Markers and Immunoprofile of Male Genital Tract Tumors

13

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13.1 Prostatic Tumors

Diagnostic antibody panel for prostatic adenocarcinoma (acinar and ductal) and basal cell carcinoma.

13.1.1 Markers for Prostatic Epithelium

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13.1.2 Markers for Basal Cells

High molecular weight Cytokeratins (CK5, CK6, CK14, CK34βE12), p40, p63, EGFR.

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13.1.2.1 Prostate-Specific Antigen

Prostate-specific antigen (PSA)		
Expression pattern: cytoplasmic		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Carcinoma of the prostate	Salivary duct carcinoma, small cell carcinoma	Prostatic secretory and ductal epithelium, periurethral glands, male anal glands, skene gland, salivary glands
Positive control: prostatic tissue		

Diagnostic Approach Prostate-specific antigen (PSA, also known as kallikrin-3) is a single-chain glycoprotein and a serine protease synthesized by the epithelium of prostatic acini and prostatic ducts and secreted into prostatic ducts playing a role in the liquefaction of seminal fluid. Normally, protease inhibitors rapidly inactivate PSA portion that enters the blood circulation. PSA is one of the most specific markers for prostatic parenchyma and prostatic carcinoma. Metastatic carcinoma positive for Pan-Cytokeratin but negative for Cytokeratins 5/7/14 and 20 suggests a primary prostatic carcinoma, and the expression of PSA and/or NKX3.1 will confirm the prostatic origin.

Diagnostic Pitfalls About 10% of high-grade prostatic carcinoma is negative for PSA. In such cases, other prostate-specific markers such as NKX3.1, prostate-specific membrane antigen, prostatic acid phosphatase, and androgen receptors are useful to confirm the diagnosis. Low levels of PSA expression are reported in tumors other than prostatic carcinoma. A weak expression level of PSA is found in a subset of salivary duct carcinoma. Weak expression of PSA is also reported in small cell carcinoma and breast carcinoma in addition to endometrioid carcinoma.

13.1.2.2 Prostein

Prostein (SLC45A3, P501S)		
Expression pattern: cytoplasmic, perinuclear Golgi pattern		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Carcinoma of the prostate	None described	Prostatic secretory and ductal epithelium, periurethral glands, male anal glands
Positive control: prostatic tissue		

Diagnostic Approach Prostein [solute carrier family 45, type 4 (SLC45A4)] is a transmembrane transporter protein found in the Golgi apparatus of prostatic secretory epithelia. Prostein is more specific in determining the prostatic origin than PSA and slightly more sensitive and is usually still preserved in poorly differentiated prostatic carcinoma. Prostein can thus be successfully used in a panel with NKX3.1 and PSA to classify metastases of unknown primary or to discriminate between prostatic, urothelial, and colorectal carcinomas [1]. Additionally, the expression of prostein is found in about 30% of small cell carcinoma of the prostate. The loss of prostein expression is associated with an unfavorable clinical course [2].

Diagnostic Pitfalls Negativity for prostein does not rule out the prostatic origin.

13.1.2.3 Prostatic Acid Phosphatase

Prostatic acid phosphatase (PAP)		
Expression pattern: cytoplasmic		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Carcinoma of the prostate	Neuroendocrine tumors, intravascular large B cell lymphoma	Acinic and ductal epithelium of the prostate, periurethral glands, male anal glands
Positive control: prostatic tissue		

Diagnostic Approach Prostatic acid phosphatase (PAP) is an enzyme secreted by prostatic epithelium and a major component of the prostatic fluid. PAP is more sensitive but less specific than PSA for prostatic glands and prostatic carcinoma. PAP can be successfully used in a panel with PSA to classify metastases of unknown primary tumors.

Diagnostic Pitfalls Similar to PSA, PAP can also be expressed in neuroendocrine carcinomas of different origins. This feature is important for the differentiation between poorly differentiated prostatic carcinoma, prostatic carcinoma with neuroendocrine differentiation, and other neuroendocrine tumors. The expression of PAP is one of the immunohistochemical characteristics of the primary neuroendocrine tumors of the rectum.

13.1.2.4 Prostate-Specific Membrane Antigen (PSMA)

Glutamate carboxypeptidase II (also known as prostate-specific membrane antigen; PSMA) is a class II membrane glycoprotein and an enzyme that catalyzes the hydrolysis of *N*-acetylaspartylglutamate to glutamate and *N*-acetylaspartate. Despite its name as prostate-specific membrane antigen, PSMA is not a prostate-specific marker, and besides normal and malignant prostatic glandular epithelium, it is expressed in other different tissue types such as salivary glands, intestinal mucosa, epithelium of proximal renal tubules, and ganglion cells of the nervous system in addition to the apical surface of neovascular endothelial cells associated with different tumors [3–6]. The expression of PSMA is strongly upregulated in high-grade PIN and prostatic adenocarcinoma and correlates with the Gleason score and disease progression with high expressed levels in hormone-refractory high-grade carcinoma.

PSMA is also highly expressed in other tumors, such as adenoid cystic carcinoma.

PSMA is now the therapeutic target for neoplasia-associated angiogenesis and some tumor types exhibiting PSMA overexpression.

13.1.2.5 Androgen Receptor

Androgen receptor		
Expression pattern: nuclear		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Carcinoma of the prostate – Breast carcinoma with apocrine differentiation/ different receptor-positive and triple-negative breast carcinoma	Bladder transitional cell carcinoma, endometrioid carcinoma, salivary duct carcinoma, sebaceous carcinoma, basal cell and squamous cell carcinoma, Paget's disease, papillary thyroid carcinoma, mesonephric adenocarcinoma, spindle cell lipoma and well-differentiated liposarcoma, osteosarcoma, meningioma	Prostatic epithelium, urinary bladder urothelium, Sertoli cells, Leydig cells, rete testis, epididymis and seminal vesicles, apocrine and sebaceous glands, skin, oral mucosa, hepatocytes, erythroid precursors
Positive control: prostatic tissue		

Diagnostic Approach The androgen receptor (AR) is a nuclear receptor and a member of the steroid hormone receptor family that includes the estrogen receptor, progesterone receptor, glucocorticoid receptor, and mineralocorticoid receptor. The androgen receptor is activated by binding to testosterone or dihydrotestosterone and takes part in the development and differentiation of both male and female reproductive organs and musculoskeletal, cardiovascular, immune, neural, and hemopoietic systems [3, 7]. The AR is expressed in different tissue types, including the prostatic gland, bone, and skin adnexa. Neoplastic prostatic glands are usually positive for AR, but studies show no direct correlation between the intensity of AR expression and the response to hormonal therapy [8]. AR is also positive in neuroendocrine tumors of the prostate.

