Current State of Neoadjuvant Radiotherapy for Rectal Cancer

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Abstract

Colorectal cancer is the third most commonly diagnosed cancer, with rectal cancer accounting for 30% of cases. The current standard of care curative treatment for locally advanced rectal cancer is (chemo)radiotherapy followed by surgery and adjuvant chemotherapy. Although neoadjuvant radiotherapy has reduced the risk of local recurrence to less than 10%, the risk of distant metastasis remained high at 30% affecting patient survival. In addition, there is a recognition that there is heterogeneity in tumor biology and treatment response with good responders potentially suitable for treatment de-escalation. Therefore, new treatment sequencing and regimens were investigated. Here, we reviewed the evidence for current neoadjuvant treatment options in patients with locally advanced rectal adenocarcinoma, and highlight the new challenges in this new treatment landscape.

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Introduction

In 2020, colorectal cancer is the third most commonly diagnosed cancer but is the second leading cause of cancer-related deaths.[1] Colorectal cancer is considered a disease of the developed world, with up to 9x incidence rates in developed countries such as Australia and Northern America, compared to developing countries. Rectal cancer accounts for approximately 30% of colorectal cancer diagnoses. In the early 2000s, the standard of care for management of locally advanced rectal cancer is neoadjuvant radiotherapy (with/ without chemotherapy) followed by surgery and adjuvant chemotherapy. The introduction of neoadjuvant radiotherapy and total mesorectal excision (TME) surgery has reduced the 5-year local recurrence rates to 10% or less.[2-5] The risk of developing distant metastatic disease, however, remained high at 30% in those with locally advance disease.[2,3,5,6] In the past decade, to improve patients' survival, patients' quality of life, treatment compliance and cost-effectiveness, novel treatment regimens were designed and trialed. In parallel of the developments of these new treatment options, there is a recognized need and advancements in the field of biomarkers to aid treatment personalization to patient's tumor biology.

Preoperative Versus Postoperative (Chemo)radiotherapy

Postoperative chemoradiotherapy was established as the standard of care for locally advanced rectal cancer in the 1990s following the GITSG 7175,[7] NCCTG 794751[8] and the NSABP R-01[9] trials demonstrating improved survival and locoregional control with adjuvant chemoradiotherapy.

With treatment-related side-effects of up to 61% in adjuvant trials, the sequencing of radiotherapy in relation to surgery was investigated in the 1990s. The proposed potential benefits of preoperative chemoradiotherapy include reduced bowel toxicity, as the irradiated tumor will be removed and less small bowel irradiation, and improved rates of sphincter-sparing surgery due to downstaging of tumor. Early trials including the Swedish Rectal Cancer Trial[10] and the Dutch CKVO 95-04[11] study investigated preoperative short course radiotherapy followed by surgery and showed improved locoregional control. The EORTC 22921[5,12] and FFCD 9203[13] studies showed improved pathological complete response and locoregional control rates in those who received combined chemoradiotherapy (5FU with long-course radiotherapy) compared to radiotherapy alone.

The NSABP R-03 study subsequently randomized patients to preoperative versus postoperative chemoradiotherapy.[14] Although the trial failed to meet target patient accrual, it demonstrated improved 5-year disease-free survival in the preoperative group (64.7% vs. 53.4%, $P = .011$). The practice-changing German Rectal Cancer Trial CAO/ARO/AIO-94 randomized 823 patients with T3/T4 or node positive rectal cancer to preoperative versus postoperative chemoradiotherapy.[4,6] It definitively showed

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improved 5-year locoregional control (6% vs. 13%, $P = .006$; with 10-year cumulative rates 7.1% vs. 10.1%, $P = .048$) and higher sphincter-sparing surgery rates (39% vs. 19%, $P = .004$) in those who received preoperative chemoradiotherapy compared to those who received postoperative chemoradiotherapy. Although an overall survival benefit was not demonstrated, preoperative chemoradiotherapy was established as the standard of care due to lower rates of treatment-related toxicity compared to postoperative treatment.

