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Commentary

NCI Rectal-Anal Task Force consensus recommendations for design of clinical trials in rectal cancer

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Abstract

The optimal management of locally advanced rectal cancer is rapidly evolving. The National Cancer Institute Rectal-Anal Task Force convened an expert panel to develop consensus on the design of future clinical trials of patients with rectal cancer. A series of 82 questions and subquestions, which addressed radiation and neoadjuvant therapy, patient perceptions, rectal cancer populations of special interest, and unique design elements, were subject to iterative review using a Delphi analytical approach to define areas of consensus and those in which consensus is not established. The task force achieved consensus on several areas, including the following: 1) the use of total neoadjuvant therapy with long-course radiation therapy either before or after chemotherapy, as well as short-course radiation therapy followed by chemotherapy, as the control arm of clinical trials; 2) the need for greater emphasis on patient involvement in treatment choices within the context of trial design; 3) efforts to identify those patients likely, or unlikely, to benefit from nonoperative management or minimally invasive surgery; 4) investigation of the utility of circulating tumor DNA measurements for tailoring treatment and surveillance; and 5) the need for identification of appropriate end points and recognition of challenges of data management for patients who enter nonoperative management trial arms. Substantial agreement was reached on priorities affecting the design of future clinical trials in patients with locally advanced rectal cancer.

The optimal management of rectal cancer is going through rapid changes (1). Recent trials have evaluated the role of total neoadjuvant therapy (TNT) (2,3) and nonoperative management (NOM) (4,5). The RAPIDO (Rectal cancer And Preoperative Induction therapy followed by Dedicated Operation) trial showed that TNT consisting of preoperative short-course radiotherapy followed by chemotherapy improved disease-related treatment failure, compared to the previous standard of preoperative long-course chemoradiation therapy and adjuvant chemotherapy (2). The UNICANCER-PRODIGE 23 trial evaluated a different TNT regimen, consisting of induction chemotherapy with FOLFIRINOX (fluorouracil, leucovorin, irinotecan, oxaliplatin) followed by long-course chemoradiation, and the study patients showed improved disease-free survival with this regimen compared to preoperative long-course chemoradiation and adjuvant chemotherapy (3). Subsequently, in the OPRA (organ preservation in rectal cancer) trial, half of the patients treated with TNT were able to undergo organ preservation, and organ preservation rates were higher with chemoradiation followed by chemotherapy than with chemotherapy followed by chemoradiation (5). Given the rapidly changing landscape of rectal cancer management, the direction and content of clinical trials must evolve and adapt. Furthermore, clinical trials in rectal cancer need to reflect patient priorities, especially given the increasing incidence of young-onset colorectal cancer (6,7). In addition, clinical trials must incorporate changing treatment paradigms for specific rectal cancer subgroups. There is growing interest in organ-sparing therapy for early-stage rectal cancer and for patients with low tumors (8-11). Given these considerations, the National Cancer Institute Rectal-Anal Task Force

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convened a series of meetings and a retreat facilitate the development of consensus on these issues and help inform the design of future clinical trials of rectal cancer.

Methods

An overview of the approach to this study is shown in Supplementary Figure 1 (available online), along with the names of the individual members of the expert panel. A Delphi approach (12) was chosen to achieve group consensus by conducting iterative rounds of questionnaires and allowing group discussion before each subsequent round.

The Rectal-Anal Task Force serves in an advisory capacity to the Gastrointestinal Steering Committee of the National Cancer Institute with a mission to increase the exchange of information at an early stage of clinical trial development and the efficiency of clinical trial collaboration. Rectal-Anal Task Force membership includes representatives from the following groups: the disease committee of the National Clinical Trial Network, the National Community Oncology Research Program, community oncologists, Specialized Programs of Research Excellence, biostatisticians, patient advocates, special clinicians/experts, and National Cancer Institute staff. Retreat planning was conducted in monthly Rectal-Anal Task Force meetings beginning in September 2020 and included all members and invited guests.

