Course on Liver Tumours

3 December 2022

A practical approach to liver metastases of unknown primary

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BSP Belgian Society of Pathology

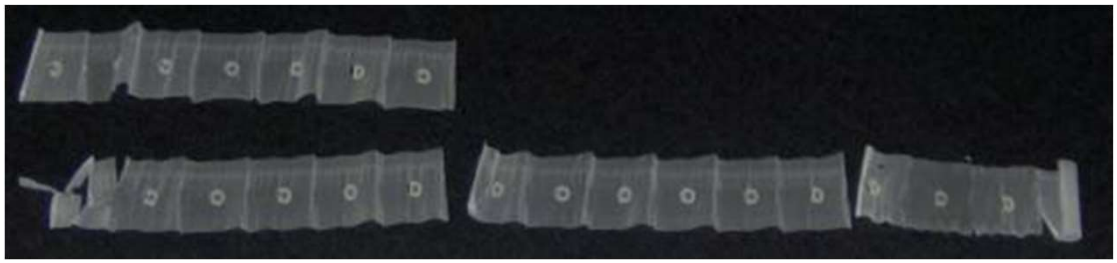
az sint-jan brugge - oostende av

Overview

- Practical aspects
- Immunohistochemical staining's
- Some pitfalls
- Example of how IHC can lead/mislead the pathologist
- Take home message and references

Biopsy handling

- Usually, a limited amount of (tumour)tissue is available
- Consider the possible need for further testing
  - Prognostic/therapeutic biomarkers
- To avoid tissue loss:
  - Divide biopsies over different paraffin blocks
  - Use of unstained slides or ‘lintjes’



Questions to address looking at the HE

- Representative for tumour?
- Primary versus secondary?
- Malignant or not?
- Epithelial or other?

Questions to address looking at the HE

- Representative for tumour?
  - Make sure the HE section is representative and covers the full length of the biopsy specimen
- Primary versus secondary?
  - Biliary tumours such as intrahepatic cholangiocarcinoma remain difficult to differentiate from metastatic adenocarcinoma
  - Neuroendocrine neoplasms
  - Soft tissue tumours

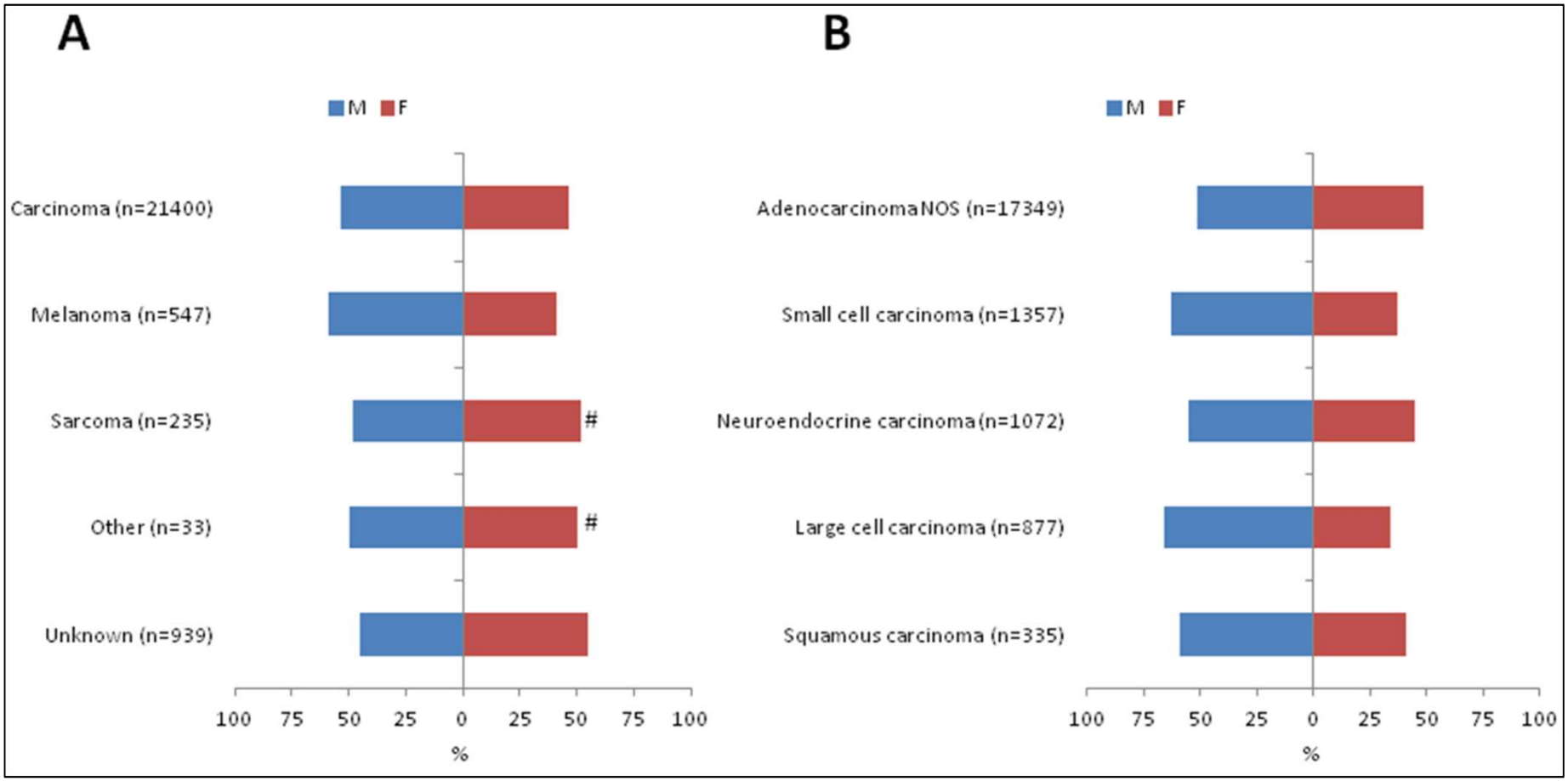
Metastatic liver disease

- Check patient history and imaging
- Age and gender

Oncotarget. 2016 Aug 23; 7(34): 55368–55376. PMCID: PMC5342423
Published online 2016 Jul 13. doi: 10.18632/oncotarget.10552 PMID: 27421135

Incidence and origin of histologically confirmed liver metastases: an explorative case-study of 23,154 patients

Jannemarie de Ridder,[1] Johannes H. W. de Wilt,[1] Femke Simmer,[2] Lucy Overbeek,[3] Valery Lemmens,[4,5] and Iris Nagtegaal[2]



Differences in gender between tumor types A. and the most important carcinoma subtypes B. #: no significant difference between women and men.

Metastatic liver disease

- 92% of the liver metastases are carcinomas of which most are adenocarcinomas (75%)
  - Colorectal
  - Pancreatic
  - Breast
- Women <50y: breast cancer
- Women >70y: GI-tract
- Men >70y: SCC-lung
- 18% presented as a CUP of which in 92% of cases the primary tumour type could be determined

Epithelial or other

- Morphology/growth pattern
  - Epithelial
  - Spindle cell
  - Vascular
  - NET
- Immunohistochemistry
  - Keratin
  - S100
  - Vimentin
  - LCA
- In Belgium, only 4 IHC tests are reimbursed

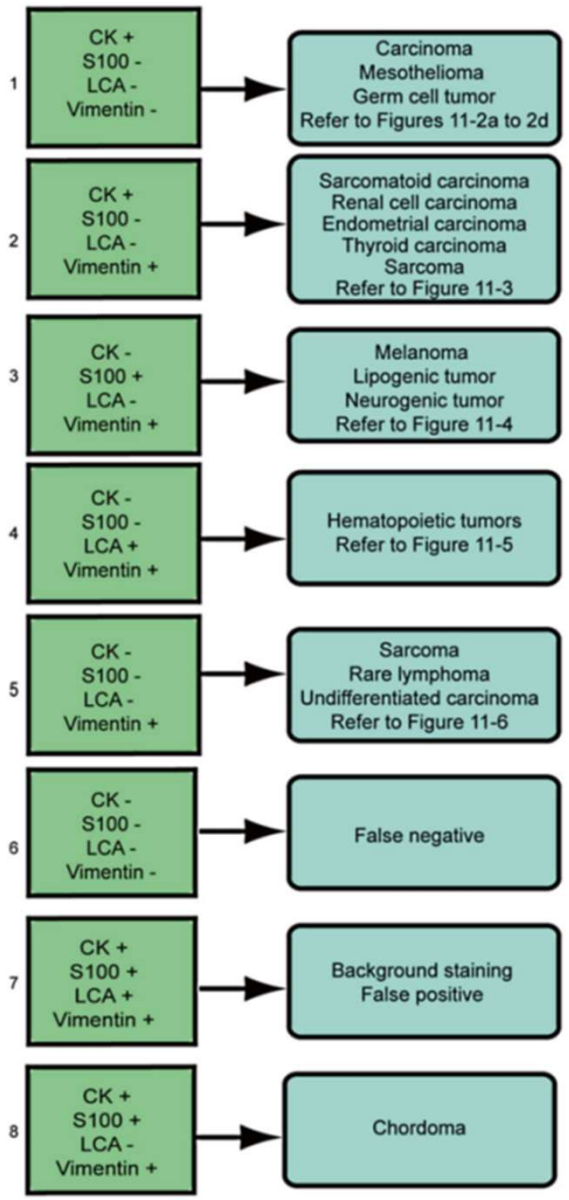


Table 11.1 Markers useful in diagnosis of undifferentiated neoplasms/unknown primaries

A. Epithelial markers:
AE1/AE3, CAM 5.2, CK7, CK20, CK5/6, CK903, CK17, CK19, EMA

B. Myoepithelial markers:
p63, S100, calponin, SMA, SMMH-1, CK14, maspin

C. Mesenchymal markers:
Vimentin, SMA, MSA, desmin, MyoD1, Myogenin, NF, S100, p63, CD10, calponin, myoglobin, MDM2, CDK4, FLI-1, CD117, DOG1, ERG, CD31, CD34, Factor XIIIa, CD99, NKX2.2

D. Melanocytic markers:
S100, HMB-45, MART-1, tyrosinase, MiTF, SOX10, SOX2

E. Mesothelial markers:
Calretinin, CK5/6, WT1, D2-40, HBME-1, mesothelin, thrombomodulin

F. Neuroendocrine markers:
Chromogranin, synaptophysin, CD56, PGP 9.5, NSE, insulin, PTH, calcitonin, thyroglobulin, prolactin

G. Germ cell tumor markers:
PLAP, OCT4, CD117 (c-kit), SALL4, LIN28, CD30, Nanog, SOX2, Alpha-fetoprotein, beta-hCG, glypican-3, GATA3, CD10, inhibin-alpha, calretinin, EMA, CAM 5.2

H. Transcription factors, receptors, and nuclear staining markers:
TTF1, SATB2, CDX-2, Ki-67 (MIB1), MSI markers (MLH1, MSH2, MSH6, PMS2), AR, ER, PR, INI-1, FLI-1, TFE3, MDM2, CDK4, p53, p63, beta-catenin, WT1, DPC4/SMAD4, OCT4, SALL4, myogenin, p16, GATA3

