Rectal Cancer – Cookbook… Update

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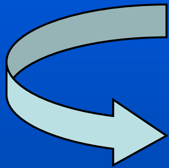
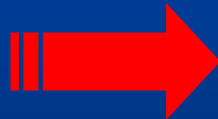
- TME is the standard surgical treatment for rectal cancer
- The pathologist has a crucial role in this process



assessment of the completeness and quality of the resection

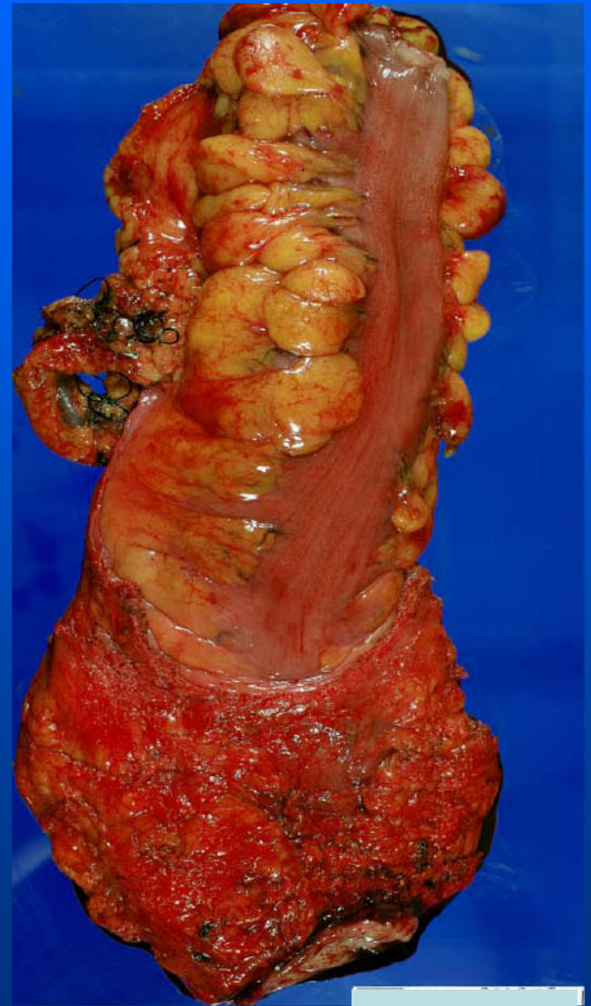


prognosis
choice of additional treatment

TME – macroscopic inspection

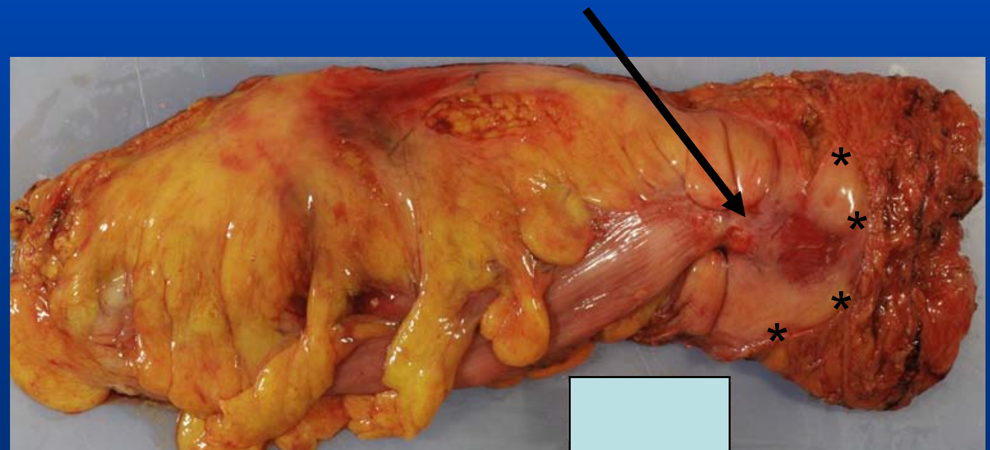
- TME resection specimens require
  - Specific macroscopic handling
  - Specific pathological work-up

Therefore, the resection specimen should be delivered fresh,unfixed to the laboratory (within 2 or 3 hours) unopened and unpinned



TME – macroscopic inspection

- It is mandatory to determine the exact topography of the tumour, with reference to the serosal surface, i.e. above, at or below the peritoneal fold of Douglas (*).



TME – macroscopic inspection

- It is mandatory to photograph the external surface of the TME : anterior and posterior surface to document the quality of the surgical specimen
- The description of the quality of the mesorectal surface is limited to the rectum <u>above</u> the sphincters

TME – macroscopic inspection

- The mesorectum is the visceral mesentery (fatty connective tissue layer enveloped by a thin fascia) surrounding the rectum.
- The mesorectal surface should be assessed
- The quality of the mesorectum can be graded.

TME – macroscopic inspection

- Grading of the quality of mesorectal excision

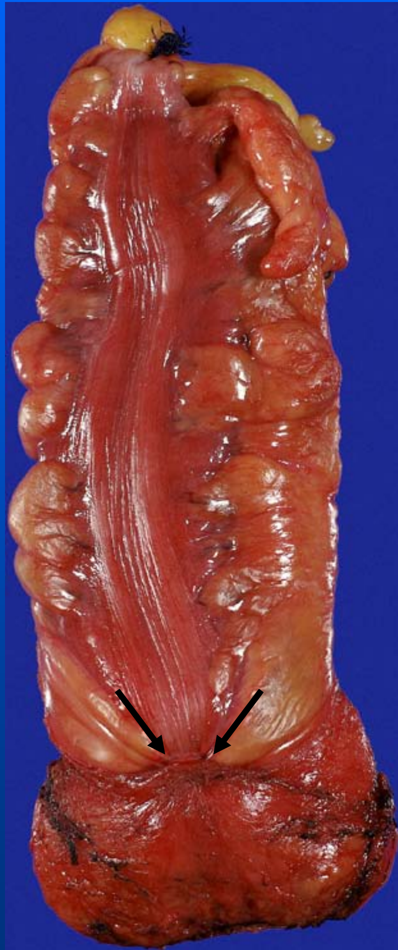
	Mesorectum	Defects	Coning	CRM
Complete (grade 3)	Intact, smooth, no violation of the fat	Not deeper than 5 mm	None	Smooth, regular
Nearly complete (grade 2)	Moderate bulk, irregular surface	No visible muscularis propria	Moderate	Mildly irregular
Incomplete (grade 1)	Little bulk, substantial loss	Down to muscularis propria	Moderate or marked	Severely irregular

