Clinical practice guidelines for the surgical treatment of rectal cancer: a consensus statement of the Hellenic Society of Medical Oncologists (HeSMO)

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Abstract

In rectal cancer management, accurate staging by magnetic resonance imaging, neo-adjuvant treatment with the use of radiotherapy, and total mesorectal excision have resulted in remarkable improvement in the oncological outcomes. However, there is substantial discrepancy in the therapeutic approach and failure to adhere to international guidelines among different Greek-Cypriot hospitals. The present guidelines aim to aid the multidisciplinary management of rectal cancer, considering both the local special characteristics of our healthcare system and the international relevant agreements (ESMO, EURECCA). Following background discussion and online communication sessions for feedback among the members of an executive team, a consensus rectal cancer management was obtained. Statements were subjected to the Delphi methodology voting system on two rounds to achieve further consensus by invited multidisciplinary international experts on colorectal cancer. Statements were considered of high, moderate or low consensus if they were voted by ≥80%, 60-80%, or <60%, respectively; those obtaining a low consensus level after both voting rounds were rejected. One hundred and two statements were developed and voted by 100 experts. The mean rate of abstention per statement was 12.5% (range: 2-45%). In the end of the process, all statements achieved a high consensus. Guidelines and algorithms of diagnosis and treatment were proposed. The importance of centralization, care by a multidisciplinary team, adherence to guidelines, and personalization is emphasized.

Keywords Guidelines, rectal cancer, surgical treatment, consensus, Delphi

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Introduction

Introduction of total mesorectal excision (TME) \cite{1,2}, accurate preoperative image staging \cite{3} and preoperative treatment when indicated, by means of radiation therapy (RT) or/and chemotherapy (ChT) \cite{4}, has resulted in considerable improvement in oncological outcomes of patients with rectal cancer during the last three decades \cite{5}. Evolving knowledge
on preoperative local staging, elaboration of preoperative RT schemes, new chemotherapeutic agents, and refinements in surgical techniques in an effort to preserve anal function, without compromising oncological outcomes, steer towards implementation of new strategies in the treatment of rectal cancer.

**Aim**

Driven by the Hellenic Society of Medical Oncology (HeSMO) a selection of an executive team was made on the grounds of their experience in colorectal cancer. The executive team was assigned to elaborate and develop a consensus document and form guidelines on the main aspects of image staging, pre-operative management and surgical treatment of rectal cancer, based on the review of literature, the principles of the evidence-based medicine, and the relevant already developed international agreements.

In the present study, the guidelines on the management of rectal cancer only are presented. Consensus documents on: a) surgical treatment of colon cancer; b) adjuvant treatment of colorectal cancer; and c) management of metastatic colorectal disease are presented elsewhere.

**Legal disclaimer**

Details on the legal aspects of these guidelines have already been reported [6].

**Methodology**

The methodology in setting our guidelines for the surgical management of rectal cancer has already been reported elsewhere [6]. The first round of the online Delphi voting process opened on September 29th 2013 and closed on December 6th 2013. The second round opened on January 6th 2014 and closed on January 24th 2014. In the final document all statements are presented as recommendations of care. Even statements achieving a consensus of <80% were included. At the end of each recommendation the level of evidence (LOE) and the strength of recommendation (SOR) are mentioned (Table 1), followed by the rate of voting consensus (ROVC).

**Discussion**

One hundred experts participated and voted for 102 statements, which entered the Delphi methodology. The median abstention rate was 12.5% (2-45%). After the first voting process, 16 statements achieved consensus by all participants, and there were 68 statements achieving a consensus of over than 90%. Three statements that achieved a rate of consensus of less than 80% and a fourth one with a consensus of over 80% entered a second round of voting, after they were amended by the executive team. At the end of the process, all four statements improved their ROVC, and there were no statements with a ROVC less than 80% (Table 2).

**General considerations**

**Background**

Optimum therapeutic strategy and adequately executed surgery for rectal cancer is best produced in volume-based referral centers by an adequately trained multidisciplinary team (MDT) which should include surgeons, radiologists, medical oncologists, radiotherapists and pathologists [7-9]. Further to centralization and adherence to clinical guidelines,

| Level of evidence | Description                                                                 |
|-------------------|-----------------------------------------------------------------------------|
| I                 | Evidence from at least one large randomized control trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted RCTs without heterogeneity |
| II                | Small RCTs or large RCTs with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity |
| III               | Prospective cohort studies                                                  |
| IV                | Retrospective cohort studies or case-control studies                        |
| V                 | Studies without control group, case reports, expert opinions                |

| Strength of recommendation | Description |
|----------------------------|-------------|
| A                          | Strong evidence for efficacy with a substantial clinical benefit, strongly recommended |
| B                          | Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended |
| C                          | Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs) optional |
| D                          | Moderate evidence against efficacy or for adverse outcome, generally not recommended |
| E                          | Strong evidence against efficacy or for adverse outcome, never recommended |

**Table 1 Evidence level and recommendation grade**

**Table 2 Rate of voting consensus of statements after the two voting processes**

| Rates of voting consensus (%) | Statement numbers after first voting process | Resubmitted statement numbers | Statements numbers at the end of process |
|-------------------------------|---------------------------------------------|---------------------------------|-----------------------------------------|
| 100                           | 16                                         | 16                             | Total: 102                              |
| 90-99                         | 68                                         | 70                             | Total: 4                                |
| 80-89                         | 15                                         | 1                              | Total: 16                               |
| 70-79                         | 3                                          | 3                              | Total: 4                                |
oncological outcomes are expected to improve by national audit registries [7,9,10]. It should be mentioned that the guidelines do not always derive from high-quality level I data, and therefore they should be applied with caution.

**Tumor classification to define therapeutic strategy**

**Background**

Rectal cancers can be divided into four groups: very early (some cT1), early (cT1–2, some cT3), more advanced (cT3, some cT4) and locally advanced (cT4). Factors other than clinical T-stage, such as tumor height, proximity to the circumferential resection margin (CRM), cN-stage, and vascular and nerve invasion are also relevant. The terms ‘favorable or early or good’, ‘intermediate or bad’ and ‘locally advanced or ugly’ can also be applied to categorize rectal cancers. Currently, in clinical practice, the term ‘locally advanced’ has been commonly used for the ‘intermediate/bad’ group, but is best reserved for the truly ‘locally advanced/ugly’ tumors. Accurate clinical staging is required to determine the need for neo-adjuvant therapy or an enhanced surgical procedure. Because oncological outcomes strongly depend on accurate diagnosis, staging and pursuing the optimal therapeutic strategies, patients with rectal cancer should be treated in specialized centers with high volume of referred cases and by an MDT which involves surgeons, histopathologists, radiologists, medical and RT oncologists [3,9,11]. An optimum therapeutic strategy and adequately executed surgery aims to lower morbidity and mortality, local recurrence rates below 10%, and overall survival above 70%. Structural surgical training and quality assurance are also prerequisites for the continuous improvement of outcomes [7,12].

**RECOMMENDATION**

1. Centralization, care by an MDT, adherence to clinical guidelines, and audit registries are necessary to improve oncological outcomes in the management of rectal cancer (LOE III; SOR A) (ROVC: 99%)

**Diagnosis and staging (Table 3)**

**Background**

Diagnostic means for initial staging [before any (neo-adjuvant or surgical) treatment]

**Table 3 Initial staging of rectal cancer**

| Aim                        | Modalities                                      |
|-----------------------------|-------------------------------------------------|
| Confirmation of diagnosis   | Endoscopy - biopsies                            |
| Localization of tumor       | Digital examination                             |
| Distance from anal verge    | Rigid recto-sigmoidoscopy                       |
| Length                      | MRI                                             |
| Circumferential spread      | Flexible endoscopy (less accurate)              |
| Synchronous colonic lesions| Total colonoscopy (1st choice)                  |
|                            | MDCT (2nd choice)                               |
|                            | MDCT colonography (in obstructive lesion)       |
|                            | MRI (if sensitivity to iodinated contrast medium)|
|                            | Double contrast barium enema (last option)      |
| T stage                     |                                                 |
| T1                          | MRI, ERUS                                       |
| T2-4                        | MRI (1st choice)                                |
|                            | MDCT (2nd choice for middle-upper rectum lesions) |
|                            | ERUS (2nd choice for lower rectum lesions)      |
| CRM status                  | MRI (1st choice)                                |
|                            | MDCT (2nd choice for middle-upper rectum lesions)|
| Levatorani & sphincter status| MRI (1st choice) |
| N stage                     | ERUS (2nd choice)                               |
|                            | MRI (1st choice)                                |
|                            | MDCT (2nd choice for middle-upper rectum lesions) |
|                            | ERUS (2nd choice for lower rectum lesions)      |
| M stage                     |                                                 |
| Liver                       | MDCT                                            |
|                            | MRI (if sensitivity to iodinated contrast medium)|
|                            | (In equivocal cases)                            |
|                            | U/S (in equivocal cases)                        |
|                            | PET/CT (if MDCT, MRI, U/S inconclusive)         |
| Lungs                       | MDCT                                            |
|                            | Chest x-ray (2nd choice)                        |
| Bones (relevant symptomatology)| Scintigraphic scan                              |
| Brain (relevant symptomatology)| Scintigraphic scan                              |

