New frontiers in rectal cancer treatment: implementing Watch and Wait in Hong Kong

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This article was published on 16 Apr 2026 at www.hkmj.org.

This version may differ from the print version.

Hong Kong Med J 2026;32:Epub
https://doi.org/10.12809/hkmj2513415

Introduction

Conventional treatment for patients with locally advanced rectal cancer involves neoadjuvant therapy (NAT) to downstage the tumour, followed by total mesorectal excision (TME) and adjuvant therapy if required. However, surgery is associated with risks, including anastomotic leakage and low anterior resection syndrome, which can substantially affect overall quality of life. Furthermore, surgery for low rectal cancer may result in the formation of a permanent colostomy.

A subset of patients with stage II/III rectal cancer develop a good clinical response to NAT, termed either complete clinical response (cCR) or near-complete response (nCR), depending on endoscopic and radiological assessment. In 2004, Habr-Gama et al[1] first proposed the concept of organ preservation, otherwise known as Watch and Wait (WW), as an option for patients who respond well to NAT, thereby avoiding the morbidity and mortality associated with surgery, as well as the potential need for a stoma. In their seminal paper, they demonstrated that patients who achieved cCR and were managed non-operatively had better 5-year overall survival and similar 5-year disease-free survival compared with those who underwent surgery and had a pathological complete response (pCR) in the resection specimen.[1]

In recent years, the use of total neoadjuvant therapy (TNT) has become increasingly popular, as it is associated with a reduced risk of distant failure,[2] greater compliance with chemotherapy, shorter time to ileostomy closure, and increased tumour response.[3] Randomised controlled trials have confirmed that TNT can enhance tumour response; both PRODIGE 23[4] and RAPIDO[5] reported a doubling of pCR rates to 28% with TNT. Given the increasing proportion of patients offered TNT, more patients will develop cCR or nCR and would therefore be eligible for WW.

Clinical assessment of patients after neoadjuvant therapy

All patients with stage II/III biopsy-proven rectal cancer who lack evidence of metastatic disease and develop a good tumour response after NAT can be considered candidates for WW. Patients should be restaged within 8 (±4) weeks of completing NAT; this should include digital rectal examination, endoscopic assessment, and magnetic resonance imaging (MRI). Endoscopic response should be graded as cCR, nCR, or incomplete clinical response (iCR) according to the MSKCC (Memorial Sloan Kettering Cancer Center) tumour regression criteria.[6] Magnetic resonance imaging response should be graded according to tumour regression grade.

Patients with an iCR should be offered standard TME surgery within 12 weeks of completing NAT. They will then undergo standard postoperative surveillance in accordance with institutional guidelines. Patients who develop a good tumour response (cCR or nCR) should be offered the option of WW. As established in the Organ Preservation for Rectal Adenocarcinoma (OPRA) trial, if there is a discrepancy between endoscopic and MRI findings regarding tumour response, the endoscopic findings take precedence.[7] Patients who agree to undergo WW should follow the intensive surveillance protocol detailed below.

Patient selection

It is important to establish which patients should be offered WW surveillance. Earlier studies focused only on patients who had achieved cCR and did not include those with nCR, owing to uncertainty regarding its underlying biology. However, there is evidence that nCR comprises two subpopulations: one group that will eventually achieve cCR, and another that will subsequently demonstrate tumour enlargement and develop iCR.

Several studies have demonstrated that increasing the interval between NAT completion and surgery increases the proportion of patients suitable for WW. Probst et al[8] reported that, in an analysis of 17 255 patients with stage II/III locally advanced rectal cancer who underwent NAT followed by surgical resection, waiting longer than 8 weeks after NAT was associated with higher odds of pCR and tumour downstaging. Furthermore, Hupkens et al[9] reported that 90% of patients with nCR at 8 to 10 weeks after NAT subsequently developed cCR (6 to 12 weeks later). Even when trimodal assessment

indicates residual tumour, 15% of patients eventually achieve cCR.[10] In a multicentre phase 2 trial, Garcia-Aguilar et al[11] demonstrated that extending the interval between neoadjuvant chemoradiotherapy and surgery increased the proportion of patients who eventually developed pCR.

