LEIDEN UNIVERSITY MEDICAL CENTER

The spectrum of haemangioendotheliomas

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Disclosure

- **No disclosure**

Terminology regarding malignant potential:

- **Benign**
- **Intermediate**
  - Locally aggressive
  - Rarely metastasizing
- **Malignant**

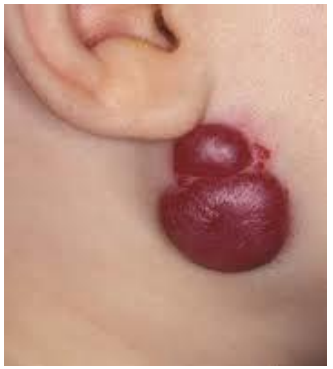
WHO classification soft tissue tumours 2013

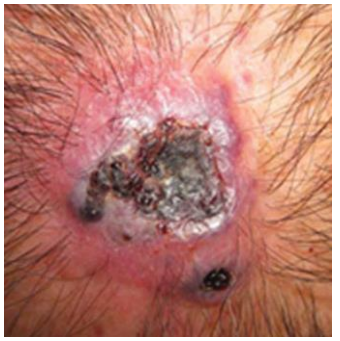
VASCULAR TUMOURS OF SOFT TISSUE	
Benign	
Haemangioma	9120/0
Synovial	
Venous	9122/0
Arteriovenous haemangioma/malformation	9123/0
Intramuscular	9132/0
Epithelioid haemangioma	9125/0
Angiomatosis	
Lymphangioma	9170/0
Intermediate (locally aggressive)	
Kaposiform haemangioendothelioma	9130/1
Intermediate (rarely metastasizing)	
Retiform haemangioendothelioma	9136/1*
Papillary intralymphatic angioendothelioma	9135/1
Composite haemangioendothelioma	9136/1
Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma	9136/1
Kaposi sarcoma	9140/3
Malignant	
Epithelioid haemangioendothelioma	9133/3
Angiosarcoma of soft tissue	9120/3

Haem-angioma

Haem-angio-endo-thelioma

Angio-sarcoma



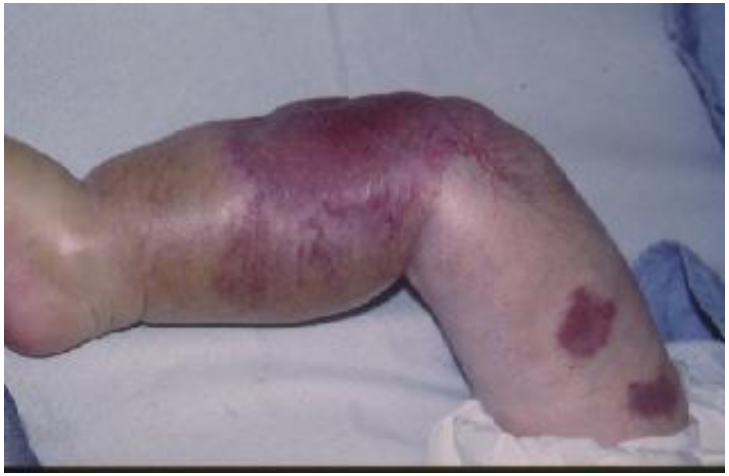


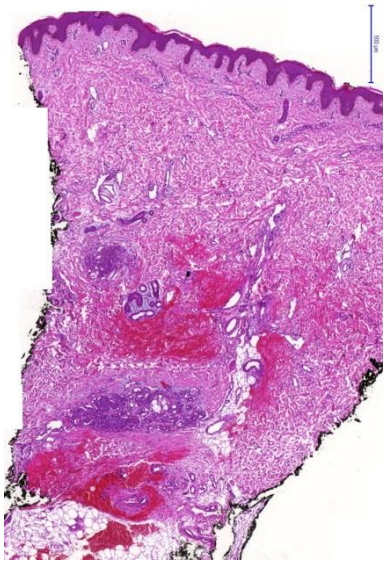
Haemangioendotheliomas

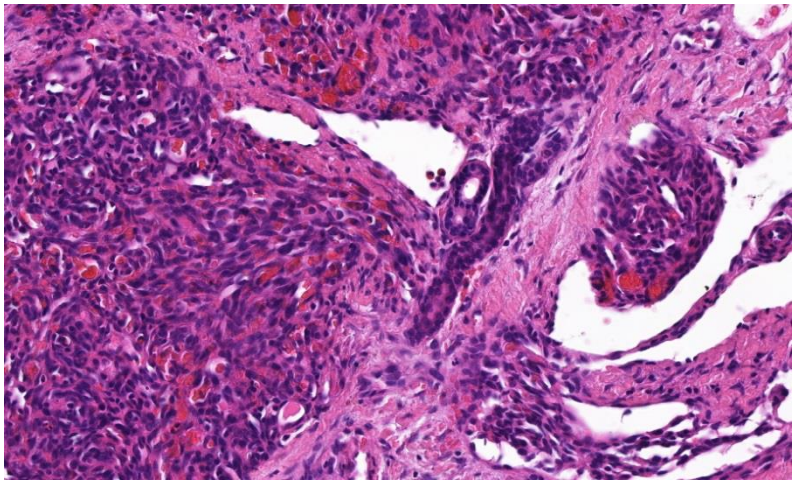
- **Kaposiform hemangioendothelioma** — Locally aggressive
- **Retiform hemangioendothelioma** — Rarely metastasizing
- **Papillary intralymphatic angioendothelioma** — Rarely metastasizing
- **Composite hemangioendothelioma** — Rarely metastasizing
- **Pseudomyogenic (epithelioid sarcoma-like) haemangioendothelioma** — Rarely metastasizing
- **Epithelioid hemangioendothelioma** — Malignant

Kaposiform haemangioendothelioma

- **Locally aggressive**
- **Nearly exclusively in children**
- **Often associated with Kassabach-Merritt phenomenon (thrombocytopenia)**
- **No tendency to regress**
- **Mortality ~10% due to local disease or thrombocytopenia**
- **Difficult to treat**

