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REVIEW ARTICLE **CME**

Watch-and-wait Approach for Clinical Complete Responders after Neoadjuvant Chemoradiotherapy for Rectal Cancer

CC Law

Department of Clinical Oncology, Queen Elizabeth Hospital, Jordan, Hong Kong

ABSTRACT

Neoadjuvant chemoradiotherapy followed by total mesorectal excision is the standard of care for locally advanced rectal cancer. The mean pathological complete response rate following neoadjuvant chemoradiotherapy has been reported to be 12% to 16%. In clinical complete responders after neoadjuvant chemoradiation, a non-operative, watch-and-wait approach is thus proposed to allow for organ preservation. This paper reviews key studies of the watch-and-wait approach following neoadjuvant chemoradiotherapy for rectal cancer to determine its oncological outcomes and safety.

Key Words: *Chemoradiotherapy; Organ preservation; Rectal neoplasms*

中文摘要

直腸腺癌新輔助放化療後臨床完全緩解者的觀察等待療法

羅志清

新輔助放化療後全直腸系膜切除是局部晚期直腸腺癌的標準治療。新輔助放化療後的平均病理完全緩解率為12%至16%。於新輔助放化療後有臨床完全緩解的直腸腺癌患者，為保存器官，有建議進行非手術的觀察和等待療法。本文回顧新輔助放化療後觀察和等待療法的重要研究以確定其腫瘤療效和安全性。

INTRODUCTION

Radical resection is the mainstay of curative treatment for non-metastatic rectal cancer. Total mesorectal excision is the standard of care and has superior oncological and functional outcomes to traditional blunt dissection.[1-3] Neoadjuvant chemoradiotherapy (NCRT) is indicated in patients with locally advanced rectal cancers. It significantly reduces local recurrence and treatment-related adverse events, compared with postoperative chemoradiotherapy, although the disease-free survival (DFS) and overall survival (OS) of both strategies are comparable.[4,5] Radical rectal surgery may result in acute and late complications. The risks of 30-day morbidity and mortality following laparoscopic total mesorectal excision have been reported to be 29.3% and 1.8%, respectively.[6] Late complications of rectal surgery may result in bowel, urinary, and sexual dysfunction.[7-9] Patients with distal rectal tumours may require abdominal perineal resection with permanent colostomy, leading to significant physical and

Correspondence: *Dr CC Law, 11/F, Block R, Queen Elizabeth Hospital, 30 Gascoigne road, Kowloon, Hong Kong.*
Email: lccz01@ha.org.hk

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psychosocial morbidity, poor body image, and impaired quality of life.[10,11] Even if the sphincter is preserved, low anterior resection often results in severe bowel dysfunction with incontinence, urgency, and frequent bowel movements (low anterior resection syndrome).[12]

To preserve the organ and to avoid the complications of surgical resection, NCRT followed by a watch-and-wait approach or local excision has been proposed. Local excision is applicable to clinically node-negative T2 and early T3 low-lying rectal cancer with good clinical response to NCRT.[13] The watch-and-wait approach is applicable to a wider range of patients with clinically stage 2-3 rectal cancer with clinical complete response to NCRT.[14] This paper reviews key studies of the watch-and-wait approach after NCRT for rectal cancer to determine its oncological outcomes and safety.

PATHOLOGICAL COMPLETE RESPONSE

NCRT can achieve pathological complete response (pCR) in 12% to 16% of patients with rectal cancer. In a meta-analysis of 14 studies and 3105 patients with locally advanced rectal cancer treated with NCRT (radiotherapy of 45-50.4 Gy in 25-28 daily fractions with fluorouracil-based chemotherapy) and surgery (6-8 weeks later), the pooled pCR rate was 16% (range, 8%-24%).[15] In a Cochrane systematic review of five randomised trials that compared NCRT with radiotherapy alone for stage 2 and 3 resectable rectal cancer, the pooled pCR rate after NCRT was 12% (range, 4.8%-15.9%).[16] In a review of phase 2 and 3 studies of 3157 patients treated with NCRT for rectal cancer, the overall pCR rate was 14%.[17]

pCR is a favourable prognostic factor associated with good OS and low rates of local recurrence and distant failure. In a meta-analysis of 16 studies and 3363 patients, patients with pCR had a weighted mean local recurrence rate and distant failure rate of 0.7% and 8.7% respectively, and the 5-year OS and DFS rates of 90% and 87%, respectively.[18] In a pooled analysis of individual patients, the 5-year DFS rate was higher in patients with pCR than in those without (83.3% vs. 65.6%, $p < 0.0001$).[15] The adjusted hazard ratio of failure in patients with pCR was 0.54, indicating a significantly higher probability of DFS than in those without pCR.

