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Outcome measures in multimodal rectal cancer trials

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There is a large variability regarding the definition and choice of primary endpoints in phase 2 and phase 3 multimodal rectal cancer trials, resulting in inconsistency and difficulty of data interpretation. Also, surrogate properties of early and intermediate endpoints have not been systematically assessed. We provide a comprehensive review of clinical and surrogate endpoints used in trials for non-metastatic rectal cancer. The applicability, advantages, and disadvantages of these endpoints are summarised, with recommendations on clinical endpoints for the different phase trials, including limited surgery or non-operative management for organ preservation. We discuss how early and intermediate endpoints, including patient-reported outcomes and involvement of patients in decision making, can be used to guide trial design and facilitate consistency in reporting trial results in rectal cancer.

Introduction

Rectal cancer is among the best examples in oncology of how progress is derived from multimodal treatment. Preoperative fluorouracil based chemoradiotherapy or short-course radiotherapy followed by total mesorectal excision have substantially reduced locoregional recurrence. However, most trials did not show an improvement in disease-free survival or overall survival.^{1,2}

In phase 3 cancer trials, overall survival is the most objectively defined endpoint and is considered the standard measure of treatment efficacy. Overall survival requires a large sample size, and long-term follow-up is costly and carries risk of the investigated treatment losing novelty by the time the trial is completed. Overall survival can be confounded by effective successive treatment lines in case of disease progression or recurrence, and competing risks for non-cancer related deaths, especially among older and frail patients, might reduce the observed treatment effect.³ There has been an increased interest in early or intermediate endpoints as surrogate measures of long-term endpoints in oncology trials.⁴

As outcome measures have been derived at several different timepoints during and after multimodal treatment, rectal cancer could address the complex interplay between early, intermediate, and long-term endpoints (figure 1). Here, we review surrogate and clinical endpoints used in non-metastatic rectal cancer in randomised multimodal clinical trials, including those of limited or non-operative management for organ preservation. The applicability, advantages and disadvantages of endpoints are summarised. This Review focuses mostly on the neoadjuvant setting. The effect of rectal cancer treatment on quality of life (QOL) has been increasingly recognised and might be as important for patients, thus we also outline patient-reported outcomes (PROs) in rectal cancer. Finally, we discuss how early and intermediate endpoints could be used to guide trial design and facilitate consistency in reporting trial results in rectal cancer.

Early endpoints for tumour response at surgery

Tumour response to chemoradiotherapy and short-course radiotherapy varies considerably in rectal cancer.

Early variables to assess tumour response, such as downstaging, pathological complete response, tumour regression grading, the neoadjuvant rectal score, completeness of local resection, and circumferential resection margin, have been proposed to reflect treatment effectiveness and patient prognosis, and have been suggested as potential surrogates for long-term outcomes, such as locoregional recurrence, disease-free survival, and overall survival (figure 1).

Tumour response is a dynamic process associated with tumour-related factors (eg, size, histology, and molecular profile) and treatment-related factors (such as radiotherapy dose and fractionation, chemotherapy, and the time between neoadjuvant treatment and surgery). The complex interplay between these factors and the varying timepoints of response assessment makes interpretation of early efficacy endpoints challenging. Although an increased tumour response might predict favourable outcomes of individual patients receiving one type of treatment, differences in early efficacy endpoints induced by different treatments might not be valid surrogates for long-term oncological outcomes. For example, the Polish I¹ and Trans-Tasman⁶ randomised trials, of short-course radiotherapy followed by immediate surgery versus fluorouracil chemoradiotherapy followed by delayed surgery, showed significantly increased pathological downstaging and pathological complete response in the fluorouracil chemoradiotherapy group, yet, no improvement in locoregional recurrence, disease-free survival, or overall survival.

The basic requirement for a surrogate endpoint is that changes of this endpoint between treatment interventions should translate to changes of the true clinical endpoints. Establishing surrogate endpoints is challenging as it requires rigorous statistical validation using large trial datasets. In 1989, Prentice proposed four criteria to validate surrogacy.⁷ First, the treatment must significantly impact on the true clinical endpoint. Second, the treatment must have a significant effect on the surrogate endpoint. Third, the surrogate endpoint must have a statistically significant effect on the true endpoint, and fourth, the full effect of treatment on the

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Figure 1: Clinical outcome measures for rectal cancer after neoadjuvant treatment and TME

Outcome measures in randomised phase 3 clinical trials used as primary endpoints (red). Outcome measures used as secondary endpoints (no colour). Different preoperative treatment options are characterised by variable length and time to surgery (grey). Timepoints of patient reported outcomes and quality of life assessment, as suggested in newer trials, are shown here. TME=total mesorectal excision. cTNM=clinical tumour node metastasis. MRF=mesorectal fascia. EMVI=extramural venous invasion. SI=sphincter involvement. PROs=patient-reported outcomes. QOL=quality of life. CRM=circumferential resection margin involved (+) or uninvolved (-). TRG=tumour regression grading. NAR=neoadjuvant rectal score. LRR=locoregional recurrence. TDRTF=time to disease-related treatment failure. DFS=disease-free survival. OS=overall survival. SCRT=short-course radiotherapy. CRT=chemoradiotherapy. TNT=total neoadjuvant therapy.

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true endpoint should be captured by the surrogate endpoint. However, the last criterion is characterised by methodological limitations in interpretation. An alternative validation method has been established based on the correlation approach that involves showing surrogacy at two levels.^{4,8} First, individual-level endpoint surrogacy reflects the correlation of surrogate outcome with clinical outcome, and can be shown in a single trial dataset using standard correlation coefficients. Secondly, trial-level endpoint surrogacy is based on meta-analysis of phase 3 trials.