MRI, magnetic resonance imaging; MDCT, multi-detector computed tomography; ERUS, endorectal ultrasound; U/S, ultrasound; PET/CT, positron emission tomography-computed tomography
The accurate diagnosis of tumor localization and local extension (T stage), lymph node involvement (N-stage), extramural vein status and potential CRM positivity is essential for defining the treatment strategy. Rectal cancers are categorized according to their distal edge measured from the anal verge, by rigid or flexible endoscopy, accompanied by biopsy, and MRI. Rigid endoscopy and MRI are more reliable in detecting the exact location and the size of the tumor. By rigid proctoscopy, rectal cancer is categorized as: low (up to 5 cm), middle (from >5 to 10 cm) or high (from >10 up to 15 cm).

**Definition of T-stage (according to TNM)**

Subclassification of T1 cancers is based upon depth of invasion into the submucosal layer: sm1 upper third, sm2 middle third and sm3 lower third. Alternatively the millimetric depth of submucosal invasion could be used, where an invaded depth of more than 1 mm is an important predictor for possible lymph node involvement [13,14]. Endorectal ultrasound (ERUS) and endorectal MRI have similar accuracy in the differentiation between T1 sm1/sm2 and sm3 and furthermore between superficial (T1 and/or T2) and T3 tumors [15]. MRI with use of an endorectal coil offers the maximum amount of information by a single modality in the staging of rectal cancer [16]. However, endorectal imaging is not an adequate method for the assessment of local tumor extent in bulky T3 or T4 tumors. Likewise, ERUS or MRI can measure sphincter infiltration with comparable accuracy.

Although ERUS is accurate in assessing early-stage low tumors (T1 and T2), with a sensitivity of 94% and specificity of 86% [17], it performs inadequately for advanced rectal tumors, leading to substantial preoperative overstaging and consequent overtreatment, because differentiation between peritumoral inflammation or fibrosis and true tumor is not possible [18,19] and the inability of the method to assess CRM or to identify lymph nodes close to the mesorectal fascia, but also to depict extramural vascular invasion (EMVI).

Thin-section MRI with 3-mm slices and a small field of view is now used to identify several prognostic features that will allow better selection of patients who will benefit from more intensive treatment [20]. MRI or multidetector-row CT (MDCT) have an equal accuracy in distinguishing T3 from T4 tumors in the middle and higher rectum [21]. However, MDCT does not correlate well enough with MRI findings to replace it in rectal cancer staging [22].

The main limitation of T staging is that T3 tumors are the majority of rectal cancers seen at presentation which, however, comprise a very heterogeneous group regarding local recurrence and survival rates. From existing pathological studies, it is clear that patients with more than 5 mm of extramural spread should be identified because they have a markedly worse prognosis than those with T3 tumors <5 mm of spread [23]. Thus, the distinction between T2 stage and T3 stage is not relevant, when the T3 tumor presents a less than 2 mm spread [3].

For low rectal cancer tumors, specific mention should be made on the MRI staging report, regarding the relationship of the infiltrating margin of the tumor with the thin mesorectum, the levators, the intersphincteric plane, and the internal and external anal sphincters [20,24,25].

**Status of CRM**

CRM involvement is an independent prognostic factor for pelvic recurrence and poor survival [26]. MRI is the method of choice for the prediction of positivity of CRM, with sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 70%, 96%, 85%, and 92%, respectively [27]. A potentially positive CRM margin is defined as tumor lying within 1 mm from the mesorectal fascia [3]. Measurements are also taken from suspicious lymph nodes, EMVI, and tumor deposits or satellite nodules within the mesorectal planes. EMVI is an additional important independent prognostic factor that can be readily identified on MRI [9,18,28].

**N-stage**

Prediction of nodal metastases has traditionally relied on size. Also, nodes are judged suspicious if they have irregular borders or/and mixed signal intensity. Nodes >8 mm in the pelvic sidewall are defined as malignant nodes. MRI and MDCT are equivalent in detection of suspect pelvic sidewall lymph nodes, defined by size >8 mm. A recent meta-analysis has shown that no significant differences existed among endorectal sonography, CT, and MRI in nodal staging using size criteria [21,29]. Particularly for mesorectal lymph nodes, a cut-off value of 10 mm gives high specificity but low sensitivity, whereas the opposite is true when a cut-off value of 3 mm is applied [30]. Nodes smaller than 5 mm in diameter and difficulty in exploring the entire mesorectum are the limitations of ERUS in determining N stage of rectal cancer [31]. Several reports show that all currently used imaging modalities lack sufficient accuracy for clinical decision making. The estimated sensitivity for ERUS, MRI and CT is 67%, 55%, and 66% respectively, with corresponding specificity estimates of 78%, 74%, and 76%, respectively [21]. By assessing the nodal morphology at MRI, namely irregular borders and signal heterogeneity, malignant nodes can be detected with a greater degree of sensitivity (85%; 95% CI 74-92%) and specificity (97%; 95% CI 95-99%) compared with nodal size measurement [29,32]. More recently, good performance of ultra-small superparamagnetic iron oxide-enhanced (USPIO) MRI for nodal staging in patients with rectal cancer has been shown with high sensitivity and specificity rates of approximately 95% for detection of malignant lymph nodes [33]. At present, USPIO is not available in the market.

Fludeoxyglucose (FDG) positron emission tomography (PET) has shown disappointing results for N staging, particularly in the mesorectal fascia, but PET-CT imaging could have a potential role in identifying lateral spread to nodes along the internal iliac chain [34].

**M-staging**

Thoracic and abdominal CT is recommended to detect or rule out distant metastases. The real value of CT is its accuracy.
in detecting distant metastases. MRI is helpful in further characterization of liver lesions suspected for metastases diagnosed by CT scan. MRI is the preferred first-line modality for evaluating colorectal liver metastases in patients who have not previously undergone therapy [35].

FDG-PET could be considered for detection of liver metastases and peritoneal disease, when there is clinical, biochemical or radiological suspicion of systemic disease [36]. FDG-PET is mainly useful in the assessment of local recurrence and metastatic disease when conventional imaging is not helpful [37]. Currently, it is considered as a primary staging modality in rectal cancers. Finally, bone scintigraphic scans and brain imaging are required, only in the presence of relative symptomatology.

In summary, MRI has been shown to accurately identify the depth of extramural invasion, the presence of lymph node metastases, EMVI and CRM involvement. By demonstration of accurate measurement of the depth of extramural tumor spread, the MERCURY Study enabled accurate preoperative prognosis [3,28].

