Role of pathology in the evalution of a liver mass

- Fine-needle aspiration cytology
- Core biopsy
- Surgical biopsy
- Resection

- Diagnosis
  - DDX of hepatocellular nodular lesions
  - DDX of primary vs. metastatic tumors
  - Assessment of an unknown primary
- Staging and grading of resected tumors
- Study of antigenic or genetic biomarkers

Needle biopsy of focal lesions, 5.2016-5.2017

• FNA specimens	110
• Needle Biopsy	120
• N. of patients	116
• Distribution of diagnoses	
• Normal/inconclusive	14
• Infection/abscess	6
• Benign hepatocellular lesions	3
• HCC	17
• CHC	5
• Metastases	64
• Other	7

Liver resection specimens, 5.2016-5.2017

• Wedge biopsy	25
• Segmentectomy	26
• Hemi-epatectomy	5
• N. of patients	56
• Distribution of diagnoses	
• HCC	14
• CHC	7
• Metastases	25
• Other tumors	3
• Non tumoral pathology	7

Diagnosis of HCC by percutanous needle biopsy

- Safe procedure
  risk if bleeding as for cirrhotic liver; seeding 0,003-0,009%
- High specificity (approaching 100%) for both FNAB and NCB
- Variable sensitivity (67-93%) due to low NPV
- Sensitivity increases combining FNAB and NBC (78% >88%)
- Accuracy depends on nodule size *(Caturelli et al. 2004)*
  88.6% ≤1 cm
  86.% 1.1-1.5 cm
  91.3% 1.6-2.0 cm
- Accuracy depends on grade of differentiation
- 90%, WD HCC vs. almost 100% MD/PD HCC
- Procedure is ‘operator-dependent’

Complications of percutaneous needle biopsy

- Rare
- 1-3% of patients is hospitalized (Tru-cut)
- 6% within 2 hours; 96% within 24 hours
- Overall mortality 1/10000

Minor complications:

- Pain
- Hypotension

Major complications

- Hemoperithoneum
- Subcapsular or intrahepatic hematoma
- Hemobilia
- Biliary perithonitis
- Transitory bacteriemia or sepsis
- Hemo/pneumothorax
- Pneumoperithoneum or puncture of viscera
- Anphylactic shock (hydatid cyst)
- Subfrenic abscess

Practice of liver biopsy in France: results of a prospective nationwide survey

(Cadranel JF, et al., Hepatology 2000)

Complications of liver biopsy (n = 2084)

Inadequate tissue	***1.5%***
Pain	
moderate	20%
severe	3%
Vaso-vagal episodes	2%
Severe complications	***0.57%***
severe vaso-vagal reaction (4) *hemoperithoneum (1)* *biliary peritonitis (3)* *pneumothorax (1)* *puncture of viscera (3)*	
Number of passes (1 vs >1)	27 vs 68%
Operator (experienced vs non-experienced)	27.4 vs 34.4%

