Some Aspects on the Role of the Pathologist in Colorectal Cancer

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- Professor of Health Sciences, Liver and Gastrointestinal Pathology.
- Consultant and Head of Surgical Pathology
- Trafford Healthcare
- Manchester
- UK

Background

- **In USA(280m) there are 150,000 new cases and 60,000 deaths per annum.**
- **In UK (60m) there are 35,000 new cases and 16,000 deaths per annum.**
- **New patterns in some parts of the world.**
- In India 6th commonest among female and 9th amongst male.

Accurate Pathological Reporting

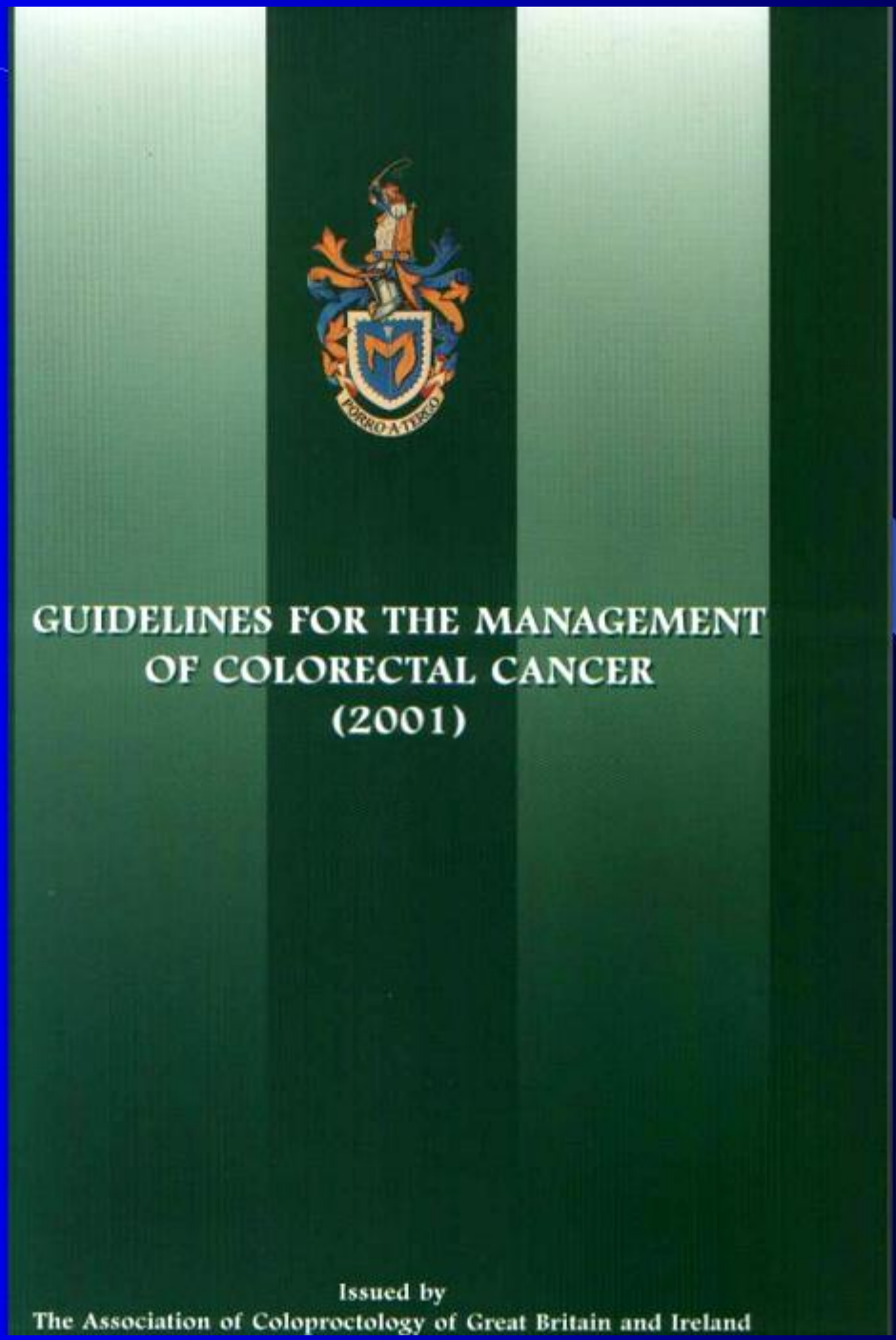
- Confirm diagnosis.
- Inform prognosis.
- Plan treatment of individual patients.
- Audit pathology services.
- Evaluate and audit the quality of other services like radiology, surgery and oncology.
- Collect accurate data for cancer registration and epidemiology.
- Facilitate high quality research.
- **Plan service delivery.**

Multi Disciplinary Team (MDT)

- Colorectal Surgeons
- Hepatobiliary (Thoracic) Surgeons.
- Radiologists.
- ***Surgical Pathologists***.
- Medical Oncologists.
- Gastroenterlogists
- Specialist Nurse.
- Stoma Nurse.
- Clinical geneticist / counsellor.
- Social worker.
- Clinical trials coordinator or research nurse.
- GP
- Dietician

MDT

- Takes place at regular intervals
- Encourages a more efficient and team working atmosphere .
- Have a consensus approach to treatment according to agreed protocols.
- Quick and appropriate referral pattern.
- Audit surgical treatment.
- Audit pathology reports.


PORRO A TERGO
GUIDELINES FOR THE MANAGEMENT
OF COLORECTAL CANCER
(2001)
Issued by
The Association of Coloproctology of Great Britain and Ireland

JOINT NATIONAL GUIDELINES MINIMUM DATA SET
COLORECTAL CANCER HISTOPATHOLOGY REPORT

Surname _____ Forenames _____ Date of birth _____ Sex ____
Hospital _____ Hospital No. _____ NHS No _____
Date of receipt _____ Date of reporting _____ Report No _____
Pathologist _____ Surgeon _____

Gross Description
Metastatic Spread
Site of tumour _____
Maximum tumour diameter _____
Distance of tumour to nearer margin (cut end) ____
Presence of tumour perforation (pT4) [ ] Yes [ ] No

For rectal tumours
Tumour is [ ] above [ ] at [ ] below
the peritoneal reflection
Distance from the dentate line _____
Yes No

Histology
Type
Adenocarcinoma [ ] Yes [ ] No
(to include mucinous and signet ring adenocarcinomas)

If No, other _____

Differentiation by predominant area
[ ] Well/moderate [ ] Poor

Local Invasion
[ ] Submucosa (pT1)
[ ] Muscularis propria (pT2)
[ ] Beyond muscularis propria (pT3)
[ ] Tumour cells have breached the peritoneal surface or invaded adjacent organs (pT4)

Margins

Tumour involvement	N/A	Yes	No
Doughnut	[ ]	[ ]	[ ]
Margin (cut end)	[ ]	[ ]	[ ]
For rectal tumours	[ ]	[ ]	[ ]
Circumferential margin involvement	[ ]	[ ]	[ ]

Histological measurement from tumour to circumferential margin .....mm

No of lymph nodes examined _____
No of positive lymph nodes _____
(pN1 1-3 nodes, pN2 4+nodes involved)

	Yes	No
Apical node positive (Dukes C2)	[ ]	[ ]
Extramural vascular invasion	[ ]	[ ]

Background Abnormalities

Adenoma(s)	[ ]	[ ]
Synchronous carcinomas(s)	[ ]	[ ]

(Complete a separate form for each cancer)

Ulcerative colitis	[ ]	[ ]
Crohn's disease	[ ]	[ ]
Familial adenomatous polyposis	[ ]	[ ]

Other comments _____

Pathological Staging
Complete resection at all margins [ ] Yes [ ] No

TNM
[ ] T [ ] N [ ] M

Dukes
[ ] Dukes A (Growth limited to wall, nodes negative)
[ ] Dukes B
(Growth beyond muscularis propria, nodes negative)
[ ] Dukes C1
(Nodes positive and apical node negative)
[ ] Dukes C2 (Apical node positive)
Histologically confirmed liver metastases [ ] Yes [ ] No

Signature _____ Date ____/____/____ SNOMED Codes ____/____

Evidence Based

Second Edition

- 2007
- Few important additions.
- www.rcpath.org

Surname _____ Forenames _____ Date of birth_____ Sex____

Hospital_____ Hospital No._____ NHS No _____

Date of receipt_____ Date of reporting_____ Report No _____

Pathologist _____ Surgeon _____

Margins

Tumour involvement	N/A	Yes	No
Doughnut	[ ]	[ ]	[ ]
Margin (cut end)	[ ]	[ ]	[ ]
For rectal tumours	[ ]	[ ]	[ ]
Circumferential margin involvement	[ ]	[ ]	[ ]

Histological measurement from tumour to circumferential margin .....mm

Assessment of RM

- **Longitudinal**
- Circumferential / lateral /Radial */ non peritonealised resection margin.*

Minimum safe Longitudinal Margin

- 5
- 3
- 2
- 1
- < 1cm

Reappraisal of 5 cm rule of distal excision for carcinoma of rectum

- **Williams , Dixon and Johnston. Br.J.Surgery 1983**

Conclusion

- The application of the 5 cm rule of distal excision may cause patients with low rectal cancer to **lose their anal sphincter unnecessarily.**

Kirwan , Drumm, Hogan, Keohane

- Determining safe margin of resection in low anterior resection for rectal cancer. Br.J.Surg 1988

- 1cm

Declining indication for APR resection in favour of AR

- Kirwan , O'Riordain and Waldron…..
- Br.J.Surg 1989

Karanjia, Schache, North and Heald

- ‘Close shave’ in anterior resection.
- Br.J.Surg. 1990
- <1cm V >1cm

Conclusion

- Reduction of resection margins (provided TME and washout is properly performed) does not increase local recurrence or compromise survival.

Additions in the 2nd edition (1)

- Documentation type of procedure .
- For rectal cancer, it is expected to have more AP than APR .

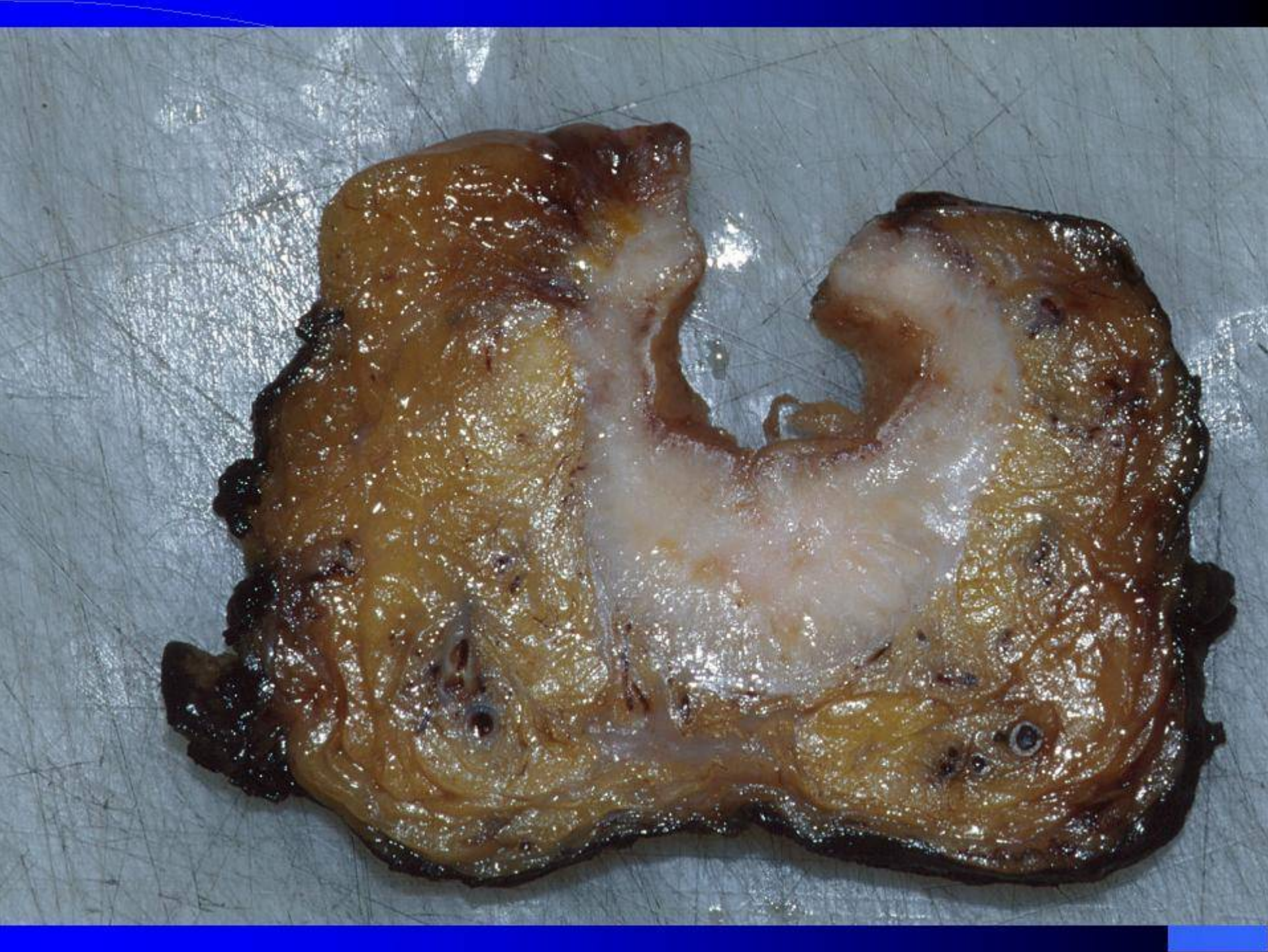
Audit

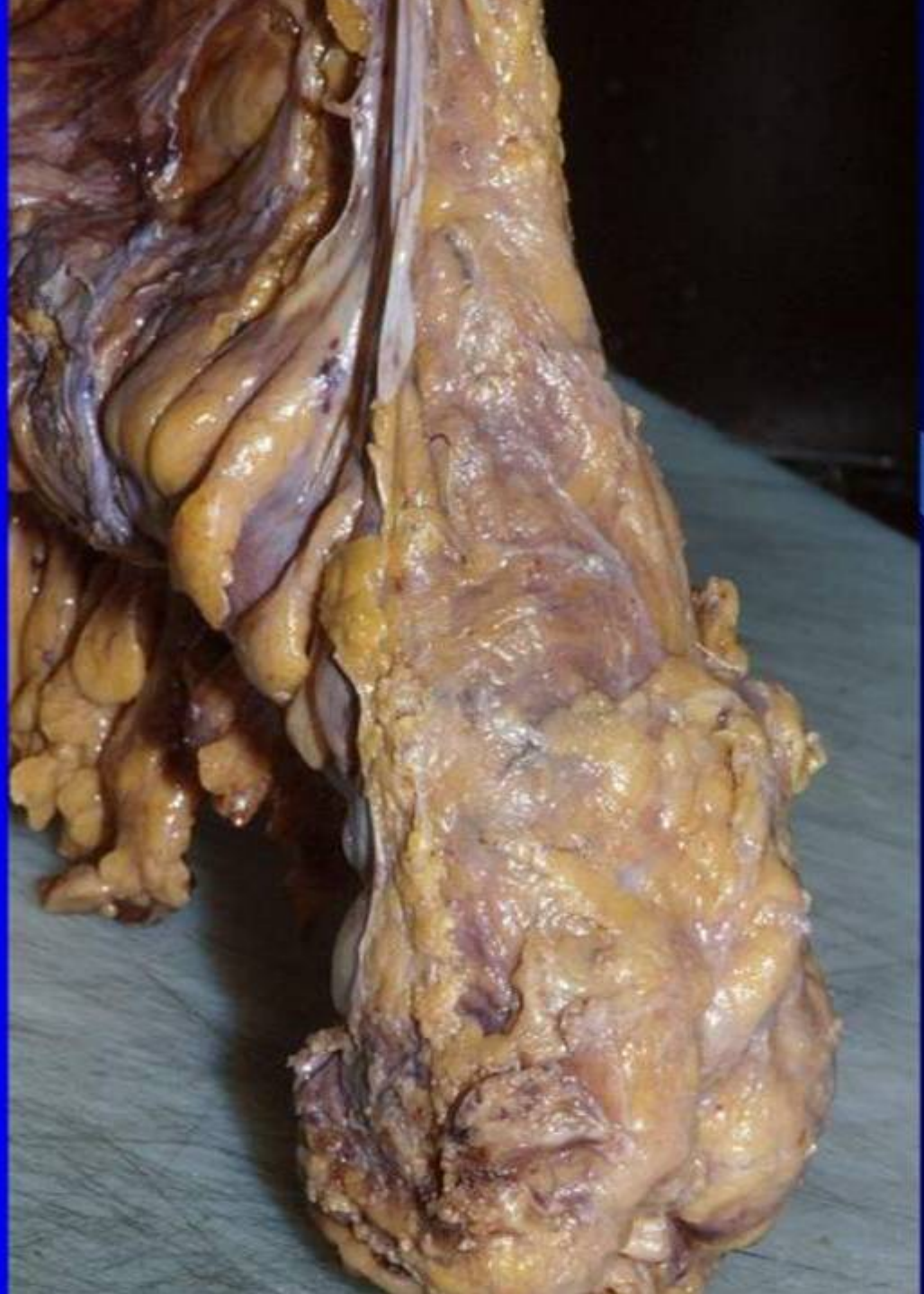
- AR 1670
- APR 746
- Hartman's 299
- There is a trend of increase the AR over APR due to:
- Better preoperative treatment
- Better imaging modalities and
- Better surgery.*Good surgeons should be able to undertake AR for tumours above 5cm from anal verge.*

