Practice parameters for early rectal cancer management: Italian Society of Colorectal Surgery (Società Italiana di Chirurgia Colo-Rettale; SICCR) guidelines

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Abstract

The introduction of new technologies for diagnosis and screening programs led to an increasing rate of early detection of colorectal cancer. This, associated with the evolution of endoscopic techniques of local excision, led to the assessment of new strategies to reduce morbidity related to treatment, especially for early rectal cancer (ERC). Nevertheless, the definition of ERC and its staging and treatment algorithm are still under debate. The Italian Society of Colorectal Surgery developed practice guidelines to provide recommendations on the diagnosis, staging and treatment of ERC. A systematic review on the topic was performed by a multidisciplinary group of experts selected based on their clinical and scientific expertise in endoscopy, endoscopic ultrasound, magnetic resonance and surgery, with the aid of an external international audit.

Keywords

Early rectal cancer Endorectal ultrasound Magnetic resonance imaging Transanal endoscopic microsurgery Local excision

Introduction

Colorectal cancer treatment has been subject to profound changes in the past few decades due to the introduction of new surgical and endoscopic technologies which, together with genetic studies and neoadjuvant chemo-radiotherapy, provided patients with better, less invasive treatment [1].

Moreover, the introduction in Italy of screening programs, based on faecal occult blood testing and colonoscopy, led to an increasing rate of early detection of cancer.
The changes were especially important in the field of rectal cancer. Unfortunately, there are not many studies on these treatment options with a high level of evidence, both for statistical reasons (due to the particular epidemiology and to ethical concerns) and because some of these treatments have been only recently introduced. Therefore, the scientific community has emphasised the importance of conferences and clinical guidelines, in which experts in the field, from different environments, try to determine what constitutes best practice, using evidence-based data when available. While the literature on early colorectal cancer treatment or multimodal treatments of rectal cancer is extensive, the literature focusing on early rectal cancer (ERC) is still limited even though there are multiple diagnostic pathways, including endoscopy imaging and ultrasound, magnetic resonance imaging (MRI) and computed tomography (CT) and a wide variety of treatments ranging from major surgery, such as total mesorectal excision (TME) with abdominoperineal resection (APR) to endoscopic resections, or transanal surgery, each eventually combined with neoadjuvant or adjuvant chemoradiotherapy [2].
The complexity of the topic has recently pushed the European Association for Endoscopic Surgery (EAES) to endorse a consensus conference on it [3], and the Italian Society of Colorectal Surgery (SICCR) has decided to complete the work with a position statement apt to define the diagnosis and the subsequent treatment of ERC in the context of the Italian healthcare system. A number of Italian experts in the field were selected and have interacted telematically with a Delphi method [4]. A literature search was conducted by searching PubMed, Embase and the Cochrane Library databases for each single topic, with the aid of the patient, intervention, comparator/control, outcome (PICO) search strategy [5]. The evidence of the outcomes has been organised according to the latest Oxford classification [6].
We describe below the work done by the work group, first agreeing on a clear definition of ERC, then focusing on the diagnostic options available today and finally concentrating on the state of the art of the different treatment options applicable in our healthcare system.

Definition

In order to clarify the field of interest of the present position statement, we thought it necessary to give a definition of ERC. In Western countries, the generally accepted definition of ERC is a stage I disease, i.e. any T1–T2 N0 M0 tumour. This is in some way different from the definition adopted in Japan which includes only Tis and T1 N0 M0 [7–9]. This is why current concepts commonly accepted in the Far East have to be translated with much care. This of course influences significantly the need to further differentiate the various treatments for different sub-stages if possible.

Endorectal ultrasound staging and restaging

Endorectal ultrasound (ERUS) can distinguish layers within the rectal wall. It provides the most accurate assessment of the depth of tumour penetration for ERCs, and perirectal spread. It is recommended as the best modality for the staging ERC [EL: II; GoR: A].
To assess the best modality to resect ERCs, it would be mandatory to have an accurate staging because of its crucial role in decision-making. High-frequency (12, 12.5, 15, 20, 25 and 30 MHz) ultrasound with mini-probes or three-dimensional (3D) ERUS provide high-resolution images of the layers of the rectal wall and can reliably identify lesions that have a low risk of spreading, suitable for local excision (LE) by the different techniques.
In a meta-analysis [10] on the accuracy of ERUS in differentiating T stages of rectal cancers, the pooled sensitivity and specificity to determine T1 stage were 87.8 and 98.3 %, respectively,

