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SPECIAL ARTICLE

Localised rectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up☆

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INTRODUCTION

This ESMO Clinical Practice Guideline (CPG) focusses on localised rectal cancer. The management of advanced and metastatic rectal cancer is covered in the ESMO CPG on metastatic colorectal cancer (CRC).[1-3]

INCIDENCE AND EPIDEMIOLOGY

Rectal cancer has an incidence rate of 13.9 cases per 100 000 per year in males and 8.6 cases per 100 000 in females, reflecting almost one-third of all CRCs.[4] Incidence is increasing, particularly in individuals aged 50-64 years, with rectal cancer accounting for 4 out of 10 CRCs in this age group.[4] Notably, mortality rates have decreased in countries with better access to screening, early diagnosis and high levels of care. Delayed diagnosis and slow adoption of modern therapy may, at least in part, explain the higher mortality rates in central and eastern European countries. Lifestyle factors, including excess body weight, obesity, consequent diabetes, lack of exercise and dietary habits, which are associated with CRC, have influenced these trends.

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DIAGNOSIS, PATHOLOGY AND MOLECULAR BIOLOGY

Diagnosis

Rectal cancer can present with symptoms; however, it is increasingly being identified via population screening programmes. After a positive screening test, colonoscopy can provide an accurate histological diagnosis of the primary tumour via biopsy or, if appropriate based on pit pattern assessment during advanced endoscopy, direct local excision (LE).

Pathology

Subsequent diagnostic work-up focusses on establishing the locoregional status. The diagnostic work-up for rectal cancer is summarised in Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.05.528. Depth of tumour invasion can determine whether the tumour is locally excisable, surgically resectable or requires neoadjuvant therapy. Further assessment of locally excised tumours can determine the risk of lymph node metastases and/or local recurrence. Risk features include tumour size, invasion depth, type, grade, presence of tumour budding, lymphatic and vascular invasion and status of resection margins. The presence of two or more of these features serves as an indication for radical resection, although this depends on national guidelines.

Molecular biology

Assessment of mismatch repair (MMR) proteins on biopsies or LE specimens can identify patients with sporadic microsatellite instability-high (MSI-H) tumours or Lynch

syndrome, who may benefit from treatment with immunotherapy and, in the case of Lynch syndrome, referral for genetic counselling [see ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) for further details — Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.05.528].

As neoadjuvant therapy can disrupt MMR staining or diminish the number of evaluable tumour cells, baseline biopsy material is preferred. Analysis of *RAS*, *BRAF* V600E, *NTRK* and human epidermal growth factor receptor 2 (HER2) status currently has no impact on the treatment of localised tumours.

Recommendations

- MSI and/or MMR status should be assessed in all patients at diagnosis using biopsy material [I, A; ESCAT score: I-B].
- Analysis of *RAS*, *BRAF* V600E, *NTRK* and HER2 status currently has no impact on the treatment of localised tumours and cannot be recommended [IV, D].

STAGING AND RISK ASSESSMENT

Increasing age, comorbidities and decreasing functional reserves are associated with higher early post-operative mortality and worse toxicity from radiotherapy (RT) and chemotherapy (ChT); therefore, for patients aged >70 years, formal geriatric assessment or screening tools for frailty may be useful before treatment.[5] Preoperative colonoscopy (to the caecal pole) is standard. Rigid rectoscopy may be used to determine tumour level; however, magnetic resonance imaging (MRI) has largely replaced rigid rectoscopy as it provides accurate information on primary tumour level and the relationship with other pelvic structures and anatomical landmarks. In case of obstruction, virtual colonoscopy can exclude synchronous colonic tumours. If no preoperative (virtual) colonoscopy was carried out, completion colonoscopy should be planned within 6 months after surgery at the latest.

MRI allows stratification for differentiated treatment of standard or high-risk rectal cancer.[6,7] Endorectal ultrasound (ERUS) outperforms MRI for T staging of localised tumours [clinical (c)T1 versus cT2]; however, its limited field of view prevents a thorough evaluation of the mesorectal and lateral compartment. MRI is, therefore, a valuable adjunct to ERUS in the work-up of localised tumours. A meta-analysis concluded that MRI is the most accurate method to identify the relationship between the tumour and the mesorectal fascia (MRF) and the involvement of the MRF.[8] Nodal staging is difficult with MRI and a 10 mm size cut-off as a criterion for malignancy with ERUS, computed tomography (CT) or MRI is inaccurate.[8] The addition of morphological criteria, such as irregular border and heterogeneous signal intensity, can improve the detection of node-positive (N+) disease but MRI nodal staging remains a challenge.[9] MRI high-risk features, such as tumour deposits, extramural venous invasion (EMVI+) and lateral lymph node involvement (LN+), are known to be independent poor prognostic indicators, but do not correlate well with histology.[10] Enlarged lateral lymph nodes (≥7 mm) with malignant features have been associated with a higher 4-year lateral local recurrence rate (17.0% versus 0% for no enlargement) and a higher 4-year distant metastasis rate (36.4% versus 24.4% for no enlargement) on univariate analysis, although there was no negative impact on overall survival (OS).[11]

The presence of high-risk features on MRI [using criteria from the RAPIDO trial: T4a, T4b, MRF invasion (MRF+), cN2 (≥4 suspicious nodes), EMVI+ and lateral lymph node enlargement of ≥7 mm[12]] should be recorded in MRI reports to identify patients who would benefit from total neoadjuvant therapy (TNT). Tumour deposits have been associated with shorter disease-free survival (DFS) and may be regarded as a high-risk factor if validated by further studies.[13]

CT of the chest and abdomen is crucial to rule out distant metastases. Positron emission tomography—CT is not used routinely for distant staging; however, it is helpful in selected patients with uncertain CT findings.[14]

Rectal cancer can be clinically classified according to the eighth edition of the Union for International Cancer Control TNM (tumour—node—metastasis) system[15] (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2025.05.528). T3 tumours can be further classified according to the criteria described in Supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2025.05.528.

Recommendations

- From diagnosis, a dedicated multidisciplinary team (MDT) of expert medical oncologists, radiologists, surgeons, radiation oncologists and pathologists should attend regular meetings to discuss patients [I, A]. Clinical guidelines should be considered in the decision-making process [I, A].
- A full medical history and physical examination, including digital rectal examination (DRE), complete blood count, liver and renal function tests and measurement of serum carcinoembryonic antigen (CEA), should be carried out [III, A].
- Preoperative colonoscopy to the caecal pole and MRI are recommended to determine tumour level [III, A].
- ERUS is recommended for T staging of localised tumours (cT1 versus cT2) [II, A].
- MRI is mandatory as part of the staging work-up to stratify for risk-adapted treatment [I, A]. MRI is a valuable option for staging localised tumours [I, B].
- MRI reports should include descriptions of tumour infiltration depth, node status, lateral lymph nodes, EMVI status and MRF status [III, A].
- The recommended high-risk criteria are cT4a or cT4b, MRF+, cN2 (≥4 suspicious nodes), EMVI+ and lateral lymph node enlargement of ≥7 mm [I, A].
- CT of the chest and abdomen is recommended for distant staging [III, A].

MANAGEMENT OF LOCALISED DISEASE

Stage I-III rectal cancer is treated with curative intent. Tumours in the lower and middle third of the rectum are particularly prone to surgical complications and local recurrence; therefore, prevention of recurrence is an important therapeutic goal. For carcinomas in the upper third of the rectum, the benefit of RT is very limited; therefore, a procedure analogous to the approach for colon carcinoma may be preferred.

Quality-assured imaging detects patients with a very low risk of local recurrence, so that neoadjuvant RT or chemoradiotherapy (CRT) can be disregarded in selected patients. The previous conservative criteria for the optional omission of RT [e.g. T3 with a maximum infiltration of 5 mm (T3a or T3b) into the perirectal fat] can be expanded according to data from the OCUM study.[16] OCUM was a large phase II study with a prospectively defined treatment algorithm, in which neoadjuvant CRT was administered only to patients whose tumour was (i) located in the middle third of the rectum and had a threatened circumferential resection margin (CRM) ($\leq$1 mm) or was T4, or (ii) located in the lower third and was T3 or T4.[16] The rate of local recurrence in patients without pretreatment (i.e. primary resection) was 2.9%.

A single standard therapy for clinical stage II or III disease can, therefore, no longer be defined. Intentions of therapy (e.g. intended organ preservation, reduction of toxicities) play a major role in the choice of treatment. For certain patient subgroups (e.g. T3 N1 tumour with free CRM in the middle third of the rectum), several evidence-based treatment options may be available. In addition, neoadjuvant CRT and short-course RT (SCRT) can be supplemented by neoadjuvant ChT. This TNT strategy may be used in high-risk tumours (e.g. T4) or in the setting of intended organ preservation. Thus, the following sections on RT cover conventional CRT and SCRT as well as TNT, and describe their use in the neoadjuvant and organ preservation settings separately.

