Evidence Table
ARS Appropriate Use Criteria
Local Excision in Rectal Cancer

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. American Cancer Society. Cancer Facts and Figures 2018. *https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/colorectal-cancer-facts-and-figures/colorectal-cancer-facts-and-figures-2017-2019.pdf* 2018	Review/Other-Dx	N/A	Summarizes basic cancer facts and figures.	Third most common cancer in the U.S. are cancers of the colon and rectum, with an estimated 95,520 new cases of colon cancer and 39,910 cases of rectal cancer diagnosed in the US in 2017. Approximately 50,260 deaths occurred from colorectal cancer in 2017, although the colorectal cancer death rate is about half compared to 1975 due to declines in incidence and improvements in detection and treatment.	4
2. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg.* 1998;133(8):894-899	Observational-Tx	519 patients	A prospective consecutive case series to examine LF and CSS after TME.	Rectal cancer can be cured by surgical therapy alone in two-thirds of patients undergoing surgical excision in all stages and in four-fifths of patients having curative resections.	2
3. Martling A, Holm T, Rutqvist LE, et al. Impact of a surgical training programme on rectal cancer outcomes in Stockholm. *Br J Surg.* 2005;92(2):225-229.	Observational-Tx	447 patients	A prospective study of surgical management of colorectal cancer compared outcomes before and after a surgical training program was conducted in TME at a single hospital in Sweden.	The proportion of APR procedures and the LF rate decreased by more than 50% and there is already evidence of a decline in rectal-cancer mortality.	2
4. Wibe A, Syse A, Andersen E, et al. Oncological outcomes after total mesorectal excision for cure for cancer of the lower rectum: anterior vs. abdominoperineal resection. *Dis Colon Rectum.* 2004;47(1):48-58	Observational-Tx	2,136 patients with rectal cancer within 12 cm of the anal verge	To assess cancer outcomes for the lower rectum, particularly LR & OS treated by LAR or APR.	Inferior oncologic outcomes were associated with T4 tumors, R1 resections, and/or intraoperative perforation of the tumor or bowel wall, which are main features of low rectal cancers. If surgery is optimized to prevent intraoperative perforation and involvement of the circumferential resection margin, the prognosis for lower rectum cancers was found not to be different from more proximal tumors.	2
5. Baxter NN, Garcia-Aguilar J. Organ preservation for rectal cancer. *J Clin Oncol.* 2007;25(8):1014-1020.	Review/Other-Tx	N/A	Review of literature regarding selection criteria and outcomes for patients undergoing organ preservation surgery with or without adjuvant therapy	Strict selection criteria are essential when considering LE, and patients should be informed of the risk of LF.. The use of adjuvant therapy with LE, particularly in patients with T2 lesions, has promise	3
6. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. *Ann Surg.* 2007;245(5):726-733.	Observational-Tx	35,179 patients with stage I rectal cancer (1989-2003); Outcome focused special study for 2,124 patients (1994-1996)	To determine rates of LE over time, and test the hypothesis that LE carries increased oncologic risks but reduced perioperative morbidity when compared with standard resection.	From 1989 to 2003, the use of LE has increased (T1, 26.6% to43.7%; T2, 5.8% to 16.8%; P<0.001 both). Special study showed lower 30-day morbidity after LE vs standard resection (5.6% vs 14.6%; P<0.001). 5-year LR after LE vs standard resection was 12.5% vs 6.9% for T1 tumors, and 22.1% vs 15.1% for T2 tumors. The 5-year OS was influenced by age and comorbidities but not the type of surgery. Study provides the best evidence for both the increasing use and the associated risks of LE vs standard resection.	2
7. Landmann RG, Wong WD, Hoepfl J, et al. Limitations of early rectal cancer nodal staging may explain failure after local excision. *Dis Colon Rectum.* 2007;50(10):1520-1525	Observational-Tx	938 patients	A prospective national study examines the accuracy of ERUS in determining nodal stage based on depth of penetration of the primary lesion (T stage).	The overall accuracy of ERUS nodal staging for the study cohort was 70 %, with a 16 % false-positive rate and 14 % false-negative rate. ERUS was more likely to overlook small metastatic lymph node deposits, especially for earlier T-stage tumors.	2
8. Endreseth BH, Myrvold HE, Romundstad P, et al. Transanal excision vs. major surgery for T1 rectal cancer. *Dis Colon Rectum.* 2005;48(7):1380-1388	Observational-Tx	291 patients	An observational study to compare long-term results of T1 rectal cancer patients treated with either TAE or major surgery.	TAE had inferior results both in terms of OS and RFS, but patient groups were not comparable.	2

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9. Madbouly KM, Remzi FH, Erkek BA, et al. Recurrence after transanal excision of T1 rectal cancer: should we be concerned? *Dis Colon Rectum.* 2005;48(4):711-719; discussion 719-721	Observational-Tx	52 patients	A retrospective review of all T1 low risk rectal cancer patients treated with LE alone considering LF, distant metastasis, disease-free interval, results of salvage surgery, DFS and OS.	5-year recurrence: 29.4%. TAE has a high rate of recurrence. Although OS rates might be regarded as satisfactory, high recurrence and low salvage rates suggest that TAE might require adjuvant therapy.	3
10. Nash GM, Weiser MR, Guillem JG, et al. Long-term survival after transanal excision of T1 rectal cancer. *Dis Colon Rectum.* 2009;52(4):577-582	Observational-Tx	145 radical resections and 137 TAE	To compare oncologic outcomes of TAE with those of radical resection. Patients were identified from a prospective database.	LR was noted in a higher proportion of TAE patients (13.2% vs 2.7%, P=0.001). After TAE the HR for LR was 11.3%, and DSS was inferior (87% vs 96% at 5 years, P=0.03, HR 2.8 [range, 1.04-7.3]). TAE has inferior oncologic results, including greater risk of cancer-related death.	2
11. Paty PB, Nash GM, Baron P, et al. Long-term results of local excision for rectal cancer. *Ann Surg.* 2002;236(4):522-529; discussion 529-530	Observational-Tx	125 patients	A retrospective review of patients treated at a single hospital by LE as definitive surgery. 31 patients received adjuvant RT, and 15 of those received adjuvant chemotherapy as well.	10-year LR and OS were 17% and 74% for T1 rectal cancers and 26% and 72% for T2 cancers. Two-thirds of patients with tumor recurrence have LF, implicating inadequate resection in treatment failure. In this study, neither adjuvant RT nor salvage surgery was reliable in preventing or controlling LR. The postoperative interval to cancer death is as long as 10 years, raising concern that cancer mortality may be higher than generally appreciated.	3
12. Wentworth S, Russell GB, Tuner, II, et al. Long-term results of local excision with and without chemoradiation for adenocarcinoma of the rectum. *Clin Colorectal Cancer.* 2005;4(5):332-335.	Observational-Tx	285 patients	Review of patients undergoing curative resection for rectal cancer, either LE, APR or LAR. 12 patients received postoperative RT and 4 received adjuvant chemotherapy.	LE 5-year OS: 76%, 10- year OS: 42%, 5-year DFS: 69%, 10-year DFS: 58%. Adjuvant therapy did not affect OS or recurrence rates in patients undergoing LE compared with other surgeries. The rate of LF (16%) is comparable to that observed in the CALGB 8984 prospective study and suggests that highly selected patients undergoing LE can expect good local control of rectal cancer.	3
13. Nam MJ, Han KS, Kim BC, et al. Long-term outcomes of locally or radically resected T1 colorectal cancer. *Colorectal Dis.* 2016;18(9):852-860	Experimental-Tx	420 patients with T1 rectal cancer	To address the long-term outcome of locally or radically resected T1 rectal cancer	Over a median follow-up of 78.4 months, disease recurred in 16 (3.7%) patients in the high-risk group, and no recurrence in the low-risk group. Resection type and vascular invasion were significantly associated with recurrence. In the vascular invasion (+) high-risk group, both 5-year DFS rate and 5-year OS rate were significantly associated with resection type (radical 94.6%, local 43.8%, P < 0.001, and radical 99.1%, local 66.7%, P < 0.001). In the vascular invasion (-) high-risk group, 5-year DFS rate was also significantly associated with resection type (radical 98.9%, local 84.7%, P = 0.001). However, 5-year OS rate was not associated with resection type (radical 98.9%, local 95.2%, P = 0.816).	2
14. Benson AB, 3rd, Venook AP, Al-Hawary MM, et al. Rectal Cancer, Version 2.2018, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw.* 2018;16(7):874-901	Review/Other-Dx	N/A	National expert consensus guidelines for the diagnosis and treatment of rectal cancer	N/A	4
15. Garcia-Aguilar J, Renfro LA, Chow OS, et al. Organ preservation for clinical T2N0 distal rectal cancer using	Experimental-Tx	72 patients T2N0	A phase II trial to assess the efficacy and safety of neoadjuvant CRT and LE	34 patients achieved a pCR (44%) and 49 (64%) tumors were downstaged (ypT0-1), but 4 patients	2

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neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. *Lancet Oncol.* 2015;16(15):1537-1546			for T2N0 rectal cancer.	(5%) had ypT3 tumors. 5 LE specimens contained lymph nodes; one T3 tumor had a positive node. All but 1 patient had negative margins. The estimated 3-year DFS for the intention-to-treat group was 88·2% (95% CI 81·3-95·8), and for the per-protocol group was 86·9% (79·3-95·3). Of 79 eligible patients, 23 (29%) had grade 3 gastrointestinal adverse events, 12 (15%) had grade 3-4 pain, and 12 (15%) had grade 3-4 hematological adverse events during CRT. Of the 77 patients who had surgery, six (8%) had grade 3 pain, three (4%) had grade 3-4 hemorrhage, and three (4%) had gastrointestinal adverse events.	
16. Greenberg JA, Shibata D, Herndon JE, 2nd, Steele GD, Jr., Mayer R, Bleday R. Local excision of distal rectal cancer: an update of CALGB8984. *Dis Colon Rectum.* 2008;51(8):1185-1191; discussion 1191-1184	Experimental-Tx	59 patients with T1 lesions; 51 patients with T2 lesions	To examine the efficacy of LE in the treatment of early-stage distal rectal cancers.	10-year rates of OS were 84% for patients with T1 and 66% for T2 rectal cancer. DFS was 75% for T1 and 64 % for T2 disease. LR rates for patients with T1 and T2 lesions were 8% and 18%, respectively, and rates of distant metastases were 5% for T1 and 12% for T2 lesions. LE alone for T1 rectal adenocarcinomas is associated with low recurrence and good OS rates that remain durable with long- term follow-up. T2 lesions treated via LE and adjuvant therapy are associated with higher recurrence rates.	2
17. Russell AH, Harris J, Rosenberg PJ, et al. Anal sphincter conservation for patients with adenocarcinoma of the distal rectum: long-term results of radiation therapy oncology group protocol 89-02. *Int J Radiat Oncol Biol Phys.* 2000;46(2):313-322.	Experimental-Tx	65 patients	Phase II study to assess the outcome of a multi-institutional, national cooperative group study attempting functional preservation of the anorectum for patients with limited, distal rectal cancer.	With median follow-up of 6.1 years, 11 patients have failed. 5-year OS was 88%. Based on these results, the authors conclude that conservative, sphincter-sparing therapy is a feasible alternative treatment for selected patients with limited cancer involving the middle and lower rectum. Risk of both local and distant failure appears to escalate with increasing depth of tumor invasion.	2
18. Perez RO, Habr-Gama A, Sao Juliao GP, Proscurshim I, Scanavini Neto A, Gama-Rodrigues J. Transanal endoscopic microsurgery for residual rectal cancer after neoadjuvant chemoradiation therapy is associated with significant immediate pain and hospital readmission rates. *Dis Colon Rectum.* 2011;54(5):545-551	Observational-Tx	36 patients 23 patients with localized rectal cancer 13 patients with benign tumors	To compare the clinical outcomes of patients undergoing TEM with and without neoadjuvant CRT.	Overall, median hospital stay was 2 days. Immediate (30-day) complication rate was 44% for grade II/III complications. Patients undergoing neoadjuvant CRT were more likely to develop grade II/III immediate complications (56% vs 23%; P = .05). Overall, the 30-day readmission rate was 30%. Wound dehiscence was significantly more frequent among patients undergoing neoadjuvant CRT (70% vs 23%; P = .03). Patients undergoing neoadjuvant CRT were at significantly higher risk of requiring readmission (43% vs 7%; P = .02).	1
19. Ding PR, An X, Cao Y, et al. Depth of tumor invasion independently predicts lymph node metastasis in T2 rectal cancer. *J Gastrointest Surg.* 2011;15(1):130-136	Observational-Dx	346 consecutive pT2 rectal cancers	To identify risk factors of LNM for T2 rectal cancer.	Age, tumor location, pathological features, and depth of invasion were independent predictors for overall LNM. Tumor location, pathological features, and depth of invasion were independent predictors for intermediate/apical LNM. Tree analysis showed that the incidence of LNM was 7.7% for	2