WATCH-AND-WAIT APPROACH

Retrospective Studies

The finding of pCR after NCRT in rectal cancer led Habr-Gama and colleagues to challenge the need for routine radical resection in patients with clinical complete response (cCR). This Brazilian group has laid the groundwork for this non-operative, watch-and-wait approach. In 2004, the Brazilian group reported a retrospective study of 265 patients with resectable distal rectal adenocarcinoma (located ≤7 cm from the anal verge) who underwent NCRT (radiotherapy of 50.4 Gy with concurrent bolus fluorouracil and folinic acid) and were assessed at 8 weeks for treatment response.[19] Patients with any significant residual ulcer or positive biopsies were considered incomplete clinical responders. Of 265 patients, 194 (73.2%) were considered incomplete clinical responders and were referred for standard surgical resection. Of them, 22 actually had pCR based on the pathological examination of the resected specimen.[19] The 71 patients without any abnormality in treatment response were considered cCR and were managed with the watch-and-wait approach that included monthly follow-up with digital rectal examination, proctoscopy and biopsy, and serum carcinoembryonic antigen level. Abdominal and pelvic computed tomography (CT) and chest radiography were taken every 6 months in the first year, and then every 2 months in the second year and 6 months in the third year. After a mean follow-up of 57.3 months in the watch-and-wait group and 48 months in the pCR group, there were three distant relapses in each group and two endorectal relapses in the watch-and-wait group; two patients in the pCR group died of the disease.[19] Respectively in the watch-and-wait group and pCR group, the 5-year OS rates were 100% and 88%, and the 5-year DFS rates were 92% and 83%.[19] In the resection group, nine definitive colostomies and seven diverting temporary ileostomies were performed. It was concluded that surgical resection might not lead to better oncological outcomes in patients with cCR after NCRT and might be associated with higher rates of stoma creation and unnecessary surgery-related morbidity and mortality.[19]

In 2006, the Brazilian group reported a larger retrospective study of 361 patients with resectable cT2-4N0 or N+ distal rectal cancers treated with the same NCRT regimen.[20] At week 8, 122 patients (33.8%) had initial cCR and were followed up monthly with digital rectal examination, serum carcinoembryonic antigen level, proctoscopy and biopsy for 1 year, and then 3 monthly for another year, and 6 monthly thereafter. At 12 months, 99 patients (27.4%) had a sustained cCR; at a mean follow-up of 60 months, 13 (13.1%) had

endorectal relapses (later salvaged by surgery) [n = 5], distant failures (n = 7), and combined relapses (n = 1), and the 5-year OS and DFS rates were 93% and 85%, respectively.[20]

In 2014, the Brazilian group reported a retrospective study of 183 patients with cT2-4 or cN+ distal rectal cancers treated with NCRT (radiotherapy of 50.4-54 Gy in 28-30 daily fractions of 1.8 Gy per fraction with the same concomitant chemotherapy).[21] Magnetic resonance imaging (MRI) of the pelvis with or without endorectal ultrasonography (ERUS) was used to evaluate treatment response. Initial cCR was achieved in 90 patients (49%) who were then managed with the watch-and-wait approach. After a median follow-up of 60 months, 28 patients (31%) had local relapses; the 5-year local relapse-free survival was 69%.[21] Of them, 26 (93%) underwent salvage therapy. Among the 62 patients without local relapse, 8 patients (13%) had systemic recurrence. The 5-year cancer-specific OS and DFS for all patients were 91% and 68%, respectively.[21] Organ preservation was ultimately achieved in 70 patients (78%).