Short Versus Long Course Radiotherapy

The Swedish Rectal Cancer Trial utilized short course preoperative radiotherapy in their trial design randomizing patients to 25Gy in 5 fractions radiotherapy followed by early surgery or surgery alone. The preoperative arm had significantly lower local recurrence rates (12% vs. 27%, $P < .001$) and better 5-year overall survival (38% vs. 30%, $P = .008$). As the study was conducted in the pre-TME surgery era, one of the main criticisms was that patients did not undergo adequate surgery, thereby contributing to the higher local recurrence rates in the surgery alone arm. The Dutch CKVO 95-04 trial was a similar study randomizing 1861 patients to short course radiotherapy followed by TME surgery or TME surgery alone.[11] The Dutch study demonstrated that even with standardized TME surgery, preoperative short course radiotherapy resulted in better 5-year locoregional control (LRR 5% vs. 11%, $P < .0001$). At median 12-year follow up, the Dutch group reported that preoperative radiotherapy significantly reduce local recurrence compared to surgery alone (5% vs. 11%, $P < .0001$), and in those with stage III disease and negative circumferential resection margin, preoperative radiotherapy improved 10-year survival compared to surgery alone (50% vs. 40%, $P = .032$).[15]

The optimal dose/fractionation for rectal cancer (ie, preoperative short vs. long course radiotherapy) were investigated by the Polish Colorectal Study Group and the Trans-Tasman Radiation Oncology Group (TROG). The Polish study randomized 312 patients with T3 or T4 rectal cancer to preoperative short course radiotherapy (25Gy in 5 fractions) followed by TME surgery within 7 days, or preoperative long course chemoradiotherapy (50.4Gy/ 28 fractions with concurrent 5FU/leucovorin) followed by TME surgery 4 to 6 weeks later.[16] Bujko et al[16] reported no difference in the 4-year locoregional recurrence rates, despite the long course arm having better downstaging effect including pathological complete response rate (16.1% vs. 0.7%) and lower positive circumferential resection margin rate (12.9% vs. 4.4%). Similarly, the TROG 01.04 study, which randomized 326 patients with T3N0-N2 rectal cancer to preoperative short course radiotherapy or long course chemoradiotherapy, followed by surgery and adjuvant chemotherapy, showed no significant difference in local recurrence, survival and late toxicity rates between the 2 arms, despite higher pathological complete response rates seen in the long course arm (15% vs. 1%).[17] For patients with distal tumors, a large but not statistically significant difference was observed between treatment arms with respect to risk of local recurrence. Additionally, there were no significant differences reported in postoperative complications between the 2 arms.[18] Both the Polish and TROG studies reported no. Additionally, no significant differences in quality of life between short course and long course radiotherapy between the 2 arms in the Polish[19] and TROG[20] studies.

The Stockholm III trial investigated dose/fractionation and timing of surgery for short course radiotherapy.[21] The Stockholm III trial was designed as a noninferiority trial and randomized 840 patients to 1 of 3 arms: short course radiotherapy with surgery within a week, short course radiotherapy with delay (surgery after 4 to 8 weeks), or long course radiotherapy (25 × 2 Gy alone) with delay (surgery after 4 to 8 weeks). Erlandsson et al[21] deemed that both short course radiotherapy with delay and long course radiotherapy with delay were noninferior to short course radiotherapy with immediate surgery, with no significant difference in overall survival, disease-free survival and postoperative complications between the 3 arms. However, when comparing the 2 short course radiotherapy arms alone, the risk of postoperative complications was lower in the short course radiotherapy with delay arm (53% vs. 41%, OR 0.61, $P = .001$). Therefore, delayed surgery is preferred if short course radiotherapy is delivered. A follow up sub study assessing tumor regression showed pathological complete response was achieved in 0.3%, 10.4% and 2.2% in short course radiotherapy with immediate surgery, short course radiotherapy with delay and long course radiotherapy with delay arms respectively. Using the Dworak system, Erlandsson et al[22] reported that a complete tumor response was associated with improved survival (HR 0.51, $P = .0046$) and time to recurrence (HR 0.27, $P = .027$).