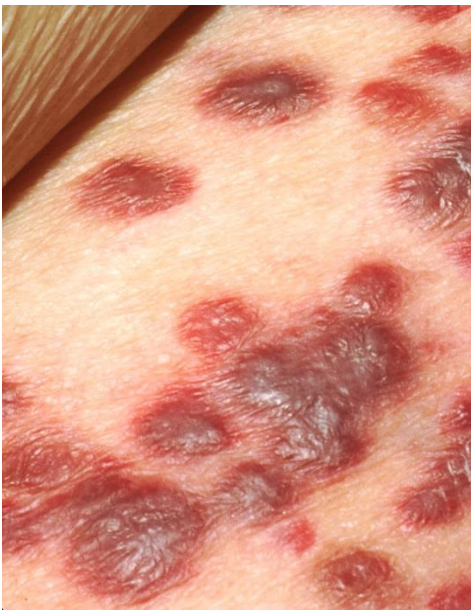


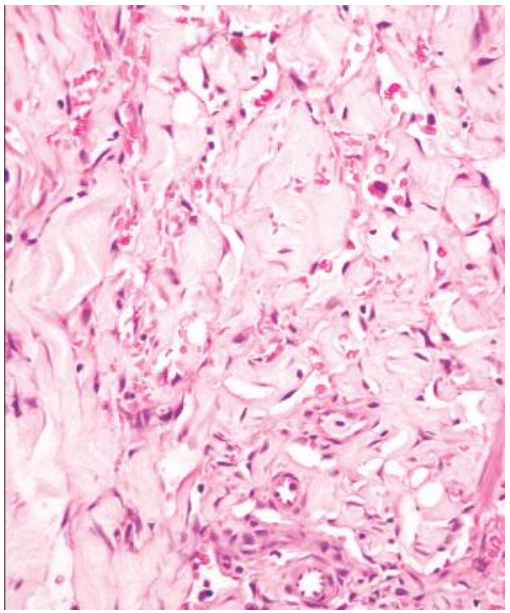


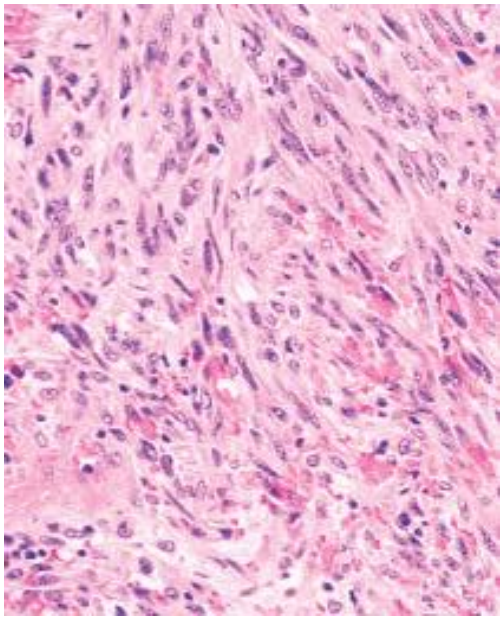


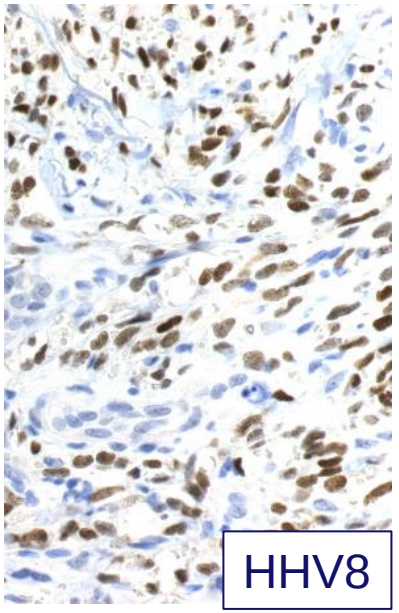
DD: Kaposi sarcoma

- **Virus induced vascular proliferation: HHV-8**
- **Locally aggressive: variable clinical behaviour**
- **Classic indolent vs. aggressive AIDS-associated**



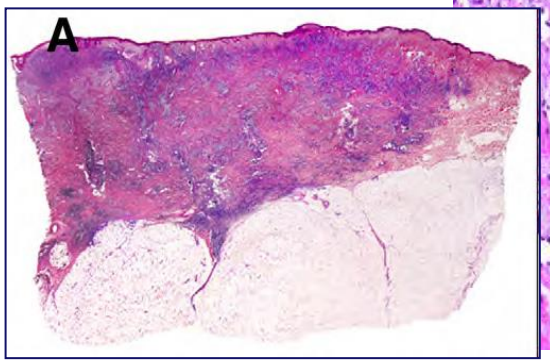


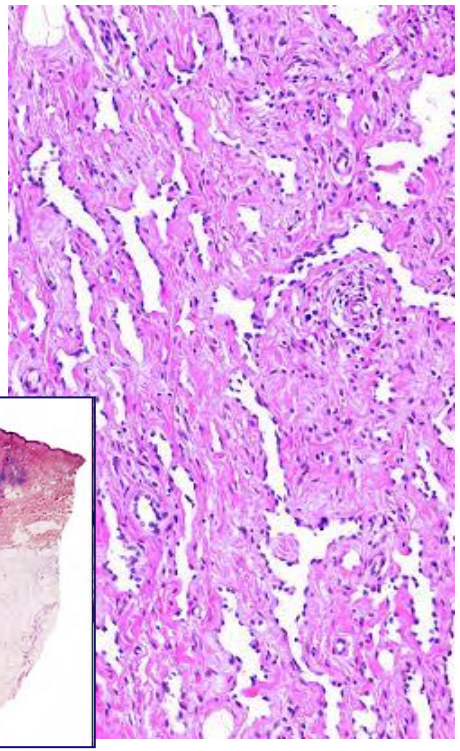


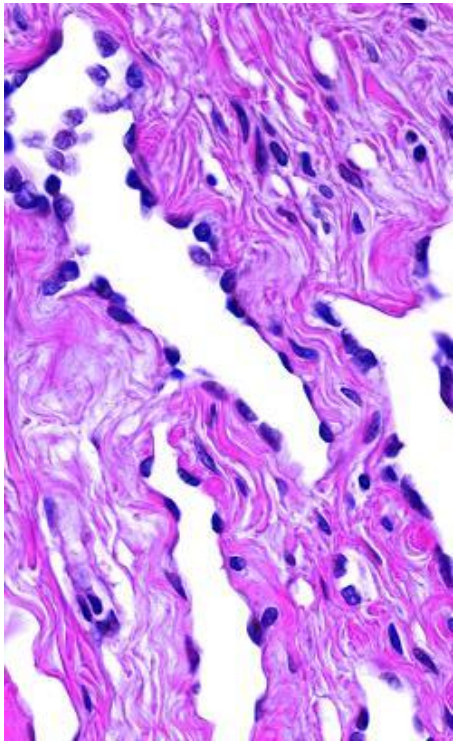


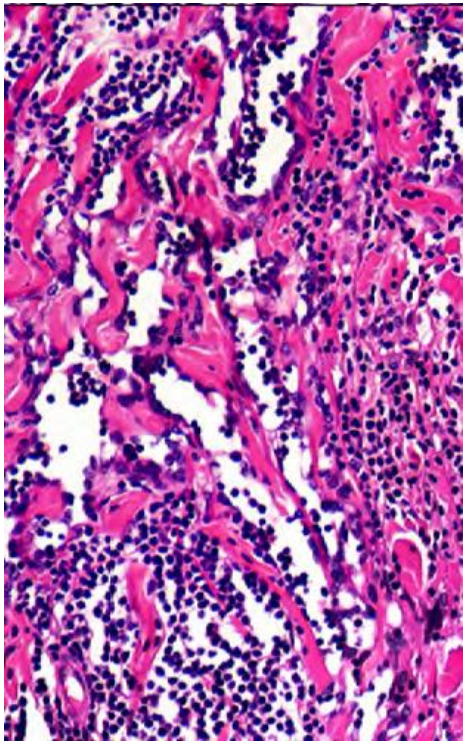
Retiform hemangioendothelioma

- **Locally aggressive, rarely metastasizing**
- **Wide age range**
- **Multiple local recurrence (60%) over many years**
- **Rarely metastases to regional lymph nodes**



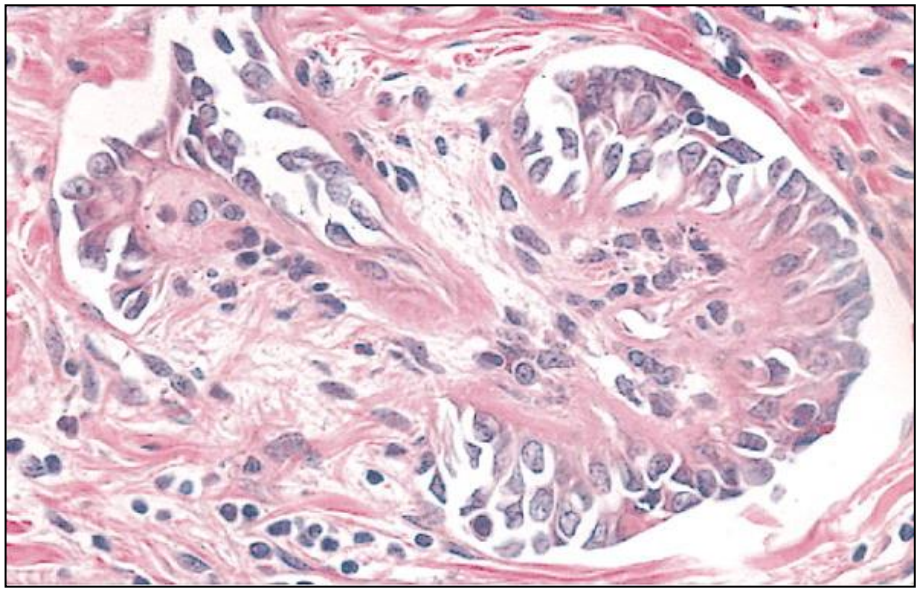


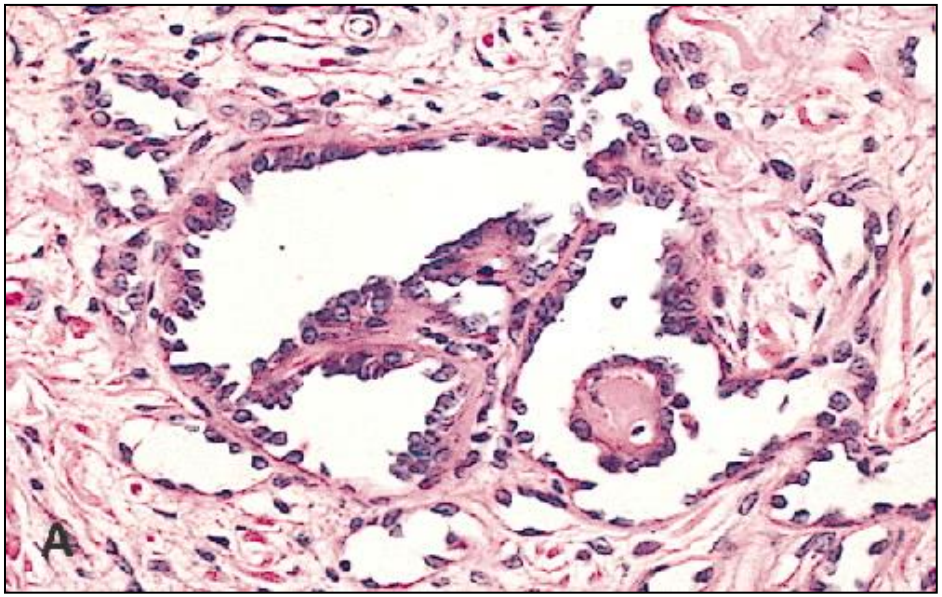




Papillary intralymphatic angioendothelioma (PILA)

