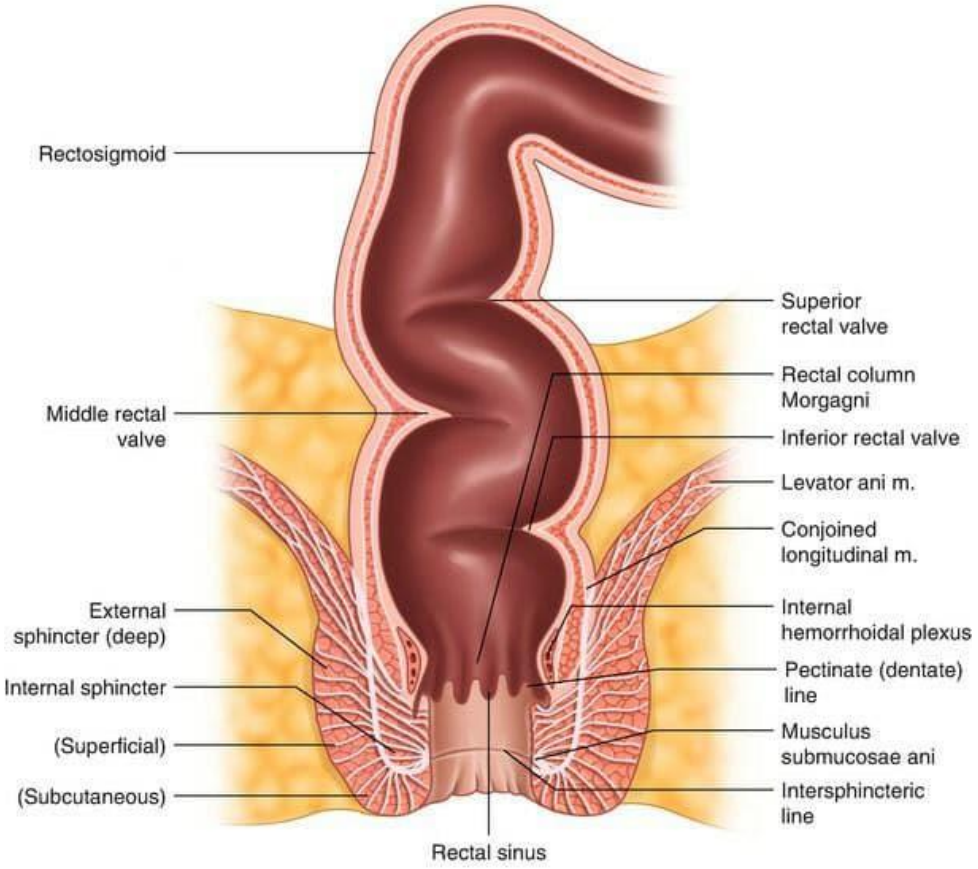
تطوير واقع جراحة الاورام في العراق

ا م د منور النقاش – فرع الجراحة

Anatomy

- The rectum begins at the rectosigmoid junction at level of S3 vertebra it is about 15 cm long. Because of differences in treatment and prognosis, the rectum is subdivided into three parts according to the distance of the lower margin of the tumor from the anal verge (assessed by rigid sigmoidoscopy): (> 10-15 cm, > 5-10 cm, 0-5 cm)
- Patients entered into postoperative adjuvant rectal trials in the United States were required to have tumors with the inferior aspect at or below the peritoneal reflection. For entry into preoperative trials, most use tumors with a distance of less than 12 cm from the anal verge for eligibility. The German trial allowed tumors at a distance of as much as 16 cm
- the rectum exhibits lateral curves usually three: two on the left side and one on the right), which corresp ond on the intraluminal aspect to Houston's valves – superior (9-10 cm from the anal verge); the middle valve, termed Kohlrausch's valve, which is the most consistent (6-8 cm from the anal verge); and inferior (4 -5 cm from the anal verge)