The OPRA trial[7] reported promising outcomes with a WW strategy in patients who developed either cCR or nCR. In this study, the 3-year TME-free survival rate was 53% among patients who underwent TNT with consolidation chemotherapy. Provided that patients with cCR show no signs of local regrowth, and those with nCR continue to demonstrate tumour regression after NAT, they remain suitable for ongoing surveillance within a WW programme.

Appropriate candidates for WW are often patients with mid- to distal rectal cancer. This trend arises because the alternatives—abdominoperineal resection with a permanent colostomy, or an ultralow or coloanal anastomosis—are both associated with poor functional outcomes. Age does not appear to affect clinical outcomes. The International Watch and Wait Database (IWWD) reported no differences in disease-specific survival, local regrowth, or risk of distant metastases between younger patients and those over 50 years of age.[12]

Certain pathological features are associated with lower cCR rates, including larger tumour size, a circumferential resection margin of smaller than 1 mm, extramural venous invasion, extensive mesorectal or pelvic lymph nodes, and mutations in *TP53* and *SMAD4*.[13] Patients with ulcerated or circumferential tumours carry a risk of severe scarring and narrowing of the rectal lumen, which may preclude endoscopic follow-up; such tumours represent a relative contraindication to WW.[14]

Surveillance

Intensive surveillance is required to detect early tumour regrowth in any patient choosing WW (Table). Surveillance is most frequent during the first 2 years, given that 88% of local regrowth occurs within this period.[15] International guidelines for WW surveillance recommend 4-monthly flexible sigmoidoscopy and measurement of carcinoembryonic antigen levels during the first 2 years, followed by 6-monthly assessments for the subsequent 3 years.[7] Magnetic resonance imaging is recommended every 6 months for the first 2 years, then annually for the following 3 years.[7] Computed tomography of the thorax, abdomen, and pelvis should be performed annually, and colonoscopy in Years 1 and 5. However, patients may be reviewed more frequently if concerns are raised by either the patient or the clinician.

During WW surveillance, patients with sustained cCR, as well as those with nCR who subsequently achieve cCR or continue to demonstrate tumour regression, should remain on the WW follow-up protocol. If there are signs of tumour regrowth in a patient who previously achieved cCR, or if a patient with nCR shows an increase in tumour size compared with the previous clinical evaluation, TME should be offered within 4 to 6 weeks.

TABLE. Five-year follow-up schedule of investigations for patients undergoing Watch and Wait surveillance: (a) Years 1-2 and (b) Years 3-5 for patients with complete clinical response or near-complete response

(a)

Investigation after entry into WW	Month 4	Month 6	Month 8	Month 12	Month 16	Month 18	Month 20	Month 24
DRE and flexible sigmoidoscopy	✓		✓	Colonoscopy	✓		✓	✓
CEA	✓		✓	✓	✓		✓	✓
Colonoscopy				✓				
MRI		✓		✓		✓		✓
CT TAP				✓				✓

(b)

Investigation after entry into WW	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60
DRE and flexible sigmoidoscopy	✓	✓	✓	✓	✓	Colonoscopy
CEA	✓	✓	✓	✓	✓	✓
Colonoscopy						✓
MRI		✓		✓		✓
CT TAP		✓		✓		✓

Abbreviations: CEA = carcinoembryonic antigen; CT TAP = computed tomography of the thorax, abdomen, and pelvis; DRE = digital rectal examination; MRI = magnetic resonance imaging; WW = Watch and Wait