- **Previously: Dabska tumor**
- **Lymphatic phenotype**
- **Infants and children, 25% in adults**
- **“Rarely metastasizing”: excellent prognosis after wide excision**





Fanburg-Smith, Am J Surg Pathol 1999

Composite haemangioendothelioma

- **Admixture of histologically distinct components**
- **Adults, females > males**
- **Longstanding history, lymphedema**
- **Locally aggressive: recurrences up to 10 years**
- **Rarely metastasizing: lymph node metastases**

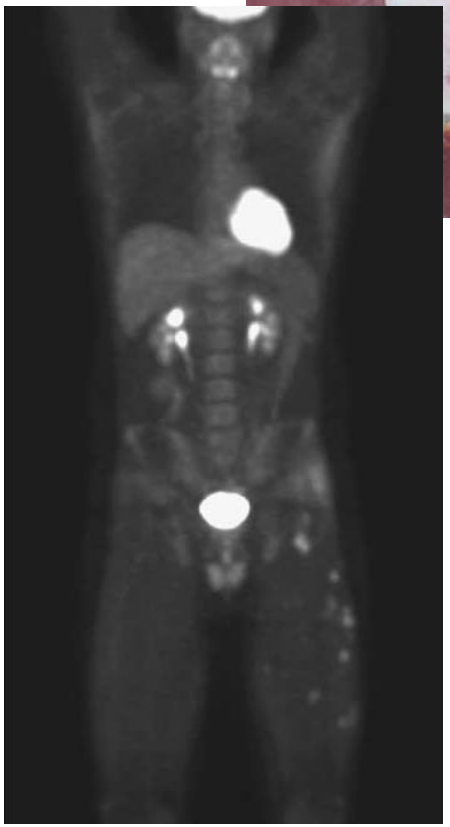
Rubin, Am J Surg Pathol 2000

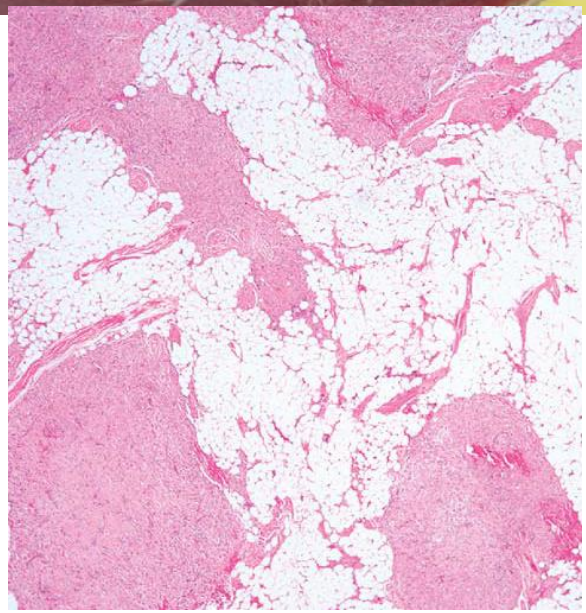
Pseudomyogenic haemangioendothelioma

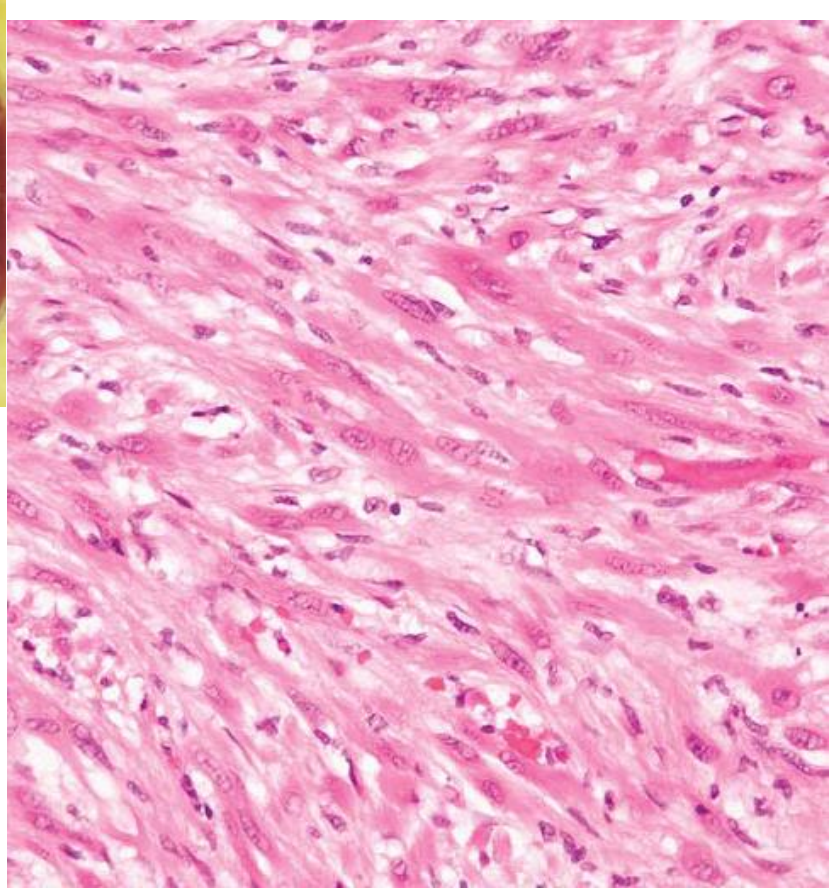
- **Young adult males**
- **Lower extremity**
- **66% multifocal: multiple discontiguous nodules in different tissue planes**
  - Cutis and subcutis
  - 50% intramuscular
  - 20% lytic bone lesions
- **Histologically resembling epithelioid sarcoma or a myoid tumor**