Algorithms for the management of localised rectal cancer in the upper third of the rectum are shown in Figures 1 and 2, and algorithms for the management of localised rectal cancer in the middle or lower thirds of the rectum are shown in Figures 3 and 4.

CRT and SCRT

Risk-adapted treatment when surgery is intended.

cT2 N0 or N+. Upfront total mesorectal excision (TME) is the standard treatment; however, LE after preoperative SCRT or CRT has been evaluated as an alternative to TME for cT2 tumours $<$4 cm, with minimal adverse impact on anorectal function 1 year after surgery and interesting short-term oncological outcomes.[17-19] This strategy is not routinely recommended but may be used for elderly or frail patients at high surgical risk, or for well-informed patients achieving a good response to CRT.

cT3 N0 or N1, lower and middle third. Preoperative CRT or SCRT reduces local recurrence rates and can be used for tumour downsizing to facilitate TME and resection with no tumour at the margin (R0); however, routine delivery of preoperative CRT or SCRT to all patients with imaging-predicted cN+ disease has become controversial due to its poor accuracy if categorised by nodal size alone.[20] Furthermore, data suggest a low risk of local recurrence in patients with MRF-negative tumours and clear levators in the case of good-quality TME and *en bloc* removal of the mesorectal nodes.[16,21] It is the responsibility of the surgeon and the pathologist to demonstrate that consistent, good-quality TME per the MERCURY classification and R0 are being achieved.[21,22] No differences in oncological outcomes between CRT and SCRT were reported in two prospective studies offering preoperative therapy to patients with cT3-cT4 or N+ disease.[23,24] In the randomised phase III Stockholm-III study, TME carried out 4-8 weeks after SCRT was associated with a lower risk of post-operative complications compared with immediate surgery after SCRT.[25]

Risk-adapted treatment when organ preservation is intended.

cT1-cT2 N0. Multimodal treatment strategies for patients with rectal cancer are increasingly incorporating a watch-and-wait approach for organ preservation. This is an option for patients with a clinical complete response (cCR) after neoadjuvant treatment to avoid the morbidities associated with radical surgery, preserve anorectal function and maintain quality of life.[26,27] Organ preservation in rectal cancer treatment has been increasingly explored in recent decades.[28] Since Habr-Gama et al. demonstrated the feasibility of a selective organ preservation approach in patients with a cCR following standard CRT,[29] several studies, including the large International Watch and Wait Database analysis in $>$800 patients,[30] confirmed that deferral of surgery in selected patients with a cCR is feasible, oncologically safe and associated with improved anorectal function, genitourinary (GU) function and quality of life.[30-35]

Patients with localised disease may be ideal candidates for organ-preserving strategies. If organ preservation is the aim in cT1-cT2 N0 disease, then SCRT or CRT can be considered; however, LE may be required in some patients with a near cCR.[31,36-38] In the prospective TREC trial,[36] SCRT followed by LE led to complete response in 30% and 41% of randomised and nonrandomised patients with cT1-cT2 N0 tumours, respectively, which is comparable to the 30%-45% reported with CRT in the ACOSOG Z6041[39] (only enrolled cT2 N0) and GRECCAR-2[40,41] (enrolled cT2-cT3 $\leq$4 cm N0) trials. The recently completed phase II/III STAR-TREC trial (NCT02945566) compared rates of organ preservation after SCRT versus CRT in patients with cT1-cT3b N0 $\leq$4 cm tumours; publication of the study results is awaited.

cT2 N+ and cT3. RT dose escalation using endorectal brachytherapy after standard external CRT can be offered to patients with cT2-cT3 N0-N1 tumours if organ preservation is the aim. The phase III OPERA trial randomised patients

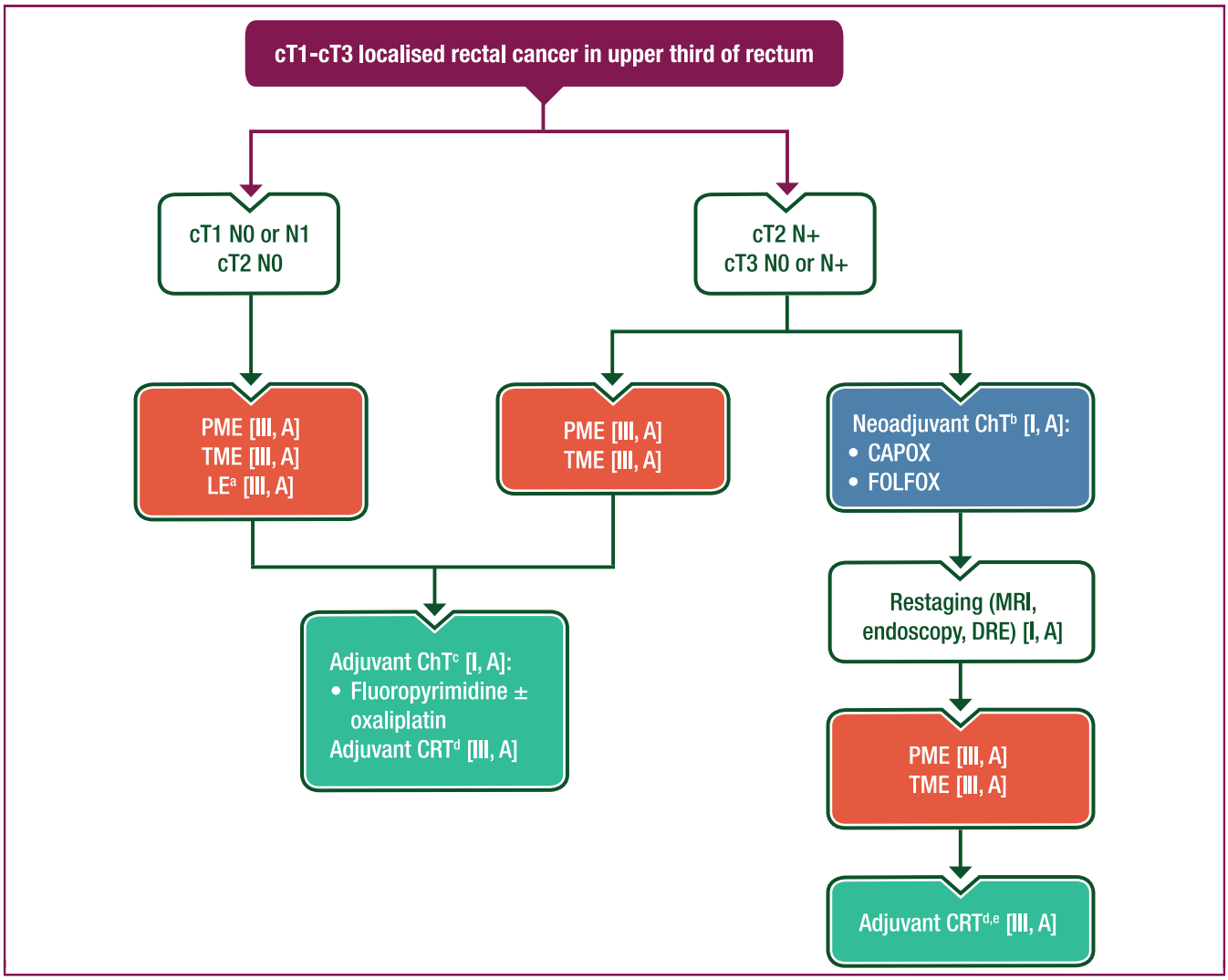

Figure 1. Management of cT1-cT3 localised rectal cancer located in the upper third of the rectum.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: nonsystemic anticancer therapies or a combination of treatment modalities; white: other aspects of management and nontreatment aspects.
c, clinical; CAPOX, capecitabine—oxaliplatin; ChT, chemotherapy; CRM, circumferential resection margin; CRT, chemoradiotherapy; DRE, digital rectal examination; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; LE, local excision; MRF, mesorectal fascia; MRI, magnetic resonance imaging; N+, node positive; p, pathological; PME, partial mesorectal excision; RT, radiotherapy; TME, total mesorectal excision.
[a]For low-risk tumours (pT1 without unfavourable pathological features).
[b]Salvage RT is recommended in case of intolerance to, or progression on, neoadjuvant ChT [I, A].
[c]Only following PME or TME alone, according to clinical risk assessment.
[d]Only in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME in patients who did not receive preoperative RT.
[e]Adjuvant ChT may be considered, but its clinical value is not proven [V, C].

with cT2-cT3b N0-N1 (<8 mm diameter) tumours <5 cm to receive preoperative CRT to 45 Gy followed by either an external beam RT boost (9 Gy in five fractions) or an endorectal boost using contact X-ray brachytherapy (90 Gy to tumour surface in three fractions).[42] After a median follow-up of 38.2 months, 3-year organ preservation rates were 59% and 81%, respectively (hazard ratio 0.36, $P = 0.0026$). Similar prospective findings were shown for high-dose external CRT and endorectal brachytherapy boost with high-dose rate afterloading.[43-45] These data provide evidence for the potential of RT dose escalation using brachytherapy to enhance cCR rates, thus allowing organ preservation in patients with localised tumours. Endorectal brachytherapy should be offered in clinical centres with relevant expertise.

