Oncotherapy of gastrointestinal tumors

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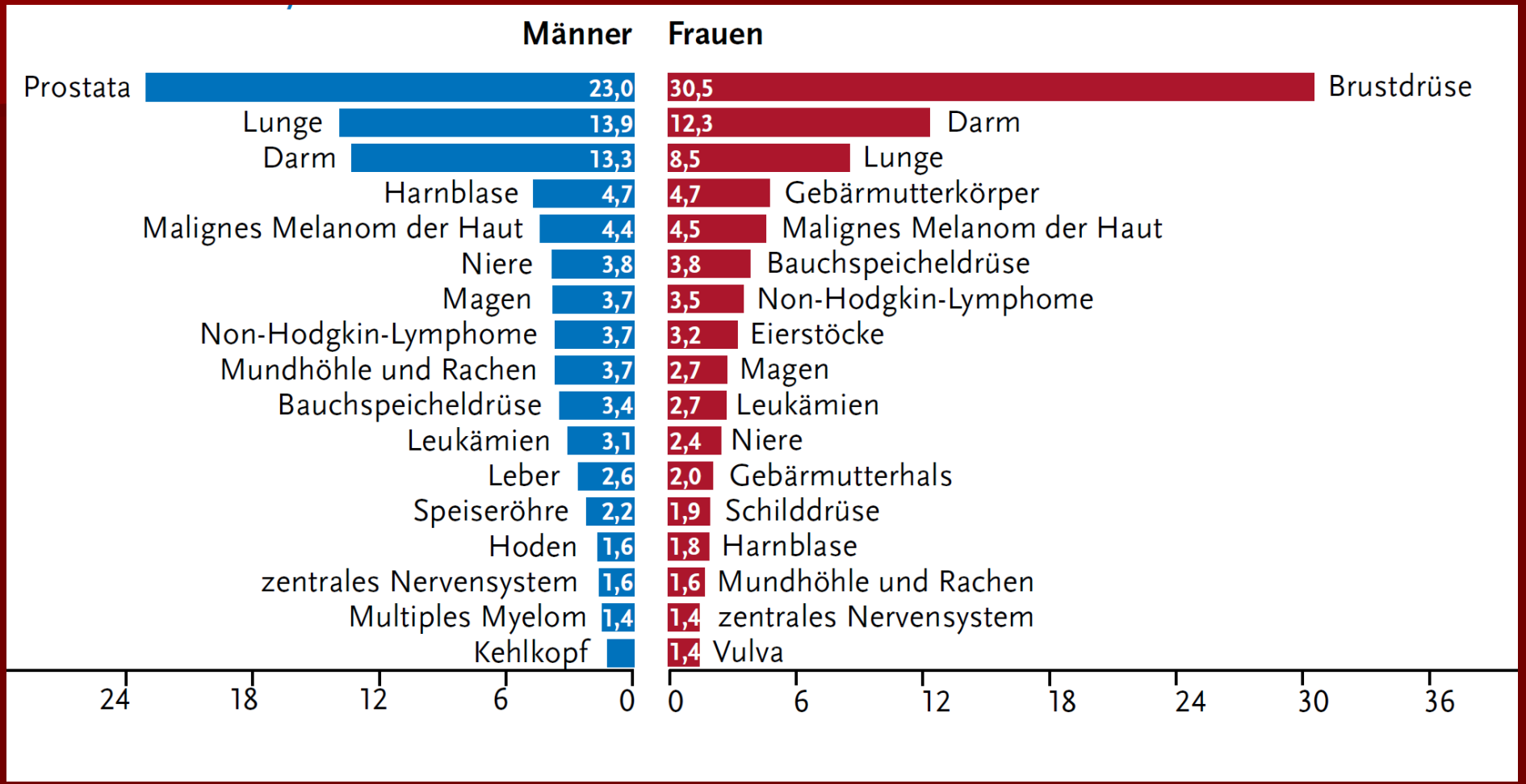
Incidecnce



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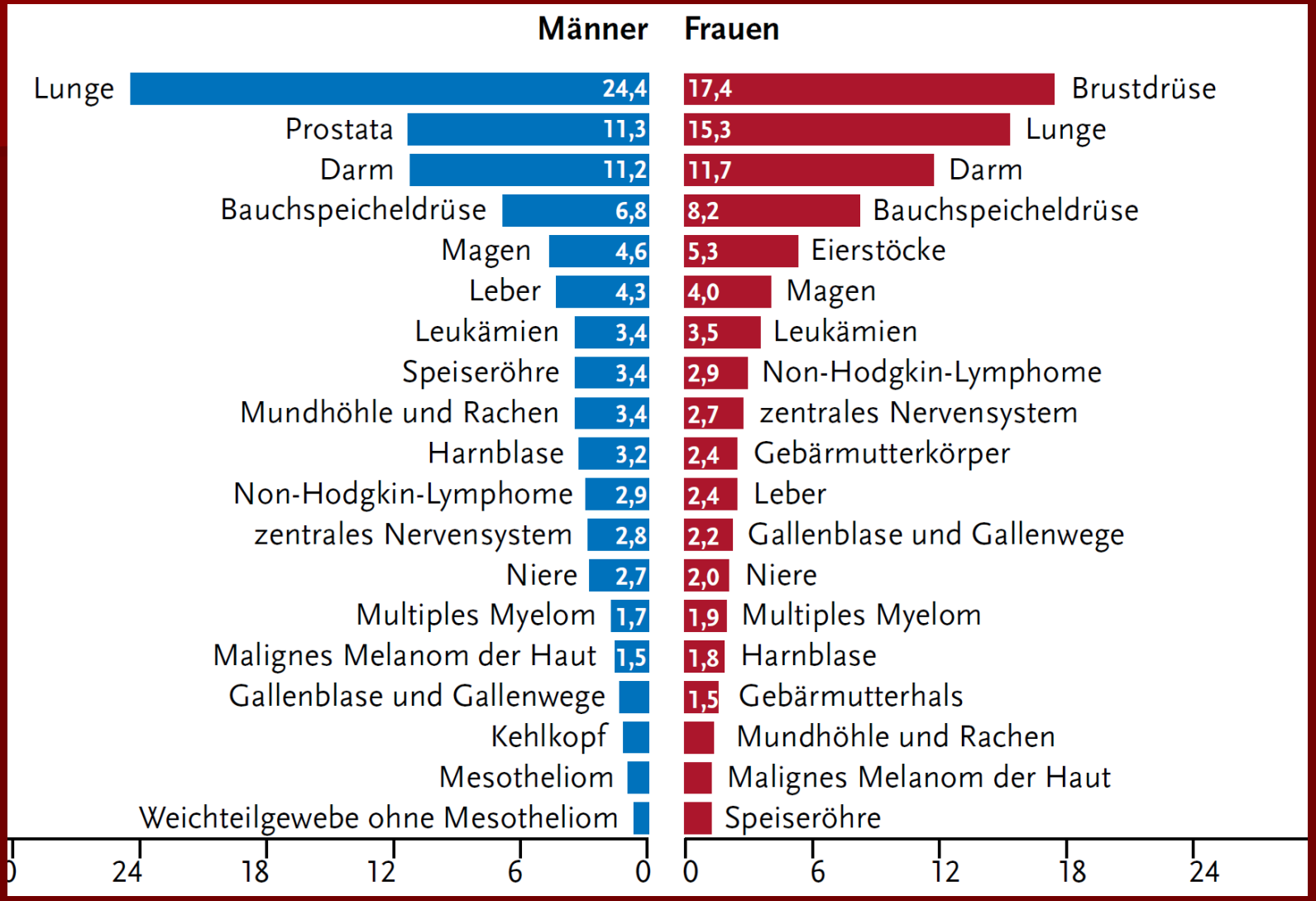
Mortality



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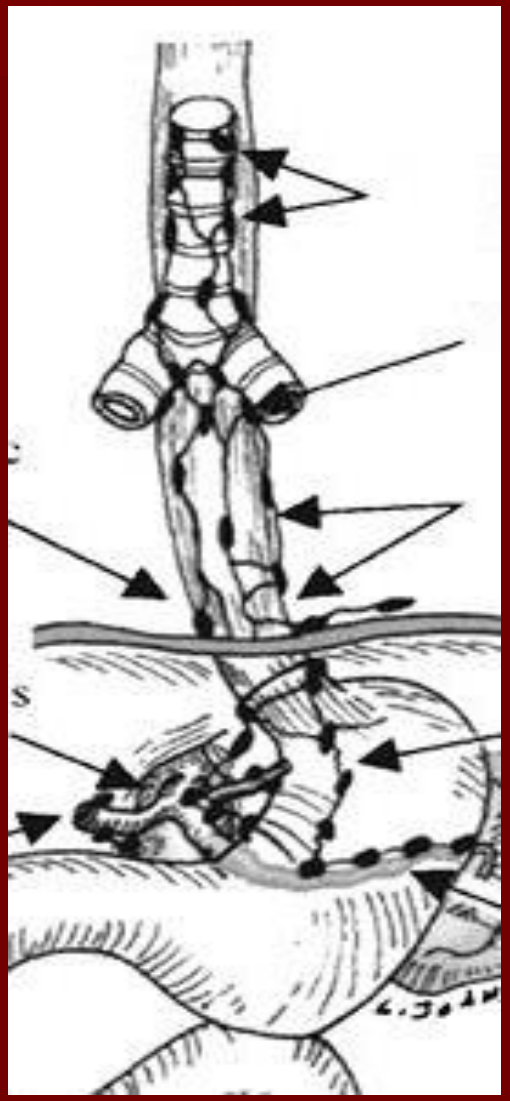
Esophageal cancer epidemiology-etiology

- **Incidence**: 5700 male / 1700 female
- **Mortality**: 4269 male / 1238 female
- **Etiology**
  - Smoking
  - Alcohol consumption
  - Hot food (>60 ˚C)
  - Obesity - GERD
  - H. pylori (squamous -, adenocc. +)
  - HPV?
  - Barrett-oesophagus