The stated objective of the meetings was to identify areas of consensus in 4 agreed-upon areas relevant to the design of rectal cancer trials. These consensus areas were the following: 1) use of short-course radiation and TNT, 2) integrating patient perceptions, 3) rectal cancer subgroups of interest, and 4) design elements unique to rectal cancer (Table 1). Consensus questions were independently developed by the 4 subject groups and sent out via survey to all Rectal-Anal Task Force members. A virtual retreat was then held on March 5, 2021, to discuss the results of the first survey. Selected questions, detailed in Tables 1-4, were edited for clarification during the virtual retreat. A second and final survey was sent out 18 days after the retreat, and the results were discussed at subsequent Rectal-Anal Task Force meetings on May 55 and July 7, 2021. The Rectal-Anal Task Force included 38 members on March 5, 2021 (listed in Supplementary Table 1, available online), and there were 38 and 29 respondents to the first and second surveys, respectively. A scale of 1 to 9 was chosen, with 1 indicating total disagreement and 9 indicating total agreement. All responses were confidential. Central tendency was measured by the median score, with a score of 7 to 9 indicating agreement (support), a score of 4 to 6 indicating a neutral response, and a score of 1 to 3 indicating disagreement (lack of support). Consensus was predefined as 70% of respondents scoring within any 3-point range.

Table 1. Objectives of consensus process[a]

Focus area	Goals
1	Provide recommendations on which radiation regimens and adjuvant/neoadjuvant treatments should be incorporated in the control arms of clinical trials for rectal cancer.
2	Provide recommendations on integrating patient perceptions in clinical trials for rectal cancer.
3	Provide recommendations on developing clinical trials for subgroups of patients, and standardizing ctDNA collection in clinical trials for rectal cancer.
4	Provide recommendations on specific design elements that should be incorporated into clinical trials for rectal cancer.

[a] ctDNA = circulating tumor DNA.

Results

Radiation and neoadjuvant therapy

With regard to selection of the control arms for clinical trials, consensus was achieved for use of TNT with long-course radiation therapy (LCRT). Consensus was achieved for lack of support for further use of the older standard of neoadjuvant LCRT followed by surgery and then adjuvant therapy (see Table 2). Consensus was also achieved for use of short-course radiation therapy (SCRT) in the sequence that was reported in the RAPIDO trial (2) as an option in a control arm.

For tumor, node, and metastasis (TNM) stage T1-2N1-2 or T3 N any, there was relative equipoise with regard to the use of induction chemotherapy followed by LCRT vs initial LCRT followed by consolidation chemotherapy (5,13). Consensus was not achieved in support of the use of the older standard of neoadjuvant LCRT followed by surgery and then adjuvant chemotherapy. Similarly, for T3 with involved circumferential radial margin or T4, consensus support was reached on the first ballot for TNT in either order, whereas SCRT followed by consolidation (the RAPIDO protocol) achieved consensus support on the second ballot.

Regarding a control arm for studies of NOM, consensus support was reached on the first ballot for LCRT followed by consolidation chemotherapy, and second-ballot consensus support was also reached for induction chemotherapy followed by LCRT. Consensus support was not reached for SCRT in a control arm of a study of NOM, with either induction or consolidation chemotherapy. Again, the older standard of neoadjuvant long-course chemotherapy followed by evaluation for surgery and then adjuvant therapy did not receive consensus support as a control arm for NOM studies.

Based on the weight of the aggregated data, a TNT approach was preferred by the group consistently across all disease categories. Although some individuals expressed concern that T3N0 patients were not well represented in TNT trials (2,3) and may be overtreated with this approach, the benefits of TNT with respect to improved outcomes in the T3N0 stage were felt to outweigh the risks of toxicity. Furthermore, clinical lymph node positivity was acknowledged to be less specific than pathological examination.

With respect to sequencing, both induction and consolidation chemotherapy were felt to be appropriate for use in control arms of clinical trials. There was a lack of consensus for SCRT in the control arm in an NOM setting. Better risk stratification and discreet categorization with imaging, genomics and circulating tumor DNA (ctDNA), plus improved response criteria in the NOM setting, were felt to be appropriate for study to select patients for treatment escalation and de-escalation in future trials. Further trials are needed to understand the long-term oncologic and functional outcomes for NOM.

Patient perceptions

Strong consensus support was achieved for increasing patient participation in trial design and for soliciting information regarding patient preferences in trial design. Consensus was also achieved regarding the need to include counseling about possible sexual dysfunction after irradiation and surgery (see Table 3). The inclusion of patient advocates at all stages of study design, vetting, and approval was also supported by consensus.

