Registration of neoplasia of the digestive system: towards a better understanding (presented 25 and 27 nov 2014)

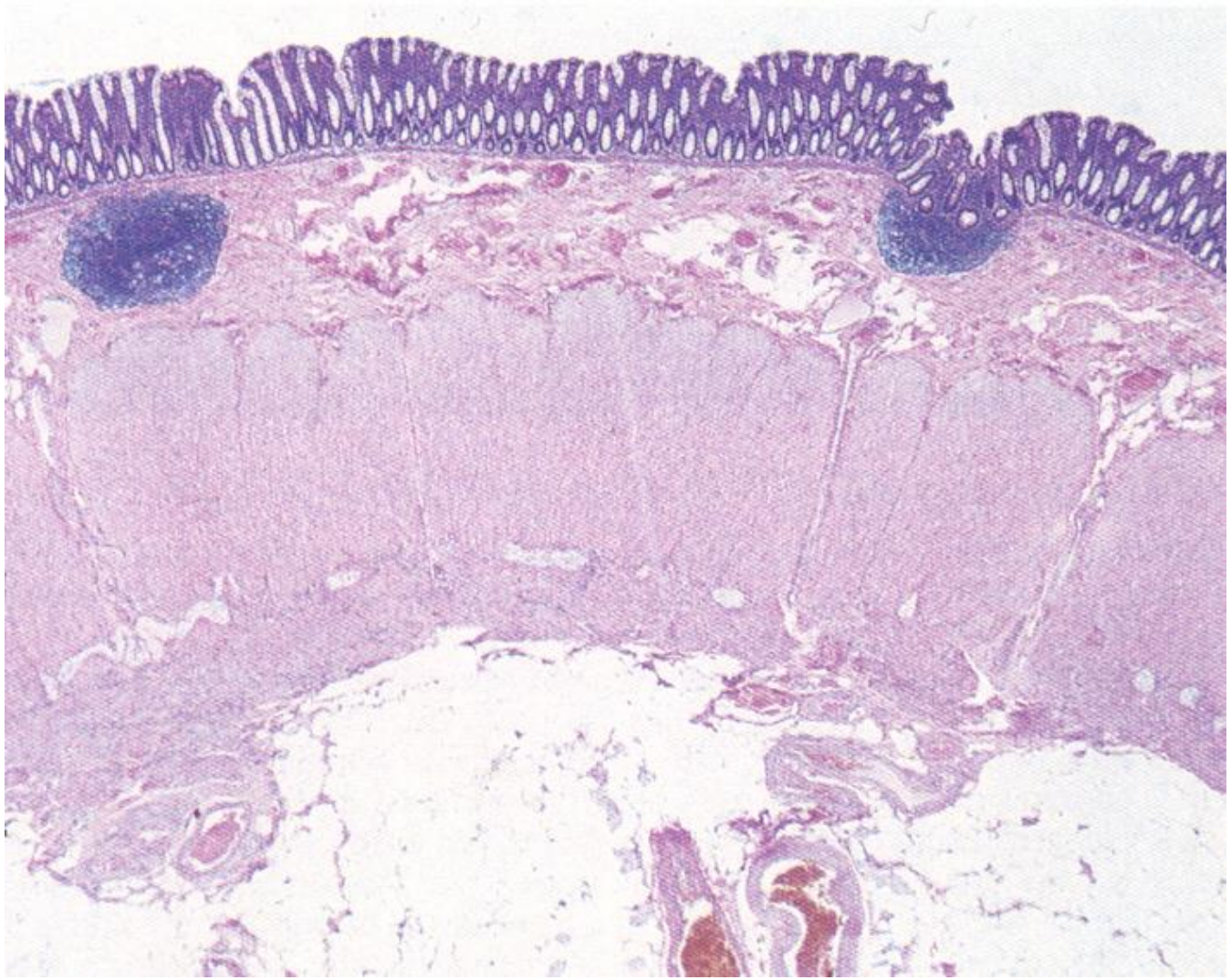
Pieter Demetter
Department of Pathology
Erasme University Hospital
Université Libre de Bruxelles (ULB)

Slightly adapted by BCR and approved by P. Demetter

THE COMPONENTS OF THE DIGESTIVE SYSTEM

- Digestive tract: oesophagus, stomach, small intestine, colon and rectum, anal canal
- Pancreas
- Liver and bile ducts

Wall of the digestive tract: general structure



mucosa

MUCOSA :
1. Epithelium
2. Basal membrane
3. Lamina propria
4. Muscularis mucosae

submucosa

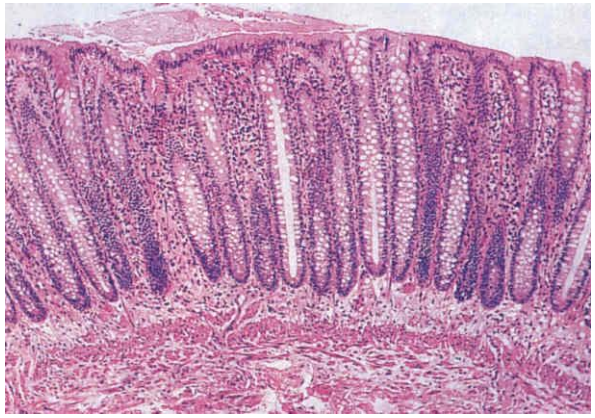
muscularis propria

subserosa

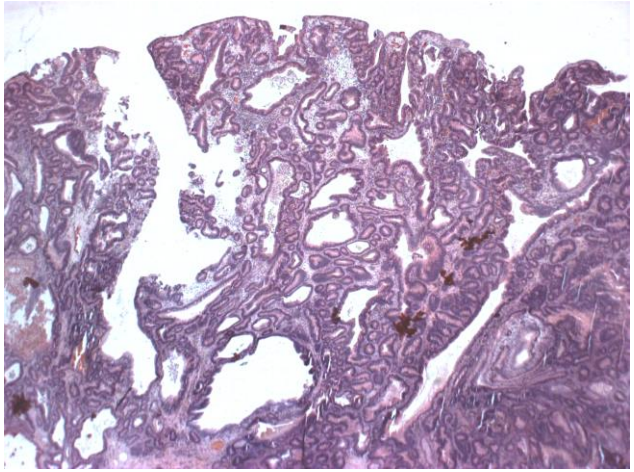
serosa

Tumours originating in the epithelium → carcinomas : the most frequent tumour of the digestive tract

normal > premalignant > malignant

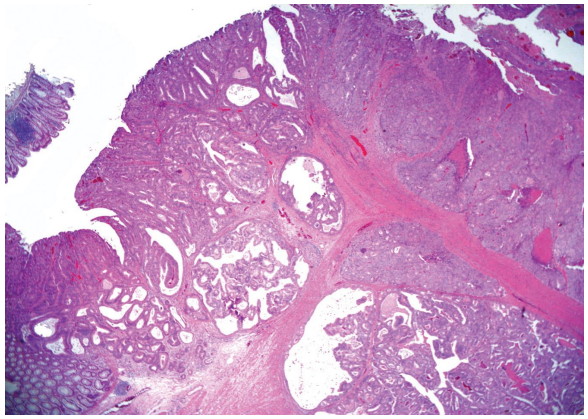


Dysplasia : alteration of cells but not yet capacity to invade other structures ; **basal membrane remains intact**

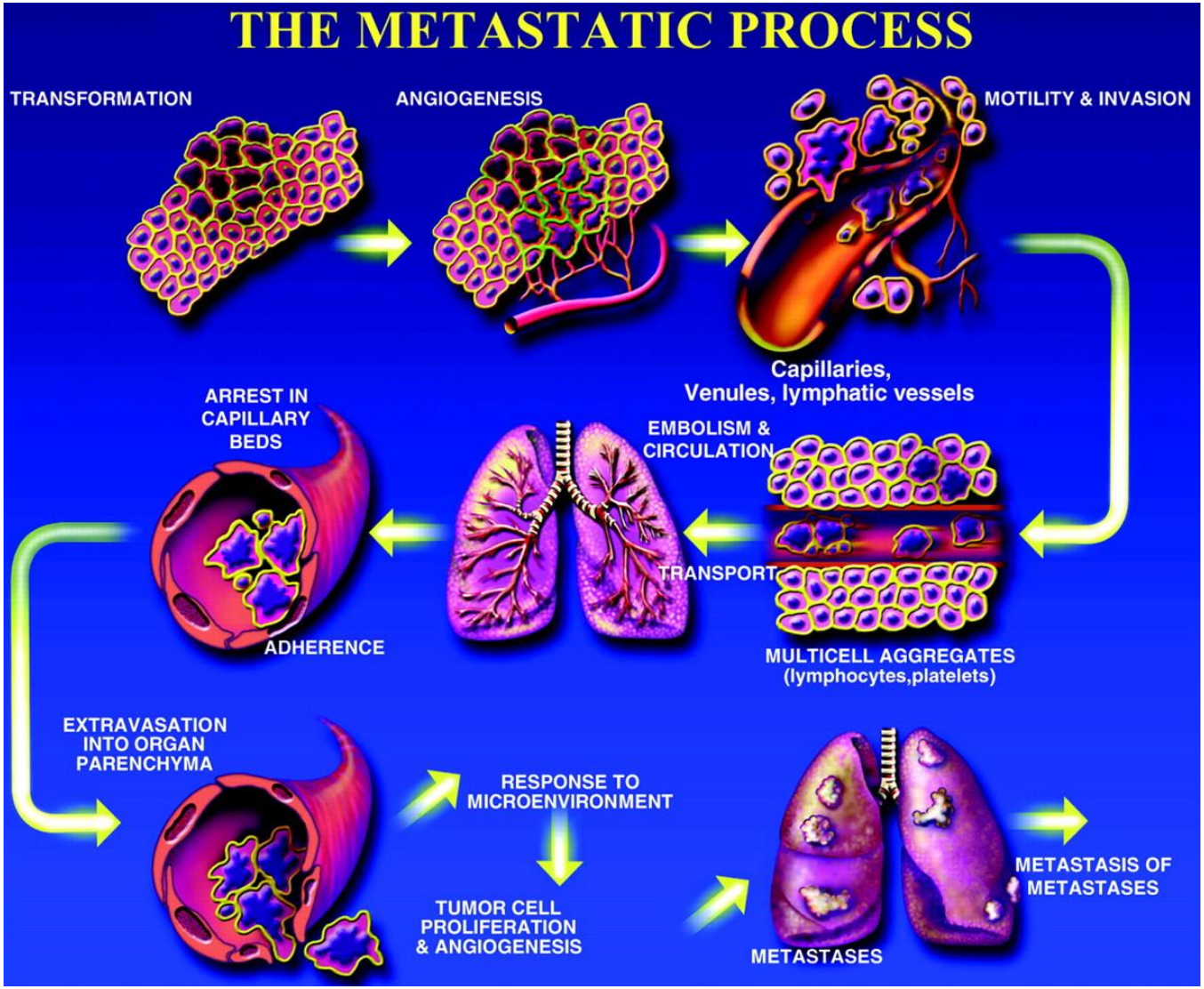


High grade dysplasia → /2 ; in situ tumour ; not yet invasive tumour

Invasive tumour (malignant tumour) : cells are capable to invade deeper structures and to spread to other organs by means of lymph/blood vessels ; **basal membrane is ruptured**

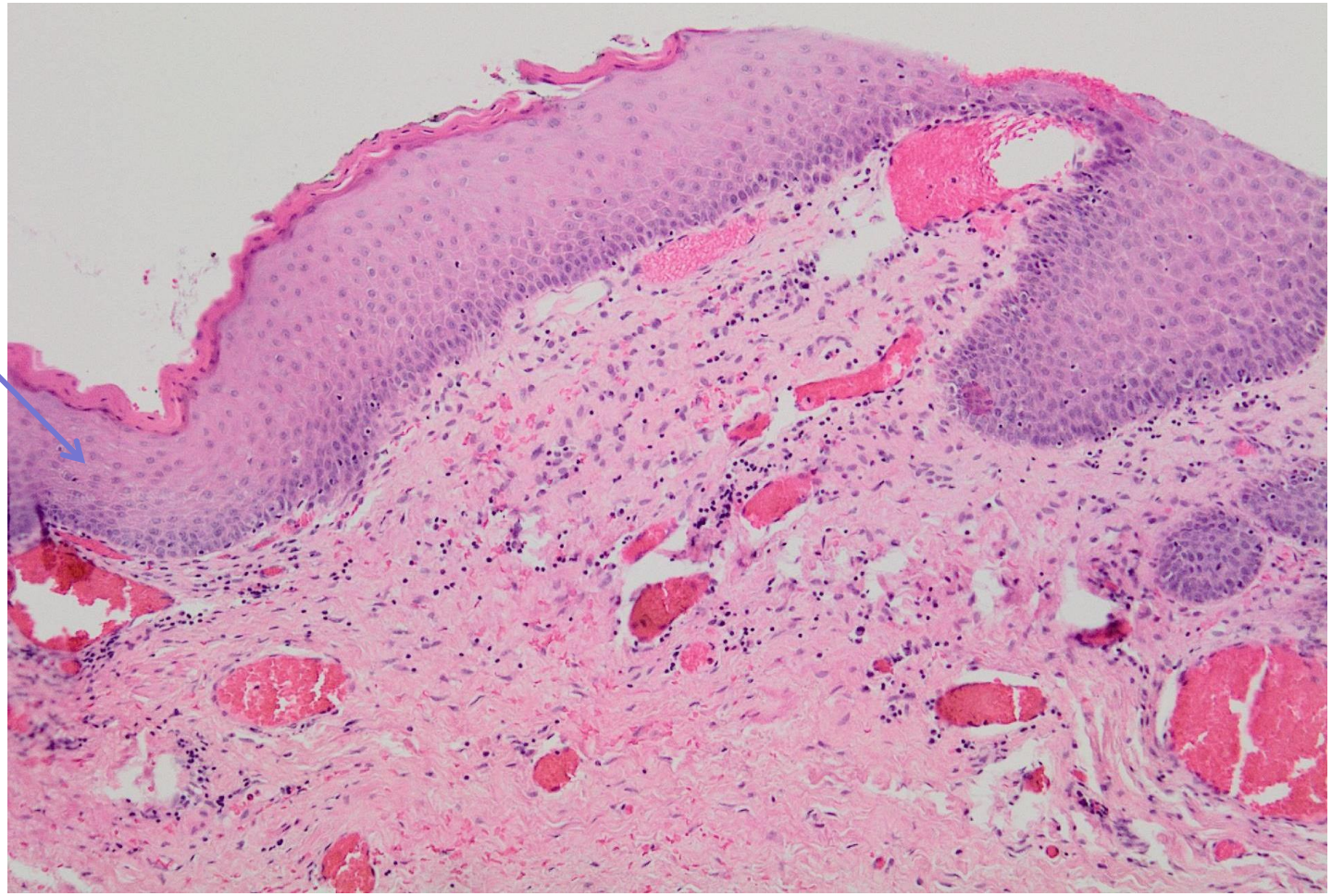


DEVELOPMENT OF METASTASES



THE NORMAL OESOPHAGUS

Normal squamous epithelium, no glands present



WHO histological classification of oesophageal tumours

Epithelial tumours	
Squamous cell papilloma	8052/0[1]
Intraepithelial neoplasia[2]	
Squamous	
Glandular (adenoma)	
Carcinoma	
Squamous cell carcinoma	8070/3
Verrucous (squamous) carcinoma	8051/3
Basaloid squamous cell carcinoma	8083/3
Spindle cell (squamous) carcinoma	8074/3
Adenocarcinoma	8140/3
Adenosquamous carcinoma	8560/3
Mucoepidermoid carcinoma	8430/3
Adenoid cystic carcinoma	8200/3
Small cell carcinoma	8041/3
Undifferentiated carcinoma	8020/3
Others	
Carcinoid tumour	8240/3

Non-epithelial tumours	
Leiomyoma	8890/0
Lipoma	8850/0
Granular cell tumour	9580/0
Gastrointestinal stromal tumour	8936/1
benign	8936/0
uncertain malignant potential	8936/1
malignant	8936/3
Leiomyosarcoma	8890/3
Rhabdomyosarcoma	8900/3
Kaposi sarcoma	9140/3
Malignant melanoma	8720/3
Others	

Secondary tumours

---

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snor Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for in situ carcinomas and grade III intraepithelial neoplasia, a malignant tumours.

[2] Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are available only for lesions categorized as glandular intraepithelial neoplasia (8148/2), squamous intraepithelial neoplasia, grade III (8077/2), and squamous cell carcinoma in situ (8070/2).

OESOPHAGUS: 2 MAIN CANCER TYPES

- Squamous cell cancer (epidermoid cancer, spinocellular carcinoma, mainly 8070/3)

Most frequent in upper third and middle third of oesophagus (but possible in the lower part!)

Risk factors : tobacco, alcohol, hot liquids, …

- Adenocarcinoma (mainly 8140/3)

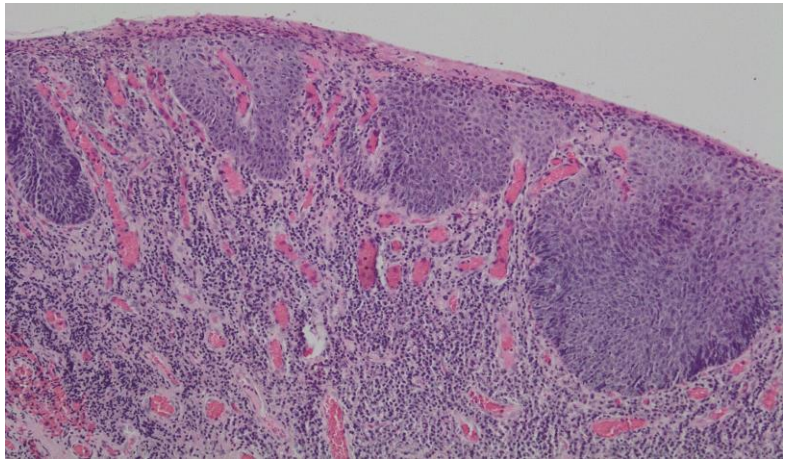
More frequent in the lower part of the oesophagus (but possible in the higher parts !)

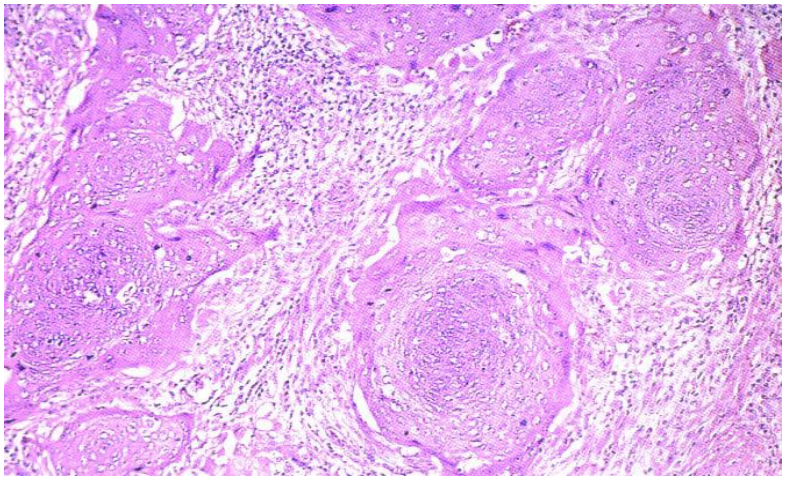
Risk factors : reflux of gastric acid, tobacco, alcohol, obesity,…

DEVELOPMENT OF SQUAMOUS CELL CANCER (mainly 8070/3)

DYSPLASIA : dysplastic cells remain in the epithelial layer : no rupture of the basal membrane

CANCER : basal membrane is ruptured → invasive tumour





Most frequently in upper 1/3 (and middle 1/3) of the oesophagus.
Risk factors: smoking, alcohol

> Search for other cancer locations (lung, ORL)

DEVELOPMENT OF ADENOCARCINOMA IN THE OESOPHAGUS (mainly 8140/3)

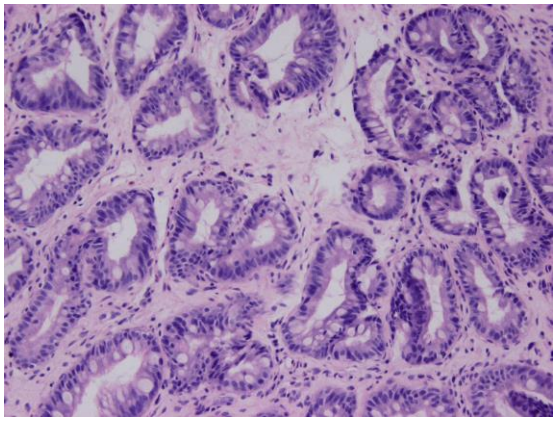
Hôpital Erasme | ULB

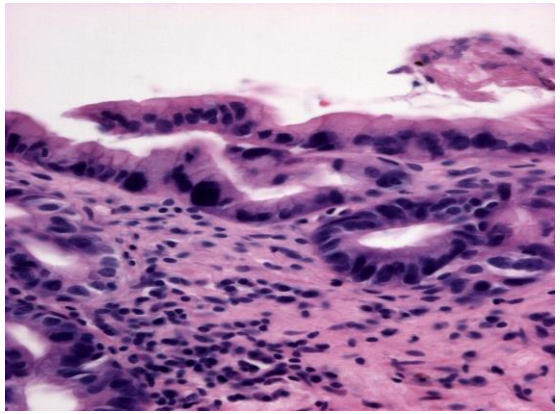
METAPLASIA

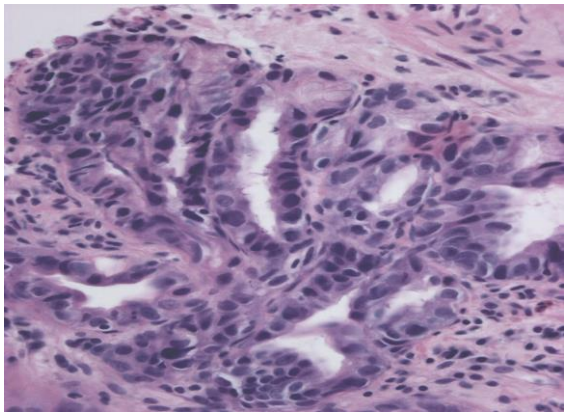
Barrett oesophagus : non-dysplastic glandular structures appear in the lamina propria

DYSPLASIA

ADENOCARCINOMA



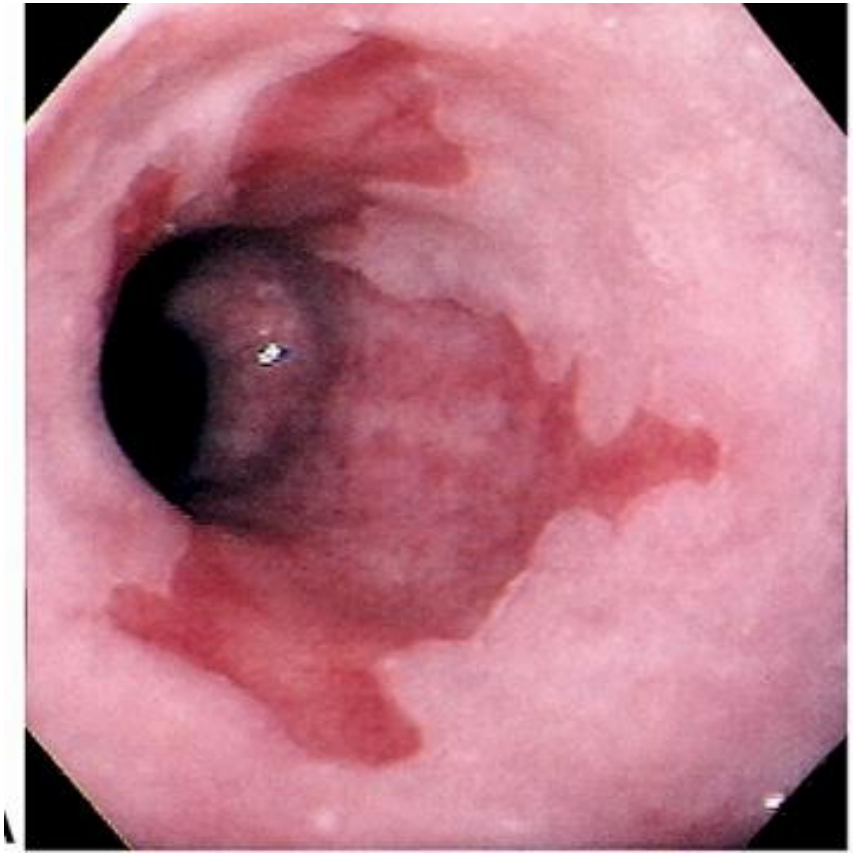


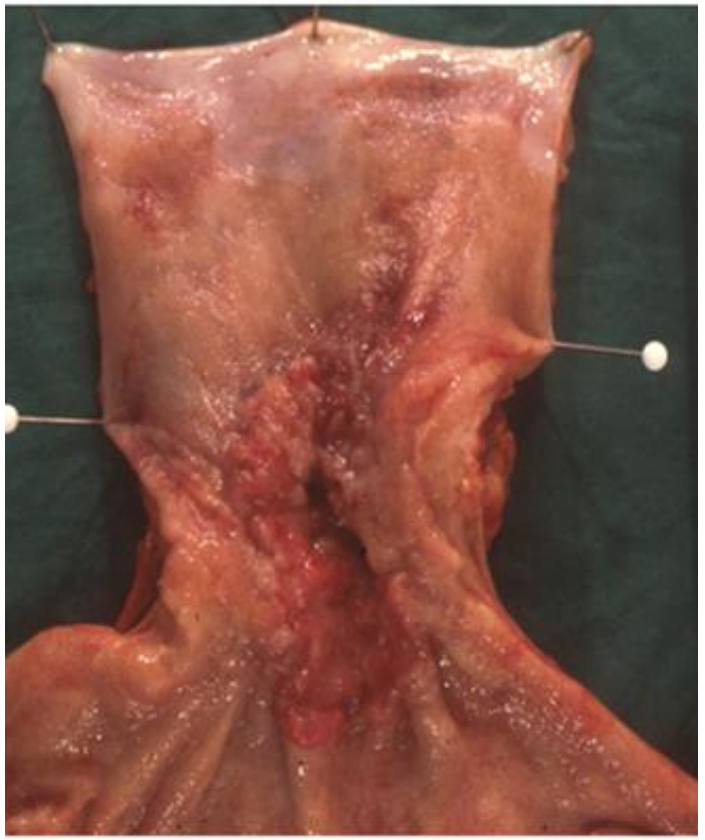


No evolution from Barrett oesophagus to squamous cell cancer !

Metaplasie = alteration in type of epithelium (not to be registered for BCR)
Dysplasie = **premalignant** alteration in epithelium (to be registered if severe/ high grade dysplasia)

BARRETT OESOPHAGUS: ENDOSCOPIC IMAGE and progression to adenocarcinoma





Barrett : always in the lower part of the oesophagus (→ adenocarcinoma appearing in higher part of the oesophagus does not originate from Barrett areas).

WHO histological classification of gastric tumours[1]

Epithelial tumours	
Intraepithelial neoplasia – Adenoma	8140/0[2]
Carcinoma	
Adenocarcinoma	8140/3
intestinal type	8144/3
diffuse type	8145/3
Papillary adenocarcinoma	8260/3
Tubular adenocarcinoma	8211/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Small cell carcinoma	8041/3
Undifferentiated carcinoma	8020/3
Others	
Carcinoid (well differentiated endocrine neoplasm)	8240/3

Non-epithelial tumours	
Leiomyoma	8890/0
Schwannoma	9560/0
Granular cell tumour	9580/0
Glomus tumour	8711/0
Leiomyosarcoma	8890/3
GI stromal tumour	8936/1
benign	8936/0
uncertain malignant potential	8936/1
malignant	8936/3
Kaposi sarcoma	9140/3
Others	
Malignant lymphomas	
Marginal zone B-cell lymphoma of MALT-type	9699/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma	9680/3
Others	

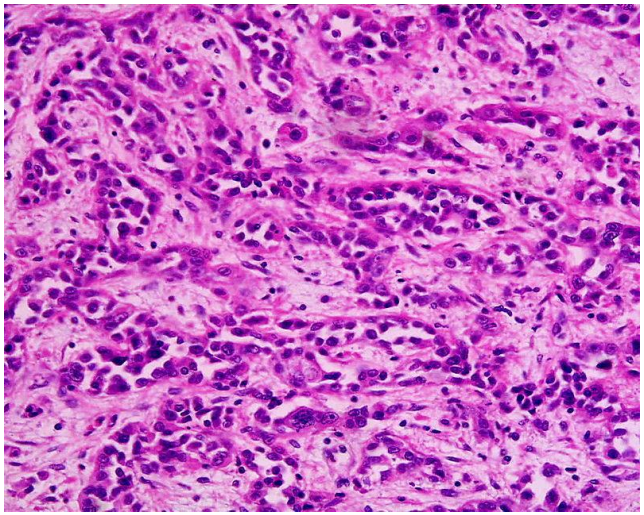
Secondary tumours

[1] The classification is modified from the previous WHO histological classification of tumours {2066} taking into account changes in our understanding of these lesions. In the case of endocrine neoplasms, the classification is based on the recent WHO clinicopathological classification {1784}, but has been simplified to be of more practical utility in morphological classification.