RECOMMENDATION

3. Based on the distance of its distal part to the anal verge, rectal cancer are categorized as low (up to 5 cm), middle (from >5 to 10 cm) or high (from >10 up to 15 cm) (LOE IV; SOR B) (ROVC: 96%)

4. Accurate diagnosis of tumor localization and local extension (T stage), lymph node involvement (N-stage), extramural vein status and potential CRM positivity are essential to define treatment strategy (LOE III; SOR A) (ROVC: 96%)

5. Rigid proctoscopy is accurate and more reliable than flexible endoscopy in defining the location of a rectal tumor (LOE IV; SOR A) (ROVC: 88%)

6. MRI is highly accurate in defining location and length of a rectal tumor (LOE III; SOR A) (ROVC: 98%)

7. Depending on availability and expertise, ERUS is preferably used in early mobile rectal tumors (T1, T2) to accurately define T stage (LOE III; SOR B) (ROVC: 89%)

8. If ERUS is not available, staging of early rectal (T1, T2) tumors can also be achieved by MRI (LOE III; SOR A) (ROVC: 89%)

9. Either ERUS or MRI may not accurately differentiate between T2 and marginal T3 (T3a) lesions (LOE III; SOR B) (ROVC: 86%)

10. For advanced (T3/4) middle or high rectal cancers, MRI should be performed to accurately define T stage (LOE III; SOR A) (ROVC: 99%)

11. Extramural depth of tumor spread can be measured with high accuracy by thin section high-resolution MRI (LOE III; SOR A) (ROVC: 100%)

12. Depth of tumor invasion into the mesorectal fat should be given in millimeters to define T3 subgroups (a-d) (LOE III; SOR A) (ROVC: 97%)

13. Depth of tumor invasion into the mesorectal fat is of the most significant prognostic factors for local recurrence and survival (LOE IV; SOR A) (ROVC: 82%)

14. Low rectal tumors should be locally staged by MRI, although for determination of sphincter infiltration ERUS could be used alternatively (LOE III; SOR A) (ROVC: 90%)

15. For determination of mesorectal fascia (CRM) positivity, MRI should be used (LOE III; SOR A) (ROVC: 99%)

16. MRI and MDCT are equivalent for the detection of suspected mesorectal and pelvic sidewall lymph nodes, defined by size ≥8 mm. Additional features of lymph node involvement are heterogeneity and irregular border, best identified by MRI (LOE III; SOR A) (ROVC: 92%)

17. Abdominal CT or MRI and chest X-ray, although chest CT is preferred, are the minimal requirements for staging of distant metastases (LOE IV; SOR B) (ROVC: 100%)

18. MDCT or MRI are the preferred modalities for the evaluation of colorectal liver metastases, but for resolving differentiation problems MRI is preferred (LOE IV; SOR B) (ROVC: 96%)

19. FDG-PET should not be used routinely for initial staging (LOE IV; SOR B) (ROVC: 99%)

20. FDG-PET is advocated when synchronous liver metastasis is present and extra-mesorectal and extra-hepatic disease must be assessed in order to define therapeutic strategy (LOE II; SOR A) (ROVC: 95%)

21. Bone scan and brain imaging should only be performed according to symptomatology (LOE V; SOR C) (ROVC: 95%)

22. MRI-based MDT discussion is highly recommended preoperatively to define prognostic factors and treatment strategy in patients with rectal cancer, to reduce CRM positivity and achieve low local recurrence rate (LOE II; SOR A) (ROVC: 99%)

Preoperative treatment

Background

The aim of preoperative treatment is to reduce the risk of local relapse, to improve resectability and to enable R0 resection in CRM-positive disease. There are two approaches to preoperative therapy: short-course (25 Gy in 5 fractions) RT and long-course (50.4 Gy in 28 fractions) RT combined with ChT.
Short-course RT

There are 11 more recent randomized trials of short-course RT versus surgery alone for resectable rectal cancer with most of them reporting a significant decrease in local recurrence [38-42]. Two most recent large studies, the Dutch TME trial and the MRC CR07 trial [43,44], confirmed the significant benefit on local control with short-course preoperative RT even with TME surgery. Both trials showed no benefit in survival, however, in the MRC CR07 trial 3-year disease-free survival was improved in the preoperative irradiated group. Acute toxicity after short-course RT is usually mild when surgery is not delayed and, although early trials revealed a significant increase in late toxicity, this has not been reported in the more recent studies [43,44].

Long-course Chemoradiotherapy (CRT)

Very limited tumor shrinkage and no tumor downstaging is expected after short-course RT and immediate surgery, while after the long-course CRT schedule the longer overall treatment time and interval to surgery results in downsizing of virtually all cancers and in pathologic complete response (pCR) in approximately 15-20% of patients. Therefore, CRT is indicated in locally advanced T3c,d, T4, N+ disease and cases with a threatened or involved CRM. The same approach is recommended for upper rectal or rectosigmoid tumors that invade adjacent structures. MRI staging may allow a selection of patients with early stage III disease (stage T3a/b) in whom preoperative treatment may not be necessary [45]. Standard long-course CRT regimens include 3D conformally planned RT for 5.5 weeks (50.4 GY total dose) and either continuous infusion of 5-fluorouracil (5-FU) or capecitabine per os. Targeted chemotherapeutic agents are not recommended in this setting.

Short- vs. long-course CRT

Three randomized trials of preoperative short- versus long-course CRT have been reported in patients with resectable T3/T4, any N rectal cancer [46,47]. Both trials showed higher rates of early RT toxicity in the CRT groups but no significant differences in late toxicity. In the Polish study [47], the sphincter preservation rate, the local recurrence rate and overall survival did not differ significantly between the two groups. In the Australian trial [47], preliminary analysis also showed no significant differences in local control or survival. The Norwegian study [46] showed that long-course CRT is associated with better local control of the disease and higher survival rates compared to short-course RT. However, the question of which schedule is superior has not been resolved since the trials are small and underpowered to detect small differences, and longer follow up is required.

CRT and sphincter preservation

There is some debate regarding the impact of long-course CRT on sphincter preservation. Contrary to the belief that reduction in tumor bulk after CRT will increase the likelihood of anterior resection, the Polish study and also two meta-analyses [47,48] showed that tumor shrinkage had no impact on the anterior resection rate [47]. Only the German study of pre-versus post-operative long-course CRT showed a significant increase in sphincter preservation [19].

pCR

Most series suggest that there is improved outcome with increasing pathological response to CRT with patients achieving a pCR having a local recurrence risk of 1.5% and overall survival over 90% [49]. A series of retrospective studies from Brazil has highlighted the rationale of a 'wait-and-see' policy for patients who achieved a pCR [50], but long-term prospective observational studies with more uniform inclusion criteria are required to evaluate the risk versus benefit of this policy.

Pre- vs. postoperative CRT

It has been shown (CAO/ARO/AIO-94 trial) that preoperative CRT followed by adjuvant ChT compared to postoperative adjuvant CRT significantly reduces local recurrence, has less acute and long-term toxicity and in addition enables a higher rate of sphincter saving surgery by downsizing and thus improves functional outcome in low rectal tumors [51,52]. Therefore, preoperative CRT is the treatment of choice for all patients at higher risk for relapse (clinical stage II/III).

Upfront ChT prior to surgery

Intensive combination ChT, with 5-FU and oxaliplatin (FOLFOX) combined with targeted agents has been proposed instead of neo-adjuvant CRT prior to surgery in T3 tumors that do not threaten the circumferential mesorectal margin, as it achieves a pCR in more than one fourth of the cases. This approach is not recommended outside clinical trials, because of limited available data.

Upfront ChT prior to preoperative CRT

In locally advanced rectal tumors, intensive and ChT with or without the addition of targeted agents prior to neo-adjuvant treatment and surgery has been associated with increased R0 rate and reduced rate of metastatic disease [53,54]. However, data are limited and the approach should not be applied outside investigational clinical trials.
Staging after preoperative CRT

Background

Given the fact that major pelvic surgery for locally advanced rectal cancer is associated with postoperative morbidity of 40-50% [55], selecting patients for observation (ypT0, ypN0) or for local excision (ypT0-2, ypN0) after CRT, although within research protocols at present, represents a major challenge. Hence accurate restaging is of paramount importance. Most of the studies suggest that none of the available imaging modalities (ERUS, standard MRI, CT, or FDG-PET) are sufficiently accurate in identifying complete remission after CRT, offering PPV as low as 17-50% [32,56,57].

Downsizing of rectal cancer after CRT to ypT0-2 tumor can be predicted accurately by using MRI, with a high PPV at the cost of a lower NPV, because of diffuse fibrosis usually seen after RT therapy and inability to distinguish between only fibrosis and fibrosis with tumor cell nests. After volumetric analysis, when the initial tumor volume is less than 50 cm³ and the decrease in volume after CRT is more than 75%, then a ypT0-2 can be predicted [3]. It has recently been shown that MRI can identify the presence of residual tumor foci with good agreement between MRI tumor regression grade and histopathologic tumor regression grade [58].

Optimally, pre and post CRT MRI scans should be done with the same, optimized high-resolution MRI protocol using the same parameters, allowing for a more accurate assessment of tumor regression, potential operability and type of surgery to be offered. Parameters to be reassessed are in particular: i) tumor height and reduction in craniocaudal length, which may have an impact on the choice of operation; and ii) new CRM status, clear of areas of fibrosis, which represents the margins of resection, rather than tumor regression, which may still harbor malignant cells [25].

Selecting patients for local transanal excision after CRT, strictly within research protocols, relies not only on accurate prediction of ypT0-2, but also on accurate prediction of ypN0 lesions [59]. The morphological criteria (i.e. signal heterogeneity, irregular borders and size) used in pre-treatment MRI for evaluation of nodal status still apply after CRT. Accurate non-invasive MRI assessment of regression of poor-prognosis stage N2 disease to N0 or N1 indicates effective therapy [60].

