

REVIEW

WATCH AND WAIT POLICY – A PATHWAY TO A BETTER QUALITY OF LIFE FOR PATIENTS WITH RECTAL CANCER: A REVIEW

Angela BLAJIN¹✉, Cristina TANASE¹, Andrei POPA¹, Vlad FILIMON¹, Florin A. GRAMA¹, Traean BURCOS¹

¹ Department of Surgery, Coltea Clinical Hospital Bucharest, Romania

Received 22 Febr 2022, Accepted 14 April 2022

<https://doi.org/10.31688/ABMU.2022.57.2.05>

ABSTRACT

The treatment of rectal cancer has significantly developed over the last few decades, the standard of care treatment for patients with locally advanced rectal cancer being the neoadjuvant chemoradiotherapy (nCRT). Nowadays, nCRT is usually followed by definitive surgery, with total mesorectal excision (TME) and adjuvant chemotherapy. Despite favourable outcomes and potential advantages, this treatment approach can result in significant toxicity. The watch-and-wait (WW) strategy is an alternative approach and has been accepted as an alternative treatment in patients with rectal cancer who have had a complete clinical response (cCR) after neoadjuvant therapy. However, there are several open questions and concerns about this strategy, including the methods of patient selection, criteria to accurately determine cCR, both clinical and radiological, optimal duration of neoadjuvant treatment, optimal follow-up strategies and future possible perspectives of this approach. The aim of this review is to summarize the current available data and evidence on the WW strategy and the proven benefits this approach may have in patients with rectal cancer.

Keywords: rectal cancer, watch-and-wait, neoadjuvant therapy.

RÉSUMÉ

La stratégie de « voir venir » – le chemin vers une meilleure qualité de la vie des patients avec du cancer rectal: une revue

Le traitement du cancer du rectum s'est considérablement développé au cours des dernières décennies, le traitement de référence pour les patients atteints d'un cancer du rectum localement avancé étant considéré comme la chimio radiothérapie néoadjuvante (nCRT). De nos jours, la nCRT est généralement suivie d'une chirurgie définitive, avec exérèse méso-rectale totale (ETM) et chimiothérapie adjuvante. Malgré les résultats favorables et les avantages potentiels qu'elle peut avoir, cette approche thérapeutique peut entraîner une toxicité importante. La stratégie « voir venir » est une approche alternative et a été acceptée comme traitement alternatif chez les patients atteints d'un cancer du rectum qui ont eu une réponse clinique complète (cCR) après un traitement néoadjuvant. Cependant, il existe plusieurs questions et préoccupations ouvertes concernant cette stratégie, notamment les méthodes de sélection des patients, les critères pour déterminer avec précision la cCR, à la fois cliniques et radiologiques, la durée optimale du traitement néoadjuvant,

✉ Address for correspondence:

Angela BLAJIN
Coltea Clinical Hospital, Bucharest, Romania
Address: 1 Ion C. Brătianu Blvd, 3rd district, Bucharest, 030167, Romania
E-mail: angela.blajin@yahoo.com

List of abbreviations

AR – anterior resection
cCR – complete clinical response
MRI – magnetic resonance imaging
nCRT – neoadjuvant chemoradiotherapy
OS – overall survival
pCR – pathologic complete response
TME – total mesorectal excision
WW – Watch and Wait/ Wait and See

INTRODUCTION

The treatment of rectal cancer continues to be one of the biggest challenges in the medical practice. There is a continuous work to reduce the risk of distant metastases, to preserve and improve the patients' quality of life and personalize treatment by identifying responders to neoadjuvant chemoradiotherapy (nCRT). According to the current definition, patients who have a pathologic complete response (pCR) in the total mesorectal excision (TME) specimen have maximal response to nCRT. This response is associated with considerable better results¹.