Diagnostic Pitfalls The expression of AR is not restricted to prostatic carcinoma and can be found in other carcinoma types occasionally with similar morphology, such as transitional cell carcinoma of the urinary bladder and urethra, endometrioid carcinoma, salivary duct carcinoma, breast carcinoma, and breast carcinoma with apocrine differentiation.

13.1.2.6 NKX3.1

NKX3.1		
Expression pattern: nuclear		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Prostatic acinar adenocarcinoma – Prostatic ductal adenocarcinoma	GCNIS, lobular breast carcinoma, a subset of T-ALL, rare sarcoma types (EWSR1-NFATC2 Ewing-like sarcoma and mesenchymal chondrosarcoma)	Prostatic tissue, salivary glands, mucinous bronchial glands, Sertoli cells
Positive control: prostatic tissue		

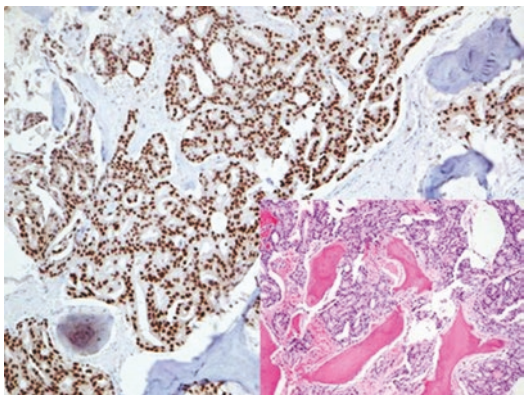


Fig. 13.1 Metastatic acinar prostatic carcinoma with strong nuclear NKX3.1 expression

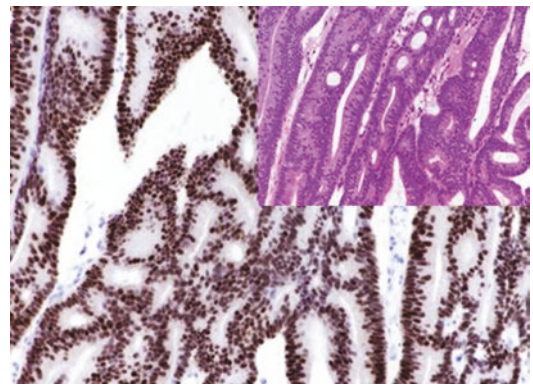


Fig. 13.2 Prostatic ductal adenocarcinoma with strong nuclear NKX3.1 expression

Diagnostic Approach NKX3.1 (also known as KX3–1, BAPX-2) is encoded by an androgen-regulated tumor suppressor gene located on chromosome 8p221.1. NKX3.1 functions as a suppressor regulating the proliferation and differentiation of prostatic luminal epithelium. NKX3.1 is strongly expressed in the nuclei of normal prostatic secretory epithelium but negative in prostatic stromal cells. NKX3.1 is a specific marker for primary acinar prostatic carcinoma and ductal adenocarcinoma, whereas the intensity of the nuclear expression correlates with the differentiation grade of the carcinoma and can be very weak in poorly differentiated carcinomas (Figs. 13.1 and 13.2) [9].

Diagnostic Pitfalls NKX3.1 is also expressed in testicular germ cells and seminoma in situ (GCNIS) but lost in invasive seminoma and embryonal carcinoma. Low to moderate NKX3.1 expression intensity is also found in a subset of estrogen- and/or androgen-positive breast carcinomas, i.e., invasive lobular carcinoma (Fig. 13.4) [10, 11]. Mucinous units of salivary glands and bronchial glands also reveal a nuclear NKX3.1 expression, which is to consider in the interpretation of small biopsies (Fig. 13.3). Furthermore, the TAL-1 genetic aberration associated with a subset of T-ALL causes the activation of NKX3.1 expression in neoplastic lymphocytes [12]. NKX3.1 is also a characteristic marker for the mesenchymal chondrosarcoma and Ewing-like sarcoma harboring the EWSR1-NFATC2 translocation [13].

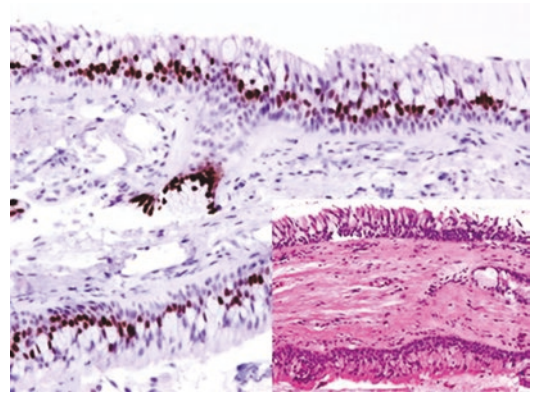


Fig. 13.3 Nuclear NKX3.1 expression in mucinous cells of bronchial mucosa

13.1.2.7 Alpha-methylacyl-CoA Racemase

Alpha-methylacyl-CoA racemase (AMACR, p504S)		
Expression pattern: cytoplasmic		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Prostatic adenocarcinoma – High-grade PIN – Papillary renal cell carcinoma	Gastrointestinal adenocarcinoma, hepatocellular carcinoma, carcinoma of breast and ovaries, endometrial clear cell carcinoma, urothelial carcinoma, extramammary Paget's disease, mucinous tubular and spindle cell carcinoma, mesothelioma, lymphoma, pancreatic islet tumor, dysplastic nevi	Periurethral glands, liver, salivary glands, sebaceous glands, renal tubular epithelium, pancreas epithelium, mesothelial cells
Positive control: prostatic carcinoma		

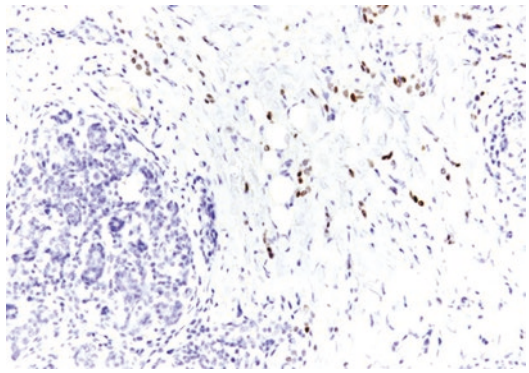


Fig. 13.4 NKX3.1 highlighting a subset of the tumor cells of invasive lobular carcinoma