Table 2. Radiation and adjuvant chemotherapy[a]

1. For patients with T1-2 N1-2 OR T3 any N rectal cancers with clear circumferential margins (by MRI), are you comfortable using the approaches listed below as an option on the control arm for NCTN clinical trials?		
M	**Consensus:**	
7.4	80% Agree	Short-course RT -> 12-16 wk of chemotherapy -> Surgery
M	**No Consensus:**	
7.2	67% Agree	Chemotherapy for 12-16 wk -> Long-course CRT -> Surgery
7.1	60% Agree	Long-course CRT -> 12-16 wk of chemotherapy -> Surgery
6.3	63% Neutral	Chemotherapy for 12-16 wk -> Short-course RT -> Surgery
6.2	60% Agree	Long-course CRT -> Surgery -> Adjuvant Chemotherapy
5.4	37% Neutral	Short-course RT -> Surgery -> Adjuvant Chemotherapy
2. For patients with T3, any N with involved or threatened margins (by MRI) OR those with T4, any N, are you comfortable using the approaches listed below as an option on the control arm for NCTN clinical trials?		
M	**Consensus:**	
7.6	82% Agree	Chemotherapy for 12-16 wk -> Long-course CRT-> Surgery (if a candidate)
7.3	76% Agree	Long-course CRT -> 12-16 wk of chemotherapy -> Surgery (if a candidate)
M	**No Consensus:**	
7.1	69% Agree	Short-course RT -> 12-16 wk of chemotherapy -> Surgery (if a candidate)
5.5	43% Agree	Chemotherapy for 12-16 wk -> Short-course RT-> Surgery (if a candidate)
3. For clinical trials of NOM in rectal cancer, are you comfortable using the approaches listed below as an option on the control arm for NCTN trials?		
M	**Consensus:**	
7.9	81% Agree	Long-course CRT -> 12-16 wk of chemotherapy -> Surgery or NOM
7.5	73% Agree	Chemotherapy for 12-16 wk -> Long-course CRT -> Surgery or NOM
M	**No Consensus:**	
6.1	53% Neutral	Short-course RT -> 12-16 wk of chemotherapy -> Surgery or NOM
5.3	47% Neutral	Chemotherapy for 12-16 wk -> Short-course RT -> Surgery or NOM
4.9	43% Neutral	Long-course CRT -> Surgery or NOM -> Adjuvant Chemotherapy

[a] CRT = chemoradiation therapy; M = median; MRI = magnetic resonance imaging; N = lymph node; NCTN = National Clinical Trial Network; NOM = nonoperative management; RT = radiotherapy; T = tumor.

The statement that "integrating patient preference is the next frontier in increasing patient participation and improving accrual for rectal and anal cancer trials" received strong consensus support. Respondents also supported the observation that clinician disinterest, lack of patient knowledge, or even patient fear may hinder patient accrual to trials. The role of patient advocates at all stages of trial design was emphasized.

Rectal cancer subgroups of interest

The following rectal cancer areas of interest were identified: early/locally advanced/metastatic disease, age based/vulnerable groups, and trials of adaptive and ctDNA-based management (Table 4).

Respondents did believe that patients with early-stage rectal cancer (8-11) should be studied separately from patients with more locally advanced tumors, but there was not consensus that T3aN0 tumors should be included with T1-2N0 tumors in the definition of early-stage rectal cancer. It was felt that patients with early-stage disease and patients who may not be able to tolerate or would prefer to avoid operative management warranted investigational NOM or local excisional options in trials. In the first iteration of the survey, "elderly" was replaced with "vulnerable" patients because the respondents felt that several types of patients other than elderly patients would prefer and warrant nonoperative or minimally invasive options. Moreover, survey respondents felt that patients known to have better outcomes, specifically good responders to neoadjuvant treatment and patients with oligometastatic disease, should be a focus in clinical trials. Younger patients (defined as age younger than 50 years) were also proposed as a focus for clinical trial activity as better functional outcomes are often a key interest in this subgroup.