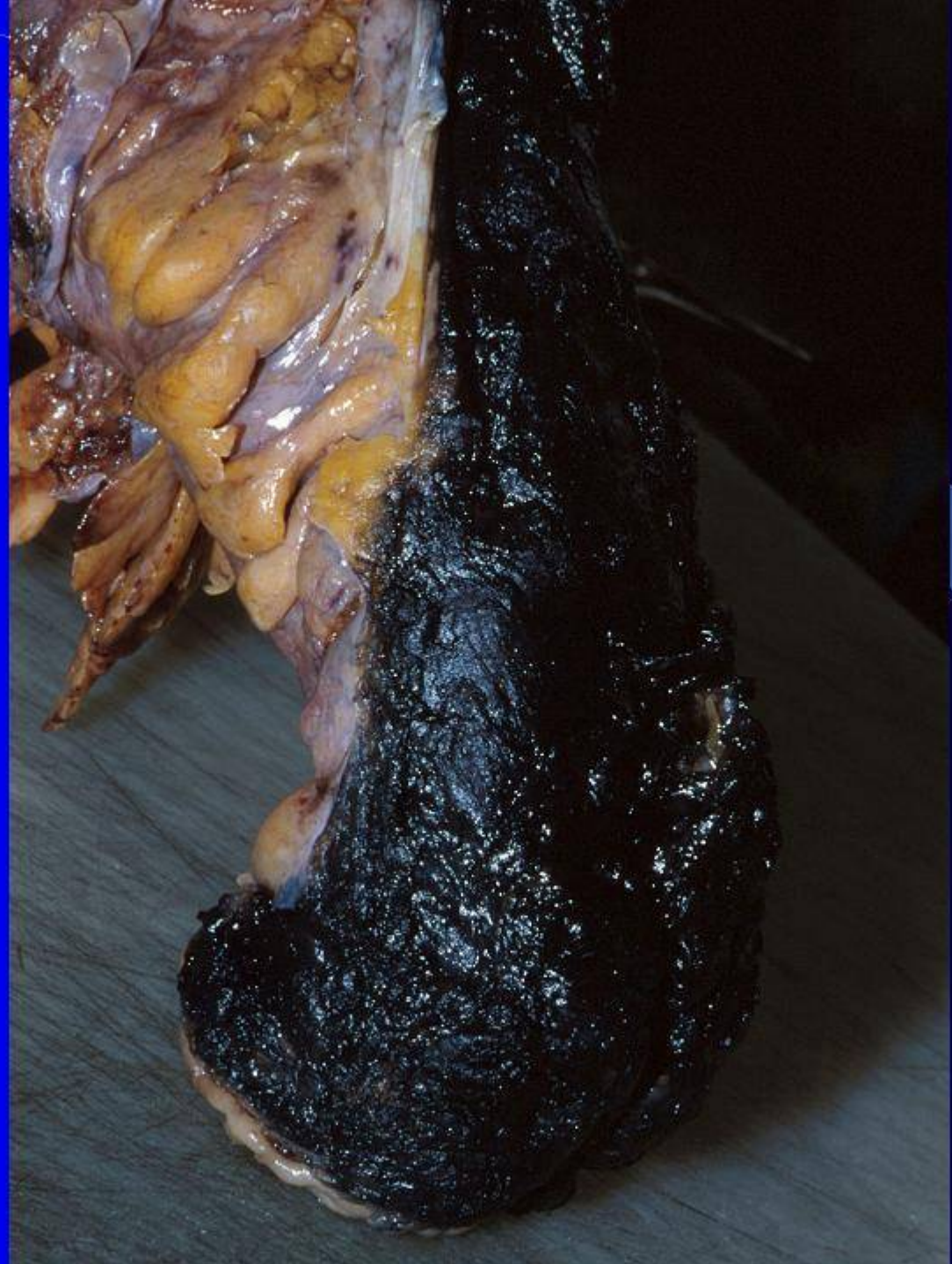
Circumferential (CRM) / Lateral / Radial / Non Peritonealised Resection Margin (NPRM)

Circumferential resection margin Involvement (CRMI) 1mm or less

- **High Local Recurrence.**
- **Low Survival.**
- **Poor Standard of Surgery.**
- **Aggressive Disease.**
- **Tumour Location.**
- ***Male gender.***





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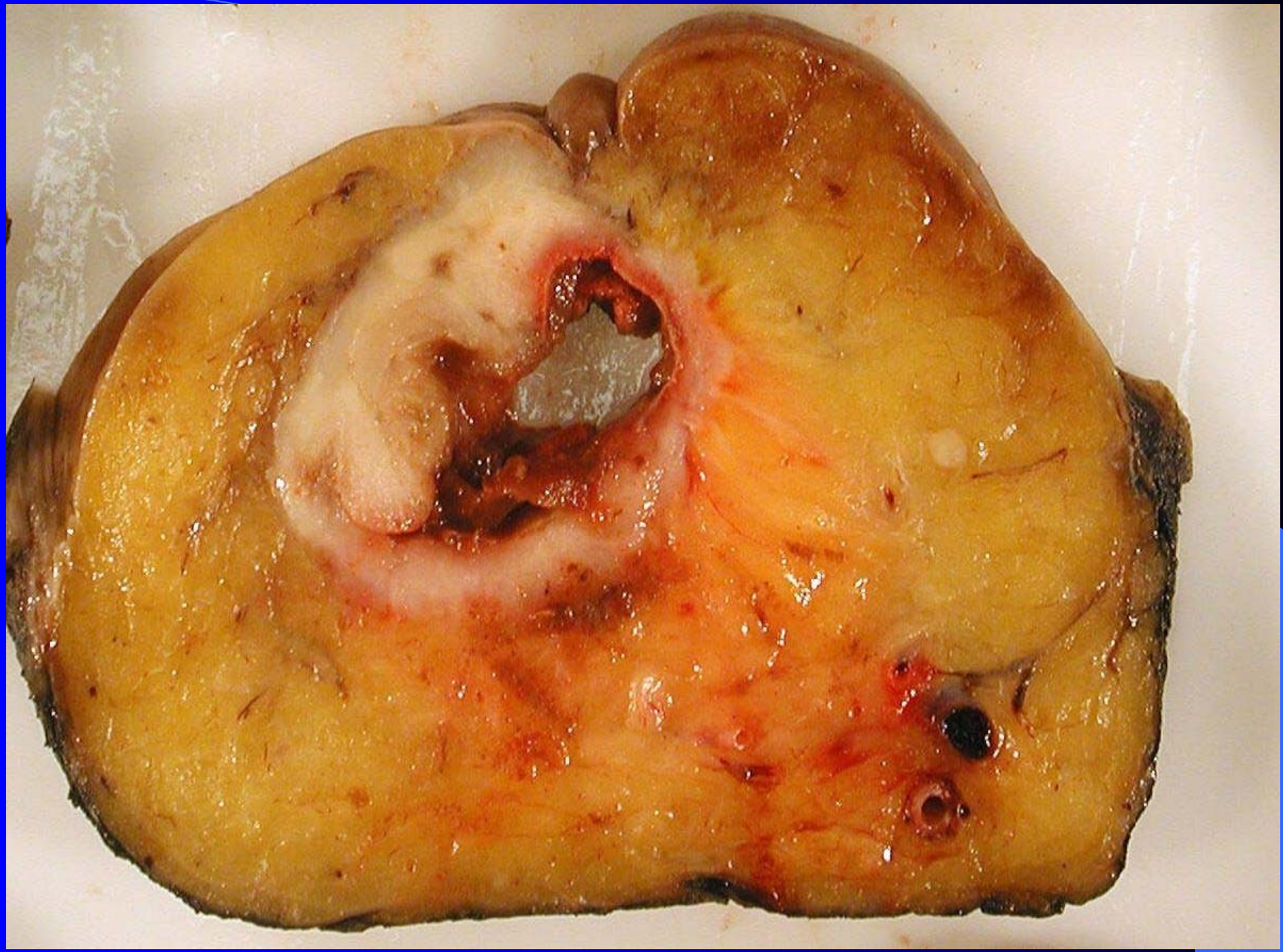
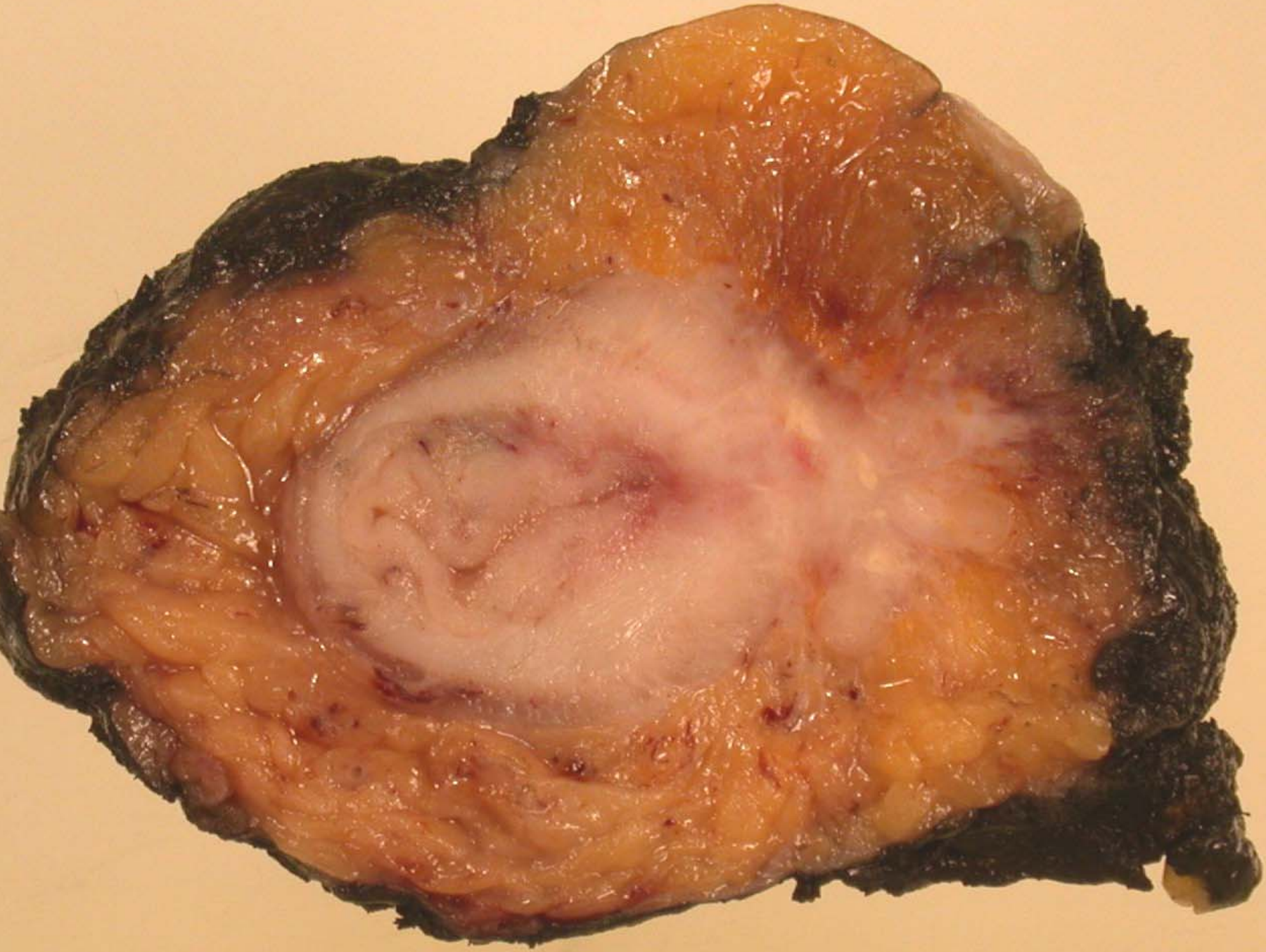
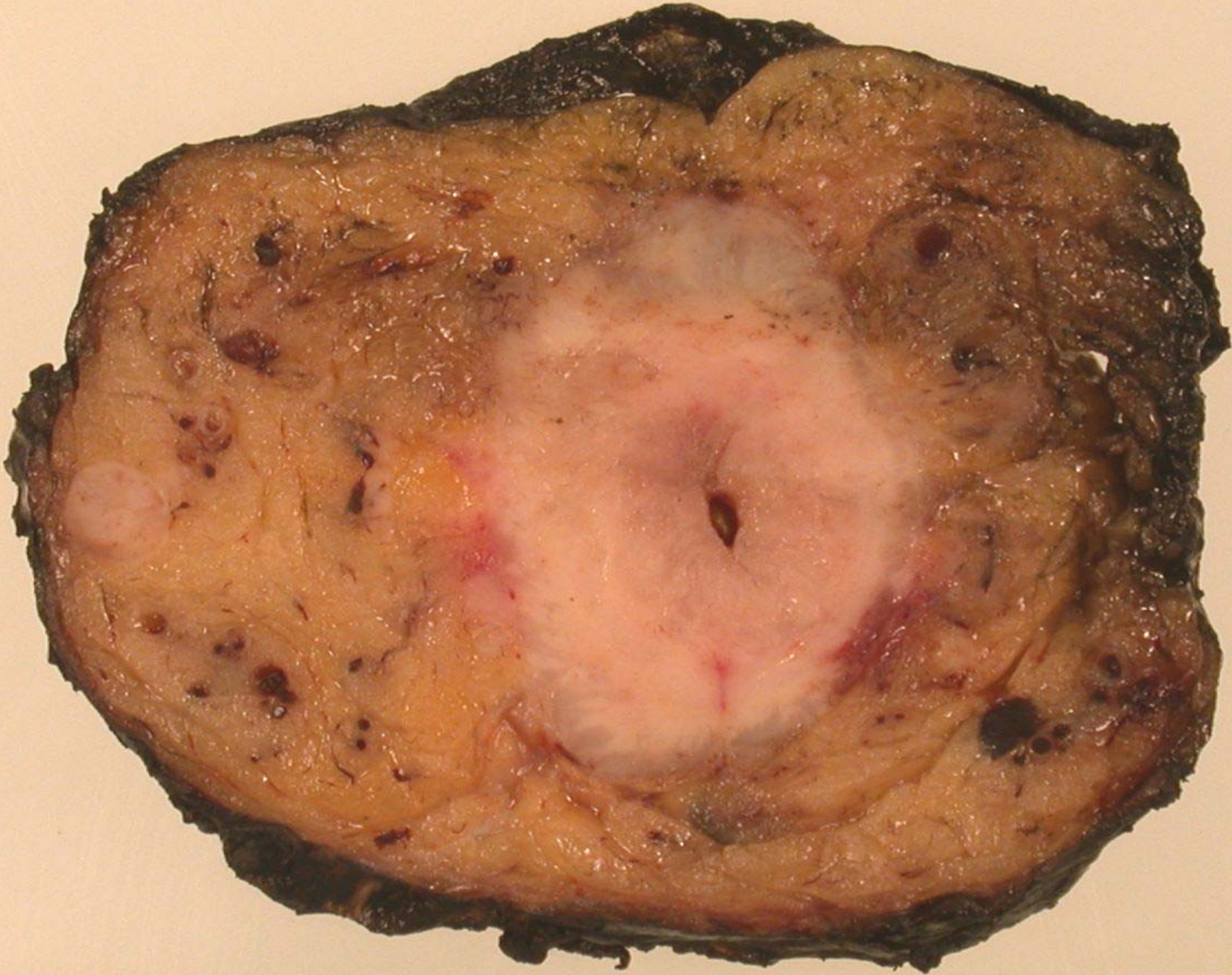






