# Assessment of GI and Pancreatic resections after neoadjuvant therapy

Georgina England

SA Pathology and Clinpath Laboratories

# Outline

- Neoadjuvant therapy (NAT)
- Rectal
  - Hepatic metastases from colorectal carcinoma
- Oesophageal squamous cell carcinoma and adenocarcinoma
- Gastric adenocarcinoma
- Pancreatic adenocarcinoma

# Neoadjuvant therapy

- Refers to any  therapy given prior to the primary therapy (usually surgical) resection.
- Types of neo-adjuvant therapy
  - Chemotherapy
  - Radiotherapy
  - Hormonal
  - Biological Agents
  - Immunotherapy

# Rationale for the use of therapy

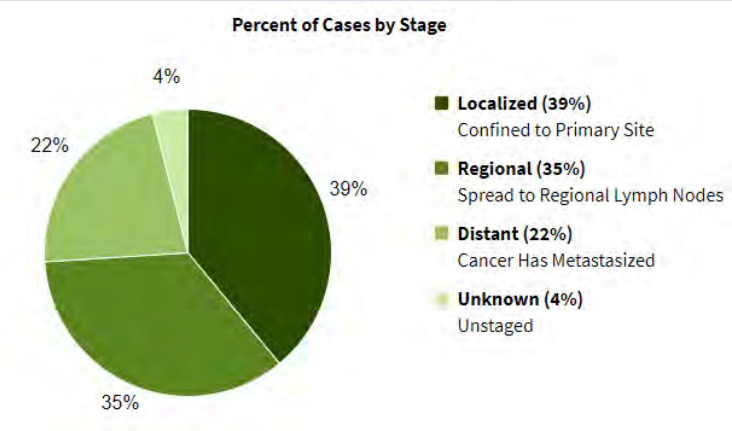
- What is the evidence base for neoadjuvant therapy?

# Rectal tumours

# Colorectal carcinoma

- SEER data (US) in 2019 :
  - Estimated New Cases: 145,600 (8.3%)
  - Estimated Deaths: 51,020 (8.4%)

| | Common Types of Cancer | Estimated New Cases 2019 | Estimated Deaths 2019 |
|---|---|---|---|
| 1. | Breast Cancer (Female) | 268,600 | 41,760 |
| 2. | Lung and Bronchus Cancer | 228,150 | 142,670 |
| 3. | Prostate Cancer | 174,650 | 31,620 |
| **4.** | **Colorectal Cancer** | **145,600** | **51,020** |
| 5. | Melanoma of the Skin | 96,480 | 7,230 |
| 6. | Bladder Cancer | 80,470 | 17,670 |
| 7. | Non-Hodgkin Lymphoma | 74,200 | 19,970 |
| 8. | Kidney and Renal Pelvis Cancer | 73,820 | 14,770 |
| 9. | Uterine Cancer | 61,880 | 12,160 |
| 10. | Leukemia | 61,780 | 22,840 |





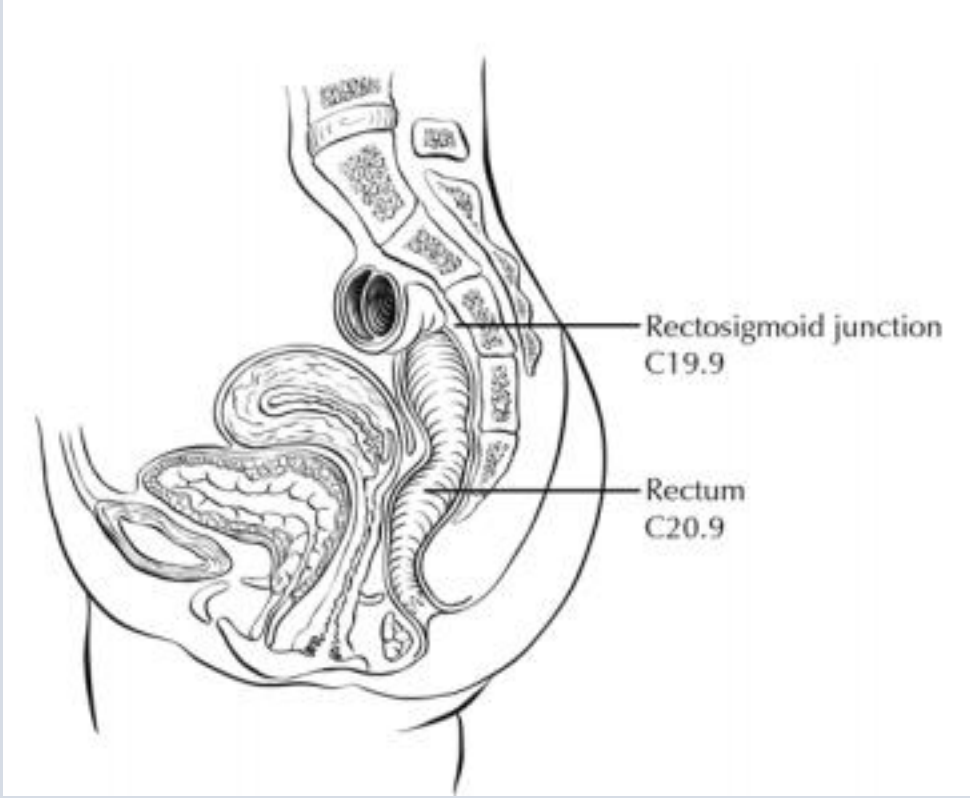

SEER Cancer Stat Facts: Colorectal Cancer. National Cancer Institute. Bethesda, MD,

# CRC - an Australian perspective

- IARC: Australia has one of the world's highest rates of colorectal carcinoma
- Environmental risk factors: Obesity, physical inactivity, smoking, high alcohol consumption, diet (high red/ processed meat consumption, low fibre)
- Second leading cause of cancer related mortality in Australia (following lung carcinoma), 9% of cases
- 2013: 14,962 new cases (8,214 males and 6,748 females).
- 1982: 6,986 new cases

# Rectal Adenocarcinoma

- Unique anatomy
  - High risk of local recurrence
  - Sphincter involvement
- Evolving literature
- Surgical aims
  - R0 resections
  - Sphincter preservation
- Surgical / therapeutic options
  - Anterior resections
  - AP resections
  - Mucosal resections
  - Watch and wait approach




*2017 College of American Pathologists Protocol for the Examination of Specimens From Patients With Primary Carcinoma of the Colon and Rectum*

# Historic approach to rectal carcinoma

- 1917: Janeway and Quick, radon beads placed directly into rectal cancer
- 1980s: Exploration of both neoadjuvant and adjuvant therapy
- 1990: NIH: Post-operative adjuvant chemoradiotherapy for Stage II and Stage II
- Total mesorectal excision (TME) becomes standard therapy: demonstrated lower risk of local recurrence

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

# Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer

Rolf Sauer, M.D., Heinz Becker, M.D., Werner Hohenberger, M.D., Claus Rödel, M.D., Christian Wittekind, M.D., Rainer Fietkau, M.D., Peter Martus, Ph.D., Jörg Tschmelitsch, M.D., Eva Hager, M.D., Clemens F. Hess, M.D., Johann-H. Karstens, M.D., Torsten Liersch, M.D., Heinz Schmidberger, M.D., and Rudolf Raab, M.D., for the German Rectal Cancer Study Group*

**Table 3. Postoperative Pathological Tumor Stage, Type of Surgery, and Completeness of Resection, According to Actual Treatment Given.***

| Variable | Preoperative Chemoradiotherapy (N=415) | Postoperative Chemoradiotherapy (N=384) | P Value |
|---|---|---|---|
| Histopathological finding (%) | | | <0.001 |
| Complete response | 8 | 0 | |
| TNM stage | | | |
| I | 25 | 18 | |
| II | 29 | 29 | |
| III | 25 | 40 | |
| IV | 6 | 7 | |
| Unknown | 6 | 6 | |
| Type of resection (%) | | | 0.45 |
| Low anterior, intersphincteric | 69 | 71 | |
| Abdominoperineal | 26 | 23 | |
| Other | 3 | 2 | |
| Unknown | 2 | 3 | |
| Completeness of local resection (%) | | | 0.69 |
| Complete | | | |
| Without distant metastasis | 91 | 90 | |
| With distant metastasis | 2 | 4 | |
| Incomplete† | | | |
| Without distant metastasis | 3 | 3 | |
| With distant metastasis | 3 | 4 | |

N Engl J Med 2004; 351:1731-1740

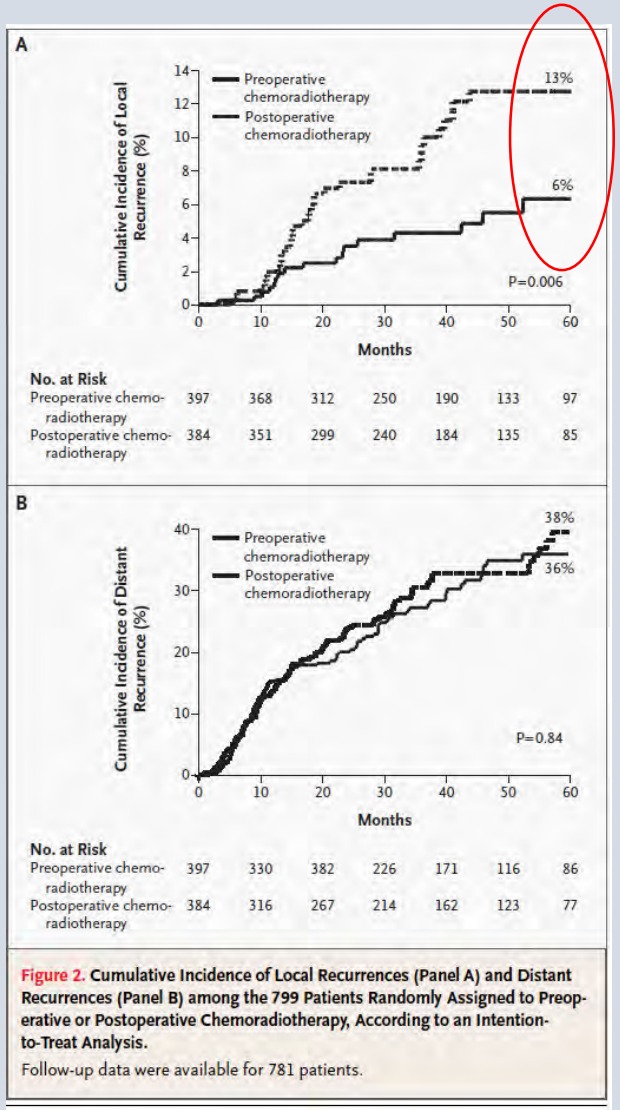



**Figure 2. Cumulative Incidence of Local Recurrences (Panel A) and Distant Recurrences (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis.**

Follow-up data were available for 781 patients.

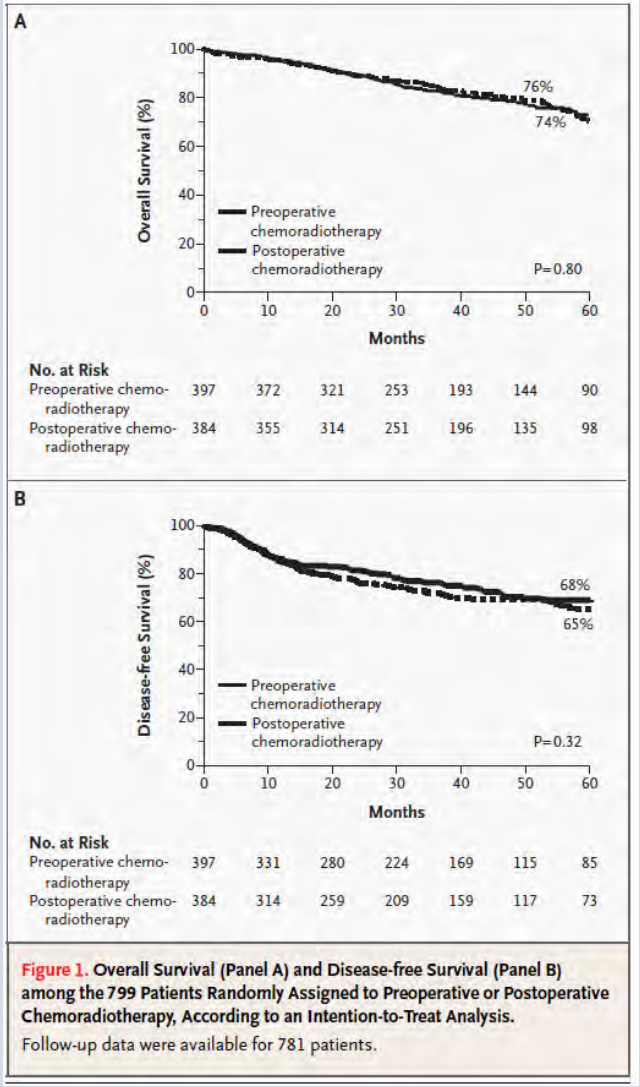



**Figure 1. Overall Survival (Panel A) and Disease-free Survival (Panel B) among the 799 Patients Randomly Assigned to Preoperative or Postoperative Chemoradiotherapy, According to an Intention-to-Treat Analysis.**

Follow-up data were available for 781 patients.

**Table 4. Rates of Sphincter-Sparing Surgery in 194 Patients Determined by the Surgeon before Randomization to Require Abdominoperineal Resection, According to Actual Treatment Given.**

| Variable | Preoperative Chemoradiotherapy (N=415) | Postoperative Chemoradiotherapy (N=384) | P Value |
|---|---|---|---|
| Abdominoperineal resection deemed necessary — no. (%) | 116 (28) | 78 (20) | |
| Sphincter-preserving surgery performed — no./total no. (%) | 45/116 (39) | 15/78 (19) | 0.004 |

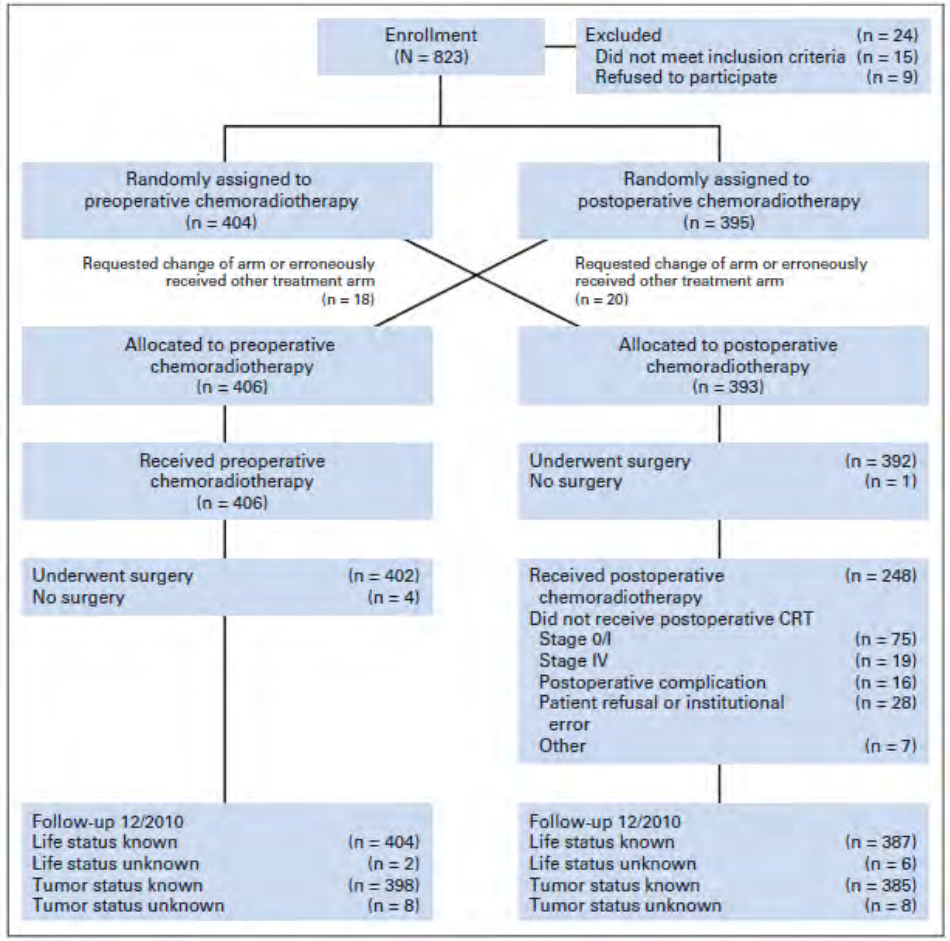
VOLUME 30 · NUMBER 16 · JUNE 1 2012

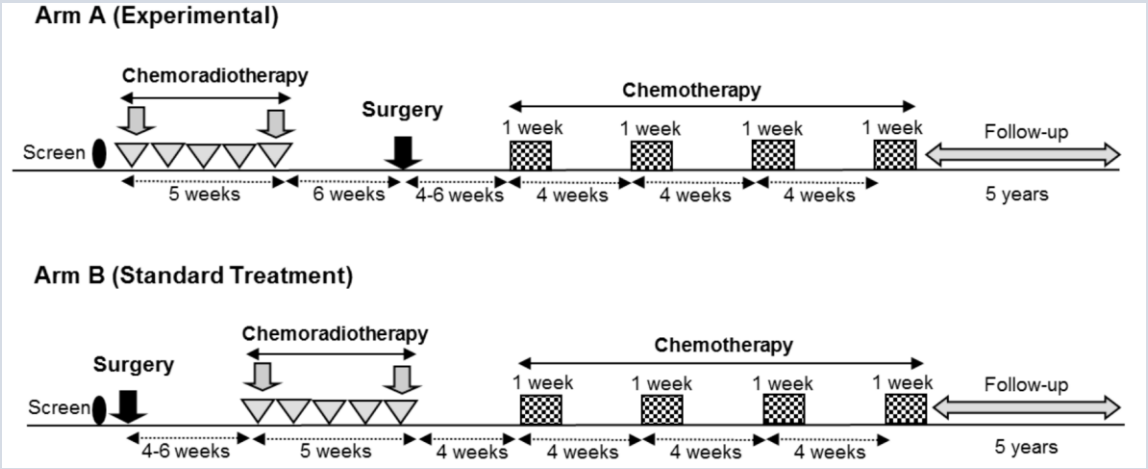
JOURNAL OF CLINICAL ONCOLOGY

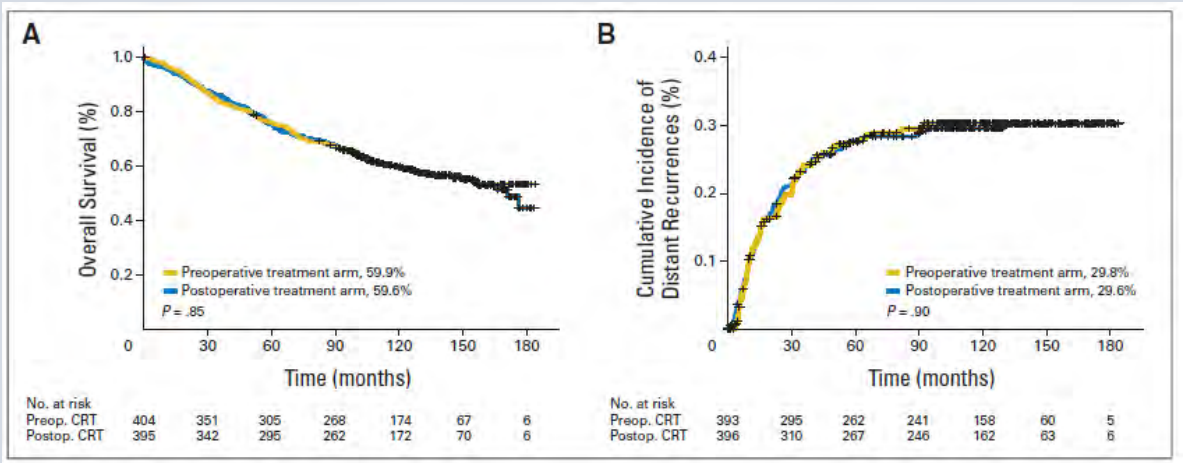
ORIGINAL REPORT

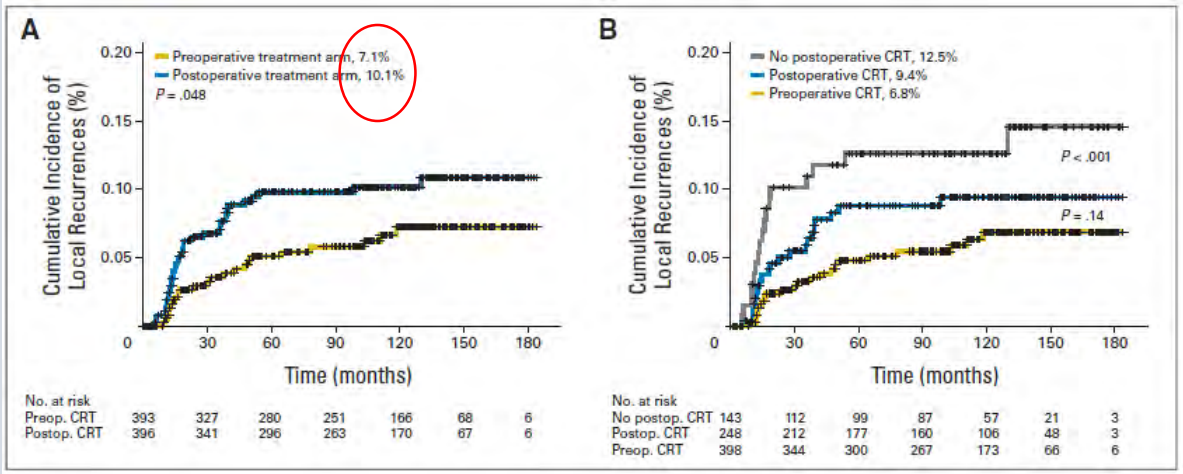
# Preoperative Versus Postoperative Chemoradiotherapy for Locally Advanced Rectal Cancer: Results of the German CAO/ARO/AIO-94 Randomized Phase III Trial After a Median Follow-Up of 11 Years