Quirke P, Histopathology 2007; Parfitt JR, J Clin Pathol 2007

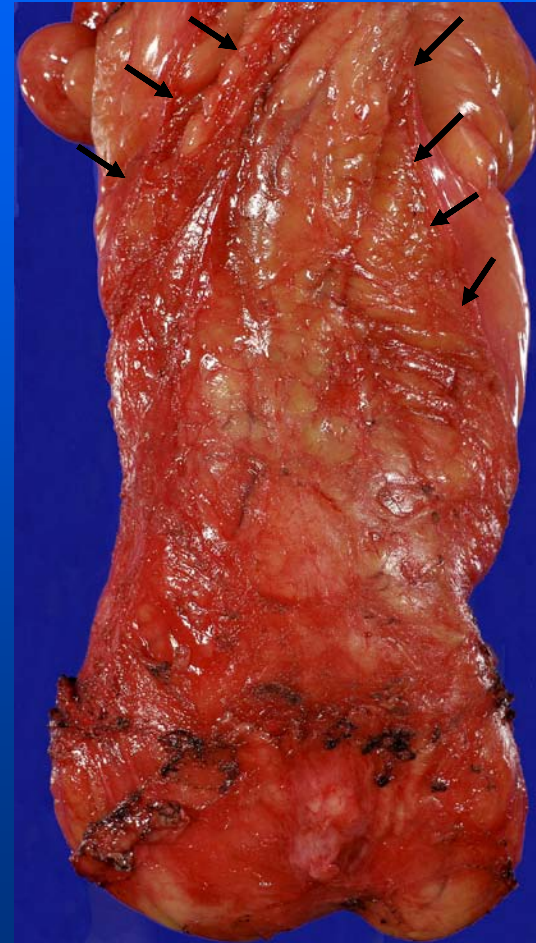
The anterior aspect is the most susceptible because there is less mesorectal tissue !

