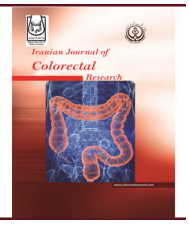
Review Article

Iran J Colorectal Res 2022;10(4):123-129.

Iranian Journal of Colorectal Research



Watch-and-wait Therapeutic Approach in Locally Advanced Rectal Cancer: An Innovative or Inevitable Option for Rectal Preservation

Mahshid Bahadori*[1], *MD;* *Nam-Phong Nguyen*[2], *MD; Faranak Bahrami*[3], *MD; Seyed Mohammad Kazem Tadayon*[3], *MD; Mohammad Mohammadianpanah*[3*], *MD

[1]*School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran*
[2]*Department of Radiation Oncology, Howard University Hospital, 2401 Georgia Avenue, NW Suite BA-07, Washington, DC 20060, USA*
[3]*Colorectal Research Center, Shiraz University of Medical Sciences, Shiraz, Iran*

Corresponding author:
Mohammad Mohammadianpanah, MD; Colorectal Research Center, Department of Radiation Oncology, Namazi Hospital, Shiraz University of Medical Sciences, 71936, Shiraz, Iran, **Tel:** +98 71 36125170; **Fax:** +98 71 36474320
Email: mohpanah@gmail.com

Received: 22-10-2022
Revised: 26-11-2022
Accepted: 26-11-2022

Abstract

Neoadjuvant chemoradiation followed by total mesorectal excision through a low anterior resection (LAR) or abdominoperineal resection (APR) is considered the standard treatment approach in most patients with locally advanced rectal cancer. While LAR allows for anatomic rectal preservation, APR leads to significant morbidity and compromised quality of life in rectal cancer patients. Approximately 10-40% of patients achieve clinical complete response (cCR) following neoadjuvant chemoradiation. Meanwhile, the pathologic complete response (pCR) rate is usually less than the cCR rate. The complete response rate may be improved by escalating the radiation dose and optimizing (total) neoadjuvant chemotherapy. Therefore, at least one-fifth of patients will have the chance of rectal preservation using the watch-and-wait strategy. In this therapeutic strategy, patients should be followed up by an active surveillance protocol to detect early tumor regrowth and undergo salvage radical surgery and will, therefore, provide comparable oncologic outcomes to those achieved in patients who undergo initial radical surgery. This study aimed to review the most recent evidence and guidelines regarding the watch-and-wait therapeutic strategy in patients with rectal cancer.

Keywords: Watchful waiting, Rectal cancer, Neoadjuvant therapy

Please cite this paper as:
Bahadori M, Nguyen N.P, Bahrami F, Tadayon SMK, Mohammadianpanah M. Watch-and-wait Therapeutic Approach in Locally Advanced Rectal Cancer: An Innovative or Inevitable Option for Rectal Preservation. *Iran J Colorectal Res*. 2022;10(4):123-129. doi: 10.30476/ACRR.2023.97583.1165.

Introduction

Colorectal cancer remains the third most frequent cancer, accounting for about 10% of global cancer incidence and mortality. Despite a decline in the incidence of colorectal cancers in highly developed countries due to a healthier lifestyle (e.g., reducing smoking) and appropriate screening programs, an increased rate in incidence and mortality has been recorded in most countries, particularly in people younger than 50 years (1).

In Iran, colorectal cancer is the third most common cancer and the fourth cause of cancer-related death. It is predicted that the incidence of this cancer will increase by more than 50% by 2025 (2). In developing countries such as Iran with limited resources, rectal

cancer tends to present as a more advanced disease and accounts for a larger proportion of all colorectal cancers (3). In young patients, the disease occurs in more advanced stages and with a greater contribution to the rectum compared to older ones. Diagnosis and treatment of rectal cancer, particularly in young people, is more challenging because of delays in referral, less suspicion of malignancy, and early and late treatment-related complications such as infertility and secondary malignancies.

