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The "Watch and wait" approach following chemoradiotherapy for rectal cancer: a case series and review of literature

Neoadjuvant chemoradiotherapy (NCRT) combined with total mesorectal excision (TME) is currently the gold standard for locally advanced low-lying rectal cancer (LACR). Around 20-30% of patients after NCRT can achieve clinical complete response (cCR); 5-44% of the patients who underwent TME achieve pathological complete response (pCR) on post-operative histopathologic studies. In the present study we perform a review of current Literature and retrospectively analyze our personal experience on "watch and wait" approach after cCR. Further studies are needed to establish an internationally accepted definition of clinical complete response, to delineate the real role of MRI in the post-treatment staging and to determine more precise predictors of sustained clinical complete response. The eventual presence of long-term morbidity and adverse effects after chemoradiation needs as well to be better evaluated. Evidence suggests that watch and wait approach is associated with substantially better quality of life and functional outcomes compared with standard surgical resection.

KEY WORDS: Chemoradiation, Neoadjuvant therapy, Rectal cancer, Remission induction

Introduction

Neoadjuvant chemoradiotherapy (NCRT) combined with total mesorectal excision (TME) is currently the gold standard for locally advanced low-lying rectal cancer (LACR). Around 20-30 % of patients after NCRT can achieve clinical complete response (cCR); 5-44 % of the patients who underwent TME achieved pathological complete response (pCR) on post-operative histopathologic studies. The question is whether they could obtain significant benefits regarding quality of life and long-term survival with a more conservative approach and a strict follow-up [1].

The idea of nonsurgical treatment for patients with cCR after NCRT was first proposed by Nakagawa and colleagues in 2004 and was then utilized in a large series of patients by Habr-Gama et al. in Brazil, when they reported the results of a retrospective cohort study of patients managed with a "watch and wait" approach after complete clinical response to neoadjuvant chemoradiation [2,3].

Actually, the watch and wait strategy constitutes a matter of debate among physicians. After adopting a non operative treatment, salvage surgery can still control local regrowth (LR) of the tumor, but the results are still controversial, as there is no accord on the criteria of follow-up and the techniques which can obtain the best sensitivity when detecting a LR. The ongoing TRIGGER trial, allows patients who have shown a good response, but in whom the possibility of residual tumour is not excluded, to be further reassessed and monitored for regrowth [4]. However, in the absence of definitive results

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from randomized trials, this approach is not the standard of care. We present a review of the literature and a personal case series.

Materials and Methods

Literature search was conducted on the following databases: PubMed, Web of Science, EMbase, Cochrane Library. Time period is set from 2002.1.1 to 2019.7.4. The search string which was used was: RECTAL and CARCINOMA or CANCER or NEOPLASM and WAIT and WATCH or SEE or WATCHFUL WAITING or NONOPERATIVE and CHEMORADIOTHERAPY. Language was restricted to English only.

Personal case series

Our personal case series included 8 patients, all of whom had cCR at the exploration after chemoradiotherapy. After extensive information, all of them had refused the proposed standard treatment with TME and signed a specific consensus to watch and wait protocol, which included information about the strict follow-up protocol the patients had to undergo. One more patient in our case series presented a residual lymph-node in the mesorectum after chemoradiation (N1), and underwent laparoscopic TME with the result of no tumor on histological analysis of the resected specimen (pCR). The protocol for intensified chemoradiation in all patients was: 55 Gy in 5 weeks with single fractions of 2.2 Gy on the the tumor and 45 Gy in 5 weeks with single fraction of 1.8 Gy on the pelvis with VMAT (Volumetric Modulated Arc Therapy) and SIB (Simultaneous Integrated Boost) image guided radiotherapy. Capecitabine was administered in all patients during the treatment at a dose of 825 mg/M2 in two daily doses. The cCR was established when no evidence of disease was found post neoadjuvant treatment on Colonoscopy with biopsy of the scar, abdominopelvic NMR and total body CT scan. The m/f ratio was 6:3; the mean age was 68,1 y/o; the mean distance of the tumor from the anal verge was 9,8 cm.