*Rolf Sauer, Torsten Liersch, Susanne Merkel, Rainer Fietkau, Werner Hohenberger, Clemens Hess, Heinz Becker, Hans-Rudolf Raab, Marie-Therese Villanueva, Helmut Witzigmann, Christian Wittekind, Tim Beissbarth, and Claus Rödel*



# Which rectal carcinomas should receive NAT?

- High / upper rectal carcinomas do not benefit from NAT
- Mid/low rectal carcinomas
  - Defined as distance from anal verge (<10 – 16 cm from anal verge)
  - Use of peritoneal reflection line insufficient
- Stage II
  - T3:  Not all T3 is the same
    - Distance of extension beyond muscularis propria in the axial plane is a prognostic factor.
      - T3a <1 mm, T3b 1-5 mm, T3c 5-15mm, T3d >15mm
      - T3a <or =5mm, T3b>5 mm
      - RCPA: Measurement of distance beyond muscularis propria
      - 'Early' cT3N0 rectal cancer (<1mm extension) is considered potentially suitable for surgery without neoadjuvant treatment.
  - T4
- Stage III
  - Nodal metastasis on pre-op imaging

# Short course RT vs Chemo-RT

- Short course:
  - 25 Gy delivered as daily 5 Gy fractions over 5 days
- Long course chemo-radiotherapy:
  - 50-50.4 Gy in 25 daily fractions, with continuous infusional 5 flurouracil (5-FU) or oral capecitabine.
- T3 rectal carcinoma:
  - No clear recurrence-free survival or overall survival benefits (SC-RT vs C-RT).
- Long-course chemoradiation is favoured:
  - Locally advanced or T4 disease (NCCN guidelines)
  - Total mesorectal excision plane is threatened

# The chemotherapeutic agents

- Neoadjuvant multiagent chemotherapy had an inferior overall survival compared with those who received neoadjuvant chemoradiotherapy
- Standard
  - Infusional 5-flurouracil (5-FU)
  - Capecitabine
- Under investigation
  - Oxaliplatin
  - Targeted therapies:
    - Bevacizumab:
      - MoAb: vascular endothelial growth factor.
      - Used in the treatment of metastatic colorectal cancer.
    - Panitumumab & Cetuximab:
      - MoAb: epidermal growth factor receptor.
      - Used in the treatment of metastatic colorectal cancer.
      - Wild-type K-ras.

# Time to surgery

- 6-8 weeks after completion of NAT.
- Pathological downstaging
- Patient recovery
- Greater delay →
  - Increase the risk of tumour regrowth
  - Metastatic potential
  - Surgical complications and challenges dt fibrosis and hypoxia

# Total mesorectal excision (TME)

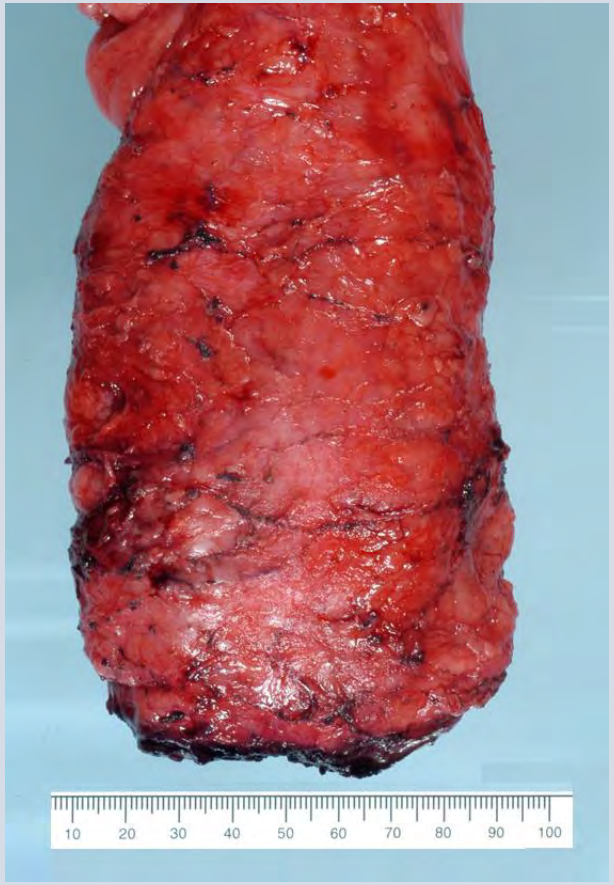
- Sharp dissection under direct vision, excision of the entire mesorectal envelope
- Challenging procedure
- Standard of therapy
  - 1986, Heald, 5 year local recurrence rate of 3.7%
  - 1998, Heald, local recurrence rate of 3% at five years and 4% and 10 years. Disease free survival was 80% at five years and 78% at 10 years.

THE LANCET, JUNE 28, 1986

Hospital Practice

**RECURRENCE AND SURVIVAL AFTER TOTAL MESORECTAL EXCISION FOR RECTAL CANCER**

R. J. HEALD R. D. H. RYALL




Intact mesorectum

# Watch and wait

- 10-20% of patient's show a complete pathological response at the time of surgery
  - However up to 1/3 of patients with a cCR may show residual viable tumour on pathological assessment
  - May be heterogenous and submucosal in location
- W&W: An investigational approach to patients who show a complete *clinical* response to chemoradiation.
- Assessment of response:
  - Endoscopy
  - Serum CEA
  - Imaging: CT, MRI & PET
- Higher risk of local recurrence
- Salvage surgery apparently shows similar rates of disease-free survival and overall survival as immediate surgery.

www.impactjournals.com/oncotarget/ Oncotarget, Vol. 7, No. 28

Review

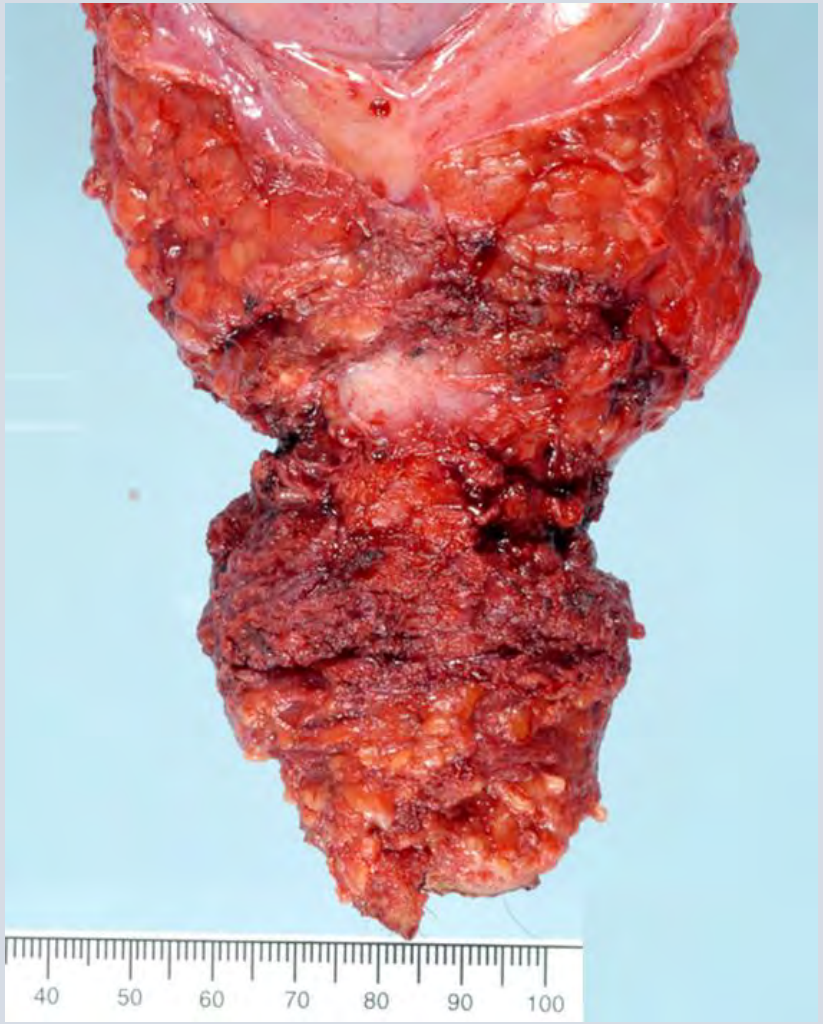
# Wait-and-see treatment strategies for rectal cancer patients with clinical complete response after neoadjuvant chemoradiotherapy: a systematic review and meta-analysis

Jun Li[1], Lunjin Li[2], Lin Yang[3], Jiatian Yuan[1], Bo Lv[1], Yanan Yao[4] and Shasha Xing[5]

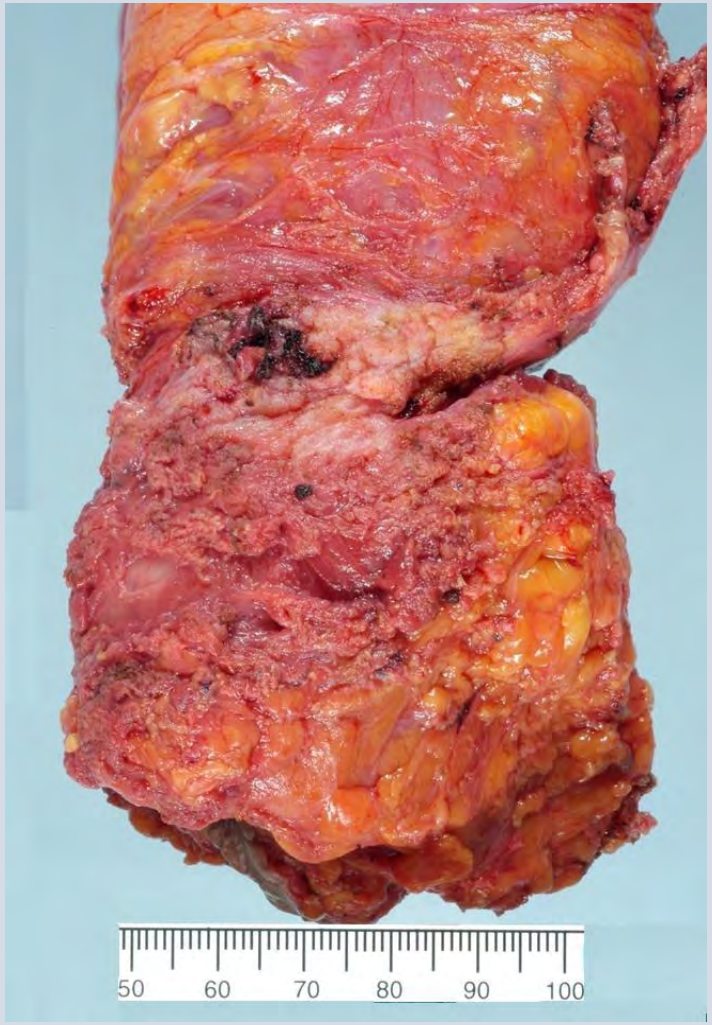
- Pooled data from 9 trials: 251 NAT & W&W / 344 NAT & radical surgery
- Local recurrence risk was significantly higher at 1, 2, 3, and 5 years among patients with clinical complete response to neoadjuvant therapy who underwent 'watch and wait' than those who underwent surger
- No significant difference in disease-free survival at 1, 2, 3 and 5 years
- No significant difference in overall survival at 1, 2, 3 and 5 years
- No significant difference in the rate of distant metastases at 1, 2, 3 or 5 year

# The role of the pathologist…

# Macroscopic assessment



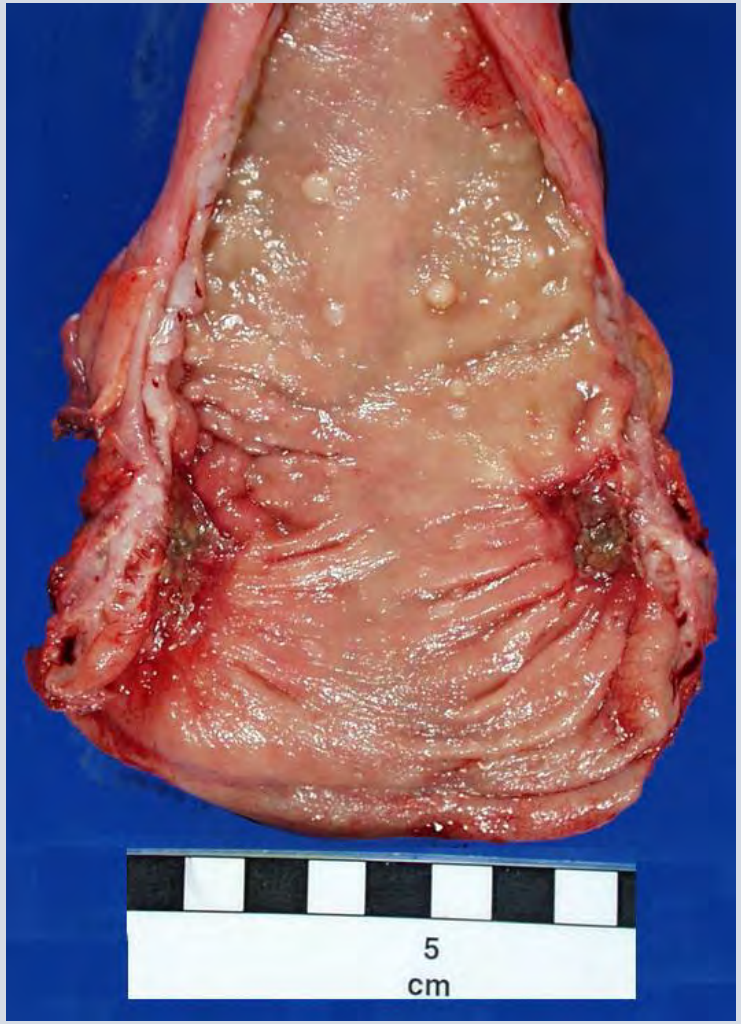

Fibrosis, irregular anterior mesorectum

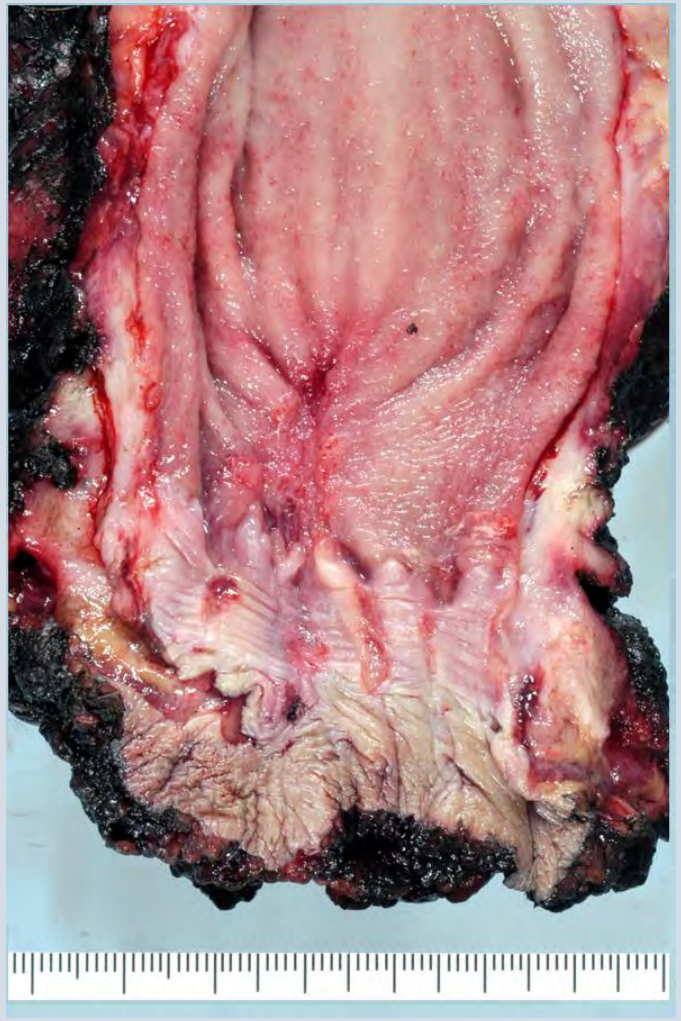



Irregular, incomplete mesorectum with perforation

- Received unopened
- Assessment of mesorectum:
  - Complete
  - Near complete
  - Incomplete
- Circumferential margin inked
- May shrink during fixation
- Margins – what is adequate
  - Positive circumferential margin: tumour within 1 mm
    - Increased local recurrence, distant metastasis, and decreased cancer specific survival
    - Direct continuity with the main tumour, tumour deposits discontinuous from the main tumour, or by tumour in veins, lymphatics or lymph nodes
  - 2cm has same outcome as 5 cm distal margin

# Assessment of mucosal surface

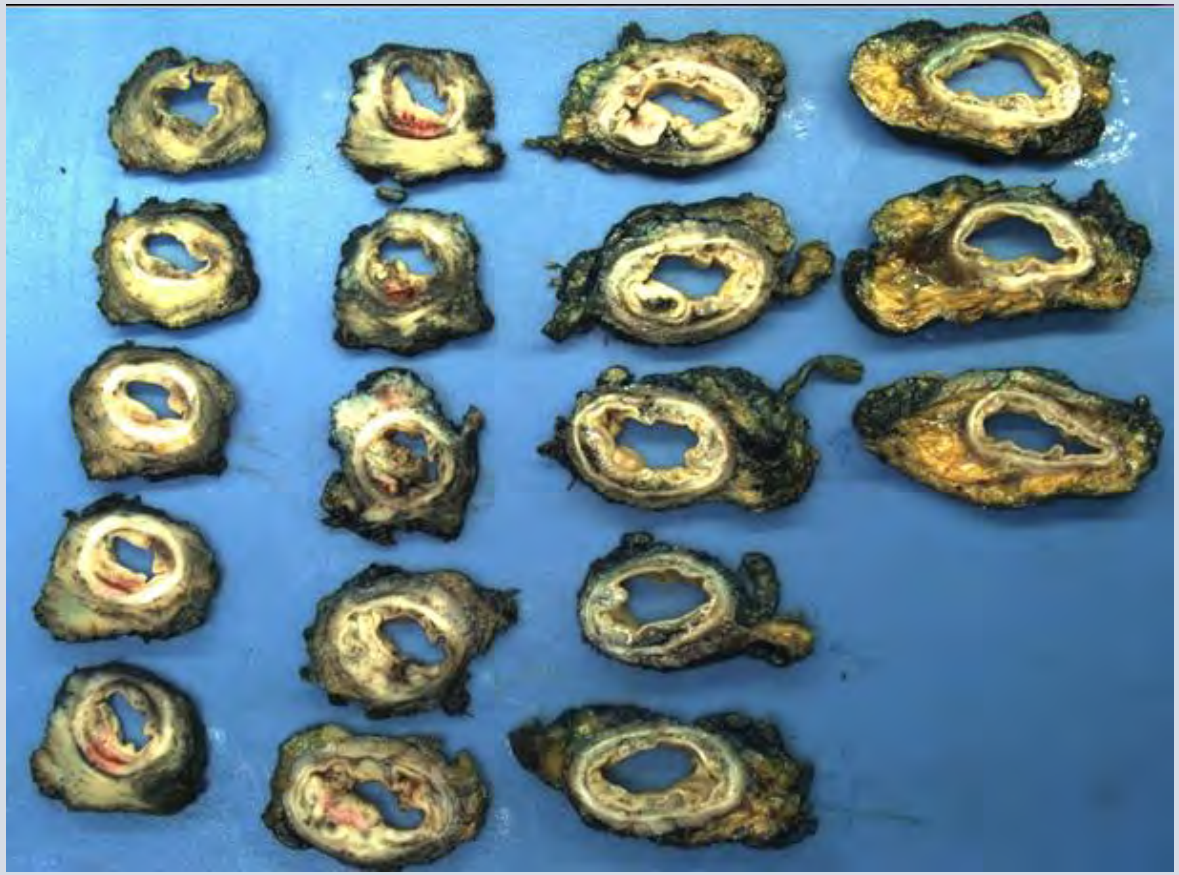


Rectal tumour after neo-adj treatment, no exophytic component but residual tumour deep to ulcer

