Vascular Sarcomas

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Aims

- Benign vascular soft tissue tumours
- Angiosarcomas
- Epithelioid hemangioendothelioma
- Primary Sarcomas great vessels
  - Intimal sarcoma
- Focus on systemic therapy

Vascular Tumors

- Hemangiomas
  - Synovial hemangioma
  - Intramuscular angioma
  - Venous hemangioma
  - Aterio venous hemangioma
- Epithelioid hemangioma
- Angiomatosis
- Lymphangioma

- Kaposiform haemangioendothelioma
- Retiform haemangioendothelioma
- Papillary intralymphatic angioendotehlioma
- Composite haemangioendothelioma

- Kaposi sarcoma
- Epithelioid haemangioendothelioma
- Angiosarcoma

WHO Classification. Tumours of Soft Tissue and Bone

Angiosarcomas

- 2-3% adult soft tissue sarcomas

- Clinical heterogeneity
  - 2/ 3 cutaneous
  - 1/ 4 arise in soft tissue

- Risk factors:
  - Predisposing syndromes
    - Recklinghausen's, Klippel-Trenaunay, Maffucci Syndromes
  - Occupational exposure (liver)
    - Arsenical insecticide
    - Polyvinyl chloride, thorium dioxide
  - Chronic lymphoedema
  - Radiation

Young R et al. Lancet Oncol 11; 983-991: 2010
Fury MG et al. Cancer 11; 241-247: 2005
Fayette J et al. Ann Oncol 18; 2030-2036: 2007

Angiosarcomas

- Localized disease:
  - Surgical resection if possible
  - +/- adjuvant radiation
- Aggressive behaviour
  - NO consistent data: adjuvant chemotherapy
- Advanced/ Metastatic disease:
  - Lung, Nodal, Bone, Soft tissue
  - Chemotherapy mainstay of palliation

Young R et al. Lancet Oncol 11; 983-991: 2010

Angiosarcomas: Pathology

- Multi nodular haemorrhagic masses
- Both epithelioid and spindled areas
- Epithelioid angiosarcoma:
  - Large rounded “epithelioid” endothelial cells
  - Abundant amphophilic or eosinophilic cytoplasm
  - Large vesicular nuclei

WHO Classification. Tumours of Soft Tissue and Bone

Angiosarcomas: Immunohistochemistry

- Positive for
  - ERG, CD31, CD34, von Willebrand factor
  - Cytokeratin about 1/3