Results of other retrospective studies of the watch-and-wait approach from the US,[22] UK,[23] and Taiwan,[24] together with the Brazilian studies,[19-21] are summarised in Table 1. They are all single-centre studies and include a small number of patients. With a median or mean follow-up duration of 26 to 50 months, the local recurrence rates have ranged from 0% to 11.1%. All patients with local recurrence could be salvaged by surgery.

Prospective Studies

Table 2 summarises the prospective studies of the watch-and-wait approach.[25-28] A prospective study reported 192 patients with MRI-staged locally advanced rectal cancer treated with NCRT (radiotherapy of 50.4 Gy in 28 fractions with concurrent capecitabine), and the treatment response was evaluated 6 to 8 weeks later.[25] cCR was defined as having no residual tumour or suspicious lymph nodes on pelvic MRI, no residual tumour at endoscopy with negative biopsies from the former tumour location, and no palpable tumour by digital rectal examination when initially palpable.[25] In 21 patients (10.9%) with cCR who were managed with the watch-and-wait approach with pelvic MRI, endoscopic examination with biopsy, CT of abdomen and pelvis, and serum carcinoembryonic antigen level

Table 1. Retrospective studies of patients with rectal cancer managed with the watch-and-wait approach.

Study	Eligibility criteria for NCRT	NCRT regimen	Definition of cCR	No. of patients	Outcome	Salvage surgery rate for LR (%)
Habr-Gama et al,[19] 2004	Resectable distal rectal cancer (≤7 cm from anal verge)	RT of 50.4 Gy, concurrent fluorouracil and folinic acid	No residual tumour by DRE, proctoscopy and biopsy, CT +/- ERUS	71	LR = 2.8%; DR = 4.2%; 5-year DFS = 92%; 5-year OS = 100%	100
Habr-Gama et al,[20] 2006	Resectable distal rectal cancer (≤7 cm from anal verge)	RT of 50.4 Gy, concurrent fluorouracil and folinic acid	No residual tumour by DRE, proctoscopy and biopsy, CT +/- ERUS	99	LR = 5%; DR = 7.1%; LR and DR = 1%; 5-year DFS = 85%; 5-year OS = 93%	100
Smith et al,[22] 2012	Distal rectal cancer, clinical stage cT3/4 or node-positive, or uT2	RT of 45-56 Gy, concurrent fluorouracil or capecitabine	No residual tumour by DRE and endoscopy	32	LR = 9.4%; LR and DR = 9.4%; 2-year OS = 96%	100
Dalton et al,[23] 2012	Rectal cancer with threatened or involved circumferential resection margin, or involved lymph node	RT of 45 Gy, concurrent capecitabine	No residual tumour by DRE, MRI, EUA and biopsy, and PET-CT	6	LR = 0%	-
Habr-Gama et al,[21] 2014	Distal rectal cancer (≤7 cm from anal verge), clinical stage cT2-4 or cN+	RT of 50.4-54 Gy, concurrent fluorouracil-based chemotherapy	No residual tumour by DRE, proctoscopy, CT, MRI +/- ERUS	90	LR = 31%; DR = 13%; 5-year cancer-specific OS = 91%; organ preservation rate = 78%	93
Lai et al,[24] 2016	Rectal cancer (≤10 cm from anal verge), clinical stage II-III	RT of 45 or 54 Gy, concurrent fluorouracil and folinic acid	No residual tumour by DRE, endoscopy and biopsy, CT, ERUS, MRI	18	LR = 11.1%; 5-year OS = 100%	100

Abbreviations: cCR = clinical complete response; CT = computed tomography of the abdomen and pelvis; DR = distal recurrence; DRE = digital rectal examination; DFS = disease-free survival; ERUS = endorectal ultrasonography; EUA = examination under anaesthesia; LR = local recurrence; MRI = magnetic resonance imaging of the pelvis; NCRT = neoadjuvant chemoradiotherapy; OS = overall survival; PET-CT = positron emission tomography–computed tomography; RT = radiotherapy.

Table 2. Prospective studies of patients with rectal cancer managed with the watch-and-wait approach.