TNT

TNT for patients with high-risk criteria when surgery is intended. For locally advanced rectal cancer, treatment decisions related to neoadjuvant therapy are informed by preoperative assessment including MRI.[46] MRI can identify factors associated with a high risk of local recurrence, as well as synchronous and subsequent metastatic disease.[47,48] MRI also aids with risk stratification by predicting the required extent of surgery and attainment of a clear CRM (>1 mm). For patients with high-risk criteria where organ preservation is not the aim or is considered unfeasible (i.e. surgical setting), two primary TNT sequences have emerged:

(i) induction ChT followed by CRT or SCRT;
(ii) CRT or SCRT followed by consolidation ChT.

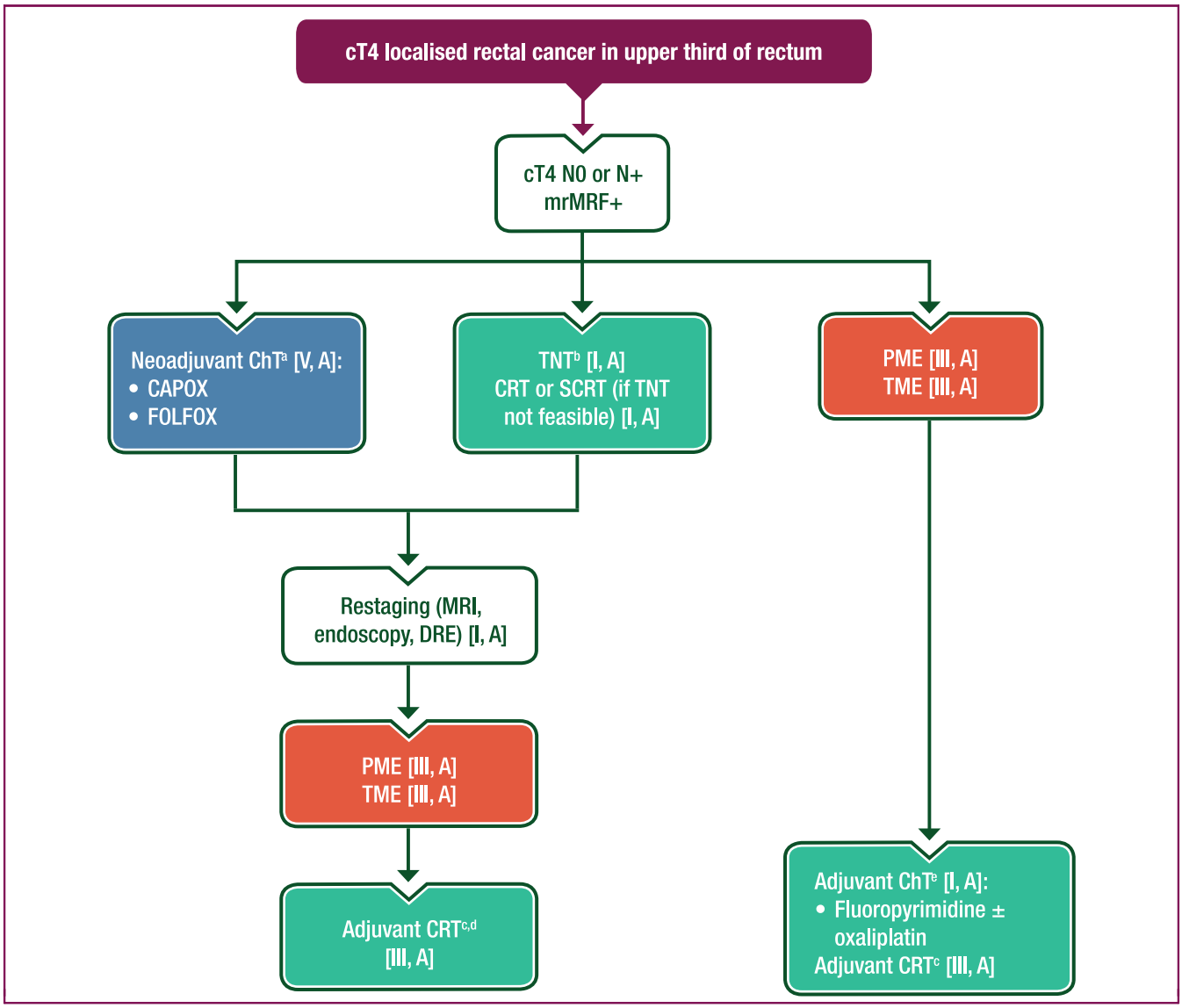

Figure 2. Management of cT4 localised rectal cancer located in the upper third of the rectum.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: nonsystemic anticancer therapies or a combination of treatment modalities; white: other aspects of management and nontreatment aspects.
c, clinical; CAPOX, capecitabine—oxaliplatin; ChT, chemotherapy; CRM, circumferential resection margin; CRT, chemoradiotherapy; DRE, digital rectal examination; EMVI+, extramural venous invasion; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; LN+, involved lymph nodes; MRF, mesorectal fascia; MRI, magnetic resonance imaging; mrMRF+, involved or threatened mesorectal fascia; N+, node positive; p, pathological; PME, partial mesorectal excision; RT, radiotherapy; SCRT, short-course radiotherapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.
[a]Salvage RT is recommended in case of intolerance to, or progression on, neoadjuvant ChT [I, A].
[b]In case of high-risk criteria (cT4, cN2, mrMRF+, EMVI+, lateral LN+).
[c]Only in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME in patients who did not receive preoperative RT.
[d]Adjuvant ChT may be considered, but its clinical value is not proven [V, C].
[e]Only following PME or TME alone, according to clinical risk assessment.

RT can be administered either as long-course CRT [50-50.4 Gy in 25-28 fractions with concomitant capecitabine or infusional 5-fluorouracil (5-FU)] or as SCRT (25 Gy in five fractions). The use of TNT is mainly based on the phase III RAPIDO[12,49] and PRODIGE 23[50,51] trials, which showed significantly improved distant control and DFS following TNT in patients with high-risk features. Further details on clinical studies of TNT are available in Supplementary Material Section 1 and Supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2025.05.528. Despite these results, the low locoregional control rates after TNT with SCRT in the RAPIDO trial[49] and the lack of DFS benefit in the Polish II[52] and STELLAR[53] trials should be taken into account when considering TNT with SCRT. PRODIGE 23 [using induction ChT with leucovorin—5-FU—irinotecan—oxaliplatin (FOLFIRINOX) followed by CRT, resection and adjuvant ChT] reported improved OS with TNT.[51] The optimal duration of consolidation or induction ChT

