International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer

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CONSENSUS STATEMENT **[Au: Strapline added for PDF production purposes, please ignore.]**

International consensus recommendations on key outcome measures for organ preservation after (chemo)radiotherapy in patients with rectal cancer **[Au: Suggested change to title OK? this is intended to reflect that organ-sparing surgical approaches might be relevant for certain patients? Feel free to revert if you disagree with this change.]**

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[Au: Affiliations have been edited to comply with journal style preferences, please check these carefully. Ideally, the style should be: department, institution, town/city, country and there should be only one affiliation listed per number. I have flagged up a few points that might not currently comply with this style] [1]Department of Radiotherapy of Oncology, University of Frankfurt, Frankfurt, Germany.

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Abstract | Multimodal treatment strategies for patients with rectal cancer are increasingly including the possibility of organ preservation, such as nonoperative management or local excision. **[Au: New sentence introduced here, OK?]** Organ preservation strategies can enable patients with a complete response or near-complete clinical responses after radiotherapy with or without concomitant chemotherapy **[Au: (chemo-)radiotherapy has been changed to radiotherapy with or without chemotherapy owing to journal style preferences, OK?]** to safely avoid the morbidities associated with radical surgery, and maintain anorectal function and quality of life **[Au: Perhaps you could also mention the improved quality of life implicit in maintaining organ function for these patients here as well?]**. However, standardization of key outcome measures of organ preservation strategies is currently lacking; this includes a lack of consensus of the optimal definitions and selection of primary end points according to the trial phase and design; the optimal time-points for response assessment; response-based decision-making; follow-up schedules; use of specific anorectal function tests; and quality of life and patient-reported outcomes. Thus, a Consensus Statement on outcome measures is necessary to ensure consistency and facilitate more accurate comparisons of data from ongoing and future trials. Here, we have convened an international group of experts with extensive experience in the management of patients with rectal cancer, including organ preservation approaches, and used a Delphi process to establish the first international consensus

recommendations for key outcome measures of organ preservation, in an attempt to standardize the reporting of data from both trials and routine practice in this emerging area.

[H1] Introduction

[Au: For the benefit of non-expert readers, I encourage you to briefly introduce the issues that organ-preservation strategies are designed to address. Presumably these would be the morbidities and functional problems associated with total mesorectal excision, which might represent overtreatment for some patients? It might also be helpful to mention the percentage of patients with rectal cancers who might be suitable for organ preservation approaches, based on typical patterns of clinical presentation. Please add a brief introductory paragraph outlining these issues.]

Organ preservation constitutes a paradigm shift in the management of rectal cancer. One of the main reasons for exploring organ preservation strategies is the avoidance of permanent colostomy, preservation of anorectal function and quality of life[1]. Bowel function deterioration including urgency, frequency, incontinence and bowel movement clustering commonly occurs in patients with rectal cancer receiving low anterior resection after neoadjuvant chemoradiotherapy. The number of clinical trials examining organ preservation strategies, such as non-operative management (NOM) or local excision only (LE), after chemoradiotherapy **[Au: CRT has been written in full throughout OK (journal style is to avoid defining one-word abbreviations?]** in patients with rectal cancer is progressively increasing **[Au: Sentence restructured for a more active voice, OK?]**[1]. Habr-Gama and colleagues were the first to implement a selective NOM approach in patients with resectable rectal cancers with a clinical complete response (cCR) following chemoradiotherapy[2]. Since this initial study, data from several studies, including the International Watch and Wait database (IWWD) analysis, indicate that deferral of surgery in patients with a cCR seems to be oncologically safe; although more randomized data are needed to confirm both the long-term oncological outcomes **[Au: changed to 'outcomes' here – I assume by 'oncological safety' you meant 'lack of disease recurrence' OK?]** and the superiority of organ preservation in terms of quality of life (QoL), as assessed using patient-reported outcomes (PROs)[3-11]. LE, using either transanal endoscopic microsurgery or transanal minimally invasive surgery, is an alternative organ-preservation approach for selected patients with small T1–T3 rectal cancers **[Au: Definition of 'low rectal cancer' added from NCCN guidelines (2015 edition) for less-expert readers, OK? Please adjust if this is not what you originally meant here]**) and a good response after chemoradiotherapy **[Au: by 'good response' did you mean a cCR?]**, as demonstrated in the

CARTS, TREC and GRECCAR2 trials[9,12-14]. The ongoing **[Au:ongoing?]** STAR-TREC trial (NCT02945566) is exploring the value of NOM and LE, depending on the degree of response after neoadjuvant treatment in patients with early stage disease **[Au: stages I and II specifically?]**. LE alone is an effective primary treatment option for selected patients with certain early stage rectal cancers (such as stage cT1N0 without adverse histopathological features) that has been shown to reduce the risk of morbidity without jeopardizing long-term oncological outcomes[15-17].

Reflective of the findings of the Definition for the Assessment of Time-to-event Endpoints in Cancer trials (DATECAN) initiative[18], we provided recommendations on the use of clinical and surrogate end points in the different phases (I–III) of rectal cancer trials in 2020[19]. However, standardization of the key outcome measures for trials involving organ-preservation approaches is currently lacking. Trials involving organ-preservation approaches thus far are characterized by marked heterogeneity in selection criteria, treatment strategies, choice of end points and design, all of which limit the accuracy of both data interpretation and comparison between studies. Hence, an international consensus is needed to ensure consistency, and thus facilitate appropriate data collection, interpretation and the comparison of organ preservation outcomes either as part of a trial ('intended' organ preservation) or outside of a trial ('incidental' organ preservation) in patients with a cCR after standard neoadjuvantly intended **[Au:neoadjuvant?]** treatment, as is now permitted by several guidelines including those provided by ESMO,[17] the NCCN[20] and ASTRO[21]). Here, we provide the first expert Consensus Statement on key outcome measures for organ preservation in patients with rectal cancer, with a particular focus on NOM. We have convened an international group of clinical trialists with extensive experience in rectal cancer, including organ preservation strategies, and used the Delphi process to collect opinions, with the aim of providing a standardized approach to outcome measurement and reporting in this setting.

[H1] Methods

[H2] Search strategy and selection criteria **[Au: Edited for length OK? H2 subheadings must contain a maximum of 39 characters, including spaces.]**

References were retrieved from electronic databases (PubMed/MEDLINE, Web of Science, the Cochrane Library, and Google Scholar) **[Au: This seems to be four databases and a search engine? Did you mean that one or more of the databases was searched using google scholar, or something else here?]**), which were searched for published articles and abstracts

from international meetings containing data from retrospective, prospective and randomized clinical trials investigating any **[Au:all/any?]** organ preservation approaches for patients with rectal cancer, published from inception to April 1, 2020 (Supplementary information). **[Au: Sentence introducing supplementary information has been removed owing to journal style preferences, OK? Journal style is to refer to supplements/display items only indirectly]**. Two investigators (E.F. and C.R.) extracted data on the key outcome measures of organ preservation from all selected studies to be included in the Delphi process, reviewed the list of retrieved articles and selected potentially relevant articles (FIG. 1).

