Chapter 20
Uterus

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Abstract This chapter is an overview of frequently used markers in the differential diagnosis of both common and less common tumors of the uterine cervix and corpus, with a focus on the effective markers employed to differentiate adenocarcinoma of the endocervix versus endometrium, low-grade versus high-grade endometrial neoplasms, benign versus malignant mimics of cervical and endometrial lesions. Other useful panels in the differential diagnosis of undifferentiated tumors of the uterine corpus and gestational trophoblastic lesions in addition to the less common carcinomas of the cervix are also addressed. There are 47 tables in this chapter with immunohistochemical markers answering questions that may arise when examining hematoxylin and eosin-stained sections. A summary of useful and frequently used markers with potential pitfalls is also provided. The effective diagnostic panels of antibodies for several entities are highlighted in several tables.

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Note for All Tables: "+" – 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.

Table 20.1 Summary of applications and limitations of useful markers

Antibodies	Staining pattern	Function	Key applications and pitfalls
AFP	C	Glycoprotein present in yolk sac tumors and cases of hepatocellular carcinoma	In differentiating metastatic hepatocellular carcinoma and hepatoid carcinomas from other primary carcinomas of the genital tract
ALK-1	C, N, M	Tyrosine kinase receptor	In differentiating leiomyosarcoma (negative) from inflammatory myofibroblastic tumors (positive)
ARP	N	DNA-binding transcription factor that regulates gene expression	Reactive in mesonephric remnants, ectopic prostate, female adnexal tumor of probable Wolffian origin (FATWO), endometrial adenocarcinoma, mesonephric carcinoma of cervix, and endometrial stromal sarcoma
ARID1A (BAF250)	N	Regulates certain gene transcription by altering the chromatin structure around them	Abnormal expression is frequent in clear cell carcinoma but rare in endometrial serous carcinoma; can be useful in differentiating high-grade endometrioid from serous carcinoma
Bcl2	C	A proto-oncogene, encoding a 25 kDa protein localized to the inner mitochondrial membrane, blocks apoptosis, and extends cell survival	Used to differentiate tubo-endometrial metaplasia and endometriosis of the cervix (diffusely positive) from adenocarcinoma in situ (AIS) (usually negative); diffusely expressed in the gland cell cytoplasm in proliferative endometrium; reduced expression in the glands of both atypical hyperplasia and endometrioid-adenocarcinomas; positive in the basal cell layer of the normal squamous epithelium of the cervix
Ber-EP4	M	Epithelial-specific antigen to a membrane-bound glycoprotein	Useful in distinguishing a serous adenocarcinoma of the ovary or peritoneum and implants in the peritoneum (positive) from mesothelial-derived lesions (negative)
CA 19-9	C	An antigen of sialyl Lewis(a) containing glycoprotein	Used to identify pancreatic, biliary, or colorectal adenocarcinoma metastatic to the genital tract; mucinous neoplasms of the ovary may be focally reactive whereas most primary ovarian adenocarcinomas are negative

Table 20.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
CA-125	C + M	A glycoprotein (mucin-like) antibody to an ovarian carcinoma antigen	Used to distinguish between a primary and a metastatic ovarian adenocarcinoma; expressed in ovarian, breast, lung, cervix, and uterine corpus adenocarcinoma; mesotheliomas and benign mesothelial cells are commonly reactive; primary ovarian mucinous carcinomas and colorectal adenocarcinomas are unreactive
Caldesmon	C	Mediator of the inhibition of Ca^{++} dependent smooth muscle contraction More specific marker of smooth muscle cells	For the differentiation between endometrial stromal neoplasms (negative) and smooth muscle neoplasms (positive); may be expressed in endometrial stromal neoplasms with smooth muscle differentiation; not as sensitive as desmin but more specific
Calretinin	C/N	Calcium-binding protein	More sensitive but less specific marker of ovarian sex cord-stromal tumors; as a part of a panel including Ber-EP4 and PAX8 in distinguishing mesothelioma [Calretinin (positive), Ber-EP4 (negative), PAX8 (negative)], and serous epithelial neoplasms [PAX8 (positive), Ber-EP4 (positive) Calretinin (negative)]; positive in FATWO, adenomatoid tumors, uterine tumor resembling ovarian sex-cord tumors, and in both benign and malignant mesonephric lesions within the cervix and female genital tract
CAM5.2	C	Cytokeratin 8	Usually positive in glandular but not squamous epithelium; Paget's cell mimics in the vulva are (negative)
CD10	C/M	Cell membrane metallopeptidase	Benign and neoplastic endometrial stromal cells; may be expressed in smooth muscle neoplasms and in myometrium surrounding invasive endometrial cancer cells, therefore, its presence will not exclude myometrial invasion; may not be expressed in less differentiated endometrial stromal neoplasms and other tumors
CD34	M	A single chain transmembrane glycoprotein leukocyte differentiation antigen; marker for myeloblasts, lymphoblasts, and fixed connective tissue cells; potential indicator of vascular differentiation	Solitary fibrous tumors (rare); in differentiating endometrial stromal neoplasms (negative) from metastatic reactive mimics (such as metastatic gastrointestinal stromal tumor (GIST), and primary GIST arising in the vulvovaginal region and rectovaginal septum)
CD56	M	Neural cell adhesion molecule (NCAM)	To establish neuroendocrine differentiation in a tumor
CD99	M	MIC2 gene product; cell surface glycoprotein involved in cell adhesion	Part of a panel for the diagnosis of small round blue cell tumor; in the diagnosis of primitive neuroectodermal tumor (PNET) (rare in the female genital system); reactivity in sex cord-like areas in endometrial stromal neoplasms and uterine tumors resembling ovarian sex-cord tumors
CD117 (c-KIT)	C	Trans-membrane tyrosine kinase receptor	Metastatic GIST; primary recto-vaginal septum; uterine leiomyosarcoma; occasionally expressed in uterine carcinosarcoma and ovarian serous carcinomas and germ cell tumors
CD146 (MEL-CAM)	C/N/M	Expressed in implantation site but not chorion-type extravillous (intermediate) trophoblast	Placental site trophoblastic tumor (PSTT) and exaggerated placental site (negative); placental site nodules and epithelioid trophoblastic tumor (negative)
CDX-2	N	A homeobox domain-containing transcription factor involved in the differentiation of the intestines	Marker for colorectal adenocarcinoma and strongest in tumors of colorectal origin; AIS and adenocarcinoma of the cervix as well as ovarian mucinous neoplasms may also be reactive, albeit usually less so
CEA	C + L	A heterogeneous family of related oncofetal glycoproteins secreted in the glycocalyceal surface of gastrointestinal cells	Widely used but may be prone to high background staining; as a component of a panel that may differentiate endometrial (negative) from endocervical (positive) adenocarcinoma; when used as part of a panel, monoclonal CEA may be helpful in distinguishing non-mucinous ovarian adenocarcinomas (usually negative) from colorectal adenocarcinoma (usually positive); a proportion of primary endometrial mucinous adenocarcinomas are positive

(continued)

Table 20.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
Chromogranin	C	Neuroendocrine marker	To establish neuroendocrine differentiation in a tumor; its significance when focally positive is less clear, particularly in undifferentiated endometrial carcinomas
CK5/6	C	Usually reacts with normal, reactive, and neoplastic mesothelial cells	Of limited use in distinguishing mesothelioma from epithelial (serous) tumors
CK7	C	Type 2 filament protein	Simultaneous CK7 and CK20 reactivity in most metastatic neoplasms from the stomach, pancreas, biliary tree, or urinary bladder; CK7 positive and CK20 negative in endometrial and endocervical adenocarcinomas and also in breast and pulmonary adenocarcinoma; many Müllerian carcinomas are CK7 negative
CK20	C	Type 1 filament protein	
CK (AE1/AE3)	C	Helps to confirm the epithelial lineage of a neoplasm	Uterine smooth muscle tumors and endometrial stromal neoplasms may also be weakly reactive; also expressed in the sarcomatous portion of carcinosarcomas; simple confirmation of the presence of an implantation site (trophoblast positive; decidual cells negative); not useful in the evaluation of trophoblastic disease
Desmin	C	Identifies smooth muscle cells	To support either skeletal or smooth muscle origin in spindle cell tumors
DPC4	N + C	Deleted in pancreatic cancer, locus 4	Helpful in differentiating metastatic pancreatic adenocarcinoma to the genital tract (negative) from primary mucinous benign or malignant lesions of the genital tract, primarily ovary (positive)
EMA	M	Glycoprotein in human milk fat globule membranes; helps confirm the epithelial lineage of a neoplasm	Usually negative in stromal and smooth muscle neoplasms that may express CAM5.2 and CK (AE1, AE3); in the differential diagnosis of an epithelial neoplasm (positive) and FATWO (negative); neoplastic and non-neoplastic trophoblastic tissue is also reactive
ER and PR	N	DNA-binding transcription factor that regulates gene expression	May be helpful in distinguishing cervical (negative) from endometrial (positive) carcinomas; often used to determine whether a given tumor might be sensitive to hormonal therapy
HCG	C	Reacts against syncytiotrophoblast but not cytotrophoblast	Used mainly to establish the presence of a trophoblastic neoplasm, particularly if syncytial cells are present, highlights trophoblastic elements in mixed germ cell tumors; may be helpful in confirming aberrant trophoblastic differentiation in poorly differentiated carcinomas
HIK1083	C	Monoclonal antibody against gastric gland cell mucin	Reactive in minimal deviation adenocarcinoma of the cervix; normal endocervical glands are not reactive; focal reactivity is encountered in the usual adenocarcinoma; and benign endocervical glandular lesions
HNF1-β	N	Transcription factor controls endoderm development	Sensitive but not entirely specific for clear cell carcinoma; should be used in a panel with other markers
HLA-G	C/M	Positive in all chorion and implantation-type intermediate trophoblast, and benign and malignant trophoblastic lesions	Used judiciously, primarily in concert with Ki-67 to distinguish early implantation from PSTT
HMB-45	C	Melanosome-associated marker	A marker for malignant melanoma, helpful mainly in classifying poorly differentiated carcinomas of the lower genital tract or metastatic carcinomas; PEComa is characteristically (positive); may also be reactive with clear cell uterine epithelioid leiomyosarcoma
HPL	C	A member of the gene family that includes human growth hormone and prolactin	Stronger and more diffuse expression in implantation site and in placental site trophoblastic tumor but not heavily used relative to inhibin
Inhibin	C	Peptide hormone expressed by granulosa and theca cells	Variably expressed by FATWO, cervical mesonephric adenocarcinoma, uterine tumor resembling ovarian sex-cord tumor, and sex cord-like areas within endometrial stromal neoplasms; also reactive in some trophoblastic cell populations, syncytiotrophoblast, and more mature extravillous trophoblast; choriocarcinoma, PSTT, and ETT; cytotrophoblastic tissue is negative

Table 20.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
Lymphoid (B and T) markers	M	Markers for B and T cells	Used in the diagnosis of the lymphoma or leukemia in the genital tract; CD20 and CD79a may help in the diagnosis of low-grade endometritis; ISH for Kappa and Lambda light chain may assist in the diagnosis of endometritis
Melan-A (MART-1)	C	Melanocytic marker	Used in identifying malignant melanoma; may stain sex cord stromal tumors but not used for this purpose
MIB-1 (Ki-67)	N	Identifies cells in non-G0 phases of the cell cycle	In benign cervical and vulvar squamous epithelium, reactivity confined to basal and parabasal layers; in cervical intraepithelial neoplasia (CIN) and vulvar intraepithelial neoplasia (VIN) reactivity increases in upper layers; helpful in distinguishing atypical atrophy from CIN; may help distinguish AIS from benign mimics but will be elevated in reactive endocervical epithelium; may distinguish exaggerated placental site (nearly absent) from PSTT (elevated and used with HLAG in a double stain) or placental site nodule from ETT
MMR (PMS2, MSH6)	N	Mismatch repair proteins	Abnormal expression is frequent in clear cell carcinoma and rare in serous endometrial carcinomas; endometrioid carcinomas of endometrium can also show MMR defects
MUC2	C + M	High molecular weight glycoprotein	Reactivity in vulvar Paget's disease favors an underlying colorectal adenocarcinoma
MUC5AC	C + M	High molecular weight glycoprotein	Distinguishes primary ovarian carcinoma (positive) from colonic adenocarcinoma (negative); pancreatic and appendiceal tumors are (positive); positive in endocervical glands
myoD1	N	Skeletal muscle marker	To demonstrate rhabdomyoblastic differentiation in carcinosarcomas; in confirming the diagnosis of rhabdomyosarcoma
Myogenin	N	Skeletal muscle marker	To demonstrate the rhabdomyoblastic differentiation in carcinosarcomas; in confirming the diagnosis of rhabdomyosarcoma
OCT4	N	Octamer transcription factor	Predominantly in dysgerminoma, embryonal carcinoma of the ovary, and in the germ cell component of gonadoblastoma
p16	N + C	Binds to cyclin D-CDK4/6 complex to control the cell cycle at G_1-S interphase	Diffuse nuclear and cytoplasmic staining in all high-grade CINs and many low-grade CINs, as well as AIS; used to distinguish neoplastic squamous and glandular lesions of the cervix from benign mimics; used to distinguish cervical (diffuse strongly positive) from endometrial (heterogeneous staining) adenocarcinoma; high-grade endometrioid and serous carcinomas of the endometrium may express diffuse reactivity
p53	N	Mutations cause stabilization of this nuclear protein involved in regulating cell growth, allowing detection by immunohistochemistry	Predominantly in distinguishing serous adenocarcinoma, endometrial intraepithelial carcinoma (EIC), and clear cell carcinoma from benign papillary endometrial proliferations and metaplasias; significant p53 positivity is reported in some endometrioid adenocarcinomas and some serous carcinomas may totally lack reactivity
p57	N	Cell cycle inhibitor of proliferation; expressed only when maternal DNA is present	Absent in the villous cytotrophoblast and villous stromal cells of the complete hydatidiform mole; reactivity present in decidua and extravillous trophoblast (control staining)
p63	N	Transcription factor that belongs to the p53 family	Reactive in immature basal and reserve squamous cells of the cervix; distinguishes small cell non-keratinizing squamous cell carcinoma of the cervix (diffuse positive) from small cell neuro-endocrine carcinoma (negative or focally positive); identifies squamous differentiation in cervical carcinomas
PAX2	N	Member of the paired box (PAX) family of transcription factors	Often negative in endometrial intraepithelial neoplasia (EIN); stains endocervical and benign endometrial epithelium; positive in renal cell carcinoma, medulloblastoma
PAX8	N	Member of the paired box (PAX) family of transcription factors	Expressed in around 80% of all Müllerian carcinomas; also positive in renal, thymic, thyroid, and pancreatic endocrine tumors; gynecologic squamous cell carcinomas are negative; occasional mesotheliomas will be positive

(continued)

Table 20.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
PLAP	C	Heterogeneous group of glycoproteins usually confined to the cell surface	Strongly (positive) in lesions of chorion-type intermediate trophoblast (placental site nodule); only focally positivity in lesions of implantation site intermediate trophoblast; metastatic ovarian dysgerminoma is (positive)
ProExC	N	Immunohistochemical cocktail composed of topoisomerase II α (TOP2A) and minichromosome maintenance protein 2 (MCM2) antibodies	Strong nuclear staining in more than half of epithelial thickness shows high positive predictive value for high-grade squamous intraepithelial lesion (HSIL); increased staining in endocervical carcinoma over endometrial carcinoma
PTEN		Mutation associated with loss of reactivity	Loss of reactivity in most endometrioid adenocarcinomas of the endometrium and their precursors; loss of reactivity is also encountered in normal cyclical and secretory endometrium
S100	N/C	Dimeric protein; Ca^{++} flux regulator; wide distribution in human tissues	Used for the diagnosis of malignant melanoma at all sites of the female genital tract; also expressed in the cartilaginous areas of carcinosarcoma and sex cord stromal tumors of the ovary
SMA	C	Smooth muscle marker	Identifies smooth muscle tumors and smooth muscle differentiation in endometrial stromal sarcoma
Synaptophysin		Neuroendocrine marker	To establish neuroendocrine differentiation in a tumor
Vimentin	C	Intermediate filament expressed in most endometrial carcinomas, normal proliferative endometrial glands, stroma, mesenchymal tissue, and neoplasms	Used in the differential diagnosis of endometrial (positive) and endocervical (negative) adenocarcinomas; to distinguish between tubo-endometrioid metaplasia and endometriosis (usually positive) and AIS (usually negative)
WT1	N	Expressed in smooth muscle tumors, benign and neoplastic endometrial stromal cells, serous carcinomas primarily arising in the ovary, peritoneum, and fallopian tube; uterine serous tumors are primarily negative	Differentiates most endometrioid, clear cell, and mucinous carcinomas (negative) from metastatic or extending ovarian (positive); does not differentiate endometrial stromal sarcomas or endometrial stroma from smooth muscle tumors