The most recent multicenter prospective study in the field (MERCURY trial) [61] evaluated the prognostic relevance of post-neo-adjuvant therapy MRI assessment of tumor stage, nodal status, CRM, and MRI assessment of tumor regression grade (mrTRG) system in association with overall survival, disease-free survival and local recurrence in patients undergoing neo-adjuvant therapy and TME surgery. The study showed a significant correlation between radiologically determined tumor response and long-term outcomes and has shown that MRI assessment of tumor regression grade after preoperative therapy predicts overall survival, disease-free survival and patient prognosis, before surgery. Therefore, high-resolution MRI protocols with assessment of post-treatment TRG and CRM status can effectively help the MDT individualize treatment options before definitive surgery.

Diffusion-weighted MRI (DWI) helps differentiate between residual tumor, which possesses a higher cellularity and shows a high signal and fibrosis [62]. By combining

RECOMMENDATIONS

23. Preoperative CRT may be omitted in good prognosis patients staged by high-resolution MRI, as cT2, T3a/T3b, N0, with no threatened mesorectal fascia (CRM). Short-scheme RT could be considered (LOE III; SOR A) (ROVC: 81%)

24. Short-course RT is effective for resectable rectal tumors with no CRM involvement, where downsizing is not necessary. Moreover, it is more cost effective and time saving as compared to long course CRT (LOE I; SOR A) (ROVC: 93%)

25. Preoperative treatment is recommended in locally advanced tumors (≥cT3, CRM+, EMVI and/or N+). It may be also considered for T2 tumors of the lower rectum (LOE III; SOR A) (ROVC: 92%)

26. Long-course CRT is superior to RT in rectal tumors, where down-sizing and down-staging is necessary (LOE I; SOR A) (ROVC: 99%)

27. Long-course CRT is the treatment of choice for patients with non-resectable rectal cancer or a positive CRM (LOE I; SOR A) (ROVC: 99%)

28. Short-course RT followed by ChT and definite surgery after an interval of 8-12 weeks for locally advanced lesions is experimental and cannot be used outside of ongoing clinical trials (LOE II; SOR A) (ROVC: 94%)

29. For tumors of the upper rectum and rectosigmoid, neo-adjuvant CRT is recommended in case of invasion of the adjacent structures and where en-bloc resection does not seem feasible (LOE III; SOR A) (ROVC: 97%)

30. In ChT, either 5-FU/LV bolus, or 5-FU infusion or capecitabine can be used. Use of targeted agents in the setting of neo-adjuvant treatment is not indicated (LOE I; SOR A) (ROVC: 99%)

31. When indicated, preoperative CRT is the standard treatment. Postoperative adjuvant CRT is indicated whenever there is an increased risk of local recurrence following surgery and neo-adjuvant treatment was indicated but not given (LOE II; SOR A) (ROVC: 93%)

32. Intensive ChT instead of CRT prior to surgery for tumors not threatening the circumferential mesorectal margin is not recommended outside clinical trials (LOE III; SOR A) (ROVC: 100%)

33. Intensive upfront ChT prior to CRT and surgery for locally advanced tumor should only be performed within the frame of clinical trials (LOE II; SOR A) (ROVC: 98%)
morphological with functional imaging information, MRI and DWI can significantly improve sensitivity for selection of complete responders and thus reduce interpretation difficulties when the primary tumor bed has become fibrotic after RT treatment, resulting in less overestimation of tumor in patients with a complete tumor response. Nevertheless, interpretation errors can still occur with DWI [59,63]. Also, adding DWI to T2-weighted imaging can improve the prediction of tumor clearance in the mesorectal fascia after neo-adjuvant CRT before curative surgery, compared with T2-weighted imaging alone in patients with locally advanced rectal cancer. However, the challenge of small tumor cell-clusters identification, difficult to detect even at histology, still remains beyond the detection level of any imaging modality.

Although PET using 18FDG tracer can be of some help in the evaluation and prediction of response to CRT, PET is less reliable in identifying complete responders after completion of CRT and cannot differentiate between ypT0-2 and ypT3-4 tumors or fibrosis with or without tumor [64]. PET is reserved for the evaluation metastatic or recurrent disease, but its role for assessing mesorectal nodes is limited because mesorectal nodes are most frequently found at the level of the tumor and the avid metabolic uptake of 18FDG tracer within the primary tumor obscures visualization of the nodes [34,65].

**RECOMMENDATION**

34. Before reporting restaging MRIs, pre-treatment images should be reviewed and pre and post CRT MRI scans should be done with the same optimized high-resolution MRI protocol, and the same parameters should be assessed (LOE V; SOR A) (ROVC: 95%)

35. Phased array MRI using high-resolution examination protocols distinguishes more accurately ypT0-2 from ypT3 rectal tumors, with a high PPV after neo-adjuvant CRT, than standard MRI, CT or ERUS (LOE III; SOR A) (ROVC: 97%)

36. High-resolution MRI for the assessment of TRG after preoperative therapy predicts overall survival, disease-free survival and prognosis, before definitive surgery (LOE III; SOR A) (ROVC: 85%)

37. MRI is used for the assessment of regression of mesorectal lymph nodes after neo-adjuvant CRT (LOE V; SOR C) (ROVC: 88%)

38. Addition of DWI to optimized rectal MRI protocol improves the selection of complete responders after CRT (LOE IV; SOR B) (ROVC: 90%)

39. ERUS, CT, standard MRI, or FDG-PET are not appropriate imaging modalities to identify true complete responders to CRT (LOE IV; SOR B) (ROVC: 86%)

**Definitive local surgical treatment**

**General measures**

Although bowel mechanical preparation prior to surgery is not recommended in resections of the colon with primary anastomosis, in rectal cancer cases where resection of the rectum with low colo-anal anastomosis is planned to be covered by a defunctioning stoma, bowel cleansing is recommended. There is substantial evidence that application of enhanced recovery programs in rectal cancer surgery is associated with reduced stress, reduced duration of postoperative ileus, better physical performance, lower morbidity and faster recovery [66-69]. Therefore, implementation of “fast-track” is strongly recommended in rectal cancer surgery.

Transabdominal resection of the rectum is the standard treatment of rectal cancer. A large range of surgical procedures aiming to cure rectal cancer is applied. The exact type of procedure depends on the location and histological characteristics of the tumor. In any case, surgical resection should be curative (R0). It is of paramount importance to locate exactly the position of the tumor (distance from anal verge - anterior, lateral or posterior location), and this is achieved with rigid proctoscopy. The procedures available include high anterior resection of the rectum, low anterior resection of the rectum (LARR), ultra-LARR, intersphincteric resection of the rectum (IS-LARR), different types of abdominoperineal resection of the rectum (APR) and local excision of the tumor (open transanal or transanal endoscopic microsurgery, TEM).

**RECOMMENDATIONS**

40. Patients with rectal cancer should be treated in specialized centers by an MDT (LOE III; SOR A) (ROVC: 100%)

41. Hemoglobin blood level should ideally be >10 g/100 mL and clotting mechanisms corrected if impaired prior to surgery (LOE II; SOR A) (RAVC: 99%)

42. Preoperative baseline determination of serum CEA levels is recommended as a first-line surveillance test (LOE III; SOR A) (ROVC: 93%)

43. Bowel mechanical preparation is recommended if a diverting stoma is planned (LOE III; SOR B) (ROVC: 91%)

44. Implementation of enhanced recovery programs should be encouraged (LOE I, SOR A) (ROVC: 100%)

45. Transabdominal resection is the standard treatment irrespective of stage of tumor. Resectional surgery should be curative (R0) (LOE III; SOR A) (ROVC: 97%)

46. The type of surgery depends on the exact tumor location (LOE III; SOR A) (ROVC: 100%)
Interval from end of neo-adjuvant treatment and definitive surgery

In case of neo-adjuvant treatment in the form of short-course RT, the time interval of surgery is 1-2 weeks [39,40,47]. Following a long course of CRT, the exact time interval to surgery has not been defined, and varies from 6 to 12 weeks [19,70]. This depends on the grade of tumor response to neo-adjuvant treatment. Even if a complete response (CR) is detected on pelvic MRI 6 weeks after the end of treatment, this should be followed by resection of the rectum. Deferral of surgery in case of CR is only allowed within the frame of a research protocol ("wait-and-watch" or "expectant" policy).

