Chapter 12
The Watch and Wait Approach After Neoadjuvant Therapy: The Australian Viewpoint

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Introduction

The current standard of care for locally advanced rectal cancer (T3-4 and/or N+) is neoadjuvant chemoradiotherapy (CRT) before total mesorectal excision (TME). This approach is taken due to the anatomical location in the narrow confines of the pelvis. By appreciating the anatomical restriction within the pelvis, the risk associated with surgery without neoadjuvant chemoradiotherapy (CRT) is a positive circumferential resection margin (CRM). This is associated with higher rates of local recurrence [1]. Historically local recurrence rates were as high as 40%, and perhaps the most prominent study showed a rate of 27% in the control arm of the Swedish rectal cancer trial conducted in 1997 for immediate surgery when compared with 11% in the short-course CRT arm [2]. Subsequently, further trials comparing neoadjuvant CRT with immediate surgery showed improvements in local disease control. Other benefits of neoadjuvant CRT include an increase in the radiation effect (as local blood supply is not damaged and tumour oxygenation is paramount for radiation sensitivity), minimising radiation toxicity, and most importantly, potential down-staging of the tumour [1–3].

Following concerns with high pelvic failure and the local recurrence rate, in 1988 Bill Heald described the ideal resection plane, also known as the "holy plane" of surgical rectal dissection [4]. Today it is the standard operative technique, and is

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best known as TME, which requires the operator to perform a meticulous dissection in the extra-fascial plane. This maintains an intact fascia envelope of the posterior, lateral and distal mesorectum as these locations harbour lymph nodes, which are the basis of a danger zone around the visible and palpable tumour. Through this innovative technique and neoadjuvant CRT, the current local recurrence rate is now quoted as 5–7% [5, 6].

The Evolution of "Watch and Wait"

The next development was a keen observation that there is a spectrum of tumour responsiveness following neoadjuvant CRT. An estimated 10–25% of locally advanced rectal cancer treated with CRT will achieve a pathological complete response (pCR), defined as no residual tumour identified by a pathologist in the resected specimen [7–9]. In addition there is the survival benefit in achieving a pCR, with a pooled local recurrence rate of 0.7%, a distant recurrence rate of 8.7%, a 5-year overall survival of 90.2% and a disease-free survival of 87% [10]. Recognising this clinical entity resulted in the recognition of a new concept that contrasted with the traditional orthodox teaching [11]. This concept involved a non-operative approach similar to the management of anal squamous carcinoma following CRT [12].

The rationale for pursuing this "watch and wait" strategy was the potential for avoiding the sequelae of radical surgery, which included long-term urinary dysfunction, sexual dysfunction and faecal incontinence. There are also immediate postoperative risks to consider such as bleeding, infection and anastomotic leak [13]. From the patient's perspective, most would also prefer to avoid the need for a temporary or even a permanent stoma, maintaining gut function and their quality of life [14]. For these reasons, there have been increasing trials assessing the safety of the "watch and wait" strategy [15–18].

The first published series of patients was by Nakagawa et al. in 2002. Ten patients who were deemed to have clinical complete response (cCR) went on to have active surveillance [11]. However, 8 patients subsequently developed local tumour regrowth within 8.8 months and the authors concluded that the "watch and wait" strategy was not a safe option. Subsequently in 2004, Habr-Gama et al. from Sao Paulo, Brazil continued research on the "watch and wait" strategy by publishing their series of 71 patients with cCR, reporting robust long-term outcomes [19]. Despite this, for a period of time they were the only advocates of the "watch and wait" strategy and in their most recent publication of 90 patients diagnosed with cCR, 28 patients (31%) had tumour regrowth with an overall salvage rate of 93% (26 patients) [18]. They then reported a 5-year cancer-specific overall survival (OS) and disease-free survival (DFS) of 91% and 68%, respectively. This led to a progressive acceptance and gradual increase in the number of trials conducted assessing the safety of this strategy [20–25].