Neoadjuvant chemoradiation followed by total mesorectal excision (TME) through a low anterior resection (LAR) or abdominoperineal resection (APR) is considered the standard treatment approach in the vast majority of patients with locally advanced rectal cancer (LARC) (4, 5). Radical surgery, particularly APR, is associated with significant morbidity and mortality in rectal cancer patients (6).

The watch-and-wait treatment strategy in rectal cancer patients who achieve a clinical complete response (cCR) following neoadjuvant chemoradiation would be an innovative approach to avoid surgery if feasible. In this treatment strategy, patients should be followed up on an active surveillance protocol to detect early tumor regrowth and immediately undergo salvage radical surgery, providing comparable oncologic outcomes to those achieved in patients who undergo initial radical surgery (7). This review aimed to present the most recent evidence and guidelines regarding the watch-and-wait strategy in patients with rectal cancer.

Morbidity and Mortality of Radical Rectal Surgery

Almost all patients with LARC are treated by neoadjuvant long-course chemoradiation or short-course radiotherapy followed by TME via a LAR or APR, mainly based on the tumor location (4). Performing TME, regardless of the surgical technique, is associated with frequent early and late complications. Up to 30% of patients during and following TME will develop short-term complications such as blood loss, anastomotic leakage, infection, pain, thromboembolic events, and bowel, nerve, urinary bladder, vaginal, or urethral injury (6, 8, 9). Likewise, many patients will suffer from long-term surgical-related complications such as LAR syndrome, sexual dysfunction, infertility, incisional hernia, fistula, bowel obstruction, and living with a temporary or permanent colostomy. Additionally, many patients will experience compromised quality of life due to gastrointestinal, urinary, and sexual dysfunction (9). On the other hand, large reported series found a 1.6–9% mortality rate in patients who underwent radical rectal surgery (6). In addition, those who require APR will be faced with the port of a life-long colostomy bag. Therefore, any effort to avoid unnecessary surgery and preserve the rectum in patients with rectal cancer will be very noteworthy.

Therapeutic Response Rate

Neoadjuvant treatment plays a critical role in the management of LARC. Long-course chemoradiation or short-course radiotherapy with or without induction (consolidation) chemotherapy is considered for the vast majority of patients with LARC (10). Following neoadjuvant treatment, more than two-thirds of patients achieve a degree of therapeutic response, and a pathologic complete response (pCR) rate of around 1–40% is observed. Systematic reviews found a mean pCR rate of 17.5% in cases who underwent radical surgery following neoadjuvant treatment (11, 12). The rate of clinical complete response (cCR) is usually more than pCR and is achievable in 10-40% of rectal cancer patients (13). Short-course neoadjuvant radiotherapy without induction and consolidation chemotherapy provides only a 1% complete response rate compared to 15% in those who receive neoadjuvant long-course chemoradiation. In the short course method with early surgery, the time interval to response assessment (or surgery) is too small to observe a tumor shrinkage. On the other hand, the response rate is much higher in the long-course chemoradiation technique due to the concurrent chemotherapy and the long interval between neoadjuvant treatment and surgery (14). Therefore, by incorporating induction or consolidation chemotherapy into short-course radiotherapy and prolonging the interval between neoadjuvant therapy and assessment time (or surgery), a comparable cCR is achievable (5, 15). This response rate may be improved by escalating the radiation dose and optimizing the neoadjuvant chemotherapy; therefore, rectal preservation is feasible in a significant number of patients (16). Optimizing chemotherapy can be achieved with total neoadjuvant chemotherapy (17, 18). Furthermore, escalating radiation dose is feasible with advanced radiotherapy techniques such as image-guided radiation therapy (IGRT), intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), and endorectal brachytherapy. These advanced radiotherapy techniques have significantly reduced grade 3-4 side effects and complications for all cancer patients regardless of age because of normal organ sparing (19-22). Patients' age, lymph node status, and tumor size, location, and histologic subtype are the most important non-treatment-related factors predicting complete response to neoadjuvant treatment. Patients with older age, smaller tumor size, distal tumor location, no clinical lymph node involvement, and the non-mucinous subtype are more likely to achieve cCR and are more eligible for the watch-and-wait strategy (23-25).