decreasing to 80.5 and 95.6 % for T2 stage, respectively, 96.4 % and 90.6 for T3 stage, 95.4 and 98.3 % for T4 stage.
Using high-resolution 3D imaging, the following ultrasonographic criteria have been proposed to determine the corresponding depth of submucosal invasion: (1) uT1 slight, superficial irregularity of the submucosa layer, corresponding to Sm1, (2) uT1 massive, complete invasion of the submucosa, without including the muscularis propria layer corresponding to Sm2 and Sm3 [11]. Adopting the above-mentioned criteria, Santoro [9] in a series of 142 patients with a clinically possible T1 rectal cancer reported an overall accuracy of 95.2 % in selecting the appropriate management. The limitation of ERUS is demonstrated by overstaging of T2 tumours as peritumoural inflammation cannot be differentiated from early invasion of the muscularis propria. Understaging may result from the failure to detect microscopic malignant invasion.
On the other hand, when applied on a wide scale, ERUS failed to demonstrate such an accurate assessment of the depth of tumour penetration. In 2011 Marusch [12] presented data of a multicenter, prospective, country-wide quality assurance study at more than 300 hospitals in Germany, including more than 7000 patients. He showed a uT–pT correspondence of 64.7 with an 18.0 % understaging and a 17.3 % overstaging. Here too, the poorest correspondence was found for T2 tumours. Case volume influenced results but not as much as expected.
The sensitivity and specificity of ERUS in assessing metastatic lymph nodes are varied but remained high [EL: II; GoR: A].
Published data on the accuracy of endoscopic ultrasound (EUS) for diagnosing nodal invasion in patients with rectal cancer have been inconsistent. The criteria for the diagnosis of metastatic lymph nodes include low echogenicity, clearly defined boundaries, diameter >5 mm and round shape. Puli [13] conducted a meta-analysis, reporting a pooled sensitivity of ERUS in diagnosing nodal involvement of 73.2 % and a specificity of 75.8 %. The positive likelihood ratio of ERUS was 2.84, and the negative likelihood ratio was 0.42.
The use of 3D ERUS could potentially further increase the accuracy [EL: III; GoR: C].
Kim [14] reported that lymph node metastases were accurately predicted in 84.8 % of patients by 3D-ERUS compared with 66.7 % by 2D-ERUS, while Santoro [15] reported a 95.6 % of accuracy of 3D-EUS for lymph node metastases.

Magnetic resonance imaging staging and restaging

In many countries MRI is now central to the investigation and management of rectal cancer. International guidelines for the management of rectal cancer recommend MRI as pivotal for staging the primary tumour.
MRI is recommended as the technique of first choice for the overall primary staging of rectal cancer. Differentiation between T1 and T2 tumours is not possible with MRI [EL: II; GoR: A]. Endorectal ultrasound remains the imaging method of first choice to differentiate between T1 and T2 tumours if local resection is being considered [16, 17].
At primary staging, MRI can differentiate between T2 and T3 tumours, N0 and N+ status free and involved mesorectal fascia using 2D T2W sequences only [EL: II; GoR: A].
Axial and coronal T2-weighted planes should be angled perpendicular and parallel to the tumour axis as possible, respectively. Because the mesorectum and its fascia taper caudally as they funnel towards the pelvis floor, this region (including the anterior pelvic organs, such as the prostate/seminal vesicles in male patients and uterus/vagina in female patients) is at increased risk of involvement by low tumours, and angulation of axial planes here is crucial [16, 18].
It is recommended to routinely perform MRI for restaging rectal cancer after neoadjuvant chemoradiation [EL: II; GoR: A].
For restaging after a long course of chemoradiotherapy (CRT), MRI should be performed routinely. In 2012 the European Society of Gastrointestinal and Abdominal Radiology (ESGAR) consensus

meeting, 75 % of the experts agreed that the combination of endoscopy and MRI is the best approach to confirm a complete response after CRT [16, 19, 20].

The minimal recommended field strength for adequate (re)staging of rectal cancer is 1.0 T MRI, but ideally higher field strengths should be used (1.5 T or 3.0 T). The use of an external coil is recommended, and the use of an endorectal coil is not recommended [EL: II; GoR: A].

There was no agreement on the optimal field strength, although most believed that 1.5 T is preferable to 3 T. If there is no access to a 1.5-T or 3.0-T system, 1.0-T MRI should only be used. Hypothetically, it is also feasible to perform staging at 1.0 Tesla, although it is important to assess whether the diagnostic performance is at a sufficient level depending on factors such as equipment (e.g. outdated versus modern magnet, closed- versus open-MRI system) [16].

It is recommended to routinely include 2D T2-weighted sequences in a standard clinical MRI protocol for the (re)staging of rectal cancer [EL: II; GoR: A].