[H2] Establishing a consensus. [Au: Edited to comply with length restrictions. Please adjust as you see fit while remaining within these restrictions.]

The guideline panel comprised a multidisciplinary and interprofessional team, including clinical oncologists, radiation oncologists, medical oncologists, surgical oncologists, pathologist, radiologists with expertise in rectal cancer and a bioinformatician. A Delphi method was used to achieve consensus recommendations based on votes from all panelists, recorded using the SurveyMonkey program (https://www.surveymonkey.com), with additional information shared via electronic communications **[Au: Did you simply mean email here?]**. A threshold of ≥70% agreement was deemed to be required to reach consensus on each item. More information is provided on the formation of a consensus panel and the Delphi method in Supplementary Information**.**

[H1] RESULTS

[H2] Literature search and review

A total of 3,090 publications were retrieved from the literature search. 667 abstracts were selected for full-text assessment, after removal of duplicates and screening of the titles and abstracts (FIG. 1). After full-text article review and exclusion of manuscripts that were either unrelated to the present topic and/or not written in English, 396 manuscripts were considered relevant to the scope of the present study. We identified the following seven outcome measures as key to an organ preservation strategy: definition of end points (methodology and criteria to define response, unequivocal nomenclature); choice of primary end point according to the trial phase and design; time-point of tumour response assessment (RA) and determination of a cCR; response-based decision algorithms and the use of biopsy sampling; follow-up methods (schedules and timelines); organ preservation-specific anorectal function tests; and QoL

assessment and PROs. The seven outcome measures were then developed into 32 clinical questions to include in the Delphi survey (Supplementary Table 1).

[H2] Consensus procedures and Delphi rounds

The questionnaires used in first and second Delphi rounds on the seven key outcome measures of organ preservation, together with the corresponding answers, are provided (Supplementary Tables 1 and 2). In a third Delphi round, the final consensus manuscript recommendations on key outcome measures were prepared and agreed upon by all members (100%) of the panel. The flow diagram of the study procedures used to establish an international consensus, including rounds 1–3, is provided (FIG. 2). The results of the consensus procedure and individual Delphi rounds are described in detail in Supplementary Information.

[H1] Recommendations

[H2] Criteria and definitions of endpoints **[Au: Edited for length, OK? (H1 and H2 headings have an upper character limit of 38). Please feel free to adjust while remaining within these restrictions.]**

[Au: Indirect reference to BOX 1 removed, OK?] As part of the Delphi process, the panel reached a consensus upon the definitions of organ preservation, locoregional regrowth after NOM and locoregional recurrence after LE or total mesorectal excision (TME), respectively (BOX 1). Definitions of an incomplete/poor response, local regrowth and local recurrence are provided separately for clarity. The various criteria used to define a cCR in the literature are described in Supplementary Table 4**.** The panel recommended that the 'Amsterdam/Maastricht' criteria[4] are best suited to define cCR and near cCR (ncCR). The panel also agreed with the definition of organ preservation-adapted disease-free survival (DFS) **[Au:originally?]** proposed in 2020[19]. The definition of TME-free DFS used in the OPRA trial was introduced for the first time at the ASCO annual meeting 2020[22,23], which explains why consensus was not reached for this end point. The definition of TME-free DFS was provided separately by the primary investigator of the OPRA trial (J.G.A.).

[H2] Choice of primary end point **[Au: Similar to a previous comment, this heading was also edited to comply with length restrictions for this type of heading, OK?]**

Comparisons of the RA time-points used to determine cCR in randomized studies of organ preservation strategies indicate substantial variability, both in terms of the time-point and the primary end point selected (TABLE 1) **[Au: This comment on the heterogeneity of end**

points used in randomized studies has been moved up from the 'Recommendations' section to here as it serves as a useful introduction to the issue in general, OK?] . The panel recommended that different primary end points should be used according to the trial design and phase **[Au: Detail added here following removal from heading, OK?]**, taking into consideration the initial tumour stage, use of standard or intensified experimental treatment regimens, intended or incidental organ preservation, NOM or LE strategies, and overall aim of treatment. Consensus was reached on several primary end points

[H3] ***Recommendations.***

- Early assessments of tumour response (such as the cCR rate) should be used as primary end points for early **[Au: Journal style does not permit underlining for emphasis, OK]**phase I/II trials designed to identify strategies that increase cCR rates and enable NOM or LE using more intensive radiotherapy, chemoradiotherapy or total neoadjuvant treatment (TNT) regimens to select tolerable and locally effective treatment regimens for further testing in larger cohorts, such as the Danish trial[7] or the recently completed CAO/ARO/AIO-16 trial (NCT03561142). Notwithstanding, both the risks and the benefits of treatment intensification should be considered carefully in these contexts.
- Organ preservation assessed at 30–36 months after commencing treatment should be the primary intermediate end point for randomized phase II/III trials using either NOM or LE (for patients with a cCR or ncCR), such as WW3 (NCT04095299), STAR-TREC (NCT02945566) or ACO/ARO/AIO-18.1 (NCT04246684) **[Au: NCT numbers have been added for these trials. Please replace with references should any be available]**. Rectal function **[Au: Changed from 'function' I assume this is what you meant?]**, toxicities and QoL should be regarded as pivotal secondary outcomes, to be considered for inclusion as composite or co-primary end points, such as in the GRECCAR2 trial[9,12].
- Organ preservation-adapted DFS at 3 years[19] should be used as a primary end point if organ preservation is permitted within, but is not the primary purpose of, a phase III trial, especially in trials enrolling patients with locally advanced tumours.

[H2] Time-points to determine cCR

Evidence on optimal timing of RA to determine a cCR is still emerging and can be influenced by many variables (such as initial tumour stage, biology, treatment duration and intensity,

interval from treatment completion, and the methodology used to assess response); however, the panel indicated the importance of providing clear consensus-based recommendations for future trials and routine clinical practice. Representative examples of specific trial designs illustrate the complexity of identifying the optimal timing for accurate RA owing to the highly variable designs and treatment durations of the various clinical trials conducted in this area (FIG. 3 and TABLE 2). **[Au: Edits OK? This sentence was moved up slightly to comply with journal style preferences to first discuss background information and then provide one or more focused recommendations]**

[H3] ***Recommendations.***

- Time-points for RA and determining cCR should be selected according to trial design and treatment strategies, as summarized in BOX 2 **[Au: Edit OK? I'm trying to provide a more concise summary of the recommendations in this area]**.

[H2] Response-based decisions and biopsy use [Au: Edited for length, OK?]

A question commonly raised is whether clinicians should wait longer before deciding on surgery if restaging after preoperative treatment reveals a ncCR. The optimal timing for evaluation of a cCR greatly depends on the context of treatment design. No consensus was reached on the timing of the second assessment, although the panel supported longer waiting in this setting **[Au: Sentence restructured, OK?]**. Notably, the decision on whether to proceed to surgery or wait longer should also take into account initial tumour stage, treatment approach and the RA timepoints, as described above.