In summary, preoperative short course radiotherapy and long course chemoradiotherapy are both good options for patients with locally advanced rectal cancer. Although short course radiotherapy is shown to be noninferior to long course chemoradiotherapy and may be more cost-effective, there has been variability in terms of implementation and use of short course radiotherapy in clinical practice. Clinicians in North America have traditionally preferred long course chemoradiotherapy whilst European clinicians prefer short course radiotherapy. The European Society for Medical Oncology (ESMO) recommends both short course and long course radiotherapy as appropriate treatments for locally advanced rectal cancer, but recommends long course chemoradiotherapy or short course radiotherapy with neoadjuvant FOLFOX for those with "ugly" risk group (cT3 with mesorectal fascia involvement, cT4a/b, or involvement of lateral pelvic node).[23] The use of these 2 radiotherapy approaches needs to be considered in the context of overall patient management, and preferences may change with the rapidly evolving landscape of rectal cancer management. Considerations include general health and age of the patient, accessibility and availability of radiotherapy facility, location and extent of the tumor. For patients undergoing a "watch and wait" nonoperative approach, long course chemoradiotherapy is more likely to achieve a pathological complete response.

Total Neoadjuvant Therapy (TNT)

Despite the use of adjuvant chemotherapy, distant disease now accounts for approximately 30% of recurrences in patients with locally advanced rectal (T3/T4) cancer.[3,5,24] Decline in patient performance status following rectal surgery compromises the intended intensity of adjuvant chemotherapy. Treatment compliance is higher in the preoperative setting when patients are fitter and more likely to complete the intended treatment. In addition,

with a shift in the treatment paradigm towards delayed surgery after radiotherapy, there were concerns of prolonged overall treatment time potentially affecting patients' compliance, and probable tumor cell metastasis during the "waiting period" before surgery. The concept of total neoadjuvant therapy (TNT) has gained popularity in recent years, whereby all treatment is delivered in the neoadjuvant setting.

By delivering chemotherapy upfront before surgery, it was postulated that patients' compliance with chemotherapy would be better than adjuvant chemotherapy. This was demonstrated in the CAO/ARO/AIO-12 study where patients were assigned to either TNT (induction FOLFOX chemotherapy) or adjuvant chemotherapy, and improved compliance with chemotherapy was achieved in the TNT arm (92% vs. 85%).[25] Similarly, the Grupo Cancer de Recto (GCR)-3 study which randomized patients to receive CAPOX chemotherapy either before radiotherapy or after surgery showed better compliance and completion of chemotherapy in those who received it in the neoadjuvant setting (94% vs. 57%).[26,27] In the OPRA trial where patients with MRI-stage II or III rectal cancer received TNT (either FOLFOX or CAPEOX before or after chemoradiation), a treatment compliance rate of more than 80% was observed.[28]

The POLISH-II trial which compared short course radiotherapy plus 3 cycles of FOLFOX4 versus oxaliplatin-based long course chemoradiotherapy, showed better overall survival at 3 years in those who received short course radiotherapy with consolidation chemotherapy (73% vs. 65%, $P = .046$) but the survival benefit faded at 8 years (OS 49% in both groups).[29] At 8 years, there was no demonstrable difference between the 2 arms in overall survival, disease-free survival, local and distant failures, and late complications rates.