- Negative
  - HHV-8

WHO Classification. Tumours of Soft Tissue and Bone

Angiosarcomas

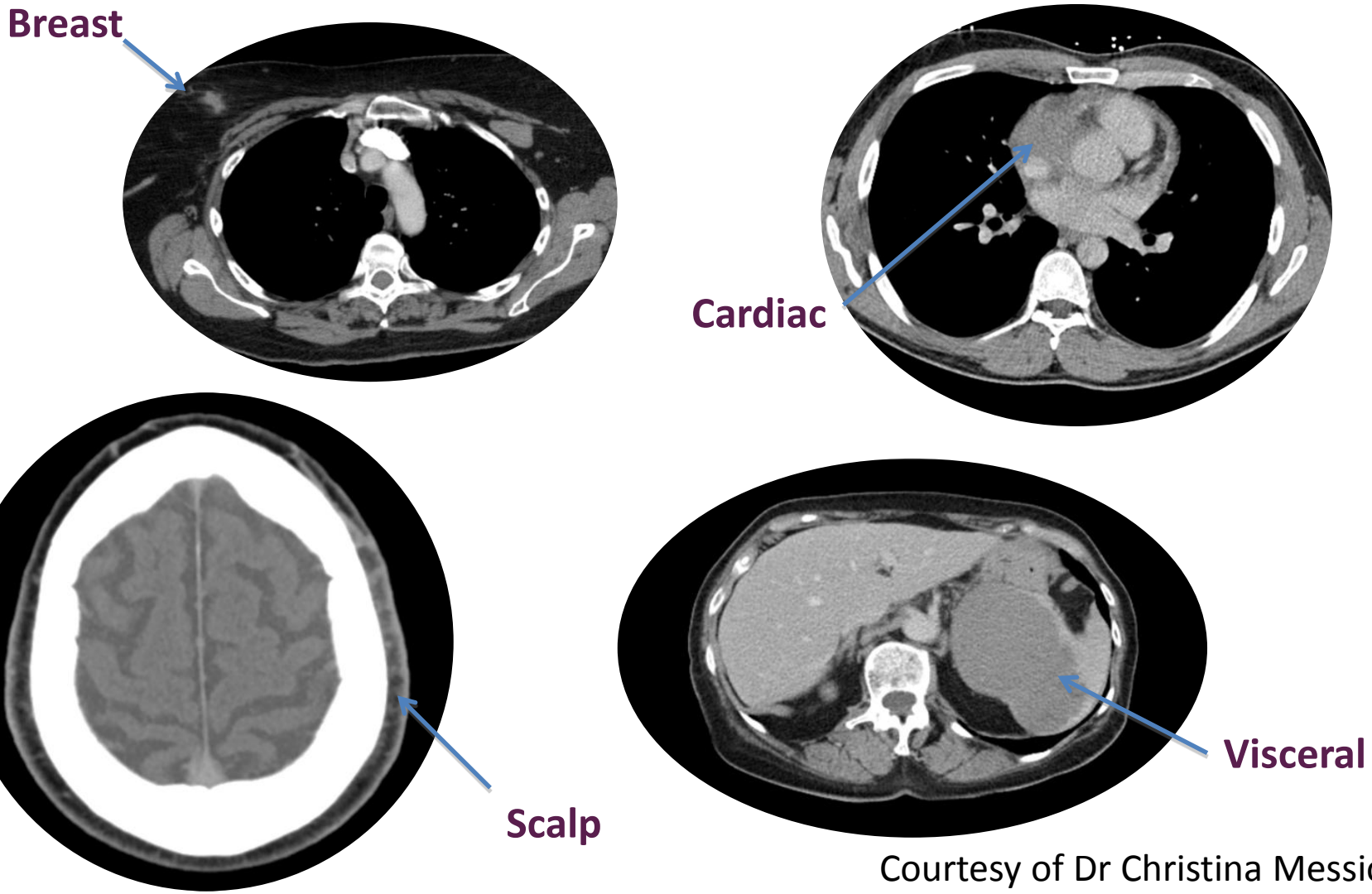
- Complex karyotype
  - Whole-genome / whole-exome sequencing
  - Recurrent mutations in 2 genes
  - *PTPRB* ([-] regulator vascular growth factor TK): 10/ 39
  - *PLCG1* (signal transducer of tyrosine kinases): 3/ 34

- Arising cavernous haemangioma
  - Sole cytogenetic abnormalities
  - Trisomy 5 and loss of Y

Behjati S et al. Nat Genet 46; 376-379: 2014
Mandahl N et al. Genes Chrom Cancer 1; 315-316:1990

Angiosarcomas: Imaging

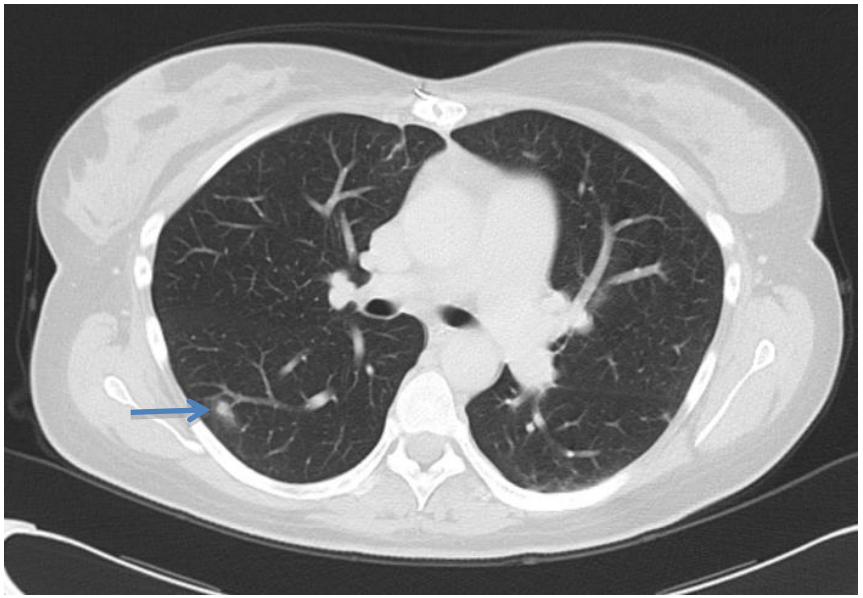
A diverse group of tumours with diverse imaging needs

