Chapter 25
Pancreas and Ampulla

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Abstract This chapter provides a practical overview of frequently used markers in the diagnosis and differential diagnosis of both common and rare pancreatic and ampullary neoplasms, with a specific focus on pancreatic ductal adenocarcinoma and its mimickers, neuroendocrine neoplasms, acinic cell carcinoma and solid and pseudopapillary neoplasm of the pancreas. The chapter contains 40 questions; each question is addressed with a table, concise note and representative pictures if applicable. In addition to the literature review, the authors have included their own experience and tested numerous antibodies reported in the literature. The most effective diagnostic panels of antibodies have been recommended for many entities, such as pVHL, maspin, S100P and IMP-3 being suggested as the best diagnostic panel for identifying pancreatic ductal adenocarcinoma. Some newly described markers such as PAX8, islet-1 and PDX-1 for neuroendocrine neoplasm have been discussed. Furthermore, immunophenotypes of normal pancreatic and ampullary tissues have been described, which tends to be neglected in the literature.

Keywords Ductal adenocarcinoma • Pancreatic neuroendocrine neoplasm • Acinar cell carcinoma • Solid-pseudopapillary neoplasm • Intraductal papillary mucinous neoplasm • Mucinous cyst neoplasm • Serous cystadenoma • CK7 • CK20 • CK17 • CK19 • pVHL • Maspin • S100P • IMP3 • MUC5AC • CEA • DPC4/SMAD4 • p53 • Chromogranin • Synaptophysin • Beta-catenin • PR • PAX8 • MIC1 • MUC2

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FREQUENTLY ASKED QUESTIONS

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Table 25.1 Summary of applications and limitations of useful markers

Antibodies	Staining pattern	Function	Key applications and pitfalls
AKR1B10	C	Aldo-keto reductase family 1B10	Positive in DAC and negative in chronic pancreatitis
Annexin A8	C	A member of the annexin family of calcium-regulated membrane binding proteins	Positive in DAC; usually negative or weakly positive in normal ducts
BCL10	C	B-cell lymphoma/leukemia 10 is a protein that in humans is encoded by the BCL10 gene and contains a caspase recruitment domain (CARD), and has been shown to induce apoptosis and to activate NF-kappa B	Positive in acinar cell carcinoma
Ber-EP4	M+C	Expressed in various adenocarcinomas and normal glandular epithelium; usually negative in mesothelioma	Positive in DAC; also positive or weakly positive in normal ducts
Beta-catenin	N or M	A subunit of the cadherin protein complex. Has been implicated as an integral component in the Wnt signaling pathway. Normally expressed in membrane of epithelial cells and is important for the function of E-cadherin. Mutation results in nuclear accumulation	N and M staining in >90 % of SPN; N staining also reported in significant numbers of PB and some ACC; M staining in normal ducts, DAC and P-NET
CA19-9	C	Also called carbohydrate antigen 19-9 or sialylated Lewis (a) antigen; overexpressed in adenocarcinoma of colon and pancreas	Positive in DAC; also positive or weakly positive in normal ducts
Carcinoembryonic antigen (CEA)	C	Expressed in various adenocarcinomas and normal glandular epithelium	Positive in DAC; usually negative in normal ducts
CDX-2	N	A caudal-related homeobox transcription factor expressed in intestinal epithelium	Positive in IPMN, CC, some MCN, and about 10 % of DAC
CEL	C	Carboxyl ester lipase	Positive in acinar cell carcinoma
Chromogranin	C	Present in the cores of amine and peptide hormone and neurotransmitter dense-core secretory vesicles	Positive in P-NET; rarely positive in SPN and ACC
CK17	M+C	Epithelial marker	Positive in DAC and usually negative in normal/reactive ducts
CK19	M+C	Epithelial marker	Positive in DAC; increasing malignant potential when positive in P-NET
CK20	M+C	Epithelial marker	Positive in most CC and MCN and some DAC
CK7	M+C	Epithelial marker	Positive in DAC; usually negative in ACC and SPN
Claudin 18	C	Component of tight junctions	Positive in DAC; usually negative or weakly positive in normal ducts
Claudin 4		Component of tight junctions	Positive in DAC; usually but also weakly positive in normal ducts

(continued)

Table 25.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
Claudin 5	M	Component of tight junctions	Positive in SPN; negative in ACC, P-NET and PB
Claudin 7	M	Component of tight junctions	Positive in ACC, P-NET and PB; negative or focal cytoplasmic positivity in SPN
DPC4/SMAD4	N	Tumor suppressor gene	Loss of expression in most invasive mucinous carcinomas and about 60 % of DACs; positive in normal ducts and ACC
E-cadherin	M	An adhesion molecule expressed in epithelial lineage	Loss of expression in SPN and undifferentiated carcinoma, some ACC and PB; M staining in others
Glypican-3	C	Glypican-3, an established immunomarker for hepatocellular carcinoma and yolk sac tumor	Can be positive in acinar cell carcinoma but not in ductal carcinomas
IMP-3	C	Also known as K homology domain-containing protein overexpressed in cancer (KOC). Encodes a protein with four K-homologous domains; regulation of tumor cell proliferation	Positive in DAC and P-NET; usually negative in normal/reactive ducts
Islet-1	N	The human insulin gene enhancer-binding protein islet-1 is a transcription factor involving in the differentiation of pancreatic endocrine cells	Islet-1 expression was noted in 90 % of P-NETs, 89 % of duodenal NETs, 100 % rectal NETS, 38 % of colonic NETs
Maspin	C+N	Related to the serpin family of protease inhibitors; plays a role in tumor invasion and metastasis	Positive in DAC; usually negative in normal/reactive ducts and acini
Mesothelin	M+C	A 40 kD protein expressed in normal mesothelium and overexpressed in some cancers, such as mesothelioma, ovarian carcinoma and DAC	Positive in DAC; usually negative in normal ducts and ACC
MOC-31	M	Expressed in various adenocarcinomas and normal glandular epithelium; usually negative in mesothelioma	Positive in DAC; also positive or weakly positive in normal ducts and acini
MUC1	C+M	A membrane-associated glycoprotein expressed in various tumor types	Positive in DAC; negative or infrequently positive in CC and IPMN
MUC2	C+M	A membrane-associated glycoprotein expressed in various tumor types	Positive in CC and frequently positive in IPMN but negative in DAC
MUC4	C+M	A membrane-associated glycoprotein expressed in various tumor types	Positive in DAC and usually negative in normal/reactive ducts
MUC5AC	C+M	A membrane-associated glycoprotein expressed in various tumor types	Positive in DAC, IPMN, and some MCN; usually negative in normal pancreatic ducts
MUC6	C	A membrane-associated glycoprotein expressed in various tumor types	Positive in CC, some IPMN and normal ducts; usually negative in DAC
p53	N	Tumor suppressor gene	Overexpression more frequently seen in DAC but can be seen in reactive conditions
PAX8	N	PAX8 is a member of the paired box (PAX) family of transcription factors, involved in development of thyroid follicular cells and expression of thyroid specific genes, and together with PAX2 involved in regulation of the organogenesis of the kidney and the Mullerian system	Positive in P-NET; also positive in thyroid follicular cell tumors, renal cell carcinomas, ovarian carcinomas, endometrial adenocarcinomas, and thymic tumors
PDX1	N	Pancreatic duodenal homeobox 1 (PDX1) is a Hox type transcription factor which regulates both exocrine and endocrine pancreatic differentiation and maintains the beta-cell function	Positive in P-NET, duodenal NET, and the vast majority of insulin and gastrin secreted NETs
PR		Progesterone receptor	Positive in approximately 60 % of P-NET and 80 % of SPN
PSCA	C	Glycosylphosphatidylinositol-anchored cell membrane glycoprotein; overexpressed in prostatic carcinoma, bladder and pancreatic carcinomas	Positive in DAC; may be positive in normal ducts and acini
pVHL	M+C	Tumor suppressor gene	Positive in both normal ducts and acini; negative in DAC, ACC, mucinous tumors and SPN
S100A6	N+C	Belongs to the family of S100 calcium-binding proteins	N and C staining in most DAC and a small portion of reactive ducts
S100P	N+C	Belongs to the family of S100 calcium-binding proteins	N and C staining in most DAC; usually negative or cytoplasmic staining in normal/reactive ducts and other entities (P-NET, ACC and SPN)

(continued)

Table 25.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
TAG 72 (B72.3)	M+C	Expressed in various adenocarcinomas and normal glandular epithelium	Positive in DAC; also positive or weakly positive in normal ducts
Trypsin	C	An enzyme of pancreatic origin; catalyzes the hydrolysis of proteins to smaller polypeptide units	Positive in ACC and negative in SPN; background staining is a common problem

N nuclear staining, *M* membranous staining, *C* cytoplasmic staining, *DAC* ductal adenocarcinoma, *SPN* solid pseudopapillary neoplasm, *P-NET* pancreatic neuroendocrine tumor, *IPMN* intraductal papillary mucinous neoplasm, *MCN* mucinous cystic neoplasm, *CC* colloid carcinoma, *ACC* acinar cell carcinoma, *PB* pancreatoblastoma, *NET* neuroendocrine tumor

References: [1–81]

Table 25.2 Summary of useful markers for common tumors

Antibodies	DAC	ACC	P-NET	SPN	PB
CK7	+	− or +	+ or −	−	+ or −
CK19	+	− or +	− or +	−	+ or −
Mesothelin	+	−	−	−	+ or −
S100P	+	−	−	−	+ or −
Maspin	+	−	−	−	+ or −
Beta-catenin	M+	M or N+	M+	N and M+	N and M+ or M+
E-cadherin	+	+	+	−	− or +
Chromogranin	−	−	+	−	− or +
CD10	−	−	+	+	− or +
IMP-3	+	−	+ or −	−	− or +
Trypsin	−	+	−	−	+
Claudin 5	ND	−	−	M+	−
Claudin 7	ND	M+	M+	− or focally C+	M+

M membranous staining, *N* nuclear staining, *C* cytoplasmic staining, *DAC* ductal adenocarcinoma, *ACC* acinar cell carcinoma, *P-NET* pancreatic neuroendocrine tumor, *SPN* solid-pseudopapillary neoplasm, *PB* pancreatoblastoma

The immunostaining results on PB are largely dependent upon the components in the tumor, such as acinar, squamous, ductal, or even endocrine component

