CLINICAL PRACTICE GUIDELINES

An ESMO Product

Rectal cancer

ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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on behalf of the ESMO Guidelines Committee

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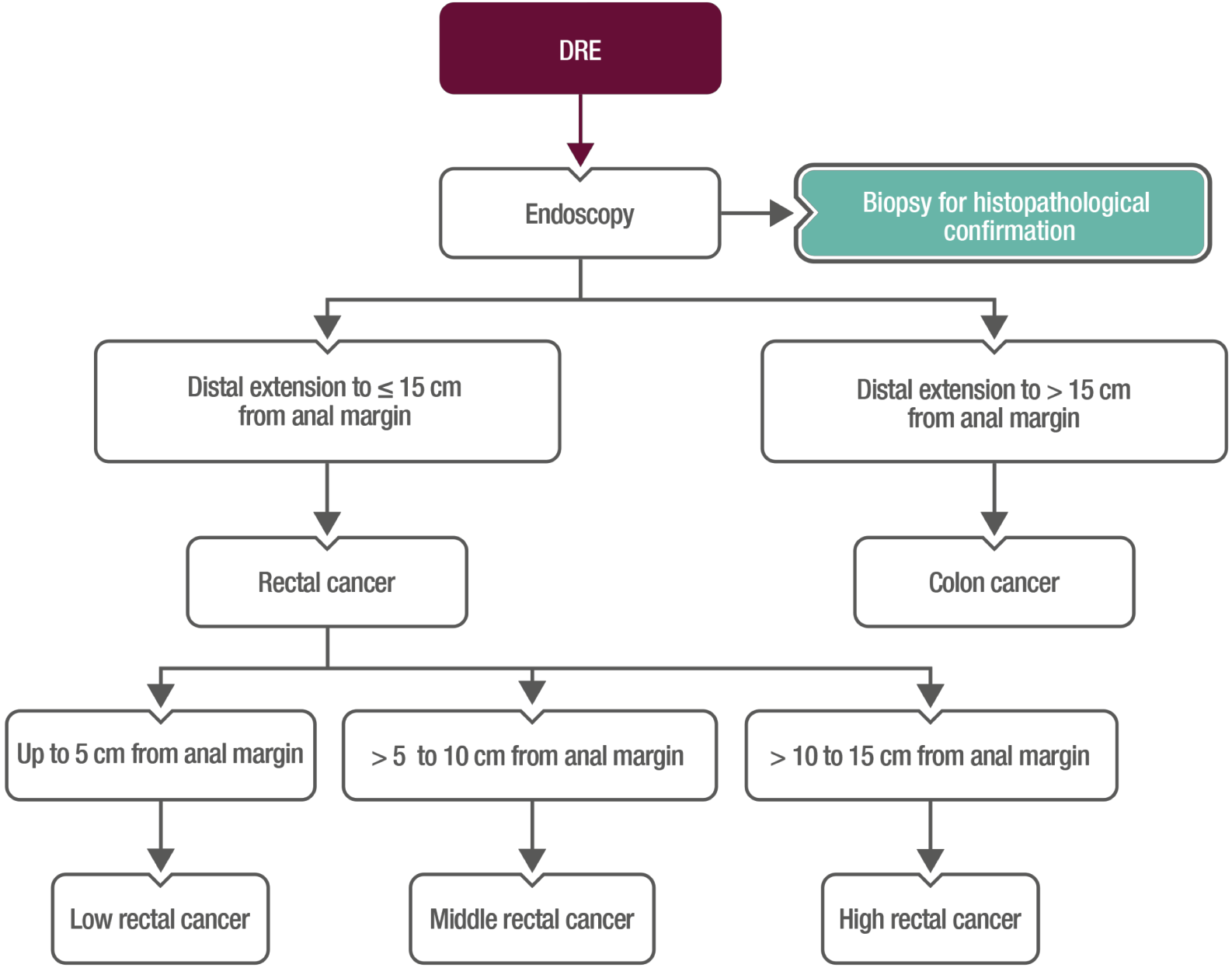
Diagnosis and pathology

Categorisation



Diagnosis is based on a DRE and endoscopy, with biopsy for histopathological confirmation

There is a wide overlap of molecular genomic profiles of left-sided / sigmoid with rectal cancer; so rectal cancer cannot be seen as a molecularly defined different entity