Downstaging

Downstaging is a decrease of the pathological versus the preoperative clinical T category or N category, or both, and has been used as an endpoint in early trials to evaluate the effectiveness of preoperative chemoradiotherapy and short-course radiotherapy. The CAO/ARO/AIO-94 trial² showed that preoperative chemoradiotherapy induced significant downstaging compared with straight surgery. The subgroup of patients who had

ypT0N0 or ypT1-2N0 disease after preoperative chemoradiotherapy had an excellent prognosis; however, patients with remaining ypT3-4 or ypN1-2 after preoperative chemoradiotherapy had a higher risk of developing distant metastases with poorer disease-free survival compared with patients with corresponding pathological tumour, node, metastasis (TNM) subgroups in the postoperative treatment group. Disease-free and overall survival remained identical in both groups, resembling the reverse Will Rogers stage migration phenomenon.⁹ Thus, downstaging might unmask different prognostic subgroups within a given treatment group, rather than reflect improved treatment efficacy between interventions. Also, there is no clear definition of downstaging, which makes its use challenging. Some investigators used a reduction of either T or N categories by at least one level, whereas others restricted this endpoint to a reduction of stage. As such, validation of downstaging as a surrogate endpoint based on large phase 3 trial cohorts is currently unavailable.

	Number of patients	Treatment schedule and time to surgery	Primary clinical endpoint
Lyon R90-01 trials ^{10,11}	210	Radiotherapy followed by 2-week interval to surgery versus radiotherapy followed by 6–8 weeks interval to surgery	Sphincter-sparing surgery
GRECCAR-6 trial ¹²	265	Fluorouracil or capecitabine chemoradiotherapy followed by 7-week interval to surgery versus chemoradiotherapy followed by 11-week interval to surgery	Pathological complete response
British trial ¹³	237	Capecitabine chemoradiotherapy followed by 6-week interval to surgery versus capecitabine chemoradiotherapy followed by 12-week interval to surgery	MRI-based T-downstaging
Turkish trial ¹⁴	327	Capecitabine chemoradiotherapy followed by less than 8-weeks interval to surgery versus capecitabine chemoradiotherapy followed by more than 8-weeks interval to surgery	Pathological complete response
Stockholm III trial ¹⁵	840	Short-course radiotherapy followed by surgery within 1-week versus short-course radiotherapy followed by surgery after 4–8 weeks versus long-course radiotherapy followed by surgery after 4–8 weeks	Time to local recurrence

Table 1: Randomised trials assessing the interval between completion of neoadjuvant treatment and surgery

Pathological complete response

Pathological complete response is the primary endpoint in numerous phase 1, 2, and 3 trials (tables 1–3). Maas and colleagues³⁹ showed a strong association of pathological complete response after chemoradiotherapy with improved disease-free survival and overall survival. The excellent prognosis of patients with pathological complete response could be, in part, explained by possible over-staging and overtreatment early-stage tumours. Pooled individual data analysis⁴⁰ from the EORTC 22921 and FFCD 9203 phase 3 trials comparing the effect of preoperative radiotherapy with or without concurrent fluorouracil showed significantly higher pathological complete response rates and reduced 3-year locoregional recurrence in the chemoradiotherapy versus radiotherapy groups, but no significant improvement in overall survival and poor trial-level surrogacy of pathological complete response for overall survival. Similarly, in a meta-analysis of 22 randomised trials⁴¹ involving 10050 patients treated with neoadjuvant radiotherapy or chemoradiotherapy, the pathological complete response was poorly correlated with 5-year overall survival, both at the individual and trial level. Thus, intensification of local neoadjuvant treatment by increasing radiotherapy dose or adding radiosensitising drugs could improve pathological complete response rates and potentially reduce locoregional recurrence; however, the natural history of the disease with respect to distant metastases might not be improved.

In the Lyon R90–01 randomised trial,¹⁰ a longer interval (6–8 weeks *vs* 2 weeks) between completion of radiotherapy and surgery led to significant increase of patients with major pathological response (pathological complete response or few residual cells) without an effect on locoregional recurrence or overall survival. Further extension beyond 8 weeks has been tested in the GRECCAR-6 trial¹² (7 weeks *vs* 11 weeks) and a British randomised trial (6 weeks *vs* 12 weeks).¹³ Although the GRECCAR-6 trial did not show an increase of pathological complete response in the longer interval group (15% *vs* 17.4%, $p=0.59$), the British study did find a statistical increase (9% *vs* 20%, $p<0.05$). Similarly, an increased pathological complete response (18% *vs* 10%, $p=0.027$)

was also reported by Akgun and colleagues¹⁴ for an interval of more than 8 weeks versus less than 8 weeks after chemoradiotherapy. Long-term outcomes of these trials are pending (table 1). The available trial data are conflicting and do not suggest that simply increasing the interval beyond 6–8 weeks will result in better long-term outcomes. Also, most studies had a small sample size, which should be considered when interpreting the findings.

Several groups have used the prolonged interval time between chemoradiotherapy or short-course radiotherapy and surgery for adding neoadjuvant, rather than adjuvant chemotherapy, known as total neoadjuvant treatment. A prospective phase 2 cohort trial⁴² used preoperative chemoradiotherapy and sequentially increased the time-point of surgery. Group 1 underwent surgery 6 weeks after completion of chemoradiotherapy. Groups 2, 3, and 4 received two, four, or six cycles of FOLFOX (leucovorin, fluorouracil, and oxaliplatin) during the waiting period before surgery that was done at 11, 15, and 19 weeks, after completion of chemoradiotherapy. The pathological complete response rate of patients treated in study group 1 was 18% compared with 25% (group 2), 30% (group 3), and 38% (group 4).⁴² Whether prolonging the interval between radiotherapy and surgery and adding systemic therapy will lead to improved disease-free survival and increased organ preservation, is currently being tested in the OPRA phase 2 trial (NCT02008656) and the RAPIDO phase 3 trial after SCRT (NCT01558921). The CAO/ARO/AIO-12 randomised phase 2 trial that compared two total neoadjuvant treatments (chemoradiotherapy with either induction or consolidation chemotherapy), showed a pathological complete response of 17% (chemoradiotherapy and induction) and 25% (chemoradiotherapy and consolidation chemotherapy).²⁰ However, long-term data are needed to show whether improved pathological complete response translates into improved disease-free survival (table 2).