I. Tumor-associated markers:
MUC1, MUC2, MUC4, MUC5AC, MUC6, CEA, Ber-EP4, MOC-31, TAG72 (B72.3), CA19-9, CA125, GCDFP15, mammaglobin, PSA, PSAP, P504S, Hep Par1, glypican 3, PAX8, PLAP, OCT4, SALL4, CD117 (c-kit), IMP-3, maspin, pVHL, S100P, RCCMa, inhibin-alpha, napsin A, CD30, KIM-1, uroplakin II, S100A6, S100A1, GFAP

J. Hematopoietic markers:
CD2, CD3, CD5, CD10, CD20, CD38, CD21, CD35, CD15, CD30, CD79a, CD43, CD138, Bcl-2, Bcl-6, cyclin D1, MUM1, CD68, CD1a, S100, MPO, SOX11, HGAL, LMO2, IRTA1, c-MYC, CD160, LEF1, EBI3, IMP-3

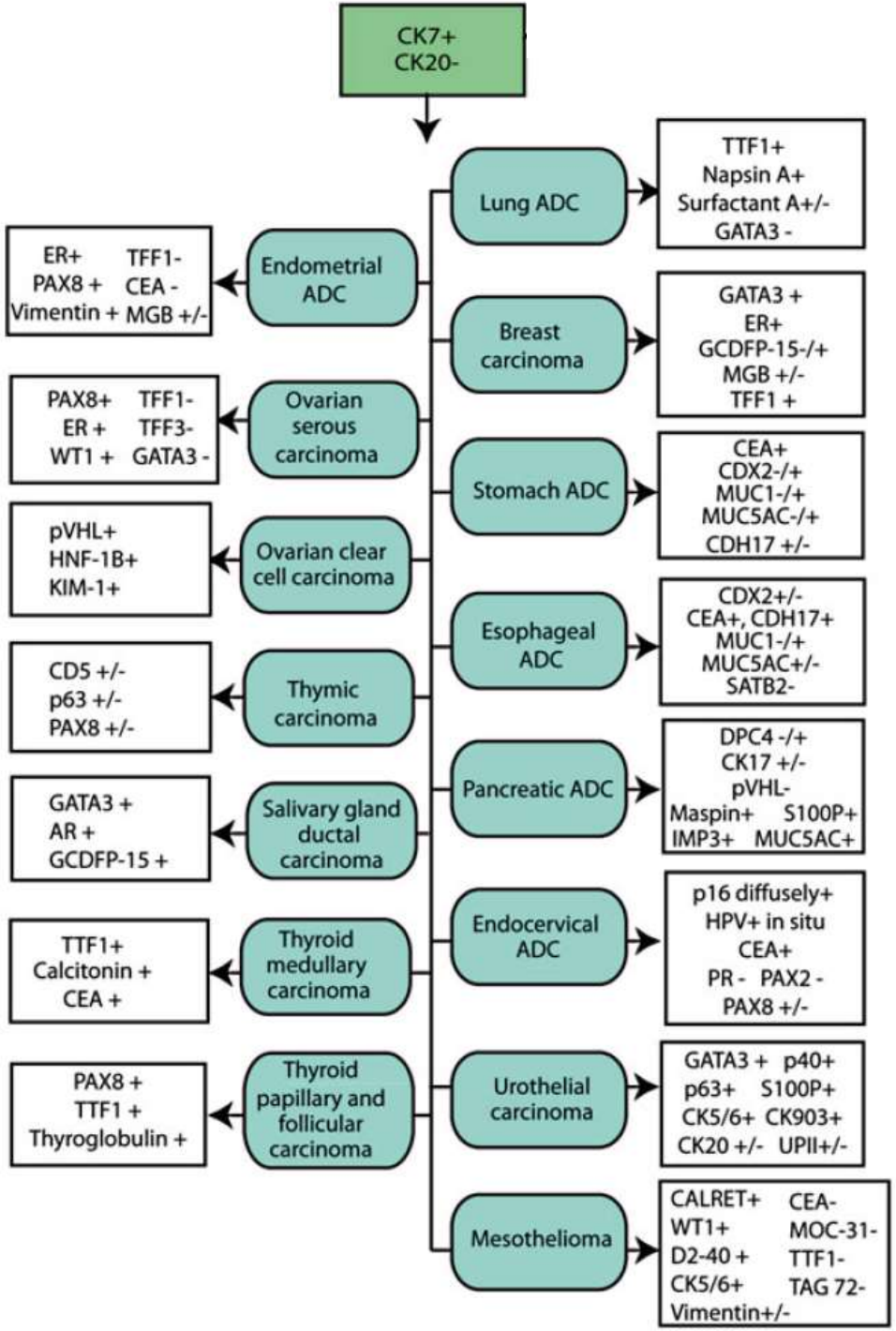
K. Markers for infectious agents:
EBV, HPV, HHV-8, Merkel cell polyomavirus (MCPV)

Table 11.6 Expression of CK7 and CK20 in various tumors

CK7+/CK20-	CK7-/CK20 +	CK7+/CK20+	CK7-/CK20-
Lung	Colorectal ADC	Urothelial CA	CRCC
Breast	Bladder ADC	Pancreatic /biliary CA	HCC
Mesothelioma	Merkel cell carcinoma	Ovarian mucinous CA	Prostatic ADC
Endometrial ADC	Appendiceal CA	Small bowel CA	ACCA
Endocervical ADC	Small bowel CA	Cholangiocarcinoma	SCC
Ovarian serous CA	PRCC, type II	Gastric CA	SQCC
Thymoma	Mucinous adenocarcinoma of the lung	Bladder ADC	Mesothelioma
Pancreatic/biliary ADC		Esophageal ADC	Neuroendocrine neoplasm
HCC—fibrolamellar variant			Medullary carcinoma of the colon
Upper GI ADC			
Thymic carcinoma			

ADC adenocarcinoma, *CA* carcinoma, *CRCC* clear cell renal cell carcinoma, *HCC* hepatocellular carcinoma, *SCC* small cell carcinoma, *SQCC* squamous cell carcinoma, *ACCA* adrenal cortical carcinoma, *GI* gastrointestinal tract

References: [1–11, 13]


CK7+
CK20-
Lung ADC
TTF1+
Napsin A+
Surfactant A+/-
GATA3 -
Breast carcinoma
GATA3 +
ER+
GCDFP-15-/+
MGB +/-
TFF1 +
Stomach ADC
CEA+
CDX2-/+
MUC1-/+
MUC5AC-/+
CDH17 +/-
Esophageal ADC
CDX2+/-
CEA+, CDH17+
MUC1-/+
MUC5AC+/-
SATB2-
Pancreatic ADC
DPC4 -/+
CK17 +/-
pVHL-
Maspin+ S100P+
IMP3+ MUC5AC+
Endocervical ADC
p16 diffusely+
HPV+ in situ
CEA+
PR - PAX2 -
PAX8 +/-
Urothelial carcinoma
GATA3 + p40+
p63+ S100P+
CK5/6+ CK903+
CK20 +/- UPII+/-
Mesothelioma
CALRET+ CEA-
WT1+ MOC-31-
D2-40 + TTF1-
CK5/6+ TAG 72-
Vimentin+/-
Endometrial ADC
ER+ TFF1-
PAX8 + CEA -
Vimentin + MGB +/-
Ovarian serous carcinoma
PAX8+ TFF1-
ER + TFF3-
WT1 + GATA3 -
Ovarian clear cell carcinoma
pVHL+
HNF-1B+
KIM-1+
Thymic carcinoma
CD5 +/-
p63 +/-
PAX8 +/-
Salivary gland ductal carcinoma
GATA3 +
AR +
GCDFP-15 +
Thyroid medullary carcinoma
TTF1+
Calcitonin +
CEA +
Thyroid papillary and follicular carcinoma
PAX8 +
TTF1 +
Thyroglobulin +
CK7+
CK20+
Pancreas ADC
DPC4-/+
pVHL-
Maspin+
S100P+
MUC5AC+
CK17 +/-
Stomach ADC
CEA+
CDX2-/+
MUC1-/+
MUC5AC-/+
SATB2 -
Esophagus ADC
CDX2+/-
CEA+
MUC1-/+
MUC5AC+/-
SATB2-
Mucinous carcinoma of ovary
DPC4+
CDX2+/-
CA-125+
Urothelial carcinoma
GATA3+ p63+
S100P+ p40+
CK5/6+ CK903+
CK20 +/- UPII+/-
Small bowel ADC
MUC5AC+/-
CDX2+
Villin+/-
CDH17+
SATB2 -/+
Lung mucinous ADC
TTF1-/+
CK7 -/+
CDX2+/-