Another important point concerns the role of biopsy sampling in patients with a ncCR or cCR. In both scenarios, consensus agreement was reached that biopsy sampling does not provide additional value and could lead to false-negative results. Long-term follow-up data from a prospective study assessing watch-and-wait after chemoradiotherapy in this setting indicates that biopsies have only limited clinical value for ruling out residual cancer[5]. A further analysis of data from this study clearly indicates that biopsy samples provide no added diagnostic value, especially when the criteria for a cCR are fulfilled[24]. In contrast to the original study where a biopsy was indicated in case of ncCR[5], the panel did not recommend a biopsy as mandatory for ncCR due to the abovementioned reasons. **[Au: Edited to avoid use of author names (this is a journal style preference) and to provide a little more detail on these studies, OK?]**. **[Au:**

"In contrast to the original study by Martens et al. in which biopsy sampling was indicated in patients with a ncCR (showing dysplastic changes)," has been removed in order to provide clearer recommendations on use of biopsy sampling, OK?]

[H3] ***Recommendations.***

- The panel does not recommend biopsy sampling as mandatory for those with either a cCR or ncCR as it does not provide any additional diagnostic value and could lead to false-negative results . **[Au:OK to cite refs 5 and 24 here?]**

- Where a biopsy sample is nevertheless obtained from a patient with an ncCR and is negative on analysis, the panel recommends that extended waiting and reassessment after 6–12 weeks could be considered, again depending on the treatment approach.

[H2] Follow-up procedures and schedule

The panel reached a consensus that serum carcinoembryonic antigen (CEA) tests, digital rectal examination (DRE), rectoscopy, pelvic MRI, and chest and abdominal CT should all be part of the follow-up of patients treated using an organ preservation approach (TABLE 2). The majority indicated that serum CEA levels should be assessed every 3 months during the first 3 years after completion of treatment, and then every 6 months during years 4–5. Consensus was also established that DRE, endoscopy and MRI should be conducted every 3–4 months during the first 2 years after completion of treatment, and then every 6 months during years 3–5. Finally, the preferred time schedule to perform CT of the thorax and/or abdomen **[Au: The term 'chest/abdomen' was used earlier in this paragraph, OK to apply it here also, for consistency?]** is every 6–12 months during the first year after completion of treatment, and annually during years 2–5 (TABLE 2). **[Au: Sentence introducing TABLE 2 has been removed owing to journal style preferences to refer to display items only indirectly where possible, OK?]**

[H2] Anorectal function measurement

The panel was asked to select the optimal method of measuring anorectal function among the various commonly used tests, combining a mix of clinician-reported and patient-reported instruments. These included the Wexner score[25], the Low Anterior Resection Syndrome (LARS) score[26], the MSKCC Bowel Function Instrument (MSKCC BFI) score[27], the Vaizey score[28] and manometry (Supplementary Table 5).

[H3] ***Recommendations.***

- The patient-reported LARS score is recommended as the best available method of measuring anorectal function. **[Au: Adapted from the previous paragraph to provide a more concise and direct recommendation, OK?]**

- A new organ preservation-specific score should be developed that includes the ability to measure other functional aspects, such as urinary and sexual dysfunction in addition to bowel dysfunction. **[Au: Adapted from the previous paragraph to provide a more concise and direct recommendation, OK?]**

[H2] QoL assessment and PROs

The panel achieved a consensus that the EORTC QLQ-C30 should be the standard method of QoL assessment and should always be used. The panel was asked to vote on five proposed QoL and function scales. These included overall QoL, physical function, role function, social function and emotional function. Consensus was achieved on the role of all five proposed scales.

The panel also agreed on the 10 most important symptomatic toxicity items from a list of 20 proposed items for evaluation as part of a patient-reported assessment. These included bowel urgency, faecal incontinence, bowel frequency, diarrhoea, tenesmus, toilet dependency, night-time bowel opening, urinary urgency, impotence and pain. Among the panel, 42% voted for the use of the EORTC QLQ-CR29 in addition to QLQ-C30. EORTC QLQ-CR29 covers many aspects of bowel, urinary, stoma and sexual function, although it does not include all bowel symptoms that can occur following NOM or LE, and in particular fails to collect information on bowel urgency and toilet dependency. These bowel issues are included in the LARS score, although this score lacks items relating to urinary and sexual dysfunction as well as stoma-related items for patients in whom organ preservation was not possible. Thus, all panel participants indicated a need to develop a new, validated, NOM and LE-specific PRO measure (or extension) (Supplementary Table 1).

Finally, the panel was provided with a list of different time-points and asked to vote on the optimal timings for measurements of symptomatic toxicities, QoL and **[Au:anorectal function**

specifically, or pelvic organ function in general?] anorectal function. The panel recommended that toxicities should be measured at baseline, 3 months, 12 months, 24 months, 36 months and 60 months after a decision on whether to undergo NOM or LE. A similar consensus was reached on using the same time-points for measurements of QoL and **[Au: pelvic organ?]** anorectal function.

[H3] ***Recommendations***.

- Overall QoL, physical function, role function, social function and emotional function should be used to document adverse events and how they affect patients
- Ten symptomatic toxicity items (bowel urgency, faecal incontinence, bowel frequency, diarrhoea, tenesmus, toilet dependency, night-time bowel opening, urinary urgency, impotence and pain) were selected as the highest priority for evaluation, with a specific time schedule for measurement
- A new, validated PRO instrument should be developed specifically for patients undergoing organ preservation approaches

[Au: Please provide a concise bullet-pointed list summarizing the recommendations on QoL assessments and PROs]

[H1] Discussion and future perspectives

Herein, we provide the first international consensus recommendations on key outcome measures for organ preservation strategies in patients with rectal cancer. Undoubtedly, these strategies are still in a transitional phase, or are only at the beginning of a new era in which evidence regarding many aspects of organ preservation is far from complete[1]. This incompleteness is reflected by the inconsistency in outcome measurements and reporting in clinical trials and retrospective or population-based series, which underlines the importance of these consensus recommendations. Ambiguous clinical outcomes have often also been reported, which reflects heterogeneity in patient inclusion criteria for specific interventions, including various radiotherapy and/or chemotherapy regimens. We recommend that investigators use these consensus recommendations as a framework when designing studies involving organ preservation approaches for patients with rectal cancer.

The use of ambiguous language in definitions of clinical end points, such as cCR, tumour regrowth, disease recurrence, organ preservation and DFS with or without considering tumour

regrowth has often led to confusion. Use of the term 'local regrowth', instead of local recurrence, to describe tumour regrowth that occurs after an initial cCR was agreed at the Champalimaud (Lisbon) meeting in 2014, owing to differences in time course, salvageability and the more favourable prognosis associated with local regrowth over local recurrence[29] **[Au: Sentence restructured, OK?]**. Nevertheless, the distinction between locoregional and local or regional regrowth (or recurrence) has often been far from clear, and rigorous definitions are often not provided. Here, consensus was reached on several exact descriptions of end points, which will hopefully avoid such disparities, and enable future cross-trial comparisons. Consensus was also reached on the improved definition of DFS (organ preservation-adapted DFS)[19] proposed in 2020, which incorporates both NOM and LE. TME-free DFS was only recently introduced as an end point and was first reported in a presentation of data from the OPRA trial at the ASCO annual meeting 2020[22,23], although the definition of this term is provided for future reference.