Use of a sagittal and axial 2D T2-weighted sequence is mandatory for the assessment of tumour height, T–N-stage, mesorectal fascia (MRF) involvement and the presence of EMVI both before and after neoadjuvant treatment. The use of a coronal 2D T2-weighted sequence is recommended. The recommended optimal slice thickness for staging and restaging MRI is uncertain and ranges between 1 and 3 mm (maximum 4 mm). The axial and coronal T2-weighted sequence should be angulated perpendicular and parallel to the tumour axis for tumours in the middle and upper part of the rectum [16].

The use of diffusion-weighted imaging (DWI) is not mandatory for primary staging but is recommended for restaging (specifically for assessment of the T-stage) after CRT [EL: II; GoR: A].

It is unclear whether DWI is helpful for nodal restaging and assessment of MRF involvement after CRT. It is unclear whether it is possible to reliably differentiate between a complete response (yT0) or residual tumour using either 2D T2-weighted sequences or diffusion-weighted sequences [16].

The use of contrast-enhanced dynamic or steady-state T1-weighted sequence is inappropriate and not recommended [EL: II; GoR: B].

The use of contrast-enhanced dynamic or steady-state T1-weighted sequences is not recommended either. While some studies have investigated dynamic contrast-enhanced MRI for tumour response evaluation [21] or lymph node-specific contrast agents [22, 23] for nodal staging, the available evidence is limited and at present there is no role for contrast-enhanced MRI sequences in either the primary MRI staging or restaging of rectal cancer [16].

In primary staging, stranding into the mesorectal fat is an equivocal sign [EL: II; GoR: B].

This may indicate either a T2 tumour with desmoplasia or a T3 tumour with tumoural strands. Criteria for lymph node staging on T2-weighted sequences are signal intensity, border contour and shape. Size is also a predictor, but there is no optimal cut-off threshold for involved nodes. The MRF should be considered involved if the distance between tumour and MRF is ≤1 mm and threatened if the distance between tumour and MRF is ≤2 mm. If on primary staging MRI stranding extends from the tumour into the MRF, this should be considered involved. The assessment of extramural venous invasion is recommended but not obligatory [16].

In restaging after neoadjuvant treatment, a normalised, two-layered rectal wall after CRT should be considered a sign of a clinically complete tumour response (yT0) [EL: II; GoR: B].

A hypointense, fibrotic residue is an equivocal feature that may indicate either residual tumour or a complete response. Size is more reliable as a criterion for lymph node staging after neoadjuvant treatment. A reduction in size and homogeneity of the nodal signal intensity is indicative of a sterilised node. It is not clear whether normalisation of the shape (oval) or border (regular) is an indicator of sterilised nodes. When a fat pad reappears between the tumour and MRF after CRT, this indicates regression from the MRF. The presence of stranding into the MRF after CRT should be considered an equivocal sign that may or may not indicate persistent MRF involvement [16, 24–26].

Treatment

While T1 cancers may be good indications for LE in selected patients, because of the risk of disease spread up to 15 %, T2 cancers treated with curative intent should undergo radical surgery [27–29] *[EL: II; GoR: B].*

For T2 cancers of the low rectum, neoadjuvant treatment may be considered, aiming at conservative surgery to reduce the risk of a definitive stoma but only within clinical trials and with patient consent considering the high percentage of severe complications [30].

LE should be proposed for T1 cancers, with low (G1) or intermediate (G2) differentiation grade, that are mobile, exophytic and not ulcerated, with no evident nodal metastasis at preoperative ERUS or MRI, with possibility to perform a full-thickness en bloc excision with a cancer free margin >1 cm [31] *[EL: II; GoR: B].*

In any case, LE should be considered the last step of the work-up and potentially the effective treatment.

LE is considered curative if the lesion is resected with clear margins and confirmed either a benign lesion or a cancer staged up to T1 N0 with favourable clinical and pathological features [EL: II; GoR: A].

The term "LE" includes several surgical procedures, ranging from endoscopic mucosectomy to full-thickness LE with partial resection of mesorectal fat.

To be effective, LE aims to achieve a R0 en bloc resection of the wall with clear resection margins. The best way to achieve this goal is to perform a full-thickness resection down to the mesorectum. Nevertheless, patients with intraperitoneal rectal cancers can be offered a full-thickness resection, with no increased morbidity and cancer-related mortality [8, 9, 32–34].

Due to the absence of adequate lymphadenectomy, any LE may be considered curative only when the incidence of lymph node metastases is very low, as for up to T1 sm1 (0–3 %), while it increases up to 15 and 25 % for T1 sm2–3 and T2, respectively [35–40].