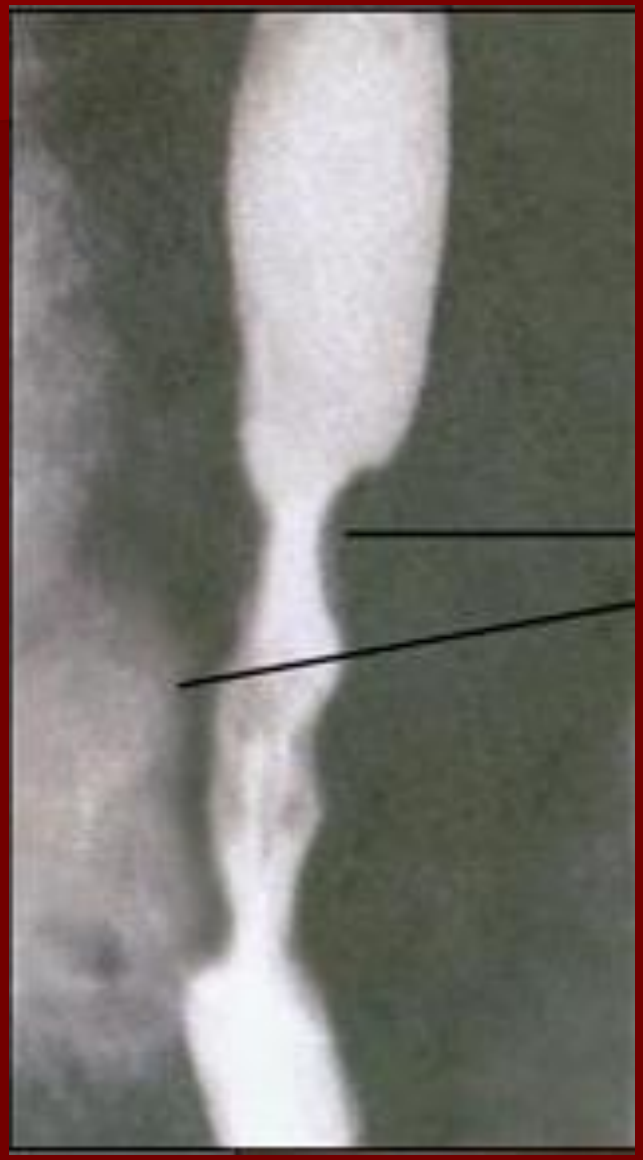
Anatomy



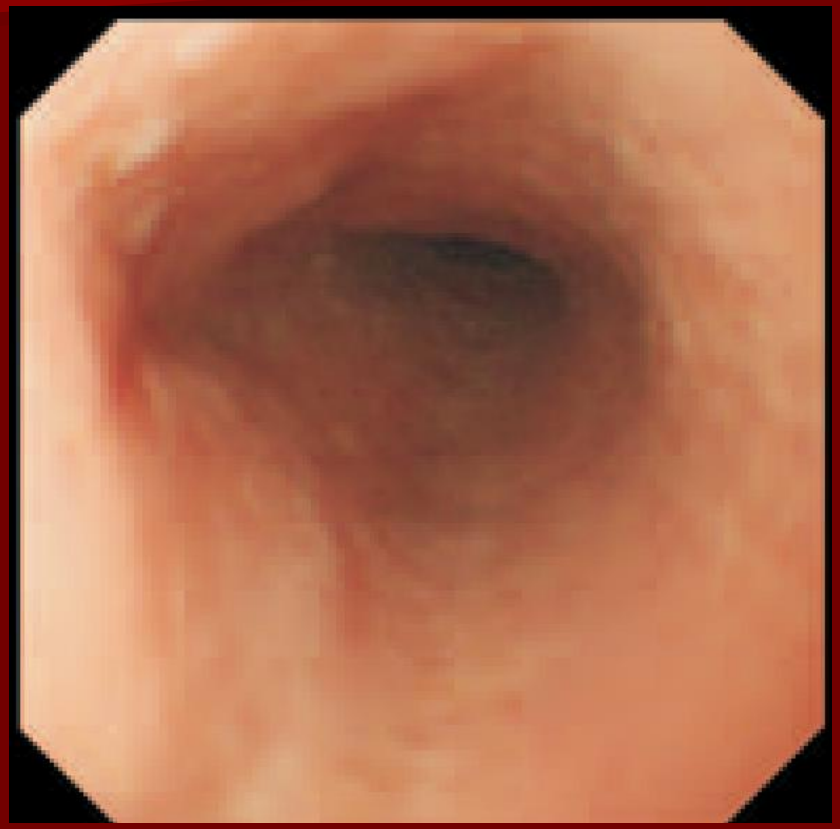
Symptoms and clinical workup

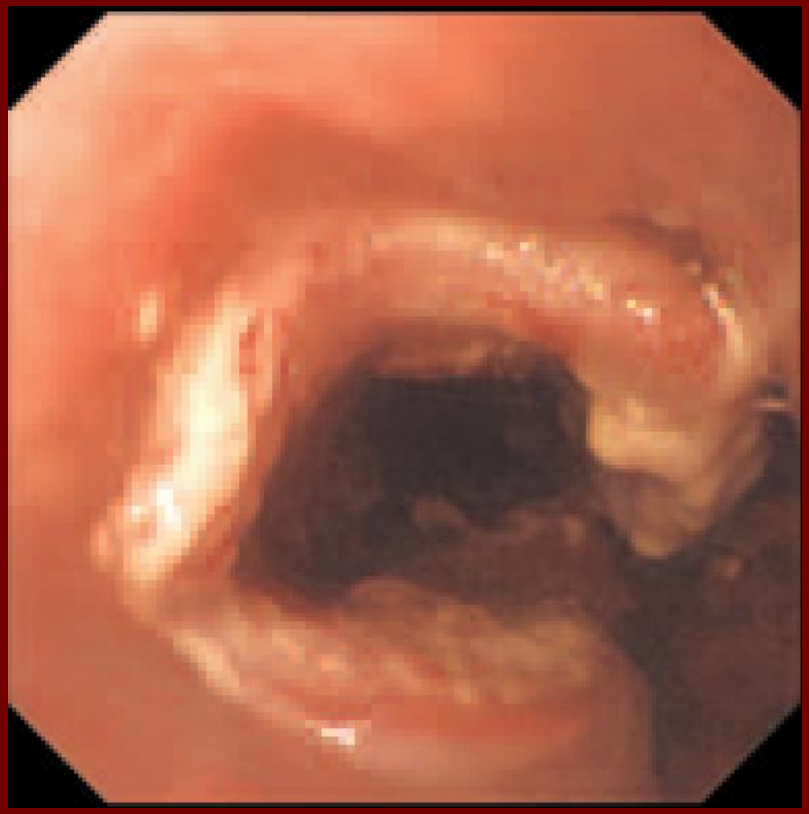
- **Symptoms**
  - Dysphagia
  - Pain
  - Bleeding
- **Imaging**
  - Barium swallow
  - Endoscopic US
  - CT
  - PET/CT
- **Histology**
  - Usually through endoscopy
  - 99% epithelial cancer
  - Squamous cell
  - Glandular cell (adenocc) incidence increasing

Barium swallow

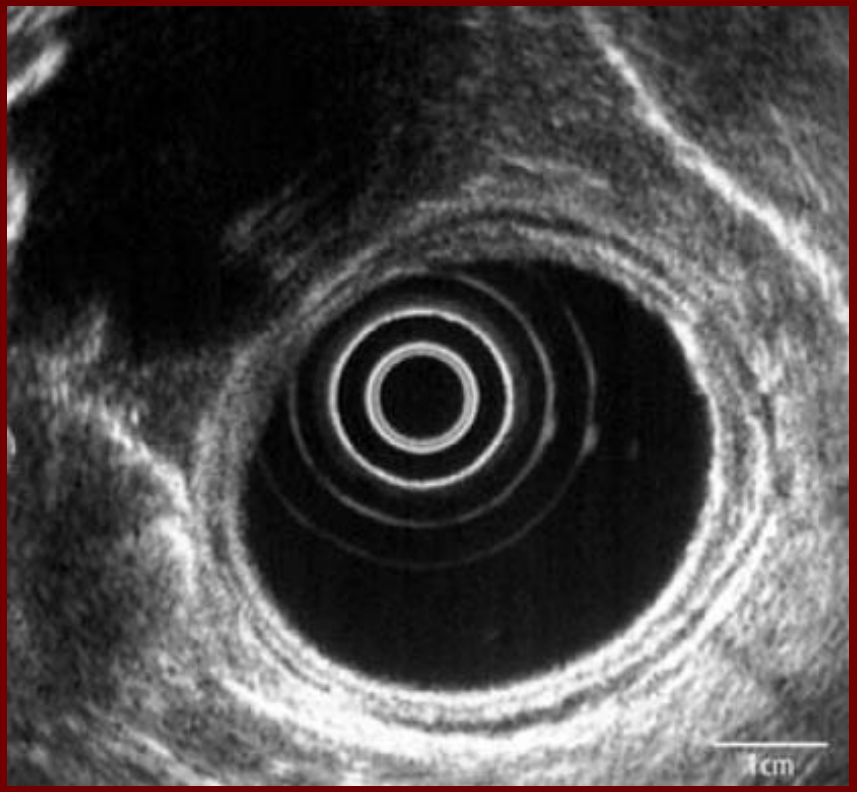


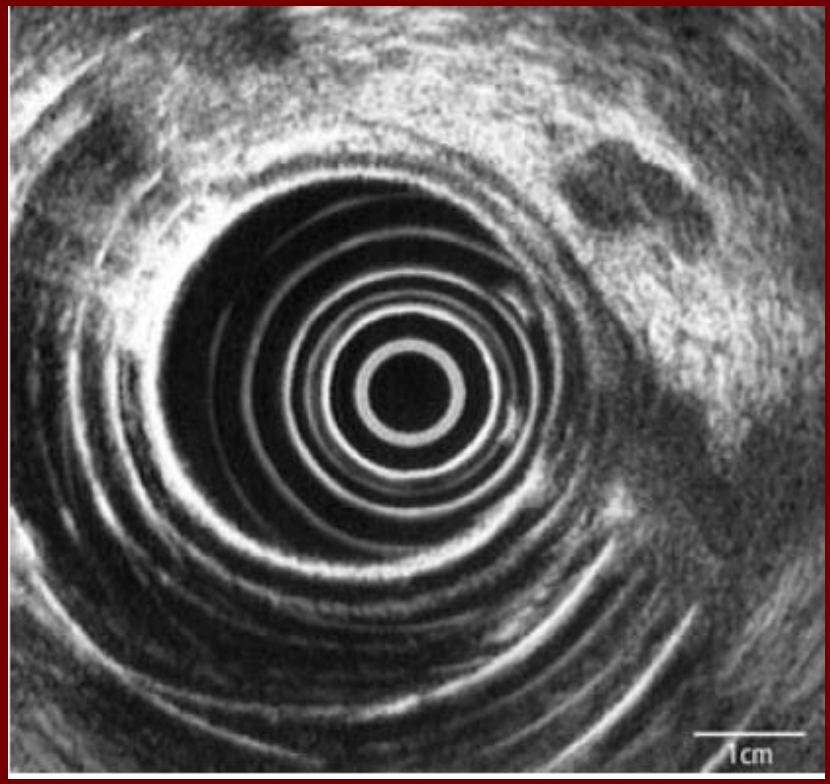
Endoscopy



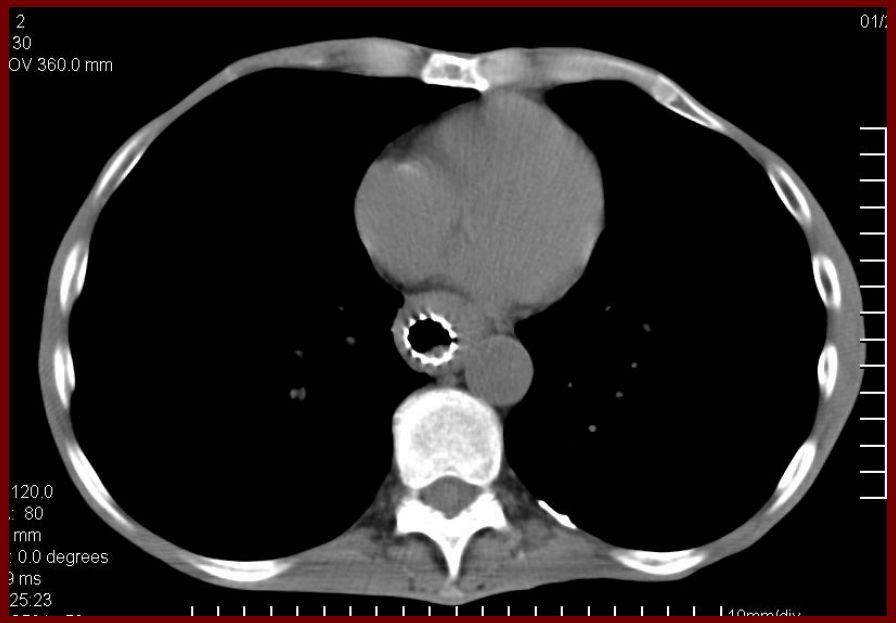


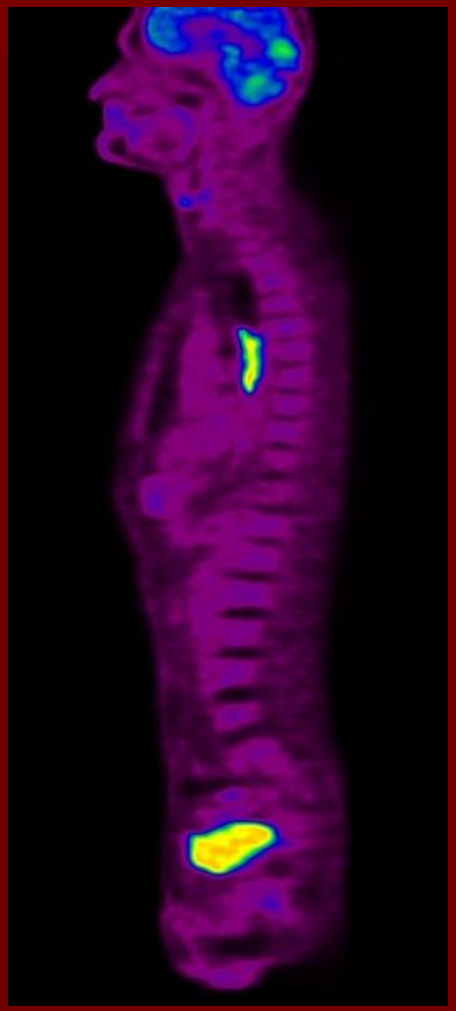
EUS

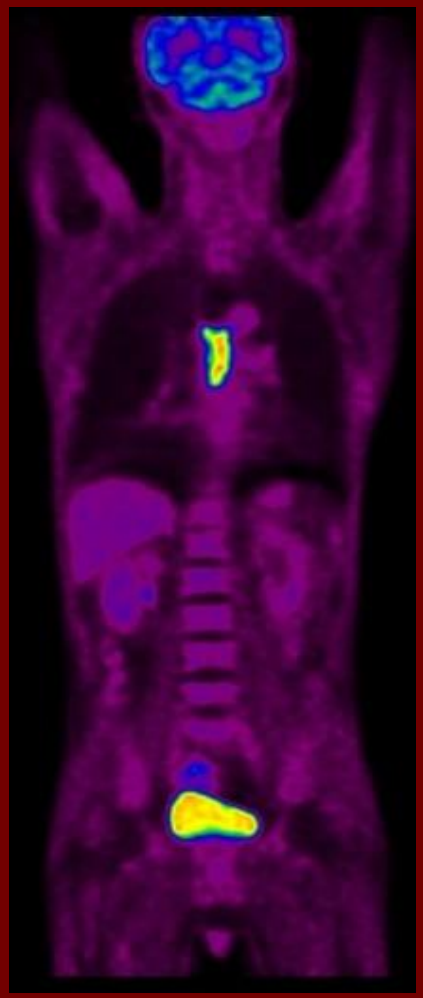




CT – PET/CT







Staging (TNM /AJCC)

Tumour (T)	
Tis	In situ carcinoma
T1a	Tumour invades the lamina propria or muscularis mucosae
T1b	Tumour invades the submucosa
T2	Tumour invades the muscularis propria
T3	Tumour invades the adventitia
T4a	Resectable tumour, invades the pleura, pericardium, or the diaphragm
T4b	Unresectable tumour, invades the aorta, vertebral body, or trachea

Lymph node status (N)	
N0	No regional lymph node metastases
N1	1-2 regional lymph node metastases
N2	3-6 regional lymph node metastases
N3	>7 regional lymph node metastases
Metastases (M)	
M0	No distant metastases
M1	Distant metastases are present

Principles of treatment

- **Upper third**
  - Concomitant chemoradiation
- **Middle-lower third**
  - Surgery
  - Concomitant chemoradiation
  - Surgery + adjuvant chemoradiation (only cardia)
  - Neoadjuvant chemoradiation +- surgery
- **Metastatic disease**
  - Chemotherapy or best supportive care
  - Targeted therapy, immunotherapy not yet established
- **Unfit patients** of any stage
  - Best supportive care

Surgery

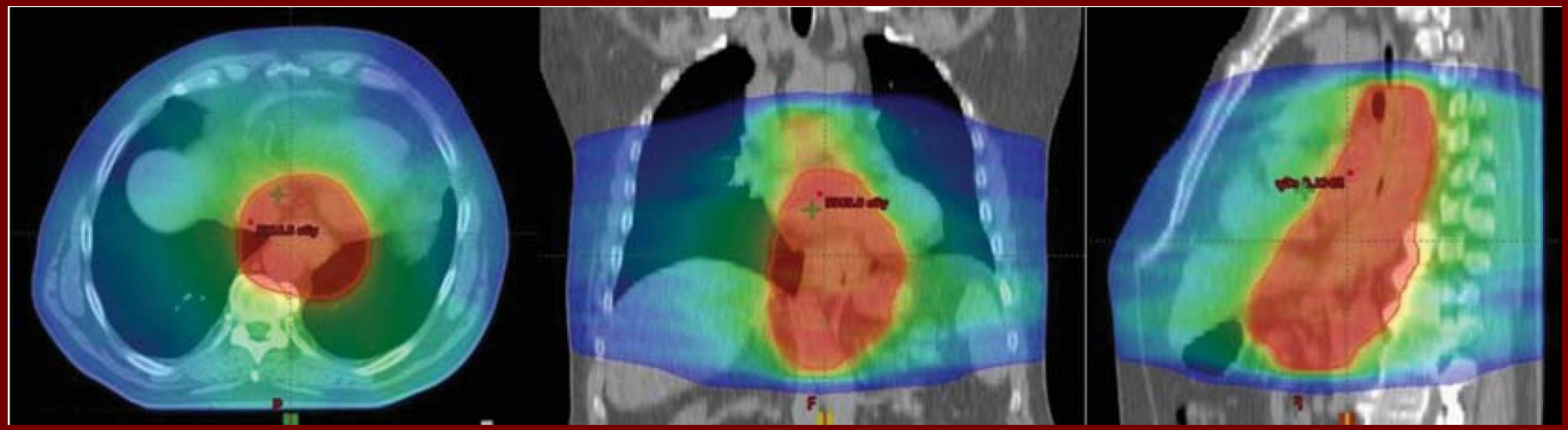
- Open and minimal invasive techniques
  - Endoscopic surgery or small tumors
  - Excision of the esophagus
  - Replacement (stomach, bowel)
  - Thoracic / abdominal or abdominal approach
- Lymphadenectomy