The recently reported phase III RAPIDO trial comparing short course radiotherapy (5 × 5 Gy) with CAPOX (6x) or FOLFOX4 (9x) chemotherapy followed by TME, versus long course chemoradiotherapy with adjuvant chemotherapy CAPOX (8x) or FOLFOX4 (12x) in patients with locally advanced (T4) rectal cancer showed improved 3-year disease-related failure (23.7% vs. 30.4%, $P = .02$) and pathological complete response rates (27.7% vs. 13.8%, $P < .001$) in those who had short course radiotherapy with consolidation chemotherapy.[30,31] Similar findings were reported in the PRODIGE-23 trial with improvement in pathological complete response rate (27.5% vs. 11.7%, $P < .001$) in the TNT arm (mFOLFIRINOX followed by long course chemoradiotherapy) compared with standard of care.[32] The trial also showed a 3-year metastasis-free survival benefit in the TNT arm (79% vs. 72%).

Although the RAPIDO trial results are encouraging, caution is required when considering implementation of TNT with short course radiotherapy in clinical practice, particularly when an overall survival benefit has not yet been demonstrated. Of note, more than half of the cohort in the long course chemoradiotherapy arm did not receive adjuvant chemotherapy, as this decision was left to the discretion of participating sites. The availability of expertise in high quality MRI is essential in the implementation of this treatment regimen.

In contrast to the RAPIDO trial, long course chemoradiotherapy is a component of the TNT regimen utilized in the PRODIGE-23 trial. This regimen may appeal to those who feel hesitant with hesitancy in adopting TNT with short course radiotherapy for locally advanced disease. Of note, an imbalance of early events in the control arm contributed to survival differences in the first 6 months, and it remains to be seen whether further survival differences will be observed with longer follow up. The PRODIGE-23 regimen was not strictly TNT as patients also received adjuvant chemotherapy.

Nonoperative Approach After Chemoradiotherapy

As up to 30% of patients who receive preoperative chemoradiotherapy reportedly achieve pathological complete response,[33-36] it was proposed that this subgroup of patients may be spared surgery. Habr-Gama et al[37] first described the long-term results of an observational study where patients who had complete clinical response after chemoradiotherapy were spared surgery. The nonoperative management surveillance approach described was stringent and rigorous with monthly follow-up visits for physical examinations and blood tests and 6-monthly imaging in the first year. With a mean follow up of 57.3 months, in a group of 71 patients who achieved clinical complete response and had nonoperative management, the recurrence rate was 7% (2 had local recurrences which were salvaged and 3 had distant recurrence).

Maas et al[38] reported similar findings in a cohort of 21 out of 192 patients who achieved clinical complete response and underwent a wait-and-see policy with only 1 patient developing local recurrence. No difference in disease-free and overall survival was observed between the surgery and wait-and-see groups. Overall, when compared to patients who had surgery, those in the wait-and-see group reported less incontinence and defecation frequency. This study also incorporated the use of MR imaging of the pelvis in their staging and follow up protocols, which provides stricter criteria for selecting patients for wait-and-see. Combining clinical evaluation and MRI (T2-weighted and DWI) assessment provides a 98% probability of predicting a complete response. However, these strict criteria meant that approximately 15% of patients that actually achieved pathological complete response were deemed to have clinical incomplete response and was not offered the option of the wait-and-see policy.[39]

With strict patient selection criteria and surveillance protocols, nonoperative strategies have consistently reported comparable survival rates to cohorts undergoing surgery. In the International Watch and Wait Database (IWWD) registry, where 47 institutions across 15 countries contributed outcomes data from patients that had nonoperative management after chemoradiotherapy, 880 out of 1009 patients had clinical complete response.[40] With a median follow up of 3.3 years, the cumulative incidence of local recurrence was 25%, and 8% of patients developed distant disease. The 5-year overall and disease-specific survival were 85% and 94%.

The OnCoRe project performed a propensity-score matched cohort analysis to compare outcomes between patients who had surgery (228 patients) and those who had watch-and-wait after achieving a clinical complete response (129 patients).[41] With a median follow up of 33 months, Renehan et al[41] showed a 38%

3-year local recurrence rate, where 88% of patients were salvaged. No difference in 3-year overall survival or disease-free survival was observed between the 2 groups, but those who had watch-and-wait management had better 3-year colostomy-free survival than the surgical group (74% vs. 47%, HR 0.445, $P< .0001$).