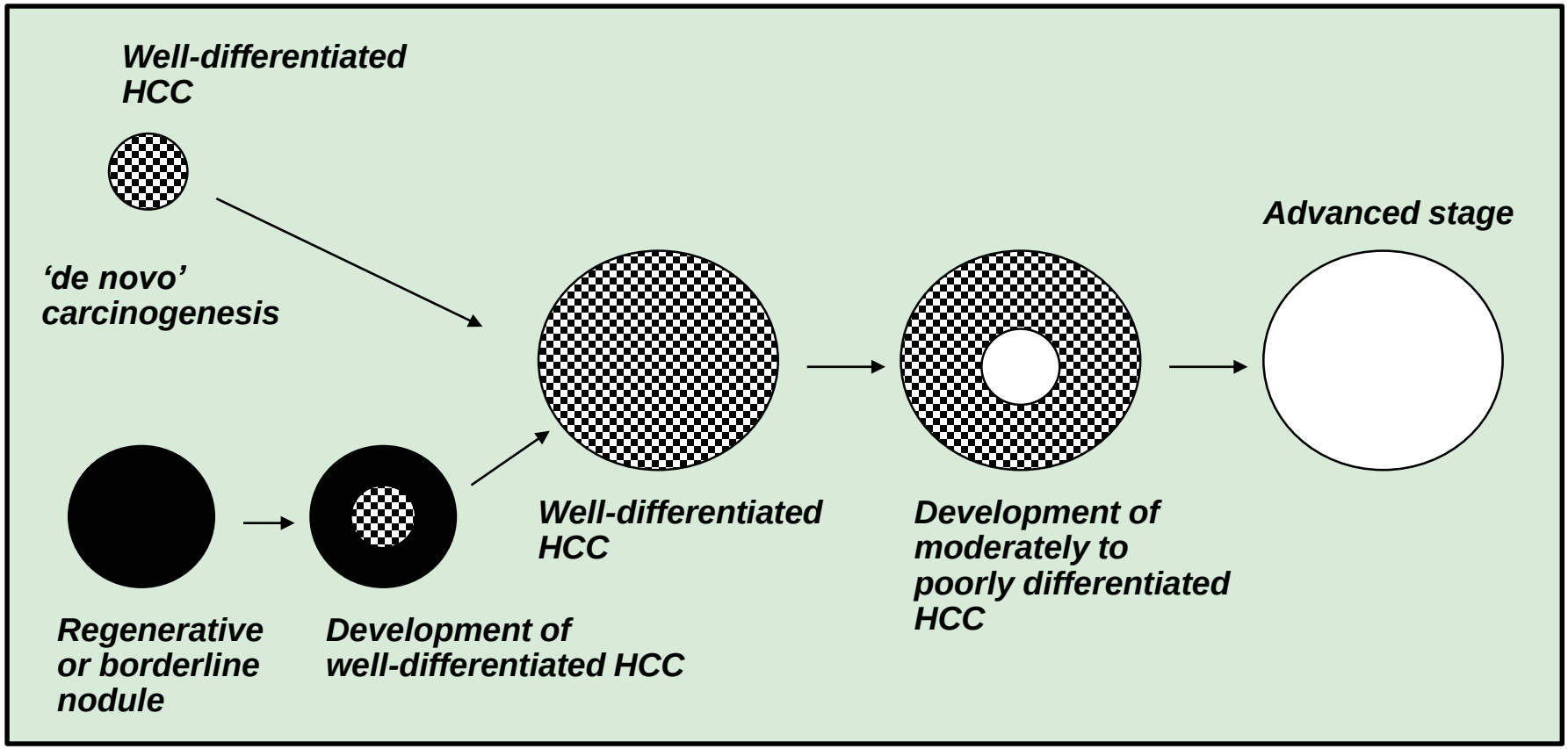
Controindications of percutaneous needle biopsy

- Anamnesis of anomalous bleeding
- Alterations of coogulation indices
- Acute biliary obstruction
- Suspect hemangioma (or othervascular tumor)
- No avalaibility of transfusion
- Suspect hydatic cyst
- Not collaborative patient
- No idoneous site for biopsy

"HCC development can be described histologically as a progressive clonal selection of increasingly aggressive cell population. HCC arises from transformation of dysplastic foci, mainly on a background of cirrhosis and in a multicentric fashion"

Proposed schema for the developmental process from evolution to an advanced stage of HCC in humans

(adapted from Kojiro M. et al, Gann Monogr. Cancer Res. 1991)



Classification of hepatocellular nodules

(International Working Party, Hepatology 1995 - 2009)

1. Regenerative lesions

- *1.1 Monoacinar regenerative nodule*
  - *1.1.1 Diffuse nodular hyperplasia without fibrous septa (NRH)*
  - *1.1.2 Diffuse nodular hyperplasia with fibrous septa or in cirrhosis*
- *1.2 Multiacinar regenerative nodule*
- *1.3 Lobar or segmental hyperplasia*
- *1.4 Cirrhotic nodule*
  - *1.4.1 Monoacinar cirrhotic nodule*
  - *1.4.2 Multiacinar cirrhotic nodule*
- *1.5 Focal nodular hyperplasia*
  - *1.5.1 Focal nodular hyperplasia, solid type*
  - *1.5.2 Focal nodular hyperplasia, teleangiectatic type*