Assessment of Response to Neoadjuvant Therapy

After completing neoadjuvant chemoradiation, we have to consider an interval to response assessment. There is no consensus regarding the optimal time

interval between neoadjuvant chemoradiation and response assessment; however, a minimum of 8 weeks is recommended by most guidelines for clinical response assessment (or surgery) (10, 26-28). Another study reported up to a two-fold increase in cCR by extending the time interval between chemoradiation and response assessment (or surgery) from 8 to 12 weeks (29). In practice, this prolonged interval may be achieved by extending the duration of consolidation chemotherapy (30).

In general, digital rectal examination, imaging studies, and serum carcinoembryonic antigen (CEA) levels are used to assess the clinical response to neoadjuvant therapy (10). Computed tomography (CT), positron emission tomography (PET), magnetic resonance imaging (MRI), and endoscopic ultrasonography (EUS) are the most important tools used for evaluating the initial disease stage and later re-staging rectal cancer following neoadjuvant treatment. CT and PET scans are mainly used to detect distant metastases. However, many studies have investigated the use of PET before and after chemoradiation to assess the correlation between tumor response, survival, and possible patient selection for observation (31-33). Compared to CT and PET scans, MRI and EUS are more accurate for locoregional staging and evaluating the response to therapy. Many studies and meta-analyses evaluated the sensitivity, specificity, and accuracy of MRI and EUS in initial locoregional staging as well as the re-staging of rectal cancer following neoadjuvant treatment. Currently, most guidelines suggest an equivalent accuracy for both MRI and EUS in locoregional staging and re-staging of rectal cancer, although MRI is suggested by the Comprehensive Cancer Network (NCCN) as the preferred diagnostic modality (10, 27).

Generally, a pelvic MRI with or without contrast with a field strength of at least 1.5 Tesla is recommended to evaluate treatment response. In practice, high-resolution T2-weighted sequences and diffusion-weighted imaging (DWI) are the most frequently used MRI images to assess clinical therapeutic responses in patients with rectal cancer. MRI provides high sensitivity and low-to-moderate specificity in detecting residual disease in the primary site and regional lymph nodes. Accordingly, MRI is mainly useful for ruling out persistent disease rather than confirming a cCR (34, 35).

Patient Selection

Careful patient selection plays a pivotal role in the watch-and-wait strategy (36). The first step is to achieve and confirm cCR following neoadjuvant chemoradiation. This step is challenging because current assessment tools, including digital rectal examination, EUS, and MRI, are not perfect tools to confirm a cCR (37-39). However, some guidelines suggest criteria for defining cCR based on endoscopy, clinical examination, serum tumor markers, and MRI findings. According to these criteria, a cCR is defined as no ulceration, palpable tumor, or irregularity on digital rectal examination, no tumor, ulcer, or nodularity on endoscopy and EUS, the absence of a visible tumor and suspicious lymph nodes in T2-weighted sequences and DWI of MRI, and a normalized serum level of CEA (10, 40-42).

Patients' age and performance status are other important factors in selecting the watch-and-wait treatment approach. Older age is a favorable factor for achieving cCR; on the other hand, it is a risk factor for a higher rate of APR and surgery-related morbidity and mortality (5, 10, 21). Therefore, older cancer patients may benefit the most from the watch-and-wait strategy due to pre-existing comorbidities which may preclude surgery.

Tumor location is the most crucial factor in selecting the type of radical surgery (LAR versus APR). Distal rectal tumors are usually treated by APR, which will result in more complications compared to LAR. Additionally, these tumors are likewise more appropriate for radiation dose escalation and endorectal brachytherapy, which will result in a higher rate of cCR. Therefore, they are a favorable factor in achieving cCR compared with upper rectal tumors (20). In terms of surveillance, distal rectal tumors are more eligible for rectal examination and proctoscopy and, consequently, more eligible for the watch-and-wait approach. Patients' compliance and adherence to the watch-and-wait treatment strategy is another important factor. Selected patients should have good compliance and regular follow-up under an active surveillance protocol.