In addition to favorable patient outcomes with nonoperative approaches, Dizdarevic et al[42] demonstrated in a cohort of 40 patients treated with 60Gy in 30 fractions with concurrent chemotherapy, followed by brachytherapy boost (5Gy) that their long-term quality of life scores were similar to baseline at 24, 48 and 60 months after treatment, with similar bowel- and bladder-related symptom scores across timepoints, similar to the study above by Maas et al.[38] Patients did report rectal bleeding at the 24-month timepoint with 81% of the cohort experiencing rectal bleeding.[42] The incidence of rectal bleeding may be related to the higher dose of radiation delivered to the rectum than standard chemoradiotherapy.

In the setting to total neoadjuvant therapy, the OPRA trial randomized 324 patients with MRI stage II and III rectal cancer to induction or consolidation chemotherapy (4 months of FOLFOX or CAPEOX) with chemoradiotherapy followed by watch-and-wait management for those that had clinical complete or near complete response.[28] Preliminary results indicated patients who had watch-and-wait approach had 3-year organ preservation rates of 43% for the induction arm and 58% for the consolidation arm.

The reported follow up period for watch-and-wait studies tend to be relatively short. To assess longer term outcomes in patients managed with the watch-and-wait strategy, Smith et al[43] retrospectively performed a single institution case series analysis in 113 patients who participated in a watch-and-wait strategy compared to a cohort of 136 who had surgery and achieved pathological complete response. With a median follow up of 43 months, the authors reported comparable disease-specific survival in both groups (90% in watch-and-wait, and 98% in surgical groups). Nine patients in the watch-and-wait group developed distant metastases compared to 5 in the surgical group. However, in those who had local recurrence in the watch-and-wait group, 36% developed distant metastasis, compared to only 1% in those without local recurrence. Although this study indicated that the watch-and-wait strategy may contribute to the risk of distant progression in those with local recurrence, the study comes with all the caveats of a retrospective study and the small numbers of events in the study. The authors also did not report on the rate of distant metastases in those who had local recurrence in the surgical group. Therefore, although this study is hypothesis-generating, a prospective study is required to test the hypothesis.

All in all, there is evidence that a nonoperative approach is feasible and strict criteria for assessing clinical response and close surveillance assessments are required, particularly in the first 3 years of follow up. Consensus guidelines or strategy for patient selection and surveillance is required. Furthermore, there is a need for multicenter phase III trial of nonoperative approach versus surgery in patients who achieved complete clinical response. Current evidence presented above are predominatly observational and/or retrospective study with the inherent limitations of such study designs.

Omission of Neoadjuvant Radiotherapy

More recently, there has been interest to explore strategies that allow for omission of neoadjuvant radiotherapy given the potential impact of late effects on patient long-term quality of life.

An early single institution phase II study examined the potential use of neoadjuvant FOLFOX (6 cycles) and bevacizumab in 32 patients with stage II-III rectal cancer, with responders to proceed to surgery without radiotherapy and nonresponders to have radiotherapy before surgery.[44] Of the 30 patients who completed neoadjuvant chemotherapy, all were responders and proceeded to surgery. The pathological complete response rate was 25%, and the 4-year local recurrence rate and disease-free survival were 0% and 84%. This study provided early data that selective omission of radiotherapy appears feasible and safe in a carefully selected group of patients, and led to the development of the phase II/III PROSPECT study (ClinicalTrials.gov identifier: NCT01515787), a randomized study comparing neoadjuvant FOLFOX followed by selective chemoradiotherapy based on response versus standard neoadjuvant chemoradiotherapy. Patients with more than 20% downstaging after chemotherapy proceeded to surgery without radiotherapy. The PROSPECT study recently completed recruitment and results are eagerly awaited.

