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Watch-and-Wait is an Option in Rectal Cancer Patients: From Controversy to Common Clinical Practice☆

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Abstract

Overview of the introduction of organ preservation in rectal cancer patients and future challenges.

Keywords: Nonoperative management; organ preservation; rectal cancer; watch and wait

Introduction

Surgery has long been the primary curative modality for rectal cancer. In locally more advanced tumours, neoadjuvant (chemo)radiation has significantly improved local control rates, but, interestingly, it has also resulted in a proportion of pathological complete responses (pCR). After long-course chemoradiation for locally advanced tumours, pCR rates up to 20% were seen [1], whereas after short-course radiotherapy and delayed surgery after a 6–8-week interval, pCR rates of 7–14% have been described [2]. Patients who achieved a pCR after neoadjuvant therapy seemed to have an excellent prognosis [3]. Although the combination of neoadjuvant (chemo)radiotherapy followed by total mesorectal excision (TME) results in a good oncological outcome, patients may experience a profound effect on quality of life, with bowel, sexual and bladder dysfunction, and with the potential impact of a permanent colostomy when an anastomosis is not feasible or desirable. In recent years, the organ-preservation approach for rectal cancer has been explored, in an attempt to improve a patient's quality of life by prevention of TME surgery and to meet the increasing preference of patients towards organ-preserving strategies [4,5]. The terminology in organ preservation can be confusing, but watchful waiting, wait-and-see and non-operative management all have in common that after a good response to radiotherapy, in selected patients, a formal TME resection is no longer required.

How It Started

In the 1970s, a series with highly selected patients described the results of resectable rectal cancers that were successfully treated by 'curative endocavitary irradiation' [6]. This is considered the precursor technique of the current contact X-ray brachytherapy (CXB). However, the use of this technique remained mainly limited to a few centres and to frail and elderly patients. The current wider interest in organ preservation started after a more widespread use of neoadjuvant (chemo)radiotherapy in the 1990s. In 2004, the landmark paper by Habr-Gama's group was published [7], in which 265 patients with resectable rectal cancer were assessed for a clinical complete response (cCR) 8 weeks after chemoradiation, of whom 71 entered a watch-and-wait (W&W) programme [7]. Their results suggested that in these patients, omitting TME surgery and follow-up in a carefully structured surveillance programme can be safe, with a 5-year overall and disease-free survival of 100% and 92%, respectively; moreover, they stated that a

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sustained cCR could be indicative of cure. The limitation of this study was that patients were included in the observation arm only after reaching cCR after 12 months of uneventful follow-up, thereby raising some concern about selection bias.

In the following years, other pioneering W&W centres compared the outcome of patients with a cCR following W&W, with matched pCR patients who underwent major resection: both overall and disease-free survival were comparable [8,9]. These studies reported small series of 21 and 31 patients, respectively, in whom non-operative management was initiated after a cCR. Subsequent reports have provided additional series of patients in which the safety of the W&W regimen was reported as a major outcome. One meta-analysis published in 2017 obtained data from 11 studies with $n = 602$ patients in total; the 2-year cumulative incidence of a local regrowth was 21.4% [10].

Two papers reported on the long-term oncological outcome in W&W patients. The first paper in 2017, a systematic review and meta-analysis of 23 series with a total of 867 patients, reported a regrowth rate at 2 years of 15.7% and a salvage surgery possibility rate of 95%. Furthermore, survival data of W&W were similar when compared with patients with a pCR following TME surgery [11]. The second paper, in 2018, was from the International Watch & Wait Database (IWWD), with pooled data of 880 patients with a cCR at 47 centres in different countries. The 2-year incidence of regrowth was 25%, with 88% of those detected in the first 2 years; most of these regrowths were salvaged by TME and the risk of locally unsalvageable disease was $<1\%$. Excellent survival data were displayed, with 5-year overall and disease-specific survival of 85% and 94%, respectively [12].

The most commonly used regimen in studies on W&W is a long course of chemoradiation (fluorouracil or capecitabine based), with only two studies reporting on short-course radiotherapy and W&W in a small cohort of patients, mainly elderly or frail patients who do not tolerate long-course chemoradiation [13,14].

Acceptance of the Watch-And-Wait Policy in a Clinical Complete Response

With increasing data on the oncological safety of W&W in a cCR after neoadjuvant therapy and a high interest of patients, there was also an increasing interest from clinicians in how to perform an optimal response assessment, how to identify a complete response and how to select patients for organ preservation. Unlike pCR, which is an objective histological determination with no tumour cells present in the surgical resection specimen, cCR is a more subjective categorisation based on the assessment triad of digital rectal examination, endoscopy and magnetic resonance imaging (MRI). Even though there have been attempts to standardise clinical, endoscopic and radiological findings, recognition of cCR requires specific expertise with a substantial learning curve. As the decision to proceed with W&W is based on the assessment of this clinical response, there is inherently some uncertainty, illustrated by the 20–25% of regrowth after an initial apparent cCR. This inherent uncertainty and risk of regrowth mandates a strict follow-up schedule to detect tumour regrowth as early as possible and to allow salvage surgery with as little as possible oncological compromise [7,15].