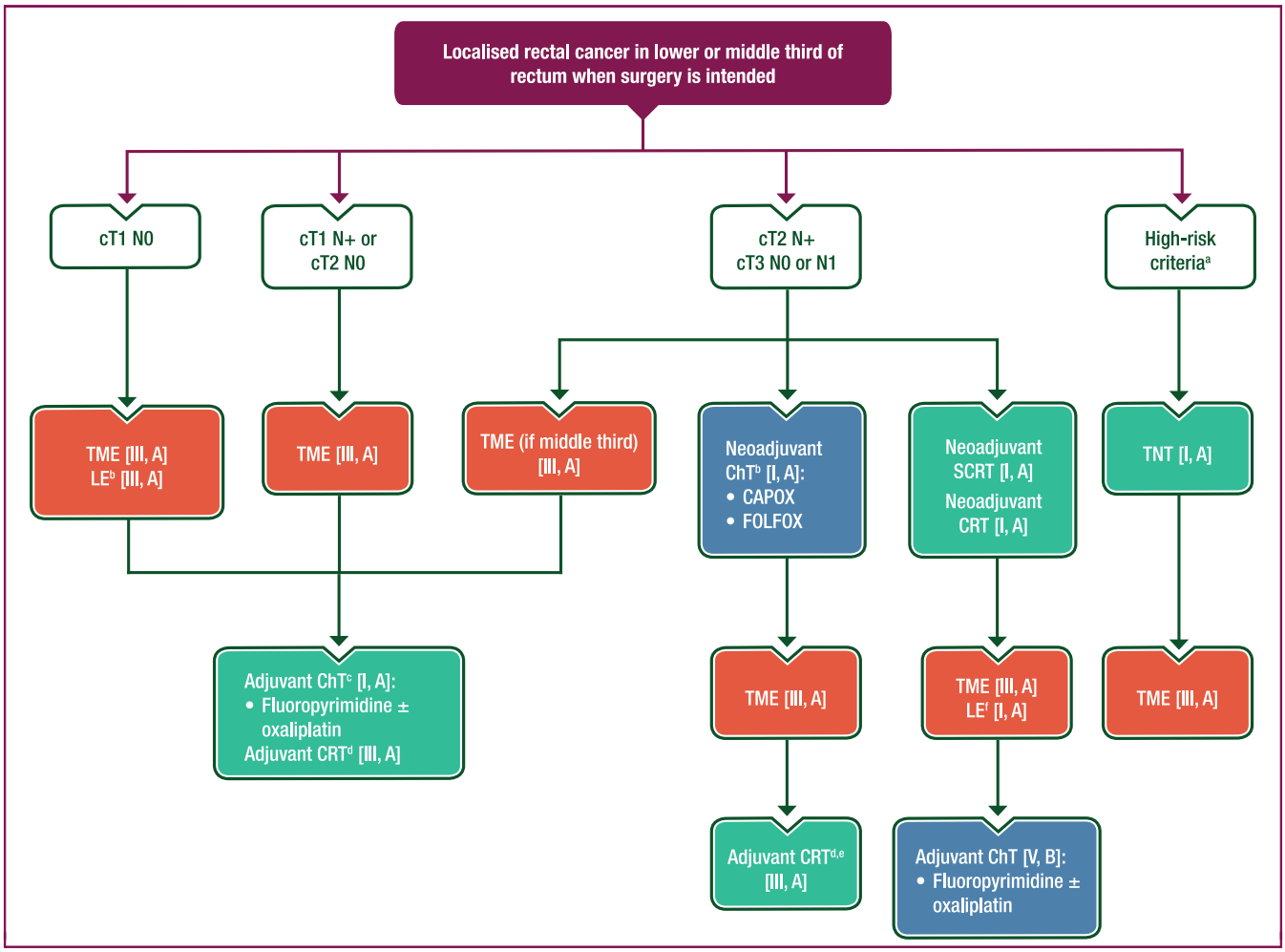

Figure 3. Management of localised rectal cancer located in the lower or middle third of the rectum when surgery is intended.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: nonsystemic anticancer therapies or a combination of treatment modalities; white: other aspects of management and nontreatment aspects.
c, clinical; CAPOX, capecitabine—oxaliplatin; ChT, chemotherapy; CRM, circumferential resection margin; CRT, chemoradiotherapy; EMVI+, extramural venous invasion; FOLFOX, leucovorin—5-fluorouracil—oxaliplatin; LE, local excision; LN+, involved lymph nodes; MRF, mesorectal fascia; mrMRF+, involved or threatened mesorectal fascia; N+, node positive; p, pathological; RT, radiotherapy; SCRT, short-course radiotherapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.
[a]cT4, cN2, mrMRF+, EMVI+, lateral LN+.
[b]Salvage RT is recommended in case of intolerance to, or progression on, neoadjuvant ChT [I, A].
[c]Following TME alone, according to clinical risk assessment.
[d]Only in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME in patients who did not receive preoperative RT.
[e]Adjuvant ChT may be considered, but its clinical value is not proven [V, C].
[f]Patients with baseline cT2 or cT3a N0 tumours.

[capecitabine—oxaliplatin (CAPOX) or leucovorin—5-FU—oxaliplatin (FOLFOX)] as part of TNT is not clear, but 3-4.5 months is reasonable.[54] The benefit of any treatment intensification beyond CAPOX or FOLFOX in TNT is unclear so far. Specifically, the role of irinotecan is uncertain, as comparative studies of FOLFIRINOX versus FOLFOX are lacking in this setting. FOLFIRINOX is associated with higher toxicity compared with FOLFOX. Surgery is optimally carried out 4-8 weeks after completion of TNT. The role of adjuvant therapy in this context is discussed in the 'Adjuvant therapy' section below.

Additional factors, such as age (elderly patients are often unsuitable for TNT due to toxicity[50,55]), functional status, comorbidities and the potential long-term adverse effects of surgery, RT and high-dose ChT, should be taken into account when considering TNT, especially in the surgical setting. Long-term adverse effects include, but are not limited to, chronic pain, anorectal dysfunction (e.g. clustering, faecal incontinence), GU dysfunction (e.g. impotence, dyspareunia, infertility) and peripheral polyneuropathy.[56] TNT should be considered on a case-by-case basis following multidisciplinary discussion using high-quality MRI. Effective communication between cancer specialists and patients is crucial to optimise shared decision making.

TNT for patients with high-risk criteria or cT2 N+ or cT3 N_{any} when organ preservation is intended. TNT is indicated in patients with high-risk criteria and can be considered for patients with cT2 N+ or cT3 N_{any} disease, if organ preservation is intended and considered reasonable. This is based on the inclusion criteria and results of RAPIDO[12]

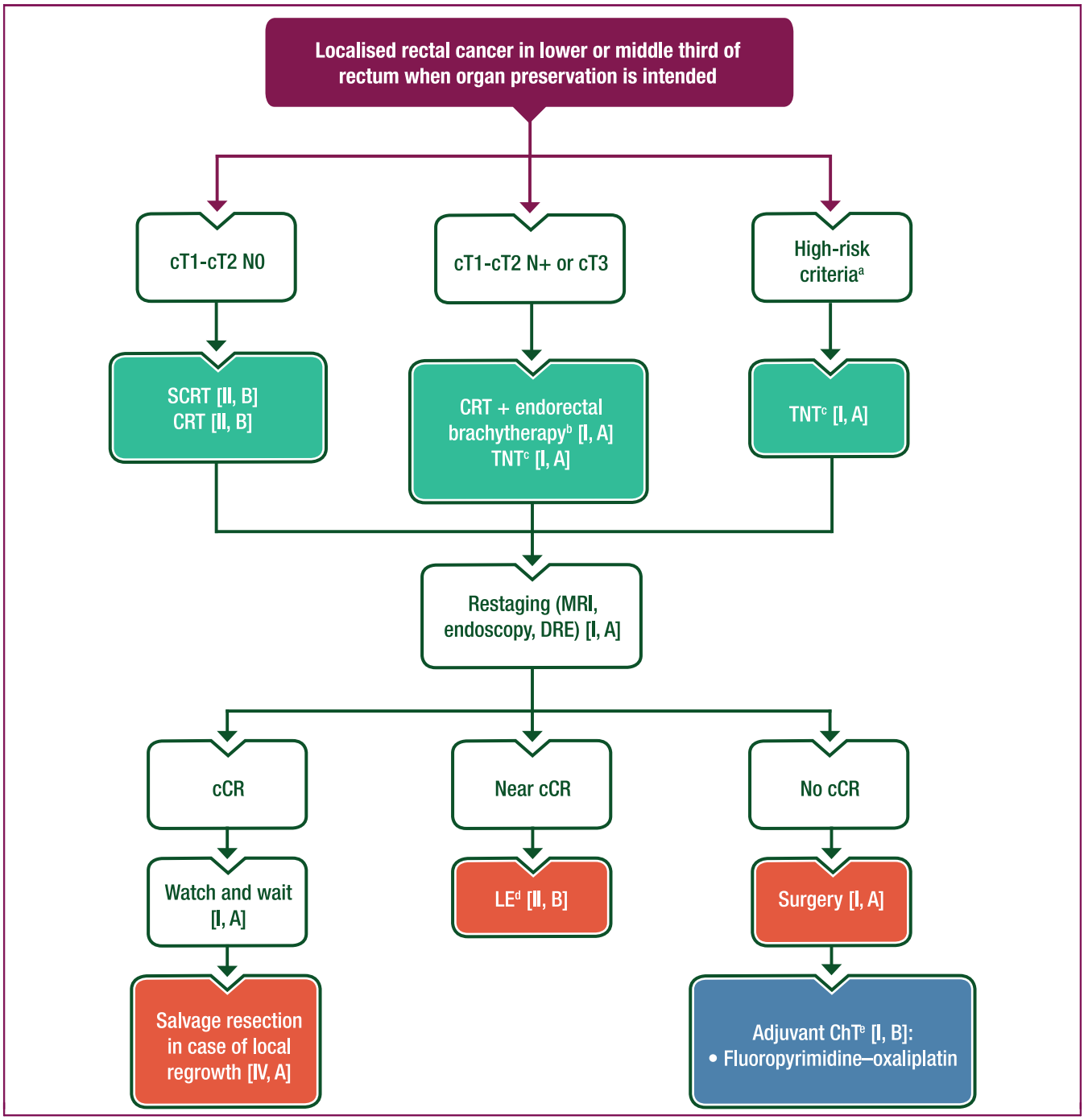

Figure 4. Management of localised rectal cancer located in the lower or middle third of the rectum when organ preservation is intended.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; turquoise: nonsystemic anticancer therapies or a combination of treatment modalities; white: other aspects of management and nontreatment aspects.
c, clinical; cCR, clinical complete response; ChT, chemotherapy; CRT, chemoradiotherapy; DRE, digital rectal examination; EMVI+, extramural venous invasion; LE, local excision; LN+, involved lymph nodes; MRI, magnetic resonance imaging; mrMRF+, involved or threatened mesorectal fascia; N+, node positive; p, pathological; SCRT, short-course radiotherapy; TNT, total neoadjuvant therapy.
[a]cT4, cN2, mrMRF+, EMVI+, lateral LN+.
[b]cT2-cT3b N0-1 tumours <5 cm.
[c]Upfront CRT followed by consolidation ChT can be recommended to increase the likelihood of cCR [I, B].
[d]Patients with baseline cT2 or cT3a N0 with a near cCR.
[e]On a case-by-case basis after fluoropyrimidine-based CRT in patients with initial cN+ disease.