TME – macroscopic inspection

Complete excision- grade 3 -



Anterior

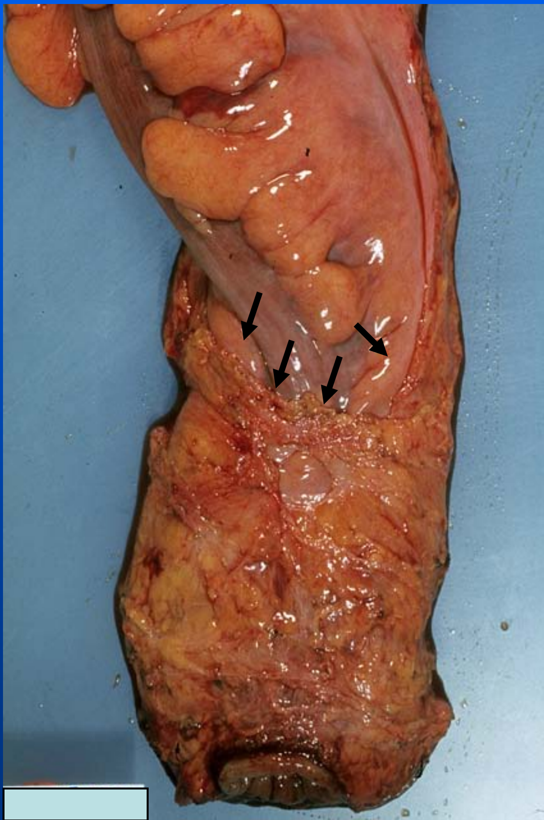


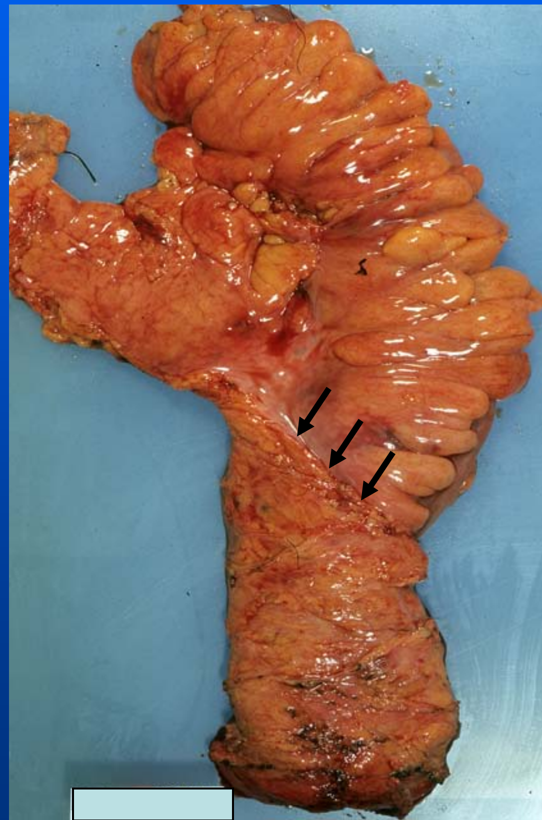
Posterior

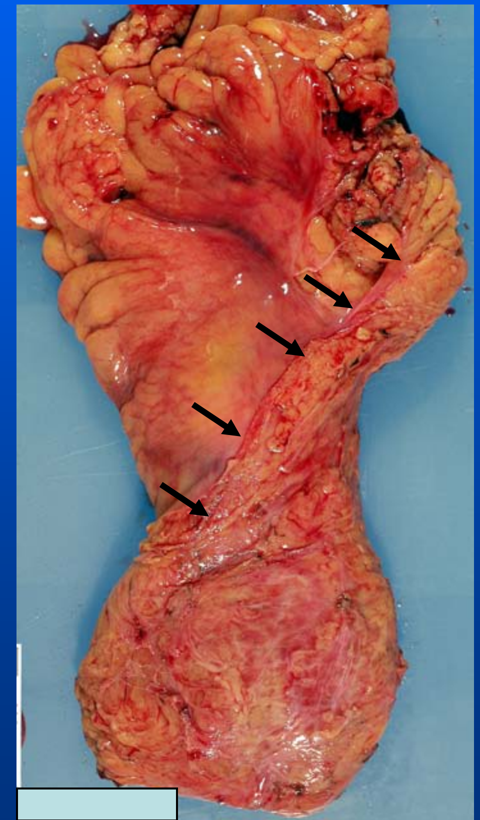
DOUGLAS FOLD

TME – macroscopic inspection

Complete excision- grade 3 -







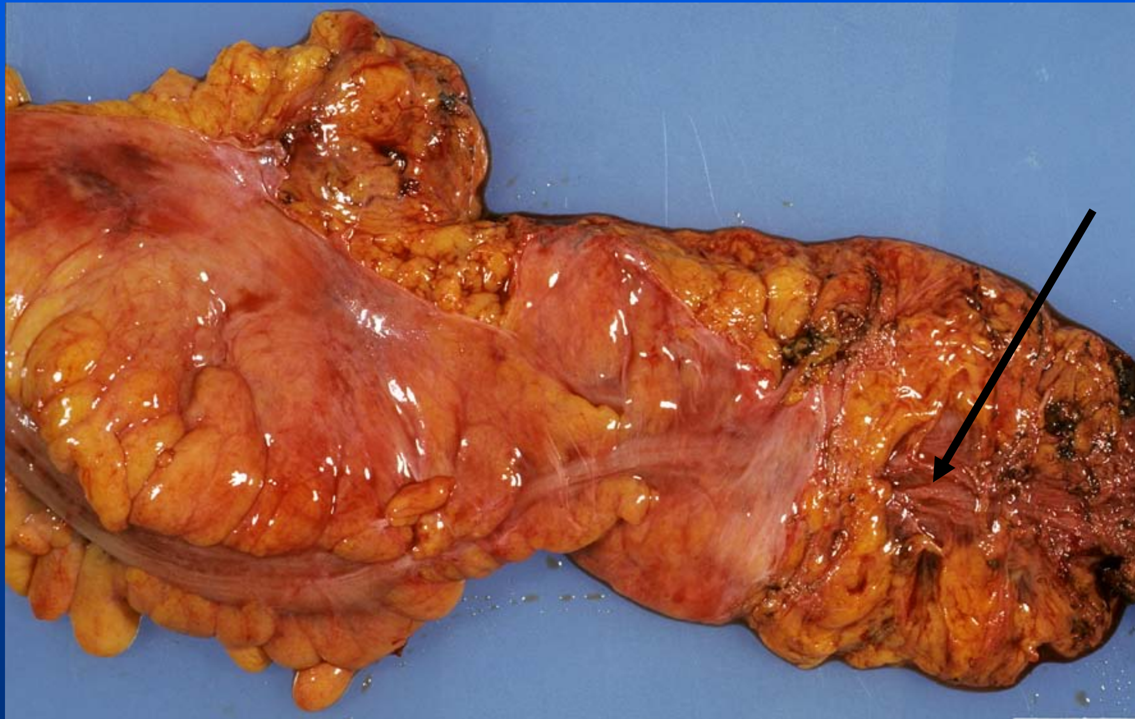
Anterior

Latero-posterior

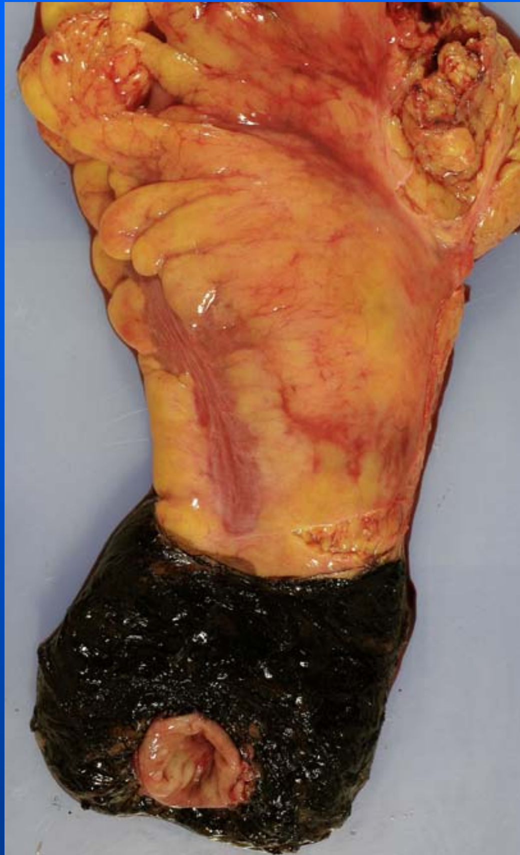
: DOUGLAS FOLD

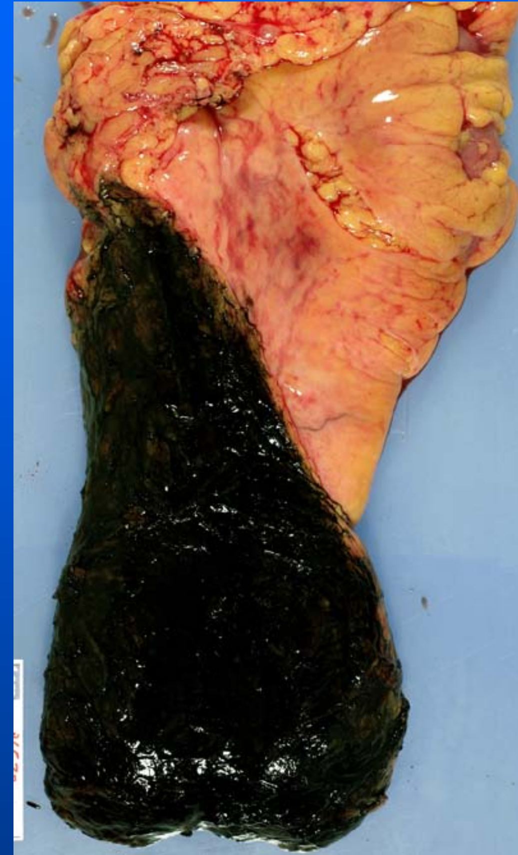
TME – macroscopic inspection

Incomplete excision – grade 1 -



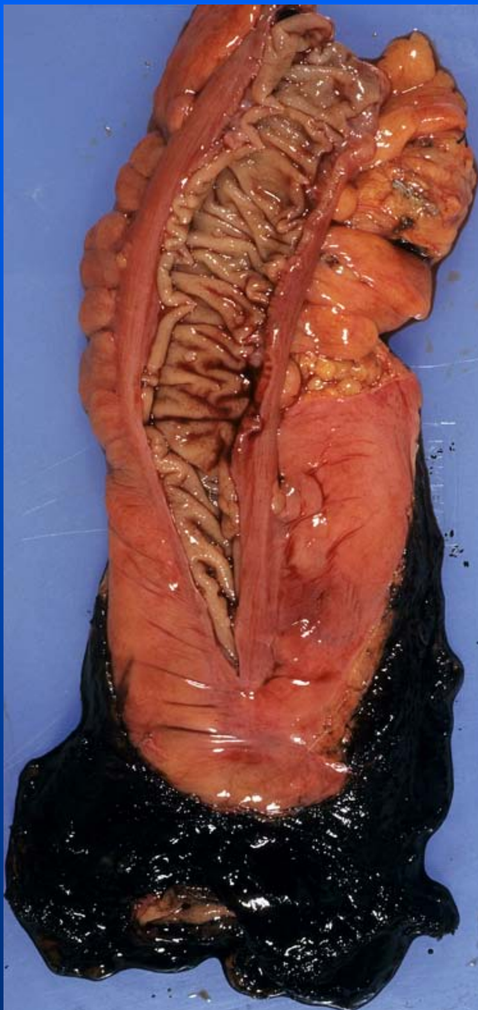
TME – macroscopic inspection





- After examination of the external surface, one should ink the mesorectum surface before opening of the specimen

