Immunohistochemical differentiation of metastatic tumours

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Key points from a review article written by Daisuke Nonaka

Intro

- Metastatic disease is the initial presentation in 10-15% of cases (higher in carcinomas)
- In up to 1/3 of cases the primary tumour site may not be identified
- Common organs involved in metastasis
  - Lung, LN's, liver, bone and brain
  - In these organs there is a higher incidence of mets than primary tumours

Intro

- In some cancers, there may be a long latent period before metastasis and therefore a detailed medical history together with radiological findings is essential.
- Such information allows you to narrow down the differential and therefore select relevant immuno
  - cost-effective and time-efficient

Undifferentiated tumours

- Can be classified into generic morphological categories :-
  - Small round blue cell neoplasm
  - Spindle cell neoplasm
  - Epithelioid neoplasm
  - Pleomorphic neoplasm

- In each category, depending on age, sex, clinical history and location of metastasis, there would be a statistically probably differential diagnosis

Immunohistochemistry

In metastatic undifferentiated tumours, immuno should aim at determination of the broad category of tumour groups –

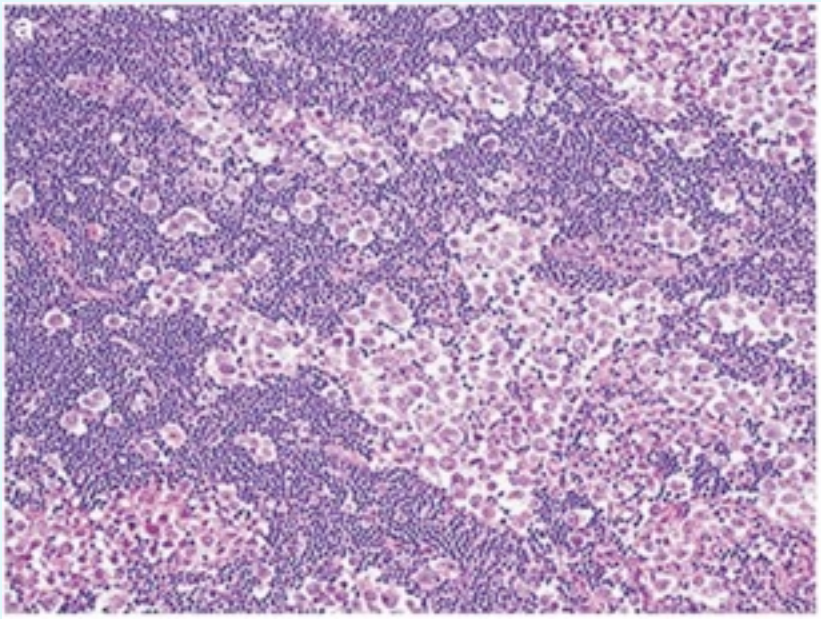
- Carcinoma – Cytokeratin
- Melanoma – S100
- Lymphoma – CD45
- Sarcoma – Vimentin
- Germ cell tumour – no pan-germ cell tumour immuno