The using of a watch-and-wait strategy (WW) for patients with rectal cancer following a clinical complete response (cCR) to nCRT is a nonstandard approach, but it has become more widely practiced with the advent of total neoadjuvant therapy and with increasing demand by patients in the context of a cCR². The main advantage of the WW approach is that it avoids all the significant morbidity and mortality risks associated with abdominoperineal resection. Although many expert care centres have reported favourable outcomes of patients undergoing WW, some medical professionals have raised concerns regarding its application outside of highly specialized settings. Notably, adoption of WW in a broader community practice has been hindered by the lack of consensus and comfort regarding the optimal response assessment. These concerns are represented by the fear that unaddressed residual disease after nCRT will ultimately progress to distant metastases and thereby decrease survival³. Many studies support these data, concluding that there are no significant differences in overall survival (OS) and local recurrence between surgically treated patients and those managed with the WW protocol². However, larger prospective studies are needed to confirm long-term outcomes and to resolve controversies surrounding the selection of candidates for WW, the accurate determination of cCR, and the optimal follow-up protocols.

Data sources, literature search and study

les stratégies de suivi optimales et les perspectives possibles de cette approche. L'objectif de cette revue est de résumer les données et les preuves actuellement disponibles sur la stratégie de surveillance et d'attente et les avantages prouvés que cette approche peut avoir chez les patients atteints d'un cancer du rectum.

Mots-clés: cancer du rectum, voir venir, thérapie néoadjuvante.

selection

A systematic search of PubMed and Science Direct databases was performed for English language literature published between January 2019 – January 2022. Studies were included if they evaluated patients with rectal cancer managed by a WW strategy after nCRT. The inclusion criteria set for this review were the English language and the timeframe above-mentioned. The research relied mostly on rectal cancer management by a WW or wait-and-see strategy, without excluding the existence of a neoadjuvant therapy.

In the search strategy developed for the current review, different combinations of the following keywords were included: „rectal cancer“, „neoadjuvant therapy“, „wait-and-see“, „watch-and-wait“, the search being performed by two independent reviewers. The initial search of PubMed data base for „rectal cancer“, „neoadjuvant therapy“, „watch and wait“ combination led to a number of 151 results. The selection criteria have been restricted to studies in English language published between January 2019 and January 2022, with an outcome of 99 results. Subsequent searches on PubMed database have led to a number of 13 results for „rectal cancer“, „neoadjuvant therapy“, „wait-and-see“ combination and 21 results for „rectal cancer“ and „wait and see“ keywords.

The initial search of ScienceDirect database using the same criteria as those used on PubMed for „rectal cancer“, „neoadjuvant therapy“, „watch and wait“ combination led to 235 results. Subsequent searches have led to a number of 164 results for „rectal cancer“, „neoadjuvant therapy“, „wait and see“ combination and 566 results for „rectal cancer“ and „wait and see“ keywords.

A total of 133 studies were retrieved from the searches of PubMed database and 203 studies were retrieved from the searches of ScienceDirect database, upon excluding reviews and meta-analyses, book chapters, guidelines, editorials, case reports, and correspondences. Duplicates check was performed for these 336 articles and 102 studies were left to determine whether these met the inclusion criteria or not. Titles and abstracts were screened for those 102

studies, which drove to a total number of 12 studies from both databases to be included in the current review. The inclusion criteria have been set considering the purpose of this review.

Risk of bias assessment

For each study included, an assessment has been made to establish if it evaluated rectal cancer managed by a WW strategy or wait-and-see strategy after neoadjuvant therapy and if the following were described: outcome of the neoadjuvant therapy and efficacy of the strategy applied, along with takeaway lessons regarding the surveillance period, management of the regrowth and relapses, survival rate.

RESULTS

Study selection and study characteristics

Twelve studies have been selected considering the inclusion criteria, being included only the studies which evaluated the evolution of rectal cancer managed by a WW approach after nCRT.

Results of individual studies

A total of 12 studies, conducted mainly in the United States and in Europe, were included in the present review. The outcome of this review established that WW therapy should be taken into consideration for every patient with rectal cancer who achieved a cCR to chemoradiotherapy since this policy is safe and effective and improves the health-related patients' quality of life.