[2] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, and /1 for unspecified, borderline or uncertain behaviour. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are available only for lesions categorized as glandular intraepithelial neoplaia grade III (8148/2), and adenocarcinoma in situ (8140/2).

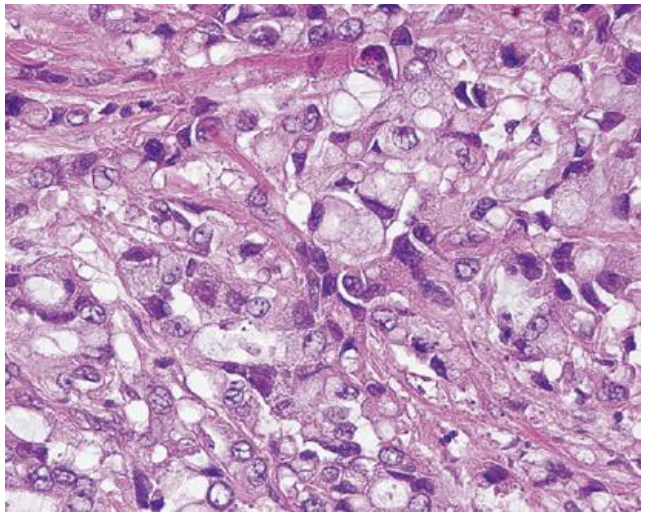
STOMACH: 2 MAIN CANCER TYPES

- Adenocarcinoma of intestinal type (8144/3)



Well organised glandular structures

- Adenocarcinoma of diffuse type (including signet-ring cell cancer) (8145/3 & 8490/3)



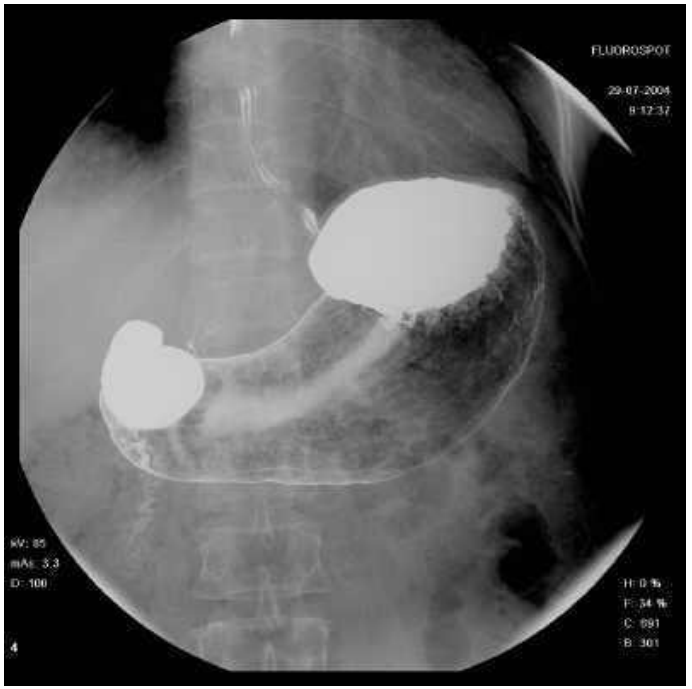
Chaotic arrangement of cells, no glandular structures, bad prognosis

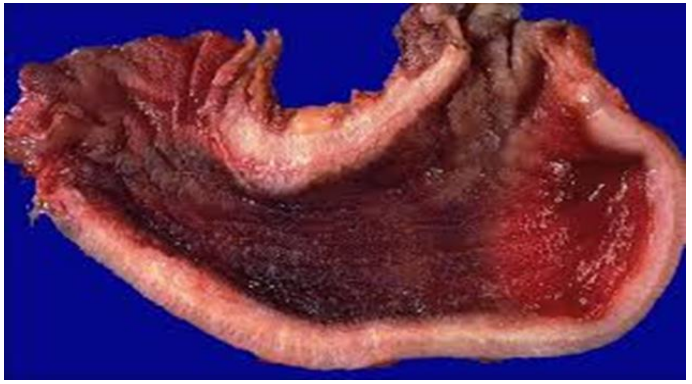
! ADENOCARCINOMA OF INTESTINAL TYPE !

- Adenocarcinoma in the intestine (8140/3) does not equal adenocarcinoma of the *intestinal type* (8144/3)!
- Adenocarcinoma of the *intestinal type* can also be found in nasal cavity, paranasal sinuses and nasopharynx!

STOMACH : LINITIS PLASTICA

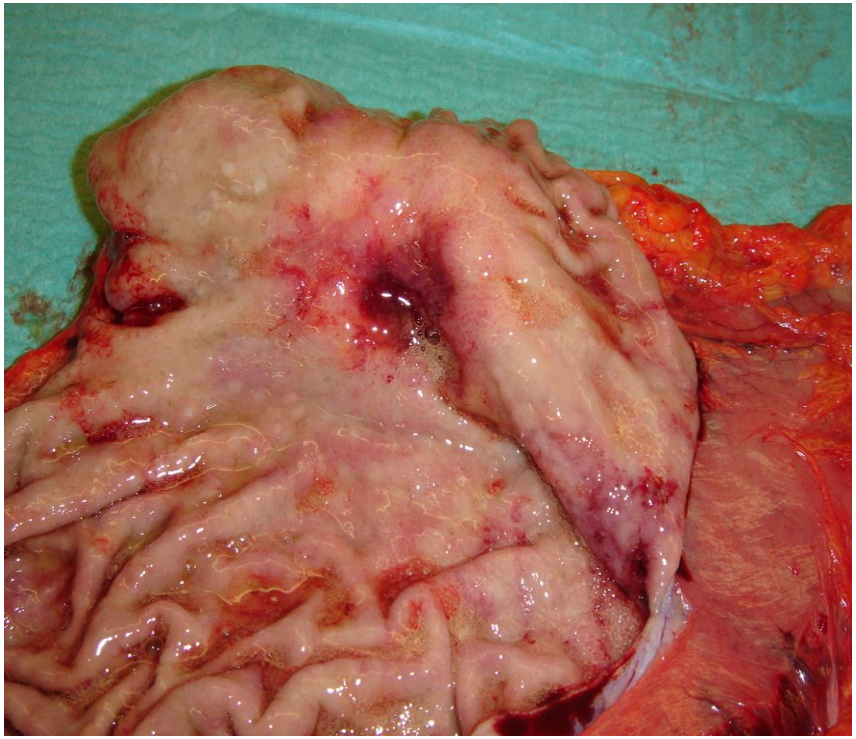
- **Linitis plastica (8142/3)** is used by clinicians and refers to radiologic/endoscopic image. If used by pathologists, the tumour can be classified as adenoca of diffuse type (8145/3).

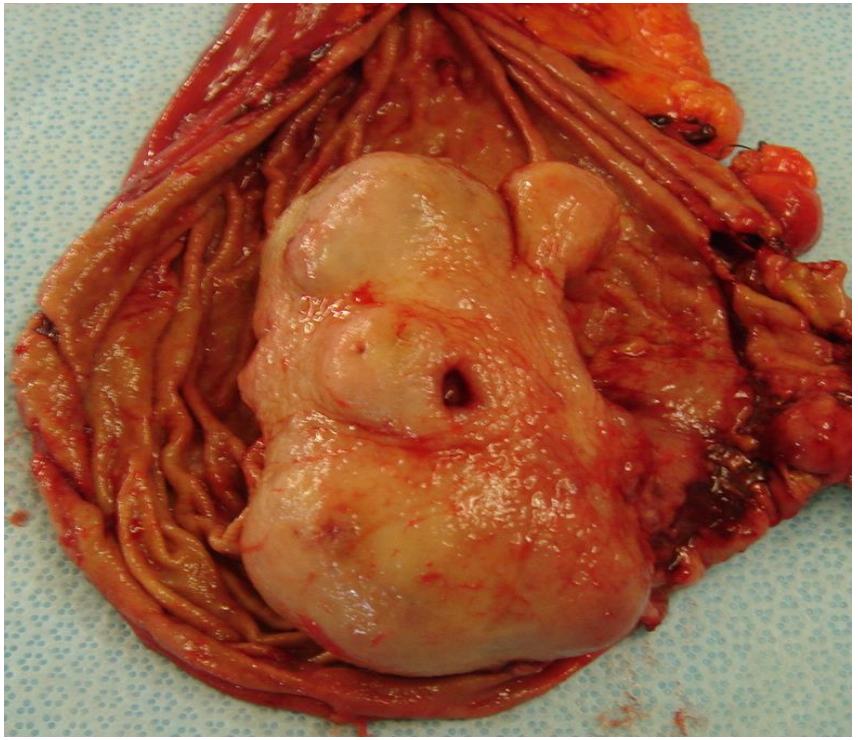




Thickened wall → stiffness

GASTRIC TUMOURS





Malignant gastric ulcus :

tumour arising in the epithelium (carcinoma)

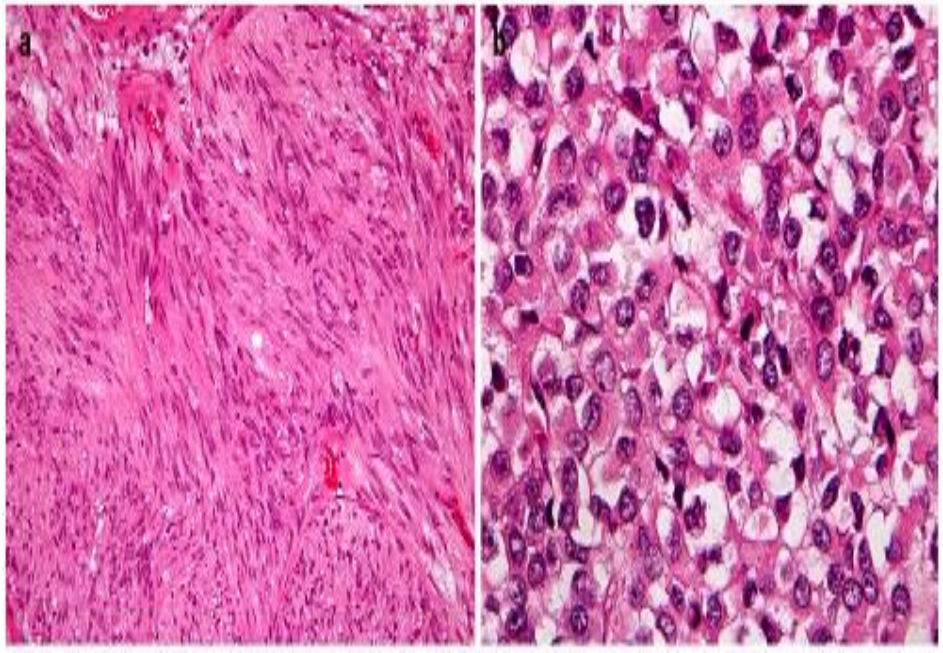
GIST (large) (8936/3) :

tumour arising in the mesenchymal part (sarcoma)

GASTRO-INTESTINAL STROMAL TUMOUR (GIST)

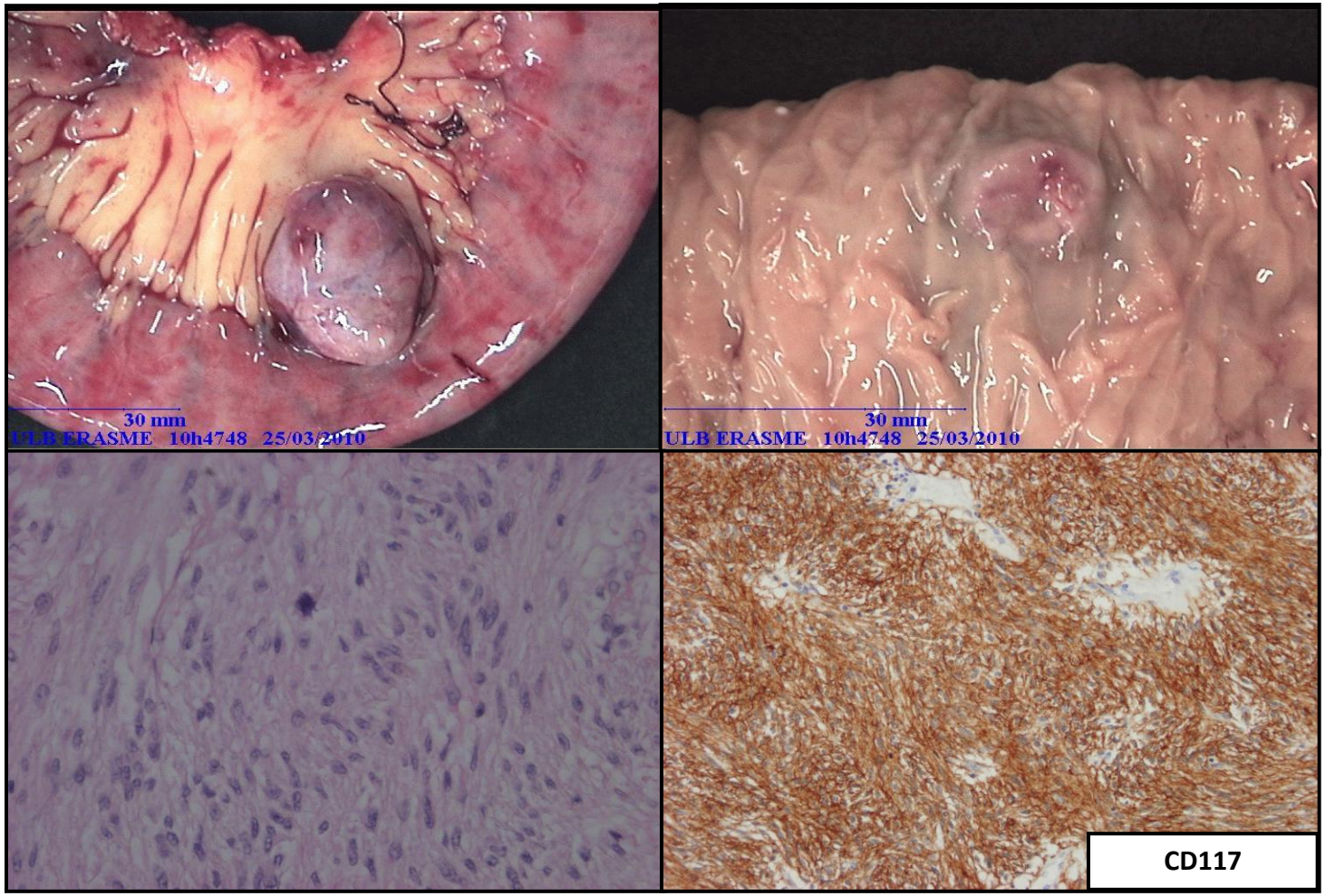
GIST (8936/3) may occur anywhere along the GI tract or elsewhere in the abdomen or retroperitoneum

GIST TUMOURS and GASTRIC CARCINOMAs have a different TNM-classification !



ALL GIST-TUMOURS HAVE A MALIGNANT POTENTIAL! → always /3 (although weak in small gists with few mitoses)

GASTRO-INTESTINAL STROMAL TUMOUR (GIST)



CD117 : typical immunohistochemical marker for GIST (present in > 95 % of GIST-tumours)

TUMOURS OF THE CARDIA / GASTRO-OESOPHAGEAL JUNCTION

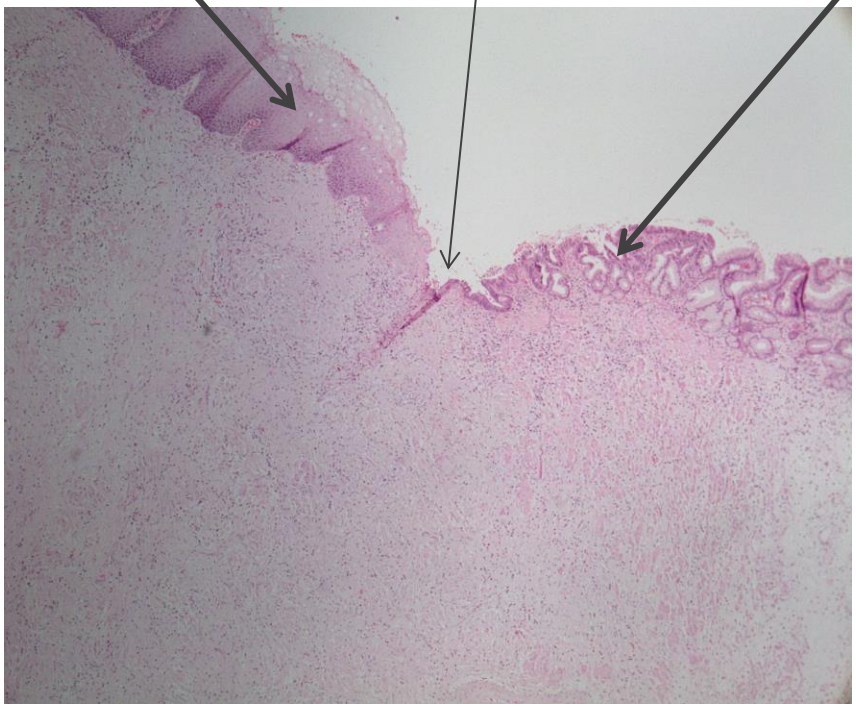
- A tumour the epicentre of which is within 5 cm of the gastro-oesophageal junction and also extends in the oesophagus is classified and staged using the oesophageal scheme. Tumours with an epicentre in the stomach greater than 5 cm from the gastro-oeophageal junction or those within 5 cm of the gastro-oesophageal junction without extension in the oesophagus are classified and staged using the gastric carcinoma scheme.

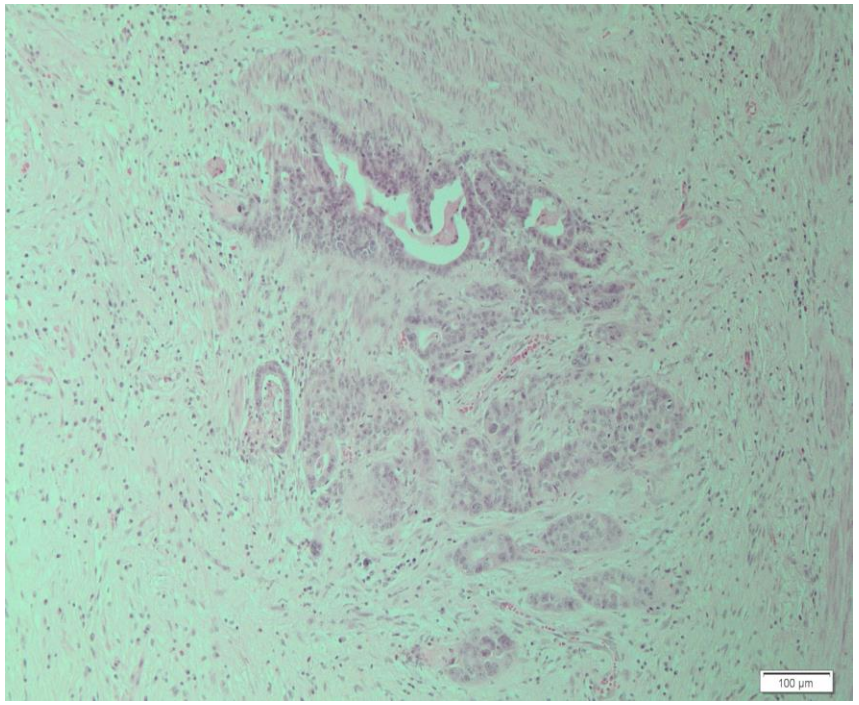
Gastro-oesophageal junction

Squamous epithelium of oesophagus

Junction

Glandular epithelium of the stomach





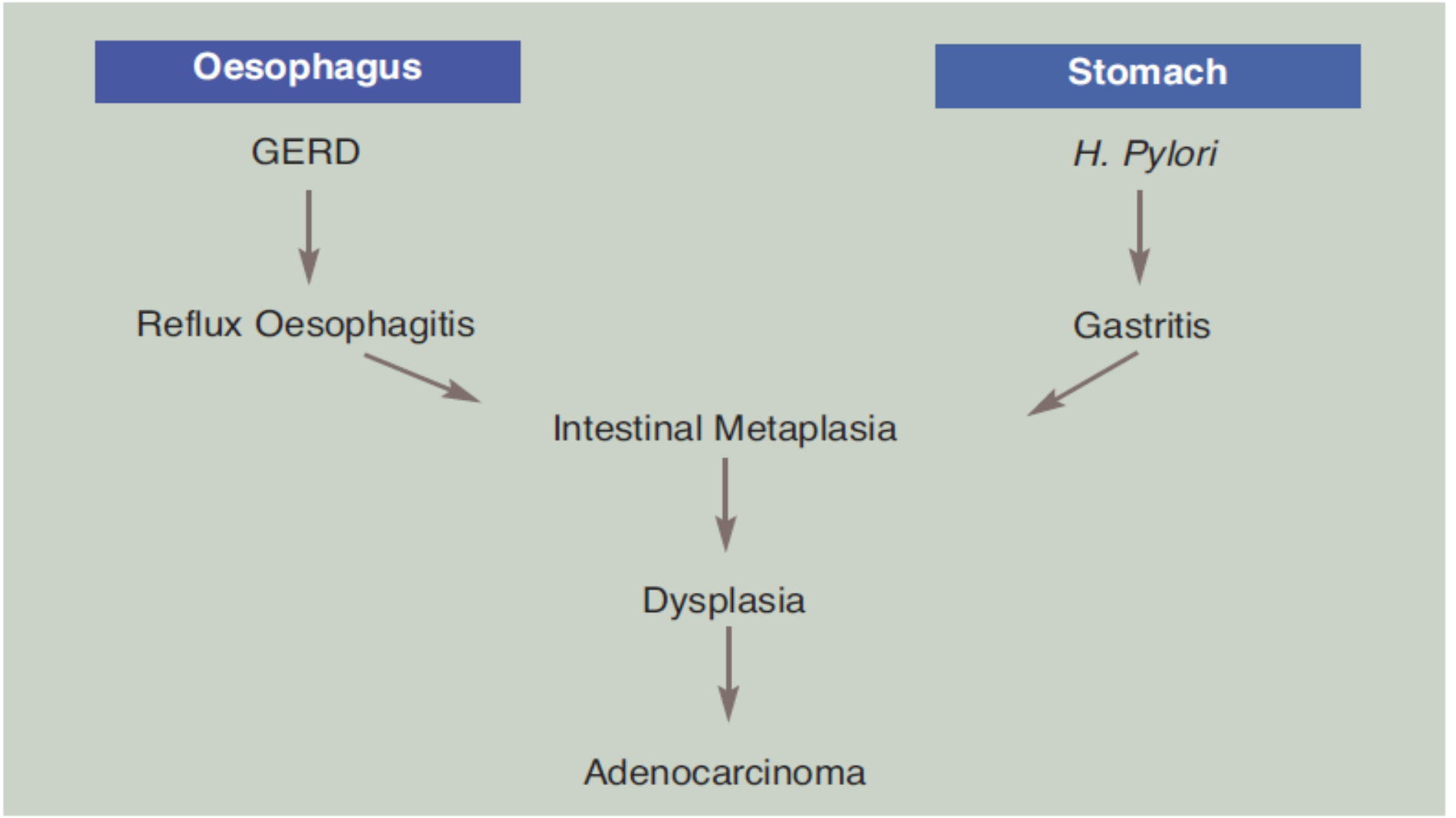
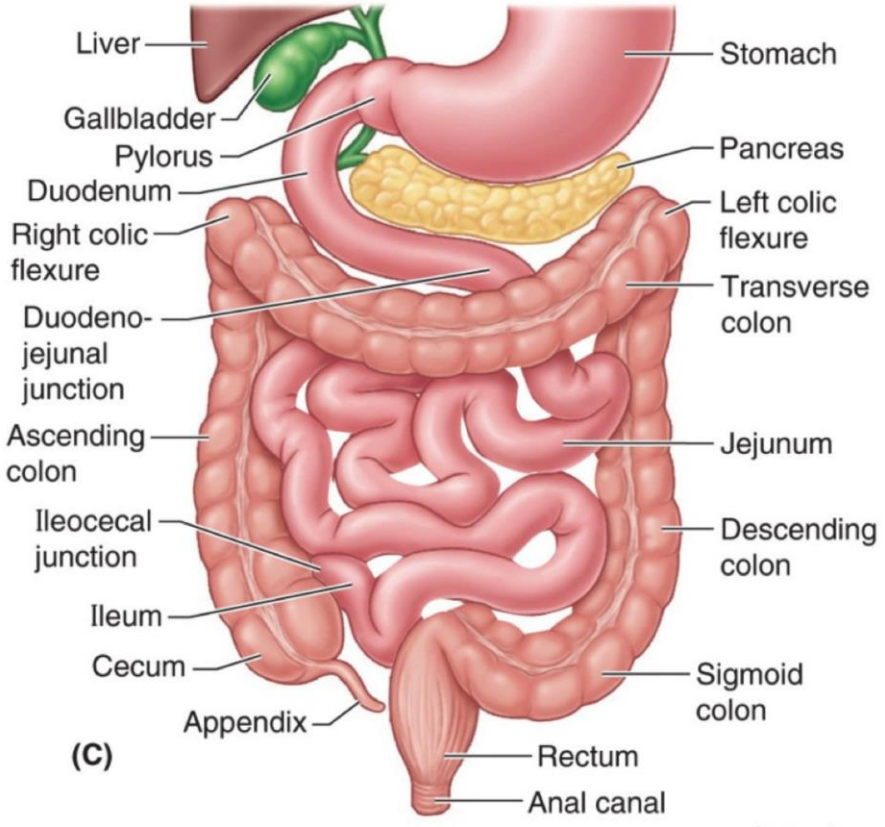


Fig. 2.03 Pathogenetic pathways operative in the evolution of oesophageal and gastric carcinoma. Intestinal metaplasia is a common precursor lesion that may result from gastro-oesophageal reflux disease (GERD) or chronic *H. pylori* infection

SMALL INTESTINE

- Duodenum, jejunum,ileum
- Complex anatomy duodenum/pancreas/bile ducts
- In the small intestine, neuroendocrine tumours are more frequent than adenocarcinomas



WHO histological classification of tumours of the small intestine[1]