Patients who refuse radical surgery or are inoperable due to underlying disease inevitably are included in the watch-and-wait strategy. Some studies found this group mostly includes the elderly, black or Asian race, women, and those with more advanced disease and government insurance (43). It is clear that no test will reliably predict a pCR, but the combination of close clinical monitoring, diagnostic studies, and repeated biopsies (if indicated) may enable us to provide patients with a complete response following chemoradiation the reassurance that local recurrence will be diagnosed early for surgical salvage.

Active Surveillance Protocol

A careful surveillance program is mandatory and plays a critical role in managing patients under the watch-and-wait strategy. In general, all clinical and diagnostic tools used in staging and re-staging after neoadjuvant treatments have been recommended in this stage. According to this protocol, patients should be followed up every three months in the first two years and every six months in the next three years. In each follow-up, clinical, endoscopic, and imaging evaluations include a careful history and physical (rectal) examination, serum CEA level, proctoscopy, and pelvic MRI. In the absence of any

suspicious rectal lesion such as a mass, ulceration, or irregularity, a blind biopsy of the normal rectum is not recommended. To detect distant failure, a chest, abdominal, and pelvic CT scan is suggested every six months in the first two years and every 6-12 months in the next three years (27).

Tumor Regrowth Rate and Treatment Outcome

Several studies and systematic reviews investigated the rate of tumor regrowth in the watch-and-wait strategy. They found a 30% (range 15-34%) locoregional recurrence rate among patients who achieved cCR following neoadjuvant treatments (7, 44-49). These studies showed a high rate (68-90%) of successful salvage surgery in patients with locoregional recurrence (40, 41, 46-50). However, approximately 2-3% of patients with underlying comorbidity or unresectable or metastatic disease may not be eligible for salvage surgery. In addition, patients who refuse surgery should be added to this percentage (51). Furthermore, many reports and systematic reviews concluded similar short- and long-term treatment outcomes and overall and disease-specific mortality for patients managed by the watch-and-wait strategy compared with those treated by upfront radical surgery (40, 45, 48, 50). Due to the higher rate of tumor regrowth in the watch-and-wait strategy, the disease-free survival rate may be better in patients with upfront radical surgery; however, there is no significant difference regarding the ultimate outcome and overall survival rate between these groups (52).

Cost Effectiveness

Some studies investigated the cost-effectiveness of the watch-and-wait strategy and found a benefit for this treatment policy. In these studies, a detailed microcosting for all services including preoperative evaluation, chemotherapy (type, cycles, and protocol), radiotherapy technique (three-dimensional conformal radiation therapy vs. IMRT) and method (short-course vs. long-course), radical surgery (LAR or APR), postoperative complications, rehabilitation, ostomy closure, and annual stoma care and surveillance have been analyzed. These studies concluded that the watch-and-wait strategy provides a comparable oncologic outcome, better quality of life, and lower total cost than upfront radical surgery (47, 53-55).

Future Perspectives

Older patients with locally advanced rectal cancer may benefit from a non-surgical approach if they develop a cCR. Thus, increasing the percentage of patients who achieve a cCR would benefit this vulnerable population. A preliminary investigation suggested that immunotherapy may benefit a subset of patients with mismatch repair-deficient tumors. In a phase II clinical trial recently published in the New England Journal of Medicine, all 12 patients with mismatch repair-deficient locally advanced rectal cancer achieved a cCR using dostarlimab, a programmed death receptor-1 blocker, with a minimum follow-up of six months (56). As immunotherapy is better tolerated than chemotherapy, this innovative strategy should be investigated in future clinical trials (57). Another innovative approach is using high dose rate (HDR) brachytherapy to deliver a higher dose to the tumor bed to increase the cCR rate. In a study, four out of six older patients with locally advanced cancer who were too frail to undergo surgery achieved cCR with an HDR boost. However, the study sample was small, so this innovative approach needs to be tested in future clinical trials (58).

