

Rectal cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

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incidence

The crude incidence of rectal cancer in the European Union is ~35% of the total colorectal cancer incidence, i.e. 15–25/100 000 per year. The mortality is 4–10/100 000 per year with the lower figures valid for females, the higher for males.

diagnosis

Diagnosis is based on a clinical rectal examination including rigid proctoscopy with biopsy for histopathological examination. Tumors with distal extension to ≤15 cm (as measured by rigid proctoscopy) from the anal margin are classified as rectal, more proximal tumors as colonic.

staging and risk assessment

Complete history and physical examination, complete blood count, liver and renal function tests, carcinoembryonic antigen (CEA), chest X-ray (alternatively CT scan) and CT or MRI or ultrasound of liver should be carried out.

Endoscopic ultrasound for the earliest tumors (cT1–T2) or rectal MRI for all others is recommended in order to select patients for preoperative treatment. Complete colonoscopy pre- or postoperatively is required.

Histopathological examination should include surgical specimen with proximal, distal and circumferential margins and regional lymph nodes (at least 12 nodes are recommended to be examined).

The TNM 2002 staging system (Table 1) should be used.

treatment

localized disease

overall strategy. An important aim is to treat so that the risk of residual disease in the pelvis, frequently causing a disabling

Table 1. TNM 2002 system

TNM	Stage	Extension to
Tis N0 M0	0	Carcinoma <i>in situ</i>
T1 N0 M0	I	Submucosa
T2 N0 M0	I	Muscularis propria
T3 N0 M0	IIA	Subserosa/perirectal tissue
T4 N0 M0	IIB	Perforation into perirectal tissue or invasion to other organs
T1–2 N1 M0	IIIA	1–3 regional nodes involved
T3–4 N1 M0	IIIB	1–3 regional nodes involved
T1–4 N2 M0	IIIC	4 or more regional nodes involved
T1–4 N1–2 M1	IV	Distant metastases

local recurrence, is very low (preferably less than ~5% in the population in whom curative treatment is intended) and, at the same time, with as little acute and late morbidity as possible. This should be possible in all but the few (≤10%) cases presenting with a fixed tumor growing into a non-readily resectable organ.

Another aim is to treat so that good sphincter function can be preserved in as many patients as possible.

need for quality assurance and control. Treatment of rectal cancer is demanding and requires great skill in the entire multidisciplinary team. Good pathology and long-term complete follow-up, also including functional aspects, are important for quality control.

risk-adapted treatment. In the earliest, most favorable cases [T1–2, some early T3, N0 (T3a according to MRI)], surgery alone, either a local procedure, e.g. using the transanal endoscopic microdissection (TEM) technique in appropriately selected cases (T1, N0) [III, A] or a sharp radical dissection using the total mesorectal excision (TME) technique [II, A].

In more locally advanced cases [most T3–T3b (c according to MRI) some T4 (e.g. vaginal or peritoneal involvement only), N+], preoperative radiotherapy is recommended followed by TME, since this reduces local recurrence rates [I, A]. A dose of 25 Gy, 5 Gy/fraction followed by immediate surgery is a convenient, simple and low-toxic treatment [I, A]. More demanding, but not more effective alternatives [II, A] are 46–50 Gy, 1.8–2 Gy/fraction without or with 5-fluorouracil (5-FU)

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(bolus, continuous infusion or peroral) [III, A]. Whenever possible, preoperative treatment is preferred since it is more effective and less toxic than postoperative treatment [I, A].

In the most locally advanced, frequently non-resectable cases (T3 crm+, T4 with overgrowth to organs not readily resectable), preoperative radiochemotherapy, 50 Gy, 1.8 Gy/fraction with concomitant 5-FU-based therapy should be used [II, A], followed by radical surgery 6–8 weeks later.

postoperative therapy. Postoperative chemoradiotherapy (e.g. 50 Gy, 1.8–2.0 Gy/fraction) with concomitant 5-FU-based chemotherapy is no longer recommended but could be used in patients with positive circumferential margins, perforation in the tumor area or in other cases with high risk of local recurrence if preoperative radiotherapy has not been given [I, A].