Resource requirements

Watch and Wait has not previously been offered in the Hong Kong public healthcare system. Several key challenges must be addressed before WW can be widely implemented locally. Watch and Wait surveillance involves regular endoscopic and MRI examinations, which require additional infrastructure and funding. Although it may be feasible for Hong Kong colorectal surgeons to arrange additional flexible sigmoidoscopies within their own departments, scheduling extra MRI scans remains challenging because of limited appointment availability. There is increasing evidence that luminal assessment is more informative than MRI for detecting tumour regrowth during WW. In the OPRA trial, when there was a discrepancy between endoscopic and MRI findings, endoscopic findings took precedence, given that rectal cancer is primarily a mucosal disease.[7] Furthermore, analysis of data from the IWWD revealed that 97% of local regrowth occurred in the bowel wall.[15] Considering the limited availability of MRI appointments within the Hong Kong public healthcare system, it may be necessary to develop a WW surveillance programme tailored to local resources, for example by arranging MRI examinations more selectively, particularly in response to an elevated carcinoembryonic antigen level.

Implementation of WW also relies on consistent and robust endoscopic assessment of tumour response.[6] Training is essential to ensure high-quality and consistent reporting. Increasing awareness of WW in Hong Kong, and educating local clinicians on the endoscopic classification of tumour response, will help ensure that the most appropriate patients are offered WW within a robust surveillance programme.

Oncological outcomes

Because WW is not yet widely adopted, there may be hesitancy among local clinicians regarding the long-term oncological outcomes of patients undergoing WW. However, these concerns are not supported by recent data. The IWWD examined 880 patients with cCR who underwent WW and reported a 2-year local regrowth rate of 25%, a 5-year overall survival rate of 85%, and a 5-year disease-free survival rate of 94%.[15] For patients who develop local regrowth, salvage surgery was feasible in more than 95% of cases[16]; pelvic control was maintained in 91% of those who underwent salvage surgery.[17] Regarding distant metastasis, data from MSKCC indicate an increased risk in patients with local regrowth compared with those without local failure,[17] and the IWWD reported an incidence of distant metastasis of 18% in patients with local regrowth compared with 5% in those without local failure.[15] However, these findings may be explained by the fact that regrowing tumours are more likely to have aggressive underlying biology, rather than reflecting an inherent risk associated with delayed surgery.

Further evidence supporting the importance of tumour biology—rather than timing of surgery—in determining oncological outcomes was provided by the OPRA trial, which demonstrated an overall distant metastasis rate of 20%, with no significant difference between patients who underwent TME at restaging and those who underwent TME after regrowth.[7] Habr-Gama et al[18] also reported no survival disadvantage in patients who underwent delayed surgery for suspected cCR compared with those who had delayed surgery for other reasons. A recent study by Thompson et al[6] demonstrated that clinical tumour response grade was associated with disease-free survival, local recurrence-free survival, distant metastasis-free survival, and overall survival; the authors reported 3-year TME-free survival (ie, organ preservation) rates of 77% for patients with cCR and 40% for those with nCR.[6] Taken together, these studies support the conclusion that underlying tumour biology, rather than timing of surgery, is the key determinant of oncological outcomes.

Patient perspectives

Patient education is essential to ensure widespread enrolment and adherence to the WW surveillance schedule. Patients' perspectives and their willingness to accept the risk of regrowth as part of organ preservation should be explored before WW is offered. Gani et al[19] showed that 83% of patients would choose WW if they achieved cCR despite higher rates of local regrowth, and 94% accepted a local regrowth rate of 25%. In another study examining patient and physician preferences for non-operative management of low rectal cancer compared with abdominoperineal resection, patients were willing to accept a higher absolute risk of local regrowth than physicians (20% vs 5%); they were also willing to accept a greater absolute decrease in overall survival (20% vs 5%).[20] These findings suggest that patients may be more willing than physicians to accept the higher risks associated with WW.

Conclusion

In Hong Kong, WW has the potential to reduce the number of unnecessary operations, and improve patient quality of life. Successful adoption depends on overcoming several challenges, including resource constraints, robust implementation of a surveillance programme, and comprehensive education of both clinicians and patients. By addressing these barriers, Hong Kong will have the opportunity to offer more personalised treatment options for rectal cancer, ultimately benefiting patients and the public healthcare system.

Author contributions

All authors contributed to the concept or design of the study, acquisition of the data, analysis or interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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