Chapter 19
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 vs. endometrium, low-grade vs. high-grade endometrial neoplasms, benign vs. 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 43 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.

Keywords Cervical dysplasia • Mesonephric carcinoma • Endocervical adenocarcinoma • Small cell undifferentiated carcinoma • Serous carcinoma • Endometrial clear cell carcinoma • Endometrioid adenocarcinoma • Undifferentiated carcinoma • Carcinosarcoma • Undifferentiated sarcoma • Endometrial stromal nodule • Endometrial stromal sarcoma • Adenomatoid tumor • PECOMA • Epithelioid trophoblastic tumor • Placental site trophoblastic tumor • Choriocarcinoma • Placental site nodule • Gestational trophoblastic tumor • Arias-Stella reaction • Hydatidiform mole • Cervical adenocarcinoma in-situ • Cervical dysplasia • Minimal deviation adenocarcinoma • Polypoid adenomyoma • Uterine leiomyosarcoma • Uterine leiomyoma • Cervical microglandular hyperplasia • Endometriosis • Exaggerated placental site • Adenosarcoma

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FREQUENTLY ASKED QUESTIONS

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Table 19.1 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
ALK1	C, N, M	Tyrosine kinase receptor	In differentiating leiomyosarcoma (−ve) from inflammatory myofibroblastic tumors (+ve)
AR	N	DNA-binding transcription factor that regulates gene expression	Reactive in mesonephric remnants, ectopic prostate, FATWO, endometrial adenocarcinoma, mesonephric carcinoma of cervix and endometrial stromal sarcoma
ARID1A (BAF250)		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 tuboendometrial metaplasia and endometriosis of the cervix (diffusely +ve) from AIS (usually −ve); 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

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Table 19.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
BerEP4	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)
CA19.9	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
CA125	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 (−ve) and smooth muscle neoplasms (+ve); 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 BerEp4 and PAX8 in distinguishing mesothelioma [Calretinin (+ve), BerEp4 (−ve), PAX8 (−ve), and serous epithelial neoplasms [PAX8 (+ve), BerEp4 (+ve) Calretinin (−ve)]; 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 8/18	Usually positive in glandular but not react squamous epithelium; Paget's cell mimics in the vulva are (−ve)
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 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 PNET (rare in the female genital system) (73); 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	PSTT and exaggerated placental site (+ve); placental site nodules and epithelioid trophoblastic tumor (−ve)
CDX2	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

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Table 19.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
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 (+ve) from endocervical (+ve) 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
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 & K20 reactivity in most metastatic
CK20	C	Type 1 filament protein	neoplasms from the stomach, pancreas, biliary tree or urinary bladder; CK7 positive and CK20 negative in endometrial and endocervical adenocarcinomas, as well as in breast and pulmonary adenocarcinoma; many müllerian carcinomas are CK7 negative
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 (−ve) from primary mucinous benign or malignant lesions of the genital tract primarily ovary (+ve)
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 (+ve) and female adnexal tumor of probable wolffian origin (FATWO) (−ve); neoplastic and non-neoplastic trophoblast is also reactive
ER and PR	N	DNA-binding transcription factor that regulates gene expression	May be helpful in distinguishing cervical (−ve) from endometrial (+ve) 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
HNF 1-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
HMB45	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 (+); may also be reactive with Clear cell uterine epithelioid leiomyosarcoma

(continued)

Table 19.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
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, may be positive; cytotrophoblast is negative
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
MELANA (MART-1)	C	Melanocytic marker	Used in identifying malignant melanoma; may stain sex cord stromal tumors but not used for this purpose
MIB1 (Ki67)	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 CIN and 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 doublestain) 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; around one half of endometrioid carcinomas of endometrium show loss of at least 1MMR
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 (+ve) from colonic adenocarcinoma (−ve); pancreatic and appendiceal tumors are (+ve); positive in endocervical glands
myoD1	N	Skeletal muscle marker	To demonstrate the 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 +ve) 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, 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+ve) from small cell neuro-endocrine carcinoma (negative or focal+ve); identifies squamous differentiation in cervical carcinomas

Table 19.1 (continued)

Antibodies	Staining pattern	Function	Key applications and pitfalls
PAX8	N	Member of the paired box (PAX) family of transcription factors	Expressed in around 80 % of all müllerian carcinoma; also positive in renal, thymic, thyroid and pancreatic endocrine tumors; gynecologic squamous cell carcinomas are negative; occasional mesotheliomas will be positive
PLAP	C	Heterogeneous group of glycoproteins usually confined to the cell surface	Strongly (+ve) in lesions of chorion-type intermediate trophoblast (placental site nodule); only focally positivity in lesions of implantation site intermediate trophoblast; metastatic ovarian dysgerminoma is (+ve)
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 and mesenchymal tissue and neoplasms	Used in the differential diagnosis of endometrial (positive) and endocervical (negative) adenocarcinomas; to distinguish between tuboendometrioid metaplasia and endometriosis (usually +ve) and adenocarcinoma *in situ* (AIS) (usually –ve)
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 –ve	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

References: [1–41]

Table 19.2 Summary of useful markers in common tumors (most commonly used markers are shaded)

Antibodies	SCCx	AdenoCx	AdenoEM	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 +	+
PAX-8	−	−	+	+	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 +
HMB45	−	−	−	−	−	−	− or +
MART-1	−	−	−	−	−	− or +	−

SCCx Cervical squamous cell carcinoma, *Adeno Cx* Cervical Adenocarcinoma, *Adeno EM* Endometrial endometrioid adenocarcinoma, *Ser EM* 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 19.3 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)
PAX-2	+	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