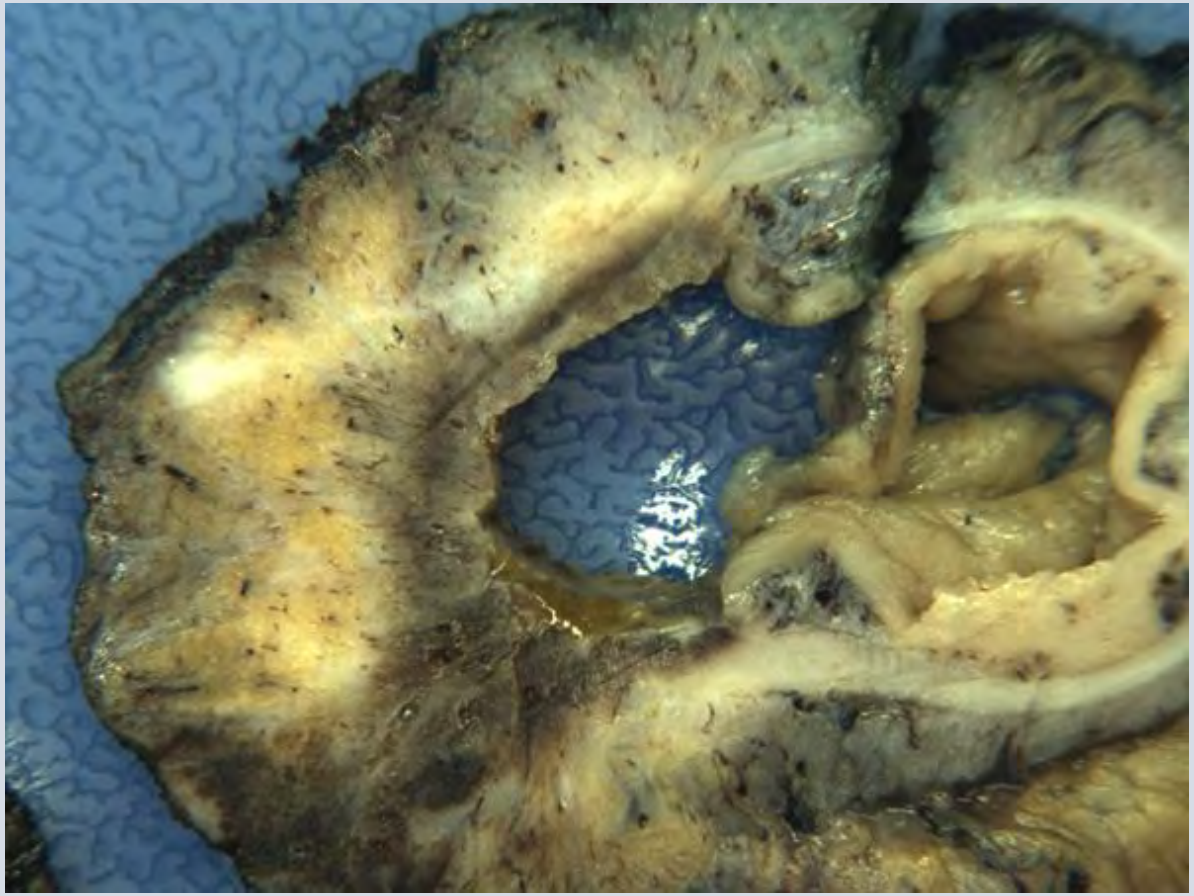
# Quirke method of sectioning

- Opened anteriorly, fixed for 48 hours (!)
- Slices cut from distal to proximal at 3-5 mm intervals and orientated as per MRI
- Extent of tumour
- Distance of the tumour to the circumferential resection margin (CRM)
- Extramural vascular invasion (stranding)
- Lymph nodes (and relationship to CRM)



# Block selection

- If less than 3 cm entirely embed the tumour bed
- Blocking of the whole area of abnormality may be required to confirm the presence of tumour.
- Lymph nodes:
  - Ideally 12,
  - If unable to obtain 12 lymph nodes, clearing of fat or additional blind sampling of the mesorectal fat.



# Histological assessment – post neoadjuvant

# Tumour assessment – post NAT

- Changes within malignant cells
  - Oncocytic cytoplasmic change
  - Vacuolisation
  - Nuclear atypia and multinucleate tumour cells
  - Mucin lakes or mucin pools in up to 30% of cases
- Grading – not performed in neoadjuvant setting
- Typing – may show neuroendocrine differentiation
- Depth of invasion
  - >5 mm beyond MP → poor prognosis

# Tumour regression

- Complete tumour regression →
  - Reduced local recurrence, metastases
  - Increased cancer-free and overall survival
- Partial regression is associated with intermediate survival
- Grading performed at the primary site (not in lymph nodes)
- Assessment of viability:
  - Exclude scars, fibrosis and acellular mucin
- According to some studies, tumour may be preferentially eradicated from the mucosa and submucosa, with residual viable tumour identified at the invasive front.

| **AJCC modification of Ryan grading** | | |
|---|---|---|
| **Grade** | | **Criteria** |
| 0 | Complete response | No viable cancer cells |
| 1 | Moderate response | Single cells or small groups of cancer cells |
| 2 | Minimal response | Residual cancer outgrown by fibrosis |
| 3 | Poor response | Minimal or no tumour kill; extensive residual cancer |

## Mandard grading

| Score | Appearances |
|---|---|
| 1 | Complete regression, Fibrosis without detectable tumour |
| 2 | Fibrosis with rare, scattered residual cancer cells |
| 3 | Fibrosis and tumour cells with a predominance of fibrosis |
| 4 | Fibrosis and tumour cells with a predominance of tumour cells |
| 5 | No changes of regression |

## Modified rectal cancer regression grade

| Score | Residual carcinoma |
|---|---|
| 1 | No tumour cells or scattered foci occupying < 5% of overall area of abnormality |
| 2 | Combination of viable tumour cells and fibrosis (5–50% of the overall area of abnormality) |
| 3 | More than 50% of the area of abnormality comprises malignant epithelium |

## College of American Pathologists grading

| Score | | Residual carcinoma |
|---|---|---|
| 0 | Complete response | No viable cancer cells |
| 1 | Near complete response | Single or rare groups of cancer cells |
| 2 | Partial response | Residual cancer with evident tumour regression, but more than single cells or rare groups of cancer cells |
| 3 | Poor or no response | Extensive residual cancer with no evident tumour regression |

## Becker grading

| Score | Residual carcinoma |
|---|---|
| 1 | 0% |
| 2 | 1-10% |
| 3 | 11-50% |
| 4 | >50% |

## Ryan grading

| Score | Residual carcinoma |
|---|---|
| 1 | Complete regression or only microscopic foci of adenocarcinoma remaining, with marked fibrosis |
| 2 | Increased number of cancer cells but fibrosis still predominates |
| 3 | Absence of regressive change or residual cancer out growing fibrosis |

## Rodel grading

| Score | Residual carcinoma |
|---|---|
| 0 | No regression |
| 1 | Regression of <25 % of tumour mass |
| 2 | Regression of 25-50 % of tumour mass |
| 3 | Regression of >50 % of tumour mass |
| 4 | Complete regression |

## Dworak grading

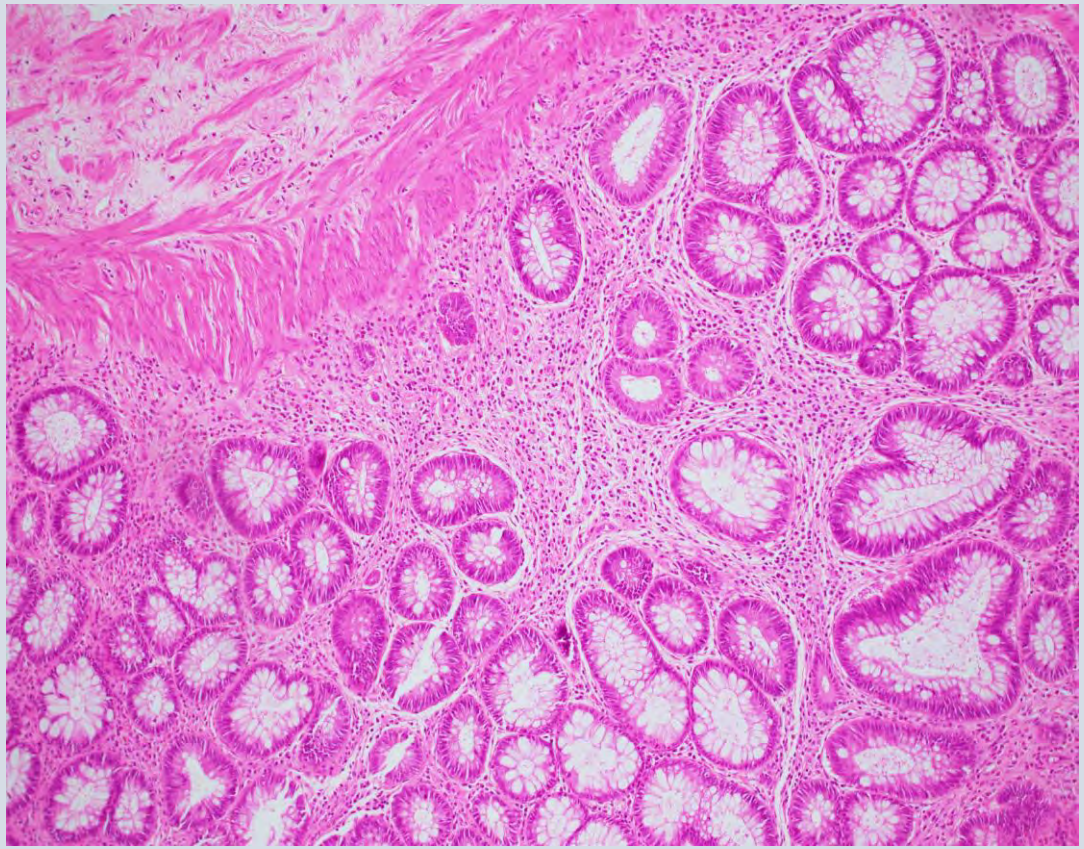
| Score | Residual carcinoma |
|---|---|
| 0 | No regression |
| 1 | Dominant tumour ass with obvious fibrosis and/or vasculopathy |
| 2 | Dominantly fibrotic changes with few tumour cells or groups (easy to find) |
| 3 | Very few tumour cells in fibrotic tissue with or without mucous substance |
| 4 | No tumour cells, only fibrotic mass (total regression) |

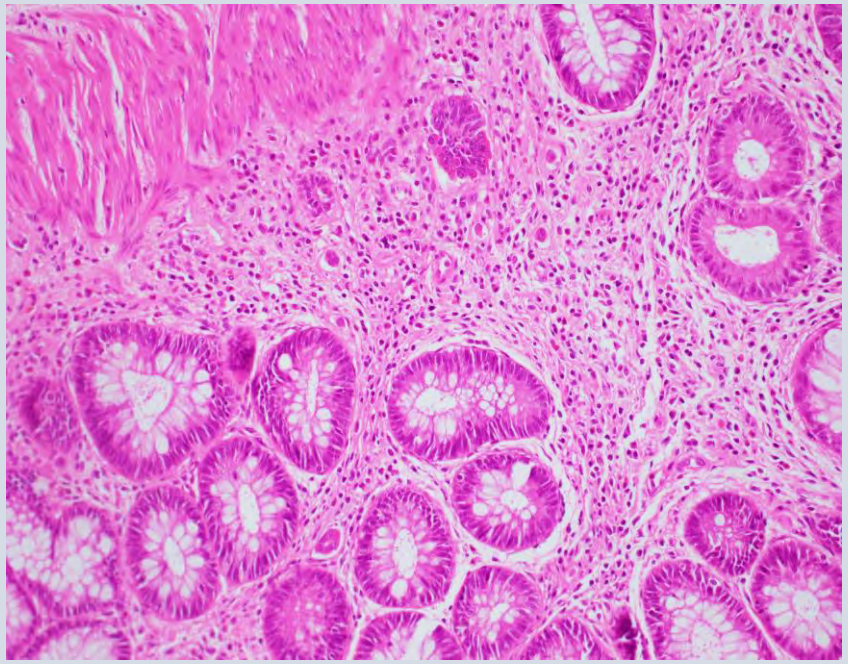
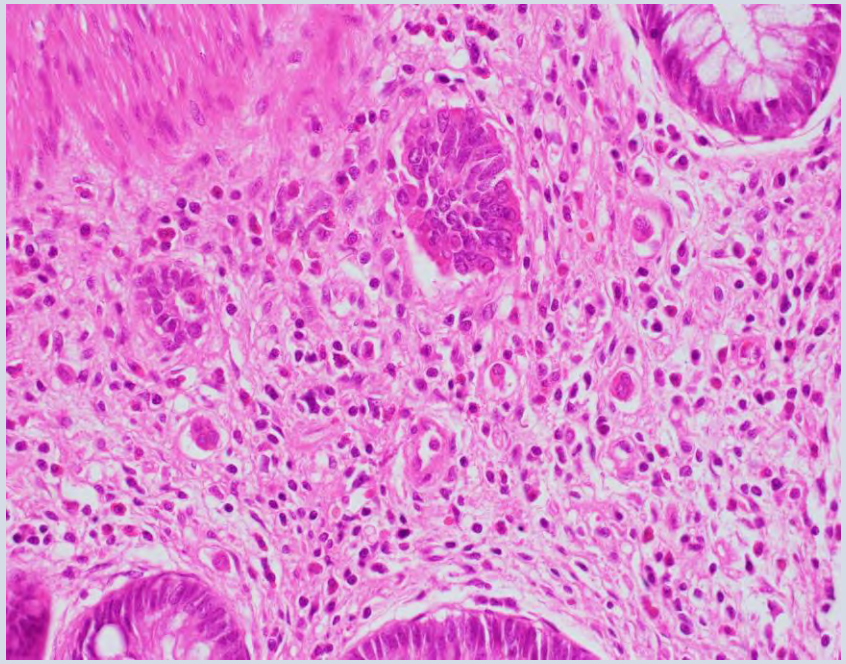
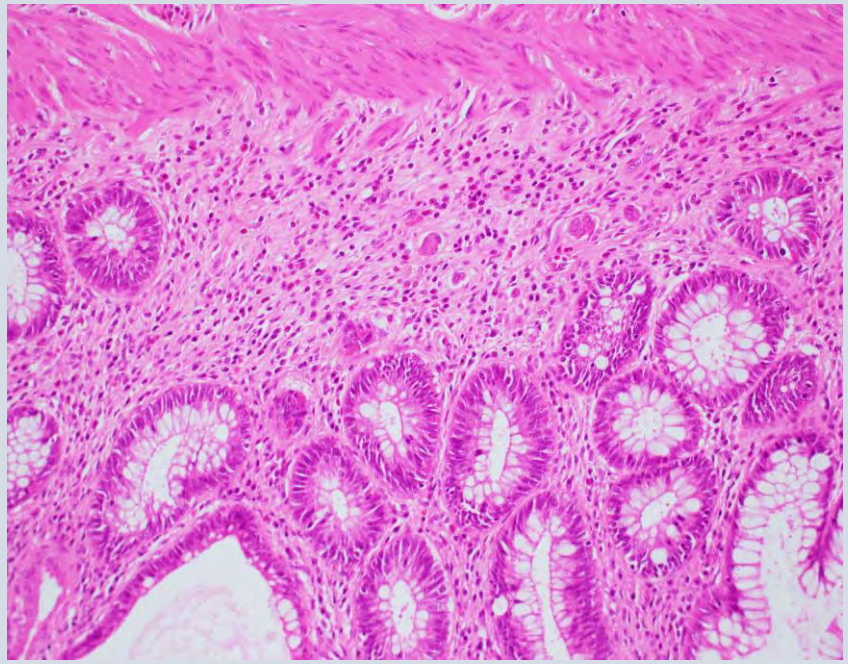
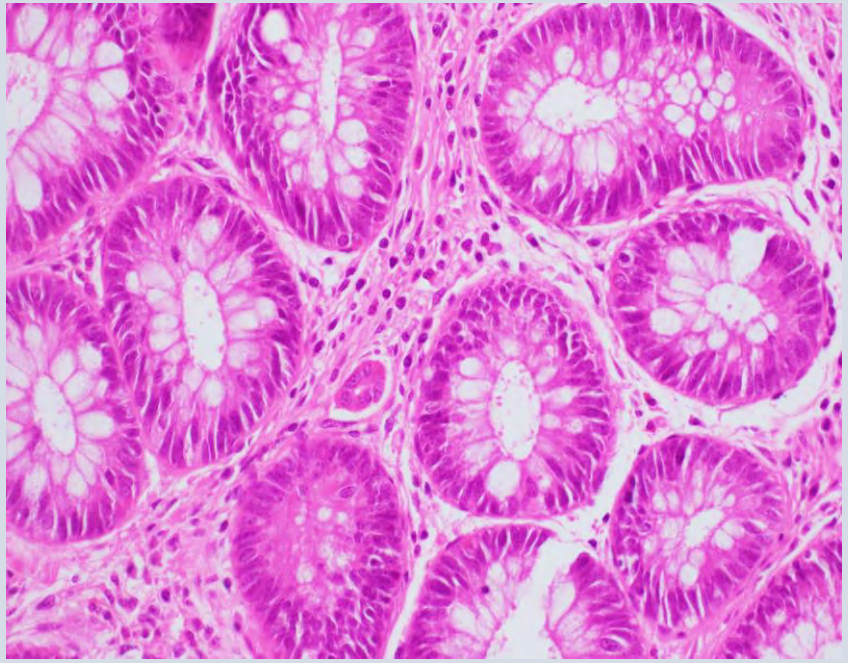
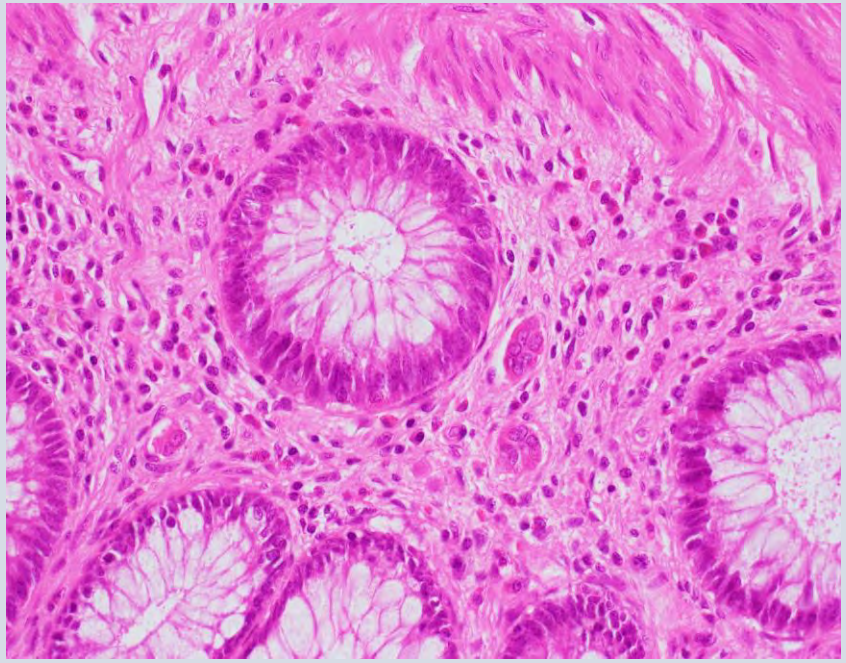
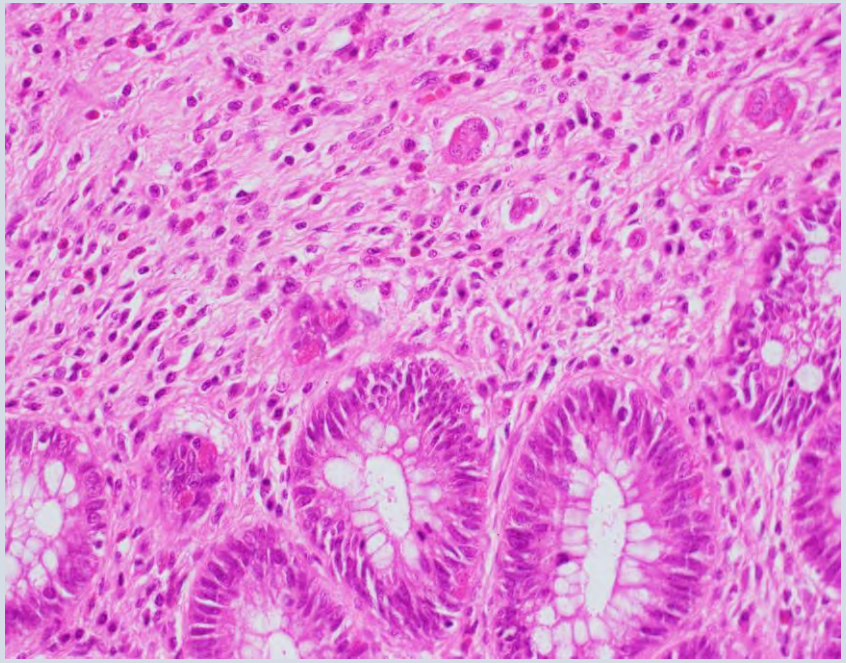
# Histological alterations – stroma