Hornick and Fletcher, Am J Surg Pathol 2011

Pseudomyogenic Haemangioendothelioma



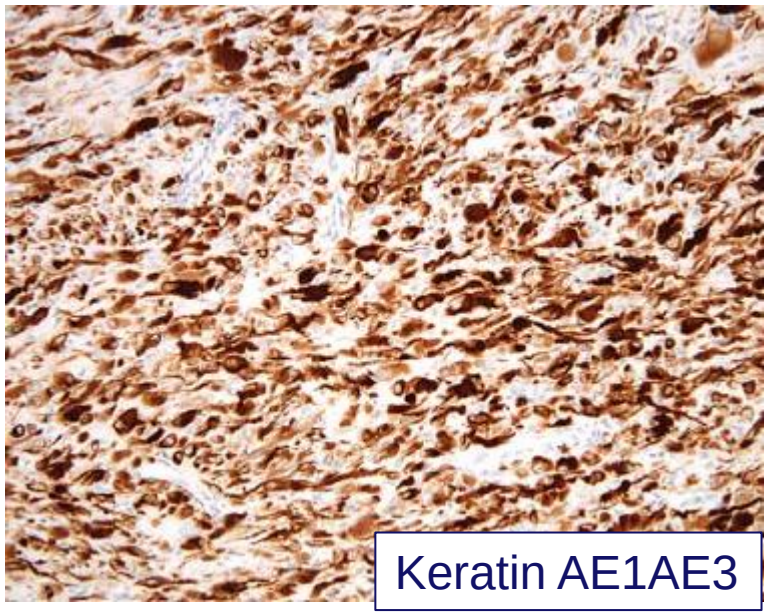


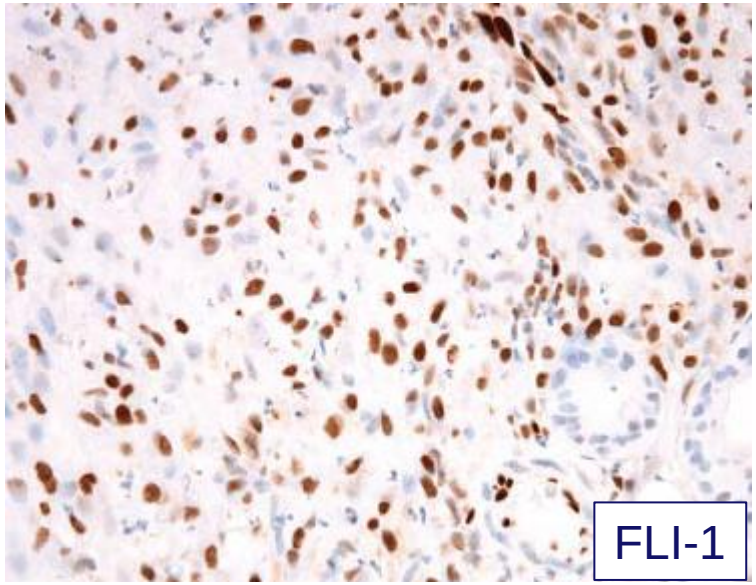


Hornick and Fletcher, Am J Surg Pathol 2011

Pseudomyogenic Haemangioendothelioma

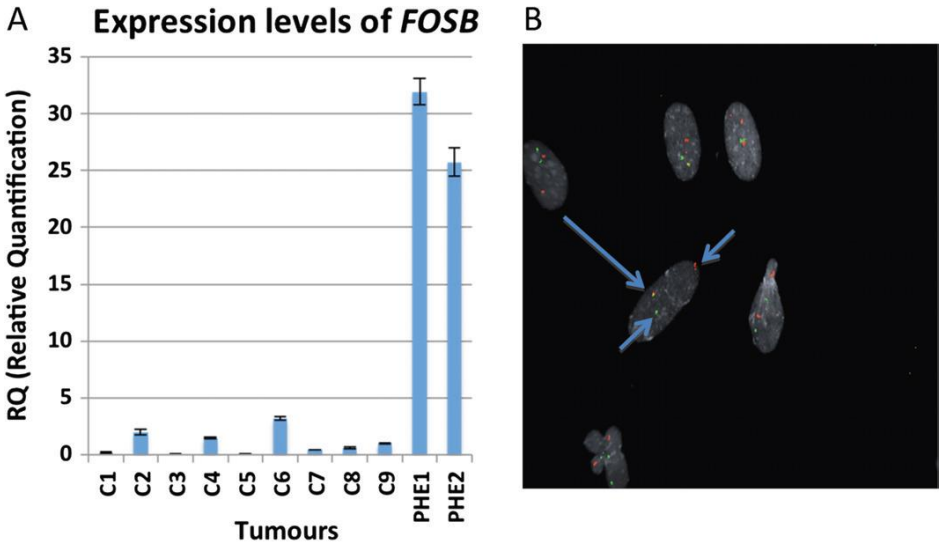
- **Diffuse expression of Keratin AE1, ERG and FLI1**
- **CD34, desmin negative**
- **CD31 in 50%**
- **Retention of INI1**





Hornick and Fletcher, Am J Surg Pathol 2011

Pseudomyogenic Haemangioendothelioma



- t(7;19)(q22;q13) in 2 cases
- SERPINE1–FOSB fusion in 8/8 cases

Walther et al, J Pathol 2014

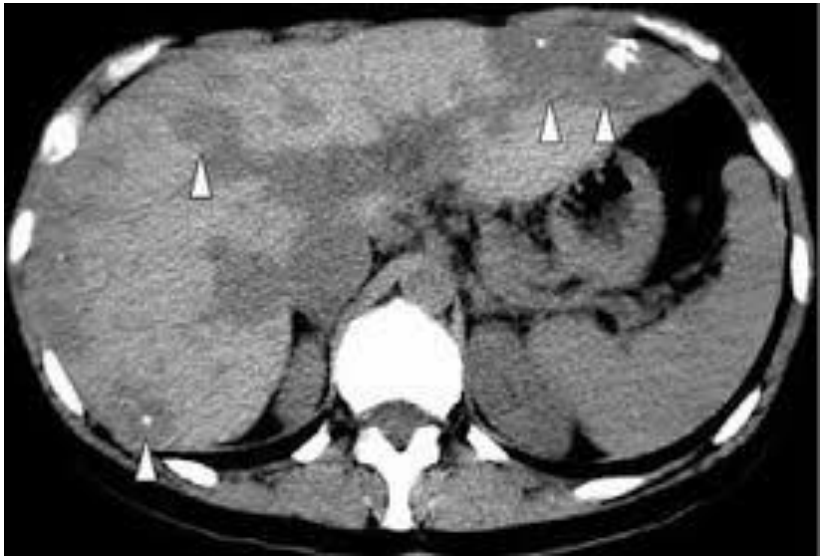
Pseudomyogenic Haemangioendothelioma

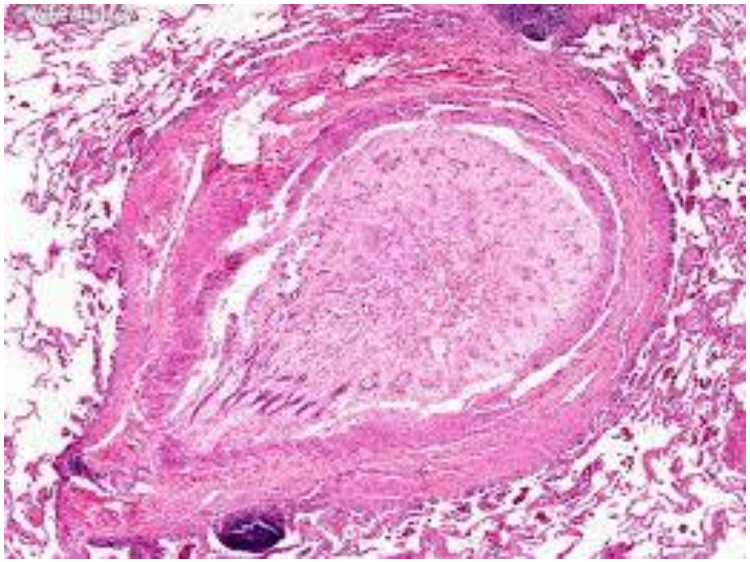
- **60 patients reported:**
  - Surgical excision
  - Locally aggressive: 60% local recurrence / additional lesions, usually within 1-2 years
  - Rarely metastasizing: 1 lymph node and 2 late distant metastases out of 60 patients

