

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 excludedGFAP +, CK8/18 -/+ (focal), CD34-positive microvascular proliferates <ul style="list-style-type: none">glioblastomaMelan 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 metastasisS100 + (diffuse nuclear and cytoplasmic) <ul style="list-style-type: none">metastasis of malignant melanomakappa/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 variationall 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) carcinomaS100 + (diffuse nuclear and cytoplasmic), HMB45 +/- <ul style="list-style-type: none">malignant melanomaCD30 + (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 variationall 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 metastasisS100 + (diffuse nuclear and cytoplasmic) <ul style="list-style-type: none">(spindle-cell) malignant melanomaCD31 + <ul style="list-style-type: none">angiosarcomah-Caldesmon + (more than single cells) <ul style="list-style-type: none">leiomyosarcomaCD30 + (membranous diffuse and in the Golgi region), Pan-CK -/+ (focal) <ul style="list-style-type: none">(sarcomatoid) anaplastic large-cell lymphomaall 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">angiosarcomaMyf4 + (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 differentiationh-Caldesmon + (more than single cells) <ul style="list-style-type: none">pleomorphic leiomyosarcomaCD30 + (membranous diffuse and in the Golgi region) <ul style="list-style-type: none">(sarcomatoid) anaplastic large-cell lymphomaother marker combination <ul style="list-style-type: none">sarcoma; needs further investigation

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

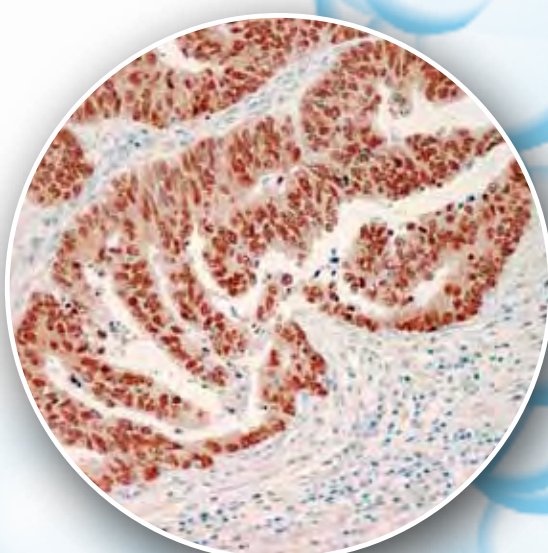
Localisation of tumour infiltrates	Antibody panel	Marker constellation and valuation
Pleura	p63, WT1, Podoplanin (D2-40), S100, Pan-CK	<ul style="list-style-type: none">p63 +, WT1 -, D2-40 (Podoplanin) +/- <ul style="list-style-type: none">pleura carcinosis due to non-keratinising squamous cell carcinomaWT1 + 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 carcinomaPan-CK +, other markers negative <ul style="list-style-type: none">Pleura carcinosis due to macrocellular carcinomaS100 + (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 α	<ul style="list-style-type: none">Ber-EP4 + or Ber-EP4 -, Pan-CK +, Calretinin - <ul style="list-style-type: none">peritoneal carcinosisCalretinin +, 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 α - <ul style="list-style-type: none">metastasis of a malignant melanomaInhibin α +, 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 carcinomaGFAP +, CK8/18 -/+ (focal) <ul style="list-style-type: none">anaplastic glioma or glioblastomaMelan A + <ul style="list-style-type: none">malignant melanoma (metastasis)OCT4 +, CD117 - <ul style="list-style-type: none">embryonary carcinomaOCT4 +, 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 metastasisS100 + (diffuse nuclear and cytoplasmic), Pan-CK -/+ (focal) <ul style="list-style-type: none">metastasis of a malignant melanomaOCT4 +, Pan-CK + (diffuse), CD30 + <ul style="list-style-type: none">metastasis of an embryonary carcinomaOCT4 +, Pan-CK -/+ (focal), CD30 - <ul style="list-style-type: none">metastasis of a seminomaCD30 + (membranous diffuse and in the Golgi region), Pan-CK -/+ (focal), CD20 - <ul style="list-style-type: none">anaplastic large-cell lymphoma, „small-cell“ variantCD20 + <ul style="list-style-type: none">diffuse large-cell B-NHL
Ovary	Pan-CK, EMA, S100, Inhibin α, OCT4, CD20	<ul style="list-style-type: none">Pan-CK +, EMA +/-, Inhibin α -, OCT4 - <ul style="list-style-type: none">carcinoma (primary tumour or metastasis)S100 + (diffuse nuclear and cytoplasmic), Pan-CK -/+ (focal), Inhibin α - <ul style="list-style-type: none">malignant melanomaInhibin α +, EMA -, S100 +/- (focal) <ul style="list-style-type: none">germ band or stroma tumourOCT4 +, Pan-CK -/+ (focal) <ul style="list-style-type: none">embryonary carcinomaOCT4 +, Pan-CK -/+ (focal) <ul style="list-style-type: none">dysgerminomaCD20 + <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 α, OCT4, CD20	<ul style="list-style-type: none">Pan-CK + (diffuse) <ul style="list-style-type: none">carcinomaS100 + (diffuse nuclear and cytoplasmic), Pan-CK -/+ (focal), Inhibin α - <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 tumourCD20 + <ul style="list-style-type: none">diffuse large-cell B-NHLCD30 + (membranous diffuse and in the Golgi region), Pan-CK -/+ (focal), CD20 - <ul style="list-style-type: none">anaplastic large-cell lymphoma, „small-cell“ variantKappa/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 metastasisS100 + (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 tumourCD31 + <ul style="list-style-type: none">epithelioid angiosarcomaCD117 + <ul style="list-style-type: none">epithelioid gastro-intestinal stroma tumour (GIST)?