Figure 19.1

References: [1, 4–18, 42, 43]
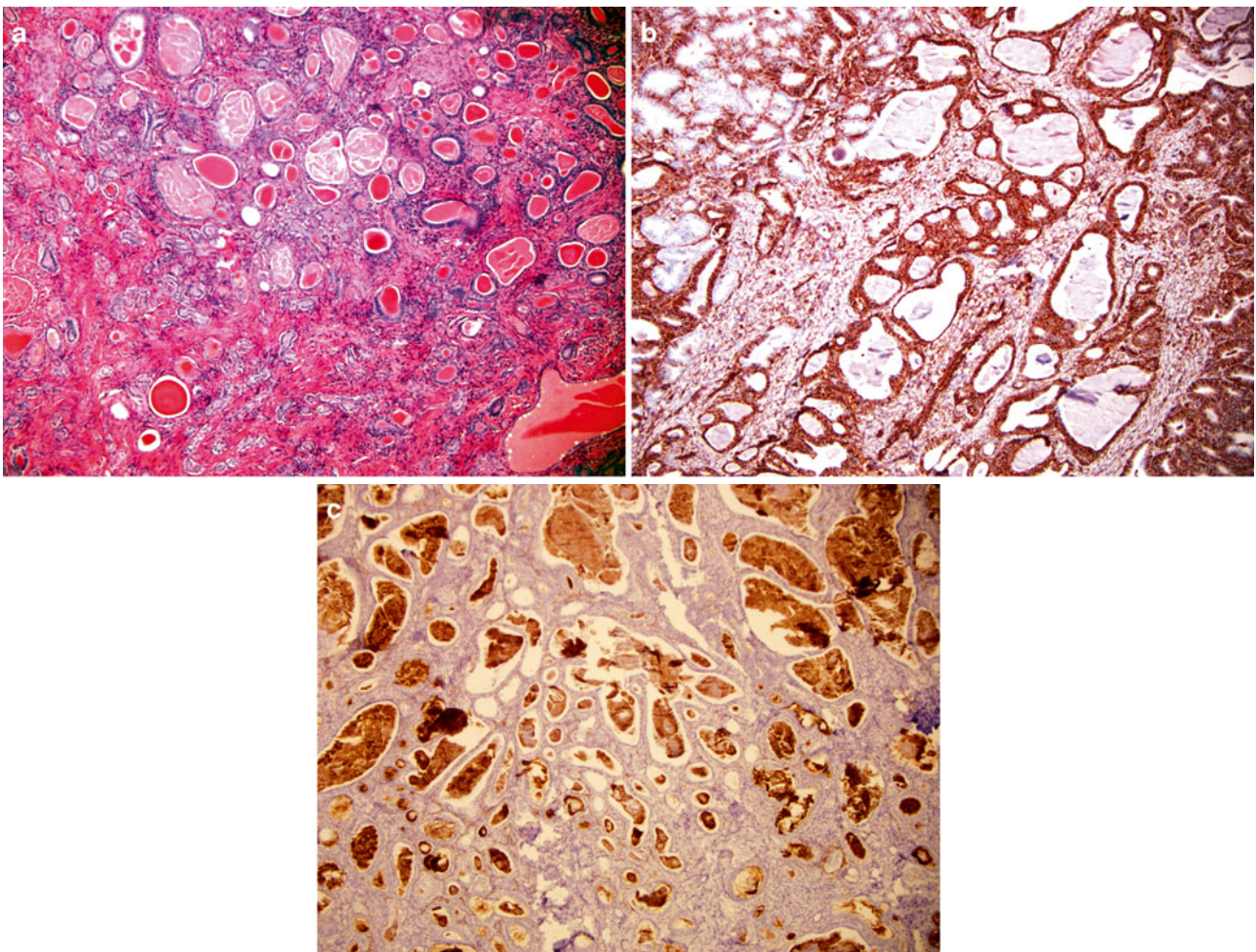
Fig. 19.1 Mesonephric remnant hyperplasia (**a**), with diffuse positive vimentin (**b**), and luminal CD10 positivity (**c**)

Table 19.4 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 towards the surface and usually diminishes deeper in the glands

Figure 19.2

References: [5, 8, 10, 17, 44]
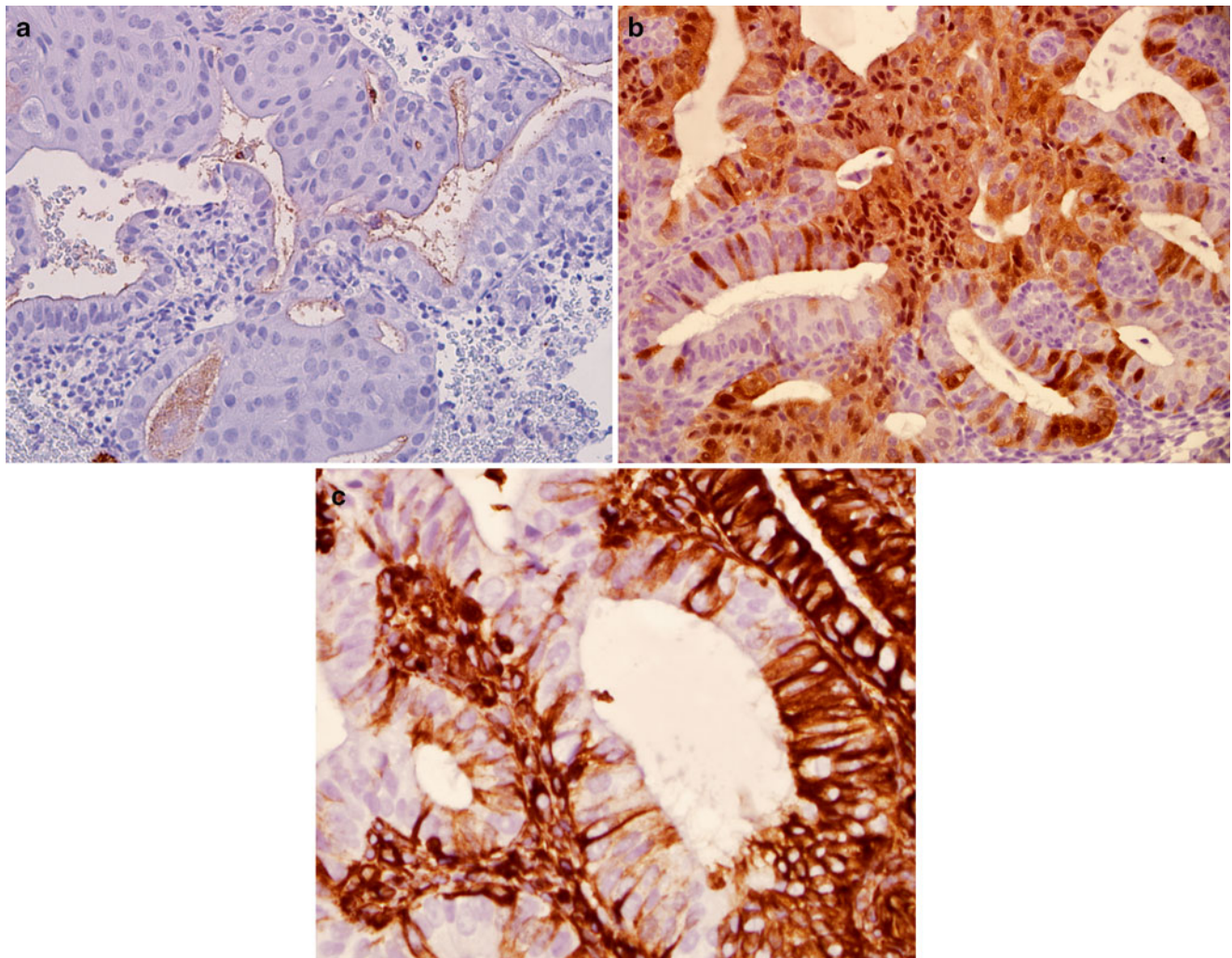
Fig. 19.2 Endometrial squamous metaplasia with lack of CEA staining (**a**), patchy staining pattern with p16 (**b**), and lack of staining with vimentin in the metaplastic foci (**c**)