Trials and Long-Term Outcomes

There have been numerous systematic reviews and meta-analyses summarising the available publications on a number of clinical end-points concerning the safety of a "watch and wait" strategy [26–29]. One of the main concerns is that there is no reliable test that can accurately stratify patients to pCR [30]. As a result, cCR was devised as a surrogate assessment for pCR. This would mean that although patients can avoid the morbidity associated with surgery, they still have a risk of tumour regrowth and consequently will need intensive surveillance.

All studies identified were case-controlled cohort studies (level II evidence) [26, 27], with only one propensity-matched multicentre trial identified from the Oncological Outcomes after Clinical Complete Response in Patients with Rectal Cancer (OnCoRe) group [25]. There was significant heterogeneity between all the studies, with no randomised controlled trials to date. In a pooled analysis by Kong et al. comparing "watch and wait" approach to TME after neoadjuvant CRT, the local tumour regrowth rate was 28.4%, distant recurrence was 1.9% and salvage surgery for tumour regrowth was possible in 83.8% of patients [26]. As for the long-term survival, no pooled analysis was performed due to reporting heterogeneity. Nonetheless in a well-constructed, propensity-score matched cohort analysis by the OnCoRe group there was reported no difference in 3-year non-regrowth DFS between "watch and wait" (88% [95% CI 75–94]) and TME (78% [63–87]). Similarly, no difference was noted in 3-year OS with the "watch and wait" approach – 96% (88–98%) when compared with a TME – 87% (77–93%).

Other authors have identified similar survival outcomes, including Maas et al. and Smith et al. who demonstrated no significant differences in 2-year OS; 100% and 97% ("watch and wait") vs 91% and 100% (TME) and 2-year DFS; 89% and 88% ("watch and wait") vs 93 and 98% (TME), respectively [22, 31]. Despite equivalent survival outcomes to date, these were small observational cohort studies with a short follow-up and should be interpreted with caution.

Patient Selection and Assessment of Clinical Complete Response

A stringent selection process is required for "watch and wait". The initial selection includes all patients with histological confirmation of rectal adenocarcinoma, radiological staging of T2-4 and/or nodal positivity confined to the radiation field and patients who will receive long course chemoradiotherapy can be considered [25, 27, 32]. The long course neoadjuvant treatment usually consists of radiotherapy (45–65 Gy), for which 50.4 Gy was the most common dose, with concurrent fluoropyrimidine-based chemotherapy [26].

Table 12.1 Assessment of clinical complete response in each study published to date

Method of assessment	Criteria for complete clinical response
Digital rectal examination	Absence of a palpable tumour [22, 25, 34]
Endoscopic visualisation (Use Maas et al. [34] assessment)	No residual tumour [22, 31] OR whitening of mucosa with telangiectasia [16] OR small ulcer with smooth edges [34]
Biopsy	Negative if there was a scar or ulcer identified [21, 22, 31]
Magnetic Resonance Imaging [27, 34]	Normal rectal wall/no residual tumour OR only subtle wall thickening OR residual fibrosis AND no involved lymph node

A consideration is the timing of assessment of the irradiated tumour bed. In this regard, it has been shown that a longer interval time between cessation of CRT to the time of surgery increases down-staging and the pCR rate [33]. Hence, in the observed studies, the interval time to assessment for selecting cCR varies between 6 and 12 weeks [19, 23–25]. Furthermore, there is currently no standardised definition for cCR and surgeons currently rely upon institution-specific definitions. A multimodality approach is used to assess these patients, and will usually include digital rectal examination (DRE), endoscopic visualisation of the previously irradiated tumour bed and magnetic resonance imaging (MRI). The commonly accepted findings for cCR for each modality are shown in Table 12.1.

Increasing Pathological Complete Response Using Different Neoadjuvant Regimens

There have been a few attempts to deliver intensified regimens to improve the rate of pCR. These include increasing the dose of radiotherapy [23] and adding a new combination of chemotherapeutic agents [35, 36]. As such, Appelt et al. had used 60 Gy to the local tumour site and 50 Gy to the lymph node basins in 30 fractions, with an additional 5 Gy boost to the endorectal region and tegafur-uracil as their preferred chemotherapeutic agent [23]. They reported a persistent cCR rate of 62% (31 out of 50 patients) and a tumour regrowth rate of 22.5% (9 out of 40 patients) after a median follow-up of 34.5 months [23]. However, in a meta-analysis assessing an intensified radiotherapy dose of ≥60 Gy from 14 studies with a total of 487 patients, they found no correlation with pCR rate [37].