The intensive follow-up (with 3-monthly MRI and endoscopy during the first 2 years of follow-up) and the required expertise may have hampered widespread dissemination of organ-preservation programmes. Moreover, some authors have postulated that further study is warranted before routine implementation of W&W [16–18]. Randomised controlled trials comparing the W&W strategy with TME surgery for a cCR after neoadjuvant chemoradiation would be ideal to confirm the efficacy and safety of such an organ-preservation strategy. However, the clear preference of most patients for a W&W approach with an anticipated better quality of life will impede patient accrual and the feasibility of such randomised controlled trials.

Considering the fact that most regrowths will develop within the first 2 years of follow-up and around 90% will occur endoluminally, the proposed strict clinical follow-up allows early detection with the possibility of successful salvage surgery [12]. Salvage surgery mainly consists of TME surgery, generally the same operation as planned initially at the time of rectal cancer diagnosis [19]. Some papers confirmed the high rate of successful pelvic control after treatment of regrowth, ranging from 88 to 95% [11,12,19,20]. These findings have promoted the acceptance of the W&W strategy as an alternative to TME, with incorporation in national guidelines, such as the updated Dutch national rectal cancer guideline in 2021.

Organ Preservation from the Perspective of the Patient

The increasing popularity of organ preservation is not only initiated by treating physicians, but patients' preference is playing an increasingly important role. Patients are highly interested in treatment strategies that preserve their rectum, their anorectal and urogenital function, their quality of life and strategies that minimise the risk of a stoma. Moreover, they are willing to make oncological compromises for this goal, and apparently more so than their doctors [4,5].

A matched controlled study compared the quality of life in W&W patients and a sustained complete response with patients who underwent chemoradiation followed by TME: W&W patients scored better on some quality of life subscales and showed fewer problems with defecation and sexual and urinary tract function [21]. Nevertheless, chemoradiation therapy on its own is not without long-term side-effects, as shown by the suboptimal functional scores in the successful W&W patients with a sustained cCR [22]. The recently reported TREC study randomised patients with early rectal cancer between TME surgery and short-course

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radiotherapy followed by transanal local excision [23]. Patients in the organ-preservation group scored significantly better in patient-reported short-term toxicities and quality of life and function scores than patients who underwent TME surgery; these improved outcomes sustained at 36 months of follow-up [23].

The pros and cons of organ preservation have to be well discussed with patients. Some patients may prefer straightforward TME surgery to the uncertainty and stress of the intensive follow-up schedule. Patients with claustrophobia and other contraindications for MRI should also be carefully counselled about the suboptimal follow-up in an organ-preservation strategy.

Primary versus Secondary Organ Preservation

Patients with locally advanced rectal cancer undergo neoadjuvant chemoradiation for an oncological indication: to lower the local recurrence rate and to obtain downsising of the tumour. The 15–20% of patients who show a cCR at restaging are obvious candidates for W&W. This can be named opportunistic or secondary organ preservation. In the last decade there has also been an increasing trend towards planned or primary organ preservation in smaller tumours that do not require neoadjuvant radiotherapy, but where it can be added with the specific goal to achieve a cCR and to omit TME surgery, or to perform a local excision in case of a small remnant. In this strategy, the role of radiotherapy is shifting from improving local control and oncological outcome towards improving and preserving function and quality of life. Several, relatively small, studies evaluating primary organ preservation for early-stage rectal cancer have reported promising results after neoadjuvant (chemo)radiation with or without additional surgical local excision, with organ preservation in over 50% of patients [23–26]. One study showed high rates of organ preservation in selected early cT2-3 rectal cancer when combining neoadjuvant chemoradiation and CXB; thereby the authors introduced the so-called planned organ preservation as an option for operable patients with early rectal cancer [27]. The high success rates in adding CXB to chemoradiation for primary organ preservation in early rectal cancer formed the basis of the more recent OPERA trial [28].

The available studies seem to indicate that primary organ preservation does not jeopardise oncological outcome. However, more evidence is also required on the overall impact on the functional outcome, taking into account that TME surgery may still be required, with a worse functional outcome than after TME surgery without neoadjuvant radiotherapy [29]. However, the TREC trial does suggest that the functional benefit of successful organ preservation is larger than the functional harm of patients still requiring TME surgery. The ongoing multicentre STAR-TREC trial (NCT02945566) addresses primary organ preservation for early cT1-3abN0M0 rectal cancer with a randomisation between short-course radiotherapy and long-course chemoradiation [30].