Lymph node status

Lymph node status after preoperative chemoradiotherapy or short-course radiotherapy is an important prognostic

	Number of patients	Treatment schedule	Primary clinical endpoint
Randomised phase 2 trials testing TNT			
GCdr-3 ¹⁶	108	Capecitabine plus oxaliplatin CRT followed by surgery and adjuvant CAPOX chemotherapy followed by capecitabine plus oxaliplatin CRT and surgery	Pathological complete response
EXPERT-C ¹⁷	165	Induction CAPOX chemotherapy and cetuximab followed by capecitabine plus cetuximab CRT and surgery versus CAPOX chemotherapy followed by capecitabine CRT and surgery	Complete clinical response and pathological complete response
GEMCAD 1402 ¹⁸	115	Induction mFOLFOX6 chemotherapy and aflibercept followed by capecitabine CRT and surgery versus induction mFOLFOX6 chemotherapy followed by capecitabine CRT and surgery	Pathological complete response
GRECCAR4 ¹⁹	194	Induction FOLFIRINOX followed by immediate surgery versus capecitabine CRT and surgery (good responders); or induction FOLFIRINOX followed by capecitabine CRT (50 Gy) and surgery versus capecitabine CRT (60 Gy) and surgery (poor responders)	Complete surgical resection rate
CAO/ARO/AIO-12 ²⁰	304	Induction mFOLFOX6 chemotherapy followed by 5-FU plus oxaliplatin CRT and surgery versus 5-FU plus oxaliplatin CRT followed by mFOLFOX6 chemotherapy and surgery	Pathological complete response
OPRA (NCT02008656)	300	Induction mFOLFOX6 chemotherapy followed by 5-FU CRT and surgery or NOM versus 5-FU CRT followed by mFOLFOX6 chemotherapy and surgery or NOM	3-year disease-free survival
NRG G1002 (NCT02921256)	178	Induction FOLFOX chemotherapy followed by capecitabine CRT versus induction FOLFOX chemotherapy followed by capecitabine plus veliparib CRT versus induction FOLFOX chemotherapy followed by capecitabine plus pembrolizumab CRT	Neoadjuvant rectal score
Randomised phase 2 and 3 trials testing NOM and LE or TEM			
Brazilian trial (NCT02052921)	150	5-FU CRT followed by observation versus 5-FU CRT followed by TME surgery after achieving complete clinical response at 12 weeks	3-year disease-free survival
TESAR (NCT02371304)	302	TME surgery versus LE followed by capecitabine CRT	3-year locoregional recurrence
OPERA (NCT02505750)	236	Capecitabine CRT followed by EBRT boost versus capecitabine CRT followed by brachytherapy boost (if complete clinical response: NOM or LE; if partial response: TME)	3-year organ preservation*
WW3 (NCT04095299)	111	Capecitabine CRT versus capecitabine CRT with SIB (if complete clinical response: NOM or LE; if partial response: TME)	2-year organ preservation*
MORPHEUS (NCT03051464)	40	Capecitabine CRT followed by EBRT boost versus capecitabine CRT followed by brachytherapy boost (if complete clinical response: NOM; if partial response: TME)	2-year organ preservation
GRECCAR12 (NCT02514278)	218	Induction mFOLFIRINOX followed by capecitabine CRT versus capecitabine CRT (if good response: LE; if poor response: TME)	12-month organ preservation†
TESS (NCT03840239)	168	Induction CAPOX chemotherapy followed by capecitabine plus oxaliplatin CRT versus capecitabine plus oxaliplatin CRT (if complete clinical response: NOM; if partial response: LE or TEM; if poor response: TME)	Sphincter preservation (stoma absence) at 18 months
STAR TREC (NCT02945566)	120	TME surgery versus capecitabine CRT followed by NOM versus SCRT followed by NOM (if complete clinical response: NOM; if partial response: TEM; if poor response: TME)	Recruitment rate at 12 and 24 months‡
TREC (ISRCTN 14422743)	..	TME surgery versus SCRT followed by TEM or NOM	Recruitment rate at 12, 18, and 24 months‡
APHRODITE (ISRCTN16158514)	104	5-FU or capecitabine CRT versus 5-FU or capecitabine CRT with SIB (if complete clinical response: NOM)	Complete clinical response at 6 months
<p>All trials shown above are phase 2, except the OPERA and GRECCAR12, which are randomised phase 3 trials. MORPHEUS is a pilot randomised trial. TNT=total neoadjuvant therapy. CRT=chemoradiotherapy. CAPOX=capecitabine and oxaliplatin. FOLFIRINOX=fluorouracil, leucovorin, irinotecan, and oxaliplatin). 5-FU=5-fluorouracil. NOM=non-operative management. FOLFOX=fluorouracil, leucovorin, and oxaliplatin. TME=total mesorectal excision. LE=local excision. EBRT=external beam radiotherapy. SIB=simultaneously integrated boost. TEM=transanal endoscopic microsurgery. SCRT=short-course radiotherapy. *In the OPERA trial, organ preservation is defined as the rate of rectum preservation, either with local excision or watch and wait strategy after neoadjuvant treatment, without non-salvageable locally progressive disease at 3 years post-treatment, or permanent stoma; in the WW3 trial, organ preservation is defined as an intact rectum, no locoregional failure, and no stoma at 2 years post-treatment. †In the GRECCAR12 trial, organ preservation is defined as the number of patients with organ preservation and absence of stoma, 1 year after surgery. ‡The aim of these studies is to assess the feasibility of recruitment within the phase 2 trial.</p>			
Table 2: Primary clinical endpoints in trials for total neoadjuvant therapy with or without NOM and LE or TEM			

factor for both local and distant recurrence.⁴³ In the CAO/ARO/AIO-04 trial,⁴⁴ the 3-year cumulative incidence of locoregional recurrence and distant recurrences were 2% and 10·6% for ypN0, 2·5% and 28·6% for ypN1, and 17·2%, and 48% for ypN2, respectively. Persistent lymph node metastases after neoadjuvant chemoradiotherapy reflect a highly aggressive tumour phenotype

resistant towards chemoradiotherapy and prone to distant metastases.