Study	Eligibility criteria for NCRT	NCRT regimen	Definition of cCR	No. of patients	Outcome	Salvage surgery rate for LR (%)
Maas et al,[25] 2011	cT4 or T3 with threatened or involved mesorectal fascia +/- >3 involved nodes +/- distal tumour with 1-3 involved nodes	RT of 50.4 Gy, concurrent capecitabine	No residual tumour by DRE, MRI, endoscopy and biopsy	21	Watch-and-wait approach vs. those of pCR after NCRT and surgery: LR = 4.8% vs. 0%; 2-year DFS = 89% vs. 93%; 2-year OS = 100% vs. 91%	100
Habr-Gama et al,[26] 2013	cT2-4 or cN1-2 distal rectal cancers (≤7 cm from anal verge)	RT of 54 Gy, concurrent fluorouracil and folinic acid (3 + 3 cycles)	No residual tumour by DRE, endoscopy and biopsy, MRI, PET-CT	47	LR = 25.5%; DR = 10.6%; 3-year DFS for patients with sustained cCR = 75%; 3-year OS for patients with sustained cCR = 94%	91.7
Appelt et al,[27] 2015	Resectable, T2 or T3, N0-N1, M0, distal rectal cancer (lower 6 cm of rectum)	IMRT of 60 Gy + 5 Gy endorectal brachytherapy boost, concurrent tegafur-uracil	No residual tumour by DRE, endoscopy and biopsy, CT and MRI	40	LR = 22.5%; cumulative LR at 1 and 2 years = 15.5% and 25.9%, respectively; DR = 7.5%	100
Renehan et al,[28] 2016	cT2-4 and N0-2, distal rectal cancer (4-8 cm from anal verge)	RT of 45 Gy, concurrent fluoropyrimidine	No residual tumour by DRE, endoscopy and biopsy, MRI	129	LR = 34%; matched cohort analysis of watch-and-wait approach vs. surgical resection: 3-year non-regrowth DFS = 88% vs. 78%; 3-year OS = 96% vs. 87%; 3-year colostomy-free survival = 74% vs. 47%	88

Abbreviations: cCR = clinical complete response; CT = computed tomography; DFS = disease-free survival; DR = distal recurrence; DRE = digital rectal examination; IMRT = intensity-modulated radiotherapy; LR = local recurrence; MRI = magnetic resonance imaging; NCRT = neoadjuvant chemoradiotherapy; OS = overall survival; pCR = pathological complete response; PET-CT = positron emission tomography–computed tomography; RT = radiotherapy.

monitoring every 3 to 6 months, only one patient developed a small endoluminal recurrence that was salvaged by transanal endoscopic microsurgery, and the remaining 20 patients remained alive without relapse at a mean follow-up of 25 months; the 2-year DFS and OS were 89% and 100%, respectively.[25] Ten patients with low-lying rectal tumours avoided abdominoperineal resection with permanent colostomy.[25] For comparison of oncological outcomes, a control cohort of 20 patients with pCR after NCRT and total mesorectal excision from another study was included. None had a local relapse; one died of complications associated with colostomy closure surgery; and one died of distant relapse. The 2-year DFS and OS for this control cohort were 93% and 91%, respectively, and were comparable with those of the watch-and-wait cohort. Bowel function was significantly better in those managed with the watch-and-wait approach than by surgery.[25]

Another prospective study reported 70 patients with MRI- or ERUS-staged cT2-T4 or cN1-2 non-metastatic distal rectal cancers who underwent intensified NCRT (radiotherapy of 54 Gy in 1.8 Gy per fraction daily with 3 cycles of concurrent bolus fluorouracil and folinic acid and 3 additional cycles of the same chemotherapy).[26] At 10 weeks after NCRT, treatment response was evaluated by digital rectal examination, endoscopy and radiological studies. Of 70 patients, 47 (67.1%) achieved initial cCR and were treated with the watch-and-wait approach; 8 of them (17%) had early tumour regrowth, and 39 (83.0%) had sustained cCR.[26] At a median follow-up of 25.5 months, four patients (10.3%) had late local relapse and were all salvaged by resection without further relapse, and five patients developed distant failure resulting in one death.[26] The 3-year DFS and OS in patients with sustained cCR were 75% and 94%, respectively.[26] Overall, 35 patients (89.7%) with sustained cCR had not undergone any type of resection after a median follow-up of 56 months.[26]