Addition to the 2nd edition (2)

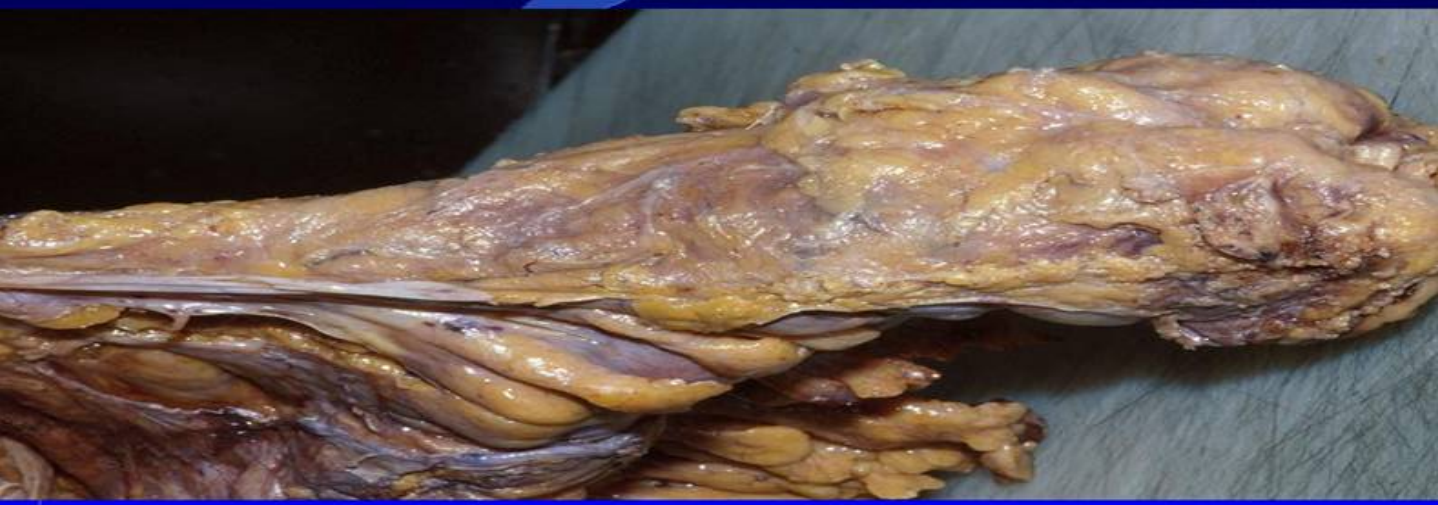
- Grading of surgical plane of resection in rectal cancer.
- The continuous feedback to surgeons may lead to improve quality of surgery.

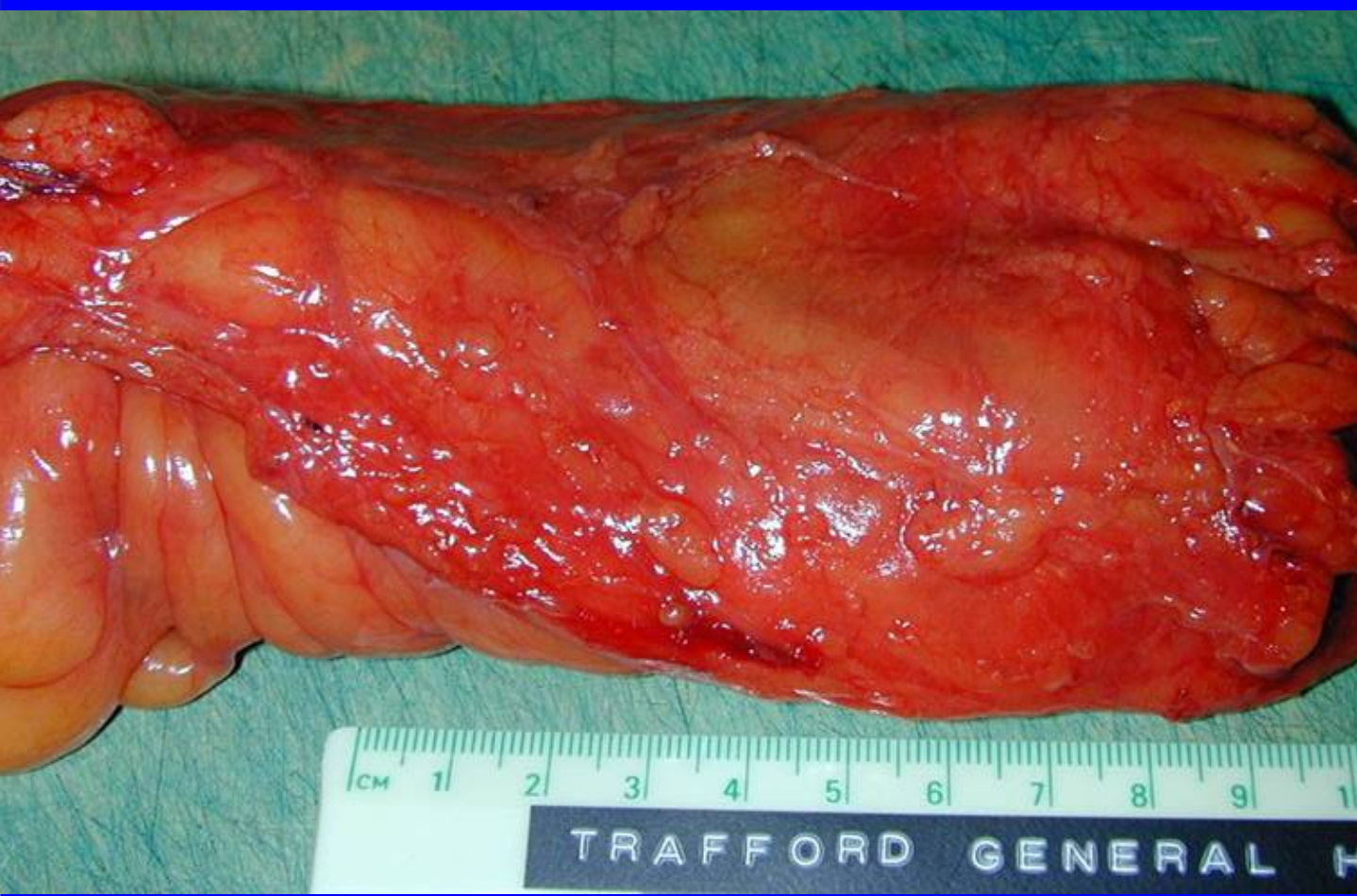
Macroscopic Evaluation of Rectal cancer Resection Specimens

- Clinical Significance of the Pathologist in Quality Control.
- 2 years follow up.
- Iris Nagtegaal et al
- J Clin Oncol 2002, 20: 1729-1734

Macroscopic Grading of TME

- A (3) (Good). Complete. Smooth, no coning, defect >5 mm and regular CRM
- C (1) (Poor). Defects down to the Muscularis ,conning, no bulk and irregular CRM
- B(2) .Nearly complete. Defect present but Muscularis is not apparent(except at the insertion of LA) and irregular CRM.

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Results

Grade	A&B - good and acceptable	C- Poor
Local Recurrence	8.7%	15%
Local recurrence and Distant Metastasis	20.3%	36.1%
2 Year Survival	90.5%	76.9%

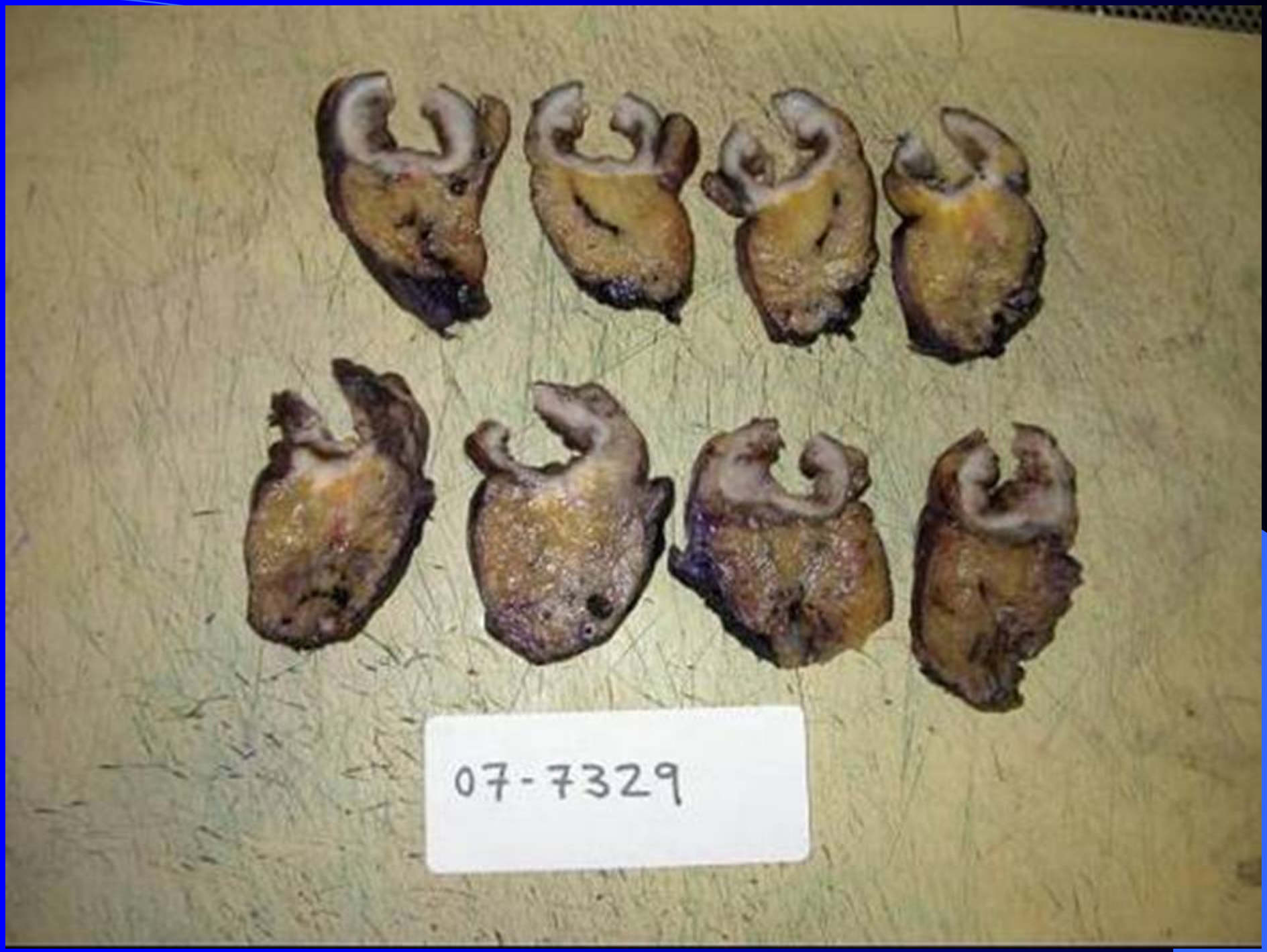
Addition to the 2nd edition (3)

- Measurement of tumour beyond the muscularis propria recorded in mm.
- This is to:

a/ facilitate audit of preoperative imaging of extramural spread as it is of importance in selecting patients of rectal cancer to choose a therapy arm .

b/ It has a prognostic implication for rectal cancer.

5mm or more is associated with adverse prognosis.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Addition to the 2nd edition (4)

- Recording tumour involvement of the NPRM in colonic tumours (in addition to rectum) like the caecum. These patients may be selected for post operative adjuvant therapy.
- Bateman et al J Clin Path 2005 and Quirke et al 2006 J Path

Addition to the 2nd edition (5)

- Recording serosal (peritoneal surface) involvement.
- ‘Tumour cells visible either on the peritoneal surface or free in the peritoneal cavity carry bad prognosis’

Influence of local peritoneal involvement on pelvic recurrence and prognosis in rectal cancer.

Shepherd, Baxter and Love

J. Clin. Path 1995

Local Peritoneal Involvement

1. Detected in 25.8% (54/209) of cases.
2. Showed considerable prognostic disadvantage in curative and non curative cases.
3. May be an important factor in local recurrence of **upper rectal** cancers.

The Prognostic Importance of Peritoneal Involvement in **Colonic** Cancer: a Prospective Evaluation

- Shepherd et al Gastroenterology 1997
- Strong predictive value for local recurrence / persistent disease specially when there is mucinous differentiation.

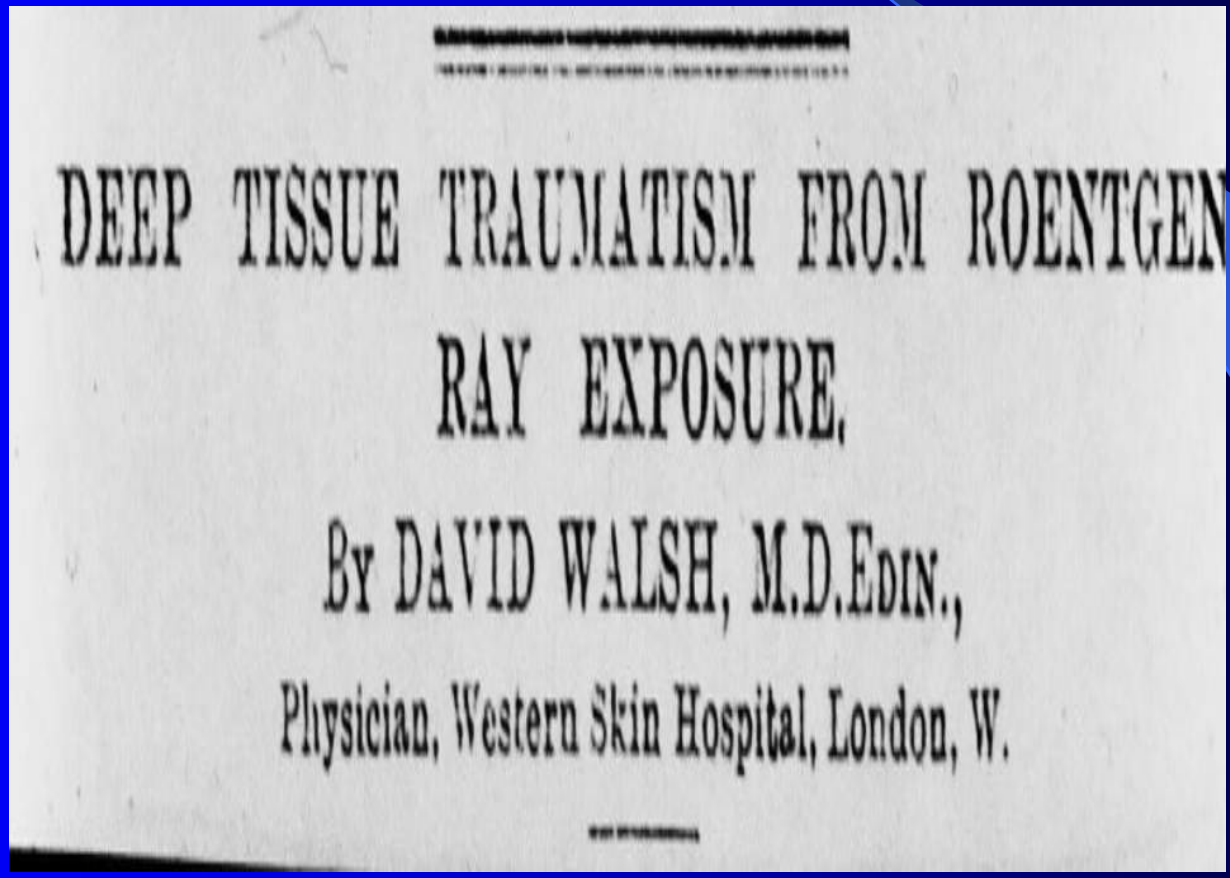
Additions in the 2nd edition (6)

- **Recording of marked or complete tumour regression in patients with rectal cancer that have received adjuvant chemo / radiotherapy (CRT)**

1895

XRT 1st used

BMJ 1897



DEEP TISSUE TRAUMATISM FROM ROENTGEN RAY EXPOSURE.