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				upper rectal cancer with favorable pathological features, and 3.4% for mid/lower rectal cancer without other identified risk factors. The incidence of intermediate/apical LNM was 5.7% for superficial T2 rectal cancer with favorable pathological features, and 3.1% for deep T2 rectal cancer locating in upper rectum with favorable pathological features.	
20. Restivo A, Zorcolo L, Marongiu L, Scintu F, Casula G. Limits of endorectal ultrasound in tailoring treatment of patients with rectal cancer. *Dig Surg.* 2015;32(2):129-134.	Observational-Dx	220 patients	To evaluate how often an ERUS-based decision leads to an appropriate treatment.	Patients were staged with ERUS who underwent a surgical resection or a LE without neoadjuvant therapy from 1997 to 2012 were included. According to ERUS, patients were divided into three groups of indication: (a) LE (Tis-1 N0), (b) direct surgery (T2 N0), (c) preoperative CRT (T3-4 or N+). Accuracy was explored by the correlation established with the final pathology. Accuracy for T and N staging was 65 and 64%, respectively. Indication to LE and to CRT was correct in 97 and 88% of patients staged by ERUS. Accuracy of indication to direct surgery was poor (37%), and 21% of patients were overtreated in this group.	2
21. Zorcolo L, Fantola G, Cabras F, Marongiu L, D'Alia G, Casula G. Preoperative staging of patients with rectal tumors suitable for transanal endoscopic microsurgery (TEM): comparison of endorectal ultrasound and histopathologic findings. *Surg Endosc.* 2009;23(6):1384-1389.	Observational-Dx	81 patients	To assess the accuracy of ERUS.	81 patients (46 males, mean age 66 years) underwent TEM. Mean distance of the tumor from the anal verge was 6.6 cm (range 2-12 cm). ERUS staged 15/27 adenomas (55%) as uT1. Of 54 carcinomas, 5 were pT0 because TEM was performed to remove resection margins of a malign polyp already snared. 5/19 pTis (26%) were overstaged uT1, while 7/17 pT1 (41%) were understaged. Overall, ERUS enabled distinction between early and advanced rectal lesion with 96% sensitivity and 85% specificity, giving accuracy of 94% (65/67). 13 patients had advanced lesions (8 pT2 and 5 pT3). Only in 2 of them (15%) was depth of invasion underestimated by ERUS (one uT0, one uT1) and thus was subsequent salvage surgery necessary.	2
22. Stepansky A, Halevy A, Ziv Y. Preoperative staging using transrectal ultrasound in high and low rectal cancer. *Isr Med Assoc J.* 2010;12(5):270-272	Observational-Dx	95 patients	To determine the accuracy of transrectal ultrasound in the staging of rectal cancer.	60 patients underwent radical surgery. Of these, 34 received no preoperative chemo-irradiation owing to microT1, was suggested to patients with adenocarcinoma that proved to be microT3. The overall accuracy rate was 80% for T stage. Overstaging was found in 13.3% and understaging in 6.7%. The N-stage was correctly assessed in 70%. The overall accuracy rate for tumors was 73.9% in the lower part and 90.9% in the upper. A trend towards a lower accuracy rate for low-lying tumors compared to high-located rectal tumors was found (P=0.532), which did not	2

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				reach statistical significance.	
23. Santoro GA, Gizzi G, Pellegrini L, Battistella G, Di Falco G. The value of high-resolution three-dimensional endorectal ultrasonography in the management of submucosal invasive rectal tumors. *Dis Colon Rectum.* 2009;52(11):1837-1843.	Observational-Dx	126 patients	1) To evaluate the accuracy of high-resolution 3D ERUS in distinguishing slight from massive submucosal invasion of early rectal tumors, and 2) to determine the technology's role in treatment selection.	3D ERUS staged 77 lesions as uT0, 25 as uT1-slight, 20 as uT1-massive, and 4 as uT2. Histologically, adenomas were found in 75 patients and tumor invasion was found in 44 lesions (24 pT1-slight, 16 pT1-massive, 4 pT2). The overall kappa for the concordance between EUS and histopathologic staging was 0.81 (95% CI, 0.72-0.89). No invasive carcinomas remained undetected. The depth of invasion was correctly determined in 87.2% of both pT1-slight and pT1-massive lesions. Considering the complete series of 126 patients, the accuracy of this modality in selecting appropriate management was 95.2% (kappa, 0.84; 95% CI, 0.71-0.96). Adequate surgery was performed in 87.5% of pT1 tumors.	2
24. Ashraf S, Hompes R, Slater A, et al. A critical appraisal of endorectal ultrasound and transanal endoscopic microsurgery and decision-making in early rectal cancer. *Colorectal Dis.* 2012;14(7):821-826	Observational-Dx	494 patients 16 with TEM	To reports its accuracy and impact of ERUS staging for patients entered on the UK TEM database.	ERUS was performed in 165 of 494 patients who underwent TEM for rectal cancer. It inaccurately staged rectal cancer in 44.8% of tumors: 32.7% were understaged and 12.1% were overstaged. There was no significant difference in the depth of TEM excision or R1 rate between the patients who underwent ERUS before TEM and those who did not (P = 0.73)	3
25. Balyasnikova S, Brown G. Optimal Imaging Strategies for Rectal Cancer Staging and Ongoing Management. *Curr Treat Options Oncol.* 2016;17(6):32	Review/Other-Dx	N/A	Review of current literature describing optimal staging techniques for rectal cancer	Imaging determines the optimal treatment for rectal cancer patients. High-resolution MRI overcomes many of the known limitations of previous methods. When performed in accordance with the recommended standards, MRI enables accurate staging of both early and advanced rectal cancer, accurate response assessment, the delineation of recurrent disease and planning surgical treatment in a safe and effective manner. Tumor-related high-risk features with known adverse outcomes can be preoperatively identified and treated with neoadjuvant CRT. Further, MRI post-treatment tumor response assessment using TRG grading system also predicts the likely survival outcomes and in the future will be used to modify treatment further by stratification into good and poor responders. There is a paucity of literature with validated outcome data concerning use of diffusion-weighted imaging and PET/CT, and in the absence of any validated methods and outcome data, their use in the initial assessment and restaging after treatment is limited to research protocols. Combination MRI and CT is essential for distant spread assessment and recurrent disease, and currently PET-CT is sometimes used for workup of patients with recurrent and metastatic disease.	3

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26. An C, Huh H, Han KH, et al. Use of Preoperative MRI to Select Candidates for Local Excision of MRI-Staged T1 and T2 Rectal Cancer: Can MRI Select Patients With N0 Tumors? *Dis Colon Rectum.* 2015;58(10):923-930	Observational-Dx	246 patients	To develop a set of criteria using preoperative MRI that would minimize the false-negative rate for the diagnosis of regional LMN.	MRI features significantly associated with LMN were identified using a χ test. 5 diagnostic criteria for LMN were created based on these predictive MRI features, and their false-negative rates were compared using the generalized estimating equation method. Small size/homogeneity of lymph nodes and no visible tumor/partially involved muscular layer were significantly associated with lower risks of LMN. When tumor invasion depth was not considered, the false-negative rate did not decrease below 10%, even when the strictest criterion for morphologic evaluation of lymph nodes (not visible or <3 mm) was used. Adding invasion depth to the diagnostic criteria significantly decreased the false-negative rate as low as 1.8%.	3
27. Bipat S, Glas AS, Slors FJ, Zwinderman AH, Bossuyt PM, Stoker J. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging--a meta-analysis. *Radiology.* 2004;232(3):773-783.	Review/Other-Dx	99 studies	To perform a meta-analysis to compare EUS, CT, and MRI in rectal cancer staging.	For muscularis propria invasion, US and MR imaging had similar sensitivities; specificity of US (86% [95% CI: 80, 90]) was significantly higher than that of MR imaging (69% [95% CI: 52, 82]) (P =.02). For perirectal tissue invasion, sensitivity of US (90% [95% CI: 88, 92]) was significantly higher than that of CT (79% [95% CI: 74, 84]) (P <.001) and MR imaging (82% [95% CI: 74, 87]) (P =.003); specificities were comparable. For adjacent organ invasion and lymph node involvement, estimates for EUS, CT, and MR imaging were comparable. Summary ROC curve for US of perirectal tissue invasion showed better diagnostic accuracy than that of CT and MR imaging. Summary ROC curves for lymph node involvement showed no differences in accuracy.	2
28. Op de Beeck B, Smeets P, Penninckx F, et al. Accuracy of pre-treatment locoregional rectal cancer staging in a national improvement project. *Acta Chir Belg.* 2017;117(2):104-109	Observational-Dx	1,168 patients	To assess the accuracy, particularly the predictive value, of locoregional clinical rectal cancer staging (cTN) and its variability in a national improvement project.	TN stages and the distance between tumor and MRF were compared with histopathological findings. Agreement between clinical and histopathological TN stages was 50%, independent of tumor location. Inter-hospital variability was within 99% prediction limits. MRI was increasingly applied, but staging accuracy did not improve. Stage II-III was correctly predicted in 69% and pStage I was over-staged in 35%. The positive predictive value of ERUS for T1 lesions was 57%. MRI-based distances to MRF correlated poorly with the circumferential resection margin (r = 0.26). A negative resection margin was achieved in 91% when the distance to the MRF was >1 mm.	2
29. Clancy C, Burke JP, Albert MR, O'Connell PR, Winter DC. Transanal endoscopic microsurgery versus standard transanal excision for the removal of rectal neoplasms: a systematic review and meta-analysis. *Dis Colon Rectum.* 2015;58(2):254-261.	Review/Other-Dx	927 local excisions	A meta-analysis to compare TEM with transanal LE	Six comparative series comparing outcomes following 927 local excisions were identified. There was no difference between techniques in postoperative complication rate (OR, 1.018; 95% CI, 0.658-1.575; p = 0.937). TEM had a higher rate of	2

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				negative microscopic margins in comparison with LE (OR, 5.281; 95% CI, 3.201-8.712; p < 0.001). TEM had a reduced rate of specimen fragmentation (OR, 0.096; 95% CI, 0.044-0.209; p < 0.001) and lesion recurrence (OR, 0.248; 95% CI, 0.154-0.401; p < 0.001) compared with LE. There was no across-study heterogeneity for any end point	
30. Hompes R, Ashraf SQ, Gosselink MP, et al. Evaluation of quality of life and function at 1 year after transanal endoscopic microsurgery. *Colorectal Dis.* 2015;17(2):O54-61	Experimental-Tx	102 patients	To evaluate the changes over time in anorectal function, urinary symptoms and QoL in patients who had TEM surgery for a rectal tumor.	A consecutive series of 102 patients underwent TEM at a single institution. Patients were asked to fill out standardized questionnaires at baseline and then at 6, 12, 26 and 52 weeks after surgery. The QoL among these patients was assessed using one generic (EQ-5D) and two disease-specific [European Organization for Research and Treatment of Cancer QLQ-C30 and QLQ-CR29 questionnaires. Anorectal and urinary symptoms were studied using the COlo-REctal Functional Outcome (COREFO) and the International Prostate Symptom Score (I-PSS) questionnaires, respectively. The response rate was 90% (92/102 patients). Postoperative complications occurred in 14% (13/92) of patients. The general QoL (as assessed using the EQ-5D) was lower 6 and 12 weeks after TEM compared with baseline QoL (P < 0.05) but returned towards baseline after 26 weeks.Anorectal function (determined using the COREFO) was worse 6 weeks postoperatively (P < 0.01) but had normalized by 12 weeks. Urinary function (determined using the I-PSS) was not affected at any time point after surgery. The total COREFO score and the American Society of Anesthesiologists (ASA) score were correlated with the deterioration in QoL.The study demonstrates that TEM has a temporary and reversible impact on QoL and anorectal function.	2
31. Christoforidis D, Cho HM, Dixon MR, Mellgren AF, Madoff RD, Finne CO. Transanal endoscopic microsurgery versus conventional transanal excision for patients with early rectal cancer. *Ann Surg.* 2009;249(5):776-782	Observational-Tx	42 TEM and 129 TAE patients	Retrospectively review information on all patients with stage pT1 and PT2 rectal adenocarcinoma to compare TEM with conventional TAE in terms of the quality of resection, LR, and survival.	In the TAE group, 52 (40%) of tumors were <5 cm from the anal verge; in the TEM group, 1 (2%). Surgical margins were less often positive in the TEM group (2%) than in the TAE group (16%). For patients with tumors ≥5 cm from the anal verge, the estimated 5- year DFS rate was similar between the TEM group (84.1%) and the TAE group (76.1%) (P=0.651). But within the TAE group, the estimated 5-year DFS rate was better for patients with tumors ≥5 cm from the anal verge (76.1%) vs <5 cm from the anal verge (60.5%) (P=0.029). In multivariate analysis, the tumor distance from the anal verge, the resection margin status, the T stage, and the use of adjuvant therapy were independent	3

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				predictors of LR and DFS. Quality of resection is better with TEM than with TAE.	
32. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. *Br J Surg.* 2012;99(9):1211-1218	Observational-Tx	100 patients T2N0 50 LE 50 laparoscopic TME	Prospective randomized study to compare the oncologic results for LE via TEM and those for laparoscopic resection via TME in the treatment of T2N0, G1-2 rectal cancer after neoadjuvant therapy with both treatments, using a 5-year minimum follow-up period.	50 patients in each group were analyzed. Overall tumor downstaging and downsizing rates after neoadjuvant CRT were 51 and 26 per cent respectively, and were similar in both groups. All patients had R0 resection with tumor-free resection margins. At long-term follow-up, LR had developed in four patients (8%) after endoluminal locoregional resection and three (6%) after TME. Distant metastases were observed in two patients (4%) in each group. There was no statistically significant difference in DFS (P = 0·686).	1
33. Lezoche E, Guerrieri M, Paganini AM, Baldarelli M, De Sanctis A, Lezoche G. Long-term results in patients with T2-3 N0 distal rectal cancer undergoing radiotherapy before transanal endoscopic microsurgery. *Br J Surg.* 2005;92(12):1546-1552.	Observational-Tx	100 patients with uT2-3 rectal cancer	To evaluate the results of LE in patients with small (less than 3 cm in diameter) T2 and T3 distal rectal tumours following neoadjuvant therapy.	Definitive histological examination revealed nine pT1, 54 pT2 and 19 pT3 tumors. A complete response (R0) or microscopic residual tumor (R1mic) was found in three and 15 patients respectively. Minor complications occurred in 11 patients and major complications in two. At a median follow-up of 55 (range 7-120) months, the LF rate was 5% and metastatic disease was found in two patients. The CSS rate at 90 months' follow-up was 89%, and the OS rate 72 %. Salvage APR was performed in three patients, two of whom were disease free at 15 and 19 months.	2
34. Marks JH, Valsdottir EB, DeNittis A, et al. Transanal endoscopic microsurgery for the treatment of rectal cancer: comparison of wound complication rates with and without neoadjuvant radiation therapy. *Surg Endosc.* 2009;23(5):1081-1087	Experimental-Tx	62 patients	Compare morbidity rates and wound complication rates for patients undergoing TEM and LE with and without neoadjuvant radiation to determine whether this could be accomplished safely. Data for all patients undergoing TEM are prospectively entered into a database.	Overall morbidity rate was 33% for the neoadjuvant therapy with radiation group and 5.3% for the non-neoadjuvant therapy with radiation group. The wound complication rates were 25.6% for the neoadjuvant therapy with radiation group (11 patients) and 0% for the non-neoadjuvant therapy with radiation group (P=0.015). 9 patients in the neoadjuvant therapy with radiation group (82%) had minor wound separations, and 2 patients (18%) had major wound separation. 10 patients with wound separations were treated as outpatients and administered long-term oral antibiotics. 1 patient required additional surgery (diverting stoma).	1
35. Stijns RCH, de Graaf EJR, Punt CJA, et al. Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer: The CARTS Study. *JAMA Surg.* 2018	Experimental-Tx	55 patients with cT1-3N0M0 rectal cancer	A phase II multicenter study to explore long-term oncological outcomes and health-related quality of life in patients with cT1-3N0M0 rectal cancer who underwent neoadjuvant CRT followed by TEM	The primary study outcome of the study was the number of ypT0-1 specimens by performing TEM. Secondary outcome parameters were locoregional recurrences and HRQOL. Of the 55 included patients, 30 (55%) were male, and the mean (SD) age was 64 (39-82) years. Patients were followed up for a median (interquartile range) period of 53 (39-57) months. Two patients (4%) died during CRT, 1 (2%) stopped CRT, and 1 (2%) was lost to follow-up. Following CRT, 47 patients (85%) underwent TEM,	2