TME – macroscopic inspection



- The specimen is opened anteriorly longitudinally from its proximal end downwards without extension into the tumour !

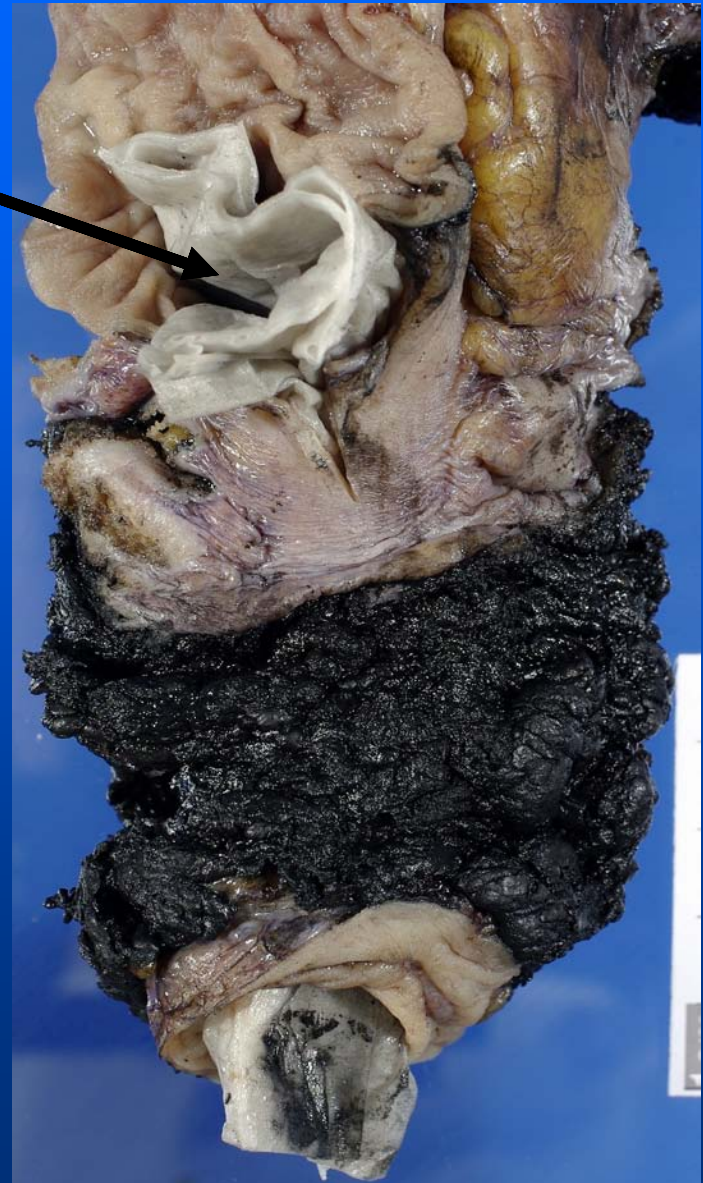
TME – handling the specimen

- The resection specimen should be pinned out on a corkboard to avoid shrinkage and left floating with the cork upwards in formalin fixative during 48 h to 72 hours (long fixation time is required to make the tissue firmer and facilitates serial cross-sectional slicing).

NB *Tumour cell density may be insufficient in treated tumours to perform Kras or MSI analysis. For this reason, it is very important to make gastroenterologist aware that they should try to obtain sufficient material in pretreatment biopsies.*