Conclusion

The watch-and-wait strategy is an innovative feasible option for a remarkable portion of patients with rectal cancer who achieve a clinical complete response (cCR). This prerequisite can be achieved by escalating the radiation dose and optimizing the neoadjuvant chemotherapy. In the watch-and-wait strategy, patients should be followed up on an active surveillance protocol to detect early tumor regrowth and schedule immediate salvage radical surgery if needed, thereby providing similar oncologic outcomes with better quality of life and lower treatment cost relative to initial radical surgery.

Authors' Contribution

Mahshid Bahadori involved in the design, writing, revising the manuscript, and approval of final version; NamPhong Nguyen involved in conception, literature review, writing the manuscript and approval of final version; Faranak Bahrami and Seyed Mohammad Kazem Tadayon involved in conception, writing, revising the manuscript, and approval of final manuscript; and, Mohammad Mohammadianpanah, involved in design, literature review, writing, revising the manuscript, and approval of final version of the manuscript. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Conflict of interest: None declared.

References

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Translational Oncology. 2021;14(10):101174.
2. Roshandel G, Ferlay J, Ghanbari-Motlagh A, Partovipour E, Salavati F, Aryan K, et al. Cancer in Iran 2008 to 2025: Recent incidence trends and short-term predictions of the future burden. International Journal of Cancer. 2021;149(3):594-605.
3. Mohammadianpanah M. Colorectal cancer incidence: does Iran follow the West? Iranian Journal of Colorectal Research. 2015;3(1):0-.
4. Keller DS, Berho M, Perez RO, Wexner SD, Chand M. The multidisciplinary management of rectal cancer. Nature Reviews Gastroenterology & Hepatology. 2020;17(7):414-29.
5. Bananzadeh A, Hafezi AA, Nguyen N, Omidvari S, Mosalaei A, Ahmadloo N, et al. Efficacy and safety of sequential neoadjuvant chemotherapy and short-course radiation therapy followed by delayed surgery in locally advanced rectal cancer: a single-arm phase II clinical trial with subgroup analysis between the older and young patients. Radiat Oncol J. 2021;39(4):270-8.
6. Alves A, Panis Y, Mathieu P, Mantion G, Kwiatkowski F, Slim K, et al. Postoperative Mortality and Morbidity in French Patients Undergoing Colorectal Surgery: Results of a Prospective Multicenter Study. Archives of Surgery. 2005;140(3):278-83.
7. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018;391(10139):2537-45.
8. van der Pas MH, Haglind E, Cuesta MA, Fürst A, Lacy AM, Hop WC, et al. Laparoscopic versus open surgery for rectal cancer (COLOR II): short-term outcomes of a randomised, phase 3 trial. Lancet Oncol. 2013;14(3):210-8.
9. Vennix S, Pelzers L, Bouvy N, Beets GL, Pierie JP, Wiggers T, et al. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev. 2014(4):Cd005200.
10. Podda M, Sylla P, Baiocchi G, Adamina M, Agnoletti V, Agresta F, et al. Multidisciplinary management of elderly patients with rectal cancer: recommendations from the SICG (Italian Society of Geriatric Surgery), SIFIPAC (Italian Society of Surgical Pathophysiology), SICE (Italian Society of Endoscopic Surgery and new technologies), and the WSES (World Society of Emergency Surgery) International Consensus Project. World J Emerg Surg. 2021;16(1):35.