Carcinomas

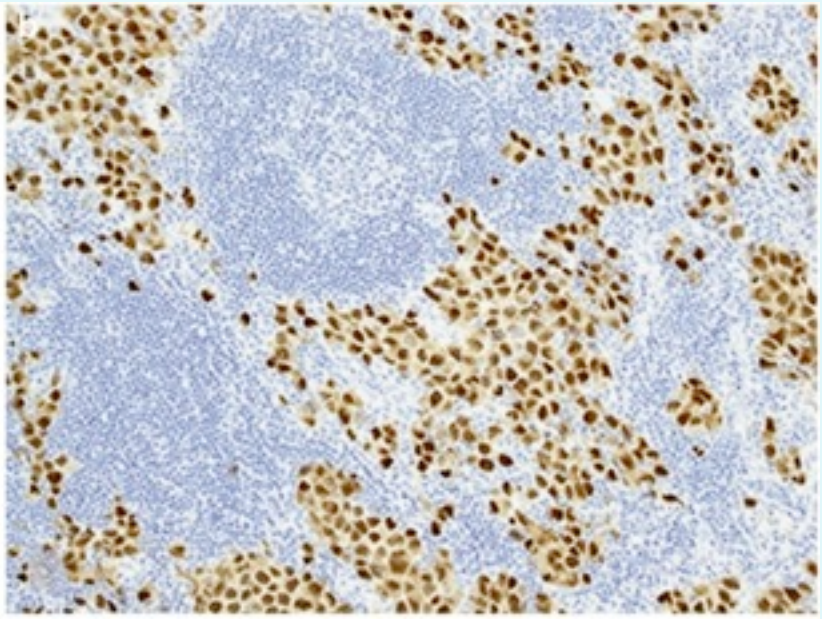
- Cytokeratins are useful screening markers
- Poorly differentiated carcinomas show variable expression to CK's
- EMA (epithelial membrane antigen) may serve as a supplement to CK's especially in sarcomatoid or undifferentiated carcinoma that are –ve for CK.
- EMA however is negative in some epithelial tumours (endocrine, medullary thyroid) and are positive in some haematopoieitc malignancies.
- Abberant CK staining in nonepithelial malignancy is weak and stains focally whereas CK staining in carcinomas is strong.

Germ cell tumours

- There is no pan-germ cell tumour immuno marker
- When germ cell tumours are suspected OCT3/4 detects components of seminoma and embryonal carcinoma
- OCT3/4 is a transcription factor and is fundamental in the maintenance of pluripotency in embryonic stem cells – its expression dissappears rapidly when cells differentiate.
- Combinations of CD30 and CD117 can help to distinguish between seminoma and embryonic carcinoma
  - Seminoma – CD30 – , CD117 +
  - Embryonal – CD30 +, CD117 –



Metastatic seminoma in a LN

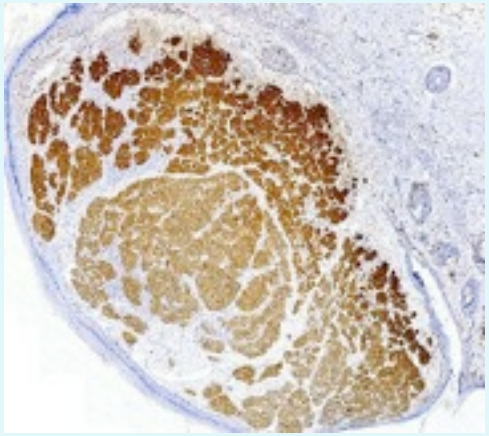


OCT3/4 immuno

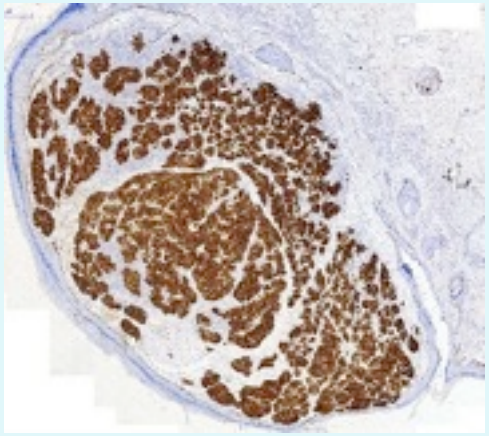
Malignant melanoma

- S100 in the screening marker for MM with >95% sensitivity.
- S100 however has a low specificity and is also expressed in other tumours –
  - Peripheral nerve sheath tumours
  - Occasional adenocarcinomas
- Therefore melanocyte-specific markers are used
  - HMB-45 (sensitivity 75-92%)
  - Melan A (sensitivity 69-93%)
- However, desmoplastic and spindle cell melanomas are negative for melanocyte-specific markers