2. Dysplastic or neoplastic lesions

- *2.1 Hepatocellular adenoma*
- ***2.2 Dysplastic focus***
- ***2.3 Dysplastic nodule***
  - ***2.3.1 Dysplastic nodule, low grade***
  - ***2.3.2 Dysplastic nodule, high grade***
- ***2.4 Hepatocellular carcinoma***

Hepatocarcinogenesis is a continuous process that for purposes of investigation and description has been divided into discrete steps

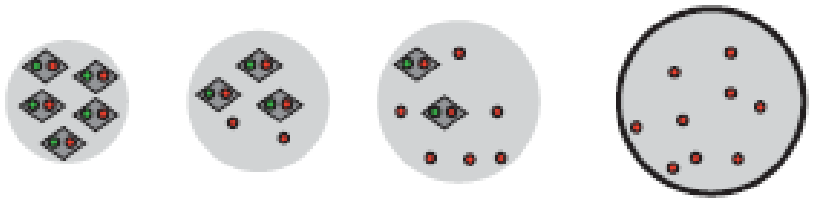
Histologic criteria to distinguish hepatocellular nodules

International Working Party, Hepatology 1995

Histologic feature	*LRN*	*LG-DN*	*HG-DN*	*WD-HCC*	*MD-HCC*
			Primary criteria		
Mitotic figures (>5/10 HPF)	-	-	-	-	+
Cell density > twice normal	-	-	-	+	+
Nuclear hyperchromasia	-	-	+	+	+
Irregular nuclear contour	-	-	-	+	+
Clone-like populations	-	+	+	+	+
Plates over 3 cells wide	-	-	-	-	+
			Secondary criteria		
Cell density < twice normal	-	-	+	+	+
Pseudoglands	+*	-	+	+	+
Cytoplasmic basophilia	-	-	+	+	+
Clear cell change	-	-	+	+	+
Reticulin loss	-	-	-	-	+
Resistance to iron storage	-	-	+	+	+
Mitotic figures (1-5/10 HPF)	-	-	+	+	+
Invasive growth	-	-	-	+	+

International consensus on small hepatocellular nodules
(Kojiro M. Oncology, 2010)

Clinicopathological consensus of nodular lesions in cirrhotic liver



IWP classification	LGDN	HGDN	WD-HCC	MD-HCC
Pathological features				
Gross appearance			vaguely nodular	distinctly nodular
Stromal invasion	(–)	(–)	+/–	+/–
Clinical (imaging)				
Arterial supply	iso/hypo	iso/hypo	iso/hypo rarely hyper	hyper
Portal supply	+	+	+	–
Clinicopathological			early HCC	progressed HCC

◆ = Portal tract; • = unpaired artery; iso = isovascular; hypo = hypovascular; hyper = hypervascular; IWP = International Working Party

- *Consensus even among experts in differentiating e-HCC from HG-DN is low, ranging from k values of 0.30 (2002) and 0.49 (2004)*

'The smaller the lesion the harder the diagnosis'

Prospective validation of non-invasive criteria for the diagnosis of HCC ≤2 cm

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
CE-US suspicious MRI suspicious (n = 40)*	66.7%	100%	100%	59.2%
CE-US suspicious MRI conclusive (n = 29)†	48.3%	100%	100%	48.3%
CE-US conclusive MRI suspicious (n = 28)‡	46.7%	100%	100%	47.5%
CE-US conclusive MRI conclusive (n = 20) AASLD criteria positive	33.3%	100%	100%	42%

Imaging diagnosis categorized as suspicious (arterial hypervascularization regardless of washout) or conclusive (arterial hypervascularization followed by venous washout). The nodules classified as suspicious include those defined as conclusive and those categorized as suggestive but nonconclusive of HCC.

*In 3 cases (1 nodule 10–15 mm and 2 nodules 16–20 mm), both techniques suggestive but inconclusive for HCC.

†Nine cases (1 nodule < 10 mm, 3 nodules 10–15 mm, and 5 nodules 16–20 mm); the CEUS was suggestive but inconclusive for HCC.

‡Eight cases (3 nodules 10–15 mm and 5 nodules 16–20 mm); the MRI was suggestive but inconclusive for HCC.