Others have reported an addition of another chemotherapeutic agent such as oxaliplatin [36], anti-epidermal growth factor and anti-vascular endothelial growth factor to the current standard treatment [38, 39]. Although showing promising results initially, larger studies concluded that these therapies do not increase the tumour response rate for locally advanced rectal cancer.

Intensive Surveillance During "Watch and Wait"

Following the selection of patients with cCR, they will then need to continue an intensive surveillance protocol in order to ensure that no local tumour regrowth has occurred. The surveillance protocol commonly consists of clinical assessment by DRE, proctoscopy or endoscopy, serum carcinoembryonic antigen (CEA) measurement and imaging modalities such as MRI to detect local/regional tumour regrowth and positron emission tomography/computed tomography (PET/CT) for the detection of distant recurrence. An example of a PET/CT response to chemoradiation is seen in Fig. 12.1.

However, there is no agreed consensus on the frequency and timing for each modality. The protocol established by Habr-Gama et al. since 2004 were DRE and CEA measurement every 2 months in the first year, every 3 months in the second year and then 6 monthly in the third year and beyond. This was followed by radiological assessment using MRI and CT of the abdomen and pelvis every 6 months for the first 2 years, followed by yearly thereafter [32]. In comparison, the OnCoRe group evaluates DRE and MRI to every 4–6 months in the first 2 years and uses other forms of assessment per their standard national guidelines; including a colonoscopy at 1 year, CEA every 6 months for 3 years and CT of the abdomen and chest with a minimum of two scans in 3 years [25].
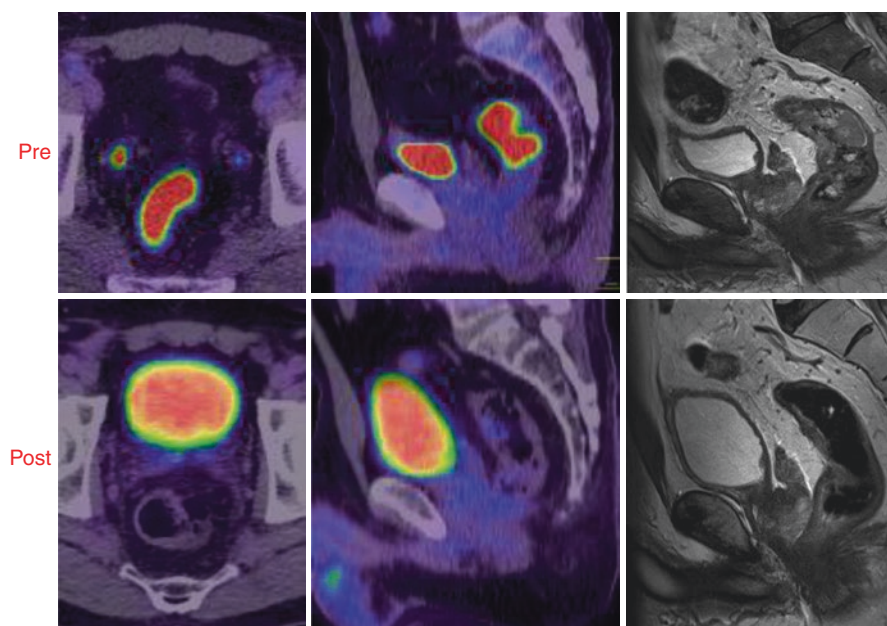
Fig. 12.1 Complete pathological response of rectal cancer on imaging (PET and MRI) pre and post neoadjuvant chemoradiotherapy

Without an agreed standardised protocol, a systematic review from Sammour et al. made recommendations from the summation of all published protocols. These include DRE, endoscopy and CEA every 3 months for the first 2 years and every 6 months thereafter, with biopsies undertaken for any suspicious lesions. Patients are also recommended for an MRI every 6 months for the first year, and a CT of the abdomen and chest every 6 months for the first year, and annually thereafter up to 5 years.

