Annals of Oncology 24 (Supplement 6): vi81–vi88, 2013
doi:10.1093/annonc/mdt240

Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†

B. Glimelius[1], E. Tiret[2], A. Cervantes[3] & D. Arnold[4], on behalf of the ESMO Guidelines Working Group*

[1]*Dept of Radiology, Oncology and Radiation Science, Akademiska sjukhuset, Uppsala University, SE-751 85 Uppsala, Sweden;* [2]*2AP-HP, Hôpital Saint-Antoine, Pierre et Marie Curie University, Paris 6, France;* [3]*Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain;* [4]*Klinik fuer Tumorbiologie, Freiburg, Freiburg, Germany*

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

incidence and epidemiology

The 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 female individuals.

The risk increases with age. Median age at diagnosis is about 70 years or slightly older in most European countries.

The literature on risk factors for colorectal cancer is extensive. Diet and dietary components are important, although the risk increases are not marked and not universally seen. Dietary fibre most likely decreases the risk, whereas excessive consumption of red or processed meat most likely increases it. Smoking increases the risk as does at least moderate and heavy alcohol use. It has been noted that an otherwise healthy lifestyle can substantially reduce the risk [1]. Regular use of NSAIDs is associated with reduced incidence. Diabetes type II increases the risk and there is probably a causal role of hyperinsulinaemia and insulin-like growth factors. Ulcerative colitis and Crohn's disease also increase the risk.

Up to about 15% of cases have a hereditary component although this is more pronounced for colon cancer than for rectal cancer. The most common disorders are Lynch syndrome and familial adenomatous polyposis.

diagnosis and pathology/molecular biology

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

The majority (95%–98%) are adenocarcinomas usually arising from an adenoma. Most rectal adenocarcinomas are characterised by chromosomal instability; microsatellite instability (MSI) is very rare (a few percent). Approximately one-third of rectal cancers are associated with aberrant DNA methylation. Several pathways are central to rectal cancer carcinogenesis, the WNT signalling pathways being the most important. The tumour suppressor gene APC is frequently mutated. Inactivation of additional tumour suppressor genes in the *P53* and *TGFβ* pathways are seen, as well as activations of oncogenes such as *KRAS* and *PI3CKA*. *BRAF* mutations are rare in rectal cancer.

staging and risk assessment

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

Endoscopic rectal ultrasound (ERUS) for the earliest tumours (cT1-T2) or rectal MRI for all tumours, including the earliest ones, is required in order to select patients for preoperative treatment and extent of surgery [2, 3] [III, A]. Preoperative complete colonoscopy is required. If the tumour is obstructive, virtual colonoscopy or barium enema is recommended also to exclude further manifestations (but regular colonoscopy should be added after resolution of the obstructive situation).

Nodal staging is very unreliable even using both ERUS and MRI. In addition to large size (which in itself is not particularly accurate), roundness, irregular border and hypoechoic nature/heterogeneous signal on ERUS provide additional information.

Histopathological examination should include surgical specimen with proximal, distal and circumferential margins and regional lymph nodes (it is recommended to examine at least 12 nodes). The pathohistological circumferential resection margin (crm) status is very important. There are uncertainties in the interpretation of this and the residual (R) tumour classification, and an expanded classification has been suggested [4]. Moreover, vascular and nerve invasion should be evaluated [III, A].

The TNM staging system should be used. In these recommendations, version 7 (from 2010) is preferred, although

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;
E-mail: clinicalguidelines@esmo.org

†Approved by the ESMO Guidelines Working Group: August 2002, last update May 2013. This publication supersedes the previously published version—Ann Oncol 2010; 21 (Suppl. 5): v82–v86.

Table 1. Diagnostic work-up in primary rectal cancer

Parameter	Method of choice
Location (distance from anal verge)	Palpation Rigid sigmoidoscopy (flexible endoscopy)
Morphological verification	Biopsy
T stage	
Early	ERUS MRI
Intermediate/advanced	MRI (ERUS)
Sphincter infiltration	MRI (ERUS, palpation)
N stage	MRI (CT, ERUS)
M stage	CT, MRI (or US) of the liver/abdomen CT/chest X-ray of the thorax
Evaluation	MDT conference

MRI, magnetic resonance imaging; ERUS, endorectal ultrasound; CT, computed tomography; US, ultrasound; MDT, multidisciplinary team. Methods within brackets are less optimal.

version 5 is still used in some European countries. There is a need for further sub-classification of cT3, as indicated in Table 1. The TNM system is shown in Table 2, and stage grouping in Table 3.