Neoadjuvant rectal score

The neoadjuvant rectal (NAR) score was proposed as a potential surrogate for overall survival in rectal cancer.⁴⁵ The NAR formula $(5 \text{ ypN} - 3[\text{cT} - \text{ypT}] + 12)^2 / 9 \cdot 61$ results

	Number of patients	Treatment schedule	Primary clinical endpoint
Swedish trial ²¹	1168	Surgery with or without preoperative SCRT	5-year overall survival
NSABP R03 ²²	267	Preoperative versus postoperative 5-FU plus LV CRT followed by surgery and adjuvant 5-FU plus LV chemotherapy	5-year disease-free survival and overall survival
Frykholm ²³	70	Preoperative methotrexate plus 5-FU plus LV CRT versus RT followed by surgery and adjuvant chemotherapy	5-year local recurrence
Dutch trial ²⁴	1861	Surgery with or without preoperative SCRT	2-year local recurrence
CAO/ARO/AIO-94 ²⁵	823	Preoperative versus postoperative 5-FU CRT followed by surgery and adjuvant 5-FU chemotherapy	5-year overall survival
Polish I trial ⁵	316	Preoperative 5-FU plus LV CRT versus SCRT followed by surgery and adjuvant chemotherapy	Sphincter preservation
Braendengen ²⁶	207	Preoperative methotrexate plus 5-FU plus LV CRT versus RT followed by surgery and adjuvant chemotherapy	5-year overall survival
EORTC 22921 ²⁷	1011	Preoperative 5-FU plus LV CRT versus RT alone followed by surgery and adjuvant 5-FU plus LV chemotherapy versus observation	5-year overall survival
FFCD 9203 ²⁸	762	Preoperative 5-FU CRT plus LV CRT versus RT followed by surgery and adjuvant 5-FU plus LV chemotherapy	5-year overall survival
MRC CR07 and NCIC-CTG C016 ²⁹	1350	Preoperative SCRT and surgery versus surgery followed by selective postoperative CRT (CRM-positive only)	3-year local recurrence
STAR-01 ³⁰	747	Preoperative 5-FU CRT versus 5-FU plus oxaliplatin CRT followed by surgery and adjuvant chemotherapy	5-year overall survival
ACCORD 12/0405 PRODIGE 2 ³¹	598	Preoperative capecitabine CRT versus capecitabine plus oxaliplatin CRT followed by surgery and adjuvant chemotherapy	Pathological complete response
NASBP R-04 ³²	1608	Preoperative capecitabine CRT versus capecitabine plus oxaliplatin CRT versus 5-FU CRT versus 5-FU plus oxaliplatin CRT, all followed by surgery and adjuvant chemotherapy	3-year Local recurrence
PETACC-6 ³³	1094	Preoperative capecitabine CRT versus capecitabine plus oxaliplatin CRT followed by surgery and adjuvant chemotherapy with or without oxaliplatin	3-year disease-free survival
Hofheinz ³⁴	401	Preoperative or postoperative 5-FU CRT versus capecitabine CRT followed by surgery and adjuvant chemotherapy	5-year overall survival
CAO/ARO/AIO-04 ³⁵	1236	Preoperative 5-FU CRT versus 5-FU plus oxaliplatin CRT followed by surgery and adjuvant chemotherapy with or without oxaliplatin	3-year disease-free survival
FOWARC ³⁶	495	Preoperative 5-FU plus LV CRT versus 5-FU plus LV plus oxaliplatin CRT versus FOLFOX6 chemotherapy followed by surgery and adjuvant chemotherapy	3-year disease-free survival
Stockholm III ³⁵	840	SCRT and surgery within 1-week versus SCRT followed by surgery after 4–8 weeks versus long-course RT followed by surgery after 4–8 weeks	Time to local recurrence
Polish II ³⁷	515	SCRT and consolidation FOLFOX4 versus 5-FU plus LV (plus oxaliplatin) CRT followed by surgery and adjuvant chemotherapy	R0 resection rate
GRECCAR-2 ³⁸	186	Preoperative CRT followed by local excision versus TME surgery	2-year composite endpoint*
ARISTOTLE (ISRCTN09351447)	600	Preoperative capecitabine CRT versus capecitabine plus irinotecan CRT followed by surgery and adjuvant chemotherapy	3-year disease-free survival
RAPIDO (NCT01558921)	920	Preoperative CRT followed by TME surgery versus SCRT followed by CAPOX or FOLFOX consolidation chemotherapy and TME surgery	Time to disease-related treatment failure
PROSPECT (NCCTG N1048/Alliance; NCT01515787)	1194	Induction FOLFOX chemotherapy followed by surgery (response>20%) or CRT and surgery (response<20%) versus CRT followed by surgery and adjuvant FOLFOX chemotherapy	Local recurrence and 3-year disease-free survival
STAR TREC (Phase 3 part; NCT02945566)	460	TME surgery versus capecitabine CRT versus SCRT (if complete clinical response: NOM; if partial response: TEM; if poor response: TME)	30-month organ preservation rate
ACO/ARO/AIO-18.1 (EudraCT: 2018-000876-14)	822	Preoperative 5-FU plus oxaliplatin CRT followed by consolidation FOLFOX chemotherapy and TME surgery (or NOM by complete clinical response) versus 5-FU CRT followed by TME surgery (or NOM by complete clinical response)	3-year disease-free survival

In the STAR TREC trial (phase 3), organ preservation is defined as an intact rectum, no locoregional failure, and no stoma. SCRT=short-course radiotherapy. 5-FU=fluorouracil. LV=leucovorin. CRT=chemoradiotherapy. RT=radiotherapy. CRM=circumferential resection margin. FOLFOX=folinic acid, leucovorin, oxaliplatin. TME=total mesorectal excision. CAPOX=capecitabine, oxaliplatin. NOM=non-operative management. *The primary clinical endpoint in the GRECCAR-2 trial was a composite outcome of death, recurrence, morbidity, and side-effects at 2-years after surgery.

Table 3: Primary clinical endpoints in phase 3 trials with neoadjuvant treatment of rectal cancer

in 24 distinct scores that range from 0 to 100. For ypT and ypN, a relative weight of 3 and 5 has been suggested to reflect the effect of these variables, based on the

nomogram of Valentini and colleagues.⁴⁶ The NAR score was classified as low (NAR<8), intermediate (NAR=8–16), and high (NAR>16) according to the score tertiles of the

randomised NSABP R-04 trial dataset. A lower NAR score was associated with improved overall survival.