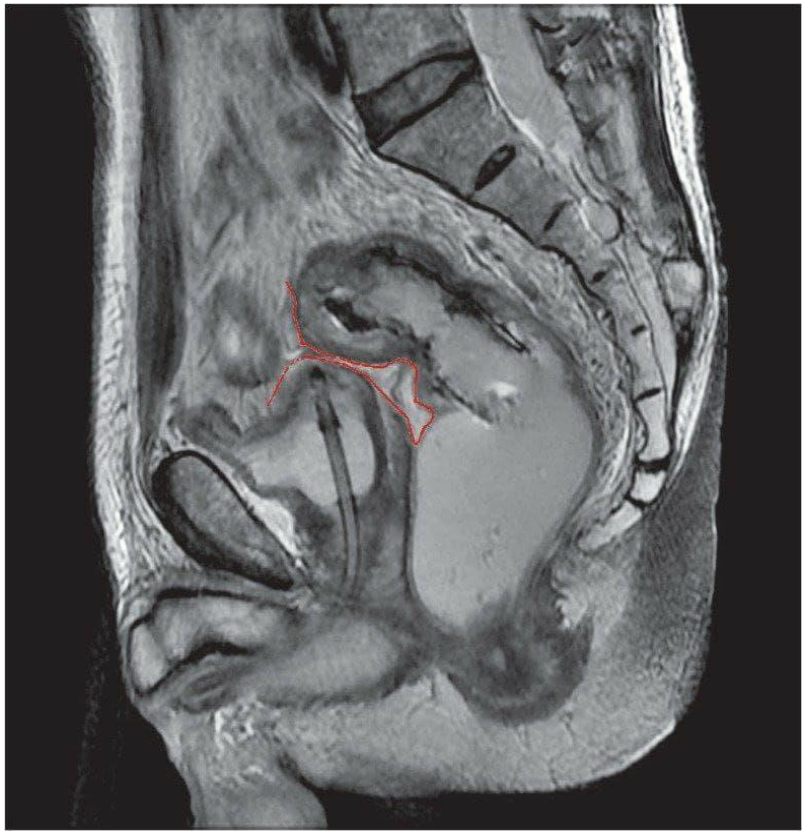


Anatomy

- The anterior peritoneal reflexion represents the point at which the rectum exits the peritoneal cavity and becomes an retroperitoneal structure (approximately 12-15 cm from the anal verge). Below this level, a layer of visceral fascia encloses both the rectum and mesorectum tissue, forming a separate compartment within the pelvis

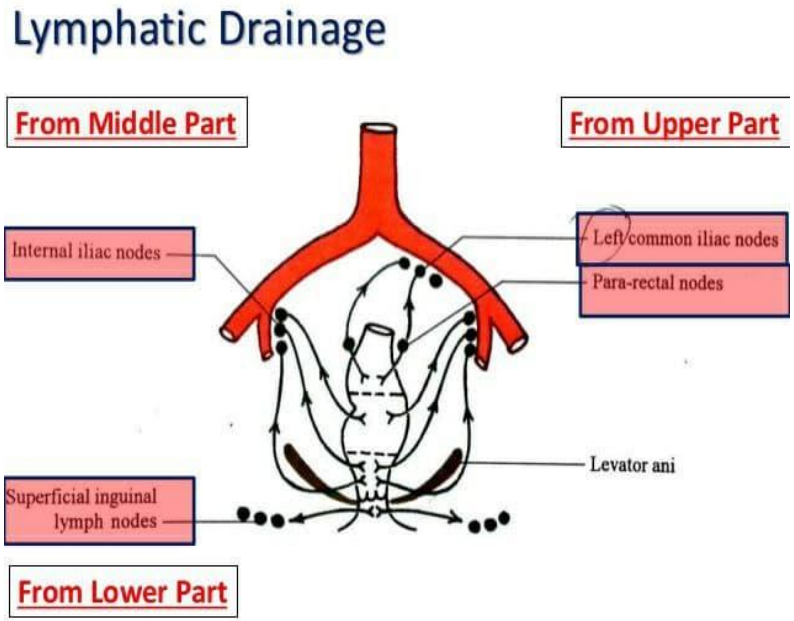
- discontinuous microscopic tumor spread (including meta- stasis in lymph nodes, solitary tumor foci, vessel and perineural invasion) can be found in the mesorectum, predominantly in a radial direction but also in a distal one, up to some centimeters from the lower tumor margin.

- Extramural venous invasion (EMVI) specifically describes tumor cells within the veins outside the muscularis propria of the bowel wall. EMVI is widely regarded as an adverse prognostic feature in rectal cancer and confers a higher risk of both local and distant recurrence.



Anatomy

- **Lymph node drainage:**
- Upper half rectum: superior hemorrhoidal → IMA → para-aortic
- Lower half rectum: Inferior + middle hemorrhoidal → internal iliac, obturator presacral nodes
- Involvement of anal canal: superficial inguinal node
- Invading anterior structures (prostate, bladder, vagina) → external iliac
- Rectal metastases travel along portal drainage to liver via the superior rectal vein; pulmonary metastases can result from drainage via the middle and inferior rectal veins to the systemic circulation