Staining pattern: *C* cytoplasmic, *M* membranous, *N* nuclear
References: [1–46]

Table 20.2 Summary of useful markers in common tumors (most commonly used markers are shaded)

Antibodies	SCCx	AdenoCx	AdnoEM	SerEM	CCEM	ESS	LMS
p16	+	+	– or +	+ or –	+ or –	–	+ or –
p53	–	– or +	– or +	+	+ or –	– or +	– or +
p63	+	– or +	– or +	– or +	– or +	–	–
WT1	ND	+ or –	– or +	– or +	–	ND	– or +
CD10	–	–	–	–	–	+	– or +
ER	–	– or +	+	– or +	– or +	+	– or +
Vimentin	–	–	+	+	+	+	+
Desmin	–	–	–	–	–	– or +	+
PAX8	–	–	+	+	ND	–	–
CEA	+ or –	+	– or +	– or +	– or +	–	–
h-Caldesmon	–	–	–	–	–	– or +	+
PR	–	– or +	+	– or +	– or +	+	+ or –
EMA	+	+	+	+	+	–	– or +
CK (AE1/AE3)	+	+	+	+	+	– or +	– or +
CK7	+	+	+	+	+	– or +	– or +
CK20	–	– or +	– or +	–	–	–	–
Calponin	–	–	–	–	–	+ or –	+
SMA	–	–	–	–	–	+ or –	+
S100	–	–	–	–	–	–	– or +
HMB-45	–	–	–	–	–	–	– or +
MART-1	–	–	–	–	–	– or +	–

SCCx cervical squamous cell carcinoma, *AdenoCx* cervical adenocarcinoma, *AdenoEM* endometrial endometrioid adenocarcinoma, *SerEM* endometrial serous carcinoma, *CCEM* endometrial clear cell carcinoma, *ESS* endometrial stromal sarcoma, *LMS* leiomyosarcoma, *ND* no data.
References: [1, 4–8, 11, 16–18, 32]

Table 20.3 Markers for normal and non-neoplastic lesions of the cervix

Marker	CG	CS	MH	MRH	FDG	E
ER	− or +	+ or −	− or +	−	− or +	+ or −
PR	− or +	+ or −	+ or −	−	− or +	+ or −
CEA	+	−	−	−	−	−
Vimentin	−	+ or −	− or +	+ or −	− or +	+ or −
CD10	−	− or + (W)	− or + (W)	+ (A + L)	−	+ (S)
AE1/AE3	+	− or +	+	+	+	+
EMA	+	−	+	+	+	+
CK7	+[a]	−	+[a]	+	+	+
CK20	−	−	− or +	−	−	−
p16	−	−	− (F)	− (F)	−	− or + (F)
PAX2	+	ND	+	+	+	+

CG endocervical glands (crypts), *CS* endocervical stroma, *MH* microglandular hyperplasia, *MRH* mesonephric remnant hyperplasia, *FDG* florid deep glands, *E* endometriosis, *W* weakly positive, *A + L* apical and luminal, *F* may be focally positive, *S* in stromal cells, *ND* no data

[a]CK7 is usually strongest on the surface, in microglandular change and at the squamocolumnar junction, diminishing higher in the endocervix and deeper in the crypts. (Fig. 20.1)

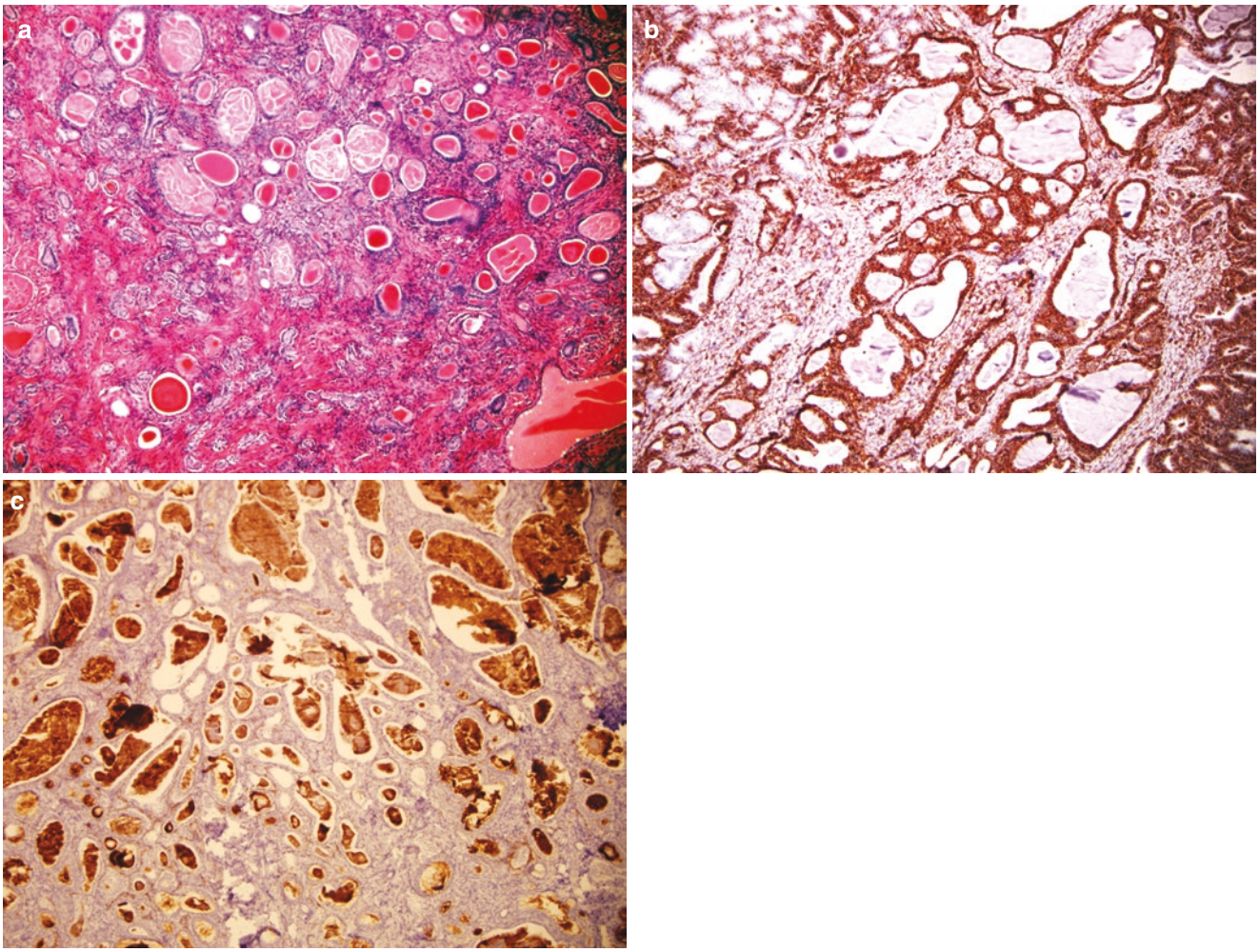

Fig. 20.1 Mesonephric remnant hyperplasia (**a**), with diffuse positive vimentin (**b**), and luminal CD10 positivity (**c**). References: [1, 4–18, 47, 48]

Table 20.4 Markers for normal and non-neoplastic lesions of the endometrium

Marker	EG	ES	SME	PSM	IM	TM	ASR
ER	+ or –	– or +	+ or –	+	+ or –	+ or –	– or +
PR	+ or –	– or +	+ or –	+ or –	+ or –	+ or –	+ or –
CEA	– or +	–	–	–	–	–	–
Vimentin	+	+	– or +	–	–	–	+
CD10	–	+	–	–	–	–	–
AE1/AE3	+	– or +	+	+	+	+	+
EMA	+	–	+	+	+	+	+
CK7	+[a]	–	+	+	– or +	+	+
CK20	–	–	–	–	+	–	–
p16	–	–	– or +	+[d]	–	+ or –[p]	– or +
p53	–	–	–	+ or –[f]	ND	+ or –[f]	–
CDX-2	–	–	–	–	+	–	–

EG endometrial glands, *ES* endometrial stroma, *SME* squamous metaplasia, *PSM* papillary syncytial metaplasia, *IM* intestinal metaplasia, *TM* tubal metaplasia, *ASR* Arias-Stella reaction, [d]diffuse, [f] focal or wild type, [p] patchy

[a]CK7 is strongest toward the surface and usually diminishes deeper in the glands (Fig. 20.2)

Table 20.5 Markers for cervical high-grade squamous intraepithelial lesion

Antibodies	Literature
p16	+[a]
Ki-67	+[b]
ProExC	+
HPV	+[c]
Stathmin-1	+[d]

[a]p16 usually shows strong nuclear and cytoplasmic staining of at least two-thirds and often the full thickness of the involved mucosa. p16 may be positive in both high-grade and low-grade lesions. In the latter, the staining is more commonly limited to the lower two-thirds of the epithelial thickness

[b]Ki-67 usually shows strong nuclear staining of at least two-third thickness of the involved mucosa but usually involves cells on the surface

[c]HPV by in situ hybridization. This is not as sensitive as p16, particularly in immature metaplastic epithelia

[d]Stathmin-1 is normally expressed in the basal layer of the ectocervix. Positivity is identified as expression in at least two-thirds of the epithelial thickness. In this regard, staining of two-thirds thickness is infrequently seen in low-grade dysplasia. Increased staining correlates with the severity of dysplasia (Fig. 20.3)

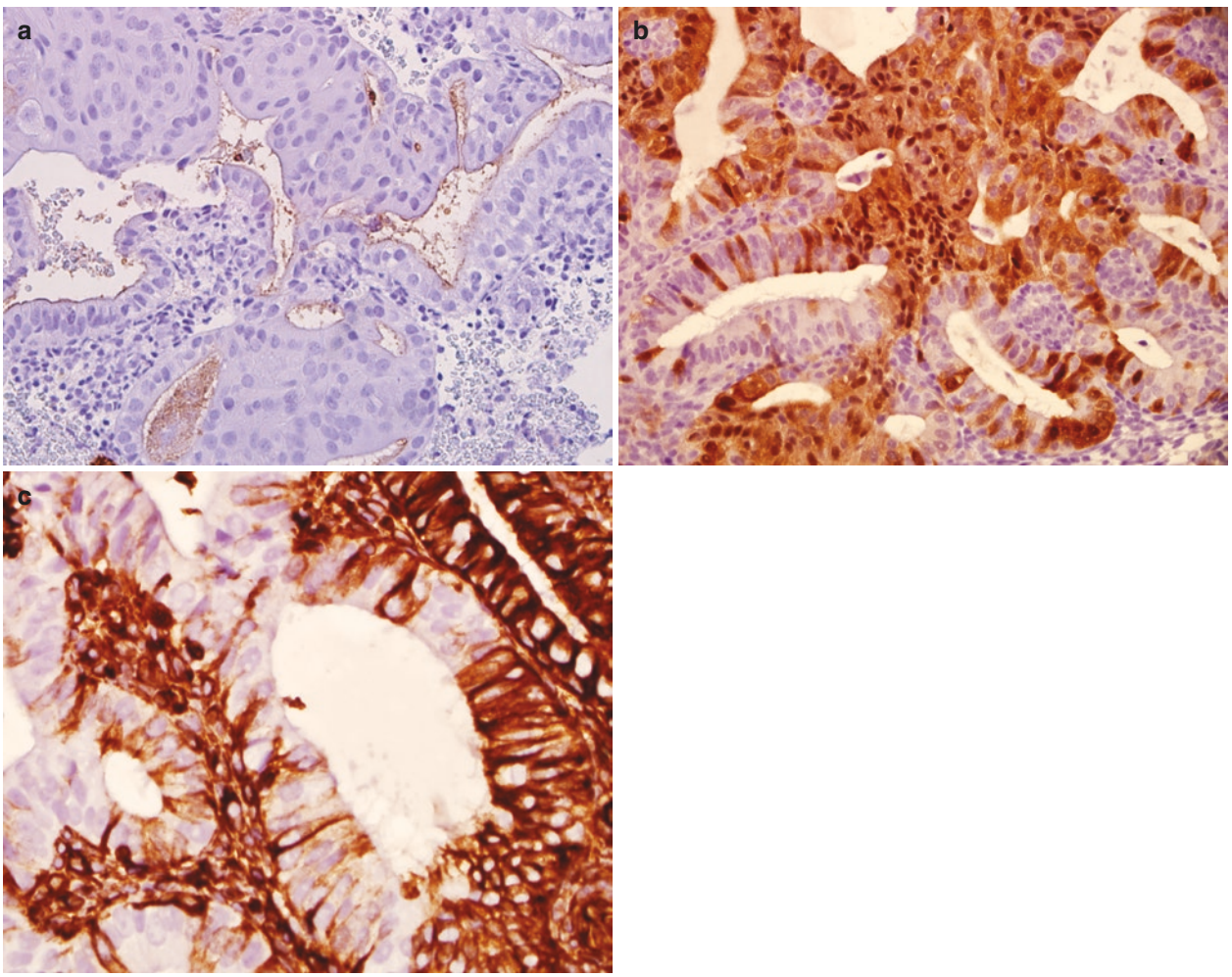

Fig. 20.2 Endometrial squamous metaplasia with lack of CEA staining (**a**), patchy staining pattern with p16 (**b**), and lack of staining with vimentin in the metaplastic foci (**c**). References: [5, 8, 10, 17, 49]

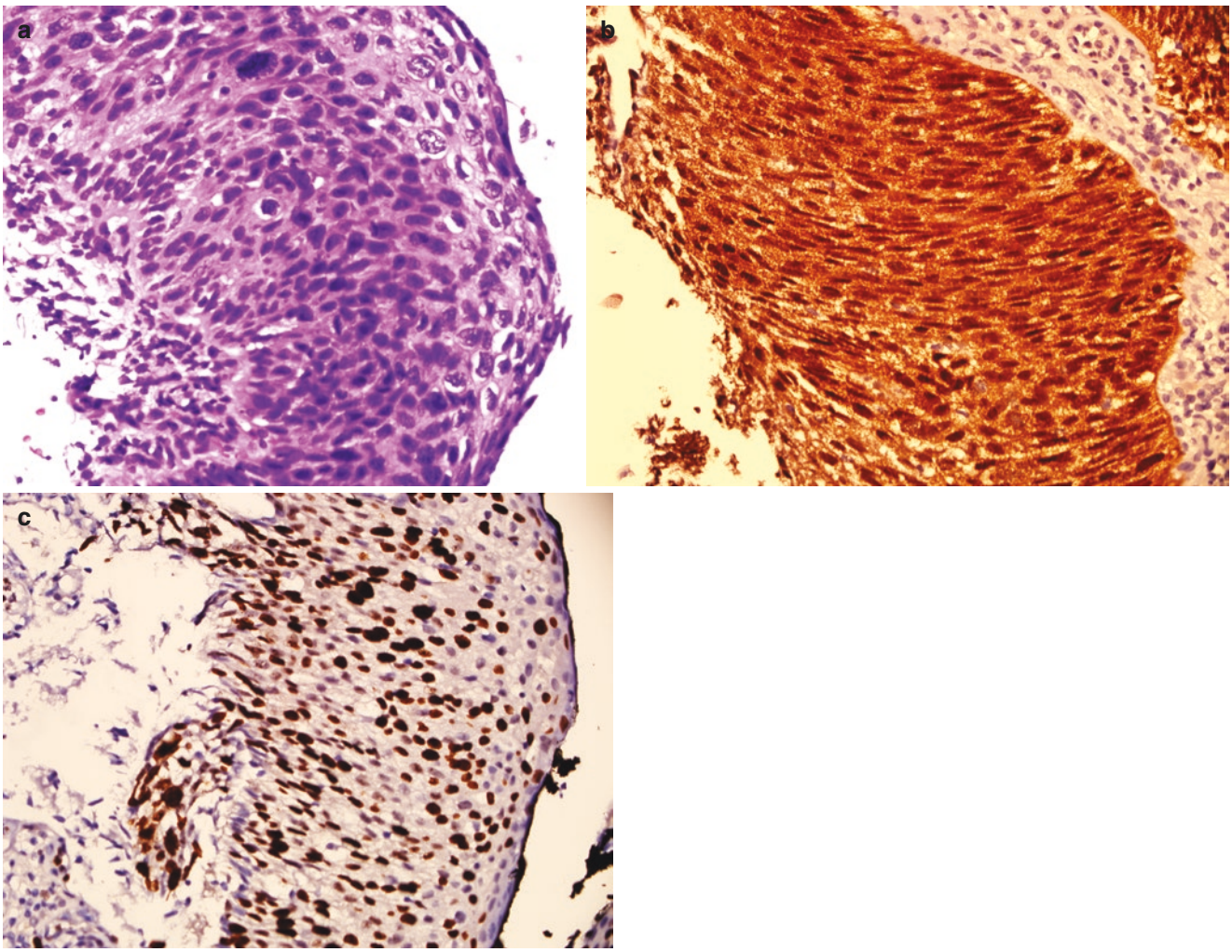

Fig. 20.3 High-grade SIL on hematoxylin and eosin (H&E) (**a**), with full thickness and intense nuclear staining with p16 (**b**), and increased Ki-67 proliferative index involving upper layers (**c**). References: [4–18, 47, 48, 50]