TME – handling the specimen

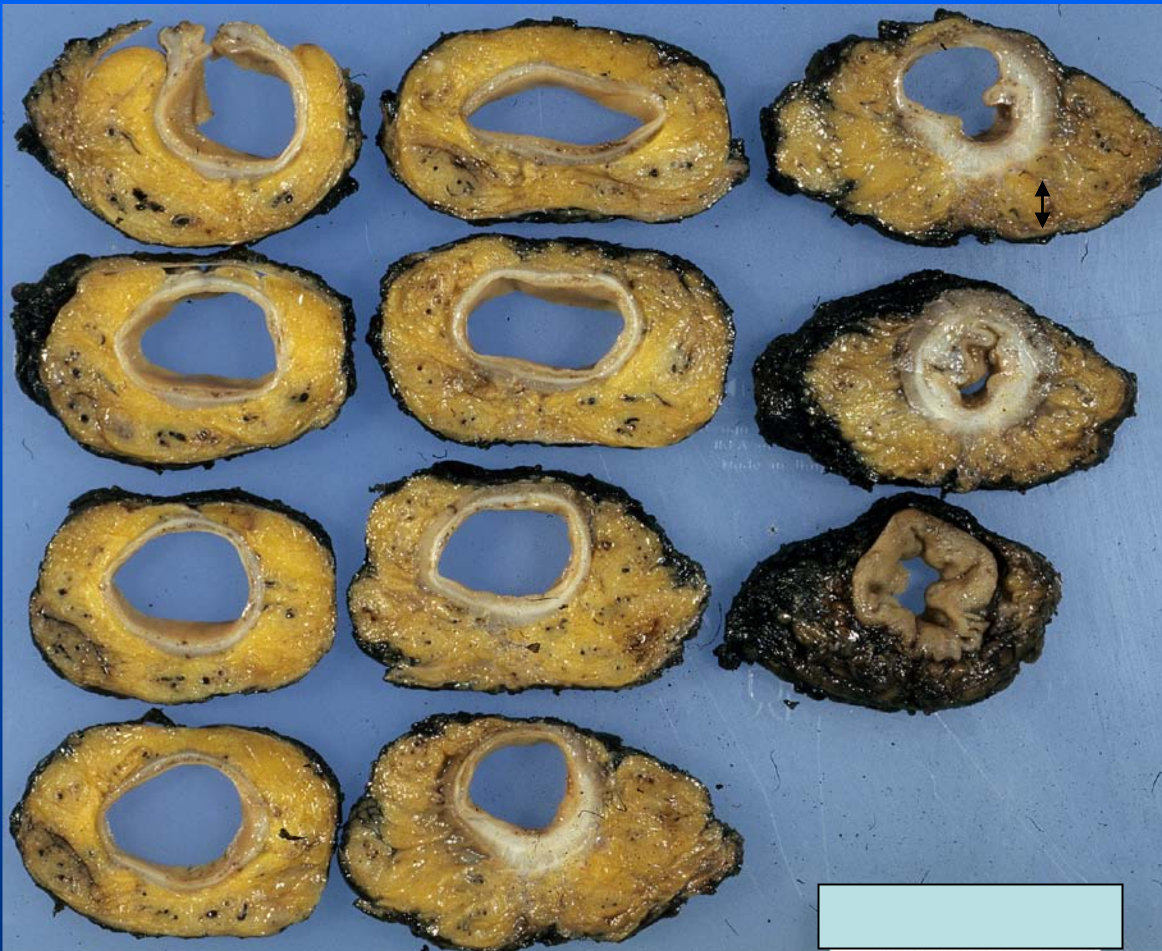
- We can place gauze or paper tissue wick soaked in formalin within the lumen of the intact bowel segment to enhance fixation



TME – handling the specimen

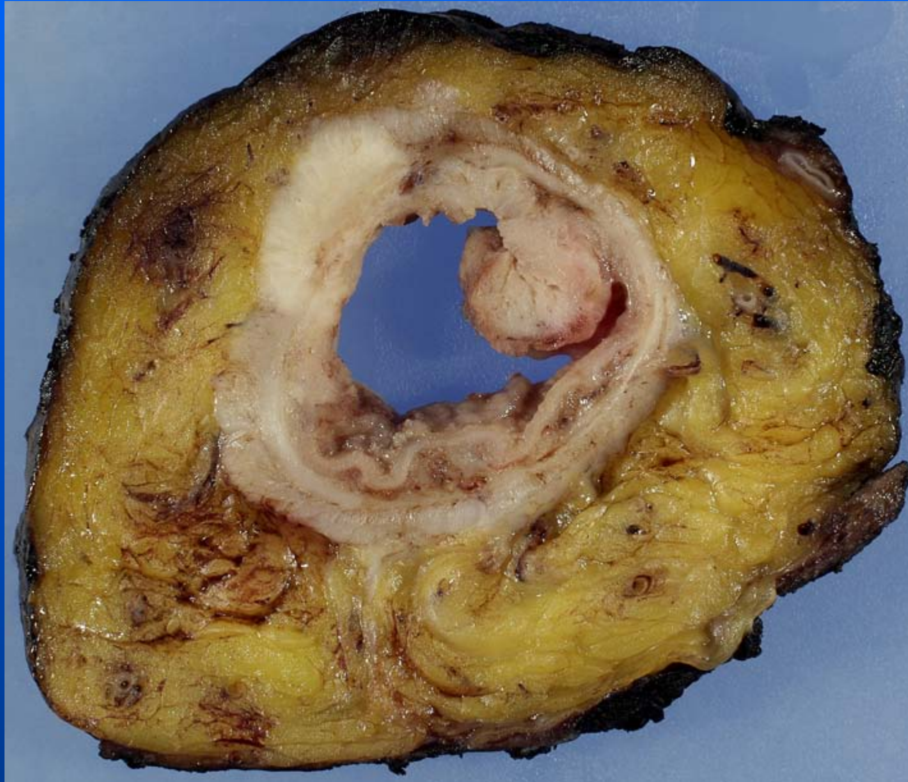
- The resection specimen should be sectioned in parallel cuts of 3 – 4 mm perpendicular to the length of the bowel allowing to assess the deepest point of invasion and to measure the distance to the nearest lateral surface to be reported in mm.

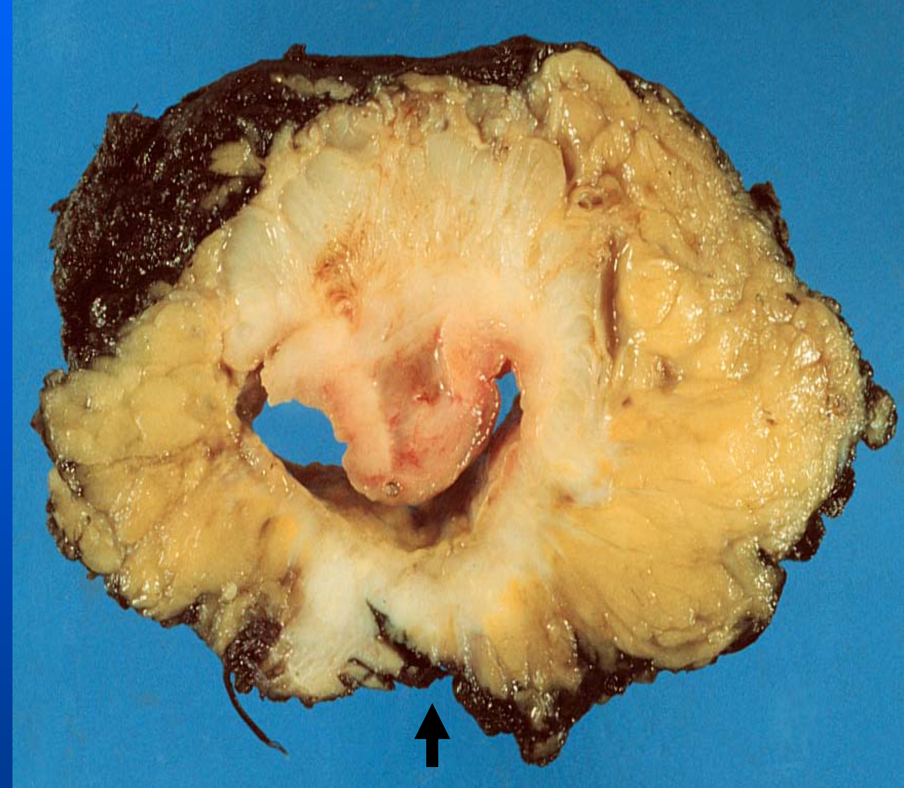
TME – handling the specimen



- Both the specimen as a whole as well as the transverse slides should be examined for adequate evaluation of the quality of mesorectal excision.
- These parallels cuts must also be photographed. In addition, they document the extend of the disease