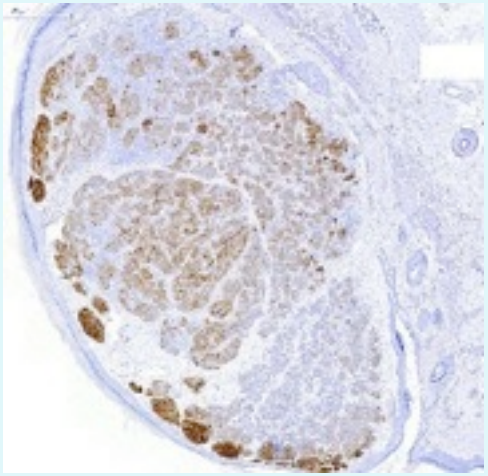
Malignant melanoma



S100



Melan A



HMB45

Haematopoietic malignancies

- CD45 has high sensitivity (97%) and specificity (nearly 100%) for lymphoid tumours
- However, CD45 is unexpressed in lymphoblastic lymphomas and variably expressed in plasma cell neoplasms and anaplastic large cell lymphomas.

CK7 & CK20

	CK7	CK20
Colorectal carcinoma	-	+
Ovarian, endometrial, lung, salivary gland or mammary gland carcinoma	+	-
<u>Urinary bladder</u> Squamous carcinoma Urothelial carcinoma	 - +	
Prostate carcinoma	-	-
Urothelial carcinoma	+	+
<u>Neuroendocrine</u> Merkel cell carcinoma Small cell carcinoma of lung	 - +	 + -

Organ specific markers

- Lung – TTF-1
- Thyroid – thyroglobulin, calcitonin
- Adrenal – Melan-A, inhibin-A and calretinin are expressed in adrenocortical carcinomas
- Breast – ER & PR
- GI & pancreas – CDX-2
- Liver – HepPar-1
- Kidney – RCC, CD10
- Ovary – CA125
- Endometrium – ER, PR
- Prostate – PSA