11. Teo MTW, McParland L, Appelt AL, Sebag-Montefiore D. Phase 2 Neoadjuvant Treatment Intensification Trials in Rectal Cancer: A Systematic Review. Int J Radiat Oncol Biol Phys. 2018;100(1):146-58.
12. De Caluwé L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev. 2013(2):Cd006041.
13. Bitterman DS, Resende Salgado L, Moore HG, Sanfilippo NJ, Gu P, Hatzaras I, et al. Predictors of Complete Response and Disease Recurrence Following Chemoradiation for Rectal Cancer. Front Oncol. 2015;5:286.
14. Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, et al. Randomized Trial of Short-Course Radiotherapy Versus Long-Course Chemoradiation Comparing Rates of Local Recurrence in Patients With T3 Rectal Cancer: Trans-Tasman Radiation Oncology Group Trial 01.04. Journal of Clinical Oncology. 2012;30(31):3827-33.
15. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. Lancet Oncol. 2021;22(1):29-42.
16. Appelt AL, Pløen J, Harling H, Jensen FS, Jensen LH, Jørgensen JC, et al. High-dose chemoradiotherapy and watchful waiting for distal rectal cancer: a prospective observational study. Lancet Oncol. 2015;16(8):919-27.
17. Garcia-Aguilar J, Patil S, Gollub MJ, Kim JK, Yuval JB, Thompson HM, et al. Organ Preservation in Patients With Rectal Adenocarcinoma Treated With Total Neoadjuvant Therapy. Journal of Clinical Oncology. 2022;40(23):2546-56.
18. Aref A, Abdalla A. Total Neoadjuvant Therapy for Locally Advanced Rectal Cancer: Induction or Consolidation Chemotherapy? Journal of Clinical Oncology. 2022;40(23):2515-9.
19. Hearn N, Atwell D, Cahill K, Elks J, Vignarajah D, Lagopoulos J, et al. Neoadjuvant Radiotherapy Dose Escalation in Locally Advanced Rectal Cancer: a Systematic Review and Meta-analysis of Modern Treatment Approaches and Outcomes. Clin Oncol (R Coll Radiol). 2021;33(1):e1-e14.
20. Omidvari S, Zohourinia S, Ansari M, Ghahramani L, Zare-Bandamiri M, Mosalaei A, et al. Efficacy and Safety of Low-Dose-Rate Endorectal Brachytherapy as a Boost to Neoadjuvant Chemoradiation in the Treatment of Locally Advanced Distal Rectal Cancer: A Phase-II Clinical Trial. Ann Coloproctol. 2015;31(4):123-30.
21. Nguyen NP, Ceizyk M, Vock J, Vos P, Chi A, Vinh-Hung V, et al. Feasibility of image-guided radiotherapy for elderly patients with locally advanced rectal cancer. PLoS One. 2013;8(8):e71250-e.
22. Vuong T, Garant A, Vendrely V, Nout R, Martin AG, Enger SA, et al. Image-Guided Brachytherapy for Rectal Cancer: Reviewing the Past Two Decades of Clinical Investigation. Cancers (Basel). 2022;14(19).
23. Huang Y, Lee D, Young C. Predictors for complete pathological response for stage II and III rectal cancer following neoadjuvant therapy - A systematic review and meta-analysis. Am J Surg. 2020;220(2):300-8.
24. Hosseini S, Nguyen N, Mohammadianpanah M, Mirzaei S, Bananzadeh AM. Predictive Significance of Mucinous Histology on Pathologic Complete Response Rate Following Capecitabine-Based Neoadjuvant Chemoradiation in Rectal Cancer: a Comparative Study. Journal of Gastrointestinal Cancer. 2019;50(4):716-22.
25. Zhang J, Xie X, Wu Z, Hu H, Cai Y, Li J, et al. Mucinous Adenocarcinoma Predicts Poor Response and Prognosis in Patients With Locally Advanced Rectal Cancer: A Pooled Analysis of Individual Participant Data From 3 Prospective Studies. Clin Colorectal Cancer. 2021;20(4):e240-e8.
26. 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):367-74.