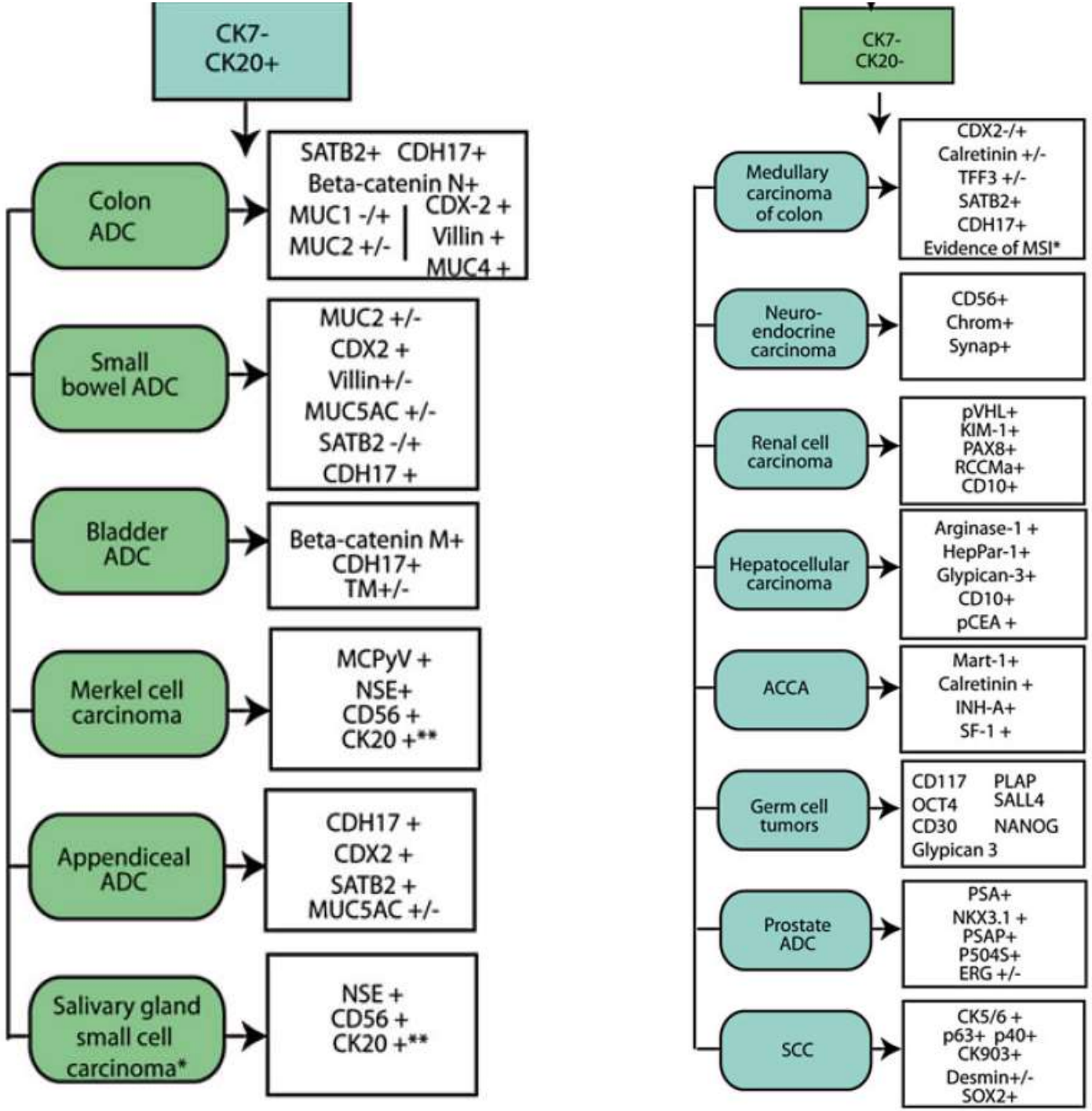

CK7-
CK20+
Colon ADC
SATB2+ CDH17+
Beta-catenin N+
MUC1 -/+
MUC2 +/-
CDX-2 +
Villin +
MUC4 +
Small bowel ADC
MUC2 +/-
CDX2 +
Villin+/-
MUC5AC +/-
SATB2 -/+
CDH17 +
Bladder ADC
Beta-catenin M+
CDH17+
TM+/-
Merkel cell carcinoma
MCPyV +
NSE+
CD56 +
CK20 +**
Appendiceal ADC
CDH17 +
CDX2 +
SATB2 +
MUC5AC +/-
Salivary gland small cell carcinoma*
NSE +
CD56 +
CK20 +**
CK7-
CK20-
Medullary carcinoma of colon
CDX2-/+
Calretinin +/-
TFF3 +/-
SATB2+
CDH17+
Evidence of MSI*
Neuro-endocrine carcinoma
CD56+
Chrom+
Synap+
Renal cell carcinoma
pVHL+
KIM-1+
PAX8+
RCCMa+
CD10+
Hepatocellular carcinoma
Arginase-1 +
HepPar-1+
Glypican-3+
CD10+
pCEA +
ACCA
Mart-1+
Calretinin +
INH-A+
SF-1 +
Germ cell tumors
CD117
PLAP
OCT4
SALL4
CD30
NANOG
Glypican 3
Prostate ADC
PSA+
NKX3.1 +
PSAP+
P504S+
ERG +/-
SCC
CK5/6 +
p63+ p40+
CK903+
Desmin+/-
SOX2+

Table 11.3 Summary of common immunostaining markers in adenocarcinomas, mesothelioma, melanoma, and germ cell tumors

Marker	Lung	Pancreas	Breast	Stomach	Ovary	Uterus	Cervix	Colon	Kidney	Bladder	Prostate	Liver	Meso	Mel	GCT
CK7	+	+	+	+	+	+	+	−	−	+	−	−	+	−	− or +
CK20	−	− or +	−	− or +	−	−	−	+	−	+ or −	−	−	−	−	−
CK5/6	−	−	−	−	−	−	−	−	−	+	−	−	+	−	−
p63	−	−	−	−	−	−	−	−	−	+	−	−	−	−	−
UPII	−	−	−	−	−	−	−	−	−	+ or −	−	−	−	−	−
TTF1	+	−	−	−	−	−	−	−	−	−	−	C+	−	−	−
CDX-2	−	− or +	−	+ or −	−	−	− or +	+	−	−	−	−	−	−	−
CDH-17	−	− or +	−	+ or−	−	−	− or+	+	−	−	−	−	−	−	−
ER	−	−	+	−	+	+	− or +	−	−	−	−	−	−	−	−
GATA3	−	− or +	+	−	−	−	−	−	−	+	−	−	−	−	− or +
CD10	−	−	−	−	−	−	−	−	+	− or +	−	+	−	− or +	− or +
RCCMa	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
pVHL	−	−	−	−	−	−	−	−	+	−	−	−	−	−	−
PAX8	−	−	−	−	+	+	+ or −	−	+	−	−	−	−	−	−
S100	− or +	−	+ or −	−	−	−	−	−	+ or −	−	−	−	−	+	−
S100P	+ or −	+	− or +	−	−	−	−	+ or −	− or +	+	−	−	−	−	−
Vimentin	−	−	−	−	−	+ or −	−	−	+	−	−	−	− or +	+	−
PSA	−	−	−	−	−	−	−	−	−	−	+	−	−	−	−
Arginase-1	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−
Glypican-3	−	−	−	−	−	−	−	−	−	−	−	+	−	−	−
HMB-45	−	−	−	−	−	−	−	−	−	−	−	−	−	+	−
SALL4	−	−	−	−	−	−	−	−	−	−	−	−	−	−	+

Meso mesothelioma, *Mel* melanoma, *GCT* germ cell tumors (includes seminoma and non-seminomatous tumors), *C* cytoplasmic staining

Lung mucinous adenocarcinoma with bronchioloalveolar carcinoma (BAC) features tends to be negative for TTF1 and can be positive for CDX-2

Typical seminoma tends to be negative for cytokeratin (such as AE1/AE3, CK7, and CK20) and can be positive for CAM 5.2. In contrast, non-seminomatous tumors are usually positive for AE1/AE3. Seminoma is usually positive for PLAP, CD117, OCT4, D2-40, and SALL4

Embryonal carcinoma is usually positive for OCT4, SALL4, SOX2, Nanog and often positive for CD30; yolk sac tumor is frequently positive for AFP, SALL4 and glypican-3, and negative for OCT4; choriocarcinoma is positive for beta-hCG, GATA3, and CD10

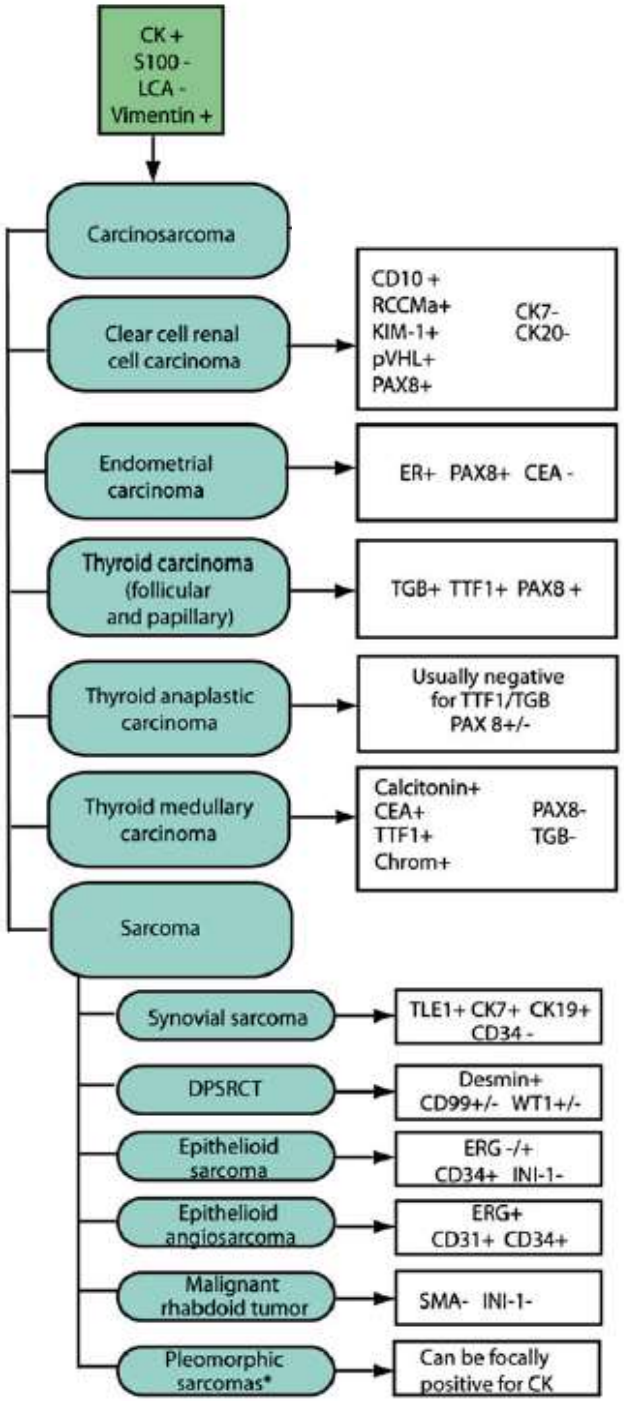
Colon: Medullary carcinomas of the colon tend to be negative or only very focally positive for CK20 and CDX-2; to complicate the matter further, some can be focally positive for CK7 but usually present with microsatellite instability (MSI: loss of expression of MLH1 and PMS2, or MSH2 and MSH6). SATB2 and cadherin-17, two recently described markers, have been demonstrated to be highly sensitive for medullary carcinoma of the colon. Caution should be taken because negativity for both CK20 and CDX-2 does not automatically exclude the possibility of a colorectal origin. If the clinical suspicion is high, additional markers including SATB2, cadherin-17, and MSI markers should be performed