References: [1–58]

Table 25.3 Markers for normal pancreatic ducts and acini

Antibodies	Pancreatic ducts	Pancreatic acini
CAM 5.2	+	+
CK7	+	+
CK20	−	−
CK19	Focally +	−
CK17	Usually −	−
S100P	− or C+	−
S100A6	− or weakly C+ or N+	−
pVHL	+	Focally +
mCEA	− or weakly + on luminal side	−
CA19-9	− or focally +	Weakly +
Trypsin	−	+
MOC-31	+	+
Ber-EP4	+	+
TAG 72 (B72.3)	−	−
IMP-3	− or very focally +	−
Maspin	Usually −	−
Annexin A8	Weakly +	Weakly +
Claudin 4	Weakly +	Weakly +
Claudin 18	Focally +	+
PSCA	+	+
Mesothelin	Weakly +	−
MUC1	Weakly + on luminal side	−
MUC2	−	−
MUC4	−	−
MUC5AC	−	−
MUC6	+	−
DPC4/SMAD4	+	+
p53	− or very weakly +	−
CDX-2	− or +	− or +

C cytoplasmic staining, *N* nuclear staining

The table is from GML data based on 40 cases on TMA sections and routine sections; the stains were performed on both the Dako and Ventana Systems

Normal and reactive pancreatic ducts are usually negative for CK20, CK17, maspin, IMP3, S100P (nuclear staining), mCEA, trypsin, MUC2, MUC4, and MUC5AC

Approximately 10 % of pancreatic ducts and acini are focally positive for CDX-2

Table 25.4 Markers for ductal adenocarcinoma of the pancreas

Antibodies	Literature	GML data (N = 70)
pVHL	–	100 % negative
Maspin	+	100 %
IMP-3	+	90 %
S100P	+	96 %
S100A6	+	96 %
CAM 5.2	+	75 %
CK7	+	96 %
CK20	– or focally +	15 %
CK17	+	60 %
CK19	+	75 %
Mesothelin	+	57 %
mCEA	+	85 %
MOC-31	+	97 %
CA19-9	+	84 %
Annexin A8[a]	+	ND
MUC1	+	95 %
MUC2	–	4 %
MUC4	+	50 %
MUC5AC	+	67 %
MUC6	– or +	17 %
Claudin 4	+	94 %
Claudin 18	+	80 %
PSCA	+ or –	56 %
DPC4/SMAD4	+ or –	41 %
p53	+ or –	60 %
CDX-2	– or +	5 %
Fascin[a]	+	85 %
CDH17	+ or –	18 % (17/95)
Annexin A10	+	ND
AKR1B10	+	ND
Plectin-1	+	ND

GML data is based on TMA sections containing 50 cases and 20 cases of routine sections

Many markers have been reported in the literature. However, our experience shows that pVHL, maspin, S100P, and IMP-3 are the best panel of markers in the distinction of DAC from normal/reactive pancreatic ducts. Representative cases for these four markers are shown in Figs. 25.1, 25.2, 25.3, 25.4, and 25.5. It should be noted that maspin is positive in both normal gastric mucosa and duodenal mucosa. Background staining for S100P sometimes is present. In this instance, S100A6 can be a good substitute, although weak nuclear and cytoplasmic staining for S100A6 can be seen in normal/reactive pancreatic ducts

Other markers including MUC1, MUC5AC, CA19-9, mesothelin and p53 are shown in Figs. 25.6, 25.7, 25.8, 25.9, and 25.10

Normal pancreatic ducts and acini are usually positive for MOC-31, PSCA, claudin 4 and claudin 18, which limits the application of these markers in the distinction between DAC and reactive ducts. Strong background staining is frequently seen with annexin A8 and fascin; in addition, many stromal cells and endothelial cells are positive for fascin

Among the group of cytokeratins being tested (CK7, CK20, CK17, CK19, CAM 5.2), CK17 appears to be the only promising marker in differentiating adenocarcinoma from normal/reactive ducts since it usually lacks expression or is only very focally positive in normal ducts

Loss of DPC4/SMAD4 expression has been reported in approximately 60 % of pancreatic DACs, which can be useful in differentiating pancreatic origin from other mucinous neoplasms, including an ovarian mucinous neoplasm. A metastatic carcinoma with loss of DPC4/SMAD4 expression is suggestive of a pancreatic origin, although it is not absolutely specific (it has been reported in other tumors, including metastatic colonic adenocarcinomas). Examples of DAC positive and negative for DPC4/SMAD4 are shown in Figs. 25.11 and 25.12

[a]Strong background staining is frequently seen in both Annexin A8 and fascin

References: [1–34, 37–39, 41–44, 58–62]

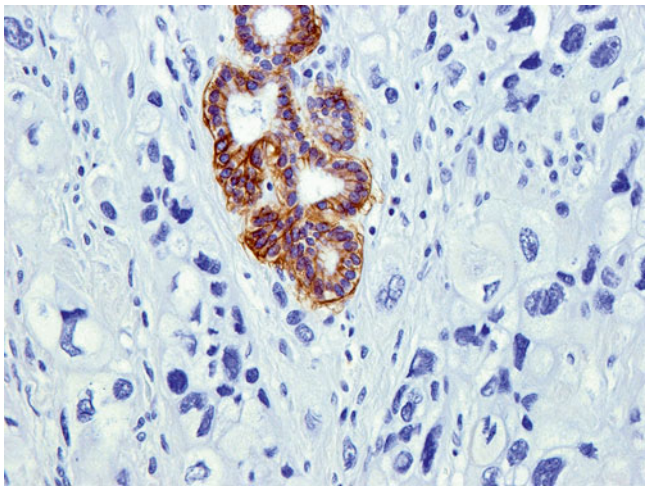

Fig. 25.1 Invasive ductal adenocarcinoma shows loss of expression of pVHL, and normal ducts show membranous and cytoplasmic staining

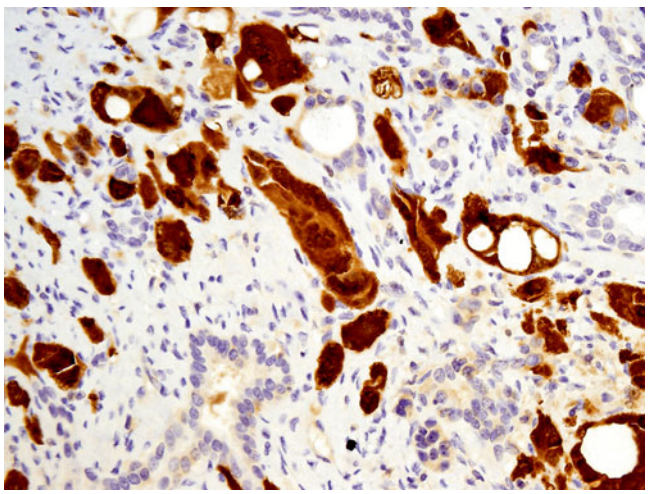

Fig. 25.2 High-grade adenocarcinoma shows nuclear and cytoplasmic staining for maspin

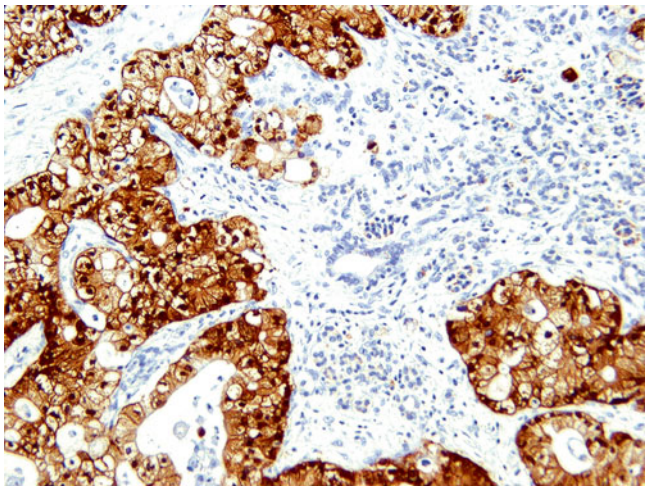

Fig. 25.3 Nuclear and cytoplasmic positivity of S100P in ductal adenocarcinoma, whereas the normal ducts are negative. Note that only nuclear staining or nuclear and cytoplasmic staining is regarded as positive

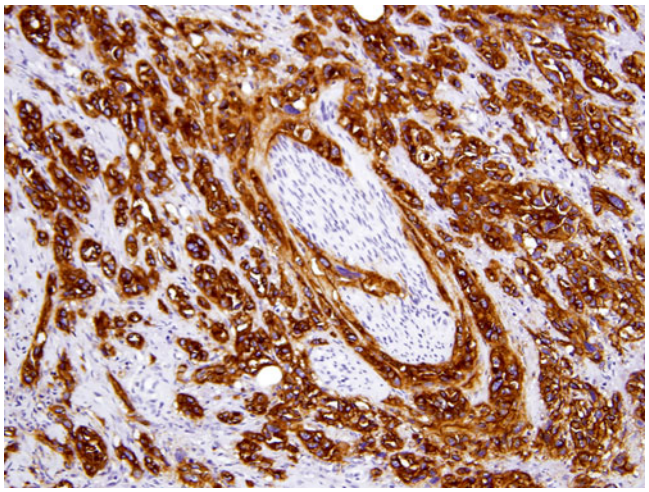

Fig. 25.6 Ductal adenocarcinoma shows strongly positive cytoplasmic staining for MUC1