A prospective observational study evaluated the effectiveness of high-dose radiotherapy with concomitant chemotherapy followed by the watch-and-wait approach in 51 patients with resectable distal (lower 6 cm) rectal adenocarcinoma, stage T2 or T3, N0-N1, M0 who underwent intensified NCRT consisting of intensity-modulated radiotherapy with

concomitant boost technique (60 Gy in 30 fractions to tumour, 50 Gy in 30 fractions to elective lymph node volumes), 5-Gy endorectal brachytherapy boost, and oral chemotherapy with tegafur-uracil.[27] At 6 weeks after NCRT, 40 patients with complete clinical tumour regression, negative tumour site biopsies, and no nodal or distant metastases on CT and MRI were managed by the watch-and-wait approach.[27] At a median follow-up of 23.9 months, 9 of them (22.5%) had local relapse and underwent salvage surgery without further local relapse; the cumulative local recurrence was 15.5% at 1 year and 25.9% at 2 years.[27] Three patients had distant metastasis. Patient-reported bowel function was good, with 72% (18 of 25 patients) reporting no stool incontinence at 1 year and 69% (11 of 16 patients) at 2 years.[27] The most common grade-3 acute adverse event was diarrhoea, with a rate of 8% (4 of 51 patients). The most common late toxicity was rectal mucosal bleeding, with a grade-3 bleeding rate of 7% (2 of 30 patients) at 1 year and 6% (1 of 17 patients) at 2 years.[27]

Another prospective observational study reported 129 patients with non-metastatic rectal cancers (cT2-4 and N0-2; located 4-8 cm from the anal verge) who underwent standard NCRT (radiotherapy of 45 Gy in 25 daily fractions with concurrent fluoropyrimidine) and achieved cCR 8 weeks or more later.[28] At a median follow-up of 33 months, 41 patients (32%) had luminal regrowth alone and 36 of them (88%) underwent salvage therapy, and three patients had synchronous luminal regrowth and distant metastasis.[28] The 3-year actuarial rate of local regrowth was 38%.[28] For comparative analyses, a one-to-one paired cohort was derived from 109 patients treated by surgical resection using propensity-score matching (including age, performance status, and tumour stage).[28] In the matched analyses, the watch-and-wait approach and surgical resection were comparable in terms of 3-year non-regrowth DFS (88% vs. 78%, log-rank $p = 0.022$; not violating the a-priori non-inferiority margin) and 3-year OS (96% vs. 87%, long-rank $p = 0.015$; not violating the a-priori non-inferiority margin).[28] The watch-and-wait approach resulted in better 3-year colostomy-free survival, compared with surgical resection (74% vs. 47%, $p < 0.0001$), with a 26% absolute reduction in patients requiring permanent colostomy at 3 years.[28]

Systematic Reviews

In a systematic review of five retrospective and four prospective observational studies that included 370 patients, local tumour regrowth occurred in 105 patients (28.4%) and distant failure without local tumour regrowth in seven patients (1.9%).[29] Salvage surgery was possible in 94 patients (89.5%) with local tumour regrowth, and four of the seven patients with distant failure underwent resection of the metastatic disease.[29] In two of these studies with comparative analysis of the cCR group and pCR group, there was no significant difference in terms of 2-year OS (100% and 97% vs. 91% and 100%) or 2-year DFS (89% and 88% vs. 93% and 98%).[29] Most patients with local tumour regrowth could be salvaged by surgery under the watch-and-wait approach; nonetheless, there was insufficient evidence to confirm its oncological safety in view of the non-randomised nature of studies, small sample size, short follow-up, and heterogeneity of studies.[29]