(only included patients with high-risk criteria), PRODIGE 23[50] (17% cT4, 35%-39% cT3c-cT3d, 26% cN2 and 22% MRF+) and OPRA[57] (77% cT3, 13% cT4 and 71% cN+). The high pathological complete response (pCR) rates in RAPIDO and PRODIGE 23 (~28%), in conjunction with the excellent TME-free survival data from OPRA in patients with lower third rectal tumours (5-year TME-free survival rate after TNT was 54% with consolidation ChT versus 39% with induction

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ChT, without compromising 5-year DFS rate[58]) support TNT as a valid strategy in this setting. Based on OPRA, if TNT is used with the aim of increasing the cCR rate to achieve organ preservation, upfront CRT followed by consolidation ChT might be the preferable sequence. Implementation of this approach should be limited to centres with proficient MDTs. Decisions regarding organ preservation after TNT should include a thorough discussion with the patient regarding the risk of regrowth after initial cCR (~25%), which necessitates salvage TME, and the need for adherence to the meticulous watch-and-wait surveillance schedule.

Neoadjuvant ChT

The use of neoadjuvant ChT alone in patients with locally advanced rectal cancer at low risk for local recurrence based on MRI criteria is based on the results of three randomised trials (PROSPECT,[59] CONVERT[60] and FOWARC[61]), which are detailed in Supplementary Material Section 2, available at https://doi.org/10.1016/j.annonc.2025.05.528. Overall, these studies demonstrated similar local recurrence and DFS outcomes with neoadjuvant ChT when compared with neoadjuvant CRT. Evidence suggests that the inclusion criteria from PROSPECT should be used when selecting neoadjuvant ChT, thus excluding patients at high risk of local recurrence; however, this approach can also be considered for patients with a higher risk profile, based on the criteria of CONVERT and FOWARC. Although not formally reported by these three trials, patients with MMR-deficient (dMMR) and/or MSI-H tumours should be excluded from neoadjuvant ChT based on unfavourable findings in dMMR colon cancer.[62] The use of intensified regimens [e.g. FOLFIRINOX or combinations with monoclonal antibodies (mAbs)] is not supported by data from randomised trials. Although the key trials included adjuvant treatment in all arms, the clinical value of post-operative ChT in this setting is unclear. Studies are required to determine the benefit of neoadjuvant ChT in terms of DFS and local recurrence rate compared with primary TME surgery.

dMMR and MSI-H tumours

Approximately 2%-3% of rectal cancers are dMMR and/or MSI-H,[63] which are associated with a poor response to ChT in the neoadjuvant treatment of colon cancer.[62] In recent years, neoadjuvant treatment with various immunotherapies has demonstrated high efficacy in localised dMMR or MSI-H colon and rectal cancers, with very high rates of cCR and pCR.[64-66] Early data have suggested that locally advanced dMMR rectal cancers can become undetectable with programmed cell death protein 1 (PD-1) blockade alone and do not require ChT, RT or surgery, although this approach is not currently approved by regulatory authorities. The best evidence to date is derived from a monocentric phase II trial in the United States.[64,65] Patients received dostarlimab, a PD-1-blocking mAb, for 6 months. Sustained cCR was defined as pCR at surgery or no evidence of tumour by MRI, endoscopy and DRE for ≥12 months following completion of therapy.[64] Response assessment was scheduled at 6, 12 and 24 weeks and every 4 months after that.[64] The most recent presentation of data from this trial reported that, of 48 patients with dMMR rectal cancers, all patients (42/42) who completed the planned 6-month treatment with dostarlimab achieved a cCR.[65] After a median follow-up of 26.3 months (range 12.4-50.5 months) in patients with a cCR, no patients have experienced clinical progression to date.[65] These findings are supported by the high efficacy of PD-1-targeted immunotherapy in locally advanced dMMR or MSI-H colon cancer. The optimal follow-up strategy is unclear; therefore, follow-up should be aligned with that of patients with MMR-proficient (pMMR) or microsatellite-stable tumours who achieve cCR with TNT management. An algorithm for the management of locally advanced dMMR or MSI-H rectal cancer is shown in Figure 5.

Restaging before surgery or organ preservation

Primary tumour response to RT and/or ChT can be substantial; therefore, restaging after initial therapy (neoadjuvant CRT, neoadjuvant ChT or TNT) is an integral part of definitive rectal cancer management. This may be critical for both surgical and nonsurgical approaches.

Patients with locally advanced disease can have baseline threatened margins (e.g. MRF) that require reassessment after treatment to determine the need for beyond-TME surgery and to plan the surgical approach to obtain an R0 resection.[67] In addition, information about the intersphincteric plane may be critical for the indication of sphincter-saving procedures or an abdominoperineal resection (APR).[68] Radiological restaging using MRI is, therefore, critical. In the rare case of tumour progression during or after treatment, the strategy has to be reconsidered by the MDT.

Patients are considered for organ-preserving strategies (including LE and nonsurgical management) based on primary tumour response. While the use of LE may be highly dependent on baseline staging information, patients considered for this approach preferably present with at least partially responsive tumours (including a reduction in tumour size) and with disease restricted to the bowel wall (i.e. no significant extension into the perirectal fat and no mesorectal or lateral pelvic compartment disease), as assessed by MRI.[19,40]

Nonsurgical strategies have become an attractive alternative for patients who achieve a cCR. Criteria for clinical, endoscopic and MRI findings defining a cCR have been standardised and used in individual series, international registries and prospective randomised trials.[26,57,69,70] The findings consistent with a near cCR are less clear.[71] The definitions as recommended by international expert consensus are shown in Supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2025.05.528.[26]