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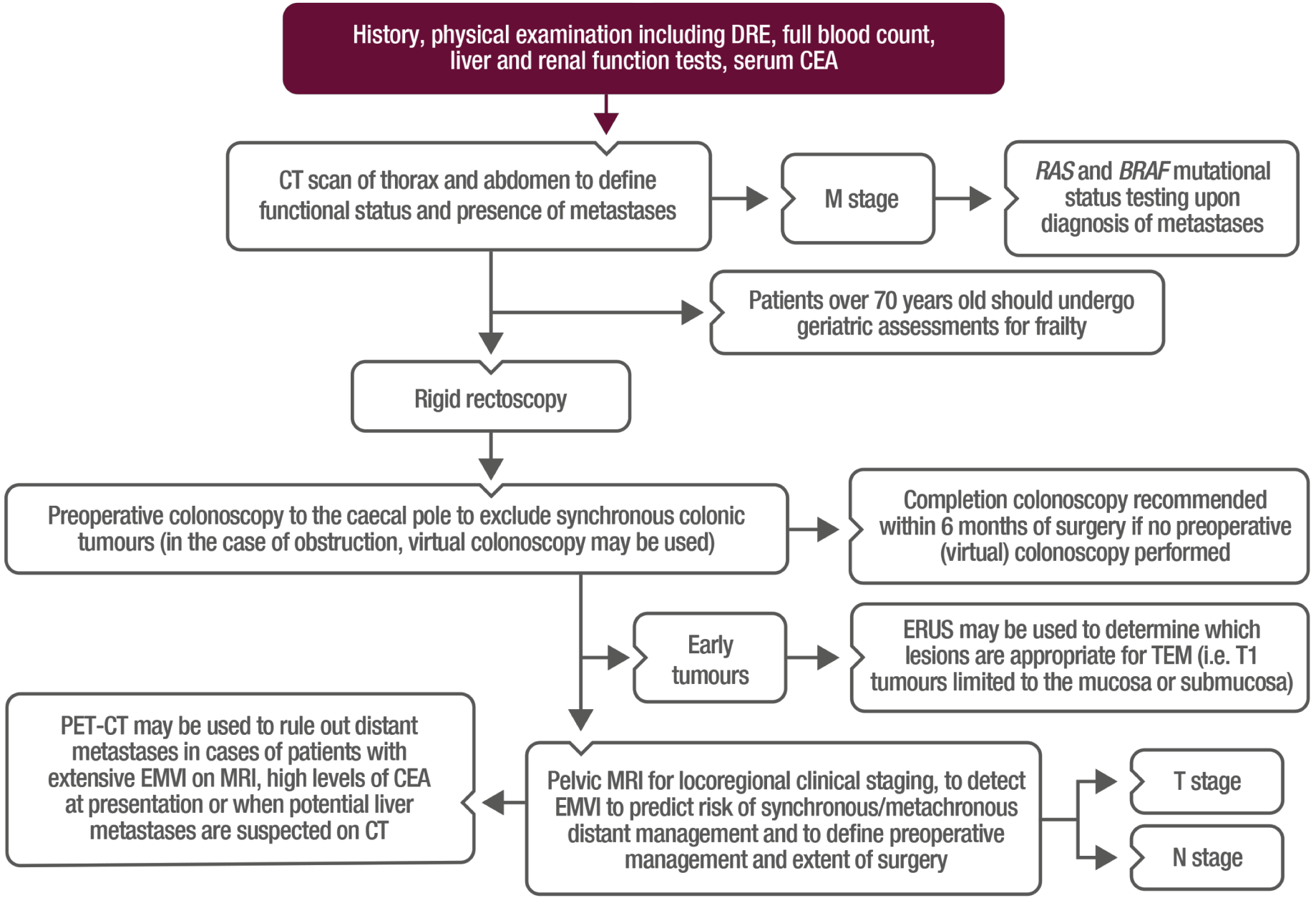
Staging and risk assessment



Management should be by an MDT of radiologists, surgeons, radiation oncologists, medical oncologists and pathologists

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Staging and risk assessment

Diagnostic work-up in primary rectal cancer

Parameter	Method of choice
Location (distance from anal verge)	DRE/Palpation Rigid sigmoidoscopy (flexible endoscopy)*
Morphological verification	Biopsy
cT stage Early Intermediate/advanced	 ERUS MRI MRI (ERUS)*
Sphincter infiltration	MRI (ERUS, palpation, EUA)*
cN stage	MRI (CT, ERUS)*
M stage	CT, MRI (or US)* of the liver/abdomen CT of the thorax PET-CT if extensive EMVI for other sites
Evaluation for all patients	MDT discussion

*Methods within brackets are less optimal

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Staging and risk assessment

The UICC TNM staging (8th edition) classification for colon and rectal cancer

TNM Clinical Classification	
T – Primary Tumour	
TX	Primary tumour cannot be assessed
T0	No evidence of primary tumour
Tis	Carcinoma *in situ*: Invasion of lamina propria*
T1	Tumour invades submucosa
T2	Tumour invades muscularis propria
T3	Tumour invades subserosa or into non-peritonealised pericolic or perirectal tissues
T4	Tumour directly invades other organs or structures†,‡,§ and/or perforates visceral peritoneum
T4a	Tumour perforates visceral peritoneum
T4b	Tumour directly invades other organs or structures

TNM Clinical Classification	
N – Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 to 3 regional lymph nodes
N1a	Metastasis in 1 regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumour deposit(s), i.e. satellites,‖ in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue *without* regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
M – Distant Metastasis	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ (liver, lung, ovary, non-regional lymph node(s)) without peritoneal metastases
M1b	Metastasis in more than one organ
M1c	Metastasis to the peritoneum with or without organ involvement

*, †, ‡, §, ‖
For details please see following slide

Brierley JD et al. TNM Classification of Malignant Tumours, 8th edition: John Wiley & Sons, Inc., Oxford, 2016. Reprinted with permission from John Wiley & Sons, Inc.

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Staging and risk assessment

Notes to previous slide:
The UICC TNM staging (8th edition) classification for colon and rectal cancer

Stage		T - Primary Tumour
Tis	Carcinoma *in situ*: invasion of lamina propria*	*includes cancer cells confined within the mucosal lamina propria (intramucosal) with no extension through the muscularis mucosae into the submucosa
T4	Tumour directly invades other organs or structures†,‡,§ and/or perforates visceral peritoneum	†Invades through to visceral peritoneum to involve the surface ‡Direct invasion in T4b includes invasion of other organs or segments of the colorectum by way of the serosa, as confirmed on microscopic examination, or for tumours in a retroperitoneal or subperitoneal location, direct invasion of other organs or structures by virtue of extension beyond the muscularis propria § Tumour that is adherent to other organs or structures, macroscopically, is classified cT4b. However, if no tumour is present in the adhesion, microscopically, the classification should be pT1–3, depending on the anatomical depth of wall invasion
N1c	Tumour deposit(s), i.e. satellites,‖ in the subserosa, or in non-peritonealised pericolic or perirectal soft tissue *without* regional lymph node metastasis	‖ Tumour deposits (satellites) are discrete macroscopic or microscopic nodules of cancer in the pericolorectal adipose tissue's lymph drainage area of a primary carcinoma that are discontinuous from the primary and without histological evidence of residual lymph node or identifiable vascular or neural structures. If a vessel wall is identifiable on H&E, elastic or other stains, it should be classified as venous invasion (V1/2) or lymphatic invasion (L1). Similarly, if neural structures are identifiable, the lesion should be classified as perineural invasion (Pn1). The presence of tumour deposits does not change the primary tumour T category, but changes the node status (N) to pN1c if all regional lymph nodes are negative on pathological examination

Brierley JD et al. TNM Classification of Malignant Tumours, 8th edition: John Wiley & Sons, Inc., Oxford, 2016. Reprinted with permission from John Wiley & Sons, Inc.