In another systematic review and meta-analysis of 23 studies including 867 patients with a median follow-up of 12 to 68 months, the pooled 2-year local regrowth rate was 15.7%, and salvage therapies were performed in 95.4% of patients with local regrowth.[30] Patients with cCR managed with the watch-and-wait approach and patients with pCR managed with surgical resection were comparable in terms of non-regrowth relapse, cancer-specific mortality, and OS.[30] The DFS was significantly better in the surgery group because of a higher risk of local regrowth in the watch-and-wait group.[30] In addition, patients with cCR managed with the watch-and-wait approach and patients with cCR managed with surgery were comparable in terms of non-regrowth recurrence, cancer-specific mortality, DFS, and OS.[30] Most patients managed with the watch-and-wait approach avoided radical surgery, and almost all patients with local regrowth could undergo salvage therapy; nonetheless, more prospective studies are needed to confirm the long-term safety in view of the limited number of patients included in the studies.[30]

Various Definitions of Complete Clinical Response and Watch-and-wait Approach

The definition of cCR was not standardised across studies. In general, cCR was defined as no residual tumour detected on digital rectal examination, endoscopic examination with biopsy, or multiple imaging modalities (Table 3[25-28]). The watch-and-wait approach also varied across studies (Table 4[21-28]). In general, it involved digital rectal examination, endoscopy and biopsy, CT of the chest and abdomen, pelvic MRI, and serum carcinoembryonic antigen measurements. Examination under anaesthesia was included in two studies,[23,28] and the use of positron

emission tomography–CT in two studies.[23,27] The frequency of follow-up also varied across studies. In general, follow-up was more frequent in the first 2 years (every 2-4 months) and less frequent thereafter.

STRATEGIES TO ENHANCE PATHOLOGICAL COMPLETE RESPONSE

Strategies to enhance pCR and ultimately organ

Table 3. Definition of clinical complete response after neoadjuvant chemoradiotherapy for rectal cancer.

Study	Definition of clinical complete response		
	DRE	Endoscopy	Imaging
Maas et al,[25] 2011	No palpable tumour when initially palpable before NCRT	No residual tumour; small residual erythematous ulcer or scar; negative biopsies from the scar, ulcer, or former tumour location	Pelvic MRI: substantial downsizing with no residual tumour or fibrosis only; no suspicious lymph node; residual wall thickening due to oedema
Habr-Gama et al,[26] 2013	Absence of residual ulceration, mass, or significant rectal wall irregularity	Absence of residual ulceration, mass, or significant rectal wall irregularity	Pelvic MRI: presence of residual low-signal intensity areas; absence of restriction to diffusion PET-CT: absence of residual fluorodeoxyglucose uptake within the rectal wall
Appelt et al,[27] 2015	No palpable tumour	Small, white scar in rectal wall; superficial erosion or ulceration without palpable tumour; if persistent ulcer or erosion, additional biopsies at the edge to ensure no evidence of disease	Pelvic MRI: primary tumour regression was not part of the formal response assessment; regional lymph node assessment (suspected node was considered malignant if diameter >5 mm)
Renehan et al,[28] 2016	Absence of residual ulceration, stenosis, or mass within the rectum	Absence of residual ulceration, stenosis, or mass within the rectum	Pelvic MRI: normal radiological imaging of the mesorectum and pelvis

Abbreviations: DRE = digital rectal examination; MRI = magnetic resonance imaging; NCRT = neoadjuvant chemoradiotherapy; PET-CT = positron emission tomography–computed tomography.

Table 4. Definition of watch-and-wait approach.

