SINGAPORE 2015 ESMO ASIA

DIFFICULT CASES IN SARCOMA

Epithelioid Sarcoma and Alveolar Soft Part Sarcoma

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Peter Mac EXCELLENCE INNOVATION COMPASSION

The Royal Melbourne Hospital

General Principles

- Very rare sarcomas
- Group of selected subtypes which have:
  - Distinctive clinical behaviour
  - Distinct biologies and/or molecular characteristics
  - Responses to agents targeting these pathways
    - Or a lack of response to conventional cytotoxics

Case 1

24 yo single man

- Computer programmer.
- Living at home with elderly parents
- No Past History of note. No Family History of cancer

- Referred to Peter MacCallum Sarcoma Service from regional hospital, 1-month post complicated resection of a distal thigh soft-tissue mass arising from left high.

24 yo man

- Suboptimal (R1) resection, approx. 3cm tumour
- Sarcoma NOS by local pathology service
- Pathology reviewed at Peter Mac
  - High grade sarcoma, morphologically consistent with epithelioid sarcoma or synovial sarcoma. Distal margin+ve
  - Expression of cytokeratin, epithelial membrane antigen, vimentin and CD34. Neg for S100, CD31. FISH -ve for t(X:18)
  - Features consistent with epithelioid sarcoma

24 yo man: epithelioid sarcoma

Next Steps:

- Restaging completed. MRI left thigh, CT-C/A/P
  - No clear evidence of residual tumour
  - No locoregional or distant metastatic disease
- Further management?:

24 yo man: epithelioid sarcoma

- Further management?:
  - Wide-Resection. Limb-sparing vs amputation?
  - Radiotherapy- pre vs post-op?
  - Systemic therapy?

24 yo man: epithelioid sarcoma

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  - Radiotherapy- pre vs post-op?
  - Systemic therapy?
- Went on to receive External beam RTx
- Surgical re-resection with wide margins
  - No residual tumour evident
- Adjuvant chemotherapy not recommended
  - Given histology and lack of clear OS benefit

24 yo man: epithelioid sarcoma

- Routine follow-up
- Nine months later:
  - Painful subcutaneous lesions distal thigh
  - Deep and infiltrative on imaging with MRI
    - Within radiation field
    - At distal end of prior tumour
    - No proximal extension
  - Biopsied
    - Recurrence confirmed
  - Increasing pain++ with ulceration of superficial disease

24 yo man: epithelioid sarcoma

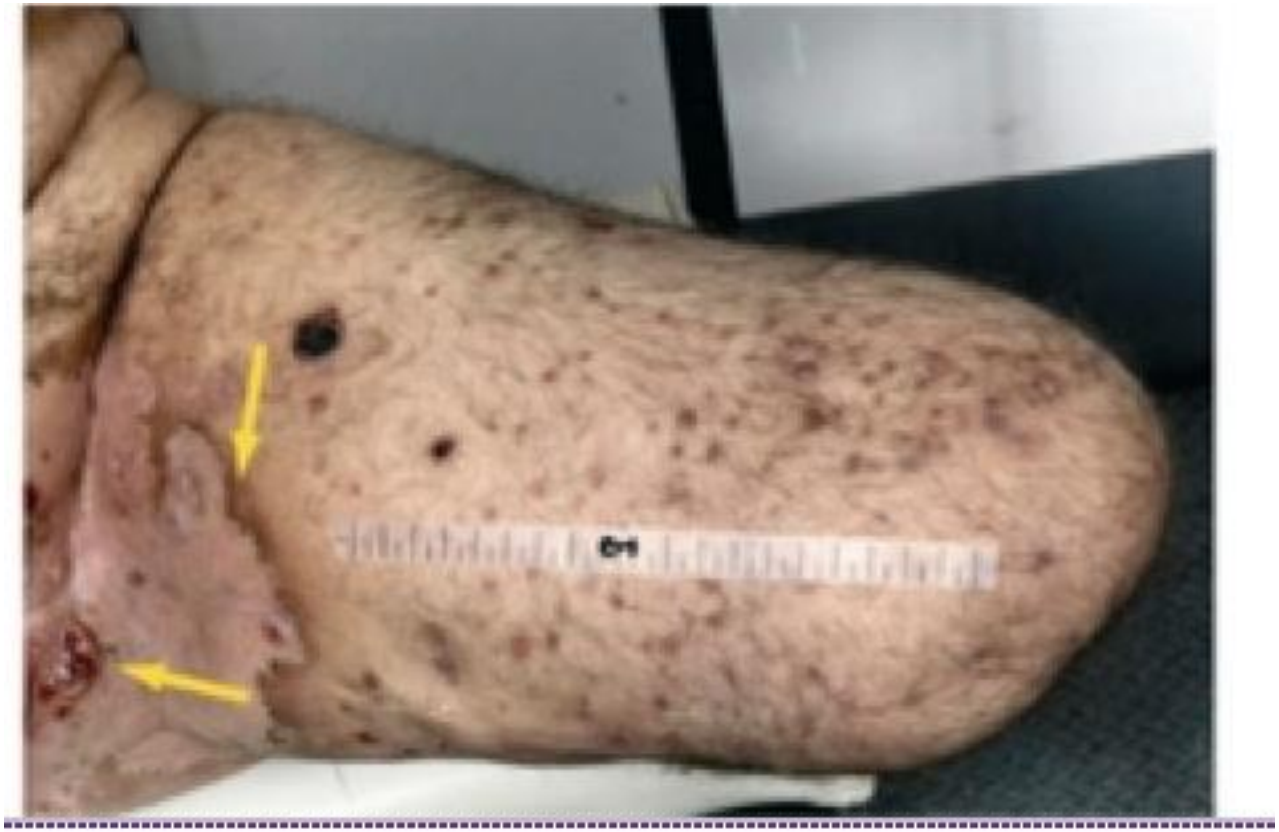
- Further management?:

24 yo man: epithelioid sarcoma

- Further management?:
  - Re-resection not thought possible
    - Above knee amputation performed
  - Remained disease-free for further 3 years
    - Now in 6-monthly follow-up
  - Re-presents with multiple subcutaneous lesions
  - Extending proximally
    - Painful superficial lesions and sacral pain++
    - Clinically, growing very rapidly

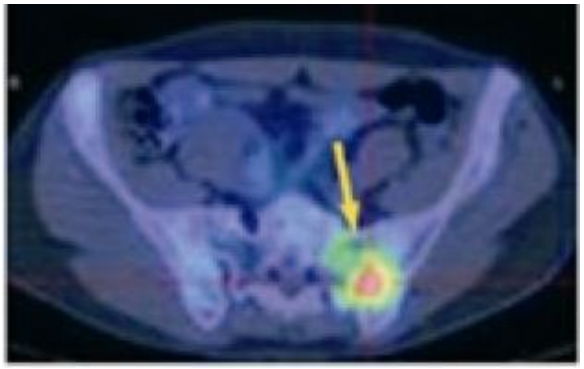
Recurrent epithelioid sarcoma

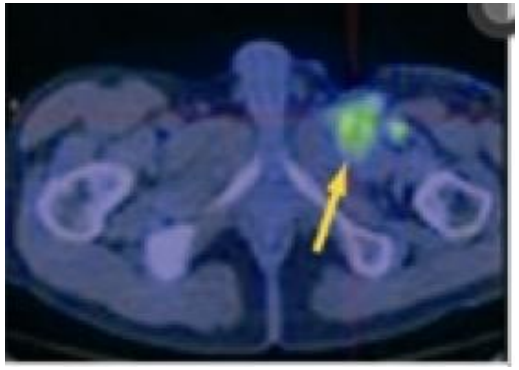
- Further management?:



Recurrent epithelioid sarcoma

- Restaging: Locoregional disease on PET/CT

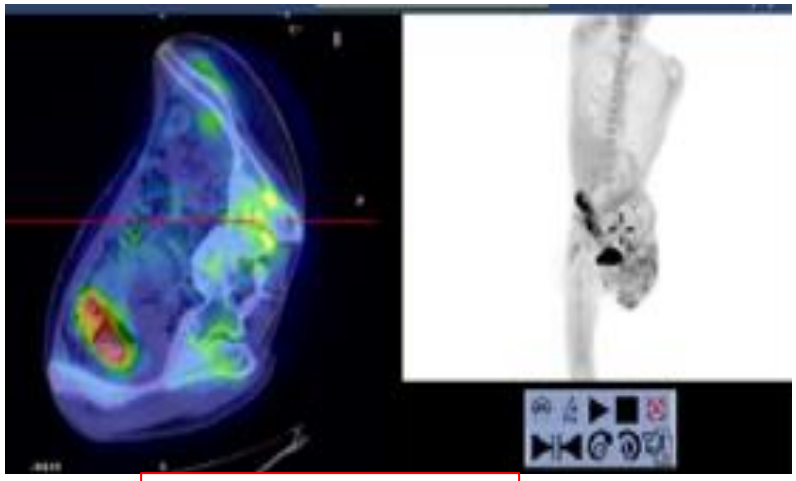




- Further management?
  - Radiotherapy considered,
    - but concerns given in-field recurrence and rapid proximal progression
  - Commenced on chemotherapy with Dox/Ifos