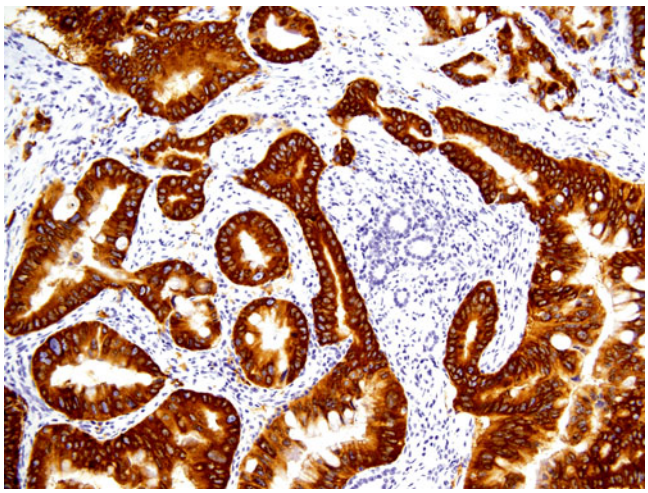

Fig. 25.4 Strong cytoplasmic staining for IMP-3 seen in ductal adenocarcinoma

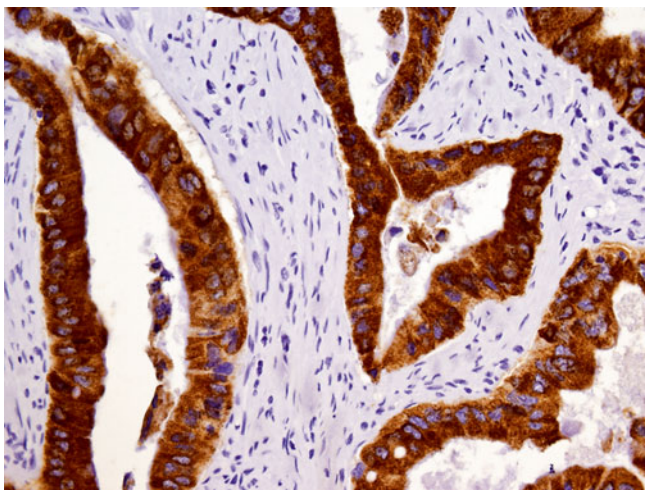

Fig. 25.7 Ductal adenocarcinoma shows strongly positive cytoplasmic staining for MUC5AC

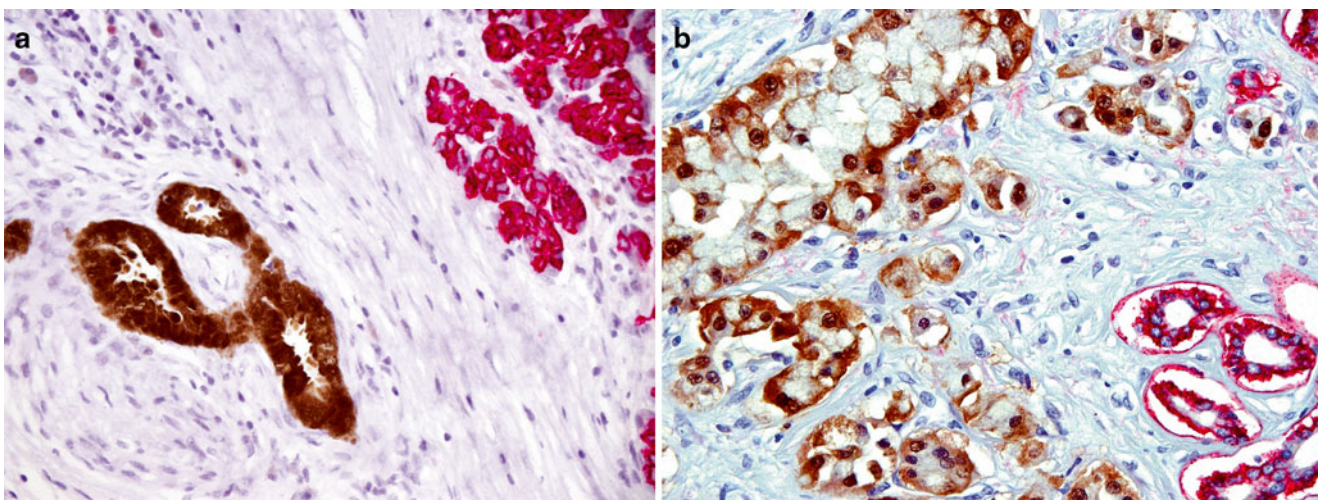

Fig. 25.5 Double-staining technique (**a**) showing carcinoma positive for maspin (brown) and normal ducts positive for pVHL (purple). Double-staining technique (**b**) showing carcinoma positive for S100P (brown) and normal ducts positive for pVHL (purple)

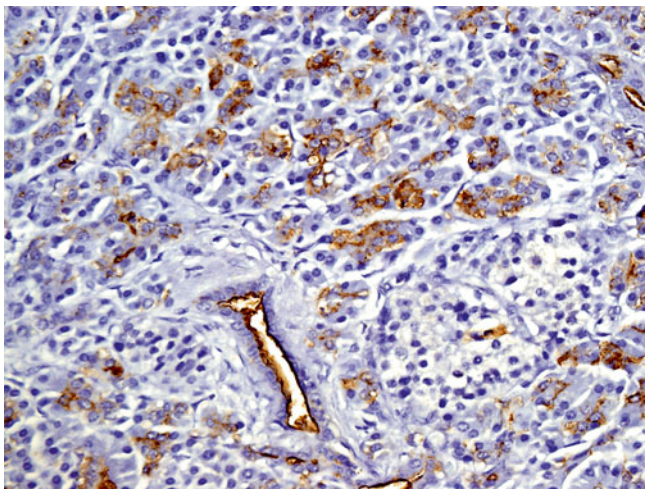

Fig. 25.8 CA19-9 is not a very useful marker since it is also expressed in normal ducts and acini

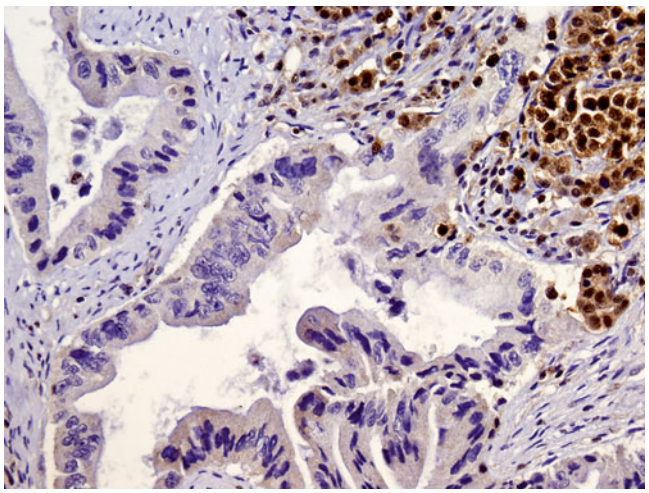

Fig. 25.11 Ductal adenocarcinoma showing loss of expression of DPC4/SMAD4. Note that inflammatory cells and stromal cells show nuclear positivity as an internal positive control

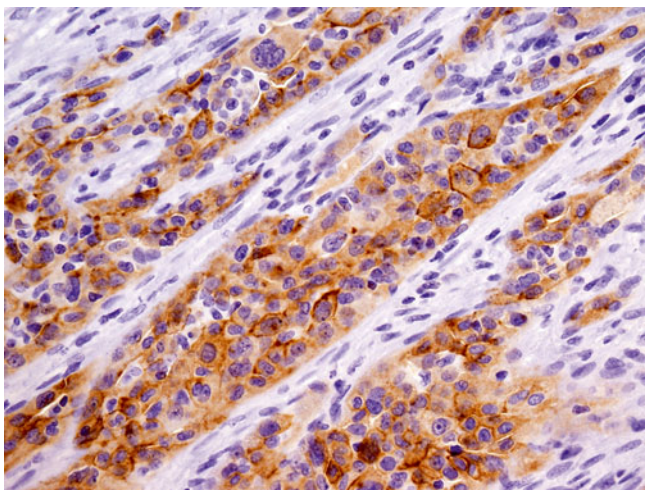

Fig. 25.9 Ductal adenocarcinoma showing membranous staining for mesothelin

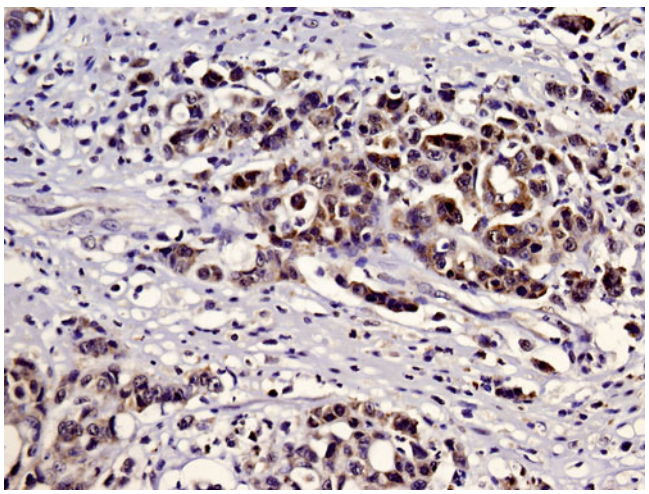

Fig. 25.12 Ductal adenocarcinoma showing positive staining for DPC4

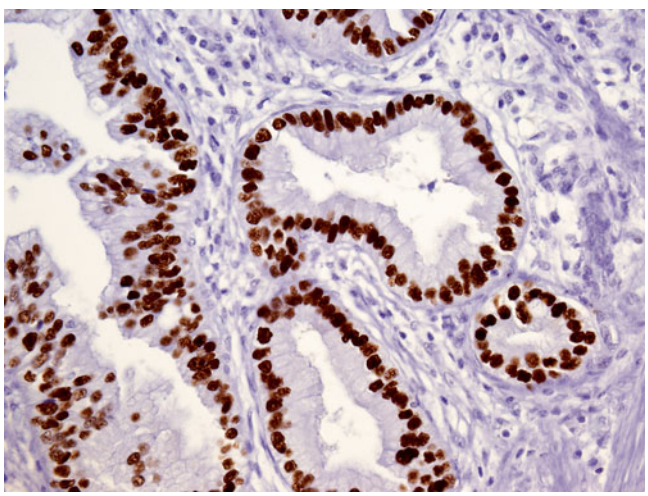

Fig. 25.10 Strong nuclear staining for p53 in ductal adenocarcinoma

Table 25.5 Markers for adenosquamous carcinoma of the pancreas

Antibodies	Literature
CK7	+
CK19	+
CEA	+
CA19-9	+
CK5/6	+
CK903	+
p63	+

Adenosquamous carcinoma can be seen in both the gallbladder and ampulla

References: [1–3]

Table 25.6 Markers for colloid carcinoma of the pancreas

Antibodies	Literature
MUC1	− or +
MUC2	+
CDX-2	+
CK7	+
CK20	+ or −
CA19-9	+
CEA	+
pVHL	−
S100P	+
IMP-3	+
Maspin	+