T1 tumours could also be classified according to Haggitt's sub-classification if the cancer is in a stalked adenoma and according to the Kikuchi (sm)-system if in a sessile adenoma [5, 6] (Tables 4–5). The two systems overlap. The level of infiltration into the submucosa (sm) predicts the risk of lymph node metastases and thus the type of surgery [7] [III, B]. In order to facilitate this sub-classification, these small lesions should be pinned-out on cork before being sent to the pathology laboratory.

Immunohistochemistry is helpful in identifying MSI tumours (although these are very rare in the rectum).

management of local/locoregional disease

overall strategy

An important aim is to treat so that the risk of residual disease in the pelvis, frequently causing a disabling local recurrence, is very low. This risk should preferably be less than about 5% in the population in whom curative treatment is intended, and, at the same time, as little acute and late morbidity as possible should be targeted. This should be possible in all but the few (≤10%) cases presenting with a fixed tumour growing into a non-readily resectable organ (some cT4b).

Another aim is to treat such that a good sphincter function is preserved.

From a practical point of view, rectal cancers could be divided into four groups:

a) very early (some cT1),
b) early (cT1-2, some cT3),
c) intermediate (cT3- some cT4a)
d) locally advanced (cT3crm +, some cT4a, all cT4b).

Table 2. TNM classification (version 7, 2010) with sub-classifications

TNM	Extension to
Tis	Carcinoma *in situ*: intraepithelial or invasion of lamina propria
T1	Submucosa
T2	Muscularis propria
T3	Subserosa/perirectal tissue
	T3a[a] <1 mm
	T3b 1–5 mm
	T3c 5–15 mm
	T3d 15+ mm
T4	Perforation into visceral peritoneum (a) or invasion to other organs (b)[b]
N1	1–3 regional nodes involved
N1a	1 lymph node
N1b	2–3 lymph nodes
N1c	Small deposits in the fat
N2	4 or more regional nodes involved
N2a	4–6 lymph nodes
N2b	7 or more lymph nodes
M1	Distant metastases
M1a	One distant organ or set of lymph nodes
M1b	More than one organ or to the peritoneum

[a]This sub-classification based upon an evaluation using MRI before treatment decision is clinically valuable, and is used in these recommendations. It can be used also in the histopathological classification but is not validated and not incorporated in any of the TNM versions (5–7).

[b]This is the sub-classification in TNM 6–7. It was the opposite in TNM 5. Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Table 3. Stage grouping

I	T1-2, N0, M0
IIA	T3, N0, M0
IIB	T4a, N0, M0
IIC	T4b, N0, M0
IIIA	T1-2, N1/N1c, M0
	T1, N2a, M0
IIIB	T3-T4a, N1/N1c, M0
	T2-T3, N2a, M0
	T1-2, N2b, M0
IIIC	T4a, N2a, M0
	T3-4a, N2b, M0
	T4b, N1-2, M0
IVA	T1-4, N1-2, M1a
IVB	T1-4, N1-2, M1b

Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Table 4. Haggitt's subclassification of polypoid T1 cancers based upon the extent of invasion of the stalk

Level	
0	Absence of invasive carcinoma
1	Invasion into the head of the polyp
2	Invasion into the neck
3	Invasion into the stalk
4	Invasion into the base

Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Table 5. Subclassification of T1 cancers based upon depth of invasion into the submucosal layer

sm	
1	Upper third
2	Middle third
3	Lower third

Note: Haggitt's levels 1–3 correspond to sm 1, Haggitt's level 4 may be sm 1–3.
Edge SB, Byrd DR, Compton CC, eds. AJCC Cancer Staging Manual. 7th ed. New York, NY.: Springer, 2010. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer Science and Business Media LLC, www.springer.com.

Factors other than clinical T stage, such as tumour height, anterior location, proximity of the tumour or lymph node growths to the mesorectal fascia (mrf), size of the mesorectum, cN stage and vascular and nerve invasion are also relevant. It is presently not possible to give a precise definition of which T and N substages belong to these groups.

The terms 'favourable' or 'early' or 'good', 'intermediate' or 'bad' and 'locally advanced' or 'ugly' can be used for categorising rectal cancers into clinical subgroups. In many of the recent studies, the term locally advanced has been commonly used for the intermediate/bad group, but is best reserved for the truly locally advanced/ugly tumours as used in the most recent European consensus documents [8–10].