How to Increase Organ-Preservation Rates: Testing Boundaries

There is great interest to increase organ-preservation rates, and there are a number of approaches to obtain this. A higher radiotherapy dose provides more response, but increasing the standard external beam radiotherapy dose above 60 Gy with conventional volumes may lead to unacceptable toxicity to the small bowel and pelvis [31]. An additional boost dose in a smaller volume could provide a better response while minimising the additional toxicity, and can be administered as an external boost or by endorectal CXB. The Lyon R96-02 randomised trial was the first prospective study to demonstrate that a CXB dose of 85 Gy (additional to 39 Gy external beam radiotherapy) increased the cCR from 2 to 24% in cT2-3 rectal cancer patients, which also resulted in a higher rate of long-term sphincter preservation and coincidentally also organ preservation [32,33]. More recently, the OPERA trial (NCT02505750) was specifically designed to evaluate the role of dose escalation using CXB in improving the chance of organ preservation with a randomisation between standard chemoradiation of 45 Gy combined with either an external boost of 9 Gy or internal CXB of 90 Gy; preliminary results are very promising, with reported organ-preservation rates of 60–80% [28]. An external beam boost is currently being investigated in the UK APHRODITE trial, assessing the value of a small volume simultaneous integrated boost to 62 Gy in 25 fractions. The aim of this study is to increase the cCR rate, with acceptable toxicity, for treatment of patients with early rectal cancer unsuitable for radical surgery [34]. New promising MR-guided radiotherapy techniques, such as MR linac, will help in the application of small volume boost doses; it permits the visualisation of tumorous and healthy tissue and online daily plan adaptations following the observed anatomical changes.

A higher response rate can also be achieved by adding systemic chemotherapy. The upfront combination of radiotherapy and chemotherapy has been labelled as total neoadjuvant therapy and is increasingly proposed as a means to increase organ preservation. Some studies were not designed for organ preservation but showed a higher pCR rate after TME resection. The Rapido trial used 5×5 Gy radiotherapy followed by six cycles of CAPOX for locally advanced tumours and showed a pCR rate of 28% [35]. The Prodige-23 trial studied six cycles of FOLFIRINOX chemotherapy followed by chemoradiation and showed a similar pCR rate of 28% [36]. The final results of the OPRA trial (NCT02008656) have been eagerly awaited, a trial comparing first induction chemotherapy followed by chemoradiation versus chemoradiation first followed by consolidation FOLFOX or CAPOX cycles in stage II or III rectal cancer, with the explicit goal of organ preservation built into the trial [37]. The 3-year disease-free survival was 76% in both the induction and consolidation chemotherapy group, and organ preservation was obtained in half of the patients by this total neoadjuvant therapy approach [38]. An ongoing French prospective multicentric phase III randomised trial (GRECCAR 12) is investigating if additional

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induction FOLFIRINOX before the start of chemoradiotherapy increases the rate of organ preservation (NCT02514278).

Another approach to increase organ-preservation rates is to apply additional local treatment in patients in whom a good, but not a cCR is seen at the first response assessment, rather than repeating the response evaluation after another 6–8-week interval with the idea that it may take longer to achieve a cCR [39,40]. Examples of such additional local treatments are surgical local excision (transanal minimal invasive surgery) or a boost with CXB. Both treatment options are currently being explored in European trials, such as the Dutch OPAXX trial (NL75896.031.20), which randomises patients with a near-complete response or a small tumour remnant <3 cm at 12 weeks between CXB (three internal boosts of 30 Gy in 4 weeks) versus repeating the response evaluation 6 weeks later and performing a local excision (transanal minimal invasive surgery) in case of a persistent tumour remnant.

Finally, the recent paper on immunotherapy in mismatch repair-deficient rectal cancer needs to be mentioned in the light of attempts to increase organ-preservation rates: in this small group of 12 patients, the microsatellite unstable tumours appeared highly sensitive to single-agent PD-1 blockade; all patients had a cCR at 6 months [41]. More results with longer follow-up data are awaited, but immunotherapy seems to be very promising in the small subset of mismatch repair-deficient rectal cancer patients.

Final Remarks

In the last two decades, W&W and organ preservation have evolved from controversy to common clinical practice after successful clinical implementation in experienced centres worldwide, and can be considered an option alongside the more common treatment approaches. With the knowledge gained from an increasing number of studies and the oncological safety data in large (non-randomised) datasets, W&E has evolved from an opportunistic waiting game to a well-documented alternative to TME with the goal to provide an improved quality of life and functional outcome. Response assessment of tumours remains crucial to identify those patients in whom organ preservation can be considered; also, a strict surveillance schedule and expertise in W&W are essential in order to detect and treat a regrowth as early as possible. Omitting TME surgery in a W&W approach leads to an improved quality of life and functional outcome, which is the main driver for a patient's preference in exploring organ preservation. Managing these preferences is becoming essential in the outpatient clinic, and shared decision making and discussing both the pros and cons of organ-preservation options has therefore become an important part of the treatment. Future research should investigate the role of systemic therapy and intensified radiotherapy, and the optimal management of patients with a small residual tumour who prefer organ preservation (primary or secondary). The toxicity of intensified neoadjuvant schedules should be carefully balanced against the benefits in terms of successful organ preservation. Finally, the research agenda on organ preservation in rectal cancer for the upcoming years should also focus on response prediction at baseline using biomarkers, radiomics, etc., especially in the light of an increasing interest of patients in primary organ preservation.

Author Contributions

Both authors contributed equally.

Conflicts of Interest

The authors declare no conflict of interest.

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