By DAVID WALSH, M.D.Edin.,

Physician, Western Skin Hospital, London, W.

For Rectal cancer

- **Preoperative Chemoradiotherapy (CRT) is considered for T2-T3 / *T4***

Rationale for adjuvant CRT for Rectal Cancer

- Increases tissue sensitivity towards radiation.
- Radiation stops proliferation.
- Significant decrease in loco-regional recurrence AND overall survival.

Irradiation of Tumour Zone

- Tumour Tissue.
- Adjacent ‘normal’ tissue.

TARGET

- DNA
  - DIRECT
  - INDIRECT
- CYTOPLASM

DIRECT DAMAGE (DNA)

- SINGLE OR DOUBLE STRANDED CHROMOSOMAL BREAK

INDIRECT EFFECT

- RADIOLYSIS OF CELLULAR WATER WITH FORMATION OF FREE RADICALS.

CELL CYCLE

- GO
- **G1**
- **G2**
- **S**
- **M**

Because different cells have different cell cycles

- Rapidly dividing cells are
  - More Chemoradiosensitive

Turn over of cells in the gut

- Epithelial cells
- Endothelial
- Stromal

Radiatiotherapy

- **Short Course**
  - 25Gys over 5 days in 5-10 fraction with the last fraction within 72 hours before surgery.
  - **Early stage.**
  - **Not well patients.**
- **Long Course**
  - 45-50 Gys over 5 weeks followed by surgery after at least 3 weeks from the last dose.
  - **Tethered ,T3 and T4.**
  - **Large.**
  - **Anterior location**

Short term preoperative radiotherapy interferes with the determination of pathological parameters in rectal cancer

- Iris Nagtegaal et al. J Path 2002,197:20-27.
  1306 patients(706 TME alone, 598 TME+RT)
- Decrease in T lymphocytes and neutrophils.
- Increase in fibroblasts.
- Decrease in no. of LN retrieval but not in +ve lymph nodes.
- No change in depth.
- Three folds decrease in local recurrence.

Long course CRT

- **Improves staging (depth and lymph node status).**

Patterns of morphologic alteration in residual rectal carcinoma following preoperative chemoradiation and their association with long term outcome

- J. shia et al (New York)
- Am J Surg Path
- 2004

66 T3 and T4 rectal Ca treated with RT with or without 5FU

- Marked fibrosis with or without prominent inflammation.
- Frequent nuclear atypia but without mitosis.
- Retention of the adenoma component in the presence of tumour regression within the wall.

Prognostic factors in CRC treated by preoperative radiotherapy and immediate surgery

- R.James, N. Haboubi, P. Schofield, M.Mellor, N Salhab
- DCR 1991

Change in the grading and staging after RT

- Under stage.
- Over grade.
- Suggest: Any clinicopathological staging should record whether there is radiation or not .

Classifications of Regression

- **Mandard :** **Cancer 1994,73;2680.** **(1-5)**
- **Dworak :** **Int CRD 1997,12;19.** **(0-4)**
- **Wheeler :** **DCR 2002,45;1051.** **(1-3)**
- **Ryan :** **Histopathol 2005,47;141.** **(1-3)**
- **PRINCIPLE**
- **Tumour Volume V Fibrosis.**

Discrepancy in Staging

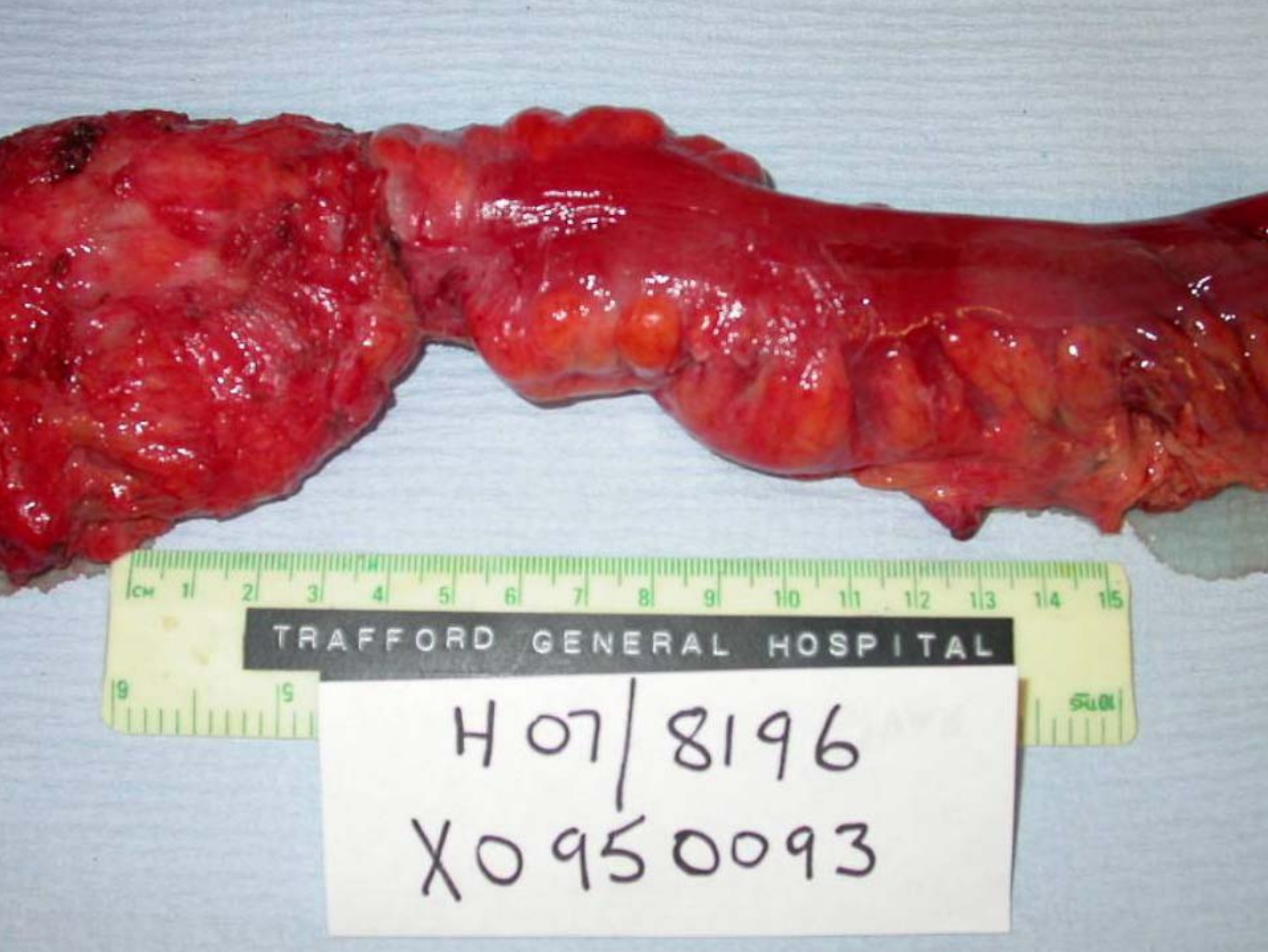
Author	Grade	Best Response	Worst Response
Mandard	1-5	1	5
Dworak	0-4	4	0
Wheeler	1-3	1	3
Ryan	1-3	1	3

Pathological response following long-course neoadjuvant CRT for locally advanced rectal cancer

- Rayan et al Histopathology:2005,47:141-146.
- 60 patients
- **G1, G2,G3.**
- **none of the G1&2 had local recurrence after mean 22 months.**