Extramural vascular invasion (EMVI) can be identified on MRI. Presence of EMVI (EMVI+) is a poor prognostic signal for development of distant metastases, and possibly also local failure. EMVI+ tumours belong at least to the intermediate group.

need for quality assurance and control

Treatment of rectal cancer is demanding and requires highly skilled practice by the entire multidisciplinary team (MDT). Competent surgery and good pathology as well as sound radiation techniques and optimally given chemotherapy, together with long-term complete follow-up including also functional aspects, are important for quality control. Many countries have launched quality control programmes in rectal cancer surgery, which has been very beneficial for the outcomes. The quality of the mesorectal excision should be evaluated by the surgeon and/or the pathologist, as described elsewhere [11].

risk-adapted treatment

In the earliest, most favourable cases, chiefly the malignant polyps (Haggitt 1-3, T1 sm 1 (-2?) N0), a local procedure, e.g. using the transanal endoscopic microsurgery (TEM) technique, is appropriate [7, 12] [III, A]. The resection should be complete with safe margins (R0) and no signs of vessel invasion or poor differentiation should be present. If this is not the case or if the tumour infiltrates deeper into the submucosa (Haggit 4, T1 sm (2?-)3) or is a T2 tumour, the risk of recurrence due to remaining tumour cells or lymph node metastases is too high (≥10%) and immediate radical standard surgery (total mesorectal excision, TME) should be recommended [II, A]. Salvage surgery for local recurrence yields poor survival for a tumour initially staged T1. Chemoradiotherapy should be carried out only if surgery is contraindicated [III, C].

Local radiotherapy [brachytherapy or contact therapy (Papillon technique)] may be used as an alternative to local surgery, alone or with (preoperative) chemoradiotherapy [III, C]. Experience with these treatments outside specialised centres is limited [13].

In early, favourable cases (cT1-2, some early cT3, N0 [cT3a(-b) and clear mrf (mrf-) according to MRI], good group) above the levators, surgery alone, meaning a sharp radical dissection using the TME technique is appropriate [II, A], since the risk of local failure is very low [8]. The role of TME in tumours situated in the upper third of the rectum has been much discussed and no strong evidence supporting TME in those cases has been reported. Instead, partial mesorectal excision can be carried out with a mesorectal margin of ≥5 cm distally to the tumour [IV, B].

In intermediate cases [most cT3 (cT3(b)c+ without threatened and involved mrf (mrf-) according to MRI], some cT4a (i.e. limited peritoneal involvement only), N+, bad group), preoperative radiotherapy is recommended followed by TME, since this reduces local recurrence rates [I, A]. Even in the absence of signs of extramural growth on ultrasound or MRI (cT2) in very low tumours (especially located anteriorly), preoperative radiotherapy may be indicated since the distance to the mrf is very small. This preoperative therapy could be given in one of two ways:

a) either as short-course radiotherapy, 25 Gy, 5 Gy/fraction during 1 week followed by immediate surgery (<10 days from the first radiation fraction) [14–16] [I, A]
b) or as 45–50.4 Gy, 1.8–2 Gy/fraction without or preferably with 5-fluorouracil (5-FU; bolus, continuous infusion or oral) [17–20] [II, A].

Whenever possible, preoperative treatment is preferred because it is more effective and less toxic than postoperative treatment [8, 21] [I, A].

Table 6. Choice of treatment according to risk category for primary rectal cancer without distant metastases

Risk group	TN substage	Therapeutic options
Very early	cT1 sm1 (-2?) N0	Local excision (TEM). If poor prognostic signs (sm ≥ 2, high grade, V1), resection (TME) (or possibly CRT)
Early (good)	cT1-2; cT3a (b) if middle or high, N0 (or cN1 if high), mrf-, no EMVI	Surgery (TME) alone. If poor prognostic signs (crm+, N2) add postop CRT or CT[a]. (CRT with evaluation, if cCR, wait-and-see, organ preservation)
Intermediate (bad)	cT2 very low, cT3mrf- (unless cT3a(b) and mid- or high rectum, N1-2, EMVI+, limited cT4aN0	Preop RT (5 × 5 Gy) or CRT followed by TME. (if CRT and cCR, wait-and-see in high risk patients for surgery)
Advanced (ugly)	cT3mrf+, cT4a,b, lateral node+	Preop CRT followed by surgery (TME + more extended surgery if needed due to tumour overgrowth). 5 × 5 Gy with a delay to surgery in elderly or in patients with severe comorbidity who cannot tolerate CRT

[a]The preoperative staging should be of such high quality so that this is rarely seen. Other factors than T and N stages are also relevant, such as distance from the anus and sphincters, direction, size of mesorectum and patient characteristics.
TEM, transanal endoscopic microsurgery; TME, total mesorectal excision; CRT, chemoradiotherapy; RT, radiotherapy; cCR, clinical complete remission; CT, chemotherapy; EMVI, extramural vascular invasion; V1, vascular invasion.