There was consensus within the group to use the degree of response to neoadjuvant therapy for clinical trials investigating adaptive treatment modalities. Consensus was achieved in support of ctDNA being prospectively evaluated in clinical trials, with a focus on the neoadjuvant and adjuvant settings. In the neoadjuvant setting, investigations were supported into whether ctDNA correlates with radiological, endoscopic, and/or clinical factors, and how such correlations might influence decisions about adaptive management strategies. Consensus was also reached regarding support for evaluation of the usefulness of ctDNA in the decision-making processes, intensity of adjuvant therapy, intensity of surveillance, and early treatment of defined minimal residual disease. It was agreed that clinical trials should examine the clinical utility of ctDNA in defining escalation/de-escalation of both pre- and postsurgical management. There was strong consensus that standardization of the ctDNA methodology regarding collection, volume, plasma storage, transport, and DNA extraction was warranted. There were endorsements regarding standardizing of time points for blood collection of ctDNA: after completion of each modality of neoadjuvant therapy, pre- and postsurgery and during surveillance. Last, consensus was reached as to when investigational blood draws for ctDNA should be performed in relation to restaging of CT scans and after surgeries, within 7 days of the CT scan to allow for accurate correlation, and more than 3-4 weeks after surgery to prevent false-positive/-negative results because of tissue trauma. A previous National Cancer Institute Colon and Rectal-Anal Task Force white paper provides additional guidelines on the application of ctDNA (14).

Trial design elements unique to rectal cancer

The design element statements focused on the following trial aspects unique to the management of rectal cancer: 1) inclusion and exclusion criteria, 2) quality assurance with respect to treatment, 3) appropriate endpoints for phase II or III clinical trials, 4) patient-reported endpoints, 5) allowance and methods to deal

Table 3. Integrating patient perceptions (all items reached consensus)[a]

M	Consensus:	
1. Importance of patient preference		
8.0	83% Agree	Integrating patient preference is the next frontier in increasing patient participation and improving accrual for rectal and anal cancer.
2. Barriers that currently exist to integration of patient preferences into clinical trials		
7.0	95% Agree	Lack of patient knowledge
7.0	95% Agree	Patient fear
7.0	93% Agree	Clinician disinterest
5.0	93% Neutral	Clinician fear
6.0	95% Neutral	Patient disinterest
3. Sexual/rectal function		
9.0	93% Agree	Trials that include radiation and surgery MUST provide information about sexual health for both women and men.
4. Incorporating patient choice into study questions		
8.0	77% Agree	When random assignment between 2 treatment groups is not considered acceptable, either by patients or clinicians, then consideration should be given to alternative designs which incorporate patient choice to help shape the question asked.
5. Should more weight/voice be given to the patient advocates on the following levels?		
7.0	97% Agree	Design Onset
7.0	97% Agree	Cooperative group vetting and approval
7.0	97% Agree	RATF group vetting and approval
7.0	95% Agree	GISC group approval process
6. Should consideration be given to putting the patient advocates into stronger positions relative to voting for/against proposed trials at each of these steps?		
7.0	97% Agree	Design onset
7.0	97% Agree	Cooperative group vetting and approval
7.0	97% Agree	RATF group vetting and approval
7.0	97% Agree	GISC group approval process

[a] GISC = Gastrointestinal Steering Committee; M = median; RATF = Rectal Anal Task Force.

with clinical complete response (cCR) and NOM, and 6) trial-defined surveillance (see Table 5).

With respect to clinical trial design, there was overall consensus on almost all of the key elements. The themes included making trials more standardized while maintaining pragmatism and flexibility, particularly for standard of care treatments that are being performed as part of a multimodal trial. This theme was balanced by consensus to ensure that quality metrics be collected and credentialing be required for surgery and radiotherapy. There was strong agreement that avoidance of an ostomy at 3 years after treatment initiation was an appropriate endpoint for a randomized phase II/III clinical trial. There was general consensus that data from patient-reported outcome measures (15), particularly those related to physical functioning, should be collected for all patients enrolled in clinical trials. A surveillance strategy with carcinoembryonic antigen, cross-sectional imaging, and colonoscopy had a high level of consensus support. Finally, there was consensus that for neoadjuvant trials, NOM is a therapeutic alternative that cannot be ignored and patients participating in clinical trials need to be counseled as to the potential benefits and risks of NOM. Trials need to be developed, and these future developments should be taken into account in the analysis study results.