Prognostic Significance of Tumour Regression After Preoperative CRT for RC

- Rodel et al .J Clin Oncol 2005,23:8688
- G 4(Good) in 10.4% DFS 86%.
- G 2&3 DFS 75%
- G 0&1(Bad) >10% DFS 63%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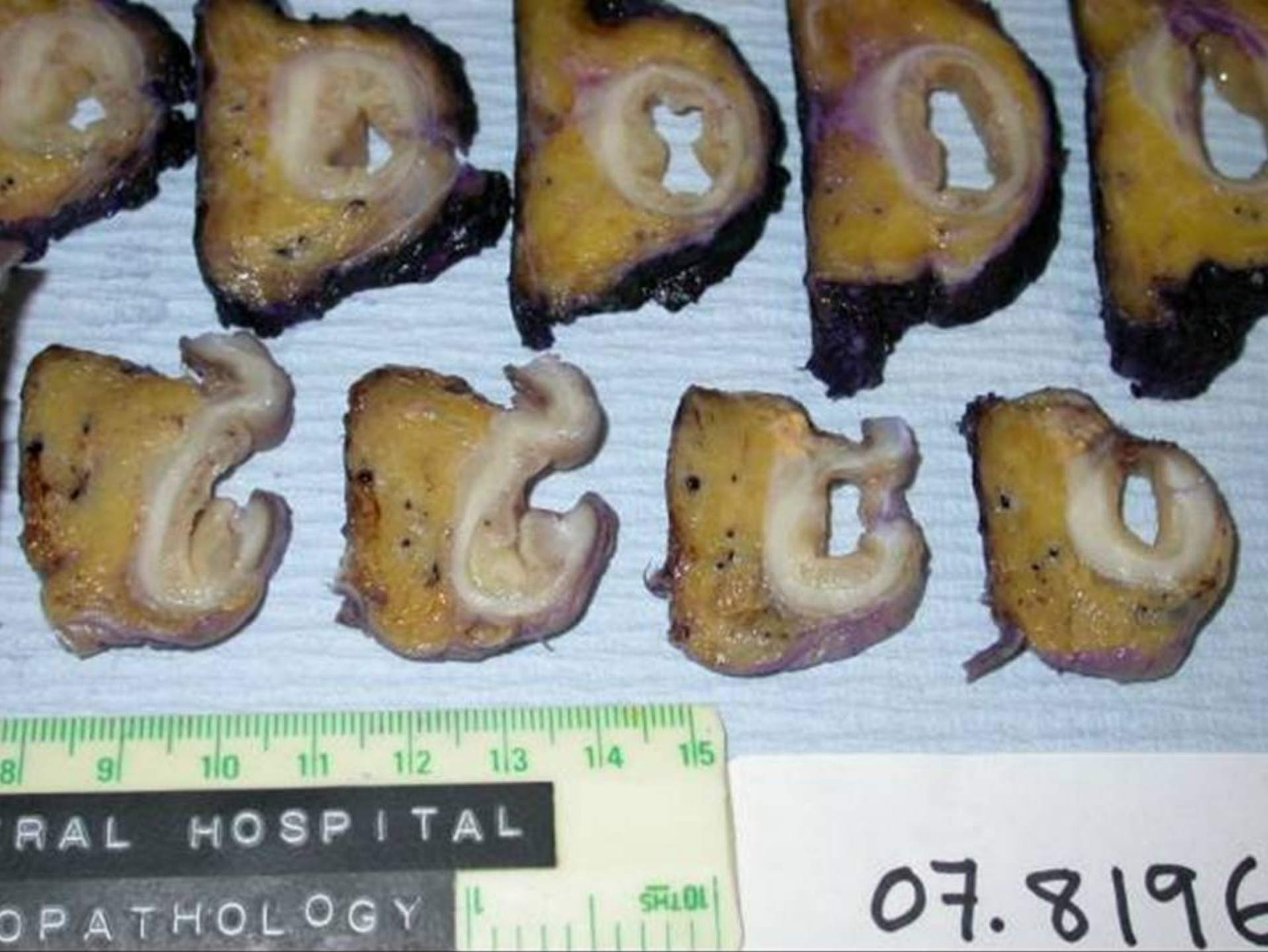
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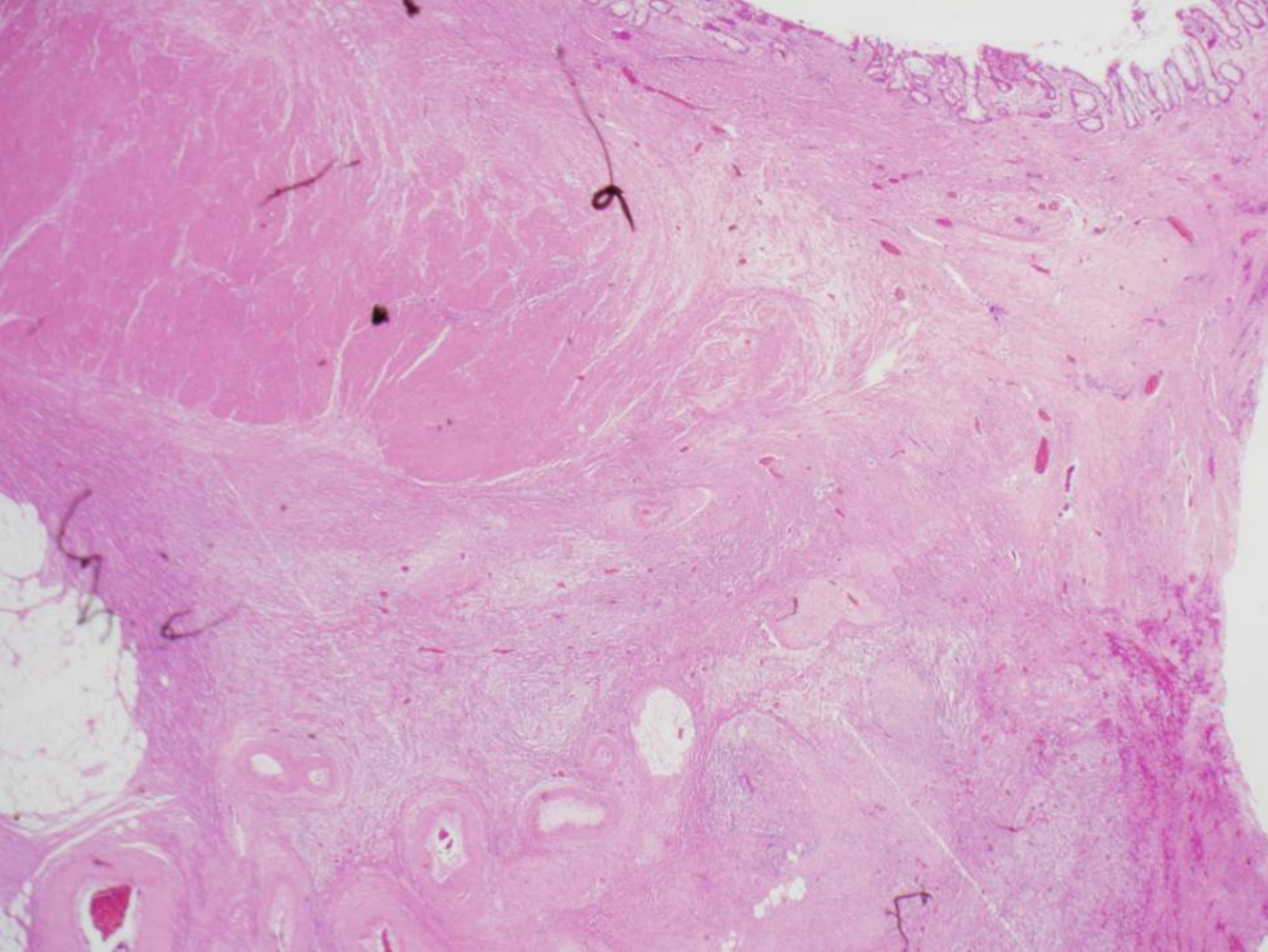
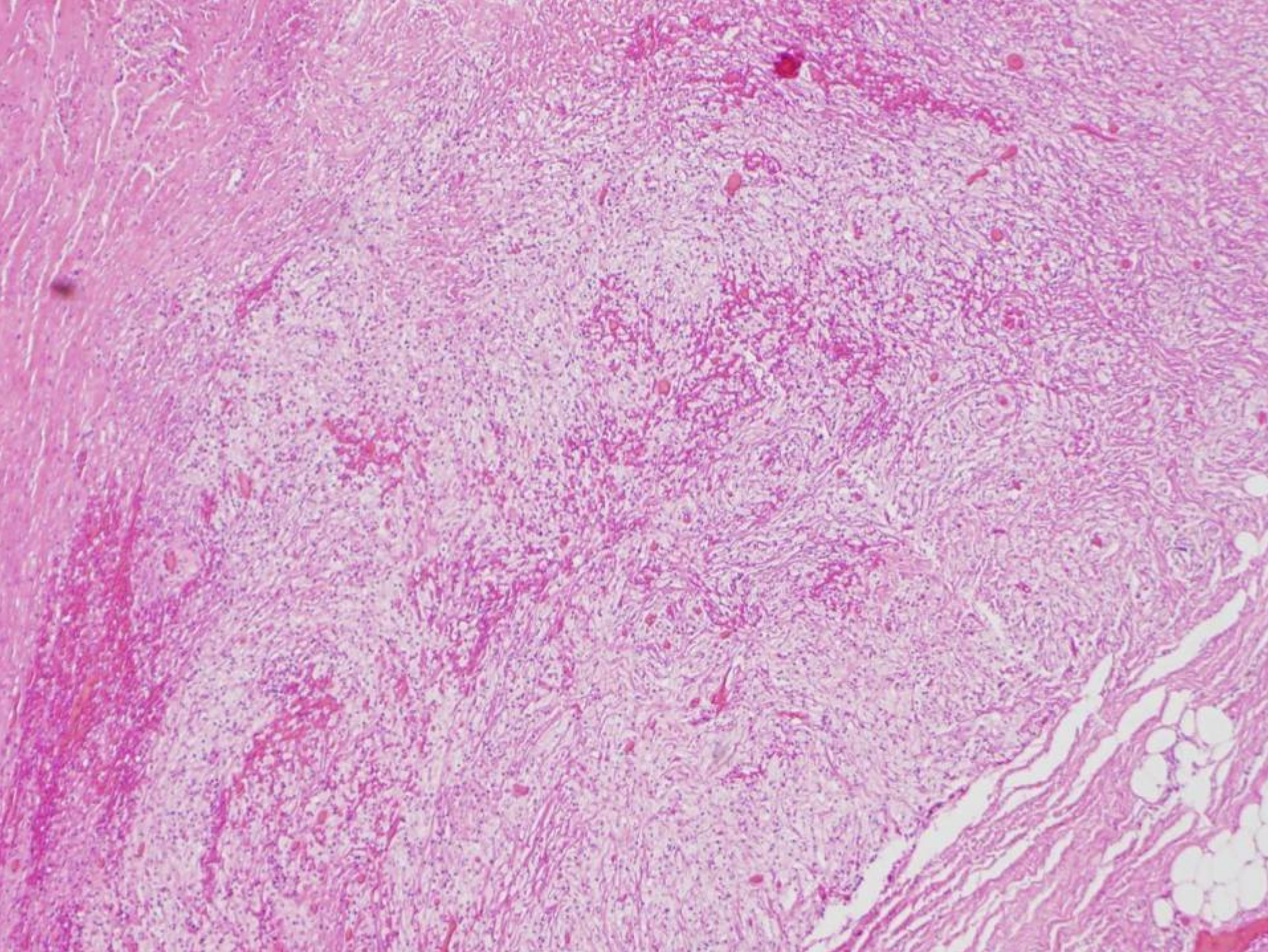
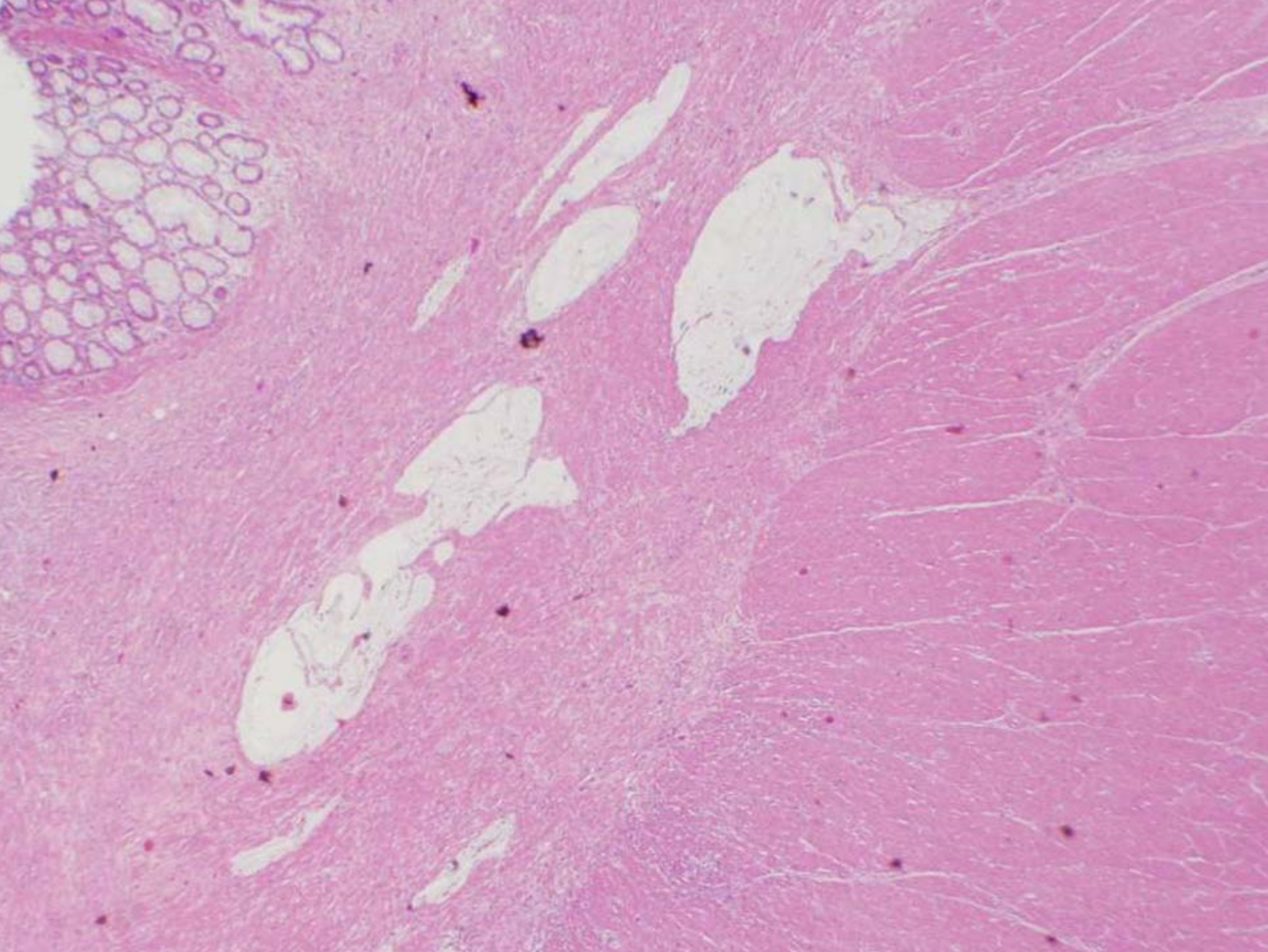
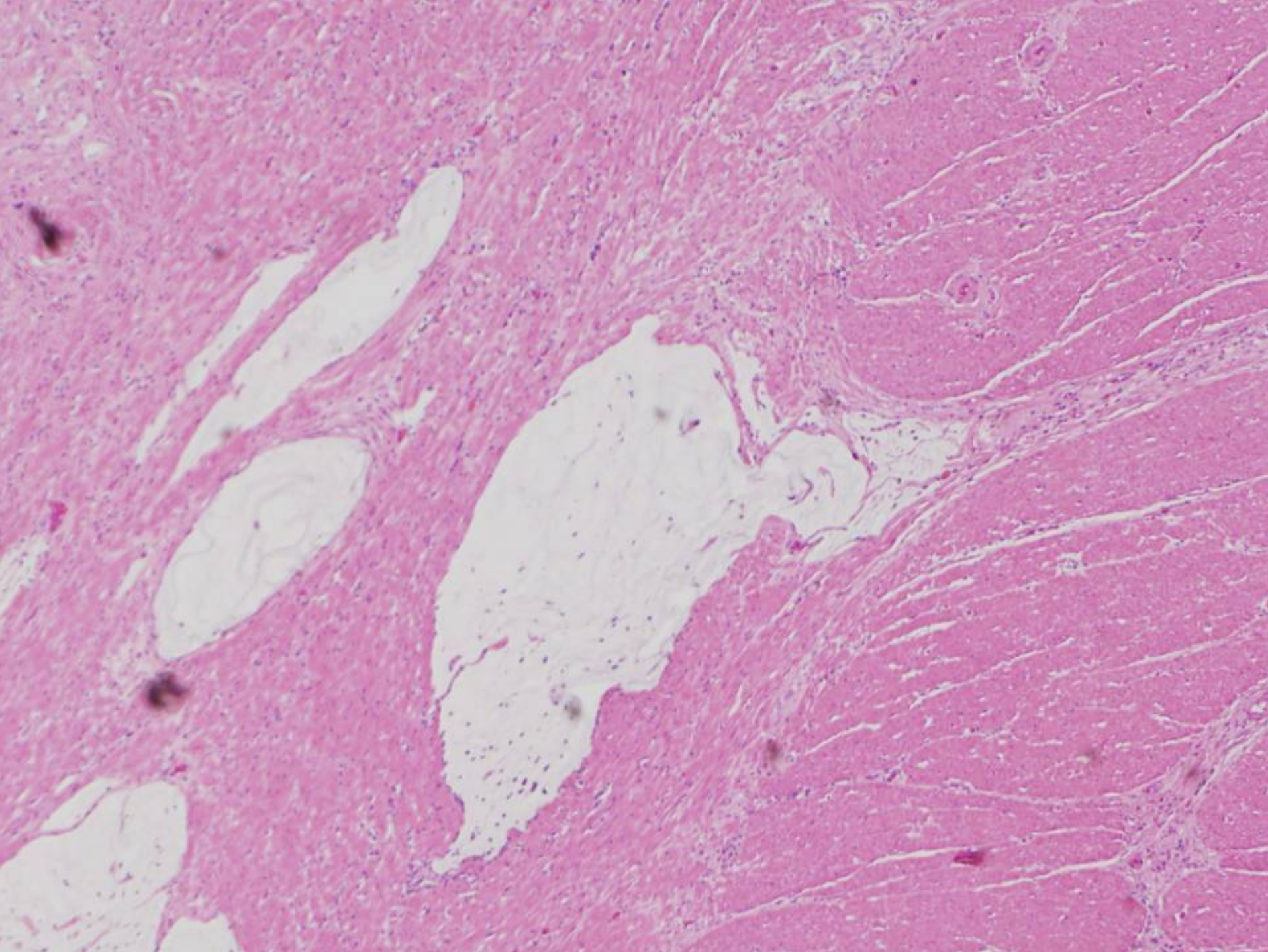








Non Cancerous Tissue

Prevalence of Toxicity

- 50% of solid malignancies will undergo RT.
- The data for radiation toxicity is poorly documented.

XRT Cervix ,Bladder Prostate ,Rectum

- May successfully downstage, control or eliminate the tumour
- Surrounding intestinal tissue may be injured

FACTORS INFLUENCING BIOLOGICAL RESPONSE

- Related to host and tissue.
- Related to therapy

Factors related to therapy

- Dose . High dose more toxic
- Field. Large field more toxic.
- Concomitant chemotherapy is more toxic
- Post operative RT is more toxic than pre operative RT

MORPHOLOGY

Acute radiation colitis in patients treated with short term preoperative radiotherapy for rectal cancer

- Leupin et al (Switzerland)
- Am J Surg. Path.
- 2002

Radiation colitis

- **Short Course**
- Sever mucosal inflammation.
- Prominent eosinophils.
- Crypt disarray
- Crypt epithelial damage.
- Nuclear abnormality
- Apoptosis of crypt epithelium.
- *Either clinically silent or quick recovery.*

- **Long Course**
- These features are either absent or rarely detected.

The Light and Electron Microscopic Features of Early and Late Radiation-Induced Proctitis