In case of locally advanced (≥T3c/T4) rectal cancer, neo-adjuvant CRT aims to downsize and downstage the local disease [71]. If response is favorable as assessed by pelvic imaging, curative resection (R0) can be achieved. There is good evidence that patients with pCR after CRT show significantly lower local recurrence and higher survival rates than those with partial response [72,73].

RECOMMENDATIONS
47. The interval between the end of neo-adjuvant short course of radiation and surgery is 1-2 weeks (LOE II, SOR A) (ROVC: 80%)
48. The interval between the end of neo-adjuvant CRT and surgery varies between 6 and 12 weeks, depending on the grade of response (LOE III, SOR B) (ROVC: 92%)
49. In cases of complete response to neo-adjuvant treatment, as assessed by high-resolution MRI 6-8 weeks after end of treatment, transabdominal resection is again the standard treatment. Deferral of surgery and "wait-and-watch policy" could be followed only within the context of clinical trials (LOE III, SOR A) (ROVC: 98%)

Transabdominal resection: surgical principles

Background

The surgical principles of radical transabdominal resection for rectal cancer include: i) central ligation and division of the inferior mesenteric artery (IMA). Although it has been claimed that there is not any significant difference in short-term outcomes and oncological results between a high tie of the IMA and a low tie after the origin of the left colic artery [74], current evidence [75] shows that high IMA ligation and apical lymph node status assessment are of critical prognostic significance; ii) ligation and division of the inferior mesenteric vein just below the pancreas; iii) mobilization of the splenic flexure if necessary; and iv) TME which involves en-bloc removal of the package of the rectum and mesorectum covered by their intact embryologic envelop, that is the posterior mesorectal fascia and the Denovillier’s fascia. This is achieved by sharp dissection in the well-confined embryological planes and by preserving the autonomic pelvic nerve plexuses [1,2]. The macroscopic assessment of the quality of the resected specimen according to specific definitions [76-78] is mandatory. A complete TME specimen with intact fascia and no coning towards the bowel wall (intramesorectal or muscularis dissection) is a strong positive prognostic factor of local recurrence prevention [79], as is the negative by 1-2 mm CRM [76]. The distal to the tumor transection of the rectum is achieved either transabdominally or transanally, and the colo-anal anastomosis is fashioned with the use of a circular stapling device or by hand respectively.

A temporary defunctioning stoma to protect the anastomosis is strongly recommended, particularly in case of a very low colo-anal anastomosis, an anastomosis in the obese male patient, and after neo-adjuvant treatment [80,81]. The defunctioning stoma can be closed 3-6 months later, provided anastomosis is complete and leak is not identified by proctoscopy or double contrast imaging.

Upper rectal tumors

For tumors located at the upper third of the rectum and the rectosigmoid junction a high anterior resection of is recommended. The procedure involves the aforementioned described central to the tumor dissection of the bowel and a clear distal margin of transection of at least 5 cm. TME is recommended, although partial mesorectal excision is an alternative option. A stapled colo-rectal anastomosis is preferable. A defunctioning stoma is also recommended in case of neoadjuvant treatment.

Mid rectal tumors

For tumors located in the middle rectum (6-10 cm from the anal verge), LARR with TME, and preservation of the pelvic nerve plexuses is indicated. A clear distal bowel margin of at least 1 cm is required. However, a distal margin <1 cm may be adequate, provided that pathology report confirms a negative margin and CRT has preceded surgery [82]. A stapled colo-rectal anastomosis is preferable. A defunctioning stoma is also recommended in almost all cases [83].

Low rectal tumors

For T1, N0 tumors or T2-3, N0 subjected and responding to CRT and in which a distal bowel clearance >1 cm does not involve a major part of the external anal sphincter, a LARR with TME and intersphincteric distal dissection with hand-sewn colo-anal anastomosis is recommended [84-86]. Intersphincteric resection for low and ultra-low rectal cancer is associated with low morbidity, local recurrence rate of approximately 7%, disease-free survival of 78% and acceptable functional results [72]. For those cases with the above tumor characteristics, but in whom a colo-anal anastomosis is
expected to be associated with poor functional results, an intersphincteric APR is recommended [87]. Either stapled or hand-sewn, colo-anal anastomosis should be protected by a diverting stoma [83].

Anastomotic leak

Of the most embarrassing and potentially catastrophic problems of restorative colorectal surgery is anastomotic leak, reported in varying rates of 1-30%. Patient- and technique-related risk factors for anastomotic leak include advanced age, male sex, obesity, comorbidities such as diabetes mellitus or immunosuppression, preoperative pelvis RT, anastomotic tension and inadequate blood supply [88]. There is substantial evidence that anastomotic leakage from a colo-rectal or colo-anal anastomosis, apart from increased immediate morbidity and mortality, is associated with increased rate of local recurrence and reduced survival [83,89], although no impact of anastomotic leak on oncological outcomes has been reported [90]. Therefore, all technical preventive measures should be taken during surgery.

RECOMMENDATIONS

50. The main principles of curative surgery include: i) central ligation of IMA; ii) resection of the sigmoid colon; and iii) dissection of rectum and mesorectum along their embryological planes (fascia propria), thus achieving a TME (LOE III; SOR A) (ROVC: 99%)

51. For tumors of the upper third of rectum, a high anterior resection of the rectum with a partial or total (TME) mesorectal excision and a distal clear bowel margin of at least 5 cm are indicated. Addition of a diverting stoma in case of neo-adjuvant CRT is recommended (LOE II; SOR A) (ROVC: 100%)

52. For tumors of the middle third of rectum a LARR with TME and a distal clear bowel margin of at least 1 cm are recommended. Pelvic nerve plexuses should be preserved during dissection (LOE III; SOR A) (ROVC: 95%)

53. Fashioning of a stapled anastomosis, if technically feasible, is preferable. Pull-through technique and hand-sewn anastomosis is an alternative technique. Addition of a diverting stoma is mandatory in all cases (LOE I; SOR A) (ROVC: 94%)

54. For low and very low T2–T3 rectal tumors in which distal bowel clearance of at least 1 cm does not involve the external anal sphincter, an intersphincteric LARR with TME after neo-adjuvant treatment, stapled or hand-sewn anastomosis and covering stoma are recommended (LOE II; SOR B) (ROVC: 96%)

55. A defunctioning stoma should be applied in case of colo-anal anastomosis to reduce the rate of anastomotic leak-related morbidity and reoperation rate (LOE I; SOR A) (ROVC: 100%)

56. In low colo-rectal anastomosis, a protective stoma is recommended in case of increased risk of anastomotic leak-related morbidity and reoperation rates [80,81,91-93]. Others [94] support the view that similar anastomosis-related morbidity is accounted between patients with and those without a protective stoma, and that standard use of a defunctioning stoma should be questioned. According to a more recent study [95], application of defunctioning stoma should be tailored to the level of anastomosis: a protective stoma in low colorectal anastomosis does not prevent anastomosis-related morbidity, whilst a protective stoma is mandatory in colo-anal anastomosis by preventing sepsis and septic shock and by reducing reoperation rate because of anastomotic leak. In conclusion, colo-anal anastomosis should always be protected with a proximal stoma. In low colo-rectal anastomosis, a defunctioning stoma should be applied in case of increased risk of anastomotic leak, such as male sex, obesity, respiratory insufficiency or preoperative CRT.

There is no clear answer which type of diversion, loop ileostomy or loop colostomy, is superior in terms of morbidity. Ileostomy is associated with significantly less prolapse, less septic complications and reoperation rates compared with colostomy. On the contrary, lower rates of dehydration and renal failure are seen after defunctioning colostomy. Therefore, it is recommended that defunctioning ileostomy should be preferred, and colostomy should be reserved for the elderly who are more likely to present with dehydration [96-98].

Closure of the defunctioning stoma is attempted 6-8 weeks after initial surgery, provided that the patient is not subjected to adjuvant treatment and the integrity of the anastomosis has been assessed. In case of adjuvant treatment, closure of the defunctioning stoma is attempted at 4–6 weeks after the end of treatment. Closure of colostomy usually requires laparotomy, while of loop ileostomy is usually performed at the stoma site. A 20% of morbidity and 8% of reoperation rate are associated with the closure of ileostomy [99].