Study	Definition of watch-and-wait approach	
	Clinical examination	Imaging
Prospective		
Maas et al,[25] 2011	Clinical assessment and CEA: every 3 months in year 1, every 6 months in years 2-5	Pelvic MRI: every 3 months in year 1; CT of chest, abdomen and pelvis every 6 months in year 1, every 12 months in years 2-5
Habr-Gama et al,[26] 2013	DRE, proctoscopy, CEA: every 2 months in year 1, every 3-4 months in year 2, every 6 months in years 3-5, every 12 months in year 6	Pelvic MRI: +/- PET-CT every 2 months in year 1, every 3-4 months in year 2, every 6 months in years 3-5, every 12 months in year 6; CT of the chest and abdomen every 6 months in years 1-2, every 12 months in year 3
Appelt et al,[27] 2015	Clinical examination and endoscopy: every 2 months in year 1, every 3 months in year 2, every 6 months in year 3, every 12 months in years 4-5	PET-CT 3 times in year 1, twice in year 2, and every year thereafter
Renehan et al,[28] 2016	DRE, EUA or endoscopy in years 1-2, CEA at least every 6 months in years 1-3	Pelvic MRI: every 4-6 months in years 1-2; CT of the chest, abdomen, and pelvis at least twice in years 1-3
Retrospective		
Smith et al,[22] 2012	DRE and flexible sigmoidoscopy: every 3 months in year 1, and every 4-6 months thereafter	CT every 6 months in years 1-2
Dalton et al,[23] 2012	EUA at 3 months and at 1 year, CEA levels	PET-CT and pelvic MRI: 6-monthly and then yearly
Habr-Gama et al,[21] 2014	DRE + rigid proctoscopy every 1-2 months and CEA levels every 2-3 months in year 1, then every 3 months after year 1, and every 6 months after 3 years	CT, pelvic MRI, +/- ERUS after 6 months and yearly thereafter
Lai et al,[24] 2016	DRE + rigid proctoscopy or colonoscopy +/- selective biopsy, and CEA every 3 months in years 1-2, then every 6 months in year 3	Chest radiography, CT, pelvic MRI after 6 months and yearly thereafter

Abbreviations: CEA = carcinoembryonic antigen; CT = computed tomography; DRE = digital rectal examination; EUA = examination under anaesthesia; ERUS = endorectal ultrasonography; MRI = magnetic resonance imaging; PET-CT = positron emission tomography–computed tomography.

preservation involve optimisation of radiotherapy, chemotherapy, and the time interval from NCRT completion to surgery.

Optimal Timing to Capture Maximal Tumour Regression

To determine the relationship between pCR and the time interval from NCRT completion to surgery, the Consortium for Optimizing the Surgical Treatment of Rectal Cancer conducted a retrospective analysis of 17,255 patients from the National Cancer Database (2006-2011) with clinical stage 2 to 3 rectal cancer treated with NCRT and surgical resection.[31] Compared with a time interval of 6-8 weeks, a time interval of >8 weeks was associated with a significant increase in the odds of pCR (13.2% vs. 11.7%) and tumour down-staging, and the cumulative pCR rate appeared to peak between 10 and 11 weeks.[31] In another study of 3298 patients with rectal cancer treated with 45-54 Gy radiotherapy in conventional fractionation, the percentage of patients who achieved pCR increased most rapidly between 4 and 8 weeks, and the rate plateaued after 10 to 12 weeks.[32] In a Korean study of 1786 patients with locally advanced rectal cancer (cT3-4N0-2M0), the pCR rate increased after 5 weeks and decreased after 10 weeks.[33] These data suggest that the cumulative pCR rate increases most rapidly at 4 to 8 weeks, peaks at 10 to 11 weeks, and levels off thereafter. The optimal time interval to evaluate treatment response after NCRT appears to lie between 8 and 11 weeks.

Escalation of Radiotherapy Dose

A radiation dose-response model study demonstrated a significant dose-response relationship in radiotherapy doses between 50.4 Gy and 70 Gy for rectal cancer regression after NCRT.[34] In a meta-analysis of patients with locally advanced rectal cancer treated with preoperative radiotherapy of ≥60 Gy, the pooled pCR rate was 20.4%,[35] which was higher than the 12% to 16% reported after conventional NCRT of 45-54 Gy.[15-17] Increasing the radiotherapy dose above the standard dose of 45-54 Gy may potentially enhance the pCR rate and therefore organ preservation.

To escalate the radiotherapy dose to the rectal tumour without exceeding surrounding normal tissue tolerance, local boost using endoluminal brachytherapy is a viable option owing to its ability to deliver a high localised dose with a rapid fall-off and hence sparing adjacent normal tissues.[36] Nonetheless, a randomised study that compared fluorouracil-based chemoradiotherapy (50.4 Gy) with the same chemoradiotherapy plus two high-dose rate brachytherapy fractions of 5 Gy each reported that the addition of brachytherapy boost did not improve the pCR rate.[37]