27. Benson AB, Venook AP, Al-Hawary MM, Azad N, Chen YJ, Ciombor KK, et al. Rectal Cancer, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2022;20(10):1139-67.
28. Akgun E, Caliskan C, Bozbiyik O, Yoldas T, Doganavsargil B, Ozkok S, et al. Effect of interval between neoadjuvant chemoradiotherapy and surgery on disease recurrence and survival in rectal cancer: long-term results of a randomized clinical trial. BJS Open. 2022;6(5).
29. Terzi C, Bingul M, Arslan NC, Ozturk E, Canda AE, Isik O, et al. Randomized controlled trial of 8 weeks' vs 12 weeks' interval between neoadjuvant chemoradiotherapy and surgery for locally advanced rectal cancer. Colorectal Dis. 2020;22(3):279-88.
30. Ma B, Gao P, Song Y, Huang X, Wang H, Xu Q, et al. Short-Course Radiotherapy in Neoadjuvant Treatment for Rectal Cancer: A Systematic Review and Meta-analysis. Clinical Colorectal Cancer. 2018;17(4):320-30.e5.
31. Perez RO, Habr-Gama A, São Julião GP, Lynn PB, Sabbagh C, Proscurshim I, et al. Predicting complete response to neoadjuvant CRT for distal rectal cancer using sequential PET/CT imaging. Tech Coloproctol. 2014;18(8):699-708.
32. Kalff V, Duong C, Drummond EG, Matthews JP, Hicks RJ. Findings on 18F-FDG PET scans after neoadjuvant chemoradiation provides prognostic stratification in patients with locally advanced rectal carcinoma subsequently treated by radical surgery. J Nucl Med. 2006;47(1):14-22.
33. Pyo DH, Choi JY, Lee WY, Yun SH, Kim HC, Huh JW, et al. A Nomogram for Predicting Pathological Complete Response to Neoadjuvant Chemoradiotherapy Using Semiquantitative Parameters Derived From Sequential PET/CT in Locally Advanced Rectal Cancer. Front Oncol. 2021;11:742728.
34. Beets-Tan RGH, Lambregts DMJ, Maas M, Bipat S, Barbaro B, Curvo-Semedo L, et al. Magnetic resonance imaging for clinical management of rectal cancer: Updated recommendations from the 2016 European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus meeting. Eur Radiol. 2018;28(4):1465-75.
35. Gollub MJ, Arya S, Beets-Tan RG, dePrisco G, Gonen M, Jhaveri K, et al. Use of magnetic resonance imaging in rectal cancer patients: Society of Abdominal Radiology (SAR) rectal cancer disease-focused panel (DFP) recommendations 2017. Abdom Radiol (NY). 2018;43(11):2893-902.
36. Marincaş AM, Prunoiu VM, Brătucu E, Cirimbei C, Ionescu S, Buzatu R, et al. Clinical and Paraclinical Criteria of Patient Selection for the Non-operative Treatment in Completely Responsive Rectal Cancer (after Neoadjuvant Radiochemotherapy). Chirurgia (Bucur). 2015;110(4):351-5.
37. 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):748-61.
38. Cote A, Florin FG, Mois E, Elisei R, Badea R, Mare C, et al. The accuracy of endorectal ultrasonography and high-resolution magnetic resonance imaging for restaging rectal cancer after neoadjuvant chemoradiotherapy. Ann Ital Chir. 2018;89:168-76.
39. de Jong EA, ten Berge JC, Dwarkasing RS, Rijkers AP, van Eijck CH. The accuracy of MRI, endorectal ultrasonography, and computed tomography in predicting the response of locally advanced rectal cancer after preoperative therapy: A metaanalysis. Surgery. 2016;159(3):688-99.
40. Smith JJ, Chow OS, Gollub MJ, Nash GM, Temple LK, Weiser MR, et al. Organ Preservation in Rectal Adenocarcinoma: a phase II randomized controlled trial evaluating 3-year disease-free survival in patients with locally advanced rectal cancer treated with chemoradiation plus induction or consolidation chemotherapy, and total mesorectal excision or nonoperative management. BMC Cancer. 2015;15:767.
41. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rödel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017;28(suppl_4):iv22-iv40.
42. Wei IH, Garcia-Aguilar J. Non-operative management of rectal cancer: understanding tumor biology. Minerva Chir. 2018;73(6):601-18.
43. Pianka K, Zhao B, Lee K, Liu S, Eisenstein S, Ramamoorthy S, et al. Factors associated with refusing surgery versus planned nonoperative management for rectal cancer. Surgery. 2022;172(5):1309-14.
44. Dattani M, Heald RJ, Goussous G, Broadhurst J, São Julião GP, Habr-Gama A, et al. Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis. Ann Surg. 2018;268(6):955-67.
45. Nasir I, Fernandez L, Vieira P, Parés O, Santiago I, Castillo-Martin M, et al. Salvage surgery for local regrowths in Watch & Wait - Are we harming our patients by deferring the surgery? Eur J Surg Oncol. 2019;45(9):1559-66.
46. Habr-Gama A, Gama-Rodrigues J, São Julião GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014;88(4):822-8.
47. Kong JC, Guerra GR, Warrier SK, Ramsay RG, Heriot AG. Outcome and Salvage Surgery Following "Watch and Wait" for Rectal Cancer after Neoadjuvant Therapy: A Systematic Review. Dis Colon Rectum. 2017;60(3):335-45.
48. On J, Shim J, Aly EH. Systematic review and meta-analysis on outcomes of salvage therapy in patients with tumour recurrence during 'watch and wait' in rectal cancer. Ann R Coll Surg Engl. 2019;101(7):441-52.
49. Chadi SA, Malcomson L, Ensor J, Riley RD, Vaccaro CA, Rossi GL, et al. Factors affecting local regrowth after watch and wait for patients with a clinical complete response following chemoradiotherapy in rectal cancer (InterCoRe consortium): an individual participant data meta-analysis. Lancet Gastroenterol Hepatol. 2018;3(12):825-36.
50. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, São Julião GP, Proscurshim I, Bailão Aguilar P, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56(10):1109-17.
51. López-Campos F, Martín-Martín M, Fornell-Pérez R, García-Pérez JC, Die-Trill J, Fuentes-Mateos R, et al. Watch and wait approach in rectal cancer: Current controversies and future directions. World J Gastroenterol. 2020;26(29):4218-39.
52. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. Lancet Gastroenterol Hepatol.

