Editorial

When watching and waiting is enough: managing locally advanced rectal cancer without surgery

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Introduction

The recently published "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" by van der Valk *et al.* in *Lancet Oncology* poses an interesting question (1). Could rectal cancer patients with locally advanced disease treated with neoadjuvant therapy sans resection patients be spared from a major operation, or possibly postponed indefinitely?

Traditionally, management of clinically staged locally advanced rectal cancer involves neoadjuvant chemoradiation followed by transabdominal resection with total mesorectal excision (2). Neoadjuvant regimens can include several options including: long course radiation (50.4–54 Gy) combined with 5-FU or capecitabine based chemotherapy, short course radiation alone (25 Gy in 5 fractions) when circumferential margin is uninvolved, FOLFOX or CAPEOX followed by combination radiation therapy with 5-FU or capecitabine. The rationale for neoadjuvant therapy is two-fold: to decrease the local tumor burden in locally advanced disease and to reduce risk of distant metastases. In addition, compared to adjuvant therapy, neoadjuvant therapy is associated with reduced acute and late toxicity, and also possible improvement in local control (LC) (3). Typically, patients then are restaged, with consideration for surgical resection unless otherwise contraindicated. If after restaging there is a complete clinical response (cCR), then patients can be considered for surveillance, also known as watch and wait (W&W), however, there is still lack of category 1 evidence to support this line of management at this time.

Precedent for W&W

Over the years, several studies both retrospective and prospective, have been reported that utilized the W&W approach in select patients with cCR, which constitutes approximately 20–25 percent of locally advanced rectal cancer patients treated with neoadjuvant treatment (4-6). These patients treated with surgery after neoadjuvant treatment appear to have good LC and clinical outcomes, with a meta-analysis, primarily driven by retrospective studies, showing 5-year overall survival (OS) and disease-free survival (DFS) of 90.2% and 87% respectively (7). What happens for patients who receive neoadjuvant treatment, but do not undergo surgery?

One of the seminal papers looking at prospective data for W&W approach for patients by Habr-Gama *et al.* in Brazil looked at 71 patients with cCR that were observed (8). Long-term follow-up showed DFS and OS of 92% and 100% at 5 years, which was comparable to the patients who lacked cCR and thus had resection in another 22 patients with stage 0 disease, with DFS and OS of 83% and 88%, respectively. The conclusion from this study was that W&W was comparable to resection for patients with stage 0 disease. Subsequent smaller studies from The Netherlands, Australia, and Memorial Sloan Kettering also showed similar results for W&W in patients with cCR (9-11).

A larger study from The Netherlands with 100 patients looked at patients with both cCR and near cCR and showed colostomy free survival CFS) of 94.8% at 3 years and LC of 84.6% (12). Similarly, a UK study looking through the Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) database with 129 patients of W&W had 3-year local regrowth of 34% and CFS was 74% which was better than those patients who had surgical resection with 47% (13). Patients with local recurrence will often undergo salvage resection. Although there have been larger studies to support W&W, the strategy has still not been widely adopted.

Largest W&W

The recent publication from van der Valk *et al.* examines the largest patient pool to date for neoadjuvant treatment in the setting of locally advanced rectal cancer sans resection. The international registry included a total number of 1,009 patients, of which 880 were determined to have a cCR and were operable candidates, were included with endpoints including local regrowth, distant metastases and 5-year DFS and OS. Median follow-up time was 3.3 years. Approximately half of the patients were from prior published studies, with the majority from Brazil, The Netherlands, and the UK.

The neoadjuvant regimens were heterogeneous, with most patients (91%) receiving chemoradiation. Radiation doses ranged from 45 to 60 Gy, with 5-FU or capecitabine, and with high compliance. There were also variations with patients receiving either radiation alone, or chemotherapy alone, and some patients also receiving brachytherapy. The cCR was determined through digital rectal examination (DRE), endoscopy, biopsy, MRI or a combination of any of these modalities. Local regrowth at 2 years was 25.2% while 3 years distant metastases rate was 8.1% and 5-year OS was 84.7%. The majority (88%) of salvage resection achieved negative margins.