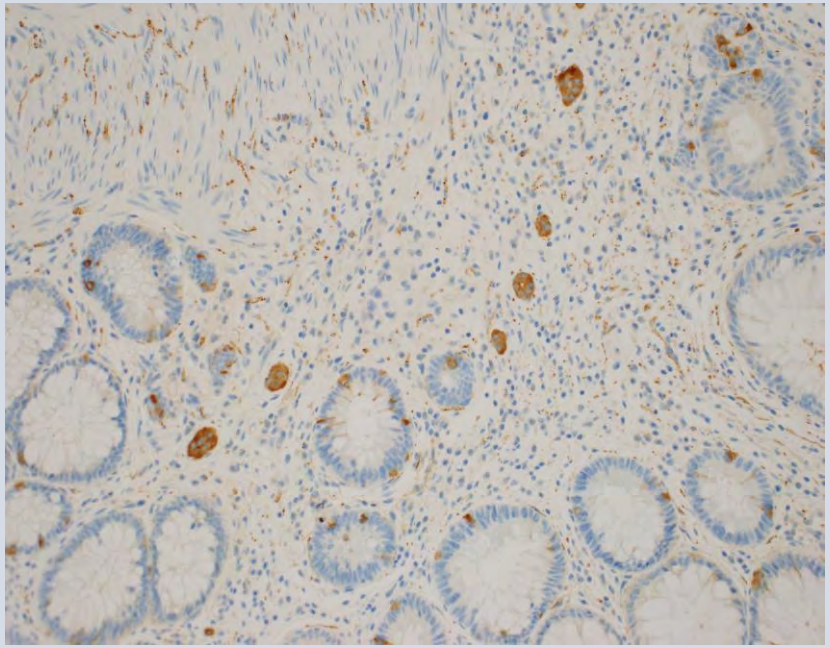
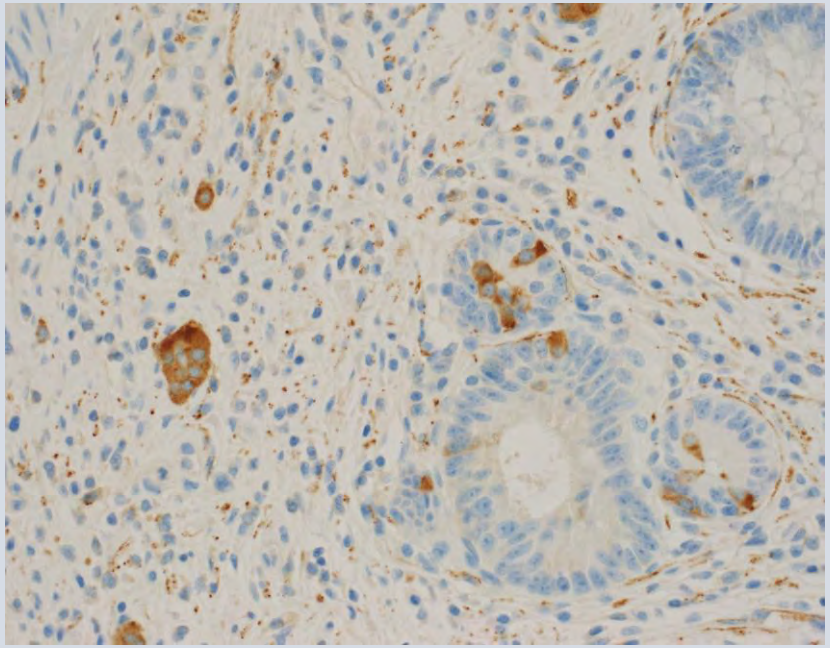
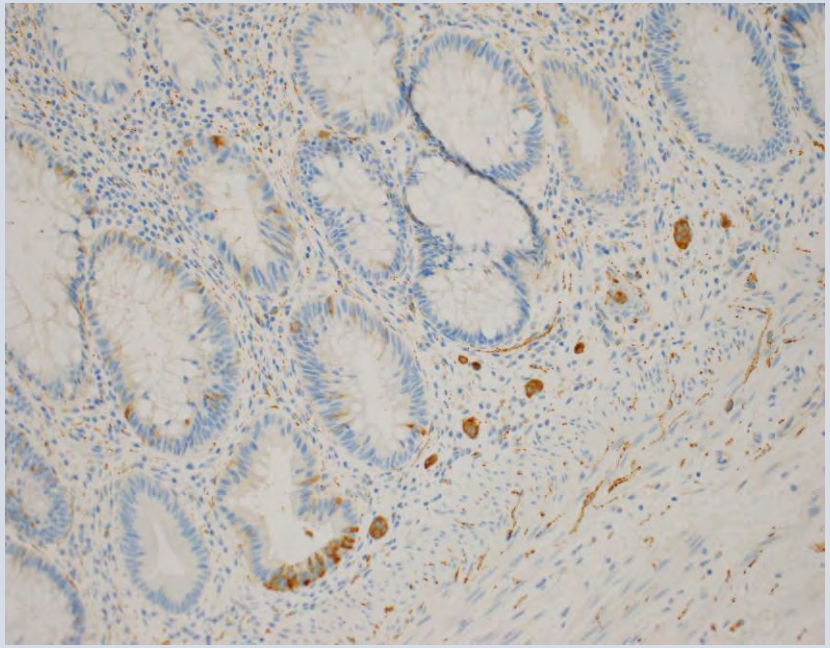
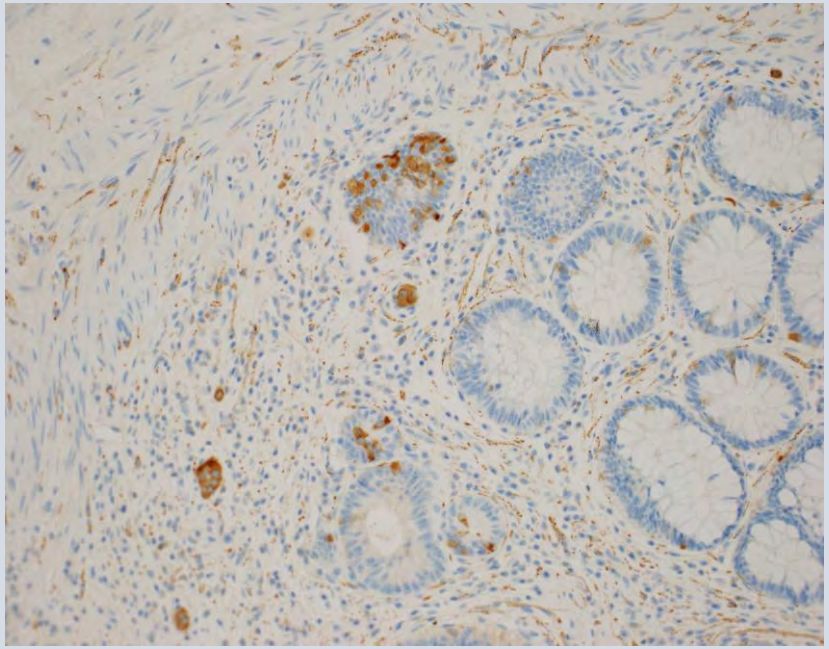
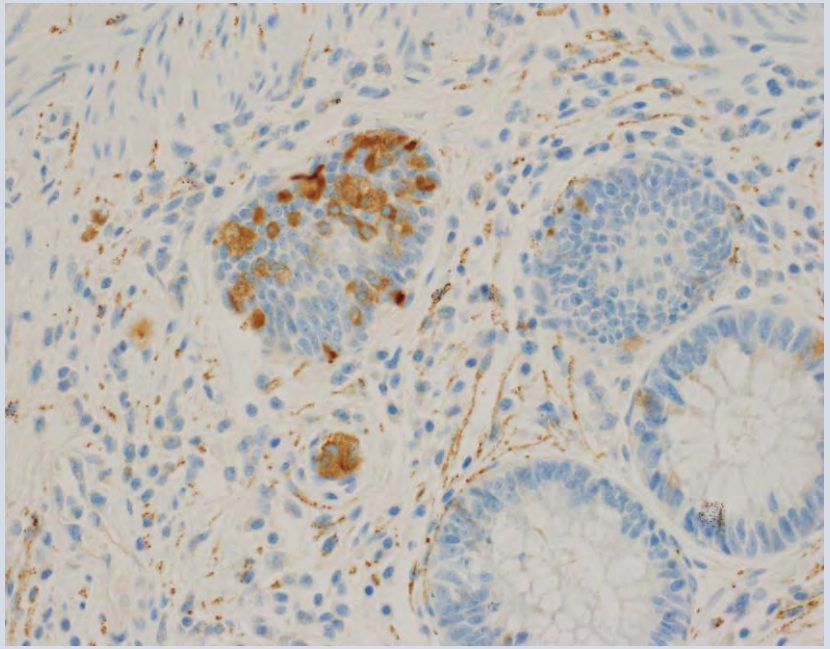
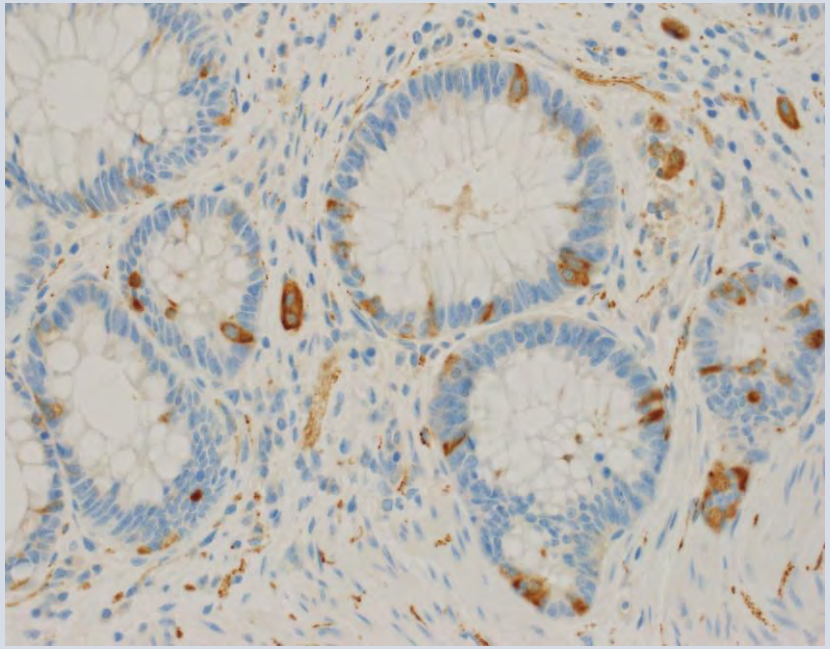
- Vascular
  - Endothelial atypia
  - Intimal hyalinisation
  - Telangiectasia
  - Organising thrombi
- Stromal
  - Fibrosis
  - Haemorrhage +/- haemosiderin deposition
  - Bizarre fibroblasts
  - Histiocytic infiltration

# Histological alterations – background mucosa

- Apoptosis
- Hyperchromasia
- Pleomorphism
- Neuroendocrine hyperplasia

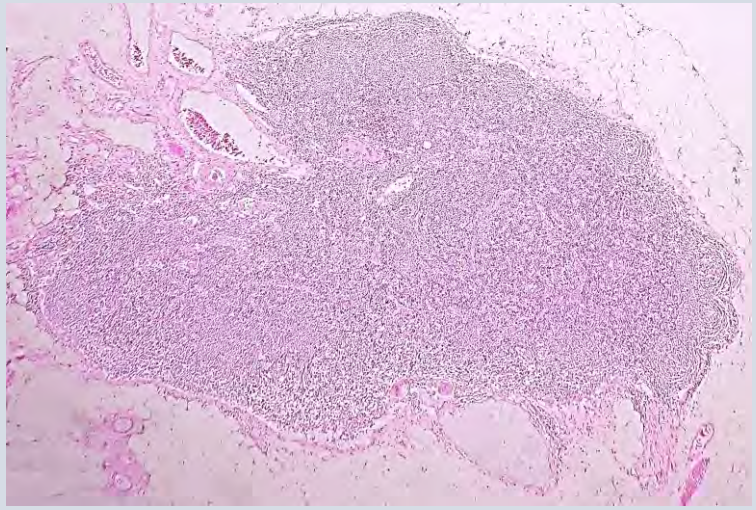


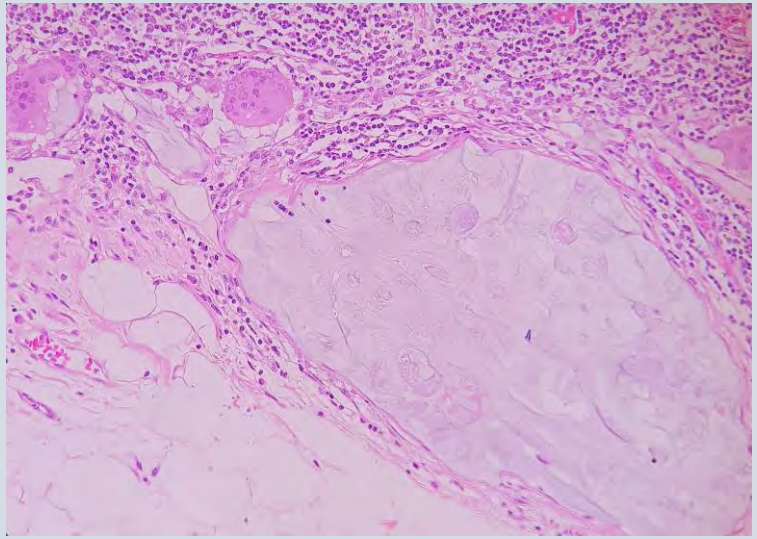







# Lymph nodes

- Minimum number:
  - AJCC: 12
  - Increased nodes have been shown to correspond to a better prognosis, regardless of status
  - Fewer nodes may be associated with increased risk of understaging
  - 12 lymph nodes are not always found in the neoadjuvant setting
- Fibrosis
- Mucin pools
- Residual viable tumour:
  - micrometastases did not impact survival
  - macrometastes (> 0.2 cm) reduced disease-free and overall survival





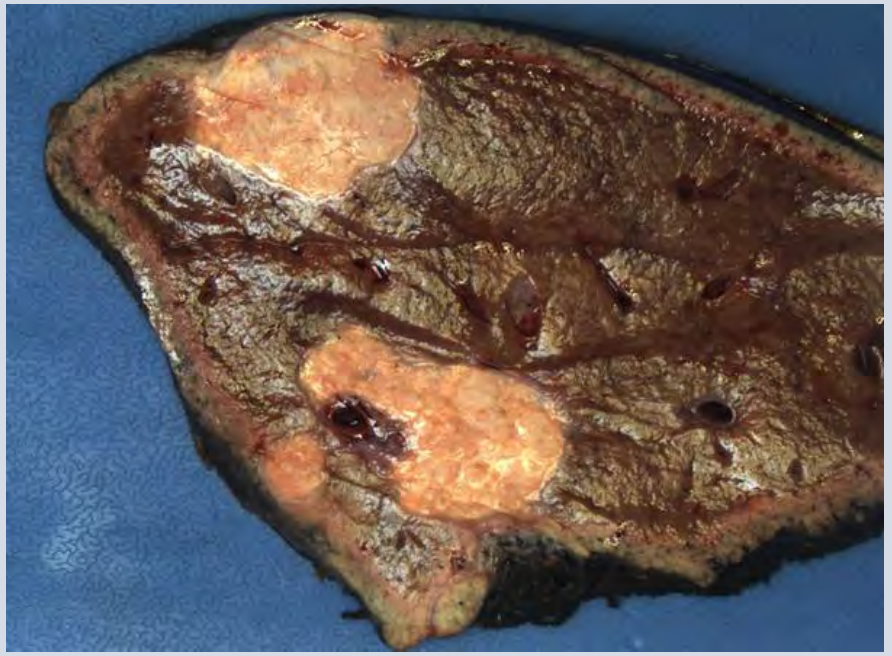
# Liver metastases

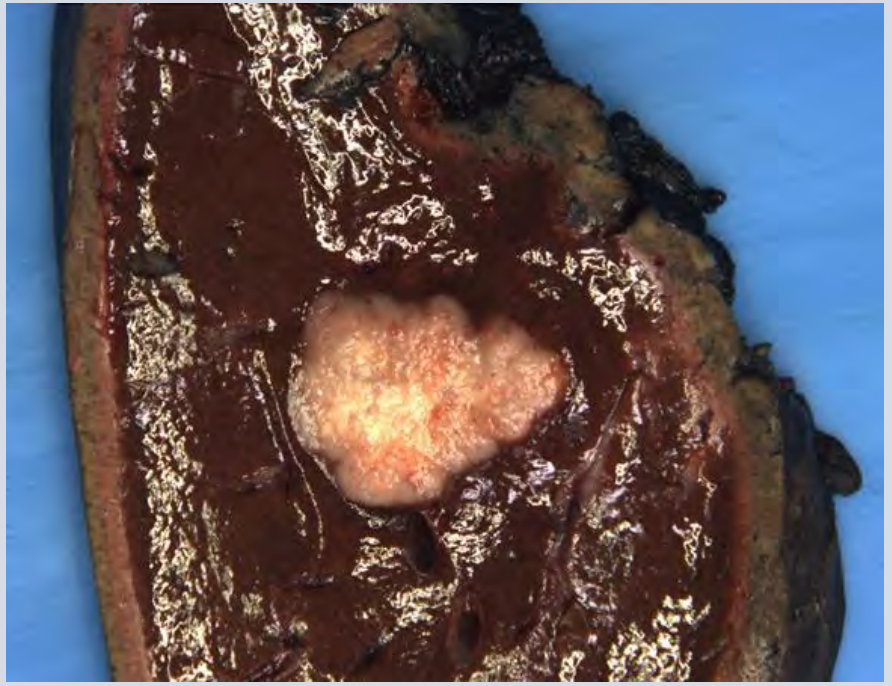
# Liver metastases in colorectal carcinoma

- 50% of patients with CRC
- Resection of liver mets 46-58% 5 year survival

# Macroscopic assessment

- Number of nodules: >4 → worse prognosis
- Size of nodule: > 5 cm → worse prognosis
- Completely embed:
  - Tumours measuring ≤15 mm
  - Nodules with complete pathological response to neoadjuvant chemotherapy
- Partially sample (1 block / 5-10mm):
  - >15 mm
- Increased fibrosis corresponds with response
- Sections from the central and peripheral areas
- Margin assessment
  - Margin only considered positive with tumour on ink
  - >1cm → better prognosis