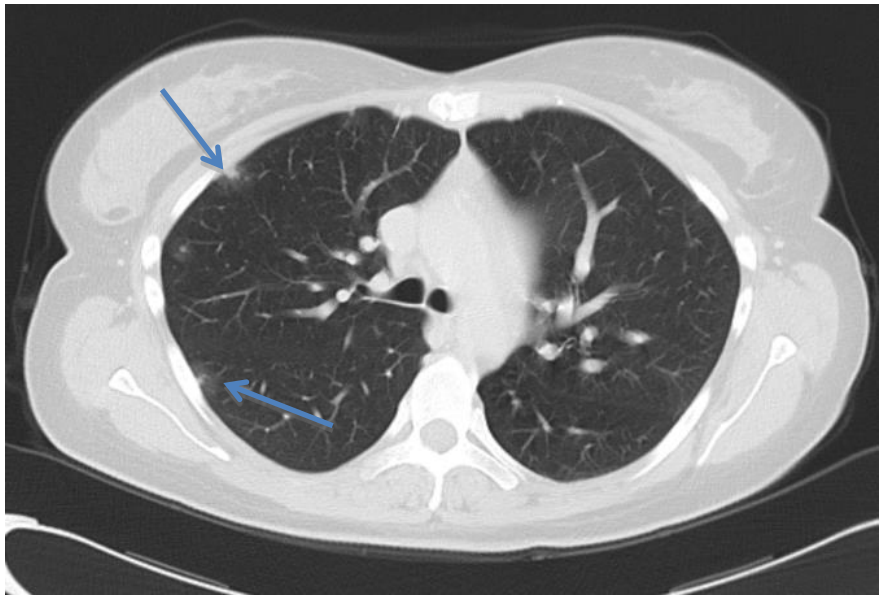


Courtesy of Dr Christina Messiou

Angiosarcomas: Imaging

Unusual morphology of metastatic disease





In any other tumour type these nodules may be classified as inflammatory.

Courtesy of Dr Christina Messiou

Angiosarcomas

- 149 patients
- Median age: 60 years

- Metastases at diagnosis: 86/ 139 (62%)

- Median overall survival 11 months

- No difference in outcome:
  - Doxorubicin vs paclitaxel

Penel N et al. Ann Oncol 23; 517-523: 2012

Angiosarcomas: EORTC Database

- N=108 locally advanced/ metastatic angiosarcoma
  - Median age: 46 years (37-58)
  - Median follow-up: 4.2 years

- Angiosarcoma
  - Response rate: 25% (27/ 108)
  - Median PFS: 4.9 months (95%CI 3.7-6.1)
  - Median OS: 9.9 months (95%CI 8.3-12.3)

- Other soft tissue sarcomas
  - Response rate: 21% (544/ 2557)
  - Median PFS: 4.3 months (95%CI 4.0-4.6)
  - Median OS: 12 months (95%CI 11.6-12.5)

Young RJ et al. EJC 50; 3178-3186: 2014

French Phase II: Weekly Paclitaxel

- N=30, 80 mg/m^2
- Median age: 67 years (range 23-85)
- 19 (63%) no previous chemotherapy

- Progression-free rate:
  - 2 months: 74%
  - 4 months: 45%

- Median follow-up 8 months
  - Median time to progression: 4 months
  - Median overall survival: 8 months