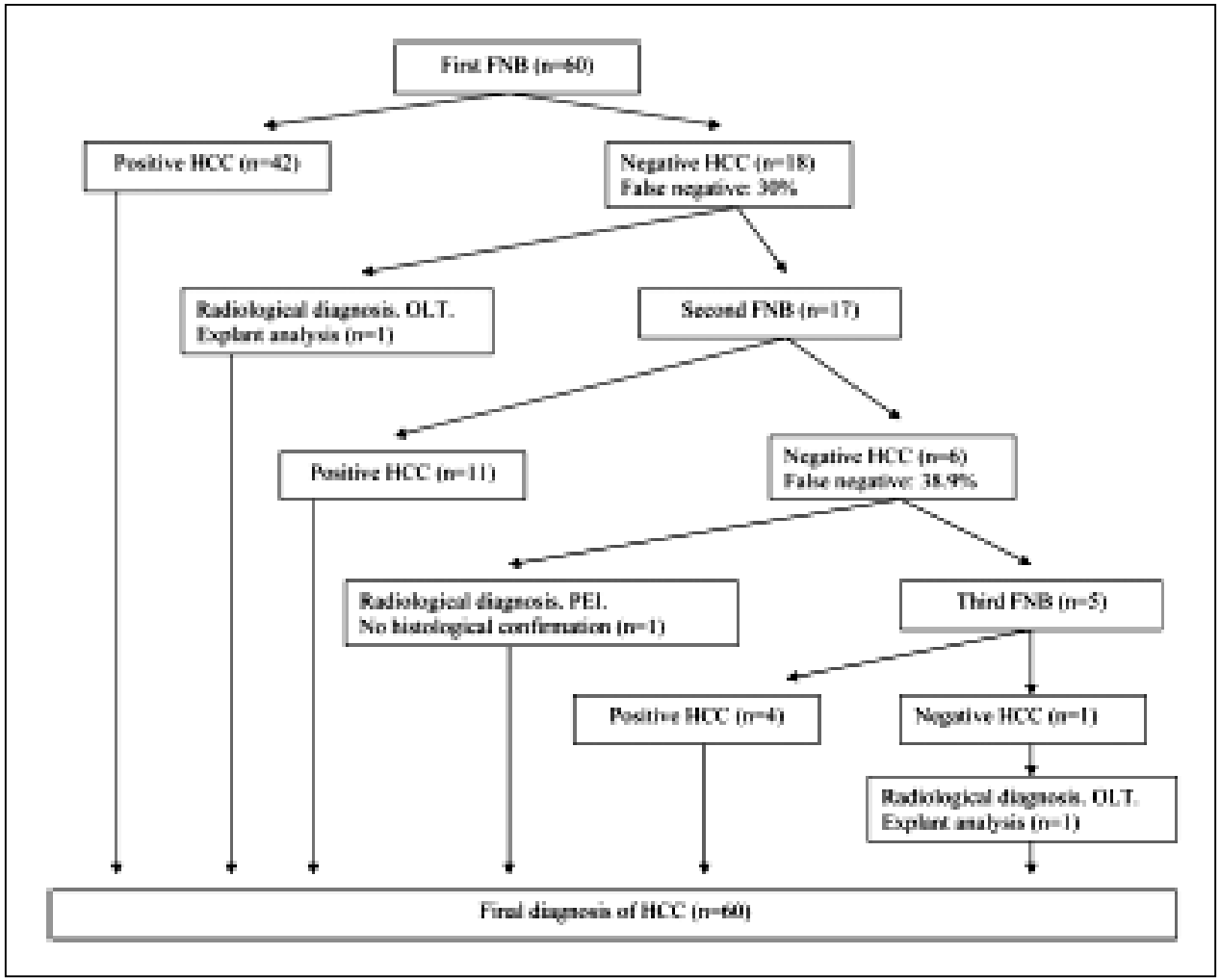
- Coincident results of two dynamic imaging techniques (CEUS, MRI) show absolute specificity and PPV but low sensitivity (33%) and NPV (42%)