There was a high level of consensus for standardized inclusion criteria, which included the location of the tumor and potential for sphincter sparing by the surgeon, use of magnetic resonance imaging as the preferred modality for preoperative local staging (16), and clarifying the definition of clinically positive lymph node metastases (by radiological imaging), and increased leeway for allowing investigators to determine whether a prior malignancy might interfere with the assessment of primary and secondary outcomes.

With respect to appropriate clinical trial endpoints for phase II and III rectal cancer trials, there was a high level of consensus in support of a 3-year sphincter preservation rate and 3-year ostomy-free survival, whereas 2-year ostomy-free survival had neutral agreement. For secondary endpoints for phase II and III rectal trials, there was a high level of consensus in support of an R0 resection rate, pathological complete response, cCR, and percentage of patients with sphincter preservation at 3 years. There was disagreement for use of the neoadjuvant response score (17) and tumor regression grade as intermediate study endpoints, and a neutral score for use of pathology margin endpoints. For patient-reported outcome measures (15), there was a high level of agreement that these measurements should be collected at both early time points (1-3 months) and later time points (3-5 years) and should include metrics related to quality of life on treatment; bowel, urinary, and sexual function; and dietary changes.

There was also a high level of consensus in favor of neoadjuvant trials to take into account patients who will experience an cCR and not wish to proceed with surgical resection (18). This option included a high level of consensus that patients should be informed of the current literature regarding NOM and offered this approach, that the analysis plan should define how patients who opt for NOM will be handled, and that a structured surveillance plan be followed for these patients, including collection of endoscopic photographs for the purposes of education and training and to standardize the definition of a cCR.

Consensus was also reached in support of all statements related to increasing the pragmatic design for clinical trials (results not shown in Table 5 because of space limitations). This pragmatic clinical trial design includes allowing both infusional and oral 5-fluorouracil, use of biosimilars and dose rounding, and standard of care chemotherapy to be given at a site other than

Table 4. Rectal cancer subgroups of interest[a]

1. Early vs locally advanced vs metastatic disease		
M	**Consensus:**	
8.0	76% Agree	Clinical trials should focus on early-stage rectal cancer (T1, T2, T3aN0) or locally advanced rectal cancer, but not include both types of tumors in the same trial.
8.0	86% Agree	Early-stage rectal cancer patients should be evaluated for de-escalation of therapy including NOM or approaches building off of local excision.
8.0	77% Agree	Patients with a defined degree of response to neoadjuvant therapy could be considered as a special subgroup for clinical trials investigating the effect of additional therapies (chemotherapy, radiation, or surgery).
8.0	73% Agree	Controversial issues in the management of primary tumor and sequencing of therapies in patients with oligometastatic stage IV rectal cancer should be studied in prospective clinical trials.
M	**No Consensus:**	
7.0	61% Agree	Early-stage rectal cancer should include T3aN0 tumors in addition to T1-2 and N0.
2. Age based/vulnerable groups		
M	**Consensus:**	
8.0	77% Agree	Trials evaluating local excision or nonoperative approaches should be designed for vulnerable patients who may not be able to tolerate operative management.
8.0	73% Agree	Patients < age 50 should be special focus for preplanned secondary analyses for tumor biology, outcomes, and patient preferences.
3. Adaptive management Strategy		
M	**Consensus:**	
9.0	100% Agree	Even though ctDNA assays are currently available for clinical use, prospective trials must be conducted to critically evaluate their clinical utility in the management of rectal cancer patients.
9.0	93% Agree	In the adjuvant setting, clinical trials should examine the clinical utility of ctDNA defined escalation/de-escalation of postsurgical management. Clinical utility of ctDNA in this setting includes decisions about intensity of adjuvant therapy, intensity of surveillance and early treatment of ctDNA defined MRD.
8.0	93% Agree	Such trials in the neoadjuvant setting should examine the clinical utility of ctDNA (in addition to clinical, endoscopic, and radiographic evaluation) in making treatment decisions regarding adaptive management strategies.
4. Recommendations for ctDNA collection in rectal cancer trials		
M	**Consensus:**	
8.0	83% Agree	All clinical trials should include prospective collection of blood for ctDNA with similar methodology across trials for blood collection, plasma separation storage, transport, and DNA extraction.
8.0	93% Agree	Volume of blood drawn should be optimized according to the clinical setting (eg, higher volumes of plasma might be required for the detection of MRD)
8.0	97% Agree	Time points for blood collection must be standardized as follows: After completion of each modality of neoadjuvant therapy
8.0	97% Agree	Presurgical (or end of all planned therapy if NOM)
8.0	100% Agree	Postsurgery prior to initiation of adjuvant therapy
8.0	100% Agree	End of adjuvant chemotherapy
8.0	83% Agree	Surveillance: with planned visits according to established guidelines until and including time of radiographic recurrence
8.0	90% Agree	Blood collection for ctDNA must be done as close as possible to imaging studies (±7 days) to allow for accurate comparisons of ctDNA and radiographic outcomes (eg, lead time between ctDNA recurrence and radiographic recurrence during surveillance).
8.0	90% Agree	Blood draw postsurgery must not be within 3 to 4 weeks of surgery to avoid false positive/negative results related to ctDNA release from tissue trauma/inflammation from surgery.