MUC2 and CDX-2 are usually positive in CC, which is useful in differentiating it from DAC. A case of CC with MUC2 and CDX-2 positivity is shown in Fig. 25.13

In contrast, DAC tends to be positive for MUC1 and negative for MUC2 and CDX-2. Other markers, including S100P, pVHL, IMP-3 and maspin, have limited value in the distinction of these two entities

Colloid carcinoma (noncystic mucinous adenocarcinoma) can be seen in both the gallbladder and ampulla

References: [1–3, 82]

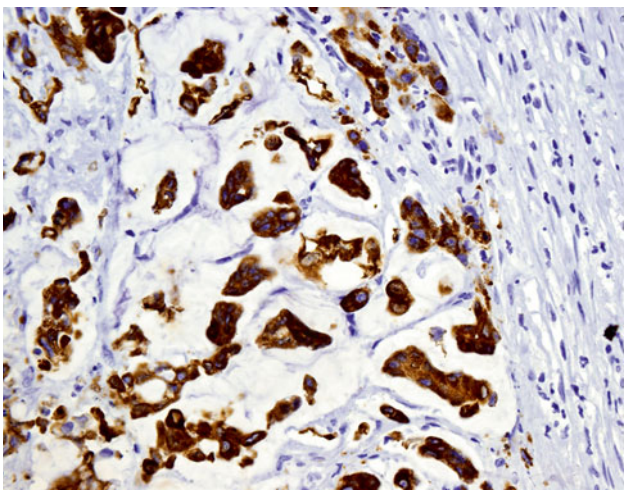

Fig. 25.13 MUC2 is frequently positive in colloid carcinoma and negative in ductal adenocarcinoma

Table 25.7 Markers for medullary carcinoma of the pancreas

Antibodies	Literature
CK7	+
CK20	–
CEA	+ or –
CA19-9	+ or –
MLH1	+ or –
MSH2	+ or –
MSH6	+ or –
PMS2	+ or –
E-cadherin	+

Approximately 30 % of reported cases demonstrate microsatellite instability (MSI) with loss of expression of either MLH1/PMS2 or MSH2/MSH6. Most reported cases show loss of expression of MLH1. K-ras mutation is an infrequent finding in medullary carcinoma compared to DAC. A representative case with loss of expression of MSH2 is shown in Figs. 25.14 and 25.15

References: [1, 2, 83–85]

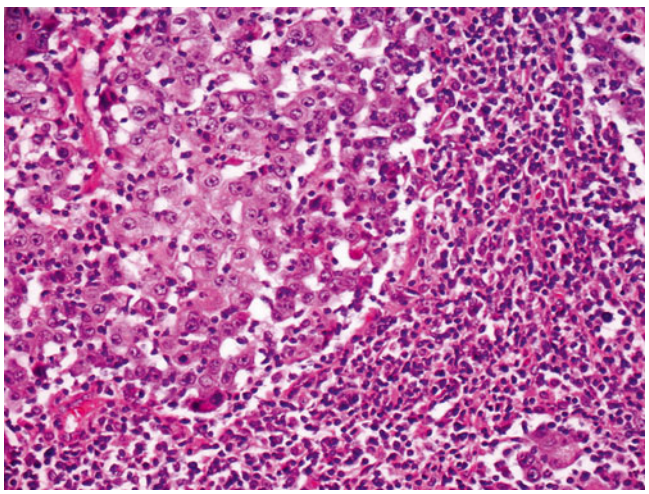

Fig. 25.14 Medullary carcinoma on H&E stained slide. Note that the lymphoid cells serve as an internal positive control

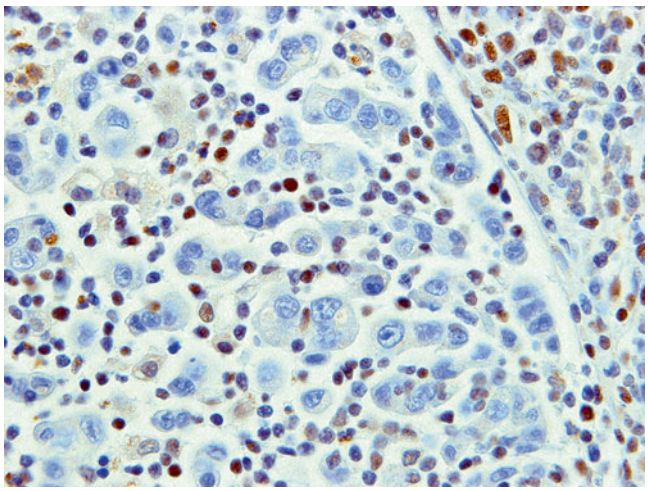

Fig. 25.15 Loss of expression of microsatellite instability marker MSH6

Table 25.8 Markers for undifferentiated carcinoma of the pancreas

Antibody	Literature
CK7	+ or –
CK19	+ or –
CEA	+ or –
MUC1	+ or –
CA19-9	+ or –
Vimentin	+ or –
CK20	–
E-cadherin	–
MSI markers	+

Loss of expression of E-cadherin in this tumor is a characteristic finding. Immunostaining for the other markers can vary depending on the degree of differentiation of the tumor. The tumor is positive for MSI markers (MLH1, MSH2, MSH6, and PMS2), which can be useful in distinction from medullary carcinoma of the pancreas since both tumors present with poorly differentiated histomorphology

References: [1, 86]

Table 25.9 Markers for hepatoid carcinoma of the pancreas

Antibodies	Literature
Hep Par 1	+
Polyclonal CEA	Canalicular +
CD10	Canalicular +
AFP	+ or –
CK7	+ or –
Bile stain[a]	+ or –

[a]Bile stain—a histochemical stain

Hepatoid carcinoma can also be seen in both the gallbladder and ampulla

References: [1, 87]

Table 25.10 Markers for signet ring cell carcinoma of the pancreas

Antibodies	Literature
CK7	+
CK20	+ or –
CEA	+
MOC-31	+
CDX-2	+ or –
CA19-9	+ or –

Signet ring cell carcinoma can also be seen in both gallbladder and ampulla

Reference: [1]

Table 25.11 Markers for undifferentiated carcinoma with osteoclast-like giant cells

Antibodies	Malignant mononuclear cells	Benign giant cells
AE1/AE3	+ or –	–
CK7	+ or –	–
CK20	–	–
CD68	–	+

References: [1–3]

Table 25.12 Markers for acinar cell carcinoma

Antibodies	Literature
CK7	– or focally +
Mesothelin	–
Trypsin	+
S100P	–
Glypican-3	+ or –
Bcl-10	+
Carboxyl ester lipase (CEL)	+
AE1/AE3	+
CK19	– or focally +
CK20	–
CEA	+ or –
MOC-31	+ or –
Beta-catenin	M+ or M and N+
pVHL	–
Vimentin	+ or –

M membranous staining, *N* nuclear staining

Approximately 25 % of ACCs may show both nuclear and membranous positivity for beta-catenin. A histochemical stain of PAS-D is usually positive in acinar cell carcinoma. Trypsin is usually positive but may give a strong background staining

Chromogranin and synaptophysin are usually negative or show only scattered positivity in endocrine cells. When greater than 25 % of tumor cells are positive for endocrine markers, the tumor would be regarded as mixed acinar and endocrine carcinoma

References: [1, 5, 7, 25–28, 33, 46, 47, 55, 63–65]

Table 25.13 Markers for pancreatic neuroendocrine neoplasm

Antibodies	Literature	GML data (N = 16)
Synaptophysin	+	100 % (16/16)
Chromogranin	+	100 % (16/16)
NSE	+	100 % (16/16)
Beta-catenin	M+	100 % (16/16)
CD56	+	44 % (7/16)
PR	– or +	56 % (9/16)
ER	–	0 (0/16)
PAX8	+ or –	47 % (15/32)
PDX1	+ or –	ND
Islet-1	+ or –	ND
CAM 5.2	+	100 % (16/16)
CK7	+ or –	0 (0/16)
CK20	–	6 % (1/16)
Vimentin	–	38 % (6/16)
CDX-2	V	6 % (1/16)
Insulin	V	13 % (2/16)
CK19	+ or –	25 % (4/16)

M membranous staining, *V* variable

The current WHO classification of P-NETs was based on counting mitoses or MIB-1 (Ki-67) proliferative index [4]. P-NETs are divided into (1) P-NET, grade 1 (0–1 mitosis/10 high power field (HPF) or <2 % MIB-1 index); (2) P-NET, grade 2 (2–20 mitoses/10 HPF or 3–20 % MIB-1 index); and (3) pancreatic neuroendocrine carcinoma (large cell neuroendocrine carcinoma or small cell carcinoma; >20 mitoses/10 HPF or >20 % MIB-1 index) [4]

Our study of a small number of cases (N = 16) showed that one case was positive for beta-catenin with both nuclear and cytoplasmic staining. CK7 and CK20 were negative in all cases except one case with focal (5 %) CK20 immunoreactivity. Nine of 16 cases were diffusely and strongly positive for PR

A representative case with vacuolated cytoplasm (lipid-rich pancreatic neuroendocrine neoplasm) is shown in Figs. 25.16 and 25.17 with positive staining for chromogranin, synaptophysin, and CD56. CD56 is the most sensitive but relatively nonspecific marker for neuroendocrine differentiation; however, in our study only 44 % of cases were positive for CD56. An example of pancreatic neuroendocrine neoplasm with positive staining for PR, PAX8 and islet-1 is shown in Figs. 25.18, 25.19, 25.20, and 25.21

CK19 positivity in P-NET may be associated with a more aggressive clinical behavior

References: [1, 4, 5, 66–73]