The choice of the most appropriate outcome measure is a crucial component of trials involving organ preservation approaches[30]. The selection of primary end points in prospective studies has often been rather arbitrary. Owing to differences in both the treatment strategies selected and their durations, the panel acknowledged that 'one size does not fit all' for organ preservation strategies, and recommended the use of specific end points according to the clinical scenario. Similar to the pCR end point used in trials involving radical surgery after neoadjuvant treatment[31], cCR was suggested as an end point for small-cohort **[Au: Please see my previous comment about 'early' ?]** phase I/II trials testing intensified treatment regimens with the aim of identifying tolerable and locally effective regimens for further testing in larger cohorts (such as a single arm trial conducted by Appelt et al.[7], in which chemoradiotherapy was combined with radiotherapy dose escalation with brachytherapy). Of note, sustained cCR at 12 months comprises part of the end point of organ preservation and was, thus, not recommended as a separate end point in this Consensus Statement. Organ preservation at 30–36 months after the start of treatment was agreed upon as the primary end point for phase II/III trials involving the use of NOM and/or LE to achieve organ preservation, and this end point is being used in the ongoing STAR-TREC (NCT02945566), OPERA (NCT02505750) and ACO/ARO/AIO-18.1 (NCT04246684) trials. The time-point for defining organ preservation varies between different studies (TABLE 2), although we recommend a 30–36-month time window after the start of treatment **[Au: Edited for a more active voice, OK?]**, reflecting the prolonged treatment time of TNT and that tumour regrowth mostly occurs within 24–30 months after completion of

treatment[8,32]. Organ preservation-adapted DFS is recommended for use in phase III trials that allow organ preservation but specifically aim to improve oncological outcomes, and especially to reduce the risk of distant metastases (such as the TRIGGER trial[33]). **[Au: Edit OK? I think this is what you meant by 'especially distant metastases']**

No perfect primary end points exist for organ preservation approaches and all end points are susceptible to certain pitfalls[34]. Furthermore, the choice of primary end point serves the statistical purpose of trial design, whereas secondary end points, especially QoL, PROs and anorectal function (one of the main arguments for deferring surgery), should be regarded as equally important[13,35-37]. Shared decision-making with patients and risk:benefit analyses (such as those exploring the balance between NOM or LE and treatment toxicity) should be considered for trials involving 'intended' organ preservation. The fact that bad responders might be overtreated **[Au: I am unsure of your meaning here. Did you mean that bad responders might receive intensified CRT in an attempt to avoid TME, but nonetheless undergo TME owing to a lack of response to CRT? Or something else here?]** should also not be underestimated, as shown in the GRECCAR2 trial, in which many patients in the LE group required completion TME, resulting in increased morbidities and adverse events[9,12]. In this context, future studies should aim to clarify which inclusion criteria should be used to advocate for LE, the optimal timing of LE depending on tumour response (cCR versus ncCR versus residual disease), and how this relates to pretreatment disease staging[38-40].

The optimal time-point for determining achievement of a cCR constitutes one of the biggest challenges to testing organ preservation approaches, as tumour response to treatment is a dynamic phenomenon affected by tumour size, histology, biology, treatment strategy, and the time interval between preoperative and/or definitive treatment and the decision to proceed to NOM or LE (or TME)[19]. This complexity is reflected in the variable time-points for RA to determine cCR across different studies owing to variations in treatment schedule and design (FIG. 3). Knowledge of the kinetics of tumour response has mainly been derived from the operative setting. In a pooled analysis of data from 4,431 patients, pCR rates increased at intervals greater than 6–7 weeks post-chemoradiotherapy, whereas a Dutch Surgical Colorectal Audit analysis comprising 1,593 patients revealed a peak in the percentage of patients with a pCR at 10 weeks post-chemoradiotherapy — 16 weeks after commencing treatment[41]. The advent of TNT, with highly variable treatment durations across different trials, has added to the complexity of this issue. For example, in a phase II trial, patients received either two, four or

six cycles of folinic acid, 5-fluorouracil and oxaliplatin (FOLFOX) chemotherapy after standard chemoradiotherapy, and underwent surgery at 6, 11, 15 and 19 weeks after completion of chemoradiotherapy; pCR rates were 18%, 25%, 30%, and 38%, respectively[42]. Whether these differences can be explained by the use of intensified chemotherapy or by the prolonged interval before surgery remains uncertain. The CAO/ARO/AIO-12 trial compared two TNT sequences: induction chemotherapy plus chemoradiotherapy vs chemoradiotherapy plus consolidation chemotherapy, demonstrating a pCR in 17% and 25% of patients, respectively[43]. Similar data favouring chemoradiotherapy plus consolidation chemotherapy were reported in the OPRA trial, which showed 3-year TME-free survival of 59% versus 43% for induction chemotherapy plus CRT[22].

The panel agreed that defining one specific time-point for assessing cCR is impossible, considering the range of different treatment strategies used; partly dependent on initial tumour stage and risk features. In a meta-analysis comprising data from 602 patients from 11 series, advanced cT stage (cT3–4 versus cT1–2) predicted a worse response and local regrowth[32]. Thus, for patients with early-stage tumours receiving chemoradiotherapy or short-course radiotherapy (SCRT), we recommend the two-step approach adopted in the STAR-TREC trial, which involves response assessments at 12 weeks and 16–20 weeks after starting treatment, analogous to the approach used for patient with anal cancer[44]. Following publication of data from the phase III RAPIDO[45] and PRODIGE[46] trials demonstrating improvement in the primary end points of disease-related treatment failure (DrTF) and DFS, respectively, TNT is expected to be integrated into the management of patients with locally-advanced rectal cancer in the next updates of treatment guidelines in this area. The panel recommends adapting the timing of cCR assessments according to the duration of TNT, that is 20–38 weeks after commencing treatment, as is the current approach in various trials, including OPERA (NCT02505750), ACO/ARO/AIO-18.1 (NCT04246684), GRECCAR12 (NCT02514278), OPRA[22] and TRIGGER[33] (FIG. 3). The optimal length of time between commencing treatment and determining cCR, in terms of both oncological safety and clinical effectiveness of treatment, remains unclear, and is particularly relevant in patients receiving prolonged TNT **[Au: Sentence restructured OK?]**. In the RAPIDO trial[45], the investigators suggested that early response imaging could be advocated to identify patients with disease progression during preoperative treatment[47]. Indeed, close monitoring is important to identify poor responders early enough to offer immediate surgery. The panel provided these practical recommendations but acknowledged that evidence on the optimal timing of cCR monitoring is far from complete.