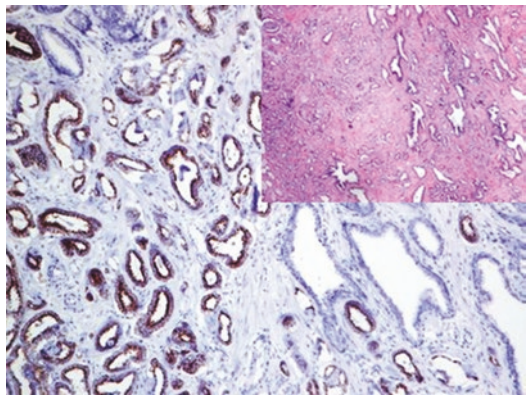


Fig. 13.5 Cytoplasmic AMACR expression in the neoplastic luminal cells of prostatic adenocarcinoma

Diagnostic Approach Alpha-methylacyl-CoA racemase (also known as p504S) is a member of the isomerase enzyme family involved in the metabolism of branched-chain fatty acids and synthesis of bile acids. It is expressed in the mitochondria and peroxisomes of various normal and neoplastic cells. P504S is overexpressed in prostatic carcinoma compared to benign prostatic glands (Fig. 13.5) [14–16]. In combination with p63, alpha-methylacyl-CoA racemase (AMACR) is now widely used for the diagnosis of prostatic carcinoma (so-called PIN cocktail). p63 is a marker for basal/myoepithelial cells exhibiting a strong nuclear stain listed in detail in previous chapters with the epithelial and renal tumor markers (see Chap. Sects. 2.5 and 12.1) [17].

The dual immunohistochemical stain with the PIN cocktail can show one of the following three expression patterns

– AMACR-positive prostatic glands lacking the p63-positive myoepithelial cells, a combination characteristic of neoplastic glands.
– AMACR-positive glands surrounded by p63-positive myoepithelial cells, characteristic of prostatic glands with high-grade PIN.
– AMACR-negative prostatic glands surrounded by p63-positive myoepithelial cells, a pattern characteristic for normal prostatic glands.

High molecular cytokeratins such as CK5/6/14 can be used as alternatives to p63 in a separate reaction (Fig. 13.6).

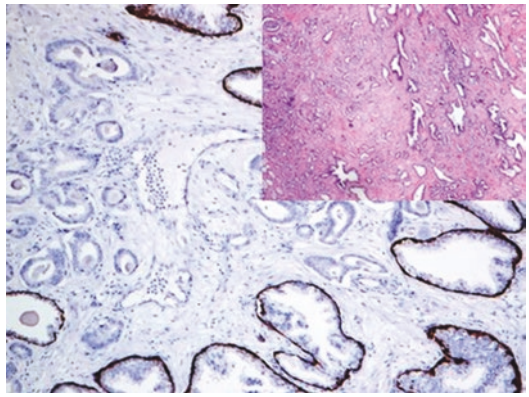


Fig. 13.6 Neoplastic glands of prostatic adenocarcinoma lacking the myoepithelial cells positive for high molecular weight cytokeratin (CK5/14)

The AMACR expression is characteristic for papillary renal cell carcinoma, mucinous tubular and spindle cell carcinoma, and Xp11 translocation renal cell carcinoma and may be also expressed in a very small subset of clear cell carcinoma but is constantly absent in chromophobe renal cell carcinoma [18, 19].

Diagnostic Pitfalls The luminal epithelium of high-grade prostatic intraepithelial neoplasia is frequently positive for AMACR, and it is also to consider that the expression of the high molecular cytokeratins may be partially lost in such lesions. Low AMACR expression levels may be also seen in benign histologic mimics of prostatic adenocarcinoma, including atrophic prostatic glands and post-atrophic hyperplasia, adenosis, seminal vesicle, and periurethral glands. The expression of AMACR is also characteristic for nephrogenic adenoma but later is positive for PAX-8 and GATA-3 and negative for NKX3.1.

In general, the expression of AMACR is found in many benign and malignant tumor types and cannot be considered a specific lineage marker of prostatic carcinoma [20].

13.1.2.8 ERG

ERG		
Expression pattern: nuclear		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Prostatic adenocarcinoma, endothelial tumors – Angiosarcoma/ endothelial tumors	Acute myeloid leukemia, B and T lymphoblastic leukemia, meningioma, GIST, solitary fibrous tumor, chondrosarcoma, chondroblastic osteosarcoma, epithelioid sarcoma, synovial sarcoma, malignant rhabdoid tumor, phosphaturic mesenchymal tumor	Endothelial cells, myeloid precursors
Positive control: blood vessels		

Diagnostic Approach **E**26 transformation-specific **r**egulated **g**ene-1 (ERG) is a member of the ETS family of transcription factors, which also includes Fli-1 and EST-1 encoded by the gene located on chromosome 21q22.3. ERG plays a role in the regulation of angiogenesis and differentiation of hematopoietic stem cells. ERG is normally expressed in endothelial cells and cells with endothelial differentiation in addition to myeloid precursors and tumors derived from these cells (Fig. 13.7) [5].

The ERG gene is the fusion partner of the TMPRSS2 gene involved in the regulation of response to androgen. This genetic mutation is the most frequent genetic abnormality associated

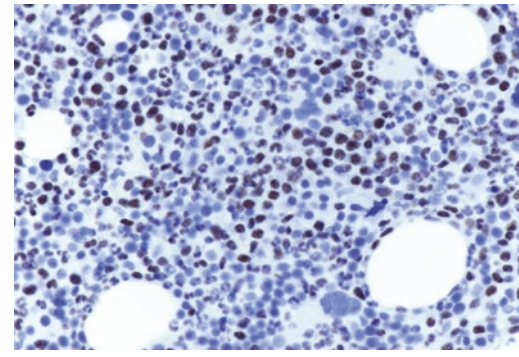


Fig. 13.7 Bone marrow with normal myeloid precursors showing nuclear ERG expression

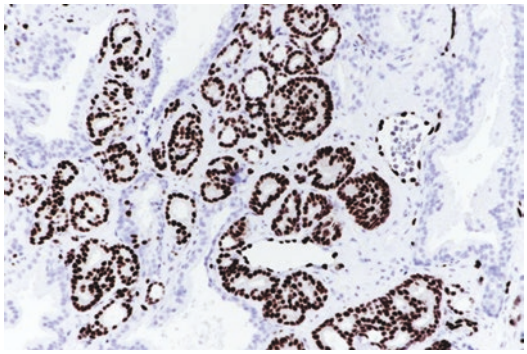


Fig. 13.8 Nuclear ERG expression in neoplastic cells of prostatic acinar adenocarcinoma; normal prostatic glands lack the ERG expression. Note that ERG also labels the endothelium of normal blood vessels

with prostatic carcinoma and is found in 40–80% of acinar adenocarcinoma and about 10% of ductal adenocarcinoma. This mutation generates the TMPRSS2-ERG gene fusion causing the overexpression of the ERG protein detected by immunohistochemistry (Fig. 13.8) in acinar prostatic carcinoma and frequently also in prostatic neuroendocrine carcinomas [21, 22].