- **WHO: intermediate, rarely metastasizing**

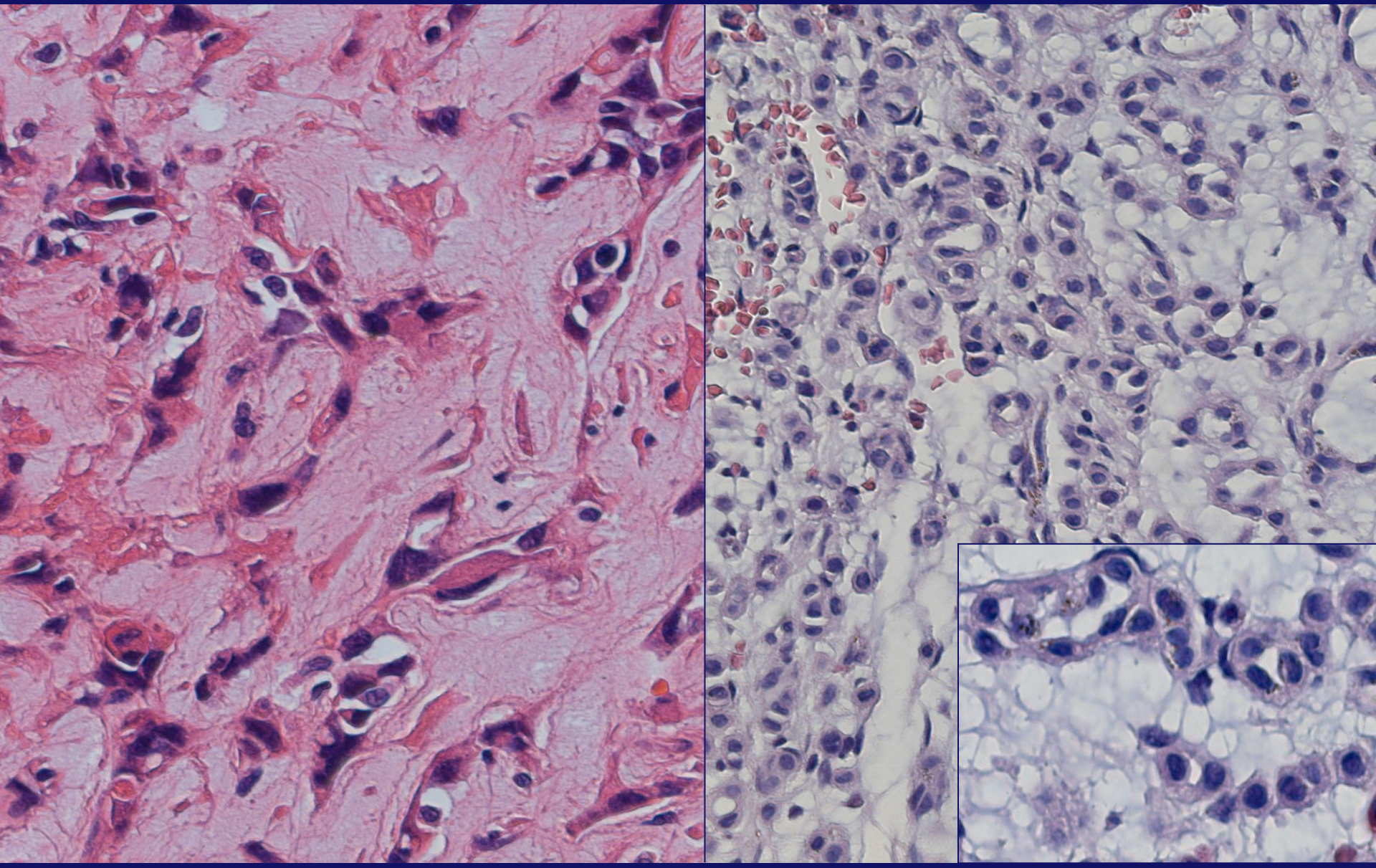
Epithelioid haemangioendothelioma

- **Wide age range, most common after 2nd decade**
- **Malignant**
- **50% multifocal, esp lung, bone, liver (monoclonal)**
- **Propensity for angiocentric growth**