1. mező
2. mező
3. mező

Radiotherapy/chemoradiation

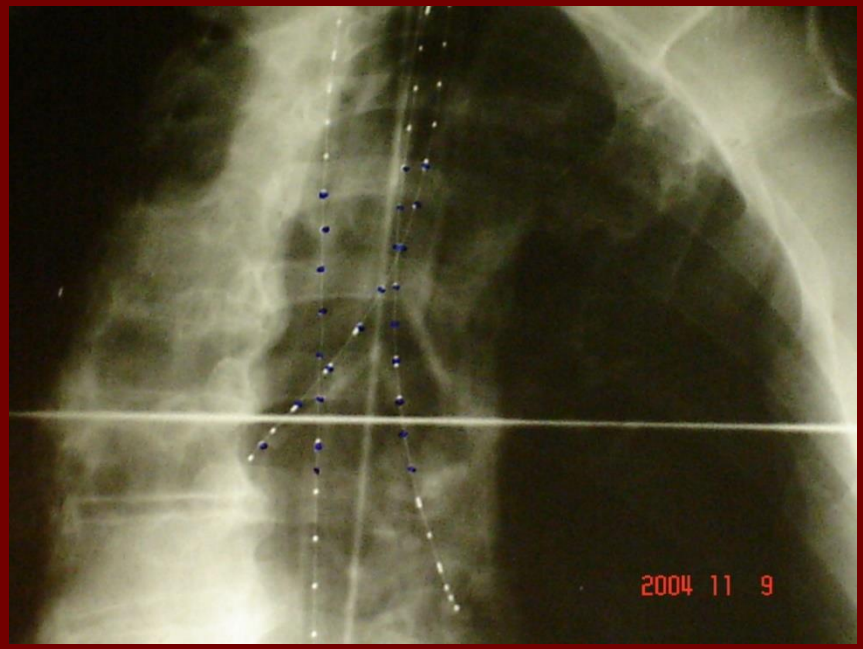
- External beam radiotherapy
  - Megavoltage X-ray / Linear accelerator
    - CT / PET fusion based conformal / IMRT
    - Dose: 45-50,4 Gy / 1,8 Gy / fraction
- Concomitant chemotherapy
  - Cisplatinum-5 FU
  - Taxane + carboplatin
  - FOLFOX