Forner A. et al., Hepatology 2008

67.4% of nodules ≤2 cm diagnosed during screening are HCCs

FNB is required for diagnosis in up 70% of cases

False negative rate of first FNB is 30%



Forner A. et al., Hepatology 2008

Stains in the diagnosis of HCC

- ***Hepatocellular markers***
  - HEPAR-1
  - Polyclonal CEA
  - Arginase
  - AFP

- ***Markers of neoplasia***
  - Loss of reticulin
  - Unpaired arteries (SMA)
  - Sinusoidal capillarization (CD34)
  - No ductular reaction (CK7)
  - Glypican-3
  - Others (HSP70, GS, CTNN1)

Carcinoma of unknown primary origin (CUP)

- ***3-5% of new malignant diagnoses***
- Among the 10 more common neoplasms in both males and females
- Only 75% can be classified even after autopsy
- Most common sites of origin include ***pancreato-biliary tract, lung and kidney***
- ***CUP eventually attributable to a specific primary site have a better prognosis that unclassifiable CUP***

- ***IHC plays a major role in the pathological work-up*** of a biopsy form a patient with CUP

CK7 and CK20 profiles of most common carcinomas

$CK7^+/CK20^-$	Breast
	Ovarian
	Pulmonary (adenocarcinoma)
	Endometrial
	Thyroid
$CK7^+/CK20^+$	Upper gastrointestinal (adenocarcinoma)
	Pancreatic (ductal)
	Urothelial
$CK7^-/CK20^+$	Colorectal
	Merkel cell
$CK7^-/CK20^-$	Prostatic
	Hepatocellular
	Renal cell
	Adrenal cortical

Adv Anat Pathol 2015;22:149–167

Markers of primary origin in carcinoma of unknown primary

Marker	Expression in Carcinomas (Primary Application)	Expression in Other Carcinomas and Select Other Tumor Types	Sensitivity in Poorly Differentiated Tumors
Mammaglobin	Breast (60%-80%)	Endometrial (10%-30%)	Low
GCDFP-15	Breast (60%-80%)	Lung (adenocarcinoma) (2%-5%)	Low
Napsin A	Pulmonary (adenocarcinoma) (60%-80%)	Ovarian, clear cell (80%-100%); renal, papillary (70%-90%); adrenal cortical (10%-20%)	Moderate
Thyroglobulin	Thyroid (80%-90%)	Ovarian, papillary serous (5%-10%)	Low
RCC marker	Renal (80%-90% primary; 50%-70% metastatic)	Adrenal cortical; colorectal; breast; prostatic; cervical; melanoma (15%-25% each)	Moderate
HepPar-1	Hepatocellular (70%-90%)	Gastric; esophageal; pulmonary (5%-15% each)	Poor
Arginase-1	Hepatocellular (80%-90%)	Prostatic (< 10%); cholangiocarcinoma (< 10%)	Moderate-high
PSA	Prostatic (85%-95%)	Breast (20%-40%); salivary (20%-40%)	Moderate-high
PAP	Prostatic (85%-95%)	Salivary (20%-50%)	Moderate
Villin	Colorectal (80%-90%)	Renal (60%-80%); endometrial (30%-40%); ovarian (< 10%); pulmonary (< 10%); gastric (60%-80%)	Moderate
Melan A/MART1	Adrenal cortical (85%-95%)	Melanoma (> 80%); sex-cord stromal tumors (> 80%)	Moderate-high
Inhibin	Adrenal cortical (85%-95%)	Sex-cord stromal tumors (> 80%)	Moderate-high
Calretinin	Adrenal cortical (85%-95%)	Sex-cord stromal tumors (> 80%); mesothelioma (> 80%)	Moderate-high
Uroplakin 3	Urothelial (15%-50%)	Rare	Low
Uroplakin 2	Urothelial (50%-80%)	Rare	Moderate

Adv Anat Pathol 2015;22:149–167

Newly available antibodies for diagnosis

International Journal of Surgical Pathology 2013, 21(6) 553– 572

Organ-related antibodies

- PAX8
- Napsin A
- Arginase-I

Antibodies providing information on cellular differentiation or tumor histogenetic type