The Japanese N-SOG 03 phase II trial evaluated the safety of neoadjuvant oxaliplatin, capecitabine and bevacizumab alone, without radiotherapy in patients with MRI-defined poor-risk rectal cancer.[45] In a cohort of 32 patients, 27 patients completed the trial treatment and 29 had curative-intent surgery. R0 resection rate was 90% with pathological complete response reported in 13%. The 5-year overall survival and locoregional failure in patients who had curative intent surgery were 89.7% and 13.9%.[46] The postoperative complication rate was 43% with wound sepsis, ileus and anastomotic leakage being most common.[45] Of note, 2 patients had severe adverse events: 1 had rectal perforation during chemotherapy requiring emergency surgery, and another patient undergoing chemotherapy had progressive local disease which was infected ultimately leading to death.

Similar R0 resection, pathological complete response and adverse event rates were also observed in the GEMCAD 0801 phase II study where patients with MRI-staged T3 rectal cancer received neoadjuvant oxaliplatin, capecitabine and bevacizumab before surgery.[47] The R0 resection and pathological complete response rates were 100% and 20%. Three deaths were reported: 2 patients died of pulmonary embolism and diarrhoea during neoadjuvant therapy, and 1 patient died of peritonitis due to an anastomotic leak. Adverse events, such as anastomotic leakage, bowel perforation and thromboembolic events may be related to bevacizumab. Therefore, the use of bevacizumab in the neoadjuvant setting needs to be carefully evaluated.

The Chinese FOWARC trial compared neoadjuvant modified FOLFOX (mFOLFOX) with or without radiotherapy and standard chemoradiotherapy in 495 patients with stage II-III rectal cancer.[48] Patients were randomized to 1 of 3 neoadjuvant treatment arms: standard radiotherapy with fluorouracil, mFOLFOX6 with concurrent radiotherapy, or mFOLFOX6 alone. At a median follow up of

45.2 months, no significant differences in the 3-year local recurrence rate, disease-free survival and overall survival were observed between the 3 arms.[49]

Imaging and Blood Biomarkers for Omission of RT or Surgery

With some recent studies indicating the potential for omission of radiotherapy or surgery in some patients, there is a need for the development of methods for identification of treatment responders to allow for optimal patient selection for these treatment strategies. Imaging, blood and tissue biomarkers have been investigated and require further validation or development of consensus guidelines for use in the clinical setting.

MRI is an established imaging modality for staging in rectal cancer at diagnosis, after chemoradiotherapy and during surveillance in nonoperative management. The MERCURY observational study established the utility of pelvic MRI in the preoperative setting.[50] In 408 patients, MR had a specificity of 92% for predicting clear circumferential resection margin (CRM), and an accuracy of 88% for predicting CRM before surgery. The MR-clear CRM group had better 5-year overall and disease-free survival compared to the MR-involved CRM group (OS: 62.2% vs. 42.2%, HR 1.97, $P< .01$; DFS: 67.2% vs. 47.3%, HR 1.65, $P< .05$).[51] Furthermore, the extramural depth (EMD) of tumor invasion measured on MRIs were within 0.5mm of histopathological measurements, highlighting the accuracy of high-resolution MRI to select for patients at high-risk disease (CRM involvement and deep EMD) and may benefit from neoadjuvant radiotherapy.[52]