TME – handling the specimen





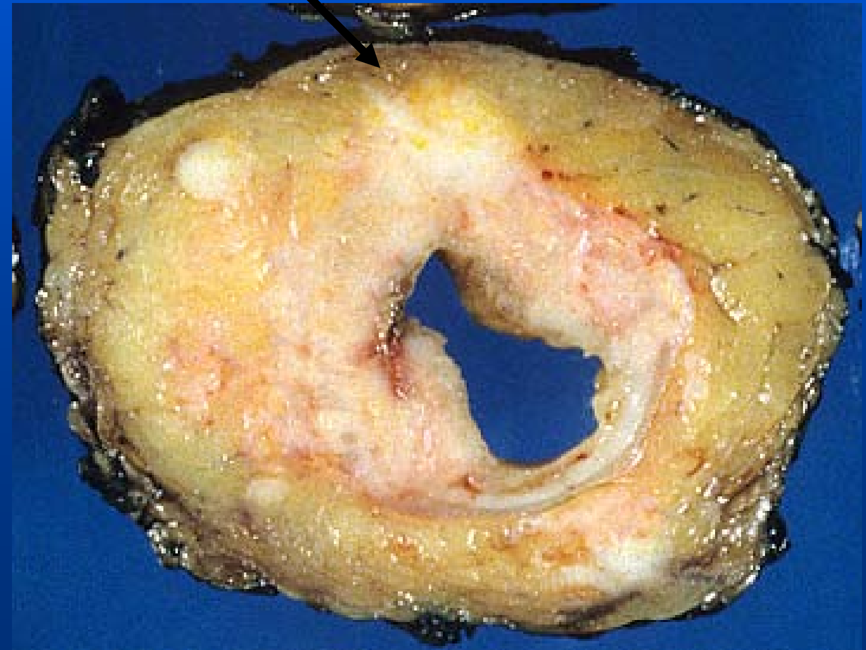
Complete mesorectum

Incomplete mesorectum

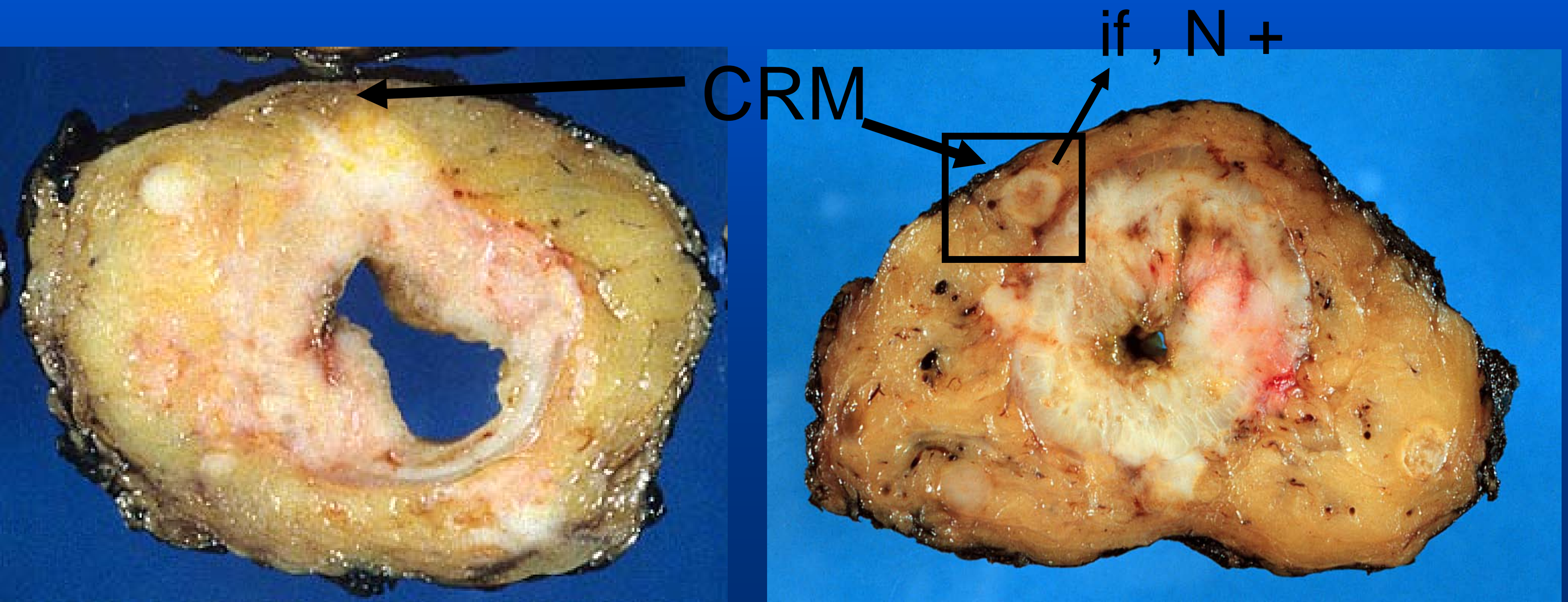
TME – handling the specimen

- The circumferential margin (CRM) is defined as the distance between the deepest point of extension of the tumour and the non peritonealised circumferential surface

- This CRM must be measured and reported in mm



- To measure the CRM: No distinction should be made between various modes of involvement i.e. direct spread, involved lymph node, lymphatic or vascular spread.



TME – handling the specimen

- The lateral margin refers to tumours located above the peritoneal reflection (above the Douglas fold) and is defined as the distance between the deepest point of extension of the tumour and the non peritonealised posterior resection margin (inked surface).