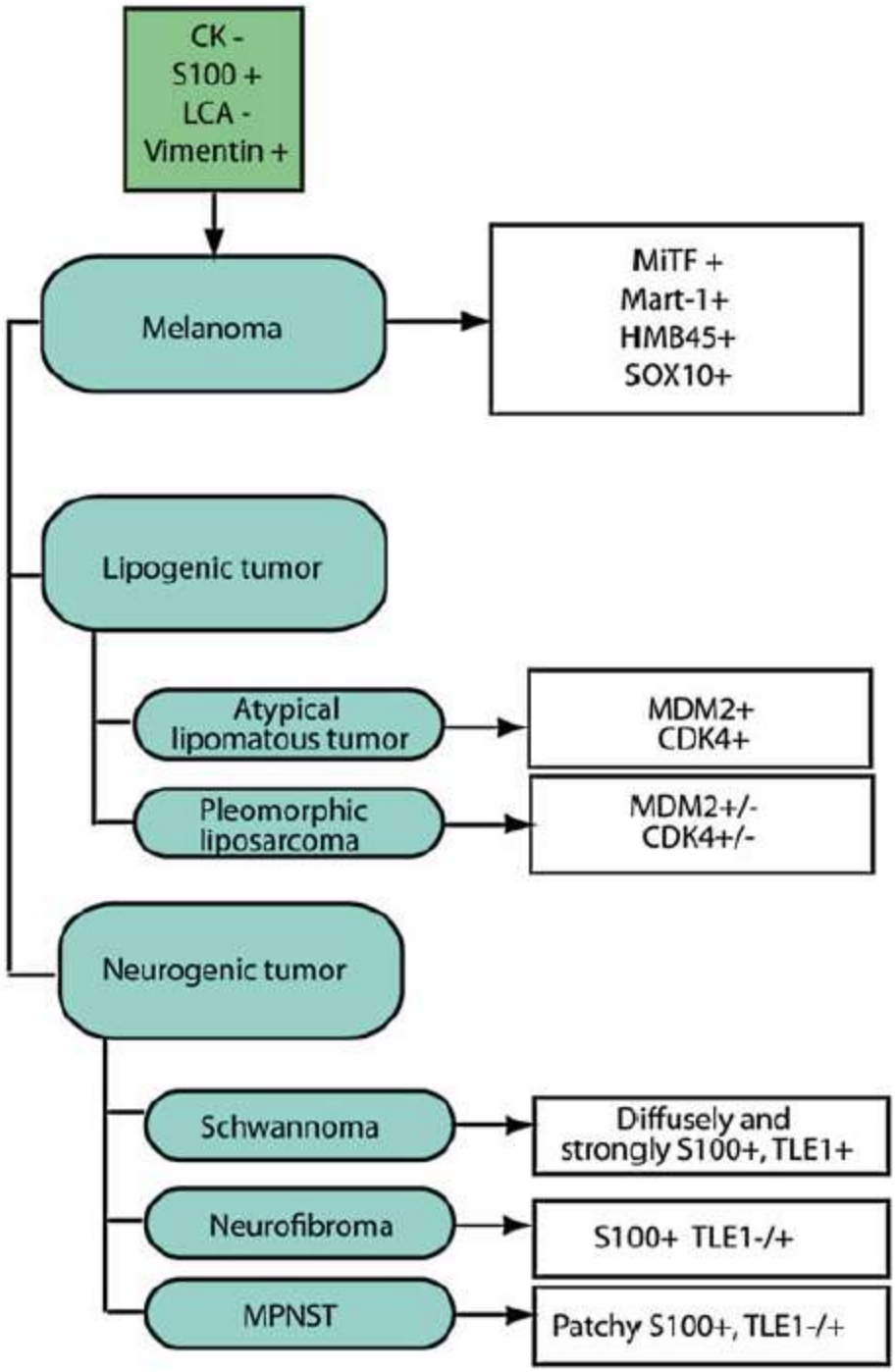
Kidney: The staining profile shown in this table is for clear cell renal cell carcinoma (CRCC). Type I papillary renal cell carcinoma (PRCC) is usually positive for CK7, P504S, KIM-1 and CD10, with the exception of the type II PRCC, which is frequently negative for CK7, strongly positive for P504S and CD10, and can be focally positive for CK20. KIM-1, RCCMa, PAX8 and pVHL are the most effective panel of markers to identify a metastatic renal cell carcinoma (RCC). CA IX is a highly sensitive marker for CRCC; however, it also expresses in a number of other carcinomas, including a majority of endocervical adenocarcinomas. pVHL is positive in most clear cell carcinomas of the ovary and uterus as well

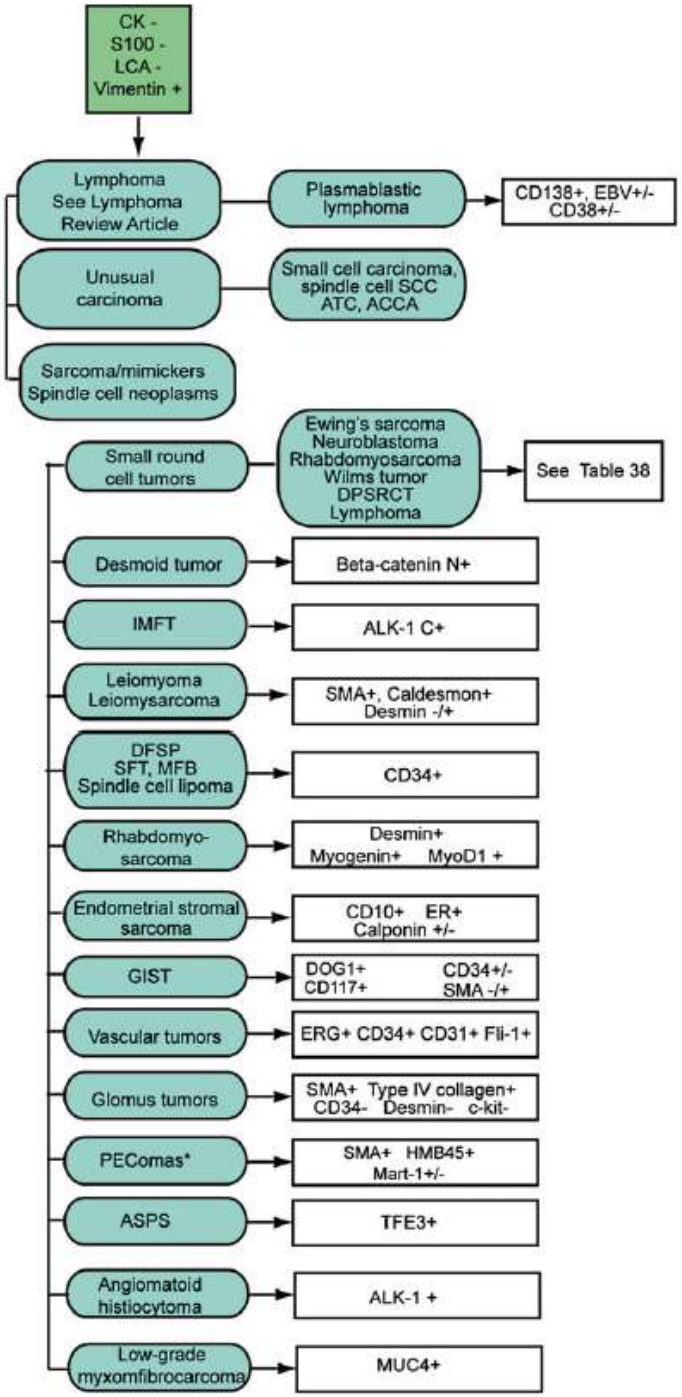
Endocervical adenocarcinoma: It is usually diffusely and strongly positive for p16 and positive for HPV by in situ hybridization. In contrast, endometrial adenocarcinoma tends to be only focally positive for p16 and also positive for ER/PR and vimentin, but negative for CEA

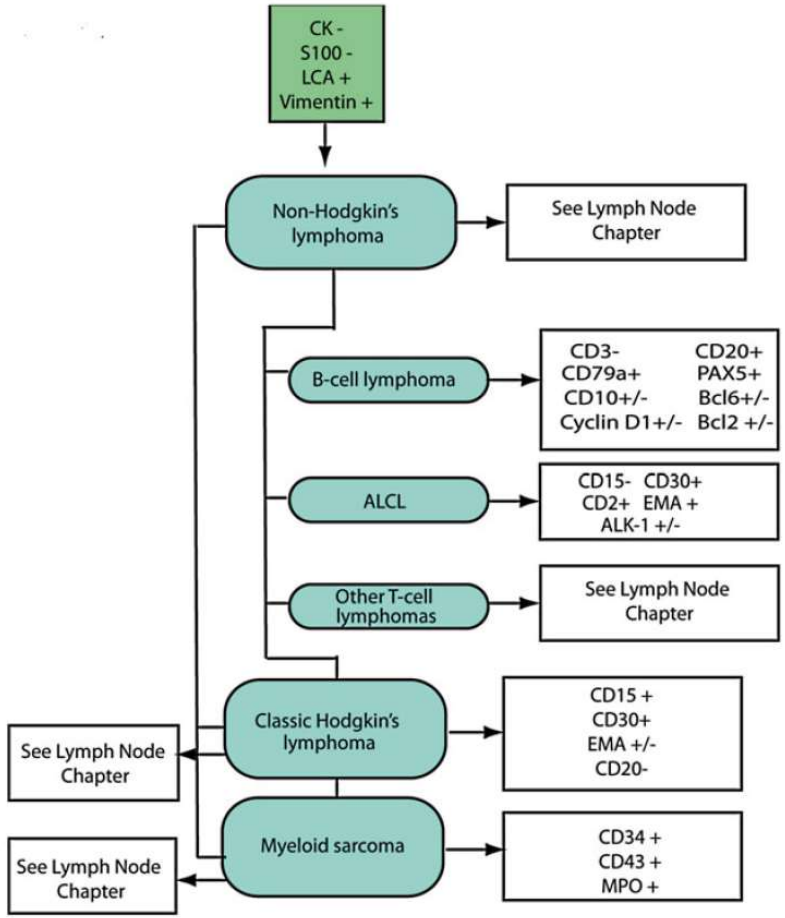
In addition to expression in the majority of breast carcinomas, including ER-negative breast carcinomas, and urothelial carcinomas, approximately 10 % of pancreatic adenocarcinomas (ADCs) can be positive or GATA3. The expression of GATA3 has been reported in most salivary gland tumors, especially salivary duct carcinoma, and mammary analogy secretory carcinoma, 80 % of paragangliomas, and some squamous cell carcinomas from various organs. Rare cases of RCC and mesothelioma can be positive for GATA3

References: [1–213]


CK +
S100 -
LCA -
Vimentin +
Carcinosarcoma
Clear cell renal cell carcinoma
CD10 +
RCCMa+
KIM-1+
pVHL+
PAX8+
CK7-
CK20-
Endometrial carcinoma
ER+ PAX8+ CEA -
Thyroid carcinoma (follicular and papillary)
TGB+ TTF1+ PAX8 +
Thyroid anaplastic carcinoma
Usually negative for TTF1/TGB
PAX 8+/-
Thyroid medullary carcinoma
Calcitonin+
CEA+
TTF1+
Chrom+
PAX8-
TGB-
Sarcoma
Synovial sarcoma
TLE1+ CK7+ CK19+ CD34 -
DPSRCT
Desmin+
CD99+/- WT1+/-
Epithelioid sarcoma
ERG -/+
CD34+ INI-1-
Epithelioid angiosarcoma
ERG+
CD31+ CD34+
Malignant rhabdoid tumor
SMA- INI-1-
Pleomorphic sarcomas*
Can be focally positive for CK


CK -
S100 +
LCA -
Vimentin +
Melanoma
MiTF +
Mart-1+
HMB45+
SOX10+
Lipogenic tumor
Atypical lipomatous tumor
MDM2+
CDK4+
Pleomorphic liposarcoma
MDM2+/-
CDK4+/-
Neurogenic tumor
Schwannoma
Diffusely and strongly S100+, TLE1+
Neurofibroma
S100+ TLE1-/+
MPNST
Patchy S100+, TLE1-/+


CK -
S100 -
LCA -
Vimentin +
Lymphoma
See Lymphoma
Review Article
Plasmablastic
lymphoma
CD138+, EBV+/-
CD38+/-
Unusual
carcinoma
Small cell carcinoma,
spindle cell SCC
ATC, ACCA
Sarcoma/mimickers
Spindle cell neoplasms
Small round
cell tumors
Ewing's sarcoma
Neuroblastoma
Rhabdomyosarcoma
Wilms tumor
DPSRCT
Lymphoma
See Table 38
Desmoid tumor
Beta-catenin N+
IMFT
ALK-1 C+
Leiomyoma
Leiomysarcoma
SMA+, Caldesmon+
Desmin -/+
DFSP
SFT, MFB
Spindle cell lipoma
CD34+
Rhabdomyo-
sarcoma
Desmin+
Myogenin+ MyoD1 +
Endometrial stromal
sarcoma
CD10+ ER+
Calponin +/-
GIST
DOG1+
CD117+
CD34+/-
SMA -/+
Vascular tumors
ERG+ CD34+ CD31+ Fli-1+
Glomus tumors
SMA+ Type IV collagen+
CD34- Desmin- c-kit-
PEComas*
SMA+ HMB45+
Mart-1+/-
ASPS
TFE3+
Angiomatoid
histiocytoma
ALK-1 +
Low-grade
myxomfibrocarcoma
MUC4+