The involvement of CRM is an independent risk factor for future development of local recurrence.[53-55] Therefore, the high accuracy of MRI for prediction of CRM involvement was further explored as an approach to guide omission of radiotherapy in patients with rectal cancer. The German OCUM trial and MERCURY study evaluated the potential role of MRI to select for patients with good prognosis or low risk disease that can avoid neoadjuvant radiotherapy. In 374 patients with stage I to III rectal cancer in the MERCURY study, approximately 1 in 3 patients were classified as MR-staged "good prognosis" tumor and the 5-year overall and disease-free survival for this subgroup of patients were 68% and 85%, respectively.[56] Local recurrence was 3% in this subgroup with good prognosis tumor who did not receive radiotherapy. In the OCUM trial, 254 patients were classified as having MR-staged low-risk disease and underwent TME surgery alone.[57] When compared to those with MR-staged high-risk disease who had neoadjuvant chemoradiotherapy, there was no difference in the 5-year local recurrence rate. As predicted, those with MR-staged high-risk disease had higher 5-year distant metastasis rate (24.9%vs. 14.4%, $P= .005$) and worse 5-year disease-free survival (66.7% vs. 76%, $P= .016$). Both these studies demonstrated the prognostic value of staging MR at diagnosis, and the potential use of MR to guide selection of patients that can have surgery alone.

Similarly, MRI was investigated as a potential modality for selecting patients suitable for nonoperative approach after radiotherapy. High quality T2-weighted MR sequence was the most investigated. The MR-modified Mandard grading system (mrTRG) which categorizes treatment response to 5 categories based on fibrosis and residual tumor T2-signal intensity has been shown to correlate with pathological findings and subsequent treatment outcomes.[58-60] As discussed earlier, studies investigating nonoperative approach in patients with good response with radiotherapy utilize MRI as part of treatment response assessment and surveillance imaging.[38-41] In addition to T2-weighted MRI, diffusion-weighted imaging (DWI) sequence has been of interest particularly in the postradiotherapy treatment response assessment setting. DWI shows the Brownian motion of the water molecules or diffusion within tissues, therefore an area of high cellularity such as tumor will demonstrate diffusion restriction (high DWI signal).[61] Apparent diffusion coefficient (ADC) is a standardized quantified value obtained from DWI and is typically low in malignant tumors compared to normal tissue. DWI was incorporated in MRI assessment in the nonoperative approach study by Maas et al,[39] as described above. Although many studies have shown that the increase in ADC value is indicative of treatment response and lower preradiotherapy ADC value is associated with better treatment response, different ADC value cut-offs and a variability in DWI b-values limited the use of DWI in the clinical setting for assessment of treatment response. Further work is required in this field is required before clinical implementation. Other functional MRI such as dynamic-contrast enhanced (DCE) MRI,[62-67] and intravoxel incoherent motion (IVIM)[68-70] which assess tissue and tumoral vasculature also showed promising results in predicting treatment responders. However, similar to DWI, there is a need for standardization of imaging acquisition and processing techniques, and further validation before these imaging techniques are ready for prime time use in clinical practice.

The value of 18F-FDG PET imaging in locoregional assessment of disease and treatment response remains to be confirmed. PET imaging is commonly used when routine diagnostic scans are equivocal for distant disease and/or locoregional disease recurrence. As PET imaging alone provides limited spatial information unlike MRI, PET is usually acquired alongside CT and/or MRI. A meta-analysis of 34 studies (total of 1526 patients) by Maffione et al[71] found that 18F-FDG PET imaging demonstrated a sensitivity of 73% and specificity of 77% for predicting pathological response to neoadjuvant chemoradiotherapy. However, studies[71-75] have used different criteria for PET interpretation and variable SUV cut-offs creating a challenging situation for its use in clinical practice to select for patients that may be suitable for omission of surgery.

To date, there is no reliable or validated blood or tissue biomarker that has been shown to predict treatment response or be useful in risk-stratification with the purpose of omitting radiotherapy or surgery in rectal cancer. CEA levels pre- and post-treatment has been shown to correlate with pathological response to neoadjuvant therapy.[76-79] However, CEA is neither highly specific nor sensitive for rectal cancer.[80]

Circulating tumor cells (CTCs) has been investigated as a promising biomarker for predicting and monitoring treatment response in rectal cancer. The CellSearch system (Menarini Silicon Biosystems, Italy) is the first U.S Food and Drug Administration (FDA) -approved CTC platform for the detection and quantification of CTCs in patients with metastatic breast, prostate and colorec-

tal cancer.[81,82] However, the detection rates of CTC, using the Cellsearch system, in patients without metastatic colorectal cancer is reportedly low of approximately 5% to 15%.[83,84] Investigators have since developed and evaluated various methods of CTC detection and quantification. Although the majority of studies indicated that treatment responders have greater decrease in CTC numbers,[85-90] various CTC detection methods and CTC number cut-offs were reported.