presentation

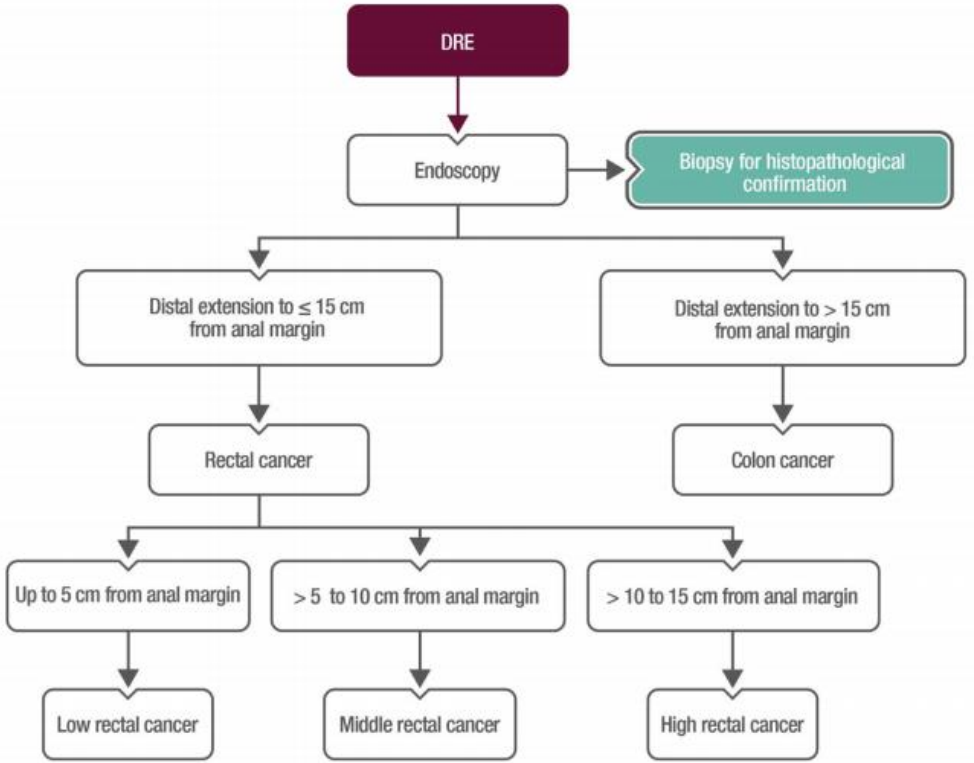
- Common symptoms include gross red blood (mixed or covering stool, or by itself, so metimes accompanied by the passage of mucus) and a change in bowel habits such as unexplained constipation, diarrhea, or reduction in stool caliber.
- Hemorrhoidal bleeding should always be a diagnosis of exclusion.
- Obstructing rectal cancers frequently present with diarrhea rather than constipation.
- In cases of locally advanced rectal cancer with circumferential growth and extensive transmural penetration, urgency, inadequate emptying, and tenesmus occur.
- Urinary symptoms and buttock or perineal pain from posterior extension are grave signs.
- Sciatic pain is indicative of tumor invasion into the sciatic notch, and surgery will likely leave gross disease.

- DRE and complete pelvic exam in women. Note size, location, ulceration, mobile vs tethered vs fixed, and sphincter function on rectal exam.

CLINICAL PRACTICE GUIDELINES

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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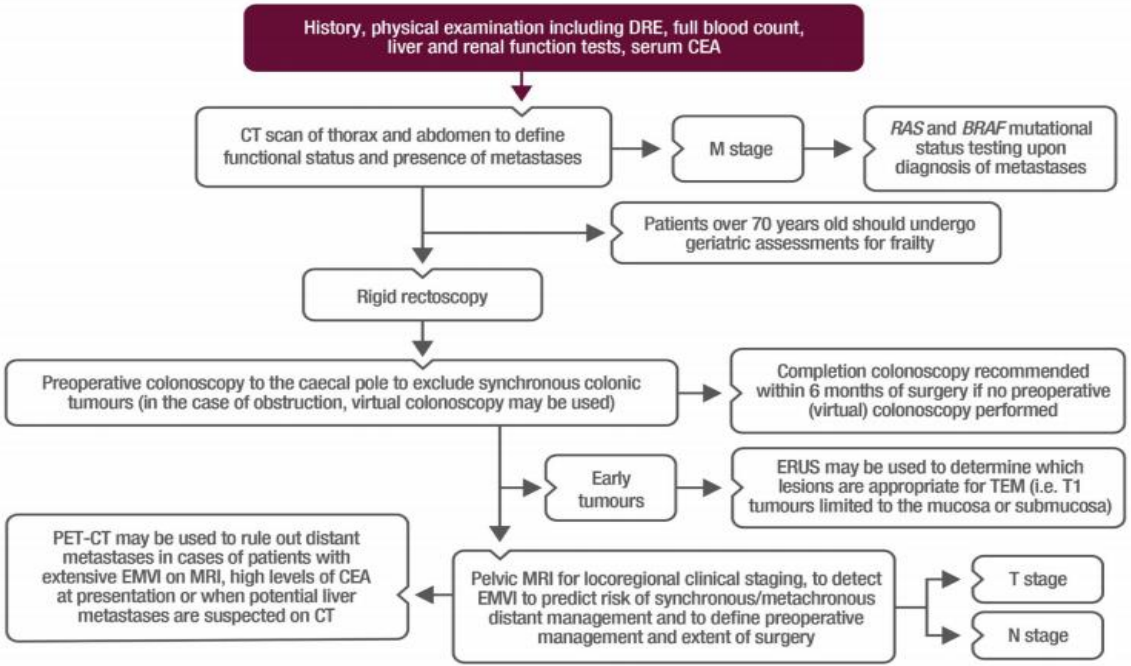
Clinical assessment

CLINICAL PRACTICE GUIDELINES

Staging and risk assessment



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

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Clinical assessment

CLINICAL PRACTICE GUIDELINES

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

4.1 Definition of Primary Tumor (T)

✓	*T Category*	*T Criteria*
	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma *in situ*, intramucosal carcinoma (involvement of lamina propria with no extension through muscularis mucosae)
	T1	Tumor invades the submucosa (through the muscularis mucosa but not into the muscularis propria)
	T2	Tumor invades the muscularis propria
	T3	Tumor invades through the muscularis propria into pericolorectal tissues
	T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
	T4a	Tumor invades through the visceral peritoneum (including gross perforation of the bowel through tumor and continuous invasion of tumor through areas of inflammation to the surface of the visceral peritoneum)
	T4b	Tumor directly invades or adheres to adjacent organs or structures

✓	*T Suffix*	*Definition*
	(m)	Select if synchronous primary tumors are found in single organ.

