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SUPPLEMENTARY MATERIAL

Pathological specimen processing for assessing pCR and TRG

Care must be taken to ensure consistent dissection and block selection methods by Pathologists, and also that this term means achievement of stage ypT0 ypN0. Inclusion of just ypT0 cases artificially elevates the pathological complete response (pCR) rate. The 8th edition of the TNM classification has recommended the use of the modified Ryan 4 group classification for assessing tumor regression grading (TRG) that has become the gold standard method[1,2].

Also, the Royal College of Pathologists (RCPath) has developed the cancer datasets for histopathological reporting to facilitate accurate and consistent grading and staging of colorectal cancer in the UK (weblink: https://www.rcpath.org/uploads/assets/c8b61ba0-ae3f-43f1-85ffd3ab9f17cfe6/G049-Dataset-for-histopathological-reporting-of-colorectal-cancer.pdf).

Definition of near clinical complete response

The term **"near cCR**" refers to tumors that show marked response to CRT/SCRT, but do not fulfill all criteria of cCR at the time of response assessment The definition of near-cCR as proposed by Martens et al. [4] is as follows: 1) Small and smooth regular irregularity on DRE; 2) Residual ulcer, or small mucosal nodules or minor mucosal abnormalities, with mild persisting erythema of the scar; 3) Regression of lymph nodes with no malignant enhancement features but size >5 mm on MRI. Patients with near cCR may either be reassessed in further, e.g., 3 months, or undergo limited surgical procedures, such as local excision (LE) and transanal endoscopic microsurgery (TEM).

Supplementary Table 1. Variable clinical, endoscopic, and imaging criteria based on the largest series and guidelines to define clinical complete response after neoadjuvant/definitive treatment

Study	Time interval from completion of treatment to response assessment	Clinical, endoscopic, imaging criteria used to define clinical complete response
Habr-Gama et al. (2004)[5]	8 weeks	DRE: normal, no palpable tumor Endoscopy: No residual ulcer, mucosal whitening +/- telangiectasia, negative biopsy CT-abdomen and pelvis/ chest x-ray: no residual tumor detectable
Martens et al. (2016)[4]	6-8 weeks	DRE: no palpable tumor, when initially palpable with DRE Endoscopy: No residual tumor and white scar; negative biopsy from scar (biopsy not mandatory) MRI (T2-weighted): substantial downsizing with no residual tumor, or residual fibrosis, or residual wall thickening because of edema; no suspicious lymph nodes MRI (diffusion weighted): low signal on high b-value
Van der Valk et al. (2018)[6]	Not specifically reported	No residual tumor on DRE, endoscopy, biopsy Imaging according to local policies (very heterogeneous criteria and combinations)
Smith et al. (2019)[7]	Not specifically reported	DRE: no palpable tumor No visible pathology other than flat scar MRI: only used after 2013
ESMO guidelines (Glynne-Jones et al. 2017)[8]	12 weeks after start of neoadjuvant treatment	DRE: no palpable tumor or irregularity Endoscopy: no visible lesion except scar, telangiectasia, or mucosal whitening, negative biopsy from the scar MRI or ERUS: no residual tumor at primary site or lymph nodes Normalised CEA-level (< 5 ng/mL), if initially elevated
NCCN guidelines (2019)[9]	Not specifically reported	No evidence of residual disease on DRE, rectal MRI, endoscopy

Abbreviations: DRE, Digital rectal examination; CT, computer tomography; MRI, magnetic resonance imaging; ERUS, endorectal ultrasound

Supplementary Table 2. Follow-up schedule for non-operative management as suggested by the Maastricht/NKI group

Year	CEA	DRE	Endoscopy	MRI pelvis	CT chest/abdomen
1	4×	4×	4×	4×	2×
2	4×	2×	2×	2×	1×
3	4×	2×	2×	2×	1×
4	2×	2×	2×	2×	1×
5	2×	2×	2×	2×	1×

Abbreviations: CEA, carcinoembryogenic antigen; DRE, digital rectal examination; MRI, magnetic resonance imaging; CT, computer tomography