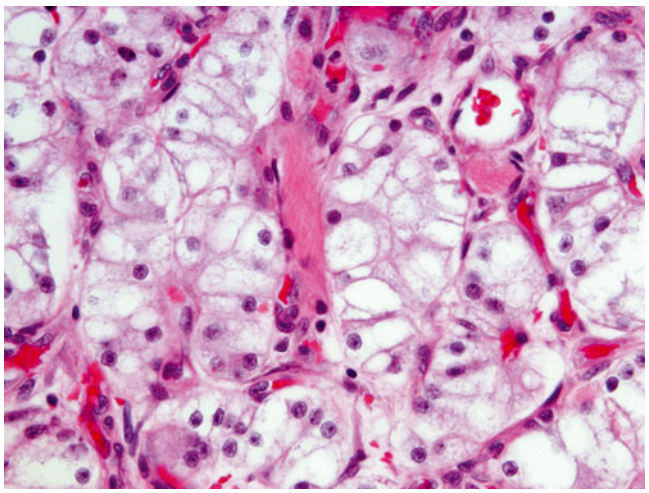

Fig. 25.16 Lipid-rich variant of pancreatic neuroendocrine neoplasm

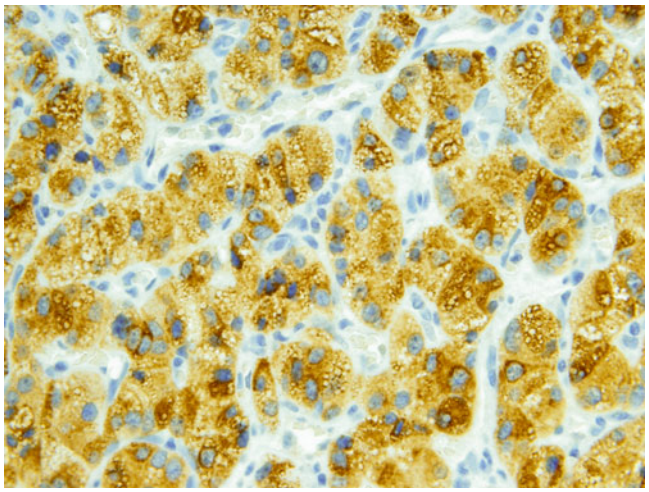

Fig. 25.17 Lipid-rich variant of pancreatic neuroendocrine neoplasm positive for chromogranin

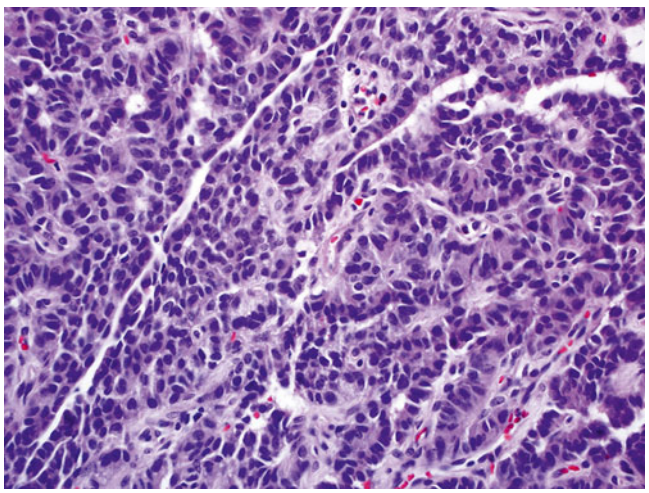

Fig. 25.18 Show examples of pancreatic neuroendocrine neoplasm

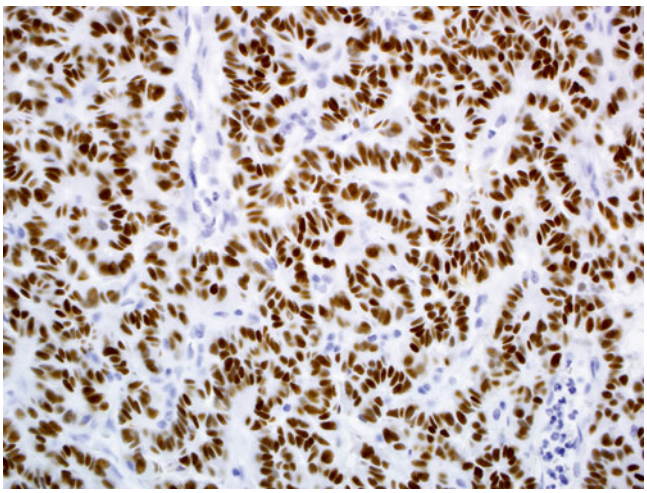

Fig. 25.19 Pancreatic neuroendocrine neoplasm with positive staining for PR

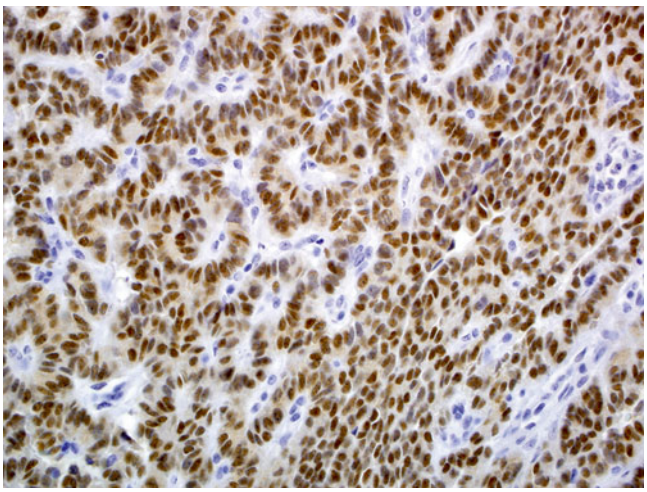

Fig. 25.20 Pancreatic neuroendocrine neoplasm with positive staining for PAX8

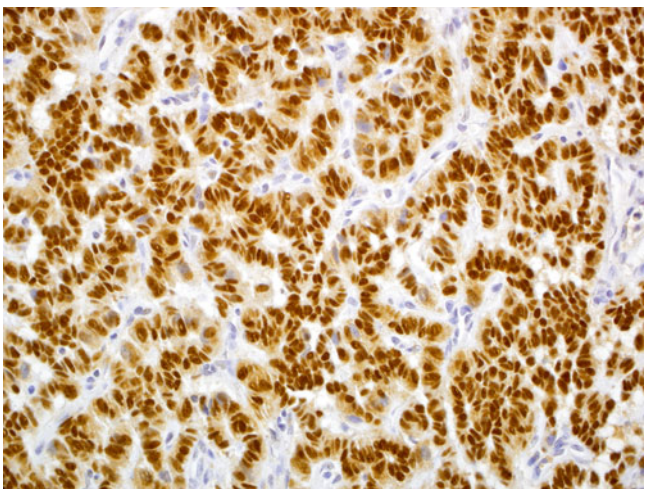

Fig. 25.21 Pancreatic neuroendocrine neoplasm with positive staining for islet-1

Table 25.14 Markers for solid-pseudopapillary neoplasm of the pancreas

Antibodies	Literature
Beta-catenin	N and M+
E-cadherin	–
Chromogranin	–
CD10	+
AE1/AE3	Focally + or –
CK7	–
Vimentin	+
Trypsin	–
Alpha-1 antitrypsin	+
CD56	+
NSE	+ or –
Synaptophysin	– or +
Claudin 5	M +
Claudin 7	– or focally C+
Progesterone receptors (PR)	+ or –
Estrogen receptors (ER)	–
CD99	+ (Cytoplasmic dot)

N nuclear staining, *M* membranous staining, *C* cytoplasmic staining

Beta-catenin, E-cadherin, CD10 and chromogranin are the effective panel of antibodies to confirm the diagnosis of solid and pseudopapillary neoplasm of the pancreas. Over 90 % of SPNs show both nuclear and membranous staining for beta-catenin. A representative case is shown in Figs. 25.22, 25.23, 25.24, and 25.25

References: [1, 5, 37, 45–52, 74]

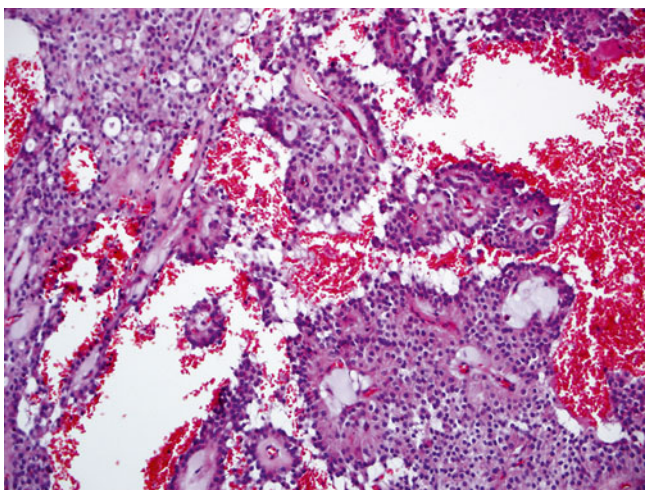

Fig. 25.22 Solid-pseudopapillary tumor

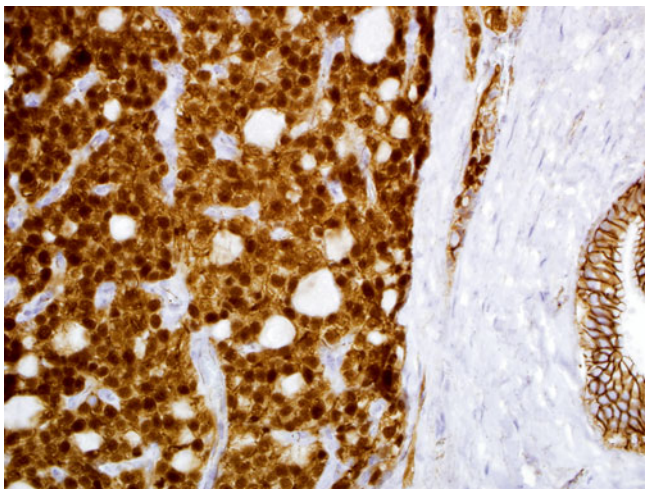

Fig. 25.23 Solid-pseudopapillary tumor showing nuclear and cytoplasmic staining for beta-catenin. Note that normal pancreatic duct shows membranous staining for beat-cadherin