Table 20.6 Markers for in situ endocervical adenocarcinoma

Antibodies	Literature
p16	+[a]
Vimentin (crypts)	–
Ki-67	+[b]
p53	+ or –
ProExC	+ or –
Bcl2	– or +
CEA-M	+
CEA-P	+
PAX8	+
CA-125	–[c]
ER (glands)	– or +
PR (glands)	– or +
ER (stromal cells)	+[d]
α-SMA (stromal cells)	+
CD10 (stroma)	–
CDX-2	– or +
HPV	+
PAX2	–
IMP-3	+

Table 20.6 (continued)

[a]p16 positivity is usually strong and diffuse in in situ adenocarcinoma. Focal reactivity is encountered in normal cervix, lower grade glandular intra-epithelial lesions, tubo-endometrioid metaplasia, and other reactive and malignant conditions. Diffuse, intense staining may be encountered in high-grade endometrial adenocarcinomas

[b]High Ki-67 proliferative index is also encountered in inflammation, proliferative endometrium, and other conditions and should be used in concert with p16. p53 staining is optional but may be valuable if the differential diagnosis includes a high-grade endometrial carcinoma. Vimentin, ER, and PR are less commonly used but should be negative in endocervical carcinomas

[c]In in situ adenocarcinoma CA-125 is absent or localized to the perinuclear region of the cytoplasm as an accumulation of atypical coarse granules. CA-125 is encountered in the secretory products of the uninvolved endocervical glands on the luminal surfaces

[d]The stromal cells surrounding crypts/glands are estrogen receptor (ER) positive and alpha-smooth muscle actin negative in in situ adenocarcinoma. The stromal cells associated with invasive adenocarcinoma show an opposite pattern (Fig. 20.4)

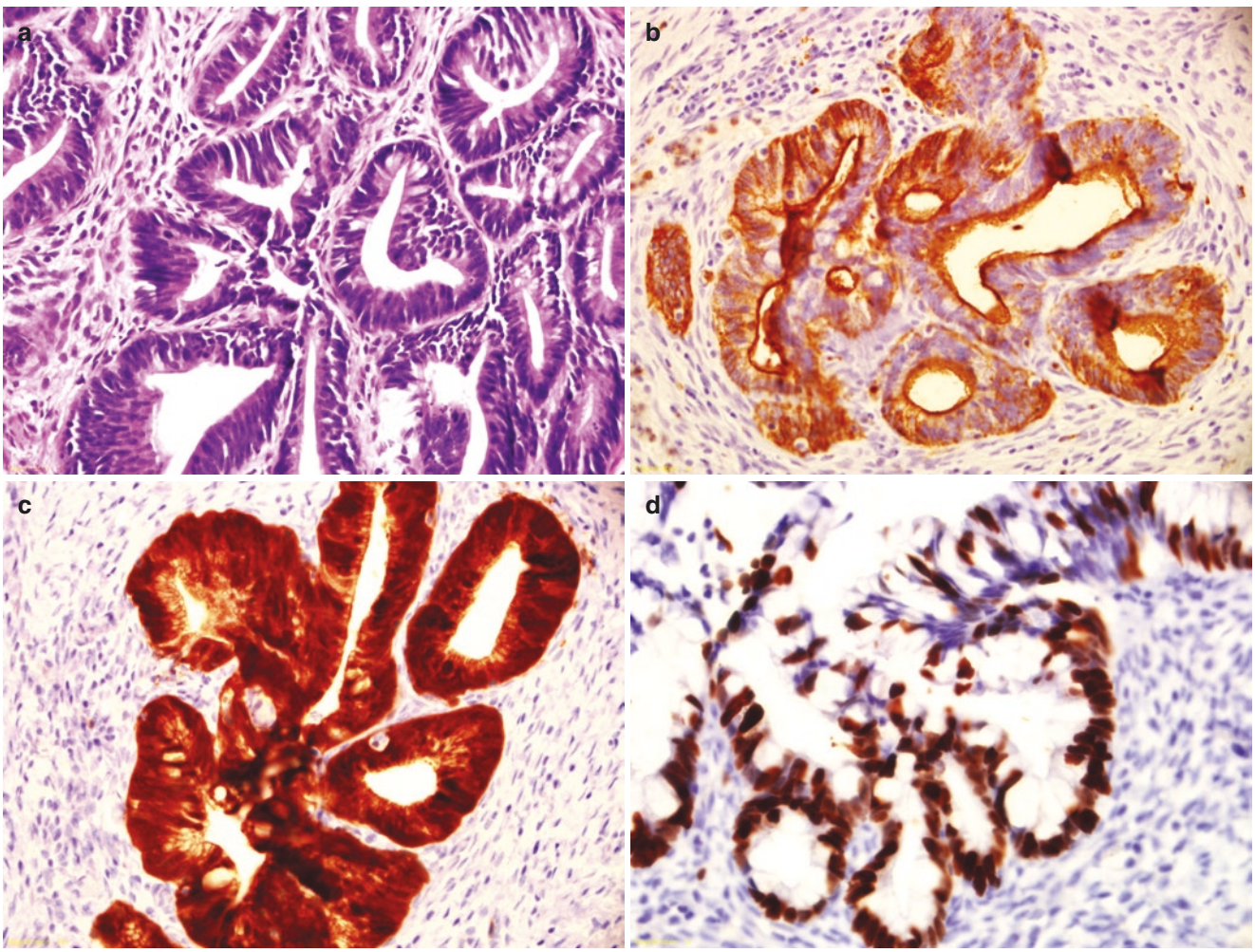

Fig. 20.4 Adenocarcinoma in situ of the endocervix on H&E (**a**), with CEA positive staining (**b**), diffuse and intense p16 nuclear and cytoplasmic staining (**c**), and increased Ki-67 proliferative index (**d**). References: [4–18, 51]

Table 20.7 Markers for invasive squamous cell carcinoma of the cervix

Antibodies	Literature
p63	+
p16	+
CK (AE1, AE3)	+
CK5/6	+
CK7	+
Bcl-2	+ or –
p53	+ or –
GATA3	– or +
CEA-P	– or +
Bcl2	– or +
PAX8	–

Additional negative markers include CD56, synaptophysin, chromogranin, napsin-A, TTF1, and HepPar1. p16 and p63 are useful in confirming a squamous and cervical origin

References: [4, 6, 7]

Table 20.8 Markers for invasive endocervical (mucinous) and endometrioid adenocarcinoma of cervix

Antibodies	Literature
CK7	+
p16[a]	+
CEA-M	+
CEA-P	+
PAX8	+
CK (AE1, AE3)	+
EMA	+
HepPar1	+
ProExC	+ or –
WT1	+ or –
CA-125	+ or –
p53	+ or –
p63	– or +
MUC2	– or +
MUC6	– or +
CDX-2	– or +
Vimentin	– or +
PAX2	–

Additional negative markers include CK20, CD10, TTF1, and PSA

[a]p16 will be diffusely positive in the endometrioid cervical carcinomas but less so in mucinous tumors and negative in HPV negative minimal deviation adenocarcinoma. CK7 and CK20 occasionally are useful for excluding metastatic colonic tumors. HPV in situ hybridization is occasionally helpful but not routinely necessary (Fig. 20.5)

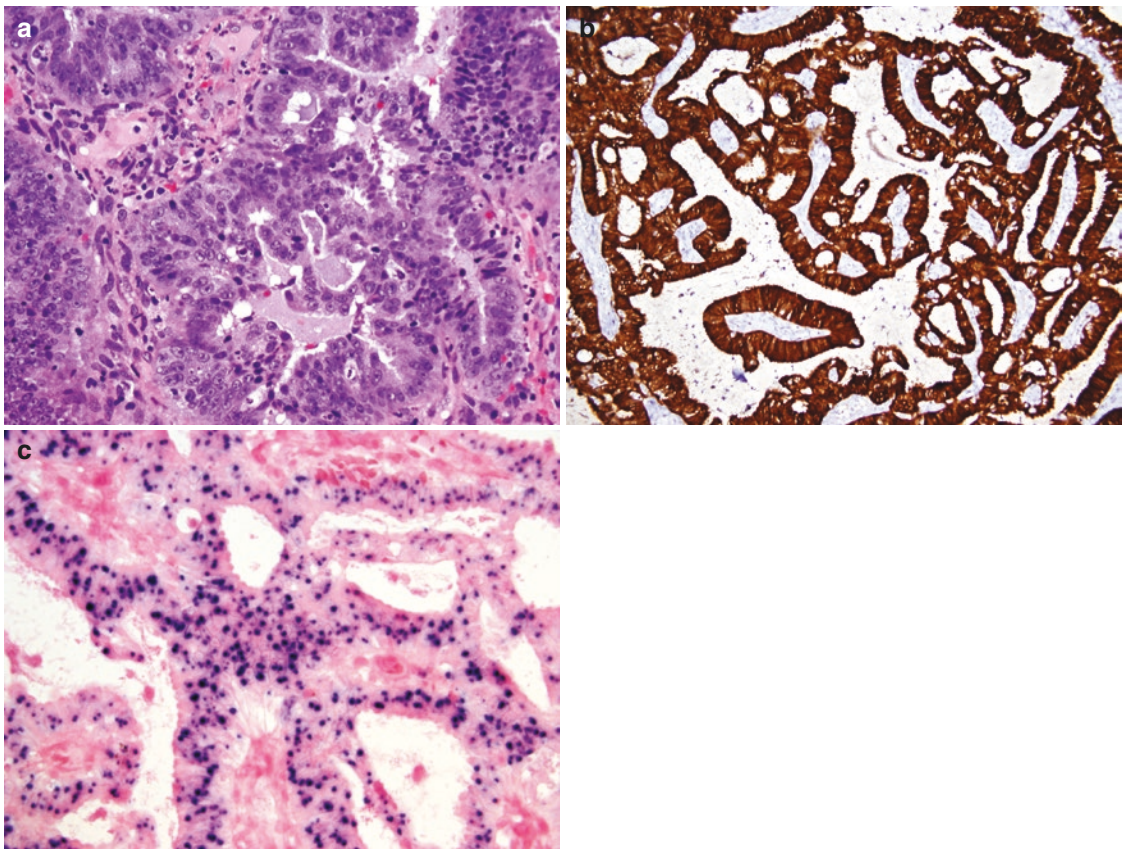

Fig. 20.5 Invasive endocervical adenocarcinoma on H&E (**a**), with p16 diffuse and intense positive staining (**b**) and positive inclusions by in situ hybridization for HPV (**c**). References: [4–18, 52]

Table 20.9 Markers for in situ and invasive gastric-type endocervical adenocarcinoma

Antibodies	Literature
CA 19-9	+
HNF-1β	+
Cytokeratin 7	+
Cytokeratin 20	+ or −
CDX-2	+ or −
CEA	+
CA-125	+
PAX2	−
PAX8	+ or −
ER	− or +
PR	− or +
MUC6	+
CAIX	+
p16	− or +
p53	− or + [a]
Her-2	−
MMR	+[b]

MMR mismatch repair stains

[a]Majority of p53 staining is wild-type pattern with fewer showing an increased mutated p53 pattern

[b]Mismatch repair proteins are retained and stain positive

References: [53–55]

Table 20.10 Markers for in situ and invasive intestinal-type endocervical adenocarcinoma

Antibodies	Literature
CK (AE1, AE3)	+
CK 7	+
CK20	−
CDX-2	+
EMA	+
CEA-M	+
CEA-P	+
p16	+[a]
pRB	+
MUC1	+
MUC5AC	+
WT1	+ or −
CA-125	+ or −
CA 19-9	− or +
MUC6	− or +
p53	− or +

[a]p16 will be diffusely positive in the endometrioid cervical carcinomas but less so in mucinous tumors and negative in HPV negative minimal deviation adenocarcinoma. CK7 and CK20 occasionally are useful for excluding metastatic colonic tumors. HPV in situ hybridization is occasionally helpful but not routinely necessary

References: [4–18, 52]

Table 20.11 Markers for minimal deviation adenocarcinoma of the cervix

Antibodies	Literature
HIK1083	+[a]
PAX2	–
p16	− or +[b]
CEA	− or +[c]
p53	− or +[d]
Ki-67	− or +
ER	−[a]
PR	−[a]
HPV	–
CD10	–

[a]Mucinous variant

[b]Positive in around 30% of mucinous variants

[c]Focal to diffusely positive in mucinous and endometrioid variants

[d]Negative or focally positive in the mucinous variant

References [1, 5, 56–61]

Table 20.12 Markers for small cell poorly differentiated carcinomas of the uterine cervix

Marker	NEC	SCNKSCC	BC	PNET	Melanoma	ERMS
Chromogranin-A	+ or −	−	−	−	−	−
Synaptophysin	+ or −	−	−	− or +	− or +	−
NSE	+	− or +	− or +	+ or −	+ or −	− or +
p63	− or +	+	+	− or +	−	
Desmin	−	−	−	−	−	+
Actin-HHF-35	−	−	−	−	−	+
SMA	−	−	−	−	− or +	− or +
BerEp4/Ep-CAM	+	+ or −	+	ND	−	−
EMA/MUC1	+	+	+ or −	− or +	−	− or +
p16	+ or −	+ or −	+	− or +	+ or −	− or +
CK7	+	−	+	− or +	−	−
CK20	− or +	−	−	−	−	−
PLAP	− or +	−	−	−	−	+
Vimentin	− or +	+ or −	− or +	+	+	+
S100	− or +	−	+ or −	− or +	+	−
HMB-45	−	−	−	− or +	+	−
MART-1	ND	−	−	−	+	−
CD99	− or +	− or +	+ or −	+	+ or −	− or +
TTF1	− or +	−	−	−	−	−

NEC neuroendocrine carcinoma, *SCNKSCC* small cell non-keratinizing squamous cell carcinoma, *BC* basaloid carcinoma, *PNET* primitive neuroectodermal tumor, *ERMS* embryonal

References: [1, 62–66]

Table 20.13 Markers for mesonephric adenocarcinoma of cervix

Antibodies	Literature
Calretinin (nuclear)	+ or −
Vimentin	+ or −
p16	− or +[a]
PAX8	+
CAM5.2	+
CK(AE1/AE3)	+
CK7	+
EMA	+
HNF-1β	+
CD10	+ or −[b]
ARP	− or +
Inhibin	− or +
ER	−
PR	−
CEA-M	−
CK20	−
CA-125	+