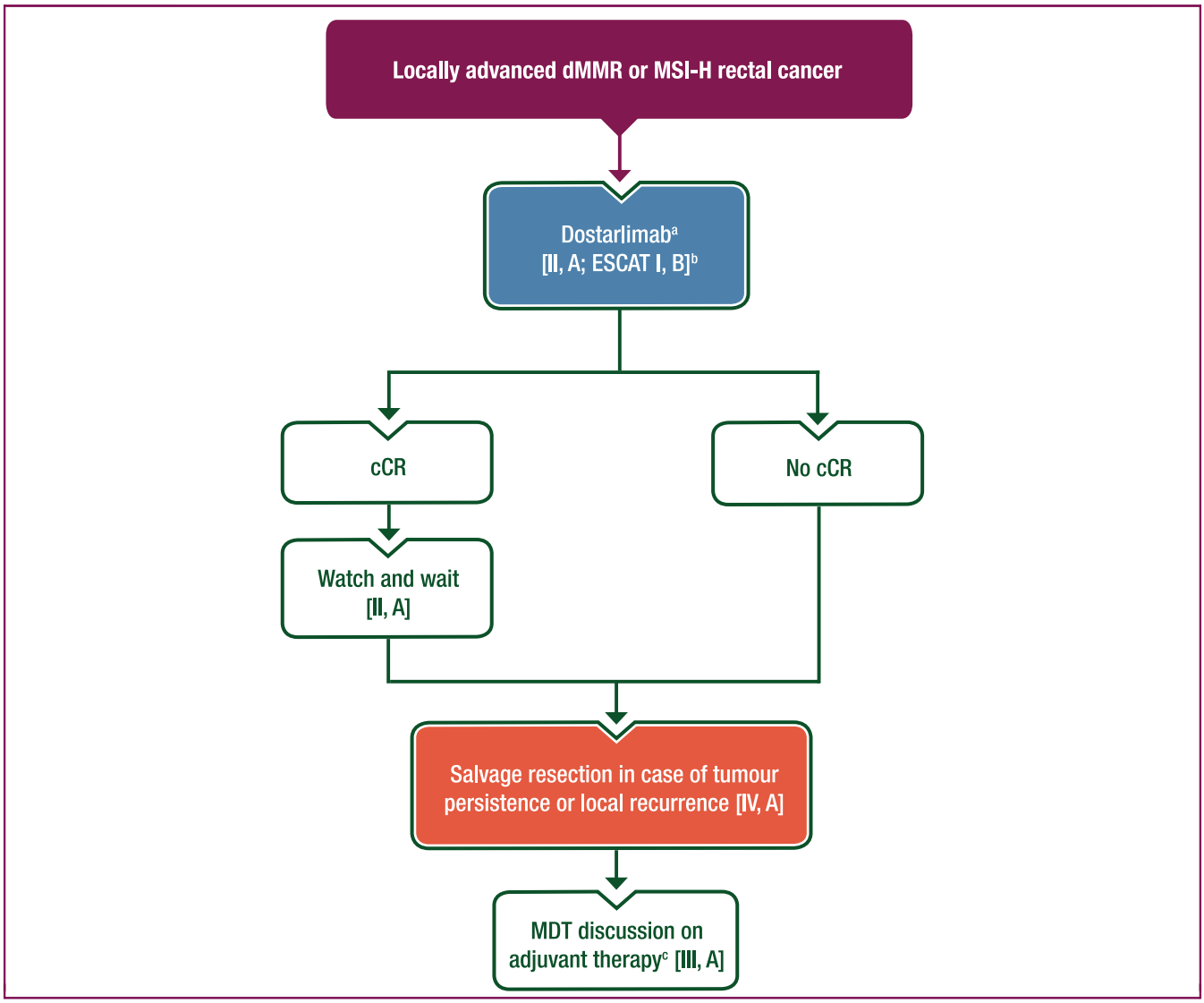

Figure 5. Management of locally advanced dMMR or MSI-H rectal cancer.
Purple: algorithm title; orange: surgery; blue: systemic anticancer therapy or their combination; white: other aspects of management and nontreatment aspects.
cCR, clinical complete response; ChT, chemotherapy; CRT, chemoradiotherapy; dMMR, mismatch repair deficient; EMA, European Medicines Agency; ESCAT, ESMO Scale for Clinical Actionability of molecular Targets; FDA, Food and Drug Administration; MDT, multidisciplinary team; MSI-H, microsatellite instability-high.
[a]Not EMA or FDA approved in this setting.
[b]ESCAT scores apply to alterations from genomic-driven analyses only. These scores have been defined by the authors and validated by the ESMO Translational Research and Precision Medicine Working Group.[105]
[c]ChT or CRT considered, according to clinical risk assessment.

The timing of assessment is critical, as tumour response appears to be time dependent. The restaging timepoints recommended here are adopted from prospective clinical trials. A prospective randomised trial failed to demonstrate an increase in pCR rate between 7 and 11 weeks from neoadjuvant CRT completion,[72] but retrospective series have reported that most patients successfully managed by organ-preservation approaches only achieved a cCR after 16 weeks from RT completion in a TNT regimen.[73] Other studies have suggested that the majority of tumour response is observed within the first few weeks following RT completion.[74,75] Finally, systemic ChT, which is included in all TNT regimens, may also lead to significant primary tumour response.[59,76] For patients interested in organ preservation, a first reassessment of tumour response could be considered 8-12 weeks after CRT completion, even though systemic consolidation ChT is ongoing. In OPRA, however, assessment of response was scheduled 28-32 weeks after completion of CRT.[58] While most patients will not achieve a cCR by 8-12 weeks after CRT, patients intended for organ preservation should exhibit significant primary tumour response (near cCR). This allows for a second reassessment of tumour response in another 8-12 weeks. Most patients achieve a cCR within 24-26 weeks from neoadjuvant CRT completion, allowing them to enter a surveillance programme.[73] Patients without a cCR should undergo surgical resection (although many will demonstrate pCR in the resected specimen) due to the risk of inferior oncological outcomes following a partial response.[77,78]

Surgery

The standard surgical approach for locally advanced tumours in the middle or lower third of the rectum remains total proctectomy with TME, which has demonstrated a substantial benefit in decreasing local recurrence rates.[21] Partial mesorectal excision (PME) is considered sufficient for upper third rectal cancers (usually located above the peritoneal reflection and clearly identified by preoperative MRI and/or confirmed intraoperatively). DRE and preoperative imaging with dedicated MRI are critical to define the surgical strategy. A distal mesorectal margin of $\geq$5 cm is preferred. The MRF status can be anticipated with MRI: the tumour should be $>$1 mm from the MRF and other organs to avoid circumferential microscopic (R1) or macroscopic (R2) involvement. Beyond-TME resection may be required for patients with a compromised or threatened MRF on MRI ($<$1 mm).[79] Evaluation of the distal wall margin drives the decision between restorative procedures (sphincter preservation) and APR. The decision for rectal conservation is made before surgery based on invasion of the intersphincteric plane, indicated by MRI.[68] In the absence of preoperative treatment, a $\geq$1 cm resection margin is preferred, while after preoperative treatment, clear distal resection margins $<$1 cm could be sufficient.[80,81] Data in this regard from TNT trials have not been published to date. In case of suspected lymph node metastases, lateral pelvic nodes (internal iliac and obturator lymph nodes) considered to be locoregional disease may also require resection.[82] The surgical approach for TME remains the surgeon's choice, since prospective randomised clinical trials comparing open surgery and minimally invasive approaches (laparoscopic or robotic) reported similar oncological outcomes but fewer complications.[83-85]

Neoadjuvant treatment has become increasingly widespread. In patients originally allocated to APR, conversion to sphincter-preserving surgery with TME and coloanal anastomosis is considered possible in 50%-80% of cases after preoperative treatment.[86-88] Decisions between sphincter-preserving procedures and APR should consider pre- and post-treatment findings.

Data from retrospective studies and OPRA suggest that most local regrowths following nonsurgical management are amenable to salvage resection.[57,89,90] While most cases have been managed by radical TME, there is evidence to suggest that LE is a good option for local recurrences detected in patients with baseline localised disease.[91] In OPRA, the 5-year DFS rate was similar in patients who underwent salvage TME for incomplete response after restaging compared with those in a watch-and-wait programme who underwent salvage TME after regrowth (both 64%).[58]

LE is an alternative to radical TME and nonsurgical management.[40] This can be carried out with endoscopic methods that have demonstrated good R0 rates and unfragmented specimens. LE is adequate for localised disease [pathological (p)T1] with favourable pathological features.[92] In case of LE showing unfavourable pathological features, TME should be considered. LE is also an option after response to neoadjuvant CRT; indeed, two prospective studies have suggested that cT2-cT3a N0 tumours with a good response to treatment are suitable for LE, with similar oncological and favourable functional outcomes when compared with radical TME.[19,40]

Watch and wait

There is increasing evidence for a watch-and-wait approach in patients achieving a cCR. The cCR is assessed by a combination of DRE, sigmoidoscopy and MRI to assess the MRI tumour regression grade. The value of biopsies in the absence of cCR is unclear. For patients who achieve a cCR and are selected for a watch-and-wait strategy, the risk of regrowth is 25%-35%.[30,33,89] Patients should consent to an appropriate protocol for close surveillance to identify endorectal regrowth at an early stage so that salvage surgery can be applied.

Updated results from OPRA showed that 94% of recurrences occurred within the first 2 years of surveillance.[58] The OPRA protocol for patients with cCR (or near cCR) consisted of DRE and flexible sigmoidoscopy every 4 months for the first 2 years from the time of initial response assessment, then every 6 months for the following 3 years. Rectal MRI was scheduled every 6 months for the first 2 years and yearly for the following 3 years. In the UK TRIGGER trial, watch and wait consisted of clinical review every 3 months from 6 months after the end of CRT up to year 2 and then every 6 months up to year 5.[93] MRI and sigmoidoscopy (or colonoscopy) were carried out every 3 months during the first year, every 6 months up to year 2 and then annually up to year 5. The ongoing RENO study of a watch-and-wait approach in Australia is using the same protocol.[94]

As watch and wait becomes a standard approach, a meticulous surveillance protocol should be undertaken with a focus on the first 2 years (Supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2025.05.528). It is not clear whether failure of watch and wait is associated with a higher risk of distant metastases and consequently decreased survival when compared with upfront surgery.[42,95,96]

Adjuvant therapy

After surgery alone for rectal cancer, individual trials and meta-analyses have indicated benefit with adjuvant 5-FU-based ChT in terms of DFS and OS,[97,98] but the magnitude of benefit is smaller than observed in colon cancer. By contrast, following SCRT or CRT with or without TME, individual randomised trials and meta-analyses have not shown a clear benefit with adjuvant 5-FU-based ChT.[99] Addition of oxaliplatin to 5-FU may improve DFS, but results are not consistent and there is no effect on OS.[100,101] A single randomised phase II study has suggested that adding oxaliplatin to adjuvant 5-FU—leucovorin improves DFS and OS (the latter was not significant)

in high-risk rectal cancers without downstaging after preoperative 5-FU-based CRT.[102] The benefit of adjuvant treatment following neoadjuvant TNT is also unclear. The RAPIDO and OPRA trials did not anticipate post-neoadjuvant systemic treatment (irrespective of whether resection was carried out), whereas the PRODIGE 23 trial recommended post-neoadjuvant treatment with CAPOX or FOLFOX for a maximum of 8 weeks. In addition to limited efficacy, the cumulative oxaliplatin dose and consequent neuropathy are a concern. Potential indications for adjuvant CRT in patients who have not received neoadjuvant RT include CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF, poor mesorectal quality and defects in the surgical specimen.