4.2 Definition of Regional Lymph Node (N)

✓	*N Category*	*N Criteria*
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	One to three regional lymph nodes are positive (tumor in lymph nodes measuring ≥ 0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
	N1a	One regional lymph node is positive
	N1b	Two or three regional lymph nodes are positive
	N1c	No regional lymph nodes are positive, but there are tumor deposits in the • subserosa • mesentery • or nonperitonealized pericolic, or perirectal/mesorectal tissues.
	N2	Four or more regional nodes are positive
	N2a	Four to six regional lymph nodes are positive
	N2b	Seven or more regional lymph nodes are positive

✓	*N Suffix*	*Definition*
	(sn)	Select if regional lymph node metastasis identified by SLN biopsy only.
	(f)	Select if regional lymph node metastasis identified by FNA or core needle biopsy only.

Staging

4.3 Definition of Distant Metastasis (M)

The terms pM0 and MX are NOT valid categories in the TNM system. Assignment of the M category for clinical classification may be cM0, cM1, or pM1. Any of the M categories (cM0, cM1, or pM1) may be used with pathological stage grouping.

✓	*M Category*	*M Criteria*
	cM0	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs (This category is not assigned by pathologists.)
	cM1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified
	cM1a	Metastasis to one site or organ is identified without peritoneal metastasis
	cM1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis
	cM1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases
	pM1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified and microscopically confirmed
	pM1a	Metastasis to one site or organ is identified without peritoneal metastasis and microscopically confirmed
	pM1b	Metastasis to two or more sites or organs is identified without peritoneal metastasis and microscopically confirmed
	pM1c	Metastasis to the peritoneal surface is identified alone or with other site or organ metastases and microscopically confirmed

5 AJCC Prognostic Stage Groups

Always refer to the specific chapter for rules on clinical and pathological classification of this disease.

✓	*When T is…*	*And N is…*	*And M is…*	*Then the stage group is…*
	Tis	N0	M0	0
	T1, T2	N0	M0	I
	T3	N0	M0	IIA
	T4a	N0	M0	IIB
	T4b	N0	M0	IIC
	T1–T2	N1/N1c	M0	IIIA
	T1	N2a	M0	IIIA
	T3–T4a	N1/N1c	M0	IIIB
	T2–T3	N2a	M0	IIIB
	T1–T2	N2b	M0	IIIB
	T4a	N2a	M0	IIIC
	T3–T4a	N2b	M0	IIIC
	T4b	N1–N2	M0	IIIC
	Any T	Any N	M1a	IVA
	Any T	Any N	M1b	IVB
	Any T	Any N	M1c	IVC

Staging

CLINICAL PRACTICE GUIDELINES

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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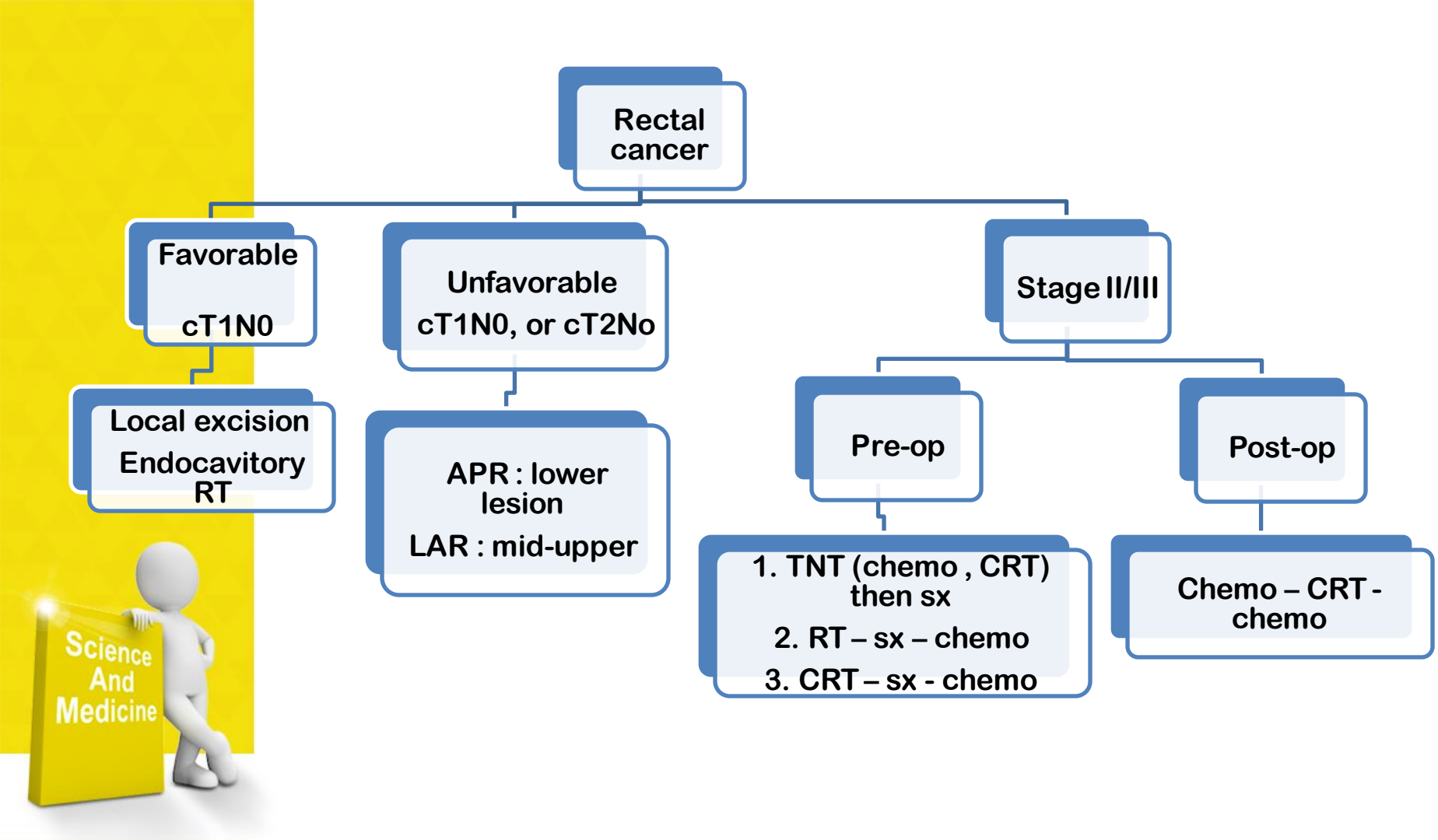