In locally advanced, sometimes non-resectable cases [cT3 mrf +, cT4 with overgrowth to organs not readily resectable (cT4b)], preoperative chemoradiotherapy (CRT), 50.4 Gy, 1.8 Gy/fraction with concomitant 5-FU-based therapy should be used [9, 22] [II, A]. This should be followed by radical surgery 6–8 weeks later. In very old patients (≥80–85 years) and in patients not fit for CRT, 5 × 5 Gy with a delay of ∼8 weeks before surgery is an option [23, 24] [IV, A].

Standard preoperative chemoradiotherapy means a dose of 45–50.4 Gy, 1.8 Gy/fraction, or alternatively 50 Gy, 2 Gy/fraction together with a fluoropyrimidine, as trials have shown that chemoradiotherapy provides better local control than the same radiotherapy alone [9, 18, 19, 22] [I, A]. The fluoropyrimidine may be 5-FU given either as bolus injections with leucovorin (at 6–10 times during the radiation) [9, 18, 19, 22] or as prolonged continuous infusion (which is likely better than bolus [II, A]) or oral capecitabine [25]. Extrapolations from other clinical situations and convenience indicate that oral 5-FU is a valid treatment [I, A]. Combinations of 5-FU with other cytotoxics such as oxaliplatin or irinotecan or targeted biologic drugs have been extensively explored in phase II trials, with more favourable results claimed (more down-sizing, higher pathological complete regression (pCR) rates), but also more acute toxic effect. Early results of several comparative randomised trials have not been favourable (e.g. [26]), and these combinations are still experimental.

The choice of treatment according to risk category for primary rectal cancer without distant metastases is shown in Table 6.

total mesorectal excision

The standard of care today in rectal cancer surgery is TME implying that all of the mesorectal fat, including all lymph nodes, should be excised [III, A]. In rare situations a local excision can be an option in patients with a T1 tumour or in fragile patients with more advanced tumours. If this is the case, TEM is the procedure of choice.

If an abdominal procedure is carried out, there are strong data indicating that a good TME without damaging the rectal fascia surrounding the mesorectal fat and rectum is prognostically relevant. If the fascia has been torn or damaged outcome is adversely affected and the local recurrence rate will increase. There is also good evidence indicating that surgeons can train and learn this technique and, once this technique has been adopted, the local recurrence rate will be reduced. If an abdominoperineal excision is planned, the dissection from above must be stopped at the tip of the coccyx and be continued from below in order to get a cylindrical specimen, without a waist effect towards the tumour carrying a risk of crm+ or an R1/2 resection [27]. This strategy has not yet been studied extensively, but the dissection plane is likely to be the most important factor for the high R1 resection rates and local recurrence rates after an abdomino-perineal resection in low-lying rectal cancers [IV, B].

In Japan, a lateral node dissection is often added to the mesorectal excision since lateral pelvic node metastases may occur. This is not practised in Europe, unless such involvement is suspected on imaging with enlarged lateral nodes. It prolongs operation time and results in greater blood loss [28]. In Europe, the addition of preoperative (C)RT is considered superior (higher efficacy and/or less morbidity) to surgical resection of the nodes, although this has not been subject to a randomised trial.

organ preservation?

Besides the earliest tumours that can be treated with a local procedure or local radiation therapy as described above, it has become increasingly popular to first give CRT, wait and then restage the tumour clinically or with multiple biopsies/excision biopsy of the previous tumour area. If no tumour can be detected and/or no viable tumour cells are found, i.e. a clinical or a pathological complete response (cCR or pCR) is achieved, no further therapy is provided (organ preservation) and the patient is monitored closely for at least 5 years [29, 30]. It is then assumed that potential lymph node metastases have been eradicated in conjunction with the excellent response of the tumour. Although this undoubtedly may occur in some patients, this strategy has not been subject to properly controlled prospective studies [IV, D].

evaluation of response after preoperative (chemo) radiotherapy

Since the response to preoperative therapy (5 × 5 Gy with a delay or prolonged chemoradiotherapy to 45–50.4 Gy) may influence prognosis, and thus subsequent therapy (both the extent of surgery and postoperative chemotherapy), there have been attempts to clinically and pathologically restage the tumours.