[a]Apical

[b]Patchy (Fig. 20.6)

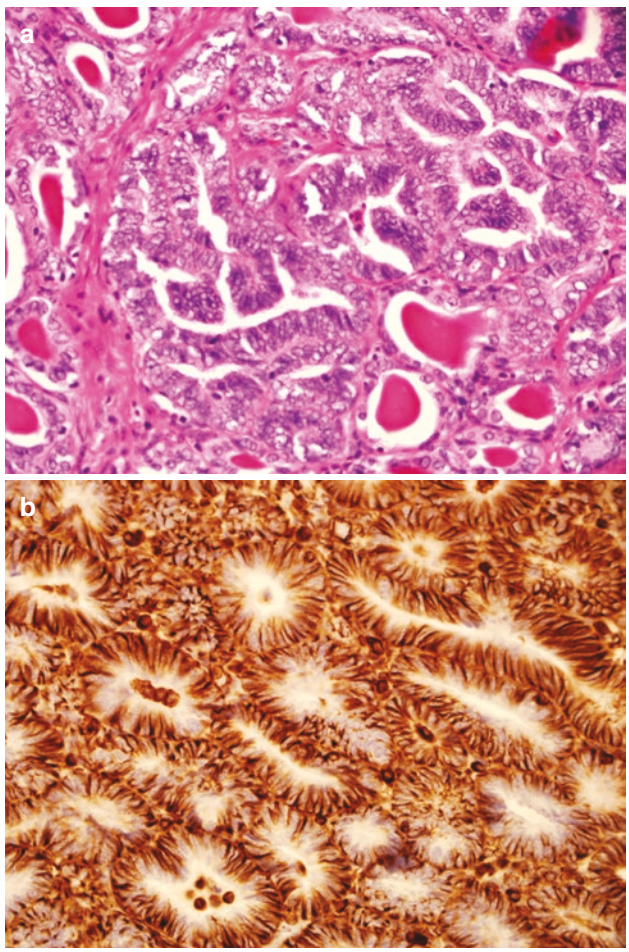

Fig. 20.6 Mesonephric carcinoma on H&E (**a**) and positive vimentin (**b**). References: [67–70]

Table 20.14 Markers for endometrioid adenocarcinoma of the endometrium

Antibodies	Literature
CK7	+
CAM5.2	+[a]
Ber-EP4	+
CK (AE1, AE3)	+[a]
EMA	+[a]
CA-125	+
ER	+
PR	+
Vimentin	+
PAX8	+
Cyclin D1	+
CK 5/6	+ or −
Beta-catenin	− or +
Mesothelin	+ or −
p53	− or +[b]
WT1	− or +[c]
PTEN	− or +
CD56	− or +
Bcl2	− or +
CDX-2	− or +
Calretinin	− or +
TTF1	− or +
CEA-P	− or +
CEA-M	− or +
MUC5AC	− or +
p63	− or +[d]
TAG72	− or +
IMP-3	− or +
CDX-2	− or +
p16	−[e]

Additional negative markers include CK20, HepPar1, HNF-1β, GCDFP-15, MUC-2, PAX2, and PAP. Napsin-A is usually (but not always) negative except in secretory carcinoma

Intact staining with MLH1/PMS2/MSH2/MSH6 in more than 95% of the cases

[a]Usually focal in undifferentiated components

[b]Weak reactivity with p53 in less than 50% of tumor cells is common in low-grade endometrioid adenocarcinoma but may be diffuse in higher grade tumors

[c]Variable

[d]Positive in the squamous areas

[e]Usually patchy but may be diffuse nuclear and cytoplasmic in high-grade tumors. p16 is usually positive in areas with squamous differentiation (Fig. 20.7)

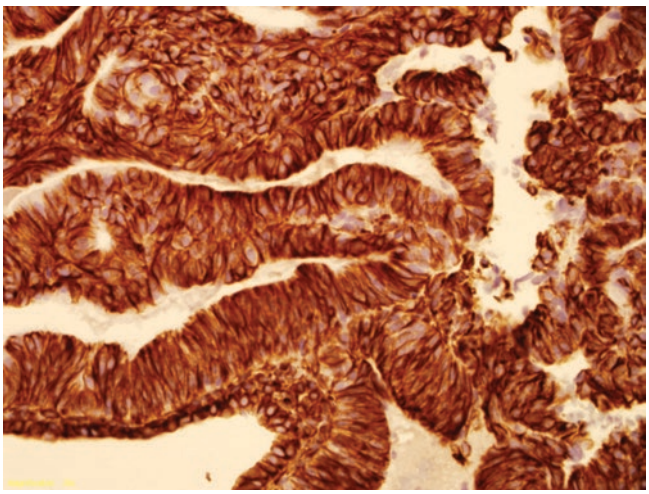

Fig. 20.7 Intense vimentin staining in endometrioid adenocarcinoma. References: [1, 34, 61, 71–80]

Table 20.15 Markers for benign hyperplasia and endometrioid intraepithelial neoplasia

Marker	Benign hyperplasia	EIN[a]
PTEN	+ or −	−
PAX2	+ or −	−

[a]Endometrioid intraepithelial neoplasia (Fig. 20.8)

References: [43, 81–83]

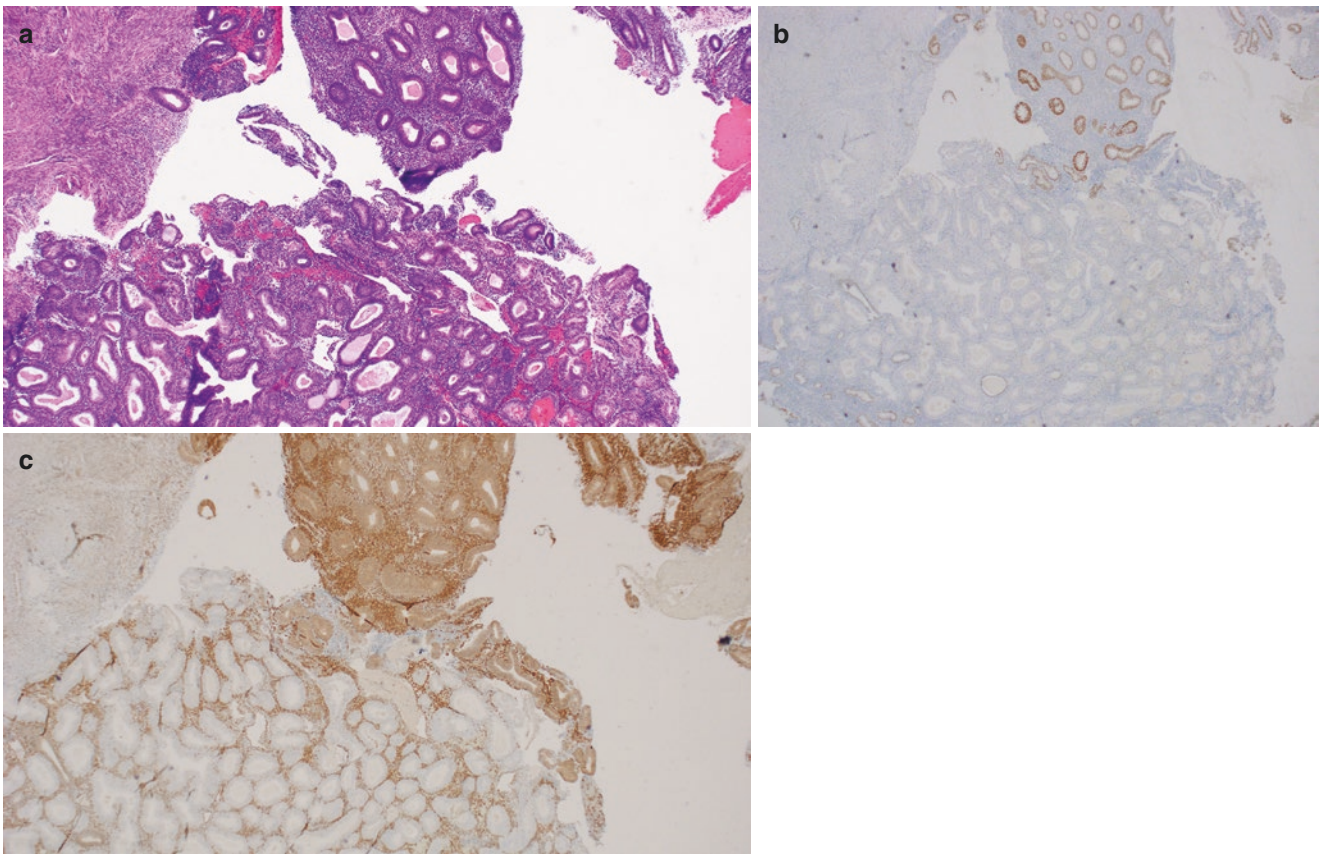

Fig. 20.8 Endometrioid intraepithelial neoplasia (EIN) present in the lower half of the image on H&E (**a**), with absent PAX2 expression (**b**), and with absent PTEN expression (**c**)

Table 20.16 Markers for serous carcinoma of the endometrium and putative precursors EIC

Antibodies	Literature
IMP-3[a]	+
p53[a]	+[b]
p16[a]	+ or –[c]
Pan-CK	+
EMA	+
Ber-EP4	+
CK7	+
CA-125	+
Vimentin	+
Ki-67	+[d]
PAX8	+
IMP2	+
ARID1A	+
WT1	– or +
CEA-M	– or +
ER	– or +
PR	– or +
Bcl2	– or +
Her-2/neu	– or +
D2-40	– or +
HNF-1β	– or +
Her-2/neu	– or +
Beta-catenin	–
CK20	–
Loss of PTEN	Almost never
Loss of MLH1	Almost never
Loss of MSH2	Almost never
Loss of MSH6	Almost never
Loss of PMS2	Almost never

[a]Some publications recommend diffuse p16 staining as the most useful. IMP-3 and p53 are also helpful. However, high-grade endometrioid carcinomas can stain for all three. WT1 should be weak or negative in endometrial versus upper genital trace serous carcinomas, but not consistently

[b]Intense nuclear staining in over 90% of tumor cells (p53-null tumors show total absence of reactivity in tumor cells)

[c]Diffuse and intense staining including nuclear staining is encountered in almost every cell

[d]Very high proliferative index exceeding 75%

References: [1, 33, 38, 78–80, 84–91]

Table 20.17 Markers for uterine serous papillary carcinoma and ovarian serous papillary carcinoma

Marker	USPC	OSPC
WT1	– or + [a]	+
IMP-3	+	+
p53	+ or –	+
p16	+	+
ER	– or +	+

USPC uterine serous papillary carcinoma, *OSPC* ovarian serous papillary carcinoma

[a]While WT1 often shows some degree of positivity, it is often not strongly, diffusely positive

References: [44, 79, 91–95]

Table 20.18 Markers for clear cell carcinoma of the endometrium

Antibodies	Literature
HNF-1	+
ER	– or +
PR	– or +
Pan-CK	+
EMA	+
Ber-EP4	+
CK7	+
Vimentin	+
p16	– or +
Napsin	+ or –
WT1	– or +
p53	– or +[a]
CK20	–
CEA	– or +
Cyclin D1	– or +[b]
E-cadherin	–
Loss of MSH6	Rare
Loss of PMS2	Rare

[a]Focal and weak

[b]Negative or weakly positive

References: [1, 19–25, 31, 72, 96–98]

Table 20.19 Markers for carcinosarcoma of the endometrium[a–c]

Antibodies	Literature
CK (AE1, AE3)	+[d]
p16	+[e]
p53	+[e]
E- and P-Cadherin	+[f]

[a]Myogenin and MyoD1 are also used to establish a rhabdomyoblastic differentiation

[b]Vimentin, ER, and PR are usually positive in endometrioid and negative in the serous carcinoma components

[c]The sarcomatous component may also express CD10, CD34, vimentin, and desmin

[d]Most commonly, an epithelial marker (CK) is used to confirm that a spindle cell component is or is not epithelial in origin

[e]Usually positive in both carcinoma and sarcoma components

[f]Indicative of epithelial-mesenchymal transition when expressed in the carcinomatous component

References: [1, 72, 99]

Table 20.20 Markers for atypical polypoid adenomyoma (most commonly used shaded)

Antibodies	Literature
SMA[a]	+[b]
Desmin[a]	+ or –[b]
CD34[a]	+ or –
CK (AE1, AE3)[c]	+
CAM5.2[c]	+
ER[c]	+
PR[c]	+

[a]In mesenchymal component
[b]Desmin or SMA might be helpful in distinguishing tumor stromal response from smooth muscle. This distinction is usually made on histologic evaluation
[c]In epithelial component
References: [100, 101]

Table 20.21 Markers for stromal nodule and low-grade endometrial stromal sarcoma[a,b]

Antibodies	Literature
CD10	+
SMA	+ or –
Desmin	– or +
h-Caldesmon	– or +
ER	+
PR	+
Vimentin	+
WT1	+
ARP	+ or –
Calponin	+ or –
Beta-catenin	+ or –
CK (AE1, AE3)	– or +
CAM5.2	– or +
Pan-CK	– or +
Actin-HHF35	– or +

Additional negative markers include CD117, EMA, inhibin, CD34, and HMB-45
[a]The metaplastic elements lose the endometrial stromal immunophenotype and acquire the corresponding metaplastic tissue immunophenotype. Usually CD10 positive and negative for smooth muscle markers, but not always (as in stromomyomas)
[b]The above table reflects predominantly the low-grade variant of endometrial stromal component. The immunohistochemical profile of high-grade uterine sarcomas (undifferentiated sarcoma) is not defined. For the workup of an undifferentiated neoplasm, it is recommended to exclude melanoma, carcinoma, lymphoma, and leukemia before rendering the diagnosis of undifferentiated uterine sarcoma
References: [102–107]

Table 20.22 Markers for high-grade endometrial stromal sarcoma[a,b]

Antibodies	Literature
Cyclin D1	+[a]
CD117[n]	+
CD10	– or +[b]
ER	–
PR	–
DOG1	–

Cyclin D1 positive/CD10 negative tumors can be analyzed further for the YWHAE-FAM22A/B gene fusion by FISH
[a]Diffusely and strongly positive
[b]Focal, weak, or negative
[c]No KIT mutations
References: [1, 108, 109]

Table 20.23 Markers for undifferentiated uterine sarcoma[a]

Antibodies	Uniform variant	Pleomorphic variant
CD10	+ or –	+ or –
Cyclin D1	–	+
ER	+	–
PR	+	–
Beta-catenin	+	–
p53	ND	+

[a]This is usually a diagnosis of exclusion. Pleomorphic variant can be cyclin D1 positive but histologically not compatible with high-grade ESS. Other tumors such as undifferentiated leiomyosarcoma, carcinosarcoma, and adenosarcoma with stromal overgrowth must be excluded
References: [102, 108, 109]

Table 20.24 Markers for low-grade Müllerian adenosarcoma[a] (stromal component)

Antibodies	Literature
Vimentin	+
WT1	+
CD10	+[b]
ER	+[b]
PR	+[b]
CK (AE1, AE3)	+ or –
SMA	+ or –
ARP	+ or –
CD34	– or +

[a]The diagnosis of adenosarcoma is based principally on growth pattern
[b]Areas with sarcomatous overgrowth (Müllerian adenosarcoma with sarcomatous overgrowth, MASO) are frequently negative for CD10, ER, and PR
References: [99, 110, 111]

Table 20.25 Markers for uterine smooth muscle tumors

Antibodies	Leiomyoma	Leiomyosarcoma
Desmin	+	+ or –
SMA	+	+
h-Caldesmon	+	+
Cyclin D1	+	+
p53	– or +	– or +
HMB-45	– or +	– or +
Calponin	+	+
Actin-HHF35	+	+
Vimentin	+	+
ER	+ or –	– or +
PR	+ or –	– or +
NSE	+ or –	+ or –
P16 INK4a	– or +	+ or –
Bcl2	– or +	– or +
HLA-DR	– or +	– or +
MITF	– or +	– or +
CD10	– or +	– or +
CD30	– or +	– or +
CD34	– or +	– or +
CD57	– or +	+ or –
CD68	– or +	– or +
CD99	– or +	– or +
MDM-2	– or +	– or +
CAM5.2	– or +	– or +
E-Cadherin	– or +	– or +
AE1	– or +	– or +
CK (AE1, AE3)	– or +	– or +
Pan-CK	– or +	– or +
EMA	– or +	– or +
CDK4	– or +	– or +
DOG1	–	–
CD34	–	–