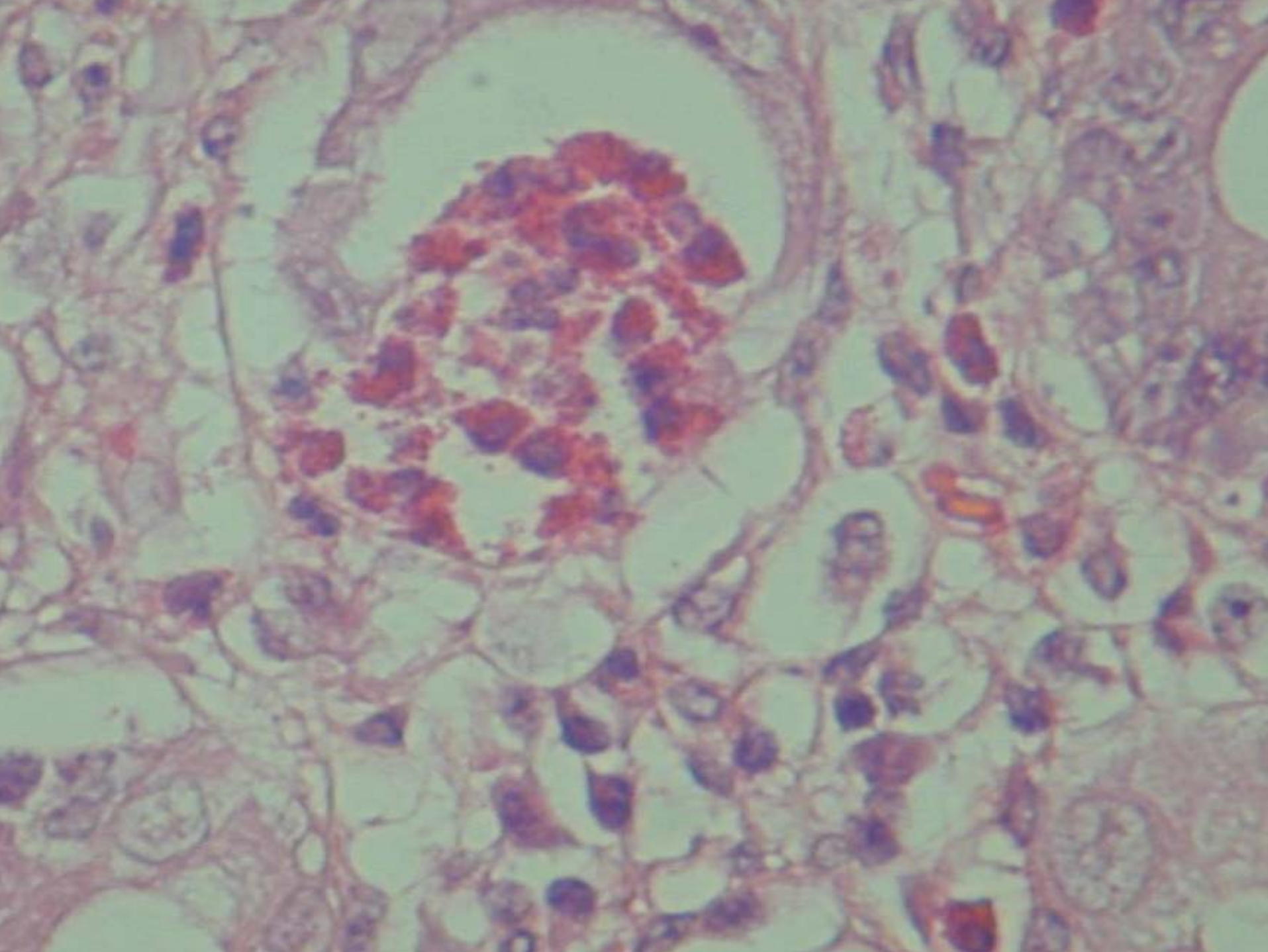
Haboubi, Rowland, and Schofield

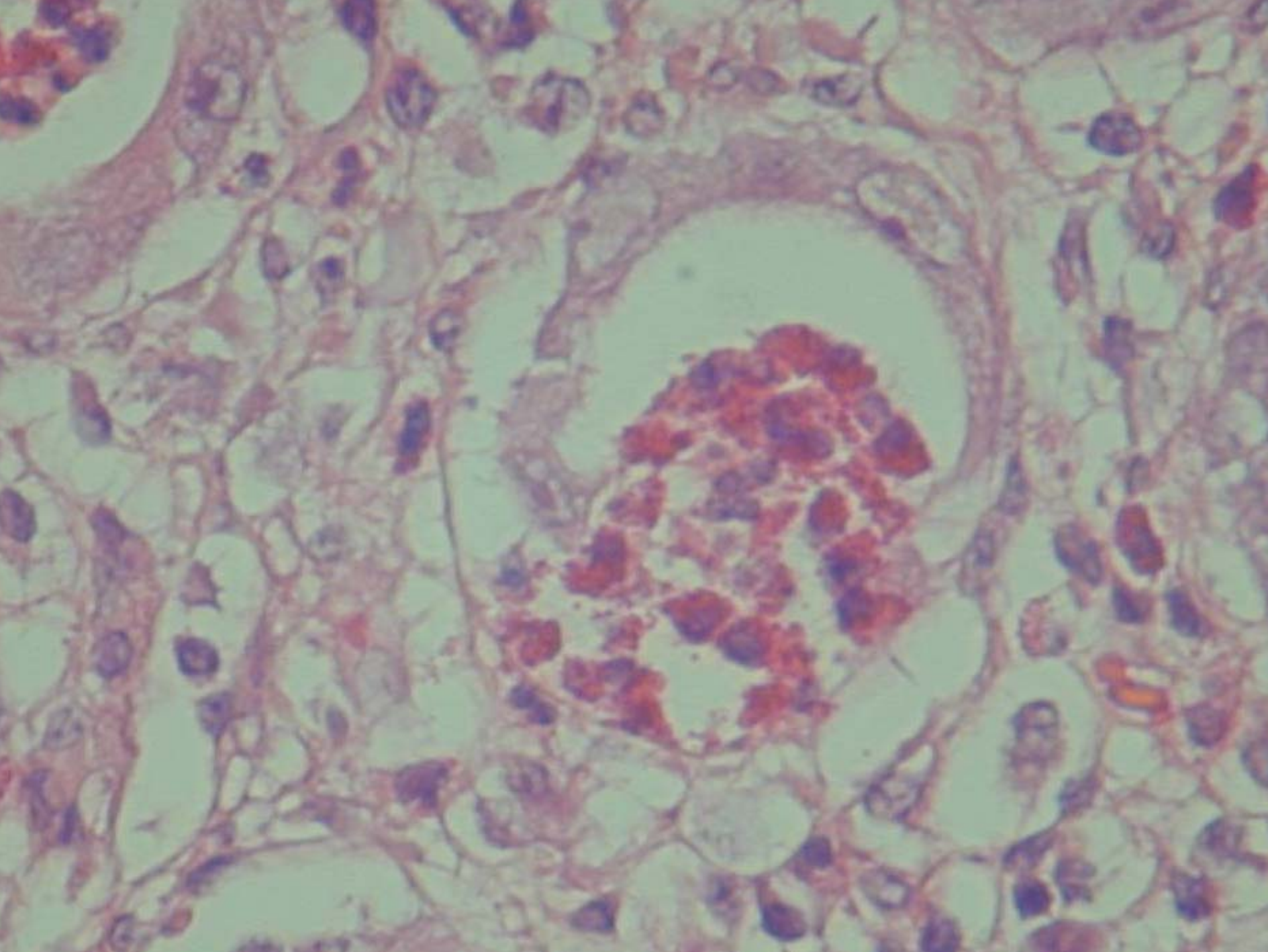
Am.J.of Gastro.

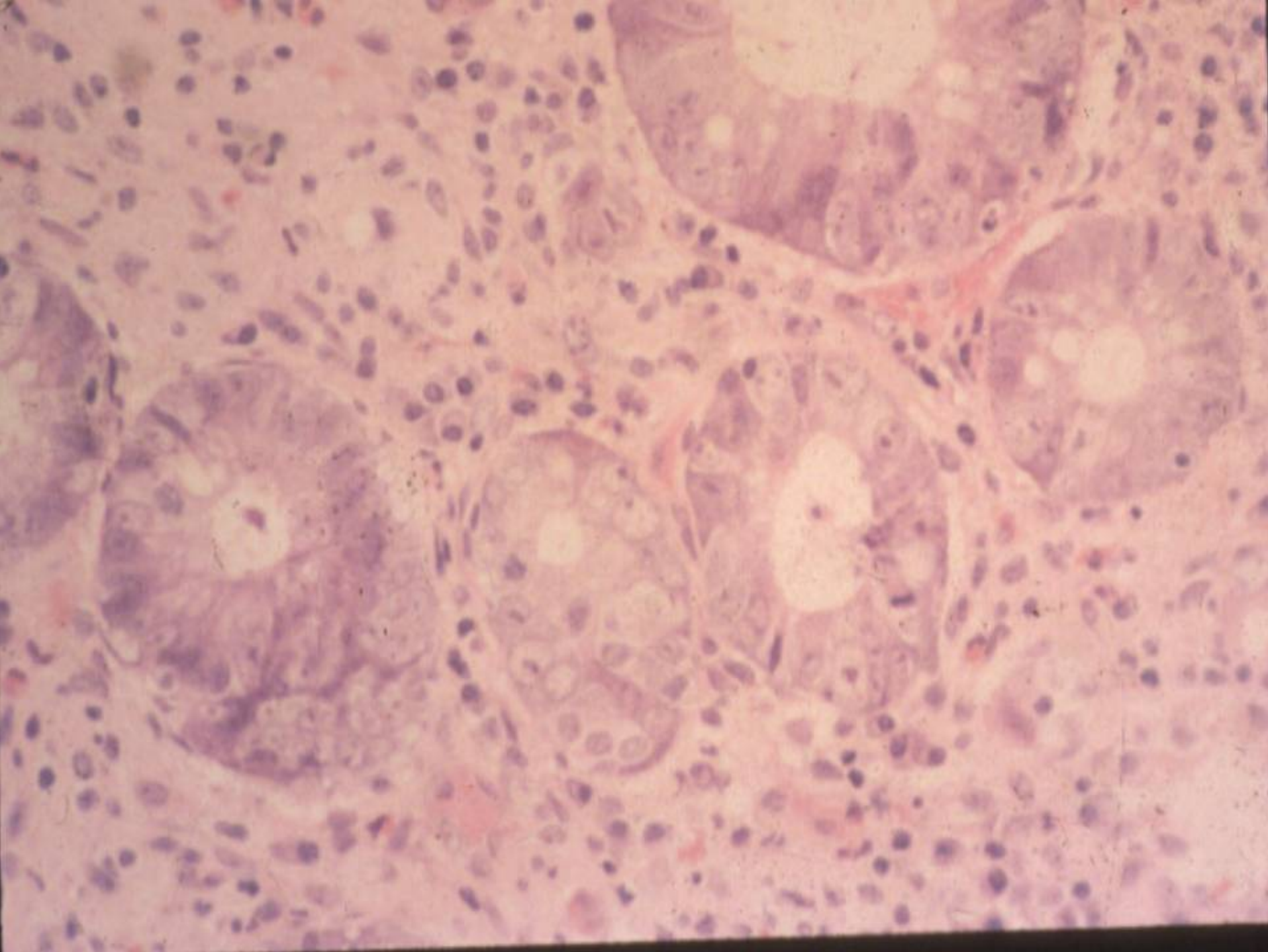
1988

ACUTE PHASE/EPITHELIAL

- **Days.**
- **Eosinophilic infiltrate**
- **Megalanucleosis .**
- *Normal blood vessels*







CAUTION

Acute phase radiation

- Appearances may resemble dysplasia

VASCULAR PHASE

Weeks

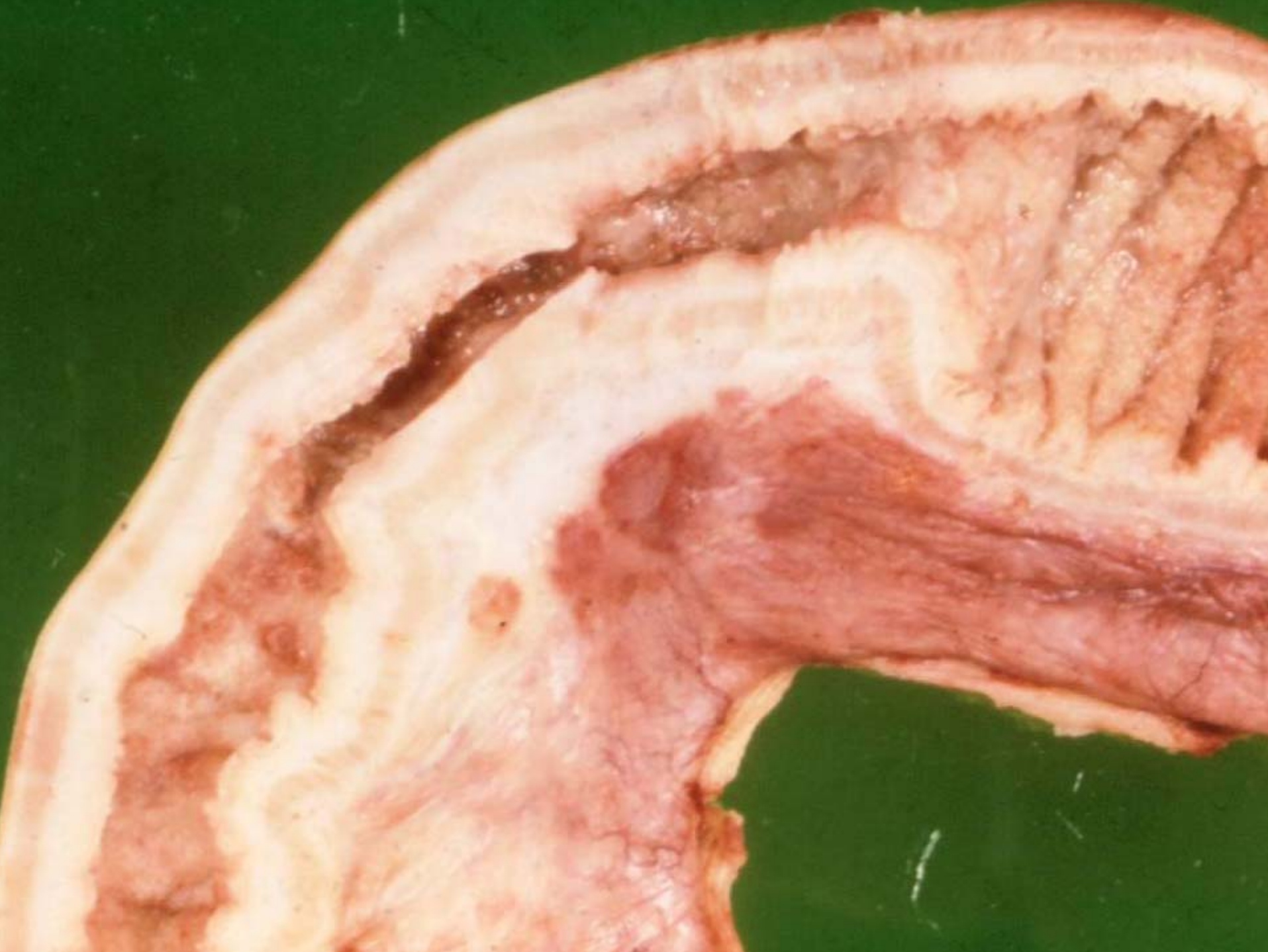
Appears after the epithelial phase.

FEATURES

- Narrowing by sub endothelial oedema
- Fibrin deposition
- On E/M there is endothelial cell necrosis and platelet thrombi formation
- Reversibility??

Late Phase

- Months/years
- Vascular component .
- Mesenchymal/ Stromal/fibrous.
- Irreversible.