Diagnostic Pitfalls The immunohistochemical results using this marker must be carefully interpreted as positive staining is observed in about 29% of high-grade PIN and occasionally benign glands. Consequently, the gold standard remains the labeling of the myoepithelial basal cells [23]. Both antibodies to ERG and p63 can be used as a cocktail for the diagnosis of prostatic carcinoma but have less sensitivity than the above-described PIN cocktail [24].

Despite this obvious lack of sensitivity, ERG positivity in metastasis of unknown epithelial primary can be considered confirmative of prostate cancer.

The aberrant expression of ERG is also characteristic for the solitary fibrous tumor because of other genetic anomalies associated with this tumor. ERG expression is also reported in a few other mesenchymal tumors, including chondrosarcoma, chondroblastic osteosarcoma, epithelioid sarcoma, synovial sarcoma, GIST, fibrous meningioma, and t(21;22)(q22;q12) associated Ewing's sarcoma [25]. ERG expression is also described in rare cases of invasive ductal carcinoma of the breast and papillary thyroid carcinoma. Moreover, EGR is expressed in a subset of acute myeloid leukemia and myeloid sarcoma in addition to B and T lymphoblastic leukemia/lymphoma.

13.1.2.9 Phosphatase and Tensin Homolog (PTEN)

PTEN is a tumor suppressor mentioned in a previous chapter (Chap. 11). The loss of PTEN is found in about 20% of primary carcinomas, with higher rates of PTEN loss in higher Gleason scores. PTEN loss is prognostically unfavorable. Diagnostically, the loss of PTEN expression may help to distinguish intraductal carcinoma (commonly lost) from high-grade PIN (often positive) if the morphological context supports this.

Immunoprofile of prostatic and seminal vesicle tumors				
Tumor type	+ in >90% (+)	+ in 50–90% (+/−)	+ in 10–50% (−/+)	+ in <10% (−)
Sclerosing adenosis of the prostate	Preserved myoepithelial basal cells positive for high molecular Cytokeratins (CK5/CK6/CK14, CK-34E12), p63, p40, LP34			
Acinar adenocarcinoma	Pan-CK, CK8/18, CK19, **PSA**, PAP, **NKX3.1**, **Prostein**, hK2, **p504S (racemase)** **Diagnostic is the loss of basal myoepithelial cell layer: negativity for high molecular Cytokeratins (CK5/6/14, CK-34E12), p63, p40**	**Androgen receptor, ERG**[a]	CK7	CK5/14, CK10, CK20, CDX-2, GATA-3, Uroplakin, CEA
Ductal adenocarcinoma	Pan-CK, CK8/18, CK19, NKX3.1, androgen receptor	PSA, Prostein, p504S (racemase), CK20		CK5/CK14, CK7, CDX-2

Intraductal carcinoma	Pan-CK, CK19, PSA, PAP, NKX3.1, p504S (racemase), **ERG** **Preserved basal myoepithelial cell layer**: positive for high molecular Cytokeratins (CK5/6/14) and p63, p40			PTEN
Adenoid cystic (basal cell) carcinoma of the prostate	CK8/18, **CK5/6/14**, **p63**, **p40**, bcl-2[c], CK7 only in luminal	**Myb**[b], HER-2	P504S (AMACR), androgen receptor	ERG, PSA, CK20
Neuroendocrine neoplasms – Adenocarcinoma with neuroendocrine differentiation – Well-differentiated neuroendocrine tumors (NET G1, G2, G3) – Neuroendocrine carcinoma of small and large cell type	Chromogranin, Synaptophysin, CD56 See neuroendocrine tumors (Chap. 14.7)		Androgen receptors, NKX3.1	
Prostatic stromal tumor of uncertain malignant potential	PgR, AR, vimentin	Desmin, actin, CD34	ER	CD117
Prostatic stromal sarcoma	Vimentin	CD34	ER, PgR	CD117, Desmin, actin
Adenocarcinoma of seminal vesicle	CK8, CK18, CK19, **PAX-8**, PAX-2, MUC-6, CA-125, CEA	CK7, androgen receptor		CK20, PAP, PSA, NKX3.1, GATA-3, Oct-4, WT-1, CDX-2
Squamous cell carcinoma of seminal vesicle	CK5/CK14, p63			CK7, CK20, PSA, CEA
Mixed epithelial and stromal tumor of seminal vesicle	*Stromal cells*: vimentin, CD34, ER, PgR, Desmin, h-Caldesmon *Epithelial cells*: CK7			Inhibin, CD117, PSA, NKX3.1, CK20

[a] Positive in tumors associated with the TMPRSS2-ERG gene fusion
[b] See adenoid cystic carcinoma of the salivary glands (Chap. 6.2)
[c] Negative in basal cell hyperplasia

13.2 Testicular and Paratesticular Tumors

13.2.1 Germ Cell Tumors

Diagnostic antibody panel for germ cell tumors.

Oct-3/4, SALL-4, NANOG, LIN28, Sox-2, Sox-17, NUT, CD117, D2 40, PLAP, AFP, CD30, CDX-2, GATA-3, β-hcG, and cytokeratin profile.

13.2.2 Sex Cord-Stromal Tumors

Diagnostic antibody panel for sex cord-stromal tumors.

Inhibin, Steroidogenic factor-1 (SF-1, Ad4BP), FOXL2, Calretinin, CD56, anti-Müllerian hormone, Melan A, CD99.

13.2.2.1 SALL-4

SALL-4		
Expression pattern: nuclear		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Seminoma/intratubular germ cell neoplasms – Embryonal carcinoma – Yolk sac tumor – Choriocarcinoma – Ovarian dysgerminoma – CNS germinoma	A subset of gastrointestinal and pulmonary adenocarcinoma, ovarian serous carcinomas, rhabdoid tumor, Wilms tumor, B cell ALL, AML	CD34-positive progenitor cells
Positive control: seminoma		

Diagnostic Approach Sal-like protein (SALL-4) is a member of the **sp**al**l**-like multi-zinc finger family functioning as a transcription factor encoded on chromosome 20q13. SALL-4 is involved in the development and maintenance of embryonic stem cell pluripotency by modulation of Oct-4, Sox-2, and NANOG [13–15]. The expression of SALL-4 is an important sensitive and specific marker for testicular, ovarian, and extragonadal germ cell tumors, including seminoma and dysgerminoma, embryonal carcinoma, immature teratoma, and mononuclear trophoblastic cells of choriocarcinoma. In contrast to Oct-4, SALL-4 strongly labels yolk sac tumor (Fig. 13.9). SALL-4 is negative in sex cord tumors.