Table 19.5 Markers for cervical high grade squamous intraepithelial lesion

Antibodies	Literature
p16	+[a]
Ki67	+[b]
ProExC	+
HPV	+[c]

[a]p16 usually shows strong nuclear and cytoplasmic staining of at least two-thirds and often the fullthickness of the involved mucosa. p16 may be positive in both high grade and low grade lesions. In the latter the staining is

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Table 19.5 (continued)

more commonly limited to the lower two thirds of the epithelial thickness

[b]Ki67 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

Figure 19.3

References: [4–18, 42, 43]
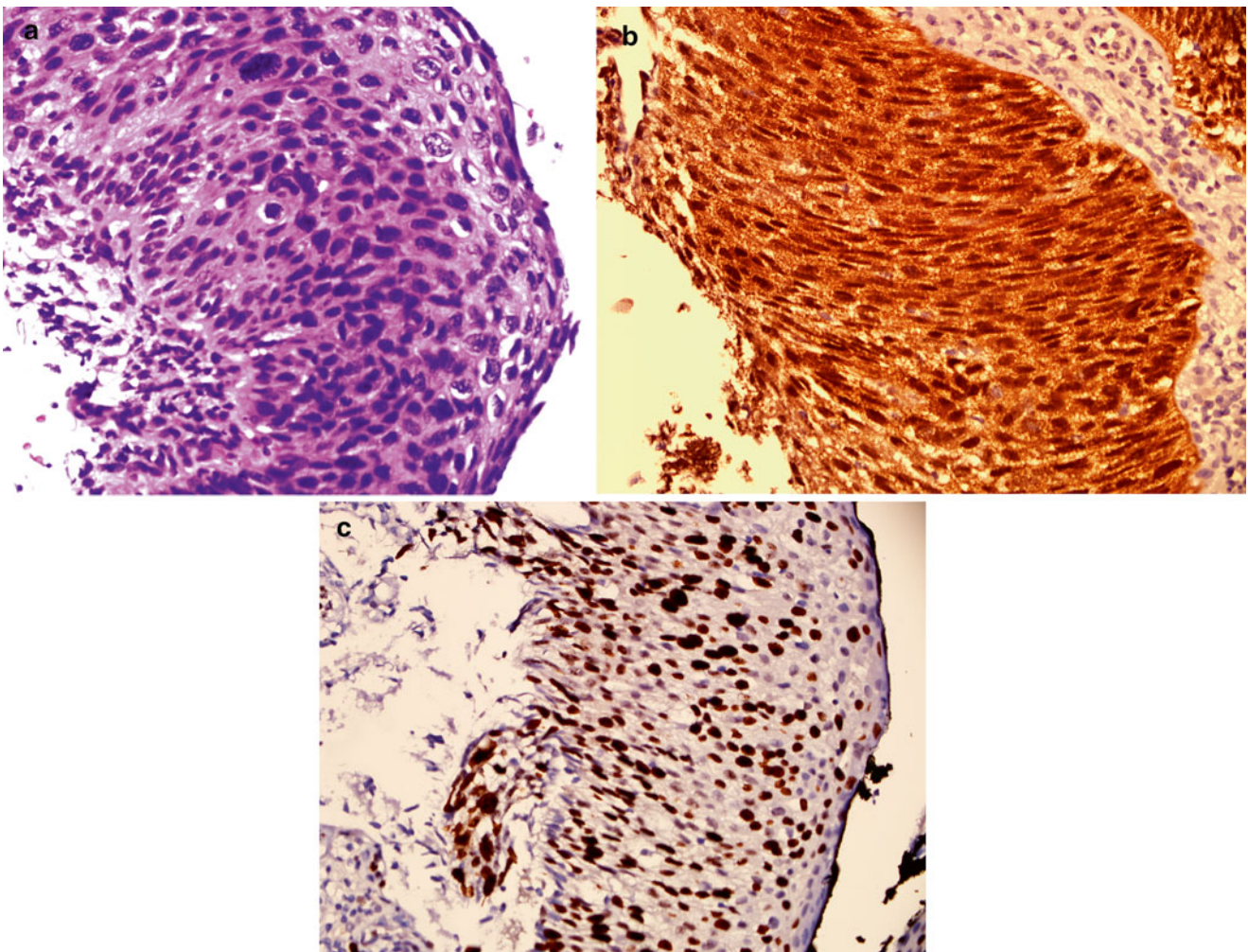
Fig. 19.3 High grade SIL on H & E (**a**), with full thickness and intense nuclear staining with p16 (**b**), and increased Ki-67 proliferative index involving upper layers (**c**)

Table 19.6 Markers for in-situ endocervical adenocarcinoma (most commonly used are shaded)

Antibodies	Literature
p16	+[a]
Vimentin (crypts)	−
Ki67	+[b]
p53	+ or −
ProExC	+ or −
Bcl2	− or +
CEA-M	+
CEA-P	+
PAX-8	+
CA125	−[c]
ER (glands)	− or +
PR (glands)	− or +
ER (stromal cells)	+[d]
Alpha-SMA (stromal cells)	+
CD10 (stroma)	−
CDX-2	− or +
HPV	+
PAX-2	−

[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-
(continued)

Table 19.6 (continued)

endometrioid metaplasia and other reactive and malignant conditions. Diffuse intense staining may be encountered in high grade endometrial adenocarcinomas

[b]High Ki67 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 CA125 is absent or localized to the perinuclear region of the cytoplasm as an accumulation of atypical coarse granules. CA125 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 stomal cells associated with invasive adenocarcinoma show an opposite pattern

Figure 19.4

References: [4–18]

Fig. 19.4 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**)

