

Efficient immunohistochemical differential diagnosis of undifferentiated neoplasia

Conventional histomorphology: pleomorph and/or high-grade spindle-cell

Localisation of tumour infiltrates	Antibody panel	Marker constellation and valuation
Central nervous system	CK8/18, Ber-EP4, GFAP, Melan A, CD34	<ul style="list-style-type: none"> CK8/18 + (diffuse), Ber-EP4 +/-, GFAP -/+ (focal) <ul style="list-style-type: none"> carcinoma metastasis if plexus carcinoma is excluded GFAP +, CK8/18 -/+ (focal), CD34-positive microvascular proliferates <ul style="list-style-type: none"> glioblastoma Melan A + <ul style="list-style-type: none"> malignant melanoma (metastasis)
Lymph node	Pan-CK, S100, CD30, CD20, kappa/lambda	<ul style="list-style-type: none"> Pan-CK + (diffuse or focal, other markers negative) <ul style="list-style-type: none"> carcinoma metastasis S100 + (diffuse nuclear and cytoplasmic) <ul style="list-style-type: none"> metastasis of malignant melanoma kappa/lambda +, CD20 - <ul style="list-style-type: none"> immature (anaplastic) plasmocytoma (myeloma) CD30 + (membranous diffuse and in the Golgi region), Pan-CK -/+ (focal), CD20 - <ul style="list-style-type: none"> anaplastic large-cell lymphoma (ALCL) CD20 +, CD30 +/- <ul style="list-style-type: none"> diffuse large-cell B-cell lymphoma, anaplastic variation all markers negative <ul style="list-style-type: none"> carcinoma with lost CK expression or histiocytic sarcoma?
Gastrointestinal tract, genito-urinary system, parenchymatous organs, head/neck area	Pan-CK, S100, HMB45, CD30, CD20	<ul style="list-style-type: none"> Pan-CK + (diffuse or focal, other markers negative) <ul style="list-style-type: none"> (sarcomatoid) carcinoma S100 + (diffuse nuclear and cytoplasmic), HMB45 +/- <ul style="list-style-type: none"> malignant melanoma CD30 + (membranous diffuse and in the Golgi region), Pan-CK -/+ (focal), CD20 - <ul style="list-style-type: none"> anaplastic large cell lymphoma (ALCL) CD20 +, CD30 +/- <ul style="list-style-type: none"> diffuse large-cell B-cell lymphoma, anaplastic variation all markers negative <ul style="list-style-type: none"> carcinoma with loss of CK expression or histiocytic sarcoma?
Skin	Pan-CK, CK5/6, CD31, S100, CD30, h-Caldesmon	<ul style="list-style-type: none"> Pan-CK +/-, CK5/6 +/-, CD31 -, h-Caldesmon -, S100 +/- (focal) <ul style="list-style-type: none"> (sarcomatoid) carcinoma, differential diagnosis metastasis S100 + (diffuse nuclear and cytoplasmic) <ul style="list-style-type: none"> (spindle-cell) malignant melanoma CD31 + <ul style="list-style-type: none"> angiosarcoma h-Caldesmon + (more than single cells) <ul style="list-style-type: none"> leiomyosarcoma CD30 + (membranous diffuse and in the Golgi region), Pan-CK -/+ (focal) <ul style="list-style-type: none"> (sarcomatoid) anaplastic large-cell lymphoma all markers negative <ul style="list-style-type: none"> atypical fibroxanthoma (Head/Neck, actinic lesion?)
Soft tissue	S100, HMB45, Myf4, CD31, h-Caldesmon, CD30	<ul style="list-style-type: none"> S100 + (diffuse nuclear and cytoplasmic), HMB45 + <ul style="list-style-type: none"> malignant melanoma, differential diagnosis clear cell sarcoma (if HMB45 - differential diagnosis malignant peripheral nerve sheath tumour, MPNST) CD31 + <ul style="list-style-type: none"> angiosarcoma Myf4 + (nuclear, attention: immunoreactivity in regenerative skeletal muscle fibres in tumour-infiltrated areas) <ul style="list-style-type: none"> pleomorphic rhabdomyosarcoma or other tumour with focal rhabdomyoblastic differentiation h-Caldesmon + (more than single cells) <ul style="list-style-type: none"> pleomorphic leiomyosarcoma CD30 + (membranous diffuse and in the Golgi region) <ul style="list-style-type: none"> (sarcomatoid) anaplastic large-cell lymphoma other marker combination <ul style="list-style-type: none"> sarcoma, needs further investigation