Gürel Neşşar et al. compared the oncological results of clinically complete responders with those patients defined as pathologically tumour-free, between 2010 and 2016, 61 patients who have received nCRT for low rectal cancer being included in the study. The patients who achieved cCR were included in the WW protocol and did not receive surgery (7 out of 61 patients). The remaining patients (51) underwent radical surgery and 7 of them were diagnosed as having a pathologically complete response. The 5-year survival was 100%. The mean follow-up was 56 months, and the average age was 50.6 years. All patients, except one, are alive without tumour recurrence in the surgery group. However, those who received surgery experienced significant morbidities related to surgery. The oncological results of the WW approach were no different from radical surgery results, the patients being diagnosed with pathologically complete response. The patients who required abdominal-perineal resection before chemoradiation should be informed about this approach if they have achieved cCR⁶.

Two studies developed in The Netherlands, conducted by Haak et al, analysed the occurrence and

detection of local regrowth in a WW cohort and tried to suggest a more efficient follow-up schedule. A total of 306 rectal cancer patients with a cCR after nCRT were prospectively and retrospectively included in a multicentre WW registry, between 2004 and 2018, with the following follow-up schedule: endoscopy and magnetic resonance imaging (MRI) at 3 months in the first year and 6 months thereafter. 50 out of 304 (16%) patients developed a local regrowth. The majority (98%) were detected at ≤ 2 years, located in the lumen (94%) and were visible on endoscopy (88%). The theoretical comparison of the different hypothetical schedules suggests that the optimal follow-up schedule should focus on the first 2 years with endoscopy at 3 months and MRI at 3–6 months. Longer intervals in the first two years will cause delays in the diagnosis of local regrowth, ranging from 0 to 5 months. After two years, the increase of the interval from 6 to 12 months did not cause important delays. The study concluded that the optimal follow-up schedule for a WW policy in patients with a cCR after chemoradiation for rectal cancer should include frequent endoscopy and to a lesser degree MRI in the first two years⁵. Longer intervals, up to 12 months, can be considered after two years. The other study focused on patients older than 75 years. 43 patients were included, the 3-year overall survival was 97%, with death mostly due to other causes. The local regrowth free rate, non-regrowth disease-free survival and overall survival at 3-years was 88%, 91% and 97%, respectively. One patient had local recurrence⁸.

A retrospective, multicentre study was performed by an international team of researchers from different countries across the world. The study used a dataset from the International Watch & Wait Database, which includes data from 47 clinics across 15 countries. Patients aged ≥ 18 years with rectal cancer who had a cCR after nCRT, and who were subsequently managed by a WW strategy between Nov 25, 1991, and Dec 31, 2015 were included. Patients who had not achieved a cCR or who had undergone any surgical procedure were excluded. The criteria used for defining a cCR and the specific surveillance strategies were at the discretion of each participating centre. 793 patients with cCR were identified in the International Watch & Wait Database, who had been managed by a WW strategy. The median follow-up was 55.2 months. The probability of remaining free from local regrowth for an additional two years if a patient had a sustained cCR for one year was 88.1% (95% CI 85.8–90.9), for 3 years was 97.3% (95.2–98.6), and for 5 years was 98.6% (97.6–100.0). The probability of remaining free from distant metastasis for further two years in patients who had a cCR