Results

The m/f ratio was 2:1 (6m, 3 F); the mean age was 68 y/o (range 48-75 y.o.); the mean distance of the tumor from the anal verge was 9,8 cm (range 2-15 cm). The TNM of the patients who underwent the "watch and wait" protocol is summarized in (Table I). The patient with asterisk is the one with the "false positive" residual lymph node metastasis. The mean follow-up was 2 years (range 5y-3mo). One patient (1,1%) had to undergo salvage surgery for relapse 9 months after chemoradiation. The patient then developed a metacronous cancer of the caecum which was reoperated, and died of post-operative pneumonia 4 years after the first diagnosis (red asterisk on Table I). All of the other analyzed patients are alive and free from disease at the current follow-up.

Discussion

Watch and wait strategy is an evolving alternative to radical surgery after a clinical complete response (cCR) to neoadjuvant treatment. The goal of this strategy is improved quality of life and comparable curves of disease-free survival [5,6]. Total mesorectal excision combined with NCRT is critical in improving rates of local recurrence and disease-free survival, but many patients experience morbidity and significant post-operative bowel, sexual and bladder disfunctions. Clinical complete response is defined as no clinical evidence of residual tumor and can be achieved in up to 67% of patients with NCRT [7]. 15-40% of the patients achieve complete pathological response (pCR) after TME, which is defined by the absence of residual tumour in the pathological specimen (no detectable tumor cells) [8]. Rectal surgery is not without morbidity and anastomotic leak is a common complication, reported in up to 12% of cases, with subsequent perioperative mortality from 3% to 13% [9].
This concept uses clinical complete response as a surrogate marker for pathological complete response (pCR), which can be determined only by surgical resection. However, pathological complete response and clinical complete response are not always concordant [10,11].

TABLE I - *Characteristics of the patients in our case series*

Initials	Sex	Age	TNM	Distance from anal verge	Follow-up (months)
R.C.	M	48	T3 N1 M0	2	58
R.F.	F	74	T2 N2 M0	15	3
A.A.	M	67	T3 N0 M0	12	7
G.F.*	M	50	T3 N1 M0	10	7
P.A.*	M	77	T3 N2 M0	10	44
C.B.	M	71	T4 N0 M0	5	28
P.R.	F	68	T2 N2 M0	15	26
C.A.	M	79	T3 N1 M0	5	26
D.C.L.	F	75	T2 N1 M0	15	11

The selection of the patients for a "watch and wait" strategy is determined by several factors regarding the patient and the tumor. Some critical points are constituted by the time for response assessment and the optimal surveillance strategy [12]. Basically, the current methods for defining cCR include digital rectal examination, CT, MRI, EUS, proctoscopy, proctoscopy rebiopsy, and serum CEA level. cCR does not necessarily correspond to pCR, the pathological result of a rebiopsy or surgical specimen does not always indicate a pCR.
Consequently, "watch and wait" will fail in a proportion of patients, and surgical resection will be required for tumor regrowth.

Selection of the patients

Two factors appear crucial in the selection of the patient for NOM (non operative management): an advanced T stage seems to be correlated with a higher incidence of local regrowth, and baseline sphincter function (patients who already present fecal incontinence could not have a real benefit from organ preservation). There are patients who are unfit for radical operation because of comorbidities or performance status, and therefore they are offered cRT or short course radiotherapy as an alternative treatment and they can achieve a cCR and subsequently be monitored. However, these patients should be excluded from trials involving watch & wait protocols.
Other patients who constitute a significant proportion in the retrospective studies are them who decline surgical treatment after CRT, and therefore they entry in a Watch and Wait program.
Other categories of patient amenable to a W & W approach are the ones with early-stage low tumours, when high risk features are present, such as third submucosal layer (sm3), invasion, positive margin, grade 3, lymphovascular invasion, and therefore local excision is not amenable and radical resection can result in permanent stoma. In addiction, nCRT is justified in patients with high-risk low tumours (unsafe low rectal surgical plane, invasion from the tumour of the anterior quadrant of the rectum, tumour height of less than 4 cm from the anal verge and the presence of extramural vascular invasion on MRI). Finally, patients with locally advanced rectal cancer typically require nCRT and those who reach a cCR could be candidate for W & W program [13].
Currently no predictive factors exist to determine which patients will respond to CRT based on preoperative data.