Conventional histomorphology: epithelioid, intermediate-cell to large-cell

Localisation of tumour infiltrates	Antibody panel	Marker constellation and valuation
Pleura	p63, WT1, Podoplanin (D2-40), S100, Pan-CK	<ul style="list-style-type: none"> p63 +, WT1 -, D2-40 (Podoplanin) -/+ <ul style="list-style-type: none"> pleura carcinosis due to non-keratinising squamous cell carcinoma WT1 + and/or D2-40 (Podoplanin) +, p63 -, Pan-CK + <ul style="list-style-type: none"> epithelioid or biphasic mesothelioma, Attention: Pleura carcinosis due to serous ovarian carcinoma Pan-CK +, other markers negative <ul style="list-style-type: none"> Pleura carcinosis due to macrocellular carcinoma S100 + (diffuse nuclear and cytoplasmic), Pan-CK -/+ (focal) <ul style="list-style-type: none"> metastasis of a malignant melanoma
Peritoneum	Ber-EP4, Pan-CK, Calretinin, S100, HMB45, Inhibin alpha	<ul style="list-style-type: none"> Ber-EP4 + or Ber-EP4 -, Pan-CK +, Calretinin - <ul style="list-style-type: none"> peritoneal carcinosis Calretinin +, Pan-CK +, Ber-EP4 - <ul style="list-style-type: none"> epithelioid or biphasic mesothelioma, S100 + (diffuse nuclear and cytoplasmic), Pan-CK -/+ (focal), Ber-EP4 -, Inhibin alpha - <ul style="list-style-type: none"> metastasis of a malignant melanoma Inhibin alpha +, Calretinin +, Ber-EP4 -, S100 -/+ (focal) <ul style="list-style-type: none"> granulosa-cell tumour? HMB45 +, S100 - <ul style="list-style-type: none"> perivascular epithelioid-cell tumour
Central nervous system	CK8/18, GFAP, Melan A, OCT4, CD117	<ul style="list-style-type: none"> CK8/18 + (diffuse), GFAP -/+ (focal) <ul style="list-style-type: none"> carcinoma metastasis after elimination of a plexus carcinoma GFAP +, CK8/18 -/+ (focal) <ul style="list-style-type: none"> anaplastic glioma or glioblastoma Melan A + <ul style="list-style-type: none"> malignant melanoma (metastasis) OCT4 +, CD117 - <ul style="list-style-type: none"> embryonal carcinoma OCT4 +, CD117 - <ul style="list-style-type: none"> germinoma
Lymph node	Pan-CK, CD20, S100, OCT4, CD30	<ul style="list-style-type: none"> Pan-CK + (diffuse), OCT4 - <ul style="list-style-type: none"> carcinoma metastasis S100 + (diffuse nuclear and cytoplasmic), Pan-CK -/+ (focal) <ul style="list-style-type: none"> metastasis of a malignant melanoma OCT4 +, Pan-CK + (diffuse), CD30 + <ul style="list-style-type: none"> metastasis of an embryonal carcinoma OCT4 +, Pan-CK +/- (focal), CD30 - <ul style="list-style-type: none"> metastasis of a seminoma CD30 + (membranous diffuse and in the Golgi region), Pan-CK -/+ (focal), CD20 - <ul style="list-style-type: none"> anaplastic large-cell lymphoma, „small-cell“ variant CD20 + <ul style="list-style-type: none"> diffuse large-cell B-NHL
Ovary	Pan-CK, EMA, S100, Inhibin alpha, OCT4, CD20	<ul style="list-style-type: none"> Pan-CK +, EMA +/-, Inhibin alpha -, OCT4 - <ul style="list-style-type: none"> carcinoma (primary tumour or metastasis) S100 + (diffuse nuclear and cytoplasmic), Pan-CK -/+ (focal), Inhibin alpha - <ul style="list-style-type: none"> malignant melanoma Inhibin alpha +, EMA -, S100 +/- (focal) <ul style="list-style-type: none"> germ band or stroma tumour OCT4 +, Pan-CK +/- (focal) <ul style="list-style-type: none"> embryonal carcinoma OCT4 +, Pan-CK +/- (focal) <ul style="list-style-type: none"> dysgerminoma CD20 + <ul style="list-style-type: none"> diffuse large-cell B-NHL
Gastrointestinal tract, Respiratory tract, genito-urinary system, parenchymatous organs, head/neck area	Pan-CK, EMA, S100, Inhibin alpha, OCT4, CD20	<ul style="list-style-type: none"> Pan-CK + (diffuse) <ul style="list-style-type: none"> carcinoma S100 + (diffuse nuclear and cytoplasmic), Pan-CK +/- (focal), Inhibin alpha - <ul style="list-style-type: none"> malignant melanoma, (if HMB45 - differential diagnosis malignant peripheral nerve sheath tumour, MPNST) HMB45 +, S100 - <ul style="list-style-type: none"> perivascular epithelioid-cell tumour CD20 + <ul style="list-style-type: none"> diffuse large-cell B-NHL CD30 + (membranous diffuse and in the Golgi region), Pan-CK +/- (focal), CD20 - <ul style="list-style-type: none"> anaplastic large-cell lymphoma, „small-cell“ variant Kappa/lambda +, CD20 - <ul style="list-style-type: none"> plasmoblastic lymphoma? (HIV + ?), ALK-1-positive diffuse large-cell B-NHL?
Soft tissue	Pan-CK, S100, CD31, HMB45, CD117	<ul style="list-style-type: none"> Pan-CK + (diffuse) <ul style="list-style-type: none"> epithelioid sarcoma, differential diagnosis carcinoma metastasis S100 + (diffuse nuclear and cytoplasmic), HMB45 +/- <ul style="list-style-type: none"> malignant melanoma, differential diagnosis clear-cell sarcoma (if HMB45 - differential diagnosis malignant peripheral nerve sheath tumour, MPNST) HMB45 +, S100 - <ul style="list-style-type: none"> perivascular epithelioid-cell tumour CD31 + <ul style="list-style-type: none"> epithelioid angiosarcoma CD117 + <ul style="list-style-type: none"> epithelioid gastro-intestinal stroma tumour (GIST)?