Table 19.7 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 +
PAX-8	−

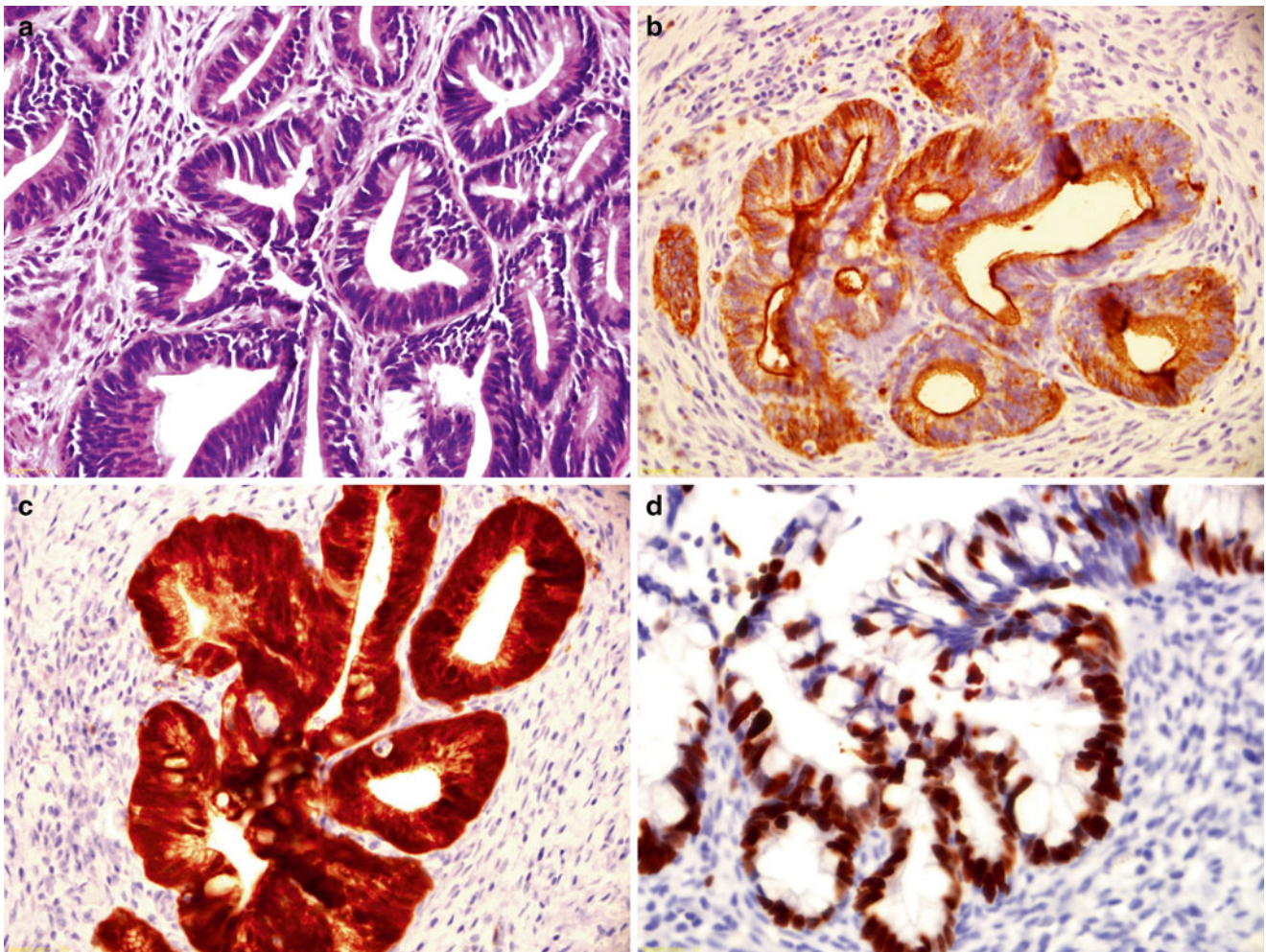Additional negative markers include CD56, Synaptophysin, Chromogranin, Napsin-A, TTF-1 and Hep-Par1. P16 and p63 are useful in confirming a squamous and cervical origin

References: [4, 6, 7]

Table 19.8 Markers for invasive endocervical (mucinous) and endometrioid adenocarcinoma of cervix

Antibodies	Literature
CK 7	+
p16*	+
CEA-M	+
CEA- P	+
PAX-8	+
CK (AE1, AE3)	+
EMA	+
HepPar1	+
ProEx C	+ or −
WT1	+ or −
CA125	+ or −
p53	+ or −
P63	− or +
MUC2	− or +
MUC 6	− or +
CDX-2	− or +
Vimentin	− or +
PAX-2	−

Additional negative markers include CK20, CD10, TTF-1 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

Figure 19.5

References: [4–18, 45]

Table 19.9 Markers for in-situ and invasive intestinal-type endocervical adenocarcinoma

Antibodies	Literature
CK (AE1, AE3)	+
CK 7	+
CK20	−
CDX2	+
EMA	+
CEA-M	+
CEA-P	+
p16	+[a]
pRB	+
MUC1	+
MUC5AC	+
WT1	+ or −
CA125	+ 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, 45]