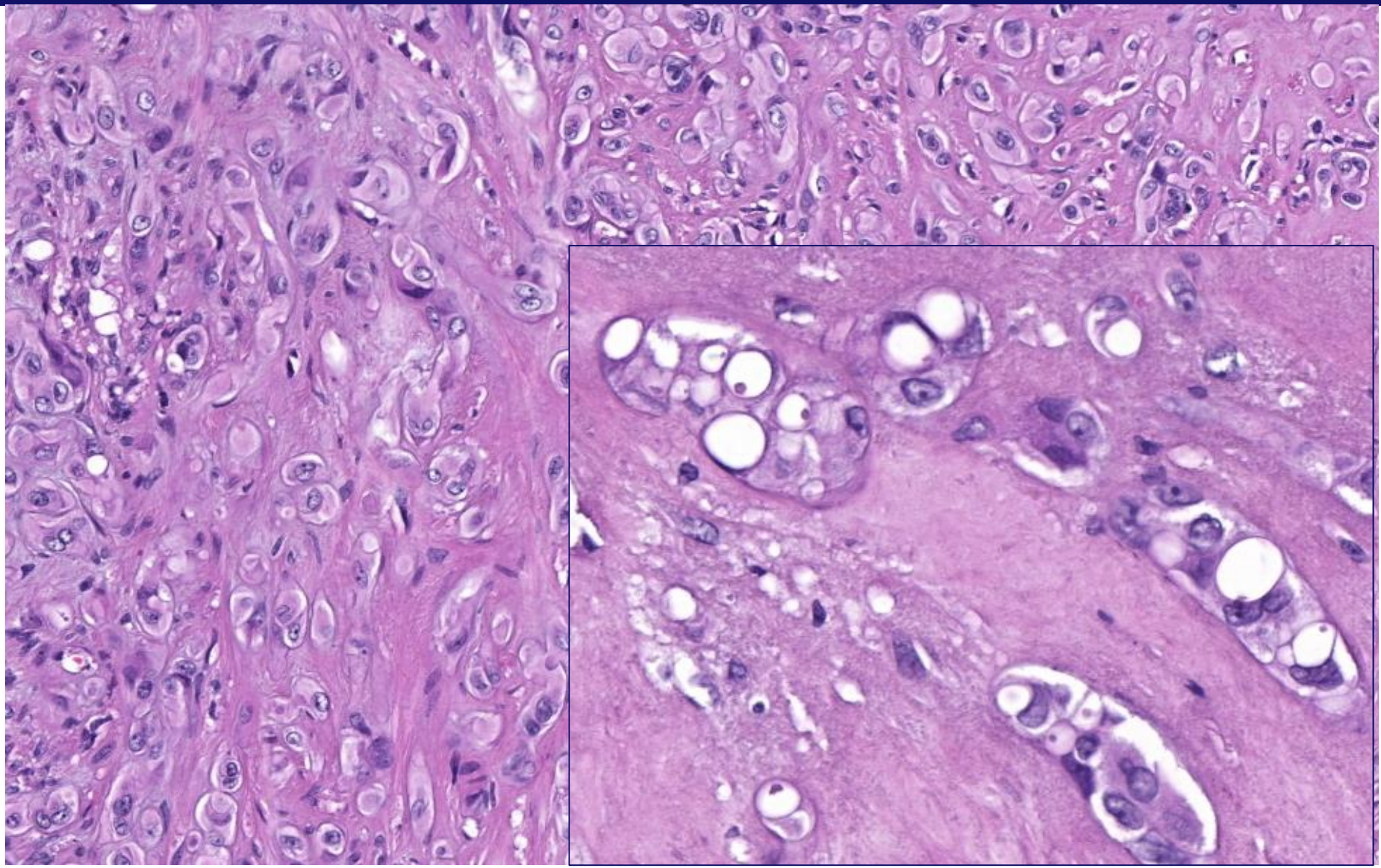




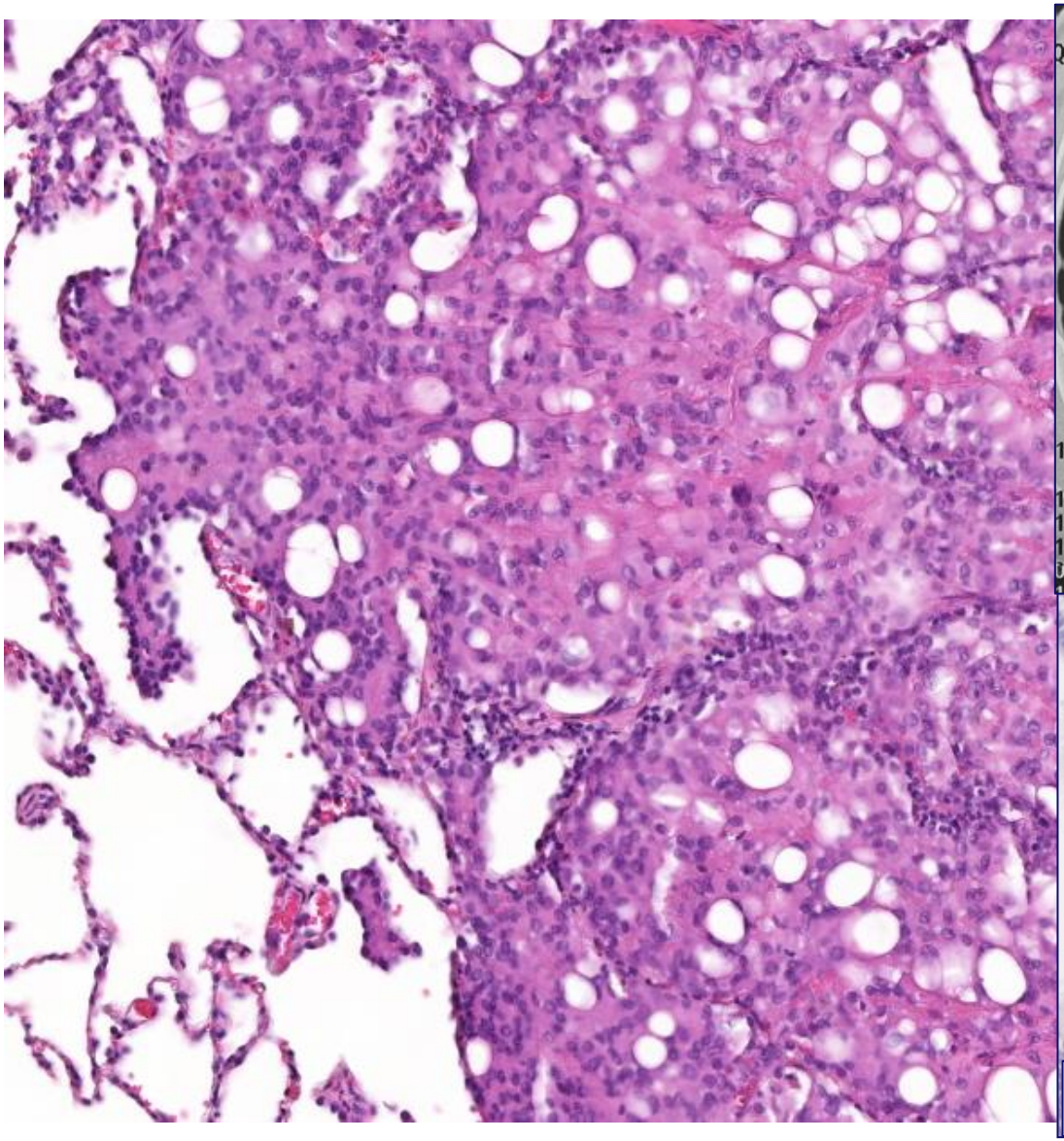
Epithelioid haemangioendothelioma

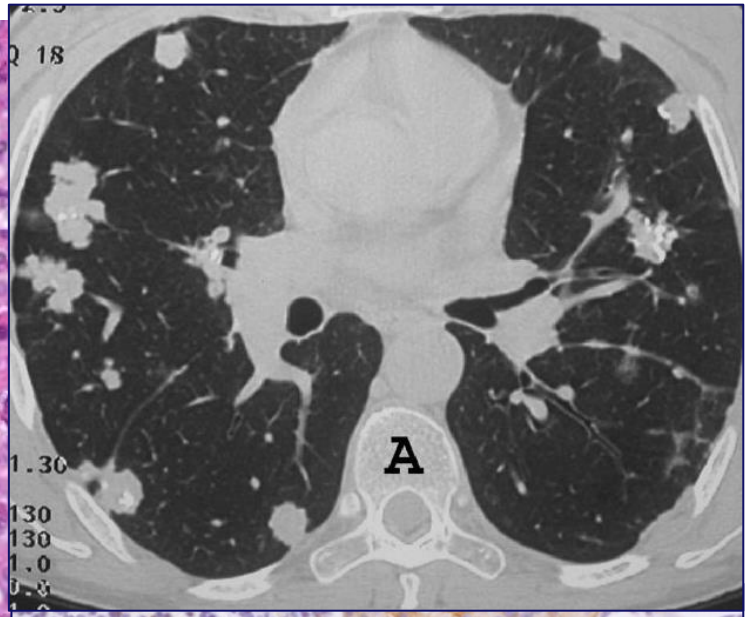


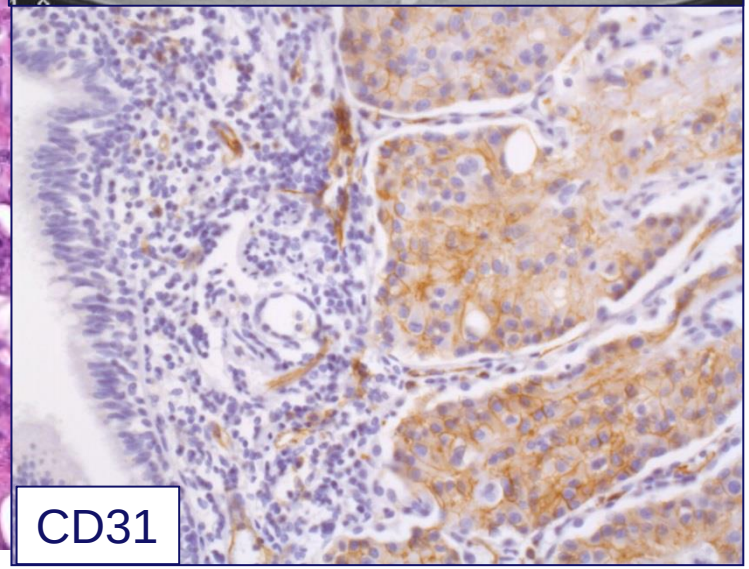
Epithelioid haemangioendothelioma



Epithelioid haemangioendothelioma of the lung

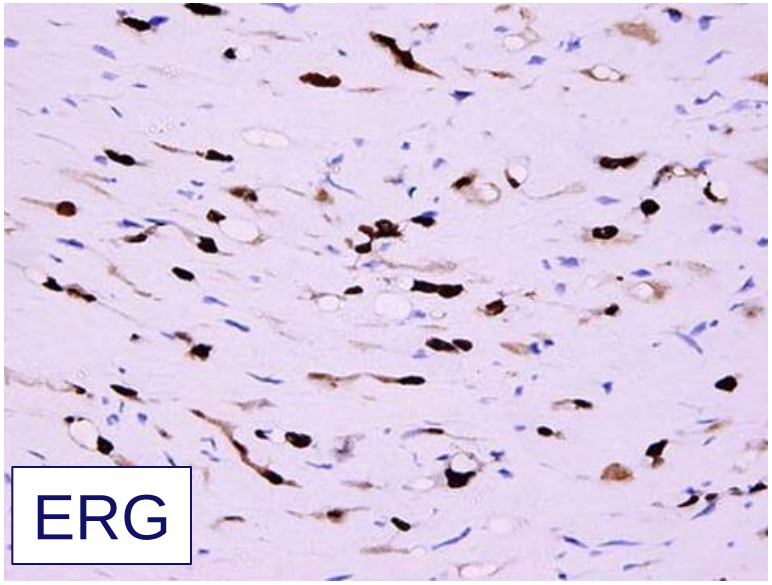






EHE; immunohistochemistry

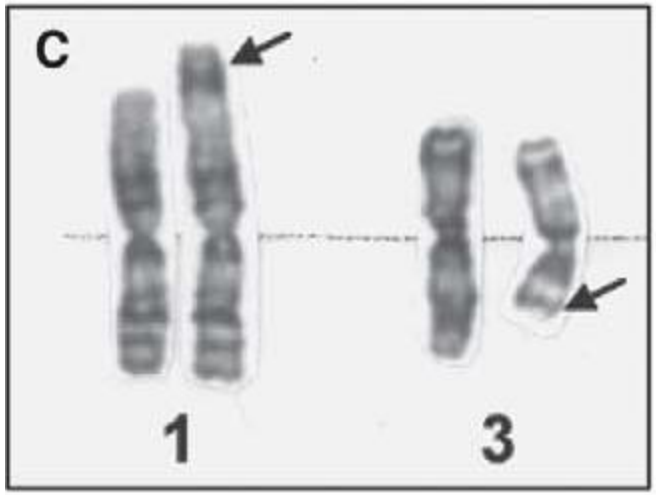
- **CD31** **100%**
- **CD34** **85%**
- **FLI1** **100%**
- **ERG** **98%**
- **Keratin** **25-38%**
- **D2-40** **54%**
- **Prox1** **47%**
- **Claudin-5** **88%**

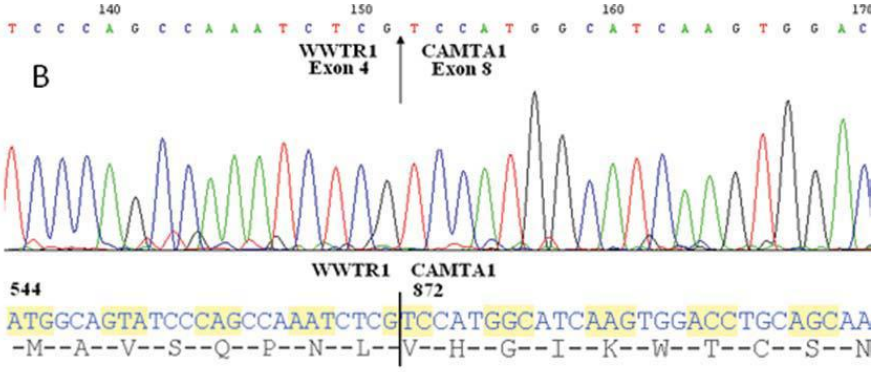


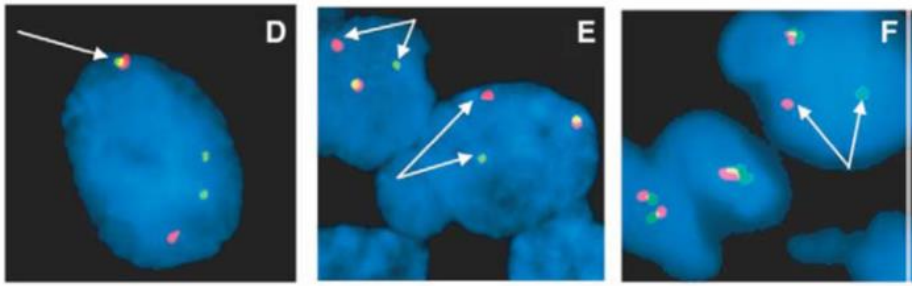
Gill et al, Arch Pathol Lab Med 2009, WHO 2002, Miettinen AJSP 2009, 2011, 2012