Similarly, there is ongoing development and investigation in circulating cell-free nucleic acids. Although cell-free nucleic acid is actively being explored in colorectal cancer, there are very studies on cell-free nucleic acid in localized rectal cancer. Higher MGMT promoter methylation levels has been reportedly associated with treatment responders.[91] There is, however, conflicting reports on KRAS mutation and its association with treatment responders.[91-94] With the advancement in laboratory technology, multigene sequencing is possible. Dynamic serial plasma monitoring before and during radiotherapy, and before and after surgery coupled with baseline and presurgery MRI assessments were performed in 119 patients by Wang et al.[95] The investigators sequenced 422 cancer-related genes from plasma and found that the addition of circulating tumor DNA (ctDNA) clearance information improved the accuracy of pathological clinical response prediction from 70.6% to 73%. Using a prediction model incorporating ctDNA and mrTRG information, the model had a significantly higher pathological complete response versus incomplete response prediction performance (AUC = 0.886) than mrTRG (AUC = 0.729) or ctDNA (AUC = 0.818) alone. The combined model also performs better in risk stratification for the development of recurrence postoperatively than either modality alone. Although promising, ctDNA requires further investigation and validation in neoadjuvant trials to determine its role in prognostication, risk stratification, treatment response assessment and surveillance of minimal residual disease.[96]

In addition, tissue molecular biomarkers have been investigated. The most studied DNA mutation in tumor tissue is TP53. In a meta-analysis of 30 studies by Chen et al, wild type p53 has been associated with good pathologic response to neoadjuvant chemoradiotherapy.[97] Other molecular markers such as bcl-2, EGFR, VEGF, COX2 and ki-67 have been evaluated as potential markers of treatment response.[98,99] Furthermore, markers of tumor immune microenvironment such as PD-L1 expression and tumor-infiltrating lymphocytes were assessed but the results were inconsistent.[99]

It has been a challenge to establish a reliable approach to accurately risk stratify and predict treatment response in patients with rectal cancer in order to guide an adaptive treatment approach. There is ongoing work and development in the area of imaging and blood/ tissue biomarkers to further guide personalization of treatment. The performance of each biomarker platform requires rigorous validation in larger trials and a consensus of appropriate method and interpretation of results to be achieved before implementation into clinical practice. In addition, rectal cancer is a heterogeneous cancer and therefore likely to require a panel of biomarkers and disease subtyping to achieve adequate sensitivity and specificity in predicting treatment response.

Conclusions

The management of locally advanced rectal cancer remained an evolving landscape. Clinicians and patients now have multiple treatment options to consider: short versus long course radiotherapy, total neoadjuvant therapy, nonoperative approach, and omission of radiotherapy. With the multitude of acceptable and reasonable treatment options, we are now in need of a strategy to "match patient to the right treatment," optimizing the therapeutic effect of each treatment modality whilst limiting treatment-related side effects and costs. Rectal cancer is a heterogeneous disease with different biological behavior and treatment response. Hence, there is a demand for developments of imaging, blood and/or tissue molecular markers for predicting treatment response and tumor behavior. Multidisciplinary and multi-institutional cooperative trials are required to provide a unified consensus and/or guidelines to the development of an optimal patient selection and risk stratification strategy, the selection of biomarker(s) for assessment of treatment response, and the modelling of a cost-effective surveillance program for patients with rectal cancer.

Declaration of Competing Interest

None.

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