Regimens of NCRT

The current protocol by Habr-Gama includes radiation therapy of 54 Gy with combination 5-fluorouracil and leucovorin chemotherapy, which extends for an additional 3 cycles beyond the neoadjuvant period for a duration of 9 wk. Patients undergoing extended nCRT were more likely to undergo organ preservation and avoid surgery at 5 years (67 vs 30%, p = 0,001) [14,15]. Their cCR rate after extended nCRT was 85,7% compared to 56.6% after standard nCRT (p < 0.001). The European Society of Medical Oncology (ESMO) guidelines recommend a regimen of 45-50 Gy in 35-28 fractions with consideration of a boost of 5.4 Gy in 3 fractions should the circumferential resection margin (CRM) be threatened and a continuous infusion of 5-FU or oral capecitabine [16]. However, an extended nCRT regimen could cause toxicity and potential poorer functional outcomes.

Timing of Assessment

Timing of assessment of the tumor response is another critical aspect in the watch & wait strategy. Some series in the literature described reassessment at a fixed time point, like 6, 8 or 10 weeks [17,18].
Others authors proposed a rather large period of time, for example 8 to 12 weeks, 4 to 10 weeks or more than 8 weeks [19-21]. A higher rate of pCR has been described when delaying surgery after nCRT in several studies [22,23].
The optimal interval between nCRT and surgery, and similarly between nCRT and response assessment in a Watch & Wait context, has not been established. In the absence of evidences, a timing interval between 6 and 12 weeks after completion of treatment should be considered by clinicians [24]. It seems that a longer interval for the declaration of cCR can increase the number of patients who can be offered W & W up to 43% [25].

Assessment of CCR

There is no consensus on the definition of cCR, but all published protocols recommend a combination of endoluminal and MRI criteria. The 2017 European Society for Medical Oncology guidelines define cCR as the absence of any irregularities or a palpable tumor on digital rectal examination and non-visible lesion on endoscopy with the exception of a flat scar, teleangiectasia or whitening of the mucosa [26].
Any suspicion lesion can be biopsied; however, some authors reported a sensitivity of 50% and a poor negative predictive value of 11% for endoscopic biopsies, which might be explained by geographical miss. The specificity and the positive predictive value were reported to be both 100%, meaning that when cancer cells were found on the biopsy, it resulted in confirmed residual cancer in the resected specimen in all cases [27].
Maas et al. defined five criteria for cCR: an absence of residual tumour at endoscopy or only a small residual erythematous scar, non-palpable tumour and negative biopsies from the scarred area or previous site of tumour, substantial downsizing with no residual tumour

or only fibrosis on diffuse weighted imaging (DWI) MRI and absence of any suspicious lymph-node on MRI [28]. Magnetic resonance imaging is a powerful tool to assess tumour response. Two different sequences can be utilized in the assessment of nCRT response: the standard MRI (mostly T2-weighted sequence) and the diffusion-weighted MRI (DW-MRI). The magnetic resonance tumour regression grade (mrTRG) correlates well with overall survival, disease-free survival and local recurrence rates [29]. According to mrTRG grading system patients are categorised in 5 groups:
– TRG1-thin fibrosis, low-density signal on T2-weighted images with no evidence of intermediate signal intensity at the site of the treated disease;
– TRG2-dense fibrosis with no macroscopic evidence of intermediate T2 signal intensity;
– TRG3-predominating low signal fibrosis with macroscopic scattered or local intermediate signal intensity;
– TRG4 and TRG5-predominating intermediate T2-weighted signal with minimal or no fibrosis present.
The mrTRG closely resembles the Mandard pathologic grade system, which showed being ten times more sensible in identifying patients with pCR compared with only clinical assessment [30]. Restaging rectal cancer after NCRT remains difficult. Some authors suggested that a multimodal assessment with High Resolution Magnetic Resonance Imaging (HR-MRI) and endorectal ultrasonography (ERUS) may be the best option for local restaging of locally advanced rectal cancer after NCRT, even if the radiotherapy tissue alteration causes a low diagnostic accuracy for both methods [31].
Panzironi et al. [32] founded that ERUS performance is significantly reduced when restaging rectal cancer after neoadjuvant treatment, with frequents errors of over staging, due to fibrotic and necrotic reactions that can hardly and extensively alter the rectal and perirectal tissues.
An alternative to repeated assessment in patients with a "near-complete response" is a local excision, preferably TEM, providing histological proof of a ypT0. Some of the disadvantages of a TEM are the raise of postoperative complications, a more difficult follow-up because of fibrotic changes, and more difficult salvage TME [28].