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Staging and risk assessment

Subclassification of T3 rectal cancer

T3 Stage	Depth of invasion beyond the muscularis propria, in mm
T3a*	< 1
T3b	1–5
T3c	6–15
T3d	> 15

*This subclassification, based on pretreatment decision MRI evaluation, is clinically valuable and can be used also in the histopathological classification, although it is not validated nor incorporated in any of the TNM versions

Edge SB et al. AJCC Cancer Staging Handbook, 7th edition: Springer, New York, 2010. Reprinted with permission.

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Staging and risk assessment

Stage grouping of colon and rectal cancer

TNM Pathological Classification			
The pT and pN categories correspond to the T and N categories			
pN0	Historical examination of a regional lymphadenectomy specimen will ordinarily include 12 or more lymph nodes. If the lymph nodes are negative, but the number ordinarily examined is not met, classify as pN0		
Stage			
Stage 0	Tis	N0	M0
Stage I	T1, T2	N0	M0
Stage II	T3, T4	N0	M0
Stage IIA	T3	N0	M0
Stage IIB	T4a	N0	M0
Stage IIC	T4b	N0	M0
Stage III	Any T	N1, N2	M0
Stage IIIA	T1, T2	N1	M0
	T1	N2a	M0
Stage IIIB	T1, T2	N2b	M0
	T2, T3	N2a	M0
	T3, T4a	N1	M0
Stage IIIC	T3, T4a	N2b	M0
	T4a	N2a	M0
	T4b	N1, N2	M0
Stage IV	Any T	Any N	M1
Stage IVA	Any T	Any N	M1a
Stage IVB	Any T	Any N	M1b
Stage IVC	Any T	Any N	M1c

Brierley JD et al. TNM Classification of Malignant Tumours, 8th edition: John Wiley & Sons, Inc., Oxford, 2016. Reprinted with permission from John Wiley & Sons, Inc.

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Histopathology

Summary of recommendations	
T1 tumours classification	• According to Haggitt's sub-classification if the cancer is pedunculated • According to Kudo/Kikuchi (sm)-system if in a sessile adenoma
Resection *en bloc*	Recommended for accurate assessment of invasion in the resection margin and the deepest area
Radical surgery	According to Japanese guidelines, radical surgery and removal of lymph nodes is recommended for high-risk pathological features
Surrogate	Involved CRM rate (i.e. < 1 mm) and TME quality are surrogates for good oncological outcomes
Lymph node examination	At least 12 regional lymph nodes should be examined and their margins documented
Mesorectal resections	Histopathological examination should include a photographic record of the surgical specimen and assessment of TME quality
Evaluation	ENE of nodal metastases, EMVI, PNI and tumour budding should be evaluated

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Histopathology

Objective grading of technical quality of TME surgery specimen	
Mesorectal plane (good plane of surgery achieved)	Intact mesorectum with only minor irregularities of a smooth mesorectal surface; no defect deeper than 5 mm; no coning; and smooth circumferential resection margin on slicing
Intra-mesorectal plane (moderate plane of surgery achieved)	Moderate bulk to mesorectum, with irregularities of the mesorectal surface; moderate distal coning; muscularis propria not visible with the exception of levator insertion; and moderate irregularities of circumferential resection margin
Muscularis propria plane (poor plane of surgery achieved)	Little bulk to mesorectum with defects down onto muscularis propria; very irregular circumferential resection margin; or both

The specimen is examined as a whole (fresh) and as cross-sectional slices (fixed) to make an adequate interpretation

A TME specimen ideally should have a smooth surface, without incisions, defects or cracks, as an indication of successful surgical excision of all mesorectal tissue. 'Coning' represents the tendency for the surgeon to cut inwards towards the central tube of the rectum during distal dissection, rather than staying outside the visceral mesorectal fascia. The specimen then shows a tapered, conical appearance representing suboptimal surgical quality