Diagnostic Pitfalls SALL-4 is strongly expressed in the neoplastic cells of intratubular germ cell neoplasms (GCNIS) but can also be expressed in adult normal testicular intratubular germ cells, specifically in undifferentiated spermatogonia; consequently, SALL-4 is not a suitable marker to highlight the cells of intratubular germ cell neoplasms. In routine immunohistochemistry, it is important to remember that the expression of SALL-4 is not restricted to germ cell tumors as it is expressed in various intensity in different non-germ cell epithelial and mesenchymal tumors, including serous ovarian carcinoma, pulmonary adenocarcinoma, gastric adenocarcinoma, cholangiocarcinoma and hepatocellular carcinoma, urothelial carcinoma, and small cell carcinoma in addition to embryonal rhabdomyosarcoma, renal rhabdoid tumor beside subsets of lymphoblastic lymphoma, and anaplastic large cell lymphomas. This aberrant expression must be carefully considered in the interpretation of this marker [28].

13.2.2.2 Oct-4

Oct-4		
Expression pattern: nuclear		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Seminoma/intratubular germ cell neoplasms – Embryonal carcinoma	Ovarian dysgerminoma, CNS germinoma, renal medullary carcinoma, diffuse large B cell lymphoma	Germ cells (pluripotent germ cells)
Positive control: seminoma		

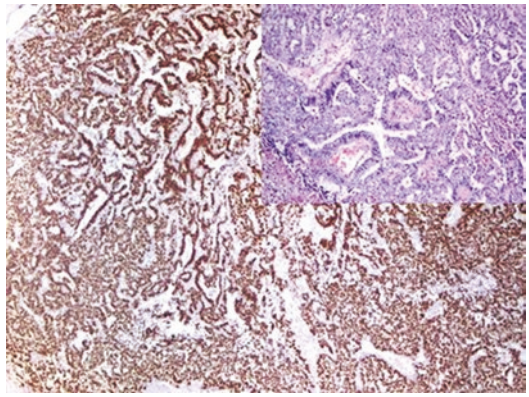


Fig. 13.9 SALL-4 labeling the nuclei of yolk sac tumor cells

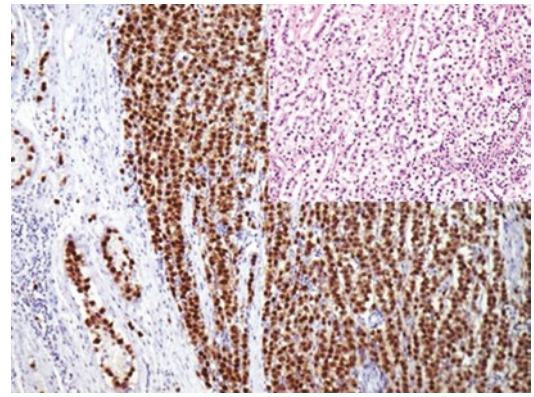


Fig. 13.10 Oct-4 staining the nuclei of seminoma cells and the cells of intratubular germ cell neoplasm (left)

Diagnostic Approach Octamer-binding transcription factor 4 (Oct-4) is a member of the POU family of transcription factors, expressed in early embryonic cells, and plays an important role in the differentiation of pluripotent germ cells and downregulated when these cells started to differentiate. A high expression level of Oct-4 is characteristic for seminoma and embryonal carcinoma, whereas spermatocytic tumor (formerly spermatocytic seminoma) lacks the expression of Oct-4 (Fig. 13.10) [29]. Oct-4 labels the nuclei of the majority of the dysplastic cells of intratubular germ cell neoplasms but not the non-neoplastic testicular cells, making Oct-4 a helpful and specific maker for intratubular germ cell neoplasms (Fig. 13.11) [30]. Atypical cytoplasmic Oct-4 expression is also found in neuroendocrine tumors with different differentiation grades.

Diagnostic Pitfalls The expression of Oct-4 is found in a subset of pulmonary non-small cell carcinoma and breast carcinoma [31]. Oct-4 expression is also found in some cases of testicular and extra-testicular diffuse large B cell lymphoma, which is to consider in the differential diagnosis [32].

13.2.2.3 Placental Alkaline Phosphatase

Placental alkaline phosphatase (PLAP)		
Expression pattern: membranous		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Germ cell tumors: seminoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma	Proximal GIT tumors, lung and ovarian carcinoma. Tumors with myogenic differentiation	Placental syncytiotrophoblasts, endocervical and fallopian tube mucosa
Positive control: seminoma		

Diagnostic Approach Alkaline phosphatases are a group of metalloenzymes catalyzing the hydrolysis of phosphoric acid monoesters. Placental alkaline phosphatase (PLAP) is a membrane-associated glycoprotein primarily expressed in placental syncytiotrophoblasts from the eighth week throughout pregnancy. PLAP is a marker for several germ cell tumors such as seminoma, dysgerminoma, and, to a lesser degree also, embryonal carcinoma, yolk sac tumor, and gonadoblastoma. Since PLAP is not specific for any germ cell tumor (but has a preference for seminoma and dysgerminoma), a panel of antibodies is required to differentiate between the PLAP-positive germ cell tumors (see below) [33–35]. PLAP is negative in spermatocytic tumors and immature teratoma.

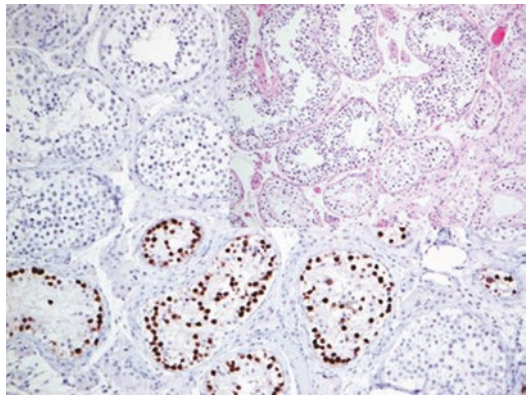


Fig. 13.11 Oct-4 highlighting the cells of intratubular germ cell neoplasm (IGCN)

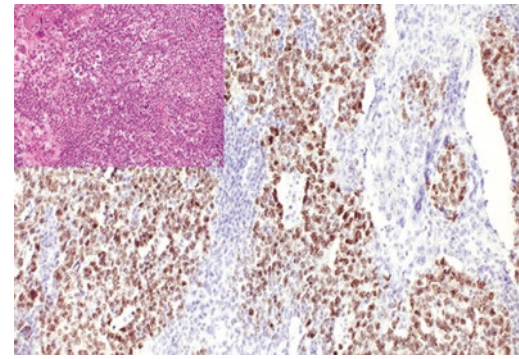


Fig. 13.12 Testicular mixed germ cell tumor with nuclear Sox-2 expression in the cells of embryonal carcinoma. Other tumor components lack the expression of Sox-2

Diagnostic Pitfalls Aberrant PLAP expression is rarely found in other non-germ cell tumor types such as breast and lung carcinoma. Additionally, it is essential to consider that a cytoplasmic PLAP stain is reported in tumors with myogenic differentiation, such as embryonal rhabdomyosarcoma and smooth muscle tumors [23].