Table 19.10 Markers for Minimal deviation adenocarcinoma of the cervix

Antibodies	Literature
HIK1083	+[a]
PAX-2	−
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, 46–51]
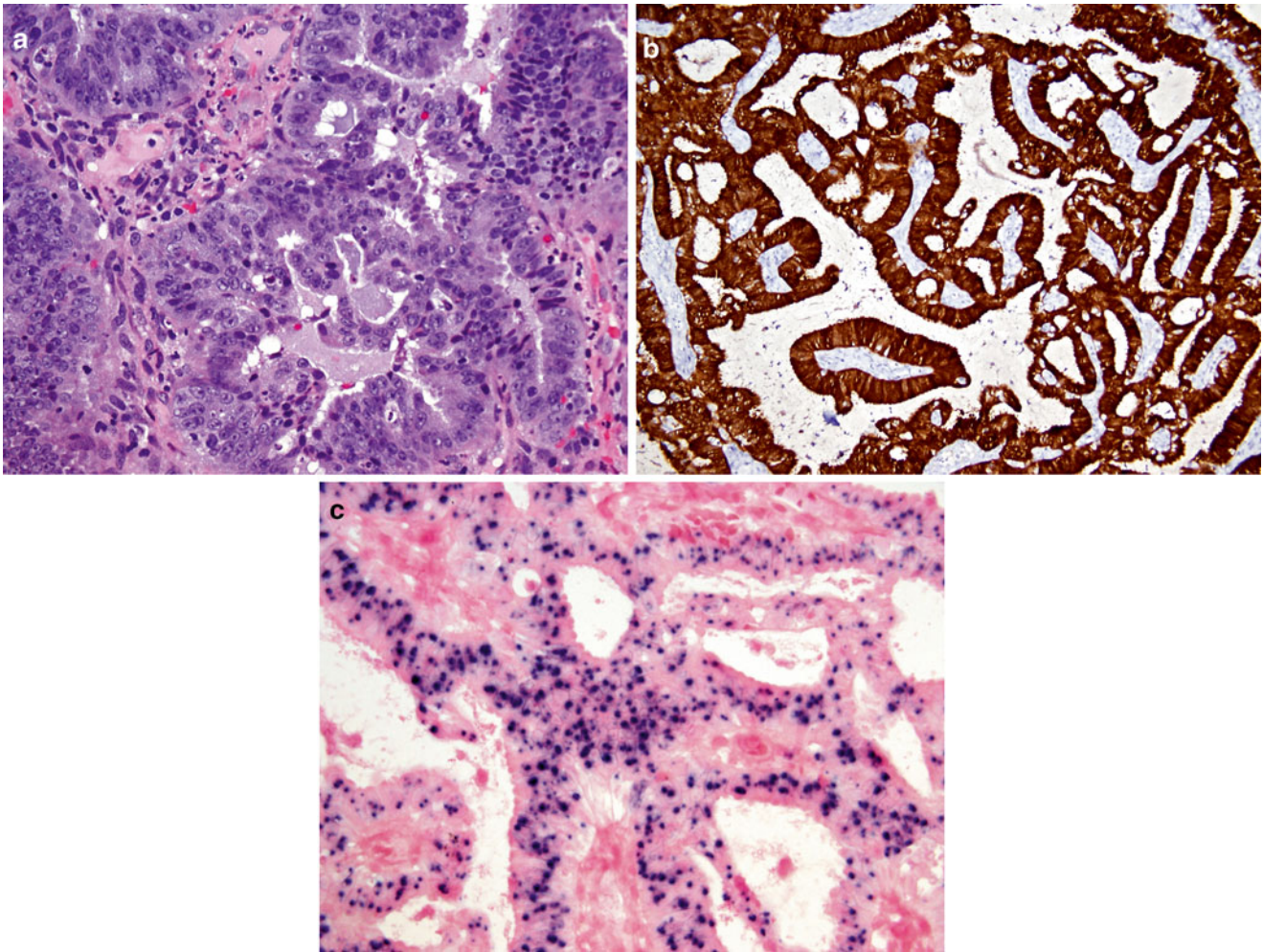
Fig. 19.5 Invasive endocervical adenocarcinoma on H & E (**a**), with p16 diffuse and intense positive staining (**b**) and positive inclusions by in-situ hybridization for HPV (**c**)

Table 19.11 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/EpCAM	**+**	+ 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 +	+	−
HMB45	−	−	−	− 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 rhabdomyosarcoma

References: [1, 52–56]

Table 19.12 Markers for mesonephric adenocarcinoma of cervix

Antibodies	Literature
Calretinin (nuclear)	+ or −
Vimentin	+ or −
p16	− or +[a]
PAX-8	+
CAM5.2	+
CK(AE1, AE3)	+
CK7	+
EMA	+
HNF-1β	+
CD10	+ or −[b]
AR	− or +
Inhibin	− or +
ER	−
PR	−
CEA-M	−
CK20	−

Additional negative markers include

Figure 19.6

[a]Apical

[b]Patchy

References: [57–59]
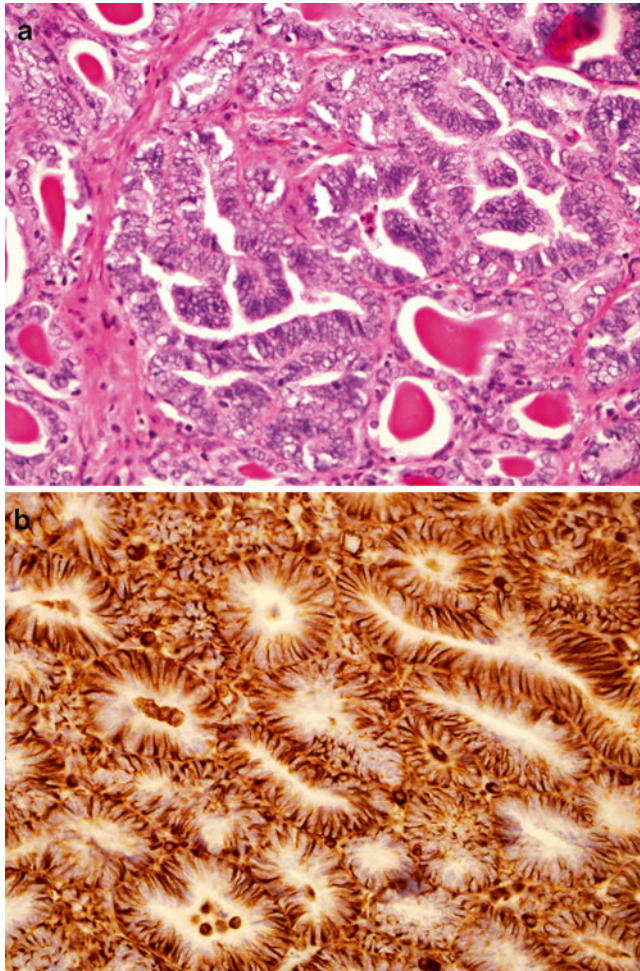
Fig. 19.6 Mesonephric carcinoma on H & E (**a**) and positive vimentin (**b**)

Table 19.13 Markers for endometrioid adenocarcinoma of the endometrium

Antibodies	Literature
CK 7	+
ER	+
Vimentin	+
PAX-8	+
CAM5.2	+[a]
BerEP4	+
CK(AE1, AE3)	+[a]
EMA	+[a]
CA125	+
PR	+
Cyclin D1	+
CK 5/6	+ or −
Beta-catenin	− or +
Mesothelin	+ or −
p53	− or +[b]
WT 1	− or +[c]
PTEN	− or +
CD 56	− or +
Bcl2	− or +
CDX2	− or +
Calretinin	− or +
TTF1	− or +
CEA-P	− or +
CEA-M	− or +
MUC5AC	− or +
p63	− or+[d]
TAG72	− or +
IMP3	− or +
CDX2	− or +
p16	−[e]

Additional negative markers include: CK20, HepPar-1, HNF-1β, GCDFP-15, MUC-2, PAX-2 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

Figure 19.7

[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

References: [1, 34, 38, 51, 60–75]
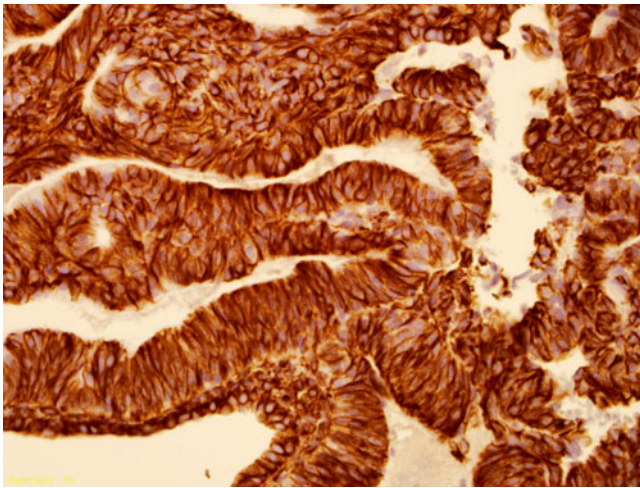
Fig. 19.7 Intense vimentin staining in endometrioid adenocarcinoma