a) There is still limited experience in evaluating tumour response by MRI or positron emission tomography (PET)-computed tomography (CT). Using MRI, reduction in size can be seen, as well as increase in fibrosis and mucous degeneration indicating response [31]. Using PET, reduction in uptake can be seen [32]. At present, the relevance of these changes is not understood and the extent of surgery should not be modified based on this [IV, D].
b) Several systems for pathological tumour regression grading have been used (e.g. by Mandard 1994; Dworak 1997; Wheeler 2002; Roedel modification of Dworak 2005). It is not known which system is the best (reproducibility, prognostic information, etc.). The tumours should at least be graded into three groups: complete response (pCR), some response and no response [IV, B]. Potentially in the future some response may be categorised as good, moderate and poor response.
c) The proportion of pCRs, meaning absence of tumour cells after a given treatment of a certain substage, is influenced by the intensity of the examination carried out by the pathologist. Standardisation is required if pCR rates are to be used as a valid end point [IV, B].

postoperative therapy

Postoperative chemoradiotherapy (e.g. about 50 Gy, 1.8–2.0 Gy/fraction) with concomitant fluoropyramidine-based chemotherapy is no longer recommended but could be used in patients with positive crm, perforation in the tumour area, defects in the mesorectum, or in other cases with high risk of local recurrence if preoperative radiotherapy has not been given [8] [I, A]. Traditionally, postoperative CRT was recommended for all patients with pT3-4 or N+ tumours, but the routine use of this has been questioned for all pT3N0 tumours [8].

As in colon cancer stage III (and 'high-risk' stage II), adjuvant chemotherapy can be given, even if the level of scientific evidence for sufficient benefit is much lower than in colon cancer [33, 34, 35] [II, B].

In Japan, postoperative adjuvant chemotherapy with uracil-tegafur is considered standard therapy since this treatment improved relapse-free and overall survival [36].

radiation therapy volumes and doses

Whenever radiotherapy is indicated to lower the risk of local failure in the intermediate group, or for down-sizing to allow radical surgery in cT3mrf+, cT4b tumours (locally advanced/ugly group), the primary tumour should be irradiated along with the mesorectum and lymph nodes outside the mesorectum, which are likely to contain tumour cells. A boost of about 4–6 Gy in 2–4 fractions to the primary tumour is often given. The appropriate dose for subclinical disease is not precisely known, but with 5-FU chemotherapy should be at least 45–46 Gy in 1.8–2 Gy fractions [III, A].

a) The entire mesorectum is at risk to have tumour deposits, often in the mesorectal lymph nodes, in all tumours except the very earliest (T1 sm1 (-2?)) and should be included in the clinical target volume (CTV). High tumours are an exception and it is sufficient to include the 4–5 cm distal to the tumour. This means that in these tumours the lower border of the beams can be about 5–6 cm distal to the tumour.
b) Besides the mesorectal nodes, the pre-sacral nodes along the superior rectal arteries up to the level of S1-2 and nodes along the internal iliac arteries up to below the bifurcation from *a iliaca communis* or to the level of about S1-2 should always be included. If pre-sacral nodes are radiologically involved, the upper border of CTV should be even higher.
c) The lateral nodes along *a rectalis inferior* and *a obturatorii* and the internal iliac nodes up to the bifurcation from *a iliac communis* should be included in tumours below the peritoneal reflection (i.e. in tumours up to about 9–12 cm from the anal verge). The risk of lateral node involvement in the Western world is not properly known, but studies from Asia show that these lymph nodes are seldom involved in low-mid rectal pT1-2 tumours and in high tumours, irrespective of T stage.
d) External iliac nodes should only be included if an anterior organ such as the urinary bladder, prostate or female sexual organs are involved to such an extent that there is a risk of involvement of these lymph node stations.
e) *Fossae ischiorectalis* should only be included when the levator muscles and the internal and external sphincters are involved.
f) The medial inguinal nodes need to be prophylactically included only when the tumour grows at or below the dentate line [37].
g) When lymph nodes are involved by metastatic disease such that this can be seen on imaging, there is always a risk of aberrant spread, and the CTV can be enlarged to include nodal stations other than those described above.

management of local recurrences

If radiotherapy was not given in the primary situation, patients with recurrence should receive preoperative radiotherapy (about 50 Gy during 5–6 weeks) with concomitant chemotherapy [III, A].

In patients previously irradiated, attempts at providing additional radiotherapy, external and/or using intraoperative radiotherapy (IORT) or different brachytherapy techniques could be tried [IV, C].

Attempts at radical surgery should take place 6–10 weeks after radiotherapy [IV, A].

In patients with prior radiotherapy for whom salvage surgery is not an option, systemic palliative chemotherapy may be tried, although experience is not favourable [V, C].

management of metastatic disease

It may be apparent in certain cases whether patients with primarily disseminated disease (synchronous metastases) should receive first locoregional treatment and then systemic treatment, or the inverse, but is otherwise poorly known [IV]. Age, comorbidity, patient preferences and, most importantly, a balanced evaluation of the extent of primary and metastatic disease must be considered and discussed in the MDT. Especially in cases where the number of metastases is limited (oligo-metastatic) and is localised at sites that can be resected or otherwise ablated (e.g. irradiated stereotactically), it is important to consider the sequence and what constitutes the greatest threat for the patient.