Table 1. Summary of studies

<i>Authors</i>	<i>Country</i>	<i>Title</i>	<i>Study type</i>	<i>No. of patients</i>	<i>Outcome</i>
Beard BW et al., 2020 ³	US	Watch-and-Wait Compared to Operation for Patients with Complete Response to Neoadjuvant Therapy for Rectal Cancer	Retrospective	95	An increasing use of nCRT experience with WW, it is anticipated an increasing demand by patients for WW to preserve quality of life.
Smith JJ et al., 2019 ²	US	Assessment of a Watch-and-Wait Strategy for Rectal Cancer in Patients with a Complete Response After Neoadjuvant Therapy	Retrospective	249	The results of this study have indicated that 82% of patients with rectal cancer managed by a WW strategy achieved rectal preservation.
Fernandez LM et al., 2021 ¹	International	Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database	Retrospective, multicentre	793	Conditional survival analysis estimates suggests that patients who sustain a clinical complete response for 3 years have 5% or lower risk of developing a local regrowth and a less than 2% risk of developing systemic recurrence thereafter.
Pascual-Russo A et al., 2020 ⁴	Argentina	Better quality of life and reduced faecal incontinence in rectal cancer patients with the watch-and-wait follow-up strategy	Prospective	30	The WW strategy in patients with locally advanced adenocarcinoma of the rectum was associated with better quality of life and reduced faecal incontinence, compared with the AR + TME strategy.
Haak HE et al., 2021 ⁵	The Netherlands	The evaluation of follow-up strategies of watch-and-wait patients with a complete response after neoadjuvant therapy in rectal cancer	Retrospective	304	The results support an intensive follow-up in the first 2 years, followed by a de-intensification after 2 years of follow-up, which will probably result in a lower burden for patients and a better efficiency.
Neşsar G et al., 2019 ⁶	Turkey	“Watch and wait” approach in rectal cancer patients following complete clinical response to neoadjuvant chemoradiotherapy does not compromise oncologic outcomes	Prospective, comparative	61	The oncological results of the WW approach patients were no different from the patients who received radical surgery and were diagnosed as having pathological complete response. Those patients who required abdominal-perineal resection before chemoradiation should be informed about this approach if they have achieved cCR clinically.
Van der Sande ME et al., 2019 ⁷	The Netherlands	Impact of radiotherapy on anorectal function in patients with rectal cancer following a watch and wait programme	Cross-sectional, prospective	33	This was the first study to investigate the late dose-volume effects on radiotherapy on the anorectal function in rectal cancer patient following a WW policy after nCRT. One third of the patients reported major low anterior resection syndrome score after a minimal follow-up of two years.
Haak HE et al., 2020 ⁸	The Netherlands	Is watch and wait a safe and effective way to treat rectal cancer in older patients?	Prospective and retrospective	43	WW for older patients with a near cCR appears to be a safe alternative to TME, with a very high pelvic control rate, and few rectal cancer related deaths.

Authors	Country	Title	Study type	No. of patients	Outcome
Kaul S et al., 2022 ⁹	United Kingdom	Is the Management of Rectal Cancer Using a Watch and Wait Approach Feasible, Safe and Effective in a Publicly Funded General Hospital?	Retrospective	63	WW policy is a safe and effective option for the management of real-world patients with a cCR to neoadjuvant therapy. It shows that cCR is durable and when mucosal regrowth occurs, it can be safely and effectively salvaged. The study also shows that the quality of life is probably improved if a WW approach is adopted.
Al-Najami I et al., 2021 ¹⁰	United Kingdom	Rectal cancer: Watch-and-wait and continuing the rectal-preserving strategy with local excision for incomplete response or limited regrowth	Prospective	42	A WW strategy for cCR is a viable pathway in the non-operative management of rectal cancer. The use of CRT + local excision is a useful option for those who hope to avoid surgery but caution should be exercised due to substantially higher risk of recurrence.
Nasir I et al., 2019 ¹¹	Portugal	Salvage surgery for local regrowth in Watch & Wait - Are we harming our patients by deferring the surgery?	Retrospective, single centre	78	Patients with an initial cCR who developed a local regrowth after WW approach may be safely managed by deferring the surgery.
Gérard JP et al., 2019 ¹²	France	Planned organ preservation for early T2-3 rectal adenocarcinoma: A French, multicentre study	Retrospective	74	Organ preservation through WW policy is a viable option for patients with T2-T3 rectal cancers. Contact X-ray brachytherapy with nCRT provides a high rate of cCR with a risk of local recurrence below 15%.

Legend: WW - Watch and Wait/ Wait and See; AR - anterior resection; TME - total mesorectal excision; nCRT - neoadjuvant chemoradiotherapy; cCR - complete clinical response

without distant metastasis for one year was 93.8% (92.3–95.9), for 3 years was 97.8% (96.6–99.3), and for 5 years was 96.6% (94.0–98.9). The results suggest that the intensity of active surveillance in patients with rectal cancer managed by a WW approach could be reduced if they achieve and maintain a cCR within the first 3 years of starting this approach¹.