Quirke P et al. Lancet 2009;373:821–8.
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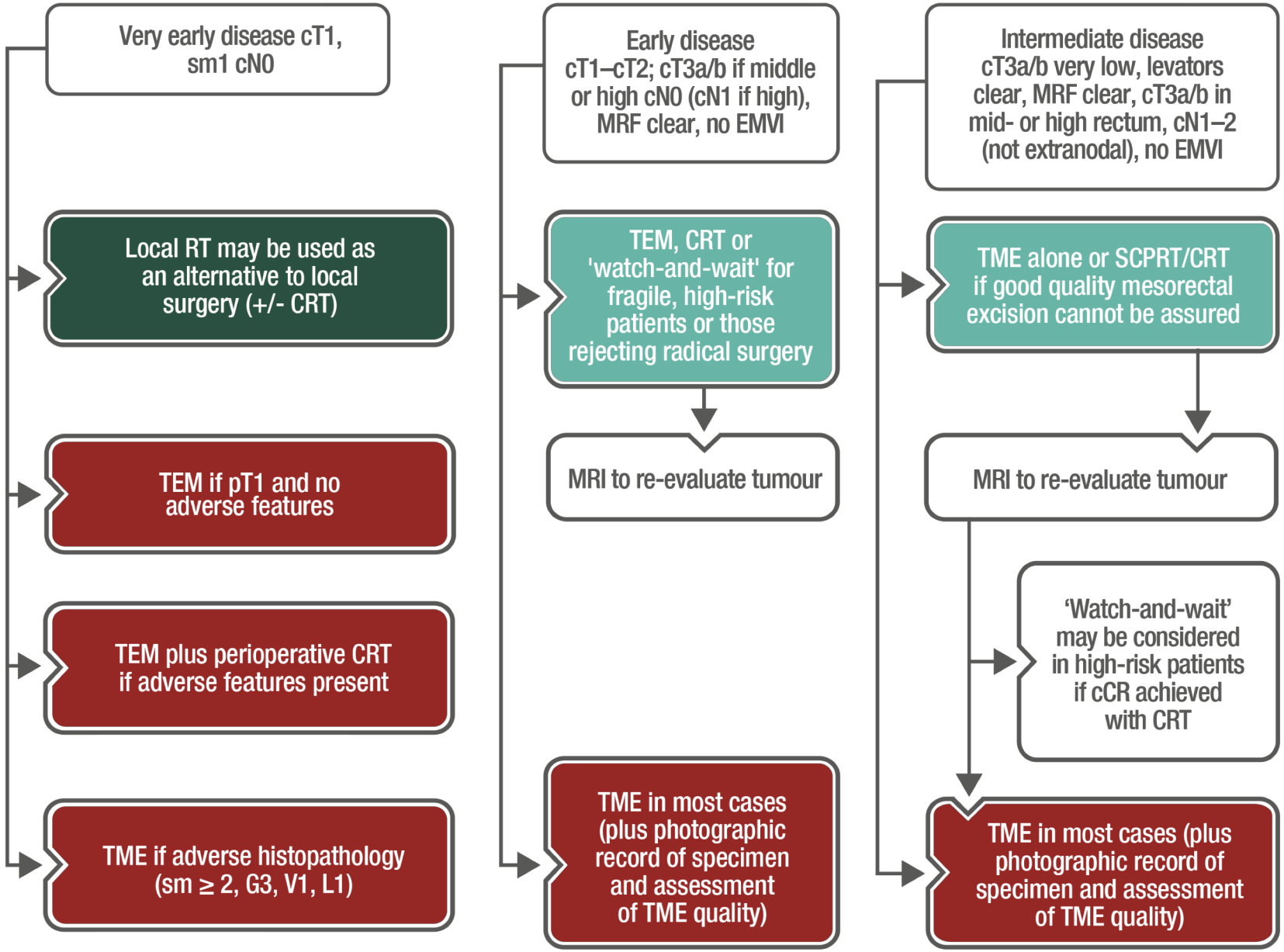
Treatment recommendations

Very early, early and intermediate disease



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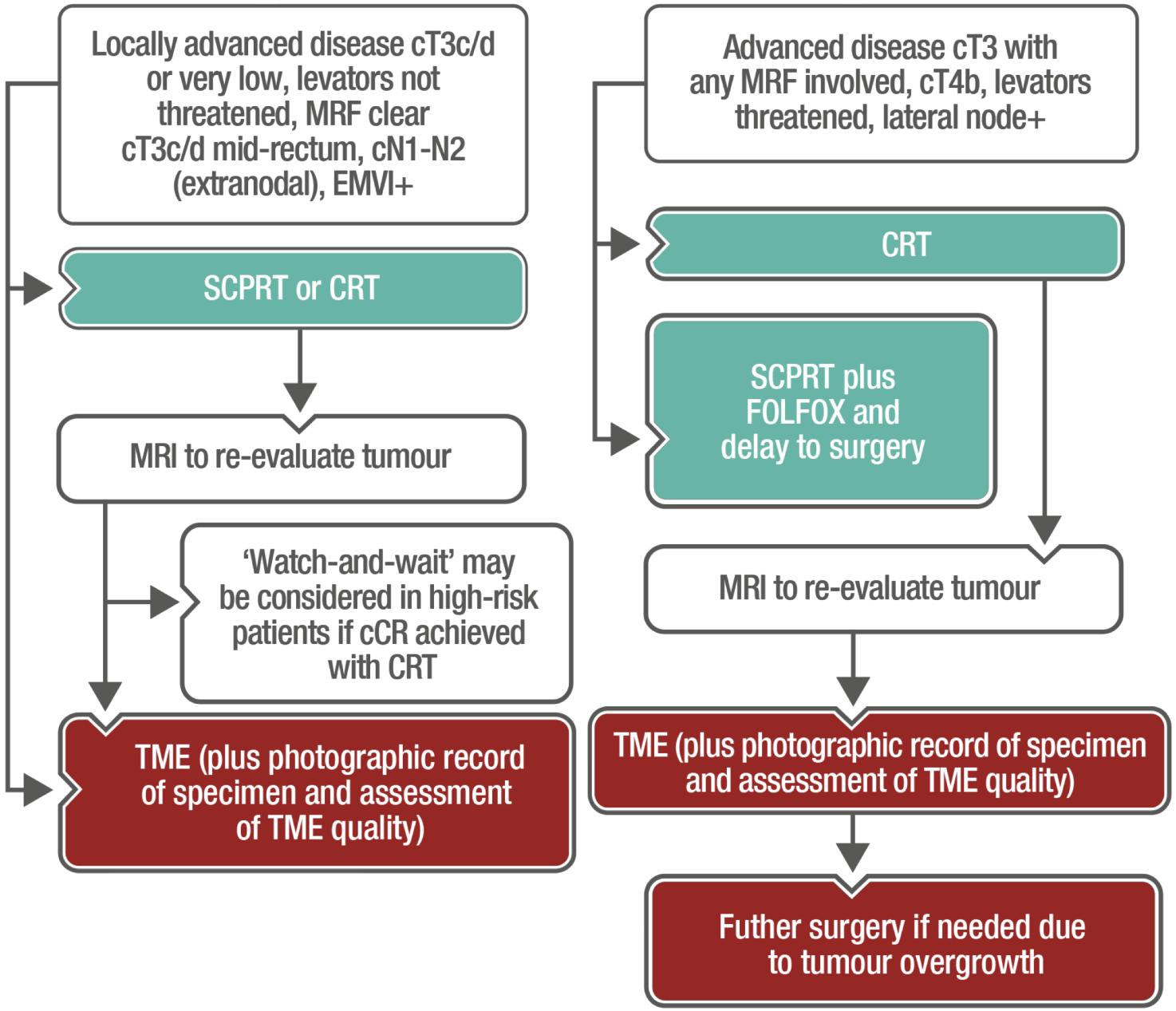
Treatment recommendations