2017;2(7):501-13.
53. Bibi S, Edilbe MW, Rao C. The Cost-effectiveness of Watch and Wait for Rectal Cancer. Clin Oncol (R Coll Radiol). 2022.
54. Rodriguez-Pascual J, Nuñez-Alfonsel J, Ielpo B, Lopez M, Quijano Y, de Vicente E, et al. Watch-and-Wait policy versus robotic surgery for locally advanced rectal cancer: A cost-effectiveness study (RECCOSTE). Surg Oncol. 2022;41:101710.
55. Dossa F, Chesney TR, Acuna SA, Baxter NN. A watch-and-wait approach for locally advanced rectal cancer after a clinical complete response following neoadjuvant chemoradiation: a systematic review and meta-analysis. The Lancet Gastroenterology & Hepatology. 2017;2(7):501-13.
56. Cercek A, Lumish M, Sinopoli J, Weiss J, Shia J, Lamendola-Essel M, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. N Engl J Med. 2022;386(25):2363-76.
57. Mi M, Ye C, Yuan Y. Neoadjuvant PD-1 blockade: a promising nonoperative strategy for mismatch repair-deficient, locally advanced rectal cancer. Signal Transduct Target Ther. 2022;7(1):361.
58. Fleischmann M, Diefenhardt M, Trommel M, Scherf C, Ramm U, Chatzikonstantinou G, et al. Image-guided high-dose-rate brachytherapy for rectal cancer: technical note and first clinical experience on an organ-preserving approach. Strahlenther Onkol. 2022;198(7):654-62.