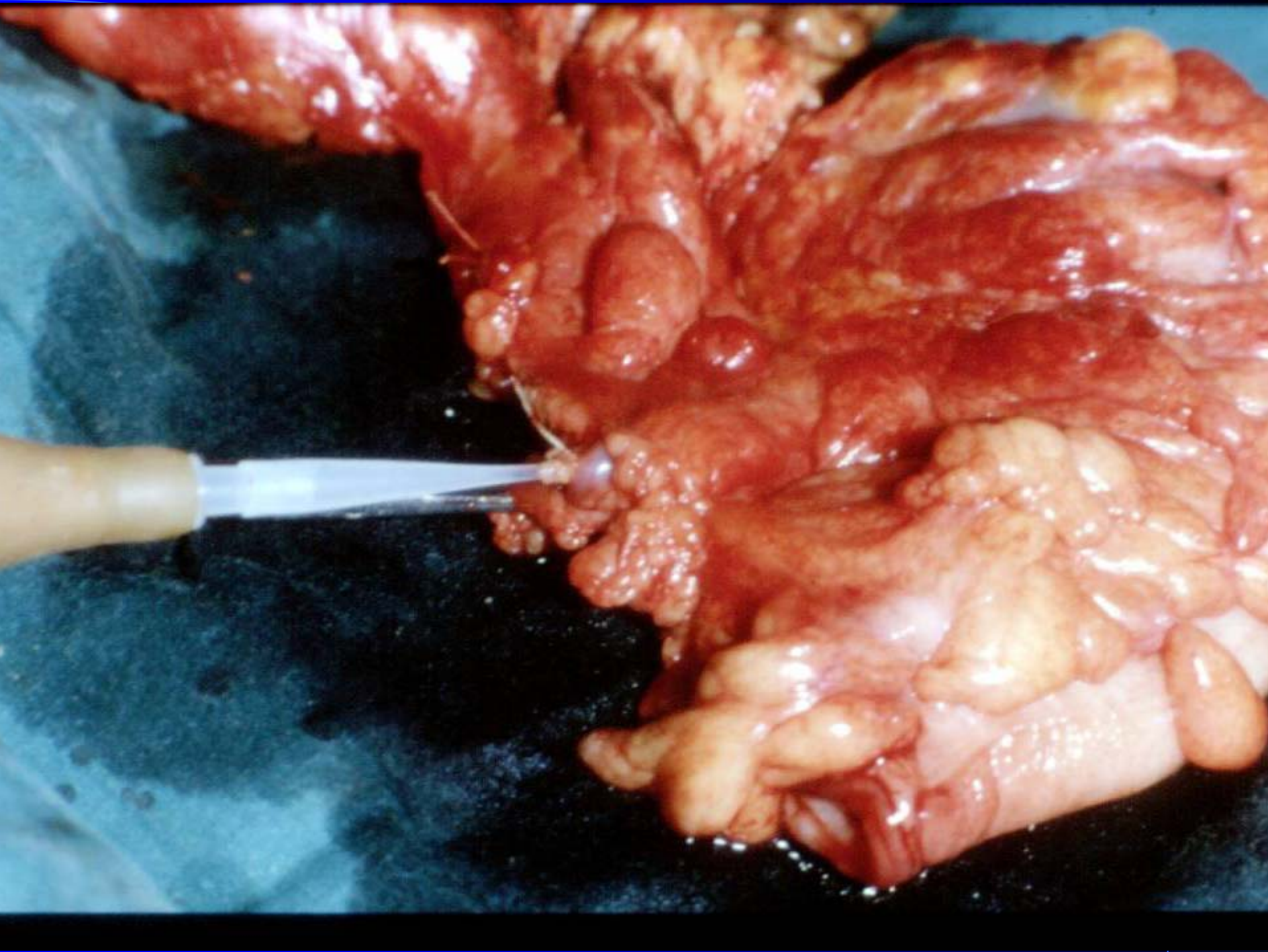
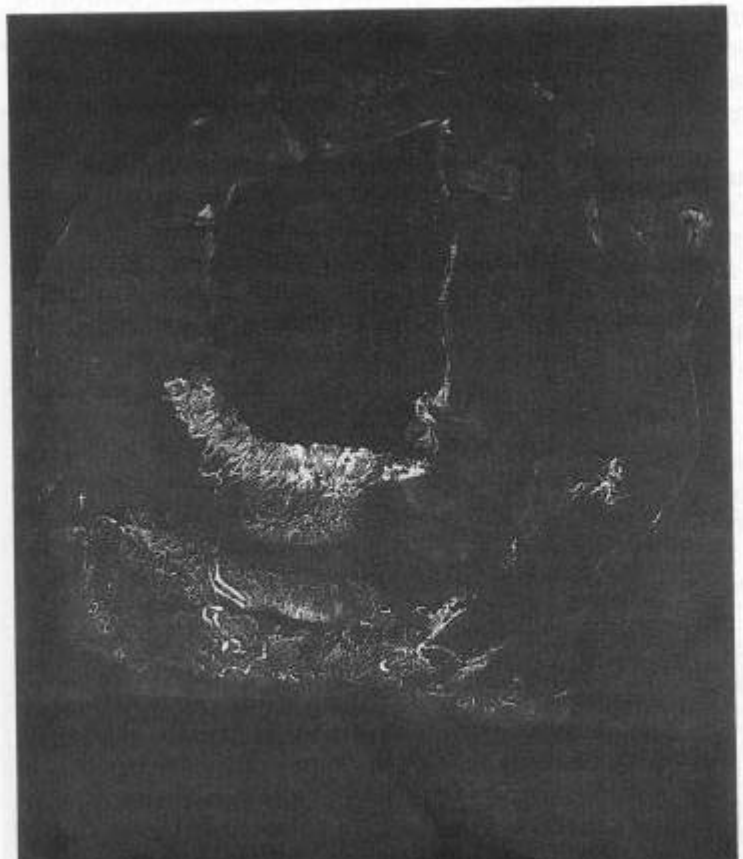


Fig. 5.16

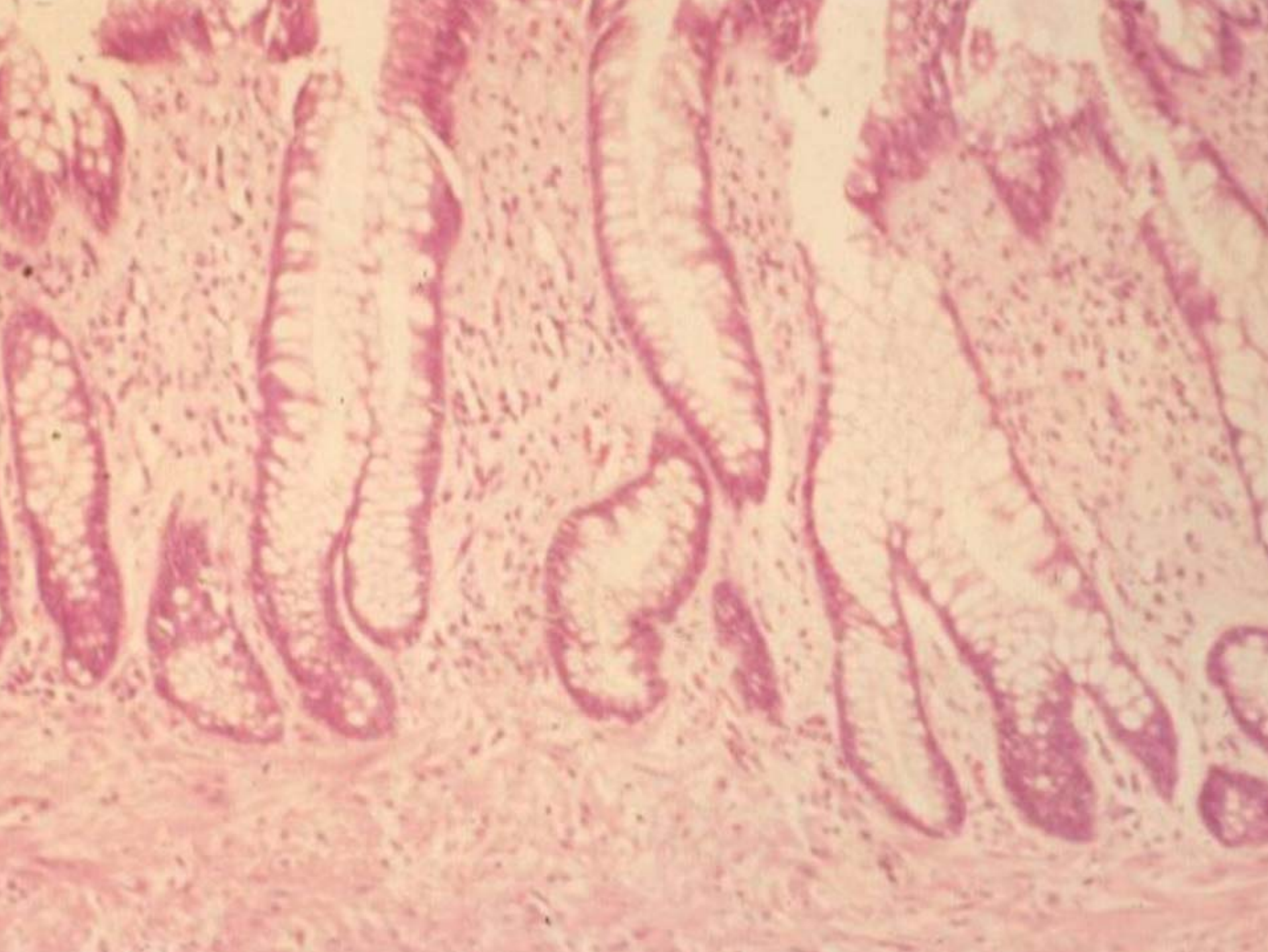


Components of Late phase

Fibrous

Vascular

Epithelial



CAUTION

Late phase radiation

- Appearance may resemble **Chronic IBD**

LATENT INJURY

More subtle DNA injury responsible for:

- Mutation
- Teratogenic effect
- Carcinogenic effect

FLOW CYTOMETRIC DNA CHARACTERISATION OF RADIATION COLITIS - A PRELIMINARY STUDY

Pearson JM, Kumar S, Butterworth DM, Haboubi NY

Anti Cancer Research 1992

AIM

To study the DNA ploidy status in cases of acute and chronic phase reaction

MATERIAL

Six cases of acute (24 days)

Six cases of chronic(755 days)

Age and sex matched

Results

- None of the acute phases biopsies showed DNA aneuploidy despite the bizarre nuclear morphology.
- 2 out of the 6 chronic phase showed DNA aneuploidy.In both there is mild nuclear atypia.

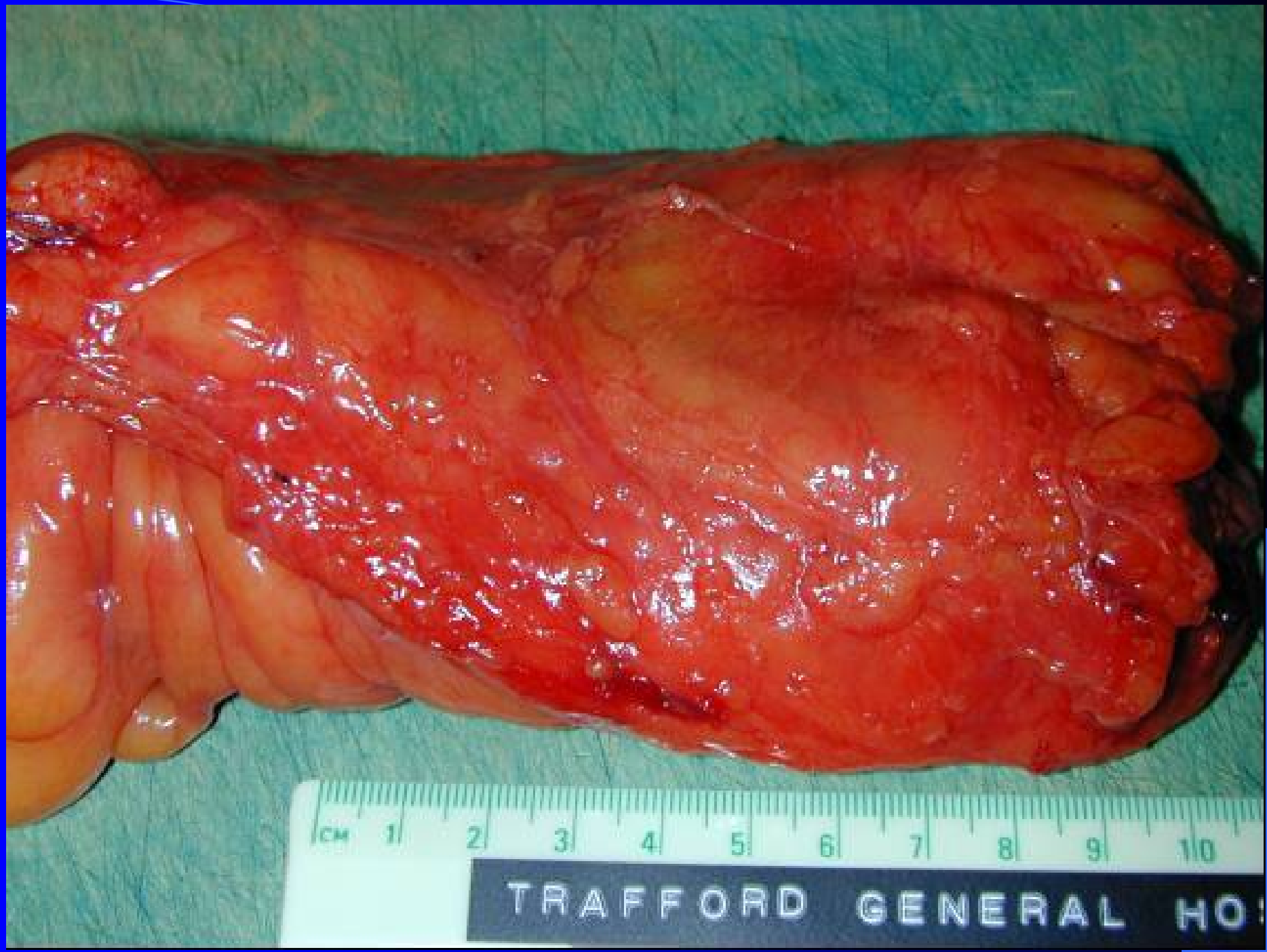
The role of the pathologist in CRC

- Diagnostic.
- Therapeutic.
- Audit.
- Research

لا تلم كفي إذا السيف نبا
صح مني العزم و الدهر أبى

The effective management of CRC requires

- The involvement of the histopathologist at various stages of treatment pathway.
- Diagnostic.
- Therapeutic.
- Audit.
- Research.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Summary

- Don’t know how common ,probably on the increase.
- Clinical and Pathological features are related to the phase (tissue type) injury.
- Satisfactory management should be in the hands of experienced team

Time relation of complication to various presentations

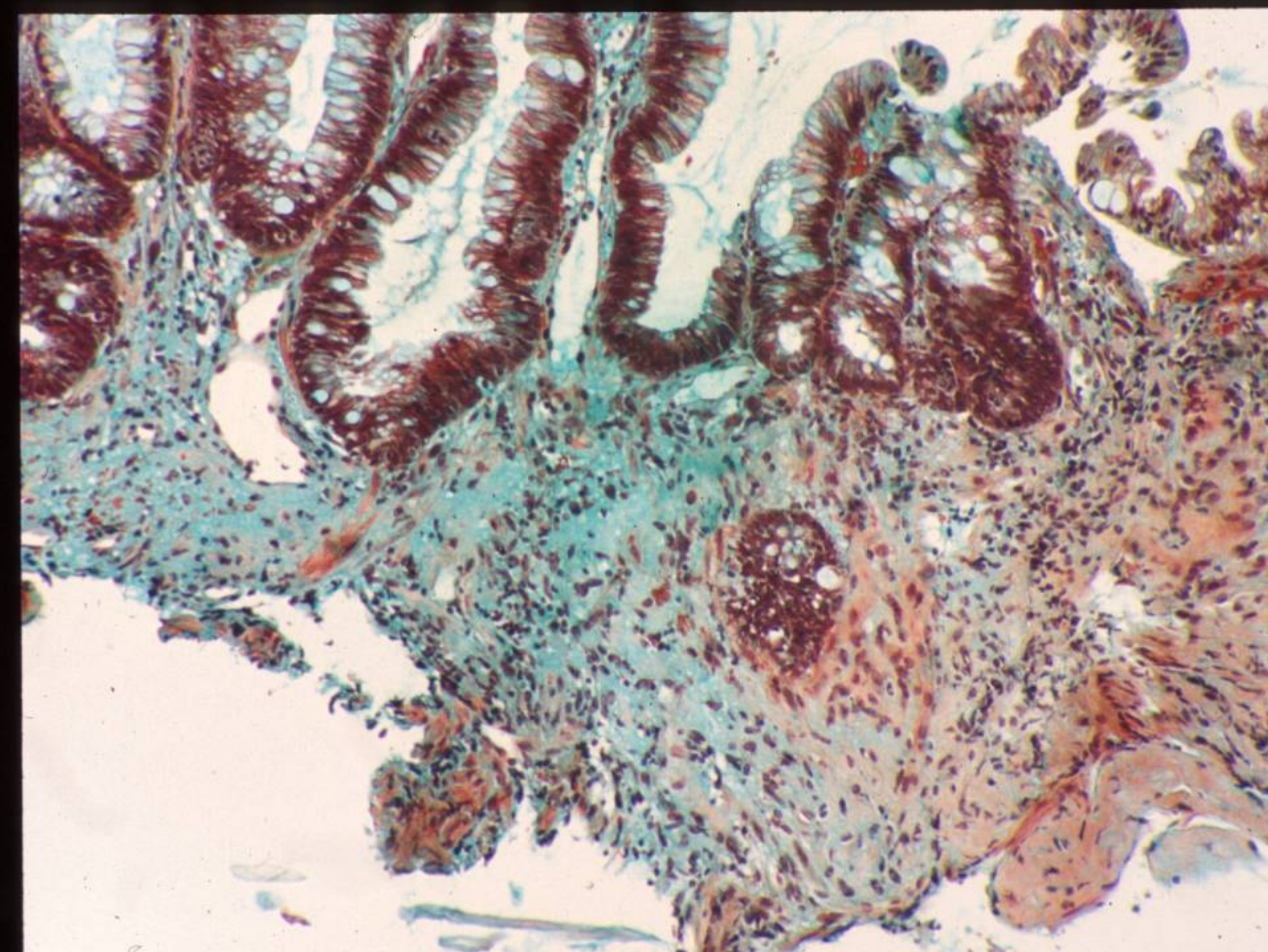
- Acute proctitis (epithelial) 0-4 weeks
- Acute enteritis (epithelial) 0-4 weeks
- Rectal bleeding(vascular) 4-12 months
- Chronic abscess(stromal) 9-15 months
- Fistula (stromal) 18-24 months
- Stricture (stromal) 2-20 years

Components of Late phase

Fibrous

Vascular

Epithelial



Radiation induced cytochrome c release causes loss of rat colonic fluid absorption by damage to crypts and pericryptal myofibroblasts

- Thiagarajah, Gourmelon, Griffiths, Lebrun,Naftalin,Pedly (Kings ,France)
- Gut 2000

Total body radiation of mice

- Mitochondrial damage .
- Loss of crypt fluid absorption and increased permeability coincide with decreased inter cellular adhesion crypt epithelial cells and loss of pericryptal sheath barrier function.