RECOMMENDATIONS
Surgical treatment of rectal cancer

**RECOMMENDATIONS**

60. For tumors of the lower third of rectum in which distal bowel clearance of at least 1 cm involves removal of the major part of the external anal sphincter, APR with TME and permanent colostomy is recommended (LOE I; SOR A) (ROVC: 98%)

61. The cylindrical or extralevator APR is supposed to offer a better quality of specimen and less CRM positivity at the level of puborectalis muscle compared with standard APR (LOE II; SOR B) (ROVC: 97%)

62. Locally advanced T4 tumors must be treated with upfront CRT, followed by extensive -beyond TME- surgery, only when an R0 resection can be achieved (LOE III; SOR A) (ROVC: 94%)

63. If an R0 resection of locally advanced T4 tumor, irresponsive to neo-adjuvant CRT, is not possible, palliative measures can be undertaken (LOE III; SOR A) (ROA: 96%)

**Locally advanced rectal tumor**

**Background**

In case of locally advanced rectal tumor, the type of resection depends on the extent of local disease, and varies from TME with LARR or APR to pelvic exenteration or/and sacral bone excision, similar to recurrent rectal cancer [114-116]. If an R0 resection is not possible, palliative measures can be undertaken [117,118].

**RECOMMENDATIONS**

62. Locally advanced T4 tumors must be treated with upfront CRT, followed by extensive -beyond TME- surgery, only when an R0 resection can be achieved (LOE III; SOR A) (ROVC: 94%)

63. If an R0 resection of locally advanced T4 tumor, irresponsive to neo-adjuvant CRT, is not possible, palliative measures can be undertaken (LOE III; SOR A) (ROA: 96%)

**Laparoscopic-assisted colectomy**

**Background**

Evidence on the laparoscopic approach for the surgical treatment of rectal cancer is accumulating rapidly, but at present fails to offer clear answers on several issues, mostly immediate postoperative morbidity, oncological outcomes and urinary and sexual function. According to the multicenter “CLASICC” trial [119,120] and several meta-analyses of comparative studies of limited quality [121-127], laparoscopic TME is as safe and effective as the open approach, both in terms of immediate postoperative outcomes and of oncological results. Moreover, laparoscopy is associated with faster recovery [128,129]. Also, quality of surgery and acquired specimen is comparable between the two approaches [123,130,131]. Therefore, the laparoscopic approach could be an alternative to the open for the surgical treatment of rectal cancer in selected scenarios.

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**APR of rectum**

**Background**

For low rectal tumors in which distal bowel clearance of >1 cm involves the major part of the external anal sphincter, an APR is indicated. Data from the Swedish Registry [100] and a review [101] show that standard APR for T3,4 rectal cancers is associated with higher local recurrence rate and a worse overall survival compared to LARR. This difference could be at first attributed to the fact that patients subjected to APR have tumors that are more advanced and exhibit different patterns of recurrence [102-104]. However, it is supported that standard APR achieves a suboptimal resected specimen with commonly threatened CRM at the level of the levator ani which translates to increased recurrence rates [105], and is usually associated with increased rate of intraoperative perforation at the level of tumor site [106]. For this reason a more extended form of APR is recommended: the so-called “extralevator” or “cylindrical” APR (ELAPE) [106-108] by which a complete resected specimen is acquired [109], and better oncological results are expected, although current evidence is not robust at present to support this expectation. The objection to the ELAPE is that impaired CRM and perforation at the tumor level practically occurs in case of anterior location of the lesion, in which case even the ELAPE cannot improve the quality of the resected specimen [106,110]. Also, according to recent reports, positivity of CRM and perforation rate do not differ between standard APR and ELAPE [110-112]. Reports on morbidity after ELAPE are conflicting, being either increased [111,112] or similar [110] to standard APR. Commonly, after the end of resection, closure of the perineal gap is achieved with the use of musculo-cutaneous flaps or biological prostheses [107,108,113]. The procedure is completed with a terminal colostomy.
cases (recommendations by the European Association for Endoscopic Surgery - EAES) [132].

Specific to the laparoscopic approach are some technical problems. Transection of the rectum distal to the tumor upon the pelvic aspect of the levator ani and a stapled colo-anal anastomosis are technically difficult, particularly in the obese male patient. These difficulties translate into increased conversion and anastomotic leak rates compared with the open approach [133]. For the above reasons, laparoscopic TME surgery for rectal cancer should only be performed by experienced surgical groups and at present within the frame of research protocols.

**RECOMMENDATIONS**

64. The laparoscopic approach for the surgical treatment of rectal cancer should be strictly applied by a very experienced surgical team. The principles of resection are the same as in the open approach. The approach is not indicated in locally advanced, perforating or obstructing tumors (LOE II; SOR A) (ROVC: 99%)

65. Predicting factors for conversion to open should be identified preoperatively, because under specific circumstances conversion may be associated with impaired short- and long-term outcomes. When conversion is anticipated with high probability the open approach should be preferred (LOE III; SOR A) (ROVC: 97%)

66. Obesity and male sex are factors associated with increased conversion and morbidity as a result of technical difficulties with distal transection of the rectum and stapled anastomosis. In these cases, alternative techniques such as hybrid laparoscopic-open approach or transanal transection and hand-sewn anastomosis are recommended (LOE III; SOR C) (ROVC: 98%)

**Transanal local excision**

**Background**

Transanal local excision is recommended for T1, N0-x or T2, N0-x lesions after neo-adjuvant CRT that are small (<3 cm), involve less than 30% of the lumen circumference, and are preferably located laterally or posteriorly and within 8 cm from the anal verge. With the application of TEM, even tumors located higher than 8 cm from the anal verge can be resected successfully. Local excision should be of full thickness and perpendicular to the rectal wall, including adjacent perirectal fat with clear rectal wall and fat margins of at least 3 mm. It is important to orient the specimen and fix it on a corkboard prior to be sent to the pathology department. If pathologic examination shows positive margins, poor tumor differentiation, perineural invasion, extramural vein invasion, tumor budding or lymphovascular invasion, a transabdominal radical resection is recommended.

Transanal excision carries the advantages of sphincter preservation, minimal morbidity, no mortality and fast recovery [134]. The disadvantage of the procedure is lack of pathological staging of regional lymph nodes and lack of information about lymph node micrometastases that tend to be as common as 10% in early rectal lesions [135-138].

As far as long-term oncological results are concerned, reports from studies of rather poor quality are conflicting. Some authors claim that local excision of T1, N0 tumors and T2, N0 after neo-adjuvant treatment is associated with recurrence rate similar to radical resection [139-141]. Opposite are the results reported by others [142], who showed a recurrence rate of 13.2% after local excision as compared to 2.7% after radical resection in 282 patients with T1 rectal tumor. They also found a 20% nodal involvement in patients subjected to radical resection. These results depict the inability to accurately stage the disease after local excision. Waiting for the results of several ongoing trials which test the oncological safety of local excision, the procedure is not recommended even for T1, with the exception of patients who refuse a radical resection or those with a poor general condition [143].

**RECOMMENDATIONS**

67. In patients with cT1 tumors, less than 3 cm in diameter and occupying less than one third of the lumen circumference, with microscopic characteristics of good prognosis, refusing transabdominal surgery, or presenting co-morbidities that precludes standard resectional surgery, transanal resection or TEM could be considered (LOE II, SOR B) (ROVC: 100%)

68. Resection should be full thickness and perpendicular to the rectal wall, including adjacent perirectal fat with clear rectal wall and fat margins of at least 3 mm (ROVC: 99%)

**Non-operative approach after combined modality therapy (CMT)**

**Background**

After neo-adjuvant CRT for locally advanced rectal cancer, pCR with no residual tumor at surgery is observed in 13-25% of the cases [73,144-146]. Also, there is substantial evidence that patients with pCR after CMT, subjected to TME, show excellent oncological outcomes, with a local recurrence rate of only 0.7%, distant metastasis rate of 8.7%, overall survival of 90% and disease-free survival of 87% [72]. Considering that definitive surgical treatment is associated with significant morbidity and that patients with pCR after CMT are of good prognosis, “expectant policy” and “deferring surgery” in case of recurrence could be a rational policy. If patients with pCR are approached non-operatively and observed closely, local and distant recurrence are seen in only 0.1-6% and 0-8.9% respectively [49,72,144-152]. However, opposite results concerning recurrence after initial pCR show rates greater
Surgical treatment of rectal cancer

than 80% within the first year [153]. Therefore, non-operative management should be reserved only for those with durable pCR. At present, non-operative treatment in patients with pCR after CRT should be applied in research protocols, and be reserved for patients unfit or unwilling to undergo surgery.