Synchronous oligo-metastatic rectal cancer can be a therapeutic challenge since cure may be achievable. In selected cases, treatment may include surgery of resectable liver or lung metastases [III, A]. Treatment must be individualised according to the patient, extent of disease and whether it is primarily resectable or requires down-sizing and/or down-staging. The following advice can be given:

a) If both primary tumour and metastases are resectable upfront and the patient can tolerate intensive treatment, therapy could start with 5 × 5 Gy to the primary and adjacent involved nodes followed by combination chemotherapy. There should be an evaluation after 6–8 weeks and surgery for the metastases and the primary after about 3 months or when this is considered appropriate. Pre- and postoperative chemotherapy of up to 6 months in total is recommended.
b) If the primary is locally advanced (ugly) and the metastases resectable, the same strategy as described above could be applied. Note that when synchronous metastases are present, short-course radiotherapy with combination chemotherapy starting 11–18 days later will result in higher dose intensity of the systemic treatment than chemoradiotherapy with a fluoropyrimidine. Evidence suggests that surgery for the primary can be safely carried out up to at least 5–6 months after the radiotherapy.
c) If the metastases are non-resectable and require down-sizing before planned surgery, the same strategy as above could again be utilised. Alternatively, treatment could start with combination chemotherapy, evaluation after 2 and 4 months and continued chemotherapy until sufficient regression has been seen. Then 5 × 5 Gy could be given, if desired, and liver surgery and subsequent rectal cancer surgery with additional adjuvant chemotherapy, if considered of value.
d) Of note, conventional chemoradiation (with fluropyrimidine) is almost never indicated as upfront treatment in synchronous metastases.

Other surgical or stenting procedures [III, A] or radiotherapy should be considered as palliative procedures [II, A]. Stenting may be difficult for lower tumours as the patient is then often unable to tolerate it.

Chemotherapy should be considered early and consists of fluoropyrimidines (5-FU/leucovorin or capecitabine) in various combinations and schedules with oxaliplatin or irinotecan, with or without a monoclonal antibody [I, A]. Inhibition of the EGFR-receptor with cetuximab or panitumumab is indicated only in wild-type *KRAS* tumours, whereas bevacizumab against VEGF can be used irrespective of *KRAS* mutation status [II, 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 [I, B].

personalised medicine

There are no molecular or other markers which can evaluate whether a patient is in need of preoperative treatment of a rectal cancer indicating that surgery will not be radical. MRI gives accurate information provided it is done appropriately. Similarly, there are no known markers that can predict response to radiotherapy or chemoradiotherapy.

In metastatic disease, *KRAS* mutant status predicts non-response to EGFR inhibition [II, A].

follow-up and long-term implications

Follow-up serves to identify patients in need of salvage surgery or other curative treatment modalities, palliative care, and to prevent secondary colorectal cancers. There is some proof that regular follow-up after successful treatment improves the outcome of patients with rectal cancer, but frequency and modality of follow-up are not yet known [38].

A minimum provisional recommendation is as follows:

Clinical assessment: if possible every 6 months for 2 years [V, D]. A completion colonoscopy should be carried out within the first year if not done at the time of diagnostic work-up (e.g. if obstruction was present) [I, A].

a) History and colonoscopy with resection of colonic polyps every 5 years up to the age of 75 years [I, B].
b) Clinical, laboratory and radiological examinations are of unproven benefit and should be restricted to patients with suspicious symptoms [IV, A].

Both rectal cancer surgery and the additional pre- or postoperative (chemo)radiotherapy may result in late sequelae, with consequences of the daily function. However, surgery is the individual modality that causes most late effects.

Prevention from local failures, with the severe morbidity which may accompany them, must be weighted against the morbidity that all treated patients can develop from (chemo)radiotherapy.

The morbidity after 5 × 5 Gy has been well described in data from the randomised trials [39]. There is less evidence of the extent of late morbidity after chemoradiotherapy with a fluoropyrimidine to 45–50.4 Gy. There is some evidence that the addition of 5-FU increases not only acute toxic effect but also late toxic effect [40].