Patterns of Local Failure

Local tumour regrowth is a term used for incomplete sterilisation of rectal adenocarcinoma on a previously irradiated tumour bed after failure with the "watch and wait" strategy. Surveillance for "watch and wait" has shown a tumour regrowth rate between 6% and 34% [25, 31, 32, 40]. In a large retrospective database collated by the International Watch and Wait Database (IWWD) which presented their series of 679 patients with cCR, there was a local tumour regrowth rate of 25% over a median follow-up of 2.6 years (0–24 years) [41]. Of their series of local tumor regrowth, 96% were endoluminal tumours whereas 4% were lymph node metastases. These were all early detections, with 84% identified within the first 12 months. This was consistent with the reported outcomes by the most experienced group led by Angelita Habr-Gama which showed that all of their cases of local tumour regrowth occurred within the first 24 months, after a median follow-up of 60 months. Hence, an intensive surveillance program was developed for early identification of local tumour regrowth with the potential for salvage surgery.

Role of Adjuvant Chemotherapy

The basis for recommending adjuvant chemotherapy came before surgical refinement to the currently known TME. Patients with stage II and III rectal cancers will typically be offered 5-fluorouracil or capecitabine and oxaliplatin [42, 43]. Subsequently a randomised controlled trial by the European Organisation for Research and Treatment of Cancer (EORTC) 22921 (Radiation Therapy, Surgery and Chemotherapy in Treating Patients with Rectal Cancer that can be Surgically Removed) [44], concluded that adjuvant fluorouracil-based chemotherapy after neoadjuvant CRT does not affect DFS or OS.

It is in that context, that the uptake of adjuvant chemotherapy in the "watch and wait" trials has been variable. There have been three studies that had included adjuvant therapy as part of their trial protocol whereas only one study was an off-protocol administration [26]. The question remains as to whether cCR patients with nodal involvement on pre-treatment imaging require additional therapy, especially with the knowledge that not all lymph node positivity will be detected by such imaging [45].

Limitations in Predicting Pathological Complete Response

One of the fundamental concerns with the "watch and wait" strategy is the risk of tumour regrowth and the ability to perform salvage surgery. As cCR is not equivalent to the gold standard histological assessment of pCR, others have searched for a better test. Identifying the extent of tumour response can be categorised as (1) clinical assessment, (2) imaging, (3) laboratory testing, (4) genomics and (5) immune profiling.
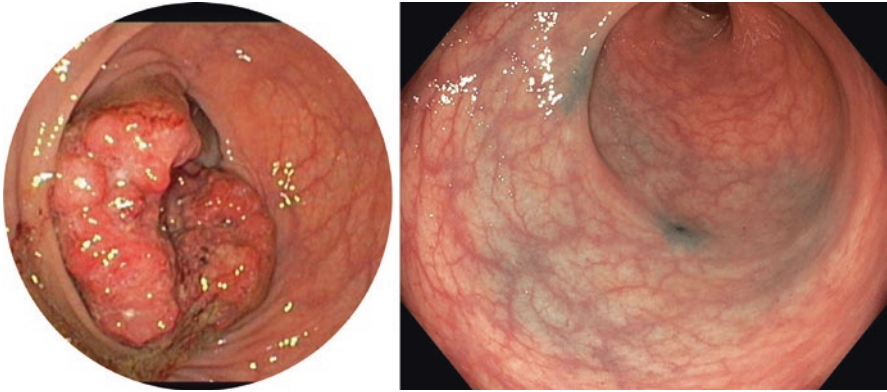
Clinical Assessment

Digital rectal examination, endoscopy and biopsy play an essential role in the assessment of cCR [26]. DRE allows assessment of tumour size, morphology, mobility, and circumference. The limitation is the discordance between the surgeon's assessment and the pathological response, as demonstrated by Guillem et al. [46]. In a single surgeon clinical assessment, before and after neoadjuvant CRT, the study found only 21% pCR were identified correctly [46]. The reasons for the poor correlation with DRE include: those cases where the tumours are beyond the reach of the examiner's finger, where there is difficulty in distinguishing between fibrosis and microscopic tumour in the bed on palpation and where there is a subjective interpretation of tumour response.