CK -
S100 -
LCA +
Vimentin +
Non-Hodgkin's
lymphoma
See Lymph Node
Chapter
B-cell lymphoma
CD3- CD20+
CD79a+ PAX5+
CD10+/- Bcl6+/-
Cyclin D1+/- Bcl2 +/-
ALCL
CD15- CD30+
CD2+ EMA +
ALK-1 +/-
Other T-cell
lymphomas
See Lymph Node
Chapter
Classic Hodgkin's
lymphoma
CD15 +
CD30+
EMA +/-
CD20-
Myeloid sarcoma
CD34 +
CD43 +
MPO +
See Lymph Node
Chapter
See Lymph Node
Chapter

Some pitfalls

- Non-epithelial epithelioid tumours
  - Melanoma
  - Mesothelioma
  - Epitheloid angiosarcoma
  - …
- Rare tumour types
  - Hepatoid gastric/pancreatic carcinoma
  - …
- False negative or positive staining's
  - May direct you in a completely opposite direction
  - Check the controls

- Rare (or not that rare) expression patterns

› Am J Surg Pathol. 2014 Feb;38(2):224-7. doi: 10.1097/PAS.0000000000000138.

TTF-1 and Napsin-A are expressed in a subset of cholangiocarcinomas arising from the gallbladder and hepatic ducts: continued caveats for utilization of immunohistochemistry panels

Lea F Surrey [1], Renee Frank, Paul J Zhang, Emma E Furth

Affiliations + expand

PMID: 24418856 DOI: 10.1097/PAS.0000000000000138

47.4% of extrahepatic cholangiocarcinoma expressed TTF-1, 33.3% of which coexpressed NapA.

› Appl Immunohistochem Mol Morphol. 2016 Jan;24(1):16-9. doi: 10.1097/PAI.0000000000000250.

CDX-2 Expression in Primary Lung Adenocarcinoma

Morgan L Cowan [1], Qing K Li, Peter B Illei

Affiliations + expand

PMID: 26469326 DOI: 10.1097/PAI.0000000000000250

CDX-2 positivity can be seen in a subset (12%) of non-enteric type lung adenocarcinoma.

Incidence and Significance of GATA3 Positivity in Pancreatic Ductal Adenocarcinoma and Cholangiocarcinoma

Agostini-Vulaj, Diana DO*; Bratton, Laura E. MD†; Dunne, Richard F. MD‡; Cates, Justin M. M. MD, PhD§; Zhou, Zhongren B.Med, PhD‖; Findeis-Hosey, Jennifer J. MD*; Yang, Qi AAS*; Ramesh, Mira K. HSD*; Gonzalez, Raul S. MD*

Author Information

GATA3 positivity was seen in 16% of PDACs and 5% of CCs

Applied Immunohistochemistry & Molecular Morphology: July 2020 - Volume 28 - Issue 6 - p 460-463

- Rare (or not that rare) expression patterns
  - This may be antibody/clone dependent

Comparative Study > Am J Clin Pathol. 2018 Oct 24;150(6):533-544. doi: 10.1093/ajcp/aqy083.

Comparison of Three Different TTF-1 Clones in Resected Primary Lung Cancer and Epithelial Pulmonary Metastases

Halla Vidarsdottir [1 2 3], Lena Tran [4], Björn Nodin [3], Karin Jirström [3 4], Maria Planck [3 5], Johanna S M Mattsson [6], Johan Botling [6], Patrick Micke [6], Per Jönsson [7 8], Hans Brunnström [3 4]

Affiliations + expand

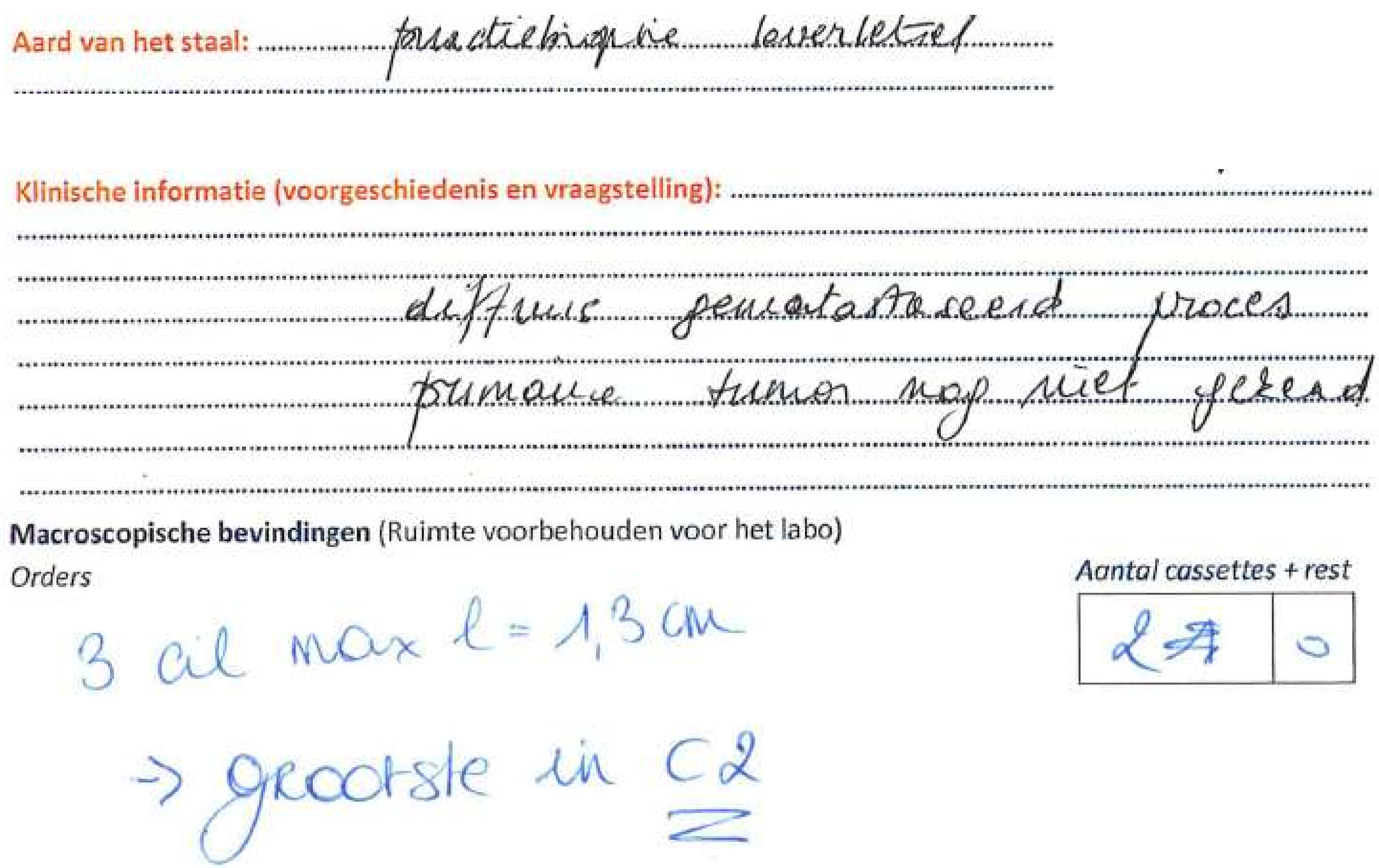
PMID: 30169783 DOI: 10.1093/ajcp/aqy083

Results: Most lung adenocarcinomas, 89%, 93%, and 93%, were positive with TTF-1 clones 8G7G3/1, SPT24, and SP141, respectively. The corresponding figures for lung squamous cell carcinomas were 0%, 6%, and 8%. In total, five (2%), 19 (7%), and 21 (8%) of the pulmonary metastases from colorectal adenocarcinomas were positive with clones 8G7G3/1, SPT24, and SP141, respectively. Other TTF-1-positive pulmonary metastases (n = 8) were thyroid, urothelial, pancreatic, small bowel, and cervix carcinomas.

Conclusions: TTF-1 expression in lung cancer and pulmonary metastases differs between clones, with 8G7G3/1 being more specific but less sensitive compared with SPT24 and SP141.

Case

- Female patient
- 57y


Aard van het staal: punctiebiopsie leverletsel

Klinische informatie (voorgeschiedenis en vraagstelling):

diffuus gemetastaseerd proces

primaire tumor nog niet gekend

Macroscopische bevindingen (Ruimte voorbehouden voor het labo)