# Microscopic assessment

- Prognostic factors:
  - Tumour regression grading
  - Invasion of local structures
    - Portal vein
    - Bile duct
    - Hepatic vein
    - Lymphatic
    - Perineural
  - Tumour pseudocapsule
  - Margins
  - Mucinous pattern
  - Tumour growth pattern
    - Infiltrative vs pushing
  - Pathological response to neoadjuvant chemotherapy.
- Background hepatic parenchyma
  - steatosis, steatohepatitis,
  - Sinusoidal dilatation, sinusoidal obstructive syndrome
  - Nodular regenerative hyperplasia
  - Fibrosis: Perivenular / Perisinusoidal

**Table 3.** Protocol for the examination of colorectal liver metastasis specimens

Specimen type:

- ☐ Noduletomy
- ☐ Segmentectomy
- ☐ Lobectomy

Number and location of liver metastases:

Tumour size:

- Greatest dimension: _____ mm

Blood vessel invasion (portal invasion)

- ☐ Not identified
- ☐ Present

Lymphatic invasion

- ☐ Not identified
- ☐ Present

Tumour growth pattern

- ☐ Infiltrative
- ☐ Pushing

Tumour pseudocapsule

- ☐ Not identified
- ☐ Present—measureof maximum thickness: __ mm

Mucinous pattern (mucinous differentiation)

- ☐ Not identified
- ☐ Present: ___% of section area

Treatment effect (applicable to carcinomas treated with neoadjuvant therapy)

- Percentage of viable cancer cells: __%
- Percentage of necrosis: __%
- Percentage of fibrosis: __%
- Percentage of acellular mucin (mucin pool):__%

Margins

- ☐ Margins are uninvolved by invasive carcinoma. Distance of invasive carcinoma from nearest margin (specify which margin): _____ mm
- ☐ Margins involved by invasive carcinoma (grossly, microscopically)

Background liver: _____

Additional information (for example: lymphnodes, if present; invasion of adjacent organs, such asdiaphragm and adrenals, among others)

*Histopathology* 2018, **72**, 377–390. DOI: 10.1111/his.13378

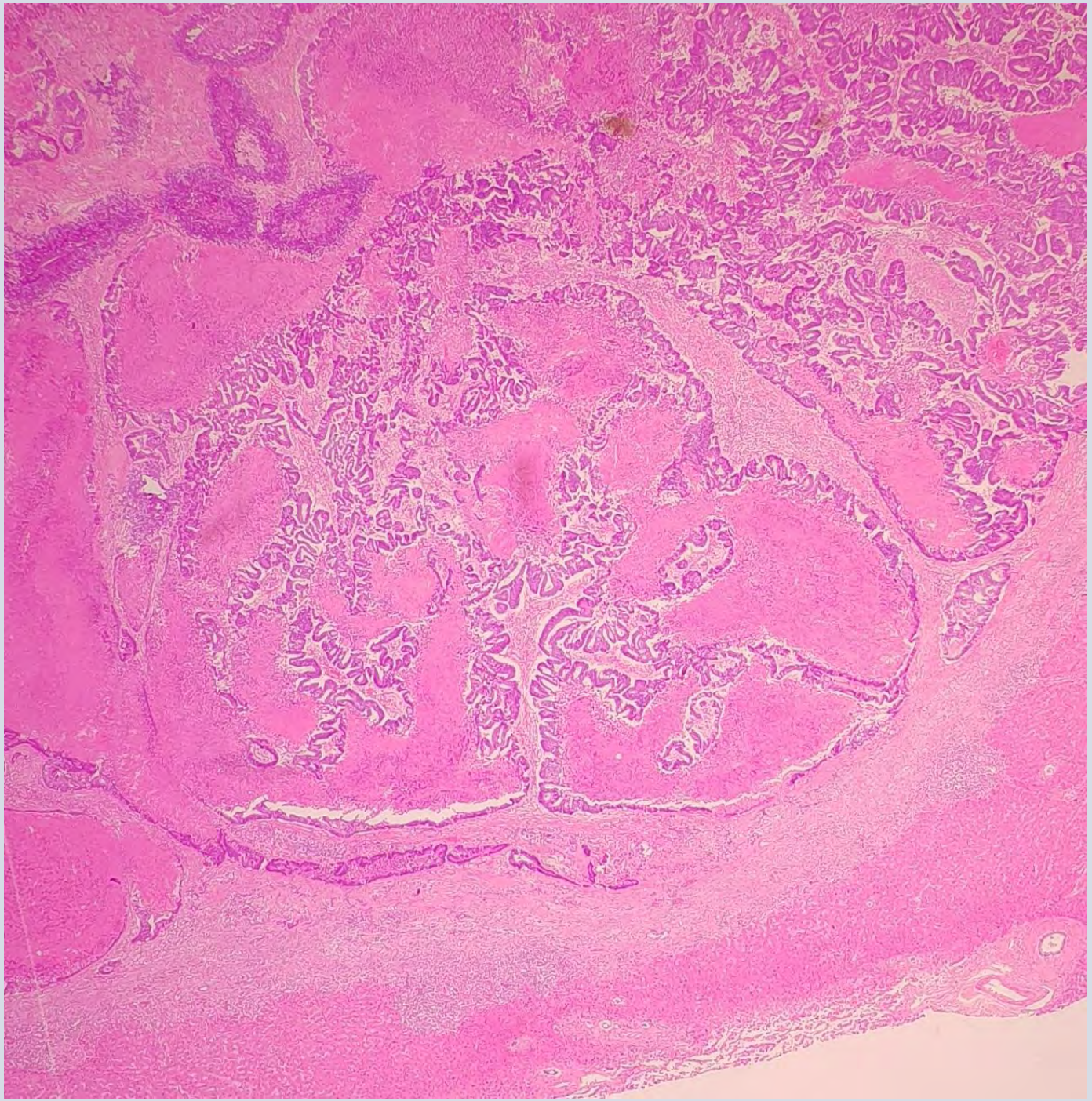
REVIEW

## Pathological factors and prognosis of resected liver metastases of colorectal carcinoma: implications and proposal for a pathological reporting protocol

Gilton M Fonseca,[1] Paulo Herman,[1] Sheila F Faraj,[2] Jaime A P Kruger,[1] Fabricio F Coelho,[1] Vagner B Jeismann,[1] Ivan Cecconello,[1] Venancio A F Alves,[2] Timothy M Pawlik[3] & Evandro S de Mello[2]

[1]*Digestive Surgery Division, Department of Gastroenterology, University of São Paulo Medical School, São Paulo, Brazil,* [2]*Department of Pathology, São Paulo State Cancer Institute, University of São Paulo Medical School, São Paulo, Brazil, and* [3]*Department of Surgery, The Ohio State University, Wexner Medical Center, Columbus, OH, USA*

Fonseca G M, Herman P, Faraj S F, Kruger J A P, Coelho F F, Jeismann V B, Cecconello I, Alves V A F, Pawlik T M & de Mello E S
(2018) *Histopathology* **72**, 377–390. https://doi.org/10.1111/his.13378



| Rubbia-Brandt regression grading | |
|---|---|
| **Score** | **Features** |
| Major response | Fibrosis without detectable tumour<br>Fibrosis with rare scattered tumour cells |
| Minor response | Fibrosis and tumour cells with > fibrosis |
| No response | Fibrosis and tumour cells with > tumour cells<br>No changes of fibrosis |

| Blazer regression grading | |
|---|---|
| **Score** | **Features** |
| Complete | No residual tumour |
| Major response | 1-50% residual carcinoma |
| Minor response | >50% residual carcinoma |

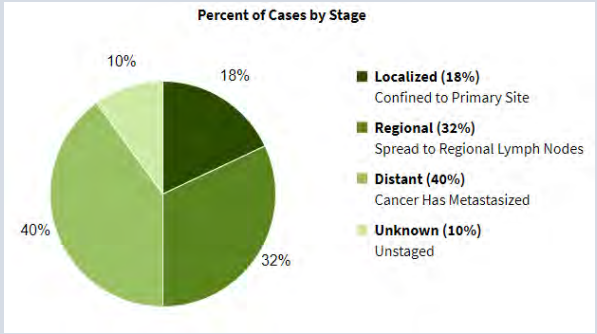
# Oesophageal carcinoma

Both squamous and adenocarcinoma

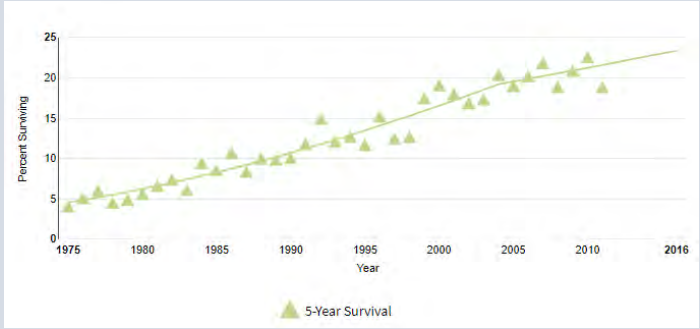
# Oesophageal carcinoma

- *Issues in the statistics and trials, which often combine SCC and AdCa*
- SEER data (US) in 2019 :
  - Estimated new cases: 17650 (1%)
  - Estimated deaths: 16,080 (2.6%)

| | Common Types of Cancer | Estimated New Cases 2019 | Estimated Deaths 2019 |
|---|---|---|---|
| 1. | Breast Cancer (Female) | 268,600 | 41,760 |
| 2. | Lung and Bronchus Cancer | 228,150 | 142,670 |
| 3. | Prostate Cancer | 174,650 | 31,620 |
| 4. | Colorectal Cancer | 145,600 | 51,020 |
| 5. | Melanoma of the Skin | 96,480 | 7,230 |
| 6. | Bladder Cancer | 80,470 | 17,670 |
| 7. | Non-Hodgkin Lymphoma | 74,200 | 19,970 |
| 8. | Kidney and Renal Pelvis Cancer | 73,820 | 14,770 |
| 9. | Uterine Cancer | 61,880 | 12,160 |
| 10. | Leukemia | 61,780 | 22,840 |
| | - | - | - |
| **18.** | **Esophageal Cancer** | **17,650** | **16,080** |







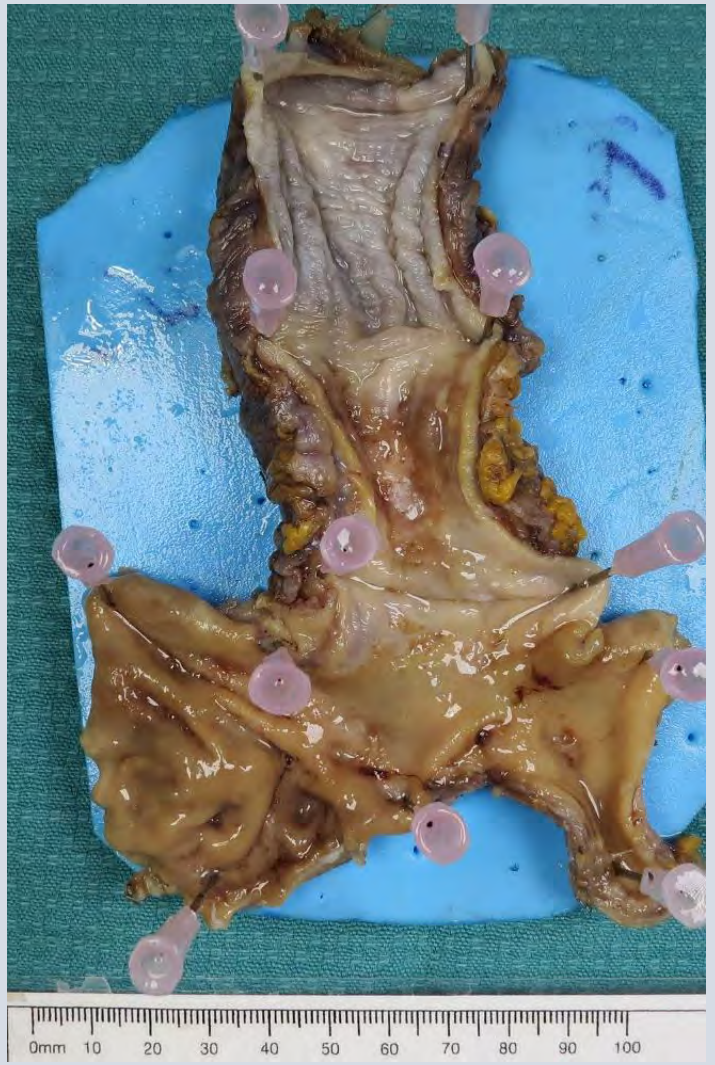

SEER Cancer Stat Facts: Esophageal Cancer. National Cancer Institute. Bethesda, MD,

# The role of neoadjuvant therapy in oesophageal carcinoma

- Neoadjuvant chemoradiotherapy is used in T2 N1 adenocarcinoma

# Macroscopic assessment post-NAT

- Shrinkage or complete loss of macroscopic abnormality
- Localised sampling: Clinical and imaging
- Following slicing, thickening or fibrosis in the submucosa and muscularis propria
- If no carcinoma is → three further levels of each block.
- If there is still no carcinoma found, embedding of the whole site is required before a complete response to neoadjuvant therapy can be reported.
- Lymph nodes:
  - Ideally 15



# Microscopic changes in Adenocarcinoma

- Changes within tumour:
  - Oncocytic cytoplasmic change
  - Vacuolisation
  - Nuclear atypia and multinucleate tumour cells
  - Mucin lakes or mucin pools in up to 10-20% of cases
    - often limited to cases with mucinous or signet ring differentiation on prior biopsy
    - Acellular mucin at radial margins has not been associated with recurrence or metastasis
- Other prognostic factors
  - Staging
  - Presence of signet ring morphology

# Microscopic changes in squamous cell carcinoma

- Degenerative changes in squamous cells:
  - Acellular keratinocytes
  - Ghost cells
- Background changes in benign cells, hampering histological assessment:
  - Squamous metaplasia within oesophageal submucosal glands
    - Clues: rounded groups without desmoplastic stromal response

# Tumour regressing grading

- Should only be performed on the tumour bed, not in the lymph nodes
- Many proposed grading systems

| College of American Pathologists 2015 grading | | |
|---|---|---|
| **Score** | | **Residual carcinoma** |
| 0 | Complete response | No viable cancer cells |
| 1 | Near complete response | Single or rare groups of cancer cells |
| 2 | Partial response | Residual cancer with evident tumour regression, but more than single cells or rare groups of cancer cells |
| 3 | Poor or no response | Extensive residual cancer with no evident tumour regression |

| Mandard grading | |
|---|---|
| **Score** | **Appearances** |
| 1 | Complete regression<br>Fibrosis without detectable tumour |
| 2 | Fibrosis with rare, scattered residual cancer cells |
| 3 | Fibrosis and tumour cells with a predominance of fibrosis |
| 4 | Fibrosis and tumour cells with a predominance of tumour cells |
| 5 | No changes of regression |

| Becker and Chirieac grading | |
|---|---|
| **Score** | **Residual carcinoma** |
| 1 | 0% |
| 2 | 1-10% |
| 3 | 11-50% |
| 4 | >50% |

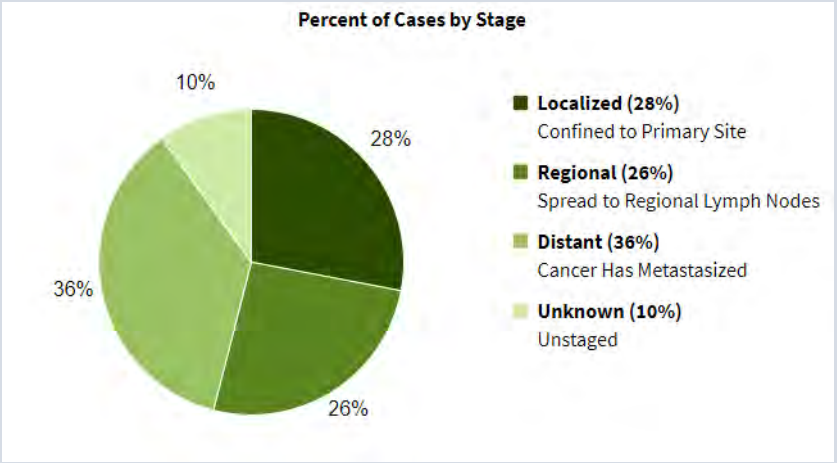
| Wu grading | |
|---|---|
| **Score** | **Residual carcinoma** |
| 0 | 0% |
| 1 | 1-50% |
| 2 | >50% |

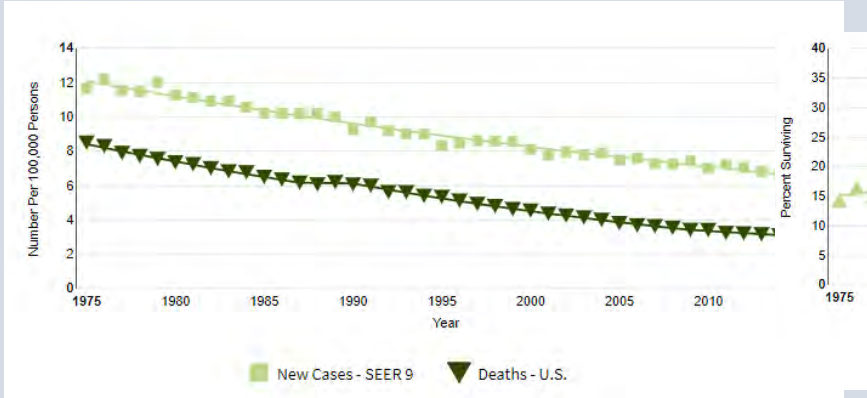
# Gastric

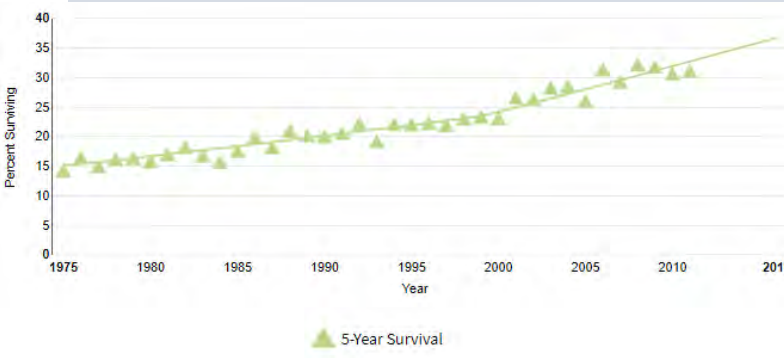
# Gastric carcinoma

- SEER data (US) in 2019 :
  - Estimated New Cases: 27,510 (1.6%)
  - Estimated Deaths: 11,140 (1.8%)

| | Common Types of Cancer | Estimated New Cases 2019 | Estimated Deaths 2019 |
|---|---|---|---|
| 1. | Breast Cancer (Female) | 268,600 | 41,760 |
| 2. | Lung and Bronchus Cancer | 228,150 | 142,670 |
| 3. | Prostate Cancer | 174,650 | 31,620 |
| 4. | Colorectal Cancer | 145,600 | 51,020 |
| 5. | Melanoma of the Skin | 96,480 | 7,230 |
| 6. | Bladder Cancer | 80,470 | 17,670 |
| 7. | Non-Hodgkin Lymphoma | 74,200 | 19,970 |
| 8. | Kidney and Renal Pelvis Cancer | 73,820 | 14,770 |
| 9. | Uterine Cancer | 61,880 | 12,160 |
| 10. | Leukemia | 61,780 | 22,840 |
| | - | - | - |
| **15.** | **Stomach Cancer** | **27,510** | **11,140** |