Locally advanced and advanced disease



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Management of local/locoregional disease

Risk of recurrence according to postoperative histology

Summary of recommendations

Postoperative histopathological features with an impact on the risk of local recurrence, include:

- pathological TNM stage
- T substage
- CRM status
- the number/proportion of involved lymph nodes
- extracapsular extension
- extranodal deposits
- tumour differentiation
- lymphovascular invasion
- extramural vascular invasion
- perineural invasion

The risk of local recurrence in patients with histologically involved nodes is reduced with good quality mesorectal excision, ensuring removal of all mesorectal lymph nodes

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Management of local/locoregional disease

Considerations for selection of the most adequate (C)RT regimen

Summary of recommendations
The standards of care for preoperative treatment are SCPRT: • 25 Gy total dose at 5 Gy/fraction during 1 week, then immediate surgery (< 10 days from the first radiation fraction) and CRT with a recommended dose of 45–50 Gy in 25–28 fractions • To be considered for preoperative RT, if CRM is threatened: boost of 5.4 Gy in 3 fractions • Postoperative RT: routinely with 5.4–9.0 Gy in 3–5 fractions according to CRM
CRT is recommended where CRM and/or R0 resection status are predicted by the MDT to be at risk
Routine addition of oxaliplatin to fluoropyrimidine-based CRT is not recommended
5-FU IV infusion / oral capecitabine, are recommended in preference to bolus 5-FU during CRT and as adjuvant systemic treatment
Preoperative RT or CRT reduces the rate of local recurrence for mid/low stage II/III rectal cancers, but is associated with significantly worse postoperative intestinal and sexual functions
Upper rectal cancers above the peritoneal reflection should be treated as colon cancer
Patients with cT4 tumours falling back into the pelvis might benefit from neoadjuvant CRT or NACT alone

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Management of local/locoregional disease

Preoperative (neoadjuvant) chemotherapy

Preoperative chemotherapy

Fluoropyrimidine and oxaliplatin-based NACT, either alone or combined with targeted agents, instead of preoperative CRT in cT3 tumours not threatening the CRM and cT4 tumours in the mid- and upper rectum, is associated with pCR in 25% of early-stage cases

(NACT alone is not recommended for localised, non-metastatic disease outside clinical trials)

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Management of local/locoregional disease

Preoperative (neoadjuvant) chemotherapy

Situation	Reassessment/response assessment after preoperative (chemo)radiotherapy
Assessment of the primary tumour response	The standard methods of clinical reassessment are clinical examination using DRE, proctoscopy and MRI re-imaging
Clinical complete response and a watch-and-wait approach	• An initially raised CEA level which returns to normal (< 5 ng/mL) after CRT is associated with an increased likelihood of cCR and pCR • Further validation of a watch-and-wait approach is required
Patients planned for surgery	• In LARC, the primary tumour/CRM should be re-evaluated with MRI after CRT prior to resection • mriTRG can predict survival outcomes but does not correlate well with histopathological TRG • CT has relatively low value in assessing local response • PET should not be routinely used as a response tool and surgery should not be modified based on the findings • Patients with persistent potential CRM involvement on imaging following CRT should be referred to a MDT for tumour removal *en bloc*

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Management of local/locoregional disease

Preoperative (neoadjuvant) chemotherapy

Situation	Reassessment/response assessment after preoperative (chemo)radiotherapy
Distant metastases	Routine restaging of chest and abdomen after neoadjuvant CRT is not recommended, but patients with cT4 cancers, threatened CRM and EMVI should be re-staged within 3 months of original staging *NB: Applicable only for earlier stage tumours when clinical progression is observed*
Pathological assessment of response	• As a minimum, tumours should be graded as having either pCR, some response or no response • Other dynamic histopathological features, i.e. amount of necrosis, regression of EMVI and downstaging of T and N stage, may also help to define outcomes • Interval to surgery • For SCPRT in resectable cancers not requiring downstaging, immediate surgery (within 7 days from the end of neoadjuvant treatment, and within 0–3 days if the patient is ≥ 75 years [< 10 days from the first radiation fraction]) is recommended

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Management of local/locoregional disease

Postoperative therapy

Summary of recommendations	
Postoperative chemoradiotherapy	May be used selectively in patients with unexpected adverse histopathological features after primary surgery, including • positive CRM • perforation in the tumour area • incomplete mesorectal resection or in other cases with high risk of local recurrence if preoperative RT has not been given
Postoperative chemotherapy	• Adjuvant ChT after preoperative CRT/RT with postoperative histology (ypTNM) stage III (and 'high-risk' yp stage II) can be considered (level of evidence is lower than in colon cancer) • The decision to use postoperative ChT (fluoropyrimidine alone or combined with oxaliplatin) should take into account the predicted toxicity and the risk of relapse

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Management of local/locoregional disease

Potential indications for postoperative CRT if preoperative CRT not given

Sufficient and necessary	Insufficient and unnecessary
CRM ≤ 1 mm	pT1/pT2
pT4b	pT3
pN2 extracapsular spread close to MRF	CRM > 2 mm
Extranodal deposits (N1c)	pT4a above peritoneal reflection
pN2 if poor mesorectal quality/defects	pN1
	If good quality smooth intact mesorectum
Sufficient	
pN2 low tumours within 4 cm of anal verge (risk of involved LPLN)	
Extensive extramural vascular invasion/perineural invasion close to MRF	
Borderline sufficient	
pN2 in mid/upper rectum if good mesorectal quality	
CRM 1–2 mm	
Circumferential obstructing tumours	