[a] ctDNA = circulating tumor-derived DNA; M = median; MRD = minimal residual disease; N = lymph node; NOM = nonoperative management; T = tumor.

the primary recruiting site, when the chemotherapy is not the primary question on the trial. There was also consensus for allowing both 3-dimensional and intensity-modulated radiation therapy and radiation to be given at a site other than the primary recruiting site (with appropriate credentialing), when the radiation is not the primary question on the trial. However, these recommendations will not be applicable to trials in which specific radiation techniques are being evaluated or radiation is the primary treatment modality. Further, there was consensus on allowing the use of either laparoscopic, robotic, or open rectal surgery when the surgery was not the primary question being addressed in the trial. Alternatively, there was a high level of agreement that when systemic therapies were being compared, both standard of care and experimental systemic therapies need to be administered at the primary trial site. There was also high level of agreement that when a trial involves a new surgical technique, credentialing should be included as part of the trial. There was also a high level of agreement that surgical and radiation quality metrics should be collected in any trial where they are included, regardless of whether they are part of the experimental question.

Discussion

The consensus meetings were held in 2020-2021. Since then, the availability of important data on rectal cancer has continued to evolve, such as data from a trial showing the role of immune checkpoint inhibition for mismatch repair–deficient rectal cancer (19). Future clinical trials will need to incorporate the most current evidence in this rapidly changing landscape.

Summary of consensus recommendations

Total neoadjuvant therapy should represent the standard arm for clinical trials, with a preference for LCRT in the NOM setting and the following recommendations: 1) Increased patient participation is needed in all stages of trial design. Patient-reported outcomes should be included in trials. 2) Patient groups of interest for clinical trials are patients with early-stage rectal cancer, those in age-based and vulnerable groups, and participants in trials of adaptive and ctDNA-based management. 3) Consensus on elements unique to the design of rectal cancer trials was achieved in the following areas: 1) inclusion and exclusion criteria, 2) treatment quality assurance, 3) appropriate endpoints for phase II and III clinical

Table 5. Trial design elements unique to rectal cancer[a]