The Amsterdam/Maastricht criteria were selected as the recommended method of defining cCR and ncCR[4]. The diagnosis of ncCR poses a challenge to clinical decision-making owing to the nonbinary nature of this end point and the role of disease trajectory, which can make imaging-based assessments difficult. The panel recommends that longer intervals after commencing treatment should be considered, as performed in several studies where RA was repeated three months later **[Au: if possible please give some examples of the extended delays used in these trials?]**[3,5]; although, for assessments of ncCR, this decision should also take into account the trial duration. Importantly, based on data from previous studies[5,24], biopsy sampling was not recommended by the panel, and should not be routinely performed owing to the risk of false-negative findings (for example owing to sampling from a fibrotic area) and a lack of evidence of value, especially when DRE, endoscopy and MRI criteria for cCR are all fulfilled[1,48]. Indeed, residual cancer cells are often found in the muscularis propia, which could explain the high risk of false-negative results with biopsy sampling, as samples are often obtained from more-superficial areas[49]. **[Au: Sentence 'Also, definition of ncCR is difficult as it is not a binary issue that can always be accurately determined by imaging, and depends on the trajectory.' has been removed – this information has been incorporated into the second sentence of this paragraph]** In contrast to an original study, in which biopsy sampling was indicated in patients with a ncCR [5], the panel does not recommend mandatory biopsy sampling to define ncCR. The definition of ncCR requires consideration of both lymph node regression and the presence of morphological features associated with node positivity (such as a round, irregular border and heterogeneous signal) combined with diameter ≥5 mm[50-53]. LE can be used in patients with a ncCR, both for diagnostic and therapeutic purposes[13,54], although this approach is also associated with increased morbidity if completion TME is required[9,12]. The criteria for completion TME after initial LE need to be further elucidated.

For patients with early stage rectal cancers with an adenomatous component, the accuracy of diagnosing a residual adenomatous polyp after chemoradiotherapy poses a great challenge to organ preservation approaches. Previous data indicate that these tumours might be suitable for primary treatment with chemoradiotherapy and organ preservation; however, residual adenomatous polyps often include high-grade dysplastic components and should therefore be removed using full-thickness LE[55,56].

Diagnostic imaging can be notoriously inaccurate at initial diagnosis and further research efforts are needed in this area **[Au: Are you still talking specifically about early-stage rectal cancers or all stages here? Also please note, I incorporated information from a sentence originally located at the end of this paragraph (on the need for more research) as it seems more appropriate to mention this here]**. Nonetheless, staging is highly relevant in the context of organ preservation as previous studies have indicated increasing cT stage, tumour volume or, alternatively, tumour length and bowel wall circumferential extent at baseline as the most important predictors of a cCR[11,62-64]. Furthermore, inaccurate staging of cT1 tumours as cT2 rectal cancers (upstaging) can lead to unnecessary treatment with chemoradiotherapy within clinical trials. LE alone without chemoradiotherapy is considered sufficient and can reduce the risk of morbidities without jeopardizing long-term oncological outcomes[57-60] for patients with pT1 tumours and no adverse-risk features[15,16]; however, completion TME is recommended for patients with adverse histopathological features (location in the middle or lower third of the submucosa (SM ≥2), grade III disease, venous invasion, lymphatic invasion, **[Au: please define what L and V refers to here, presumably this is some sort of indicator of local invasiveness?]**) detected in the resected LE specimen. **[Au: without CRT?]** **[Au: please define what L and V refers to here, presumably this is some sort of indicator of local invasiveness?]**) Alternatively, for patients with pT1 and adverse histopathological features **[Au: on biopsy or initial LE?]**, LE plus salvage (or adjuvant) chemoradiotherapy has been explored, although further studies are required to clarify the role of chemoradiotherapy in this setting[17,61].

[Au: The sentence "Further effort should be made to develop expertise for accurate imaging at diagnosis." Has been removed and this information has been incorporated at the start of the paragraph, OK?]

Retrospective and prospective studies have explored various different methods and follow-up schedules, most of which were designed empirically and extrapolated from guidelines on operative management[2-4,6,7,10,65,66]. This heterogeneity was reflected in the large discrepancy of panel participant votes on the most appropriate follow-up schedule after Delphi round 1. The panel recommended that follow-up should comprise serum CEA testing, DRE, rectoscopy, pelvic MRI and chest and abdominal CT, and agreed a specific follow-up schedule in order to avoid inconsistencies (TABLE 2). Local regrowth after initial cCR typically occurs within the first 2–3 years of treatment; therefore, a period of 3 years of monitoring using all available

methods was strongly recommended in order to capture as many events as possible. Precautionary further monitoring in the fourth and fifth years was also recommended.

Regarding individual methods for organ preservation, a meta-analysis of data from 602 patients[32] indicates that serum CEA level is not predictive of local regrowth after an initial cCR; however, serum CEA values were missing in 45% of patients, which should be considered when interpreting these findings. Thus, the predictive value of serum CEA remains unclear and more prospective studies are required to clarify any possible role. MRI and endoscopy have been demonstrated to have complementary roles in determining cCR and predicting local regrowth, although failures have also been reported[67-70]. The role of chest and abdominal CT requires further exploration. We recommend CT every 6–12 months within 1 year of treatment, and annual CT during years 2–5, partly because watching and waiting **[Au: I assume this is what you meant by W&W? Also of note, would it be appropriate to call this 'active surveillance' if 'watching' include regular imaging, for example]** is not routinely established and long-term safety data from randomized studies are currently unavailable. In the IWWD registry analysis, distant metastases were diagnosed in only 8% of 880 patients with a cCR following chemoradiotherapy **[Au: with a cCR following chemoradiotherapy? If possible please clarify?]**, mostly during the first 3 years after treatment[8]. In a systematic review of data from 17 (mostly retrospective) studies including a total of 1,387 patients who received NOM, the maximum risk of distant metastases was 5.5% in patients with a sustained cCR but 23.1% in those with regrowth after an initial cCR, a scenario requiring a high level of caution[71]; similar data were reported from a retrospective comparison of these two approaches[10]. Furthermore, the 5-year incidence of metastases was 28% in poor responders (ypT2–3) after chemoradiotherapy in the GRECCAR2 trial[12] and, thus, special caution is also required in this patient subgroup if LE is explored. Of note, in the updated IWWD report published in December 2020 (after completion of the second round of Delphi process for this Consensus Statement), the probability of remaining free from local regrowth for an additional 2 years if a patient had a sustained cCR for 1 year or 3 years was 88.1% and 97.3%, respectively[72] **[Au: Mention of median follow-up removed – this is adequately implied by the durations mentioned, OK?]**. These data indicate that the intensity of watch and waiting can safely be reduced in patients with a sustained cCR for the first 3 years after treatment **[Au: I removed 'W&W' here as you already used the term 'active surveillance' OK?]**.

One of the main arguments for exploring the efficacy of NOM is the potential for preservation of both sphincter and anorectal function. Previous research demonstrated inferior anorectal function with major LARS after chemoradiotherapy plus surgery (in up to 67% of patients) compared with chemoradiotherapy alone (in up to 36% of patients); however, comparisons between different studies are complicated by the seemingly arbitrary use of different anorectal function scores[35-37,73]. Despite the lack of evidence from randomized cohorts comparing TME surgery **[Au:Specifically TME?]** with NOM or LE, the panel recommended that LARS score[26] is the most practical PRO measure for routine use. The panel also acknowledged the limitations of LARS score (including a lack of specific validation for organ preservation approaches and reporting being limited to symptoms related to bowel dysfunction) and recommended that a new PRO designed and validated specifically for patients with rectal cancer undergoing treatment with organ preservation approaches should instead be developed.