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Management of local recurrence

Summary of recommendations
Surgical salvage should be carried out by specialist team
If RT has not already been administered, patients should be considered for standard dose preoperative CRT (45–50 Gy in 5–6 weeks), or SCPRT followed by a fluoropyrimidine and oxaliplatin-based ChT, prior to attempted resection
In patients previously irradiated, re-irradiation to lower doses (with concomitant ChT) is safe and can be used to facilitate a curative resection or to palliate symptoms
Systemic palliative ChT to downstage a tumour and enable salvage surgery may be considered
Palliative surgical diversion procedures and brachytherapy are effective palliative options

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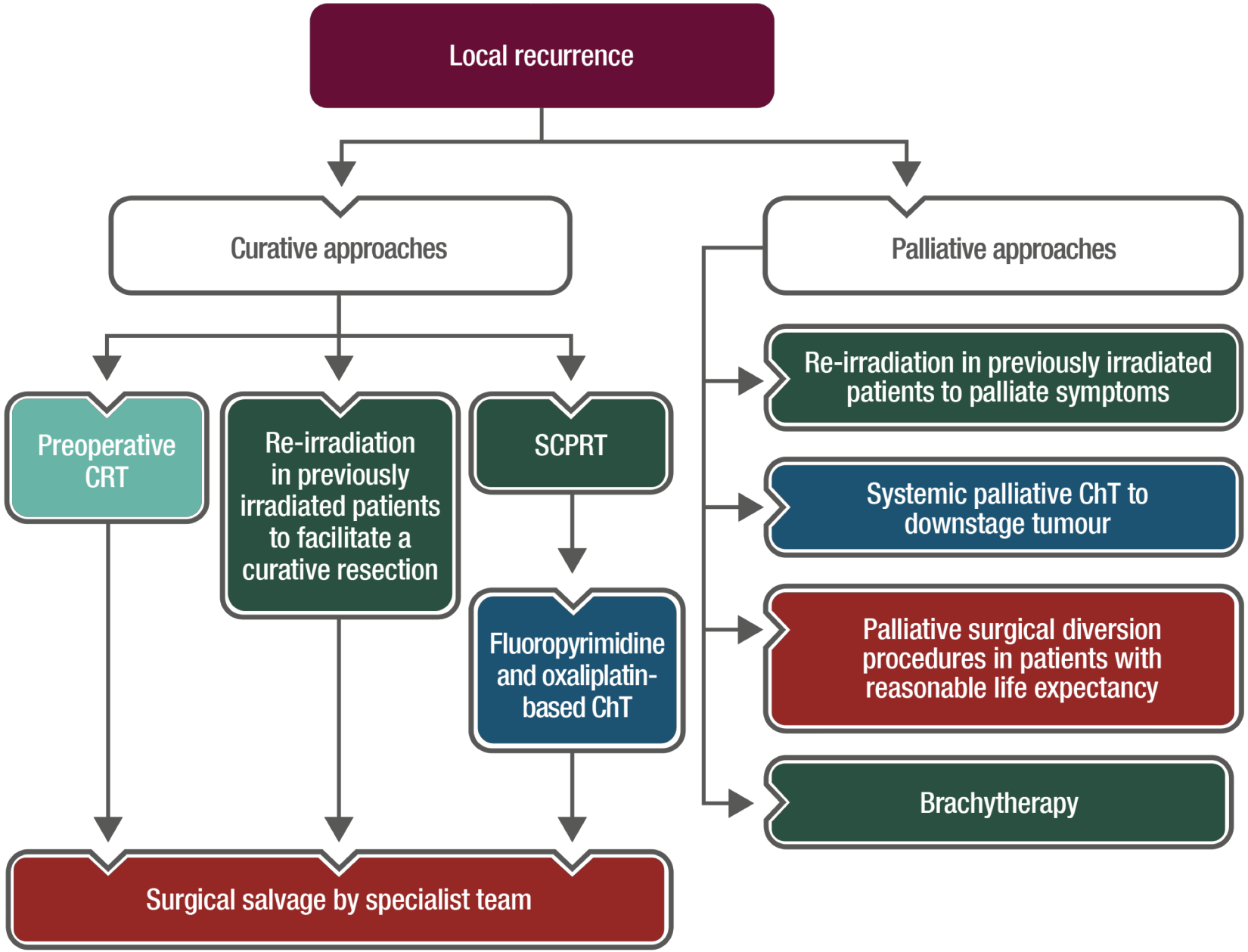
Management of local recurrence



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Management of advanced/ metastatic disease

Summary of recommendations
Metastatic rectal cancer management should reflect tumour-, disease-, patient- and treatment-related factors
ChT alone may be insufficient where the primary tumour remains *in situ* and untreated and local RT palliation of rectal symptoms may be required
SCPRT is preferable to CRT
Rapid local control with effective systemic ChT and appropriate sequence/timing of metastasectomy is the aim of treatment where cure is a possibility
SPCRT with capecitabine/oxaliplatin/bevacizumab can be used to facilitate resection borderline resectable liver metastases and primary tumour
The MDT should be responsible for critical treatment decisions in patients with potentially curable metastatic disease