Conventional histomorphology: small-cell

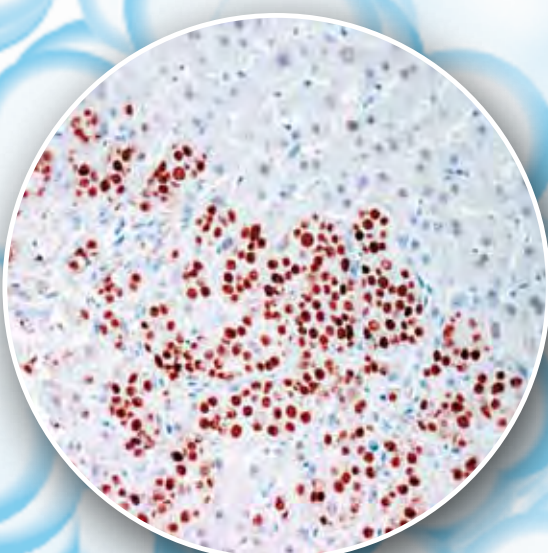
Localisation of tumour infiltrates	Antibody panel	Marker constellation and valuation
Central nervous system	CK8/18, GFAP, Melan A, TTF-1, Synaptophysin	<ul style="list-style-type: none">CK8/18 + (diffuse), Synaptophysin +, TTF-1 +/- <ul style="list-style-type: none">metastasis of a small-cell carcinomaGFAP +, CK8/18 -/+ (focal), Synaptophysin - <ul style="list-style-type: none">small-cell fraction of a glioblastomaMelan 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 carcinomaCD99 + (membranous diffuse), Pan-CK -/+ (focal), Synaptophysin +/-, Tdt -, S100 +/- (focal), MPO - <ul style="list-style-type: none">PNETSynaptophysin +, 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 melanomaMelan 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)