As in colon cancer, circulating tumour DNA (ctDNA) has been evaluated to define minimal residual disease status and to predict the risk of systemic recurrence and the potential benefit of systemic treatment. The randomised DYNAMIC-Rectal trial showed that a ctDNA-based strategy (with ctDNA positivity predicting indication for 4 months of systemic adjuvant treatment) versus standard treatment (clinical decision making) may help select patients who can benefit most from adjuvant treatment.[103] Further data are needed, however, to determine its use in routine practice.

Recommendations

The following recommendations refer to the modality used in each case. For the sequence of modalities according to clinical or pathological stage, please refer to Figures 1-5.

RT and CRT

- For lower or middle third tumours when surgery is intended:
  - Preoperative RT followed by LE cannot generally be recommended in patients with cT2 N0 tumours <4 cm [III, D] but may be considered for selected patients (e.g. elderly or frail patients at high surgical risk).
  - Neoadjuvant SCRT or CRT (not TNT) is recommended for patients with cT2 N+, cT3 N0 or cT3 N1 tumours [I, A].
- For lower or middle third tumours when organ preservation is intended:
  - SCRT or CRT can be recommended for patients with cT1-cT2 N0 tumours [II, B].
  - Standard external CRT followed by RT dose escalation using endorectal brachytherapy is recommended for patients with cT1-cT2 N+ or cT3 N0-1 tumours <5 cm [I, A].

TNT

- Decisions on the use of TNT should be made within an MDT using high-quality MRI and taking patient factors into account [V, A].
- RT should be offered as long-course CRT (50-50.4 Gy in 25-28 fractions with concomitant capecitabine or infusional 5-FU) or SCRT (25 Gy in five fractions) [I, A].
- Consolidation or induction ChT (CAPOX or FOLFOX) should be administered for 3-4.5 months [I, A].
- If irinotecan is used, it should be administered in line with the protocol of the PRODIGE 23 trial [I, A].
- For upper third tumours:
  - TNT should be offered to patients with cT4 or involved or threatened MRF [I, A].
  - CRT or SCRT should be considered if TNT is not feasible [I, A].
- For lower or middle third tumours when surgery is intended:
  - TNT should be offered to patients with high-risk criteria [I, A].
- For lower or middle third tumours when organ preservation is intended:
  - TNT is recommended for patients with high-risk criteria and patients with cT2 N+ or cT3 N_{any} tumours [I, A].
  - Upfront CRT followed by consolidation ChT can be recommended to increase the likelihood of cCR [I, B].

Neoadjuvant ChT

- When considering neoadjuvant ChT, the inclusion criteria of the PROSPECT study should be used (T2 N+, T3 N_{any}, distance to the CRM $\geq$3 mm, continence-preserving surgery possible) [I, A].
- Neoadjuvant ChT should comprise 3 months of CAPOX or FOLFOX [I, A]. Neoadjuvant FOLFIRINOX or mAbs cannot be recommended [V, D].
- For upper third tumours:
  - Neoadjuvant ChT is recommended for patients with cT2 N+ or cT3 N_{any} disease [I, A].
  - Neoadjuvant ChT is recommended for patients with cT4 N_{any} disease [V, A].
- For lower or middle third tumours when surgery is intended:
  - Neoadjuvant ChT is recommended for patients with cT2 N+, cT3 N0 or cT3 N1 disease [I, A].
- Neoadjuvant ChT cannot be recommended for dMMR and MSI-H tumours [V, D].
- Salvage RT is recommended in case of intolerance to, or progression on, neoadjuvant ChT [I, A].
- Watch and wait cannot be recommended in case of a cCR [I, D].

dMMR and MSI-H tumours

- Patients with locally advanced dMMR or MSI-H tumours in the upper, middle or lower third of the rectum should receive dostarlimab for a planned treatment duration of 6 months [II, A; ESCAT score: I-B; not European Medicines Agency (EMA) or Food and Drug Administration (FDA) approved in this setting].
- Follow-up procedures should be aligned with those for patients with pMMR tumours achieving a cCR after TNT (i.e. watch and wait) [II, A].

- Salvage resection is recommended in case of tumour persistence or local recurrence [IV, A].
- MDT discussion is recommended to consider adjuvant ChT or CRT, according to clinical risk assessment [III, A].

Restaging before surgery or organ preservation

- Restaging should comprise MRI, endoscopy and DRE [I, A].
- ERUS cannot be recommended for restaging [V, D].
- In case of a cCR, biopsies cannot be recommended to determine a watch-and-wait approach, as their value in this setting is unclear [V, D].
- The recommended timings for restaging are:
  - For restaging with intended surgery:
    - 2-4 weeks after CRT with consolidation ChT [I, A].
    - 6-7 weeks after induction ChT and CRT [I, A].
    - 4-8 weeks after the start of SCRT when delayed surgery is planned [I, A].
    - 4-7 weeks after completion of neoadjuvant CRT [I, A].
    - 3-4 weeks after completion of neoadjuvant ChT [I, A].
  - For restaging to determine cCR for a watch-and-wait approach:
    - 4-8 weeks after completion of consolidation ChT in TNT [I, A].
    - 12 weeks after the start of RT in SCRT or CRT; in case of near cCR, further restaging can be recommended after another 4-8 weeks [I, B].
    - 14 weeks after the start of RT in CRT—brachytherapy; in case of near cCR, further restaging can be recommended after another 6-10 weeks [I, B].
    - 12 weeks after initiation of dostarlimab in patients with dMMR or MSI-H tumours and a second restaging 24 weeks after initiation of immunotherapy [III, A].

Surgery

- PME and TME are the recommended surgical procedures for rectal cancer [III, A].
- Open surgery and minimally invasive approaches are both recommended as they lead to similar oncological results [I, A].
- A distance of >1 mm from tumour to CRM and other organs can be recommended [III, B]. In case of MRF+ or T4b, beyond-TME surgery is recommended [III, A].
- The distal mesorectal margin should be ≥ 5 cm [III, A].
- In the absence of preoperative treatment, a distal resection margin of ≥ 1 cm is recommended [III, A]. After neoadjuvant therapy, a distal resection margin of <1 cm may be acceptable, although there are no data to support this following TNT [III, C].
- Lateral lymph nodes with a short axis of ≥ 7 mm should be resected after neoadjuvant treatment [IV, A].
- For upper third tumours:
  - PME and TME are both equally recommended [III, A].
  - LE is recommended as an alternative to PME or TME for low-risk tumours (pT1 without unfavourable pathological features) [III, A].
- For lower or middle third tumours when surgery is intended:
  - TME is the recommended surgical procedure [III, A].
  - LE should be considered as an alternative to TME for low-risk tumours (pT1 without unfavourable pathological features) [III, A].
  - LE is recommended as an alternative to TME after a good response to neoadjuvant CRT or SCRT in baseline cT2 or T3a N0 tumours [I, A].
- For lower or middle third tumours when organ preservation is intended:
  - Surgery, with the resection method depending on clinical assessment, is recommended for patients who do not achieve a cCR following CRT or TNT [I, A].
  - LE can be considered to achieve organ preservation in patients with baseline cT2 or cT3a N0 with a near cCR [II, B].
- In case of local (endorectal) regrowth after a watch-and-wait procedure, salvage resection should be offered to all patients [IV, A]. LE cannot be recommended as its value in this setting is unclear [IV, D].

Watch and wait

- For lower or middle third tumours, a watch-and-wait strategy is recommended in patients with cCR when organ preservation is intended [I, A].
- For all dMMR or MSI-H rectal tumours, a watch-and-wait strategy is recommended in patients with cCR after treatment with a PD-1 inhibitor [II, A].
- Discussion with patients about the importance of adherence to strict follow-up investigations is mandatory [V, A].
- Follow-up examinations should comprise MRI, endoscopy and DRE every 3 months for the first 2 years and every 6 months thereafter [I, A]. CT scans of the chest and abdomen should be carried out every 6 months for the first 2 years and annually thereafter [I, A].