As for endoscopic visualisation and biopsy, it had similar accuracy to DRE, with only 59% diagnosed correctly in one prospective study [47]. Poor detection rates can be explained by a single study investigating the distribution of residual rectal cancer after neoadjuvant CRT within different layers of the bowel wall [48]. A total of 79 patients were recruited, and the distribution of residual rectal cancer for ypT2-4 (where yp denotes staging after neoadjuvant CRT) in the mucosa, submucosa, and muscularis propria was 20%, 36.7%, 69.2%, respectively. This resulted in an overall sensitivity of 12.9% and a specificity of 94.1%. The study concluded that the rectal cancer residuum was primarily located in the deeper layers of the bowel wall, and that the biopsy results for primary rectal lesions were unreliable [48]. Moreover neither DRE nor endoscopy can assess nodal involvement after neoadjuvant CRT. An example of an endoscopic response is seen in Fig. 12.2.

Imaging

Restaging after neoadjuvant CRT in locally advanced rectal cancer is not routine practice. Imaging modalities can include endorectal ultrasound (ERUS), MRI and PET/CT.

Fig. 12.2 Endoscopic view of rectal cancer before and after neoadjuvant chemoradiotherapy after complete clinical response

Endorectal Ultrasound

Assessment by ERUS has been shown not to be accurate, owing to the inflammation, necrosis and desmoplastic changes identified after neoadjuvant CRT. The overall ypT stage accuracy was highly variable, between 43% and 73%. However ERUS may have a role in confirming lymph node negativity after pre-operative treatment, with a ypN stage accuracy of 72–77% in those with pCR [49–53]. In one study, six of six patients were correctly diagnosed with absence of lymph node involvement [52] and in three studies, the negative predictive values were between 81% and 88% [47, 52, 54].

Magnetic Resonance Imaging

Pre-operative MRI has been the key imaging modality to assess T and N stage as a guide to clinical management. In the last 6 years, two emerging groups (Regina Beets-tan et al. and Gina Brown et al.) have investigated the utility of re-staging MRI to assess pCR. Similar to DRE, the limitations of MRI are the inability to differentiate residual tumour from fibrosis, desmoplastic reaction, inflammation and oedema surrounding the tumour bed post-therapy [34, 55]. An extensive systematic review performed by Ryan et al. showed the accuracy of standard MRI in assessing T and N stage were 45–67% and 65–75% respectively. [30]

Championing the usage of restaging MRI is the Magnetic Resonance Imaging and Rectal Cancer European Equivalence (MERCURY) group, whose focus was to assess the accuracy of MRI in determining multiple facets of tumour response after neoadjuvant CRT in relation to short-term (tumour regression) and long-term DFS

Table 12.2 The criteria for the assessment of mrTRG

mrTRG	Definitions
1	No/minimal fibrosis visible (tiny linear scar and no tumour signal)
2	Dense fibrotic scar (low signal density) but no macroscopic tumour signal (indicates no or microscopic tumour)
3	Fibrosis predominates but obvious measurable areas of tumour signal visible
4	Tumour signal predominates with little/minimal fibrosis
5	Tumour signal only (no fibrosis, includes progression of tumour)

and OS [55–57]. In the process, the authors have developed the MRI tumour regression grade (mrTRG), to stratify good and poor responders [55]. In addition, they discovered extra-mural venous invasion (EMVI) was significantly predictive of poor responders in their updated series, when added to the mrTRG (Table 12.2) [58]. In their multivariate Cox-regression analysis, mr-vTRG 4–5 increased the risk of disease recurrence with an estimated HR of 5.75, and they concluded that it can be used to identify high risk patients for more intensive therapy. Because patients were stratified as good versus poor responders, the accuracy to predict pCR using re-staging MRI is uncertain.

In a large (1566 patients from 33 studies) meta-analysis performed by van der Paardt assessing the accuracy of re-staging MRI in predicting pCR, they found a re-staging MRI sensitivity and specificity of 19% and 94%, respectively. This result was enhanced by applying diffusion weighted imaging (DWI), with a significant increase in sensitivity to 84% but with a lower specificity of 85% [59]. Because of the heterogeneous results with re-staging MRI accuracy, this modality cannot be relied upon to dictate a non-surgical rectal conserving approach.