Table 19.14 Markers for serous carcinoma of the endometrium and putative precursors EIC EIC (most commonly used shaded)

Antibodies	Literature
IMP3[a]	+
p53[a]	+[b]
p16[a]	+ or −[c]
PanCK	+
EMA	+
BerEP4	+
CK7	+
CA125	+
Vimentin	+
Ki67	+[d]
PAX-8	+
IMP2	+
WT1	− or +
CEA-M	− or +
ER	− or +
PR	− or +
Bcl2	− or +
Her2neu	− or +
D2-40	− or +
HNF-1β	− or +
HER2/neu	− or +
B-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. IMP3 and p53 are also helpful. However, high grade endometrioid carcinomas can stain for all three. WT1 should be weak or negative in endometrial vs. upper genital trace serous carcinomas, but not consistently

Table 19.14 (continued)

[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, 67–76]

Table 19.15 Markers for clear cell carcinoma of the endometrium[a]

Antibodies	Literature
HNF-1	+
ER	− or +
PR	− or +
PanCK	+
EMA	+
BerEP4	+
CK7	+
Vimentin	+
p16	− or +
WT-1	− or +
p53	− or +[b]
CK20	−
CEA	− or +
Cyclin-D1	− or +[c]
E-cadherin	−
Loss of MSH6	Rare
Loss of PMS2	Rare

[a]Additional markers such as Napsin and ACAR are under study (most of the data is in ovarian clear cell cancers)

[b]Focal and weak

[c]Negative or weakly positive

References: [1, 19–25, 31, 61, 77]

Table 19.16 Markers for Carcinosarcoma of the endometrium[a,b,c]

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

[a]Myogenin and Myo-D1 are also used to establish a rhabdomyoblastic differentiation

[b]Vimentin, ER, 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, 61, 78]

Table 19.17 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, however

[c]In epithelial component

Table 19.18 Markers for stromal nodule and low grade endometrial stromal sarcoma[a,b]

Antibodies	Literature
CD10	+
SMA	+ or −
Desmin	− or +
h-Caldesmon	− or +
PR	+
PR	+
Vimentin	+
WT1	+
AR	+ or −
Calponin	+ or −
B-catenin	+ or −
CK (AE1, AE3)	− or +
CAM5.2	− or +
Pan-CK	− or +
ACTIN-HHF35	− or +

Additional negative markers include CD117, EMA, Inhibin, CD34 and HMB45

[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: [79–85]

Table 19.19 Markers for high grade endometrial stromal sarcoma[a,b]

Antibodies	Literature
Cyclin-D1	+[a]
CD117[n]	+
CD10	− or +[b]
ER	−
PR	−
DOG-1	−

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

[n]no KIT mutations

References: [1, 86, 87]

Table 19.20 Markers for undifferentiated uterine sarcoma[a]

Antibodies	Uniform variant	Pleomorphic variant
CD10	+/−	+/−
Cyclin-D1	−	+
ER	+	−
PR	+	−
B-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, adenosarcoma with stromal overgrowth must be excluded

References: [85–87]

Table 19.21 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 −
AR	+ 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: [78, 88, 89]

Table 19.22 Markers for uterine smooth muscle tumors

Antibodies	Leiomyoma	Leiomyosarcoma
Desmin	+	+ or −
SMA	+	+
h-Caldesmon	+	+
Cyclin D1	+	+
p53	− or +	− or +
HMB45	− 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 +
DOG-1	−	−
CD34	−	−

Additional negative markers include: S100, Alk1, p63, Calretinin, Beta-Catenin (nuclear), CD31, CD117, CD163, Tyrosinase, Myogenin, Inhibin, Myoglobulin, MART1, GFAP, NFP, Factor VIIIR AG, CK19 and HepPar-1

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

References: [90–106]

Table 19.23 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	+
Vimentin	+ or −
BerEP4	− or +
CK 5/6	− or +
PAX-8	−

Additional negative markers include CEA-P, CEA-M, TAG72, CD15, CD31, CD34, Factor 8, 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: [107, 108]

Table 19.24 Markers for PECOMAs

Antibodies	Literature
HMB45	+
MelanA	+ or −
MiTF	+ or −
CD1a	+ or −
S100	−
Inhibin	−
CK (AE1, AE3)	−
Desmin	+ or −
SMA	+ or −
Calponin	+
Vimentin	+
FVIIIRAG	+
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: [109–113]

Table 19.25 Markers for gestational trophoblastic lesions

Marker	PSN	PSTT	ETT	CC
β-HCG	+ or −	− or +a	− or +	+
HLA-G	+	+	−	+
P63	+	− or +	+	+ or −
Ki-67 index	≤10 %	15–25 %	10–25 %	>50–70 %
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: [114–124]

Table 19.26 Differentiating high grade SIL from benign mimics and low grade SIL

Marker	HGSIL	AR	RC	AT	ISM	TM	LGSIL
P16	+a	−	−	−	−	−	+ or −b
Ki67	+a	− or +b	− or +b	− or +b	− or +b	− or +b	+b
HPVc	+	−	−	−	−	−	+

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

aDiffuse, strong nuclear staining involving the superficial two thirds of the involved mucosa

bOnly the basal layer is involved

cBy in-situ hybridization

References: [4–18, 42, 43]

Table 19.27 Differentiating in-situ adenocarcinoma of cervix and endometriosis or tubal-endometrial metaplasia

Antibodies	In-situ Adenocarcinoma	Endometriosis
CEA-P	+	−
PAX-2	−	+
P16	+a	+ or −b
Ki67	+ or −	− or +
ER	− or +	+
PR	− or +	+
CD10	− or +	− or +
Vimentin	− or +	−
Chromogranin-A	− or +	−
EpCAM/BerEP4	+	+
CK7	+	+
CK20	− or +	−
P53	− or +	−

aStrong diffuse

bMostly patchy

References: [4–18]

Table 19.28 Differential diagnosis of cervical microglandular hyperplasia

Antibodies	MICROGH	MDA (M)	MDA (E)	ADENOCX	ENDOMCA
MIB1	<1 %	ND	ND	High	High
PAX-2	+[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	–	+
CA125	+[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]PAX-2 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, 45–51]

Table 19.29 Endocervical vs. low grade endometrial adenocarcinoma[a]

Antibodies	Cervix	Endometrium
CEA	+	–
Vimentin	–	+
P16	+	– or +
ER	– or +	+
IMP3	+	– or +
MUC5AC	– or +	+
PR	– or +	+
HPV DNA	+	–

[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.