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				of whom 35 (74%) were successfully treated with LE alone. TME was performed in 16 patients (4 with inadequate responses, 8 with completion after TEM, and 4 with salvage for LR. The actuarial 5-year LR rate was 7.7%, with 5-year disease-free and OS rates of 81.6% and 82.8%, respectively. Health-related quality of life during follow-up was equal to baseline, with improved emotional well-being in patients treated with LE (mean score at baseline, 72.0; 95% CI, 67.1-80.1; mean score at follow-up, 86.9; 95% CI, 79.2-94.7; P = .001). Major, minor, and no low anterior resection syndrome was experienced in 50%, 28%, and 22%, respectively, of patients with successful organ preservation.	
36. Brunner W, Widmann B, Marti L, Tarantino I, Schmied BM, Warschkow R. Predictors for regional lymph node metastasis in T1 rectal cancer: a population-based SEER analysis. *Surg Endosc.* 2016;30(10):4405-4415	Observational-Dx	1,592 patients with radical resection for T1 rectal cancer	To identify cT1 rectal cancer patients at risk of regional LMN	In all patients minimum of 12 retrieved regional lymph nodes were identified. The overall LNM rate was 16.3 % (N = 260). A low risk of LNM was observed for small tumor size (P = 0.002), low tumor grade (P = 0.002) and higher age (P = 0.012) in multivariable analysis. The OR for a tumor size exceeding 1.5 cm was 1.49 [95 % CI 1.06-2.13], for G2 and G3/G4 carcinomas 1.69 (95 % CI 1.07-2.82) and 2.72 (95 % CI 1.50-5.03), and for 65- to 79-year-old and over 80-year-old patients 0.65 (95 % CI 0.43-0.96) and 0.39 (95 % CI 0.18-0.77), respectively. 5-year CSS for patients with LNM was 90.0 % (95 % CI 85.3-95.0 %) and for patients without LNM 97.1 % (95 % CI 95.9-98.2 %, hazard ratio = 3.21, 95 % CI 1.82-5.69, P < 0.001).	2
37. Kobayashi H, Mochizuki H, Kato T, et al. Is total mesorectal excision always necessary for T1-T2 lower rectal cancer? *Ann Surg Oncol.* 2010;17(4):973-980	Observational-Dx	567 patients	To clarify the determinants of LE for patients with T1-T2 lower rectal cancer.	The independent risk factors for LNM were female gender, depth of tumor invasion, histology other than well-differentiated adenocarcinoma, and lymphatic invasion. According to the first 3 parameters that can be obtained preoperatively, only 0.99% of the patients without risk factors had LNM. On the other hand, even if the lower rectal cancer was at stage T1, women with histological types other than well-differentiated adenocarcinoma had an approximately 30% probability of having LNM. Lymphatic invasion was most useful to predict nodal involvement among patients with T2 lower rectal cancer. The rates of LNM in T2 patients with and without lymphatic invasion were 32.9% and 9.1%, respectively.	3
38. Nascimbeni R, Burgart LJ, Nivatvongs S, Larson DR. Risk of lymph node metastasis in T1 carcinoma of the colon and rectum. *Dis Colon Rectum.* 2002;45(2):200-206.	Review/Other-Dx	7,543 patients reviewed, 353 patients met criteria	A review of clinical records of patients with sessile T1 colorectal cancer to identify risk factors for LNM	Only patients with sessile T1 lesions who underwent colorectal resection were included in the study, yielding an analysis cohort of 353 patients. The following carcinoma-related variables were assessed: size, mucinous subtype, carcinomatous component, grade, site in colon and rectum, LVI,	3

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				and depth of submucosal invasion. For the depth, the submucosa was divided into upper third (sm1), middle third (sm2), and lower third (sm3). Chi-squared tests and logistic regression were used to evaluate the variables as potential risk factors for LMN. The incidence of T1 lesions was 8.6 %. In the analysis cohort, the LMN rate was 13 percent. Significant predictors of LMN both univariately and multivariately were sm3 (P = 0.001), LVI (P = 0.005), and lesions in the lower third of the rectum (P = 0.007). Poorly differentiated carcinoma was significant univariately (P = 0.001) but not in the multivariate model. No other parameter was associated with a significant risk. T1 colorectal carcinomas with LVI, sm3 depth of invasion, and location in the lower 1/3 of the rectum have a high risk of LNM.	
39. Rackley TP, Ma RM, Brown CJ, Hay JH. Transanal Local Excision for Patients With Rectal Cancer: Can Radiation Compensate for What Is Perceived as a Nondefinitive Surgical Approach? *Dis Colon Rectum.*2016;59(3):173-17	Review/Other-Dx	93 patients with T1, T2 and T3 rectal cancer	To report oncological outcomes of patients with rectal cancer treated with LE and adjuvant radiation.	5-year OS, local control, and PFS for patients treated with LE and adjuvant RT were 78.5%, 86.1%, and 83.8%. In T1 disease, local control was 92.5%.	3
40. Chakravarti A, Compton CC, Shellito PC, et al. Long-term follow-up of patients with rectal cancer managed by local excision with and without adjuvant irradiation. *Ann Surg.* 1999;230(1):49-54	Observational-Tx	99 patients	A retrospective study to compare long-term outcomes for patients treated with either: LE alone; or LE + adjuvant pelvic irradiation.	After 5-years: local control was 76% for LE alone, and 90% for LE + adjuvant pelvic irradiation. RFS was 66% for LE alone, and 74% for LE + adjuvant pelvic irradiation.	2
41. Borschitz T, Heintz A, Junginger T. Transanal endoscopic microsurgical excision of pT2 rectal cancer: results and possible indications. *Dis Colon Rectum.* 2007;50(3):292-301	Observational-Tx	44 patients	To determine the value of LE for T2 rectal carcinomas, prognostic factors, and the need for reoperation.	LR rates after local R0 resection alone of low-risk T2 carcinomas were 29%, whereas patients with unfavorable criteria developed recurrences in 50%. After immediate reoperation, the LR risk in patients without lymph node filiae was reduced to 7%.	2
42. Folkesson J, Johansson R, Pahlman L, Gunnarsson U. Population-based study of local surgery for rectal cancer. *Br J Surg.* 2007;94(11):1421-1426	Observational-Tx	10,181 patients; 643 had a LE	To determine long-term survival and recurrence rates after LE of rectal cancer from a prospectively registered population-based database.	5-year CSS for 256 patients with stage I disease who had LE was 95.3%. The 5-year LR rate was 7.2%. After adjustment for age, sex, tumor stage and preoperative RT, the relative risk of death from cancer was the same as that after major resection.	2
43. Garcia-Aguilar J, Mellgren A, Sirivongs P, Buie D, Madoff RD, Rothenberger DA. Local excision of rectal cancer without adjuvant therapy: a word of caution. *Ann Surg.* 2000;231(3):345-351	Observational-Dx	82 patients with T1 (n = 55) and T2 (n = 27) rectal cancer	Retrospective study to evaluate the results of LE alone for the treatment of rectal cancer, applying strict selection criteria.	Ten of the 55 patients with T1 tumors (18%) and 10 of the 27 patients with T2 tumors (37%) had recurrence at 54 months of follow-up. Average time to recurrence was 18 months in both groups. Seventeen of the 20 patients with LR underwent salvage surgery. The OS rate was 98% for patients with T1 tumors and 89% for patients with T2 tumors. Preoperative staging by ERUS did not influence LR or CSS.	3
44. Lezoche E, Baldarelli M, De Sanctis A, Lezoche G, Guerrieri M. Early rectal cancer: definition and management. *Dig Dis.* 2007;25(1):76-79	Observational-Tx	135 patients 24 with pT0 66 with pT1 45 with pT2	To analyze the results of patients with early stage low rectal cancer treated with LE by TEM.	Minor complications were observed in 12 patients (8.8%) whereas major complications were seen only in 2 patients (1.5%). At a median follow-up of 78 (36-125) months, LRs occurred in 4 patients and	2

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				distal metastasis in 2 patients (all patients were staged preoperatively T2). DFS rates in T1 and T2 patients were 100 and 93% respectively.	
45. Min BS, Kim NK, Ko YT, et al. Long-term oncologic results of patients with distal rectal cancer treated by local excision with or without adjuvant treatment. *Int J Colorectal Dis.* 2007;22(11):1325-1330	Observational-Tx	76 patients with rectal cancer; 3 cases of uT0, 55 cases of uT1 and 18 cases of uT2	To review long-term oncologic results of LE and to investigate the validity and feasibility of LE as a treatment option for distal rectal cancer.	Preoperative transrectal EUS revealed 3 cases of uT0, 55 cases of uT1 and 18 cases of uT2. Postoperative pathologic examination revealed 10 cases of pT0 (where no residual cancer cells remained), 11 cases of pTis, 37 cases of pT1, 16 cases of pT2, and 2 cases of pT3. Eleven out of 37 patients with pT1 tumors received adjuvant RT. Among 16 patients with pT2 tumor, 7 undertook salvage operation and 8 received adjuvant therapy. The median follow-up period was 84.9 months. LR was observed in six patients. The 5-year LRFS was 89.4% in the pT1 group and 75.0% in the pT2 group (p = 0.012). Among the patients with pT1 cancer, those who received adjuvant RT demonstrated a 5-year LFS 100%, compared to those who did not, 76.0% (p = 0.038).	3
46. Lezoche G, Guerrieri M, Baldarelli M, et al. Transanal endoscopic microsurgery for 135 patients with small nonadvanced low rectal cancer (iT1-iT2, iN0): short- and long-term results. *Surg Endosc.* 2011;25(4):1222-1229	Observational-Tx	135 patients 24 with pT0 66 with pT1 45 with pT2	To analyze the short- and long-term results for a series of 135 patients with small nonadvanced low rectal cancer who underwent LE by TEM.	Minor complications were observed in 12 patients (8.8%) and major complications in 2 patients (1.5%). During a median follow-up period of 97 months (range, 55-139 months), LRs occurred for 4 patients and distant metastases for 2 patients. The patients who experienced a recurrence had been preoperatively staged as iT2 and were low or nonresponders to neoadjuvant treatment (ypT2). At the end of the follow-up period, the DFS rates were 100% for iT1 patients and 93% for iT2 patients.	2
47. Ramirez JM, Aguilella V, Valencia J, et al. Transanal endoscopic microsurgery for rectal cancer. Long-term oncologic results. *Int J Colorectal Dis.* 2011;26(4):437-443	Observational-Tx	88 patients	To analyze survival and recurrence of patients with rectal cancer who were operated by TEM with curative intention.	After definitive histological findings, 54 patients were to group A, 28 to group B, and 6 had immediate radical surgery. 1 patient was lost for follow-up. At a mean follow-up of 71 months, 7 (4 from group A and 3 from group B) out of 81 patients recurred. 5-year OS was of 94% and cancer-specific survival of 96%.	2
48. Bach SP, Hill J, Monson JR, et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. *Br J Surg.* 2009;96(3):280-290	Observational-Tx	487 patients	To examine a predictive model for local recurrence after TEM. A national database, collated prospectively from 21 regional centers, detailed TEM treatment in patients with rectal cancer.	Postoperative morbidity and mortality were 14.9% and 1.4% respectively. The Cox regression model predicted LR with a concordance index of 0.76 using age, depth of tumor invasion, tumor diameter, LVI, poor differentiation and conversion to radical surgery after histopathological examination of the specimen.	2
49. Peng J, Chen W, Venook AP, et al. Long-term outcome of early-stage rectal cancer undergoing standard resection and local excision. *Clin Colorectal Cancer.* 2011;10(1):37-41	Observational-Tx	350 patients	To explore the long-term outcome and prognostic factors for early stage rectal cancer patients undergoing standard resection or LE.	The 5-year LR rate was 14.1% in LE group vs 3.3% in standard resection group (P= .0004), and the 10-year OS rate was not significantly different between the 2 groups. Multivariate analysis suggested that LE was an independent risk factor for 5-year local recurrence rate and 10-year OS rate. Tumor grade was found related to 5-year LR, and T stage was found related to 10-year OS. Tumor size of 2.5 cm is	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				found as a possible cut-off for predicting 5-year LR rate in LE group, with a sensitivity of 77.8% and a specificity of 75.9%. In patients with LE, the 5-year LR rate for tumors ≥2.5 cm was 40%, compared with 4.3% for tumors <2.5 cm (P=.001).	
50. Morino M, Allaix ME, Caldart M, Scozzari G, Arezzo A. Risk factors for recurrence after transanal endoscopic microsurgery for rectal malignant neoplasm. *Surg Endosc.* 2011;25(11):3683-3690	Observational-Dx	355 patients	A prospective database was analyzed with the intent to identify risk factors for recurrence after TEM.	Among 355 patients subjected to TEM, 107 had an adenocarcinoma: 48 pT1, 43 pT2, and 16 pT3. Comparing pre- and postoperative data, histological discrepancy was 20% and staging discrepancy was 34%. 0% mortality, morbidity was 9%. Mean follow-up was 54.2 months (range = 12-164), follow-up rate was 100%. The 5-year DFS rate was 85.9%, 78.4%, and 49.4% for pT1, pT2, and pT3, respectively (P=0.006). Recurrence rate was 0% (0/26) in pT1sm1 cancers and 22.7% (5/22) in sm2-3 (P<0.05). A submucosal infiltration was a significant risk factor for recurrences: 0% sm1, 16.7% sm2, and 30% sm3. Recurrence in pT2 was 0% in patients who had neoadjuvant therapy and 26% in the others. At univariate analysis, diameter, sm3 stage, pT stage, tumor grading, margin infiltration, and LVI demonstrated statistical significance. Multivariate analysis indicated sm3 stage, pT stage, and tumor grading as independent predictors of recurrence.	2
51. Peng J, Chen W, Sheng W, et al. Oncological outcome of T1 rectal cancer undergoing standard resection and local excision. *Colorectal Dis.* 2011;13(2):e14-19	Observational-Dx	567 patients	To clarify the determinants of LE for patients with T1-T2 lower rectal cancer.	The independent risk factors for LNM were female gender, depth of tumor invasion, histology other than well-differentiated adenocarcinoma, and lymphatic invasion. According to the first 3 parameters that can be obtained preoperatively, only 0.99% of the patients without risk factors had LNM. On the other hand, even if the lower rectal cancer was at stage T1, women with histological types other than well-differentiated adenocarcinoma had an approximately 30% probability of having LNM. Lymphatic invasion was most useful to predict nodal involvement among patients with T2 lower rectal cancer. The rates of LNM in T2 patients with and without LVI were 32.9% and 9.1%, respectively.	3
52. Rasheed S, Bowley DM, Aziz O, et al. Can depth of tumour invasion predict lymph node positivity in patients undergoing resection for early rectal cancer? A comparative study between T1 and T2 cancers. *Colorectal Dis.* 2008;10(3):231-238.	Observational-Dx	303 patients	Retrospective study to examine the risk of LNM according to the depth of tumor invasion in patients undergoing resection for rectal cancer.	The incidence of LNM in the T1 group was 12.7% (7/55), compared to 19% (47/247) in the T2 group. The node positive and negative groups were similar with regard to patient demographics, although the former contained a significantly higher number of poorly differentiated (P=0.001) and extramural vascular invasion tumors (P=0.002). No significant difference in the number of patients with sm1-3, or T2 tumor depths within the lymph node positive and negative groups. On multivariate analysis the presence of extramural LVI (OR = 10.0) and tumor	3