The study performed by Pascual-Russoa et al. aimed to analyse and compare the functional anorectal disorders and quality of life in patients with locally advanced adenocarcinoma of the rectum treated with nCRT, divided into two different groups: group 1 (G1), WW; and group 2 (G2), anterior resection (AR). 30 patients (G1: n = 20 and G2: n = 10) who had finished nCRT at least 12 months prior were included. The mean patients' age was 59.5 years (range: 41-79). The functional anorectal disorders were evaluated through clinical history, 21-day bowel diary, Jorge and Wexner faecal incontinence scale, anorectal manometry and faecal incontinence quality of life scale.

The study showed that there are no significant differences between the two groups regarding bowel diary and anorectal manometry, but significant regarding faecal incontinence scale: faecal incontinence in G1 was significantly less severe than in G2. Quality of life: significant difference between the two groups (G1: 3.7 vs. G2: 2.8; $p < 0.03$). The study concluded that the WW follow-up strategy in patients with locally advanced rectal cancer was associated with better quality of life and reduced faecal incontinence⁴.

The long-term anorectal function was assessed in rectal patients following a WW policy after chemoradiotherapy by van der Sande in 2019. The study also investigated the dose-volume effects of radiotherapy on the rectal function. 33 patients who were treated with chemoradiotherapy and a WW policy with a minimum follow-up of two years were included. The anorectal function was assessed using anorectal manometry and patient reported outcomes (Vaizey faecal incontinence score and low anterior resection

syndrome score). The most frequent complaints were clustering of defecation and faecal urgency. Trends towards a higher Vaizey and low AR syndrome score after higher anal sphincter complex dose were observed, although these associations were not statistically significant⁷.

Beard et al. reviewed the records of patients treated with nCRT for nonmetastatic rectal cancer. From January 2015 to February 2019, 465 patients completed nCRT; 406 patients had response assessment, of which 95 (23%) had a complete endoscopic response. Of these patients, 53 patients underwent WW and 42 patients had surgery. The median follow-up was 35 months. In the WW group, the rate of 3-year free from local regrowth was 85%. In the surgical and WW groups, 3-year overall survival, rectal cancer-specific survival, and freedom from nongrowth recurrence were 100% vs 88% ($p=0.03$), 100% vs 95% ($p=0.16$), and 92% vs 85% ($p=0.36$), respectively. Of the six WW patients with local regrowth, five (83%) eventually developed distant recurrence. The study concluded that WW instead of surgery appears to be a safe and feasible treatment approach for patients achieving cCR to nCRT. A careful evaluation to confirm cCR after nCRT is valuable in selecting patients for WW³.

Also in the USA, Smith et al. conducted a retrospective case series analysis in a comprehensive cancer centre in New York, including patients who received a diagnosis of rectal adenocarcinoma between January 1, 2006, and January 31, 2015. The study analysed the outcomes of WW among patients with rectal cancer who had a cCR to nCRT. Patients had a cCRT after completing nCRT and agreed to a WW strategy of active surveillance and possible salvage surgery ($n = 113$), or patients underwent TME and were found to have a pathologically complete response at resection ($n = 136$). No pelvic recurrences occurred in the pathologically complete response group. Rectal preservation was achieved in 93 of 113 patients (82%) in the WW group (91 patients with no local regrowth plus two patients with local regrowth salvaged with trans anal excision). A higher rate of distant metastasis was observed among patients in the WW group who had local regrowth vs those who did not have local regrowth (36% vs 1%, $p < 0.001$). The study concluded that a WW strategy for selected rectal cancer patients who had a cCR after nCRT resulted in excellent rectal preservation and pelvic tumour control; however, in the WW group, a worse survival was noted along with a higher incidence of distant progression in patients with local regrowth vs those without local regrowth². The long-term outcomes and the quality of life in patients managed with WW policy were reported by Kaul et al. in a retrospective

study of 63 patients. The rate of cancer recurrence was 25.4% (95% confidence interval 16.3-37.3%) in patients from the WW program. Thirteen patients out of 63 had mucosal regrowth, 12 with mucosal regrowth alone, and one patient had metastatic disease, local-nodal recurrence, and mucosal regrowth. There was no significant difference in the incidence of metastatic disease between surgical and WW cohort. The 5-year survival was 79% in the WW group and 76% in the surgical group⁹.