SEER Cancer Stat Facts: Stomach Cancer. National Cancer Institute. Bethesda, MD,

# Rationale for neoadjuvant therapy

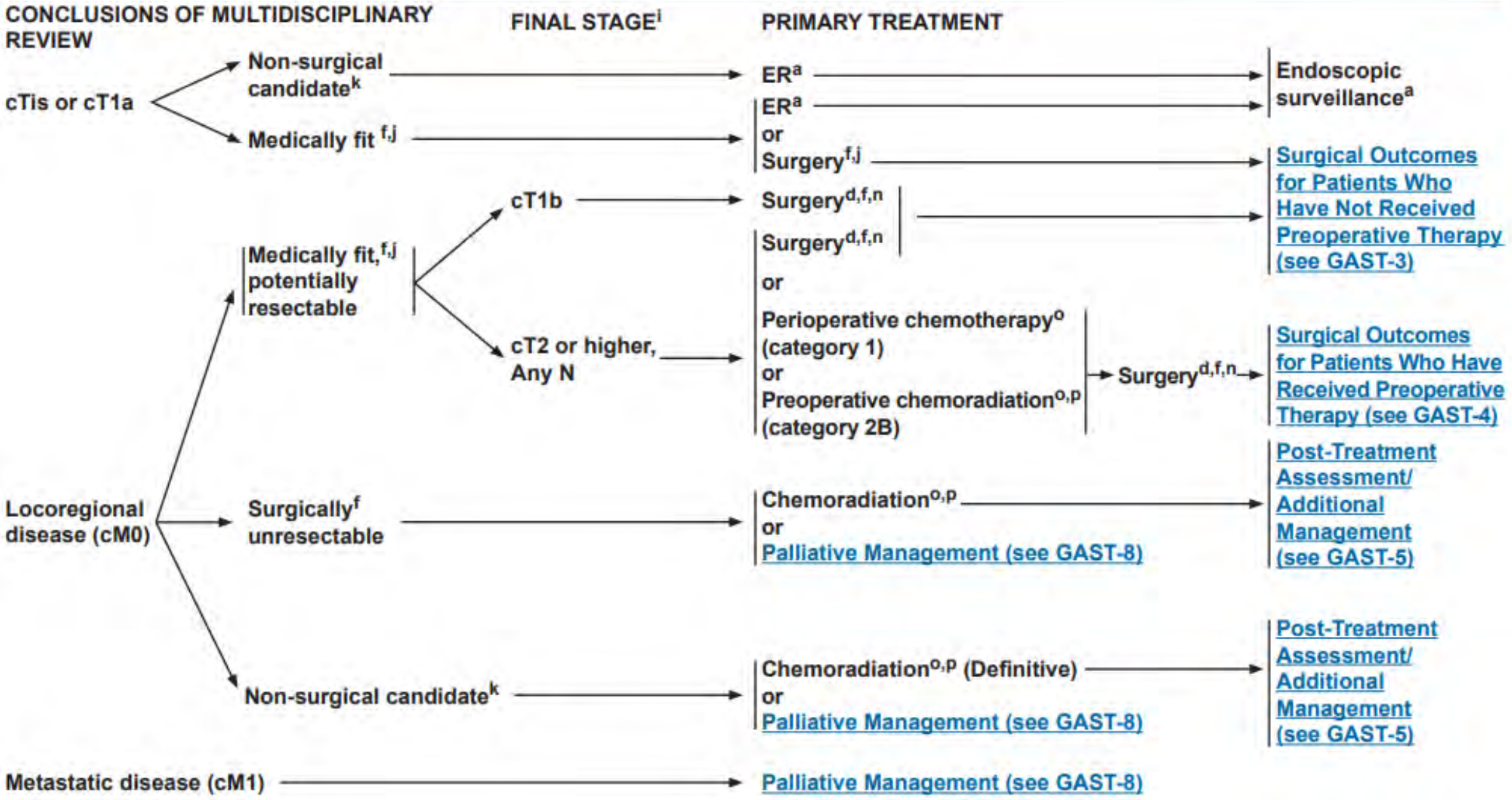
- Neoadjuvant therapy leads to:
  - 24% reduction in death
  - Increased R0 resection rates
  - Reduced risk of recurrence (34% vs 19%)
- Pathological response and tumour regression corresponds to survival
- May be delivered via two protocols:
  - Peri-operative therapy
  - Preoperative therapy

**Perioperative Chemotherapy**
(3 cycles preoperative and 3 cycles postoperative):
- Fluorouracil and cisplatin (category 1)[1]
- Fluoropyrimidine and oxaliplatin*
- ECF (epirubicin, cisplatin, and fluorouracil) (category 2B)[2]
- ECF modifications (category 2B)[3,4]
  - Epirubicin, oxaliplatin, and fluorouracil
  - Epirubicin, cisplatin, and capecitabine
  - Epirubicin, oxaliplatin, and capecitabine

**Preoperative Chemoradiation**
- Infusional 5-FU can be replaced with capecitabine
- Preferred Regimens:
  - Paclitaxel and carboplatin (category 1)[5]
  - Fluorouracil and cisplatin (category 1)[6,7]
  - Fluorouracil† and oxaliplatin (category 1)[8,9]
- Other Regimens:
  - Paclitaxel and fluoropyrimidine (fluorouracil or capecitabine)[10] (category 2B)

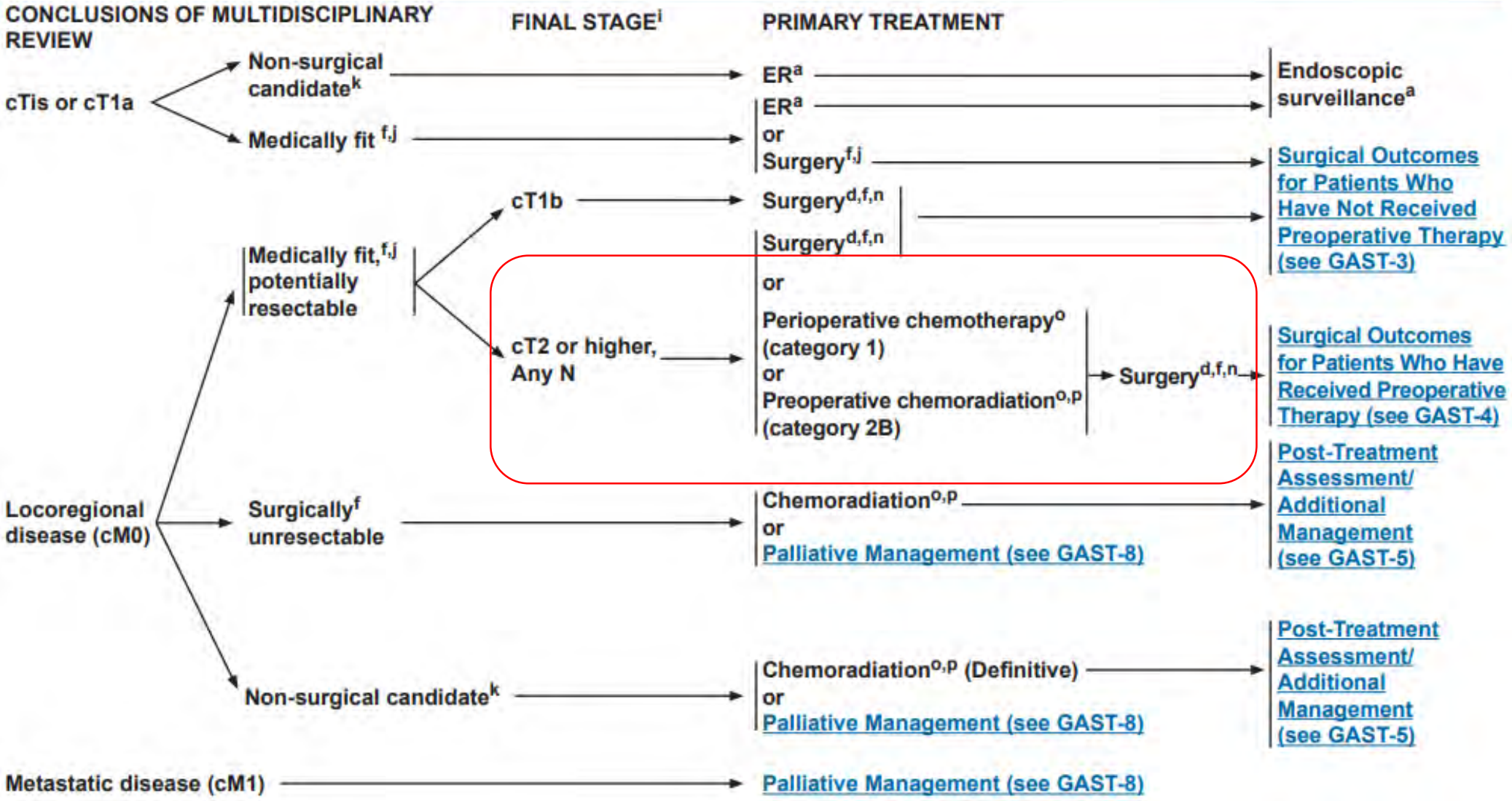
National Comprehensive Cancer Network®

# NCCN Guidelines Version 5.2017
# Gastric Cancer



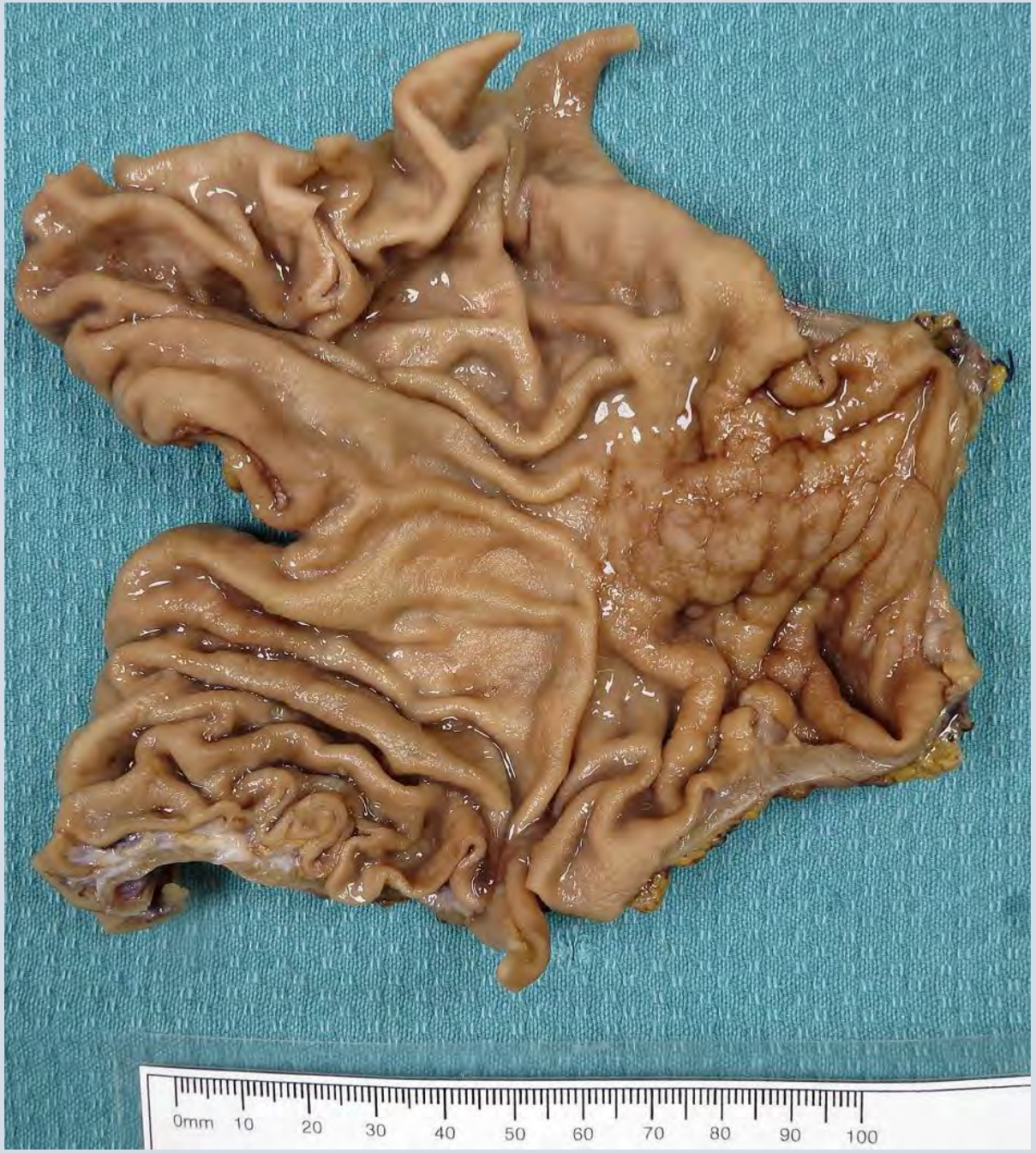
National Comprehensive Cancer Network®

# NCCN Guidelines Version 5.2017
# Gastric Cancer

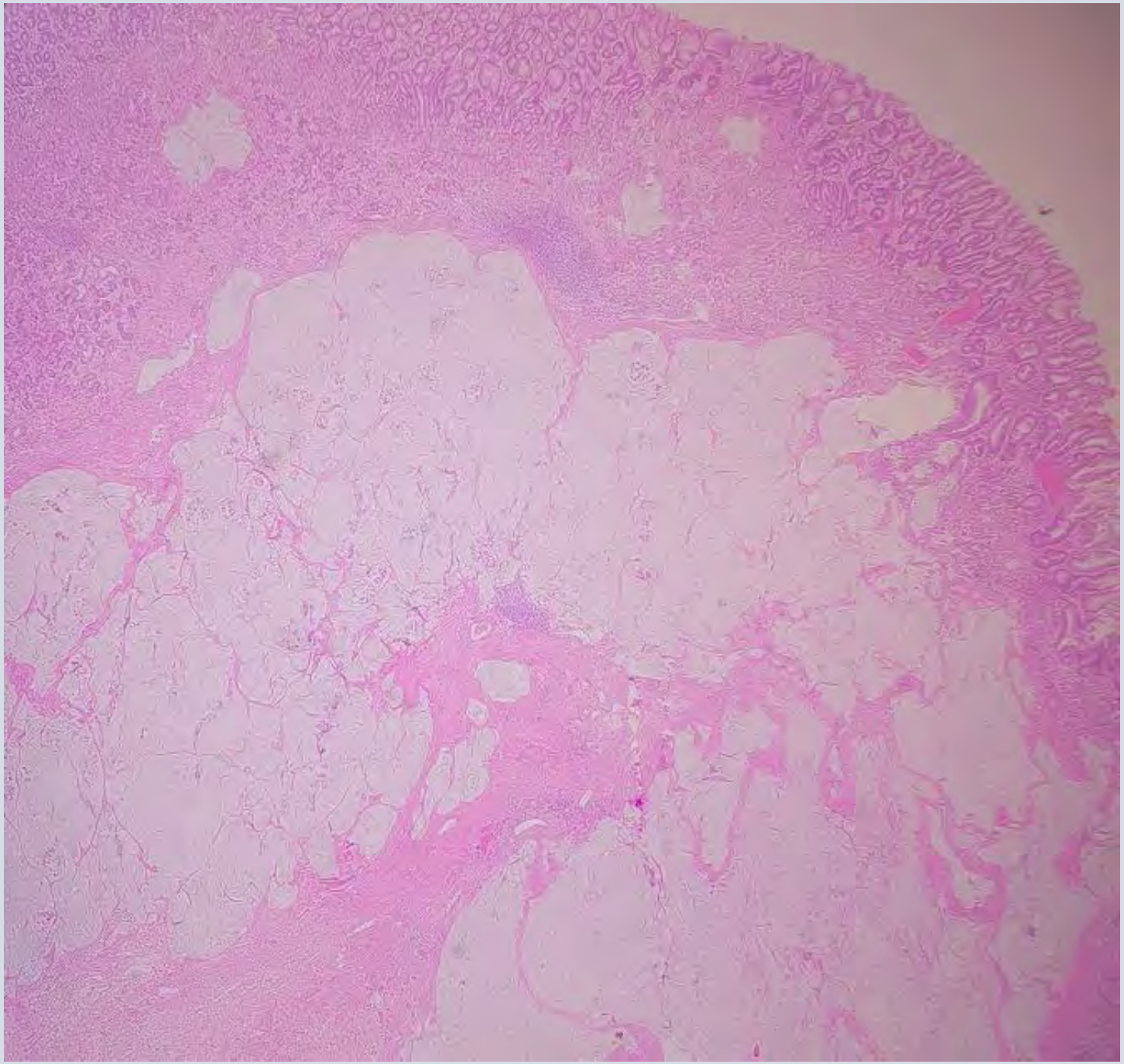


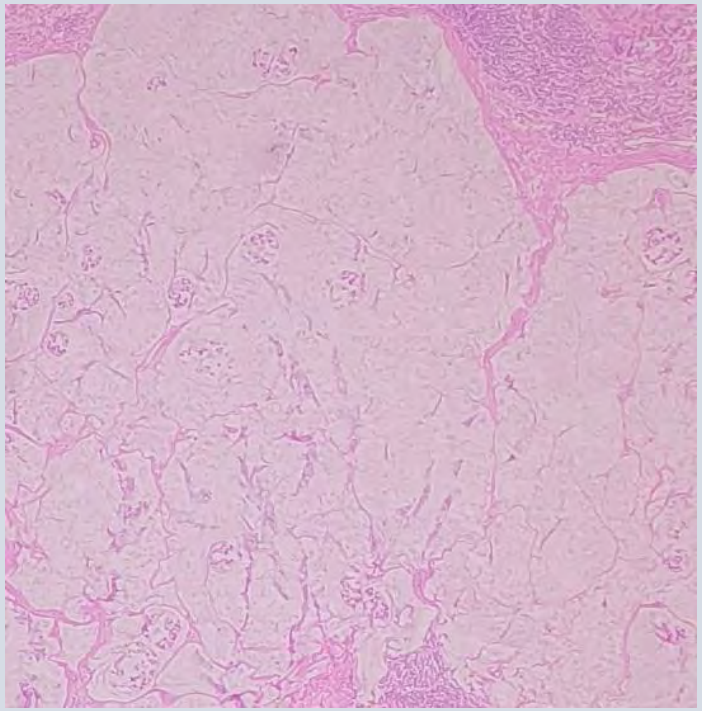
# Macroscopic assessment

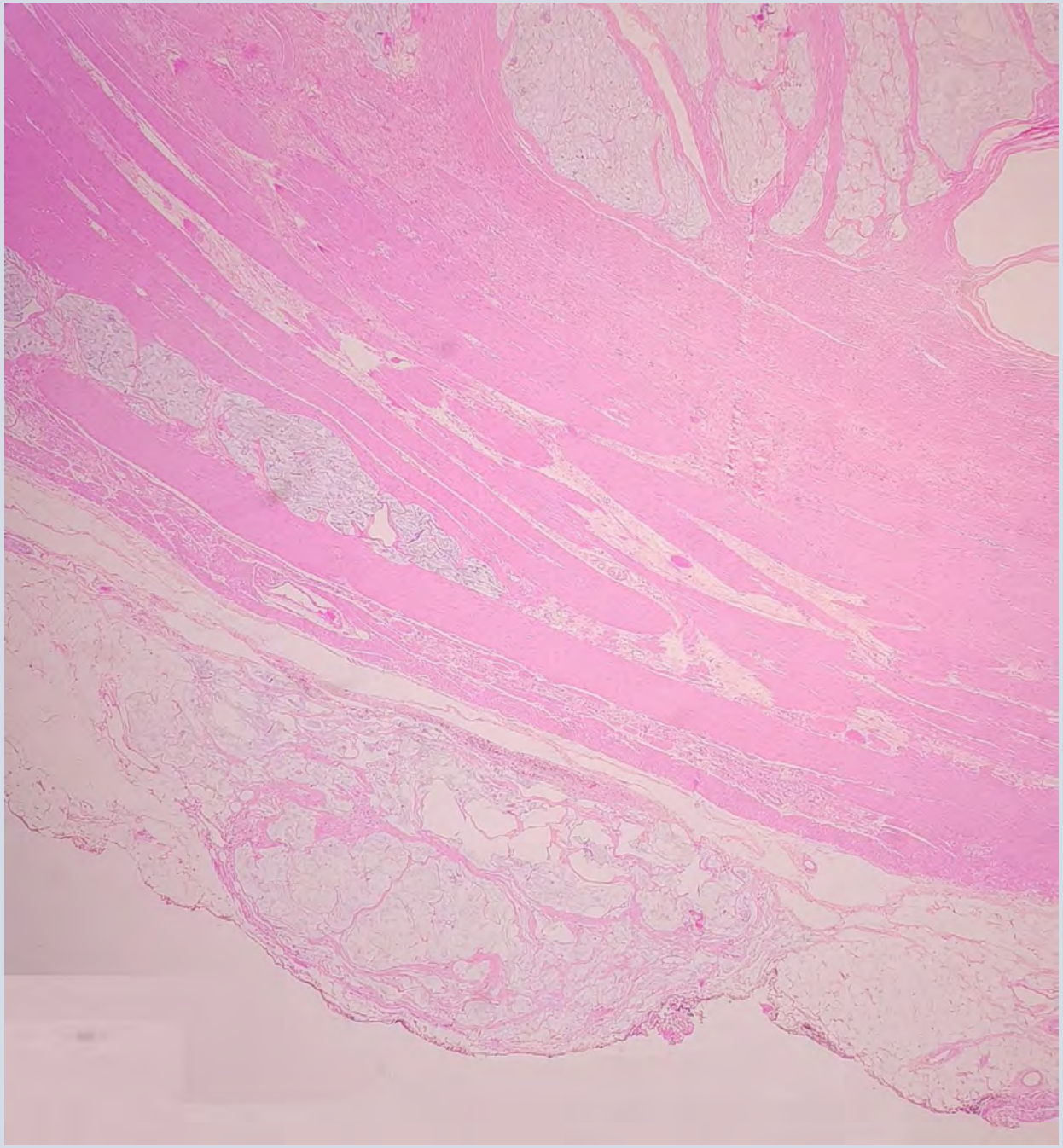
- Neoadjuvant chemotherapy may result in the shrinkage or complete loss of macroscopic abnormality.
- Clinical and radiologic data regarding tumour location is used to localise sampling.
- Following slicing, thickening or fibrosis in the submucosa and muscularis propria may indicate the site of previous tumour.
- Minimum of five blocks from the tumour site should be taken.
- If no carcinoma, examine three levels of each block.
- If no carcinoma is found, embedding of the whole site is required before a complete response to neoadjuvant therapy can be reported.