13.2.2.4 Sox-17

Sox-17 (SRY-box transcription factor 17) is a member of the SOX family of transcription factors detailed in Chap. 11.6. In germ cell tumors, Sox-17 is positive in seminoma, dysgerminoma, and yolk sac tumor, whereas embryonal cell carcinoma and choriocarcinoma lack the expression of Sox-17 [36].

13.2.2.5 Sox-2

Sox-2		
Expression pattern: nuclear		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Embryonal carcinoma	Squamous cell carcinoma, prostatic carcinoma, neuroendocrine tumors, gliomas	Brain tissue
Positive control: seminoma		

Diagnostic Approach Sox-2 is a member of the Sox family of transcription factors (**s**ex-determining region Y-b**ox 2**). Sox-2 forms a trimeric complex with Oct-4 on DNA and controls the expression of several genes involved in the embryonic development of the respiratory tract, nervous system, and germ cells. In germ cell tumors, Sox-2 shows strong nuclear expression in embryonal carcinoma but is negative in seminoma, yolk sac tumor, and choriocarcinoma (Fig. 13.12) [36, 37]. Sox-2 is also expressed in glial brain tumors and supratentorial PNET [38]. Ectopic Sox-2 expression is found in a subset of pulmonary squamous cell carcinomas and adenocarcinomas. Variable Sox-2 expression is also reported in some neuroendocrine carcinomas [26].

13.2.2.6 Podoplanin (D2–40)

Podoplanin (D2–40) is a type I transmembrane mucoprotein listed in detail with the markers of vascular tumors (Chap. 25). D2–40 is an excellent seminoma marker that also stains intratubular neoplastic germ cells but is negative in all other non-seminomatous germ cell tumors. As D2–40 stains both seminoma cells and lymphatic vessels, it can be used as a marker to highlight the lymphovascular invasion in surgical specimens (Fig. 13.13).

13.2.2.7 Human Chorionic Gonadotropin

Human chorionic gonadotropin (HCG)		
Expression pattern: cytoplasmic		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Syncytiotrophoblast in germ cell tumors (choriocarcinoma) – Non-seminomatous testicular tumors	Pulmonary large cell carcinoma and adenocarcinoma, high-grade urothelial carcinoma	Trophoblasts
Positive control: placenta		

Diagnostic Approach Human chorionic gonadotropin is a hormone produced by syncytiotrophoblasts composed of α- and β-chains. The β-chain reveals a unique structure and is more specific for syncytiotrophoblasts and related tumors. The α-chain shares amino acid sequences with other hormones such as LH, FSH, and TSH of the pituitary gland.

Diagnostic Pitfalls Low expression levels of β-HCG could be found in other non-syncytiotrophoblastic tumors such as pulmonary and colonic carcinomas and rarely lymphomas [39, 40]. Focal expression is also noted in high-grade urothelial carcinoma. Generally, the expression of β-HCG in nontrophoblastic tumors indicates aggressive behavior.

13.2.2.8 CD30

CD30 is a membrane-bound glycoprotein listed in detail in a later section as an essential marker for Hodgkin and anaplastic lymphomas (Chap. 16.6). Additionally, the expression of CD30 is characteristic for embryonal carcinoma (Fig. 13.14). In rare cases, CD30 may faintly stain yolk sac tumor, which is to consider in the differential diagnosis of combined germ cell tumors.

13.2.2.9 Inhibin A

Inhibin A		
Expression pattern: cytoplasmic		
Main diagnostic use	**Expression in other tumors**	**Expression in normal cells**
– Sex cord-stromal tumors (granulosa cell tumor, Leydig cell tumor, Sertoli cell tumor, steroid cell tumor, thecoma and fibrothecoma) – Adrenocortical tumors	Choriocarcinoma and trophoblastic lesions and placental site nodule, hepatocellular carcinoma	Sertoli cells, granulosa cells, theca interna, intermediate trophoblasts, syncytiotrophoblasts, adrenal cortex, brain tissue
Positive control: granulosa cell tumor/adrenal gland		

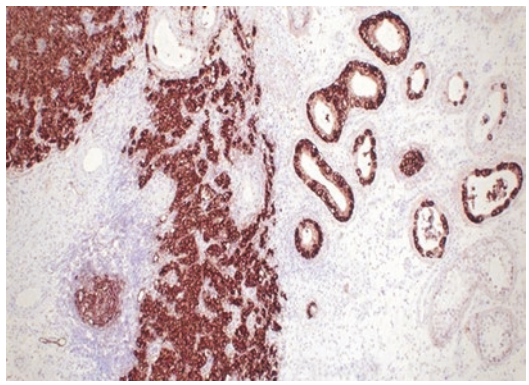


Fig. 13.13 Seminoma associated with intratubular neoplastic germ cells. Podoplanin stains both tumor components in addition to small lymphatic vessels

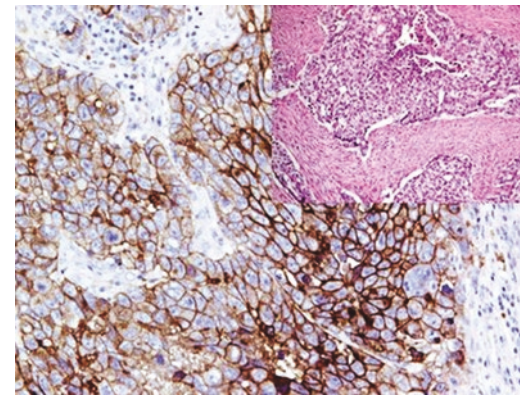


Fig. 13.14 Embryonal carcinoma, tumor cells with strong membranous CD30 expression

Diagnostic Approach Inhibin is a member of the transforming growth and differentiation factor family, a glycoprotein hormone composed of α- and β-subunits expressed in the ovarian granulosa cells, gonads, and adrenal gland, functioning as an inhibitor for the pituitary follicle-stimulating hormone (FSH) secretion and stimulating the synthesis of androgen in ovarian theca cells. Antibodies to Inhibin A, anti-Müllerian hormone, and Melan A are important diagnostic markers for sex cord tumors, including adult and juvenile granulosa cell tumor, Leydig cell tumor, Sertoli cell tumor, steroid cell tumors, thecoma, fibrothecoma, and hyperthecosis [40]. Inhibin and anti-Müllerian hormone are consistently negative in ovarian surface epithelial-stroma tumors, seminoma, and embryonal carcinoma.