CEA

Several studies have found the CEA level, either prior to any treatment or after nCRT before radical surgery, to be a strong factor of tumour regression and pCR, although two rectal cancer patients with the same overall burden of disease can express different carcinoembryonic antigen (CEA) levels [33-35].

PET/TC

Positron emission tomography and CT (PET-CT) is an imaging modality who has a growing interest in identifying cCR. Variation in total lesion glycolysis can be used as a predictor of cCR [36]. In practical terms, up to 98% of cCR could be identified by combining Digital Rectal Examination, endoscopy and MRI (T2 weighted and DWI), although the dosage of CEA and the Positron emission tomography could have a role in the near future in increasing the percentage [37].
However, the accuracy of PET-TC for prediction of complete pathologic response is estimated at 44%, so it is not actually included in a standard evaluation protocol of locally advanced rectal cancer [38].

Timing of Assessment

The most appropriate interval for assessment of cCR remains a matter of debate. A longer interval after radiation therapy is associated to a highest rate of cCR, thus avoiding unnecessary surgery in more patients [25]. An optimal interval has not been established, but most authors utilize an interval between 6 and 12 weeks. The majority of patients with a near cCR response 8-10 weeks after nCRT will evolve into a cCR at a second reassessment 6-12 week later, offering a Watch and Wait approach up to 43% of patients [39]. Patients with near cCR can benefice of a "consolidation chemotherapy" with reassessment 6-2 weeks later[25]. One common problem in Watch & Wait strategy is residual lymph node metastases within the mesorectum despite complete primary tumor regression (ypT0). A rate between 2 and 9 % of patients with clinical stage II-III disease who were ypT0 following nCRT were found to have microscopic lymph node metastases, which led to a recurrence of disease [39]. Even in this case, a longer interval between nCRT and surgery can lead to a higher chance of nodal sterilization [40]. However, randomized trials are necessary regarding timing of response assessment at 6 versus 12 weeks because it is unclear whether the late responders share the same favorable prognosis.

Follow Up

Habr-Gama et al. proposed an algorithm which includes monthly follow-up with Digital Rectal Examination and rigid proctoscopy with or without biopsy at every visit for the first 3 months and every 2 to 3 months during the first year, with determination of CEA levels every 2 months. Twice annual or annual MRI and computed tomography is recommended, with the intensity of follow up tending to decrease in frequency after 2 years. Approximately 25% of patients will develop local regrowth and the majority of this patient can undergo to a salvage surgery [41]. Follow up should be continued over 5 years. The intensity of follow-up tends to be

reduced after the 2-year mark, because the vast majority of regrowth occur in the first two years after completion of management. Patients should be aware of the implications of such an intensive program and their compliance is of primary importance in the detection of regrowth. Standard follow-up protocols for watch & wait have not been established and surveillance regimens vary.

Local Recurrence, Salvage Surgery, Disease-Free Survival and QoL

Outcomes and management of regrowth and relapse have been systematically revised by Dossa and Colleagues. In their meta-analysis they didn't find significant differences between patients managed with watch & wait and patients treated with surgery in terms of non-regrowth recurrence, cancer-specific mortality, disease-free survival or overall survival [42]. Among patients with local regrowth, the pooled rate of salvage therapy was 95,4%. However, patients managed with watch & wait had a poorer disease-free survival than those who underwent radical surgery with pathological complete response. This finding was probably correlated by the opportunity for local regrowth among these patients.

Chadi and Colleagues [43] in their meta-analysis found evidence that increasing cT stage was associated with increased risk of local regrowth, while Hupkens et al in their matched-controlled study concluded that watch & wait was associated with substantial better quality of life and functional outcomes compared with standard surgical resection [5]. In other studies, patients selected for Watch & Wait group were reported to have equivalent Overall Survival and Disease Free Survival compared with the cohort undergoing surgery [44-47]. A high proportion of patients managed by watch and wait approach who develop tumor regrowth can be salvaged with definitive surgery with non-statistically significative differences in the rate of distant recurrence. A Randomized controlled trial would provide the best evidence, comparing the "watch and wait" approach with immediate total mesorectal excision for patients with a cCR after nCRT, assessing long-term oncological and functional outcomes. The next best level evidence is likely to come through well documented, prospective studies, applying appropriate analytical methods to reduce confounding and biases, such as the initiative of the International Watch and Wait database [47].