WWTR1-CAMTA1 fusion in EHE

t(1;3)(p36;q25) in 89-100%







G	WWTR1		CAMTA1	
	Positive /total	%	Positive /total	%
Epithelioid hemangioendothelioma	42/47	89%	39/45	87%
Angiosarcoma, NOS	0/42	0%	0/39	0%
Epithelioid angiosarcoma	0/7	0%	0/7	0%
Intimal sarcoma	0/5	0%	0/3	0%
Kaposi's sarcoma	0/4	0%	0/4	0%
Malignant hemangioendothelioma, NOS	0/1	0%	0/1	0%
Retiform hemangioendothelioma	0/1	0%	0/1	0%
Kaposiform hemangioendothelioma	0/3	0%	0/2	0%
Epithelioid hemangioma	0/5	0%	0/4	0%
Arteriovenous malformation	0/2	0%	0/2	0%
Angiomatosis	0/1	0%	0/1	0%
Hemangioma, NOS	0/3	0%	0/3	0%
Capillary/pyogenic hemangioma	0/5	0%	0/5	0%
Cavernous hemangioma	0/5	0%	0/5	0%
Juvenile hemangioma	0/1	0%	0/1	0%
Spindle cell hemangioma	0/4	0%	0/4	0%
Synovial hemangioma	0/1	0%	0/1	0%
Intramuscular hemangioma	0/6	0%	0/5	0%
Littoral cell hemangioma	0/6	0%	0/2	0%
Malignant hemangiopericytoma	0/1	0%	0/1	0%
Hemangiopericytoma, NOS	0/1	0%	0/1	0%
Sinonasal hemangiopericytoma	0/1	0%	0/1	0%
Glomus tumor	0/1	0%	0/1	0%
Atypical glomus tumor	0/2	0%	0/2	0%
Lymphangioma	0/7	0%	0/7	0%
Lymphangioleiomyomatosis	0/1	0%	0/1	0%
Papillary endothelial hyperplasia	0/2	0%	0/2	0%
Total cases	165		151	

Tanas Sci Transl Med 2011, Errani GCC 2011

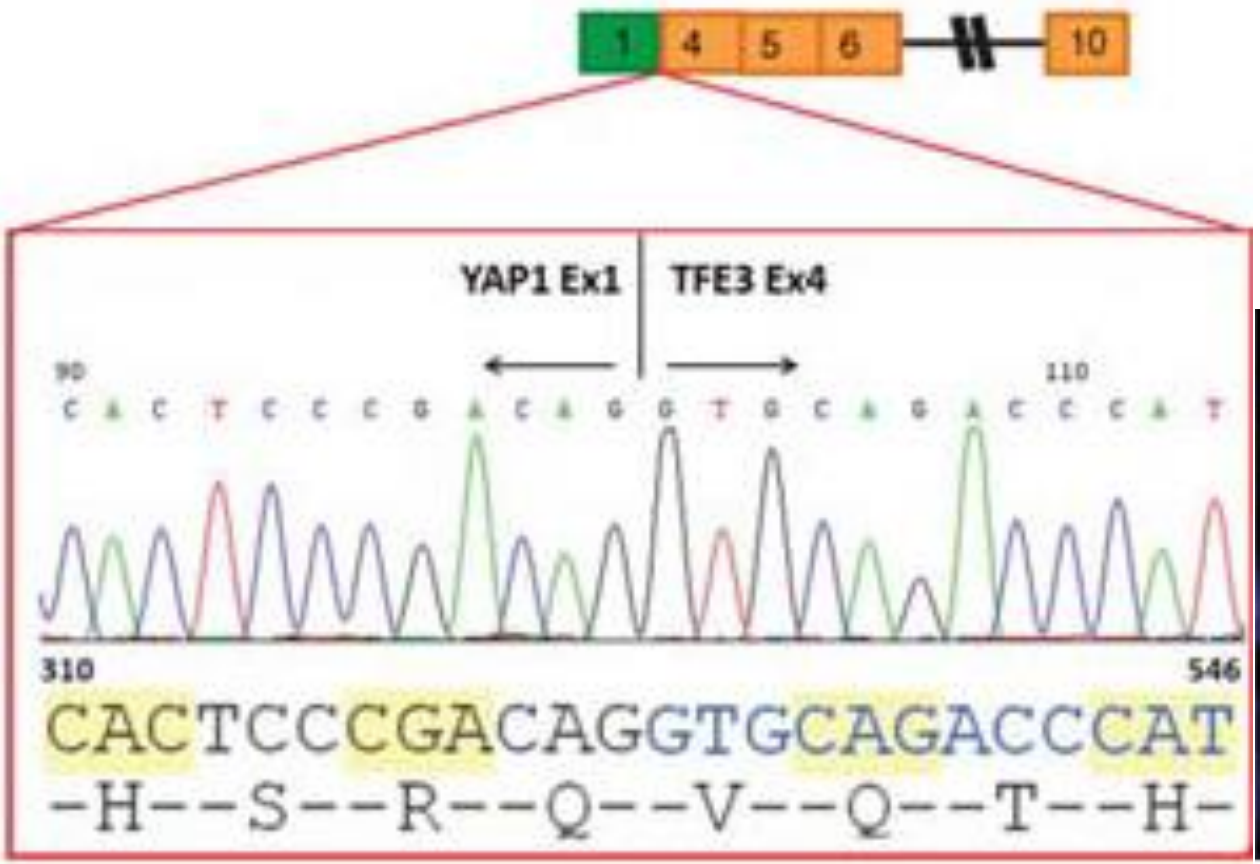
Epithelioid haemangioendothelioma

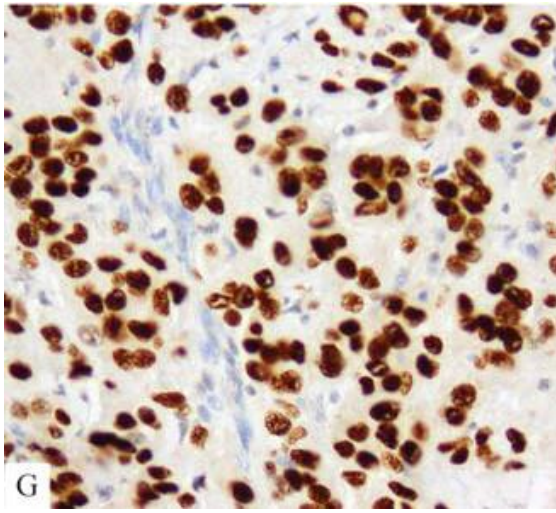
- **Variable clinical behaviour: OS 5 yrs 73%**
  - Most are indolent
  - 20-30% metastasize
  - 15% mortality

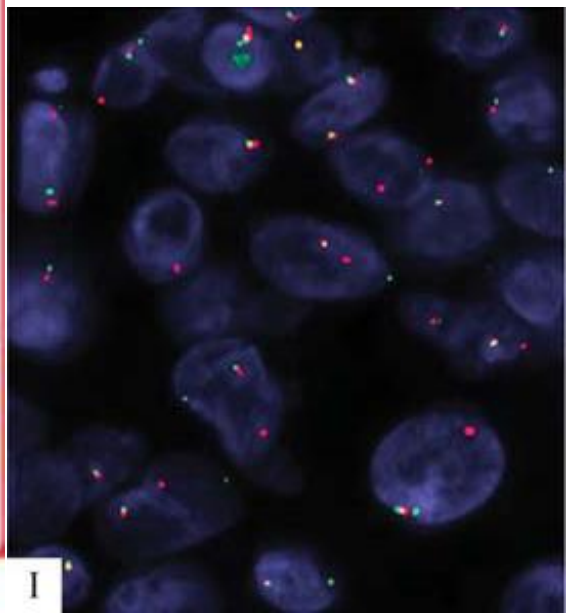
- **Risk stratification**
  - >3 cm, >3 mit/50 HPF — 5 yr survival 59%, metastatic rate 32%
  - <3 cm, <3 mit/50 HPF — 5 yr survival 100%

