Spotlight

Surgery or a watch-and-wait approach for rectal cancer?

Opening opinion: Surgery

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Chemoradiotherapy followed by total mesorectal excision is the standard of care in rectal cancer. Watch-and-wait was first tested by a Brazilian team, who showed a complete clinical response in a subgroup of patients treated with chemoradiotherapy for rectal cancer. After 57 months follow-up, 5-year overall survival and disease-free survival did not differ between patients with complete pathological tumour response treated by total mesorectal excision or watch-and-wait. The first meta-analysis on studies of patients with rectal adenocarcinoma managed by watch-and-wait after complete clinical response to neoadjuvant chemoradiation includes mainly retrospective studies (19 [83%] of 23) with a few patients (15 studies had data for less than 30 patients). The pioneers of watch-and-wait must be congratulated for pushing surgeons to improve the quality of life of some patients with rectal cancer who can avoid surgery. Although there is no doubt that watch-and-wait will be part of the future management of patients with rectal cancer, the literature shows that treatment without surgery cannot be recommended as a new standard of care in this setting in 2018.

The first limitation of a watch-and-wait approach is the absence of a correlation between complete clinical response, assessed by clinical, endoscopic, or radiological examinations, and pathological complete response, which explains local recurrence in 16–28% of patients after chemoradiotherapy due to the heterogeneity of responders, many of whom present with residual scars formed mainly by fibrotic tissue and a low concentration of tumour cells that can only be detected by histology.

The second limitation of a watch-and-wait approach is relying on salvage surgery, required in a third of patients who did not have upfront surgery. Although salvage surgery has been reported as feasible in 80–90% of these cases, local recurrence occurs more frequently after salvage than upfront surgery (three [3%] of 98 *vs* 0 of 136 patients; p=0·04). Regarding other endpoints, the meta-analysis showed that disease-free survival improved with surgery compared with watch-and-wait, but there was no difference in terms of recurrence and cancer-specific mortality. However, the small number of patients included in this analysis warrants cautious interpretation. To date, there are no data on morbidity and functional outcomes after salvage surgery, however definitive colostomy is required in 50% of patients who undergo salvage surgery.

The third limitation of watch-and-wait is the absence of prospective evidence regarding this approach. There is no standardisation in patient selection, neoadjuvant therapy regimen, diagnostic technique for clinical response assessment, definition of local recurrence, and follow-up protocols. The meta-analysis shows that most patients selected for watch-and-wait were treated for locally advanced tumours (67% had T3 rectal tumours) and watch-and-wait was incidentally chosen due to high-risk characteristics or patient's refusal to surgery. Considering patients with localised disease, eligible for organ preservation as an alternative to total mesorectal excision, surgery might achieve better outcomes than observation after neoadjuvant treatment.

The GRECCAR 2 trial randomly assigned patients with stage T2T3 lower rectal tumours, of maximum size 4 cm, who had a good clinical response to neoadjuvant chemoradiotherapy (residual tumour ≤2 cm) to local excision (n=74) or total mesorectal excision (n=71). As per protocol, a third of patients with pT2 or pT3 stage tumours in the local excision group received a completion total mesorectal excision due to the theoretical risk of lymph node micrometastases. The high frequency of side effects observed in the local excision group, mainly due to the high crossover to total mesorectal excision, did not permit to demonstrate the benefit of local excision compared to total mesorectal excision. However, the fact that completion total mesorectal excision was not necessary in 90% of cases because only 8% of patients had positive lymph nodes suggests good disease control with local

Declaration of interests
ER and ROP declare no competing interests

For more on the **Brazilian experience on watch-and-wait** see *Ann Surg* 2004; **240:** 711–18

For more on the **meta-analysis on watch-and-wait** see Articles *Lancet Gastroenterol Hepatol* 2017; **2:** 501–13

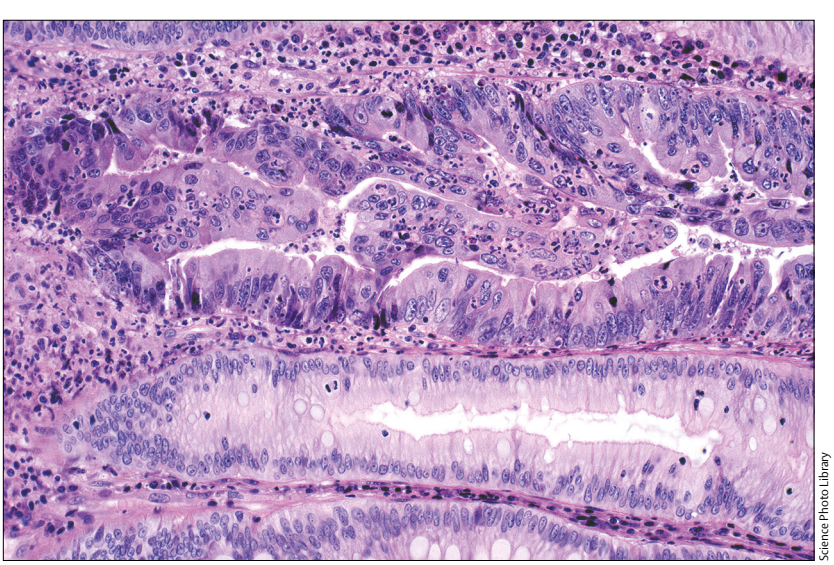
For more on **salvage surgery after watch-and-wait** see *Dis Colon Rectum* 2017; **60:** 335–45