Rectal cancer
Favorable
cT1N0
Local excision
Endocavitory RT
Unfavorable
cT1N0, or cT2No
APR : lower lesion
LAR : mid-upper
Stage II/III
Pre-op
1. TNT (chemo , CRT) then sx
2. RT – sx – chemo
3. CRT – sx - chemo
Post-op
Chemo – CRT - chemo
Science And Medicine

Favorable cT1N0

1. 8 cm from anal verge
2. < 3 cm size
3. < 30% of circumference
4. Margin > 3 mm
5. No LVI nor PNI
6. Not fixed
7. No ulceration
8. Well – moderately differentiated
9. Non signet ring histology

Local recurrence after excision is 5-10%

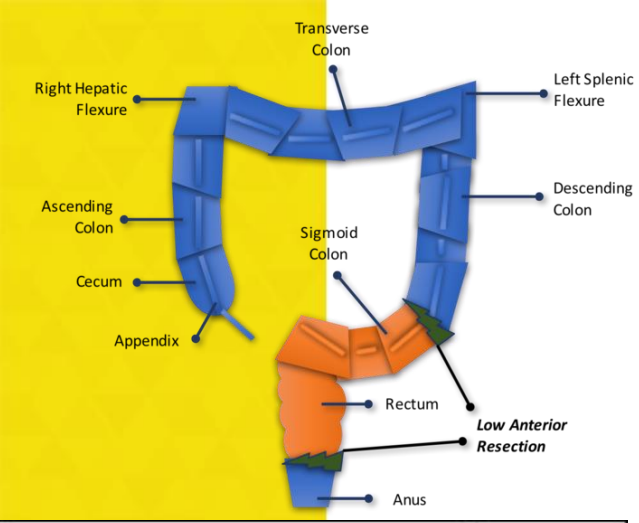
Favorable cT1N0

Can be treated by :

- Endocavitory irradiation (papillion technique) before delivery the anus is dilated and 4 cm proctoscope is introduced. A low-energy X ray unit is placed through the scop e almost against the tumor. 50 Kv is delivered at 30 Gy/Fx in 3-4 Fx over 1 month
- local excision : transanal local excision , post proctocomy, trans-sphincteric excision

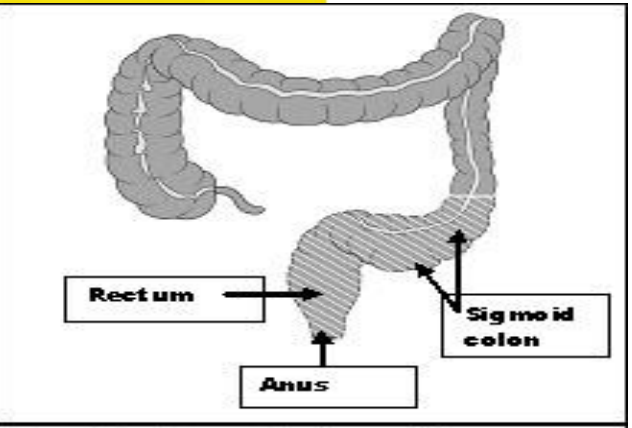
{regardless the technique, the excision should be 1. full thickness 2. non fragmented 3. negative margin

For unfavorable cT1N0 -T2N0 local recurrence afer excision is 17% & incidence of positive pelvic LNs = 10-15%