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				grade (OR for poorly vs well-differentiated = 11.7) were independent predictors of LNM.	
53. Han SL, Zeng QQ, Shen X, Zheng XF, Guo SC, Yan JY. The indication and surgical results of local excision following radiotherapy for low rectal cancer. *Colorectal Dis.* 2010;12(11):1094-1098.	Observational-Tx	83 patients	To evaluate the outcome of LE followed by adjuvant RT for rectal cancer for curative purposes.	The procedures of LE were TAE in 83 patients, trans-sacral resection in 16, trans-sphincteric LE in 5, and trans-vaginal resection in 3. The overall DFS rate was 80.4% (86/107), including 90.0% (54/60) for T1 and 72.3% (34/47) for T2 tumors, respectively. 82/107 patients underwent adjuvant postoperative RT after LE, and 25 did not, and the DFS rates between radiation and nonradiation group were significantly different for T2 [81.6% (31/38) vs 33.3% (3/9), P<0.05], but not for T1 tumors (90.9%vs 87.5%, P>0.05). The rates of LR and distant metastasis were 13.1% (14/107) and 4.7% (5/106), respectively, and the median time to relapse was 15 months (range: 10-53) for local recurrence and 30 months (21-65) for distant recurrence. The risk factors for LR were large tumor (≥3 cm), poorly differentiated adenocarcinoma and T2 tumor.	3
54. O'Neill CH, Platz J, Moore JS, Callas PW, Cataldo PA. Transanal Endoscopic Microsurgery for Early Rectal Cancer: A Single-Center Experience. *Dis Colon Rectum.* 2017;60(2):152-160.	Observational-Tx	92 patients T1-2, N0M0	A chart review of early stage rectal cancer patients treated with TEM to determine lesion characteristics, as well as operative and treatment characteristics. Complications and recurrences were recorded.	Median follow-up was 4.6 years. Negative margins were obtained in 98.9%. Length of stay was 1 day for 95.4% of patients. The complication rate was 10.9% (n = 10), including urinary retention at 4.3% (n = 4) and postoperative bleeding at 4.3% (n = 4). Preoperative staging included 54 at T1 (58.7%) and 38 at T2 (41.3%). Adjuvant therapy was recommended for all of the T2 and select T1 lesions with adverse features on histology. The final pathologic stages of tumors were ypT0 at 8.7% (n = 8), pT1 at 58.7% (n = 54), pT2 at 23.9% (n = 22), and ypT2 at 8.7% (n = 8). The 3-year LR risk was 2.4% (SE = 1.7), and overall recurrence was 6.7% (SE = 2.9). There were no recurrences among patients with pCR to neoadjuvant therapy. Mean time to recurrence was 2.5 years (SD = 1.43). A total of 89.2% of patients with very low tumors underwent curative resection without a permanent stoma (33/37). The 3-year DSS rate was 98.6% (95% CI, 90.4%-99.8%), and OS rate was 89.4% (95% CI, 79.9%-94.6%).	3
55. Jeong JU, Nam TK, Kim HR, et al. Adjuvant chemoradiotherapy instead of revision radical resection after local excision for high-risk early rectal cancer. *Radiat Oncol.* 2016;11(1):114	Experimental-Tx	83 patients with high risk pT1 or T2 rectal cancer	To evaluate the efficacy of adjuvant concurrent CRT for reducing recurrence after LE in these patients.	Patients with high-risk pT1 or pT2 rectal cancer underwent postoperative adjuvant concurrent CRT after LE. They authors defined high-risk features as pT1 having tumor size ≤3 cm, and/or resection margin (RM) ≤3 mm, and/or LVI , and/or non-full thickness excision such as endoscopic mucosal resection (EMR) or endoscopic submucosal dissection, or unknown records regarding those features, or pT2 cancer. RT was administered with a	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				median dose of 50.4 Gy in 1.8 Gy fraction size over 5-7 weeks. Concurrent 5-FU and leucovorin were administered for 4 days in the first and fifth weeks of RT. The median interval between LE and RT was 34 (range, 11-104) days. Fifteen patients (18.1 %) had stage pT2 tumors, 22 (26.5 %) had RM of ≥3 mm, and 21 (25.3 %) had tumors of ≥3 cm in size. Thirteen patients (15.7 %) had LVI. TAE was performed in 58 patients (69.9 %) and 25 patients (30.1 %) underwent EMR or ESD. The median follow-up was 61 months. The 5-year OS, LRFS, and DFS rates for all patients were 94.9, 91.0, and 89.8 %, respectively. Multivariate analysis did not identify any significant factors for OS or LRFS, but the only significant factor affecting DFS was the pT stage (p = 0.027).	
56. Sasaki T, Ito Y, Ohue M, et al. Postoperative Chemoradiotherapy After Local Resection for High-Risk T1 to T2 Low Rectal Cancer: Results of a Single-Arm, Multi-Institutional, Phase II Clinical Trial. *Dis Colon Rectum.* 2017;60(9):914-921.	Experimental-Tx	57 patients	A prospective single arm phase II trial to determine the efficacy of CR combined with LE in the treatment of T1 to T2 low rectal cancer.	Patients were treated with LE after additional external beam irradiation (45 Gy) plus continuous 5-week intravenous injection of 5-FU (250 mg/m per day) at 10 domestic hospitals. Fifty-three patients had clinical T1N0 lesions, and 4 had T2N0 lesions in the low rectum, located below the peritoneal reflection. The completion rate for full-dose CRT was 86% (49/57). Serious, nontransient treatment-related complications were not reported. With a median follow-up of 7.3 years after LE, the 5-year DFS rate was 94% for the 53 patients with T1 lesions and 75% for the 4 patients with T2 lesions. There were 2 LRs during the entire observation period. Anal function after LE and CRT were kept at almost the same levels as observed before treatment. The study was limited by the small number of registered T2 rectal cancers, retrospective evaluations of quality of life, and the exclusion of poorly differentiated adenocarcinoma (a high-risk feature of T1 lesions).	3
57. Cutting JE, Hallam SE, Thomas MG, Messenger DE. A systematic review of local excision followed by adjuvant therapy in early rectal cancer: are pT1 tumours the limit? *Colorectal Dis.* 2018;20(10):854-863.	Review/Other-Dx	22 studies; 804 patients	A systematic search focusing on LE with adjuvant therapy for adenocarcinoma of the rectum. Primary outcome measures were LF, OS and morbidity. Studies providing neoadjuvant therapy or LE alone were excluded.	Indications for LE included favorable histology, patient choice and comorbidities. T1, T2 and T3 tumors accounted for 35.1%, 58.0% and 6.9% of cases, respectively. TAE was used in 77.7%. Adjuvant therapy included long-course CRT or RT. Median follow-up was 51 months (range 1-165). The pooled LF was 5.8% (95% CI 3.0-9.5) for pT1, 13.8% (95% CI 10.1-17.9) for pT2 and 33.7% (95% CI 19.2-50.1) for pT3 tumors. The overall median DFS was 88% (range 50%-100%) with a pooled overall morbidity of 15.1% (95% CI 11.0-18.7).	2
58. Lee L, Kelly J, Nassif GJ, et al. Chemoradiation and Local Excision for T2N0 Rectal Cancer Offers Equivalent Overall Survival Compared to Standard Resection: a	Review/Other-Dx	4,822 patients T2N0M0 rectal cancer undergoing LE with neoadjuvant	Analysis of data from a national data base to compare combined CRT and LE versus RS for T2 rectal cancer.	Mean follow-up was 48.6 (SD28.5) months. There were no differences in patient characteristics, but more high-risk features in the LE + Adj-CRT group.	2

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National Cancer Database Analysis. *J Gastrointest Surg.* 2017;21(10):1666-1674		CRT (242) or adjuvant CRT (213) or radical surgery (4,367)		There were no differences in 90-day mortality. 5-year OS was similar (RS 77.4% vs. CRT + LE 76.1% vs. LE + Adj-CRT 79.7%, p = 0.786). Older age, male gender, and higher Charlson score were independently associated with worse OS, whereas treatment type was not. If 90-day mortality was excluded, LE + Adj-CRT was independently associated with worse OS compared to RS.	
59. Borstlap WA, Coeymans TJ, Tanis PJ, et al. Meta-analysis of oncological outcomes after local excision of pT1-2 rectal cancer requiring adjuvant (chemo)radiotherapy or completion surgery. *Br J Surg.* 2016;103(9):1105-1116	Review/Other-Dx	14 studies=-405 patients treated with adjuvant CRT and 7 studies -130 patient treated with completion TME	Systematic review and meta-analysis to determine oncological outcomes of adjuvant CRT as a rectum-preserving alternative to completion TME.	Owing to heterogeneity it was not possible to compare the two strategies directly. However, the weighted average LR rate for locally excised pT1/pT2 rectal cancer treated with adjuvant CRT was 14 (95 % CI 11 to 18) %, and 7 (4 to 14)% %following completion TME. The weighted averages for distance recurrence were 9 (6 to 14) and 9 (5 to 16) % respectively. Weighted averages for LF rate after adjuvant CRT and completion TME for pT1 were 10 (4 to 21) and 6 (3 to 15) % respectively. Corresponding averages for pT2 were 15 (11 to 21) and 10 (4 to 22)% respectively.	2
60. Guerrieri M, Baldarelli M, Organetti L, et al. Transanal endoscopic microsurgery for the treatment of selected patients with distal rectal cancer: 15 years experience. *Surg Endosc.* 2008;22(9):2030-2035	Observational-Tx	196 patients	Authors report their experience with TEM used to manage selected cases of distal rectal cancer without evidence of nodal or distant metastasis (N0M0).	CSS rate at the end of the follow-up period was 100% for pT1, 90% for pT2, and 77% for pT3 patients. Patients with T1 cancer and favorable histologic features may undergo LE alone, whereas those with T2 and T3 rectal cancer require preoperative CRT.	2
61. Guerrieri M, Gesuita R, Ghiselli R, Lezoche G, Budassi A, Baldarelli M. Treatment of rectal cancer by transanal endoscopic microsurgery: experience with 425 patients. *World J Gastroenterol.* 2014;20(28):9556-9563.	Observational-Tx	425 patients with rectal cancer (120 T1, 185 T2, 120 T3 lesions)	To describe a single institution experience in treating rectal cancer by TEM report morbidity and mortality and oncological outcome.	Patients staged by digital rectal examination, rectoscopy, transanal EUS, MRI and/or CT. Patients with T1-N0 lesions and favorable histological features underwent TEM immediately. Patients with preoperative stage T2-T3-N0 underwent preoperative high-dose RT; from 1997 those aged less than 70 years and in good general health also underwent preoperative chemotherapy. Patients with T2-T3-N0 lesions were restaged 30 d after RT and were then operated on 40-50 d after neoadjuvant therapy. There were neither perioperative mortality nor intraoperative complications. Conversion to other surgical procedures was never required. Major complications (urethral lesions, perianal or retroperitoneal phlegmon and rectovaginal fistula) occurred in six (1.4%) patients and minor complications (partial suture line dehiscence, stool incontinence and rectal haemorrhage) in 42 (9.9%). Postoperative pain was minimal. Definitive histological examination of the 425 malignant lesions showed 80 (18.8%) pT0, 153 (36%) pT1, 151 (35.5%) pT2, and 41 (9.6%) pT3 lesions. Eighteen (4.2%) patients (ten pT2 and eight pT3) had a LR and 16 (3.8%) had distant	2