The individual-level endpoint surrogacy of NAR for disease-free survival was shown in the CAO/ARO/AIO-04 trial⁴⁷ using Prentice criteria. Addition of oxaliplatin to preoperative fluorouracil chemoradiotherapy resulted in significant disease-free survival improvement, which was reflected in a pronounced shift towards lower NAR scores at surgery. The NAR score was an independent predictor, capturing the treatment effect on disease-free survival. Yothers and colleagues⁴⁸ showed a small but significant association between change in NAR score and improvement in overall survival ($r^2=0.13$) by meta-analysis of five randomised trials of neoadjuvant treatment. This trial-level association was nominally better than the association for pathological complete response and overall survival ($r^2=0.02$).⁴⁸ The prognostic value of NAR was also confirmed in the PAN-EX,⁴⁹ a pooled analysis of the EXPERT and EXPERT-C phase 2 trials that tested induction chemotherapy followed by chemoradiotherapy in patients with high-risk rectal cancer.

NAR is currently used as primary endpoint in the NRG GI002 phase 2 trial⁵⁰ (NCT02921256) for total neoadjuvant treatment to assess novel radiosensitisers (table 2). The addition of veliparib, a PARP inhibitor, to standard chemoradiotherapy after induction of FOLFOX chemotherapy did not reach the primary endpoint of the trial, which was a 4-point reduction in the NAR score.

Tumour regression grading

Tumour regression grading (TRG) is a semiquantitative assessment of residual tumour cells versus fibroinflammatory tissue in the rectal wall after preoperative treatment. There is no consensus for a universally approved standardisation method, and the studies using TRG were characterised by heterogeneity regarding methodological assessment, patient cohort, treatment modality, and the time interval between chemoradiotherapy and surgery.⁵² Data from the CAO/ARO/AIO-94 and CAO/ARO/AIO-04 studies^{2,35} suggest that TRG identified distinct prognostic groups independent of prognostic factors, such as the TNM classification system, and fulfilled the Prentice criteria for individual-level surrogacy,^{43,44} similarly to the NAR score.⁴⁷ A shift of 24 scores as in the case of NAR, or 3–5 tier semiquantitative TRG, could reflect treatment effects induced by different neoadjuvant regimens more accurately than binary endpoints, such as downstaging or pathological complete response, and these treatment-induced changes are potentially better candidate surrogate endpoints for overall survival (appendix p 1).

The MRI-based TRG (MRI-TRG) was used as an endpoint in the MERCURY trial⁵³ to stratify patients with a poor response (MRI-TRG 4–5) and a good response (MRI-TRG 1–3). A significantly worse disease-free survival and overall survival was reported among patients with a poor response. A weak correlation between MRI-TRG and pathological TRG was reported in the

EXPERT and EXPERT-C phase 2 trials,⁵⁴ thus further studies to assess the applicability of MRI-TRG as an endpoint are needed. The TRIGGER randomised feasibility trial (NCT02704520) is currently assessing the potential of MRI to guide treatment selection, including deferral of surgery, according to the MRI-TRG after chemoradiotherapy.

Circumferential resection margin

The circumferential resection margin (CRM) is the most important surgical margin, created around the mesorectum. Nagtegaal and Quirke⁵⁵ have shown that locoregional recurrence is greatly increased and overall survival halved when a tumour can be seen at or within 1 mm from the radial surgical plane of resection. Involved CRM (≤ 1 mm) was more common in patients with advanced stage, ulcerative growth pattern, poor differentiation, vascular invasion, poor TME quality, and abdominoperineal resection. The prognostic value of CRM for locoregional recurrence was even higher after neoadjuvant chemoradiotherapy or short-course radiotherapy than with no preoperative therapy. CRM is also a powerful predictor of distant metastases and overall survival.⁵⁵

Despite their strong prognostic relevance, R status and CRM have only been used as secondary endpoints in phase 3 trials. The randomised Polish II trial³⁷ looking at fixed T3 and T4 rectal cancer is the only exception, as the primary aim was the conversion of a primarily unresectable tumour to an R0 resectable one. The PROSPECT phase 2 and 3 randomised trial (NCT01515787) compares standard preoperative chemoradiotherapy versus preoperative chemotherapy with selective chemoradiotherapy restricted to poor responders. This trial incorporated R0 resection and time to locoregional recurrence as early stopping criteria for phase 2, and proceeded to phase 3 when stopping criteria (thresholds for both complete surgical resection and the time to local recurrence) were not met. Co-primary endpoints of phase 3 are the time to locoregional recurrence and disease-free survival. Positive resection margins have been substantially reduced ($<5\text{--}7\%$) with modern MRI staging, improved chemoradiotherapy, short-course radiotherapy, and surgery, and might be used as benchmark quality measure rather than an efficacy endpoint. The FOWARC phase 3 trial⁵⁶ also assessed the value of preoperative chemotherapy alone as an alternative strategy in a randomisation to either fluorouracil chemoradiotherapy followed by surgery and adjuvant fluorouracil, or the same treatment plus oxaliplatin on day one of each cycle, or four to six cycles of mFOLFOX6 followed by surgery and adjuvant mFOLFOX6.⁵⁶ Despite the significantly higher rates of pathological complete response and tumour downstaging in the chemoradiotherapy groups, the primary endpoint, 3-year disease-free survival, was similar between the groups.^{36,56} This study had important limitations such as complete absence of data on the use of

See Online for appendix

Figure 2: Clinical outcome measures for rectal cancer after neoadjuvant or definitive treatment and NOM or LE

Different preoperative or definitive treatment options are characterised by variable length and time to restaging (grey). Only endpoints used in randomised phase 2 and 3 trials are illustrated. Primary endpoints shown in red. The composite endpoint refers to novel primary endpoint of the GRECCAR 2 trial.³⁸ Timepoints of patient reported outcomes and quality of life assessment, as suggested in newer trials, are shown here. NOM=non-operative management. LE=local excision. TME=total mesorectal excision. DRE=digital rectal examination. CEA=carcinoembryonic antigen. cTNM=clinical tumour node metastasis. MRF=mesorectal fascia. EMVI=extramural venous invasion. SI=sphincter involvement. PROs=patient-reported outcomes. QOL=quality of life. MRI-TRG=magnetic resonance imaging-tumour regression grading. DFS=disease-free survival. LRR=locoregional recurrence. SCRT=short-course radiotherapy. CRT=chemoradiotherapy. EBRT=external beam radiotherapy. *The follow-up protocol of NOM and definitions of complete clinical response and near complete clinical response, as proposed by Martens and colleagues,⁵⁸ are shown in the main text and appendix pp 1–2.

radiotherapy in T4 or CRM-positive tumours, no formal non-inferiority hypothesis, high rates of protocol violation (18%) or lost to follow-up, and a dropout rate of 13%.^{36,56}

Sphincter-sparing surgery

Sphincter-sparing surgery indirectly reflects tumour response to preoperative treatment and was used in the Polish I trial as the primary endpoint.⁵⁷ Despite better response in the chemoradiotherapy arm with higher pathological complete response rates and less CRM involvement, no improvement in sphincter preservation was achieved.