Deyrup et al, Am J Surg Pathol 2008

YAP1-TFE3 Fusion in distinct subset EHE







EHE treatment

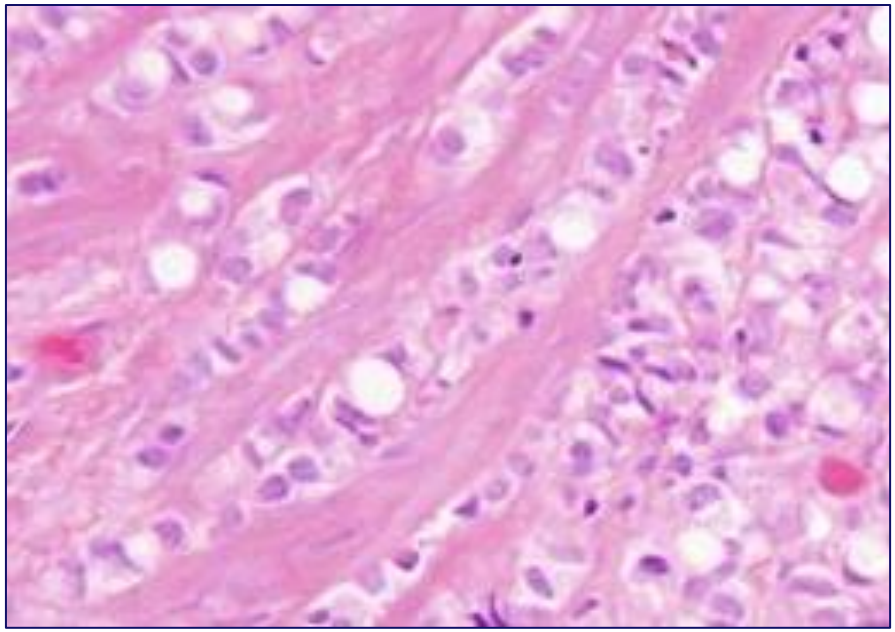
- **Wide surgical resection if possible**
- **Evaluation of regional lymph nodes**
- **Liver transplantation for multifocal liver disease**
- **Systemic therapy: poorly studied**
  - Anti-angiogenic agents
    - *phase II bevacizumab seven patients: two PR (29 %), four SD (57 %), and one PD (14 %)*
    - *Phase II sorafenib, progressive EHE: four of 13 SD, two PR*
- **Problem in evaluating therapy: highly variable growth rate of the tumor**

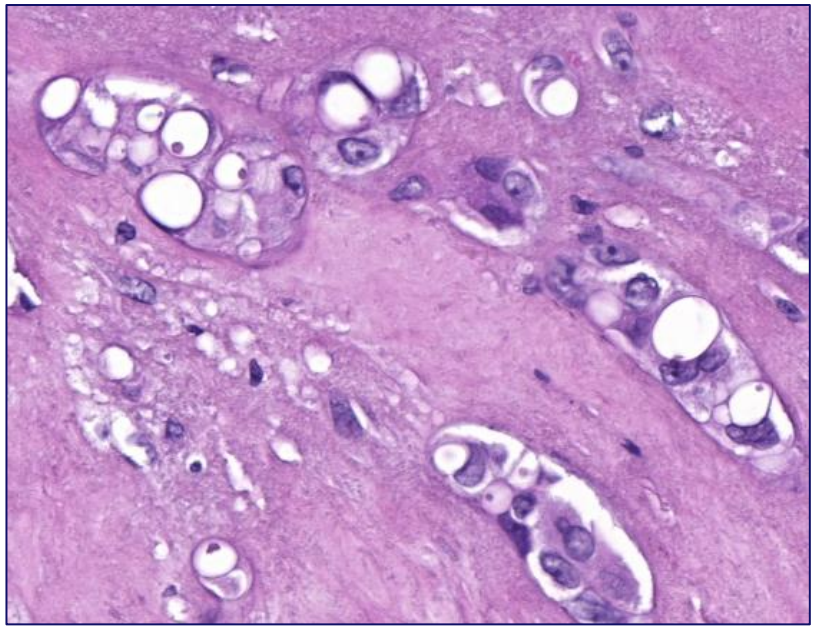
- **MET inhibitor in TFE3 rearranged EHE?**

Ravi and Patel, Curr Oncol Rep 2013

EHE; differential diagnosis

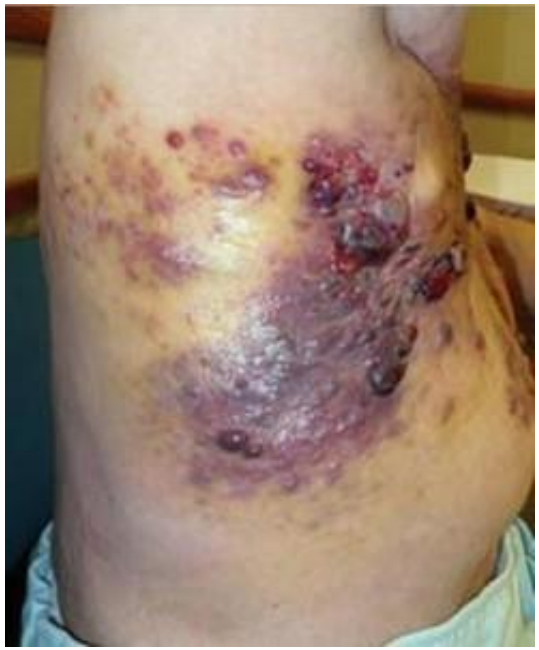
- **Epithelioid hemangioma**
  - Stroma in EHE: myxochondroid or dense sclerotic
  - More mature vessels with open lumina in EH
- **Metastatic carcinoma**
- **Epithelioid angiosarcoma**

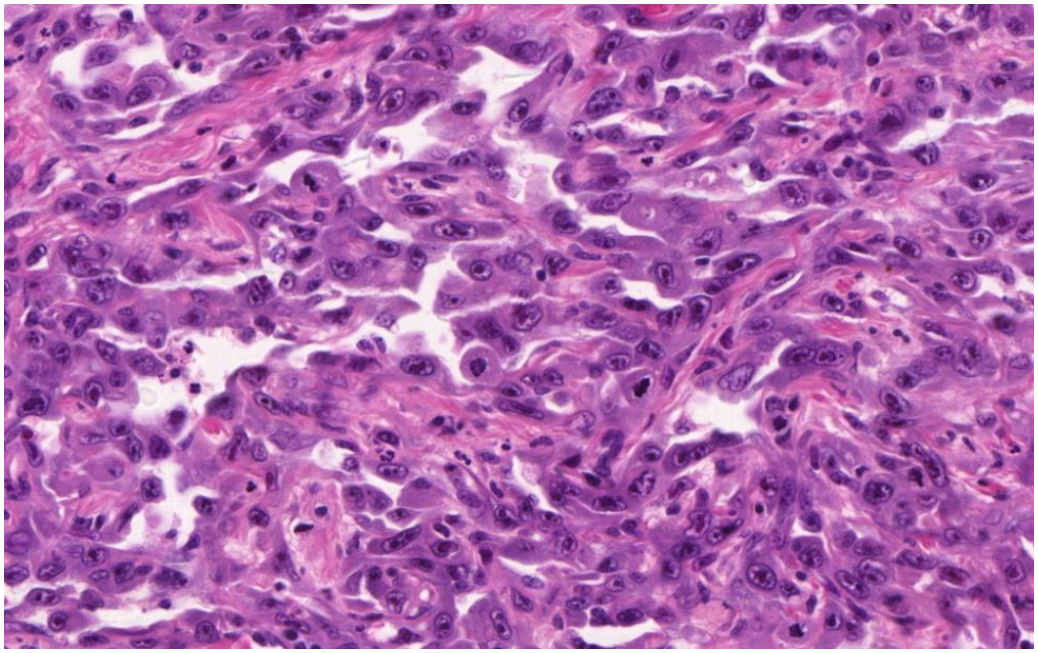




DD: angiosarcoma

- **7th decade, male > female**
- **Any part of the body, esp head and neck, also visceral**
- **Highly aggressive**
- **Primary and secondary to radiation**
- **Different molecular subtypes**





The spectrum of hemangioendotheliomas

- **Kaposiform hemangioendothelioma** — Locally aggressive
- **Retiform hemangioendothelioma** — Rarely metastasizing
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