When unfavourable pathologic features, including depth of tumour invasion beyond pT1 sm1, poorly differentiated tumour grading, lymphovascular invasion or positive resection margins, are found in the LE specimen, rectal resection with TME is recommended [EL: II; GoR: B].

The current evidence supports LE only in the treatment of "low-risk" ERCs, while "high-risk" ERCs should be addressed with rectal resection with TME in order to minimise the risk of recurrence [41–43].

Radical surgery is more difficult after a local full-thickness excision of a rectal lesion, with a higher risk of complications and of permanent stoma, due to the fibrotic reaction consequent to the first surgery [44, 45].

A surgical LE should not follow a partial non-curative resection with endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) for a histology report of a deep margin infiltration by cancer tissue [EL: II; GoR: B].

According to the Guidelines of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) published in 2010, a positive deep margin for remnant disease is a forced indication for radical surgery, rather than a surgical full-thickness EL [46].

This is because part of the disease has already been removed by flexible endoscopy, with no correct pathology staging, and therefore not only the risk of residual disease but also the risk of possible lymph node metastases should be addressed. When flexible endoscopy fails to achieve an R0 resection in presence of cancer tissue, the patient must be treated with radical surgery or TME.

Transanal endoscopic microsurgery (TEM) should be considered the transanal surgical technique for the treatment of ERCs.

Traditional transanal excision (TE), due to the high local recurrence rates, should be limited to a few cases of highly selected distal rectal lesions if TEM is not feasible for technical reasons [EL: II; GoR: A].

A few comparative studies have focused on the surgical outcomes of patients undergoing TEM or TE for large rectal adenomas and ERCs [9, 47–49]. In all these studies TEM showed a benefit compared with TE in terms of rate of positive margins, fragmented specimens and recurrence.
Transanal minimally invasive surgery (TAMIS) is a promising technique, but burdened by the difficulties in suturing iatrogenic peritoneal defects, requiring conversion to laparoscopy, which limits its field of application to clearly extraperitoneal lesions only.
Small case series with a short follow-up have demonstrated the feasibility and safety of this platform in the treatment of extraperitoneal ERCs. To date, there are no clinical prospective studies comparing TEM and TAMIS. It must be emphasised that the technique often requires conversion to laparoscopic surgery, for cases with iatrogenic peritoneal defects, due to the difficulties in achieving a tight closure of the wound.
Based on the evidence available, TEM should be considered the transanal surgical technique of choice for the treatment of ERCs. TE should be limited to a few cases of highly selected distal rectal lesions and TAMIS should be used if TEM is not available.
ESD also aims at achieving an en bloc curative resection. In the absence of credible comparative studies, a recent systematic review and single-arm meta-analysis [50] comparing safety and effectiveness of ESD and full-thickness TEM in the treatment of non-invasive large rectal neoplasms (>2 cm), showed a significantly higher en bloc resection rate and R0 resection rate after TEM ($p < 0.001$), though equivalent post-operative morbidity rate and recurrence, but further abdominal surgery for the treatment of complications or for oncologic reasons was necessary in 8.4 % of ESD patients compared with 1.8 % of TEM patients.
LE following neoadjuvant treatments might be offered to frail patients with less favourable clinical and pathological features to reduce the clinical risk of a radical operation and to major responders finalised to a conservative approach [EL: II; GoR: B].
LE has also been proposed for frail patients or in those refusing major surgery to remove more invasive rectal cancers (T2 and T3), despite the significantly higher risk of recurrence [51–54]. In these cases, a neoadjuvant (chemo)radiotherapy might improve the oncologic outcomes but more clinical data are needed [55, 56].
Taking advantage of the significant tumour regression, tumour downstaging and sterilization of perirectal lymph nodes in locally advanced rectal cancer treated with neoadjuvant CRT or short-course chemoradiotherapy (SCRT), TEM may be offered in combination after neoadjuvant treatment [57–61]. Patients responding to preoperative (chemo)radiation are those who may benefit most from TEM. More precisely, ypT0 has a null local recurrence rate, ypT1 only 2 %, while ypT2 is associated with local recurrence rates up to 20 % [55].
The most frequent complications (sometimes >60 %) after TEM performed in patients treated with neoadjuvant long-course CRT are related to the rectal wound-healing process, although it has to be made clear that all of these patients are treated conservatively.
Two ongoing studies, the TREC and CARTS groups have combined their phase II protocols (STAR–TREC) to produce a single phase III trial that will randomize patients to one of three treatments: (a) standard radical surgery, (b) SCRT + TEM and (c) CRT and TEM.

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