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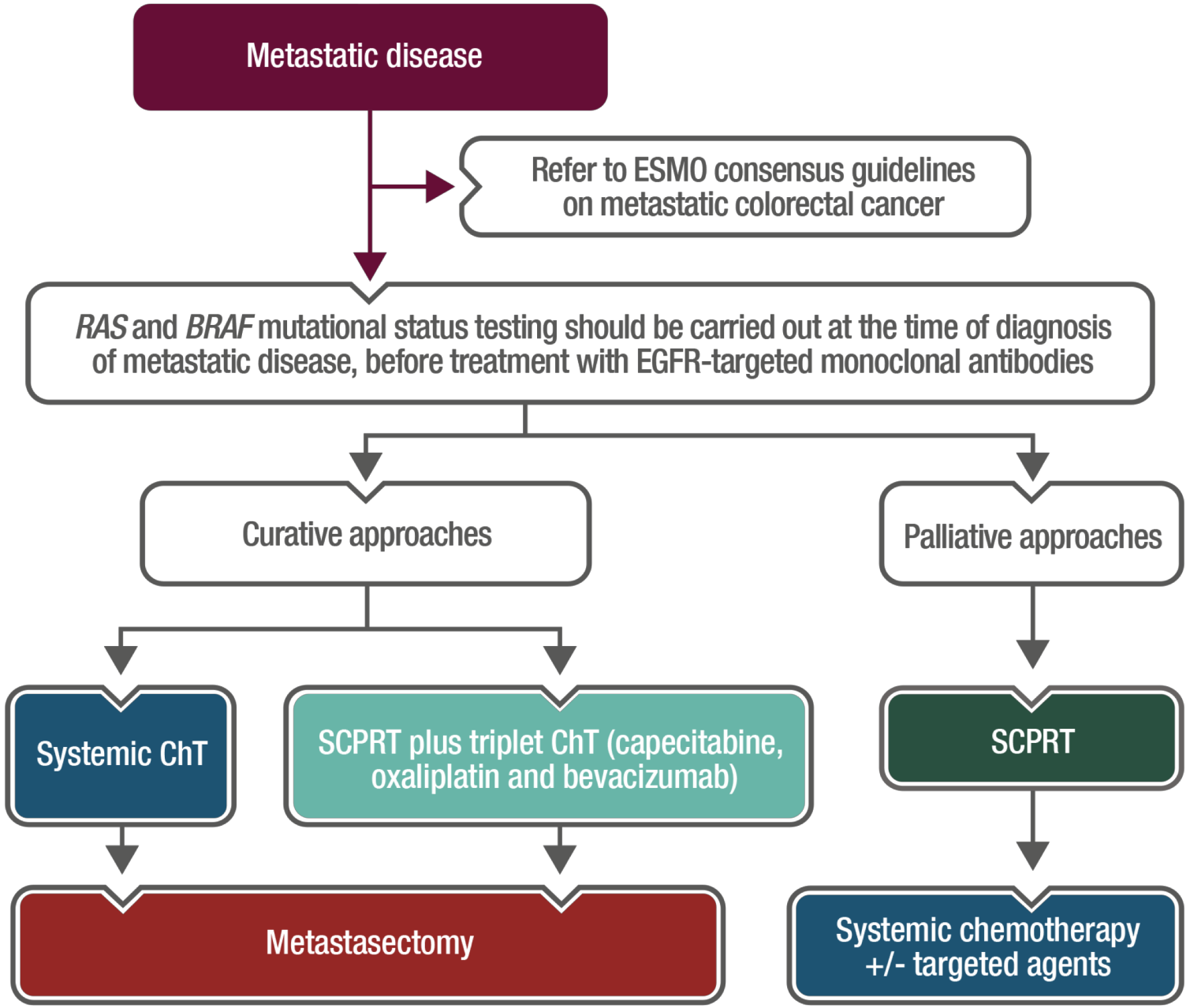
Management of advanced/ metastatic disease



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Personalised medicine

Summary of recommendations
There are no molecular markers to guide treatment approaches or to predict response to RT or CRT
Rectal cancers with distant metastases should be studied for *RAS* and *BRAF* mutational status and the other requirements addressed in the ESMO consensus guidelines on metastatic colorectal cancer

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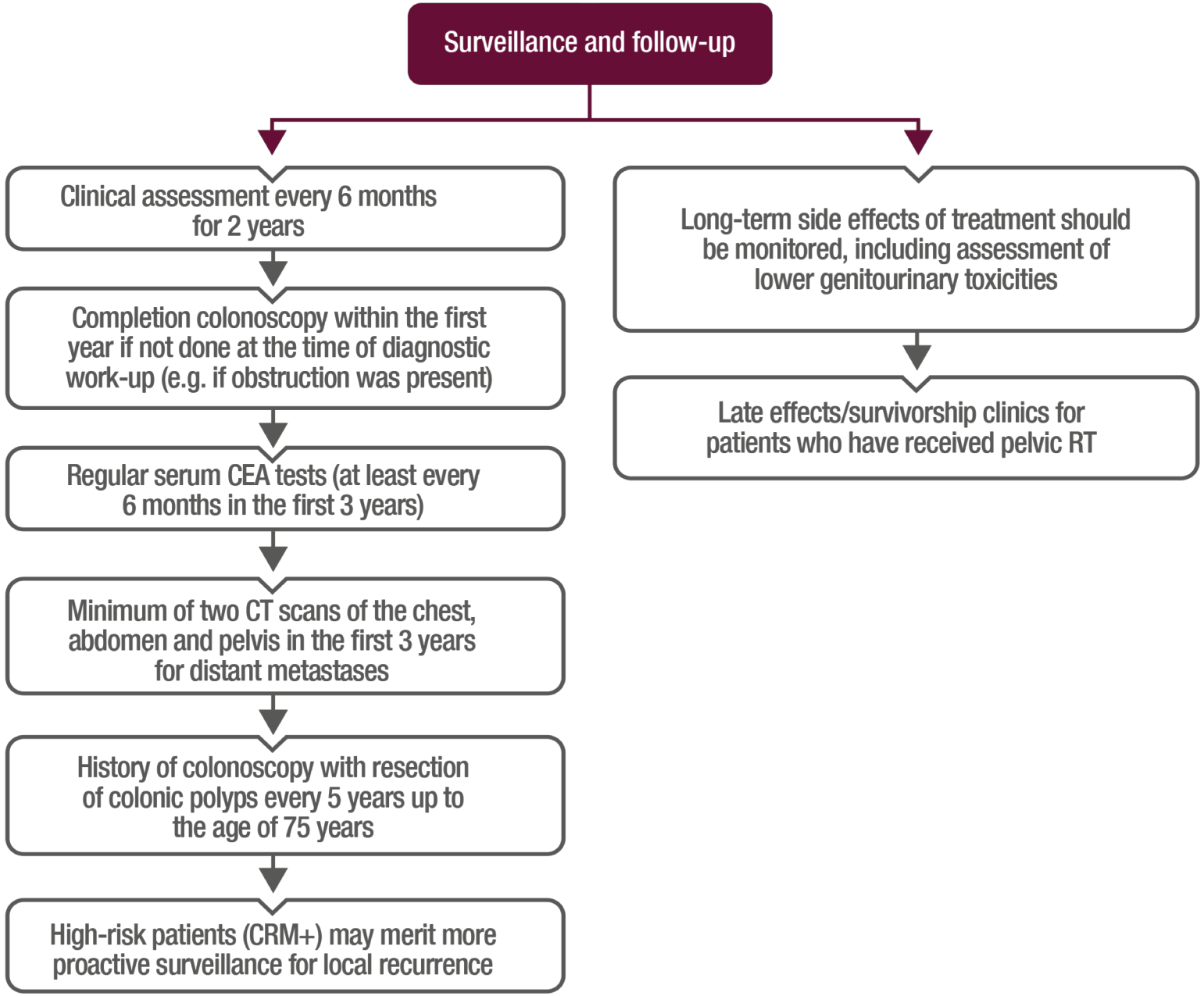
Follow-up, long-term implications and survivorship