RECOMMENDATIONS

69. Non-operative approach and expectant policy for rectal cancer with clinical CR after neo-adjuvant CRT is performed only in the context of clinical trials. It can also be offered to patients unfit or unwilling to undergo standard resectional surgery (LOE III; SOR A) (ROVC: 99%)

70. Candidates for “expectant policy” after clinical CR are patients with initially small, well-differentiated, non-mucinous, T2N0 tumors (LOE III; SOR B) (ROVC: 89%)

71. A very intensive follow-up schedule, including pelvic MRI every 3 months for 5 years is necessary (LOE III; SOR A) (ROVC: 82%)

72. The evidence regarding feasibility and outcomes of salvage surgery in recurrent cases with initial clinical CR is low (LOE IV; SOR C) (ROVC: 92%)

Stage-based strategies of treatment (Figs. 1-3)

The stage of the disease, assessed at the initial diagnostic process and possibly modified by the pathological examination of the resected specimen, defines the therapeutic strategy. The following groups are in use for the stratification of treatment: a) very early rectal tumor; b) early rectal tumor; c) more advanced rectal tumor; d) locally advanced rectal tumor; and e) synchronous metastatic disease.

Very early rectal tumor

Although evidence is limited and well-designed clinical trials are required for cT1,sm1 tumors with low-risk features, standard transanal excision or excision by means of TEM, if technically feasible, is recommended as definitive treatment [154,155]. For cT1,sm2 tumors with low-risk features definitive treatment (TME) is the treatment of choice. Local excision is not recommended outside clinical trials, unless the patient refuses definitive treatment or has co-morbidities [154,155]. If histopathology shows deeper invasion or additional high-risk features (poor differentiation, lympho-vascular, venous or neural invasion) CRT can be added with or without definitive surgery.

Early rectal tumor

For cT1,sm3 and T2 tumor neo-adjuvant treatment is not necessary and definitive transabdominal surgery with TME is recommended. cT3a,b, N0, CRM (-) or non-threatening tumors of the middle and upper rectum are treated either with upfront short-course RT followed by transabdominal TME or with transabdominal TME alone. According to the CR07 trial, there is a marginal but significant benefit, in terms of local recurrence for early rectal tumors even of the upper rectum after preoperative short-course RT, but long-term morbidity must be taken into account [44]. If quality of surgery has been compromised or pathology shows positive CRM and neo-adjuvant treatment has not been given, postoperative CRT is recommended, with the expense of rather poor functional results.

More advanced rectal tumor

For cT3c/d, or cT tumors of the middle and upper rectum non-threatening or not involving the CRM, EMVI(-) preoperative treatment, either short-course RT or long-course CRT, followed by transabdominal TME surgery is recommended. In this group, cT3a/b tumors of the lower rectum, non-threatening or not involving the CRM, EMVI(-) are included. Also, preoperative treatment, either short-course RT or long-course CRT, followed by transabdominal TME surgery is recommended. There is not enough evidence in favor of either neo-adjuvant approach, short-course RT or long-course CRT. The former is less costly and is associated with acute toxicity; the latter can achieve significant downstaging and down-sizing.

Locally advanced rectal tumor

For cT3, CRM (threatening or +), or/and EMVI(+) and T4 tumors, neo-adjuvant long-course CRT is recommended. If response is favorable and R0 is possible, transabdominal TME -and beyond if necessary- surgery is recommended. Otherwise, palliative measures are recommended (see below). In this group, patients with involved lymph nodes of the lateral pelvic wall (obdurator, internal ileac nodes) are included, and neo-adjuvant CRT with extended lateral field is recommended. Surgery follows, if a R0 resection can be achieved by either TME or/and more extended pelvic surgery including removal of the lateral pelvic lymph nodes [156].

Synchronous metastatic disease (Fig. 4)

Background

In case of a rectal tumor with synchronous metastatic disease, treatment should be personalized and aim to achieve R0 resection at all sites. There are the following options:

a) non-symptomatic, ≤T3b, CRM(-), EMVI(-) rectal tumor: 3-month perioperative CRT followed by assessment of the response of the metastatic lesion. If response is favorable and resection of metastatic disease is feasible,
Figure 1 Treatment strategy for very early rectal tumors

surgery should be considered: i) primary tumor surgery first followed by metastatic disease resection at a second stage; ii) metastatic disease resection first followed by resection of primary disease at a second stage; and iii) one-stage resection of primary and metastatic disease. In all instances, postoperative CRT (FOLFOX) is given [157]. If response of metastatic disease is not favorable and primary tumor is asymptomatic, no surgery is required. Also, if R0 resection of the primary lesion is not feasible, no surgery is required. In both latter cases palliative measures can be undertaken.

b) symptomatic, >T3b, CRM(+), EMVI(+) rectal tumor: CRT followed by CRT at the resting period or upfront CRT followed by CRT and assessment of the response of both the primary and the metastatic lesion. Depending on the response the following therapeutic measures are taken. If response of both primary and metastatic disease is favorable, with anticipated R0 resection of both: i) resection of primary and metastatic disease at one stage; ii) metastatic disease resection first, followed by resection of primary disease at a second stage; iii) primary tumor surgery first, followed be metastatic disease resection at a second stage. If response of metastatic disease is not favorable and primary tumor becomes asymptomatic, no surgery is required. Also, if R0 resection of the primary lesion is not feasible, no surgery is required. In both latter cases palliative measures can be undertaken.

RECOMMENDATIONS
73. Treatment of synchronous metastatic disease is based on the stage of the primary and metastatic lesions, should be personalized, and aim at R0 resection (LOE II; SOR A) (ROVC: 100%)
Recurrent rectal cancer

Background

After introduction of neo-adjuvant treatment and implementation of TME with clear CRM, local recurrence of rectal cancer dropped from around 30% to below 10% [158]. Predictive factors for local recurrence of rectal cancer are surgeon’s experience to perform TME and adequate volume of cases, completeness of TME with clear CRM and distal margin, and specific tumor characteristics such as differentiation and lymphatic invasion [1,26,77,85,159]. History, physical examination and increase in carcinoembryonic antigen (CEA) raise suspicion for local recurrence, which is confirmed by imaging of the pelvis (CT, MRI, PET/CT) and positive biopsy of the mass [89].

Only fit patients should be subjected to further investigation for the assessment of local extent of the disease and the identification of possible distant recurrence. This procedure should be undertaken only by an MDT in highly specialized referral centers [85]. By imaging, local recurrence is classified as central-axial (anastomotic, mesorectal, perineal), anterior (involvement of genitourinary pelvic system), posterior (involvement of presacral fascia and sacrum) and lateral (involvement of lateral pelvic soft tissues, and lateral osseous pelvis) [160]. Anastomotic and anterior recurrences are more likely to be subjected to R0 resection than presacral-posterior or lateral [160].

If neo-adjuvant treatment has not been given at primary surgery, it should be administered prior to attempting resection of recurrent disease. Even if neo-adjuvant treatment has been given at primary surgery, an additional 30-40 Gy could be administered [161]. Also, if available, intraoperative RT of the pelvis can be considered [162].

The only curative treatment of locally recurrent rectal cancer is a complete R0 resection, possible in less than 50%. The surgical team should include colorectal surgeons, orthopedic

Figure 2 Treatment strategy for early rectal tumors

RECOMMENDATIONS

74. For early non-symptomatic primary rectal lesion with resectable metastatic disease, perioperative CRT followed by image assessment of response and then surgery is recommended. Adjuvant CRT is given (LOE II; SOR B) (ROVC: 91%)

75. For advanced primary rectal lesion with resectable metastatic disease, induction CRT, followed by R0 resection of metastases, followed by CRT if required, followed by CRT at the resting period is indicated. If response of primary tumor is favorable, surgery follows and adjuvant CRT is given. If an R0 resection of the rectal lesion is not feasible, palliative treatment is recommended (LOE III; SOR B) (ROVC: 92%)

76. In case of non-resectable metastatic disease at initial assessment, CRT is recommended. If response allows an R0 resection of the metastatic disease, surgery follows. If metastatic disease does not allow an R0 resection, palliative measures are recommended (LOE IV; SOR A) (ROVC: 100%)

77. Sequence of resection -primary or metastatic disease first-is personalized (LOE III; SOR A) (ROVC: 94%)
spine surgeon, surgeon of the genitourinary system and plastic surgeons. Absolute contraindications for resection are involvement of the external iliac vessels, tumor extension to the sciatic notch, edema of the lower limb resulting from venous or lymphatic occlusion and poor general status of the patient [163]. Relative contraindications for resection are distant metastases, primary stage IV disease, extensive involvement of the lateral pelvic wall, tumor extension to S2 vertebra and above, and predicted R1 or R2 resection [89,114-116].