Improvements in QoL constituted one of the main arguments for avoiding surgery, although randomized evidence of the superiority of SCRT and/or chemoradiotherapy for organ preservation is lacking, apart from the TREC study, which demonstrated high levels of organ preservation in 19 of 27 randomized patients (70%), with improvements in QoL after SCRT compared with surgery that were sustained at 36 months of follow-up monitoring **[Au: Details added OK?]**[14]. Other data are mostly derived from series that used a wide variety of different questionnaires to assess QoL and PROs, none of which are validated for use in an organ preservation setting[35-37,73]. Thus, the panel agreed upon several recommendations for future studies: 1) Five QoL and function scales should always be used to document adverse events and how they affect patients; 2) Ten symptomatic toxicity items were selected as the highest priority for evaluation; 3) a specific time schedule for measurement; and 4) a new validated questionnaire, or short extension to an existing instrument (such as EORTC-QLQ CR29 or LARS) should be developed specifically for patients with rectal cancer undergoing organ preservation approaches; **[Au: Edit OK? I think this is what you meant, rather than organ preservation more generally?]** designed to capture both symptomatic toxicities (bowel, urinary and sexual dysfunction) as well as the effects of more intensive active surveillance protocols on QoL, for use both within trials and in clinical practice. Importantly, the aspects of QoL and PROs discussed here are the first international consensus and provide an important foundation for attempts to harmonize outcome measures and data documentation.

Our study has several limitations. First, the panel of trialists was selected arbitrarily **[Au: Please clarify 'by design', do you simply mean it was selected arbitrarily here, or something else?]**, which could lead to bias. Second, the consensus recommendation process was based on online surveys. Holding face-to-face meetings to discuss discrepancies that arose during the process was not possible, and such issues were further clarified through email correspondence. Third, although the threshold of 70% required to reach a consensus has been used previously in several other statements[74-76], this remains an arbitrary threshold that constitutes a methodological limitation of Delphi surveys[77]. Prospective evidence on the safety and effectiveness organ preservation is continuously emerging, and this will likely lead to certain outcome measures requiring adaptation in the future. Thus, the present consensus should serve as guide to enable further augmentation rather than to fully replace clinical judgment. Several key questions and uncertainties regarding organ preservation approaches for patients with rectal cancer remain to be addressed (BOX 3). Fourth, only physicians and researchers **[Au: Is this entirely accurate? (I think you mentioned that one expert is in fact a bioinformatician). Would it be better to say 'physicians and researchers' here?]** participated in the surveys, whereas other stakeholders (such as industry sponsors and patient representatives) were not involved. This limited inclusiveness was considered essential given that organ preservation constitutes a new area of clinical investigation and that consensus on several highly complex key outcome measures was needed as a first step. This project will, in the near future, be extended to a wider group comprising multiple stakeholders including patient representatives **[Au: or their representatives?]** in order to achieve greater consensus, which will also include the development of a new EORTC organ-preservation-specific QoL set of items or module. Indeed, patients often have differing perceptions of what they consider most relevant in discussions about their treatment, and differences have been described between the importance assigned by patients and clinicians to specific clinical and functional outcomes in the context of organ preservation[35,78,79].

[H1] Conclusions

In summary, to the best of our knowledge, this is the first international expert consensus statement to provide comprehensive and rigorous recommendations on the key outcome measures to be assessed and reported both in trials and in routine clinical practice for patients with rectal cancer who are eligible for organ preservation. Implementation of this consensus has important implications as it will promote the harmonized recording and reporting of data from organ preservation strategies in patients with rectal cancer, thus improving the

interpretation and comparison of new trial findings in addition to the standardization of routine clinical practice.

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Author contributions

E.F., A.A., A.G., D.S.M. and C.R. contributed to the literature search and preparation of the Delphi questionnaires. All authors contributed to writing and editing of the manuscript, and approved the final manuscript. **[Au: Details on joint authorship removed – these are typically only presented in the main author list, OK?]**

Competing interests

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Peer review information

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Table 1. Variations in outcome measures across different trials of organ preservation approaches in rectal cancer.

[Au: Table title shortened to one line, as per journal style preferences, OK?]

[Au: Table edited to comply with journal style preferences, OK?]

Study details[a,b]	Disease stage and other clinical features	Treatment schedule	RA time point	Primary end point
TREC, phase II[14] *n* = 55	cT1–T3N0, maximum diameter ≤30 mm	TME vs SCRT followed by TEM	9–11 weeks after treatment start	Recruitment rate at 12, 18 and 24 months
STAR-TREC, phase III (NCT02945566) *n* = 460	cT1–T3bN0, ≤10 cm AV	TME or LE vs CRT followed by NOM/LE vs SCRT followed by NOM/LE (NOM for patients with a cCR, TEM for patients with a PR, TME in patients with a poor response)	12 and 20 weeks after treatment start	30-month organ preservation
WW3, phase II (NCT04095299) *n* = 111	cT1–T3bN0, ≤10 cm AV	CRT vs CRT with SIB (NOM or LE for patients with a cCR, TME for those with a PR)	16 weeks after treatment start	2-year organ preservation
OPERA, phase III (NCT02505750) *n* = 236	cT2–T3bN0–1, ≤10 cm AV	CRT followed by EBRT boost vs CRT followed by brachytherapy boost (NOM or LE for patients with a cCR, TME for patients with a PR)	14 and 20–24 weeks after treatment start	3-year organ preservation
HERBERT-II, phase III (NL7795) *n* = 106	Elderly and frail patients (unfit for surgery due to co-morbidity, unlikely to maintain activities of daily living) with **[Au: Please objectively define 'elderly and frail'?]** cT1–3N0–1, ≤10 cm AV	EBRT vs EBRT plus brachytherapy boost	26 weeks after treatment end	cCR rate at 26 weeks
GRECCAR12, phase III (NCT02514278) *n* = 218	cT2-T3N0-1, ≤10 cm AV	mFOLFIRINOX followed by CRT vs CRT (LE for patients with a good response, TME for patients with a poor response)	24 weeks after treatment start	12-month organ preservation
ACO/ARO/AIO-18.1, phase III (NCT04246684) *n* = 702	cT3c–T4N0–2, ≤12 cm AV	SCRT followed by consolidation FOLFOX and TME surgery (or NOM in patients with a cCR) vs CRT followed by consolidation FOLFOX and TME (or NOM in patients with a cCR)	24 weeks after treatment start	3-year organ preservation
OPRA[22,23], phase II *n* = 300	cT3–T4N0–2, ≤6 cm AV	Induction mFOLFOX6 followed by CRT and surgery or NOM vs CRT followed by consolidation mFOLFOX6 and surgery or NOM	34–38 weeks after treatment start	3-year DFS
TRIGGER[33], phase II/III *n* = 90	cT3c–T4N0–2, ≤15 cm AV	CRT followed by surgery and adjuvant CAPOX or FOLFOX vs CRT followed by either NOM (mrTRG I–II) or CAPOX or FOLFOX (mrTRG	12, 24 and 36–38 weeks after	Recruitment rate (phase II); 3-year