In contrast to brachytherapy, intensity-modulated radiotherapy enables higher doses to both the primary rectal tumour and involved lymph nodes. In a prospective study of patients with locally advanced rectal cancer treated with intensity-modulated radiotherapy and concurrent capecitabine, 46 Gy in 23 fractions was given to the planning target volume encompassing the rectal tumour, mesorectum, and pelvic lymph nodes, whereas a higher dose of 57.5 Gy in 23 fractions was given to the boost planning target volume using simultaneous integrated boost.[38] The patients underwent surgery 6 to 8 weeks after chemoradiotherapy, and 22 of them (30.6%) achieved pCR, and the 3-year estimated OS and DFS rates were 95.4 and 85.9%, respectively.[38] No patient had local relapse, but 10 patients (13.8%) developed distant metastases; there was no grade-4 acute radiotherapy-related toxicity.[38]

Intensification of Chemotherapy

In randomised phase-3 trials of the STAR-01,[39] ACCORD 12,[40,41] NSABPR04,[42,43] and PETACC-6[44] to investigate the addition of oxaliplatin to the standard fluorouracil-based NCRT in locally advanced rectal cancer, there was no significant improvement in the pCR rate with the addition of oxaliplatin to preoperative fluoropyrimidine-based NCRT. Besides, addition of oxaliplatin resulted in significantly higher acute toxicity and thus reduced treatment compliance, but comparable local relapse rate, DFS, and OS. In contrast, the German CAO/ARO/AIO-04 randomised phase-3 trial showed a significantly increased pCR rate with the addition of oxaliplatin to the fluorouracil-based combined regimen.[45,46] The addition of oxaliplatin to standard fluoropyrimidine-based NCRT does not appear to be a better option with regard to the goal of organ preservation.

The typical time interval between the end of NCRT and surgery is 6 to 8 weeks. The addition of systemic chemotherapy within this time interval is expected to be effective in enhancing pathological regression and allowing earlier administration of systemic therapy to eradicate distant micro-metastasis, as compared with traditional postoperative adjuvant chemotherapy.

In a prospective phase-2 trial of NCRT (radiotherapy

of 50.4-54 Gy with concurrent continuous infusion fluorouracil) and delayed total mesorectal excision, 292 patients with locally advanced rectal cancer stage cT3-4 or Tany, N1-2 were treated with NCRT followed by surgery at 6 weeks (n = 71), or 2 cycles (n = 74), 4 cycles (n = 71), or 6 cycles (n = 76) of interval chemotherapy mFOLFOX6 and then surgery at 11, 15, and 19 weeks after completion of NCRT, respectively.[47] The respective pCR rates were 18%, 25%, 30%, and 38%, respectively (p = 0.0036); adding interval chemotherapy significantly increased pCR rates.[47]

Alternatively, chemotherapy can be given as induction therapy prior to NCRT. Induction chemotherapy has better compliance than postoperative chemotherapy. In the phase-2 EXPERT trial to investigate 105 patients with MRI-defined poor-risk rectal cancer who underwent four cycles of induction chemotherapy CAPOX (capecitabine and oxaliplatin) followed by NCRT (54 Gy with capecitabine) and total mesorectal excision 6 weeks later, the pCR rate was 20%.[48] In the Spanish randomised phase II GCR-3 study of 108 patients randomised to receive either four cycles of induction chemotherapy CAPOX (capecitabine and oxaliplatin) followed by NCRT and surgery or NCRT followed by surgery and 4 cycles of adjuvant chemotherapy CAPOX, the two arms were similar in terms of the pCR rate (14.3% vs. 13.5%) and DFS, but the induction chemotherapy arm resulted in lower grade ≥3 toxicity (19% vs. 54%, p = 0.0004) and higher treatment compliance (91% vs. 54%, p < 0.0001).[49,50]

CONCLUSION

In patients with cCR, the watch-and-wait approach following NCRT for rectal cancer is a viable option to achieve organ preservation and spare surgical morbidities and mortalities. The evidence mainly comes from prospective observational studies and retrospective single-centre series; no evidence from randomised controlled trial is yet available. Further studies on optimisation of chemoradiotherapy, timing of response evaluation, definition of cCR, and monitoring protocol are warranted before routine implementation of this approach.

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