Diagnostic Pitfalls Inhibin is also expressed in other tumors, mainly tumors of the adrenal cortex.

13.2.2.10 Anti-Müllerian Hormone

Anti-Müllerian hormone (AMH) is a member of the transforming growth factor-beta gene family. The expression of AMH is regulated by SF-1, GATA factors, DAX1, and follicle-stimulating hormone. Anti-Müllerian hormone mediates male sexual differentiation by inhibiting the development of the Müllerian duct and preventing the transformation of the Müllerian duct into the uterus, fallopian tubes, and other Müllerian structures and plays a role in testicular differentiation. If no AMH is produced, the Müllerian ducts undergo differentiation, while the Wolffian ducts become atrophic. In the postnatal period, AMH is also expressed in both males and females by Sertoli cells and, to a lesser degree, by granulosa cells. Anti-Müllerian hormone is an immunohistochemical marker for Sertoli cell and granulosa cell tumors [41]. Other sex cord-stromal tumors are usually negative for AMH.

13.2.2.11 Adrenal 4 Binding Protein (SF-1)

Steroidogenic factor 1 (SF-1) is listed in detail with the markers of adrenocortical tumors (Chap. 14.6). SF-1 is expressed in normal testicular Sertoli and Leydig cells in addition to granulosa cells. SF-1 is a sensitive marker for Sertoli cell tumors and granulosa cell tumors. Leydig cell tumor lacks the expression of SF-1.

13.2.2.12 Glypican-3

Glypican-3 was listed in detail in a previous chapter (Chap. 9.1). In germ cell tumors, Glypican-3 is a specific marker for yolk sac tumor and choriocarcinoma, whereas embryonal carcinoma and seminoma usually lack the expression of Glypican-3.

13.2.2.13 CDX-2

Caudal-related homeobox 2 (CDX-2) is an intestine-specific transcription factor protein regulating the differentiation and proliferation of intestinal epithelial cells and is popularly used as a marker for gastrointestinal adenocarcinomas (see Chap. 7.1). CDX-2 is also a sensitive and specific marker for yolk sac tumor (Fig. 13.15) [42].

13.2.2.14 GATA-3

GATA-3, also known as endothelial transcription factor 3, is one of the six members of the GATA family of transcription factors listed in detail with the markers of breast and urothelial in addition to salivary gland tumors (Chaps. 6.2, 10, and 12.2). GATA-3 is also a transcription factor important for the differentiation of trophoblasts and is strongly expressed in trophoblasts and trophoblastic tumors, including choriocarcinoma and gestational trophoblastic tumors. GATA-3 is also expressed in the neoplastic cells of yolk sac tumor (Fig. 13.16) [43].

13.2.2.15 CD56

CD56 (neural cell adhesion molecule) is listed in later chapters as a marker for NK lymphomas and neuroendocrine tumors (Chap. 16.5). CD56 is a sensitive marker for ovarian and testicular sex cord-stromal tumors but lacks specificity as it is expressed in a wide range of other tumors. The combination of CD56 with SF-1, Inhibin, and Melan A will make the diagnosis of sex cord tumors more precise.

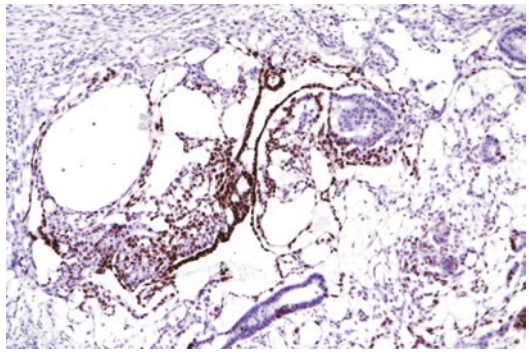


Fig. 13.15 Testicular mixed germ cell tumor with strong nuclear CDX-2 expression in yolk sac tumor component

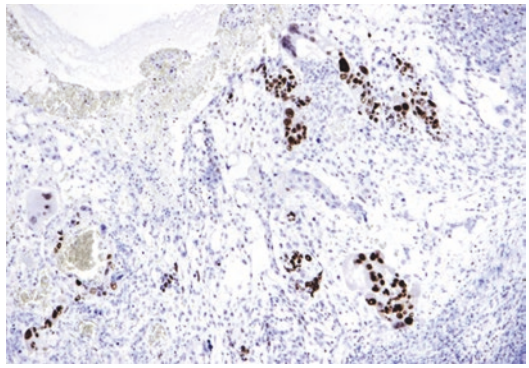


Fig. 13.16 Testicular mixed germ cell tumor with nuclear GATA-3 expression in the neoplastic trophoblasts and syncytiotrophoblasts besides few cells of yolk sac tumor. Cells of embryonal carcinoma lack the GATA-3 expression

13.2.2.16 Melan A and CD99

Melan A and CD99 are further markers that label the neoplastic cells of sex cord-stromal tumors. Both markers are listed in detail in later chapters: Melan A as a melanoma marker (Chap. 22) and CD99 as a marker for Ewing sarcoma (Chap. 29).

13.3 Paratesticular Tumors

Diagnostic antibody panel for paratesticular tumors.

Cytokeratin profile, PAX-8, PAX-2, Calretinin.