Additional negative markers include: S100, ALK-1, p63, calretinin, beta-catenin (nuclear), CD31, CD117, CD163, tyrosinase, myogenin, inhibin, myoglobulin, MART1, GFAP, NFP, Factor VIIIR AG, CK19, and HepPar1

Desmin, SMA, and caldesmon are the staples for confirming a smooth muscle tumor. HMB-45 and cyclin D1 can be used if needed for excluding PEComa and high-grade ESS, respectively

References: [112–128]

Table 20.26 Markers for adenomatoid tumor

Antibodies	Literature
Calretinin	+
D2-40	+
WT1	+
ER	+[a]
PR	+[a]
CK (AE1, AE3)	+[b]
CK7	+[b]
CK18/19	+
EMA	+
CAM 5.2	+
HBME-1	+
Vimentin	+ or –
Ber-EP4	– or +
CK 5/6	– or +
PAX8	–

Additional negative markers include CEA-P, CEA-M, TAG72, CD15, CD31, CD34, Factor VIII, thrombomodulin, MOC-31, POU5F1, and h-caldesmon

[a]Usually positive in fallopian tube and negative in uterine tumors

[b]Staining is perinuclear and cytoplasmic

References: [129–131]

Table 20.27 Markers for PEComas

Antibodies	Literature
HMB-45	+
MelanA	+ or –
MiTF	+ or –
CD1a	+ or –
S100	–
Inhibin	–
CK (AE1, AE3)	–
Desmin	+ or –
SMA	+ or –
Calponin	+
Vimentin	+
FVIIIRAG	+
Cathepsin K	+
h-Caldesmon	+ or –
Desmin	+ or –
S100	– or +
NSE	– or +
CD117	– or +
CD34	– or +
PR	– or +
ER	– or +
CD68	– or +
Tyrosinase	– or +
CD10	– or +
TFE3	– or +

Additional negative markers include CD57, CAM 5.2, CEA-P, EMA, GFAP, HepPar-1, NFP, chromogranin, and synaptophysin

References: [132–137]

Table 20.28 Markers for uterine tumor resembling ovarian sex cord tumor

Antibodies	Literature
Calretinin	+
CD99	+
WT1	+
CK (AE1, AE3)	+ or –
Inhibin	– or +
EMA	– or +
SMA	– or +
Desmin	– or +
CD10	+ or –
CD117	– or +

References: [138–140]

Table 20.29 Markers for gestational trophoblastic lesions

Marker	PSN	PSTT	ETT	CC
β-HCG	+ or –	– or +	– or +	+
HLA-G	+	+	–	+
p63	+	– or +	+	+ or –
Ki-67 index	≤10%	15–25%	10–25%	>50–75%
CK (AE1, AE3)	+	+	+	+
CK18	+	+	+	+
EMA	+	+	+	+ or –
HPL	+ or –	+	– or +	+
Inhibin	+	+	+	+
p16	–	–	–	– or +
CD146	+ or –	+	– or +	+
PLAP	+	– or +	+	– or +
E-cadherin	+		+	
CD68	–	–	–	–
CEA-P	+	+	+	– or +
Vimentin	+	+ or –	–	–
CD10	+	+	+	+

PSN placental site nodule, *PSTT* placental site trophoblastic tumor, *ETT* epithelioid trophoblastic tumor, *CC* choriocarcinoma

References: [141–151]

Table 20.30 Differentiating high-grade SIL from benign mimics and low-grade SIL

Marker	HGSIL	AR	RC	AT	ISM	TM	LGSIL
P16	+[a]	–	–	–	–	–	+ or –[b]
Ki-67	+[a]	– or +[b]	– or +[b]	– or +[b]	– or +[b]	– or +[b]	+[b]
HPV[c]	+	–	–	–	–	–	+

HGSIL high-grade squamous intraepithelial lesion, *AR* atypical repair, *RC* radiation change, *AT* atrophy, *ISM* immature squamous metaplasia, *TM* transitional metaplasia, *LGSIL* low-grade squamous intraepithelial lesion

[a]Diffuse, strong nuclear staining involving the superficial two-thirds of the involved mucosa

[b]Only the basal layer is involved

[c]By in situ hybridization

References: [4–18, 47, 48]

Table 20.31 Differentiating in situ adenocarcinoma of cervix and endometriosis or tubal-endometrial metaplasia

Antibodies	In situ Adenocarcinoma	Endometriosis
CEA-P	+	–
PAX2	–	+
p16	+[a]	+ or –[b]
Ki-67	+ or –	– or +
ER	– or +	+
PR	– or +	+
CD10	– or +	– or +
Vimentin	– or +	–
Chromogranin-A	– or +	–
Ep-CAM/Ber-EP4	+	+
CK7	+	+
CK20	– or +	–
p53	– or +	–

[a]Strong, diffuse

[b]Mostly patchy

References: [4–18]

Table 20.32 Differential diagnosis of cervical microglandular hyperplasia

Antibodies	MICROGH	MDA (M)	MDA (E)	ADENOCX	ENDOMCA
MIB-1	< 1%	ND	ND	High	High
PAX2	+[a]	–	–	–[b]	–[b]
p16	–	– or +	ND	+[c]	– or +[d]
CEA	+[e]	+[f]	+[f]	+ or –[f]	– or +
p63	+[g]	–	–	–	–
p53	–	– or +	– or +	–	– or +[h]
Vimentin	– or +	–	ND	+	+
ER	+	–	ND	–	+
PR	+	–	ND	–	+
CA-125	+[e]	–	ND	+	+ or –
Chromogranin	–	+ or –	ND	–	–[i]
HIK 1083	– or +	+	–	– or +	–
HPV (IS)	–	–	–	+	–
CD10[J]	– or + (w–m)	ND	ND	–	+ (s)
CD34[J]	+	ND	ND	–	– or + (w)

MICROGH endocervical microglandular hyperplasia, MDA (M) mucinous variant of minimal deviation adenocarcinoma, MDA (E) endometrioid variant of minimal deviation adenocarcinoma, ADENOCX endocervical adenocarcinoma (in situ and invasive), ENDOMCA endometrioid adenocarcinoma, ND no data, w weak, m moderate, s strong, IS by in situ hybridization

[a]May be positive (patchy)

[b]PAX2 is predominantly positive in high-grade tumors

[c]Strong, diffuse

[d]Patchy and focal, but may be diffuse in high-grade tumors

[e]Luminal, may be cytoplasmic in squamous metaplasia

[f]Cytoplasmic

[g]In reserve cells

[h]Diffuse, strong reactivity in high-grade tumors, but wild-type pattern in low-grade tumors. May also be completely negative (p53 null)

[i]Except in cases with neuroendocrine differentiation

[j]Stromal cells

References: [1, 4–18, 52, 56–61]

Table 20.33 Endocervical versus low-grade endometrial adenocarcinoma[a]

Antibodies	Cervix	Endometrium
CEA	+	–
Vimentin	–	+
p16	+	– or +
ER	– or +	+
IMP-3	+	– or +
MUC5AC	– or +	+
PR	– or +	+
HPV DNA	+	–
ProExC	+	– or +[b]

[a]Low-grade endometrial adenocarcinoma is usually bland in appearance and a comparable low-grade endocervical adenocarcinoma might also be HPV and p16 negative. Vimentin is among the more reliable

[b]ProExC has shown some positivity for serous endometrial carcinomas but is primarily negative for low-grade endometrioid endometrial carcinoma

References: [4–18, 45]

Table 20.34 Differentiating epithelioid trophoblastic tumor and cervical squamous cell carcinoma

Antibodies	Epithelioid trophoblasti tumor	Squamous cell carcinoma
Inhibin	+	–
HLA-G	+	–
HPL	+	–
CD146	+	–
p63	+	+
PLAP	+ or –	– or +
CK (AE1/AE3)	+	+
EMA	+	+
AFP	–	–
Ki-67	+	+
CEA-P	+	– or +
GATA-3	+	–

References: [4, 6, 7, 141–152]

Table 20.35 Differentiating adenoid cystic (ACC), adenoid basal (ABC), basaloid squamous cell (BSCC), and small cell neuroendocrine (SCNEC) carcinomas[a]

Antibodies	ACC	ABC	BSCC	SCNEC[a]
p63	–	+[b]	+	–
S100	–	– or +	–	– or +
EMA	+[c]	+	+	+ or –
CEA-M	+[c]	+	–	– or +
p16	+[d]	+[d]	+	+ or –
p53	– or +	+[d]	+ or –	+ or –
PAX8	ND	ND	–	–
TTF1	–	–	–	– or +
HPV	– or +	+	+	+

ACC adenoid cystic carcinoma, *ABC* adenoid basal carcinoma, BSCC basaloid squamous cell carcinoma, *SCNEC* small cell neuroendocrine carcinoma

[a]The only practical distinguishing markers are neuroendocrine markers to separate SCNEC. Other types are very rare and separated on histologic grounds

[b]In the peripheral cells of basaloid tumor and in dysplastic cells

[c]In glandular lumen

[d]Diffusely positive

References: [62, 153–155]

Table 20.36 Arias-Stella reaction and clear cell carcinoma of endometrium[a]

Antibodies	Arias-Stella reaction	Clear cell carcinoma
MIB-1	+ in less than 5% nuclei	+ in more than 5% nuclei
p53	+ in less than 25% nuclei	+ in more than 25% nuclei

[a]Distinction could be very difficult in a postmenopausal woman. Neither p53 nor MIB-1 will likely distinguish them all

References: [156, 157]

Table 20.37 Endometrial adenocarcinoma and carcinosarcoma (MMMT)[a]

Antibodies	Adenocarcinoma	Carcinosarcoma
CD10	–	+ Usually M + C
CK (AE1, AE3)	+	+
CA-125	+	–
Calretinin	–	– or +
CAM5.2	+ C	+ C
CEA-P	– or +	–
CK5/6	+ or –	–
CK7	+	+ or –
CK20	–	–
EMA	+	+
HepPar1	–	–
Inhibin	–	–
PLAP	– or +	– or +
S100	+	–
Thrombomodulin	–	–

M membranous, *C* cytoplasmic

[a]Based primarily on CK staining and perhaps a reticulin stain

References: [72, 78, 99, 116]

Table 20.38 Clear cell carcinoma (CCC) versus malignant mimics with clear cytoplasm [glycogen-rich squamous cell carcinoma (GRSCC), clear cell sarcoma (CCS), metastatic renal cell carcinoma (MCCRCC), and yolk sac tumor (YST)]

Marker	CCC	GRSCC	CCS	MCCRCC	YST
PAX8	+ or –	–	ND	+	–
CK7	+	+	–	–	–
SALL4	–	–	–	–	+
BerEp4	+	+	–	–	ND
Vimentin	+	–	+	+	–
Desmin	–	–	–	–	–
Melan-A	–	–	+	+ or –	–
HMB-45	–	–	+	– or +	–
S100	– or +	–	+	+	–
p16	+ or –	+	+ or –	ND	ND
ER	– or +	–	– or +	–	–
PR	– or +	–	– or +	–	–
CEA-P	– or +	+	–	–	– or +
p53	+ or –	–	– or +	–	
AFP	–	–	–	–	+
Glypican-3	–	–	–	–	+
CD10	–	–	– or +	+	–
RCCMa	–	–	–	+	–

References: [19–26, 156, 158]

Table 20.39 Endometrial serous versus endometrioid versus clear cell adenocarcinoma

Antibodies	Serous	Endometrioid	Clear cell
Beta-catenin (N)	–	+ or –	–[a]
HNF-1β[b]	– or +	– or +	+
ER	– or +	+	– or +
PR	– or +	+	– or +
p16	+	– or +	– or +
IMP-3	+	– or +	+ or –
ARID1A	+ or –	+ or –	+ or –
PTEN	+	–	+[a]
PMS2	+	– or +	ND
MSH6	+	– or +	ND
Napsin A	– or +	–	+
p53	+[c]	– or +[d]	– or +[d]
PAX8	+	+	+
Vimentin	+	+	+
CK7	+	+	+
TTF1	– or +	– or +	ND
WT1	–	– or +	–
CEA-M	– or +	– or +	– or +
Cyclin D1	–	–	–[e]

[a]Insufficient data point to the lack of abnormalities

[b]Also expressed in secretory and gestational endometrium

[c]Strong, diffuse, exceeding 75% of tumor cells or may be completely negative (p53 null)

[d]Weak, focal, or wild type

[e]May be minimally or focally expressed

References: [38, 72, 79, 80, 84–86, 97, 159]

Table 20.40 Useful markers in the differential diagnosis of endometrial undifferentiated carcinoma (UC)

Antibodies	UC	EAC	SERC	US	EPS	NE	LYM
CAM 5.2	+ or –[a]	+	+	–	+	+ or –	–
CK (AE1/AE3)	– or +[a]	+	+	–	+	+	–
EMA	+ or –[a]	+	+	–	+	+	–
MMR	– or +	+ or –	+	ND	ND	ND	ND
ER	– or +	+	– or +	V	ND	ND	–
PR	– or +	+	– or +	V	ND	ND	–
Desmin	–	–	–	– or +[a]	– or +	–	–
MSA	–	–	–	–	– or +	–	–
CD138	–	ND	ND	ND	– or +	– or +	– or +
CD56	– or +[ab]	–	–	–	– or +	+	+
SYNAP	– or +[ab]	–	–	–	ND	+ or –	–
CHROM	– or +[ab]	–	–	–	ND	+ or –	–
NSE	– or +[ab]	–	–	–	– or +	+ or –	–
LYMARK	–	–	–	–	–	–	+

EAC high-grade endometrioid adenocarcinoma, *SERC* high-grade serous carcinoma, *US* undifferentiated sarcoma, *EPS* epithelioid sarcoma, *NE* neuroendocrine carcinoma, *LYM* lymphoma, *MMR* mismatch repair proteins MSH6 and PMS2, *SYNAP* synaptophysin, *CHROM* chromogranin, *LYMARK* lymphoma markers, *V* negative in pleomorphic variant and positive in uniform variant, *ND* no data

[a]Focal

[b]In less than 10% of tumor cells

References: [26–31, 72]

Table 20.41 Differentiating leiomyosarcoma and endometrial stromal sarcoma (ESS)

Antibodies	Leiomyosarcoma	ESS
Actin-HHF-35	+	– or +
Bcl2	– or +	+
CD10	– or +	+
EGFR	– or +	+
Beta-catenin (N[a])	–	+ or –
SMMHC[b]	+	+ or –
CK (AE1, AE3)	– or +	– or +
Vimentin	+	+
Desmin	+	– or +
h-Caldesmon	+	–
SMA	+	+ or –
Calponin	+	+ or –
Cyclin D1	+	– or +
ER	– or +	+
PR	– or +	+
CD99	– or +	–
WT1	– or +	+
p53	– or +	– or +
Pan-CK	– or +	– or +
EMA	– or +	–
CAM5.2	– or +	– or +
Calretinin	–	– or +
S100	– or +	–
HMB-45	– or +	–
ALK-1	– or +	–
CD117	–	– or +
CD34	– or +	–
p63	– or +	–

Additional *negative* markers for both tumors include myoglobin, HepPar1, DOG1, inhibin, and CD163

[a]*N* Nuclear

[b]*SMMHC* Smooth muscle myosin heavy chain

References: [102–112, 121–126, 160, 161]