Supplementary Table 3. Primary clinical endpoint in randomised trials assessing the role of adjuvant chemotherapy

Randomised trials	Patient number	Treatment schedule	Primary clinical endpoint
ADORE[10]	321	Preoperative 5-FU CRT followed by surgery and adjuvant chemotherapy using 5-FU vs FOLFOX	DFS
EORTC 22921[11]	1011	Preoperative 5-FU CRT vs RT alone followed by surgery and adjuvant 5-FU chemotherapy vs follow-up	OS
I-CNR-RT[12]	655	Preoperative 5-FU CRT followed by surgery and adjuvant 5-FU chemotherapy vs follow-up	OS
CHRONICLE[13]	113	Preoperative 5-FU or Capecitabine CRT followed by surgery and adjuvant XELOX chemotherapy vs follow-up	DFS
PROCTOR/SCRIPT[14]	437	Preoperative 5-FU CRT (or SCRT) followed by surgery and adjuvant 5-FU or capecitabine chemotherapy vs follow-up	OS

Abbreviations: 5-FU, 5-Fluorouracil; CRT, chemoradiotherapy; XELOX, capecitabine/oxaliplatin; SCRT, short-course radiotherapy; DFS, disease-free survival; OS, overall survival

Supplementary Table 4. Clinical endpoints and their characteristics

Endpoint	Advantages	Disadvantages	Comment
Overall survival (OS)	Standard measure of clinical benefit; easy assessment; availability also through patient registries; universal acceptance of clinical benefit	Requires large patient numbers and long-term follow-up; costly; can be affected by confounding factors such as treatment crossover, salvage therapy, comorbidities and cancer-unrelated death	Previously use as primary endpoint in rectal cancer randomized trials; masking is not required
Disease-free survival (DFS)	Earlier endpoint; requires smaller size and shorter-follow-up than OS; masked review recommended;	Lack of statistical validation as a surrogate endpoint for OS; variable definition and measurement among trials; open-label trials can lead to statistical bias;	Previously used as primary endpoint in randomized trials; adjuvant setting; 2-year DFS suggested as surrogate endpoint
Locoregional recurrence (LRR)	Earlier endpoint; requires smaller size and shorter follow-up than OS; clear defintion	Subject to assessment bias; difficult to reflect benefit in the modern era due to excellent local control; lack of statistical validation as a surrogate endpoint for OS; depends on frequency of follow-up examination	Previously used as primary endpoint in randomized trials; should not be preferred as primary endpoint in future trials; commonly assessed as part of DFS

Distant control	Earlier endpoint; requires smaller size and shorter follow-up than OS; clear defintion	Subject to assessment bias; lack of statistical validation as a surrogate endpoint for OS; depends on frequency of follow-up examination	Lack of use as primary endpoint in randomized trials; should not be preferred as primary endpoint in future trials; commonly assessed as part of DFS
Pathological complete response (pCR)	Early assessment; small patient numbers required; feasible in single-arm trials;	Reflective of benefit only in a patient subgroup; not a direct measure of clinical benefit; subject to immortal time bias; was not shown to be surrogate for overall survival	Requires surgical intervention; currently used in single arm or randomized trials;
Complete clinical response (cCR)	Early assessment; small patient numbers required; feasible in single-arm trials;	Reflective of benefit only in a patient subgroup; not a direct measure of clinical benefit; subject to immortal time bias;	Main endpoint in organ-preservation; currently used in single arm or randomized trials; masking should be preferred in comparative studies; suggested as early surrogate endpoint; lack of consensus on the definition of cCR when used as clinical endpoint
Patient-reported outcomes (PROMs)	Reflect how patient feels and functions; objective assessment of patient perspective regarding treatment and clinical benefit	Challenging to interpret regarding its clinical relevance; masking can be difficult; lack of validated assessment tools; multiple evaluations as essential; commonly reported for the entire patient group/arm rather than individual patient	Recently introduced in small masked studies; lack of large trial data

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