References: [4–18]

Table 19.30 Differentiating epithelioid trophoblastic tumor and cervical squamous cell carcinoma (most commonly used shaded)

Antibodies	Epithelioid trophoblastic tumor	Squamous cell carcinoma
Inhibin	+	–
HLA-G	+	–
HPL	+	–
CD146	+	–
p63	+	+
PLAP	+ or –	– or +
CK (AE1, AE3)	+	+
EMA/MUC1	+	+
AFP	–	–
Ki67	+	+
CEA-P	+	– or +

References: [4, 6, 7, 114–124]

Table 19.31 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 –
PAX-8	ND	ND	–	–
TTF-1	–	–	–	– 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 marker is neuroendocrine 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: [52, 125–127]

Table 19.32 Arias-Stella reaction and clear cell carcinoma of endometrium[a]

Antibodies	Arias-stella reaction	Clear cell carcinoma
MIB1	+ 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 MIB1 will likely distinguish them all

References: [128, 129]

Table 19.33 Endometrial adenocarcinoma and carcinosarcoma (MMMT)[a]

Antibodies	Adenocarcinoma	Carcinosarcoma
CD10	–	+ Usually M + C
CK(AE1, AE3)	+	+
CA125	+	–
Calretinin	–	– or +
CAM5.2	+ C	+ C
CEA-P	– or +	–
CK5/6	+ or –	–
CK7	+	+ or –
CK20	–	–
EMA	+	+
HepPar1	–	–
Inhibin	–	–
PLAP	– or +	– or +
S100	+	–
Thrombomodulin	–	–

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

References: [61, 67, 78, 94]

Table 19.34 Clear cell carcinoma (CCC) vs. 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
PAX-8	+ or –	–	ND	+	–
CK7	+	+	–	–	–
SALL4	–	–	–	–	+
BerEp4	+	+	–	–	ND
Vimentin	+	–	+	+	–
Desmin	–	–	-	–	–
Melan-A	–	–	+	+ or –	–
HMB45	–	–	+	– 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 +	+	–
RCC Ma	–	–	–	+	–

References: [19–26, 128, 130]

Table 19.35 Endometrial serous vs endometrioid and clear cell adenocarcinoma

Antibodies	Serous	Endometrioid	Clear cell
β-catenin (N)	−	+ or −	−[a]
HNF-1[b]	− or +	− or +	+
ER	− or +	+	− or +
PR	− or +	+	− or +
p16	+	− or +	− or +
IMP3	+	− or +	+ or −
ARID1A	+ or −	+ or −	+ or −
PTEN	+	−	+[a]
PMS2	+	− or +	ND
MSH6	+	− or +	ND
p53	+[c]	− or +[d]	− or +[d]
PAX-8	+	+	+
Vimentin	+	+	+
CK 7	+	+	+
TTF1	− or +	− or +	ND
WT-1	−	− 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, 61, 68–72, 131]

Table 19.36 Useful markers in the differential diagnosis of endometrial undifferentiated carcinoma (UC)

Antibodies	UC	EAC	SERC	US	EPS	NE	LYM
CAM 5.2	+ or −[f]	+	+	−	+	+ or −	−
AE1, AE3	− or +[f]	+	+	−	+	+	−
EMA	+ or −[f]	+	+	−	+	+	−
MMR	− or +	+ or −	+	ND	ND	ND	ND
ER	− or +	+	− or +	V	ND	ND	−
PR	− or +	+	− or +	V	ND	ND	−
Desmin	−	−	−	− or +[f]	− or +	−	−
MSA	−	−	−	−	− or +	−	−
CD138	−	ND	ND	ND	− or +	− or +	− or +
CD56	− or +[fa]	−	−	−	− or +	+	+
SYNAP	− or +[fa]	−	−	−	ND	+ or −	−
CHROM	− or +[fa]	−	−	−	ND	+ or −	−
NSE	− or +[fa]	−	−	−	− or +	+ or −	−
LYMARK	−	−	−	−	−	−	+

EAC High grade endometrioid adenocarcinoma, *SER* 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

f focal, *V* negative in pleomorphic variant and positive in uniform variant, *ND* No data

[a]In less than 10 % of tumor cells

References: [26–31, 61]

Table 19.37 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 +
SMA	+	+ or −
Calponin	+	+ or −
Cyclin-D1	+	− or +
ER	− or +	+
PR	− or +	+
CD99	− or +	−
WT1	− or +	+
P53	− or +	− or +
Pan-CK	− or +	− or +
EMA/MUC1	− or +	−
CAM5.2	− or +	− or +
Calretinin	−	− or +
S100	− or +	−
HMB45	− or +	−
ALK1	− or +	−
CD117	−	− or +
CD34	− or +	−
P63	− or +	−

Additional <u>negative</u> markers for both tumors include: Myoglobin, Hep-Par-1, DOG-1, inhibin and CD163

[a]N = Nuclear

[b]SMMHC = Smooth muscle myosin heavy chain

References: [79–90, 99–104]

Table 19.38 Differentiating leiomyosarcoma and PEComa

Antibodies	Leiomyosarcoma	PEComa
MelanA 103	−	+
FVIIIRAg	−	+
CD31	−	+
HMB45	− or +	+
S100	−	− or +
Vimentin	+	+
Desmin	+	+ or −
SMA	+	+
Calponin	+	+
CD117	−	− or +
MITF	− or +	+
CD34	− or +	− or +
CD57	+	−

(continued)

Table 19.38 (continued)

Antibodies	Leiomyosarcoma	PEComa
CD99	− or +	−
ER	− or +	− or +
PR	− or +	− or +
Tyrosinase	−	− or +
Pan-CK	− or +	−
ALK1	− or +	−
CD68	− or +	− or +
EMA/MUC1	− or +	−
CK(AE1, AE3)	− or +	−
CAM5.2	− or +	−
BerEP4	−	−
HepPar1	−	−

References: [1, 90, 93, 101–104, 109, 111–113]

Table 19.39 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]	+
Myo-D1	− or +	ND	−	+
Myogenin	−	ND	ND	+
Myoglobin	−	ND	ND	+ or −
DOG-1	−	+	−	−
ALK-1	−	−	+ or −[b]	− or +
CD34	− or +	+	−	− or +
CD117	+	+	−	− or +