1. Inclusion and exclusion criteria		
M	**Consensus:**	
8.0	77% Agree	Prior to enrollment, accurate tumor location is required, by surgical evaluation or radiography
8.0	97% Agree	At enrollment, the feasibility of sphincter sparing surgery should be documented
9.0	90% Agree	Dedicated MRI pelvis is preferred local staging modality, but CT pelvis and endoscopic ultrasound scanning are acceptable alternatives
9.0	97% Agree	MRI criteria to define positive pelvic lymph nodes should be defined in the protocol and recorded
8.5	100% Agree	Definition of clinically positive specifications of nonabdominal lymph nodes in the protocol
2. Quality assurance with respect to treatment		
M	**Consensus:**	
9.0	93% Agree	Surgical quality metrics (LN harvest, distal margin, CRM re-operation) must be collected
9.0	97% Agree	Operative techniques require defined credentialing and/or quality control
9.0	97% Agree	Patients with a prior or concurrent malignancy, whose treatment will not interfere with the safety or efficacy of the trial, are eligible to participate
3. Appropriate end points for phase II or III clinical trials		
M	**Consensus:**	
A. End points could include:		
8.0	83% Agree	3-year ostomy-free survival
8.0	83% Agree	% patients with 3-year sphincter preservation
9.0	93% Agree	% patients with temporary and/or permanent ostomy
M	**No Consensus:**	
5.5	47% Disagree	2-year ostomy-free survival
M	**Consensus:**	
B. For phase II/III trials, intermediate endpoints should include:		
8.0	76% Agree	R0 resection rate (vs R1 and R2)
8.0	86% Agree	Pathological complete response rate (pCR)
8.0	83% Agree	Clinical complete response rate (cCR)
9.0	93% Agree	When pCR, cCR, NAR or TRG surrogate endpoints are used, the interval between RT and primary efficacy assessment must be fixed
M	**No Consensus:**	
6.0	54% Neutral	Proximal, distal, and radial margin distance
6.0	59% Disagree	Neoadjuvant response score (NAR)
6.5	55% Disagree	Tumor regression grade (TRG)
4. Patient-reported endpoints (baseline, during treatment, early (1 to 3 months) and late points (3 to 5 years)		
M	**Consensus:**	
9.0	97% Agree	Patient-reported bowel function, LARS
8.0	69% Agree	Patient-reported endpoint: dietary changes
8.0	83% Agree	Patient-reported endpoints: urinary function
8.0	100% Agree	Patient reported endpoint: sexual dysfunction
8.0	90% Agree	Patient-reported endpoint: treatment-related quality of life
5. Allowance and methods to deal with cCR and NOM		
M	**Consensus:**	
9.0	97% Agree	Protocols should include plans, such as NOM (NOM) in the event of cCR, and the implications for data analysis
9.0	100% Agree	Patients with cCR should be informed about NOM and 'watch and wait' (WW) strategies
8.0	89% Agree	For WW patients developing local regrowth, complete surgical resection should be considered 'disease free' for endpoint analysis
6. Trial defined surveillance		
M	**Consensus:**	
9.0	97% Agree	Surveillance should include annual cross-sectional imaging of chest/abdomen and pelvis for at least 3 years
8.0	90% Agree	Annual imaging should include chest CT scan (± contrast) and abdominal CT (+ iodine contrast) or abdominal MRI (+ gadolinium contrast) or abdominal MRI (no contrast) or PET-CT
8.0	86% Agree	CEA should be measured every 6 months for 5 years
9.0	97 Agree	Colonoscopy, to evaluate synchronous and metachronous lesions and anastomosis, should be performed at 1 year and then at not < every 5 years
8.0	97% Agree	NOM patients should receive endoscopy and DRE every 4 months for 2 years and every 6 months for years 3 to 5, and pelvic MRI every 6 months for years 1 to 2 and every 12 months in years 3 to 5
8.0	90% Agree	For cCR patients, endoscopic photographic images should be collected to standardize and document the features associated with a successful WW strategy

[a] cCR = complete clinical response; CEA = carcinoembryonic antigen; CRM = circumferential resection margin; CT = computed tomography; DRE = digital rectal exam; LARS = low anterior resection syndrome; LN = lymph node; M = median; MRI = magnetic resonance imaging; NAR = neoadjuvant response score; NOM = nonoperative management; pCR = pathological complete response rate; PET-CT = positron emission tomography/computed tomography; RT = radiotherapy; TRG = tumor regression grade; WW = watch and wait.

trials, 4) patient-reported endpoints, 5) allowance and methods to deal with cCR and NOM, and 6) trial-defined surveillance.

Significant consensus was reached on almost all of the key elements related to the design of future clinical trials for the treatment of rectal cancer. Consensus was reached in all 4 areas of evaluation, namely, radiation and neoadjuvant therapy, patient input, special subgroups, and trial design elements unique to rectal cancer. These areas of consensus should provide guidance for the design of new research protocols for the optimal treatment of rectal cancer.

Data availability

The data underlying this article are available in a shared folder hosted on Dropbox serving as an online repository that can be accessed at the following link: https://www.dropbox.com/s/0nu8u6jwtg5c93u/RA%20TF%20Rectal%20Cancer%20Retreat%20Survey%202_Results_v1.0.xlsx?dl=0.

Author contributions

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Conflicts of interest

All authors report no conflicts of interest.

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