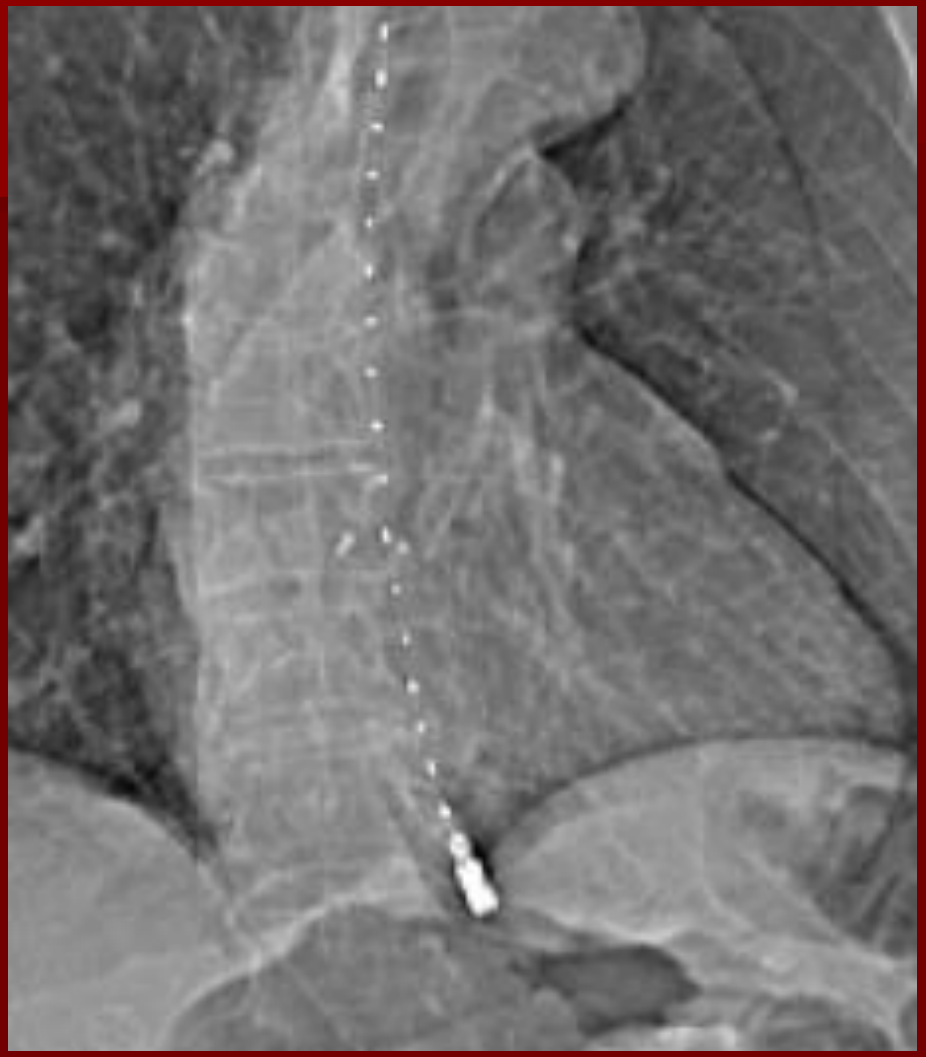
External beam radiotherapy

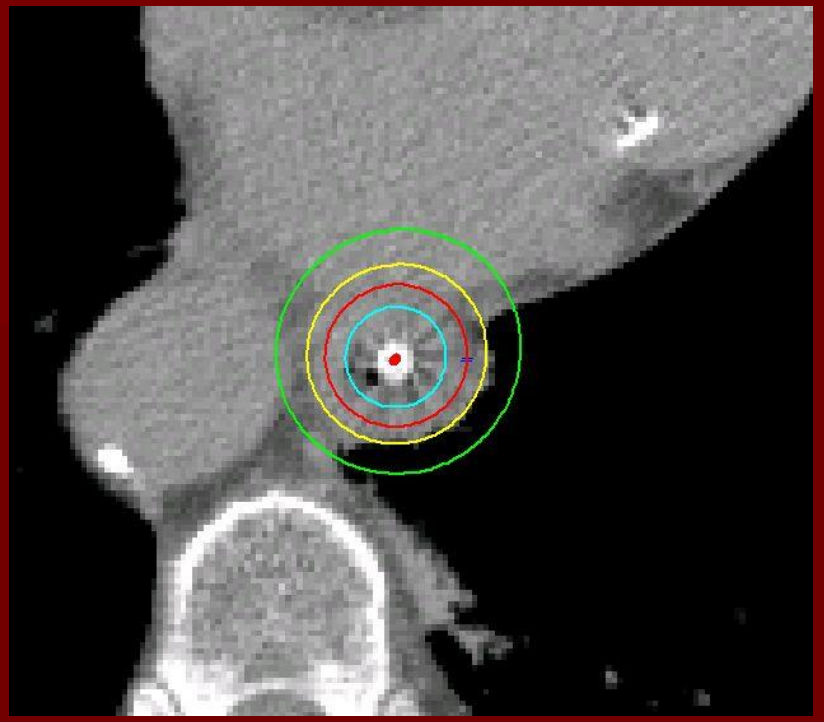


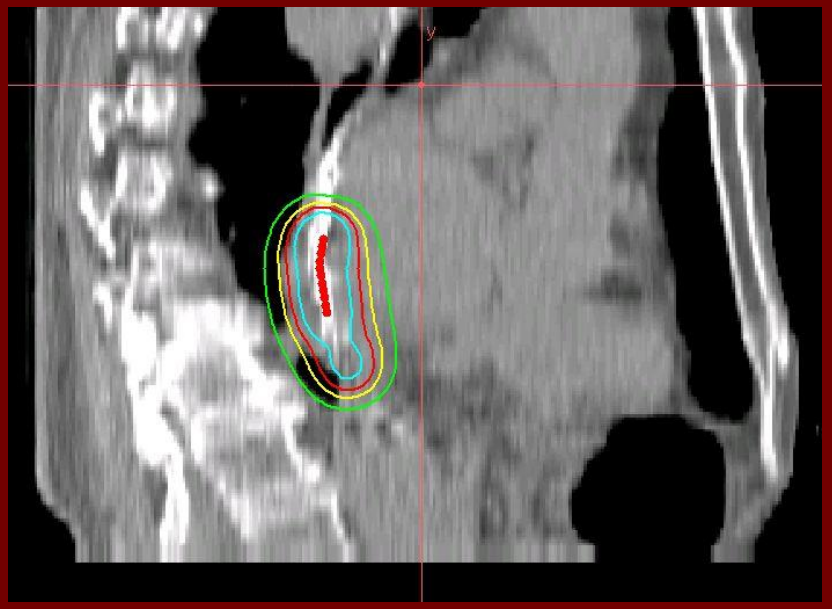
Dysphagia management

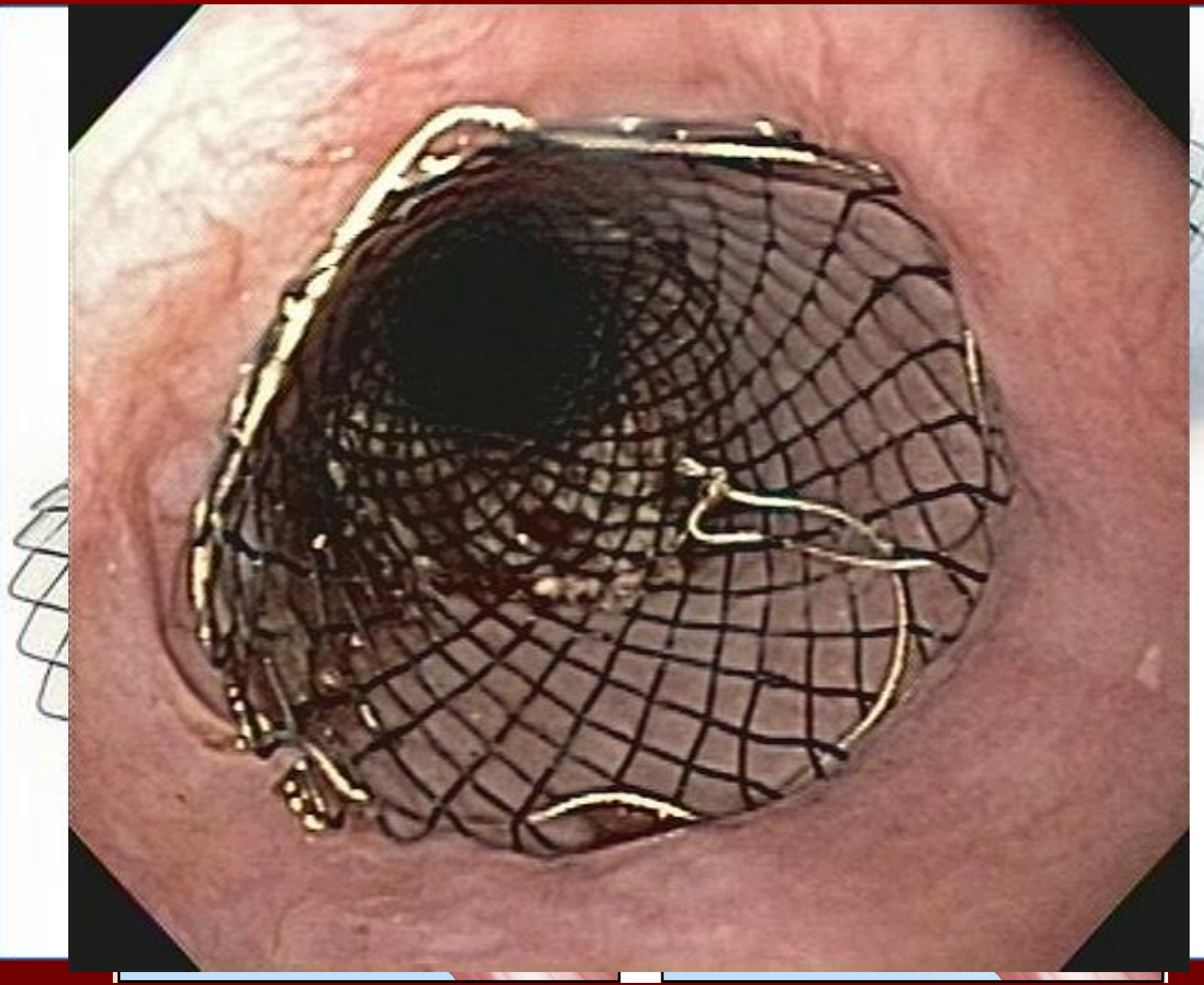
Brachytherapy











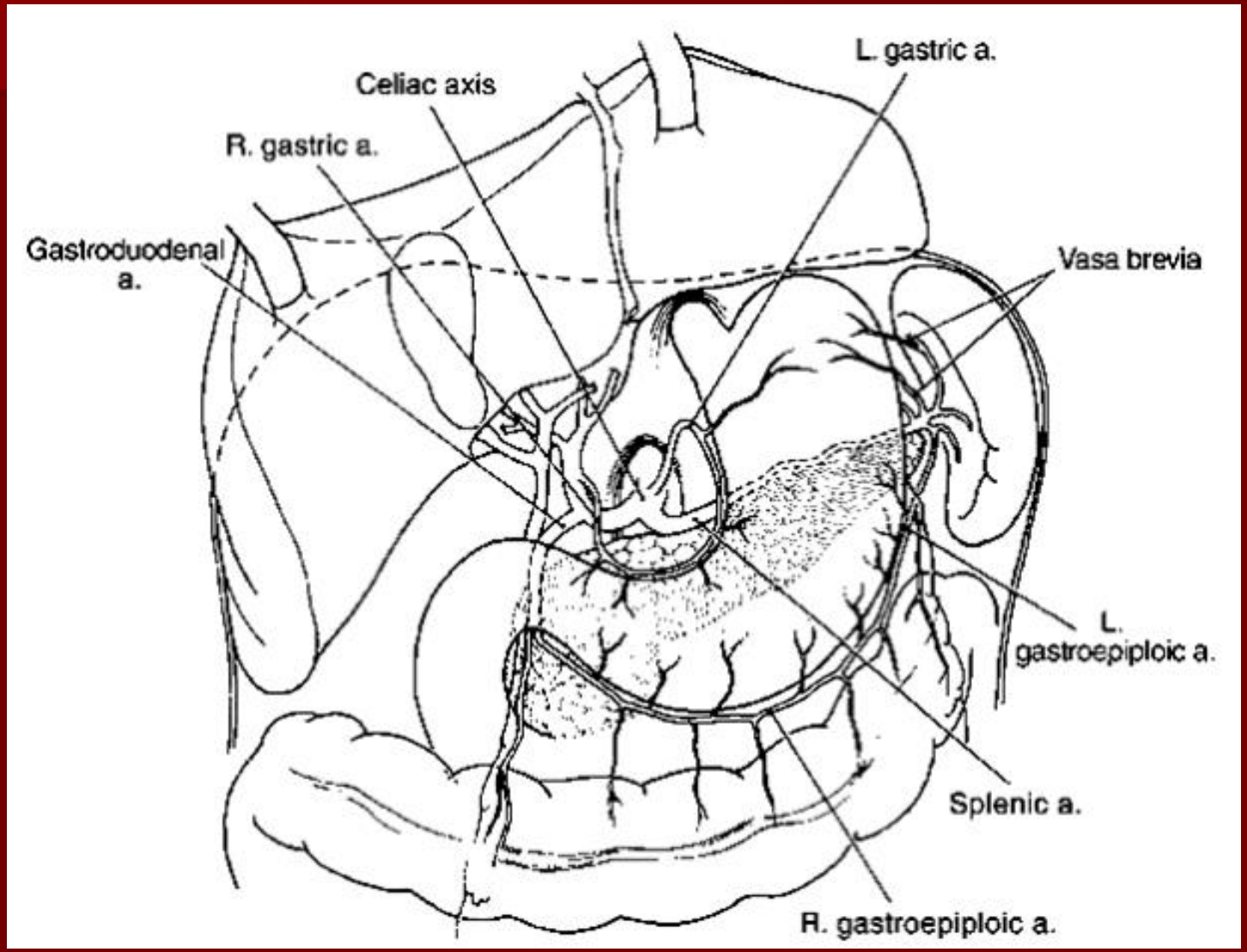
Results of therapy per stage

Stage	TNM	5-year survival (%)
0	Tis N0 M0	100
I	T1 N0 M0	57
II/A	T2 N0 M0 T3 N0 M0	40
II/B	T1 N1 M0 T2 N1 M0	25
III	T3 N1 M0 T4 N0-1 M0	10
IV	M1	~5

Gastric cancer

- **Incidence**: 9100 male, 5600 female
- **Mortality**: 5429 male, 3829 female
- **Etiology**
  - Diet: salt, nitrates (drinking water), smoked food
  - Coal mining, tyre / rubber industry
  - Smoking
  - H. pylori, Epstein-Barr Virus (EBV)
  - Previous Billroth II-type resection
- **Symptoms**
  - Anemia, weight loss, lack of appetite abdominal pain, bloody vomit, and tarry stool

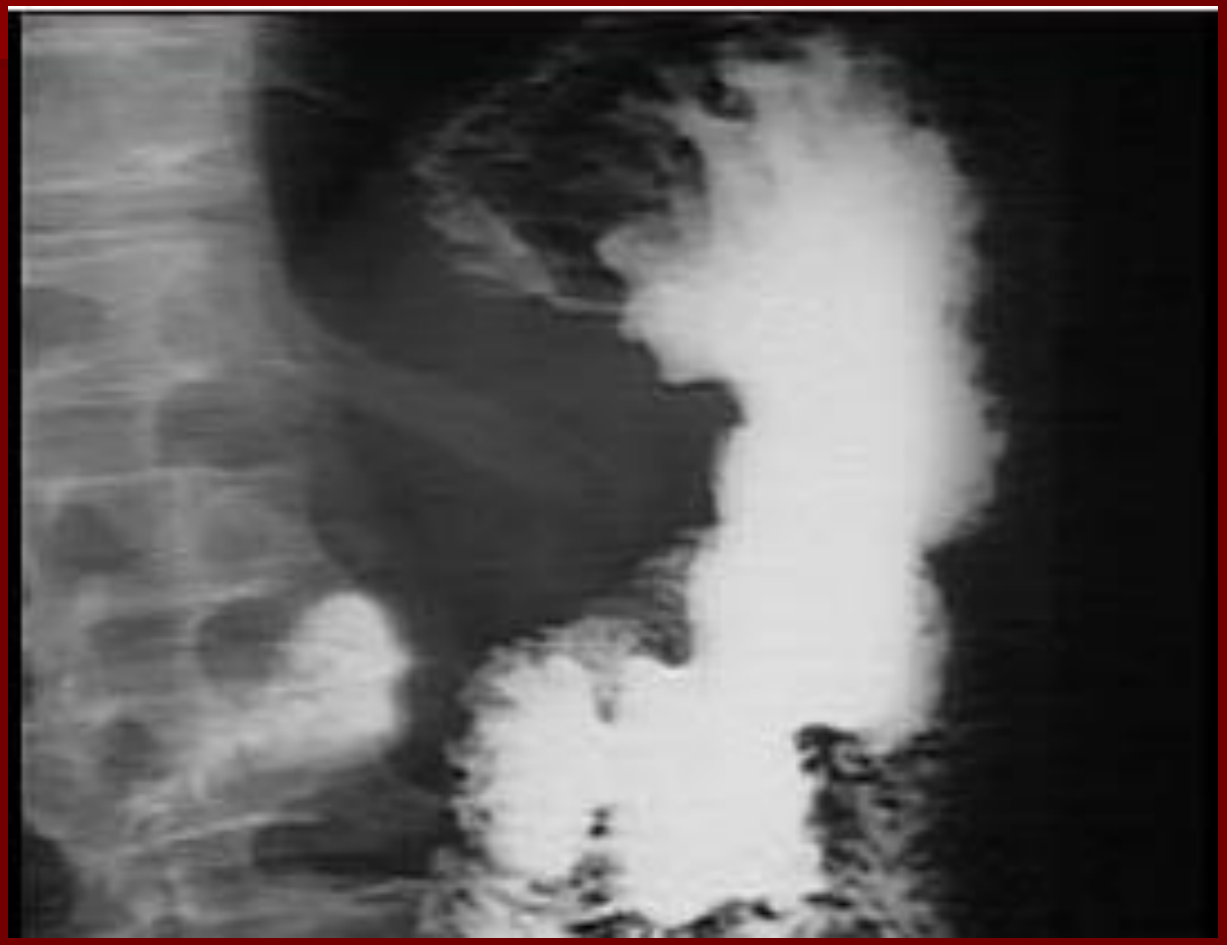
Anatomy


L. gastric a.
Celiac axis
R. gastric a.
Gastroduodenal a.
Vasa brevia
L. gastroepiploic a.
Splenic a.
R. gastroepiploic a.

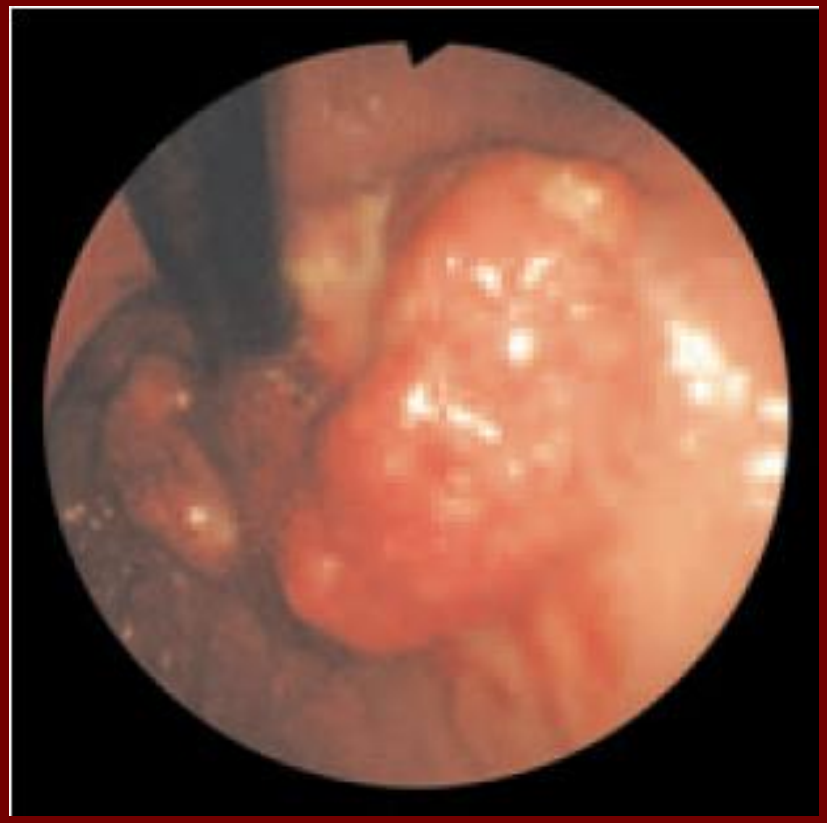
Clinical workup

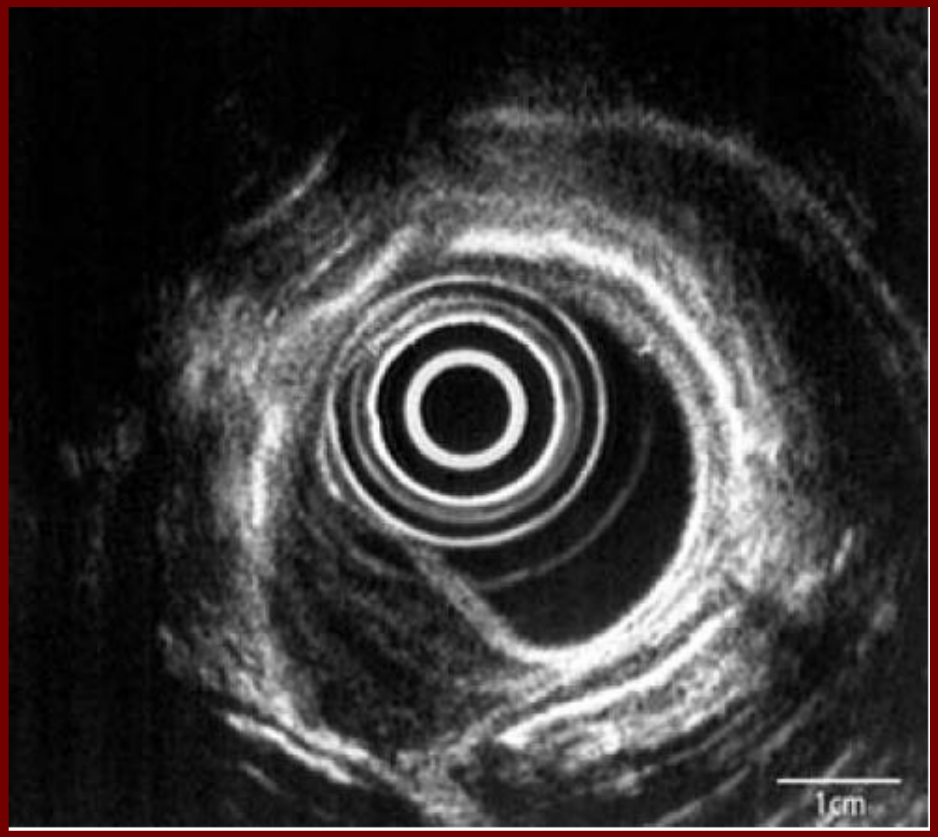
- **Histology**
  - Endoscopy
  - Mostly adenocarcinoma
    - Several subtypes (Lauren, Bormann)
    - Diffuse vs instestinal
- **Imaging**
  - Barium swallow
  - EUS
  - CT
  - PET/CT