For more on **organ preservation for rectal cancer** see Articles *Lancet* 2017; **390:** 469–79

For more on **mortality after total mesorectal excision** see *Dis Colon Rectum* 2015; **58:** 159–71

For more on the **International Watch-and-Wait study** see *Lancet* Articles 2018; **391:** 2537–45

For more on the **pooled analysis** see *Ann Surg* 2018; **268:** 955–67



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excision in most patients with small stage T2T3 tumours. Compared with watch-and-wait, local excision can cause temporary rectal bleeding and pain, but it can avoid salvage total mesorectal excision (in 5% of patients in the GRECCAR 2 trial), and offers the opportunity to de-escalate surgical treatment to subcomplete clinical responders.

Total mesorectal excision remains the standard of care after neoadjuvant therapy for big rectal tumours (T3T4) because of insufficient evidence from watch-and-wait and the uncertain outcomes of salvage surgery, and minor surgery is a safe option in patients with small rectal tumours (T2T3) who achieve complete clinical responses after neoadjuvant therapy.

Counter opinion: Watch-and-wait

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Expert surgeons often have a natural tendency to minimise the negative effects of surgical procedures. Frequently, surgical procedures take longer and are more difficult to complete than anticipated. The same applies for rectal cancer surgery. In this setting, total mesorectal excision following neoadjuvant chemoradiotherapy may seem a straightforward procedure when described by a colorectal surgeon, who might justify total mesorectal excision in the absence of residual cancer for the sole reason of providing pathological confirmation of a complete clinical response after neoadjuvant chemoradiotherapy.

Surgeons will often argue that surgery can be done in a minimally invasive approach to improve postoperative recovery compared with open surgery while still achieving good oncological outcomes. However, recent randomised studies (NCT00726622, ACTRN12609000663257) have failed to show non-inferiority of laparoscopic and robotic surgery compared with open surgery.

Surgeons often state that a definitive stoma might not be necessary as a low colo-anal anastomosis is frequently possible with acceptable postoperative function. However, surgeons forget that even though a colostomy is only required in less than 10% of patients upfront for surgical reasons, more than 22% of patients undergoing a primary anastomosis will require a definitive colostomy long-term. Even among those patients who avoid a definitive stoma, at least 50% of patients who had a total mesorectal excision will have poor fecal incontinence scores. Finally, 10% of these patients who ultimately avoid a definitive stoma will require an endoscopic cecostomy to use daily anterograde enemas and achieve minimally acceptable function.

Surgeons often state that overall morbidity and mortality are considerably low after total mesorectal excision. However, a multicentre, retrospective study showed that, depending on patients' comorbidities and age, total mesorectal excision-associated mortality is as high as 16%.

Surgeons also often state that life returns to normal a few months after surgery. However, patients who have rectal cancer surgery are more likely to be dependent on disability pensions compared with age-counterparts who did not have surgery.

Surgeons often state that an excisional biopsy provides a definitive confirmation of pathological complete response of the primary tumor after neoadjuvant therapy while preserving the rectum. However, they often forget that this full-thickness excision of the irradiated rectal wall results in delayed wound healing, pain, and substantial consequences to anorectal function.

The recognition of all of these problems associated with rectal cancer surgery led surgeons to challenge the role of radical surgery in the setting of a complete clinical response. In the presence of objective findings of clinical, endoscopic, and radiological results consistent with no residual disease after neoadjuvant treatment, patients can be managed by no immediate radical surgery and, instead, enrolled in a strict surveillance programme with frequent reassessments of tumour response, the watch-and-wait approach. This strategy allows for the identification of patients who achieve durable responses to neoadjuvant therapy and can avoid the sometimes devastating consequences of radical surgery.

Although 25% of patients will have tumour regrowth after an initial complete clinical response to neoadjuvant therapy, improved patient selection through baseline staging and neoadjuvant treatment characteristics has the potential to achieve durable complete clinical responses and minimise the risk of developing recurrent disease.

Still, provided there is appropriate and regular follow-up, available evidence suggests that most patients are unharmed by the watch-and-wait approach. More than 90% of local recurrences after neoadjuvant therapy reside within the rectal wall or lumen, allowing straightforward identification. These local recurrences are frequently resectable by salvage surgery achieving negative resection (R0) margins. Furthermore, delaying surgical treatment does not appear to negatively affect overall survival. Finally, a meta-analysis suggests that even the incidence of distant metastasis appears to be similar between watch-and-wait and upfront surgery. Ongoing research on molecular markers to assess response might provide additional tools for optimal selection of patients who can safely avoid surgery and inform precise surveillance schedules in the near future allowing a truly personalised management of patients with rectal cancer. Until then, surgeons should think twice before operating on a complete clinical responder. As is often quoted, "a good surgeon knows how to operate, the better surgeon knows when to operate, but the best surgeon knows when not to operate".