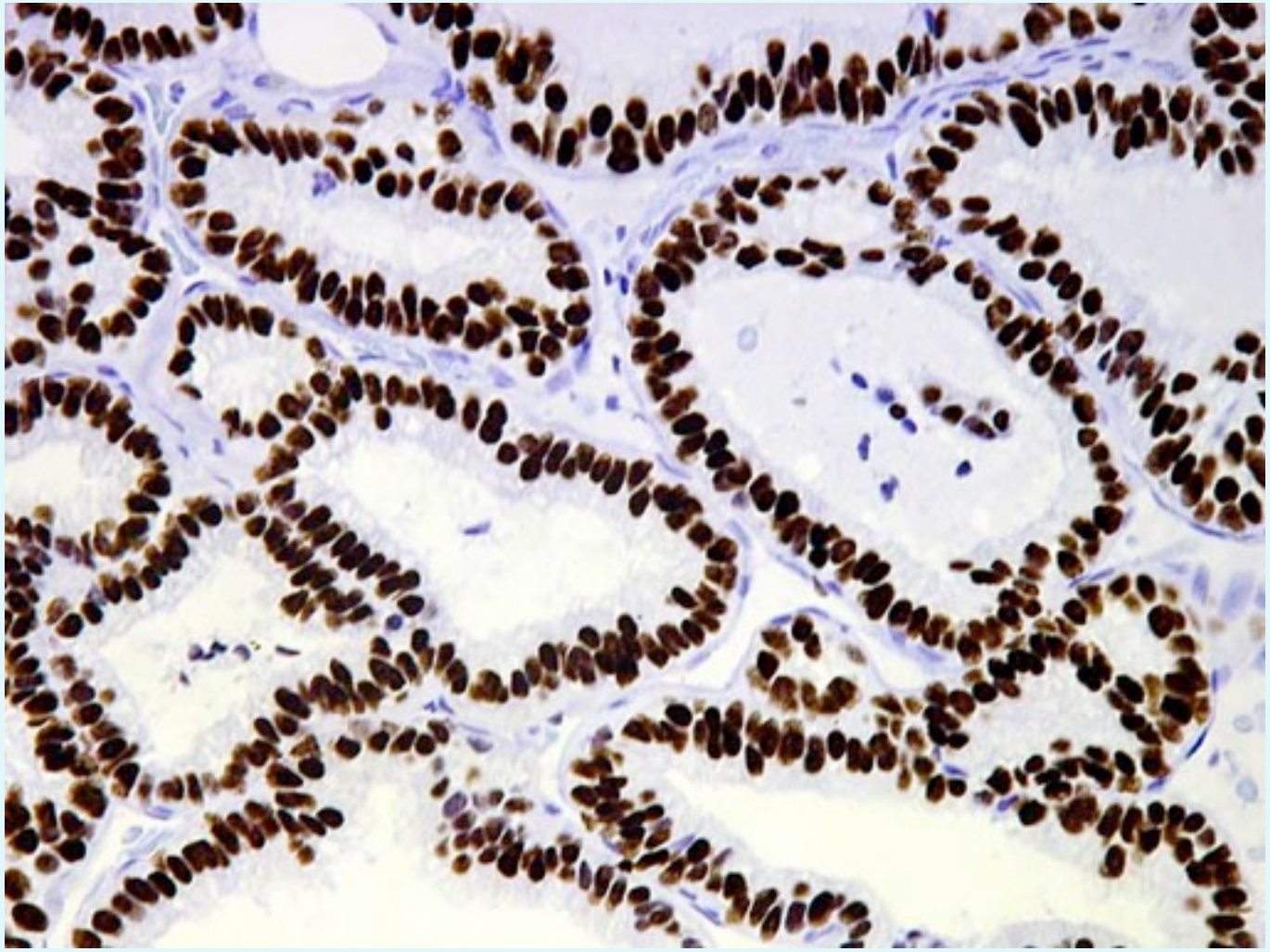
Transcription factors

- Proteins that control the first step of gene expression.
- Orchestrate the complex pathways of cellular growth and differentiation.
- Some are tissue/organ specific therefore helpful for determining cell lineage of tumour

TTF-1

- Expressed in lung, thyroid and ventral forebrain
- Expressed in 75% of lung adenocarcinomas
- Usually negative in mucinous carcinomas and bronchogenic squamous cell carcinomas
- Consistently expressed in papillary, follicular Hürthle cell and poorly differentiated carcinomas of the thyroid
- Expressed in 18% of anaplastic and variably in medullary thryroid carcinomas.

Metastatic thyroid follicular carcinoma stained for TTF-1.



WT-1

- Normally expressed in developing human organs – kidneys, ovarian surface epithelium and mesothelium

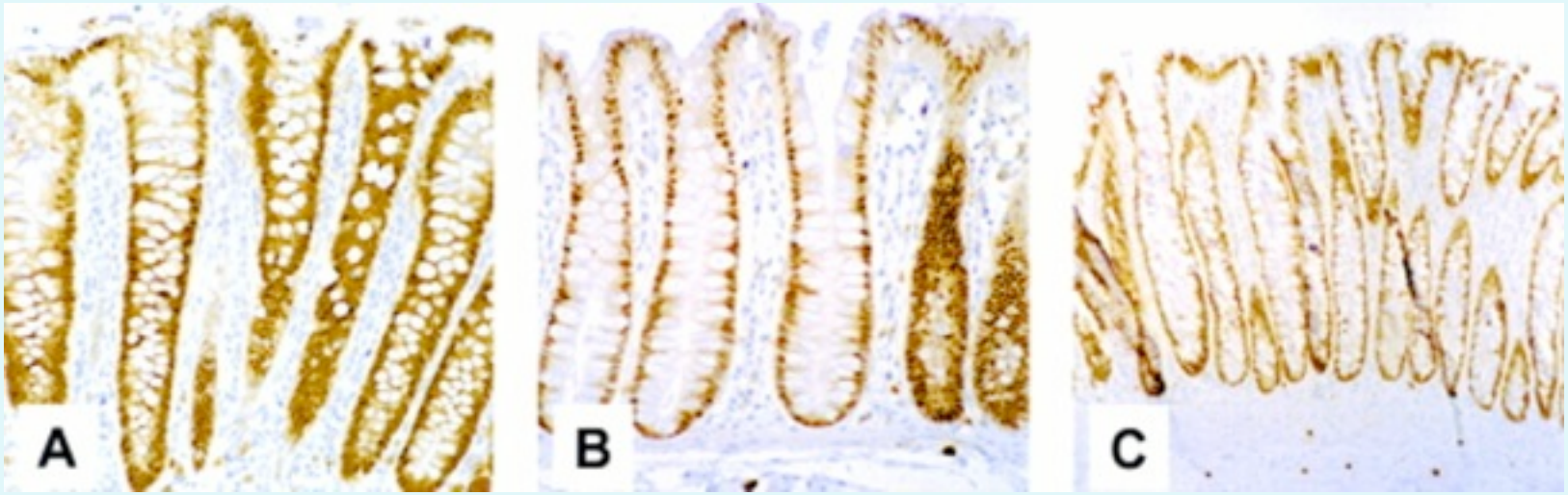
- Usually negative in all endometrial carcinomas
- In ovarian carcinomas
  - positive in serous adenocarcinoma, transitional carcinoma, and small cell carcinoma
  - negative in clear cell, endometrioid and mucinous carcinomas