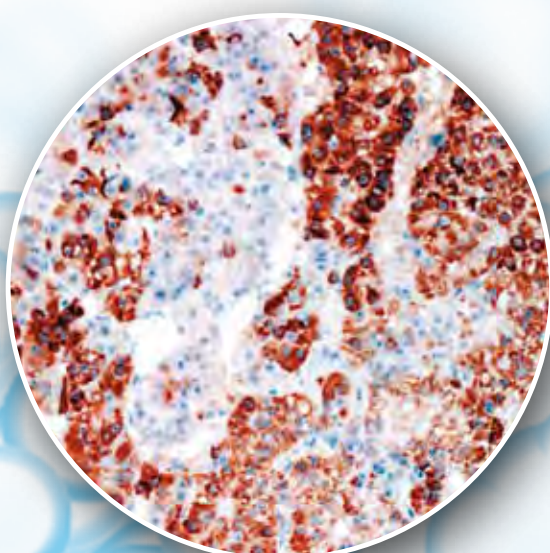
Marker	Predicted localisation of primary tumour	Type of carcinoma	Comments
AFP	liver	HCC	Positive in yolk sack tumours
CDX-2 (a)	colorectum, ovary, bladder (diffuse immunoreactivity)	adenocarcinomas (ovary only in case of gastrointestinal mucinous differentiation)	Adenocarcinomas of stomach, oesophagus, 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+)	
DP4/SMAD4	pancreas, biliary ducts	adenocarcinomas	Only the loss of expression is relevant for diagnosis!
GCDFP-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



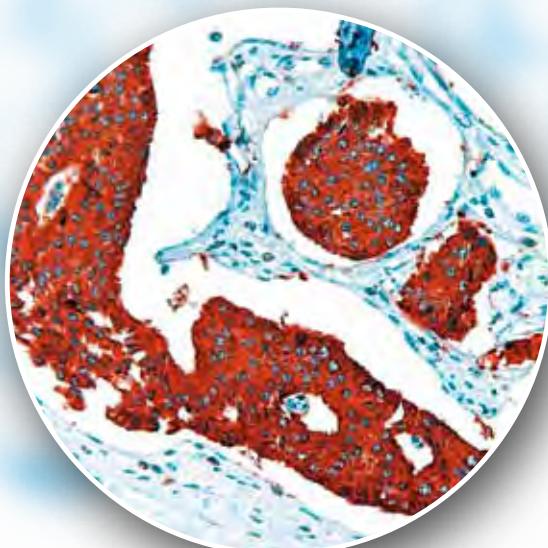
CDX-2, liver metastasis of colon carcinoma



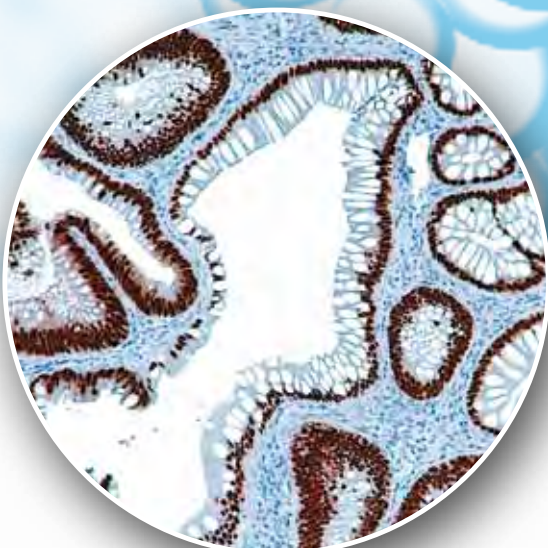
Estrogen Receptor, liver metastasis of breast carcinoma