CT after curative surgery is recommended, although there is no robust evidence. Immediate postoperative morbidity and mortality are 15-80% and 0-8%, respectively. After R0 resection, 5-year survival rates are reported at around 35%. Patients after R0 resection live longer by 38 and 53 months compared with those after R1 and R2 respectively. As R2 resections carry similar overall benefit to palliative treatment, they should be avoided [164,165].

**RECOMMENDATIONS**

78. Patients with rectal cancer should be treated in highly specialized centers by an MDT, supported by urologists, plastic surgeons, vascular surgeons and orthopedic surgeons (LOE III; SOR A) (ROVC: 96%)

79. Staging of the disease involves pelvic MRI, abdominal and chest CT and PET/CT (LOE III; SOR A) (ROVC: 93%)

80. CRT should be given, if not offered prior to initial surgery, in case of recurrent rectal tumor (LOE III; SOR A) (ROVC: 97%)

81. Surgery is the standard option of treatment of recurrent rectal cancer, provided that a curative (R0) resection can be achieved. The extent of resection depends on the location and the local extent of the...
Pathology

Background

The guidelines of the Royal College of Pathologists in the United Kingdom have gained widespread acceptance as the minimum standard for reporting this disease. They are available at https://www.rcpath.org/asset/E94CE4A2-DD2-44A7-84B9D-6829413CFC/.

Preparation and assessment of specimen

The macroscopic examination of the specimen is critical and of prognostic significance. The surgical specimen should be photographed to document the planes of surgical dissection. The lateral resection margin of the fresh surgical specimen must be inked. Macroscopic assessment of the resected fresh rectal specimen should include: quality of TME (mesorectal, intramesorectal, intramuscularis); distal margin length of clearance; quality of Denovillier’s fascia;
and width of peritoneal reflection. The APR specimen is assessed regarding presence of levator musculature at the anorectal junction as submucosal, sphincteric or extralevator. Also, the specimen is assessed for the presence of perforation, in particular at the site of the tumor. Then the specimen is opened leaving intact the tumor area and 2 cm below and above it, and is then fixed in formalin solution for 48 h [3]. The specimen from local excision of an early rectal cancer is spread but not stretched on a board and thickness and perpendicularly to the rectal wall, including adjacent perirectal fat with clear rectal wall and fat margins, are assessed and measured in mm. Histological examination of the colorectal specimen is based on a method described by Quirke and Morris [166]. After fixation, the specimen is sliced transversely at 3-4-mm intervals, looking for continuous spread and/or discontinuous tumor deposits and for involved lymph nodes at the CRM. The macroscopic CRM is measured with a ruler. The microscopic CRM measurement is best done by using a sheet of graph paper that is photocopied onto a sheet of acetate and cut to size, than by using the Vernier scale [166,167]. To record any perforation and the plane of surgical dissection anterior and posterior surfaces should be photographed [23,151,168-170].

The gross description of the histology report must include: i) location of the tumor (at or below the peritoneal reflection, or the distance from the dentate line if an abdominoperineal excision is performed, the tumor size (3 dimensions), the length of proximal and distal margins, the depth of invasion, tumor perforation, other lesions not related with the tumor such as Crohn's disease, ulcerative colitis, polyp, familial adenomatous polyposis, and the number of lymph nodes retrieved. Blocks should be taken from the area closest to the CRM and any area where the tumor extends to within less than 3 mm from the margin [166,167,169,171].

Standard microscopic description must include: i) histologic type, according to WHO classification. Mucinous component, presence of signet ring carcinoma (>50% signet ring), and medullary carcinomas should be mentioned, as these elements affect prognosis [166,168,170,172]; ii) histologic grade (low grade: >50% glandular formation; high grade: <50% glandular formation) [168,171,172]; iii) T status. In pT1 lesions, distance of tumor from the resection margin, vascular or lymphatic invasion and the depth of invasion into submucosa must be reported [172]; iv) total number and number of involved lymph nodes (≥12 lymph nodes must be found to predict actual lymph node status). Any node containing malignant cells, irrespective of size and even with smooth contour is considered as involved. Extramural tumor nodules measured >3 mm without evidence of residual lymph node tissue are considered as positive lymph nodes [23,167,168,171,172]; v) blood, lymphatic vessel, tumor budding, and perineural invasion (each one an independent prognostic factor) [23,166,168,170,172]; vi) presence of tumor infiltrating lymphocytes; and vii) surgical margin status and residual tumor classification [R classification system with surgical margin status, CRM status; and tumor regression after preoperative treatment (TRG)].

**RECOMMENDATIONS**

83. Surgical quality of TME should be recorded according to the MERCURY classification (LOE III; SOR A) (ROVC: 99%)

84. The resected fresh rectal specimen should be photographed at all aspects (LOE IV; SOR A) (ROVC: 100%)

85. By microscopic examination of the resected rectal specimen the following morphological rectal...
specimen the following morphological parameters are assessed: i) mesorectal surface quality (mesorectal, intramesorectal, muscularis); ii) distal margin length of clearance; iii) quality of Denovillier’s fascia; and iv) width of peritoneal reflection (LOE III; SOR A) (ROVC: 92%)

86. Any perforation of the specimen at the tumor site should be reported (LOE II; SOR A) (ROVC: 100%)

87. At the macroscopic assessment of rectal specimen after APR, beyond TME classification, resection at the level of anorectal junction should be classified as submucosal, sphincteric or extralevator (LOE III; SOR A) (ROVC: 100%)

88. Specimen is opened leaving intact the tumor area and 2 cm below and above it, and fixed in formalin solution for 48 h (LOE II; SOR A) (ROVC: 97%)

89. Histopathologic assessment of the local excision specimen should include: i) status and measurements of the circumferential and basal resection margins; ii) depth of invasion into the submucosa (sm1,2,3) or/and muscularis propria or/and mesorectal fat; iii) possible invasion of lymph vessels; and iv) grade of differentiation (LOE II; SOR A) (ROVC: 99%)

90. Microscopic description should include the histologic type and histologic grade of the tumor. Low-grade tumor presents with >50% glandular formation. In the high-grade tumor, a <50% glandular formation is observed (LOE I; SOR A) (ROVC: 99%)

91. Tumor invasion into the mesorectum is measured in mm (LOE III; SOR A) (ROVC: 99%)

92. CRM should be assessed as negative (>1 mm from tumor) or involved-threatened (<1 mm from tumor) (LOE III; SOR A) (ROVC: 94%)

93. Tumor regression after preoperative treatment should be graded (LOE III; SOR A) (ROVC: 99%)

94. In patients without preoperative treatment at least 12 lymph nodes (ASCO guidelines)/12 lymph nodes (TNM/NICE guidelines) have to be assessed. All identified lymph nodes should be examined (LOE III; SOR A) (ROVC: 96%)

95. A discrete extramural tumor nodule with smooth contours, irrespective of size, is considered as a positive lymph node (SOR A) (ROVC: 89%)

96. Extramural tumor deposits without evidence of residual lymph node tissue are considered as metastatic disease (SOR A) (ROVC: 83%)

97. Distance of a positive lymph node or a tumor deposit close to mesorectal fascia should be reported separately (ROVC: 97%)

98. The minimum number of lymph nodes required for accurate staging after neo-adjuvant treatment is unknown (ROVC: 92%)

99. Extramural venous invasion or small vessels in the bowel wall and the presence of perineural invasion are reported, and are considered a bad prognostic factor (LOE; SOR) (ROVC: 100%)

100. The intratumoral lymphocytic infiltration is associated with microsatellite instability and is considered an independent favorable prognostic factor (LOE; SOR) (ROVC: 94%)

101. Using the R classification system, surgical margin status should be reported (SOR A) (ROVC: 100%)

102. Rectal cancer is classified according to the pTNM system or ypTNM (5-7) system in resection specimens after CRT. The exact classification system should be reported (SOR A) (ROVC: 99%)

Follow up

See relative chapter in Part II: Surgical treatment of colon cancer [6].

Concluding remarks

Members of the HeSMO and other experts formed an MDT, assigned to develop guidelines on rectal cancer management. Embracing background knowledge and current evidence, the executive committee constructed a document from which derived statements were subjected to Delphi methodology to achieve as maximum consensus as possible. The aim of the present effort was to improve quality in the diagnosis, staging and treatment of rectal cancer, within the frame of the local National healthcare system.

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