Adjuvant therapy

- Adjuvant treatment after surgery should be discussed by an MDT on a case-by-case basis, taking into account tolerability, response to treatment and patient preference [V, A].
- For upper third tumours:
  - Adjuvant ChT with a fluoropyrimidine and (potentially) oxaliplatin should be offered (according to clinical risk assessment) following PME or TME alone [I, A].

- In patients who did not receive preoperative RT, adjuvant CRT should be offered in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME [III, A].

- For lower or middle third tumours after surgery:
  - Adjuvant therapy with a fluoropyrimidine and (potentially) oxaliplatin should be offered (according to clinical risk assessment) following TME alone [I, A] and can be considered after neoadjuvant CRT or SCRT [V, B].

- In patients who did not receive preoperative RT, adjuvant CRT should be offered in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME [III, A].

- For lower or middle third tumours with organ preservation:
  - An adjuvant fluoropyrimidine—oxaliplatin combination can be offered on a case-by-case basis after RT or fluoropyrimidine-based CRT in patients achieving cCR with initial cN+ disease [I, B].

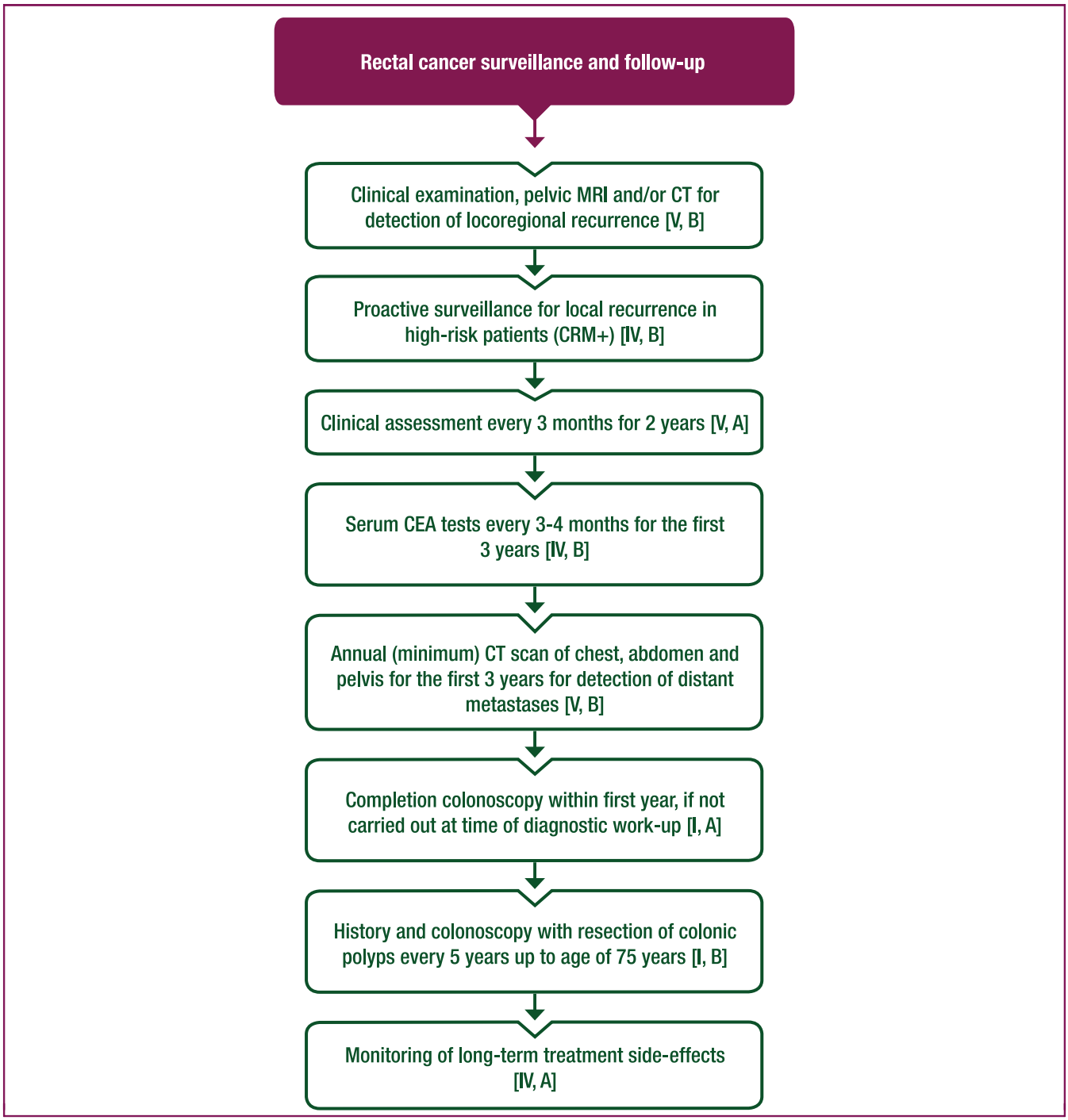

Figure 6. Rectal cancer surveillance and follow-up.
Purple: algorithm title; white: other aspects of management and nontreatment aspects.
CEA, carcinoembryonic antigen; CRM+, involved circumferential resection margin; CT, computed tomography; MRI, magnetic resonance imaging.

- Post-neoadjuvant systemic treatment following TNT (irrespective of surgical or nonsurgical local approach) cannot be generally recommended due to toxicity considerations [I, D]. This approach should be discussed individually within an MDT.
- Adjuvant ChT may be considered after neoadjuvant ChT, but its clinical value has not been proven [V, C].
- Post-operative ctDNA status cannot currently be recommended for use in adjuvant therapy decisions [II, D].

FOLLOW-UP, LONG-TERM IMPLICATIONS AND SURVIVORSHIP

Follow-up aims to improve outcomes through early detection and salvage of local and systemic recurrences and to prevent and detect metachronous CRC (Figure 6). Details of follow-up modalities are provided in Supplementary Material Section 3, available at https://doi.org/10.1016/j.annonc.2025.05.528.

Surgery and pre- and/or post-operative therapies can result in late morbidities that impact daily function,[56] including gastrointestinal and lower GU toxicities (such as erectile dysfunction, dyspareunia and urinary incontinence) and an increased risk of secondary cancers in the RT area.[104] With more effective treatments, the number of long-term survivors is increasing, who may suffer treatment-related sequelae related to stomas, poor mobility or other age-related comorbidities. Surveillance should address the social, financial and emotional impacts of rectal cancer and its treatment, as well as practical and functional issues, to maximise the long-term well-being of survivors. Proactive detection of common long-term effects is important, and educational programmes can promote engagement with the health care system and a healthy lifestyle before and after treatment.

Recommendations

- Clinical examination, pelvic MRI and/or CT can be recommended for detection of locoregional recurrence [V, B].
- Proactive surveillance for local recurrence can be considered in patients at high risk of recurrence (e.g. involved CRM) [IV, B].
- Clinical assessment should be carried out every 3 months for 2 years [V, A].
- Serum CEA measurements can be recommended every 3-4 months for the first 3 years [IV, B].
- Annual (minimum) CT scan of the chest, abdomen and pelvis can be recommended for the first 3 years for detection of distant metastases [V, B].
- A completion colonoscopy is recommended within the first year if not carried out at the time of diagnostic work-up (e.g. if an obstruction was present) [I, A].
- Medical history and colonoscopy with resection of colonic polyps can be recommended every 5 years up to the age of 75 years [I, B].
- Long-term side-effects of treatment should be monitored [IV, A].

METHODOLOGY

This CPG was developed in accordance with the ESMO standard operating procedures for CPG development (https://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology). All recommendations provided are based on current scientific evidence and the authors' collective expert opinion. Where recommendations for multiple different treatment options exist, prioritisation is illustrated by ordering these options according to the level of evidence (LoE) and grade of recommendation (GoR), where equal, by alphabetical order. The relevant literature has been selected by the expert authors. A table of ESCAT scores is included in Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2025.05.528. ESCAT scores have been defined by the authors, assisted if needed by the ESMO Translational Research and Precision Medicine Working Group.[105] The FDA/EMA or other regulatory body approval status of new therapies/indications is reported at the time of writing this CPG. LoEs and GoRs have been applied using the system shown in Supplementary Table S8, available at https://doi.org/10.1016/j.annonc.2025.05.528.[106] Statements without grading were considered justified standard clinical practice by the authors. For future updates to this CPG, including Express Updates and Living Guidelines, please see the ESMO Guidelines website: https://www.esmo.org/guidelines/guidelines-by-topic/esmo-clinical-practice-guidelines-gastrointestinal-cancers/rectal-cancer.

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