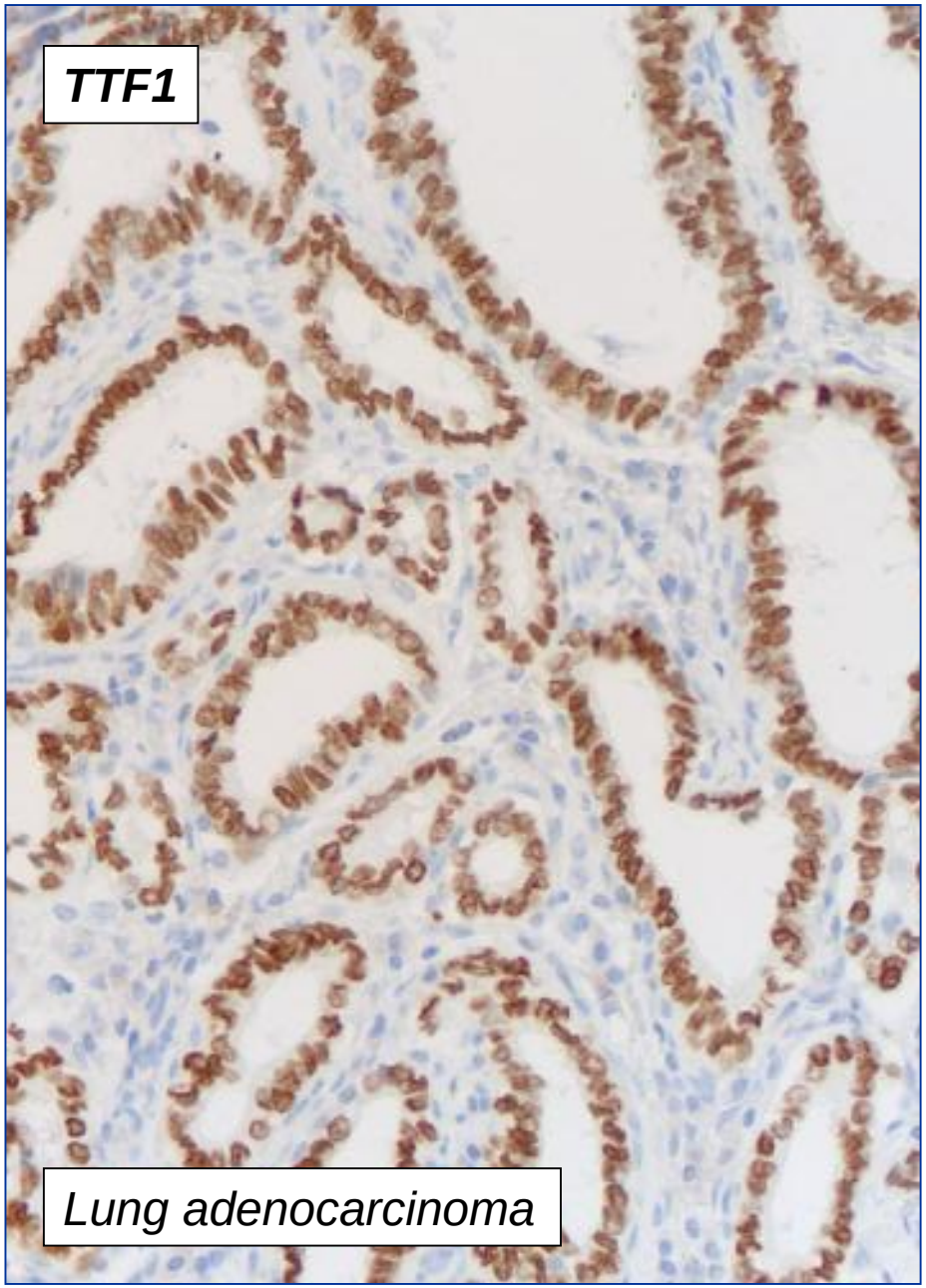
- ERG
- SOX10
- DOG1
- OCT3/4
- SALL4
- MUC4
- Langerin
- SOX11