- Good marker for epithelioid malignant mesothelioma
- Useful to distinguish mesothelioma from adenocarcinoma of the lung

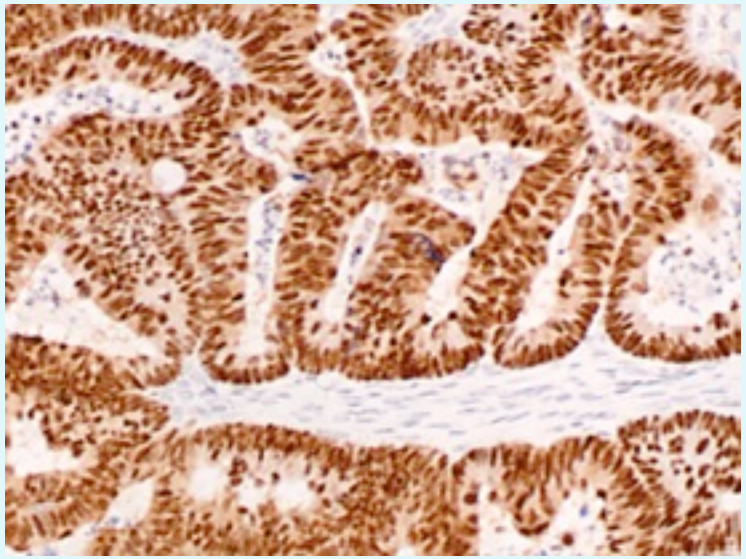
CDX-2

- Plays a critical role in the development of the intestines
- Useful marker for intestinal differentiation
- Expressed in 70-85% of colorectal adenocarcinomas which is also retained in metastatic foci
- Its expression declines in poorly differentiated carcinomas
- Also seen in adenocarcinomas of GOJ, stomach, ampulla and small intestine.
- Seen in 5-30% of pancreas ductal adenocarcinomas, cholangiocarcinmas and gall bladder adenocarcinomas.