Early endpoints used for limited surgery or non-operative management

Complete clinical response

Complete clinical response has been introduced as a clinical endpoint after the implementation of organ preservation (figure 2). Habr-Gama and colleagues⁵⁹ were the first to pioneer the selective non-operative management approach in patients with complete clinical response after conventional fluorouracil chemoradiotherapy. The International Watch and Wait database reported clinical outcomes in 880 patients with complete clinical response after neoadjuvant treatment

and non-operative management in 47 institutions within 15 countries.⁶⁰ After a median follow-up time of 3·3 years, the 2-year cumulative incidence of local regrowth was 25·2%, of which 97% of tumours occurred intraluminally. The 5-year overall survival and disease-specific survival were 85% and 94%, respectively.⁶⁰ Similar data were shown in the OnCoRe project,⁶¹ the study by Martens and colleagues,⁵⁸ and the Memorial Sloan-Kettering Cancer Center (MSKCC) database.⁶² There is no consensus on the best definition of complete clinical response, which would facilitate consistency among current and future clinical trials (appendix pp 1–2). Imaging modalities, namely T2-weighted MRI, diffusion-weighted MRI, PET-CT, and endoscopic ultrasound, all have limitations in predicting the pathological complete response and identifying patients with complete clinical response.

Martens and colleagues⁵⁸ previously provided a pragmatic definition of complete clinical response as follows: substantial downsizing with no residual tumour or some residual fibrosis (with low signal on diffusion-weighted MRI), sometimes associated with residual wall thickening due to oedema; no suspicious lymph nodes on MRI; no residual tumour at endoscopy or a small residual erythematous ulcer or scar; negative biopsies from scar, ulcer, or previous tumour location; and initially

palpable tumour becomes non-palpable (not mandatory). First assessment should be initiated 6–8 weeks after chemoradiotherapy and repeated every 3 months. Importantly, many tumours are unreachable during a digital rectal examination and cannot be objectively documented, opposed to endoscopic or MRI images. Endoscopy and MRI do not always complement each other, which adds complexity and makes the interpretation of response challenging in the non-operative management setting.⁵⁸ Randomised trials currently testing organ preservation by non-operative management, local excision, or transanal endoscopic microsurgery, and the corresponding endpoints are shown in table 2.

Intermediate and long-term endpoints after surgery or non-operative management

Locoregional recurrence

Locoregional recurrence was previously the most important indicator of unsuccessful treatment in rectal cancer. Preoperative chemoradiotherapy, short-course radiotherapy, and improved TME quality have considerably reduced locoregional recurrence. The early Swedish trial,²¹ conducted before the routine use of TME, had randomly assigned patients to preoperative short-course radiotherapy versus surgery alone. Locoregional recurrence decreased from 27% to 11% after addition of short-course radiotherapy, resulting in a significant overall survival benefit. The Dutch trial²⁴ investigated preoperative short-course radiotherapy plus TME versus TME alone, and the MRC CR07 trial²⁹ compared preoperative short-course radiotherapy with postoperative chemoradiotherapy in patients with positive CRM. Both trials used locoregional recurrence as the primary endpoint and showed a significant advantage for short-course radiotherapy. However, the numerically smaller differences in locoregional recurrence (11% with surgery alone vs 4–5% in the preoperative short-course radiotherapy groups at 3 years) did not improve overall survival, although disease-free survival was significantly improved in the MRC CR07 trial.²⁹ The Stockholm III trial¹⁵ showed non-inferiority of short-course radiotherapy with immediate versus delayed surgery or long-course radiotherapy, using time to locoregional recurrence as the primary endpoint.

In the past decade, locoregional recurrence has been criticised as a primary endpoint in trials because of the low incidence of events and the need for long term follow-up to identify late recurrences. A phase 3 trial by Allegra and colleagues³² compared preoperative chemoradiotherapy with capecitabine versus fluorouracil, both with or without oxaliplatin. The 3-year rate of locoregional recurrence was the primary endpoint, among patients who underwent R0 resection ranging from 3.1% to 5.1%, with no significant differences between treatment groups.

Local regrowth

Local regrowth occurs in approximately 20–30% of patients with initial complete clinical response, who are

managed by nonoperative management. Unlike locoregional recurrence after radical surgery, which is typically extraluminal, difficult to salvage, and might occur beyond 5 years of follow-up, local regrowth after complete clinical response usually occurs within 2 years of follow up, is mostly intraluminal, and can be easily salvaged by curative surgery.⁶⁰ Thus, randomised trials testing non-operative management, local excision, or transanal endoscopic microsurgery use 12-month, 24-month, or 3-year organ preservation rates, or disease-free survival, as the primary endpoint (table 2, figure 2).

Distant control

Distant control has not been used as a primary endpoint in phase 3 trials. Despite improvement in locoregional recurrence after preoperative chemoradiotherapy or short-course radiotherapy, overall survival was not improved in the Dutch TME and CAO/ARO/AIO-94 trials.¹² New chemotherapy drugs including oxaliplatin and irinotecan have been tested as part of phase 1–3 trials in preoperative chemoradiotherapy. A recent meta-analysis⁶³ evaluated the addition of platinum derivatives to fluorouracil-based neoadjuvant chemoradiotherapy used for rectal cancer. In ten randomised controlled trials with 5599 patients, addition of oxaliplatin to chemoradiotherapy led to a significantly increased pathological complete response ($p=0.002$) and reduced distant recurrence ($p=0.004$). However, these benefits were accompanied by higher rates of grade 3–4 toxic effects with no significant improvements in disease-free survival ($p=0.07$) or overall survival ($p=0.23$).