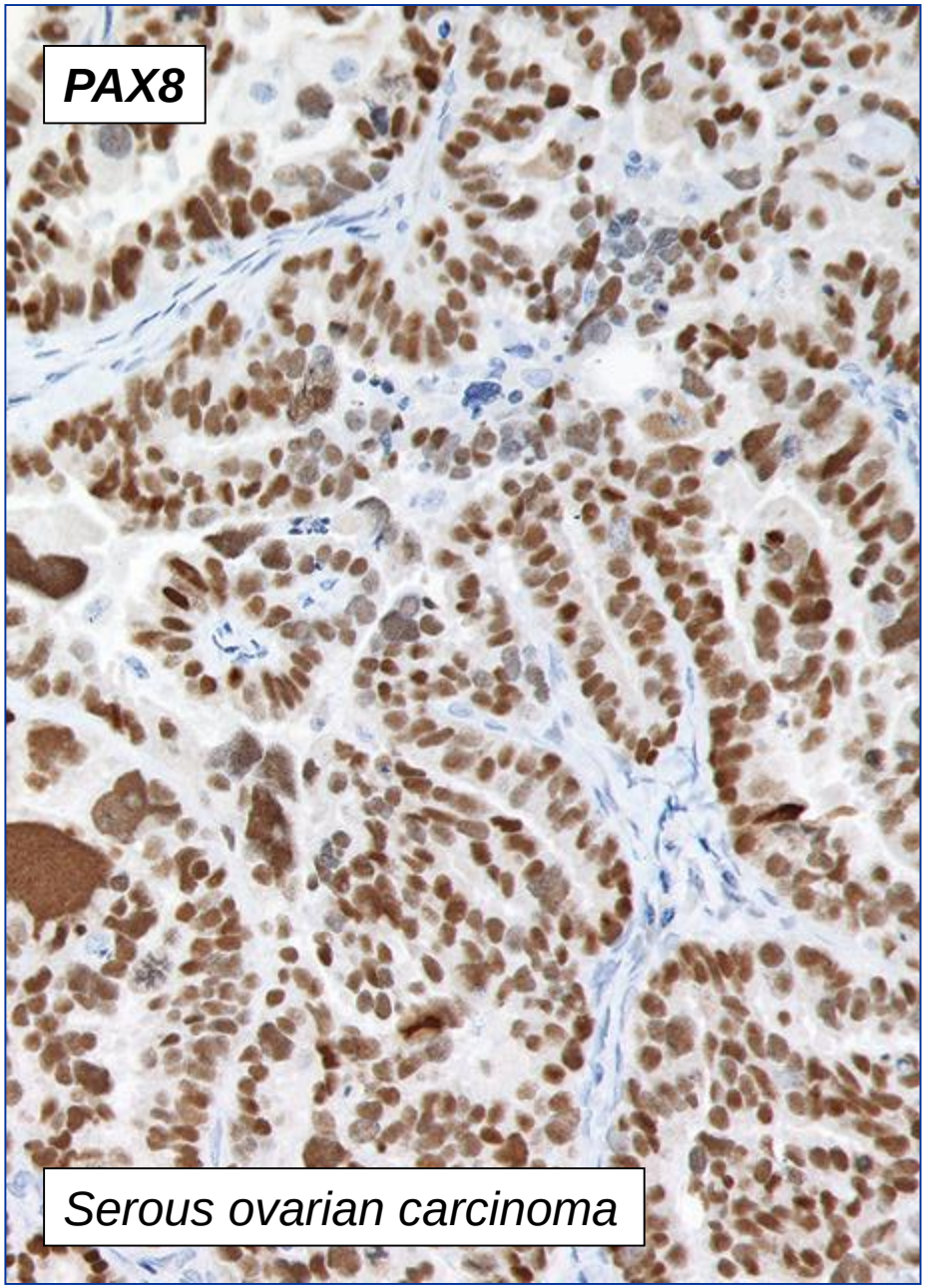
Antibodies against infective agents

- *Treponema pallidum*
- SV40

Antibodies with predictive value in tumors

- ALK (new-generation antibodies against ALK)
- Succinate dehydrogenase B


TTF1
Lung adenocarcinoma


PAX8
Serous ovarian carcinoma