Barium swallow

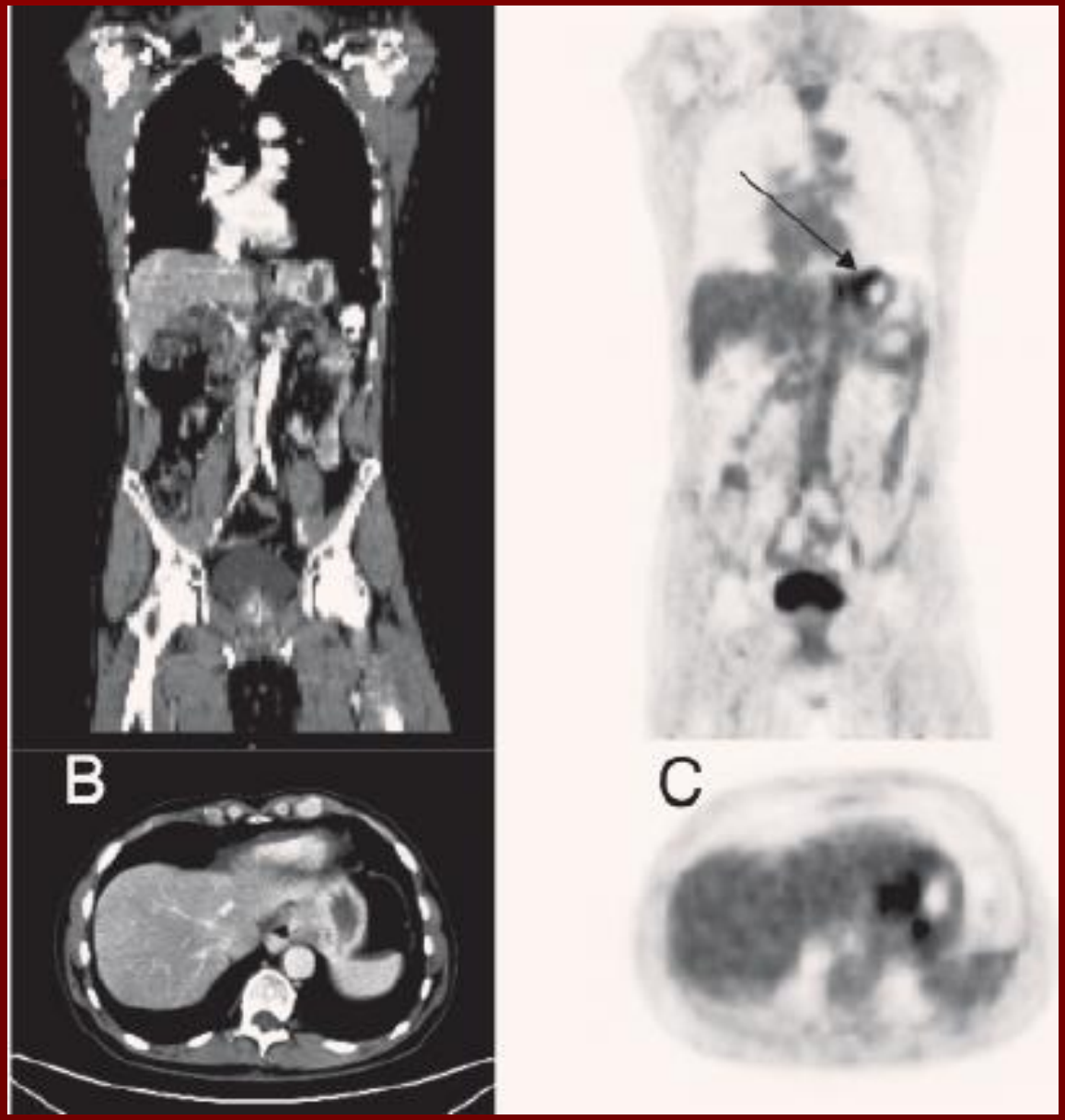


Endoscopy + EUS





CT – PET/CT



Staging

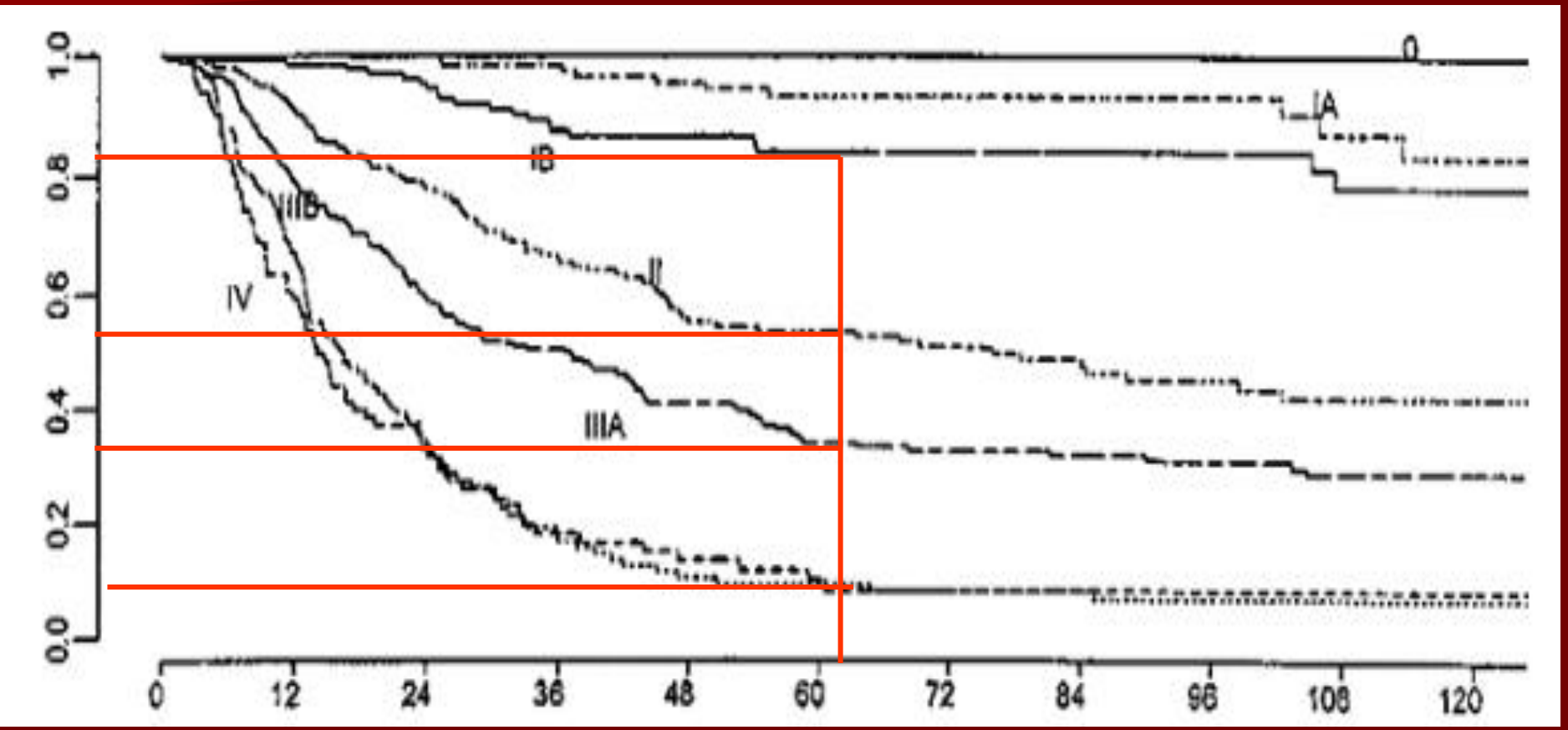
Tumour (T)	
Tis	In situ carcinoma
T1a	Tumour invades the lamina propria or muscularis mucosae
T1b	Tumour invades the submucosa
T2	Tumour invades the muscularis propria
T3	Tumour invades the subserosa, but not the peritoneum
T4a	Tumour invades visceral peritoneum
T4b	Tumour invades adjacent structures

Lymph node status (N)	
N0	No regional lymph node metastases
N1	1-2 regional lymph node metastases
N2	3-6 regional lymph node metastases
N3a	7-15 regional lymph node metastases
N3b	>16 regional lymph node metastases
Metastases (M)	
M0	No distant metastases
M1	Distant metastases are present

Principles of therapy

- Perioperative chemotherapy
  - 3 x chemotherapy – surgery – 3 x chemotherapy
- Primary surgery
  - Observation if low risk
  - Adjuvant chemoradiation if high risk
- Irresectable, non-metastatic
  - Perioperative chemotherapy
  - Chemoradiation
- Metastatic / recurrent
  - Chemotherapy (FLOT)
  - Biological therapy (trastuzumab, ramucirumab)
  - Immunotherapy (MSI, PD-L1 high)

Overall survival by stage



Pancreatic cancer

- **Incidence**: 8550 male, 8580 female
- **Mortality**: 8231 male, 8384 female
- **Etiology**
  - Smoking
  - Diabetes mellitus
  - Cirrhosis
  - Pancreatitis (alcoholic)
  - Obesity, high-fat diet
  - Chemicals (solvents with chloride)

Clinical workup

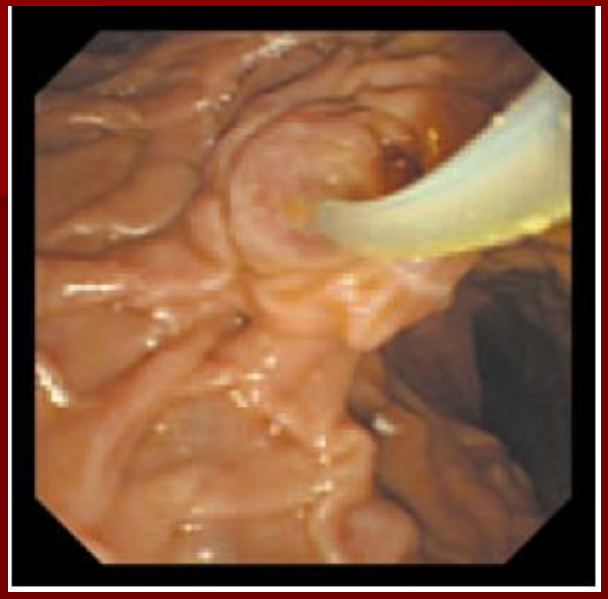
- **Symptoms**
  - belt-like pain, painless obstruction of the gallbladder, acute jaundice, asthenia, weight loss, anorexia, dark urine, nausea, back pain, steatorrhea, thrombosis, Curvoisier's sign
- **Biopsy / histology**
  - **Endoscopic way (ERCP, EUS guided)**
  - **CT guided**
  - **Laparoscopic biopsy**
- **Histology**
  - **Adenocarcinoma**
  - **Neuroendocrine cc.**
  - **Endocrine tumors**
    - **Insulinoma, glucagonoma etc.**
- **Imaging**
  - **Endoscopy/ERCP**
  - **EUS**
  - **US**
  - **CT / MR**
  - **PET/CT**

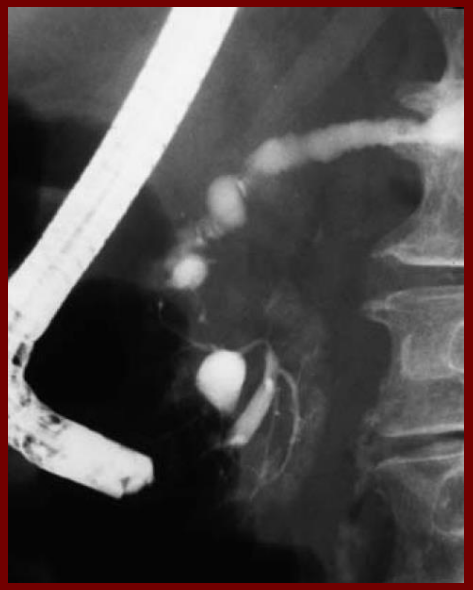
Staging

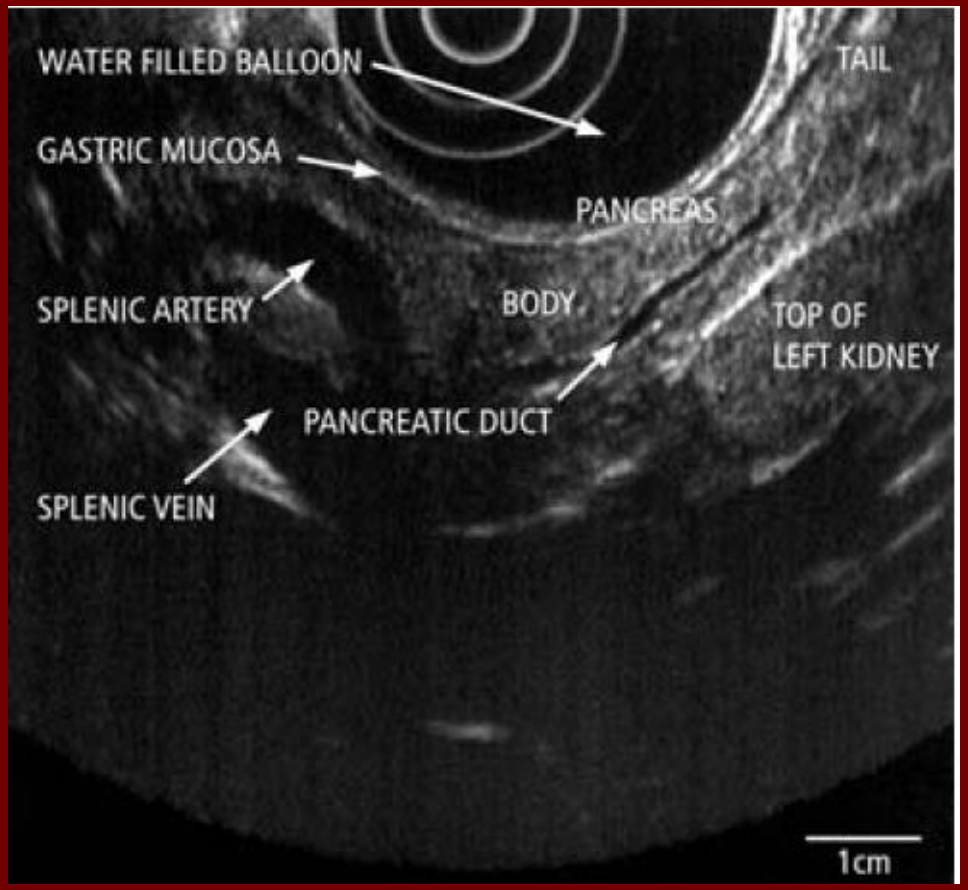
T Tumour	
Tis	Carcinoma in situ
T1	<2 cm tumour, confined to the pancreas
T2	>2 cm tumour, confined to the pancreas
T3	Tumour invades past the pancreas, but does not infiltrate large blood vessels
T4	Tumour infiltrates large blood vessels; unresectable tumour

N Lymph node	
N0	No lymph node metastases
N1	Regional lymph node metastases are present
M Metastases	
M0	No distant metastases
M1	Distant metastases are present