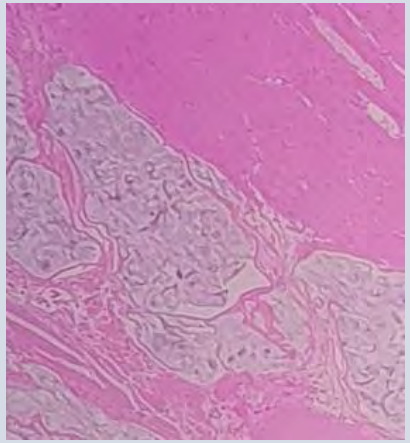

0mm 10 20 30 40 50 60 70 80 90 100

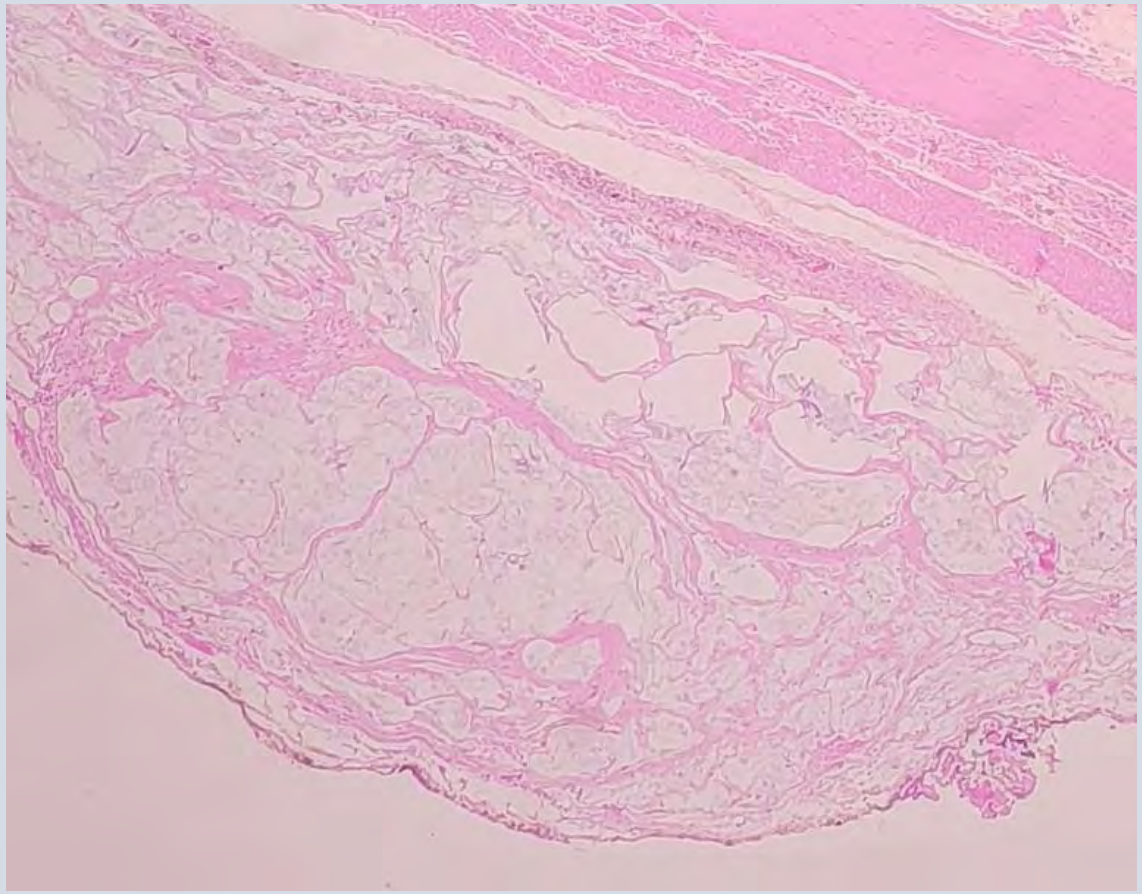

0mm 10 20 30 40 50 60 70 80 90 100











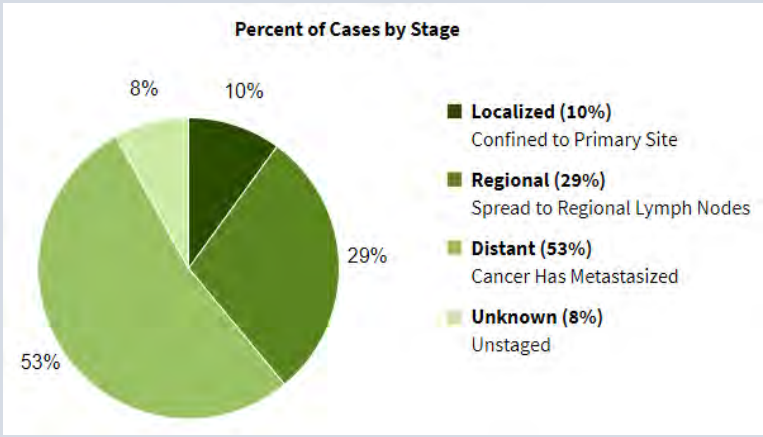
# Pancreatic ductal carcinoma

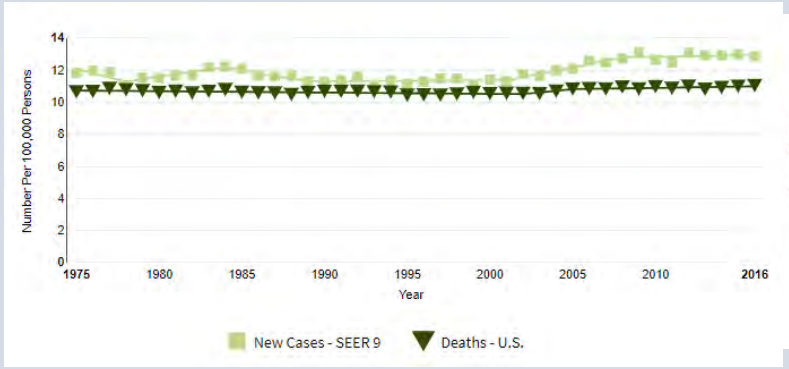
# Pancreatic carcinoma

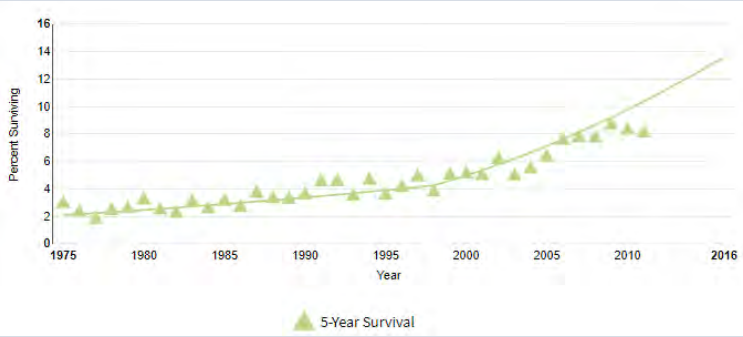
- SEER data (US) in 2019 :
  - Estimated New Cases: 56,770 (3.2%)
  - Estimated Deaths: 45,750 (7.5%)

- 4th leading cause of cancer associated deaths

| | Common Types of Cancer | Estimated New Cases 2019 | Estimated Deaths 2019 |
|---|---|---|---|
| 1. | Breast Cancer (Female) | 268,600 | 41,760 |
| 2. | Lung and Bronchus Cancer | 228,150 | 142,670 |
| 3. | Prostate Cancer | 174,650 | 31,620 |
| 4. | Colorectal Cancer | 145,600 | 51,020 |
| 5. | Melanoma of the Skin | 96,480 | 7,230 |
| 6. | Bladder Cancer | 80,470 | 17,670 |
| 7. | Non-Hodgkin Lymphoma | 74,200 | 19,970 |
| 8. | Kidney and Renal Pelvis Cancer | 73,820 | 14,770 |
| 9. | Uterine Cancer | 61,880 | 12,160 |
| 10. | Leukemia | 61,780 | 22,840 |
| | - | - | - |
| **11.** | **Pancreatic Cancer** | **56,770** | **45,750** |




SEER Cancer Stat Facts: Pancreatic Cancer. National Cancer Institute. Bethesda, MD,

# Treatment of pancreatic ductal adenocarcinoma

- Resectable disease
  - 10-20%
  - ASCO guidelines: Upfront surgery, followed by adjuvant FOLFIRINOX (fluorouracil infusion, irinotecan, oxaliplatin)
  - *Neoadjuvant therapy in a trial setting*
- Borderline resectable disease:
  - Neoadjuvant chemotherapy
    - Early treatment of disease
    - Assessment of responsiveness to chemotherapy
    - Downstaging of nodal disease
    - Improved operability with R0 resections
- Unresectable disease
  - Palliative chemotherapy / radiotherapy

# Borderline tumours???

- Tumours which involve mesenteric vasculature to a limited extent
- Tumours in which resection is likely to be compromised by a positive resection margin in the absence of pre-operative therapy

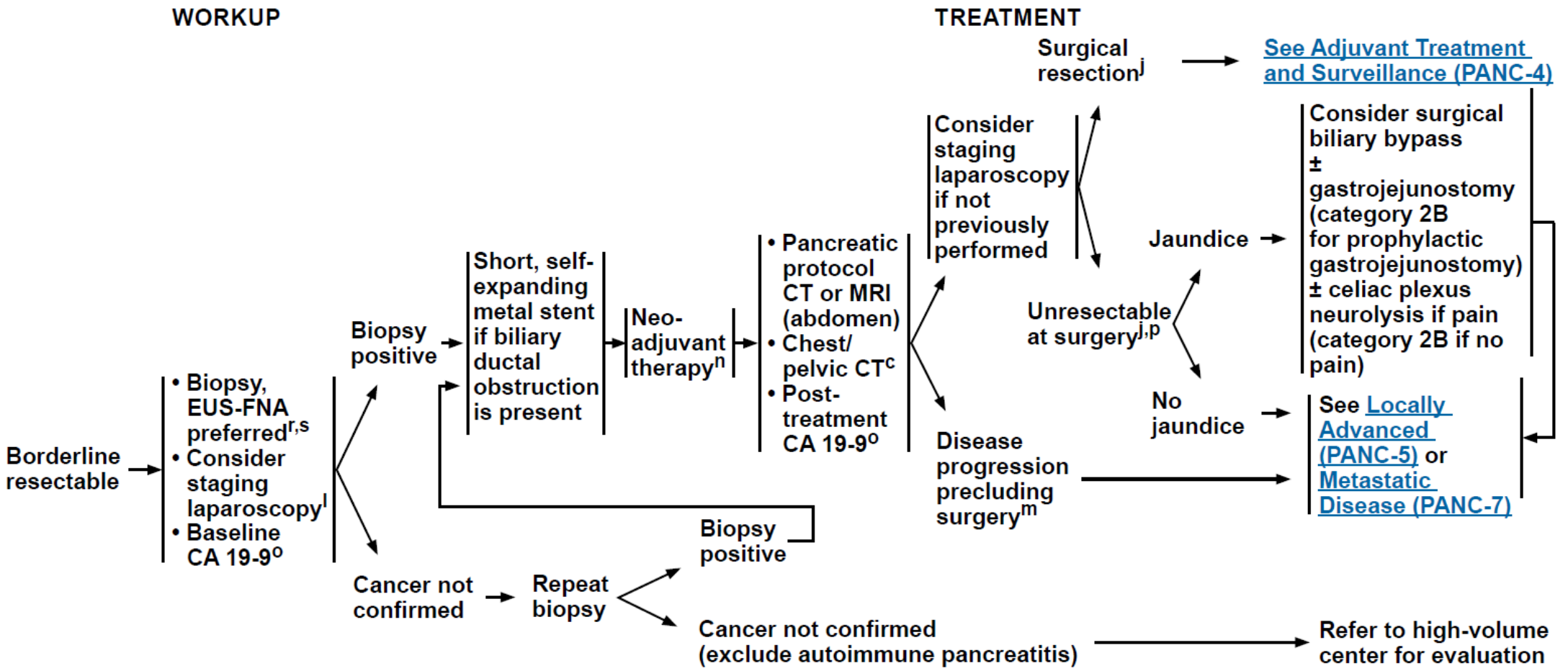
| | | |
|---|---|---|
| **Borderline Resectable**[b] | **Pancreatic head/uncinate process:**<br>• Solid tumor contact with CHA without extension to CA or hepatic artery bifurcation allowing for safe and complete resection and reconstruction.<br>• Solid tumor contact with the SMA of ≤180°<br>• Solid tumor contact with variant arterial anatomy (ex: accessory right hepatic artery, replaced right hepatic artery, replaced CHA, and the origin of replaced or accessory artery) and the presence and degree of tumor contact should be noted if present, as it may affect surgical planning.<br>**Pancreatic body/tail:**<br>• Solid tumor contact with the CA of ≤180°<br>• Solid tumor contact with the CA of >180° without involvement of the aorta and with intact and uninvolved gastroduodenal artery thereby permitting a modified Appleby procedure [some panel members prefer these criteria to be in the unresectable category]. | • Solid tumor contact with the SMV or PV of >180°, contact of ≤180° with contour irregularity of the vein or thrombosis of the vein but with suitable vessel proximal and distal to the site of involvement allowing for safe and complete resection and vein reconstruction.<br>• Solid tumor contact with the inferior vena cava (IVC). |

NCCN National Comprehensive Cancer Network®

National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018
# Pancreatic Adenocarcinoma

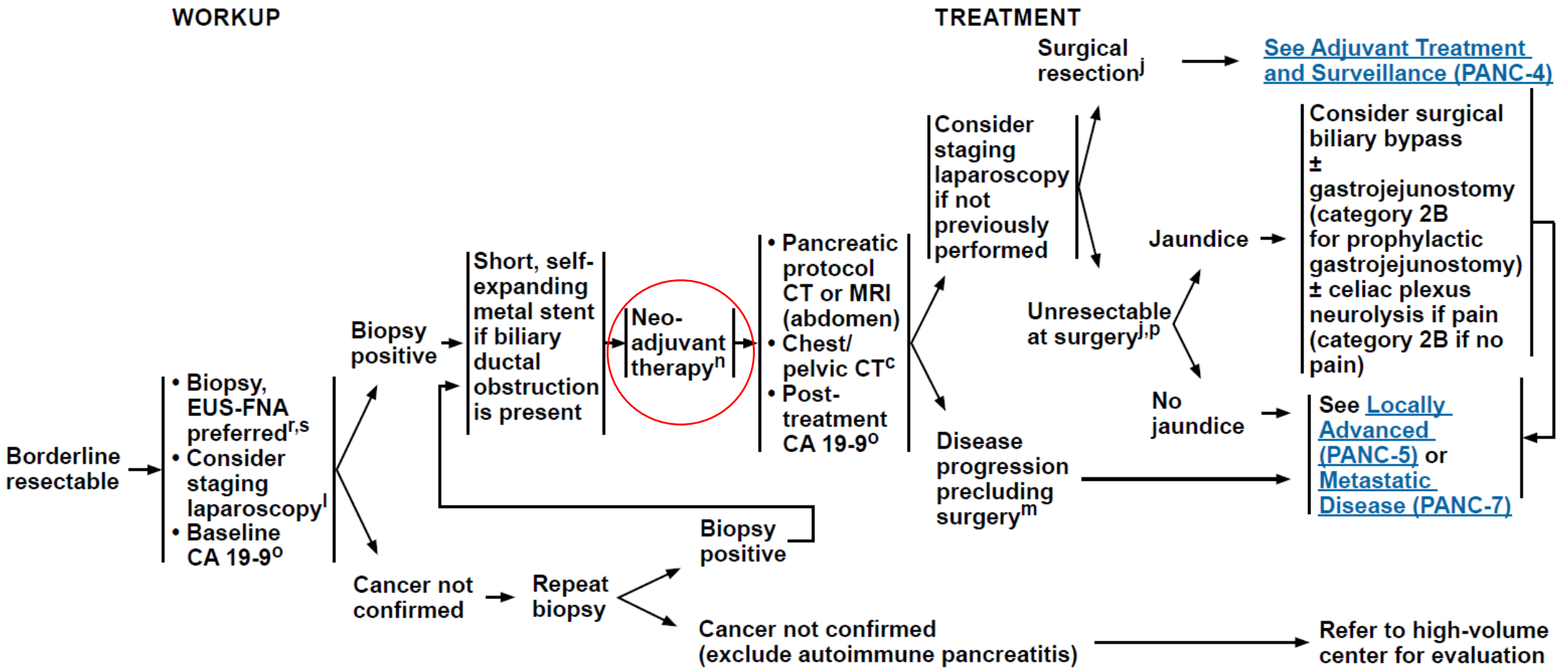
## BORDERLINE RESECTABLE[i,q] NO METASTASES



National Comprehensive Cancer Network®

# NCCN Guidelines Version 2.2018
# Pancreatic Adenocarcinoma

## BORDERLINE RESECTABLE[i,q] NO METASTASES



# Neoadjuvant therapy

- Outcomes
  - Increase in R0 resection rate in *operable* pancreatic carcinoma (82%)
  - 33% resected with an R0 resection rate of 79% in previously *inoperable* carcinomas
- Protocols
  - FOLFIRINOX+/- chemoradiation (capecitabine and 5FU or gemcitabine)
  - Gemcitabine + paclitaxel +/- chemoradiation
  - BRCA1/BRCA2: Gemcitabine + cisplatin (2-6 cycles) + chemoradiation

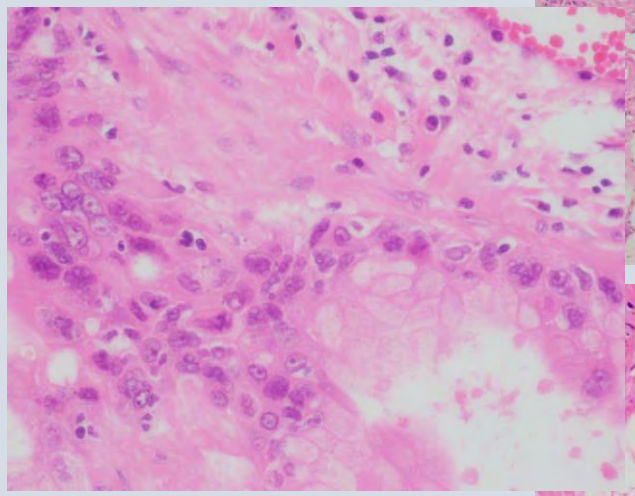
Gillen S, Schuster T, Meyer Zum Buschenfelde C, Friess H, Kleeff J . Preoperative/neoadjuvant therapy in pancreatic cancer: a systematic review and meta-analysis of response and resection percentages. PLoS Med. 2010;7(4):e1000267.