Table 20.42 Differentiating leiomyosarcoma and PEComa

Antibodies	Leiomyosarcoma	PEComa
MelanA 103	–	+
FVIIIRAg	–	+
CD31	–	+
HMB-45	– or +	+
S100	–	– or +
Vimentin	+	+
Desmin	+	+ or –
SMA	+	+
Calponin	+	+
CD117	–	– or +
MITF	– or +	+
CD34	– or +	– or +
CD57	+	–
CD99	– or +	–
ER	– or +	– or +
PR	– or +	– or +
Tyrosinase	–	– or +
Pan-CK	– or +	–
ALK-1	– or +	–
CD68	– or +	– or +
EMA	– or +	–
CK (AE1, AE3)	– or +	–
CAM5.2	– or +	–
Ber-EP4	–	–
HepPar1	–	–

References: [1, 112, 115, 123–126, 132, 134–136]

Table 20.43 Differentiating leiomyosarcoma (LMS), gastrointestinal stromal tumor (GIST), inflammatory myofibroblastic tumor (IMT), and spindle cell rhabdomyosarcoma (RHABDO)

Antibodies	LMS	GIST	IMT	RHAB
SMA	+	– or +	+	– or +
Desmin	+	– or +	– or +[a]	+
MyoD1	– or +	ND	–	+
Myogenin	–	ND	ND	+
Myoglobin	–	ND	ND	+ or –
DOG1	–	+	–	–
ALK-1	–	–	+ or –[b]	– or +
CD34	– or +	+	–	– or +
CD117	+	+	–	– or +

[a]Frequently focal
[b]Patchy, granular cytoplasmic
References: [2, 3, 5, 16, 116, 120, 121, 125]

Table 20.44 Complete hydatidiform and partial hydatidiform mole

Antibodies	Complete mole	Partial mole
p57 (N)	– or +	+

N nuclear
References: [141–143]

Table 20.45 Epithelioid trophoblastic tumor and poorly differentiated endometrial adenocarcinoma

Antibodies	Epithelioid trophoblastic tumor	Poorly differentiated Endometrial adenocarcinoma
Inhibin	+	–
HLA-G	+	–
E-cadherin	+	– or +
CEA-P	+	– or +
CD146	+	–
p63	+	– or +
Vimentin	–	+
EMA	+	+
CK (AE1, AE3)	+	+
PLAP	+ or –	– or +
CD68	–	–
S100	–	+ or –
ER	+ or –	+ or –
EGFR	+	+ or –

References: [1, 145–149]

Table 20.46 Differentiating placental site trophoblastic tumor and mimics [exaggerated placental site, epithelioid trophoblastic tumor, choriocarcinoma, epithelioid smooth muscle tumor, metastatic carcinoma, and malignant melanoma]

Marker	PSTT	EPS	ETT	CC	ESMT	MC	MM
HLA-G	+	+	+	+	–	–	–
CK (AE1/AE3)	+	+	+	+	+	+	–
p63	–	+ or –	+	+ or –	–	+ or –	–
Beta-HCG	– or +	– or +	– or +	+	–	–	–
Ki-67	+ >10%	< 10%	+ or –	+++	+ or –	+	+ or –
S100	–	–	–	–	+ or –	–	+
HPL	+	+	– or +	+	–	–	–
CD146	+	+	– or +	+	–	–	–
CK18	+	+	+	+	– or +	+ or –	–
EMA	+	+	+	+	–	+	–
Inhibin	+	+	+	+	–	–	– or +
HMB-45	–	–	–	–	+ or –	–	+

PSTT placental site trophoblastic tumor, *EPS* exaggerated placental site, *ETT* epithelioid trophoblastic tumor, *CC* choriocarcinoma, *ESMT* epithelioid smooth muscle tumor, *MC* metastatic carcinoma, *MM* malignant melanoma (Fig. 20.9)

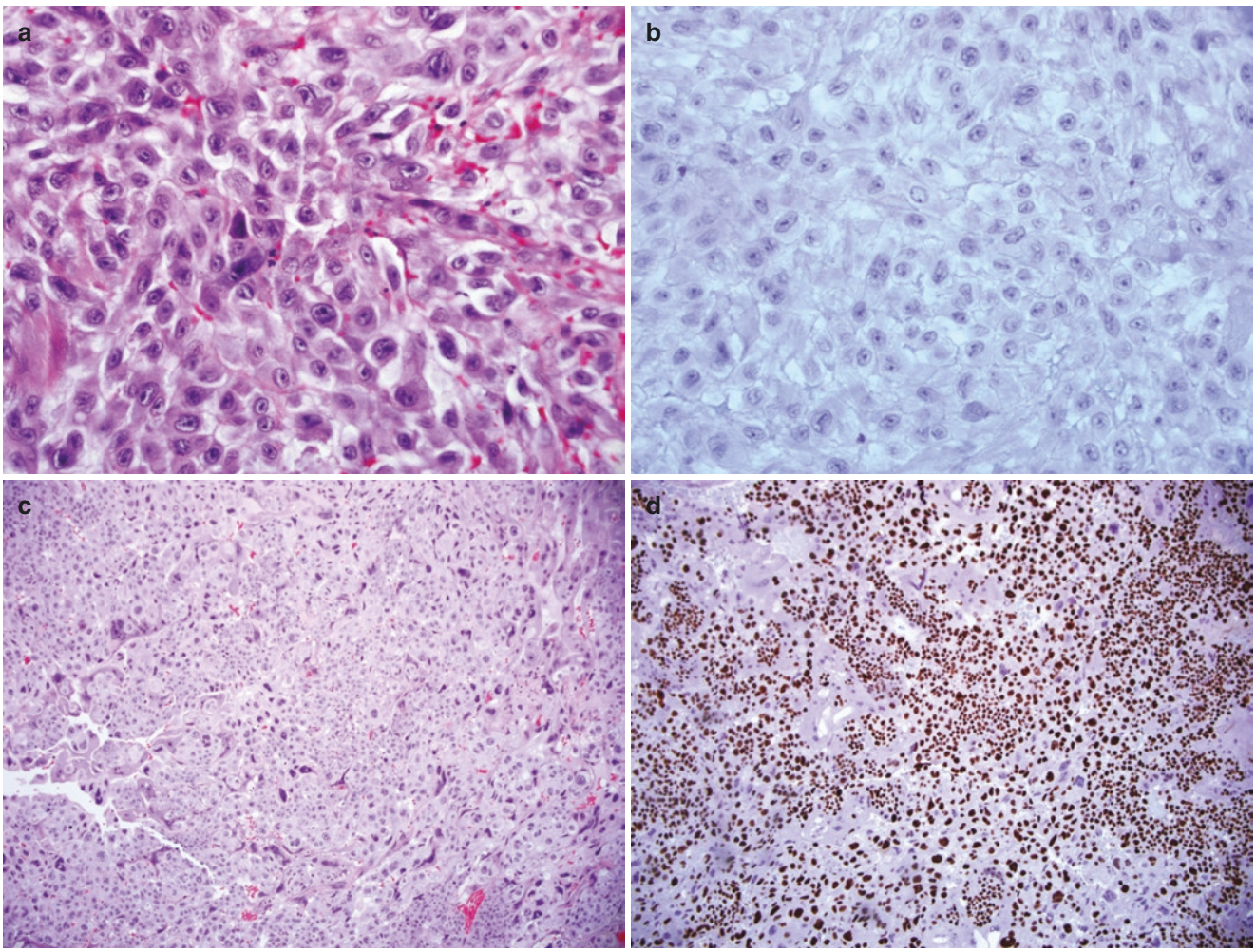

Fig. 20.9 Exaggerated placental site on H&E (**a**) with negative Ki-67 (**b**) compared to choriocarcinoma on H&E (**c**) that demonstrates extremely very high Ki-67 proliferative index (**d**). References: [141–151]

Table 20.47 Summary of common markers of primary uterine carcinoma and the more common metastatic *carcinomas* (recommended markers highlighted)

Marker	Cervix	Uterus	Ovary	Stomach	Breast	Colon	Kidney	Lung	Bladder
CK7	+	+	+	+	+	–	–	+	+
CK20	–	–	–	– or +	–	+	–	+	+ or –
p63	+ or –	–	–	–	–	–	–	–	+
TTF1	–	+ or –	+ or –	–	–	–	–	+	–
CDX-2	– or +	–	–	+ or –	–	+	–	–	–
ER	–	+	+	–	+	–	–	–	–
RCCMa	–	–	–	–	–	–	+	–	–
Vimentin	–	+ or –	–	–	–	–	+	–	–
PAX8	+	+	+	–	–	–	+	–	–
GATA3	– or +[a]	–	–	–	+ or –[b]	–	–	–	+[c]
CD10	–	–	–	–	–	–	+	–	–
CK5/6	+ or –	–	–	–	–	–	–	–	+
CK903	–	–	–	–	–	–	–	–	+

[a]Positive cases are reported in squamous cell carcinoma of cervix
[b]Negative cases are reported in triple negative and metaplastic carcinoma of the breast
[c]Negative cases are reported in adenocarcinoma, squamous cell, clear cell, and signet cell carcinoma of the bladder
References: [1, 16, 18, 19]

References

1. Rabban JT, Longacre TA. Immunohistology of the female genital tract. In: Dabbs DJ, editor. Diagnostic immunohistochemistry – theranostic and genomic applications. Philadelphia, PA: Elsevier Saunders; 2014. p. 653–709.
2. Fuehrer NE, Keeney GL, Ketterling RP, Knudson RA, Bell DA. ALK-1 protein expression and ALK gene rearrangements aid in the diagnosis of inflammatory myofibroblastic tumors of the female genital tract. Arch Pathol Lab Med. 2012;136(6):623–6.
3. Rabban JT, Zaloudek CJ, Shekitka KM, Tavassoli FA. Inflammatory myofibroblastic tumor of the uterus: a clinicopathologic study of 6 cases emphasizing distinction from aggressive mesenchymal tumors. Am J Surg Pathol. 2005;29(10):1348–55.
4. Rose PG, Cibas ES, Rose PG, Peters WA III. Cervical squamous neoplasia. In: Crum CP, Nucci MR, Lee KR, editors. Diagnostic gynecologic and obstetric pathology. Elsevier Saunders: Philadelphia, PA; 2011. p. 245–327.
5. McCluggage WG. Immunohistochemical and functional biomarkers of value in female genital tract lesions. Int J Gynecol Pathol. 2006;25(2):101–20.
6. O'Neill CJ, McCluggage WG. p16 expression in the female genital tract and its value in diagnosis. Adv Anat Pathol. 2006;13(1):8–15.
7. Herfs M, Yamamoto Y, Laury A, Wang X, Nucci MR, McLaughlin-Drubin ME, et al. A discrete population of squamocolumnar junction cells implicated in the pathogenesis of cervical cancer. Proc Natl Acad Sci U S A. 2012;109(26):10516–21.
8. Pinto AP, Schlecht NF, Woo TY, Crum CP, Cibas ES. Biomarker (ProEx C, p16(INK4A), and MiB-1) distinction of high-grade squamous intraepithelial lesion from its mimics. Mod Pathol. 2008;21(9):1067–74.
9. Kong CS, Balzer BL, Troxell ML, Patterson BK, Longacre TA. p16INK4A immunohistochemistry is superior to HPV in situ hybridization for the detection of high-risk HPV in atypical squamous metaplasia. Am J Surg Pathol. 2007;31(1):33–43.
10. Herfs M, Parra-Herran C, Howitt BE, Laury AR, Nucci MR, Feldman S, et al. Cervical squamocolumnar junction-specific markers define distinct, clinically relevant subsets of low-grade squamous intraepithelial lesions. Am J Surg Pathol. 2013;37(9):1311–8.
11. Herfs M, Crum CP. Laboratory management of cervical intraepithelial neoplasia: proposing a new paradigm. Adv Anat Pathol. 2013;20(2):86–94.
12. Singer G, Kurman RJ, McMaster MT, Shih IM. HLA-G immunoreactivity is specific for intermediate trophoblast in gestational trophoblastic disease and can serve as a useful marker in differential diagnosis. Am J Surg Pathol. 2002;26(7):914–20.
13. Ou-Yang RJ, Hui P, Yang XJ, Zynger DL. Expression of glypican 3 in placental site trophoblastic tumor. Diagn Pathol. 2010;5:64.
14. Kindelberger DW, Krane J, Lee KR. Glandular neoplasia of the cervix. In: Crum CP, Nucci MR, Lee KR, editors. Diagnostic gynecologic and obstetric pathology. Philadelphia, PA: Elsevier Saunders; 2011. p. 328–78.
15. Negri G, Egarter-Vigl E, Kasal A, Romano F, Haitel A, Mian C. p16INK4a is a useful marker for the diagnosis of adenocarcinoma of the cervix uteri and its precursors: an immunohistochemical study with immunocytochemical correlations. Am J Surg Pathol. 2003;27(2):187–93.
16. McCluggage WG. Immunohistochemistry as a diagnostic aid in cervical pathology. Pathology. 2007;39(1):97–111.
17. Kong CS, Beck AH, Longacre TA. A panel of 3 markers including p16, ProExC, or HPV ISH is optimal for distinguishing between primary endometrial and endocervical adenocarcinomas. Am J Surg Pathol. 2010;34(7):915–26.
18. McCluggage WG. Ten problematical issues identified by pathology review for multidisciplinary gynaecological oncology meetings. J Clin Pathol. 2012;65(4):293–301.
19. DeLair D, Soslow R, Gilks B, Macias A, Oliva E. The morphologi spectrum of immunohistochemically characterized clear cell carcinoma of the ovary: a study of 83 cases [USCAP abstract 961]. Mod Pathol. 2009;89:211A-A.
20. Fadare O, Liang SX. Diagnostic utility of hepatocyte nuclear factor 1-beta immunoreactivity in endometrial carcinomas: lack of specificity for endometrial clear cell carcinoma. Appl Immunohistochem Mol Morphol. 2012;20(6):580–7.
21. Tsuchiya A, Sakamoto M, Yasuda J, Chuma M, Ohta T, Ohki M, et al. Expression profiling in ovarian clear cell carcinoma: identification of hepatocyte nuclear factor-1 beta as a molecular marker and a possible molecular target for therapy of ovarian clear cell carcinoma. Am J Pathol. 2003;163(6):2503–12.
22. Kato N, Sasou S, Motoyama T. Expression of hepatocyte nuclear factor-1beta (HNF-1beta) in clear cell tumors and endometriosis of the ovary. Mod Pathol. 2006;19(1):83–9.
23. Yamamoto S, Tsuda H, Aida S, Shimazaki H, Tamai S, Matsubara O. Immunohistochemical detection of hepatocyte nuclear factor 1beta in ovarian and endometrial clear-cell adenocarcinomas and nonneoplastic endometrium. Hum Pathol. 2007;38(7):1074–80.
24. Kobel M, Kalloger SE, Carrick J, Huntsman D, Asad H, Oliva E, et al. A limited panel of immunomarkers can reliably distinguish between clear cell and high-grade serous carcinoma of the ovary. Am J Surg Pathol. 2009;33(1):14–21.
25. Hoang LN, Han G, McConechy M, Lau S, Chow C, Gilks CB, et al. Immunohistochemical characterization of prototypical endometrial clear cell carcinoma–diagnostic utility of HNF-1beta and oestrogen receptor. Histopathology. 2014;64(4):585–96.
26. McConechy MK, Ding J, Cheang MC, Wiegand K, Senz J, Tone A, et al. Use of mutation profiles to refine the classification of endometrial carcinomas. J Pathol. 2012;228(1):20–30.
27. Al-Loh S, Al-Hussaini M. Undifferentiated endometrial carcinoma: a diagnosis frequently overlooked. Arch Pathol Lab Med. 2013;137(3):438–42.
28. Altrabulsi B, Malpica A, Deavers MT, Bodurka DC, Broaddus R, Silva EG. Undifferentiated carcinoma of the endometrium. Am J Surg Pathol. 2005;29(10):1316–21.
29. Silva EG, Deavers MT, Malpica A. Undifferentiated carcinoma of the endometrium: a review. Pathology. 2007;39(1):134–8.
30. Silva EG, Deavers MT, Bodurka DC, Malpica A. Association of low-grade endometrioid carcinoma of the uterus and ovary with undifferentiated carcinoma: a new type of dedifferentiated carcinoma? Int J Gynecol Pathol. 2006;25(1):52–8.
31. Soslow RA. Endometrial carcinomas with ambiguous features. Semin Diagn Pathol. 2010;27(4):261–73.
32. McCluggage WG. New developments in endocervical glandular lesions. Histopathology. 2013;62(1):138–60.
33. Yemelyanova A, Ji H, Shih Ie M, Wang TL, Wu LS, Ronnett BM. Utility of p16 expression for distinction of uterine serous carcinomas from endometrial endometrioid and endocervical adenocarcinomas: immunohistochemical analysis of 201 cases. Am J Surg Pathol. 2009;33(10):1504–14.
34. Chiesa-Vottero AG, Malpica A, Deavers MT, Broaddus R, Nuovo GJ, Silva EG. Immunohistochemical overexpression of p16 and p53 in uterine serous carcinoma and ovarian high-grade serous carcinoma. Int J Gynecol Pathol. 2007;26(3):328–33.
35. Saad RS, Mashhour M, Noftech-Mozes S, Ismiil N, Dube V, Ghorab Z, et al. P16INK4a expression in undifferentiated carcinoma of the uterus does not exclude its endometrial origin. Int J Gynecol Pathol. 2012;31(1):57–65.