The study has several strengths. The most obvious selling point is the sheer size of the study, which is several-fold larger, than most other studies in the reported literature. For surveillance, MRI was incorporated and prioritized as an imaging modality with more than 95% patients having endoscopy at baseline. The exclusion of patients who were not medically operable or did not want surgery was appropriately stringent to capture the patient population that would have the option of surgical resection as not only salvage but also as a primary means of treatment. Most patients were from more recent years, i.e., 2010 or later, which should reflect more modern practices. The study also collected the patterns of failure with W&W, including the most common local regrowth location being the bowel wall in 97% of patients and 3% in regional lymph nodes.

Naturally, a study which is not a randomized phase 3 trial, i.e., the "gold standard" will have its limitations. One of the drawbacks of the study is the relatively short follow-up time, with a reported median of 3.3 years for at time of publication. Although the majority of observed local regrowths were seen in the first 2 years, the local regrowth curve does not immediately plateau and there may be further detriment to LC than currently seen. An updated analysis with longer median follow-up, e.g., 5 years, may provide a clearer picture. The only site with significantly longer follow-up time was Instituto Angelita e Joaquim Gama, Brazil. One of the major criticisms for W&W in the past has been the heterogeneity of studies and smaller sample sizes especially as reported via meta-analysis (14). Although the database collecting information for this registry has a uniform set of data fields, the practices at each institution were different and not controlled for so that weakness stemming from heterogeneity still remains. For example, there is a large variation between the amounts of known information for co-morbidities from 2% unknown in Brazil to 89% unknown from OncoRe, as well as clinical T staging missing/unknown from baseline for 73% of Brazil patients to 1% unknown from OncoRe. This discordance could lead to mismatched comparisons.

The local regrowth rate of 25.2% at 2 years is also higher than most reported studies in the literature, which are usually in the 15–20% range. The authors note that this difference may be due to more stringent requirements from other studies for the patient population, however, there is notably an increased rate of local regrowth from both the site in Brazil and the UK which may skew the numbers, and either patient or practice specific. Regardless, OS numbers are promising which seem to indicate despite local regrowth, salvage therapy is often successful for W&W patients.

A valuable piece of information missing from the study would have been any prognostic factors that may have predisposed patients to have local regrowth, whether that is clinical T/N stage at baseline, gender, age, or country. A formal analysis comparing such characteristics across reported sites is lacking. Since the authors discuss that W&W might be appropriate in select patients, it would helpful to have more information to determine which

patients might be at more risk for local regrowth, and thus not suitable for W&W and vice-versa.

Enhancing W&W

A head-to-head comparison of W&W vs surgical resection in a subset of patients will provide the most robust information. Although a randomized trial may be difficult to accomplish, a similar database study collecting information prospectively between patients treated with W&W *vs.* surgical resection may provide some formal analysis per institution. Having more information from sites with more uniform practices would also add to the discussion.

In addition, the neoadjuvant regimen could be adjusted to reflect alternative radiation schedules and systemic agents. Short-course radiation therapy, i.e., 25 Gy in 5 fractions, is being employed prior to resection (15,16). This study, however, only included patients with long course radiation. With contemporary radiation techniques, it may be possible to also increase the dose of radiation safely delivered, and there are ongoing trials going regularly to 59.4/60 Gy as target dose nearing completion (NCT03200249, NCT02603302) (17,18). Incorporating targeted therapies and also immunotherapies may help increase the potential number patients that could be managed with W&W, and also improve the clinical outcomes. A multi-center phase 2 trial in China is examining FOLFOXRI with Cetuximab for patients with EGFR wild type locally advanced rectal cancer as neoadjuvant treatment is underway (NCT03391843) (19). A phase 2 study at Johns Hopkins will be looking at nivolumab and relatlimab in patients with metastatic or locally advanced microsatellite stable colorectal cancer (NCT03642067) (20). Extending these treatment options to the W&W setting for locally advanced rectal cancer patients may prove to be advantageous in the long run as more and more developments occur in the systemic therapy sphere.

Conclusions

Although the database study by van der Valk *et al.* has its shortcomings inherent to the design, the sheer number of patient data is a plus and lends credibility to the W&W strategy. The results show excellent OS and salvageable situations for patients that recurred locally. The appeal of avoiding surgery for a majority of patients remains an attractive option. We anticipate that these results may encourage other providers so that W&W becomes increasingly adopted, thus leading to larger, more robust studies to be conducted. The final results from such investigations may ultimately make watching and waiting a more widely practiced and accepted option for locally advanced rectal cancer patients.

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Footnote

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