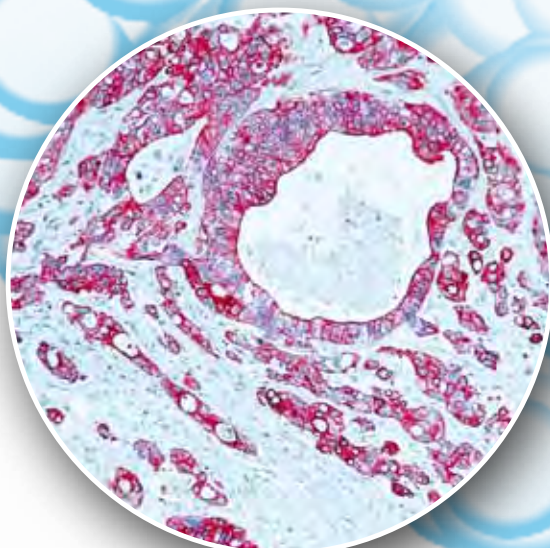
HepPar1, hepatocellular carcinoma



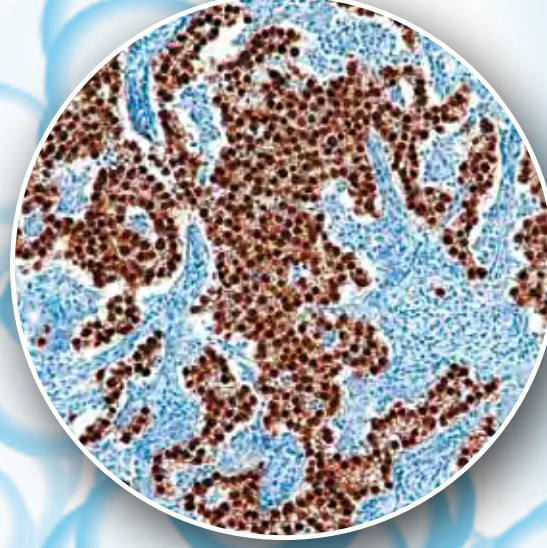
Synaptophysin, neuroendocrine tumour



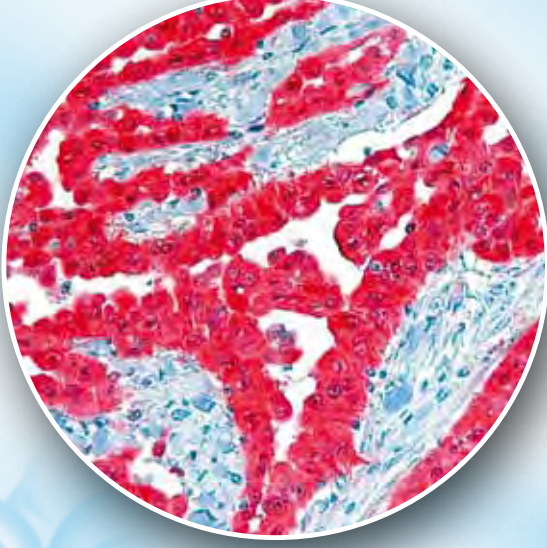
CDX-2, colon carcinoma



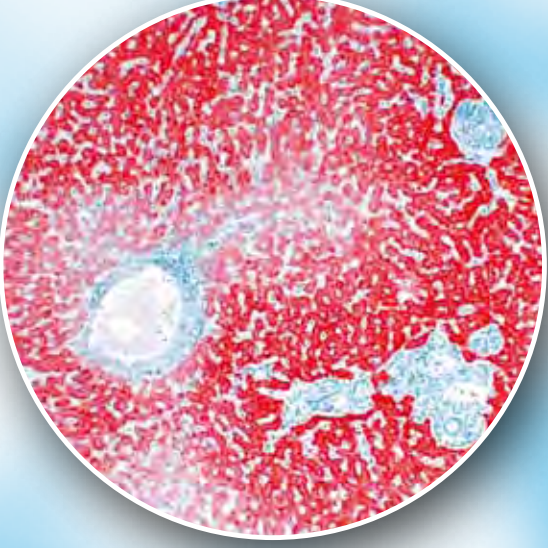
Cytokeratin 20, colon carcinoma



Oct-4, seminoma



Calretinin, mesothelioma



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

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.
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We kindly would like to thank Dr. med. habil. Olaf Kaufmann for his expert advice in the preparation of this diagram.
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