TME – handling the specimen

- Number of blocks from the tumour:
  - 3 to 5 at minimum.
  - One block should at least include the transition from the surrounding normal mucosa to the tumour
  - At least one other should include the deepest point of invasion to measure CRM.
  - One block should include to prove microscopically incomplete mesorectum (grade 1)

TME – handling the specimen

- Proximal and distal section margins do not have to be embedded if the tumour is situated at a distance of more than 3 cm from these margins.

- If the tumour is close to a margin, it is useful to sample this margin and to demonstrate the relationship to the tumour by **perpendicular** sections.

TME – handling the specimen

- Tissue blocks have to be taken to assess the circumferential (radial) or lateral margin

- Following radiotherapy, it is often impossible to distinguish therapy-induced fibrosis from tumour invasion. In this case, sufficient tissue blocks should be taken from all macroscopically suspected areas

TME – handling the specimen

- Tissue slices can be embedded as large –area (macro block) **or** as conventional small blocks

TME – handling the specimen

- All lymph nodes included in the resection specimen are considered to be regional.
- The regional lymph nodes of the rectum are : perirectal, sigmoid mesenteric, inferior, lateral sacral, presacral, internal iliac, sacral promontory (Gerota's), internal iliac, superior rectal (haemorrhoidal), middle rectal (haemorrhoidal), inferior rectal (haemorrhoidal).

TME – handling the specimen

- As much as possible lymph nodes should be found and embedded.
- One microscopic section should be taken through each lymph node.
- However it may be difficult to find lymph nodes in rectum resection, in particular after preoperative radiochemotherapy.
- The number of lymph nodes retrieved depends mainly on the effort of the pathologist.
- There is insufficient scientific evidence to recommend micro-dissection techniques or fat clearance.

TME – handling the specimen

- Associated lesions (polyps, IBD…) also have to be sampled

TME - Pathology report –

- The pathology report is standardized providing all important macroscopic and microscopic data
- The check list should be used
- PROCARE uses TNM 5th edition with some additional items

TME - Pathology report - macroscopic data

- Measurements of specimen(s)
- Tumour:
  - Localisation in relationship to
    - the peritoneal lining.
    - the proximal, distal and circumferential or lateral section margins
  - Maximal length of tumour
  - Macroscopic appearance
  - Perforation
  - Peritoneal deposits
- Associated lesions

Pathology report – microscopic data

- pT : Depth of invasion:
  - T0 No evidence of primary tumour
  - Tx Tumour cannot be assessed
  - Tis Intra-epithelial or intra-mucosal carcinoma
  - T1 Tumour invades but limited to submucosa
  - T2 Tumour invades but limited to muscularis propria
  - T3 Tumour invades through muscularis propria into subserosa (for peritonealised tumour)

Pathology report – microscopic data

- T3a mesorectal invasion < 1mm beyond muscularis propria
- T3b mesorectal invasion 1-4 mm beyond muscularis propria
- T3c mesorectal invasion 5-15 mm beyond muscularis propria
- T3d mesorectal invasion > 15 mm beyond muscularis propria

- T4a Tumour perforates visceral peritoneum (is not circumferential resection margin positive !)
- T4b Tumour invades adjacent organs

Pathology report – microscopic data

- pN **:** Lymph node involvement**:**
  - Number of positive lymph nodes/ Number of lymph nodes analysed
  - insufficient scientific evidence to mandate semi-serial sectioning or to perform immunohistochemical stains.
  - N0 No regional lymph node metastasis
  - Nx Regional lymph node metastasis cannot be assessed
  - N1 Metastasis in 1 to 3 perirectal lymph nodes
  - N2 Metastasis in 4 or more perirectal lymph nodes

Pathology report – microscopic data

- Extramural deposits: TNM 7 Controversial ! *

- For PROCARE, we continue to use TNM 5th edition

  - Extramural deposits that are not obviously within lymph nodes are regarded as discontinuous extensions of the main tumour if they measure<3mm
  - Extramural deposits are regarded as lymph node involvement if they measure > 3 mm in diameter.

* Quirke et al , J Pathol 2010

Pathology report – microscopic data

- pM : Distant metastasis:
  - Mx distant metastasis cannot be assessed
  - M0 no distant metastasis
  - M1 distant metastasis confirmed at histologic examination (cytological fluid + = M1cy+)

Pathology report – microscopic data

- **Resection margins:**
  - R0 Negative section margins
  - R1 Microscopic tumour remains after resection
  - R2 Macroscopic tumour remains after resection

a positive CRM is defined as tumour extension or the presence of a positive lymph node < 1mm from the radial non peritonealised margin

Pathology report – microscopic data

- Vascular invasion into extramural veins should be described.
- Presence of perineural and/or lymphatic invasion may be mentioned.
- The V and L substaging can be used to identify the presence of vascular or lymphatic invasion.

Pathology report – microscopic data

- Histologic type according to the WHO classification :
  - Adenocarcinoma
    - Mucinous carcinoma (colloid carcinoma)
    - Signet ring cell carcinoma
  - Adenosquamous carcinoma or squamous carcinoma
  - Small cell carcinoma
  - Medullary carcinoma
  - Undifferentiated carcinoma

Pathology report – microscopic data

- Histologic grade:
  - Four tiered system:
    - Well differentiated (G1)
    - Moderately differentiated (G2)
    - Poorly differentiated -mucinous and signet ring cell carcinoma -(G3)
    - Undifferentiated –medullary carcinoma-(G4)
  - Two tiered system:
    - Low grade >50% of glandular structures(G1 + G2)
    - High grade < 50% of glandular structures(G3 + G4)

ADDENDUM : Pathology report after neoadjuvant therapy

- The regression grade: Dworak

Grade 0: no regression

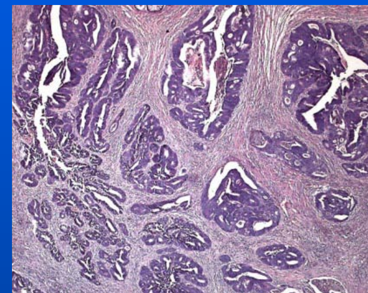
Grade 1: dominant tumour mass with obvious fibrosis and/or vasculopathy

Grade 2: dominantly fibrotic changes with few tumour cells or groups (easy to find)