		III–IV) and restaging with subsequent NOM or surgery (depending on mrTRG at restaging)	treatment start	DFS (phase III)
Brazilian[c], phase III (NCT02052921) *n* =150	cT3–T4N0–2, ≤10 cm AV	CRT followed by W&W vs 5-FU-containing CRT followed by TME after a cCR at 12 weeks post-CRT	12 weeks after treatment start	3-year DFS
TESAR, phase II (NCT02371304) *n* = 302	pT1–2cN0, ≤10 cm AV	TME vs LE followed by CRT	NA	3-year LRR
MORPHEUS, phase II (NCT03051464) *n* = 40	cT2–T3bN0, ≤10 cm AV	CRT followed by EBRT boost vs CRT followed by brachytherapy boost (NOM in patients with a cCR: TME in patients with a PR)	14 weeks after treatment start	2-year organ preservation
TESS, phase II, (NCT03840239) *n* = 168	cT3–4aN0–2, ≤5cm AV	Induction CAPOX followed by CRT vs CRT (NOM in patients with a cCR; LE or TEM in patients with a PR; TME in patients with a poor response)	20–24 weeks after treatment start	Sphincter preservation (absence of a stoma) at 18 months
APHRODITE, phase II (ISRCTN16158514) *n* = 104	cT1-T3bN0, ≤10 cm AV	CRT vs CRT with SIB (NOM in patients with a cCR)	24 weeks after treatment start	cCR at 6 months
GRECCAR2[9,12], phase III *n* = 186	cT2-3N0–1, ≤5 cm AV, maximum initial size 4 cm, residual tumour size ≤2 cm	CRT followed by local excision vs preoperative CRT followed by TME	12–14 weeks after treatment start	2-year composite end point
ELRR vs LTME, phase III (NCT01609504) *n* = 100	cT2N0, ≤6 cm AV	CRT followed by LE vs CRT followed by TME	NA	Local and distant recurrence (time-point unspecified)

AV, anal verge **[Au:OK?]**; CAPOX, capecitabine and oxaliplatin; cCR, clinical complete response; CRT, chemoradiotherapy; DFS, disease-free survival; EBRT, external beam radiotherapy; FOLFOX, folinic acid, 5-fluorouracil and oxaliplatin; LE, local excision; LRR, locoregional recurrence; mFOLFIRINOX, modified folinic acid, 5-fluorouracil, irinotecan and oxaliplatin regimen; mFOLFOX6, modified folinic acid, 5-fluorouracil and oxaliplatin; mrTRG, magnetic resonance-based tumour regression grading; NOM, non-operative management; PR, partial response; RA, response assessment; SIB, simultaneous integrated radiation boost **[Au:OK?]**; SCRT, short-course radiotherapy; TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; TdrTF, time to disease-related treatment failure; TNT, total neoadjuvant treatment; W&W, watch and wait. [a]Only randomized studies were included in this table. [b]Tumour location, especially for rectal cancers close to the anal sphincter where abdominoperineal resection with permanent stoma is often the only available surgical option, can influence the use of CRT as a method of achieving organ preservation in patients with early stage disease, as reflected in many trials that included patients with stage cT2 rectal cancer. [c]The Brazilian trial was closed prematurely (May 2020) owing to poor patient accrual. This was the first clinical trial to randomize patients with a cCR after preoperative CRT to W&W vs surgery, and used DFS as a primary end point.

Table 2. Consensus [Au: OK to change to 'Recommended' or 'Consensus' here?] follow-up methods and intervals for organ preservation strategies.

[Au: Intervals have been changed from '3X' etc to specify monthly intervals OK – I assume these intervals are intended to be spread evenly across the follow-up period?]

Year	Serum CEA	DRE	Endoscopy	Pelvic MRI	Chest and/or abdominal CT
1	4 months	3–4 months	3–4 months	3–4 months	6 months
2	4 months	3–4 months	3–4 months	3–4 months	Annually
3	4 months	6 months	6 months	6 months	Annually
4	6 months	6 months	6 months	6 months	Annually
5	6 months	6 months	6 months	6 months	Annually

First follow-up assessments typically occur at 6–8 weeks following completion of preoperative or definitive treatment. CEA, carcinoembryonic antigen; DRE, digital rectal examination. **[Au: FYI We consider MRI and CT to be common abbreviations, no need to define here, OK?]**

FIGURE LEGENDS

Figure 1. The article selection process. Seven key outcome measures of organ preservation strategies in rectal cancer were identified following a thorough literature search.

Figure 2. Summarized overview of the Delphi process.

[Au: I suggest that figures 1 and 2 are presented as supplementary information, OK?]

Figure 3. Representative examples of RA time-points to determine cCR and primary end points in organ preservation trials involving patients with rectal cancer [Au: Title edited for brevity, OK?]. The different preoperative or definitive treatment options are characterized by variable durations and time to response assessment (RA), and therefore time to making a decision on organ preservation strategies versus total mesorectal excision (TME) surgery, as illustrated below the *x* axis. Examples of corresponding clinical trials, including details on the TNM stages of the enrolled patients and the treatment arms are shown on the left side in dark blue boxes (also summarized in TABLE 1**,** which, similar to the figure, only includes randomized studies). The time-point of RA and, hence, the determination of clinical complete response (cCR) used in the different trials is indicated by orange boxes. The primary end point of the trials is shown on the right side in light blue boxes. The advent of total neoadjuvant therapy, often with a highly variable treatment duration, has added to the complexity of selecting the optimal RA time-point. AV, anal verge; CEA, carcinoembryonic antigen; CRT, chemoradiotherapy; cTNM, clinical tumour/node/metastasis staging; DFS, disease-free survival; DRE, digital rectal examination; LE, local excision; NOM, non-operative management; OP, organ preservation; SCRT, short-course radiotherapy; SIB, simultaneous integrated boost of radiotherapy.

BOX 1. Definitions of clinical end points for organ preservation strategies in rectal cancer.

[Au: This table has been converted to a BOX owing to journal style preferences, OK?]

[Au: These definitions have been minimally edited in order to make these more accessible to lay readers. Please feel free to revert all or any of these changes if you feel they detract from the intended meaning.]