Orders

3 cil max l = 1,3 cm

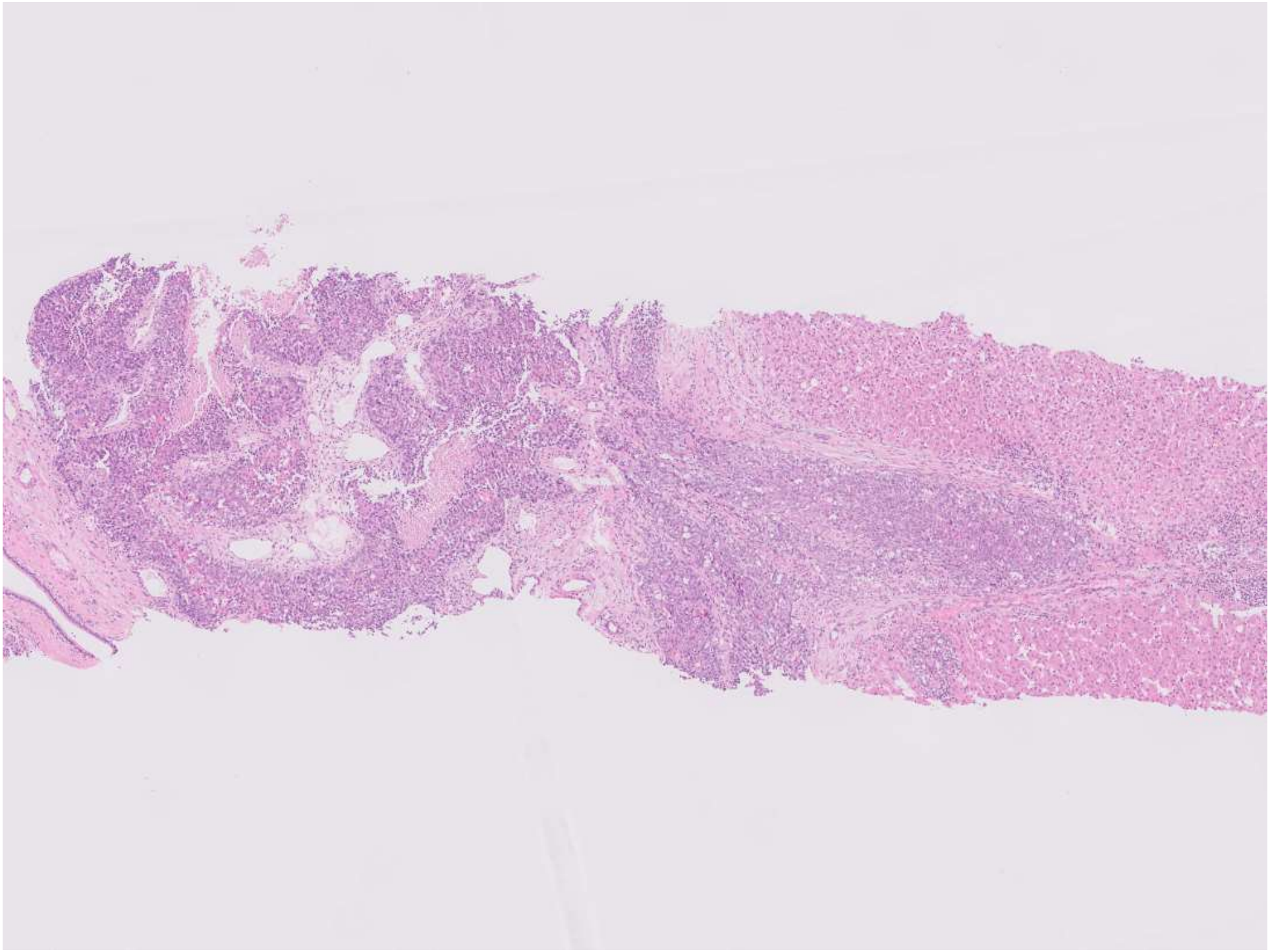
-> grootste in C2

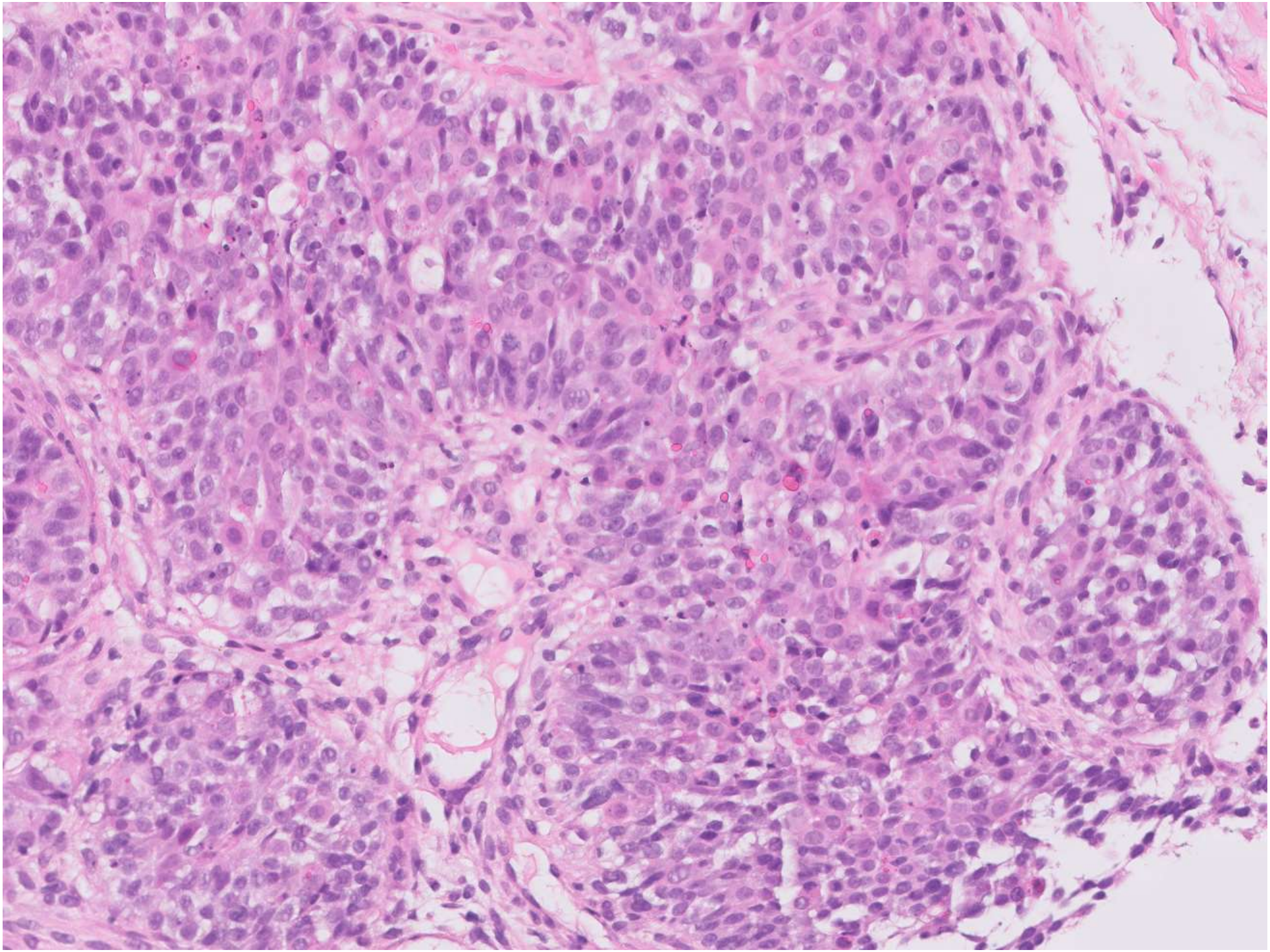
Aantal cassettes + rest

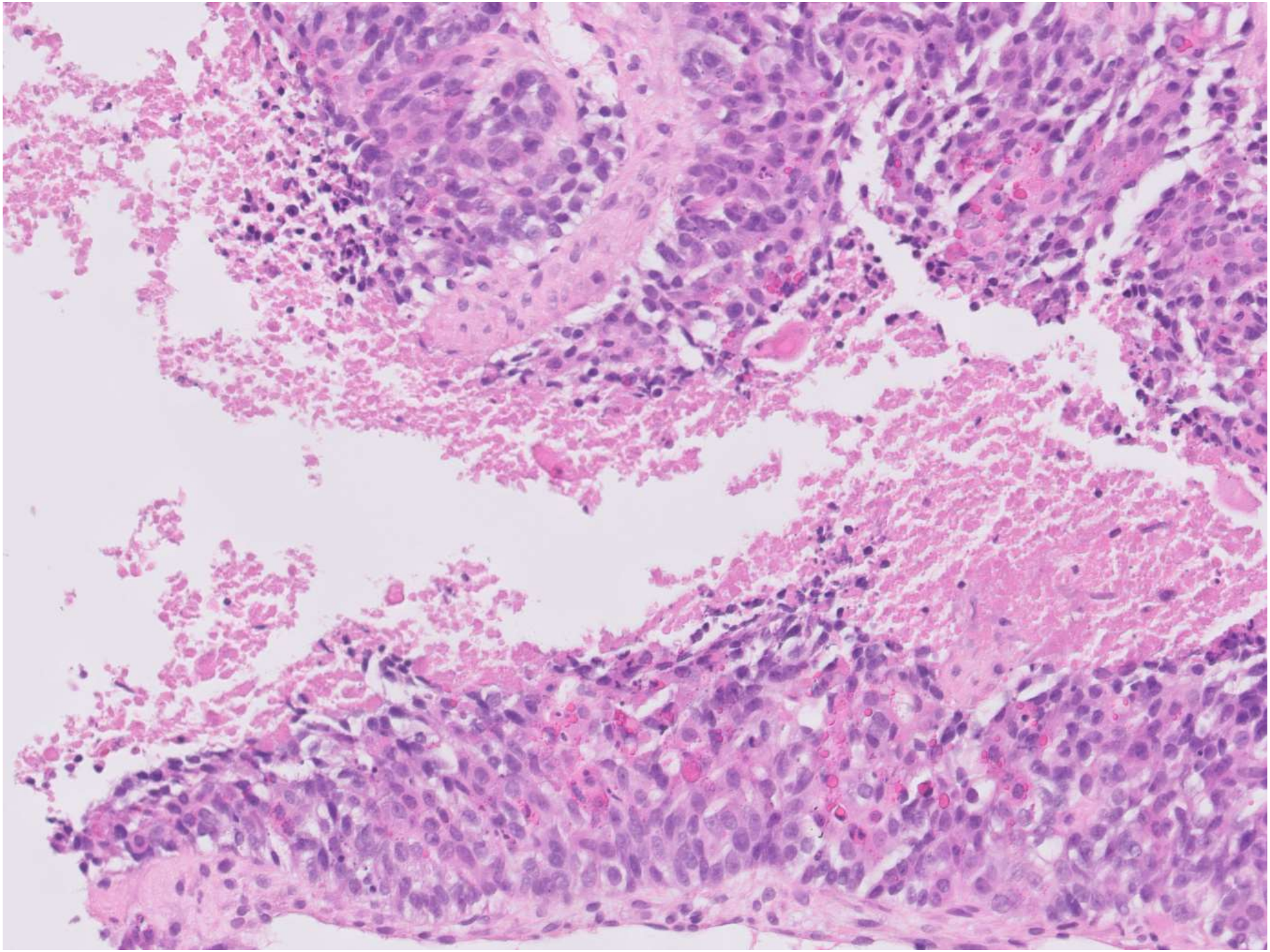
2	0

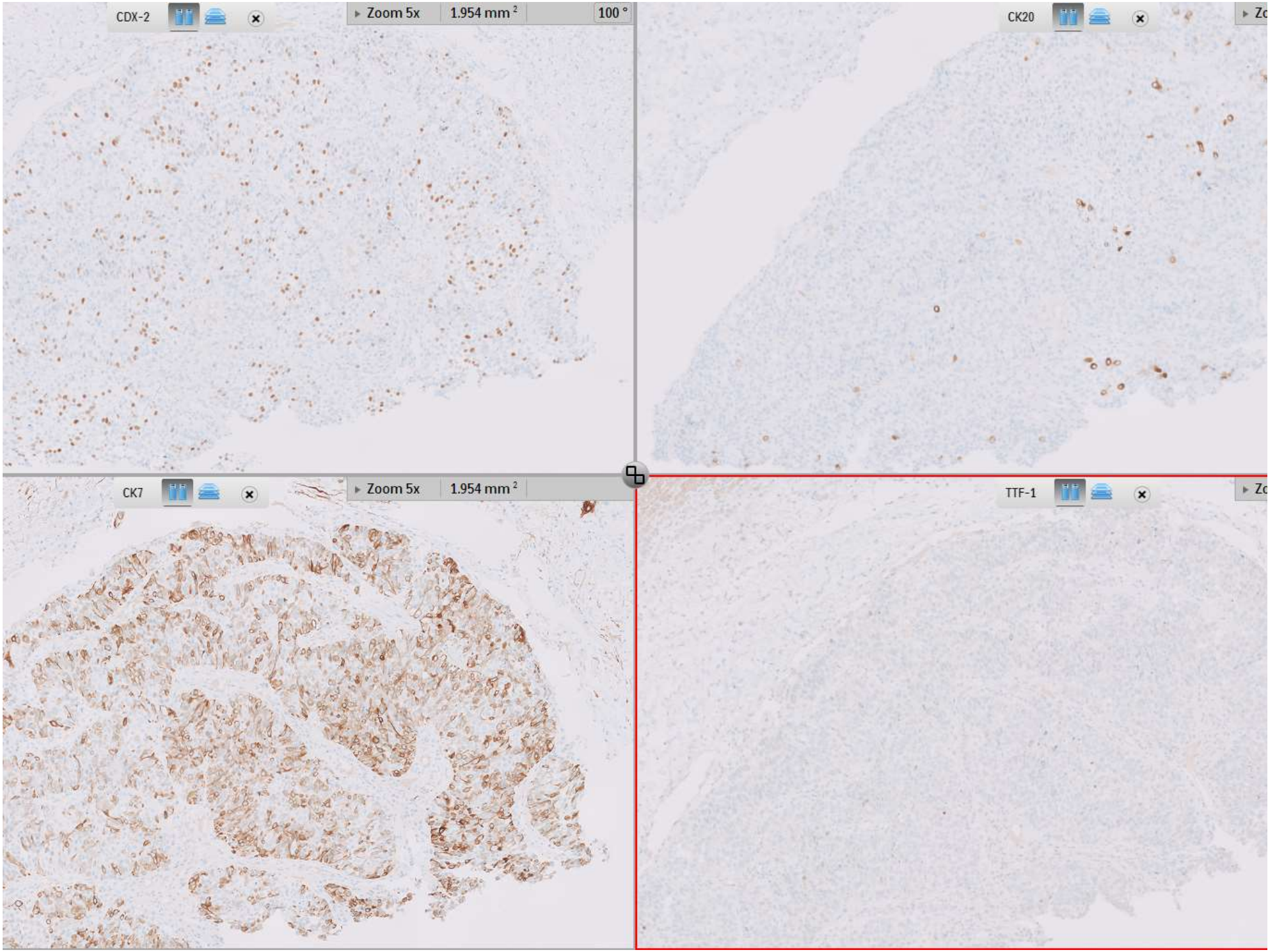

HE
3000
/1
20-10-2021
AZSJ
LOT 40444


HE
3000
/2
20-10-2021
AZSJ
LOT 40444