[a]Frequently focal

[b]Patchy, granular cytoplasmic

References: [2, 3, 5, 16, 94, 98, 99, 103]

Table 19.40 Complete hydatidiform and partial hydatidiform mole

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

N Nuclear

References: [114–116]

Table 19.41 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/MUC1	+	+
CK(AE1, AE3)	+	+
PLAP	+ or −	− or +
CD68	−	−
S100	−	+ or −
ER	+ or −	+ or −
EGFR	+	+ or −

References: [1, 118–122]

Table 19.42 Differentiating placental site trophoblastic tumor and mimics [exaggerated placental site (EPS), epithelioid trophoblastic tumor (ETT), choriocarcinoma (CC), epithelioid smooth muscle tumor (ESMT), metastatic carcinoma (MC) and Malignant Melanoma (MM)]

Marker	PSTT	EPS	ETT	CC	ESMT	MC	MM
HLA-G	+	+	+	+	−	−	−
CK (AE1, AE3)	+	+	+	+	+	+	−
p63	−	+ or −	+	+ or −	−	+ or −	−
Beta-HCG	− or +	− or +	− or +	+	−	−	−
Ki67	+ >10 %	<10 %	+ or −	+++	+ or −	+	+ or −
S100	−	−	−	−	+ or −	−	+
HPL	+	+	− or +	+	−	−	−
CD146	+	+	− or +	+	−	−	−
CK18	+	+	+	+	− or +	+ or −	−
EMA	+	+	+	+	−	+	−
Inhibin	+	+	+	+	−	−	− or +
HMB45	−	−	−	−	+ or −	−	+

Figure 19.8

EPS exaggerated placental site, *ETT* epithelioid trophoblastic tumor, *CC* Choriocarcinoma, *ESMT* epithelioid smooth muscle tumor, *MC* metastatic carcinoma, *MM* malignant melanoma
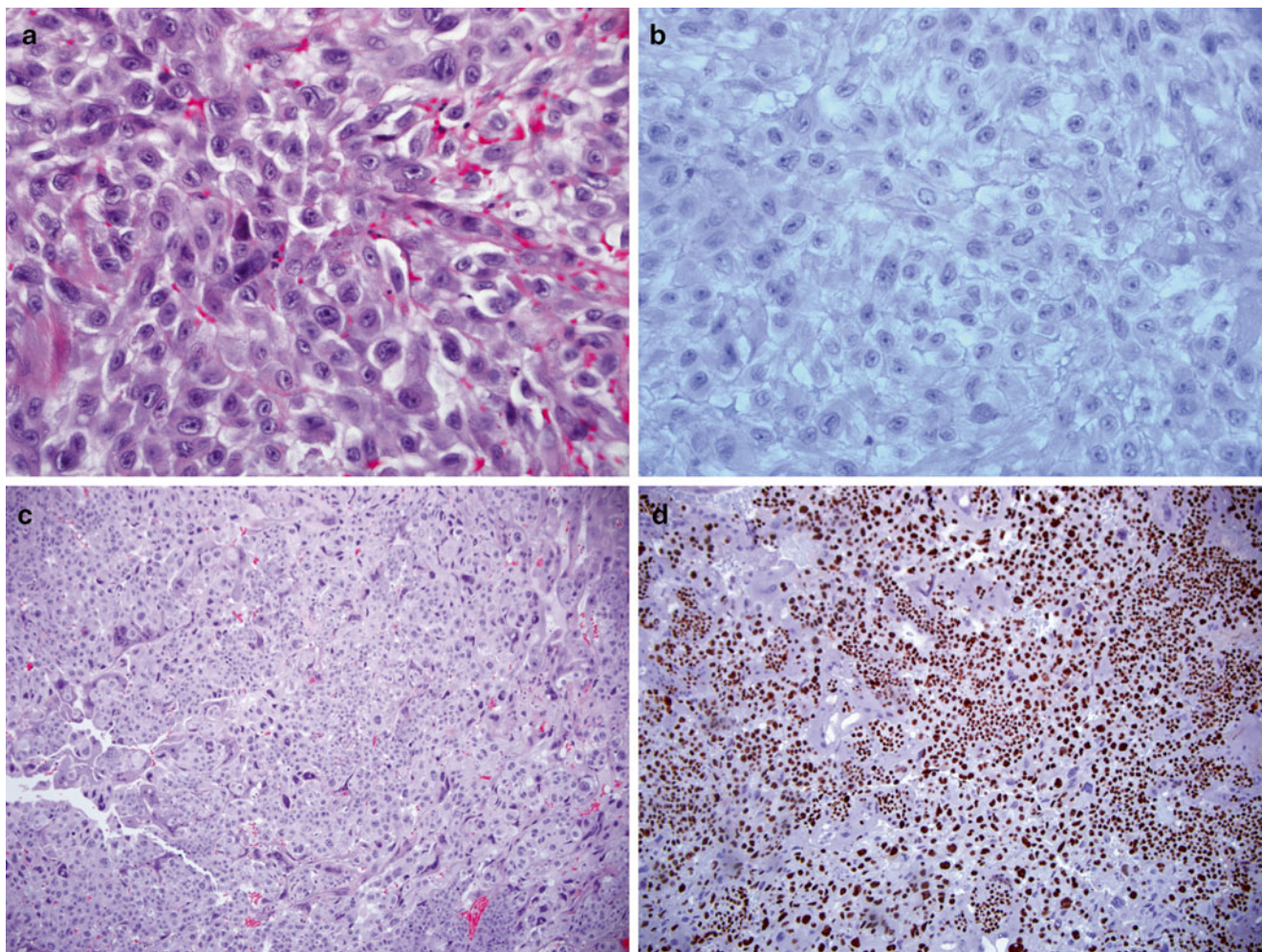
References: [114–124]

Fig. 19.8 Exaggerated placental site on H & E (**a**) with negative Ki-67 (**b**) compared to Choriocarcinoma on H & E (**c**) that demonstrates extremely elevated Ki-67 proliferative indes (**d**)

Table 19.43 Summary of common markers of primary uterine carcinoma and the more common metastatic <u>carcinomas</u> (recommended markers highlighted)

Marker	Cervix	Uterus	Ovary	Stomach	Breast	Colon	Kidney	Lung	Bladder
CK7	+	+	+	+	+	−	−	+	+
CK20	−	−	−	− or +	−	+	−	+	+ or −
p63	+ or −	−	−	−	−	−	−	−	+
TTF1	−	+ or −	+ or −	−	−	−	−	+	−
CDX2	− or +	−	−	+ or −	−	+	−	−	−
ER	−	+	+	−	+	−	−	−	−
RCC Ma	−	−	−	−	−	−	+	−	−
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]

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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