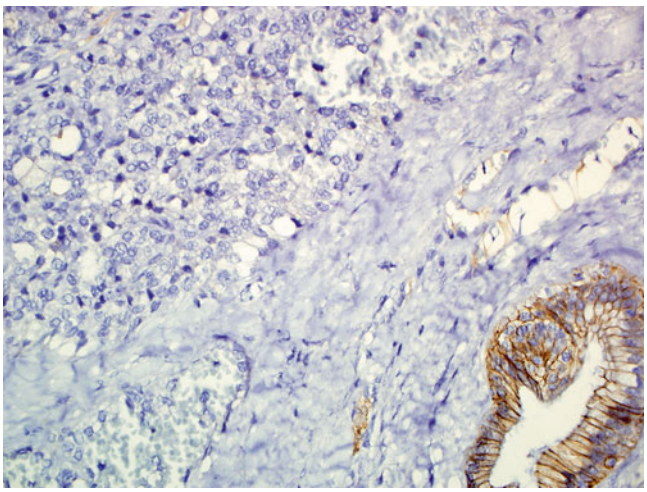

Fig. 25.24 Solid-pseudopapillary tumor showing loss of E-cadherin. Note that normal pancreatic ducts positive for E-cadherin

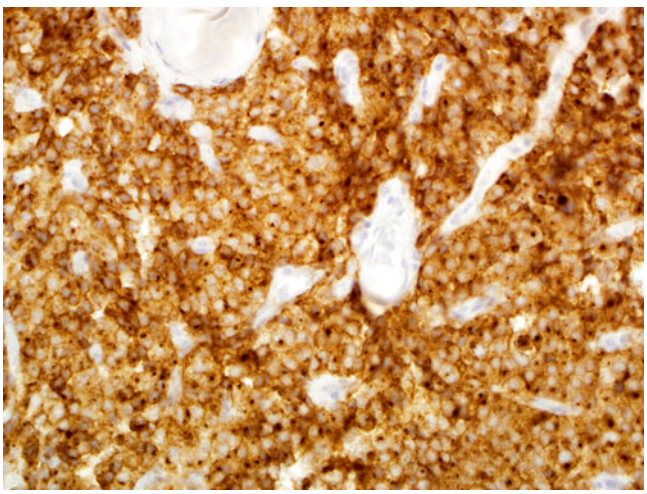

Fig. 25.25 Solid-pseudopapillary tumor positive for CD10

Table 25.15 Markers for pancreatoblastoma

Antibodies	Acinar	Endocrine	Ductal
CK7	+	–	+
CK19	+	–	+
CAM 5.2	+	+	+
Trypsin	+	–	–
NSE	–	+	–
Synaptophysin	–	+	–
Chromogranin	–	+	–
CEA	–	–	+
TAG 72 (B72.3)	–	–	+

Note: Most pancreatoblastomas consist of both acinar and squamous components; some may also contain endocrine and ductal components. The immunostaining results are largely dependent upon the components in the tumor. Nuclear staining of beta-catenin has been reported in a significant percentage of cases, which is similar to the findings in SPN and ACC. The "squamous component" usually lacks the typical squamous phenotype; i.e., positive for CK5/6, CK14 and CK17. Instead, it is usually positive for EMA, CK8, CK18 and CK19, but negative for CK7

Alpha-fetoprotein may be positive in some cases, which is in keeping with the primitive nature of this neoplasm

References: [1, 5, 7, 53, 54, 56, 57]

Table 25.16 Markers for serous cystadenoma

Antibodies	Literature	GML data (N=13)
pVHL	+	100 % (13/13)
MUC6	+ or –	92 % (12/13)
Inhibin-alpha	+	92 % (12/13)
NSE	+	54 % (7/13)
CK7	+	100 % (13/13)
CK20	–	0 (0/13)
S100P	–	0 (0/13)
Synaptophysin	+ or –	0 (0/13)
CD56	+ or –	ND
Chromogranin	–	0 (0/13)
TAG 72 (B72.3)	–	0 (0/13)
CEA	–	0 (0/13)
CA19-9	– or +	31 % (4/13)
MOC-31	–	70 % (9/13)
PAS[a]	+	100 % (13/13)
Mucicarmine[a]	–	0 (0/13)

Both pVHL and MUC6 tend to show diffuse and strong cytoplasmic and membranous staining; in contrast, both NSE and inhibin-alpha more frequently show focal and weak staining. One should be aware that a significant number of cases may be positive for MOC-31 and CA19-9, which are also positive in a high percentage of pancreatic mucin-producing neoplasms and ductal carcinomas

An example of tumor diffusely and strongly positive for pVHL, MUC6, and inhibin-alpha is shown in Figs. 25.26, 25.27, 25.28, and 25.29

[a]PAS for glycogen is usually positive, and mucicarmine for mucin is usually negative

References: [12, 75, 88]

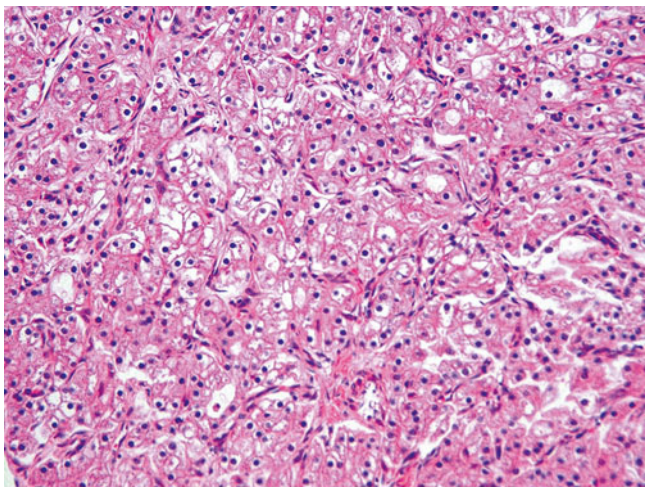

Fig. 25.26 Solid variant of serous microcystic adenoma

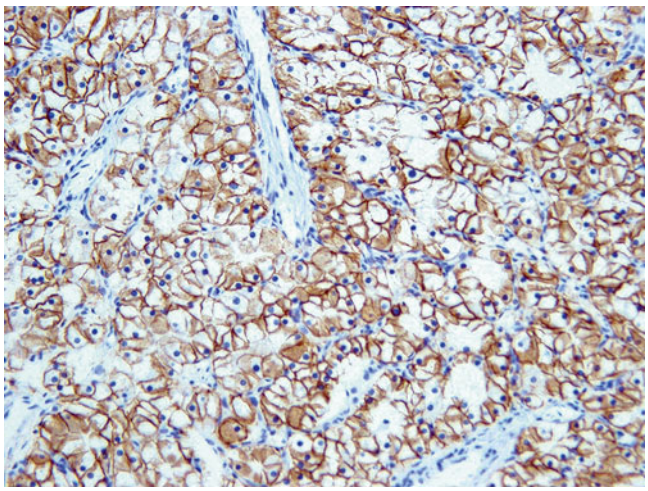

Fig. 25.27 Solid variant of serous microcystic adenoma positive for pVHL

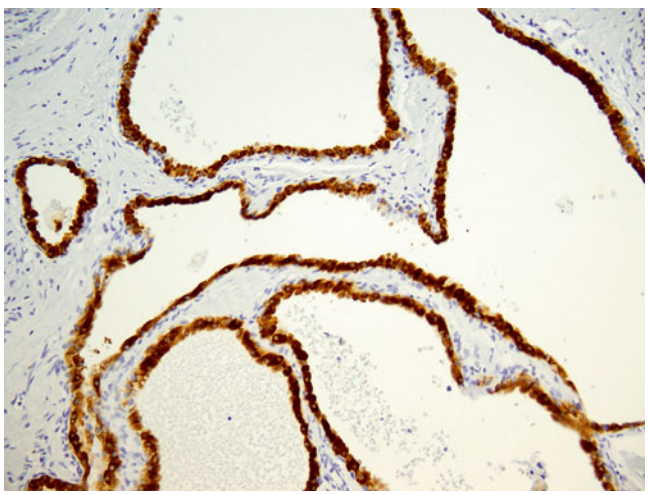

Fig. 25.28 Solid variant of serous microcystic adenoma positive for MUC6

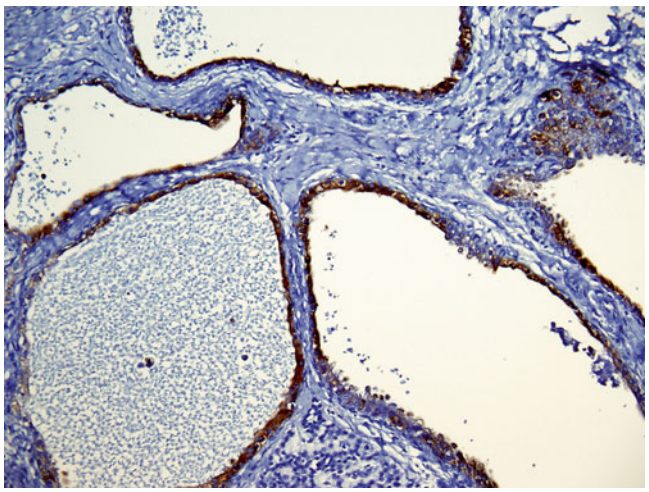

Fig. 25.29 Solid variant of serous microcystic adenoma positive for inhibin-alpha

Table 25.17 Markers for mucinous cystic neoplasm

Antibodies	Literature	GML data (N = 12)
CK7	+	100 % (12/12)
S100P	+	67 % (8/12)
pVHL	–	33 % (4/12)
CD10	+	33 % (4/12)
Estrogen receptor (ER)	+	25 % (3/12)
Inhibin-alpha	+ or –	67 % (8/12)
Progesterone receptor (PR)	+ or –	50 % (6/12)
CK20	– or +	33 % (4/12)
CAM 5.2	+	100 % (12/12)
CEA	+	100 % (12/12)
CA19-9	+	92 % (11/12)
CDX-2	–	25 % (3/12)
MUC1	–	17 % (2/12)
MUC2	– or +	0 (0/12)
MUC5AC	+	67 % (8/12)
MUC6	–	50 % (6/12)
DPC4/SMAD4	+	100 % (12/12)

The ovarian type stroma in MCN is usually positive for ER, PR, CD10, and inhibin-alpha. Expression of different types of mucins is not very useful in differentiating MCN from IPMN. MUC2 is frequently expressed in goblet cells of MCN

Our data showed that all four S100P-negative cases were positive for pVHL; CDX-2 was only focally positive; CD10 was also expressed on the lining mucinous epithelium in two cases. The staining for ER, PR and inhibin-alpha tended to be focal (less than 10 % of the tumor stained) and weak. The positivity rate for ER was lower than reported in the literature, which may be due to inadequate fixation in formalin since the majority of specimens were grossed in a fresh status

References: [1, 2, 76, 89]