Disease-free survival

Disease-free survival in adjuvant treatment trials for colon cancer is defined as the time from randomisation to local or distant recurrence, second cancer, or death from any cause.⁶⁴ In a meta-analysis,⁶⁵ the benefit of adjuvant treatments on 3-year disease-free survival was significantly associated with improved 5-year overall survival. Thus, 3-year disease-free survival has been accepted as a surrogate for overall survival in resectable colon cancer. Although 2-year disease-free survival was a stronger predictor for overall survival than pathological complete response after preoperative treatment in 2795 patients with rectal cancer across five phase 3 studies,⁶⁶ it has not been adopted as an endpoint. The definition of disease-free survival varies between multimodal rectal cancer trials, especially regarding surgery. Some trials included patients receiving only radical surgery, whereas others included patients with progressive disease before surgery, incomplete resection, or no surgery in the definition. Adjuvant chemotherapy following standard neoadjuvant chemoradiotherapy or short-course radiotherapy, was assessed in five randomised trials (appendix p 3), but its role remains unclear because these studies (except the small ADORE trial [appendix p 3]) had low accrual, poor treatment

compliance, suboptimal regimens, and did not show a clinical benefit for the primary endpoints, disease-free survival, or overall survival.⁶⁷

Composite endpoints

Composite endpoints reduce the required sample size and cost of a trial by increasing event rates. Composite endpoints should ideally incorporate components that occur with similar frequency, are of comparable importance to patients, and are affected to a similar degree by the intervention. Criticism has been raised that these conditions are unlikely to be met in practice.^{68,69} The GRECCAR 2 phase 3 trial³⁸ randomly assigned 148 patients with T2 or T3 lower rectal tumours, and residual tumours of 2 cm or less after chemoradiotherapy, to receive either local excision or total mesorectal excision. The primary endpoint was the occurrence of death, local or distant recurrence, severe surgical complications, or major morbidity 2 years after surgery. Patients with ypT0–1 in the local excision group were followed up and a completion total mesorectal excision was required for patients with ypT2–3 tumours. In the local excision group, 35% of patients needed a completion total mesorectal excision which significantly increased morbidity and side-effects. After 2 years, one or more events occurred in 56% patients in the local excision group and 48% in the total mesorectal excision group ($p=0.43$). A similar 3-year locoregional recurrence rate was observed between the two groups (5% vs 6%, $p=0.68$).³⁸ The endpoint of this trial was novel, but its interpretation remains challenging because of competing risks between different individual endpoint components.^{68,69}

Patient-reported outcomes

Patient-reported outcomes were implemented to study the effect of disease and treatment on QOL. Few phase 3 trials have reported QOL in rectal cancer. Marijnen and colleagues⁷⁰ found few differences in QOL of patients treated using total mesorectal excision with or without short-course radiotherapy, as part of the Dutch trial in 990 disease-free patients up to 2 years after randomisation. In a follow-up study, Peeters and colleagues⁷¹ examined toxic effects in 597 patients using an in-house questionnaire. After a median follow up of 5.1 years, patients after short-course radiotherapy had significantly higher proportions of faecal incontinence with pad wearing and bowel dysfunction, and worse sexual functioning.^{70,71} The Nordic trial⁷² that compared QOL using the EORTC QLQ-C30 questionnaire after chemoradiotherapy versus radiotherapy, reported higher incidence of social dysfunction, dyspnoea, and diarrhoea in the chemoradiotherapy group, but similar overall QOL in both groups. In the Polish I trial⁷³ that tested short-course radiotherapy versus chemoradiotherapy, no significant differences in anorectal and sexual functions, or QOL were observed between the two groups based on the QLQ-C30 questionnaire. The PRODIGE 2, phase 3 trial⁷⁴ randomly

assigned patients to capecitabine chemoradiotherapy either with or without oxaliplatin and showed similar QOL in both groups using the QLQ-C30 and CR38 questionnaires.

Discussion

The Definition for the Assessment of Time-to-event Endpoints in CANcer trials project⁷⁵ has been developed to provide consensus-based recommendations for clinical endpoints and facilitate consistency in reporting clinical data, but no consensus regarding the choice of endpoint in different phase trials exists to date for rectal cancer. There has been a large variability regarding primary endpoints in phase 2 and phase 3 trials, leading to intertrial inconsistency and difficulty in data interpretation.

Undoubtedly, the perfect clinical endpoint is unlikely to be established, as all endpoints have advantages and disadvantages (appendix pp 3–4). Despite these limitations, defining the most appropriate endpoints for each trial phase is important to advance progress. For rectal cancer, we propose a pragmatic approach to adjust measurement of efficacy to the specific clinical question.

For phase 1 trials, an assessment of dose-limiting toxic effects and definition of recommended dose level for phase 2 testing remain standard primary endpoints. Unlike phase 1 trials in patients with metastatic disease refractory to previous lines of treatment, phase 1 trials in rectal cancer are commonly done in treatment-naïve patients treated with curative intent. Thus, when testing the toxicity and feasibility of new chemotherapy, targeted, or immunotherapy drugs added to standard chemoradiotherapy or short-course radiotherapy, or radiotherapy dose escalation, more complex phase 1 designs such as the time-to-event continual reassessment method⁷⁶ might be indicated.

In phase 2 trials where preoperative chemoradiotherapy or short-course radiotherapy are used followed by radical surgery, NAR and TRG might be more appropriate than pathological complete response for three reasons: pathological complete response did not correlate with improved overall survival in surrogate analyses and was inferior to other endpoints such as 2-year disease-free survival;^{40,41,66} pathological complete response represents a binary histological variable, whereas NAR and TRG might reflect treatment response and cancer biology better as they indicate a continuum of tumour regression; NAR and TRG have been validated as individual-level surrogate markers for disease-free survival.^{44,47} The NAR score takes pre-treatment cT category into account, incorporates prognostically most relevant ypN-category, and has a slightly better prognostic value for overall survival compared with pathological complete response in rectal cancer trials.^{45,48} NAR is also not characterised by the inherent limitations of TRG assessment, including lack of a universally approved classification system.