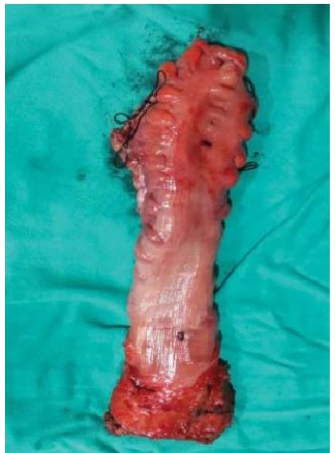


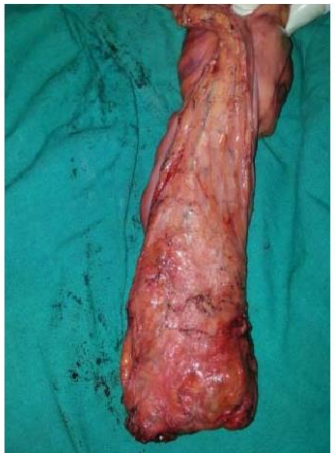
Surgical principles

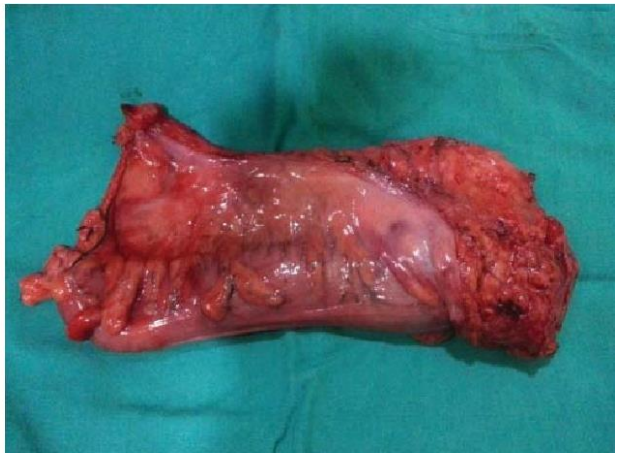
- Total mesorectal excision TME and sharp dissection of the entire mesorectur are the standard of care. It generally extends 4-5 cm b elow distal edge of tumor, but for distal tumors (<5 cm from anal ver ge) 1-2cm negative margin maybe acceptable.
- Low anterior resection LAR : is used for mid-upper tumors, it's a sphi ncter preserving procedure with LN dissection > 12
- Abdominoperineal resection APR : for lower lesions , permanent colos tomy , > 12 LNs dissected



An abdominoperineal resection removes the anus, rectum, and sigmoid colon portions of the large intestine.







Pre op RT VS. surgery alone

- 2 randomized trials of short course RT pre operative. All except for dutch trial were in pre-TME era. Most trials showed a decrease in local recurrence rate

Swedish Rectal Cancer Trial : Phase III. 1168 patients with resectable rectal CA cT1-3 randomized to pre-op RT (25 Gy/5 fx) and surgery vs surgery alone (non-TME). Pre-op RT improved 5-year LR and 5-year OS. Thirteen- year OS was 38% vs 30% favoring RT.

Study		Outcome
Swedish Rectal cancer Trial Folkesson J et al JCO 2005	•PreopRT vs sug alone, cT1-3 •1168 •25Gy/5Fr/5days→Sug •Med FU 13 years	•OS 38% vs30%, p 0.008 •LRR 9%vs 26% p 0.008
Dutch study CKVO 95-04 Willem VG et al Lancet oncol 2011	PreopRT vs TME alone, cT1-3 1861 patients 25Gy/5Fr/5days→TME Med FU 10 years	OS 48%vs 49% p 0.86 LR 5% vs 11% p 0.0001

Dutch TME : Phase III. 1861 patients with resectable rectal CA randomized to pre-op RT (25 Gy/5 fx) and surgery vs surgery alone (TME surgery). Pre-op RT improved10-year LR (5% vs 11%). RT reduced cancer specific survival but not overall survival. Subset analyses showed improved survival for patients with stage III disease and negative circumferential resection margins. At 5 years, RT increased fecal incontinence (62% vs 38%), pad wearing, bleeding (11% vs 3%), and mucous discharge.

Chemoradiation

- Chemoradiation can be delivered preoperatively or postoperatively. For patients with cT1-2N0 disease, the initial treatment is surgery. If the tumor is pT3-4N0 or TanyN1-2, this is commonly followed by postoperative chemoradiation. For patients with cT3-4N0 or TanyN+ lesions,
- preoperative chemoradiation is given, followed by surgery (alone or plus intraoperative radiotherapy [IORT] for T4 lesions) and postoperative adjuvant chemotherapy.

Pre-op vs Post-op ChemoRT

- Compared with post-op RT, pre-op RT reduces risk of local recurr ence, increases sphincter preservation, and decreases toxicity. Ho wever, some patients may receive unnecessary radiation, as up to 20% of patients are overstaged.

Pre-op vs. post-op Chemo RT

Randomized trial of the German Rectal Cancer study Group (Sauer R et al. N Engl J Med 2004;351:1731-40):

- cT3 or cT4 or node-positive rectal cancer
- 50,4 Gy (1.8 Gy per day)
- 5-FU: 1000 mg/m² per day (d1-5) during 1. and 5. week

	Preop CRT	Postop CRT	
Patients	N=415	N=384	
5 y. OS	76%	74%	p=0.8
5 y. local relapse	6%	13%	p=0.006
G3,4 toxic effects	27%	40%	p=0.001

- Increase in sphincter-preserving surgery with preop Th.

German Rectal Cancer Study Group Phase III. 823 patients with T3/4 or N+ rectal CA randomized to pre-op (50.4 Gy + 5-FU) vs post-op chemoRT (54 Gy + 5-FU). All patients received an additional 4 cycles of bolus 5-FU.
Pre-op chemoRT improved 5-year LR rate (6% vs 13%), increased sphincter preservation (39 % vs 19%), and decreased grade 3–4 acute and late toxicity and late anastomotic strictures. 25 % of pre-op group compared to 40% post-op had +LN, and there was pCR in 8% of pre-op group. In post-op arm, 18% of initially eligible patients were over staged and excluded due to finding of pT1-2N0 disease at time of surgery. No difference in survival.