Table 25.18 Markers for intraductal papillary mucinous neoplasm

Antibodies	Literature	GML data (N = 18)
CK7	+	100 % (18/18)
S100P	+	18/18 (100 %)
pVHL	–	0 (0/18)
Maspin	+	N/D
CK19	+	75 % (12/16)
CK20	– or +	62.5 % (10/16)
CDX-2	+ or –	37.5 % (6/16)
CEA	+	100 % (18/18)
CA19-9	+	62.5 % (10/16)
MUC1	V	50 % (9/18)
MUC2	V	44 % (8/18)
MUC5AC	+	100 % (18/18)
MUC6	ND	78 % (14/18)
DPC4/SMAD4	+	100 % (18/18)

Intestinal-type IPMN is usually positive for MUC2, CDX-2 and CK20

Gastric foveolar-type IPMN is usually negative for both MUC1 and MUC2. Pancreatobiliary-type IPMN is usually positive for MUC1 and negative for MUC2 and CDX-2

Expression of S100P and loss of expression of pVHL are present in all types of IPMN. Expression of DPC4/SMAD4 was present in all tested cases. MUC6 tends to be expressed in the basal layer of epithelial cells; the papillary structures projecting into the cystic space are frequently negative for MUC6

References: [1, 2, 40, 77, 78, 89, 90]

Table 25.19 Markers for intraductal oncocytic papillary neoplasm

Antibodies	Literature
TAG 72 (B72.3)	+
Mesothelin	+
Hep Par 1	+
MUC1	+
CEA	+ or –
CA19-9	+ or –
CDX-2	–
Claudin 4	–
pVHL	–
S100P	+

References: [1, 33]

Table 25.20 Markers for pancreatic intraepithelial neoplasia 1 and 2

Antibodies	Literature
S100P	+
pVHL	–
p53	– or +
Maspin	+ or –
IMP-3	+ or –
Annexin A8	– or +
Mesothelin	– or +
Claudin 18	– or +

References: [1, 6, 10–13, 17, 19–22, 26–30, 33–35, 42, 43]

Table 25.21 Markers for pancreatic intraepithelial neoplasia 3

Antibodies	Literature
pVHL	–
S100P	+
Maspin	+
IMP-3	+
MUC1	+
MUC2	–
MUC4	+
MUC5AC	+
MUC6	+
DPC4/SMAD4	+
p53	+ or –
Claudin 18	+
Annexin A8	+
Mesothelin	+

References: [1, 6, 10–13, 17, 19–22, 26–30, 33–35, 42, 43]

Table 25.22 Markers for intraductal tubular neoplasm of the pancreas

Antibodies	Literature
CK7	+
CK20	–
CK19	+
CEA	+
CA19-9	+
MUC5AC	+
MUC6	+
MUC1	– or +
MUC2	–
Ki-67	Low
Mucicarmine	+

Reference: [1]

Table 25.23 Markers for chronic pancreatitis

Antibodies	Literature	GML data
S100P	– or cytoplasmic only	– or cytoplasmic only
pVHL	+	+
Maspin	–	–
IMP-3	–	–
Mesothelin	–	Weakly +
PSCA	–	+
Annexin A8	–	Weakly +
Claudin 18	–	Weakly +
mCEA	+ or –	Weakly + on luminal side
MOC-31	+	+
CA19-9	+	+

Our experience showed 100 % of benign and reactive pancreatic ductal cells are positive for pVHL; in contrast, ductal carcinomas are negative for pVHL in nearly 100 % of cases. Non-neoplastic ducts are usually negative for S100P, IMP-3 and maspin. In an autoimmune pancreatitis, the infiltrating plasma cells were predominately IgG4-positive. An immunostain for IgG4 may be helpful in diagnosing a difficult case [79–81]. It should be cautioned, however, that the presence of abundant IgG4-positive plasma cells does not preclude the diagnosis of pancreatic DAC because in a small subset of pancreatic DAC cases the cancer-adjacent tissue may show features of autoimmune pancreatitis

An example of autoimmune pancreatitis with many IgG4-posiitve plasma cells is shown in Figs. 25.30 and 25.31

References: [1, 9–13, 17, 19–22, 26–29, 32, 34, 35, 79–81]

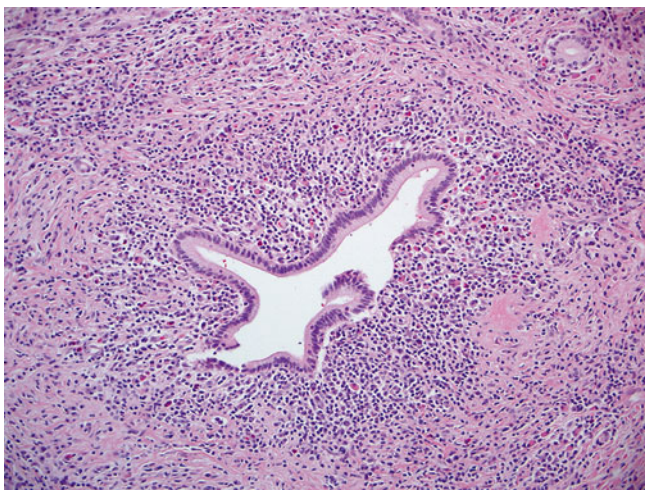

Fig. 25.30 Show an example of autoimmune pancreatitis

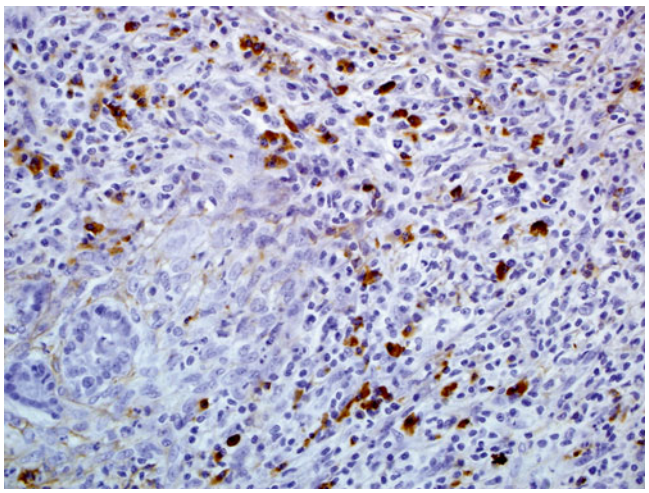

Fig. 25.31 Show an example of autoimmune pancreatitis with many IgG4-positive plasma cells

Table 25.24 Ductal adenocarcinoma vs. chronic pancreatitis

Antibodies	DAC	Pancreatitis
Maspin	+	–
pVHL	–	+
S100P	+	– or cytoplasmic + only
IMP-3	+	–
MUC5AC	+ or –	–
CK17	+ or –	Usually –
DPC4/SMAD4	– or +	+
p53	+ or –	– or very weakly +
mCEA	+	Usually – or focally +
Mesothelin	+	–
MUC1	+	+ or –
Annexin A8	+	–
Claudin 18	+	– or weakly +

DAC ductal adenocarcinoma

It has been demonstrated that 100 % of benign and reactive pancreatic ductal cells are positive for pVHL; in contrast, ductal carcinoma is negative for pVHL in nearly 100 % of cases. Our experience showed that maspin, IMP-3 and S100P are the three best positive markers for identifying adenocarcinoma. Very weak positivity in non-neoplastic ducts can be seen in maspin and IMP-3 stains. Reactive ducts may show cytoplasmic staining for S100P. Markers like TAG 72 (B72.3), MOC-31 and Ber-EP4 are usually positive in adenocarcinoma, but they are frequently positive or weakly positive in normal or reactive ducts as well

References: [1, 9–13, 17, 19–22, 26–29, 32–35, 38, 39, 42–44]

Table 25.25 Pancreatic neuroendocrine tumor vs. solid pseudopapillary neoplasm

Antibodies	P-NET	SPN
Beta-catenin	M+	M+, N+
E-cadherin	+	–
Chromogranin	+	–
Cytokeratin	+	–
Vimentin	–	+
PR	– or +	+ or –
CD10	–	+
Claudin 5	–	M +
Claudin 7	M +	– or focally C+

M membranous staining, *N* nuclear staining, *C* cytoplasmic staining, *P-NET* pancreatic neuroendocrine tumor, *SPN* solid pseudopapillary neoplasm

Over 90 % of SPNs show nuclear and cytoplasmic positivity for beta-catenin and loss of expression of E-cadherin. Expression of chromogranin in SPN has not been reported. Our study showed that PR was positive in 56 % of P-NET cases (N = 16)

References: [1, 2, 45–52]

Table 25.26 Pancreatic neuroendocrine neoplasm vs. acinar cell carcinoma

Antibodies	P-NET	ACC
Chromogranin	+	Usually –
CK7	+	– or focally +
Trypsin	–	+
Beta-catenin	M+	M or N + M
E-cadherin	+	+ or –

P-NET pancreatic neuroendocrine tumor, *ACC* acinar cell carcinoma, *M* membranous staining, *N* nuclear staining

References: [1, 55]

Table 25.27 Pancreatic neuroendocrine tumor vs. pancreatoblastoma

Antibodies	P-NET	PB
Beta-catenin	M+	Usually N + M
E-cadherin	+	Usually –
Chromogranin	+	Usually –
CK7	+	– or +

P-NET pancreatic neuroendocrine neoplasm, *PB* pancreatoblastoma, *N* nuclear staining, *M* membranous staining

This panel of immunostaining markers is very useful for a PB mainly composed of acinar and squamous components. In a PB case with additional ductal and endocrine components, the staining results would be more complicated. In general, nuclear positivity for beta-catenin and loss of E-cadherin expression are highly suggestive of PB after the exclusion of acinar cell carcinoma and SPN

References: [1, 53, 54, 56, 57]

Table 25.28 Acinar cell carcinoma vs. solid pseudopapillary neoplasm

Antibodies	ACC	SPN
CD10	–	+
Beta-catenin	M or M + N	M + N
Trypsin	+	–
E-cadherin	+	–
AE1/AE3	+	– or focal +
PR	–	+ or –
Bcl-10	+	–
Claudin 5	–	M+
Claudin 7	M+	– or focally C +
CEA	+ or –	–
Alpha-1 antitrypsin	–	+