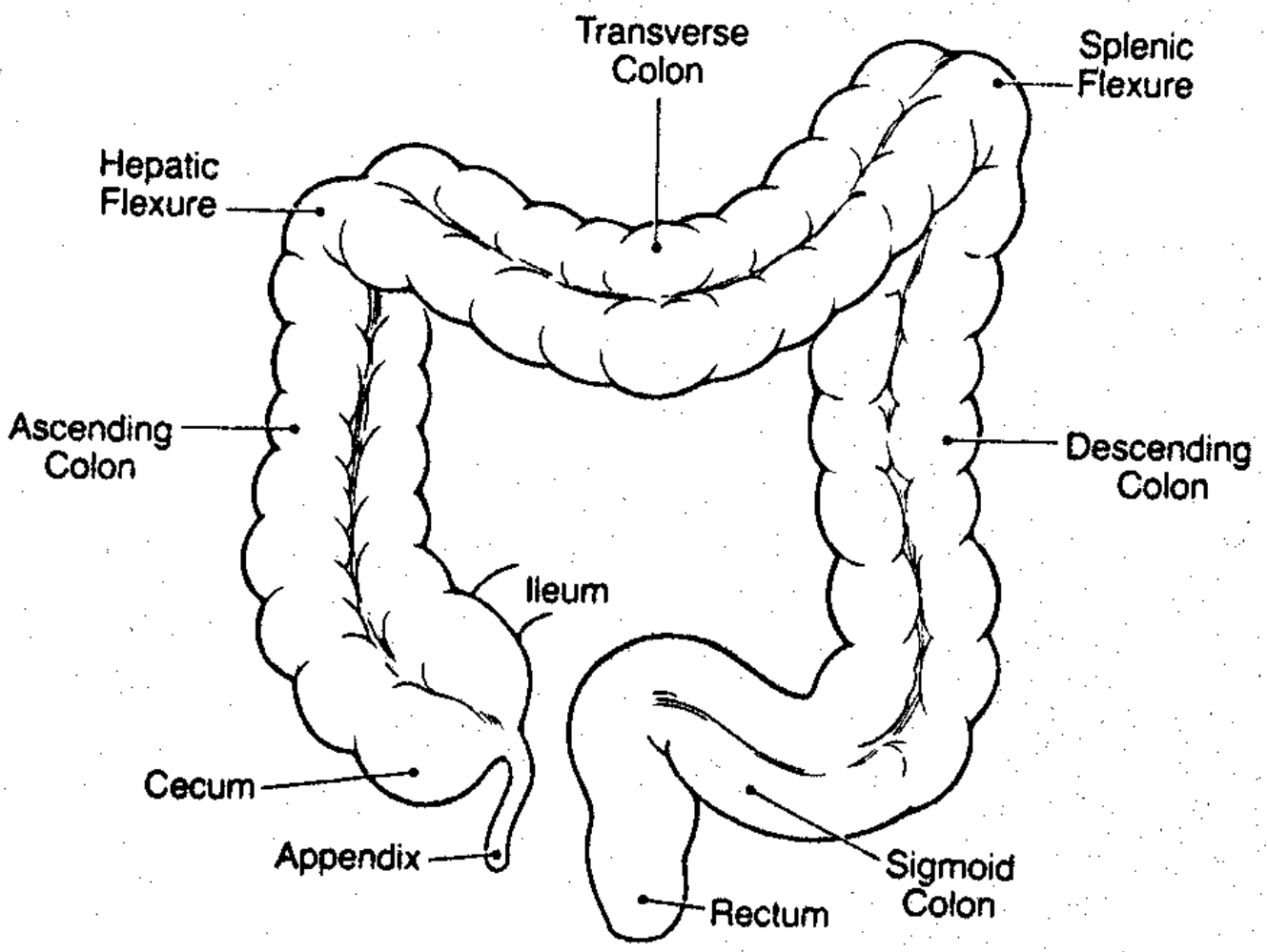
Epithelial tumours	
Adenoma	8140/0[2]
Tubular	8211/0
Villous	8261/0
Tubulovillous	8263/0
Intraepithelial neoplasia[2] (dysplasia) associated with chronic inflammatory diseases	
Low-grade glandular intraepithelial neoplasia	
High-grade glandular intraepithelial neoplasia	
Carcinoma	
Adenocarcinoma	8140/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3
Small cell carcinoma	8041/3
Squamous cell carcinoma	8070/3
Adenosquamous carcinoma	8560/3
Medullary carcinoma	8510/3
Undifferentiated carcinoma	8020/3
Carcinoid (well differentiated endocrine neoplasm)	8240/3
Gastrin cell tumour, functioning (gastrinoma) or non-functioning	8153/1
Somatostatin cell tumour	8156/1
EC-cell, serotonin-producing neoplasm	8241/3
L-cell, glucagon-like peptide and PP/PYY producing tumour	
Mixed carcinoid-adenocarcinoma	8244/3
Gangliocytic paraganglioma	8683/0
Others	

Non-epithelial tumours	
Lipoma	8850/0
Leiomyoma	8890/0
Gastrointestinal stromal tumour	8936/1
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Others	
Malignant lymphomas	
Immunoproliferative small intestinal disease (includes α-heavy chain disease)	9764/3
Western type B-cell lymphoma of MALT	9699/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma	9680/3
Burkitt lymphoma	9687/3
Burkitt-like /atypical Burkitt-lymphoma	9687/3
T-cell lymphoma	9702/3
enteropathy associated	9717/3
unspecified	9702/3
Others	
Secondary tumours	
Polyps	
Hyperplastic (metaplastic)	
Peutz-Jeghers	
Juvenile	

[1] This classification is modified from the previous WHO histological classification of tumours {845} taking into account changes in our understanding of these lesions. In the case of endocrine neoplasms, it is based on the recent WHO classification {1784} but has been simplified to be of more practical utility in morphological classification.

[2] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for in situ carcinomas and grade III intraepithelial neoplasia, and /1 for unspecified, borderline or uncertain behaviour. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are available only for lesions categorized as glandular intraepithelial neoplasia grade III (8148/2), and adenocarcinoma in situ (8140/2).

GROSS ANATOMY OF THE COLON



Hôpital Erasme ULB

WHO histological classification of tumours of the colon and rectum[1]

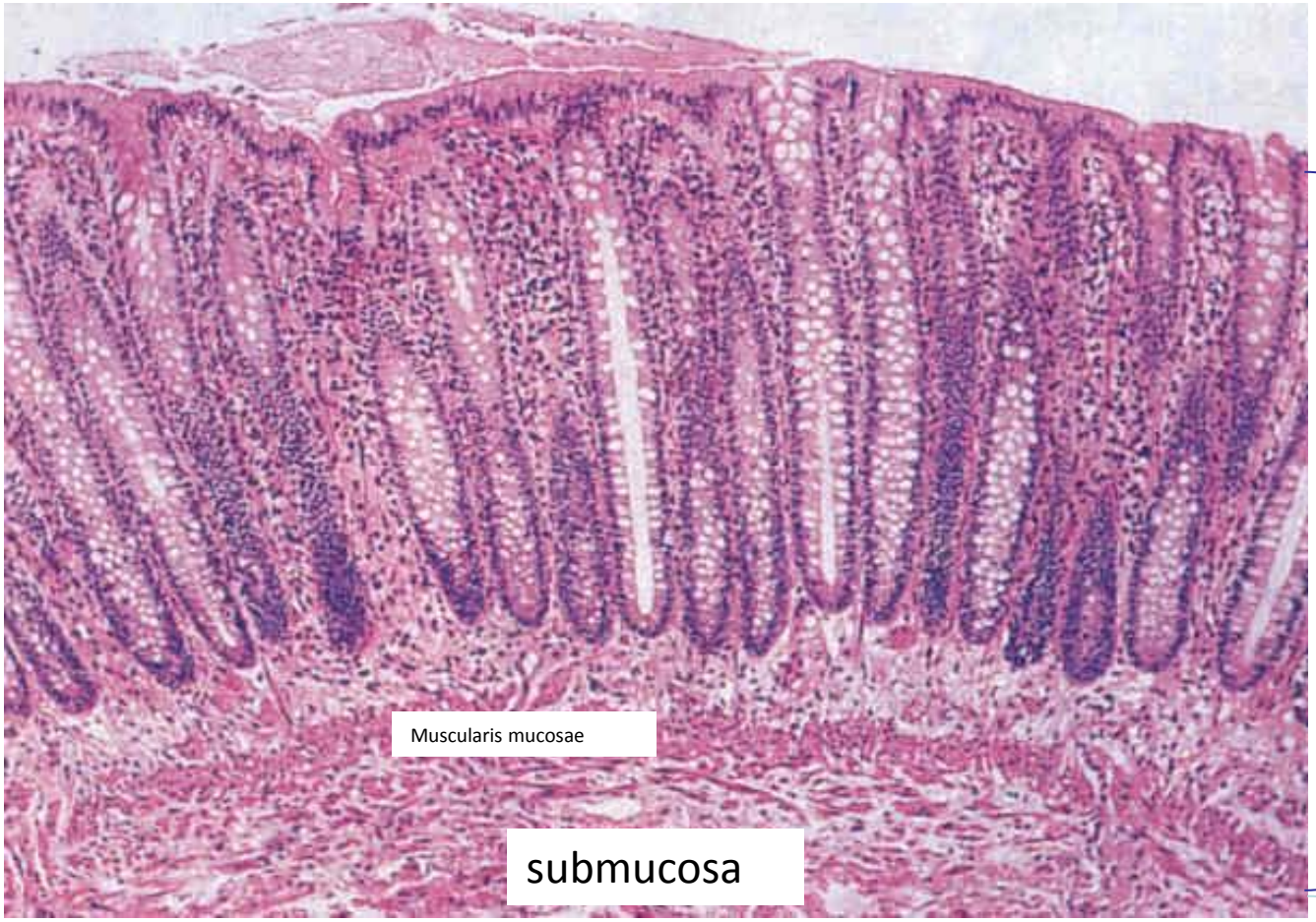
Epithelial tumours	
Adenoma	8140/0
Tubular	8211/0
Villous	8261/0
Tubulovillous	8263/0
Serrated	8213/0
Intraepithelial neoplasia[2] (dysplasia) associated with chronic inflammatory diseases	
Low-grade glandular intraepithelial neoplasia	
High-grade glandular intraepithelial neoplasia	
Carcinoma	
Adenocarcinoma	8140/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3
Small cell carcinoma	8041/3
Squamous cell carcinoma	8070/3
Adenosquamous carcinoma	8560/3
Medullary carcinoma	8510/3
Undifferentiated carcinoma	8020/3
Carcinoid (well differentiated endocrine neoplasm)	8240/3
EC-cell, serotonin-producing neoplasm	8241/3
L-cell, glucagon-like peptide and PP/PYY producing tumour	
Others	
Mixed carcinoid-adenocarcinoma	8244/3
Others	

Non-epithelial tumours	
Lipoma	8850/0
Leiomyoma	8890/0
Gastrointestinal stromal tumour	8936/1
Leiomyosarcoma	8890/3
Angiosarcoma	9120/3
Kaposi sarcoma	9140/3
Malignant melanoma	8720/3
Others	
Malignant lymphomas	
Marginal zone B-cell lymphoma of MALT Type	9699/3
Mantle cell lymphoma	9673/3
Diffuse large B-cell lymphoma	9680/3
Burkitt lymphoma	9687/3
Burkitt-like /atypical Burkitt-lymphoma	9687/3
Others	
Secondary tumours	
Polyps	
Hyperplastic (metaplastic)	
Peutz-Jeghers	
Juvenile	

[1] This classification is modified from the previous WHO histological classification of tumours {845} taking into account changes in our understanding of these lesions. In the case of endocrine neoplasms, it is based on the recent WHO classification {1784} but has been simplified to be of more practical utility in morphological classification.

[2] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /3 for malignant tumours, /2 for in situ carcinomas and grade III intraepithelial neoplasia, and /1 for unspecified, borderline or uncertain behaviour. Intraepithelial neoplasia does not have a generic code in ICD-O. ICD-O codes are available only for lesions categorized as glandular intraepithelial neoplasia grade III (8148/2), and adenocarcinoma in situ (8140/2).

NORMAL COLON MUCOSA

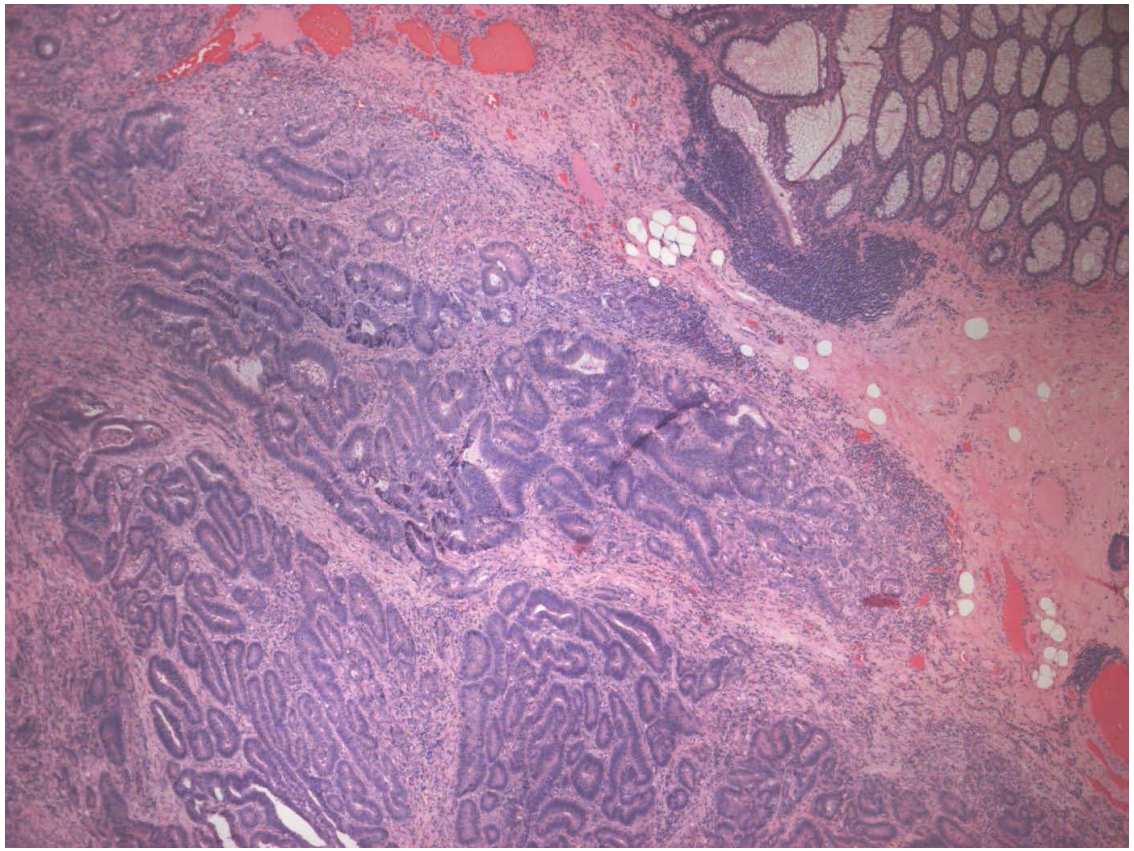


Mucosa with
- Epithelium
- Basal membrane
- Lamina propria
- Muscularis Mucosae

ONLY IN COLO-RECTUM (exceptional situation)
All intramucosal tumours, regardless intact or ruptured basal membrane → /2

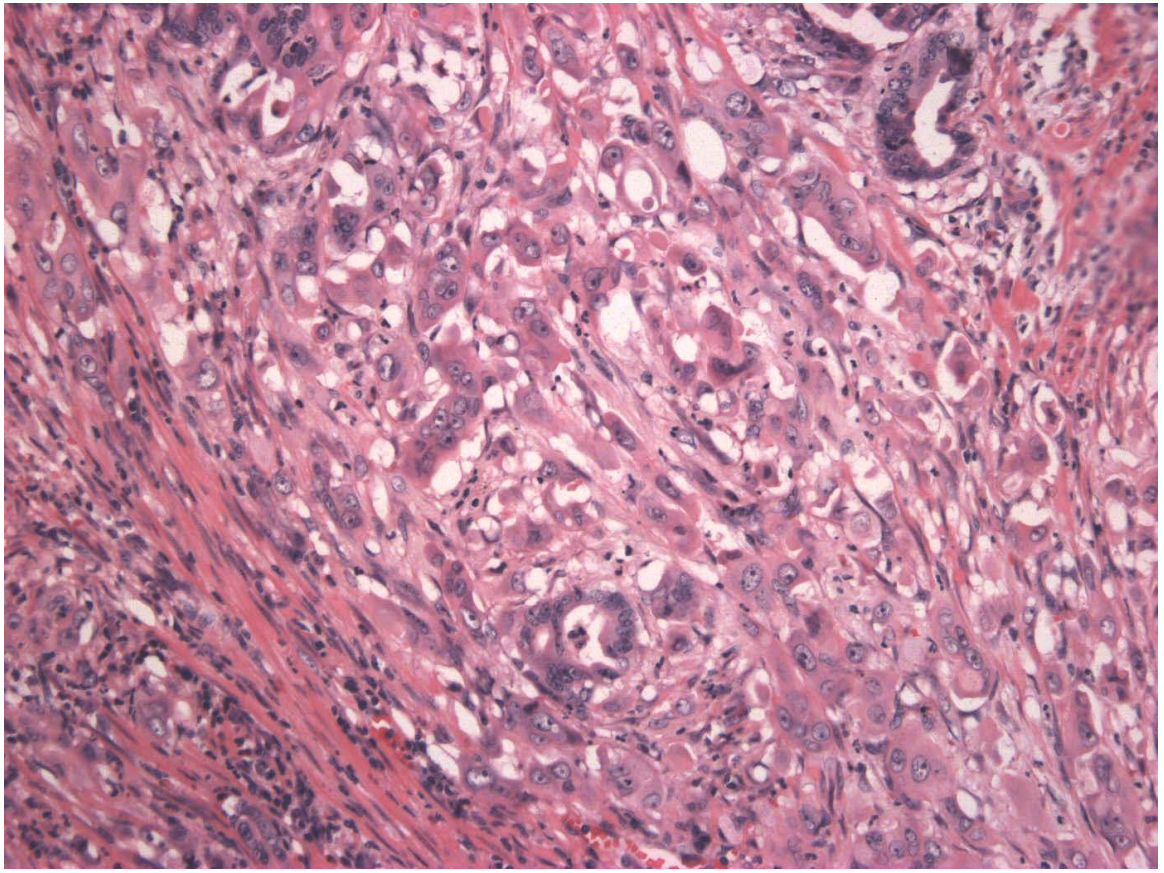
Submucosa

WELL DIFFERENTIATED ADENOCARCINOMA



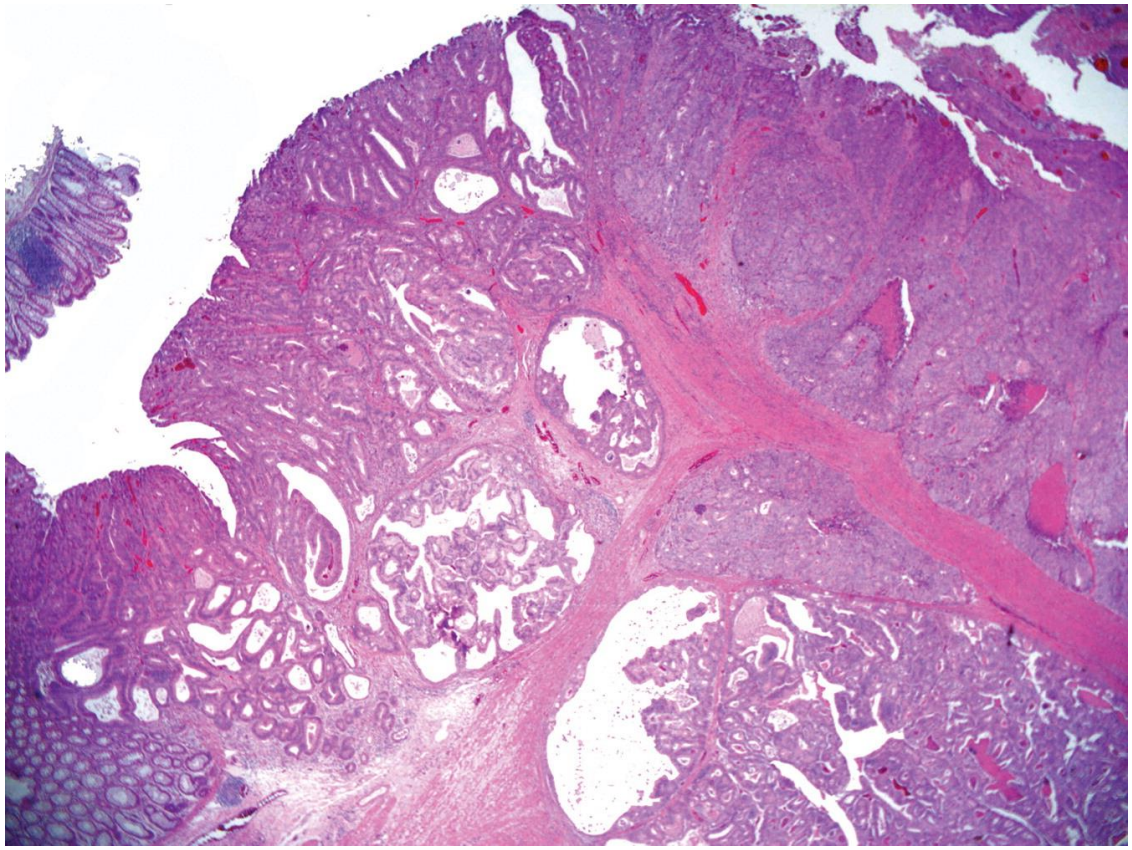
Well differentiated : nice glandular structures with a good resemblance to normal glands

POORLY DIFFERENTIATED ADENOCARCINOMA



Poorly differentiated : less resemblance to normal glandular structures → bad prognosis

THE PROBLEM OF GRADING

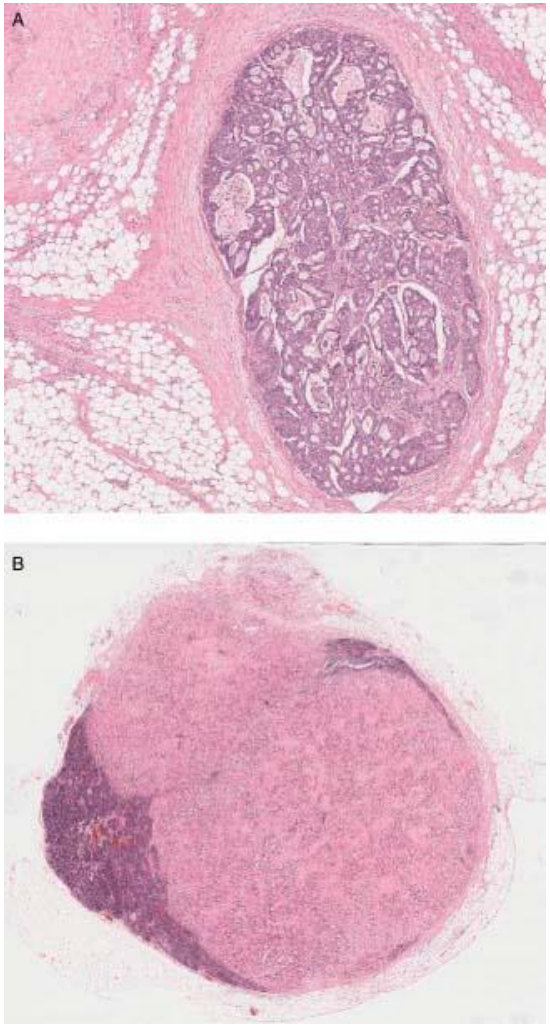


No consensus : what has to be reported by the pathologist ?

- The grade that is present in the largest part of the tumour?
- The worst grade that is present, even in only a (very) small part of the tumour?

Datamanagers have to report the worst grade, mentioned by the pathologist

THE PROBLEM OF DEFINING A LYMPH NODE

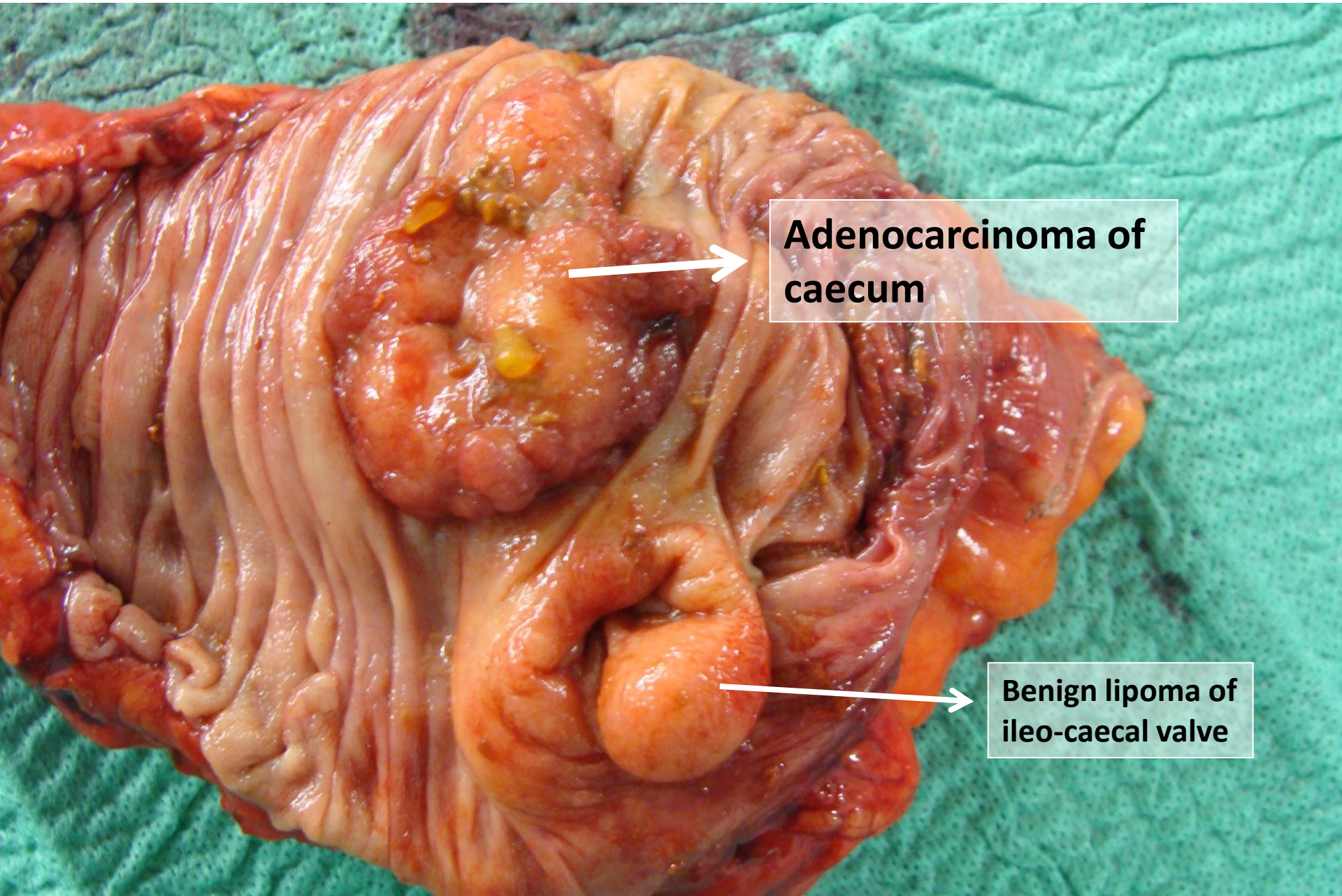


When a tumour nodule still contains some lymphoid tissue, one can consider the nodule as a positive lymph node. But what with a nodule in a lymph drainage area without residual lymphoid cells ?

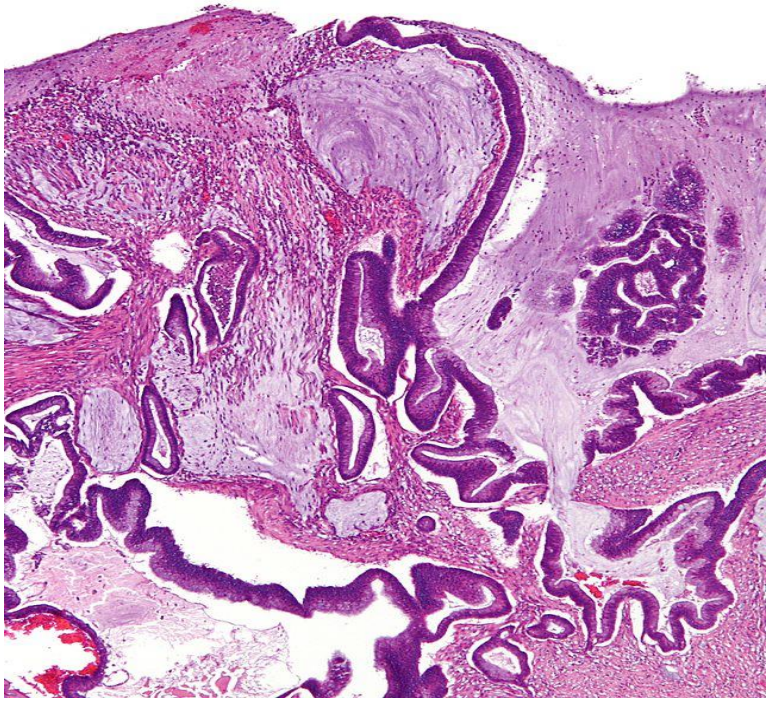
According to the TNM 7th edition, the pathologist may choose himself how to consider a tumoural nodule in a lymph drainage area :

- as a lymph node that has been completely replaced by tumour cells (→ N-classification)
- as discontinuous spread of the primary tumour (→ T-classification)
- as venous invasion (→ V-classification) (no existing classification for arterial invasion)

This lack of consensus may cause multiple problems when staging the tumour !


