (2015) Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy. Dis Colon Rectum. https://doi.org/10.1097/dcr.0000000000000281
27. Oh BY, Huh JW, Lee WY et al (2018) Are we predicting disease progress of the rectal cancer patients without surgery after neoadjuvant chemoradiotherapy? Cancer Res Treat. https://doi.org/10.4143/crt.2017.069
28. Abrams MJ, Koffer PP, Leonard KL (2016) The emerging non-operative management of non-metastatic rectal cancer: a population analysis. Anticancer Res 36:1699–1702
29. Cassidy RJ, Switchenko JM, Cheng E et al (2017) Health care disparities among octogenarians and nonagenarians with stage II and III rectal cancer. Cancer. https://doi.org/10.1002/cncr.30896
30. Lee DY, Teng A, Pedersen RC et al (2017) Racial and socioeconomic treatment disparities in adolescents and young adults with stage II–III rectal cancer. Ann Surg Oncol. https://doi.org/10.1245/s10434-016-5626-0

31. Smith JJ, Garcia-Aguilar J (2015) Advances and challenges in treatment of locally advanced rectal cancer. J Clin, Oncol
32. Stijns RCH, Tromp MSR, Hugen N, de Wilt JHW (2018) Advances in organ preserving strategies in rectal cancer patients. Eur J Surg, Oncol