ACC acinar cell carcinoma, *SPN* solid pseudopapillary neoplasm, *M* membranous staining, *N* nuclear staining, *C* cytoplasmic staining

Interpretation of trypsin and alpha-1 antitrypsin may be difficult due to the presence of background staining

Up to 25 % of ACCs may show both nuclear and cytoplasmic staining for beta-catenin

References: [1, 45–52, 54]

Table 25.29 Acinar cell carcinoma vs. ductal adenocarcinoma

Antibodies	ACC	DAC
CK7	– or very focally +	+
Mesothelin	–	+ or –
S100P	–	+
Trypsin	+	–
Glypican-3	+/–	–
Bcl-10	+	–
IMP-3	–	+
Vimentin	+ or –	–
CK19	– or focally +	+ or –
DPC4/SMAD4	+	+ or –

ACC acinar cell carcinoma, *DAC* ductal adenocarcinoma

References: [1, 25–29, 31, 32, 54, 63–65]

Table 25.30 Acinar cell carcinoma vs. pancreatoblastoma

Antibody	ACC	PB
Beta-catenin	M+ or M and N+	M and N+, or M+
E-cadherin	M+	– or M+
CK7	– or focally +	Focally +
Trypsin	+	+

Identification of squamous component/squamous differentiation is the key to making a distinction between these entities. However, the "squamous component" usually lacks the typical squamous phenotype; i.e., positive for CK5/6 and other high molecular weight cytokeratins. Approximately 30 % of ACCs may show nuclear beta-catenin staining and loss of expression of E-cadherin; in contrast, over 90 % of PBs show nuclear and cytoplasmic beta-catenin positivity and loss of expression of membranous E-cadherin

ACC acinar cell carcinoma, *PB* pancreatoblastoma, *M* membranous staining, *N* nuclear staining

References: [1, 53–57]

Table 25.31 Solid pseudopapillary neoplasm vs. pancreatoblastoma

Antibody	SPN	PB
Claudin 5	M+	–
Claudin 7	– or focally C +	M+
PR	+ or –	–
CD10	+	Usually –
Trypsin	–	+
Cytokeratin	– or focally +	+
CK7	–	– or focally +
Beta-catenin	N and M+	N and M+ or M+
E-cadherin	–	– or +
Alpha-1 antitrypsin	+	–

Interpretation of trypsin and alpha-1 antitrypsin may be difficult due to the presence of background staining

Expression of beta-catenin and E-cadherin has a limited value in the distinction between SPN and PB

SPN solid pseudopapillary neoplasm, *PB* pancreatobiliary blastoma, *M* membranous staining, *C* cytoplasmic staining, *N* nuclear staining

References: [1, 45–57]

Table 25.32 Markers for hematopoietic malignancies in the pancreas

Markers	B-cell lymphoma	Myeloid sarcoma	Plasmacytoma/MM	Hodgkin's lymphoma
CD3	–	+ or –	–	–
CD20	+	–	–	–
CD15	–	–	–	+
CD30	– or +	–	–	+
CD38	–	–	+	–
CD138	–	–	+	–
CD117	–	+	–	–
CD34	–	+	–	–
CD43	+ or –	+	–	–
EMA	–	–	+ or –	–

CD43 is a sensitive but not specific marker for myeloid sarcoma (granulocytic sarcoma); CD138 is a sensitive but not specific marker for MM/plasmacytoma; MM is frequently positive for both CD138 and EMA, which may mislead one to call it epithelial neoplasm

References: [1, 91]

MM multiple myeloma

Table 25.33 Metastases in the pancreas

Markers	PDC	Kidney	Lung-A	Melanoma	Stomach	Lung-S	Colon	Breast
CK7	+	–	+	–	+	+ or –	–	+
CK20	–	–	–	–	+ or –	–	+	–
S100	–	–	+ or –	+	–	–	–	– or +
TTF1	–	–	+	–	–	+	–	–
CDX-2	–	–	–	–	+ or –	–	+	–
PAX8	–	+	–	–	–	–	–	–
KIM-1	–	+	–	–	–	–	–	–
CD10	–	+	–	–	–	–	–	–
ER	–	–	–	–	–	–	–	+
GATA3	– or +	–	–	–	–	–	–	+
Synap	–	–	–	–	–	+	–	–
DPC4	– or +	+	+	+	+	+	+	+

PDC pancreatic ductal carcinoma, *Lung-A* lung adenocarcinoma, *Lung-S* lung small cell carcinoma

Mucinous adenocarcinomas of the lung are frequently positive for CDX-2 and negative for TTF1; in addition, a small percentage of lung adenocarcinomas can be positive for ER

S100 is a highly sensitive (98 %) but not specific marker for screening melanoma. Caution should be taken if the sample is fixed in alcohol, since the S100 antigen is not preserved well after alcohol fixation. If melanoma is suspected, then other markers including MART-1 and HMB-45 should be done. If a spindle cell melanoma or desmoplastic melanoma is suspected, SOX10 is another sensitive and specific marker to use.

GATA3 is a recently described marker, which has been reported to be positive in approximately 80 % of urothelial carcinomas and over 90 % of breast carcinomas including 50–60 % of ER-negative breast carcinomas. The expression of GATA3 has also been reported in approximately 80 % of paragangliomas and a significant percentage of salivary gland tumors including 100 % of salivary duct carcinomas and mammary analogue secretory carcinomas. Our unpublished data also showed that approximately 10 % of pancreatic DACs can be positive for GATA3. A small percentage of squamous cell carcinomas may express GATA3. Aberrant expression of GATA3 has been reported in other organs as well.

Some metastatic small cell carcinomas of the lung can be negative for both synaptophysin and chromogranin, but they are very infrequently negative for CD56. Ki-67 proliferative index tends to be very high (>50 %); it would be extremely unusual to have a small cell carcinoma with a low Ki-67 index. The majority (>90 %) of the metastatic colonic adenocarcinomas are positive for both CK20 and CDX-2; however, it should be noted that medullary carcinoma of the colon with MSI frequently shows loss of expression of both CDX-2 and CK20. In this case, the tumor cells would demonstrate loss of expression of either MLH1/PMS2 or MSH2/MSH6.

References: [1–3, 5–8, 58, 70, 92–96, 110]

Table 25.34 Prognostic markers in pancreatic adenocarcinoma

Markers	Literature	Association
DNMT1	Overexpression	Advanced stage
HDAC1	Overexpression	Advanced stage
uPAR	Gene amplification	Poor prognosis
Dkk-3	Low expression	Poor prognosis
MicroRNAs	Overexpression of 155, 203, 210 and 222	Poor prognosis
ALCAM/CD166	Overexpression	Poor prognosis
DPC4/SMAD4	Loss of expression	Poor prognosis
S100A6	Nuclear Positivity	Poor prognosis

DNMT1 DNA methyltransferase 1, *HDAC1* histone deacetylase-1, *uPAR* urokinase type plasminogen activator receptor, *ALCAM* activated leukocyte cell adhesion molecule, *Dkk-3* Dickkopf-related protein 3

References: [1, 97–100]

Table 25.35 Predictive markers for pancreatic neuroendocrine neoplasm

Markers	Literature	Association
CK19 (RCK 108 antibody)	+	Poor prognosis
Ki-67	>5 %	Metastatic disease
67-kD laminin receptors	+	Metastatic disease
CD44 isoforms (v6 and v9)	+	Good prognosis
Topoisomerase II alpha	Overexpression	Malignant
CD99	Loss of expression	Poor prognosis
Survivin	Nuclear +	Poor prognosis

References: [1, 101–107]

Table 25.36 Markers for normal ampulla of Vater

Antibodies	GML Data (N = 20)
CK7	80 % (16/20)
CK20	100 % (20/20)
CK17	0 (0/20)
CK19	100 % (20/20)
MUC1	0 (0/20)
MUC2	100 % (20/20)
pVHL	60 % (12/20)
S100P	50 % (10/20)
Maspin	95 % (19/20)
IMP-3	40 % (8/20), focal
Villin	90 % (18/20)
CDX-2	100 % (20/20)
Hep Par1	85 % (17/20)
CEA	100 % (20/20)
Ber-EP4	100 % (20/20)
MOC-31	100 % (20/20)

The data is from GML based on 20 cases of ampullary biopsy specimens

pVHL, maspin, IMP-3 and S100P are a panel of very useful markers in the distinction of normal pancreatic ducts from pancreatic DAC. The frequent expression these four markers makes them less useful in the diagnosis of ampullary adenocarcinoma

Table 25.37 Markers for ampullary adenocarcinoma—intestinal type

Antibodies	Literature
CK7	– or +
CK20	+
CDX-2	+
Hep Par 1	+
Villin	+
MUC2	+
CK17	–
MUC1	–
MUC5AC	–

References: [2, 8, 33, 108, 109]

Table 25.38 Markers for ampullary adenocarcinoma—pancreatobiliary type

Antibodies	Literature
S100P	+
pVHL	–
CK17	+
CK7	+ or –
CK20	–
CDX-2	–
Hep Par 1	–
MUC2	–
Villin	+ or –
MUC1	+
MUC5AC	+

References: [8, 33, 108, 109]

Table 25.39 Ampullary adenocarcinoma, intestinal type vs. pancreatobiliary type

Antibodies	Pancreatobiliary type	Intestinal type
MUC1	+	–
MUC2	–	+
CK20	–	+
CDX-2	–	+
Hep Par 1	–	+
CK17	+	–
CK7	+ or –	– or +
S100P	+	ND
MUC5AC	+	–
Villin	V	+

References: [2, 8, 33, 92, 109]

Table 25.40 Ampullary adenocarcinoma vs. pancreatic adenocarcinoma

Antibodies	ADCI	ADCP	DAC
CK7	+	+	+
CK20	+	–	– or +
CDX-2	+	–	–
Mesothelin	ND	ND	+
IMP-3	ND	ND	+
Hep Par 1	+	–	–
MUC1	–	+	+
MUC2	+	–	–

ADCI ampullary adenocarcinoma intestinal type, *ADCP* ampullary adenocarcinoma pancreatobiliary type, *DAC* ductal adenocarcinoma

References: [1, 2, 8, 33, 108]

Note for All Tables

Note: "+", usually greater than 70 % of cases are positive; "–", less than 5 % of cases are positive; "+ or –", usually more than 50 % of cases are positive; "– or +", less than 50 % of cases are positive. *ND* no data available, *V* variable.

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