Penel N et al. JCO 26; 5269-5274: 2008

U.S. Phase II: Sorafenib

- Angiosarcoma, n=40, 0-1 prior lines

- Sorafenib 400 mg twice per day
  - PFS: 3.8 months (95%CI 2.8-5.5)
  - OS: 14.9 months (95%CI 9.4-)
- 3 month PFR: 64%
- 6 month PFR: 31%

- Response:
  - CR: n=1
  - PR: n=4
  - SD: n=21
  - PD: n=11

Maki RG et al. JCO 27; 3133-3140: 2009

French Phase II: Bevacizumab

- Paclitaxel (90 mg/m^2)
- +/- bevacizumab (10 mg/kg)
- N=50, ≤2 lines systemic therapy

- Median follow-up 14.5 months

- Paclitaxel: No drug related serious adverse event

- Combination: 10 drug related serious adverse events
- In 8 patients
  - Hematoma, anemia (n=2), dyspnea
  - Cardiac failure, pulmonary embolism
  - Peritonitis, intestinal occlusion, diarrhea (n=2)

Ray-Coquard I et al. JCO 33; 2797-2802: 2015

Angiosarcomas: Phase II trials

	Penel et al 2008	Ray-Coquard et al 2012	Aglunik et al 2013	Ray-Coquard 2015	Ray-Coquard 2015
Therapy	Paclitaxel	Sorafenib	Bevaciz	Paclitaxel	Paclitaxel + Bevaciz
No patients	30	41	23	24	25
Response	5 (16.6%)	4 (9.7%)	2 (8.7%)	11 (45.8%)	7 (28%)
Median PFS (Months)	3.8	2	3	6.6	6.6
Median OS (Months)	8.3	9.7	13.2	19.5	15.9

Angiosarcomas: EORTC Pazopanib

- Retrospective data collection
  - Angiosarcoma
  - Epithelioid hemangioendothelioma
  - Intimal sarcoma
- Documented progressive disease prior to pazopanib:
  - Response rate
  - Progression-free survival (PFS)
  - Overall survival (OS)

		Patients (N=40) N (%)
Study		
	Non-study	31 (77.5)
	Study	9 (22.5)
Age		
	<=40	3 (7.5)
	40-50	10 (25.0)
	50-70	18 (45.0)
	>70	9 (22.5)
Gender		
	Female	12 (30.0)
	Male	28 (70.0)

- Concerning the Study patients, 6 come from EORTC-62043 and 3 from EORTC-62072.
- A total of 14 institutions contributed to the patient population considered in this report.

Angiosarcomas: EORTC Pazopanib

- Angiosarcoma
  - N=24
  - Response: 5/ 24 (20.8%)
  - Stable disease: 5/ 24
  - Median PFS: 3 months

- Epithelioid Hemangioendothelioma
  - N=9
  - Response: 2/ 9 (22.2%)
  - Stable disease: 4/ 9 (44.4%)
  - Median PFS: 26.3 months

- Intimal sarcoma
  - N=1
  - Partial response

Angiosarcomas: Clinical Trials

- NCT01462630 **Pazopanib**
  - Phase II, n = 30
- NCT02048722 **Regorafenib**
  - Chemotherapy-Refractory
  - Phase II, n = 31
- EVA GISG-06
  - Paclitaxel 70 mg/m² plus Pazopanib 800 mg/day
  - Phase II, n=44
- **TRC 105** (anti endoglin antibody, CD105)
  - Pazopanib +/- TRC 105
  - Phase III trial

Epithelioid Hemangioendothelioma

- Very rare
  - Precise incidence difficult to determine
- Wide age range
- Affects both sexes
- Spectrum of clinical behaviour
  - Unpredictable
  - Multi focal disease at presentation
- Liver, lung, soft tissues, bone

Epithelioid Haemangioendothelioma

- Fusiform intravascular mass
- Epithelioid endothelial cells arranged in short cords and nests
  - Set in a distinctive myxohyaline stroma
- IHC:
  - CD31, CD34 positive
- Characteristic chromosomal translocation:
  - *WWTR1* (3q25)
  - *CAMTA1* (1p36)
  - t(1;3)(p36;q25)