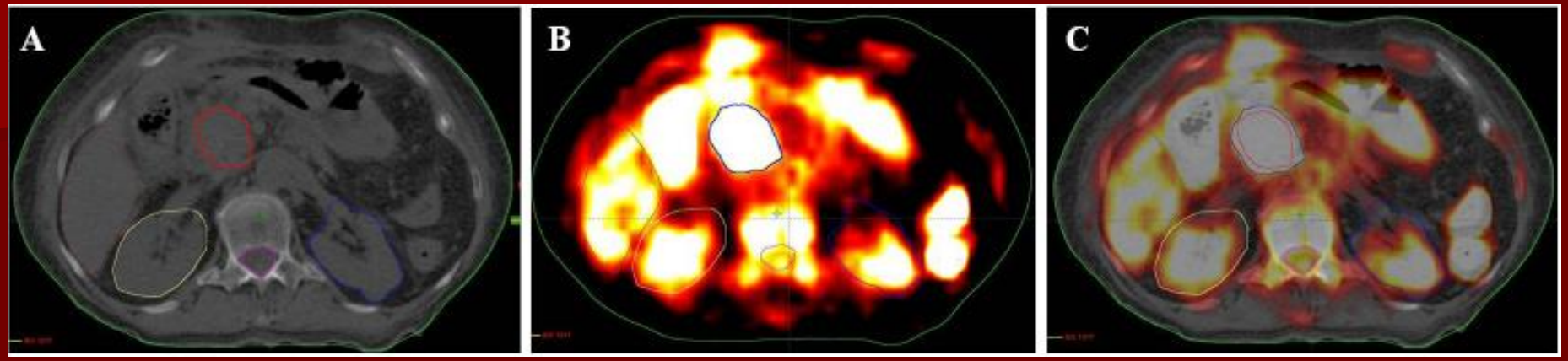
ERCP / Endoscopic US

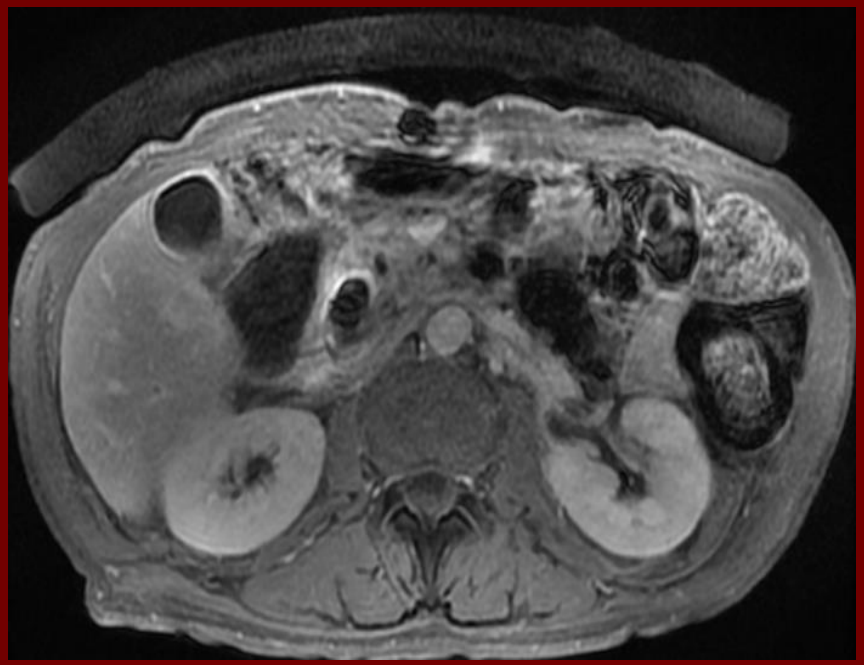






CT – PET/CT / MR





Principles of treatment

- **Resectable**
  - Surgery (20% resectable)
  - Postoperative chemotherapy
  - Postoperative chemoradiation (USA)
- **Locally advanced (LAPC)**
  - Chemotherapy
  - (Chemoradiation)
- **Metastatic**
  - Chemotherapy
- **Palliative treatment**
    - Jaundice, nutrition

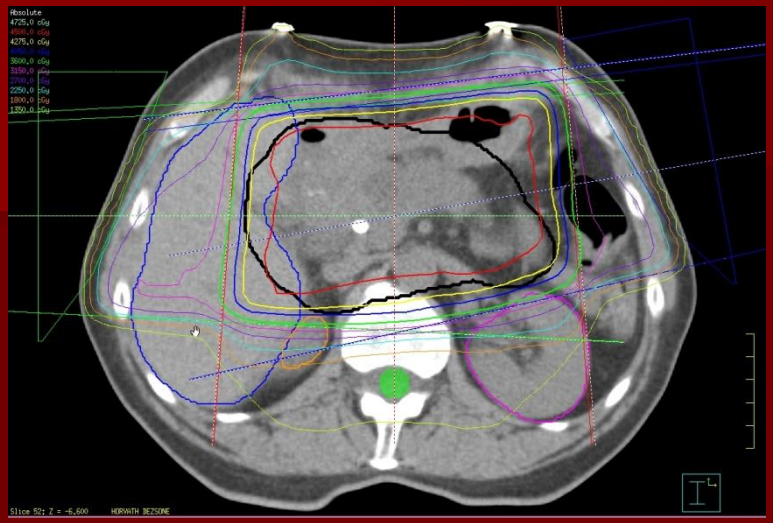
Surgery

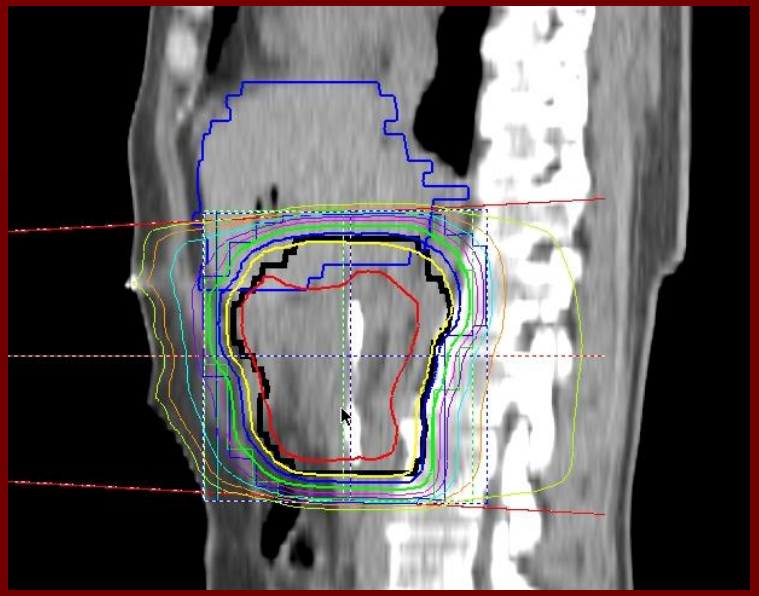
- **Criteria of resecability**
  - Resectable
  - Borderline resectable
    - Extends to retroperitoneum or vessels but possibly manageable with extended resection
  - Irresectable
    - Large vessel invasion, significant extension to retoperitoneum or adjacent organs
- **Whipple**-procedure (open or minimal invasive)
  - Pancreatico-duodenectomy with anastomosing the pancreatic stump, the choledochal duct, and the gastric stump into the jejunum

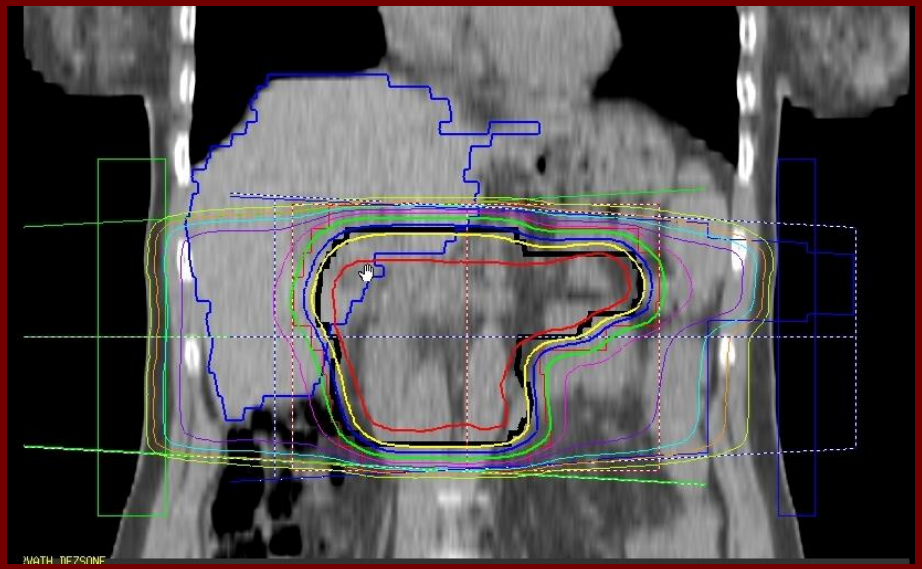
Radiotherapy / chemoradiation

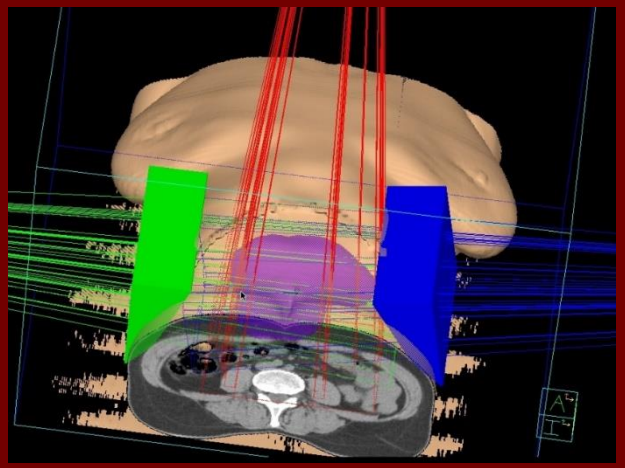
- **External beam radiotherapy**
  - Hig energy linear accelerator photon
    - CT / image fusion based conformal (IMRT) radiotherapy
    - 45-50,4 Gy, 1,8 Gy fractions
  - Stereotactic radiotherapy (SBRT)
    - 6x7-8 Gy
- **Concomittant chemotherapy**
  - Concomittant usually after induction chemo
  - 5 FU, gemcitabin (Gemzar)

External beam radiotherapy









Pharmacuetical therapy

- **Adjuvant** after R0 resection
  - Gemcitabine and capecitabine (oral 5FU)
  - Addition of radiotherapy remains controversial
- **LAPC**
  - FOLFOX (oxaliplatin, 5-Fluorouracil, folinic acid)
  - Gemcitabine +nab-paclitaxel
  - Gemcitabine + 5-Fluorouracil
  - Addition of radiotherapy remains controversial
- **Metastatic** (patient selection!)
  - FOLFIRINOX (5FU/irinotecan/oxaliplatin)
  - Gemcitabine +nab-paclitaxel

Results of therapy

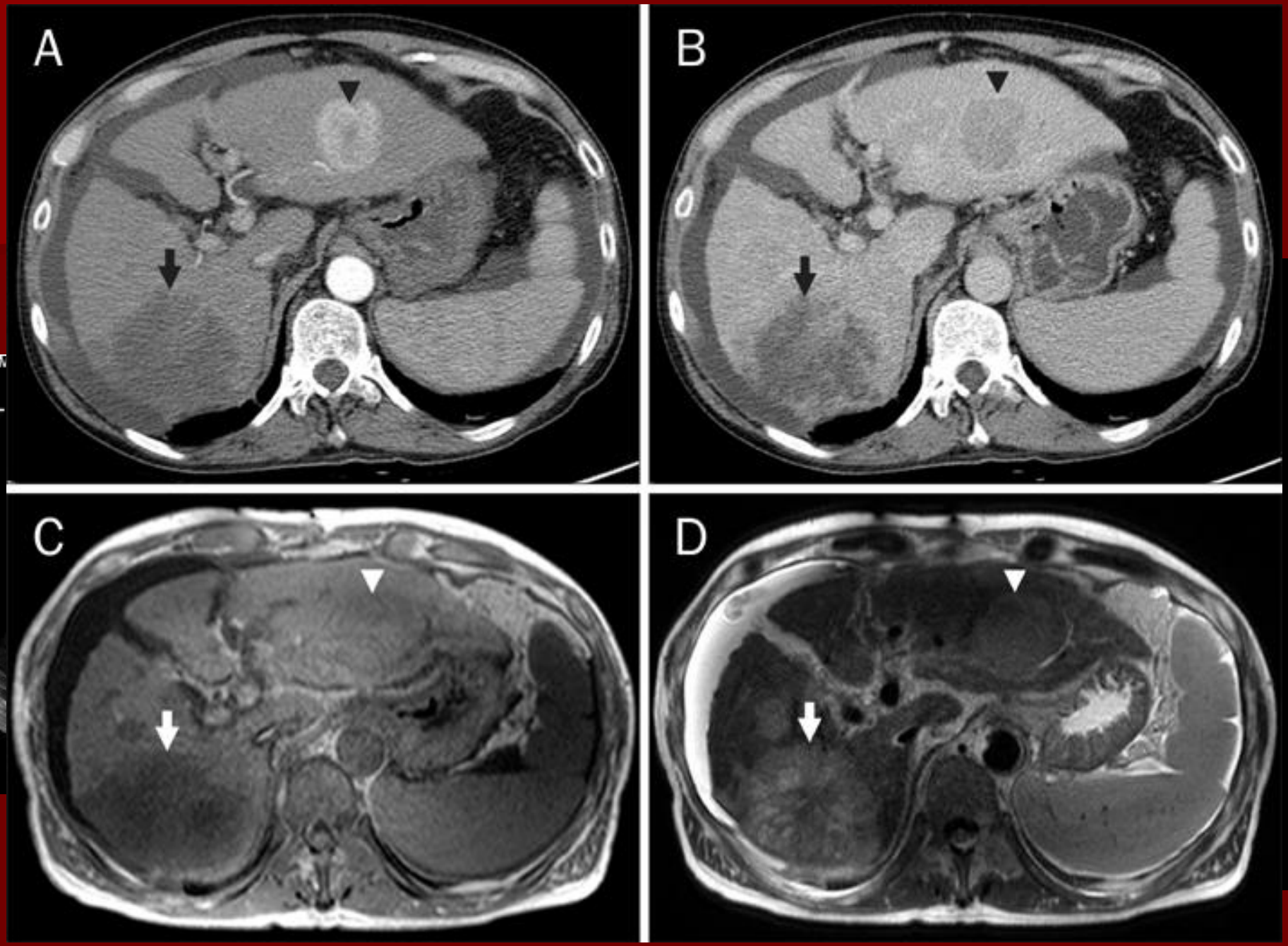
- Median overall survival
  - Resection + adjuvants therapy
    - ~20-22 months
  - LAPC
    - ~ 15 months
  - Metastatic
    - 4-6 months

Liver cancer

- **Incidence**: 6370 male, 2710 female
- **Mortality**: 5246 male, 2440 female
- **Etiology**
  - Cirrhosis
    - Alcoholic
    - Non-aclocholic
    - Hepatitis B, C
    - aflatoxin

Liver cancer

- **Symptoms**
  - Non-specific
  - Weight loss, loss of appetite, feeling full after a small meal, nausea or vomiting, enlarged liver, spleen, pain in the abdomen or near the right shoulder blade, swelling or fluid in the abdomen, itching jaundice
- **Biopsy / histology**
  - US guided
- **Histology**
  - Hepatocellular cc
  - Cholangiocellular cc
- **Imaging**
  - US
  - MRI