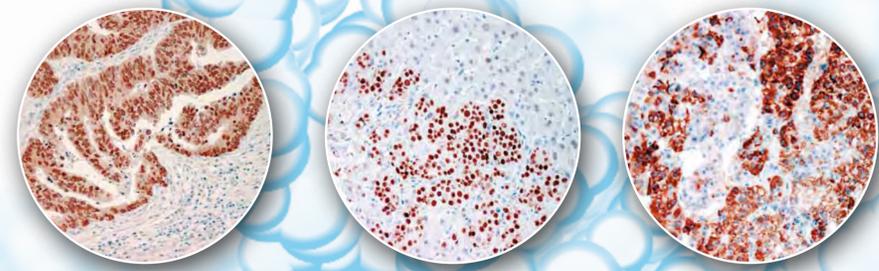
Conventional histomorphology: small-cell

Localisation of tumour infiltrates	Antibody panel	Marker constellation and valuation
Central nervous system	CK8/18, GFAP, Melan A, TTF-1, Synaptophysin	<ul style="list-style-type: none"> CK8/18 + (diffuse), Synaptophysin +, TTF-1 +/- <ul style="list-style-type: none"> metastasis of a small-cell carcinoma GFAP +, CK8/18 -/+ (focal), Synaptophysin - <ul style="list-style-type: none"> small-cell fraction of a glioblastoma Melan A + <ul style="list-style-type: none"> small-cell malignant melanoma (metastasis)
other localisation	Pan-CK, S100, CD99, Desmin, Synaptophysin, TdT, Myeloperoxidase (MPO), CK20	<ul style="list-style-type: none"> Pan-CK + (diffuse), Desmin -, CK20 -, Synaptophysin +/- <ul style="list-style-type: none"> small-cell carcinoma (if Synaptophysin - differential diagnosis small-cell squamous cell carcinoma) CK20 + (punctual perinuclear), Synaptophysin + <ul style="list-style-type: none"> merkel cell carcinoma CD99 + (membranous diffuse), Pan-CK -/+ (focal), Synaptophysin +/-, TdT -, S100 +/- (focal), MPO - <ul style="list-style-type: none"> PNET Synaptophysin +, CD99 -, Pan-CK -, S100-positive sustentacular cells <ul style="list-style-type: none"> olfactory neuroblastoma? (rhinopharynx) S100 + (diffuse nuclear and cytoplasmic) <ul style="list-style-type: none"> small-cell malignant melanoma Melan A + <ul style="list-style-type: none"> small-cell malignant melanoma (metastasis) TdT +, CD99 +/-, Pan-CK -, MPO - <ul style="list-style-type: none"> desmoplastic small- and round-cell tumour? MPO + <ul style="list-style-type: none"> myeloid sarcoma

Marker for immunohistochemical diagnostics of CUP (Carcinoma of Unknown Primary)