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Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				metastasis. CSS rates at end of follow-up were 100% for pT1 patients (253 m), 93% for pT2 patients (255 m) and 89% for pT3 patients (239 m).	
62. Kundel Y, Brenner R, Purim O, et al. Is local excision after complete pathological response to neoadjuvant chemoradiation for rectal cancer an acceptable treatment option? *Dis Colon Rectum.* 2010;53(12):1624-1631	Observational-Tx	320 patients	To evaluate the correlation between pathological T and N stages following neoadjuvant CRT for locally advanced rectal cancer and the outcome of patients with mural pCR undergoing LE.	After CRT, 93% patients had radical surgery, 6% had LE, and 3% did not have surgery. In the 291 patients undergoing RS, the pathological T stage correlated with the N stage (P=.036). We compared the outcome of patients with mural pCR (n = 37) who underwent RS (group I) and those (n = 14) who had LE only (group II). With a median follow-up of 48 months, 4 patients in group I had a recurrence and none in group II had a recurrence; 1 patient died in group I and none died in group II. DFS, pelvic RFS, and OS rates were similar in both groups.	3
63. Perez RO, Habr-Gama A, Sao Juliao GP, et al. Transanal local excision for distal rectal cancer and incomplete response to neoadjuvant chemoradiation - does baseline staging matter? *Dis Colon Rectum.* 2014;57(11):1253-1259	Observational-Tx	36 patients	To compare the clinical outcomes of patients undergoing TEM with and without neoadjuvant CRT.	Overall, median hospital stay was 2 days. Immediate (30-d) complication rate was 44% for grade II/III complications. Patients undergoing neoadjuvant CRT therapy were more likely to develop grade II/III immediate complications (56% vs 23%; P=.05). Overall, the 30-day readmission rate was 30%. Wound dehiscence was significantly more frequent among patients undergoing neoadjuvant CRT therapy (70% vs 23%; P=.03). Patients undergoing neoadjuvant CRT therapy were at significantly higher risk of requiring readmission (43% vs 7%; P=.02).	2
64. Shin YS, Yoon YS, Lim SB, et al. Preoperative chemoradiotherapy followed by local excision in clinical T2N0 rectal cancer. *Radiat Oncol J.* 2016;34(3):177-185.	Experimental-Tx	34 patients	Retrospective study to investigate whether preoperative CRT followed by LE is feasible approach in clinical T2N0 rectal cancer patients.	All patients received TAE or transanal minimally invasive surgery. Of 34 patients, 19 patients (55.9%) presented pCR. The 3-year LRFS and DFS were 100.0% and 97.1%, respectively. There was no recurrence among the patients with pCR. Except for 1 case of grade 4 enterovesical fistula, all other late complications were mild and self-limiting.	2
65. Wawok P, Polkowski W, Richter P, et al. Preoperative radiotherapy and local excision of rectal cancer: Long-term results of a randomised study. *Radiother Oncol.* 2018;127(3):396-403	Experimental-Tx	51 analyzable patients 29 short course RT 22 long course CRT	Randomized phase III study to investigate the optimal preoperative dose/fractionation schedule prior to LE for patients with cT1-2N0M0 or borderline cT2/T3N0M0 < 4 cm rectal adenocarcinomas	YpT0-1R0 was observed in 66% of patients in the short-course group and in 86% in the CRT group, p = 0.11. Completion TME was performed only in 46% of patients with ypT1R1/ypT2-3. The median follow-up was 8.7 years. LF incidences and OS at 10 years were respectively for the short-course group vs. the CRT group 35% vs. 5%, p = 0.036 and 47% vs. 86%, p = 0.009. In total, LR at 10 years was 79% for ypT1R1/T2-3 without TME. This trial suggests that in the LE setting, both LR and OS are worse after short-course RT than after CRT.	1
66. Belluco C, De Paoli A, Canzonieri V, et al. Long-term outcome of patients with complete pathologic response after neoadjuvant chemoradiation for cT3 rectal cancer:	Observational-Tx	139 patients	To analyze long-term outcome of cT3 rectal cancer treated by neoadjuvant CRT therapy in relation to pCR and type of surgery.	Tumors of 42 patients (30.2%) were classified as complete pathologic response. After a median follow-up of 55.4 months, comparing patients with	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
implications for local excision surgical strategies. *Ann Surg Oncol.* 2011;18(13):3686-3693.				pCR to patients with no pCR, 5-year DSS was 95.8% vs 78.0% (P=0.004), and 5-year DFS was 90.1% vs 64.0% (P=0.004). In patients with pCR, no statistically significant outcome difference was observed between TME and LE. In patients treated by LE, comparing patients with pCR to patients with no pCR, 5-year DFS was 100% vs 65.5% (P=0.024), and 5- year local RFS was 92.9% vs 66.7% (P=0.047).	
67. Belluco C, Forlin M, Olivieri M, et al. Long-Term Outcome of Rectal Cancer With Clinically (EUS/MRI) Metastatic Mesorectal Lymph Nodes Treated by Neoadjuvant Chemoradiation: Role of Organ Preservation Strategies in Relation to Pathologic Response. *Ann Surg Oncol.* 2016;23(13):4302-4309	Observational-Tx	226 patients with cN+ locally advanced rectal cancer who underwent CRT followed by surgery including TME(n = 179) and full-thickness LE (LE) (n = 47). At staging, 123 patients (54.4 %) were cN+.	To explore the value of organ preservation for patients achieving a pCR at the primary tumor site following neoadjuvant CRT for patients with locally advanced rectal cancer with cN+ disease	Tumors with mesorectal lymph nodes larger than 5 mm shown on EUS, pelvic MRI, or both were staged as cN+. Following neoadjuvant therapy mesorectal lymph nodes (ypN+) were detected in 41.6 % of the cN+ patients and in 2.8 % of the cN0 patients (P < 0.01). Among the cN+ patients, 16 % of the ypT0 cases were ypN+ compared with 51.8 % of the no-ypT0 cases (P < 0.01). Among the cN+ patients who underwent TME, the 5-year DSS and DFS rates were respectively 100 and 91.6 % for the ypT0 patients compared with 71.2 and 58.0 % for the no-ypT0 patients (P = 0.01). Among the ypN+ patients, the 5-year DSS and DFS rates were both 100 % for the ypT0 cases compared with 59.1 and 43.3 % for the no-ypT0 patients. Among the cN+ and ypT0 patients, the 5-year DSS and DFS were respectively 100 and 85.7 % for the TME patients compared with 100 and 91.6 % for the LE patients. In the multivariate analysis, ypT0 was the only independent prognostic factor.	2
68. Rizzo G, Zaccone G, Magnocavallo M, et al. Transanal endoscopic microsurgery after neoadjuvant radiochemotherapy for locally advanced extraperitoneal rectal cancer. *Eur J Surg Oncol.* 2017;43(8):1488-1493.	Observational-Tx	36 patients treated with TEM after neoadjuvant CRT	To provide a prospective analysis of post-operative and oncological outcomes in patients affected by locally advanced rectal cancer, who obtained a major/complete clinical response after pre-operative CRT and were treated with LE by TEM to confirm a pCR after to neo-adjuvant CRT	The median post-operative hospital stay was 5 days. The post-operative morbidity was 41.6% (no grade ≥3). At pathological analysis, 23 specimens were ypT0 TRG1, and 4 were ypT1 TRG2. In 9 cases (ypT>1 and/or TRG>2), RS with TME was proposed but 3 refused it. Median follow-up was 68 months. One LR and 4 distant metastases occurred. The 5-yr actuarial local control, OS and DFS were 96.0%, 92.0% and 82.8%.	2
69. Lynn PB, Renfro LA, Carrero XW, et al. Anorectal Function and Quality of Life in Patients With Early Stage Rectal Cancer Treated With Chemoradiation and Local Excision. *Dis Colon Rectum.* 2017;60(5):459-468.	Observational-Tx	(98%) evaluated at enrollment and 66 (92%) at 1 year.	To prospectively assess anorectal function and HRQOL of patients with T2N0 rectal cancer who were treated with an alternative approach using data from patients treated on ACOSOG Z6041	Compared with baseline, no significant differences were found on Fecal Incontinence Severity Index scores at 1 year. Fecal Incontinence QoL results were significantly worse in the lifestyle (p < 0.001), coping/behavior (p < 0.001), and embarrassment (p = 0.002) domains. There were no differences in the Functional Assessment of Cancer Therapy overall score, but the physical well-being subscale was significantly worse and emotional well-being was improved after surgery. Treatment with the original CRT regimen predicted worse depression/self-	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				perception and embarrassment scores in the Fecal Incontinence QoL, and male sex was predictive of worse scores in the Functional Assessment of Cancer Therapy overall score and trial outcome index. Small sample size, relatively short follow-up, and absence of information before cancer diagnosis were study limitations. CRT followed by LE had minimal impact on anorectal function 1 year after surgery. Overall QoL remained stable, with mixed effects on different subscales.	
70. Rullier E, Rouanet P, Tuech JJ, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. *Lancet.* 2017;390(10093):469-479	Experimental-Tx	186 patients with T2T3 lower rectal carcinoma, of maximum size 4 cm	A prospective, randomized, open-label, multicenter, phase III trial to compare LE and TME in patients with a good response after CRT for lower rectal cancer.	Patients with good clinical response to neoadjuvant CRT (residual tumor ≤2 cm) were centrally randomly assigned by the surgeon before surgery to either LE or TME surgery. In the LE group, a completion TME was required if tumor stage was ypT2-3. All patients received CRT . 148 good clinical responders were randomly assigned to treatment, three were excluded (because they had metastatic disease, tumor >8 cm from anal verge, and withdrew consent), and 145 were analyzed: 74 in the LE group and 71 in the TME group. In the LE group, 26 patients had a completion TME. At 2 years in the modified ITT population, one or more events from the composite primary outcome occurred in 41 (56%) of 73 patients in the LE group and 33 (48%) of 69 in the TME group (OR 1·33, 95% CI 0·62-2·86; p=0·43). In the modified ITT analysis, there was no difference between the groups in all components of the composite outcome, and superiority was not shown for LE over TME.	1
71. Hallam S, Messenger DE, Thomas MG. A Systematic Review of Local Excision After Neoadjuvant Therapy for Rectal Cancer: Are ypT0 Tumors the Limit? *Dis Colon Rectum.* 2016;59(10):984-99	Review/Other-Dx	22 studies (14 cohort, 5 comparative cohort, and 1 randomized controlled trial), describing 1068 patients	A systematic literature review to determine the oncological outcomes and morbidity of LE after neoadjuvant therapy.	Pretreatment T2 and T3 tumors accounted for 46.4% and 30.7% of cases. Long-course treatment was administered in all of the studies, except to a cohort of 64 patients who received short-course RT. Pooled complete clinical response was 45.8% (95% CI, 31.4%-60.5%), and pooled complete pathological response was 44.2% (95% CI, 36.4%-52.0%). Median follow-up was 54 months (range, 12-81 months). ypT0 tumors had a pooled LR rate of 4.0% (95% CI, 1.9%-6.9%) and a median DFS rate of 95.0% (95% CI, 87.4%-100%). Pooled LF and median DFS rates for ypT1 tumors or higher were 21.9% (95% CI, 15.9%-28.5%) and 68.0% (58.3%-69.0%). Pooled incidence of complications was 23.2% (95% CI, 15.7%-31.7%), with suture-line dehiscence reported in 9.9% (95% CI, 4.8%-16.7%).	2
72. Verseveld M, de Graaf EJ, Verhoef C, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). *Br J Surg.* 2015;102(7):853-	Experimental-Tx	55 patients cT1 N0 (10) cT2 N0 (29) cT3 N0 (16)	A prospective multicenter study was performed to quantify the number of patients with minimal residual disease (ypT0-1) after neoadjuvant CRT and TEM for rectal cancer.	Patients with clinically staged T1-3 N0 distal rectal cancer were treated with long-course CRT. Clinical response was evaluated 6-8 weeks later and TEM performed. TME was advocated in patients with	2