Metastatic epithelioid sarcoma

- Dox/Ifos: initial stabilisation after 2 cycles, followed by further progression at C4



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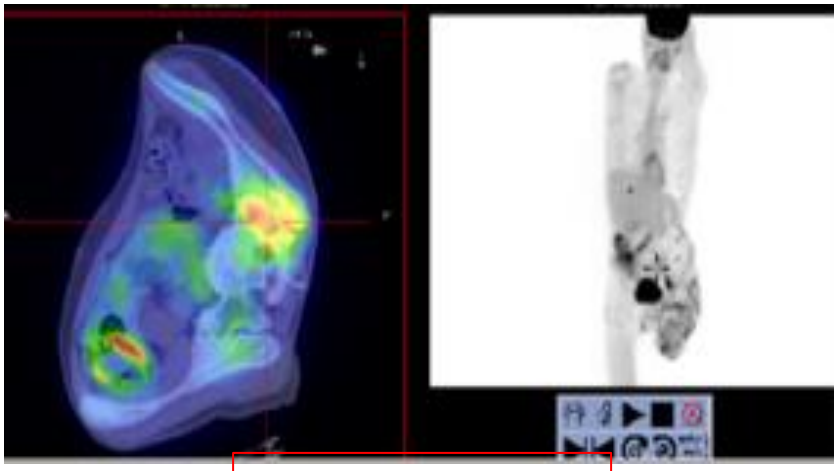

POST

- Enrolled onto a Phase Ib clinical trial with

  Docetaxel and a novel PDGF inhibitor

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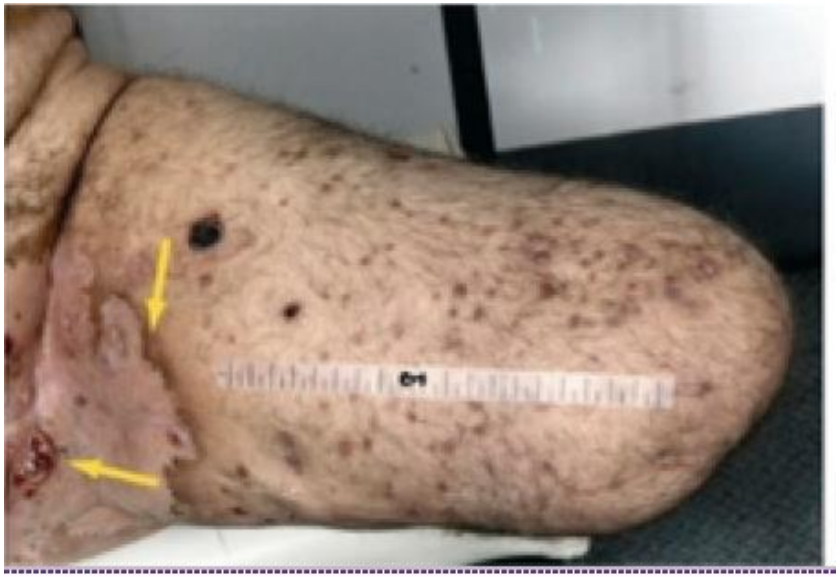

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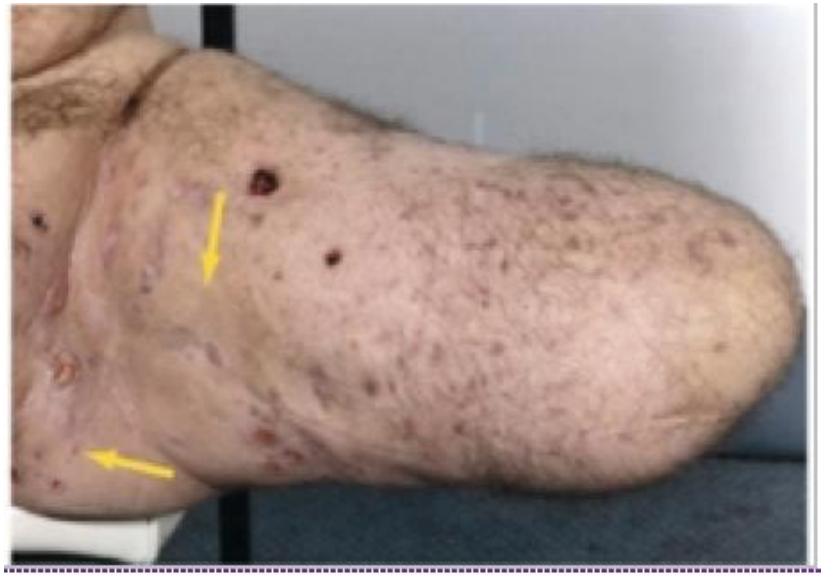