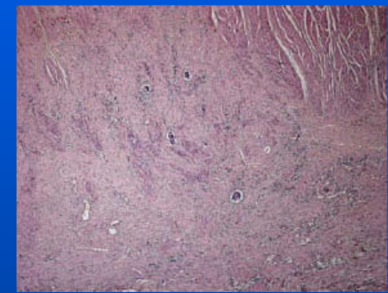
Grade 3: very few (difficult to find microscopically) tumour cells in fibrotic tissue with or without mucous substance

Grade 4: no tumour cells, only fibrotic mass (total regression or response)

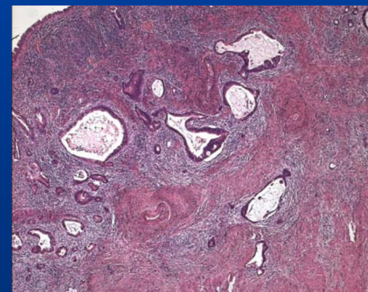
Dworak O.et al, Int J Colorectal Dis 1997



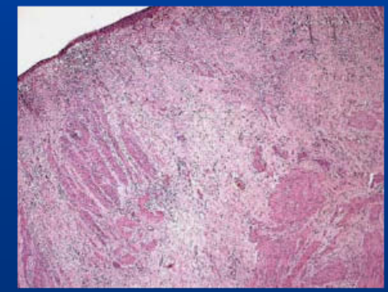
Grade 1



Grade 3



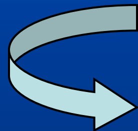
Grade 2



Grade 4

To confirm Dworak 4

- Sufficient sampling is necessary
  - 5 initials blocks from the site of tumour
  - If still no tumour observed , whole area embedded
  - If still no tumour, 3 levels from each block
  - If still no tumour



complete response : Dworak 4

After neoadjuvant therapy

- Mucus lake without tumour cells in a lymph node should be considered as ypN0

Check list

PATHOLOGY REPORT CHECKLIST AFTER SURGICAL RESECTION (excl. local excision: cf. specific form) REQ

Patient's name: .... Registration number (provided by the data center): ....

Patient's first name: .... Hospital/Laboratory: ....

Date of birth: .... Pre-operative treatment (no/yes + what): ....

RECTAL CANCER: Distance from anal verge ... .cm
cTNM staging:..
ycTNM staging: ....

TYPE OF SURGICAL INTERVENTION

☐ Anterior resection rectum (PME)
☐ Restorative rectum resection (TME)
☐ Abdominoperineal rectum excision (APER)
....

MACROSCOPIC EXAMINATION

External surface TME (also for APER)
☐ fresh ☐ smooth, regular
☐ fixed ☐ mildly irregular
☐ severely irregular

APER lowest tumor level
☐ ... mm above dentate line
☐ ... mm below dentate line

Photos fresh specimen before inking:
Anterior face: ☐ yes – ☐ no
Posterior face: ☐ yes - ☐ no

APER shape
☐ cylindrical
☐ standard (waist)

Photos of macro slices: ☐ yes - ☐ no

Rectal tumor location:
☐ ventral ☐ ....
☐ lateral ☐ above peritoneal reflection
☐ dorsal ☐ below peritoneal reflection
☐ multifocal: if second location, please use separate sheet

Length of resected specimen: .... cm
Distance tumor – resection margin:
proximal: ....cm
distal: ....cm

Rectal tumor appearance:
☐ exophytic ☐ ulcerating ☐ infiltrating ☐ flat

Tumor perforation yes ☐ no ☐

Associated lesions

	yes	no
Polyp(s)	☐	☐
Synchronic cancer(s)	☐	☐
Ulcerative colitis	☐	☐
Crohn's disease	☐	☐
Familial polyposis	☐	☐

Additional samples: ☐ frozen
☐ other fixation ....

HISTOLOGICAL EXAMINATION

☐ Adenocarcinoma
☐ well ☐ low grade
☐ moderate ☐ high grade
☐ poorly differentiated (incl. mucinous >50%, and signet cells >50%
☐ undifferentiated
☐ Other: ....

Depth of invasion

☐ Tx: primary tumor cannot be assessed
☐ T0: no evidence of primary tumor
☐ Tis: intra-mucosal or intra-epithelial (not beyond musc. mucosae)
☐ T1: limited to submucosa
☐ T2: limited to muscularis propria
☐ T3: subserosal invasion (for peritonealised tumor)
☐ T3a: mesorectal invasion <1 mm beyond muscularis propria)
☐ T3b: mesorectal invasion 1-4 mm beyond muscularis propria)
☐ T3c: mesorectal invasion 5-15 mm beyond muscularis propria)
☐ T3d: mesorectal invasion >15 mm beyond muscularis propria)
☐ T4a: invasion through serosal/peritoneal surface (is not circumferential resection margin positive!)
☐ T4b: invasion in adjacent organ(s)

Margins:
Longitudinal surgical resection margins:
Proximal: ☐ free ☐ invaded
Distal: ☐ free ☐ invaded
Lateral margins above peritoneal reflection: ☐ free - ☐ invaded
Mesorectal circumferential resection margin (CRM): ....mm remote from tumor

Extension:
Number of lymph nodes examined:..
Number of invaded lymph nodes: ....
Number of extramural deposits < 3 mm ....
Number of extramural deposits > 3 mm: ....

Nx Regional lymph nodes cannot be assessed.
N0 No regional lymph node metastasis.
N1 Metastasis in 1 to 3 regional lymph nodes
N2 Metastasis in 4 or more regional lymph nodes

Extramural vascular invasion:
☐ yes ☐ no

Metastasis (liver, peritoneum, ...)
☐ yes ☐ no ☐ impossible to determine

Rectal cancer regression grade (Dworak):
☐ grade 0 (no regression) ☐ grade 3 (>50% fibrosis)
☐ grade 1 (≤25% fibrosis) ☐ grade 4 (total regression)
☐ grade 2 (26-50% fibrosis)

RECTAL CANCER

☐ pTNM ☐ ypTNM
☐ Tx ☐ T0 ☐ Tis ☐ T1 ☐ T2 ☐ T3 ☐ T4
☐ Nx ☐ N0 ☐ N1 ☐ N2
☐ Mx ☐ M1

Other classification : ....

Signature: Date:

PATHOLOGY-CHECKLIST PROCARE – prospective registration

In summary

- Photographs of anterior and posterior mesorectal surface of **unfixed, uninked and unopened** specimen
- Photographs of overview of all transverse sections, detail of lesional section and CRM
- Sufficient sampling for histological investigation