Do patients with pathological node-negative rectal cancer require pelvic irradiation?

- Patients who undergo high quality TME, who have more than 12 LNs examined and have pT3N0 disease do not nee d the radiation component of chemoradiation depending on the adequacy of radial and distal margins of resection.
- The small benefit in local control with irradiation is not worth the risks, especially in women of reproductive age.
- However, patients with pT3N0 tumors with adverse pathological features, who undergo resection without TME, or who have fewer than 12 nodes examined should still receive postoperative chemoradiation.

Pre op chemoradiation

- Based on the German CAO/ARO/AIO 94 trial, preoperative chemoradiation is standard treatment for patients with cT3-4N0 or Tany N+ disease. The disadvantage of preoperative therapy is the possible overtreatment of patients with either early-stage disease (pT1-2N0) or undetected metastatic disease.
- There has been some debate as to which fluoropyrimidine (5-FU or capecitabine) is the preferred radiosensitizer. Two trials have examined this question. The NSABP R-04 trial and Hofheinz et al. both reported that 5-FU– and capecitabine-based chemoradiation regimens are equivalent.
- The role of post op adjuvant chemotherapy following preoperative chemoradiation is controversial. There are two randomized trials (EORTC 22921 , FFCD 9203) both of which reported a significant improvement in local control but no survival benefit
- A subset analysis of the EORTC trial revealed that patients who respond to pre op CRT had a survival benefit of post op chemotherapy
- Almost all trials of preoperative chemoradiation report an increase in pCR with a longer interval between chemoradiation and surgery. Historically, the interval was 4 to 6 weeks, which has increased to 6 to 10 weeks in many recent series

Preoperative Short-Course Radiation Versus Long-Course Chemoradiation

- Short-course radiation was established as a standard therapy in the Dutch CKVO and Swedish trials, and chemoradiation was established as a standard therapy by the German Rectal Cancer Trial CAO/ARO/ AIO-94.
- The Dutch and Swedish trials cannot be directly compared to the German trial because patients selected for treatment with short course radiation included patients with cT1-3 disease, whereas 95% of the patients in the German trial had cT3 and/or N+ disease.
- Recently, randomized trials of short-course radiation have included patients with stage cT3 or N+, thereby allowing a more relevant comparison between these two approaches.
- Historically : short course Rt has not been recommended for patients with cT3,N+this is because of
- 1. its lack of sphincter preservation
- 2. inability to safely combine it with adequate doses of chemotherapy
- 3. associated late toxicity
-

Sphincter preservation

- When the tumor is located in close proximity to the dentate line, the de crease in tumor volume with chemoradiotherapy may allow the surgeon to perform a sphincter-conserving procedure, such as a coloanal anasto mosis. However, if the tumor directly invades the anal sphincter, sphin cter preservation is unlikely even when a clinical complete response is ac hieved.
- When the goal of preoperative therapy is sphincter preservation, standard course chemoradiation with conventional irradiation doses and techniques followed by surgery in 6 to 10 weeks is recommended. Data from the Lyon R90-01 trial of preoperative irradiation suggest that an interval of longer than 2 weeks following the completion of irradiation increases the chance of downstaging.

Does short-course radiotherapy increase sphincter preservation?

- An analysis of 1316 patients who received short-course preoperative irradiation revealed that downstaging was most pronounced when the interval between the completion of irradiation and surgery was at least 10 days. In the Dutch CKVO 95-04 trial, in which the interval was 1 week , there was no downstaging.

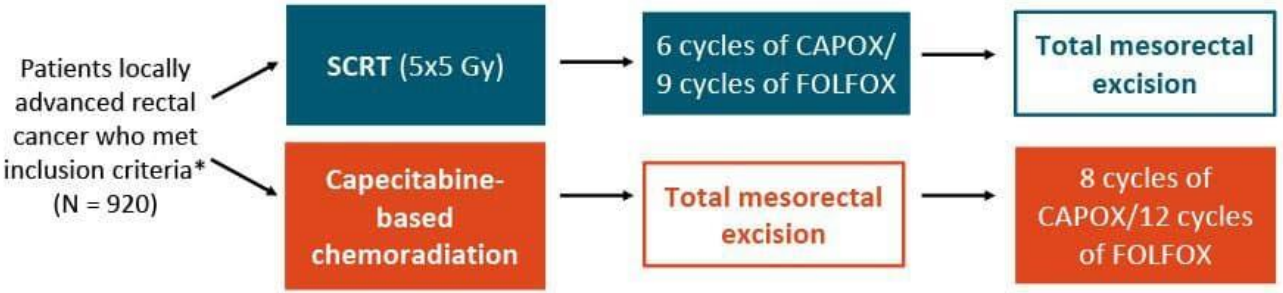
Stockholm III

- Stockholm III : Phase III. 303 patients randomized to short-course RT (25 Gy/5 fx) and early surgery (with in 1 week), short-course and delayed surgery (after 4–8 weeks), and long-course RT (50 Gy/2 fx). The post-op complication rates were 46%, 40%, and 32 % for the arms, respectively.