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860				residual disease (ypT2 or more). CRT-related complications of at least grade 3 occurred in 23 of 55 patients, with two deaths from toxicity, and two patients did not have TEM or major surgery. Among 47 patients who had TEM, ypT0-1 disease was found in 30, ypT0 N1 in one, ypT2 in 15 and ypT3 in one. LR developed in three of the nine patients with ypT2 tumors who declined further surgery. Postoperative complications grade I-IIIb occurred in 13 of 47 patients after TEM and in 5 of 12 after (completion) surgery. After a median follow-up of 17 months, four LRs had developed overall, 3 in patients with ypT2 and 3 with ypT1	
73. Park IJ, You YN, Agarwal A, et al. Neoadjuvant treatment response as an early response indicator for patients with rectal cancer. *J Clin Oncol.* 2012;30(15):1770-1776	Observational-Tx	725 patients	To assess and compare oncologic outcomes associated with the degree of pathologic response after CRT.	In all, 725 patients were classified by tumor response: complete (131; 18.1%), intermediate (210; 29.0%), and poor (384; 53.0%). Age, sex, cN stage, and tumor location were not related to tumor response. Tumor response (complete vs intermediate vs poor) was associated with 5-year RFS (90.5% vs 78.7% vs 58.5%; P<.001), 5-year distant metastasis rates (7.0% vs 10.1% vs 26.5%; P<.001), and 5-year LR only rates (0% vs 1.4% vs 4.4%; P=.002).	3
74. Engelen SM, Beets-Tan RG, Lahaye MJ, et al. MRI after chemoradiotherapy of rectal cancer: a useful tool to select patients for local excision. *Dis Colon Rectum.* 2010;53(7):979-986.	Observational-Dx	79 patients	To determine whether post CRT MRI in rectal cancer can accurately identify ypT0 to 2/ypN0, because both features are essential for identification of good responders.	79 patients (4 hospitals) underwent post-CRT MRI, 62 received a lymph node-specific contrast agent (ultrasmall superparamagnetic iron oxide). For prediction of whether a tumor penetrated the bowel wall, there was a negative predictive value of 0.90 and 0.76 for the expert and general radiologist, respectively. The negative predictive value for prediction of nodal status was 0.95 and 0.85 for expert and general radiologist, respectively.	3
75. Memon S, Lynch AC, Bressel M, Wise AG, Heriot AG. Systematic review and meta-analysis of the accuracy of MRI and endorectal ultrasound in the restaging and response assessment of rectal cancer following neoadjuvant therapy. *Colorectal Dis.* 2015;17(9):748-761.	Review/Other-Dx	63 articles	Systematic review and meta-analysis of the accuracy of MRI and ERUS in the restaging and response assessment of rectal cancer following neoadjuvant therapy	63 articles were included in the systematic review. 12 restaging MRI studies and 18 restaging ERUS studies were eligible for meta-analysis of T-stage restaging accuracy. Overall, ERUS T-stage restaging accuracy (mean [95% CI]: 65% [56-72%]) was nonsignificantly higher than MRI T-stage accuracy (52% [44-59%]). Restaging MRI is accurate at excluding circumferential resection margin involvement. Restaging MRI and ERUS were equivalent for prediction of nodal status: the accuracy of both investigations was 72% with over-staging and under-staging occurring in 10-15%.The heterogeneity amongst restaging studies is high, limiting conclusive findings regarding their accuracies. The accuracy of restaging imaging is different for different pathological T stages and highest for T3 tumors. Morphological assessment of	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				T- or N-stage by MRI or ERUS is currently not accurate or consistent enough for clinical application. Restaging MRI appears to have a role in excluding circumferential resection margin involvement.	
76. Park JS, Jang YJ, Choi GS, et al. Accuracy of preoperative MRI in predicting pathology stage in rectal cancers: node-for-node matched histopathology validation of MRI features. *Dis Colon Rectum.* 2014;57(1):32-38.	Observational-Dx	341 lymph nodes analyzed	A prospective observational cohort study to determine whether preoperative MRI could detect LMN accurately in the node-by-node analysis.	Specimens were assessed using MRI for clinical staging. After surgical resection of the tumor, the specimens were again imaged with ex vivo ultrasound scan to localize the perirectal node. The locations of each lymph node were precisely matched with its corresponding MRI to enable a node-for-node comparison of MRI and histologic findings. Agreement between MRI and histologic assessment of T stage was 82.5%. Of the 341 nodes harvested, 120 were too small (<3 mm) to be depicted on magnetic resonance images, and 18 of these contained metastasis (15%). A correlation between the results of MRI and histopathology was feasible for 205 lymph nodes, and the overall success rate of matching between the 2 techniques was 91.1% (205 of 221). Preoperative MRI revealed a node-by-node sensitivity and positive predictive value of 58.0%, and 61.7%. There was no difference in the diagnostic accuracy between the primary surgery subgroup and preoperative RT subgroups. The study is limited by its heterogeneity of cohorts including the subgroup with preoperative CRT and the lack of preoperative EUS assessment.	2
77. Kang JH, Kim YC, Kim H, et al. Tumor volume changes assessed by three-dimensional magnetic resonance volumetry in rectal cancer patients after preoperative chemoradiation: the impact of the volume reduction ratio on the prediction of pathologic complete response. *Int J Radiat Oncol Biol Phys.* 2010;76(4):1018-1025	Observational-Dx	84 patients	To determine the correlation between tumor volume changes assessed by 3D MRI volumetry and the histopathologic tumor response in rectal cancer patients undergoing preoperative CRT.	There were no significant differences in the post-treatment tumor volume and the volume reduction ratio shown by 3D MRI volumetry with respect to T and N downstaging and the TRG. In a multivariate analysis, the tumor volume reduction ratio was not significantly associated with T and N downstaging. The volume reduction ratio (>75%, P=0.01) and the pretreatment CEA level (≤3 ng/ml, P=0.01), but not the post-treatment volume shown by 3D MRI (≤5 ml), were significantly associated with increased pCR rate.	2
78. van der Sande ME, Beets GL, Hupkens BJ, et al. Response assessment after (chemo)radiotherapy for rectal cancer: Why are we missing complete responses with MRI and endoscopy? *Eur J Surg Oncol.* 2018.	Observational-Dx	36 patient with unrecognized pCR after neoadjuvant CRT who underwent restaging MRI	To evaluate what features on restaging MRI and endoscopy led to a false clinical diagnosis of residual tumor in patients with a pCR after rectal cancer surgery.	An unrecognized complete response was defined as a clinical incomplete response at MRI and/or endoscopy with a pCR of the primary tumor after surgery. The morphology of the tumor bed and the lymph nodes were evaluated on post-CRT T2-weighted MRI (T2-MRI) and diffusion weighted imaging (DWI). Post-CRT endoscopy images were evaluated for residual mucosal abnormalities. MRI and endoscopy features were correlated with	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				histopathology. 36 patients with an unrecognized pCR were included. Mucosal abnormalities were present at restaging endoscopy in 84%, mixed signal intensity on T2-MRI in 53%, an irregular aspect of the former tumor location on T2-MRI in 69%, diffusion restriction on DWI in 51% and suspicious lymph nodes in 25%. Overstaging of residual tumour after (chemo)radiotherapy in rectal cancer is mainly due to residual mucosal abnormalities at endoscopy, mixed signal intensity or irregular fibrosis at T2-MRI, diffusion restriction at DWI and residual suspicious lymph nodes.	
79. Stitzenberg KB, Sanoff HK, Penn DC, Meyers MO, Tepper JE. Practice patterns and long-term survival for early-stage rectal cancer. *J Clin Oncol.* 2013;31(34):4276-4282	Review/Other-Dx	201,764 patients	A NCDB study to examine practice patterns and OS for early-stage rectal cancer.	LE was used to treat 46.5% of patients with T1 and 16.8% with T2 tumors. Use of LE increased steadily over time (P < .001). LE was most commonly used for women, black patients, very old patients, those without private health insurance, those with well-differentiated tumors, and those with T1 tumors. Proctectomy was associated with higher rates of tumor-free surgical margins compared with LE (95% v 76%; P < .001). Adjuvant RT use decreased over time independent of surgical procedure or T stage. For T2N0 disease, patients treated with LE alone had significantly poorer adjusted OS than those treated with proctectomy alone or multimodality therapy. Guideline-concordant adoption of LE for treatment of low-risk stage I rectal cancer is increasing. However, use of LE is also increasing for higher-risk rectal cancers that do not meet guideline criteria for LE. Treatment with LE alone is associated with poorer long-term OS.	2
80. Sajid MS, Farag S, Leung P, Sains P, Miles WF, Baig MK. Systematic review and meta-analysis of published trials comparing the effectiveness of transanal endoscopic microsurgery and radical resection in the management of early rectal cancer. *Colorectal Dis.* 2014;16(1):2-14.	Review/Other-Tx	10 trials including 942 patients with T1-2 rectal cancer	A systematic review and meta-analysis of trials reporting the effectiveness of TEM and RS in the treatment of T1 and T2 rectal cancer	10 trials including 942 patients were retrieved. There was a trend toward a higher risk of LR (OR 2.78; 95% CI 1.42, 5.44; z = 2.97; P < 0.003) and overall recurrence (P < 0.01) following TEM compared with RS. The risk of distant recurrence, OS (OR 0.90; 95% CI 0.49, 1.66; z = 0.33; P = 0.74) and mortality was similar. TEM was associated with a shorter operation time and hospital stay and a reduced risk of postoperative complications (P < 0.0001). The included studies, however, were significantly diverse in stage and grade of rectal cancer and the use of neoadjuvant CRT. Transanal endoscopic microsurgery appears to have clinically measurable advantages in patients with early rectal cancer.	2
81. Lu JY, Lin GL, Qiu HZ, Xiao Y, Wu B, Zhou JL. Comparison of Transanal Endoscopic Microsurgery and Total Mesorectal Excision in the Treatment of T1 Rectal Cancer: A Meta-Analysis. *PLoS One*.	Review/Other-Tx	1 randomized controlled trial and 6 non-randomized controlled trials including	A systematic review and meta-analysis of trials to compare the efficacy of TEM and TME for the treatment of T1 rectal cancer.	Analysis revealed that all 7 studies reported LR rates, and there was a significant difference between the TEM and TME groups [OR = 4.62, 95% CI (2.03, 10.53), P = 0.0003]. A total of 5 studies	2