WHO Classification. Tumours of Soft Tissue and Bone
Tanas MR et al. Science Translational Med 3(98); 2011

Epithelioid Hemangioendothelioma

- Surgical resection if possible
- Metastatic EHE:
  - Indolent: surveillance
  - No standard systemic therapy
    - Doxorubicin, Paclitaxel, Interferon
    - Sunitinib, Bevacizumab, Lenalidomide, Pazopanib
  - Local therapy for solitary area of progression / symptomatic disease

Kelly H et al. Lancet Oncol 6; 813-815: 2005
Gaur S et al. Cancer Biol Med 9; 133-36: 2012
Bally et al. Clin Sarcoma Res 5; 12: 2015

U.S. Phase II: Bevacizumab

Table 2. Best response to bevacizumab treatment

All patients, $N = 30$	n (%)
PR	4 (13)
SD	15 (50)
PD	11 (37)
Angiosarcoma, $N = 23$	n (%)
PR	2 (9)
SD	11 (48)
PD	10 (43)
Epithelioid hemangioendothelioma, $N = 7$	n (%)
PR	2 (29)
SD	4 (57)
PD	1 (14)

PR, partial response; SD, stable disease; PD, progressive disease.

Aglunik M et al. Ann Oncol 24; 257-263: 2013

Primary sarcomas great vessels

- **Intimal (luminal):**
  - Large arteries, extend along intima surface
  - Multi focal intramural growth
  - Further subdivided morphologically distinct
    - Undifferentiated
    - Differentiated
  - IHC: Variable positivity SMA. Some are desmin (+)

- **Mural:**
  - Medial smooth muscle large veins
  - Leiomyosarcoma

Sebenik M et al. Am J Surg Pathol 29; 1184-1193: 2005
WHO Classification. Tumours of Soft Tissue and Bone

Intimal Sarcoma

- Very rare
  - First described Mandelstamm in 1923
- Sarcoma of large arteries
  - Sub-endothelial cells of vessel wall
  - Intra-luminal growth
  - Pulmonary 2x common as aortic
- Presentation
  - Not specific/ related to tumour emboli
  - Constitutional symptoms
  - Broad age range:
    - Pulmonary 48 years
    - Aortic 62 years

WHO Classification. Tumours of Soft Tissue and Bone
Mandelstamm M. Virchows Arch 245; 43-47: 1923

Intimal Sarcoma

- Management is challenging….

- Case reports and series:
  - Localised disease
    - Surgery
      - Margins often involved
    - Radiation
    - Chemotherapy
  - Metastatic disease
    - Chemotherapy + radiation
    - Repeat Surgery

Mussot S et al. Eur J Cardiothorac Surg 43; 787-789: 2013
Grazoli V et al. J Thoracic Cardiovasc Surg 148; 113-118: 2014
Wong HH et al. Clin Sarcoma Res 5; 3: 2015
Penel N et al. J Thoracic Surg 3; 907-911: 2008

Intimal Sarcoma

- CGH
  - Amplifications 12q13-14
- Amplifications of genes encoding for[4]
  - *PDGFRA*
  - *MDM2*
  - *CDK4*
  - *GLI1*
- Scope for therapy??

[1]Bode-Lesniewska B et al. Virchows Archives 438; 57-65: 2001
[2]Neuville A et al. Am J Surg Path 38; 461-469: 2014
[3]Dewaele B et al. Cancer Res 70; 7304-7314: 2010
[4]Zhao J et al. Genes Chrom Cancer 34; 48-57: 2002

Conclusions

- Angiosarcomas
  - Aggressive, heterogeneity within subtype
  - Possible to perform subtype specific trials
  - Durability of response
- Epithelioid Hemangioendothelioma
  - Very rare, unpredictable behaviour
  - Underlying biology – novel therapies
- Intimal Sarcoma
  - Very rare, non-specific symptoms
  - Consensus for management

Thank you – any questions?

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