Similar to the situation in colon cancer stage III (and ‘high-risk’ stage II), adjuvant chemotherapy can be provided, even if the scientific support for sufficient effect is less [II, A].

local recurrences

Patients with recurrence (if radiotherapy was not given in the primary situation) should receive preoperative radiotherapy with concomitant chemotherapy [II, A].

In patients previously irradiated, attempts at providing additional radiotherapy, externally or using intraoperative radiotherapy could be tried [IV, D].

Attempts at radical surgery should take place 6–8 weeks after radiotherapy [II, A].

In patients with prior radiotherapy for whom salvage surgery is not an option, systemic chemotherapy should be considered as an option.

disseminated disease

Whether patients with primarily disseminated disease (synchronous metastases) should receive first locoregional treatment and then systemic treatment, or the reverse, may be apparent in certain cases, but is otherwise poorly known [IV, D]. Age, co-morbidity, patient preference, extent of primary and metastatic disease must be considered.

In selected cases treatment may include surgery of resectable liver or lung metastases [III, A]. Other surgical or stenting procedures [III, A] or radiotherapy should be considered as palliative procedures [II, A].

First-line palliative chemotherapy should be considered early and consists of 5-FU/leucovorin in various combinations and schedules with oxaliplatin or irinotecan, with or without bevacizumab [I, A].

Second-line chemotherapy should be considered for patients with maintained good performance status [I, A] and third-line therapy for selected patients, also in good performance status. [II, A].

follow-up

Follow-up serves to identify patients in need of salvage surgery or palliative care and to prevent second colorectal cancers. There is no strong proof that regular follow-up after successful

treatment improves the outcome of patients with rectal cancer. A provisional recommendation is:

- History and rectosigmoidoscopy (if possible) every 6 months for 2 years [V, D]. A completion colonoscopy if not done at the time of diagnostic work-up (e.g. obstruction) should be performed within the first year.
- History and colonoscopy with resection of colonic polyps every 5 years [I, B].
- Clinical, laboratory and radiological examinations are of unproven benefit and should be restricted to patients with suspicious symptoms [A].

note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the expert authors and the ESMO faculty.

literature

1. MacFarlane JK, Ryall RD, Heald RJ. Mesorectal excision for rectal cancer. *Lancet* 1993; 341: 457–460.
2. Kapiteijn E, Marijnen CAM, Nagtegaal ID et al. Preoperative radiotherapy in combination with total mesorectal excision improves local control in resectable rectal cancer. Report from a multicenter randomized trial. For the Dutch Colo Rectal Cancer Group and other cooperative investigators. *New Engl J Med* 2001; 345: 638–646.
3. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8507 patients from 22 randomised trials. *Lancet* 2001; 358: 1291–1304.
4. Jeffery GM, Hickey BE, Hider P. Follow-up strategies for patients treated for non-metastatic colorectal cancer. *Cochrane Database Syst Review* 2002; 1: CD002200.
5. Beets-Tan R, Beets G, Vliegen R et al. Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. *Lancet* 2001; 357: 497–504.
6. Sauer R, Becker H, Hohenberger W et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351: 1731–1740.
7. Folkesson J, Birgisson H, Pählman L et al. Swedish Rectal Cancer Trial: Long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005; 23: 5644–5650.
8. Bipat S, Glas AS, Slors FJ et al. Rectal cancer: local staging and assessment of lymph node involvement with endoluminal US, CT, and MR imaging—a meta-analysis. *Radiology* 2004; 232: 773–783.
9. Sebag-Montefiore D for the NCR1 colorectal cancer study group and CRO et al. Routine short course pre-op radiotherapy or selective post-op chemotherapy for resectable rectal cancer? Preliminary results of the MRC CR07 randomized trial. *ASCO Annual Meeting Proceedings Part 1 2006 (18 Suppl): 24 (Abstr 3511)*.
10. Smalley SR, Benedetti JK, Williamson SK et al. Phase III trial of fluorouracil-based chemotherapy regimens plus radiotherapy in postoperative adjuvant rectal cancer: GI INT 0144. *J Clin Oncol* 2006; 24: 3542–3547.
11. Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Long-term results of a randomised trial comparing preoperative short-course radiotherapy vs preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006; 93: 1215–1223.