Adenocarcinoma of caecum
Benign lipoma of ileo-caecal valve

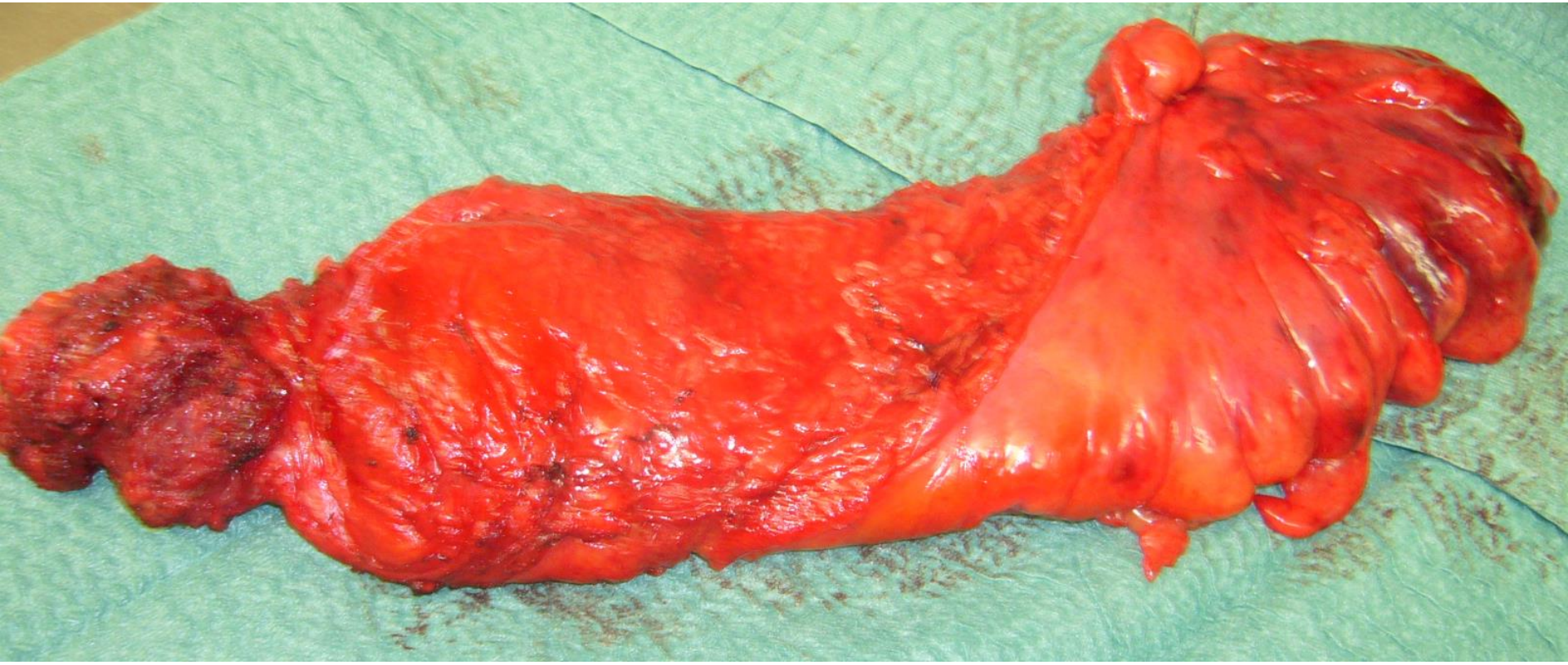
Mucinous adenoCA >< adenoCA with mucinous differentiation



In mucinous/colloid adenocarcinoma (8480/3), at least 50% of the mass is composed of mucus ;

If less than 50 % of mucus, use 8481/3 for mucin producing adenocarcinoma

RECTAL CANCER : TME – resection (PROCARE)



TME – resection : the rectum (with the rectal carcinoma) with the intact mesorectum (in which lymph nodes can be found) is resected

DEFINITION OF RECTUM

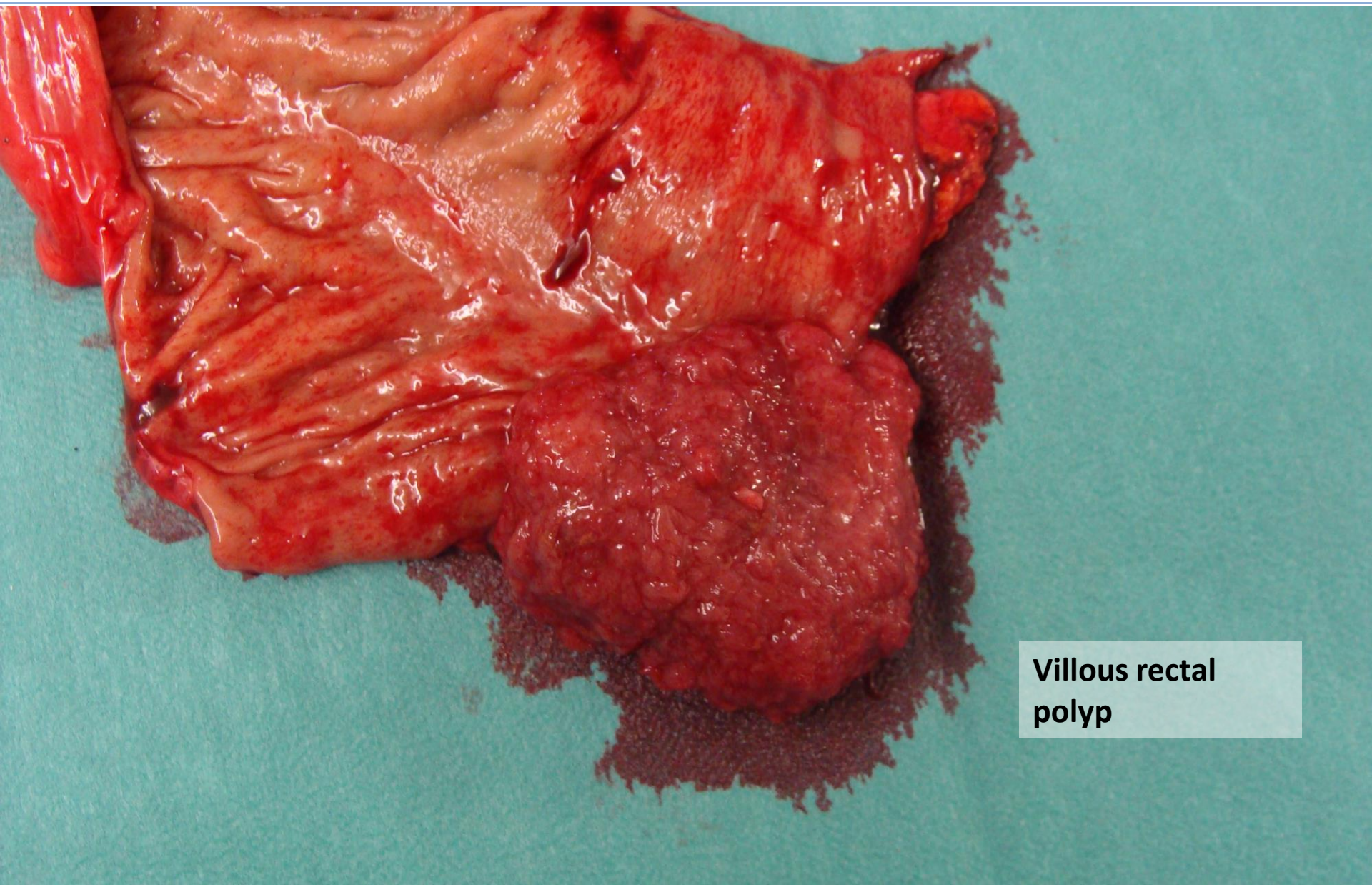
Last 15 cm of glandular mucosa

Lower than rectum: anal canal or anus!

Rectal adenocarcinoma is typically treated by radiochemotherapy before surgery > can lead to complete disappearance of tumour cells! (→ ypT0)

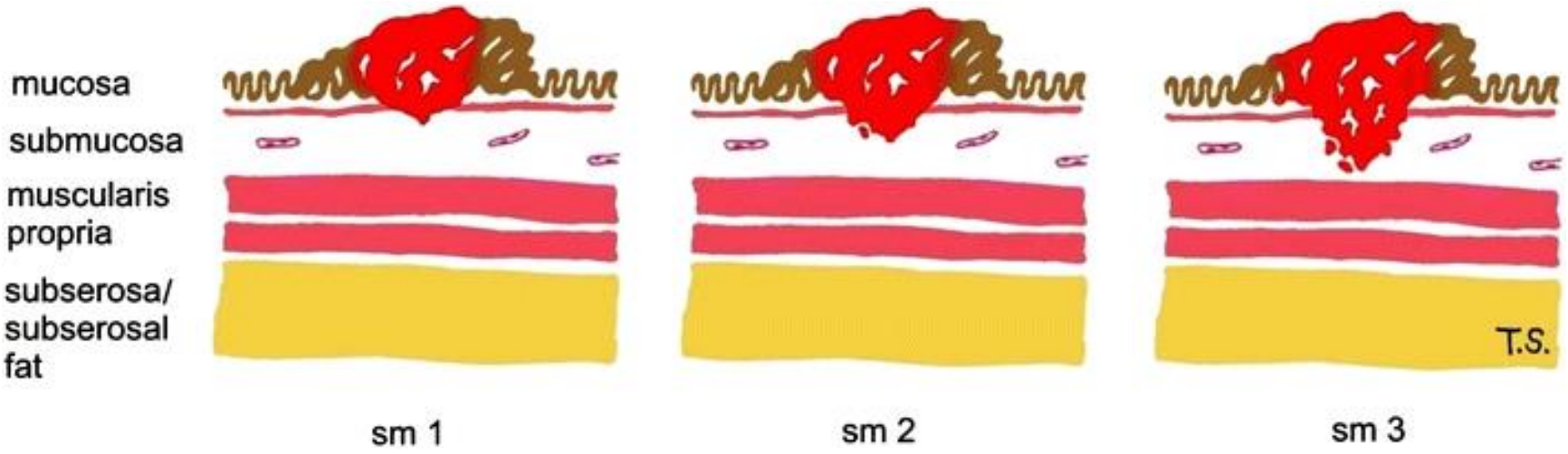
Do **not** take into account mucus without viable cells for ypTNM-staging! (viable cells stain positively for pancytokeratin)

The problem of malignant polyps



Villous rectal polyp

STAGING OF MALIGNANT SESSILE POLYPS

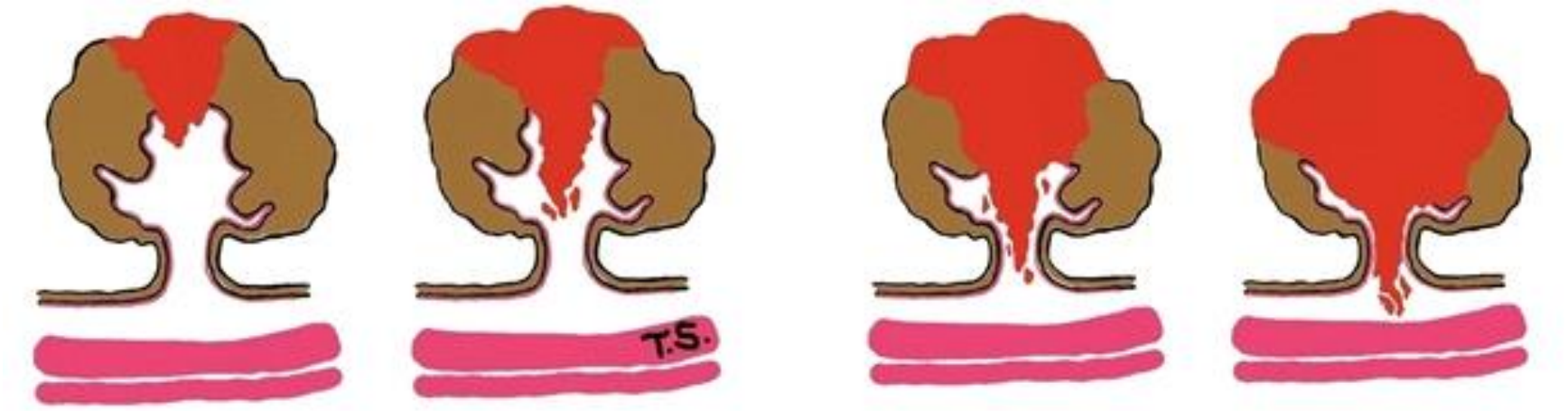


sm1 – sm2 – sm3 currently **not** in TNM-classification.
Classification according to Kikuchi.

The Kikuchi classification gives an idea about the depth of **submucosal invasion.**

After complete local resection of sm1-lesion → no additional surgery with lymph node resection necessary (one can assume that lymph nodes will be negative)
After complete local resection of sm3-lesion → additional surgery with lymph node resection is recommended because 10% of these tumours are accompanied by positive lymph nodes

STAGING OF MALIGNANT PEDUNCULATED POLYPS



Level 1: invasion of the submucosa but limited to the head of the polyp

Level 2: invasion extending into the neck of polyp

Level 3: invasion into any part of the stalk

Level 4: invasion beyond the stalk but above the muscularis propria

Classification according to Haggitt.
! Sampling error !

If biopsy of polyp says 'in situ' but metastasis (at distance or in lymph nodes) present : tumour has to be considered to be invasive (and at least with submucosal infiltration → /3)

Microsatellite instability (MSI)

15% of colorectal cancers (3 % of these are associated with the Lynch syndrome)

Associated with better prognosis

Associated with resistance to 5-fluorouracil (5-FU = classical chemo for colon cancer which means that other chemo has to be administered).

MSI indicates a condition in which one is very sensible for DNA-mutations/errors, arising during replication. Normally, these errors will be corrected which is called DNA MisMatchRepair. In MSI, the repair mechanism is impaired so the errors will not be corrected but will accumulate. The micro-satellite DNA fragments will influence other genes in their neighbourhood who are responsible for cell proliferation or cell death.

Lynch syndrome

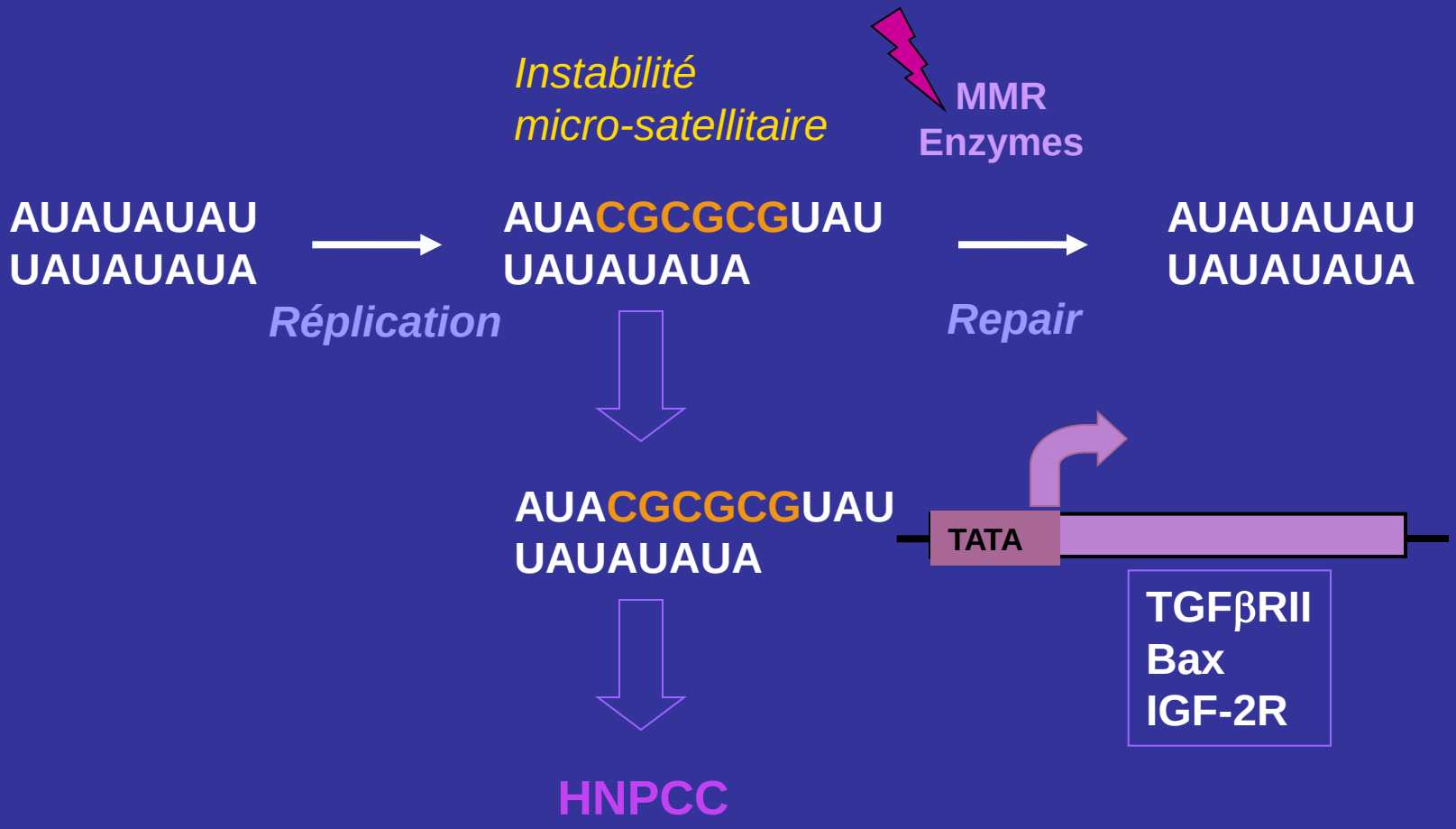
Hôpital Erasme

ULB

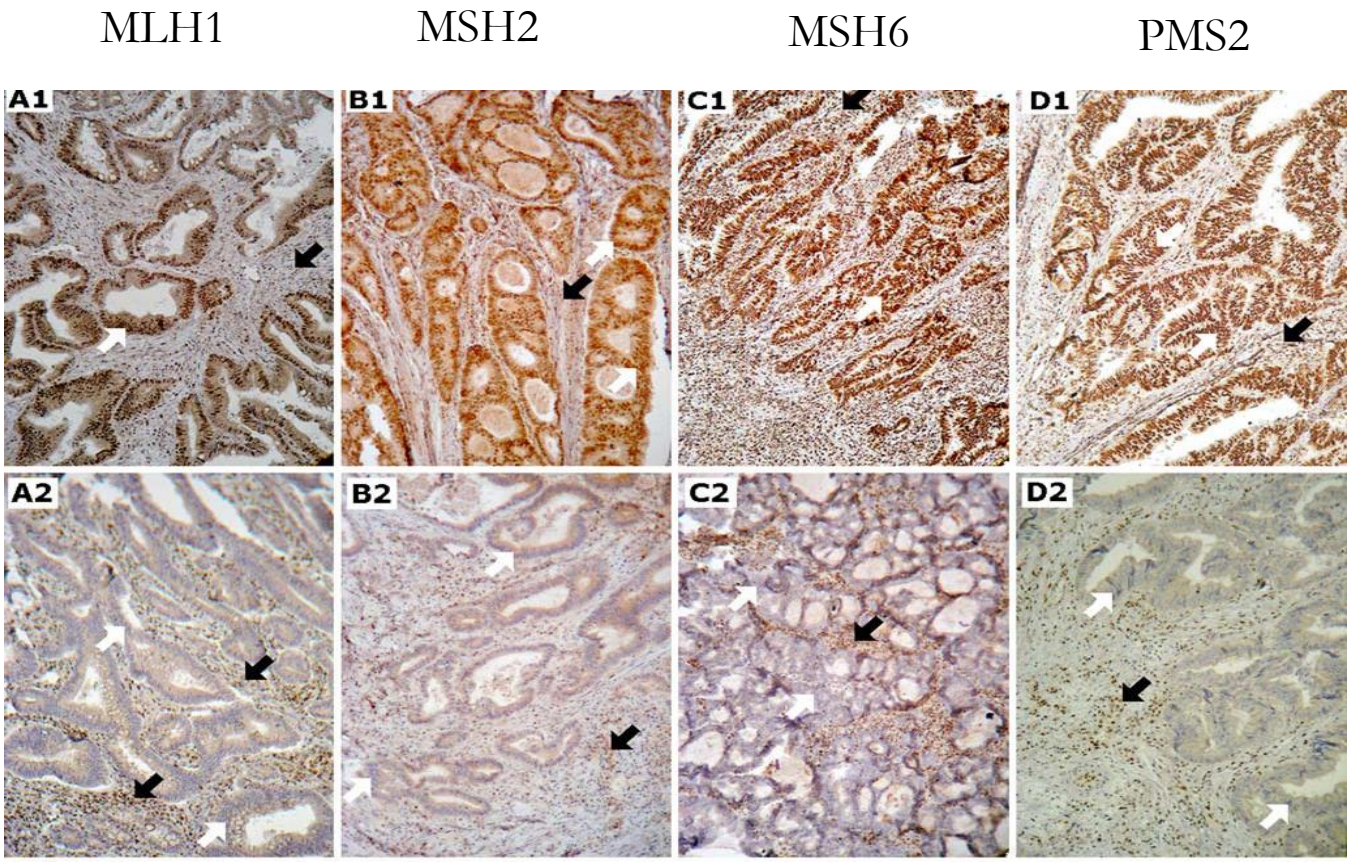
What is Lynch syndrome?

Lynch syndrome, often called hereditary nonpolyposis colorectal cancer (HNPCC), is an inherited disorder that increases the risk of many types of cancer, particularly cancers of the colon (large intestine) and rectum, which are collectively referred to as colorectal cancer. People with Lynch syndrome also have an increased risk of cancers of the stomach, small intestine, liver, gallbladder ducts, upper urinary tract, brain, and skin. Additionally, women with this disorder have a high risk of cancer of the ovaries and lining of the uterus (the endometrium). People with Lynch syndrome may occasionally have noncancerous (benign) growths (polyps) in the colon, called colon polyps. In individuals with this disorder, colon polyps occur earlier but not in greater numbers than they do in the general population.

Les régions MS sont des séquences répétitives d'ADN qui sont situés autour de gènes importants dans le contrôle de la prolifération ou l'apoptose

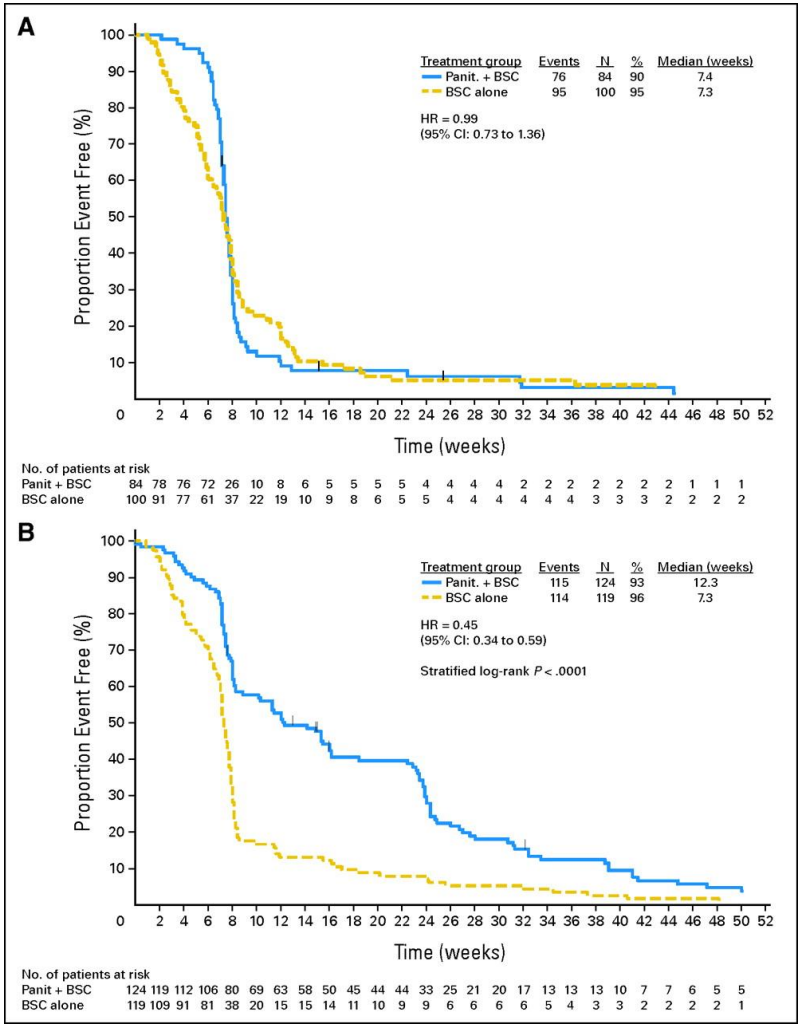


DNA MISMATCH REPAIR PROTEINS and MSI



Some proteins (MLH1, MSH2, MSH6, PMS2, …) are involved in the repair mechanism of DNA-errors (DNA Mismatch repair proteins) :
When they are present → no MSI (first row)
When they are absent → MSI + (second row)

Progression-free survival by treatment within KRAS groups



Amado RG, *J Clin Oncol* 2008

Mutations of the KRAS oncogenes are considered to be negative predictors of response to anti-epidermal growth factor receptor antibodies.

This means that therapy with anti-EGFR is useless when KRAS mutation is present.

This information is – together with information about MSI – important to choose the correct treatment for the patient with colorectal cancer !

ASSAY METHODS

Table 2. Established Technologies for *KRAS* Mutation Analysis

Method	Technology	Sensitivity, MT/WT%[a]	Time to Result	Pros	Cons
Direct sequencing					
Cycle sequencing	Sanger sequencing using dye-labeled dideoxynucleotide chain termination	15–25	4 d–2 wk (paraffin)	Gold standard Detects all mutations	Insensitive Labor intensive
Pyrosequencing	Measures pyrophosphate release during DNA extension	5–10	Fast	High-throughput Precise/reproducible Suitable for partially degraded samples	Expensive
PCR-based methods					
ARMS[a]	Mutation-specific PCR amplification	1	Rapid: <2 d (paraffin)	High sensitivity Rapid results	Detects single mutation per reaction Requires engineered primer/probe
TheraScreen[a]	Combination of ARMS, Scorpions[b] (allele-specific probe), and real-time PCR	1–5	Rapid: 2 d 2 h to process samples	Rapid results High sensitivity Commercially available	Detects only 7 common mutations Requires more tissue Very expensive
Allele-specific oligonucleotide hybridization					
Allele-specific probes	Probes hybridize to wild-type or mutant sequence impacting melting temperature	10	Rapid: <2 d (paraffin)	Rapid results	Low sensitivity
ViennaLab[b]	Hybridization of PCR products to array of allele-specific oligonucleotides	1	Rapid: 6 h to process samples	Detects 13 common mutations Less expensive than TheraScreen[b]	Complicated data interpretation

Abbreviations: ARMS, amplification-refractory mutation system; MT, mutant; PCR, polymerase chain reaction; WT, wild-type.

[a] DxS, Manchester, United Kingdom.
[b] ViennaLab Diagnostics GmbH, Vienna, Austria.