Positron Emission Tomography/Computed Tomography

PET/CT is a nuclear medicine imaging technique that acquires a 3-D image of the body. A small amount of radioactive fluorodeoxyglucose (FDG) tracer is injected through a vein, and will be taken up by all active tissue. But, because cancer cells grow rapidly, there is an increased uptake at the cancer site when compared with normal healthy tissue. Hence, the degree of metabolic response (measured by FDG uptake), before and after neoadjuvant CRT, correlates with the tumour regression grade allowing differentiation of responding from non-responding tumours with an overall accuracy of 80% [60]. Other authors have reported similar accuracy rates for different standardized uptake value (SUV) mean reductions. Cascini et al. found that a threshold of 52% decrease in the SUVmean resulted in an accuracy of 100% when distinguishing histologic responders from non-responders. When using SUVmax values, a cut-off of 42% decrease in the SUV max identified responders from non-responders with an overall accuracy of 94% [61].

There are still reservations about relying upon PET/CT as a predictor of pCR, due to the limited number of studies and the fact that there is as yet no set standardized assessment of tumour response or a designated cut-off mean value in the reduction of metabolic activity. Furthermore, false positive tests have been reported due to inflammatory changes without any residual disease being found in the tumour bed [62].

Combining Clinical Assessment with Imaging Modalities

A potential method to improve the accuracy of predicting pCR is to combine clinical assessment (digital rectal examination, endoscopy for mucosal assessment and biopsy of suspicious lesions) with imaging. The addition of radiological assessment has shown encouraging results in increasing the detection of pCR [34, 63–65]. Two of the most promising modalities in combination with clinical assessment are (PET/CT) [65] and magnetic resonance imaging with diffusion weighted imaging (MRI DWI) [34].

Habr-Gama's group from Sao Paulo investigated the utility of PET/CT in predicting cCR, reporting an accuracy approaching 91% [65]. When clinical assessment was combined with PET/CT, the accuracy increased to 96%. The high fidelity in these results is likely due in part to the vast experience accrued over the last two decades by this pioneering group as evidenced by their serially published updates [19, 32]. In the same manner, Maas et al. reported a clinical assessment sensitivity and specificity of 53% and 97%, respectively, which when combined with MRI DWI led to a post-test probability of predicting cCR of 98% [34]. Both MRI and PET have shown great promise when combined with clinical assessment as part of a multi-modal technique in evaluating the tumour response rate after neoadjuvant CRT. What is currently lacking is a randomised, single-blinded trial of PET/CT or MRI, although the current TRIGGER trial, a multicentre randomised controlled trial assessing the utility of the magnetic resonance tumour regression grade (mrTRG) as a novel biomarker designed to stratify patients between good and poor responders to chemotherapy, may provide some answers to this question.

Laboratory Testing

Two distinct markers have been consistently associated with pCR; namely, the carcinoembryonic antigen (CEA) level [66, 67] and the neutrophil-lymphocyte ratio (NLR) [68, 69]. Both are routinely performed as part of the patient's clinical work-up for rectal cancer management. However, discrepancy in the mean cut-off point or reduction value makes it difficult to ascertain the true value and significance of these markers. A study by Perez et al., with 170 patients who received neoadjuvant CRT

followed by surgery, found that a post-treatment CEA level of <5 ng/ml was associated with increased rates of pCR [66] whereas in another study by Wallin et al. recruiting 530 patients treated with preoperative CRT and radical surgery, 96 patients had pCR, with pre-treatment CEA levels of 3.4 versus 9.6 ng/ml being strongly associated with pCR [70]. Similar results can be extrapolated from NLR [68, 69], and it is likely there is a range of cut-off points that need to be established through a much larger, multicentre study so as to ensure clinical applicability.

Genomics

It is thought that a panel of genes will be able to stratify patients into high or low risk categories, providing an objective test which informs patient risk and which justifies the use of adjuvant chemotherapy. The first commercially available gene expression panel was the Oncotype Dx colon cancer test, a multi-gene test for predicting the risk of recurrence in patients with stage II and III colon cancer [71]. Other gene expression panels are also available such as ColoPrint and ColDx, both reported to be robust diagnostic platforms in refining the prognosis of Stage II and III colon cancer [72, 73]. Although promising in colon cancer cohorts, currently there are no data on the relevance of these commercially available gene expression panels in rectal cancer after neoadjuvant CRT.