36. Hirschowitz L, Ganesan R, McCluggage WG. WT1, p53 and hormone receptor expression in uterine serous carcinoma. Histopathology. 2009;55(4):478–82.
37. McCluggage WG, Soslow RA, Gilks CB. Patterns of p53 immunoreactivity in endometrial carcinomas: 'all or nothing' staining is of importance. Histopathology. 2011;59(4):786–8.
38. Mutter GL, Ince TA, Baak JP, Kust GA, Zhou XP, Eng C. Molecular identification of latent precancers in histologically normal endometrium. Cancer Res. 2001;61(11):4311–4.
39. Mutter GL, Lin MC, Fitzgerald JT, Kum JB, Baak JP, Lees JA, et al. Altered PTEN expression as a diagnostic marker for the earliest endometrial precancers. J Natl Cancer Inst. 2000;92(11):924–30.
40. Latta E, Chapman WB. PTEN mutations and evolving concepts in endometrial neoplasia. Curr Opin Obstet Gynecol. 2002;14(1):59–65.
41. Mutter GL, Duska LR, Crum CP. Preinvasive endometrial neoplasia. In: Crum CP, Nucci MR, Lee KR, editors. Diagnostic gynecologic and obstetric pathology. Philadelphia, PA: Elsevier Saunders; 2011. p. 457–89.
42. Shukla A, Thomas D, Roh MH. PAX8 and PAX2 expression in endocervical adenocarcinoma in situ and high-grade squamous dysplasia. Int J Gynecol Pathol. 2013;32(1):116–21.
43. Joiner AK, Quick CM, Jeffus SK. Pax2 expression in simultaneously diagnosed WHO and EIN classification systems. Int J Gynecol Pathol. 2015;34(1):40–6.
44. Buza N, Hui P. Immunohistochemistry in gynecologic pathology: an example-based practical update. Arch Pathol Lab Med. 2017;141(8):1052–71.
45. Esheba GE. ProExC is a novel marker for distinguishing between primary endometrial and endocervical adenocarcinomas. J Egypt Natl Canc Inst. 2013;25(2):87–93.
46. Burger MC, Brucker DP, Baumgarten P, Ronellenfitsch MW, Wanka C, Hasselblatt M, et al. PAX2 is an antiapoptotic molecule with deregulated expression in medulloblastoma. Int J Oncol. 2012;41(1):235–41.
47. Park KJ, Bramlage MP, Ellenson LH, Pirog EC. Immunoprofile of adenocarcinomas of the endometrium, endocervix, and ovary with mucinous differentiation. Appl Immunohistochem Mol Morphol. 2009;17(1):8–11.
48. Quade BJ, Yang A, Wang Y, Sun D, Park J, Sheets EE, et al. Expression of the p53 homologue p63 in early cervical neoplasia. Gynecol Oncol. 2001;80(1):24–9.
49. Ip PP, Irving JA, McCluggage WG, Clement PB, Young RH. Papillary proliferation of the endometrium: a clinicopathologic study of 59 cases of simple and complex papillae without cytologic atypia. Am J Surg Pathol. 2013;37(2):167–77.
50. Howitt BE, Nucci MR, Drapkin R, Crum CP, Hirsch MS. Stathmin-1 expression as a complement to p16 helps identify high-grade cervical intraepithelial neoplasia with increased specificity. Am J Surg Pathol. 2013;37(1):89–97.
51. Danialan R, Assaad M, Burghardt J, Newcomb P, Cartun RW, Mandavilli S. The utility of PAX8 and IMP3 immunohistochemical stains in the differential diagnosis of benign, premalignant, and malignant endocervical glandular lesions. Gynecol Oncol. 2013;130(2):383–8.
52. Riethdorf L, Riethdorf S, Lee KR, Cviko A, Loning T, Crum CP. Human papillomaviruses, expression of p16, and early endocervical glandular neoplasia. Hum Pathol. 2002;33(9):899–904.
53. Carleton C, Hoang L, Sah S, Kiyokawa T, Karamurzin YS, Talia KL, et al. A detailed immunohistochemical analysis of a large series of cervical and vaginal gastric-type adenocarcinomas. Am J Surg Pathol. 2016;40(5):636–44.
54. Lu S, Shen D, Zhao Y, Kang N, Wang X. Primary endocervical gastric-type adenocarcinoma: a clinicopathologic and immunohistochemical analysis of 23 cases. Diagn Pathol. 2019;14(1):72.
55. Wada T, Ohishi Y, Kaku T, Aman M, Imamura H, Yasutake N, et al. Endocervical adenocarcinoma with morphologic features of both usual and gastric types: clinicopathologic and immunohistochemical analyses and high-risk HPV detection by in situ hybridization. Am J Surg Pathol. 2017;41(5):696–705.
56. Gilks CB, Young RH, Aguirre P, DeLellis RA, Scully RE. Adenoma malignum (minimal deviation adenocarcinoma) of the uterine cervix. A clinicopathological and immunohistochemical analysis of 26 cases. Am J Surg Pathol. 1989;13(9):717–29.
57. Mikami Y, Kiyokawa T, Moriya T, Sasano H. Immunophenotypic alteration of the stromal component in minimal deviation adenocarcinoma ('adenoma malignum') and endocervical glandular hyperplasia: a study using oestrogen receptor and alpha-smooth muscle actin double immunostaining. Histopathology. 2005;46(2):130–6.
58. Utsugi K, Hirai Y, Takeshima N, Akiyama F, Sakurai S, Hasumi K. Utility of the monoclonal antibody HIK1083 in the diagnosis of adenoma malignum of the uterine cervix. Gynecol Oncol. 1999;75(3):345–8.
59. Park KJ, Kiyokawa T, Soslow RA, Lamb CA, Oliva E, Zivanovic O, et al. Unusual endocervical adenocarcinomas: an immunohistochemical analysis with molecular detection of human papillomavirus. Am J Surg Pathol. 2011;35(5):633–46.
60. Kusanagi Y, Kojima A, Mikami Y, Kiyokawa T, Sudo T, Yamaguchi S, et al. Absence of high-risk human papillomavirus (HPV) detection in endocervical adenocarcinoma with gastric morphology and phenotype. Am J Pathol. 2010;177(5):2169–75.
61. Rabban JT, McAlhany S, Lerwill MF, Grenert JP, Zaloudek CJ. PAX2 distinguishes benign mesonephric and mullerian glandular lesions of the cervix from endocervical adenocarcinoma, including minimal deviation adenocarcinoma. Am J Surg Pathol. 2010;34(2):137–46.
62. Emanuel P, Wang B, Wu M, Burstein DE. p63 Immunohistochemistry in the distinction of adenoid cystic carcinoma from basaloid squamous cell carcinoma. Mod Pathol. 2005;18(5):645–50.
63. Gardner GJ, Reidy-Lagunes D, Gehrig PA. Neuroendocrine tumors of the gynecologic tract: a Society of Gynecologic Oncology (SGO) clinical document. Gynecol Oncol. 2011;122(1):190–8.
64. Li JD, Zhuang Y, Li YF, Feng YL, Hou JH, Chen L, et al. A clinicopathological aspect of primary small-cell carcinoma of the uterine cervix: a single-centre study of 25 cases. J Clin Pathol. 2011;64(12):1102–7.
65. Houghton O, McCluggage WG. The expression and diagnostic utility of p63 in the female genital tract. Adv Anat Pathol. 2009;16(5):316–21.
66. Young RH, Clement PB. Endocervical adenocarcinoma and its variants: their morphology and differential diagnosis. Histopathology. 2002;41(3):185–207.
67. Ordi J, Nogales FF, Palacin A, Marquez M, Pahisa J, Vanrell JA, et al. Mesonephric adenocarcinoma of the uterine corpus: CD10 expression as evidence of mesonephric differentiation. Am J Surg Pathol. 2001;25(12):1540–5.
68. Ordi J, Romagosa C, Tavassoli FA, Nogales F, Palacin A, Condom E, et al. CD10 expression in epithelial tissues and tumors of the gynecologic tract: a useful marker in the diagnosis of mesonephric, trophoblastic, and clear cell tumors. Am J Surg Pathol. 2003;27(2):178–86.
69. Silver SA, Devouassoux-Shisheboran M, Mezzetti TP, Tavassoli FA. Mesonephric adenocarcinomas of the uterine cervix: a study of 11 cases with immunohistochemical findings. Am J Surg Pathol. 2001;25(3):379–87.
70. Kenny SL, McBride HA, Jamison J, McCluggage WG. Mesonephric adenocarcinomas of the uterine cervix and corpus: HPV-negative neoplasms that are commonly PAX8, CA125, and HMGA2 positive and that may be immunoreactive with

TTF1 and hepatocyte nuclear factor 1-beta. Am J Surg Pathol. 2012;36(6):799–807.
71. Gilks CB, Oliva E, Soslow RA. Poor interobserver reproducibility in the diagnosis of high-grade endometrial carcinoma. Am J Surg Pathol. 2013;37(6):874–81.
72. Soslow R. High-grade endometrial carcinomas – strategies for typing. Histopathology. 2013;62(1):89–110.
73. Darvishian F, Hummer AJ, Thaler HT, Bhargava R, Linkov I, Asher M, et al. Serous endometrial cancers that mimic endometrioid adenocarcinomas: a clinicopathologic and immunohistochemical study of a group of problematic cases. Am J Surg Pathol. 2004;28(12):1568–78.
74. Lomo L, Nucci MR, Lee KR, Lin MC, Hirsch MS, Crum CP, et al. Histologic and immunohistochemical decision-making in endometrial adenocarcinoma. Mod Pathol. 2008;21(8):937–42.
75. Reid-Nicholson M, Iyengar P, Hummer AJ, Linkov I, Asher M, Soslow RA. Immunophenotypic diversity of endometrial adenocarcinomas: implications for differential diagnosis. Mod Pathol. 2006;19(8):1091–100.
76. Alkushi A, Clarke BA, Akbari M, Makretsov N, Lim P, Miller D, et al. Identification of prognostically relevant and reproducible subsets of endometrial adenocarcinoma based on clustering analysis of immunostaining data. Mod Pathol. 2007;20(11):1156–65.
77. Risinger JI, Hayes K, Maxwell GL, Carney ME, Dodge RK, Barrett JC, et al. PTEN mutation in endometrial cancers is associated with favorable clinical and pathologic characteristics. Clin Cancer Res. 1998;4(12):3005–10.
78. Fukuchi T, Sakamoto M, Tsuda H, Maruyama K, Nozawa S, Hirohashi S. Beta-catenin mutation in carcinoma of the uterine endometrium. Cancer Res. 1998;58(16):3526–8.
79. Goldstein NS, Uzieblo A. WT1 immunoreactivity in uterine papillary serous carcinomas is different from ovarian serous carcinomas. Am J Clin Pathol. 2002;117(4):541–5.
80. Lax SF, Kendall B, Tashiro H, Slebos RJ, Hedrick L. The frequency of p53, K-ras mutations, and microsatellite instability differs in uterine endometrioid and serous carcinoma: evidence of distinct molecular genetic pathways. Cancer. 2000;88(4):814–24.
81. Ayhan A, Mao TL, Suryo Rahmanto Y, Zeppernick F, Ogawa H, Wu RC, et al. Increased proliferation in atypical hyperplasia/endometrioid intraepithelial neoplasia of the endometrium with concurrent inactivation of ARID1A and PTEN tumour suppressors. J Pathol Clin Res. 2015;1(3):186–93.
82. Lee H, Choi HJ, Kang CS, Lee HJ, Lee WS, Park CS. Expression of miRNAs and PTEN in endometrial specimens ranging from histologically normal to hyperplasia and endometrial adenocarcinoma. Mod Pathol. 2012;25(11):1508–15.
83. Allison KH, Upson K, Reed SD, Jordan CD, Newton KM, Doherty J, et al. PAX2 loss by immunohistochemistry occurs early and often in endometrial hyperplasia. Int J Gynecol Pathol. 2012;31(2):151–9.
84. Pallares J, Bussaglia E, Martinez-Guitarte JL, Dolcet X, Llobet D, Rue M, et al. Immunohistochemical analysis of PTEN in endometrial carcinoma: a tissue microarray study with a comparison of four commercial antibodies in correlation with molecular abnormalities. Mod Pathol. 2005;18(5):719–27.
85. Peiro G, Diebold J, Lohse P, Ruebsamen H, Lohse P, Baretton GB, et al. Microsatellite instability, loss of heterozygosity, and loss of hMLH1 and hMSH2 protein expression in endometrial carcinoma. Hum Pathol. 2002;33(3):347–54.
86. Schlosshauer PW, Ellenson LH, Soslow RA. Beta-catenin and E-cadherin expression patterns in high-grade endometrial carcinoma are associated with histological subtype. Mod Pathol. 2002;15(10):1032–7.
87. Quick CM, Laury AR, Monte NM, Mutter GL. Utility of PAX2 as a marker for diagnosis of endometrial intraepithelial neoplasia. Am J Clin Pathol. 2012;138(5):678–84.
88. Liang SX, Chambers SK, Cheng L, Zhang S, Zhou Y, Zheng W. Endometrial glandular dysplasia: a putative precursor lesion of uterine papillary serous carcinoma. Part II: molecular features. Int J Surg Pathol. 2004;12(4):319–31.
89. Zheng W, Liang SX, Yu H, Rutherford T, Chambers SK, Schwartz PE. Endometrial glandular dysplasia: a newly defined precursor lesion of uterine papillary serous carcinoma. Part I: morphologic features. Int J Surg Pathol. 2004;12(3):207–23.
90. Alkushi A, Kobel M, Kalloger SE, Gilks CB. High-grade endometrial carcinoma: serous and grade 3 endometrioid carcinomas have different immunophenotypes and outcomes. Int J Gynecol Pathol. 2010;29(4):343–50.
91. Chen W, Husain A, Nelson GS, Rambau PF, Liu S, Lee CH, et al. Immunohistochemical profiling of endometrial serous carcinoma. Int J Gynecol Pathol. 2017;36(2):128–39.
92. Zhang Y, Garcia-Buitrago MT, Koru-Sengul T, Schuman S, Ganjei-Azar P. An immunohistochemical panel to distinguish ovarian from uterine serous papillary carcinomas. Int J Gynecol Pathol. 2013;32(5):476–81.
93. Al-Hussaini M, Stockman A, Foster H, McCluggage WG. WT-1 assists in distinguishing ovarian from uterine serous carcinoma and in distinguishing between serous and endometrioid ovarian carcinoma. Histopathology. 2004;44(2):109–15.
94. Waqar S, Khan SA, Sarfraz T, Waqar S. Expression of Estrogen Receptors (ER), Progesterone Receptors (PR) and HER-2/neu receptors in Endometrial Carcinoma and their associations with histological types, grades and stages of the tumor. Pak J Med Sci. 2018;34(2):266–71.
95. Kobel M, Rahimi K, Rambau PF, Naugler C, Le Page C, Meunier L, et al. An immunohistochemical algorithm for ovarian carcinoma typing. Int J Gynecol Pathol. 2016;35(5):430–41.
96. Delair D, Soslow R. Endometrial clear cell carcinoma with and without aberrant p53 expression: a study of 16 cases [abstract]. Mod Pathol. 2012;25(Suppl 2):265A.
97. Fadare O, Desouki MM, Gwin K, Hanley KZ, Jarboe EA, Liang SX, et al. Frequent expression of napsin A in clear cell carcinoma of the endometrium: potential diagnostic utility. Am J Surg Pathol. 2014;38(2):189–96.
98. Iwamoto M, Nakatani Y, Fugo K, Kishimoto T, Kiyokawa T. Napsin A is frequently expressed in clear cell carcinoma of the ovary and endometrium. Hum Pathol. 2015;46(7):957–62.
99. Mikami Y, Hata S, Kiyokawa T, Manabe T. Expression of CD10 in malignant mullerian mixed tumors and adenosarcomas: an immunohistochemical study. Mod Pathol. 2002;15(9):923–30.
100. Terada T. Atypical polypoid adenomyoma of the uterus: an immunohistochemical study on 5 cases. Ann Diagn Pathol. 2011;15(5):338–41.
101. Soslow RA, Chung MH, Rouse RV, Hendrickson MR, Longacre TA. Atypical polypoid adenomyofibroma (APA) versus well-differentiated endometrial carcinoma with prominent stromal matrix: an immunohistochemical study. Int J Gynecol Pathol. 1996;15(3):209–16.
102. Kurihara S, Oda Y, Ohishi Y, Kaneki E, Kobayashi H, Wake N, et al. Coincident expression of beta-catenin and cyclin D1 in endometrial stromal tumors and related high-grade sarcomas. Mod Pathol. 2010;23(2):225–34.
103. Jung CK, Jung JH, Lee A, Lee YS, Choi YJ, Yoon SK, et al. Diagnostic use of nuclear beta-catenin expression for the assessment of endometrial stromal tumors. Mod Pathol. 2008;21(6):756–63.
104. McCluggage WG, Sumathi VP, Maxwell P. CD10 is a sensitive and diagnostically useful immunohistochemical marker of normal endometrial stroma and of endometrial stromal neoplasms. Histopathology. 2001;39(3):273–8.
105. Oliva E, Young RH, Clement PB, Bhan AK, Scully RE. Cellular benign mesenchymal tumors of the uterus. A comparative mor-