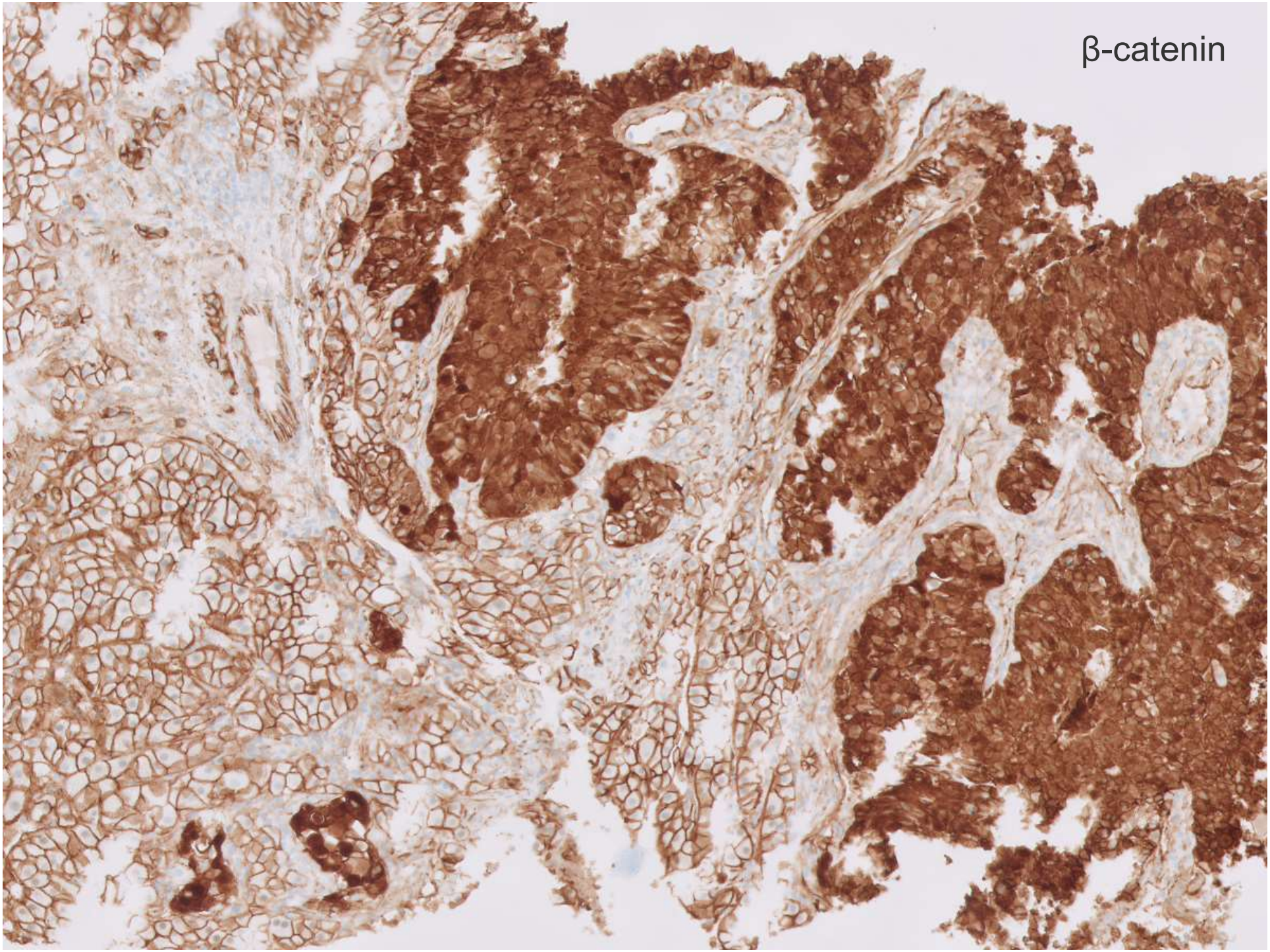





CDX-2
Zoom 5x
1.954 mm²
100 °
CK20
CK7
Zoom 5x
1.954 mm²
TTF-1

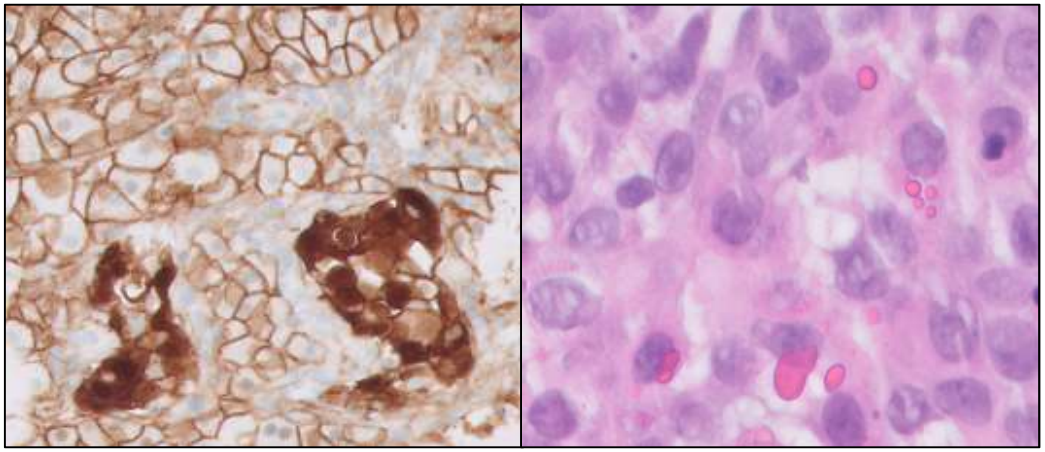
Additional IHC

- P63, GATA3, ER, PAX8: negative
- TTF1: negative
- Synaptofysin, chromogranin: negative
- Chymotrypsin, BCL10, Trypsin: negative


β-catenin

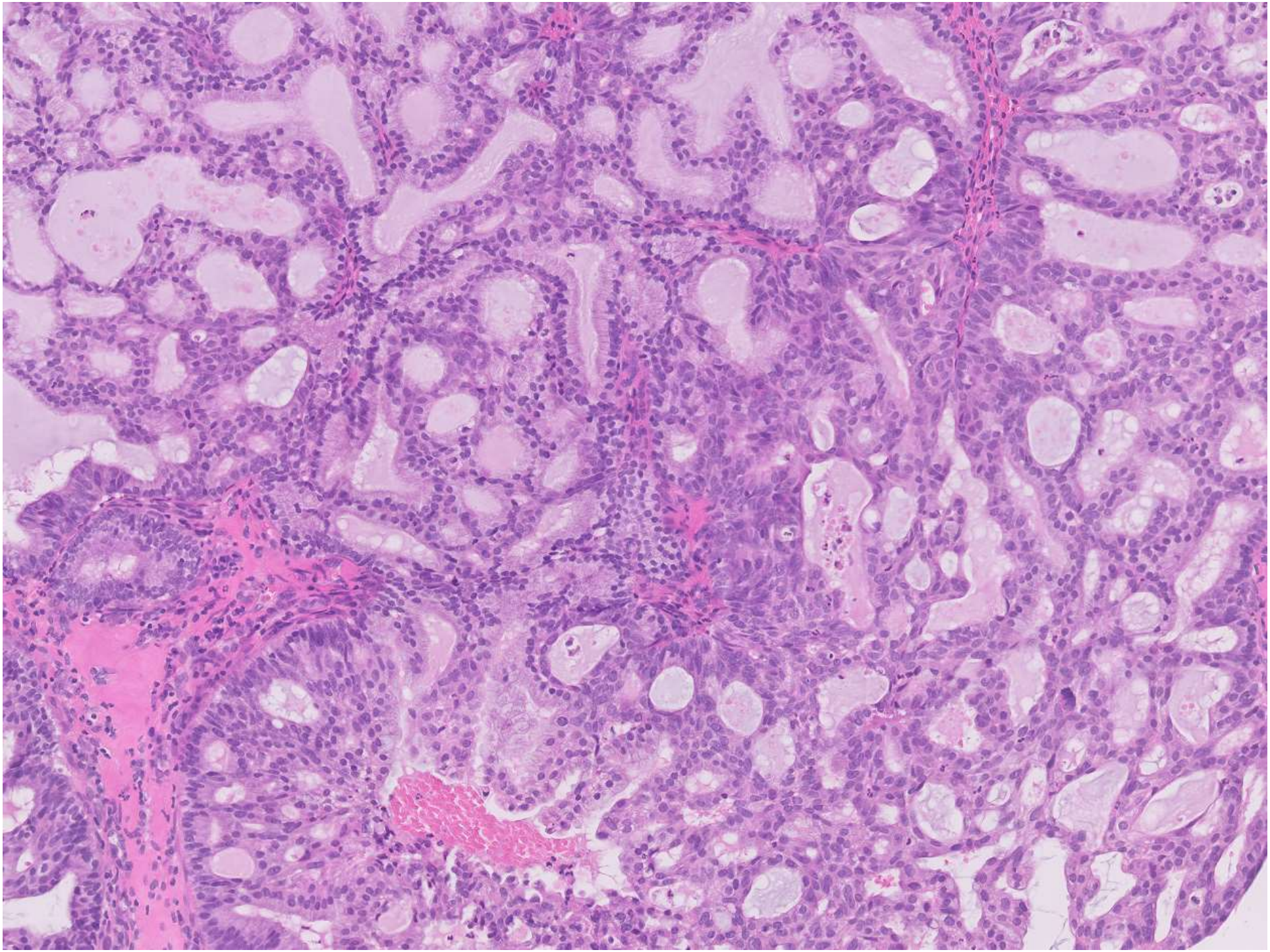
Liver biopsy:

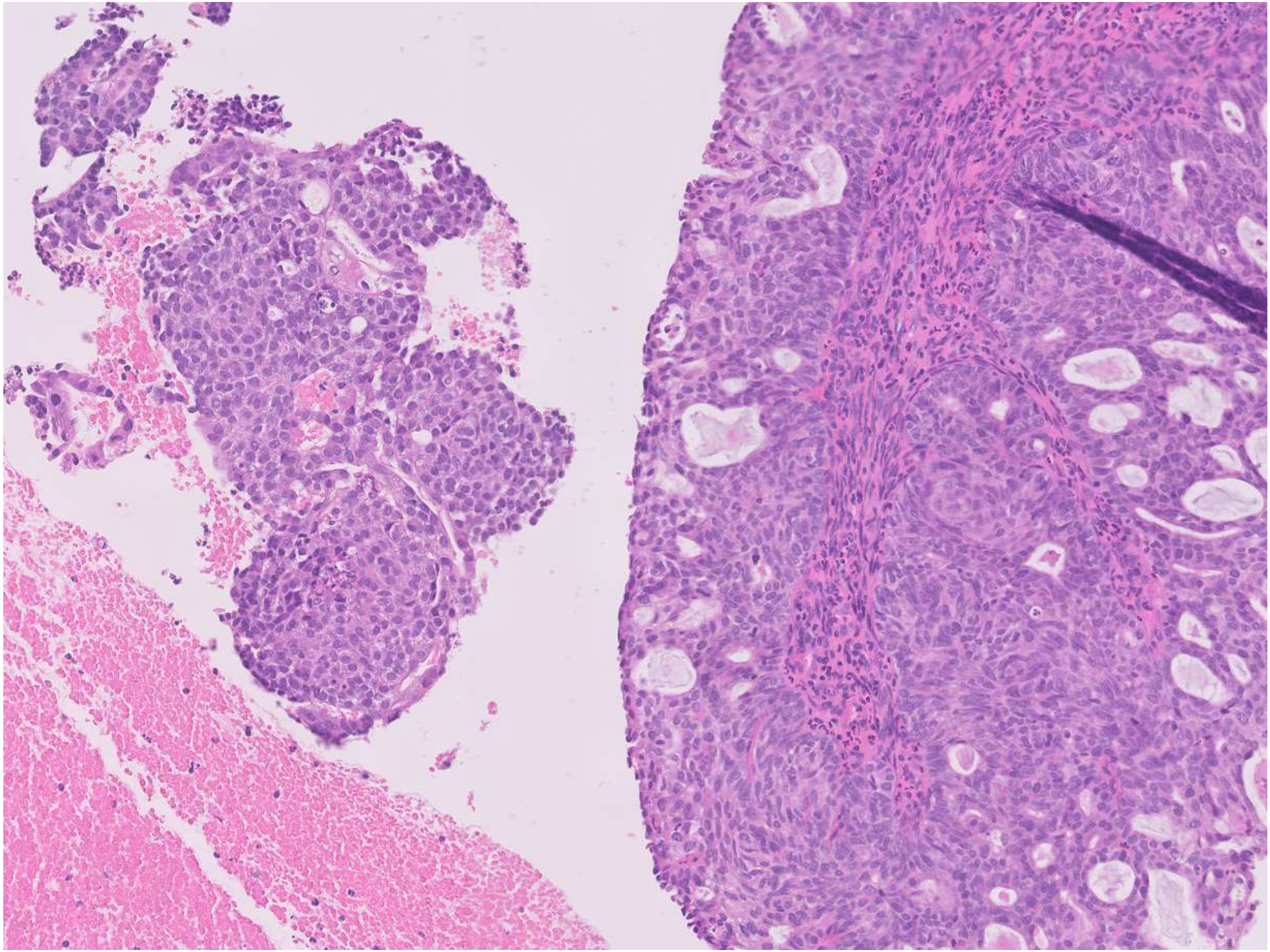
- Based on the immunohistochemical profile, the primary origin is most likely the upper GI-tract, including pancreas and biliary tract.
- The possibility of a solid pseudopapillary neoplasm must be considered.

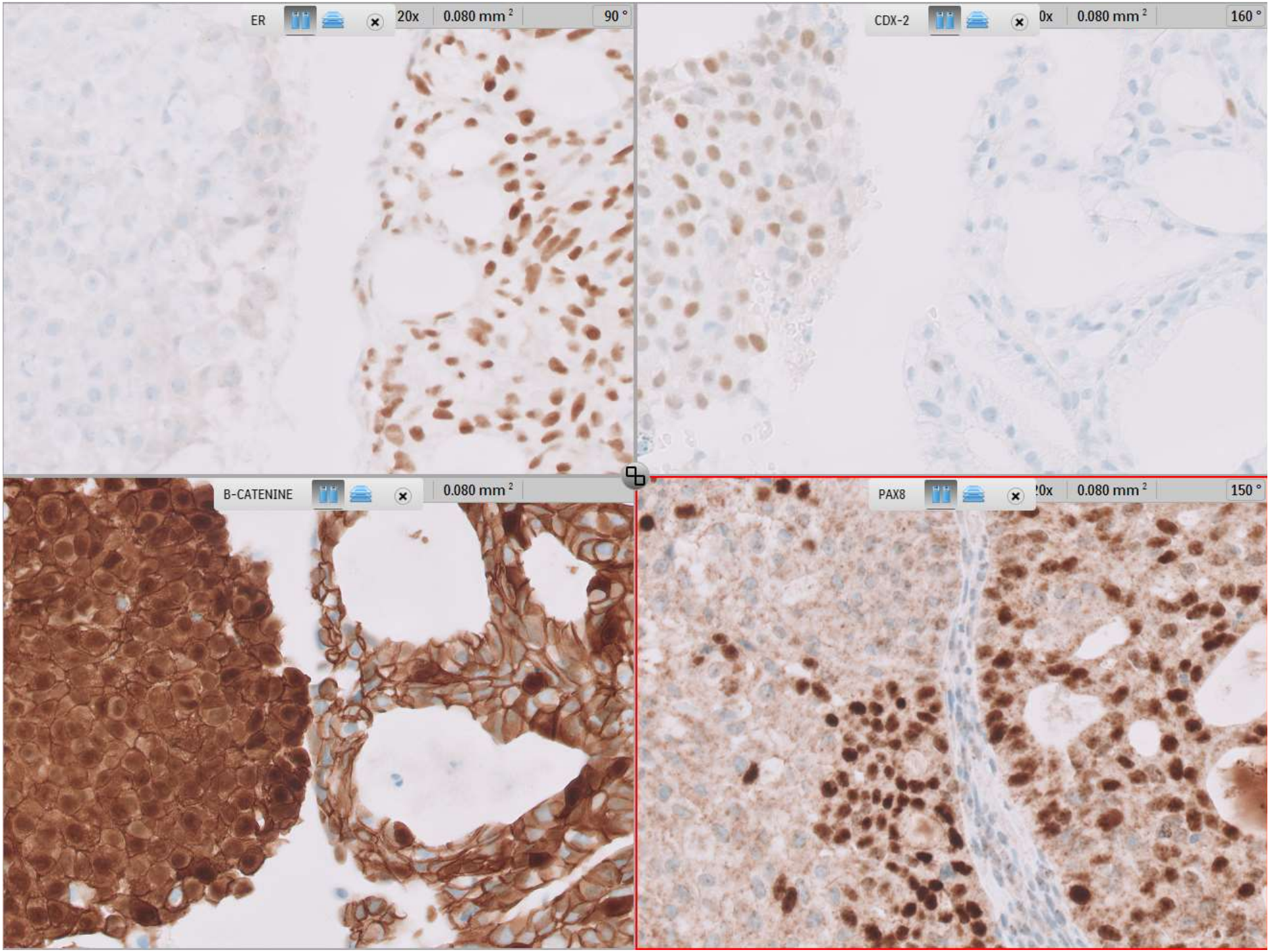


Further investigations (MRI and PET-CT)

- Diffuse metastasis to the lung, intra-abdominal lymph nodes and liver
- No pancreatic tumours
- Lesion in the uterine cavity





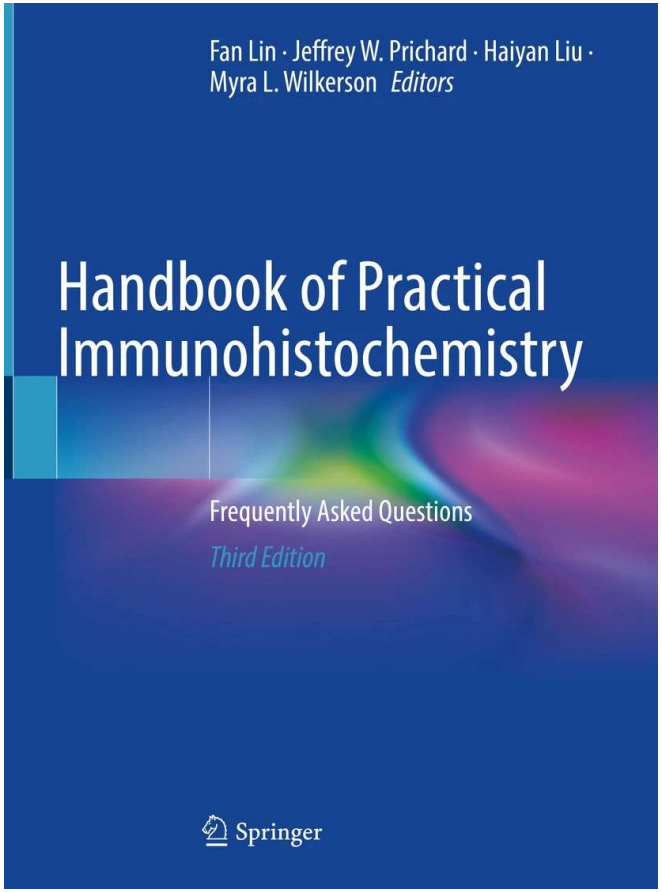

ER
20x
0.080 mm²
90 °
CDX-2
0.080 mm²
160 °
B-CATENINE
0.080 mm²
PAX8
0.080 mm²
150 °

Additional comment on the liver biopsy

- Based on the comparison of the immunohistochemical profiles, it cannot be excluded that the liver lesion is a metastatic location of the solid component of the endometrial carcinoma.

- Further systemic treatment for endometrial carcinoma was given.

- Use the available tissue sparingly
- Stepwise approach
- Always correlate with the clinical information and patients history
- Know the markers you use
- Beware of false negative or positive immunohistochemical staining's



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