Table 7. Summary of key recommendations in primary rectal cancer

- Requires morphological verification pre-decision
- Staging preferably with MRI in all cases
- Multidisciplinary team conference
- Individualise therapy according to clinical characteristics and MRI stage
- Discuss in terms of three major prognostic and therapeutic groups
  a) Early (or designated 'Good')—surgery alone sufficient, should result in extremely few local recurrences (<3%–4% after 5 years)
  b) Intermediate (or 'Bad')—surgery alone will give too many recurrences locally (>8%–10% after 5 years if surgery alone, give preop RT (5 × 5 Gy) or CRT
  c) Locally advanced (or 'Ugly')—CRT needed to achieve high probability of R0 surgery and few local recurrences
  d) Local surgery (TEM) for the very early polypoid cancers (pT1sm1 (-2?))
- Preoperative (C)RT is more efficient and less toxic than postoperative (C)RT
- Individualise therapy if synchronous metastases. The distant metastases kill most patients but uncontrolled pelvic growth can be a disaster

MRI, magnetic resonance imaging; RT, radiotherapy; CRT, chemoradiotherapy; TEM, transanal endoscopic microsurgery.

Short-course or 5 × 5 Gy radiotherapy increases the risks of poor anal and sphincter sexual function, small bowel toxic effect with obstruction and secondary malignancies. The relative increase is in the order of 1.5- to 2-fold: for example, if the risk of any anal incontinence is 40% after surgery alone, it is about 60% after radiotherapy plus surgery. More severe incontinence problems are, for example, increased from about 8% to about 12%. Late bowel obstruction is seen in 6% after surgery alone and between 8% and 10% after RT plus surgery. The risk of a second malignancy is increased from about 4% to 9% (relative risk 1.85, 95% confidence interval 1.23–2.78) after a follow-up between 14 and 20 years.

Knowledge about the extent of late toxic effect comes from trials where the radiotherapy was much less sophisticated than today. Thus, less late toxic effect can be anticipated with the treatments we give today than was seen in the follow-up studies of the radiotherapy delivered during the 1980s–1990s. More sophisticated treatment techniques such as those based on intensity modulation of the beams, presently introduced, may decrease the risks even further.

note

A summary of key recommendations is given in Table 7. Levels of evidence and grades of recommendation have been applied using the system shown in Table 8. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

conflict of interest

Prof. Arnold has reported research grants from Roche and Sanofi. The other authors have reported no potential conflicts of interest.

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials 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, experts opinions
Grades of recommendation	
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

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. Clin Infect Dis 2001; 33: 139–144.

references

1. Kirkegaard H, Johnsen NF, Christensen J et al. Association of adherence to lifestyle recommendations and risk of colorectal cancer: a prospective Danish cohort study. BMJ 2010; 341: c5504.
2. Puli SR, Reddy JB, Bechtold ML et al. Accuracy of endoscopic ultrasound to diagnose nodal invasion by rectal cancers: a meta-analysis and systematic review. Ann Surg Oncol 2009; 16: 1255–1265.
3. Al-Sukhni E, Milot L, Fruitman M et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol 2012; 19: 2212–2223.
4. Wittekind C, Compton C, Quirke P et al. A uniform residual tumor (R) classification: integration of the R classification and the circumferential margin status. Cancer 2009; 115: 3483–3488.
5. Haggitt RC, Glotzbach RE, Soffer EE, Wruble LD. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. Gastroenterology 1985; 89: 328–336.
6. Kikuchi R, Takano M, Takagi K et al. Management of early invasive colorectal cancer. Risk of recurrence and clinical guidelines. Dis Colon Rectum 1995; 38: 1286–1295.
7. Sgourakis G, Lanitis S, Gockel I et al. Transanal endoscopic microsurgery for T1 and T2 rectal cancers: a meta-analysis and meta-regression analysis of outcomes. Am Surg 2011; 77: 761–772.
8. Valentini V, Aristei C, Glimelius B et al. Multidisciplinary rectal cancer management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2). Radiother Oncol 2009; 92: 148–163.
9. Glimelius B, Holm T, Blomqvist L. Chemotherapy in addition to preoperative radiotherapy in locally advanced rectal cancer—a systematic overview. Rev Recent Clin Trials 2008; 3: 204–211.
10. Schmoll HJ, Van Cutsem E, Stein A et al. ESMO Consensus Guidelines for management of patients with colon and rectal cancer. a