- Among patients receiving short-course RT, patients in the delayed surgery arm had lower ypT stages, higher rates of pCR (11.8% vs 1.7%), and higher likelihood of tumor regression (10.1% vs 1.7%).

RAPIDO: Preoperative Short-Course Radiotherapy and Chemotherapy for Locally Advanced Rectal Cancer

- Randomized, international, multicenter phase III trial



*Inclusion criteria: biopsy-proven primary adenocarcinoma of the rectum, 18 years or older, absence of distant metastases, MRI with high-risk features (T4a/b, extramural vascular invasion +N2, mesorectal fascia + enlarged lymph nodes).

- Primary endpoints: disease-related treatment failure
- Secondary endpoints: OS, R0 rate, pCR, toxicity, surgical complications, QoL at 3 yrs

Bahadoer. ASCO 2020. Abstr 4006.

Slide credit: clinicaloptions.com

Stay at home messages

SCRT → CAPOX → TME

- ✓ 7% lower Disease-related Treatment Failure: 30.4 to 23.9%
- ✓ 7% lower Distant Metastases rate: 26.8 to 20.0%
- ✓ Doubled pCR rate: 14 to 28%
- ✓ 3-year overall survival 89% in both treatment groups
- ✓ No unexpected toxicity
- ✓ No differences in surgery, postoperative complication and QoL

- Yeo retrospective review if inguinal LNs were not irradiated, 5-yr LR is 3.5% for anal ccanal invasion, 0.2% if no invasion
- IMRT maybe considered for inguinal LNs irradiation o decrease dose to genitalia, those who need dose escalation or SIB
- Concurrent chemotherapy :

1. Continous infusion 5FU 225mg/m2 over 24 hrs 7 days a week during RT
2. Xeloda 825 mg/m2 twice daily 5 days a week is an acceptable alternative according to randomized data (hofheinz, oconnell)

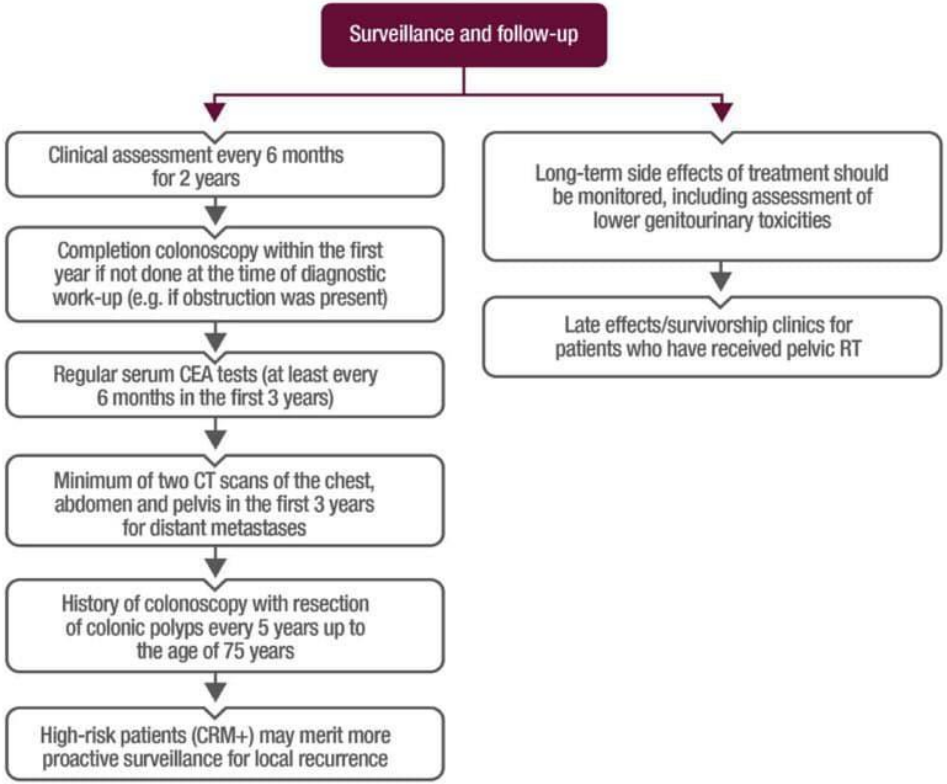
DOSE PRESCRIPTIONS

- Pre-op chemoRT: Pelvis: 45 Gy/25 fx. Tumor bed boost: 5.4 Gy/3 fx. Alternatively, IMRT with simultaneous integrated boost, 45 Gy to pel vis and 50 Gy to tumor + margin in 25 fx.
- Pre-op short-course pelvic RT: 25 Gy in 5 fx.
- Post-op chemoRT: 45–50.4 Gy to pelvis, boost tumor bed additional 5.4–9 Gy.
- Unresectable/inoperable chemoRT: Pelvis to 45 Gy, boost primary to 55.8–59.4 Gy. Consider IMRT to limit small bowel dose. 45 Gy to the whole pelvis, 50.4 Gy to the primary and sacral hollow, 55.8–59.4 Gy to the primary tumor.

CLINICAL PRACTICE GUIDELINES

Follow-up, long-term implications and survivorship

Surveillance and follow-up



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Thank you