Marker	Predicted localisation of primary tumour	Type of carcinoma	Comments
AFP	liver	HCC	Positive in yolk sack tumours
CDX-2 (a)	colorectum, ovary, bladder (diffuse immunoreactivity)	adenocarcinomas (ovary only in case of gastrointestinal mucinous differentiation)	Adenocarcinomas of stomach, oesophagus, pancreas, and biliary ducts frequently show heterogeneous immunoreactivity. Adenocarcinomas of the lung are rarely positive.
CDX-2 (b)	middle intestine (appendix, ileum)	well-differentiated neuroendocrine tumours	
CK7/CK20	colorectum	adenocarcinomas (CK7-/CK20+)	
DPC4/SMAD4	pancreas, biliary ducts	adenocarcinomas	Only the loss of expression is relevant for diagnosis!
GCDPF-15	breast, skin adnex	adenocarcinomas	Rare immunoreactivity in adenocarcinomas of the lung.
Glypican-3	liver	HCC (Hepato Cellular Carcinoma)	Positive in malignant melanomas and in yolk sack tumours; otherwise more sensitive and specific than HepPar1 and TTF1 (cytoplasmic)
HepPar1	liver	HCC (Hepato Cellular Carcinoma)	Positive in appr. 50% of all adenocarcinomas of stomach and to a lesser degree in other primary localisations (colon, lung, pancreas); therefore minor positive predictive value for differentiation from HCC and liver metastases.
Estrogen Receptor	Mamma, ovary, corpus uteri	adenocarcinomas	
Parathyroid hormone	parathyroid gland	adenomas and carcinomas	
PAX-2	kidney, ovary	clear-cell and papillary kidney-cell carcinoma, serous ovary carcinoma	Mesotheliomas and HCC negative
PSA	prostate	adenocarcinomas	
RCC	kidney	carcinomas	Immunoreactivity in appr. 10-30% of mesotheliomas, breast carcinomas, prostate carcinomas, ovary carcinomas, lung carcinomas, and adrenocortical neoplasias. Adenomas of the parathyroid gland are 100% positive; clear-cell tumours of the skin with varying histogenesis are negative.
Thyreoglobulin	thyroid gland	differentiated and insular thyroid gland carcinomas	
TTF1 (a) nuclear (only clone 8G7G3/1, other clones mostly less specific)	lung	adenocarcinomas, large-cell non-neuroendocrine carcinomas; not applicable for small-cell carcinomas (expression not localisation-specific) and squamous cell carcinomas (no expression)	With clone 8G7G3/1 also rare immunoreactivity in endometrial adenocarcinomas.
TTF1 (b) nuclear	lung	carcinoid	
TTF1 (c) nuclear	thyroid gland	differentiated and insular carcinomas	
TTF1 cytoplasmic (only clone 8G7G3/1)	liver	HCC (Hepato Cellular Carcinoma)	Similar sensitivity but slightly more specific than HepPar1
Uroplakin III	urinary tract	urothelial carcinoma	Brenner tumours of the ovary are positive
WT1 (nuclear)	ovary	serous adenocarcinoma	Mesotheliomas are also positive

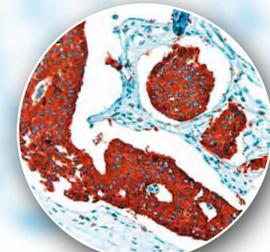
This IHC algorithm was prepared to the best of our knowledge. However, in special cases (for example childhood tumours) the information can be incomplete and the user has to be aware of this. The use of this diagram is solely the responsibility of the user. Under no circumstances shall Zytomed System be liable for any damages arising out of the use of this table. We kindly would like to thank Dr. med. habil. Olaf Kaufmann for his expert advice in the preparation of this diagram. © ZYTOMED SYSTEMS 2009



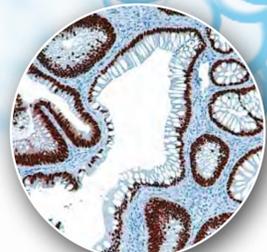
CDX-2, liver metastasis of colon carcinoma

Estrogen Receptor, liver metastasis of breast carcinoma

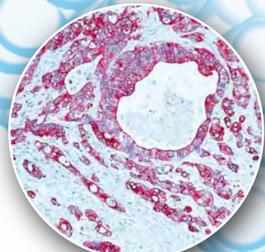
HepPar1, hepatocellular carcinoma



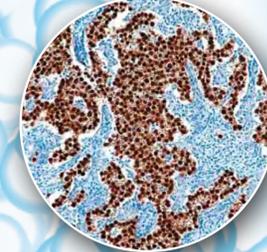
Synaptophysin, neuroendocrine tumour



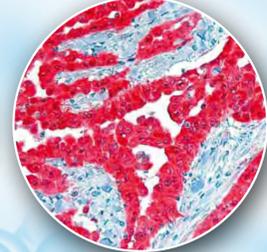
CDX-2, colon carcinoma



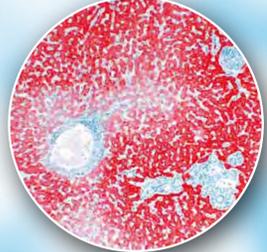
Cytokeratin 20, colon carcinoma



Oct-4, seminoma



Calretinin, mesothelioma



TTF-1 (clone 8G7G3/1), normal liver tissue