# Macroscopic assessment

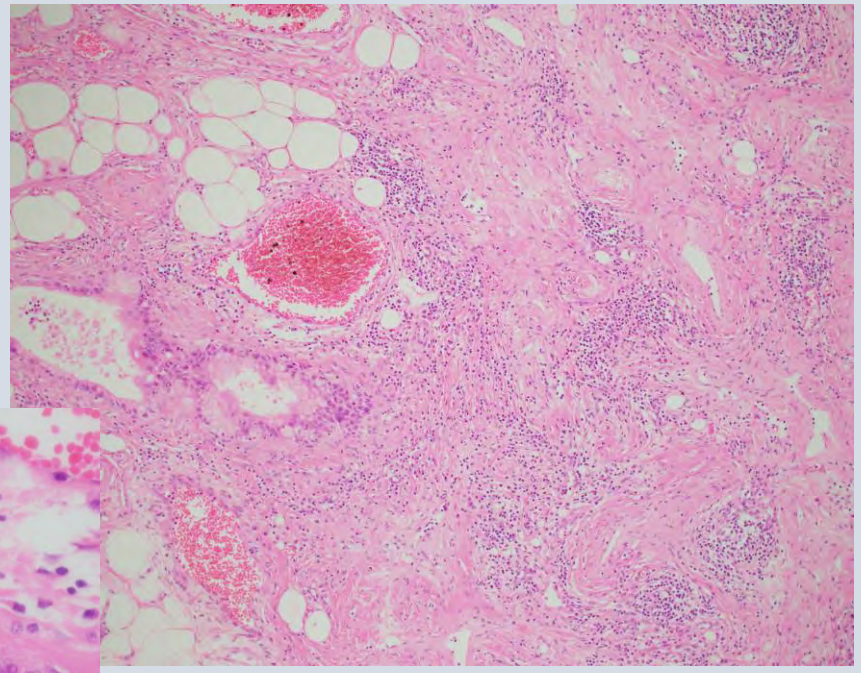
- Whipple's: Axial sections
- Distal pancreatectomy: Sagittal sections
- Margins
  - R1 → 6% 3 year survival
  - R0 → 22% 5 year survival
  - Radial sections of: SMA margin, portal vein
- Lymph nodes:
  - 12 lymph nodes.
  - Fewer lymph nodes may be found following neoadjuvant therapy

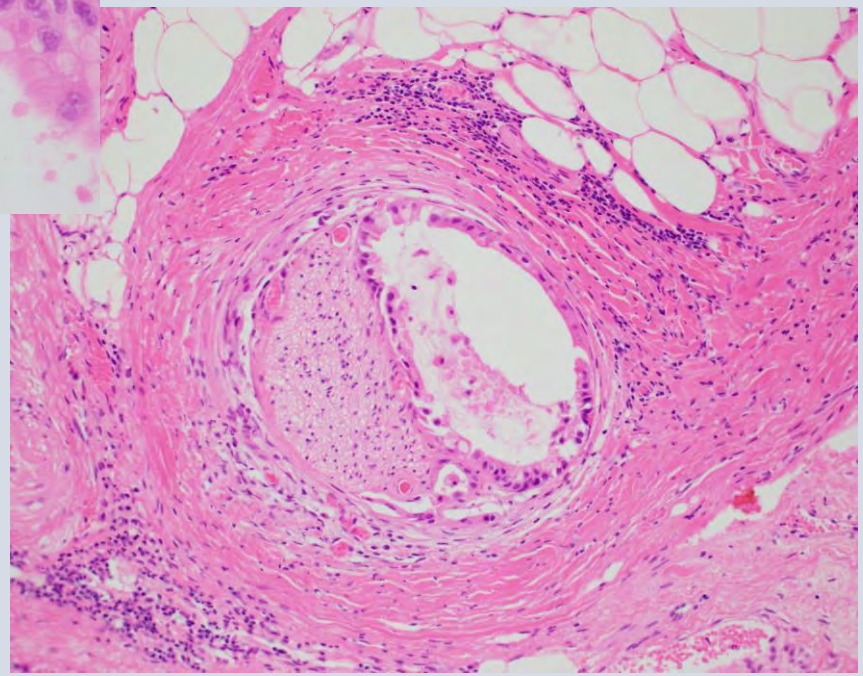
# Microscopic assessment

- In tumour:
  - Clear cell change, resembling lipoblasts
  - Karyorrhexis
  - Nuclear atypia
  - Oncocytic  or rhabdoid morphology



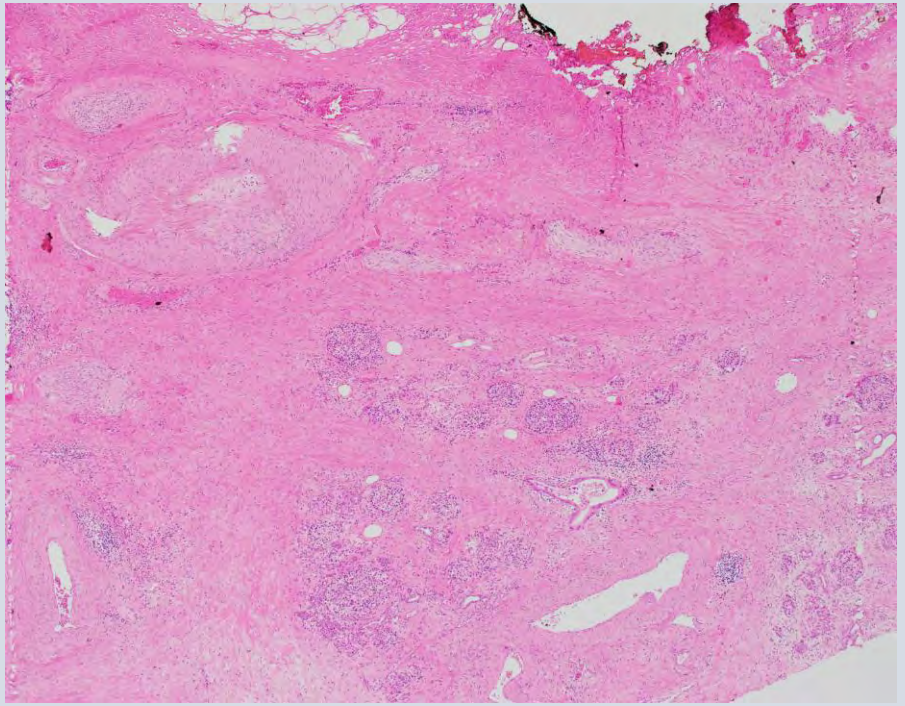
- In stroma:
  - Fibrosis separating tumour cells
    - Keloidal
    - Nodular fasciitis-like
  - Mucin pools, foamy macrophages,  foreign body-type multinucleate giant cells

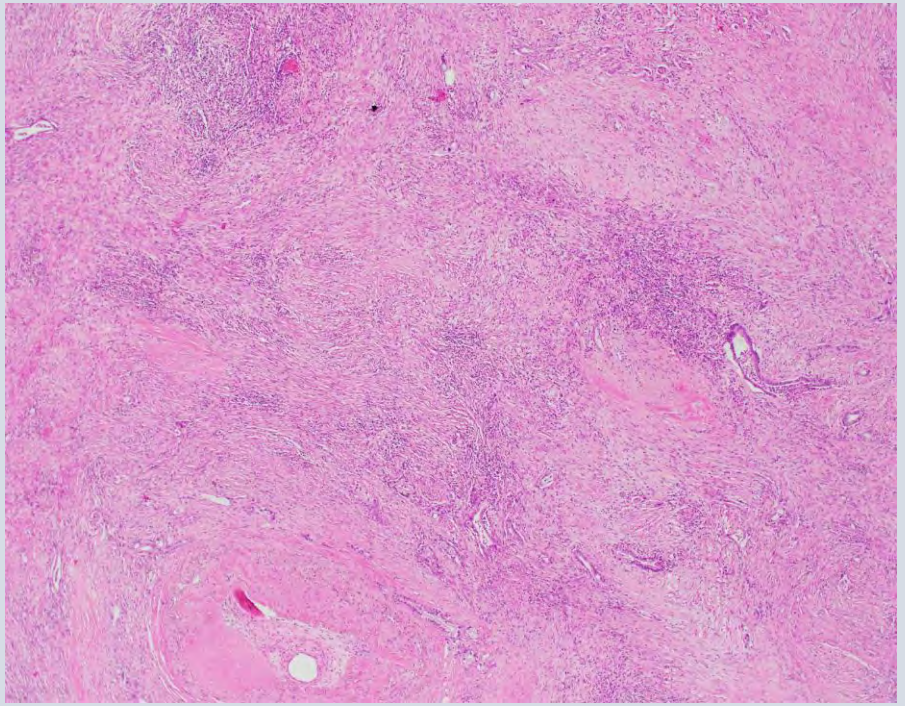


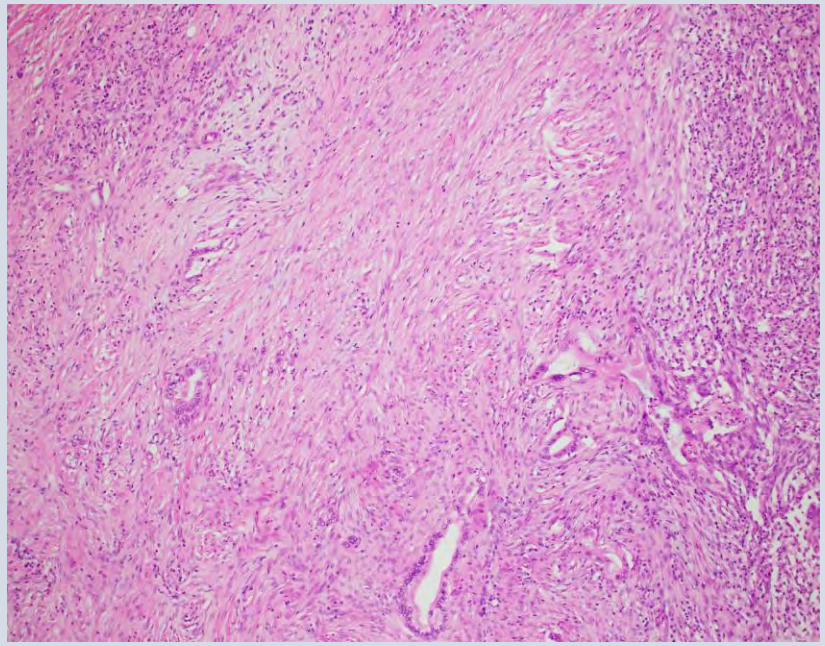
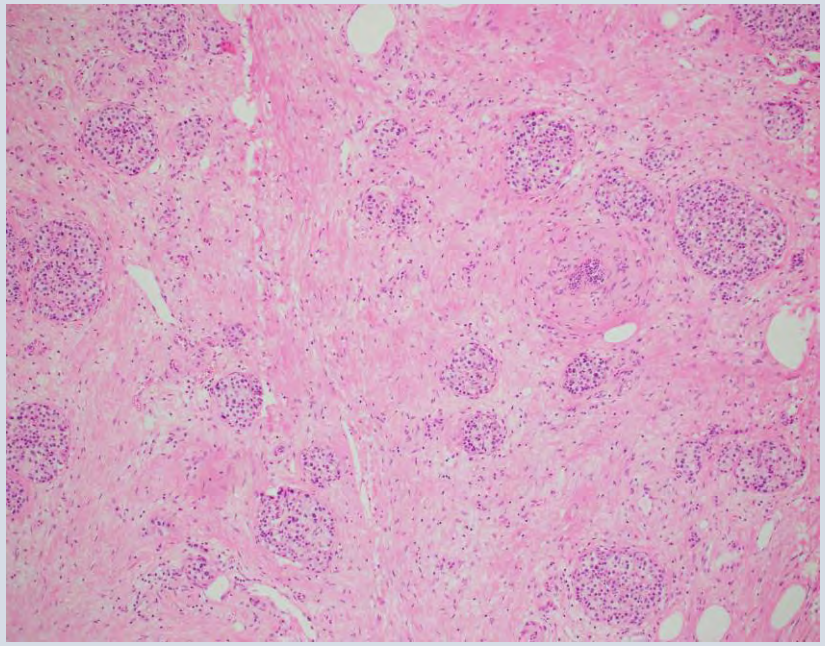
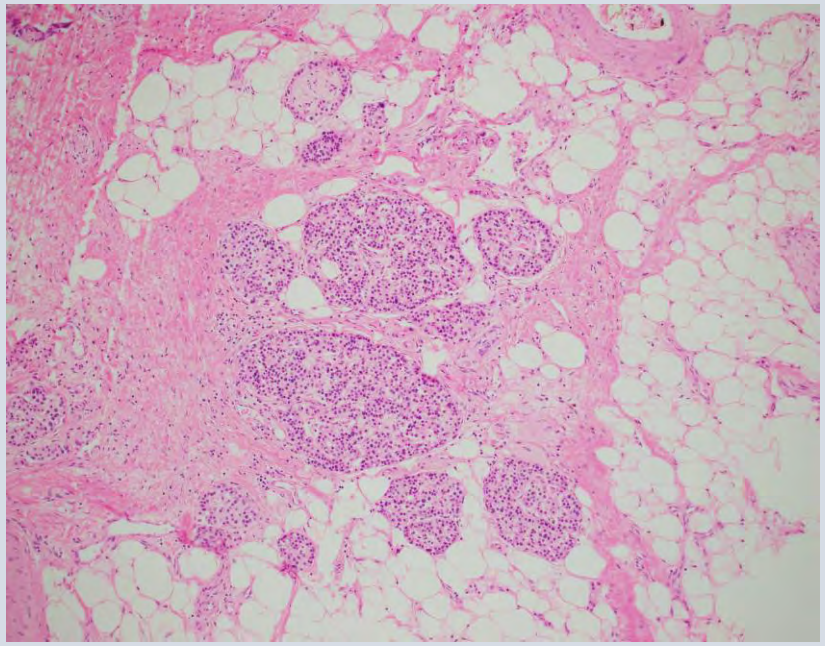
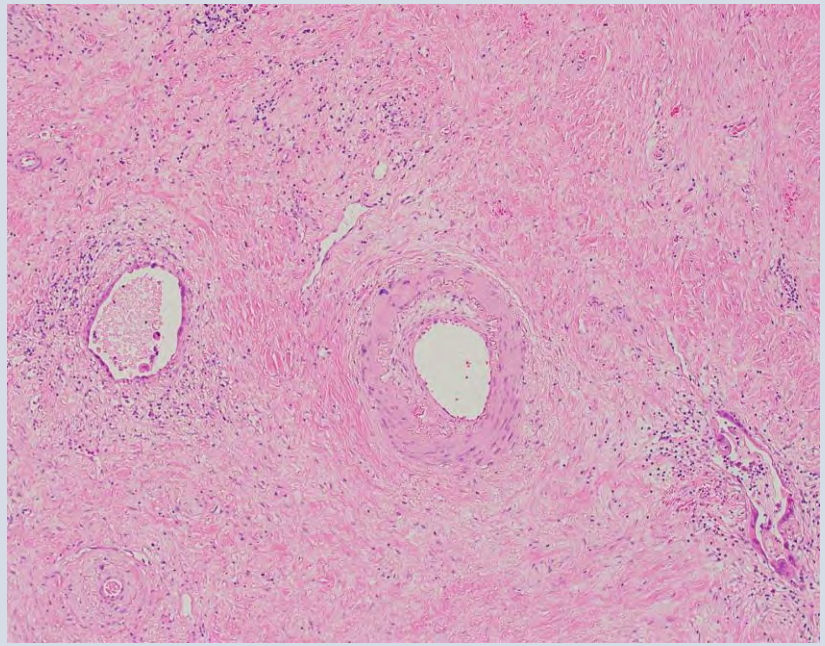
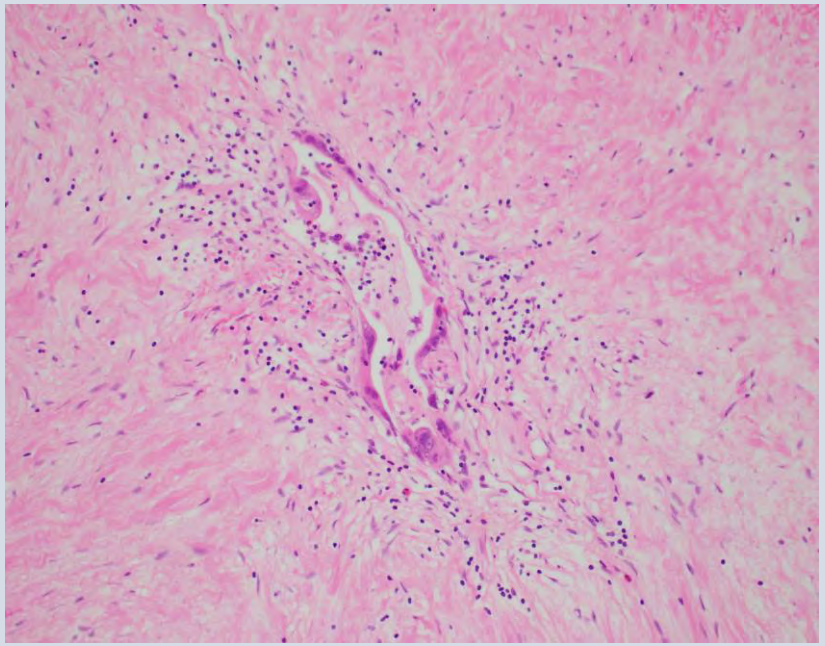
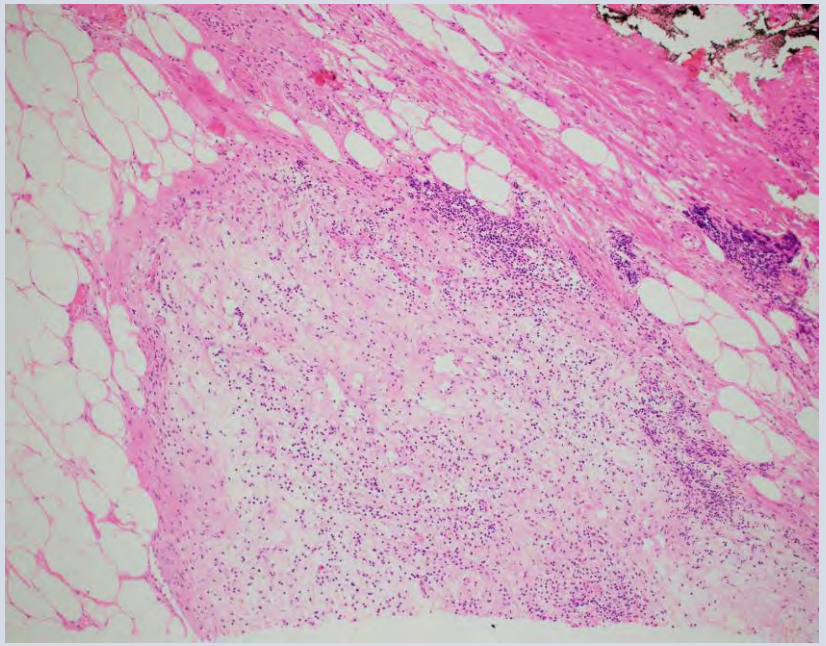


# Microscopic assessment

- In background pancreas:
  - Pancreatic acinar atrophy
    - Residual islets, nerves and ducts
  - Ductal changes:
    - Reduced PanIn
    - Squamous metaplasia
  - Fibrosis
  - Neuroma like nerve proliferation in the peri-pancreatic soft tissue
  - Elastotic vascular alteration





# Tumour regression grade in Pancreatic ductal adenocarcinoma

- Often a poor response , with <2% showing a complete response to NAT

## Evans grading

| Score | Residual carcinoma |
|---|---|
| I | < 10% or no tumour cell destruction |
| II | IIa: Destruction of 10-50% of tumour cells |
| | IIb: Destruction of 51-90% of tumour cells |
| III | < 10% tumour cells present |
| | IIIM: < 10% tumour cells present in mucin pools |
| IV | No viable tumour cells present |
| | IVM: No viable tumour cells present with acellular mucin pools |

## College of American Pathologists grading

| Score | | Residual carcinoma |
|---|---|---|
| 0 | Complete response | No viable cancer cells |
| 1 | Near complete response | Single or rare groups of cancer cells |
| 2 | Partial response | Residual cancer with evident tumour regression, but more than single cells or rare groups of cancer cells |
| 3 | Poor or no response | Extensive residual cancer with no evident tumour regression |

## Chatterjee grading

| Score | Residual carcinoma |
|---|---|
| 0 | No residual carcinoma (complete response) |
| 1 | Minimal residual carcinoma (single cells or rare groups of cancer cells, <5% residual carcinoma) |
| 2 | >5% residual carcinoma |

# Where to from here?

- Important role in the multidisciplinary management of GI and pancreatic malignancies.
- Aware of the histologic alterations post neoadjuvant therapy and potential pitfalls.
- Other therapeutic options / trials
  - Immunotherapy:
    - NEOadjuvant Immunotherapy in Resectable PANCreatic Ductal Adenocarcinoma (NEOiPANC)