A
B
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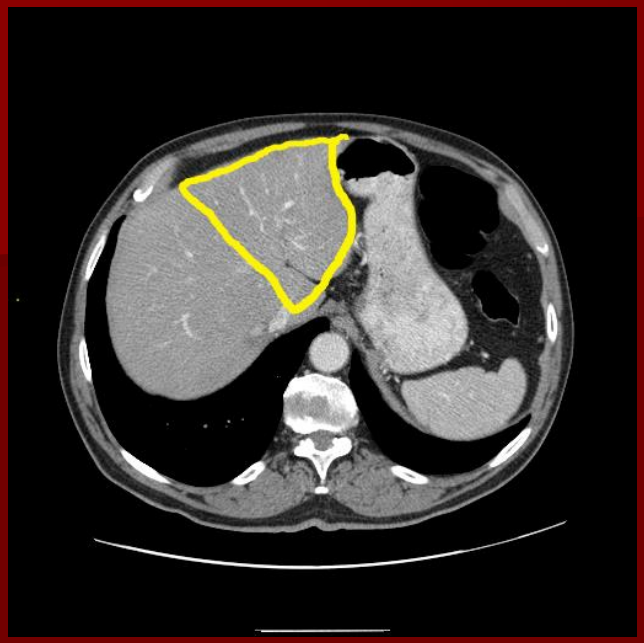
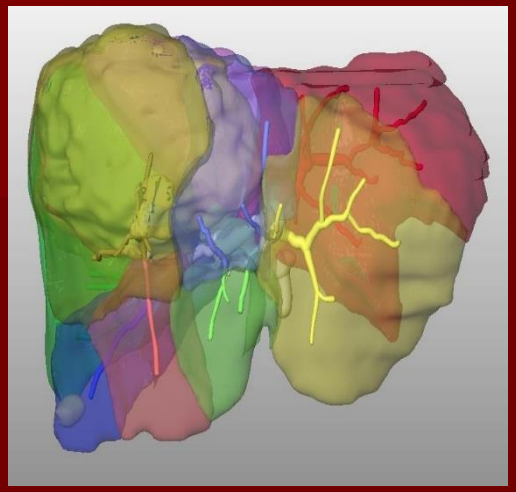
Staging

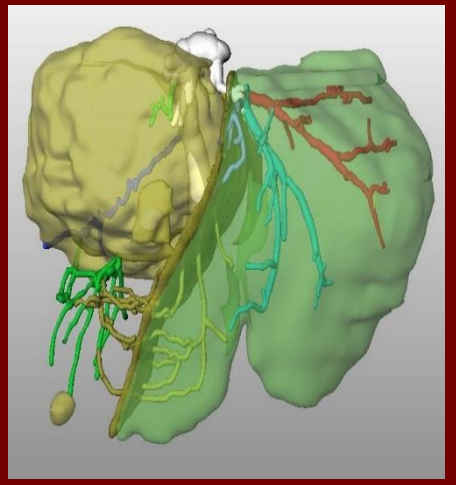
- Tumour is confined to the liver with a maximum of 1-5 nodules; surgically **resectable**; no evidence of extrahepatic manifestation or other metastases
- Tumour is confined to the liver; no evidence of extrahepatic manifestation; surgically **unresectable** (too many nodules, the resection is not technically feasible)
- Tumour is confined to the liver with locoregional lymph node metastases; **no** evidence of systemic **metastases**
- Tumour has **metastasized** to distant organs

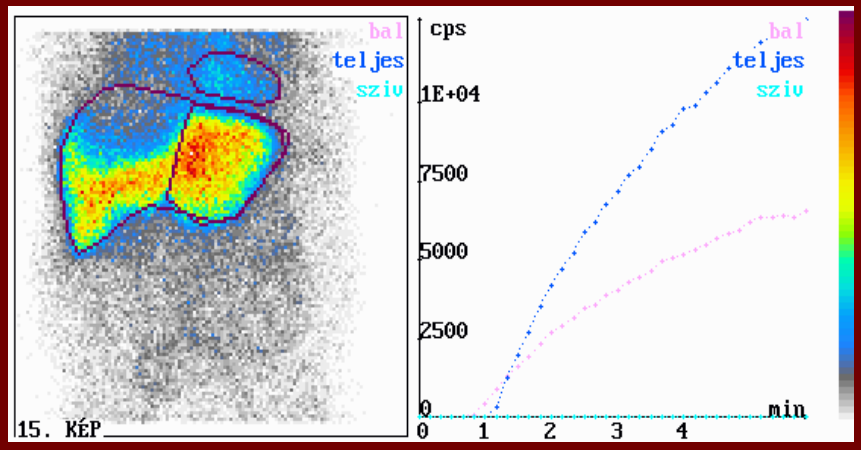
Princilpes of treatment

- Surgery if resectable
  - Minimally invasive or open
  - The question what remains not what is resectable





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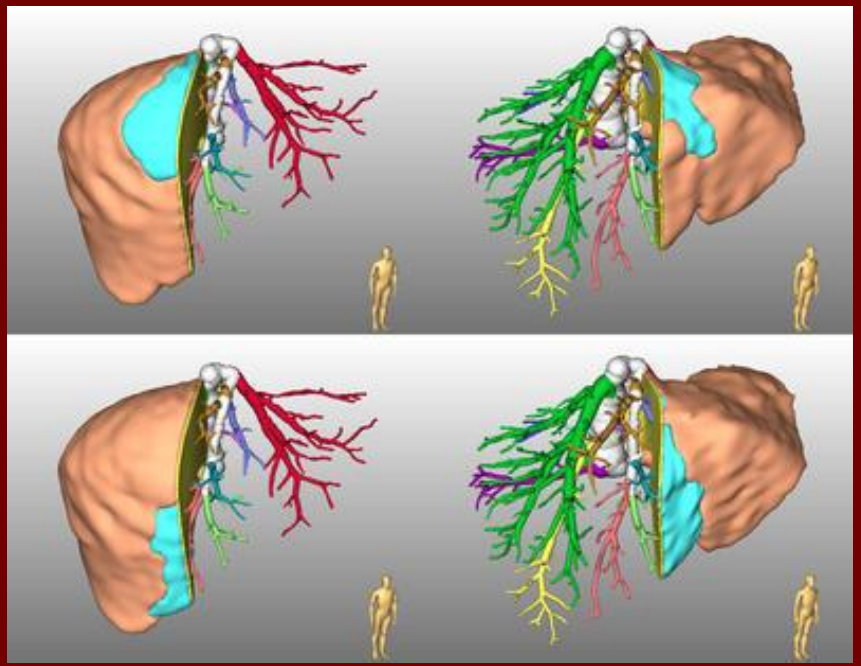


Principles of treatment

CHILD-PUGH SCORE

Chemical and Biochemical Parameters	Scores (Points) for Increasing Abnormality		
	1	2	3
Encephalopathy (grade)[1]	None	1–2	3–4
Ascites	Absent	Slight	Moderate
Albumin (g/dL)	>3.5	2.8–3.5	<2.8
Prothrombin time[2] Seconds over control INR	 <4 <1.7	 4–6 1.7–2.3	 >6 >2.3
Bilirubin (mg/dL) • For primary biliary cirrhosis	<2 <4	2–3 4–10	>3 >10

Class A = 5–6 points; Class B = 7–9 points; Class C = 10–15 points.

- Many are under invastigation e.g. immunotherapy

Colorectal cancer epidemiology/etiology

- **Incidence**: 31120 male, 27890 female
- **Mortality**: 13580 male, 11932 female
- **Etiology**
  - Non-infulencable
    - Inflammatory bowel disease (Crohn, ulcerative colitis)
    - Familial
      - FAP (familial adenomatous polyposis), APC gene
      - Lynch syndrome, mismatch repair gene
  - Influencable
    - Physical activity, NSAID, high-fibre diet, vit D reduces risk
    - Smoking, obestiy, red meat, alcochol increases risk

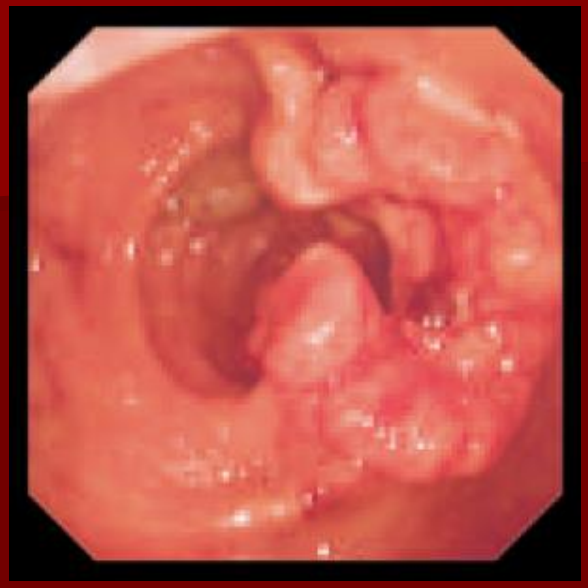
Colorectal cancer screening

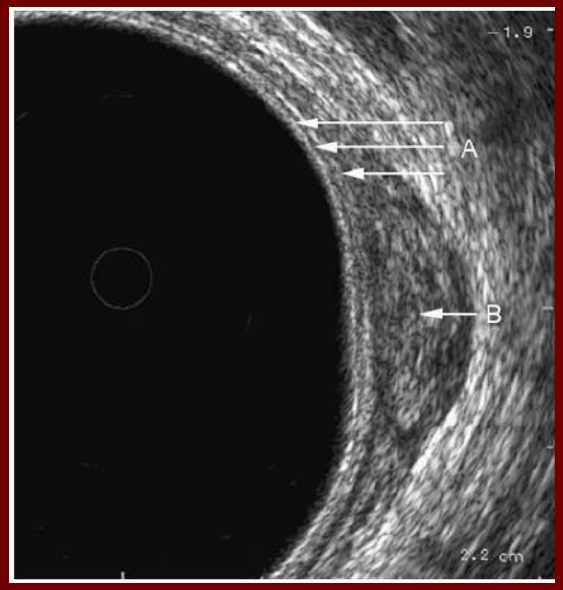
- Fecal occult blood (FOB)
- Endoscopy / capsular endoscopy
- Fecal tumor DNA
- CT colography
- PET-colography

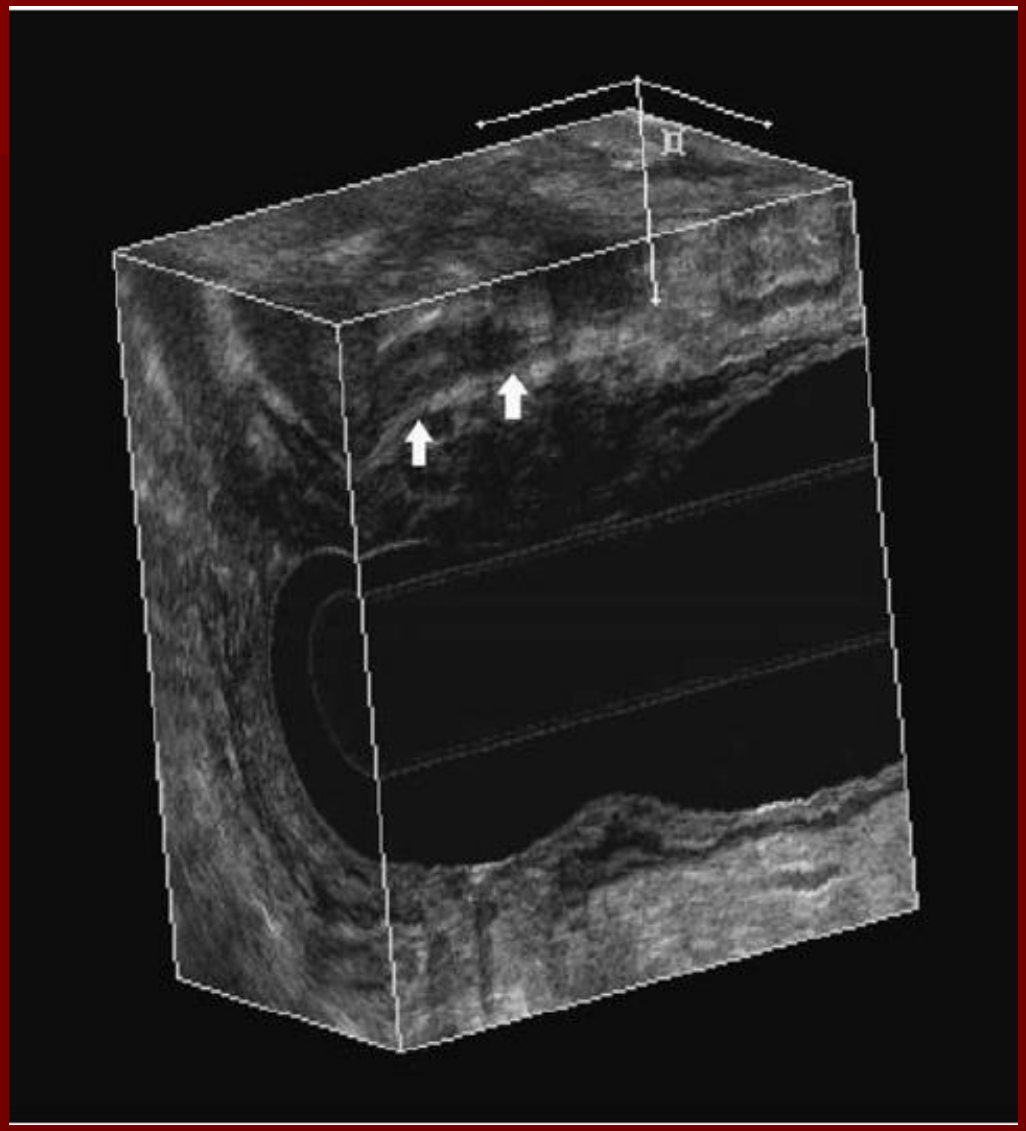
Clinical workup

- **Symptoms**
  - Fecal blood, altered defecation habits, loss of appetite, weight loss, abdominal complaints, bloating, discomfort, pain, obstipation
- **Biopsy**
  - Usually through endoscopy
  - Sometimes from metastasis
- **Histology**
  - **Adenocarcinoma**
    - **APC,p53,KRAS,BRAF**
    - **MSI**
    - **CIMP phenotype**
- **Imaging**
  - **CT**
  - **US**
  - **MR**
  - **PET-CT**