	Disease-free survival	Time from randomisation until*
No resection of primary tumour because of local progression or the patient being unfit for surgery	E	Date of exploratory surgery or scheduled, but not done surgery
No resection of primary tumour because of a clinical complete response and patient opts for NOM	I	..
Limited surgery (LE or TEM) of primary tumour because of near clinical complete response including curative completion TME after LE or TEM	I	..
Non-radical resection of primary tumour (R2-resection)	E	Date of surgery
Locoregional recurrence after R0 or R1 resection of the primary tumour	E	Date of locoregional recurrence
Local re-growth after initial clinical complete response followed by curative salvage operation (R0 or R1)†	I	..
Non-salvageable local regrowth in case of NOM management (no operation or R2 salvage resection)	E	Date of diagnosis of non-salvageable regrowth or date of R2 salvage surgery
Any distant metastatic disease before, at, or after surgery, or NOM management	E	Date of distant metastases
Second primary colorectal cancer	E	Date of second colorectal primary
Second primary other cancer	E	Date of second primary, other cancer
Treatment-related death	E	Date of death
Death from same cancer	E	Date of death
Death from other cancer	E	Date of death
Non-cancer-related death	E	Date of death
Lost to follow up	Censor	Date of last follow up

E=event. I=ignore. NOM=non-operative management. LE=local excision. TEM=transanal endoscopic microsurgery. TME=total mesorectal excision. *Time from randomisation until, whichever event occurs first. †If local excision is performed for local regrowth after initial clinical complete response, and a local recurrence occurs, then a salvage operation should be done; if the salvage operation for local recurrence is performed in curative intent (R0 or R1), it should not count as an event (ignore); if, however, no operation, or only an R2 resection is possible, or there is a recurrence after salvage surgery, this should count as an event.

Table 4: Proposal for definition of disease-free survival for randomised neoadjuvant treatment trials incorporating the option of NOM

In phase 2 trials with the aim of non-operative management, complete clinical response and sustained complete clinical response during follow-up need to be reported, along with local regrowth rates and results of salvage surgery. If a local excision or transanal endoscopic microsurgery is performed for near complete clinical response, further management is guided by histopathological assessment, although criteria for completion total mesorectal excision versus follow-up (eg, ypT0–1 vs ypT2–3) require further validation. For non-operative management, local excision, or transanal endoscopic microsurgery, organ preservation without non-salvageable, locally progressive disease, or permanent stoma is the most meaningful endpoint. Also, a validated measure for anorectal function after non-operative management, local excision, or transanal endoscopic microsurgery, needs to be developed.

Single-arm phase 2 trials are flawed because of a necessary comparison with historical controls. Randomised phase 2 trials will overcome this shortcoming. A randomised phase 2 design was recently adopted²⁰ by the CAO/ARO/AIO-12 and the OPRA trial

Search strategy and selection criteria

We did a literature search using PubMed, MEDLINE, Web of Science, and the Cochrane Library for fully published articles and abstracts from international meetings from Jan 1, 1993, to Sept 1, 2019, supplemented by hand searching of abstracts from international meetings between Jan 1, 2010 and Sept 1, 2019. MeSH terms or combined free terms included “rectal cancer”, “clinical endpoint”, “surrogate”, “surrogate endpoint”, “composite endpoint”, “randomised trials”, “phase 2/3” (or phase II/III), “survival”, “radiotherapy”, “short-course radiotherapy”, “chemoradiation”, “preoperative”, “neoadjuvant”, “organ preservation”, “non-operative management”, “quality of life (QOL)”, and “PROMs”. Only papers published in English were reviewed. Only randomised phase 2 and phase 3 clinical trials with clearly defined clinical endpoints were selected, whereas single arm, prospective non-randomised trials, and studies that did not have a clear clinical endpoint definition were excluded. Unpublished ongoing randomised phase 2 and phase 3 studies were cited using either the NCT trial number, the ISRCTN registry, or the EudraCT number. Of the 625 full-text articles or abstracts assessed for eligibility, 71 publications were relevant. The final reference list was generated on the basis of relevance to the broad scope of the present review.

(NCT02008656) for total neoadjuvant treatment, the GEMCAD 1402¹⁸ trial for inclusion of aflibercept, and the NRG GI002 trial (NCT02921256) for testing new radiosensitisers.

For phase 3 trials, disease-free survival constitutes the most suitable primary clinical endpoint, despite the lack of validation as a surrogate for overall survival in rectal cancer. In the era of organ preservation, incorporating the non-operative management into disease-free survival for patients with complete clinical response is essential. Our proposal (table 4) is based on the consensus agreement for disease-free survival in the adjuvant setting for colon cancer,⁶⁴ but additionally includes events occurring during neoadjuvant treatment and at surgery, also incorporating the non-operative management and local excision, or transanal endoscopic microsurgery.⁶⁴

Future perspectives

The choice of primary endpoint in clinical trials remains challenging. Relying on surrogates and intermediate endpoints carries the risk of trials that might not improve long-term clinical outcome. The potential biological mechanisms that could underline poor correlation of surrogate endpoints with survival in some studies remain unclear. In the context of tumour heterogeneity, the local treatment effect on the primary tumour, as reflected by pathological complete response, might not fully encapsulate the tumour cell propensity for micro-metastatic seeding.⁷⁷

In the era of personalised medicine, the opinion of patients' needs to be considered and they should be

increasingly engaged in decision making. Future trials should aim to use endpoints, agreed between patients, clinicians, and regulatory authorities, as exemplified by the core outcome measures in effectiveness trials⁷⁸ and the core outcome set for clinical trials of chemoradiotherapy interventions,⁷⁹ initiatives in anal cancer. More data on PROs are needed, especially in the increasingly adopted setting of non-operative management.

Altogether, efforts should be made to continue evaluating surrogate and clinical endpoints using robust statistical methods. We recommend that data from large, randomised clinical trials in rectal cancer become available to establish an international database, as suggested for other clinical settings⁸⁰ to allow access to all interested parties and stakeholders.

Contributors

All authors contributed to the literature search, writing or review of the manuscript, and approved the final manuscript.

Declaration of interests

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