Ross JS, *Arch Pathol Lab Med* 2012

WHO histological classification of tumours of the appendix[1]

Epithelial tumours	
Adenoma	8140/0[2]
Tubular	8211/0
Villous	8261/0
Tubulovillous	8263/0
Serrated	8213/0
Carcinoma	
Adenocarcinoma	8140/3
Mucinous adenocarcinoma	8480/3
Signet-ring cell carcinoma	8490/3
Small cell carcinoma	8041/3
Undifferentiated carcinoma	8020/3
Carcinoid (well differentiated endocrine neoplasm)	8240/3
EC-cell, serotonin-producing neoplasm	8241/3
L-cell, glucagon-like peptide and PP/PYY producing tumour	
Others	
Tubular carcinoid	8245/1
Goblet cell carcinoid (mucinous carcinoid)	8243/3
Mixed carcinoid-adenocarcinoma	8244/3
Others	

Non-epithelial tumours

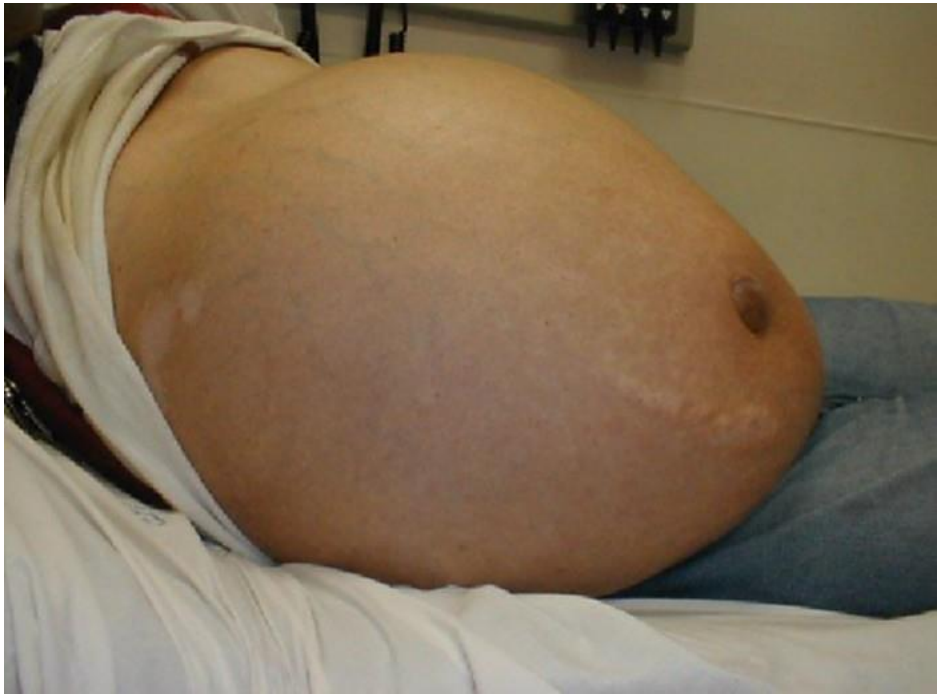
Neuroma
Lipoma
Leiomyoma
Gastrointestinal stromal tumour
Leiomyosarcoma
Kaposi sarcoma
Others

Malignant lymphoma

Secondary tumours

Hyperplastic (metaplastic) polyp

Pseudomyxoma peritonei



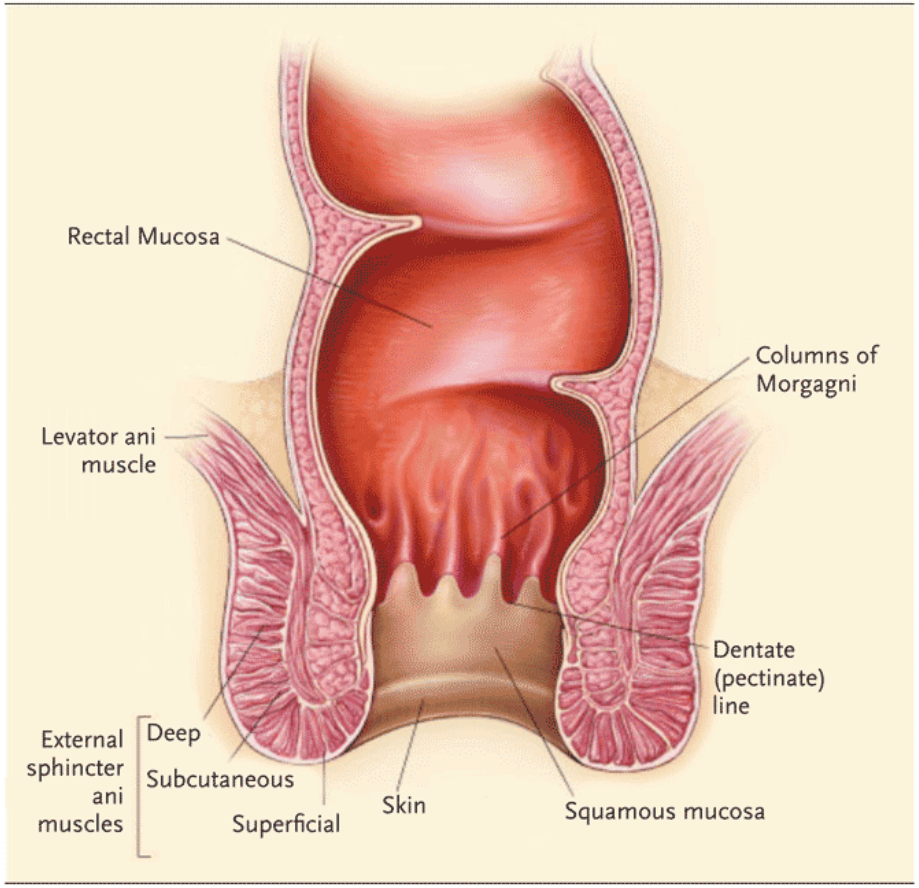
Jelly belly : gelatinous ascites, abdomen full of mucine

Pseudomyxoma peritonei is a clinical diagnosis (not a pathological one) and can be seen after a *benign or malignant* tumour of the appendix or ovary.

If originating from a mucinous adenocarcinoma (8480/3) of the appendix → metastasis outside the abdomen possible.
If originating from a low grade appendiceal mucinous neoplasm (LAMN) (8480/1) → never gelatinous metastasis outside the abdomen (but even then serious disease)

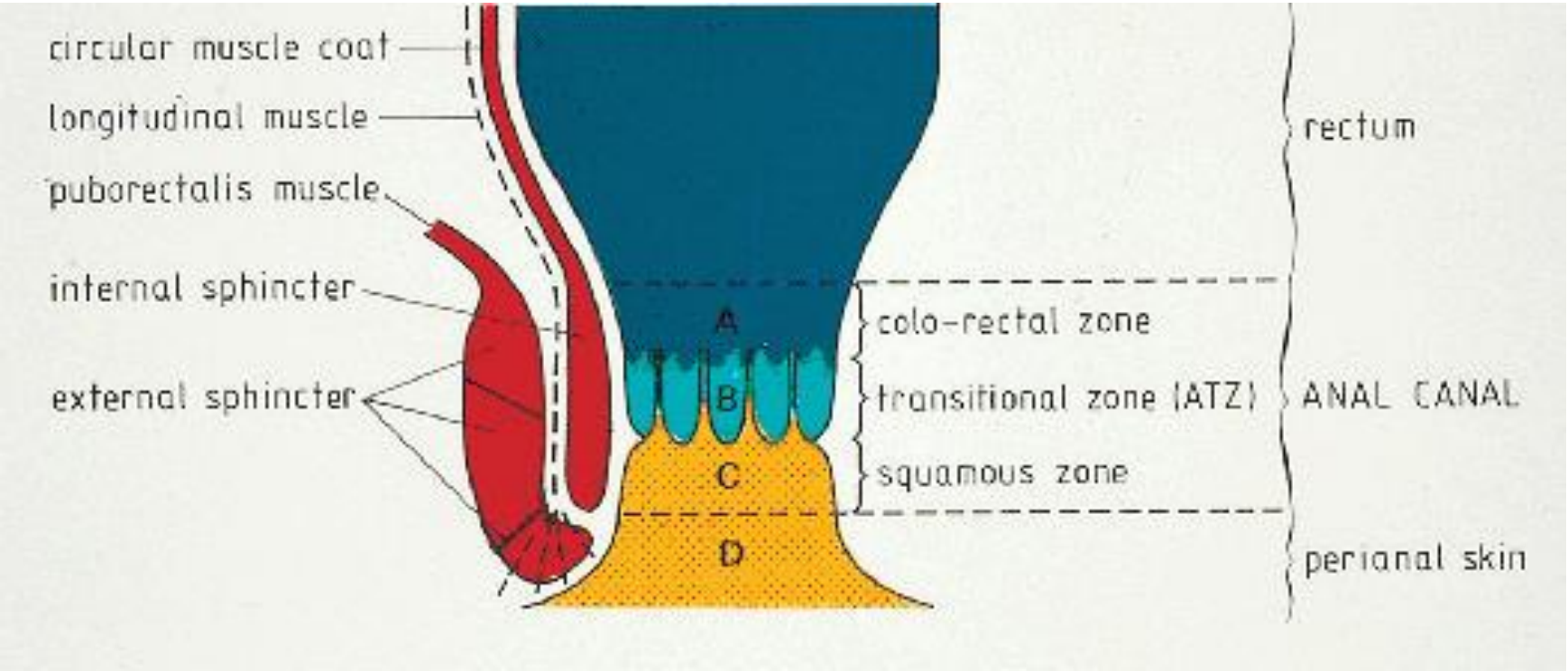
Anal canal and anus

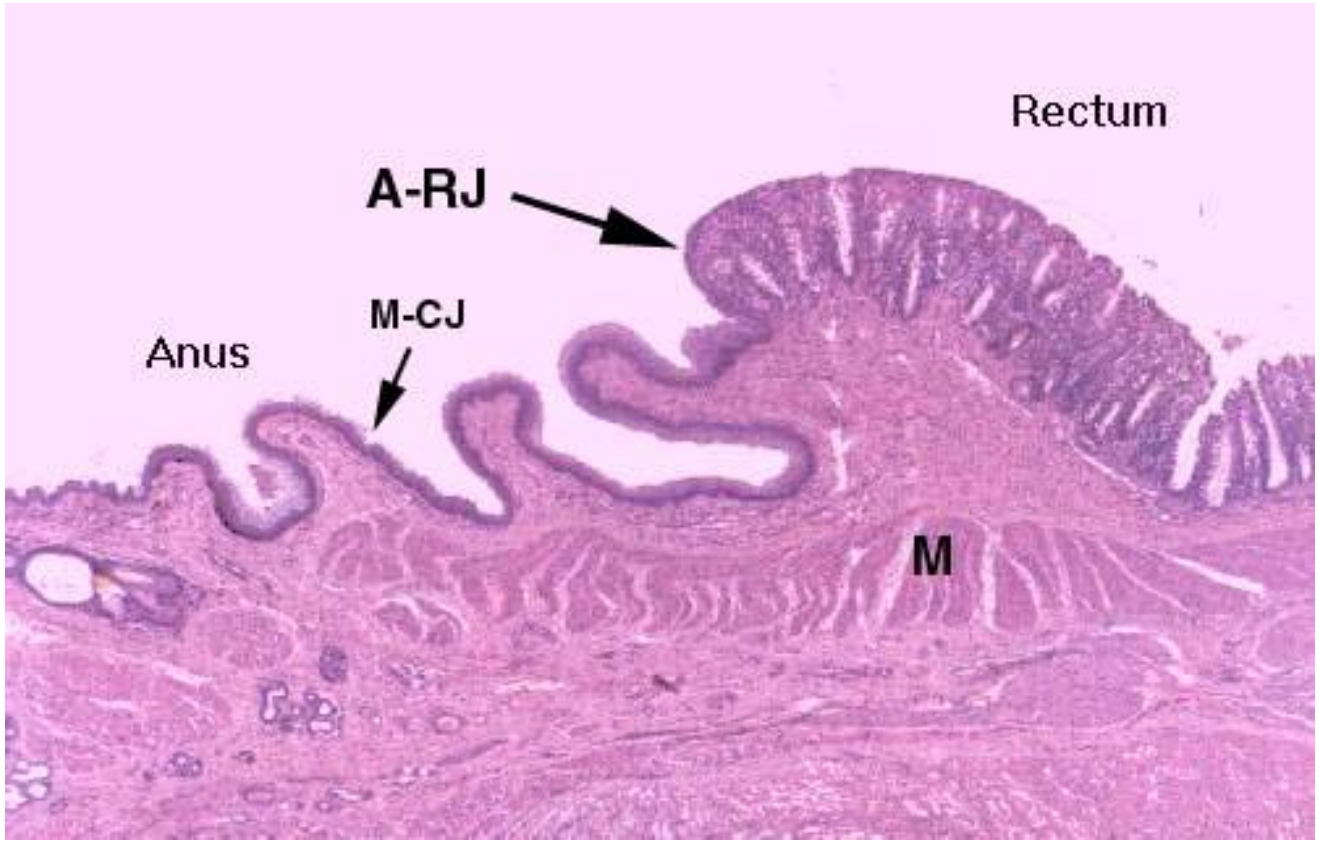
Figure 4. Anatomy of the Anus



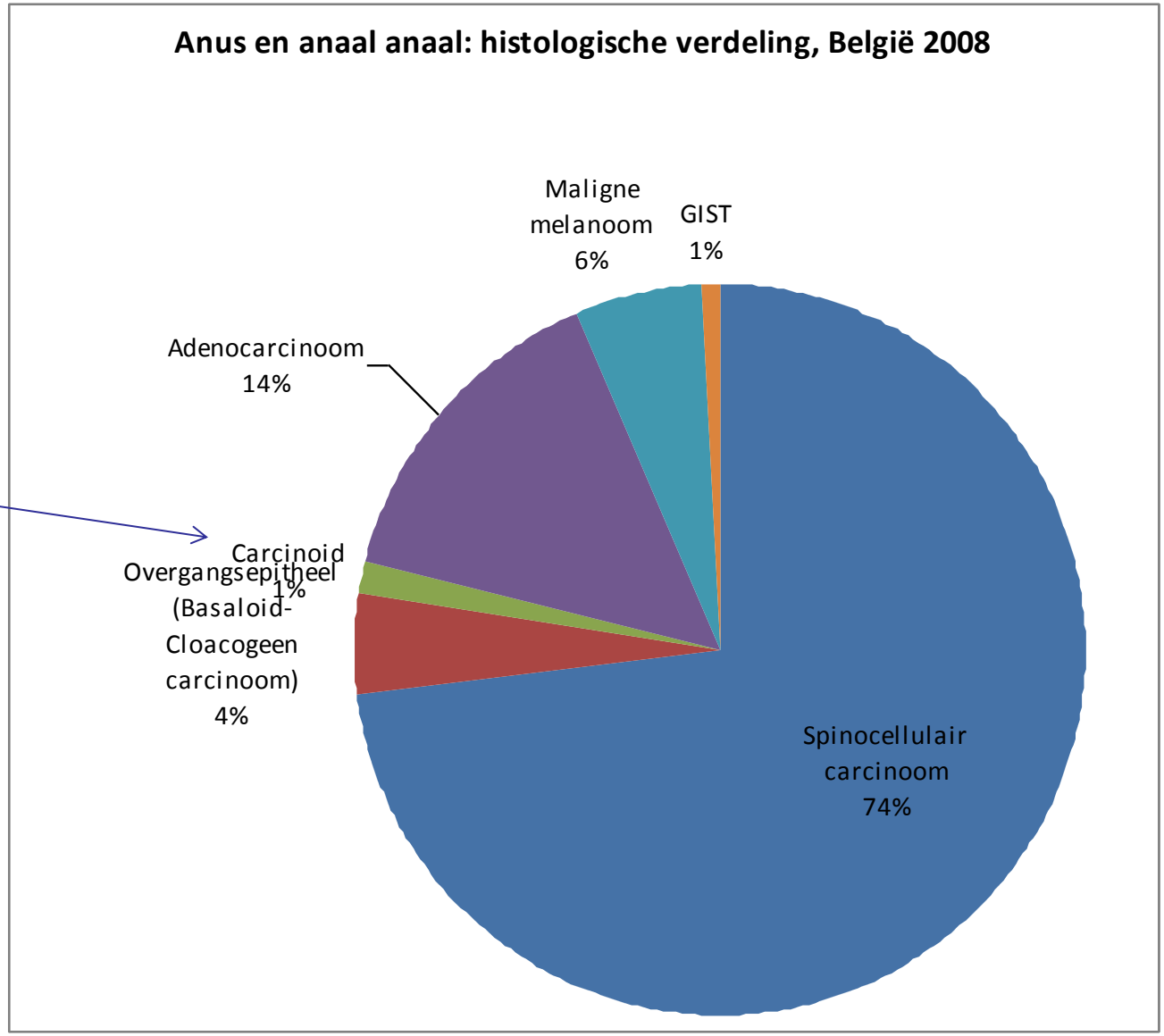
From Ryan D, Compton C, and Mayer R. Medical progress: carcinoma of the anal canal. *N Engl J Med.* 2000;342(11):792-800. Reprinted with permission from the publisher. Copyright © 2000 *Massachusetts Medical Society.* All rights reserved.

Anal canal and anus





A-RJ = ano-rectal junction (anus – rectum)
M-CJ = muco-cutaneous junction (anal mucosa – anal skin)

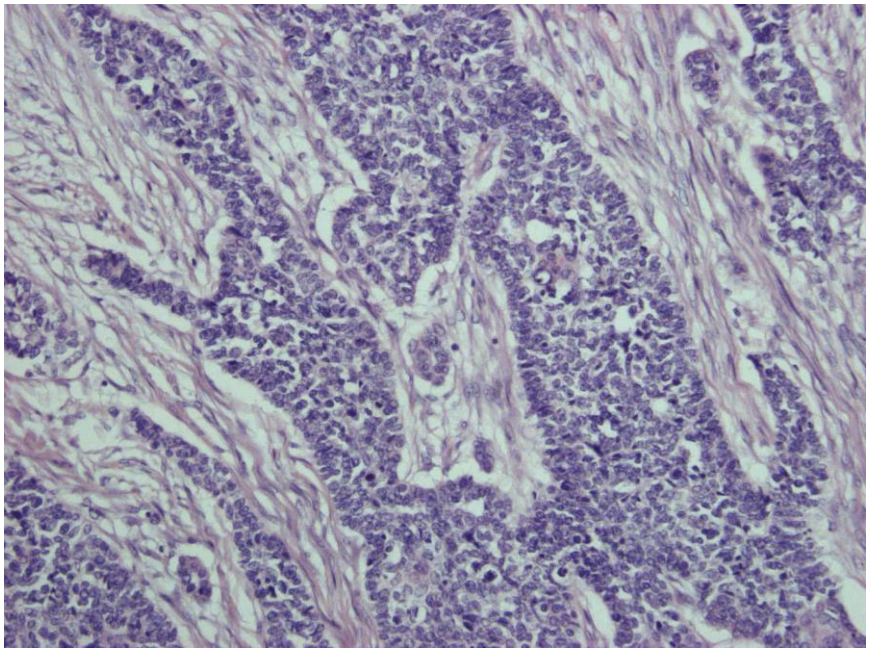


No endocrine tumours in anal canal since WHO 2010 (→ to locate in rectum)

This figure dates from 2008, so endocrine tumours could be registered in the anal canal

Squamous cell carcinoma (8070/3) : subtypes

- Large cell keratinising subtype (8071/3)
- Large cell nonkeratinising subtype (8072/3)
- Basaloid subtype (cloacogenic carcinoma) (8123/3 – 8124/3)



Not always clear difference between those different types → very subjective interpretation of the pathologist.

Prognosis similar for the 3 types.

Frequently more than one subtype present in one tumour.

↓

Future evolution towards 1 type (squamous carcinoma ; 8070/3) possible.

Main risk factor: human papillomavirus (HPV)

Hôpital Erasme ULB

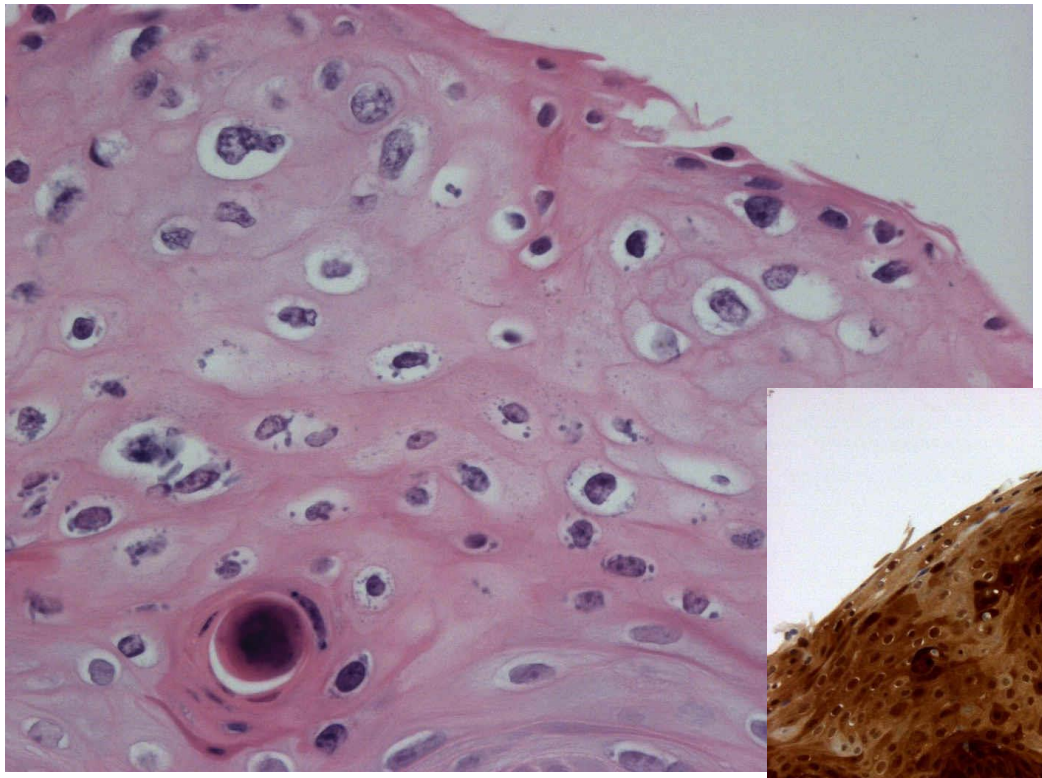
TABLE II – PREVALENCE OF HPV IN BIOPSIES OF INVASIVE ANAL CANCER AND PREVALENCE ODDS RATIOS BY HISTOLOGICAL TYPE, REGION, HPV DNA SPECIMEN TYPE, PRIMER, STUDY YEAR, CASE SOURCE AND GENDER

	No. of cases	HPV prevalence (%)	OR (95% CI)[1]	Adjusted[2] OR (95% CI)
Histological type				
SCC[1] or unspecified	951	78.3	1.0[3]	1.0[3]
Basaloid	34	82.3	1.3 (0.5–3.2)	2.5 (0.8–7.6)
ADC[1]	7	42.9	0.2 (0.0–0.9)	0.1 (0.0–0.8)
Region				
North America	268	76.9	1.0[3]	1.0[3]
Asia	46	58.7	0.4 (0.2–0.8)	0.2 (0.1–0.7)
Europe	678	79.9	1.2 (0.9–1.7)	0.5 (0.2–1.1)
HPV DNA Specimen Type				
Fixed biopsies	922	78.2	1.0[3]	1.0[3]
Fresh or frozen biopsies	70	78.6	1.0 (0.5–1.8)	1.0 (0.5–2.0)
Primer				
MY09/11	214	76.6	1.0[3]	1.0[3]
GP5+/6+ or L1C1/C2	358	86.9	2.0 (1.3–3.1)	1.9 (0.8–4.3)
TS[1] (Early proteins)	256	78.5	1.1 (0.7–1.7)	5.9 (2.6–13.2)
Combo MY09/11	111	64.9	0.6 (0.3–0.9)	1.0 (0.4–2.4)
Other[4]	53	52.8	0.3 (0.2–0.6)	0.9 (0.3–2.6)
Study Year				
1989–1998	380	64.7	1.0[3]	1.0[3]
1999–2004	538	87.0	3.6 (2.6–5.1)	8.8 (3.4–22.6)
2005–2007	74	83.8	2.8 (1.5–5.4)	7.4 (3.2–17.4)
Case Source				
Hospital-based studies	482	69.1	1.0[3]	1.0[3]
Population-based studies	510	86.9	3.0 (2.1–4.1)	0.7 (0.2–2.4)
Gender				
Males	90	76.7	1.0[3]	–
Females	171	86.5	1.9 (1.0–3.8)	–

[1]OR, odds ratio; CI, confidence interval; SCC, squamous cell carcinoma; ADC, adenocarcinoma; TS, type-specific.–[2]Adjusted for histological type, region, HPV DNA source, primer and study year.–[3]Referent.–[4]PU-1M/31B ($N = 33$), SK38/39 ($N = 6$), TS L1 ($N = 14$).