Al-Najami et al. compared the complete responders to nCRT patients who were on a WW program with a group of patients who were treated with an additional local excision for persistent tumour. Regrowth was noted in 26% (11/42) patients in the WW group after 2 years surveillance; disease-free survival was 94.5% (80-99%) at one year and 74.9% (44-76.4%) at three years. Recurrence was noted in 45% (10/22) in the nCRT + local excision group, disease-free survival at one and three years was 74% (53.4-88.1) and 66.2% (45.6-82.4), respectively¹⁰. In another study conducted by Nasir et al., patients with local regrowth following WW therapy were operated – regrowth deferred surgery (RDS) group – and compared to those with persistent disease after nCRT who did undergo surgery – non-deferred surgery (NDS) group. 78 (63%) with cCR entered WW. Twenty-three developed regrowth and underwent surgery, while 55 remain under surveillance. RDS group had smaller tumours than NDS group (2.3 ± 2 cm vs 4.5 ± 3 cm, $p=0.002$). All regrowth patients underwent minimally invasive surgery. Anastomotic leaks, 30-day morbidity, reintervention and readmission rates were similar. The pathological features and 3-year oncological outcomes were identical between groups¹¹.

DISCUSSION

This review provides an overview of the WW approach for patients with rectal cancer, that can avoid the total mesorectal excision, which is associated with significant morbidity and mortality, especially when radiotherapy is given pre-operatively¹³.

As advocated by Habr-Gama, surgery deferral and WW might be an important option for patients with an excellent or cCR after nCRT. The cCR may be an „apparent“ cCR and local regrowth may appear¹⁴, hence deferred surgery or contact X-ray brachytherapy are therapies which should be taken into consideration to reduce the local recurrence rate^{11,12}. All the patients included in these studies were followed-up for more than two years and they were monitored every three months in the first year, and six months thereafter, up to 2, 3 or 5 years, depending on the

study. The WW approach required more investigations than the standard tests performed in rectal cancer treated with the standard therapy. The theoretical comparison of the different hypothetical schedules, as demonstrated by Haak et al. and Fernandez et al. suggests that the optimal follow-up schedule should focus on the first two years, with endoscopy every 3 months and MRI every 3–6 months^{1,5}. Longer intervals in the first two years will cause delays in the diagnosis of local regrowth. After two years, increasing the interval from 6 to 12 months did not cause important delays. The study concluded that the optimal follow-up schedule for a WW policy in patients with cCR after chemoradiation for rectal cancer should include frequent endoscopy and to a lesser degree MRI in the first 2 years. Hence, the intensity of active surveillance in patients with rectal cancer managed by a WW approach could be reduced if they achieve and maintain a cCR within the first three years of starting this approach^{4,6,7}.

Incidence of mucosal regrowth, metastatic disease and recurrence of cancer were reported in the included studies. In most cases, mucosal regrowth occurred within two years of the completion of treatment. There is little evidence in the literature on how to treat this regrowth, even if some data have already been published. As showed in our review, deferred surgery is a viable option along with non-operative treatment^{11,12}.

Even if the studies demonstrated that quality of life after a WW policy is better than after TME, the anorectal function of patients who followed the WW therapy was impaired, with one third of the patients reporting major bowel dysfunction¹⁵. The anorectal function in the studies included here was assessed using low AR syndrome score and Vaizey faecal incontinence score questionnaire and by manometry. No association between higher planned radiotherapy dose to the anal sphincter complex and lower anal pressures was found. However, faecal incontinence in patients treated with neoadjuvant therapy is less severe than in patients who had anterior resection or TME^{3,6}.

CONCLUSIONS

Considering the data summarized in the present review, it can be assumed that WW policy may be a safe option for patients with a cCR after nCRT and it can be an alternative for patients who either present a high surgical risk or refuse surgical treatment. Furthermore, this review highlights the improvement of quality of life in patients who underwent a WW policy in comparison with those who underwent surgery. However, more studies are needed to

demonstrate the efficacy of this approach and to optimize the therapy protocol for patients who choose this strategy.