CDX-2 staining in normal bowel



Ascending colon Descending colon Rectum



Adenocarcinoma of the colon

P-63

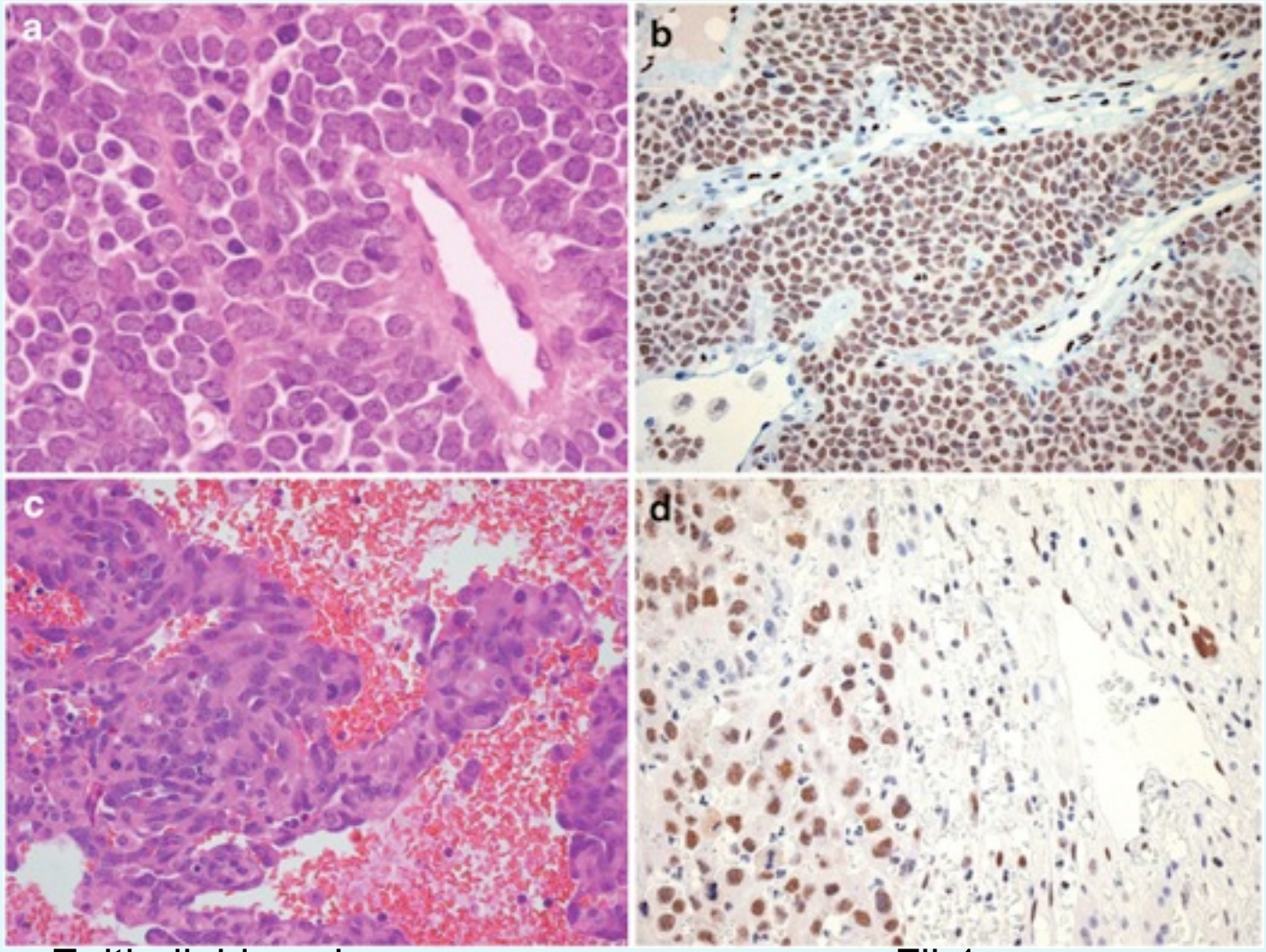
- Pivotal in the development and maintenance of stratified epithelia
- Expressed by
  - squamous epithelium, urothelium and thymic epithelium as well as
  - myoepithelial cells in breast, salivary, bronchial and sweat glands
  - basal cells of prostate
  - Bronchus
- Almost always expressed by SCC, thymomas, BCC, urothelial carcinomas and myoepithelial carcinomas

Fli-1

- Master regulator of the haemangioblast, a common precursor of blood and endothelium
- Expressed by endothelial cells of all types of vessel
- Positive in Ewing's sarcoma/PNET, lymphoblastic lymphomas and malignant vascular tumours (angiosarcoma, epithelioid haemangioendotheliomas and Kaposi sarcomas)
- Also expressed in subset of Merkel cell carcinomas, malignant melanomas, synovial sarcomas, adenocarcinomas of the lung and breast.

Ewing's sarcoma

Fli-1



Epithelioid angiosarcoma

Fli-1

Nectrotic tumours

- Immuno may not work due to loss of antigenicity or may result in false positivity
- Immuno hay be helpful in some situations
  - HMB-45 & Melan-A in maligant melanoma
  - CK, OCT3/4, CD30 &CD117 in germ cell tumours
- The necrotic cells that retain immunoreactivity correspond to areas where the outline of tumour cells (ghost cells) are recognised on H&E

Be careful when using immuno as there are no definite rules.

Use immuno to confirm your suspected diagnosis not to give the initial diagnosis.