personalized approach to clinical decision making. Ann Oncol 2012; 23: 2479–2516.
11. Quirke P, Steele R, Monson J et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. Lancet 2009; 373: 821–828.
12. Doornebosch PG, Tollenaar RA, De Graaf EJ. Is the increasing role of transanal endoscopic microsurgery in curation for T1 rectal cancer justified? A systematic review. Acta Oncol 2009; 48: 343–353.
13. Gerard JP, Ortholan C, Benezery K et al. Contact X-ray therapy for rectal cancer: experience in Centre Antoine-Lacassagne, Nice, 2002–2006. Int J Radiat Oncol Biol Phys 2008; 72: 665–670.
14. Sebag-Montefiore D, Stephens RJ, Steele R et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 2009; 373: 811–820.
15. Folkesson J, Birgisson H, Påhlman 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.
16. van Gijn W, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. Lancet Oncol 2011; 12: 575–582.
17. Bujko K, Nowacki MP, Nasierowska-Guttmejer A et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006; 93: 1215–1223.
18. Gérard JP, Conroy T, Bonnetain F et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3–4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006; 24: 4620–4625.
19. Bosset JF, Collette L, Calais G et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 355: 1114–1123.
20. Ngan SY, Burmeister B, Fisher RJ et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. J Clin Oncol 2012; 30: 3827–3833.
21. Sauer R, Liersch T, Merkel S et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 Randomized Phase III Trial after a median follow-up of 11 years. J Clin Oncol 2012; 30: 1926–1933.
22. Braendengen M, Tveit KM, Berglund Å et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in non-resectable rectal cancer. J Clin Oncol 2008; 26: 3687–3694.
23. Radu C, Berglund Å, Påhlman L, Glimelius B. Short course preoperative radiotherapy with delayed surgery in rectal cancer—a retrospective study. Radiother Oncol 2008; 87: 343–349.
24. Pettersson D, Holm T, Iversen H et al. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. Br J Surg 2012; 99: 577–583.
25. Hofheinz RD, Wenz F, Post S et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. Lancet Oncol 2012; 13: 579–588.
26. Gérard JP, Azria D, Gourgou-Bourgade S et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. J Clin Oncol 2012; 30: 4558–4565.
27. Holm T, Ljung A, Häggmark T et al. Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. Br J Surg 2007; 94: 232–238.
28. Fujita S, Akasu T, Mizusawa J et al. Postoperative morbidity and mortality after mesorectal excision with and without lateral lymph node dissection for clinical stage II or stage III lower rectal cancer (JCOG0212): results from a multicentre, randomised controlled, non-inferiority trial. Lancet Oncol 2012; 13: 616–621.
29. Habr-Gama A, Perez RO, Nadalin W et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg 2004; 240: 711–717.
30. Maas M, Beets-Tan RG, Lambregts DM et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol 2011; 29: 4633–4640.
31. Lambrecht M, Vandecaveye V, De Keyzer F et al. Value of diffusion-weighted magnetic resonance imaging for prediction and early assessment of response to neoadjuvant radiochemotherapy in rectal cancer: preliminary results. Int J Radiat Oncol Biol Phys 2012; 82: 863–870.
32. van Stiphout RG, Lammering G, Buijsen J et al. Development and external validation of a predictive model for pathological complete response of rectal cancer patients including sequential PET-CT imaging. Radiother Oncol 2011; 98: 126–133.
33. Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy? A systematic review of randomised trials. Ann Oncol 2010; 21: 1743–1750.
34. Petersen SH, Harling H, Kirkeby LT et al. Postoperative adjuvant chemotherapy in rectal cancer operated for cure. Cochrane Database Syst Rev 2012; 3: CD004078.
35. Valentini V, van Stiphout RG, Lammering G et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. J Clin Oncol 2011; 29: 3163–3172.
36. Akasu T, Moriya Y, Ohashi Y et al. Adjuvant chemotherapy with Uracil–Tegafur for pathological stage III rectal cancer after mesorectal excision with selective lateral pelvic lymphadenectomy: a multicenter randomized controlled trial. Jpn J Clin Oncol 2006; 36: 237–244.
37. Taylor N, Crane C, Skibber J et al. Elective groin irradiation is not indicated for patients with adenocarcinoma of the rectum extending to the anal canal. Int J Radiat Oncol Biol Phys 2001; 51: 741–747.
38. Baca B, Beart RW, Jr, Etzioni DA. Surveillance after colorectal cancer resection: a systematic review. Dis Colon Rectum 2011; 54: 1036–1048.
39. Birgisson H, Påhlman L, Gunnarsson U, Glimelius B. Late adverse effects of radiation therapy for rectal cancer—a systematic overview. Acta Oncol 2007; 46: 504–516.
40. Braendengen M, Tveit KM, Bruheim K et al. Late patient-reported toxicity after preoperative radiotherapy or chemoradiotherapy in nonresectable rectal cancer: results from a randomized phase III study. Int J Radiat Oncol Biol Phys 2011; 81: 1017–1024.