Surveillance and follow-up



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Disclaimer and how to obtain more information

This slide set provides you with the most important content of the full ESMO Clinical Practice Guidelines (CPGs) on the management of rectal cancer. Key content includes diagnostic criteria, staging of disease, treatment plans and follow-up.

The ESMO CPGs are intended to provide you with a set of recommendations for the best standards of care, using evidence-based medicine. Implementation of ESMO CPGs facilitates knowledge uptake and helps you to deliver an appropriate quality of focused care to your patients.

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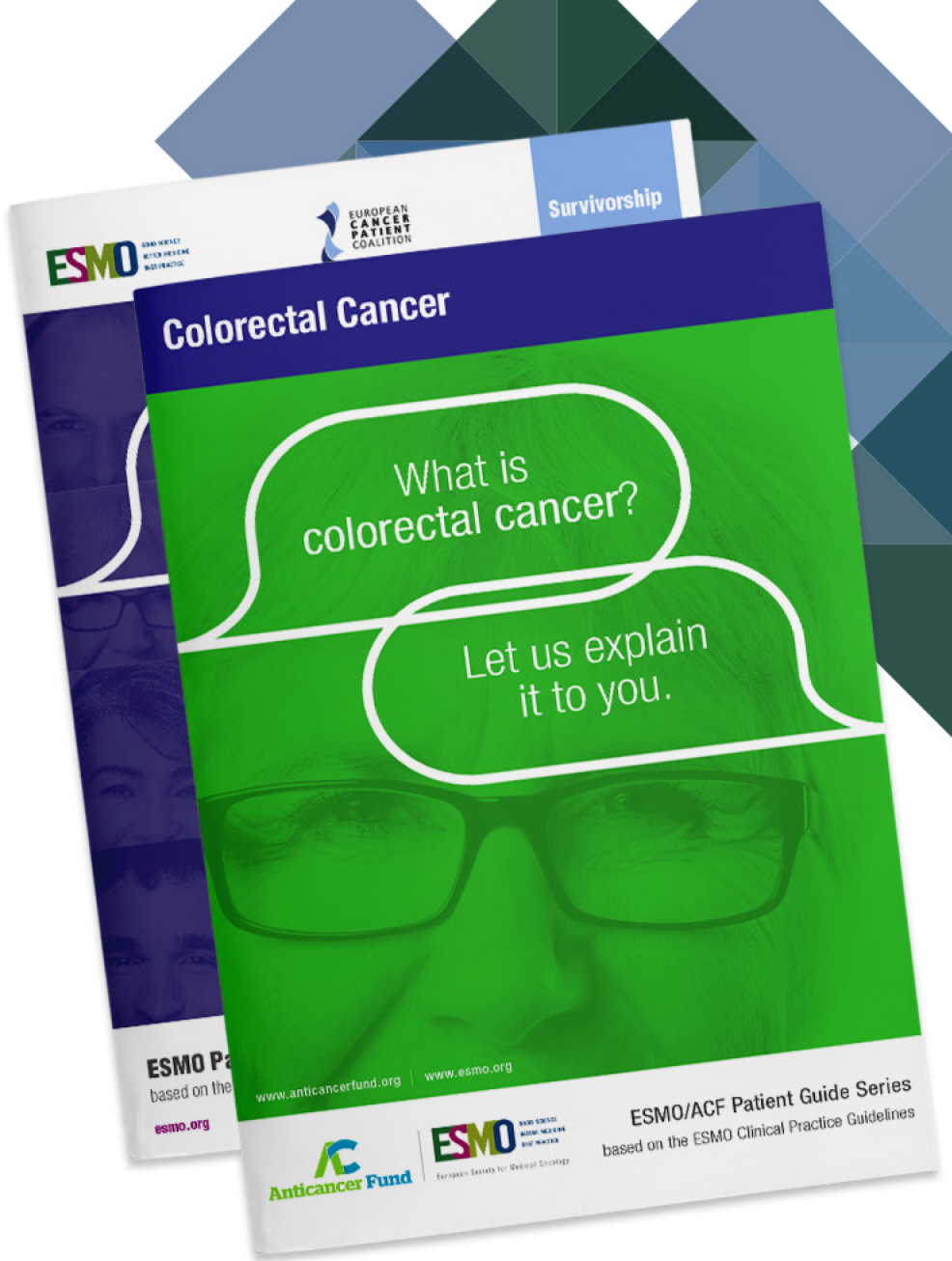

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