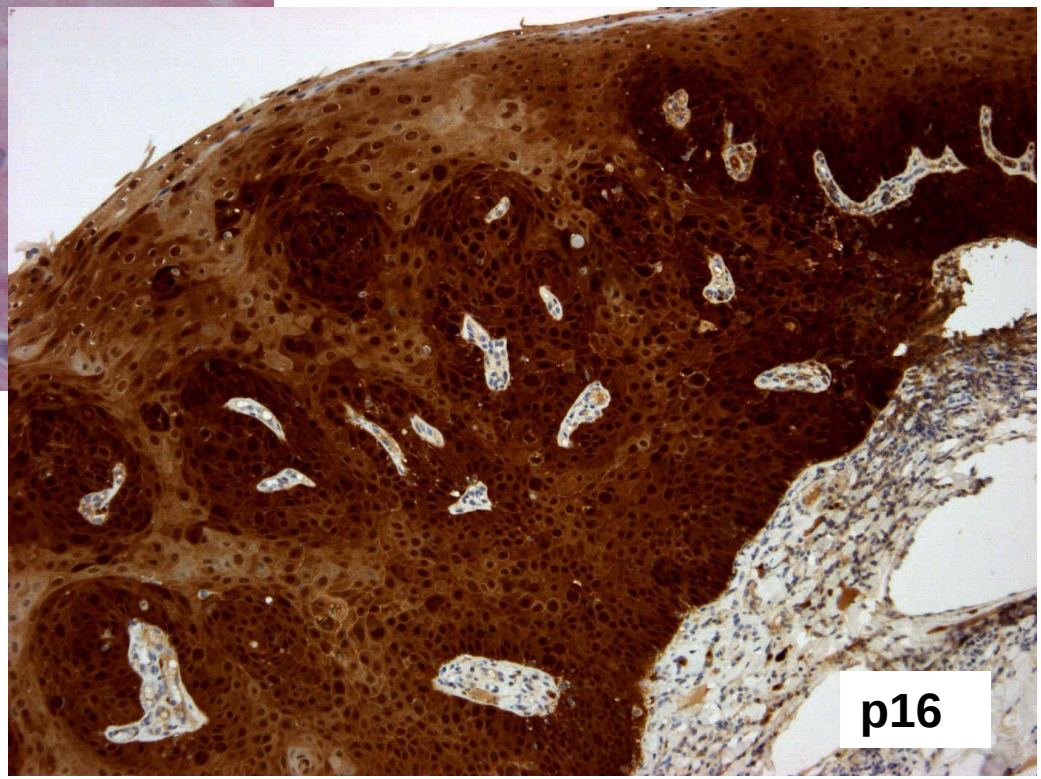
75 – 80 % of squamous anal tumours HPV+

Incidence of HPV+ tumours ↗



Condyloma with typical koilocytes → related to HPV infection and may give rise to carcinoma

Detection of HPV by PCR is expensive and not easily accessible ; p16 immunohisto-chemistry can be used as an alternative test (p16+ → HPV+)



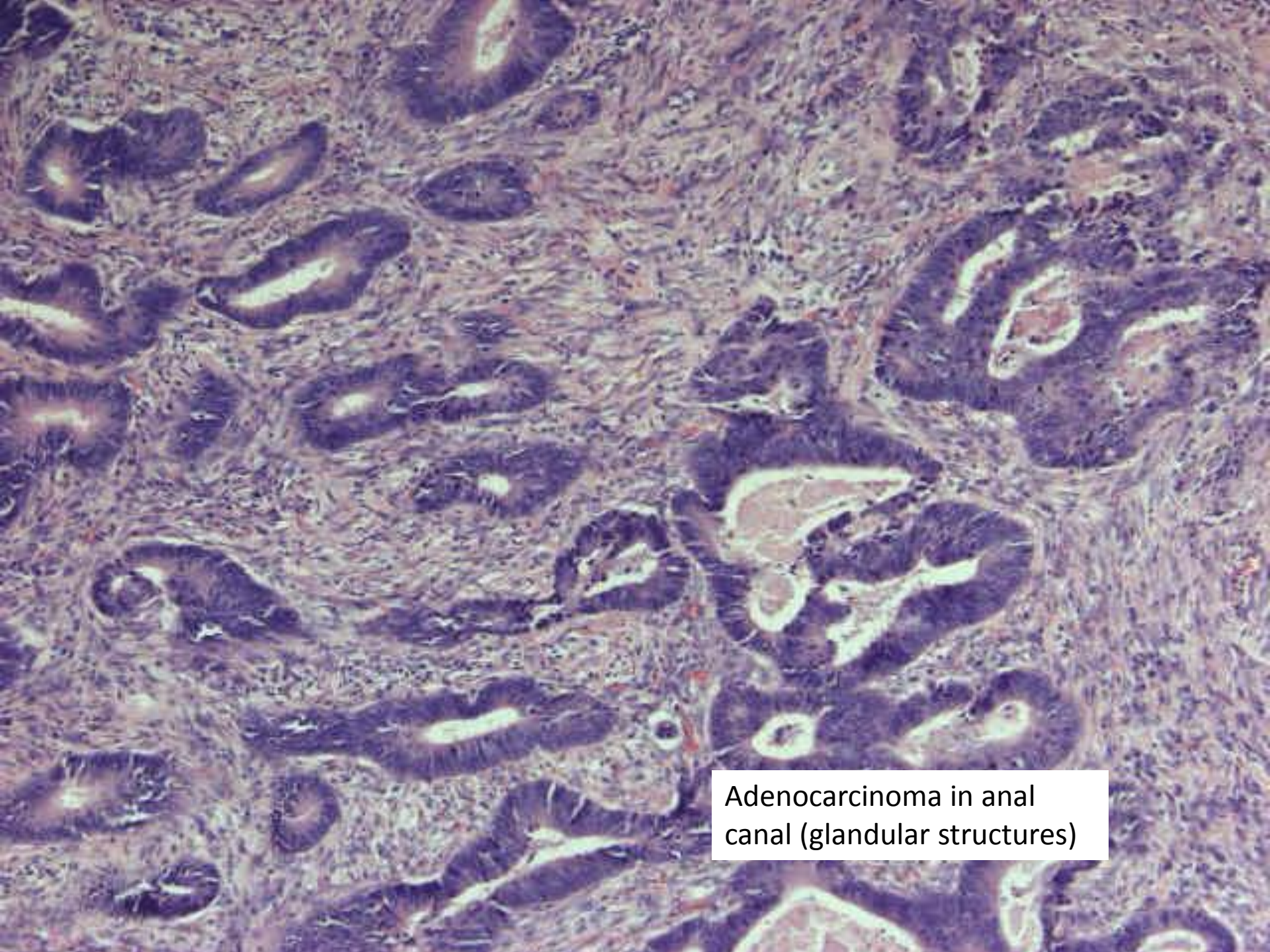
Squamous cell carcinoma: precursor lesions

- Chronic HPV infection
- Intraepithelial neoplasia
  (to be registered only if high grade dysplasia → HSIL = High-grade Squamous Intra-epithelial Lesion)(8077/2 – topo C21.1)
- Anal Squamous Intraepithelial Neoplasia (ASIN)
  (to be registered only if high grade dysplasia) (8077/2 – topo C21.1)
- Perianal Squamous Intraepithelial Neoplasia (PSIN) (Bowen's disease)
  (always to be registered because in situ lesion : 8081/2 – topo C44.5)

Anal adenocarcinoma (15 % of anal tumours)

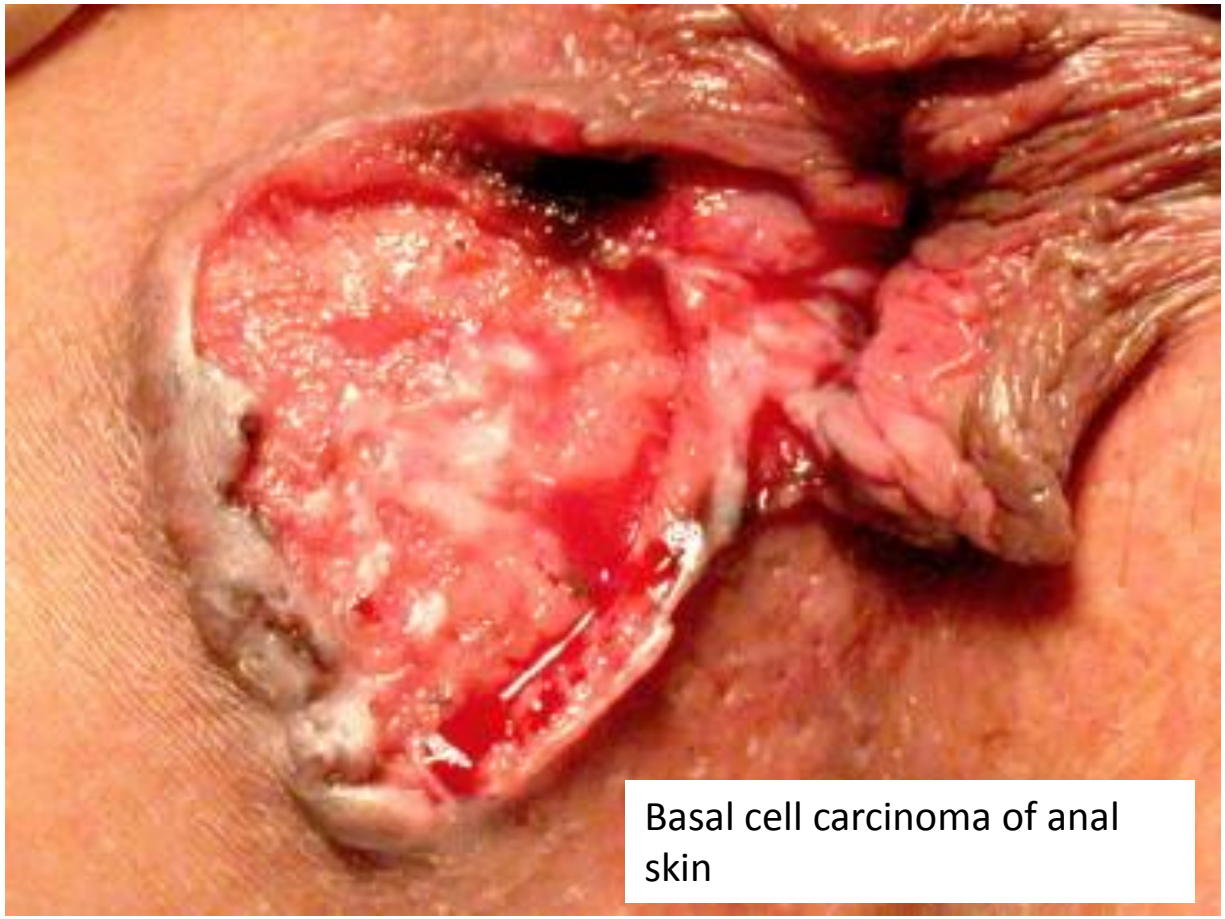
- → mainly 8140/3
- Adenocarcinoma arising in anal mucosa
- Extramucosal (perianal) adenocarcinoma
- Adenocarcinoma within anorectal fistulae (e.g. in Crohn's disease)
- Adenocarcinoma of anal glands

- Prognosis poorer than for squamous cell carcinoma (less respons to radiotherapy when compared to squamous lesions)


Adenocarcinoma in anal canal (glandular structures)

Basal cell carcinoma of the anal margin (skin tumour)

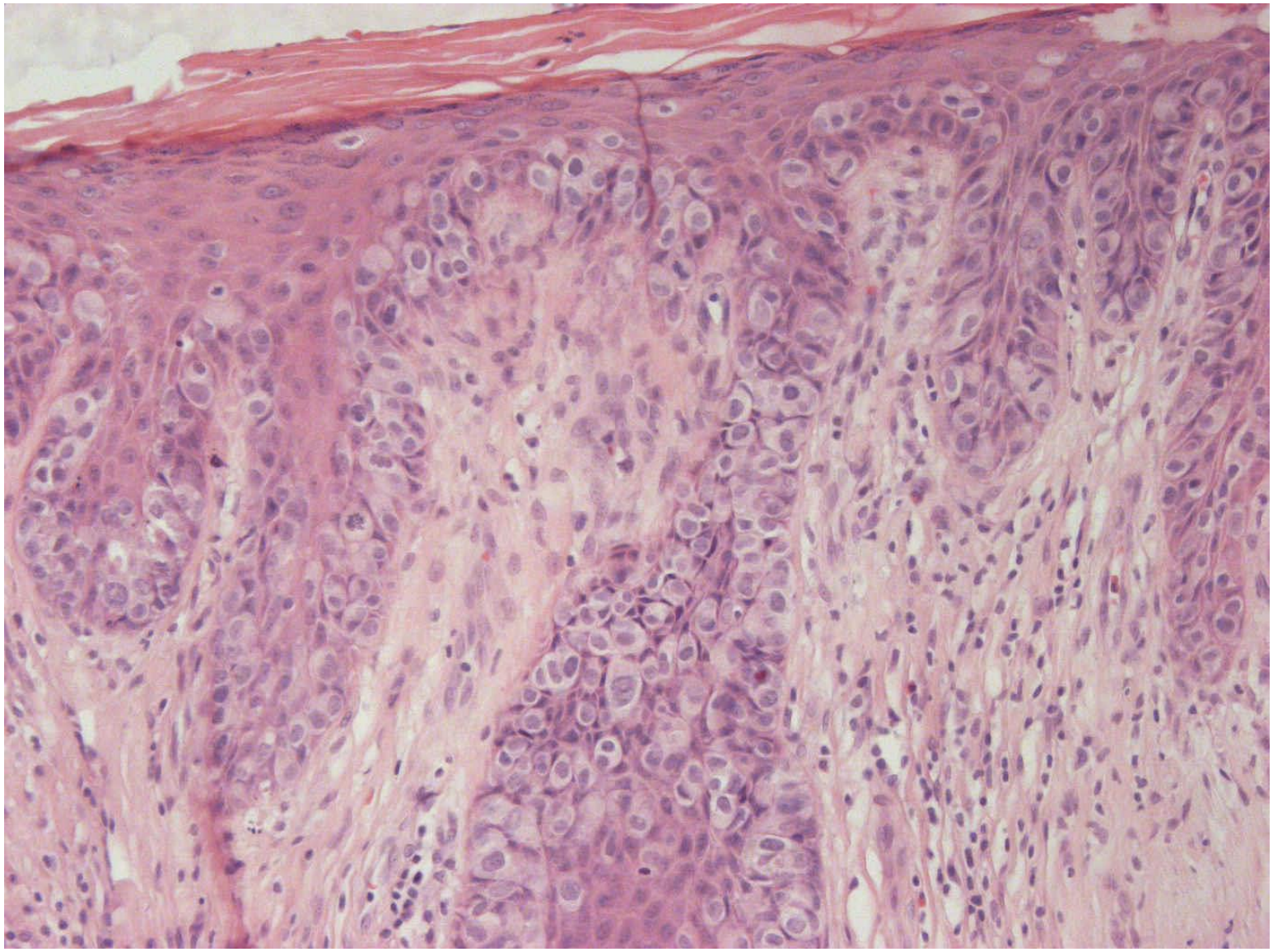
- → mainly 8090/3 ; topo C44.5
- >100 cases reported
- No evidence for role of HPV infection



Basal cell carcinoma of anal skin

Simo AC, *Gastroenterol Clin Biol* 2008

Paget's disease of perianal skin (8542/2 ; topo C44.5)



Paget's disease

- At sites with high density of glands (anus, breast)
- Often associated with invasive adenocarcinoma (e.g. adenoca of the rectal mucosa)
- To be registered as in situ lesion (8542/2) unless pathologist confirms invasion

ICD-O-3 / CIM-O-3 in which 8542/3 can be found

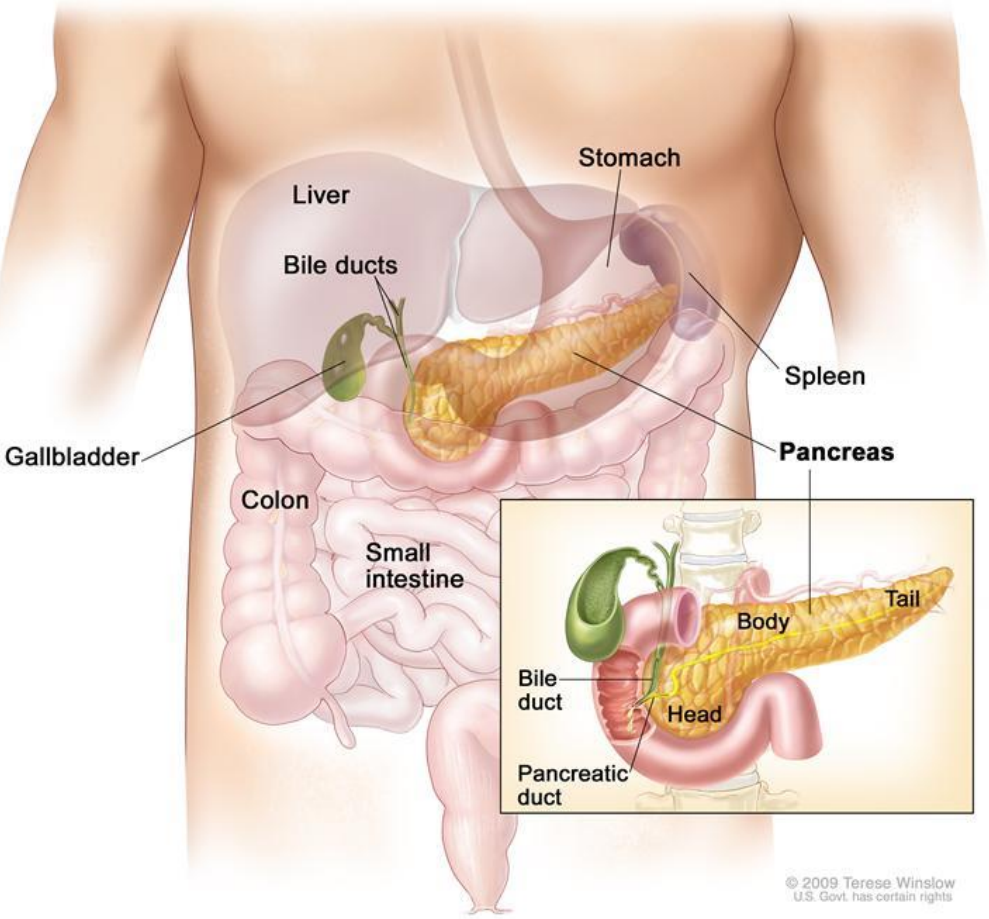
To know which tumour is involved, immunohistochemistry can help the pathologist :

Table 1. Common special stains and immunohistochemical markers that are useful in differentiating poorly differentiated neoplasms of the anal canal

Tumour types	Stains for mucin	S100	CK7/20	NSE/ chromogranin/ synaptophysin	CD20/ EBV	CK5/6 and p63	Keratin AE1/ AE3
SCC	–	–	+/–	–/–/–	–/–	+/+	+
Adenocarcinoma	+	–	+/+	–/–/–	–/–	–/–	+
Neuroendocrine	–	–	–/–	+/+/+	–/–	–/–	+
Melanoma	–	+	–/–	–/–/–	–/–	–/–	–/+
Lymphoma	–	–	–/–	–/–/–	+/+	–/–	–
Undifferentiated carcinoma	–	–	–/–	–/–/–	–/–	–/–	+

Balachandra B, *Histopathology* 2007

ANATOMY OF THE PANCREAS



Possible problems with pancreatic tumours due to its particular localisation :

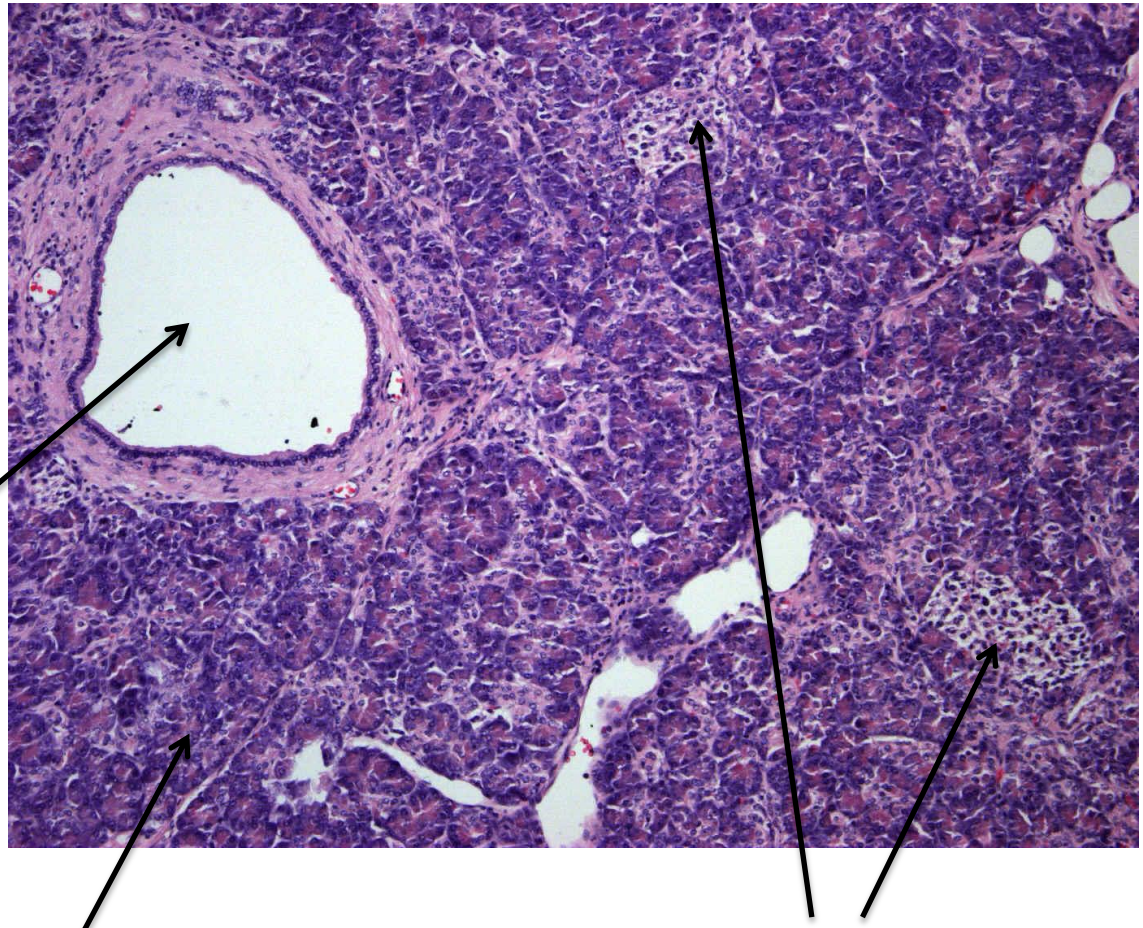
- Gastric tumour with invasion of the adjacent pancreas or just the opposite ?
- Tumour of the pancreas, the bile ducts or the duodenum ?

THE NORMAL PANCREAS

Hôpital Erasme

ULB

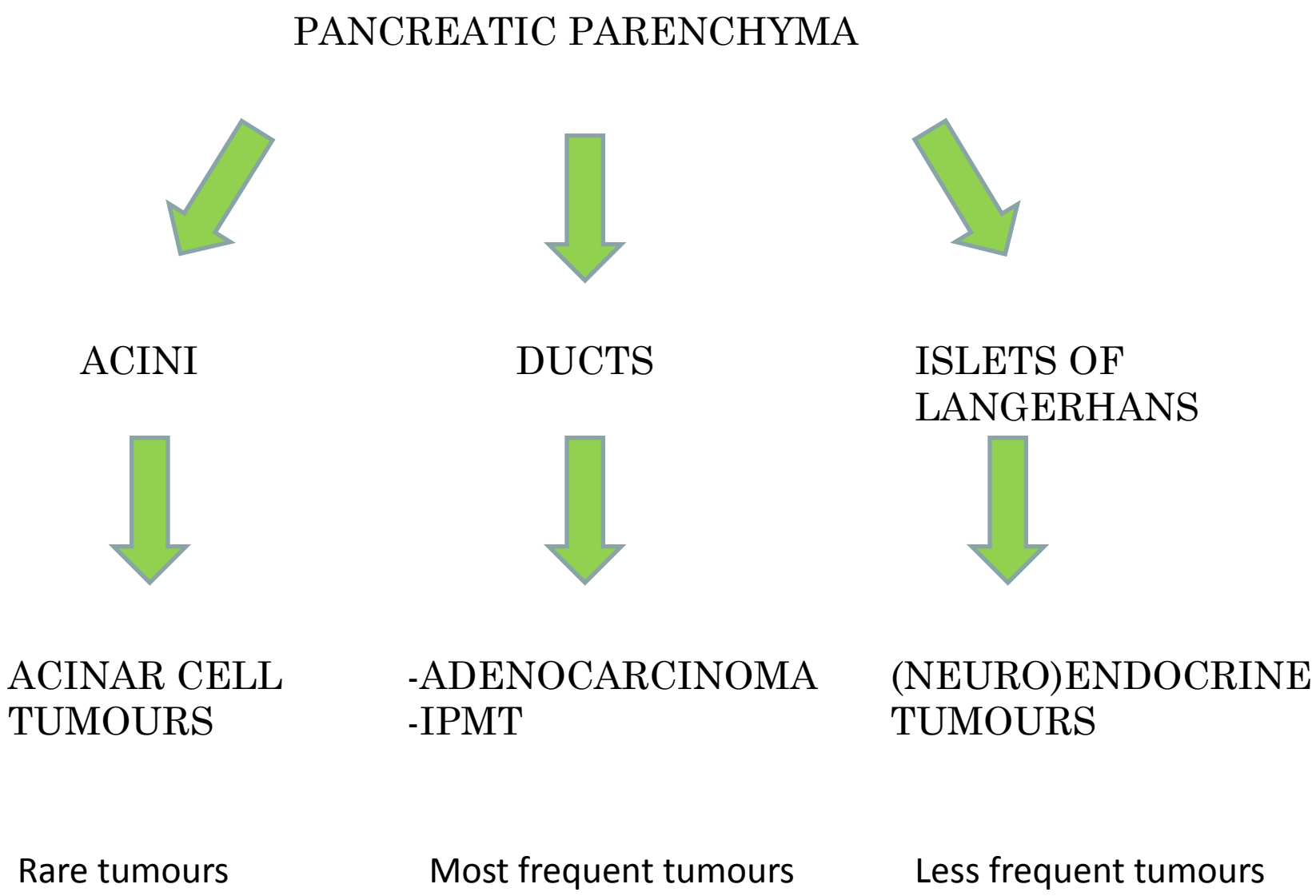
Enzymes, produced by the exocrine part of the pancreas and important for the digestion of the food, are released in the **pancreatic ducts**



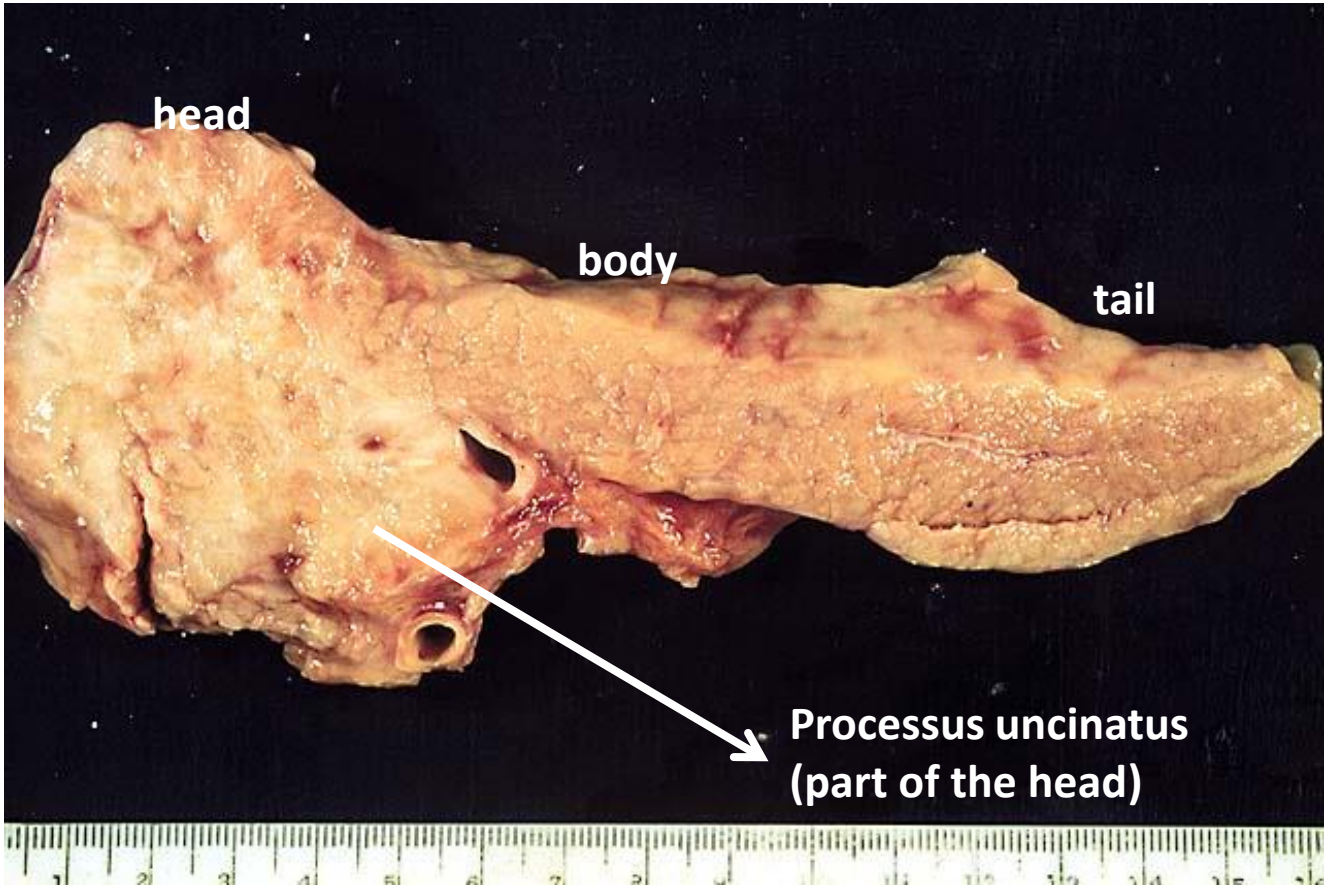
The **acini** are composed of exocrine cells, producing enzymes to digest the food (enzymes are released in the pancreatic ducts)

The islets of Langerhans are composed of endocrine cells, producing hormones (eg insulin) directly released into the bloodstream