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2015;10(10):e0141427.		Total 860 T1 rectal cancers: 303 TEM and 557 TME		reported distant metastasis rates, and there was no significant difference between the TEM and TME groups [OR = 0.74, 95%CI (0.32, 1.72), P = 0.49]. A total of 6 studies reported postoperative OS of the patients, and there was no significant difference between the TEM and TME groups [OR = 0.87, 95%CI(0.55, 1.38), P = 0.55]. In addition, 2 studies reported the postoperative DFS rates of patients, and there was no significant difference between the TEM and TME groups [OR = 1.12, 95%CI (0.31, 4.12), P = 0.86]. For patients with T1 rectal cancer, the distant metastasis, overall survival and disease-free survival rates did not differ between the TEM and TME groups, although the local recurrence rate after TEM was higher than that after TME.	
82. Chen YY, Liu ZH, Zhu K, Shi PD, Yin L. Transanal endoscopic microsurgery versus laparoscopic lower anterior resection for the treatment of T1-2 rectal cancers. *Hepatogastroenterology.* 2013;60(124):727-732.	Experimental-Tx	60 T1-2N0 rectal cancer patients 30 LE 30 LAR	To compare the surgical and oncological effectiveness as well as safety of TEMS and LAR in T1-2 rectal cancer patients.	T1-2N0 rectal cancer patients were prospectively and randomly assigned to LE using TEMS (n=30) or radical resection using LAR (n=30). The operative duration of TEMS was significantly shorter than that of LAR (130.3±16.7 minutes vs. 198.7±16.8 minutes, p<0.01). The TEMS group restarted bowel movement significantly earlier than the LAR group (51.4±5.4h vs. 86.2±8.7h, p<0.01). The postoperative complications were mild and self-limited in the 2 groups. LR occurred in 2 T2 patients (2/28, 7.1%) at 8 months and 16 months following TEMS, respectively; no patient (0/30, 0%) developed LR following LAR.	2
83. Winde G, Nottberg H, Keller R, Schmid KW, Bunte H. Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection. *Dis Colon Rectum.* 1996;39(9):969-976.3	Experimental-Tx	50 patients stage uT1N0 rectal cancer 24 TEM 26 Anterior resection	A prospective randomized trial to compare LE for early rectal carcinomas using TEM or anterior resection.	Patients' ages and rectal tumor locations showed insignificant differences of distribution in comparison of TEM with AR (Welsh's alternate t-test; t-test). LR (4.2 %) and 5-year OSrates (96 %) differed insignificantly (log-rank test). Early postoperative mortality was zero. Significant differences were found comparing time of hospitalization, loss of blood, operation time, and opiate analgesia (Welsh's alternate t-test; Wilcoxon's test; each P < 0.05). Early and late morbidity differed considerably. Lower morbidity, similar LR, and OS rates favor TEM.	1
84. Shaikh I, Askari A, Ouru S, Warusavitarne J, Athanasiou T, Faiz O. Oncological outcomes of local excision compared with radical surgery after neoadjuvant chemoradiotherapy for rectal cancer: a systematic review and meta-analysis. *Int J Colorectal Dis.* 2015;30(1):19-29	Review/Other-Dx	8 studies	A systematic review and meta-analysis to determine whether differences exist in LR, OS and DFS between patients treated with CRT + LE and CRT + RS.	Eight studies were suitable for pooled analyses of LR whereas 5 and 4 studies were analyzed for OS and DFS, respectively. When RS was used as the reference group, LR rate was higher in the LE group. However, this was non-significant (OR1.29, CI 0.72-2.31, p = 0.40). Similarly, no difference was observed in 10-year OS (OR 0.96, CI 0.38-2.43, p = 0.93) or 5-year DFS (OR 1.04, CI 0.61-1.76, p = 0.89). There was evidence of publication bias in studies used for DFS. Subgroup analysis of above outcomes in T3/any N stage cancers showed no	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				difference in LE versus RS. In the current evidence synthesis, there was no statistical difference in the LR, OS and DFS rates observed between patients treated with LE and RS for rectal cancer post-CRT.	
85. Kidane B, Chadi SA, Kanters S, Colquhoun PH, Ott MC. Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis. *Dis Colon Rectum.* 2015;58(1):122-140.	Review/Other-Dx	1 randomized controlled trial and 12 observational studies 2,855 patients	A systematic review and meta-analysis to compare LE with RS in terms of oncologic control (OS and LR), postoperative complications, and the need for a permanent stoma in adult patients with T1N0M0 rectal adenocarcinoma.	The randomized controlled trial was inadequately powered. Observational study meta-analysis showed that LE was associated with significantly lower 5-year OS (72 more deaths per 1000 patients; 95% CI 30-120). However, the TEM subgroup did not yield significantly lower OS than radical resection. LE was associated with higher LR but with lower perioperative mortality (relative risk 0.31, 95% CI 0.14-0.71), major postoperative complications (relative risk 0.20, 95% CI 0.10-0.41), and need for a permanent stoma (relative risk 0.17, 95% CI 0.09-0.30). Findings were robust to sensitivity analyses. Meta-regression suggests that the higher OS associated with radical resection may be explained by increased use of LE on tumors in the lower third of the rectum, which have poorer prognosis. LE does not offer oncologic control comparable to RS. However, this finding may be driven by the higher prevalence of cancers with poorer prognosis in LE groups. LE is associated with lower postoperative complications, mortality, and the need for a permanent stoma. LE with TEM appears to offer oncologic control similar to that of radical resection while offering all the benefits of LE.	2
86. Veereman G, Vlayen J, Robays J, et al. Systematic review and meta-analysis of local resection or transanal endoscopic microsurgery versus radical resection in stage i rectal cancer: A real standard? *Crit Rev Oncol Hematol.* 2017;114:43-52	Review/Other-Dx	2 meta-analyses and 1 randomized trial	A systematic review and meta-analysis to review the evidence on endoscopic approach vs. radical resection for stage I rectal cancer.	Randomized controlled trials provide no evidence on the superiority of local vs. radical resection for stage I rectal cancer (T1-T2, N0) regarding OS and DFS. The available data on OS after 1 and 5 years show no difference. Based on observational studies alone, no conclusion can be reached regarding the primary outcomes. The evidence on LR and distant metastases is of very low quality and allows no conclusion	2
87. Xu ZS, Cheng H, Xiao Y, et al. Comparison of transanal endoscopic microsurgery with or without neoadjuvant therapy and standard total mesorectal excision in the treatment of clinical T2 low rectal cancer: a meta-analysis. *Oncotarget.* 2017;8(70):115681-115690	Review/Other-Dx	1 randomized controlled and 3 non randomized controlled trials ; 121 patients with TEM 59 with neoCRT+TEM 62 with TEM alone 174 TME	A systematic review and meta-analysis to evaluate the oncological outcomes of TEM with or without NT comparing with conventional total TME for the treatment of clinical T2 rectal cancer	Compared with TME, there were no significant differences in the outcomes of LR overall recurrence, OS between TEM + neoCRT group. However in compassion with TME, TEM without neoCRT was associated with an increased LF, overall recurrence, and a shorter OS, with individual ORs being 3.04 (95% CI: 1.17-7.90; I2 = 0%), 5.67 (95% CI: 1.58-20.38; I2 = 0%) and 0.12 (95% CI: 0.02-0.65; I2 = 0%), respectively. Compared with TME, TEM after neoCRT may be a feasible and safe organ preservative approach for patients with clinical T2 low rectal cancer. But for those without neoCRT, TEM always seem be associated with worse	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				oncological outcomes.	
88. Serra-Aracil X, Pericay C, Golda T, et al. Non-inferiority multicenter prospective randomized controlled study of rectal cancer T2-T3s (superficial) N0, M0 undergoing neoadjuvant treatment and local excision (TEM) vs total mesorectal excision (TME). *Int J Colorectal Dis.* 2018;33(2):241-249	Experimental-Tx	To include 173 patients with rectal cancer less than 10 cm from the anal verge and up to 4 cm in size, staged as T2 or T3-superficial N0-M0.	To describe an ongoing multicenter randomized controlled trial to demonstrate the preservation of the rectum after preoperative CRT and TEM in rectal cancer stages T2-3s, N0, M0 and to determine the ability of this strategy to avoid the need for RS (TME). Patients will be randomized to two areas: CRT plus TEM or RS (TME). Postoperative morbidity and mortality will be recorded and patients will complete the quality of life questionnaires before the start of treatment, after CRT in the CRT/TEM arm, and 6 months after surgery in both arms. The estimated sample size for the study is 173 patients. Patients will attend follow-up controls for local and systemic relapse.	Pending	4
89. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann Surg.* 2004;240(4):711-717; discussion 717-718	Experimental-Tx	265 patients with distal rectal cancer	To overall long-term results of stage 0 rectal cancer following neoadjuvant CRT and compare long-term results between operative and nonoperative treatment.	OS and DFS rates at 10-year were 97.7% and 84%. In 71 patients (26.8%) CCR was observed following CRT (Observation group). 22 patients (8.3%) showed incomplete clinical response and pT0N0M0 resected specimens (Resection group). There were no differences between patient's demographics and tumor's characteristics between groups. In the Resection group, 9 definitive colostomies and 7 diverting temporary ileostomies were performed. Mean follow-up was 57.3 months in Observation Group and 48 months in Resection Group. There were 3 systemic recurrences in each group and 2 LRs in Observation Group. Two patients in the Resection group died of the disease. Five-year OS and DFS rates were 88% and 83%, respectively, in Resection Group and 100% and 92% in Observation Group.	2
90. Habr-Gama A, Sao Juliao GP, Vailati BB, et al. Organ Preservation in cT2N0 Rectal Cancer After Neoadjuvant Chemoradiation Therapy: The Impact of Radiation Therapy Dose-escalation and Consolidation Chemotherapy. *Ann Surg.* 2019;269(1):102-107	Experimental-Tx	T2N0 rectal cancer 35 patients 50.4 Gy + 5-FU and 46 patients 54 Gy + 5-FU CRT	To demonstrate the difference in organ-preservation rates and avoidance of definitive surgery among cT2N0 rectal cancer patients undergoing 2 different CRT regimens.	Patients undergoing standard CRT (50.4 Gy and 2 cycles of 5-FU-based chemotherapy) were compared with those undergoing extended CRT (54 Gy and 6 cycles of 5-FU-based chemotherapy). Patients were assessed for tumor response at 8 to 10 weeks. Patients with complete clinical response (cCR) underwent organ-preservation strategy ("Watch and Wait"). Patients were referred to salvage surgery in the event of local recurrence during follow-up. Patients undergoing extended CRT were more likely to undergo organ preservation and avoid definitive surgical resection at 5years (67% vs 30%; P = 0.001). After development of a cCR, surgery-free survival is similar between extended and standard CRT groups at 5 years (78% vs 56%; P = 0.12).	2
91. Habr-Gama A, Lynn PB, Jorge JM, et al. Impact of Organ-Preserving Strategies on Anorectal Function in Patients with Distal Rectal Cancer Following Neoadjuvant Chemoradiation. *Dis Colon Rectum.* 2016;59(4):264-269	Experimental-Tx	29 near complete response patients underwent TEM 53 complete response	To compare anorectal function following these 2 organ-preserving strategies (TEM and watch and wait) for rectal cancer with complete or near-complete response to neoadjuvant CRT.	Consecutive patients with distal rectal cancer undergoing neoadjuvant CRT (50.4-54 Gy and 5-FU-based chemotherapy) were prospectively studied. Patients with complete clinical response	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
		patients observed		were managed by watch and wait. Patients with near-complete response (≤3 cm, ycT1-2N0) were managed by TEM. Functional outcomes were determined by anorectal manometry and Fecal Incontinence Index and Quality of Life assessment. Two groups of patients were included in the study. Twenty-nine patients with near-complete response undergoing TEM and 53 with complete response after watch and wait were assessed. Baseline features were similar between groups. Patients undergoing TEM had worse resting/squeeze pressures (p = 0.004) and rectal capacity (p = 0.002). In addition, their incontinence scores (2.3 vs. 6.5; p < 0.001) and quality-of-life questionnaire responses (in all domains; p ≤ 0.01) were significantly worse in comparison with patients undergoing watch and wait.	
92. Habr-Gama A, Perez RO. No Surgery After Chemoradiation Is Not Equal to Nonoperative Management After Complete Clinical Response and Chemoradiation. *J Clin Oncol.* 2016;34(33):4051	Review/Other-Dx	N/A	Review of the literature supporting the watch and wait approach in patients who have a complete clinical response following neoadjuvant therapy for rectal cancer	N/A	4
93. Creavin B, Ryan E, Martin ST, et al. Organ preservation with local excision or active surveillance following chemoradiotherapy for rectal cancer. *Br J Cancer.* 2017;116(2):169-174	Experimental-Tx	785 patients with locally advanced rectal cancer	To report single institution data for locally advanced rectal cancer treated with organ preservation with LE or active surveillance following CRT	Patients staged ⩾T3 or any stage N+ were referred for neoadjuvant CRT (50-54 Gy and 5-FU), and were reassessed 6-8 weeks post treatment. An active surveillance program ('watch and wait') was offered to patients who were found to have a complete endoluminal response. TAE was performed in patients who were found to have an objective clinical response and in whom a residual ulcer measured ⩽3 cm. Patients were followed up clinically, endoscopically and radiologically to assess for LR or disease progression. Sixty out of three hundred and sixty-two (16.5%) patients were treated with organ-preserving strategies - 10 with 'watch and wait' and 50 by TAE. Fifteen patients were referred for salvage TME post LE owing to adverse pathological findings. There was no significant difference in OS (85.6% vs 93.3%, P=0.414) or DFS rate (78.3% vs 80%, P=0.846) when the outcomes of RS were compared with organ preservation. Tumor regrowth occurred in 4 out of 45 (8.9%) patients who had organ preservation.	2
94. Sloothaak DA, Geijsen DE, van Leersum NJ, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg.* 2013;100(7):933-939	Observational-Tx	1593 rectal cancer patients from the Dutch Surgical Colorectal Audit.	To analyze the influence of variations in clinical practice regarding timing of surgery on pathological response at a population level.	The median interval between CRT and surgery was 14 (range 6-85, interquartile range 12-16) weeks. Outcome measures were calculated for intervals of less than 13 weeks (312 patients), 13-14 weeks (511 patients), 15-16 weeks (406 patients) and more than 16 weeks (364 patients). Age, tumor location and R0 resection rate were distributed equally	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				between the four groups; significant differences were found for clinical tumor category (cT4: 17.3, 18.4, 24.5 and 26.6 % respectively; P = 0.010) and clinical metastasis category (cM1: 4.4, 4.8, 8.9 and 14·9 % respectively; P < 0.001). Resection 15-16 weeks after the start of CRT resulted in the highest pCR rate (18.0 %; P = 0.013), with an independent association (HR 1.63, 95 % CI 1.20 to 2.23). Results for secondary endpoints in the group with an interval of 15-16 weeks were: tumor downstaging, 55.2 % (P = 0.165); nodal downstaging, 58.6 % (P = 0.036); and (near)-complete response, 23.2 % (P = 0.124). Delaying surgery until the 15th or 16th week after the start of CRT (10-11 weeks from the end of CRT) seemed to result in the highest chance of a pCR.	
95. Wolthuis AM, Penninckx F, Haustermans K, et al. Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. *Ann Surg Oncol.* 2012;19(9):2833-2841	Observational-Tx	365 consecutive patients with clinical stage II and II rectal cancer	Retrospective study to to evaluate whether the interval between neoadjuvant therapy and surgery had an impact on pathologic response and on surgical and oncologic outcome.	Median age was 63 years, and 65 % were men. All patients received neoadjuvant CRT (45 Gy) with a continuous infusion of 5-FU. Data on neoadjuvant-surgery interval, type of surgery, pathology, postoperative complications, length of hospital stay, disease recurrence, and OS were reviewed. Patients were divided into two groups according to the interval between neoadjuvant therapy and surgery: ≤ 7 weeks (short interval, n = 201) and >7 weeks (long interval, n = 155). The pCR rate was 21 %. It was significantly higher after a longer interval (28 %) than after a shorter interval (16 %, p = 0.006). A longer interval did not affect morbidity or length of hospital stay. After a median follow-up of 4.9 years, the 5-year CSS rate was 83 % in the short-interval group versus 91 % in the long-interval group (p = 0.046), and the free-from-recurrence rate was 73 versus 83 %, respectively (p = 0.026).	3
96. Appelt AL, Ploen J, Harling H, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. *Lancet Oncol.* 2015;16(8):919-92	Experimental-Tx	55 patients with primary, resectable, T2 or T3, N0-N1 adenocarcinoma in the lower 6 cm of the rectum	A prospective observational trial to assess whether high-dose CRT followed by observation (watchful waiting) was successful for non-surgical management of low rectal cancer.	Patients received CRT (60 Gy in 30 fractions to tumor, 50 Gy in 30 fractions to elective lymph node volumes, 5 Gy endorectal brachytherapy boost, and oral tegafur-uracil 300 mg/m(2)) every weekday for 6 weeks. Endoscopies and biopsies of the tumor were done at baseline, throughout the course of treatment (weeks 2, 4, and 6), and 6 weeks after the end of treatment. Patients with cCR negative tumor site biopsies, and no nodal or distant metastases on CT and MRI 6 weeks after treatment were allocated to the observation group (watchful waiting). All other patients were referred to standard surgery. Patients under observation were followed up closely with endoscopies and selected-site biopsies, with surgical resection given for local recurrence. Of 51 patients who were eligible, 40 had clinical complete response and were allocated to observation. Median	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				follow-up for local recurrence in the observation group was 23.9 months (IQR 15·3-31·0). Local recurrence in the observation group at 1 year was 15.5% (95% CI 3.3-26.3). The most common acute grade 3 adverse event during treatment was diarrhea, which affected four (8%) of 51 patients. Sphincter function in the observation group was excellent, with 18 (72%) of 25 patients at 1 year and 11 (69%) of 16 patients at 2 years reporting no fecal incontinence at all and a median Jorge-Wexner score of 0 (IQR 0-0) at all timepoints. The most common late toxicity was bleeding from the rectal mucosa; grade 3 bleeding was reported in two (7%) in 30 patients at 1 year and one (6%) of 17 patients at 2 years. There were no unexpected serious adverse reactions or treatment-related deaths.	
97. Nahas SC, Rizkallah Nahas CS, Sparapan Marques CF, et al. Pathologic Complete Response in Rectal Cancer: Can We Detect It? Lessons Learned From a Proposed Randomized Trial of Watch-and-Wait Treatment of Rectal Cancer. *Dis Colon Rectum.* 2016;59(4):255-263	Experimental-Tx	118 consecutive patients with stage T3 to T4N0M0 or T(any)N+M0 cancer located within 10 cm from anal verge or T2N0 within 7 cm from anal verge	To verify our ability to identify complete clinical response in patients with rectal cancer based on clinical and radiologic criteria.	Patients were staged and restaged 8 weeks after completion of CRT (5-FU, 50.4 Gy) by digital examination, colonoscopy, pelvic MRI, and thorax and abdominal CT scans. Six patients were considered cCR (2 randomly assigned for surgery (1 ypT0N0 and 1 ypT2N0) and 4 patients randomly assigned for observation (3 sustained clinic complete response and 1 had tumor regrowth)). The 112 clinic incomplete responders underwent TME, and 18 revealed pCR. These 18 patients were not cCR at restaging because they presented at least 1 of the following conditions: mucosal ulceration and/or deformity and/or substenosis of rectal lumen at digital rectal examination and colonoscopy (n = 16), ymrT1 to T4 (n = 16), ymrN+ (n = 2), involvement of circumferential resection margin on MRI (n = 3), extramural vascular invasion on MRI (n = 4), MRI tumor response grade 2 to 4 (n = 15), and pelvic side wall lymph node involvement on MRI (n = 1). Sensitivity for identification of ypT0N0 or sustained cCR was 18.2%.	2
98. Martens MH, Maas M, Heijnen LA, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *J Natl Cancer Inst.* 2016;108(12)	Experimental-Tx	100 patients	To establish the oncological and functional results of organ preservation with a watch-and-wait approach and selective TEM in patients with a cCR or near-complete response after neoadjuvant CRT for rectal cancer.	oOgan preservation was offered if response assessment with digital rectal examination, endoscopy, and MRI showed (near) cCR. Watch-and-wait was offered for cCR, and two options were offered for near cCR: TEM or reassessment after three months. Follow-up included endoscopy and MRIs every three months during the first year, and every six months thereafter. Long-term outcome was assessed with Kaplan-Meier curves. Functional outcome was assessed wit Sixty-one had cCR at initial response assessment. Thirty-nine had near cCR, of whom 24 developed cCR at the second assessment and 15 patients underwent TEM (9	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				ypT0, 1 ypT1, 5 ypT2). Fifteen patients developed a LR (12 luminal, 3 nodal), all salvageable and within 25 months. Five patients developed metastases, and five patients died. Three-year OS was 96.6% (95% CI = 89.9% to 98.9%), distant metastasis-free survival was 96.8% (95% CI = 90.4% to 99.0%), local regrowth-free survival was 84.6% (95% CI = 75.8% to 90.5%), and DFS was 80.6% (95% CI = 70.9% to 87.4%). Colostomy-free survival was 94.8% (95% CI = 88.0% to 97.8%), with a good continence after watch-and-wait (Vaizey = 3.4, SD = 3.9) and moderate after TEM (Vaizey = 9.7, SD = 5.1).h colostomy-free survival and Vaizey incontinence score (0 = perfect continence, 24 = totally incontinent).	
99. Habr-Gama A, Perez RO, Sabbaga J, Nadalin W, Sao Juliao GP, Gama-Rodrigues J. Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. *Dis Colon Rectum.* 2009;52(12):1927-1934	Experimental-Tx	34 rectal cancer patients	To evaluate toxicity rates and the impact of an extended neoadjuvant CRT regimen on pCR rates.	Patients were managed by 54 Gy and 5-FU/leucovorin-based chemotherapy given for 3 consecutive days every 21 days for 6 cycles (3 cycles concomitant with RT). Tumor response assessment was performed at 10 weeks from RT completion. Patients with cCRwere strictly monitored and were not immediately operated on. Patients with incomplete clinical response were referred to surgery.29 patients had completed 12 months of follow-up and were included in this preliminary analysis. Twenty-eight (97%) successfully completed treatment. Fifteen of 16 patients had Grade III toxicities that were skin-related (93%). Median follow-up was 23 months. Fourteen patients (48%) were considered as cCR sustained for at least 12 months (median, 24 months) after CRT completion by clinical assessment alone. An additional 5 patients (17%) were considered as pCR with ypT0 results after full-thickness local excision. Overall, the complete response rate was 65%.	2
100. Lai CL, Lai MJ, Wu CC, Jao SW, Hsiao CW. Rectal cancer with complete clinical response after neoadjuvant chemoradiotherapy, surgery, or "watch and wait". *Int J Colorectal Dis.* 2016;31(2):413-419	Experimental-Tx	18 patients who opted for a "watch and wait" policy and 26 patients who underwent radical surgery after achieving a cCR to neoadjuvant CRT	To compare the outcomes of patients treated with CRT with a complete clinical response followed by either a "watch and wait" strategy or a TME	Patients had no documented treatment complications under the watch and wait policy, while 13 patients who underwent TME experienced significant morbidity. There were two LRs in the watch and wait group; both were treated with salvage resection and had no associated mortality. In the TME group, 1 patient showed an incomplete pathologic response (ypT0N1), and the remaining 25 patients showed pCR; 1 had a distant recurrence, which was managed non-operatively, and 2 patients died of unrelated causes. The 5-year OS rate and median DFS time were 100% and 69.78 months in the watch and TME group.	2
101. Renehan AG, Malcomson L, Emsley R, et al. Watch-and-	Experimental-		To address the shortage of evidence regarding the safety of	259 patients were treated with 45 Gy and concurrent	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet Oncol.* 2016;17(2):174-183	Tx		the watch-and-wait approach by comparing oncological outcomes between patients managed by watch and wait who achieved a cCR and those who had surgical resection (standard care).	5-FU, 228 of whom underwent surgical resection at referring hospitals and 31 of whom had a cCR, managed by watch and wait. A further 98 patients were added to the watch-and-wait group via the registry. Of the 129 patients managed by watch and wait (median follow-up 33 months [IQR 19-43]), 44 (34%) had LR (3-year actuarial rate 38% [95% CI 30-48]); 36 (88%) of 41 patients with non-metastatic LR were salvaged. In the matched analyses (109 patients in each treatment group), no differences in 3-year non-LR DFS were noted between watch and wait and surgical resection (88% [95% CI 75-94] with watch and wait vs 78% [63-87] with surgical resection; time-varying p=0·043). Similarly, no difference in 3-year OS was noted (96% [88-98] vs 87% [77-93]; time-varying p=0·024). By contrast, patients managed by watch and wait had significantly better 3-year CFS than did those who had surgical resection (74% [95% CI 64-82] vs 47% [37-57]; HR 0·445 [95% CI 0·31-0·63; p<0·0001), with a 26% (95% CI 13-39) absolute difference in patients who avoided permanent colostomy at 3 years between treatment groups.	
102. Smith JD, Ruby JA, Goodman KA, et al. Nonoperative management of rectal cancer with complete clinical response after neoadjuvant therapy. *Ann Surg.* 2012;256(6):965-972	Observational-Tx	32 rectal cancer patients with cCR following CRT	A retrospective study to review the outcomes of patients managed with selective non-operative management (NOM) after a cCR to neoadjuvant treatment and compared these with patients who underwent standard rectal resection with pCR	Among 265 treated by CRT and rectal resection, 57 patients (22%) had a pCR and formed the control group (median follow-up 43 months). Factors associated with selective use of NOM included lower pretreatment stage, older age, and distal tumor location (P < 0.05). In the NOM group, 6 had LR (median 11 months, range 7-14), 3 of whom also had concurrent distant recurrence. All 6 LFs were controlled by salvage rectal resection with no further LR of disease (median follow-up 17 months). In the rectal resection/pCR group, there were no LF. The 2-year distant DFS (88% vs 98%, P = 0.27) and OS (96% vs 100%, P = 0.56) were similar for NOM and rectal resection/pCR groups.	3
103. Sun Z, Adam MA, Kim J, Shenoi M, Migaly J, Mantyh CR. Optimal Timing to Surgery after Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer. *J Am Coll Surg.* 2016;222(4):367-374	Review/Other-Dx	11,760 patients with stage II and III rectal cancer who received CRT followed by surgery	A NCDB study to analyze the impact of time to surgery following completion of CRT on resection margin positivity and pathologic downstaging.	Multivariable regression modeling with restricted cubic splines was used to evaluate the adjusted association between time to surgery and study endpoints, and to establish an optimal time threshold for surgery. Median time to surgery was 53 days (interquartile range [IQR] 43 to 63 days). After adjusting for patient demographic, clinical, tumor, and treatment characteristics, our model determined an inflection point at 56 days after end of radiotherapy associated with the highest likelihood of complete resection and pathologic downstaging. With adjustment, the risk of margin positivity was increased in those who underwent	2