phologic and immunohistochemical analysis of 33 highly cellular leiomyomas and six endometrial stromal nodules, two frequently confused tumors. Am J Surg Pathol. 1995;19(7):757–68.
106. Sumathi VP, Al-Hussaini M, Connolly LE, Fullerton L, McCluggage WG. Endometrial stromal neoplasms are immunoreactive with WT-1 antibody. Int J Gynecol Pathol. 2004;23(3):241–7.
107. Yilmaz A, Rush DS, Soslow RA. Endometrial stromal sarcomas with unusual histologic features: a report of 24 primary and metastatic tumors emphasizing fibroblastic and smooth muscle differentiation. Am J Surg Pathol. 2002;26(9):1142–50.
108. Croce S, Hostein I, Ribeiro A, Garbay D, Velasco V, Stoeckle E, et al. YWHAE rearrangement identified by FISH and RT-PCR in endometrial stromal sarcomas: genetic and pathological correlations. Mod Pathol. 2013;26(10):1390–400.
109. Lee CH, Ali RH, Rouzbahman M, Marino-Enriquez A, Zhu M, Guo X, et al. Cyclin D1 as a diagnostic immunomarker for endometrial stromal sarcoma with YWHAE-FAM22 rearrangement. Am J Surg Pathol. 2012;36(10):1562–70.
110. Amant F, Steenkiste E, Schurmans K, Verbist L, Abeler VM, Tulunay G, et al. Immunohistochemical expression of CD10 antigen in uterine adenosarcoma. Int J Gynecol Cancer. 2004;14(6):1118–21.
111. Soslow RA, Ali A, Oliva E. Mullerian adenosarcomas: an immunophenotypic analysis of 35 cases. Am J Surg Pathol. 2008;32(7):1013–21.
112. Gannon BR, Manduch M, Childs TJ. Differential immunoreactivity of p16 in leiomyosarcomas and leiomyoma variants. Int J Gynecol Pathol. 2008;27(1):68–73.
113. Mittal K, Demopoulos RI. MIB-1 (Ki-67), p53, estrogen receptor, and progesterone receptor expression in uterine smooth muscle tumors. Hum Pathol. 2001;32(9):984–7.
114. Oliva E, Clement PB, Young RH. Epithelioid endometrial and endometrioid stromal tumors: a report of four cases emphasizing their distinction from epithelioid smooth muscle tumors and other oxyphilic uterine and extrauterine tumors. Int J Gynecol Pathol. 2002;21(1):48–55.
115. Silva EG, Deavers MT, Bodurka DC, Malpica A. Uterine epithelioid leiomyosarcomas with clear cells: reactivity with HMB-45 and the concept of PEComa. Am J Surg Pathol. 2004;28(2):244–9.
116. Winter WE 3rd, Seidman JD, Krivak TC, Chauhan S, Carlson JW, Rose GS, et al. Clinicopathological analysis of c-kit expression in carcinosarcomas and leiomyosarcomas of the uterine corpus. Gynecol Oncol. 2003;91(1):3–8.
117. Iwata J, Fletcher CD. Immunohistochemical detection of cytokeratin and epithelial membrane antigen in leiomyosarcoma: a systematic study of 100 cases. Pathol Int. 2000;50(1):7–14.
118. Fukunaga M, Nomura K, Endo Y, Ushigome S, Aizawa S. Carcinosarcoma of the uterus with extensive neuroectodermal differentiation. Histopathology. 1996;29(6):565–70.
119. Kanamori T, Takakura K, Mandai M, Kariya M, Fukuhara K, Sakaguchi M, et al. Increased expression of calcium-binding protein S100 in human uterine smooth muscle tumours. Mol Hum Reprod. 2004;10(10):735–42.
120. Carvalho JC, Wasco MJ, Kunju LP, Thomas DG, Shah RB. Cluster analysis of immunohistochemical profiles delineates CK7, vimentin, S100A1 and C-kit (CD117) as an optimal panel in the differential diagnosis of renal oncocytoma from its mimics. Histopathology. 2011;58(2):169–79.
121. Lee CH, Turbin DA, Sung YC, Espinosa I, Montgomery K, van de Rijn M, et al. A panel of antibodies to determine site of origin and malignancy in smooth muscle tumors. Mod Pathol. 2009;22(12):1519–31.
122. O'Neill CJ, McBride HA, Connolly LE, McCluggage WG. Uterine leiomyosarcomas are characterized by high p16, p53 and MIB1 expression in comparison with usual leiomyomas, leiomyoma variants and smooth muscle tumours of uncertain malignant potential. Histopathology. 2007;50(7):851–8.
123. D'Angelo E, Espinosa I, Ali R, Gilks CB, Rijn M, Lee CH, et al. Uterine leiomyosarcomas: tumor size, mitotic index, and biomarkers Ki67, and Bcl-2 identify two groups with different prognosis. Gynecol Oncol. 2011;121(2):328–33.
124. Hakverdi S, Gungoren A, Yaldiz M, Hakverdi AU, Toprak S. Immunohistochemical analysis of p16 expression in uterine smooth muscle tumors. Eur J Gynaecol Oncol. 2011;32(5):513–5.
125. Ip PP, Cheung AN, Clement PB. Uterine smooth muscle tumors of uncertain malignant potential (STUMP): a clinicopathologic analysis of 16 cases. Am J Surg Pathol. 2009;33(7):992–1005.
126. Akhan SE, Yavuz E, Tecer A, Iyibozkurt CA, Topuz S, Tuzlali S, et al. The expression of Ki-67, p53, estrogen and progesterone receptors affecting survival in uterine leiomyosarcomas. A clinicopathologic study. Gynecol Oncol. 2005;99(1):36–42.
127. Chen L, Yang B. Immunohistochemical analysis of p16, p53, and Ki-67 expression in uterine smooth muscle tumors. Int J Gynecol Pathol. 2008;27(3):326–32.
128. Kefeli M, Yildiz L, Kaya FC, Aydin O, Kandemir B. Fascin expression in uterine smooth muscle tumors. Int J Gynecol Pathol. 2009;28(4):328–33.
129. Otis CN. Uterine adenomatoid tumors: immunohistochemical characteristics with emphasis on Ber-EP4 immunoreactivity and distinction from adenocarcinoma. Int J Gynecol Pathol. 1996;15(2):146–51.
130. Schwartz EJ, Longacre TA. Adenomatoid tumors of the female and male genital tracts express WT1. Int J Gynecol Pathol. 2004;23(2):123–8.
131. Chen H-F, Liu X-L, Liu A-Z, Shi J-S, Cui Y, Gao P. Uterine adenomatoid tumor: a clinicopathologic study of 102 cases. Int J Clin Exp Pathol. 2017;10(9):9627–32.
132. Fadare O. Perivascular epithelioid cell tumors (PEComas) and smooth muscle tumors of the uterus. Am J Surg Pathol. 2007;31(9):1454–5; author reply 5–6.
133. Ye HY, Chen JG, Luo DL, Jiang ZM, Chen ZH. Perivascular epithelioid cell tumor (PEComa) of gynecologic origin: a clinicopathological study of three cases. Eur J Gynaecol Oncol. 2012;33(1):105–8.
134. Wu JH, Zhou JL, Cui Y, Jing QP, Shang L, Zhang JZ. Malignant perivascular epithelioid cell tumor of the retroperitoneum. Int J Clin Exp Pathol. 2013;6(10):2251–6.
135. Folpe AL, Mentzel T, Lehr HA, Fisher C, Balzer BL, Weiss SW. Perivascular epithelioid cell neoplasms of soft tissue and gynecologic origin: a clinicopathologic study of 26 cases and review of the literature. Am J Surg Pathol. 2005;29(12):1558–75.
136. Vang R, Kempson RL. Perivascular epithelioid cell tumor ('PEComa') of the uterus: a subset of HMB-45-positive epithelioid mesenchymal neoplasms with an uncertain relationship to pure smooth muscle tumors. Am J Surg Pathol. 2002;26(1):1–13.
137. Conlon N, Soslow RA, Murali R. Perivascular epithelioid tumours (PEComas) of the gynaecological tract. J Clin Pathol. 2015;68(6):418–26.
138. Pradhan D, Mohanty SK. Uterine tumors resembling ovarian sex cord tumors. Arch Pathol Lab Med. 2013;137(12):1832–6.
139. Irving JA, Carinelli S, Prat J. Uterine tumors resembling ovarian sex cord tumors are polyphenotypic neoplasms with true sex cord differentiation. Mod Pathol. 2006;19(1):17–24.
140. Hurrell DP, McCluggage WG. Uterine tumour resembling ovarian sex cord tumour is an immunohistochemically polyphenotypic neoplasm which exhibits coexpression of epithelial, myoid and sex cord markers. J Clin Pathol. 2007;60(10):1148–54.
141. Fisher RA, Hodges MD, Rees HC, Sebire NJ, Seckl MJ, Newlands ES, et al. The maternally transcribed gene p57(KIP2) (CDNK1C)

is abnormally expressed in both androgenetic and biparental complete hydatidiform moles. Hum Mol Genet. 2002;11(26): 3267–72.
142. Jun SY, Ro JY, Kim KR. p57kip2 is useful in the classification and differential diagnosis of complete and partial hydatidiform moles. Histopathology. 2003;43(1):17–25.
143. Sebire NJ, Rees HC, Peston D, Seckl MJ, Newlands ES, Fisher RA. p57(KIP2) immunohistochemical staining of gestational trophoblastic tumours does not identify the type of the causative pregnancy. Histopathology. 2004;45(2):135–41.
144. Shih IM, Kurman RJ. Immunohistochemical localization of inhibin-alpha in the placenta and gestational trophoblastic lesions. Int J Gynecol Pathol. 1999;18(2):144–50.
145. Kommoss F, Schmidt D, Coerdt W, Olert J, Muntefering H. Immunohistochemical expression analysis of inhibin-alpha and -beta subunits in partial and complete moles, trophoblastic tumors, and endometrial decidua. Int J Gynecol Pathol. 2001;20(4):380–5.
146. Shih IM, Kurman RJ. Ki-67 labeling index in the differential diagnosis of exaggerated placental site, placental site trophoblastic tumor, and choriocarcinoma: a double immunohistochemical staining technique using Ki-67 and Mel-CAM antibodies. Hum Pathol. 1998;29(1):27–33.
147. Wong SC, Chan AT, Chan JK, Lo YM. Nuclear beta-catenin and Ki-67 expression in choriocarcinoma and its pre-malignant form. J Clin Pathol. 2006;59(4):387–92.
148. Shih I-M. Trophogram, an immunohistochemistry-based algorithmic approach, in the differential diagnosis of trophoblastic tumors and tumorlike lesions. Ann Diagn Pathol. 2007;11(3):228–34.
149. Kalhor N, Ramirez PT, Deavers MT, Malpica A, Silva EG. Immunohistochemical studies of trophoblastic tumors. Am J Surg Pathol. 2009;33(4):633–8.
150. Lee Y, Kim KR, McKeon F, Yang A, Boyd TK, Crum CP, et al. A unifying concept of trophoblastic differentiation and malignancy defined by biomarker expression. Hum Pathol. 2007;38(7):1003–13.
151. Shih IM, Kurman RJ. p63 expression is useful in the distinction of epithelioid trophoblastic and placental site trophoblastic tumors by profiling trophoblastic subpopulations. Am J Surg Pathol. 2004;28(9):1177–83.
152. Banet N, Gown AM, Shih Ie M, Kay Li Q, Roden RB, Nucci MR, et al. GATA-3 expression in trophoblastic tissues: an immunohistochemical study of 445 cases, including diagnostic utility. Am J Surg Pathol. 2015;39(1):101–8.
153. Albores-Saavedra J, Latif S, Carrick KS, Alvarado-Cabrero I, Fowler MR. CD56 reactivity in small cell carcinoma of the uterine cervix. Int J Gynecol Pathol. 2005;24(2):113–7.
154. Wang HL, Lu DW. Detection of human papillomavirus DNA and expression of p16, Rb, and p53 proteins in small cell carcinomas of the uterine cervix. Am J Surg Pathol. 2004;28(7):901–8.
155. Grayson W, Taylor LF, Cooper K. Adenoid cystic and adenoid basal carcinoma of the uterine cervix: comparative morphologic, mucin, and immunohistochemical profile of two rare neoplasms of putative 'reserve cell' origin. Am J Surg Pathol. 1999;23(4):448–58.
156. Vang R, Whitaker BP, Farhood AI, Silva EG, Ro JY, Deavers MT. Immunohistochemical analysis of clear cell carcinoma of the gynecologic tract. Int J Gynecol Pathol. 2001;20(3):252–9.
157. Vang R, Barner R, Wheeler DT, Strauss BL. Immunohistochemical staining for Ki-67 and p53 helps distinguish endometrial Arias-Stella reaction from high-grade carcinoma, including clear cell carcinoma. Int J Gynecol Pathol. 2004;23(3):223–33.
158. McCluggage WG. Morphological subtypes of ovarian carcinoma: a review with emphasis on new developments and pathogenesis. Pathology. 2011;43(5):420–32.
159. Mhawech-Fauceglia P, Yan L, Liu S, Pejovic T. ER+ /PR+ /TFF3+ /IMP3- immunoprofile distinguishes endometrioid from serous and clear cell carcinomas of the endometrium: a study of 401 cases. Histopathology. 2013;62(7):976–85.
160. Kurihara S, Oda Y, Ohishi Y, Iwasa A, Takahira T, Kaneki E, et al. Endometrial stromal sarcomas and related high-grade sarcomas: immunohistochemical and molecular genetic study of 31 cases. Am J Surg Pathol. 2008;32(8):1228–38.
161. Nucci MR, O'Connell JT, Huettner PC, Cviko A, Sun D, Quade BJ. h-Caldesmon expression effectively distinguishes endometrial stromal tumors from uterine smooth muscle tumors. Am J Surg Pathol. 2001;25(4):455–63.