Predicting local recurrence of carcinoma of the rectum after preoperative radiotherapy and surgery

- D.Jones, Zaloudik,Roger James,N.Haboubi,M.Moore,P.Schofield
- BJS 1989.

Prospective randomised study

- Tethered rectal cancer
- 97 surgery alone
- 89 preoperative RT and Surgery
- DNA ploidy by flowcytometry.

Results

- Aneuploidy was seen in 62% of the surgery alone group V 33% of the combined group.

The surgery of today is based on Pathology.

- Unless he build on that solid foundation, the surgeon is no better than a hewer of flesh and a drawer of blood.
- William Boyd. Surgical pathology 1925

Factors related to host

- **Diabetes**
- **Hypertension.**
- **Arterial disease**
- **Smoking.**

Factors related to therapy

- Dose .
- Field.
- Concomitant chemotherapy.
- Previous surgery.

Prior abdominal or pelvic surgery

- Adhesions
- Prolapse into abnormal positions
- **Entrapment of intestinal loops in the field.**

ACUTE PHASE/L.M.

- Eosinophilic infiltrate
- **Megalanucleosis and abnormal mitotic figurers**.
- Normal blood vessels

Turn over of cells in the gut

- Epithelial cells
- Endothelial
- Stromal / fibrous cells

Early Phase

- Nuclear and cytoplasmic changes are mostly reversible.


KINGS OF
EUROPE

Adjuvant therapy

- Lymph nodes involvement(if age and co morbidity allows).
- No LN involvements but with other adverse pathological features like

a/ perforation

b/ extramural venous invasion

c/ serosal involvement

d/ incomplete resection

e/ Involved CRM in rectal cancer.

OUTCOME of Radiation Damage

- **Limited Complete repair.**
- **Extensive Partial or no repair inhibition of mitosis or promotion of apoptosis**

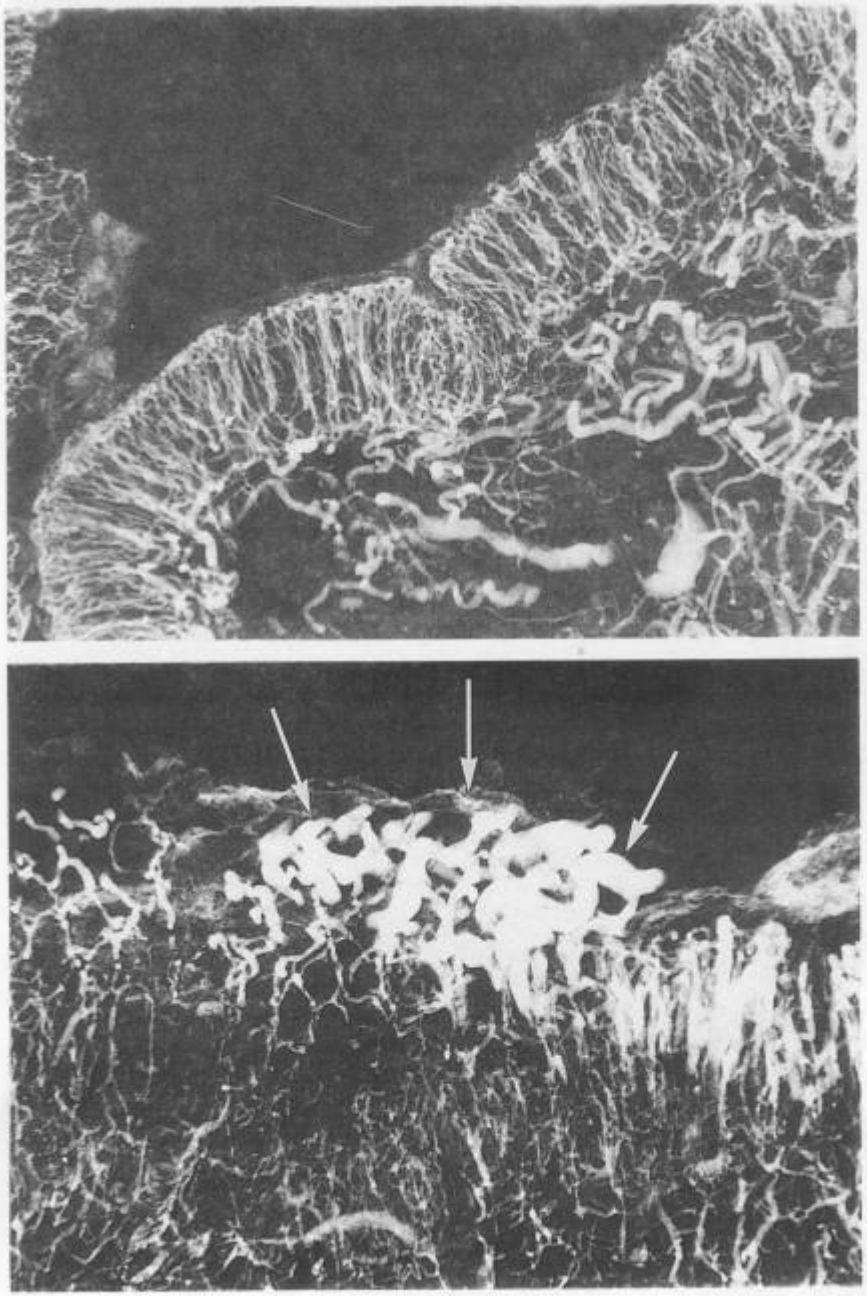


Fig. 5.18. Microradiographs comparing normal colonic mucosa (*top*) with that in RBD (*bottom*). The latter shows telangiectasia (*arrows*) of mucosal capillaries. (TS ×50)

Gross Description

Metastatic Spread

Site of tumour _____

Maximum tumour diameter _____

Distance of tumour to nearer margin (cut end) _____

Presence of tumour perforation (pT4) [ ] Yes [ ] No

Histology

Type

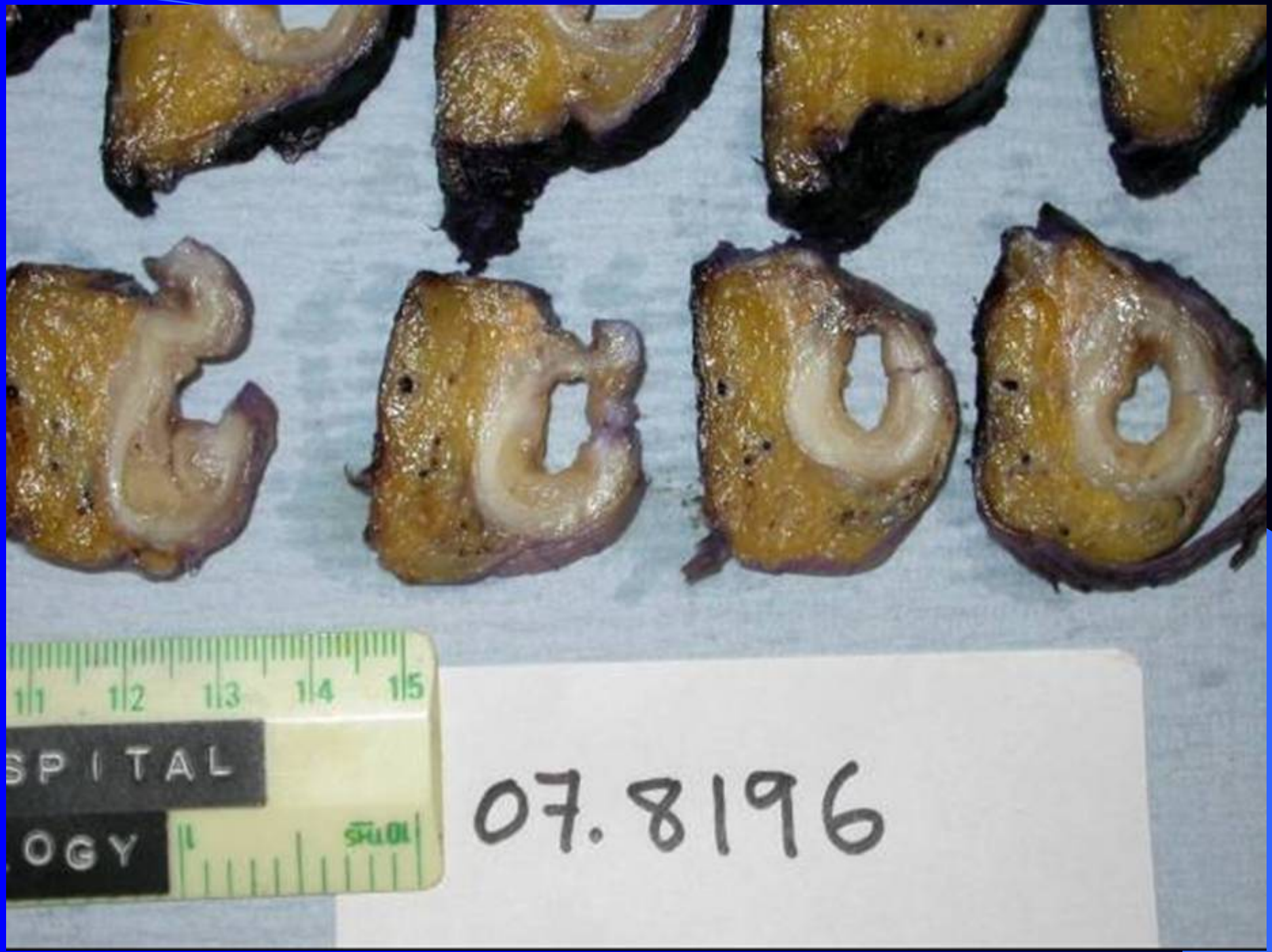
Adenocarcinoma [ ] Yes [ ] No

(to include mucinous and signet ring adenocarcinomas)

If No, other _____

Differentiation by predominant area

[ ] Well/moderate [ ] Poor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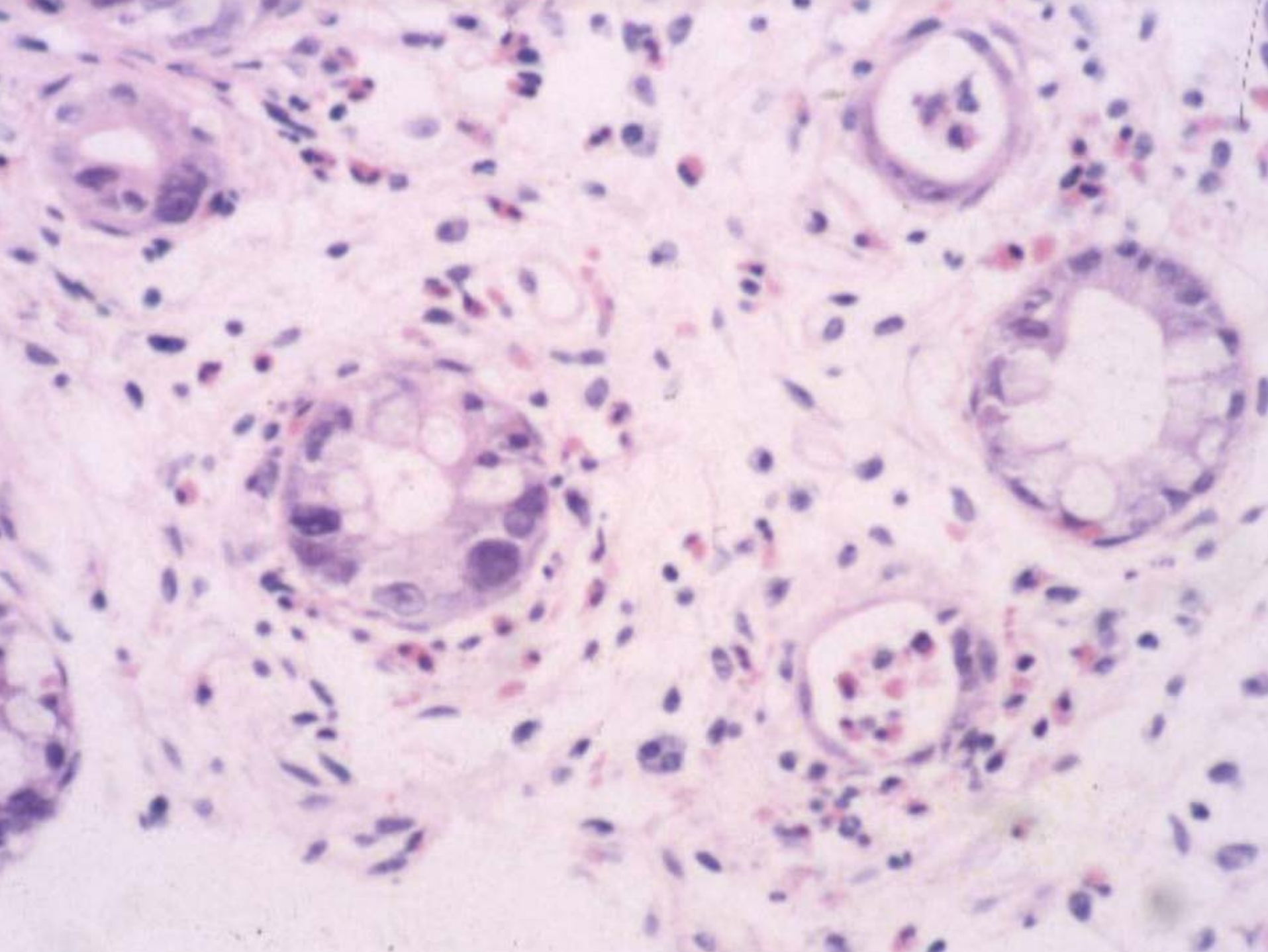

Topics

- Resection Margins.
- Grading Total Mesorectal Excision (TME).
- Recording distance of mesorectal extension.
- Recording of tumour extension to Non Peritonealised Resection Margin(NPRM).
- Recording Peritoneal involvement.
- Recording of Tumour Regression Grade.
- *Radiation Bowel Disease.*

‘It is only necessary to examine the margins histologically if tumour extends macroscopically to within 30mm of one end’

Exceptions

- Signet ring
- Small cell
- Undifferentiated
- Extensive lymphatic or vascular permeation.

High quality reporting

- Confirms that radical surgery was necessary, place the patient in an accurate prognosis category and if there is a need for post operative adjuvant therapy.
- Facilitate improvement of quality of rectal surgery. Good surgery produce less recurrence rate.

Factors that influence adequacy of TME for rectal cancer

- S.Jaeyarajah et al
- CRD 2007
- No relation between the mesorectal scoring and local recurrence rate.
- Male gender &AR are relevant factors.

Aim of CRT

- Tumour regression.
- Protect the non tumourus tissue.

Classifications of Regression Grades

- Mandard. Cancer 1994,73;2680. (1-5)
- Dworak Int CRD 1997,12;19. (0-4)
- Wheeler DCR 2002,45;1051. (1-3)
- Ryan Histopathol 2005,47;141. (1-3)

Tumour Regression

- Quantification of histologic regression of rectal cancer after irradiation(chaemo).
- Wheeler et al DCR 2002,45: 1051-1056.
- 3 stages instead of the ‘traditional’ 5 stage of Mandard et al (Cancer 1994; 73:2680-2686).

Regression Grades

- G1=Good response. Either no tumour or only microscopic foci of carcinoma.
- G2= Marked fibrosis +Macroscopic tumour still visible.
- G3= Bad response. Little fibrosis +Abundant macroscopic disease