Ongoing Research, Trials

TRIGGER trial
STARTREC trial
WOW trial (NCT03125343)

A multicentre randomized controlled trial (STAR-TREC) is currently ongoing. Patients with rectal tumour ≤ T3b N0 M0 are recruited to standard TME surgery or organ preservation arm [49]. The primary endpoint of this phase II study is to demonstrate sufficient international recruitment in order to sustain a phase III study incorporating pelvic failure as the primary endpoint. Patients with cCR post nCRT will be recruited into the W & W arm whereas patient with incomplete response will be recruited into the local excision arm. This study could clarify the actual controversy regarding the management of patients with early rectal cancer.

The TRIGGER trial is attempting to address MRI'S role in assessing response after nCRT using mrTRG (magnetic resonance tumour regression grade) as a biomarker to stratify patients into good or poor response, hence determining the optimal strategy be it W and W or surgical intervention [4].

The WoW trial in Sweden is a multicenter prospective clinical trial with all patients scheduled for neoadjuvant treatment with (chemo) radiotherapy or short course radiotherapy with delayed surgery 6-8 weeks for rectal cancer staged as cT4bNX/any cT any cN and cMRF+/any cT any cN and lateral lymph nodes on MRI. All patients that are considered to have complete response will be offered a "Watch and wait" approach with follow-up according to the protocol. They will then be followed at one of the Regional University Hospital within their catchment area.

All patients with a palpable rectal cancer staged as cT4bNX/any cT any cN and cMRF+/any cT any cN and lateral lymph nodes on MRI (and patients that have been offered short course radiotherapy with delayed surgery due to various reasons) that does not achieve complete response will serve as control and will be treated with surgery as planned prior to initiation of (chemo)radiotherapy [50].

Conclusions

There are several key areas for future research. First, there is a need to establish an internationally accepted definition of clinical complete response, and to establish the role of MRI in this definition. Research is also needed to determine other predictors of sustained clinical complete response. Several approaches exist including imaging, blood biomarkers, and tumour molecular phenotyping. Evidence suggests that watch and wait is associated with substantially better quality of life and functional outcomes compared with standard surgical resection. But a major caveat is that chemoradiotherapy itself might be associated with long-term morbidity. All three pathways (chemoradiotherapy plus resection vs chemoradiotherapy plus watch and wait vs tailored resection alone) need to be investigated. Only then can we truly appraise the role of watch and wait in the overall standard care management of locally advanced rectal cancer. There is a legitimate concern that organ preservation in rectal cancer could negate the improvements in onco-

logical outcome that have been achieved by optimal use of a good surgical TME technique and (neo)adjuvant treatment. The concern is that the increased number of local recurrences will lead to a decreased survival because some may not be amenable to salvage therapy and because some may cause metastases later. In the absence of randomized data and very large series, it is difficult to calculate an exact oncological risk, but based on our review of the series described above we estimate the excess oncological risk of dying with a watch-and-wait policy in the order of 2% to 3% or less. In the shared decision process with the patient, this needs to be carefully balanced against the operative risk and loss of function of major rectal surgery. We experienced that patients are often willing to take this small potential risk in order to avoid major surgery, potentially poor functional outcome, or a colostomy.

Riassunto

La Radiochemioterapia neoadiuvante (NRCT) associata all'escissione totale del mesoretto (TME) è attualmente il gold standard per i tumori del retto basso localmente avanzati (LACR). Circa il 20-30% dei pazienti dopo radiochemioterapia neoadiuvante possono ottenere una risposta clinica completa (cCR); il 5-44% dei pazienti sottoposti a TME ottengono una risposta patologica completa (pCR) all'esame istologico del pezzo operatorio. Nello studio presente presentiamo una review della letteratura corrente sull'argomento ed analizziamo retrospettivamente la nostra personale esperienza sull'approccio definito "watch and wait" dopo risposta clinica completa. Ulteriori studi sono necessary per stabilire una definizione clinica accettata a livello internazionale di risposta clinica completa, per delineare il reale ruolo della Risonanza Magnetica Nucleare nella stadiazione post trattamento radiochemioterapico e per stabilire dei predittori più precisi di risposta clinica completa sostenuta. Deve inoltre essere valutata la presenza di morbidità e di effetti avversi dopo trattamento radiochemioterapico. Le evidenze attualmente presenti in letteratura suggeriscono che l'approccio "watch and wait" è associato con una sostanziale migliore qualità della vita e migliori esiti funzionali, comparato con la resezione chirurgica standard.

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