Nonetheless, a wide variety of genetic and molecular markers have been implicated in the prediction of response to neoadjuvant CRT, and some of these were highlighted in a comprehensive systematic review by Spolverato et al. [74]. In the review, the authors showed that epithelial growth factor receptor (EGFR), thymidylate synthase genes, bcl-2/bax and cyclooxygenase-2 were promising biomarkers in predicting the response to neoadjuvant CRT, but the value of p53, Ki-67 and p21 testing remains controversial. Hence, no specific biomarker(s) have yet been conclusively proven to be robust for clinical utility and a better predictive tool is still required.

Immune Profile

The immune system is a host defence mechanism capable of protecting against a number of threats including cancer. In a seminal paper by Galon et al. cytotoxic tumour infiltrating lymphocytes (TILs), were described as key arbiters of a good prognosis [75], and subsequently a similar correlation was demonstrated with the image analysis densities of CD8 + cytotoxic TILs detected in the pre-treatment biopsies of the good pathological response patients who had received long-course CRT for their locally advanced rectal cancer [76]. These findings have led to a number of studies assessing the predictive value of cytotoxic TILs [77–79], however there are several limitations with these studies. Firstly, the cut-off values for

stratifying patients to either high- and low-density TILs were different between studies with each requiring a pre-determination for new institutions; a finding which Galon et al. have demonstrated during the initial creation of their in-house Immunoscore [75]. Secondly, the dichotomization of outcomes, (between a good and a poor response), does not specifically answer the question of the accuracy for predicting response to therapy in individual patients. Thirdly, there is the observation that a subset of patients with a high TIL density can have a poor response. Consequently, at the present moment the assessment of the density and type of TILs derived from pre-treatment biopsies is not the standard of care and more studies are required in order to assess the feasibility and accuracy of predicting pCR.

Should Patients "Watch and Wait"?

As research to identify a robust investigation continues, clinicians will need to weigh the risk and benefits of the "watch and wait" strategy with the individual patient. The avoidance of radical surgery (and a stoma) needs to be weighed against local tumour regrowth risk and the need for intensive follow-up for at least 2 years. There are still uncertainties with longer survival outcomes with both rectal preservation and salvage surgery, especially with respect to functional impact. Therefore the "watch and wait" strategy should be recommended with caution, and in a multidisciplinary team environment with the ability to deal with surveillance, decision making for adjuvant chemotherapy and local tumour regrowth. Those patients who are high surgical risk and with a shorter life expectancy, such as the elderly or those requiring an abdominoperineal resection can be considered after appropriate informed consent.

Given the uncertainty of long-term outcomes, meticulous prospective data collection must be enforced with continuous audits to ensure a high quality of assessment and care delivered to patients during a "watch and wait" strategy. An alternative is a formal collaboration with the International Watch and Wait Database group so as to facilitate and refine practices associated with the rectal preservation approach.

Future Direction

The research focus into novel therapies has now shifted towards harnessing the patient's immune response so as to increase the pCR rate. Collectively these treatments, the immunotherapies are being assessed with a number of Phase I/II clinical trials underway in the neoadjuvant setting. These include the ExIST study of Galunisertib (a transforming growth factor-beta kinase inhibitor; clinical trial identifier NCT02688712) and the R-IMMUNE study of atezolizumab (an antiprogrammed cell death-ligand 1; clinical trial identifier NCT03127007).

Furthermore, data from the TRIGGER trial (clinical trial identifier: NCT02704520) designed to assess the utility of mrTRG in stratifying patients for the management of rectal cancer patients, are eagerly awaited.

Summary

The "watch and wait" strategy is currently not the standard of care for locally advanced rectal cancer. This is due to an inability to predict pCR accurately compounded by uncertainty in the long-term survival and functional outcomes. There is a small subset of patients which might prove appropriate for such a strategy, however, the data from these ongoing trials are awaited.

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