THE ORIGIN OF PANCREATIC TUMOURS



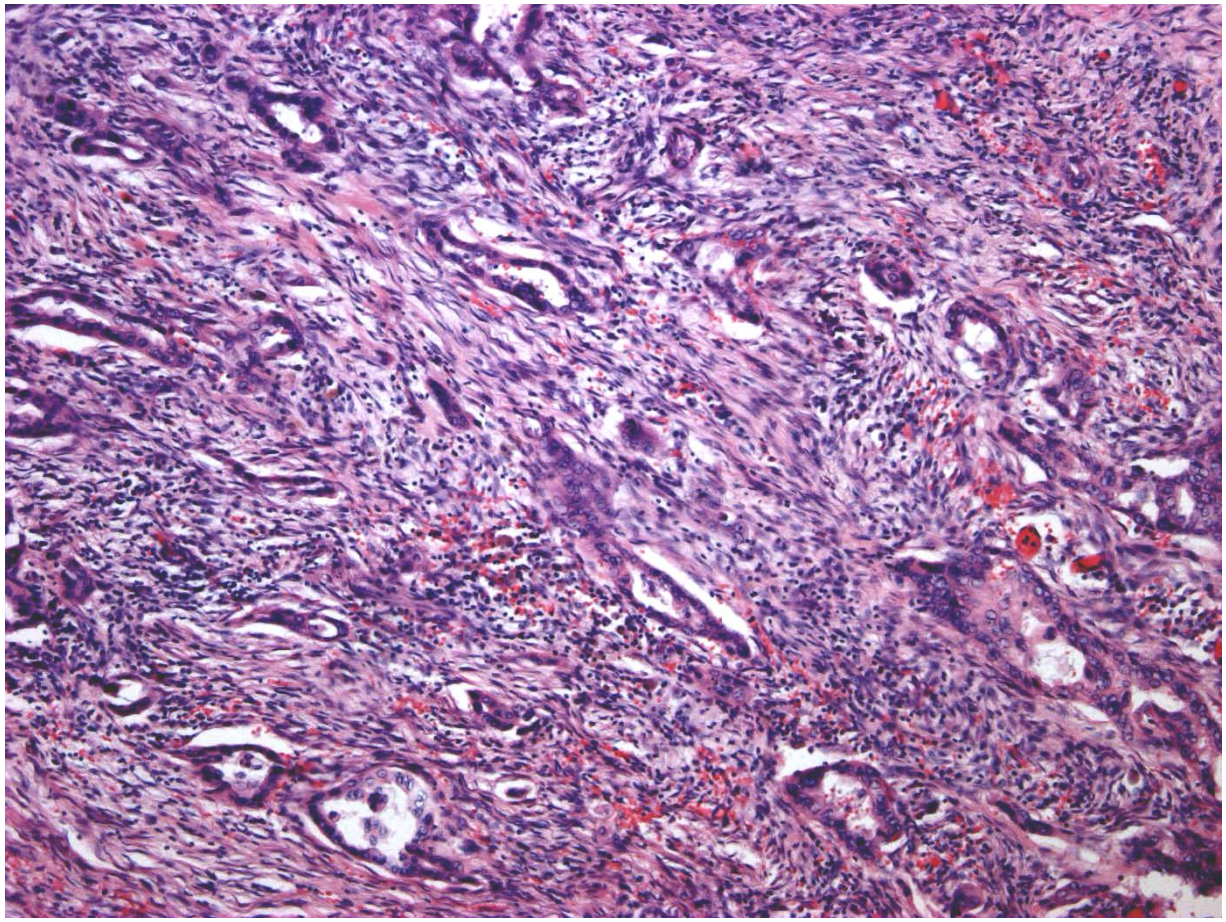
PANCREATIC ADENOCARCINOMA



Adenocarcinoma mostly in the pancreatic head

(neuro)endocrine tumours more frequent in the pancreatic tail

PANCREATIC ADENOCARCINOMA



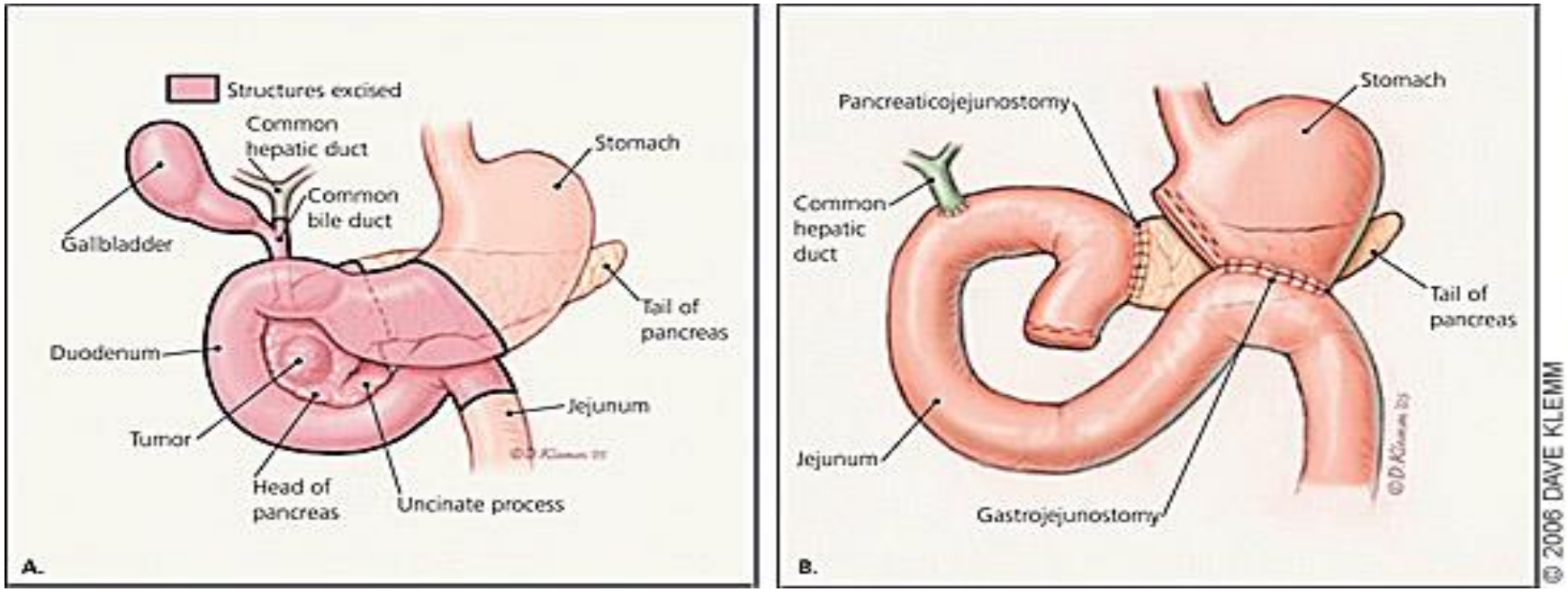
Glandular cells and a lot of fibrous stroma (less blood vessels) → little respons to chemotherapy → bad prognosis

SURGICAL TREATMENT OF PANCREATIC TUMOURS

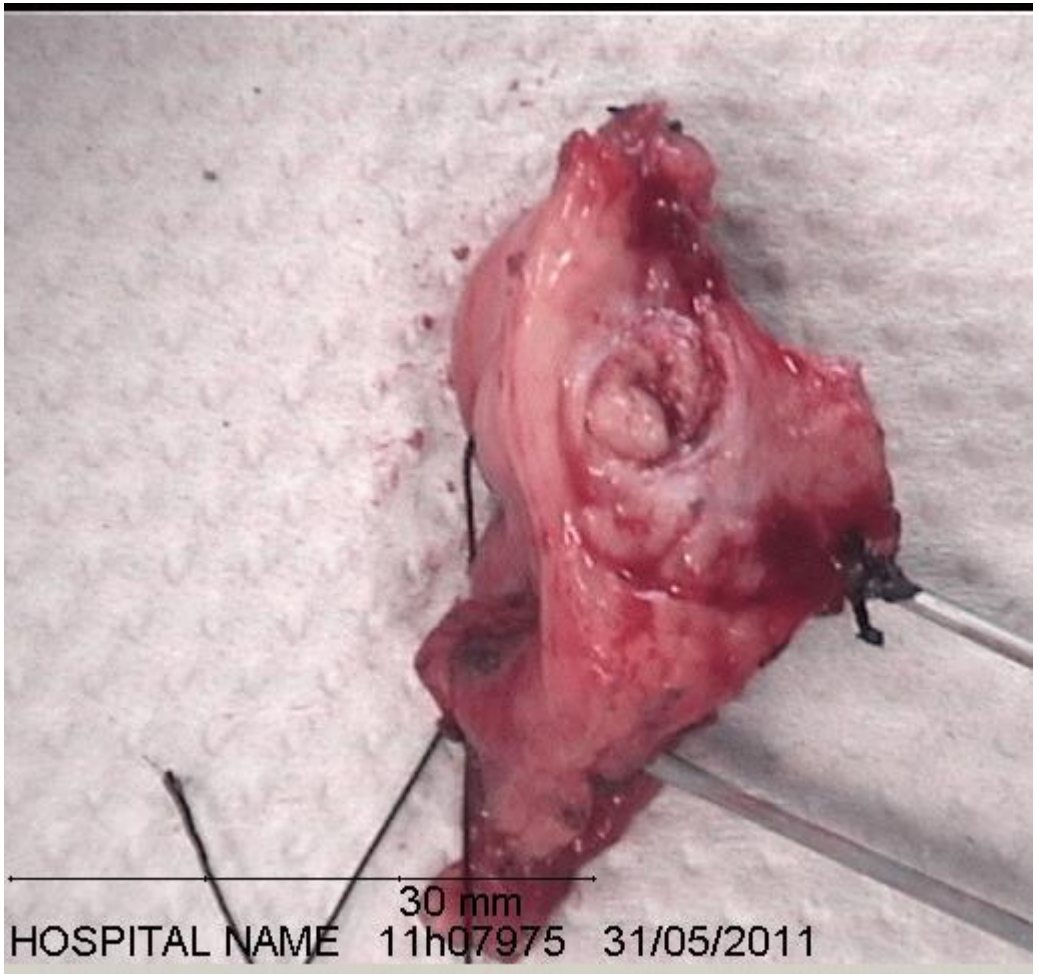
Hôpital Erasme

ULB

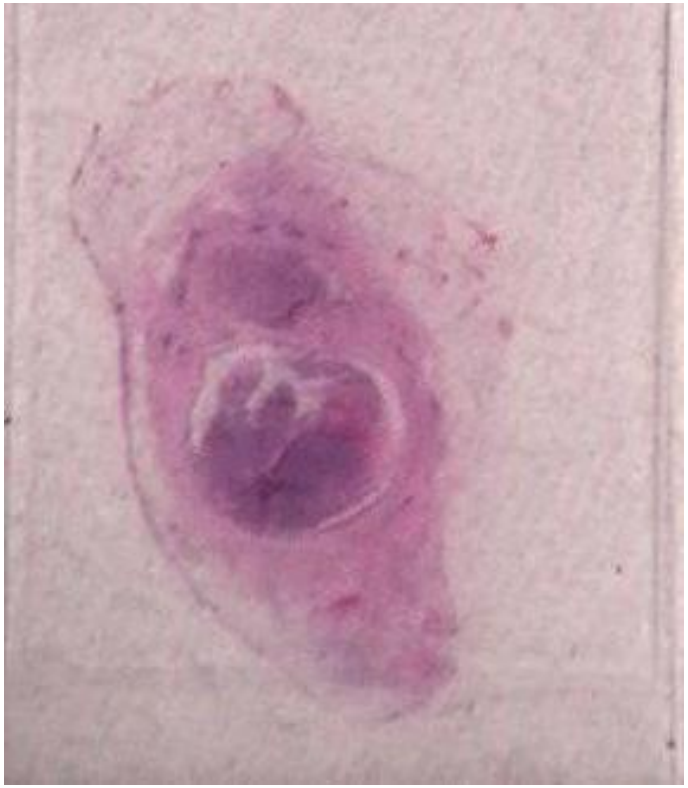
The Whipple procedure (pancreatoduodenectomy) is an operation to remove a portion of the pancreas, as well as a portion of the stomach, small intestine (duodenum), the gallbladder and part of the bile duct. The remaining organs are reattached to allow digestion of food.



INTRADUCTAL PAPILLARY MUCINOUS TUMOUR



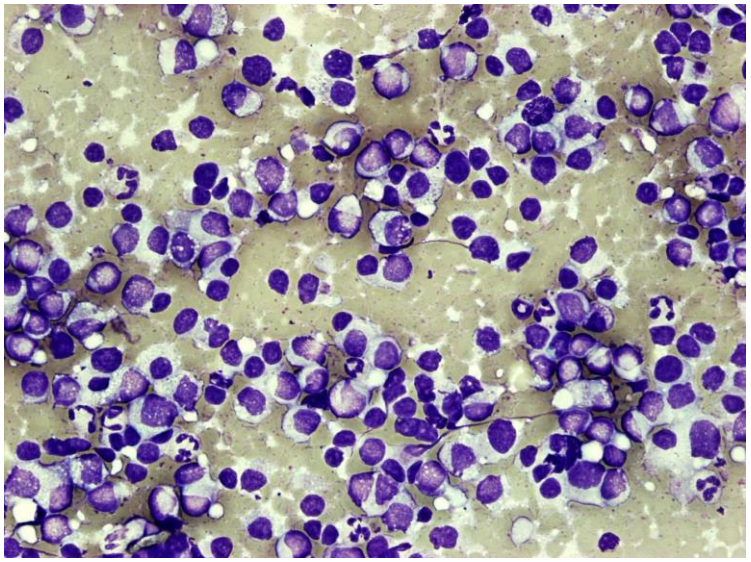
Tumour growing in the main duct of the pancreas (Wirsung)



IPMT with severe dysplasia has to be registered (once the basal membrane is ruptured → no longer IPMT but invasive ductal adenoca arising from IPMT)

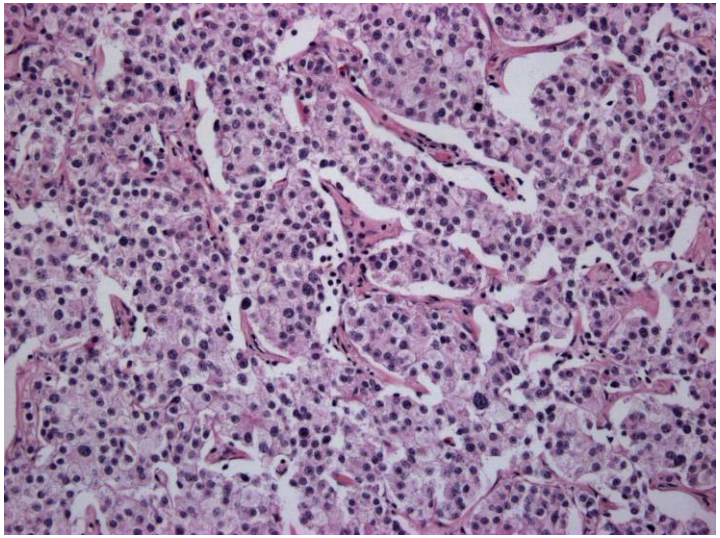
NEURO-ENDOCRINE TUMOURS

Macroscopic appearance



Cytology : only cells available for analysis : less accurate (adenoca or endocrine ca?)

Histology : tissue available for analysis : more accurate than cytology

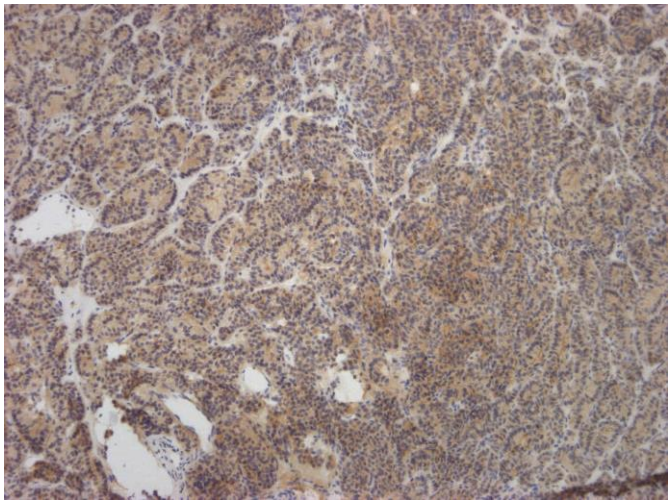


IMMUNOHISTOCHEMISTRY FOR NEURO-ENDOCRINE TUMOURS

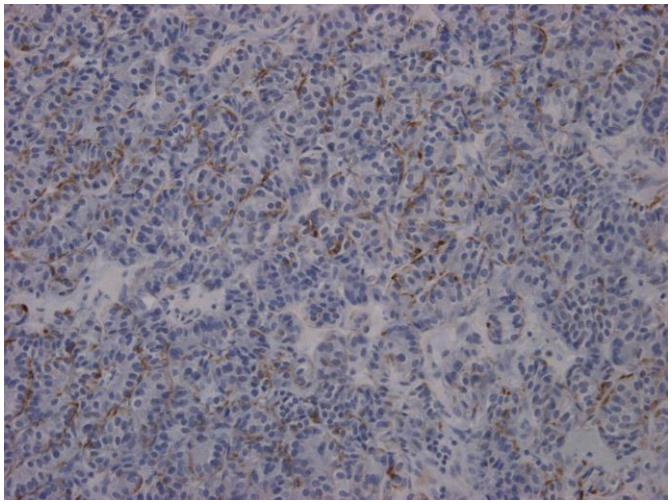
Hôpital Erasme ULB

Frequently 2/3 or 3/3 colorations + if real endocrine tumour.

If only 1/3 + (CD56 OR chromogranin OR synaptophysin), be careful because this can also be seen with classical adenocarcinoma !

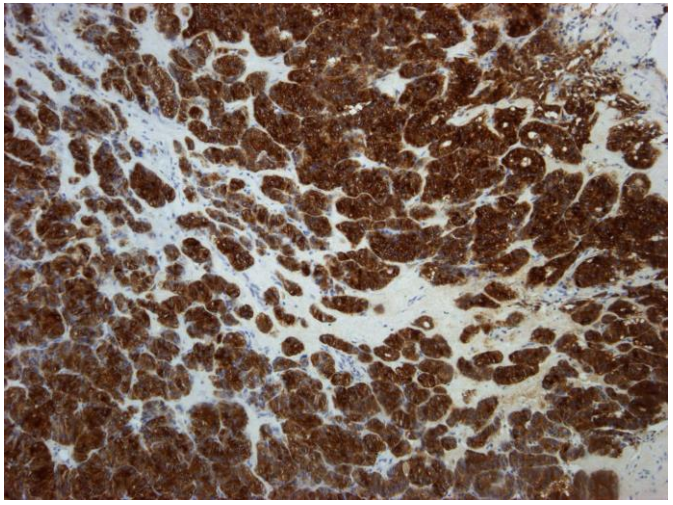


CD56

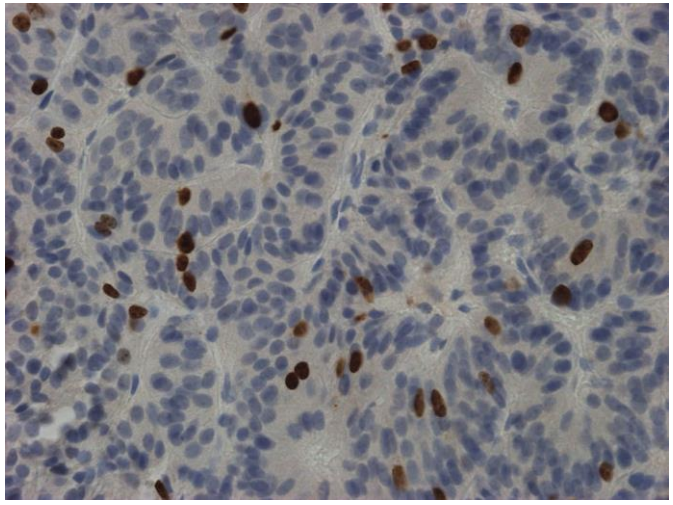


chromogranin

The higher the value of Ki-67, the more aggressive the behaviour of the tumour !



synaptophysin



Ki-67

Rindi classification for grading of neuro-endocrine tumours

Table 4 Grading proposal for foregut (neuro)endocrine tumors

Grade	Mitotic count (10 HPF)[a]	Ki-67 index (%)[b]
G1	<2	≤2
G2	2–20	3–20
G3	>20	>20

[a] 10 HPF: high power field=2 mm^2, at least 40 fields (at 40× magnification) evaluated in areas of highest mitotic density

[b] MIB1 antibody; % of 2,000 tumor cells in areas of highest nuclear labeling

Neuro-endocrine tumours

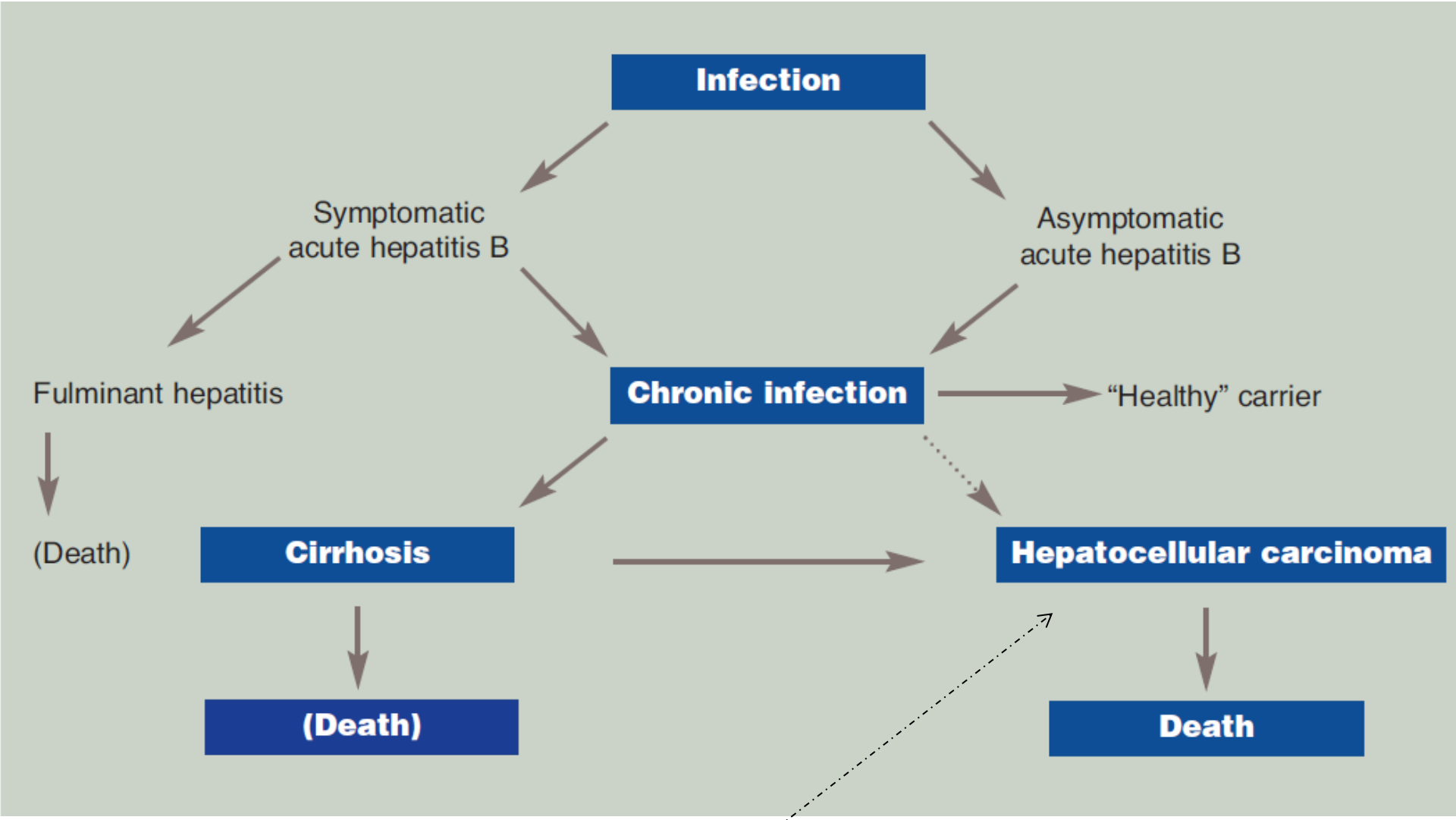
- Neuro-endocrine tumour >< tumour with some neuro-endocrine differentiation (e.g. when CD56 OR chromogranin OR synaptophysin is positive)

- Mixed adeno-neuro-endocrine tumour (MANEC): at least 30% of each component : very rare and bad prognosis !

WHO histological classification of tumours of the liver and intrahepatic bile ducts

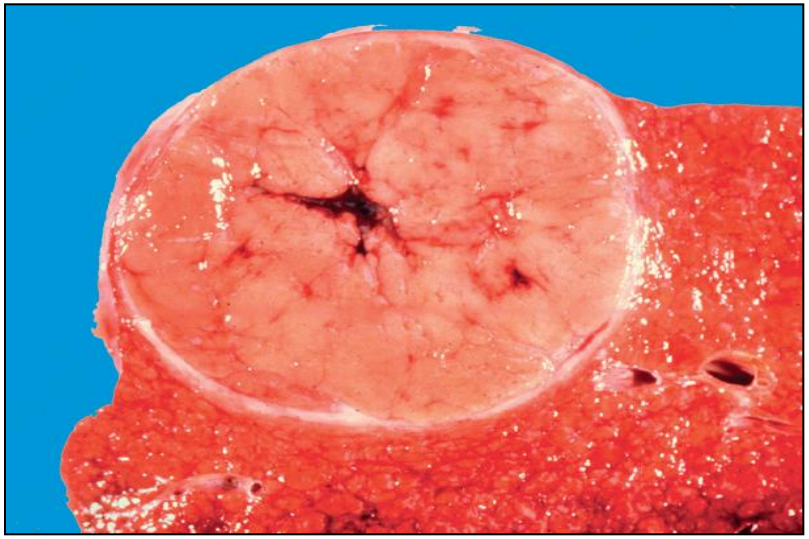
Epithelial tumours	
Benign	
Hepatocellular adenoma (liver cell adenoma)	8170/0[1]
Focal nodular hyperplasia	
Intrahepatic bile duct adenoma	8160/0
Intrahepatic bile duct cystadenoma	8161/0
Biliary papillomatosis	8264/0
Malignant	
Hepatocellular carcinoma (liver cell carcinoma)	8170/3
Intrahepatic cholangiocarcinoma (peripheral bile duct carcinoma)	8160/3
Bile duct cystadenocarcinoma	8161/3
Combined hepatocellular and cholangiocarcinoma	8180/3
Hepatoblastoma	8970/3
Undifferentiated carcinoma	8020/3
Non-epithelial tumours	
Benign	
Angiomyolipoma	8860/0
Lymphangioma and lymphangiomatosis	9170/0
Haemangioma	9120/0
Infantile haemangioendothelioma	9130/0
Malignant	
Epithelioid haemangioendothelioma	9133/1
Angiosarcoma	9120/3
Embryonal sarcoma (undifferentiated sarcoma)	8991/3
Rhabdomyosarcoma	8900/3
Others	
Miscellaneous Tumours	
Solitary fibrous tumour	8815/0
Teratoma	9080/1
Yolk sac tumour (endodermal sinus tumour)	9071/3
Carcinosarcoma	8980/3
Kaposi sarcoma	9140/3
Rhabdoid tumour	8963/3
Others	
Haemopoietic and lymphoid tumours	
Secondary tumours	
Epithelial abnormalities	
Liver cell dysplasia (liver cell change)	
Large cell type (large cell change)	
Small cell type (small cell change)	
Dysplastic nodules (adenomatous hyperplasia)	
Low-grade	
High-grade (atypical adenomatous hyperplasia)	
Bile duct abnormalities	
Hyperplasia (bile duct epithelium and peribiliary glands)	
Dysplasia (bile duct epithelium and peribiliary glands)	
Intraepithelial carcinoma (carcinoma in situ)	8500/211
Miscellaneous lesions	
Mesenchymal hamartoma	
Nodular transformation (nodular regenerative hyperplasia)	
Inflammatory pseudotumour	

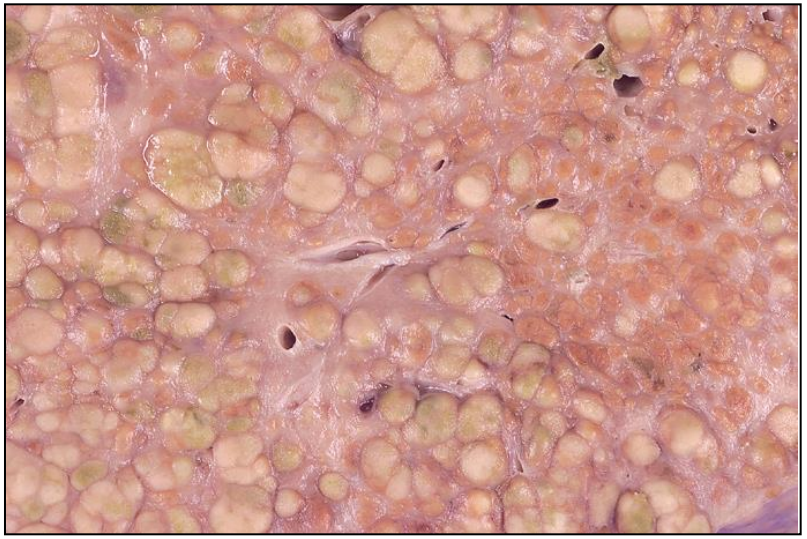
[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline or uncertain behaviour, /2 for in situ carcinomas and grade III intraepithelial neoplasia and /3 for malignant tumours.