- **Organ preservation**
  - Rectum intact, owing to no radical total mesorectal excision (TME), no locoregional regrowth unless amenable to limited, curative (R0) salvage surgery by local excision (LE) and no permanent stoma (including a never reversed protective stoma, or a stoma owing to toxicities and/or poor functional outcomes).
- **Clinical complete response (cCR)**[a]
  - DRE and rectoscopy: no palpable tumour material present, no residual tumour material or only a small residual erythematous ulcer or scar.
  - MRI[b]: substantial downsizing with no observable residual tumour material, or residual fibrosis only (with limited signal on diffusion-weighted imaging), sometimes associated with residual wall thickening owing to oedema, no suspicious lymph nodes.
  - Endoscopic biopsy: not mandatory to define cCR, biopsy should not be performed, especially if the DRE, rectoscopy and MRI criteria for cCR are all fulfilled.
- **Near cCR (ncCR)**
  - Digital rectal examination (DRE) and rectoscopy: the presence of small and smooth regular irregularities including residual ulcer, or small mucosal nodules or minor mucosal abnormalities, with mild persisting erythema of the scar.
  - MRI: obvious downstaging with residual fibrosis but heterogeneous or irregular aspects and signal or regression of lymph nodes with no malignant enhancement features, but with a size >5 mm
  - Endoscopic biopsy[c]: not mandatory to define near cCR.
- **Poor response**
  - The presence of a palpable tumour mass and visible macroscopic tumour and/or lack of regression of involved lymph nodes (patients that do not fulfill the criteria for either a cCR or near clinical complete response (ncCR)).
- **Locoregional regrowth**
  - An event involving either the bowel wall, mesorectum and/or pelvic organs that occurs after an initial cCR and watch and wait (W&W)
- **Local regrowth**
  - An event involving the bowel wall only that occurs after an initial cCR and W&W
- **Locoregional recurrence**
  - An event involving either the bowel wall, mesorectum and/or pelvic organs that occurs after LE or TME
- **Local recurrence**
  - An event involving the bowel wall only that occurs after LE or TME **[Au: For this and the previous three points, would it be possible to define 'an event' in more detail. Presumably this would be 'a recurrence event' or possibly 'a detectable tumour mass' or similar?]**
- **TME-free disease-free survival (DFS)**[d]
  - Time from randomization to one of the following events: radical TME owing to an incomplete response at restaging, any locoregional regrowth after initial cCR requiring salvage TME, any locoregional recurrence after LE or non-salvageable regrowth (a regrowth that cannot be removed with an R0 resection), the development of distant metastases or death (all cause), whichever occurs first.

- **Organ preservation-adapted DFS**[e]
    - Time from randomization to one of the following events: no resection of primary tumour owing to local disease progression or the patient being unfit for surgery; nonradical resection of the primary tumour (R2 resection); locoregional recurrence after R0/1 resection of the primary tumour; nonsalvageable local regrowth (no operation or, alternatively, only R2 salvage resection possible) in patients undergoing non-operative management (NOM); any distant metastatic disease before, at, or after surgery or NOM; the occurrence of a second primary colorectal cancer, a second primary other cancer, treatment-related death, death from the same cancer, death from another type of cancer or non-cancer related death.

[a]All criteria of DRE, including rectoscopy and MRI, should be fulfilled to define a cCR. [b]Gadolinium contrast medium is no longer compulsory for MRI conducted with the intention of defining a cCR. [c]In contrast to the study by Martens et al.[5], in which biopsy sampling was suggested for patients with a ncCR (showing dysplastic changes), the panel did not recommend mandatory biopsy sampling to define ncCR in the present Consensus Statement owing to the risks of a false-negative result and a lack of added diagnostic value. [d]Consensus was not reached for the definition of TME-free DFS that was provided separately by the primary investigator of the OPRA trial (J.G.A.). [e]If a salvage operation for the local regrowth is performed with curative intent (R0/1), it should not count as an event. If, however, no operation, or only an R2 resection is possible, and/or disease recurrence occurs after salvage surgery, this should count as an event.

BOX 2. Consensus recommendations on the optimal RA time-points for cCR determination.

- Standard short-course radiotherapy (SCRT; duration of 5 days) or chemoradiotherapy (CRT; duration of ~6 weeks) for patients with early stage tumours.
    - A two-step approach is recommended, involving initial measurement at 12 weeks from the start of treatment and then, in patients with a near clinical complete response (ncCR) at initial assessment, a repeat assesment at 16–20 weeks should be used to determine clinical complete response (cCR), as performed in the STAR–TREC trial (NCT02945566). **[Au: To clarify, should only patients with a ncCR undergo repeat assessment? for example, or does this recommendation also apply to patients with stable disease at 12 weeks?]**
- CRT followed by brachytherapy (duration of 12 weeks).
    - cCR should be determined at 14 weeks after start of treatment and should be repeated at 20–24 weeks in patients with a ncCR at initial assessment, as performed in the OPERA trial (NCT02505750).
- Total neoadjuvant treatment (TNT) with CRT and either induction or consolidation chemotherapy (duration of 16–20 weeks).
    - cCR should be determined at 24 weeks after start of treatment, as performed in the GRECCAR12 (NCT02514278) and ACO/ARO/AIO-18.1 (NCT04246684) trials.
- TNT with SCRT or CRT followed by prolonged consolidation chemotherapy (duration: 26-34 weeks).
    - cCR should be determined at 34–38 weeks after start of treatment, as performed in the OPRA[22] and TRIGGER trials[33].

RA, response assessment. [a]The panel recommended that cCR should be determined from the start of treatment. Owing to variations in preoperative treatment design and duration across the different trials, recommendations regarding a time-point enabling the earlier detection of patients with a poor response before the recommended time-point cannot be provided as a result of insufficient evidence. Nevertheless, caution is needed especially in patients with tumours featuring certain high-risk characteristics (such as advanced cT stage[32]), and selective **[Au: selective?]** earlier imaging could be advocated to enable the identification of poor responders who might have disease progression during preoperative treatment in order to offer immediate surgery.

BOX 3. Key outstanding questions and uncertainties regarding the use of organ preservation approaches in patients with rectal cancer

- Which criteria should we use to include patients in studies of organ preservation approaches?
- Can modern technologies (such as artificial intelligence, including neural networks) help to improve the accuracy of rectal cancer imaging at initial diagnosis, and thus enable more accurate assessments of tumour responses to treatment?
- How long is it oncologically safe and meaningful to wait before assessing tumour response and determining whether or not a clinical complete response (cCR) has occurred, especially after prolonged total neoadjuvant therapy (TNT)?
- What is the role of local excision (LE) as a primary treatment, and for selected patients with good responses to chemoradiotherapy?
- What is the optimal timing of LE in the context of each type of **[Au: each type of?]** response (cCR versus near-cCR versus residual disease)?
- Which criteria should we use to advocate LE for organ preservation?
- What is the optimal surgical method of managing regrowth after an initial cCR?
- Can we define robust selection criteria to guide safe reductions in the frequency **[Au: by 'intensity' did you mean 'frequency' here…ie reducing the number of imaging appointments, or something else?]** of follow-up imaging in patients with a cCR?
- What are the long-term effects of the various different strategies used to deliver 'intended' organ preservation (such as selective chemoradiotherapy with LE, radiotherapy dose escalation, TNT, and others) on quality of life, organ function as well as both the short-term and long-term toxicities?
- Which items and function scales should be included in a patient-reported outcome (PRO) measure designed specifically for patients receiving treatment with an organ preservation approach?
- Can circulating biomarkers (such as serum carcinoembryonic antigen or cell-free DNA) be used to predict a cCR and/or tumour regrowth after an initial cCR, enabling treatment to be tailored for each patient?