Author Contributions:

A.B. and F.A.G. conceived the original draft preparation. A.P. and V.F. were responsible for conception and design of the review. C.T. and A.P. were responsible for the data acquisition. A.F. and F.A.G. and T.B. were responsible for the collection and assembly of the articles/published data, and their inclusion and interpretation in this review. A.B. and F.A.G. contributed equally to the present work. All authors contributed to the critical revision of the manuscript for valuable intellectual content. All authors have read and agreed with the final version of the manuscript.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article.“

„No funding for this study“

Acknowledgements:

None

REFERENCES

1. Fernandez LM, São Julião GP, Figueiredo NL, et al. International Watch & Wait Database Consortium. Conditional recurrence-free survival of clinical complete responders managed by watch and wait after neoadjuvant chemoradiotherapy for rectal cancer in the International Watch & Wait Database: a retrospective, international, multicentre registry study. *Lancet Oncol.* 2021;22(1):43-50.
2. Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. *JAMA Oncol.* 2019;5(4):e185896.
3. Beard BW, Rettig RL, Ryoo JJ, Parker RA, McLemore EC, Attaluri V. Watch-and-wait compared to operation for patients with complete response to neoadjuvant therapy for rectal cancer. *J Am Coll Surg.* 2020;231(6):681-692.
4. Pascual-Russo A, Milito D, Facio L, et al. Better quality of life and reduced faecal incontinence in rectal cancer patients with the watch-and-wait follow-up strategy. *Rev Gastroenterol Mex (Engl Ed).* 2020;S0375-0906(20)30090-2.
5. Haak HE, Žmuc J, Lambregts DMJ, et al. Dutch Watch-and-Wait Consortium. The evaluation of follow-up strategies of watch-and-wait patients with a complete response after neoadjuvant therapy in rectal cancer. *Colorectal Dis.* 2021;23(7):1785-1792.
6. Neşşar G, Demirbağ AE, Mısırlıoğlu HC, Sezer S. „Watch and wait“ approach in rectal cancer patients following complete clinical response to neoadjuvant chemoradiotherapy does not compromise oncologic outcomes. *Turk J Gastroenterol.* 2019;30(11):951-956.
7. van der Sande ME, Hupkens BJP, Berbée M, et al. Impact of radiotherapy on anorectal function in patients with rectal

- cancer following a watch and wait programme. *Radiother Oncol.* 2019;132:79-84.
8. Haak HE, Maas M, Lambregts DMJ, Beets-Tan RGH, Beets GL; Dutch Watch-and-Wait Consortium. Is watch and wait a safe and effective way to treat rectal cancer in older patients? *Eur J Surg Oncol.* 2020;46(3):358-362.
 9. Kaul S, Rao C, Mane R, et al. Is the management of rectal cancer using a watch and wait approach feasible, safe and effective in a publicly funded general hospital? *Clin Oncol (R Coll Radiol).* 2022;34(1):e25-e34.
 10. Al-Najami I, Jones HJ, Dickson EA, et al. Rectal cancer: Watch-and-wait and continuing the rectal-preserving strategy with local excision for incomplete response or limited regrowth. *Surg Oncol.* 2021;37:101574.
 11. Nasir I, Fernandez L, Vieira P, et al. Salvage surgery for local regrowth in Watch & Wait – Are we harming our patients by deferring the surgery? *Eur J Surg Oncol.* 2019;45(9):1559-1566.
 12. Gérard JP, Barbet N, Gal J, et al. Planned organ preservation for early T2-3 rectal adenocarcinoma: A French, multicentre study. *Eur J Cancer.* 2019;108:1-16.
 13. van Gijn W, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomized controlled TME trial. *Lancet Oncol* 2011;12(6): 575e82.
 14. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer. *Dis Colon Rectum* 2013;56(10):1109e17.
 15. Hupkens BJP, Martens MH, Stoot JH, et al. Quality of life in rectal cancer patient safer chemoradiation: watch-and-wait policy versus standard resection – a matched-controlled study. *Dis Colon Rectum* 2017;60:1032-40.