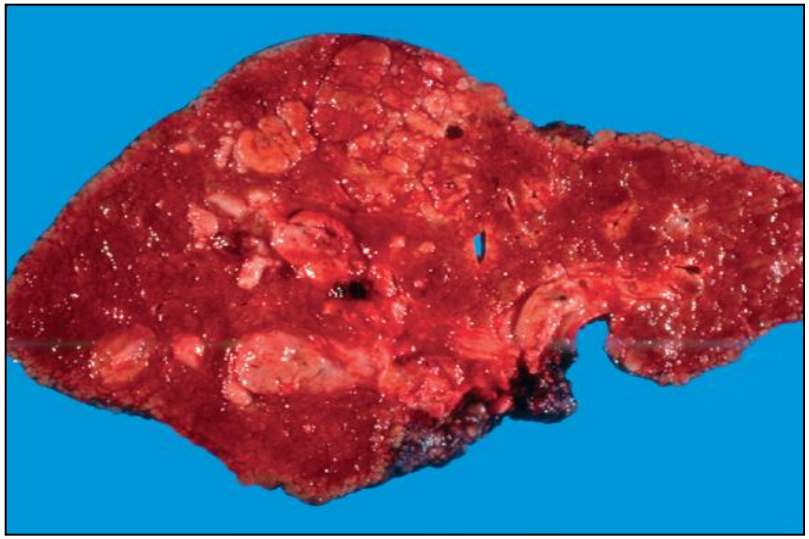


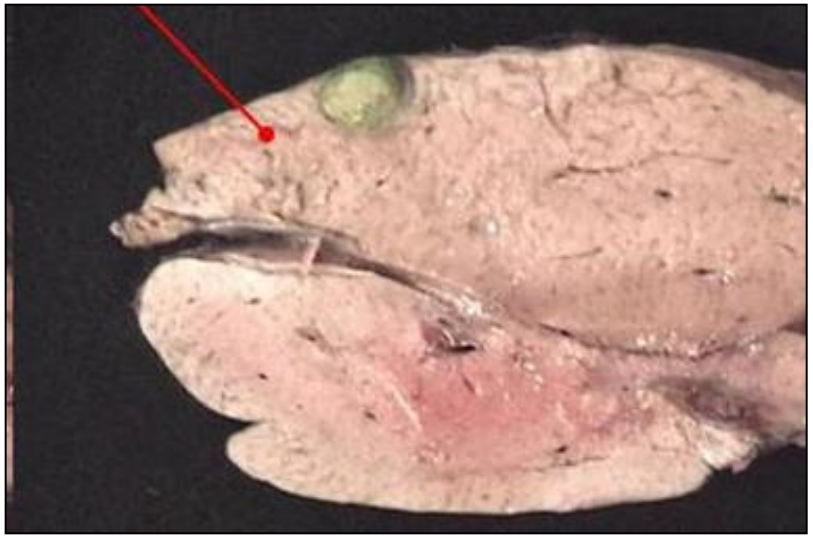
Hepatocellular carcinoma is also possible in non-cirrhotic livers !

Hepatocellular carcinoma (HCC) (8170/3): macroscopy

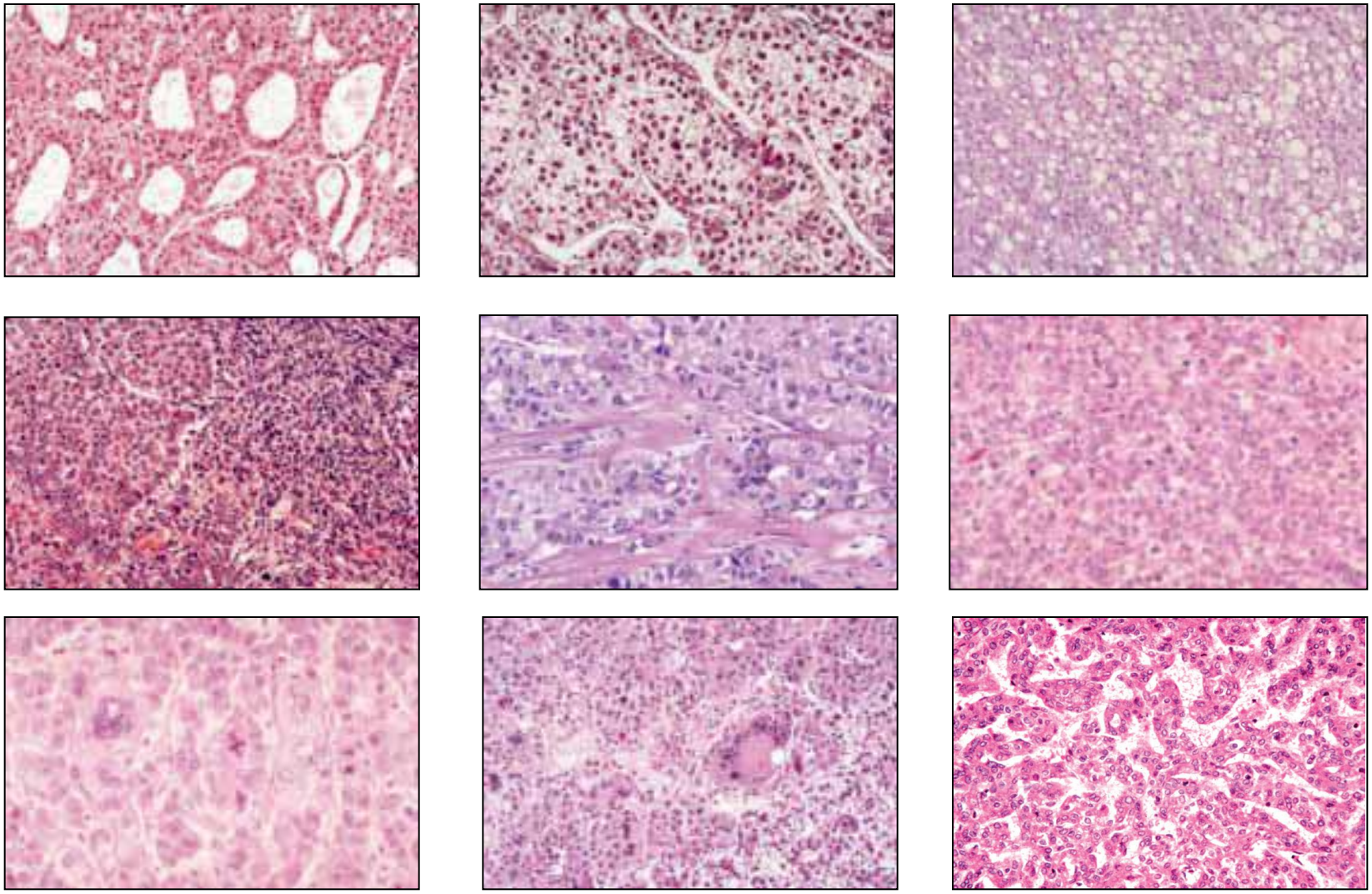








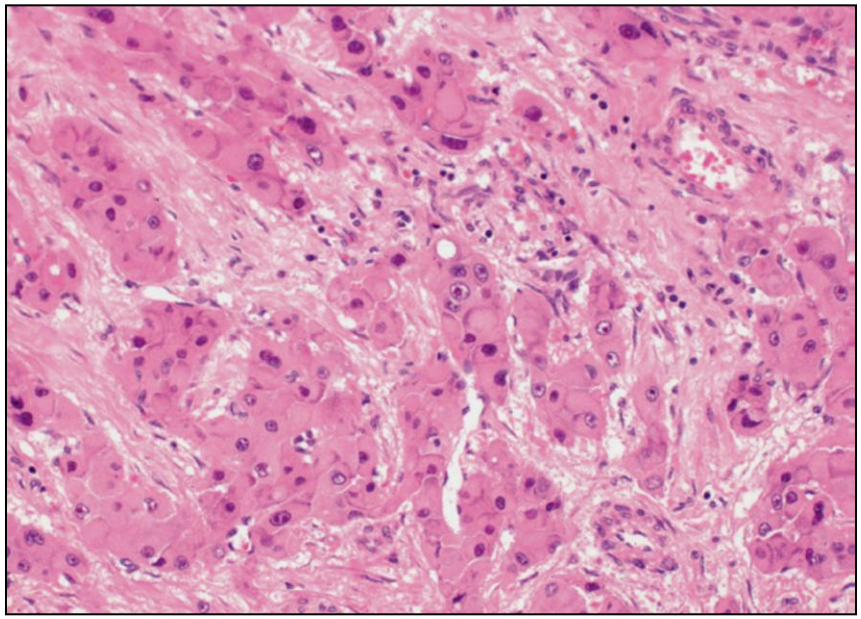
Hepatocellular carcinoma (HCC)(8170/3) : microscopy



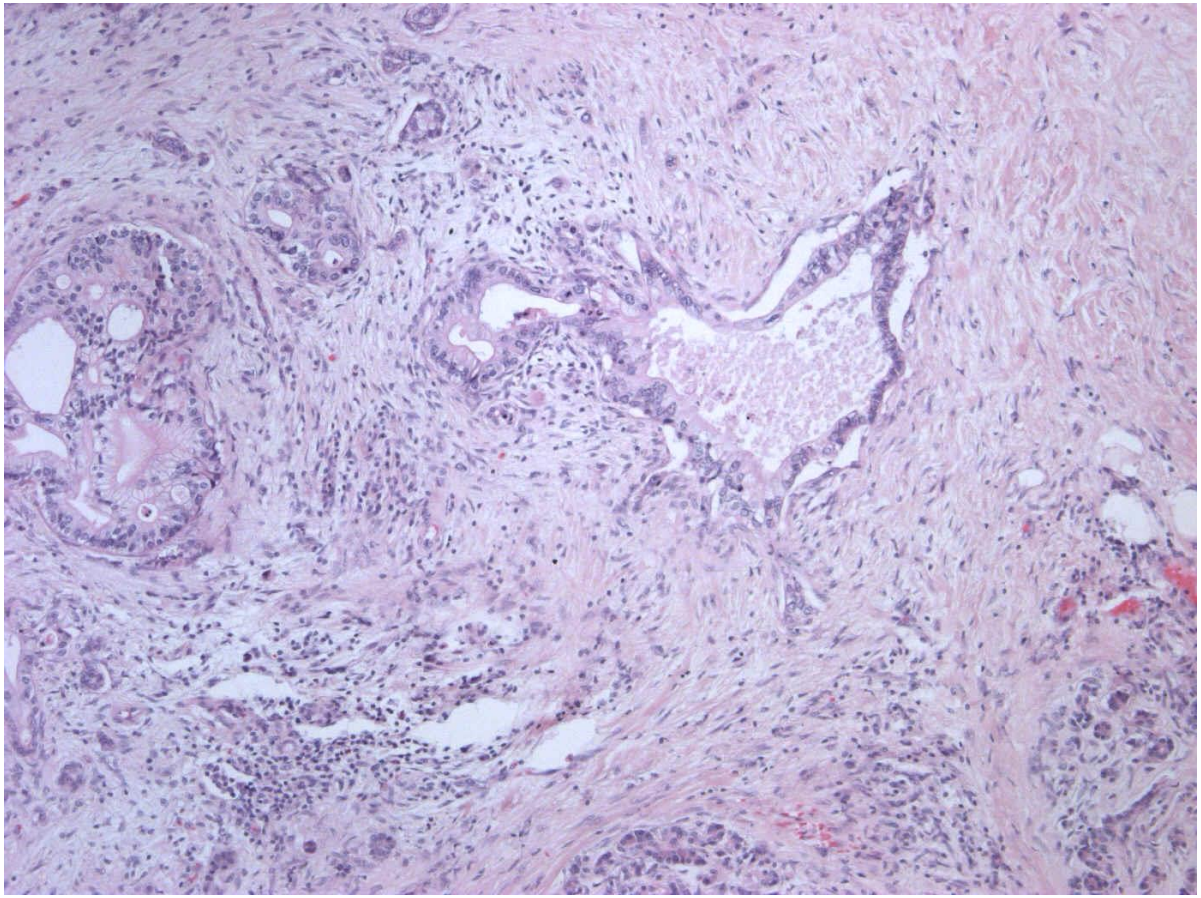
Different subtypes of HCC without prognostic relevance…

Fibrolamellar carcinoma (8171/3)

- Particular subtype of hepatocellular carcinoma
- Children and young adults
- On non-cirrhotic liver
- No known risk factors
- Better prognosis



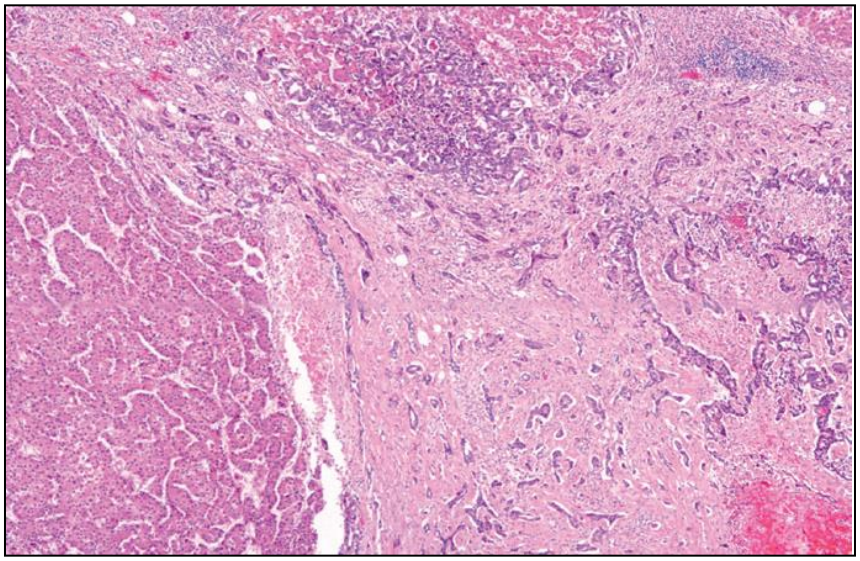
Cholangiocarcinoma



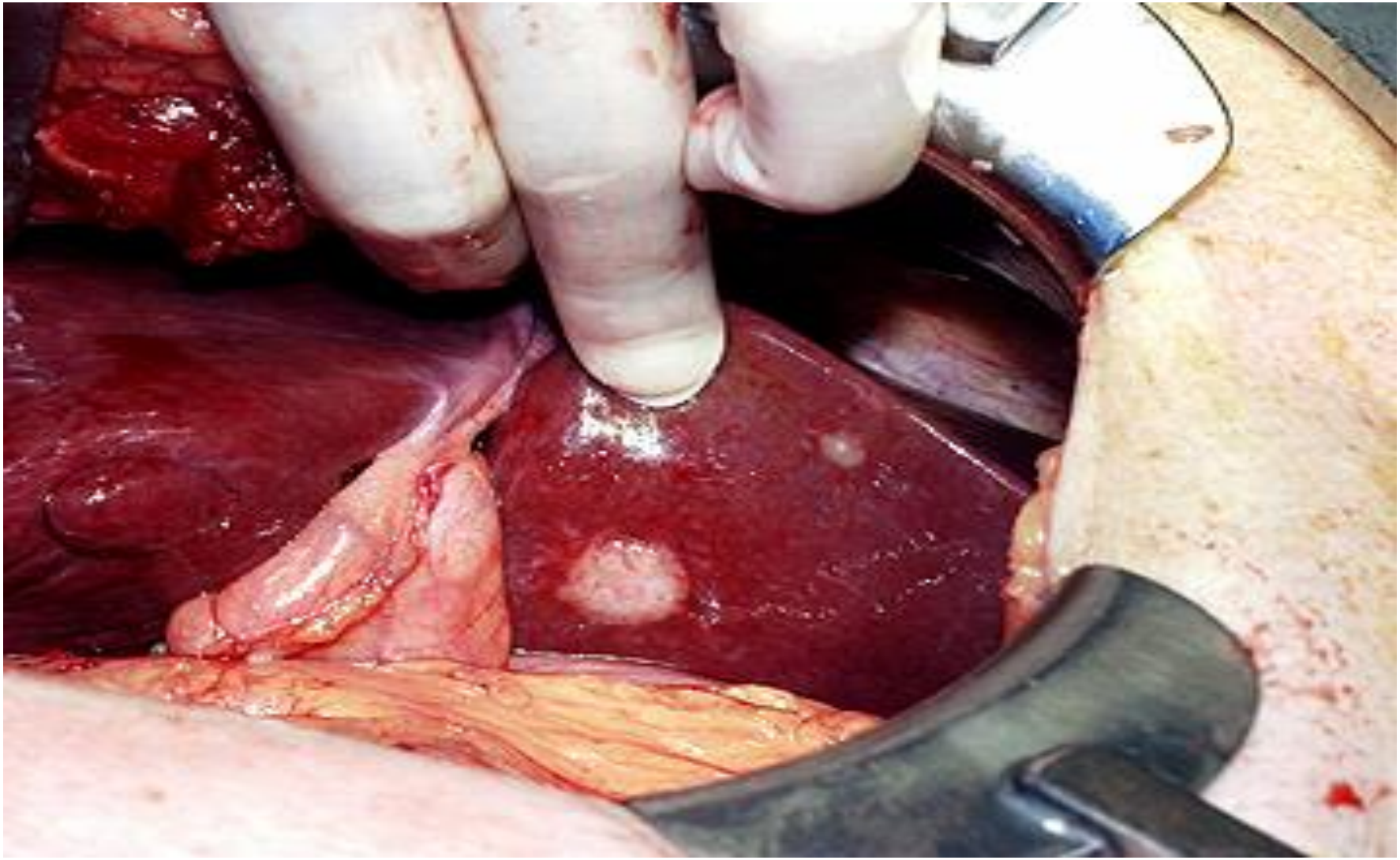
A lot of fibrous tissue (desmoplastic reaction) → less blood vessels → little reaction to chemotherapy → bad prognosis

Mixed hepatocellular/cholangiocarcinoma (8180/3)

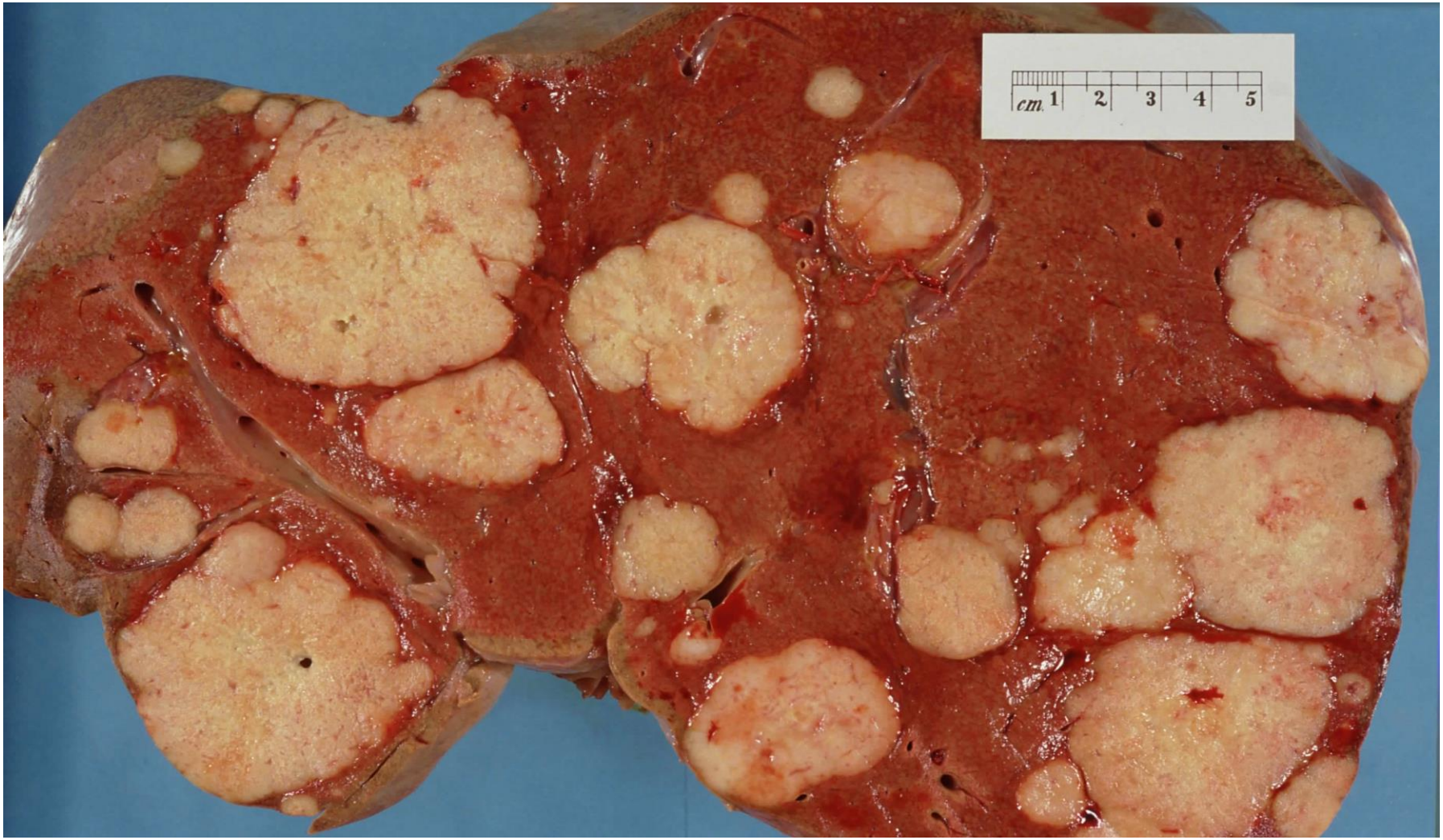
- Rare tumour with features of both
- Bad prognosis (prognosis of this mixed tumour is determined by the cholangiocarcinoma-part)



Liver: site of metastasis of other tumours



Liver metastasis



Hepatocellular carcinoma >< cholangiocarcinoma > < metastasis

Hôpital Erasme ULB

Immunohistochemistry of HCC.

Antigen	Result
Hepatocyte (Dako)	Positive (most useful in diagnosis)
Polyclonal carcinoembryonic antigen	Positive (canalicular pattern)
Alpha fetoprotein	Positive or negative
Fibrinogen	Positive or negative
Cytokeratins 8 and 18	Usually positive
Cytokeratins 7 and 19	Usually negative
Cytokeratin 20	Usually negative
Epithelial membrane antigen	Negative
BER EP4	Negative

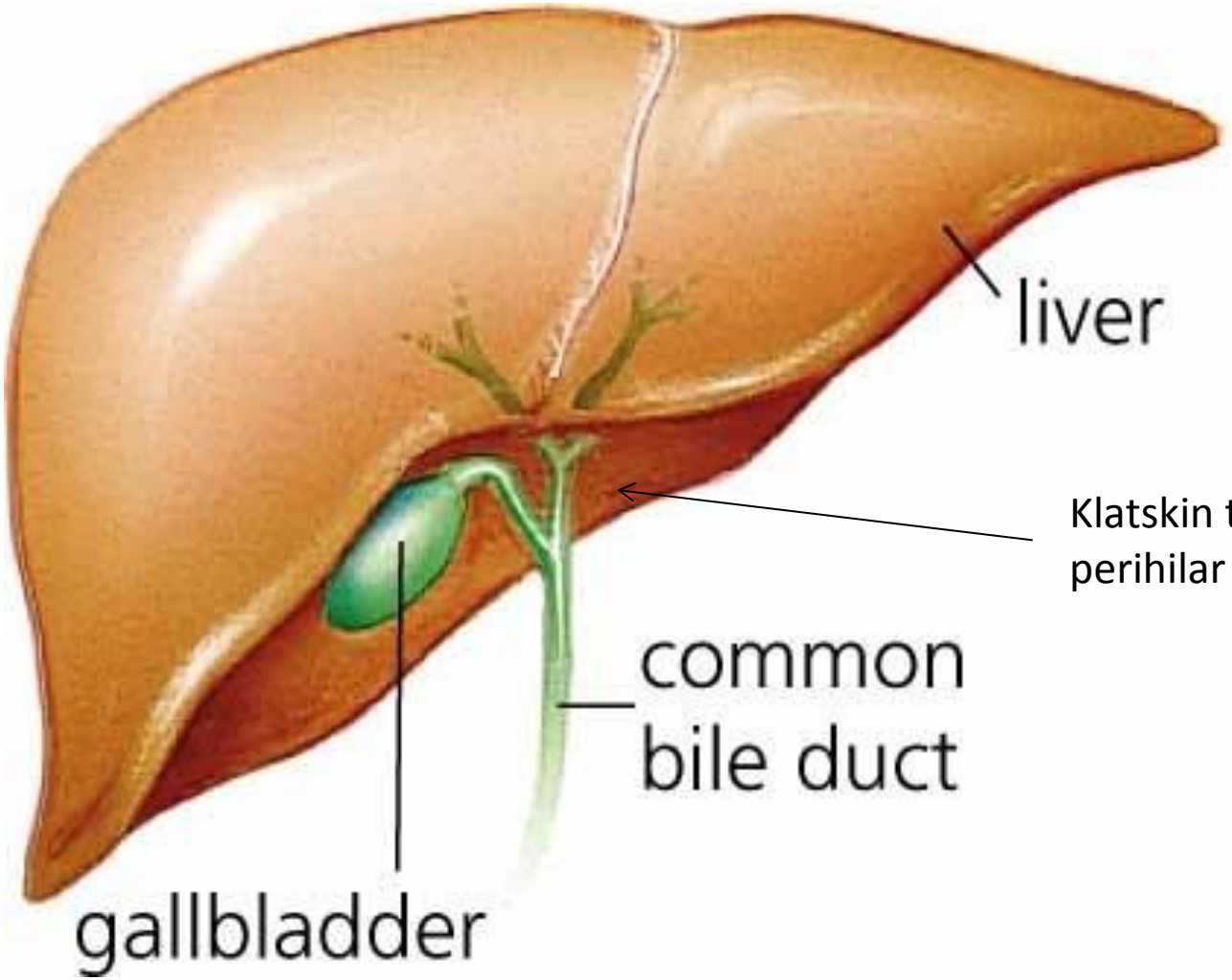
Immunohistochemistry of cholangiocarcinoma :

- Cytokeratins 7 and 19 : usually positive
- Cytokeratin 20 : positive or negative

Immunohistochemistry of metastasis of colonic cancer :

- Cytokeratins 7 and 19 : usually negative
- Cytokeratin 20 : usually positive

The different locations of cholangiocarcinoma



BILE DUCT CANCER

Hôpital Erasme

ULB

TNM classification:
gallbladder ><intrahepatic bile ducts >< extrahepatic bile ducts

Extrahepatic bile ducts – perihilar (Klatskin) >< extrahepatic bile ducts – distal >< extrahepatic bile duct named ductus cysticus (see TNM galbladder)

WHO histological classification of tumours of the gallbladder and extrahepatic bile ducts

Epithelial tumours	
Benign	
Adenoma	8140/0[1]
Tubular	8211/0
Papillary	8260/0
Tubulopapillary	8263/0
Biliary cystadenoma	8161/0
Papillomatosis (adenomatosis)	8264/0
Intraepithelial neoplasia (dysplasia and carcinoma in situ)	
Malignant	
Carcinoma	
Adenocarcinoma	8140/3
Papillary adenocarcinoma	8260/3
Adenocarcinoma, intestinal type	8144/3
Adenocarcinoma, gastric foveolar type	
Mucinous adenocarcinoma	8480/3
Clear cell adenocarcinoma	8310/3
Signet-ring cell carcinoma	8490/3
Adenosquamous carcinoma	8560/3
Squamous cell carcinoma	8070/3
Small cell carcinoma	8041/3
Large cell neuroendocrine carcinoma	8013/3
Undifferentiated carcinoma	8020/3
Biliary cystadenocarcinoma	8161/3
Carcinoid tumour	8240/3
Goblet cell carcinoid	8243/3
Tubular carcinoid	8245/1
Mixed carcinoid-adenocarcinoma	8244/3
Others	
Non-epithelial tumours	
Granular cell tumour	9580/0
Leiomyoma	8890/0
Leiomyosarcoma	8890/3
Rhabdomyosarcoma	8900/3
Kaposi sarcoma	9140/3
Others	
Malignant lymphoma	
Secondary tumours	

[1] Morphology code of the International Classification of Diseases for Oncology (ICD-O) {542} and the Systematized Nomenclature of Medicine (http://snomed.org). Behaviour is coded /0 for benign tumours, /1 for unspecified, borderline, or uncertain behaviour, /2 for in situ carcinomas and grade III intraepithelial neoplasia and /3 for malignant tumours.

STAGING OF TUMOURS

- Degree of extension in organ, in draining lymph nodes and at distance
- TNM classification: Tumour, Nodes, Metastasis