13.3.1 PAX-8 and PAX-2

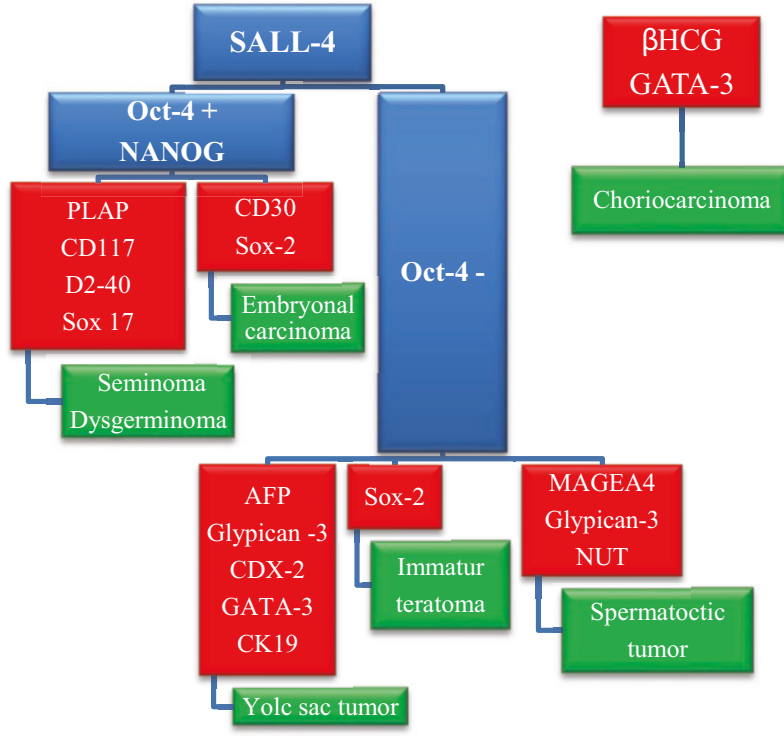
Both PAX-8 and PAX-2 are transcription factors expressed in the organs derived from Wolffian and Müllerian ducts and strongly stain the rete testis, epididymal and seminal vesicle epithelium, and carcinomas derived from these cells. They can be used to differentiate between prostatic carcinoma and carcinoma of seminal vesicles (see markers of renal cell tumors; Chap. 12.1) (Algorithm 13.1).

Immunoprofile of testicular and paratesticular tumors				
Tumor type	+ in >90% (+)	+ in 50–90% (+/−)	+ in 10–50% (−/+)	+ in <10% (−)
A. Germ cell tumors				
Intratubular germ cell neoplasms (GCNIS)	**Oct-4**, **PLAP**, **D2–40**, **TCL-1**, SALL-4[a], SOX-17, sCD143, LIN28 angiotensin-converting enzyme (ACE), NSE	Ferritin, CD117		AFP, βhcG, Glypican-3, inhibin, CD30
Seminoma/ dysgerminoma	**SALL-4**, **Oct-3/4**, **NANOG**, **PLAP**, Sox-17, **TCL-1**, LIN28, tCD143	CD117, **D2–40**, CK8, AP-2γ, Glut-3, vimentin	CK18, NSE, CK7	**CD30**, **Sox-2**, **Glypican-3**, GATA-3, EMA, CK19, CK20, CEA, AFP, βhcG, inhibin
Spermatocytic tumor (formerly spermatocytic seminoma)	**SALL-4**, **NUT**, MAGEA4, Oct-2	CD117, vimentin, CK8/CK18, NSE		AFP, **Oct-4**, **PLAP**, ßhcG, CEA, EMA, CD30, CD143, **D2–40**

Embryonal carcinoma	**Oct-3/4**, **SALL-4**, **NANOG**, **Sox-2**, **PLAP**, **CD30**, LIN28, CK8, CK18	CK7, CK19, NSE	βhcG, AFP, vimentin	EMA, CK20, CEA, GATA-3, **Sox-17**, **CD117**, **Glypican-3**, D2–40
Yolk sac tumor	**AFP**, **SALL-4**, **Glypican-3**, **CDX-2**, **CK19**, Pan-CK, LIN28	PLAP, CD34, GATA-3, NUT[b]	CD117, HepPar1, NSE, GFAP	**NANOG**, **Sox-2**, **Oct-3/4**, **CK7**, EMA, βhcG, CD30, CEA, vimentin
Choriocarcinoma Syncytiotrophoblastic cells Cytotrophoblastic cells	**βHCG**, inhibin, GATA-3, CD10, Pan-CK, CK8/CK18, CK19, Glypican-3, EGFR CD10, Pan-CK, CK8/CK18, CK19, CEA	PLAP, human placental lactogen, EMA, CEA Glypican-3, PLAP	Vimentin	CD30, AFP, Oct-4, NANOG, Sox-2, Sox-17, D2–40 βhcG, inhibin, EMA, CD30, AFP, Oct-4
Immature teratoma	**SALL-4**, **Sox-2**			**Oct-4**, **NANOG**, CD117, CD30
Polyembryoma Embryonal bodies	AFP, Pan-CK	PLAP		
B. Sex cord-stromal tumors				
Leydig cell tumor	**Inhibin**, **CD56**, **Melan-A**, **SF-1**, Calretinin, vimentin	CD99, FOXL-2	Pan-CK, S100, Synaptophysin, chromogranin	EMA, PLAP, AFP, WT-1, β-catenin(n), anti-Müllerian hormone, Oct-4, SALL-4
Sertoli cell tumor	**SF-1**, **inhibin**, **FOXL2**, **anti-Müllerian hormone**, CD56, **β-catenin (n)**, vimentin	AFP, CD99, pan-CK, chromogranin, Synaptophysin, Calretinin, SOX-9	NSE, S100	EMA, PLAP, Oct-4, SALL-4
Granulosa cell tumor	**Inhibin**, **FOXL2**, **SF-1**, CD56, vimentin	CD99, anti-Müllerian hormone	CK8, CK18, actin, S100	EMA, Desmin
Gonadoblastoma	The immunoprofile of both germ cell and sex cord-stromal components			
C. Paratesticular tumors				
Adenomatoid tumor	**Calretinin**, Pan-CK, CK5/CK6, CK7, WT-1, Thrombomodulin (CD141), vimentin			CD31, CD34, CEA
Adenocarcinoma of collecting ducts and rete testis	Pan-CK, CK7, EMA, vimentin	**PAX-8**, WT-1, CD10	CEA	Inhibin, AFP, PLAP, Oct4, Sall-4, GATA-3, NKX3.1
Ovarian type tumors of collecting ducts and rete testis	See ovarian tumors			
Adenocarcinoma of the epididymis	Pan-CK, CK7, PAX-2, PAX-8, CEA			Oct-4, WT-1, CDX-2, NKX3.1, PSA
Melanotic neuroectodermal tumor	*Large pigmented cells:* Pan-CK, EMA, NSE, HMB45, Synaptophysin *Small cells:* NSE, HMB45, CD57, Synaptophysin, CD56	S100	GFAP Pan-CK, GFAP, PAX-5, CD99, Calretinin	

[a] SALL-4 is not a suitable marker to highlight the cells of intratubular germ cell neoplasms
[b] Positive only in hepatoid variant of yolk sac tumor [42]

Algorithm 13.1
Immunoprofile of germ cell tumors



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