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				surgery after 56 days from end of radiotherapy (OR 1.40, 95% CI 1.21 to 1.61, p < 0.001). The likelihood of downstaging was increasing up to 56 days after CRT (≥56 days vs <56 days, OR 1.2, 95% CI 1.02 to 1.23, p = 0.01).	
104. Probst CP, Becerra AZ, Aquina CT, et al. Extended Intervals after Neoadjuvant Therapy in Locally Advanced Rectal Cancer: The Key to Improved Tumor Response and Potential Organ Preservation. *J Am Coll Surg.* 2015;221(2):430-440	Review/Other-Dx	17,255 patients with stage II and III rectal cancer who received CRT followed by surgery	A NCDB study to examine the relationship between a longer interval after nCRT and pCR in a nationally representative cohort of rectal cancer patients.	Multivariable logistic regression analysis was used to assess the association between the CRT-surgery interval time (<6 weeks, 6 to 8 weeks, >8 weeks) and the odds of pCR. The relationship between CRT-surgery interval, surgical morbidity, and tumor downstaging was also examined. An CRT-surgery interval time >8 weeks was associated with higher odds of pCR (OR 1.12, 95% CI 1.01 to 1.25) and tumor downstaging (OR 1.11, 95% CI 1.02 to 1.25). The longer time delay was also associated with lower odds of 30-day readmission (OR 0.82, 95% CI 0.70 to 0.92).	2
105. Petrelli F, Sgroi G, Sarti E, Barni S. Increasing the Interval Between Neoadjuvant Chemoradiotherapy and Surgery in Rectal Cancer: A Meta-analysis of Published Studies. *Ann Surg.* 2016;263(3):458-464	Review/Other-Dx	3,584 rectal cancer patients	A systematic literature search and meta-analysis to demonstrate whether a longer interval between the end of CRT and surgery is associated with a better rate of pCR in rectal cancer.	PubMed, EMBASE, the ISI Web of Science, and The Cochrane Library (CENTRAL) were searched systematically for prospective or retrospective studies reporting oncological results for intervals longer or shorter than 6 to 8 weeks between the end of CRT and surgery, in rectal cancer. The primary endpoint, reported as relative risk (RR), was the rate of pCR. Secondary endpoints were OS, DFS, R0 resection rates, sphincter preservations, and wound/anastomotic complications. A meta-analysis was performed, using the fixed- or random-effects model, with Review Manager 5.1.Thirteen trials, including 3584 patients, were identified, and overall, an interval longer than 6 to 8 weeks from the end of neoadjuvant CRT and surgery significantly improved the pCR (RR = 1.42, 95% confidence interval: 1.19-1.68; P < 0.0001). pCR rates increased from 13.7% to 19.5% in the longer interval group, and the OS, DFS, R0 resection rates, sphincter preservation, and complication rates were similar in the 2 groups.	2
106. Lefevre JH, Mineur L, Kotti S, et al. Effect of Interval (7 or 11 weeks) Between Neoadjuvant Radiochemotherapy and Surgery on Complete Pathologic Response in Rectal Cancer: A Multicenter, Randomized, Controlled Trial (GRECCAR-6). *J Clin Oncol.* 2016;34(31):3773-3780.	Experimental-Tx	265 patients with cT3/T4 or Tx N+ tumors of the mid or lower rectum randomized to surgery following CRT at 7 weeks (n = 133) and 11 weeks (n = 132)	A phase III, multicenter, randomized, open-label, parallel-group controlled trial to evaluate the effect of increasing the interval between the end of CRT and surgery on the pCR rate.	The majority of the tumors were cT3 (82%). After CRT, surgery was not performed in 9 patients (3.4%) because of the occurrence of distant metastasis (n = 5) or other reasons. Two patients underwent local resection of the tumor scar. A total of 47 (18.6%) specimens were classified as ypT0 (4 had invaded lymph nodes [8.5%]). The primary end point (ypT0N0) was not different (7 weeks: 20 of 133, 15.0% *v* 11 weeks: 23 of 132, 17.4%; *P* = .5983). Morbidity was significantly increased in the 11 weeks group (44.5% *v* 32%; *P* = .0404) as a	1

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				result of increased medical complications (32.8% *v* 19.2%; *P* = .0137). The 11 weeks group had a worse quality of mesorectal resection (complete mesorectum [I] 78.7% *v* 90%; *P* = .0156).	
107. Barina A, De Paoli A, Delrio P, et al. Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study. *Tech Coloproctol.* 2017;21(8):633-640.	Review/Other-Dx	N/A	To describe an ongoing study is to evaluate the effectiveness of rectum-sparing approaches at 2 years after the completion of neoadjuvant treatment.	N/A	4
108. Kim TH, Chie EK, Kim DY, et al. Comparison of the belly board device method and the distended bladder method for reducing irradiated small bowel volumes in preoperative radiotherapy of rectal cancer patients. *Int J Radiat Oncol Biol Phys.* 2005;62(3):769-775	Observational-Tx	20 patients	To determine the most effective method to reduce the irradiated small bowel volume when using a belly board device, a distended bladder, or both in patients with rectal cancer undergoing preoperative pelvic RT.	All patients underwent 4 sets of CT scan under the conditions of 4 different methods as follows: Group I = empty bladder without the use of belly board; Group II = empty bladder with the use of belly board; Group III = distended bladder without the use of belly board; Group IV = distended bladder with the use of belly board. The authors found that the volume of irradiated small bowel decreased in the order of Group I, Group II, Group III, and Group IV at all dose levels (P<0.05). Compared with Group I, the mean volume reduction rate (reduced volume) of irradiated small bowel in Group II varied between 14.5% and 65.4% (15.5-80.4 cm^3, in Group III it varied between 48.1% and 82.0% (21.6-163.1 cm^3), and in Group IV between 51.4% and 96.4% (28.6-167.1 cm^3).	2
109. Siddiqui F, Shi C, Papanikolaou N, Fuss M. Image-guidance protocol comparison: supine and prone set-up accuracy for pelvic radiation therapy. *Acta Oncol.* 2008;47(7):1344-1350.	Observational-Tx	30 patients	To investigate the impact of prone vs supine patient set-up and use of various image-guidance protocols on residual set-up error for RT of pelvic malignancies and to aim to identify an optimal frequency and protocol for image-guidance.	Of 5 Image-guidance RT protocols analyzed, the protocol with the highest imaging frequency, alternate day imaging with a running mean (50% imaging frequency), provided the best set-up error reduction. This protocol would have reduced the average length of 3D corrective vector shifts derived from daily image-guidance from 15.2 and 13.5 mm for prone and supine set-up, to 5 and 5.4 mm, respectively. A No Action Level protocol, averaging shifts of the first 3 fractions (No Action Level3), would have reduced the respective set-up variability to 6.3 (prone), and 7.5 mm (supine). An extended No Action Level protocol, averaging shifts of the first 3 fractions plus weekly imaging, would have reduced the daily positioning variability to 6 mm for both prone and supine set-ups. Daily image-guidance yielded set-up corrections >10 mm in 64.3% for prone and 70.3% for supine position. Use of the No Action Level3 protocol would have reduced the respective frequency to 14.4%, and 21.2%	3

Reference	Study Type	Patients/Events	Study Objective (Purpose of Study)	Study Results	Study Quality
				for prone, and supine positioning. In comparison, the alternate day running mean protocol would have reduced the frequency of shifts >10 mm to 5.5% (prone), and 8.3% (supine), respectively.	
110. Drzymala M, Hawkins MA, Henrys AJ, Bedford J, Norman A, Tait DM. The effect of treatment position, prone or supine, on dose-volume histograms for pelvic radiotherapy in patients with rectal cancer. *Br J Radiol*. 2009;82(976):321-327	Observational-Tx	19 patients	To evaluate the volume of bowel and dose received in the prone and supine positions in patients undergoing preoperative rectal cancer CRT.	Using CT planning, 19 consecutive patients with rectal cancer with a full bladder underwent CT scanning first in the prone position and then immediately afterwards in the supine position. The planning target volume was outlined for the prone position and transcribed to the supine scan using pre-set criteria. The bladder and small bowel were outlined in both positions. RT was planned using 3D conformal planning, and treatment was delivered using 3 fields with multileaf collimators in 2 phases: phase I, pelvis 45 Gy/25 fractions; and phase II, tumor 9 Gy/5 fractions. For both positions, the volume of bowel receiving doses in 5 Gy increments from 5-45 Gy was calculated using dose-volume histograms. At 5 Gy and 10 Gy dose levels, a significantly higher volume of bowel was irradiated in the supine position ($P<0.001$). At 15 Gy, it was marginally significant ($P=0.018$). From 20-45 Gy, there was no significant difference in the volume of bowel irradiated with each 5 Gy increment.	2

ARS Appropriateness Criteria
Evidence Table Key
Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:

    a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
    b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
    c) the study is an expert opinion or consensus document.

Abbreviations Key
5-FU = 5-Fluorouracil
ACOSOG = American College of Surgeons Oncology Group
AJCC = American Joint Commission on Cancer
APR = Abdominoperineal resection
CALGB = Cancer and Leukemia Group B
cCR = clinical complete response

Evidence Table
ARS Appropriate Use Criteria
Local Excision in Rectal Cancer

CI = confidence interval
CRT = chemoradiation
CSS = Cancer specific survival
CT = computed tomography
DFS = Disease-Free Survival
DSS = disease-specific survival
Dx = Diagnostic
ERUS = Endorectal ultrasound
EUS = Endoscopic ultrasound
HRQOL = health related quality of life
LE = local excision
LF = local failure
LNM = lymph node metastases
LR = local recurrence
LRFS = locoregional relapse-free survival
MRF = mesorectal fascia
MRI = magnetic resonance imaging
NCCN = National Comprehensive Cancer Network
NCDB = National Cancer Data Base
OR - Odds Ratio
OS = Overall Survival
pCR = pathologic complete response
PET = positron emission tomography
PFS = Progression-free survival
QoL = Quality of Life
RFS = relapse-free survival
ROC = receiver operator characteristic
RS = Radical Surgery
RT = Radiation Therapy
RTOG = Radiation Therapy Oncology Group
Sm3 = deepest 1/3 or the submucosa
TAE = transanal excision
TEM = Transanal endoscopic microsurgery
TME = total mesorectal excision
TRG = tumor regression grade
Tx = Treatment