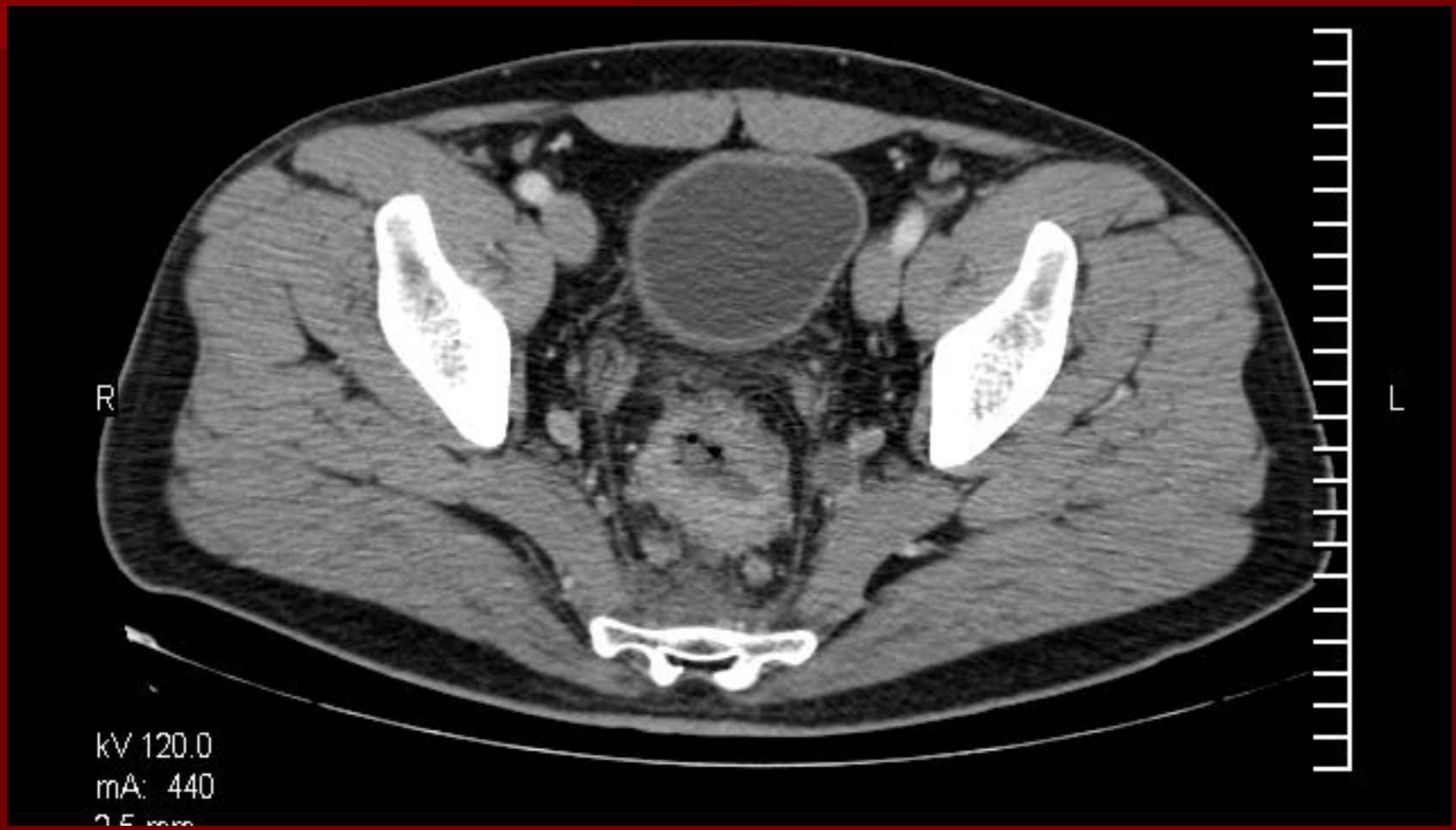
Endoscopy / EUS / TRUS



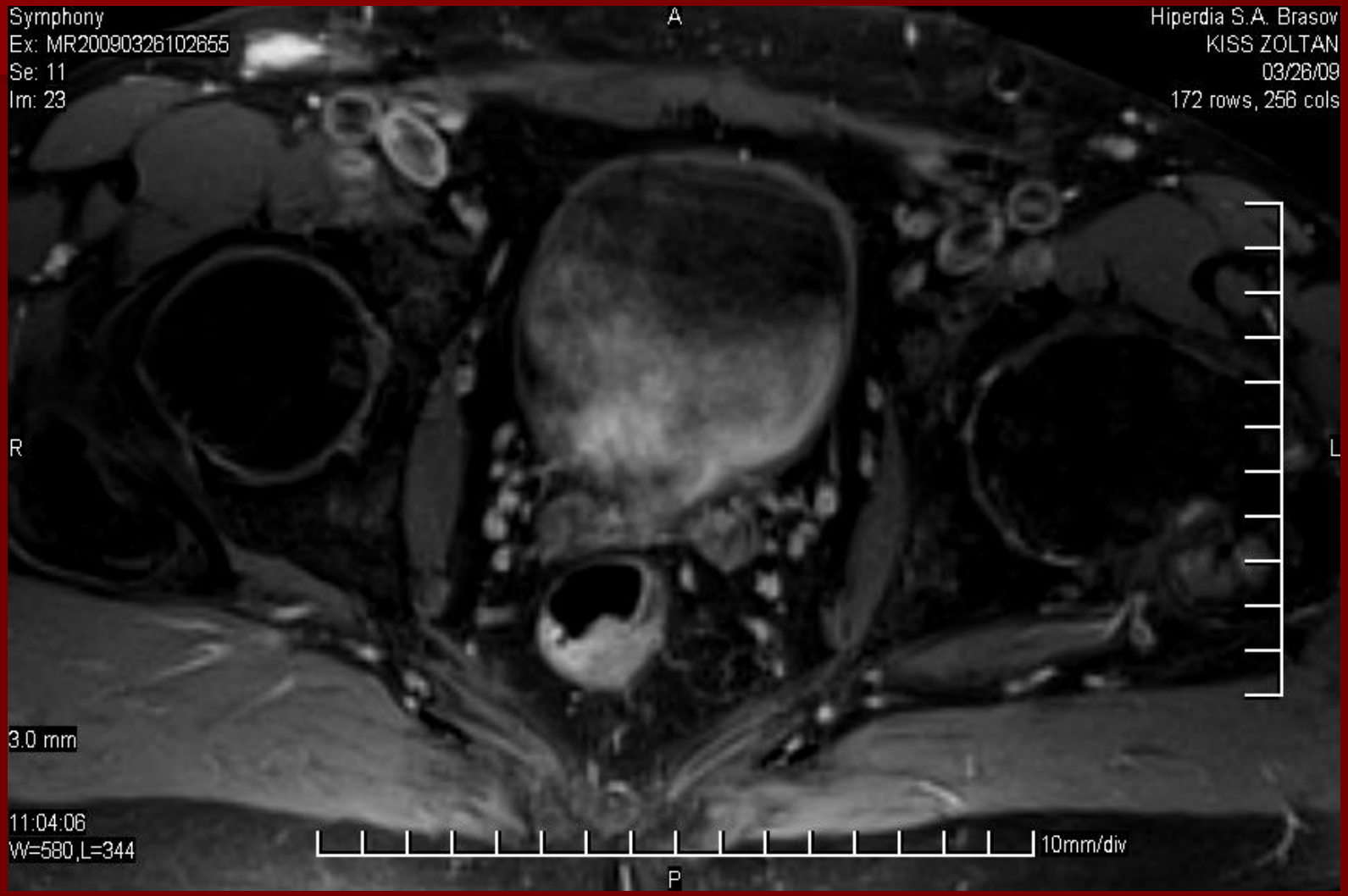




CT – MR – PET/CT



CT – MR – PET/CT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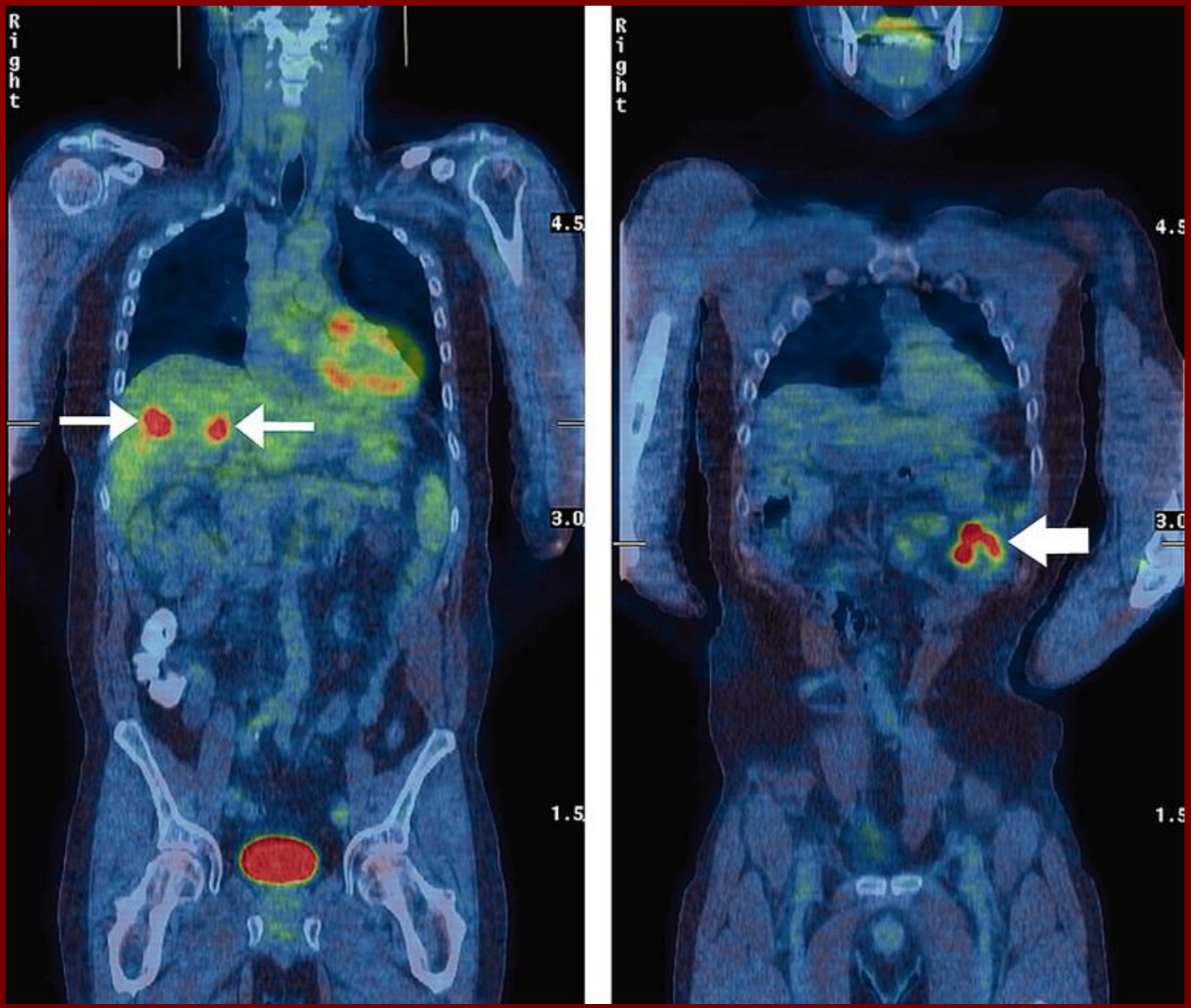
Right
4.5
3.0
1.5
Right

Staging

pT stage	
pT0	No tumour can be detected
pTis	carcinoma in situ – tumour is intraepithelial or invades the lamina propria (intramucosal tumour)
pT1	Tumour invades the submucosa
pT2	Tumour invades the muscularis propria
pT3	Tumour invades pericolorectal tissues
pT4a	Tumour penetrates the surface of the visceral peritoneum
pT4b	Tumour invades adjacent organs or structures

pN stage	
pN0	No lymph node metastases
pN1	Tumour has metastasised to 1-3 regional lymph nodes
pN1a	Tumour has metastasised to 1 regional lymph node
pN1b	Tumour has metastasised to 2-3 regional lymph nodes
pN1c	Tumour deposits in the pericolorectal connective tissue without structural evidence of lymph nodes if there are no lymph node metastases
pN2	Tumour has metastasised to 4 or moreregional lymph nodes
pN2a	Tumour has metastasised to 4-6 regional lymph nodes
pN2b	Tumour has metastasised to 7 or more regional lymph nodes

Staging

M stage	
M0	No evidence of distant metastases
M1	Distant metastases are present
M1a	Tumour has metastasised to one organ/site, with no peritoneal metastases
M1b	Tumour has metastasised to two or more organs/sites, with no peritoneal metastases
M1c	Peritoneal metastases with our without other metastases

Stage	T	N	M	Dukes	MAC
0	Tis	N0	0	–	–
I.	T1 T2	N0 N0	0 0	A A	A B1
IIA	T3	N0	0	B	B2
IIB	T4a	N0	0	B	B3
IIC	T4b	N0	0	B	B3
IIIA	T1-2 T1	N1 N2a	0 0	C	C1
IIIB	T1-2 T2-3 T3-4a	N2b N2a N1	0 0 0	C	C2/3
IIIC	any T	N2	0	C	C1-3
IVA	any T	any N	1a	–	D
IVB	any T	any N	1b	–	D
IVC	any T	any N	1c	–	D

Principles of treatment-colon

- **Tis, small T1a**
  - Endoscopic surgery
- **Local-locally advanced colon tumor**
  - Radical surgery
    - Hemicolectomy, transversal segment colectomy, subtotal-total colectomy
  - Adjuvant chemotherapy (>pT3, N+)
    - 5FU / FOLFOX

Principles of treatment-rectal

- **Tis, small T1a**
  - Endoscopic surgery (TEM, TAMIS, TAE)
- **Local-locally advanced rectal cancer**
  - Neoadjuvant radiotherapy /chemoradiation
    - 5x5 Gy immediate surgery (< 7 days)
    - 50,4 Gy+5FU /capecitabine, surgery in 8 weeks
  - Followed by radical surgery
    - Total Mesorectal Excision (TME)
  - Adjuvant chemotherapy
    - 5FU / FOLFOX

Treatment of metastatic CRC

- Always **multidisciplinary**
- Aim is to make the patient **tumor-free**
- Primary treatent is usually medical therapy
  - Chemotherapy + targeted therapy
  - wtKRAS : cetuximab, panitumumab
  - KRAS mutant: bevacizumab / ramucirumab
  - Regorafenib, TAS 102
- Evaluation for local treatment/oligometastasis
  - Surgery, RFA, SABRT

Results of treatment

- 5-year survival
  - Local (T1-2 N0 M0) ~90 %
  - Locally advanced (T1-3 N+ M0) ~68%
  - Metastatic ~ 10-15%
    - median OS now 36 months!

Anal canal cancer

- **Epidemiology-etiology**
  - Rare disease
  - HPV associated, anal injury
  - Histology: squamous cell cancer
- **Treatment**
  - Small tumors: local excision
  - Standard treatment: primary chemoradiation
  - Residual/recurrent disease: “salvage surgery”
- Chemoradiation
  - 45-59,4 Gy + mytomycin C és 5FU
  - 5-year survival: 75%
  - colostomy ~ 20%