POST 2 CYCLES

Metastatic epithelioid sarcoma

- Disease control on and off therapy for additional 9 months

- Progression with proximal abdominal and nodal disease
  - Eventual lung metastases
  - Died from complications of metastatic disease

Metastatic epithelioid sarcoma: Take home messages

- What should/could have been done differently?
  - Initial surgery
  - Radiotherapy? And re-resection?
  - Follow-up? Imaging
  - Challenges with continued proximal migration of disease
- Use of systemic chemotherapy for met disease
  - Other options?
  - Molecular drivers/molecular testing?
    - Multiple targets implicated including EGFR, cyclin D1, VEGF, mTOR

Metastatic epithelioid sarcoma: Literature/Data

- No meaningful prospective data. Retrospective:
- 1) Royal Marsden (R Jones et al. Am J Clin Oncol. 2012 Aug),
  - 1990-2009 database
  - Proximal vs Distal
  - 55 patients, 20 treated with chemotherapy (Dox+/-Ifos)
    - Partial responses in 25%, but short-lived
- Lots of anecdotes, and individual patient responses on trials with agents including pazopanib, eribulin, navelbine, trabectedin

- Take home message: explore novel options early, sequential single agents

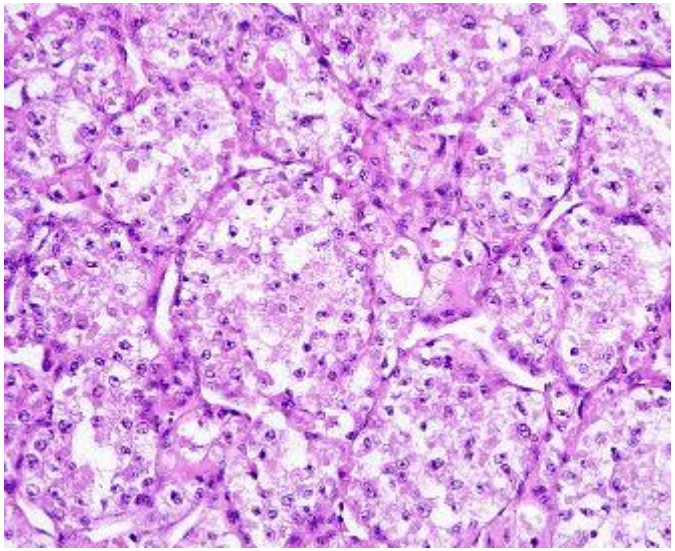
Case 2

27 yo married woman, 2 yo child

- No Past History of note. No Family History of cancer
- Presents with right forearm lesion, present for at least 12 months, slowly growing
- Staging CT scans demonstrate 3 small pulmonary metastases,
  - RLL x 2 and LUL:. 10, 9 and 7mm in size
  - FDG avid on PET
- Biopsy of left forearm lesion:

Case 2: 27 yo woman

- Biopsy of left forearm lesion:
- Nests of epithelioid cells separated by fibrovascular septae and vascular channels



- "Pseudo-alveolar pattern"

- Diagnosis of Alveolar Soft Part Sarcoma

Case 2: 27 yo woman

- Resection of forearm lesion

- Options for management of pulmonary mets discussed including
  - Staged resection
  - Watch and wait
    - Staged resection for diagnostic and treatment purposes
    - Confirmed as metastatic disease

Case 2: 27 yo woman

- Over following 3 years
  - 2 further resections for single/oligometastatic disease.
  - All via wedge resections
- Now presents with
  - multiple lung metastases (approx 10 lesions), largest 5mm
  - Bone metastasis with scapulae metastasis
    - Symptomatic
    - Treated with Radiotherapy (palliative)

Case 2: 27 yo woman

- Options for management of systemic disease?
  - Systemic chemotherapy
  - Watch and wait
  - Other options?

Alveolar Soft Part Sarcoma

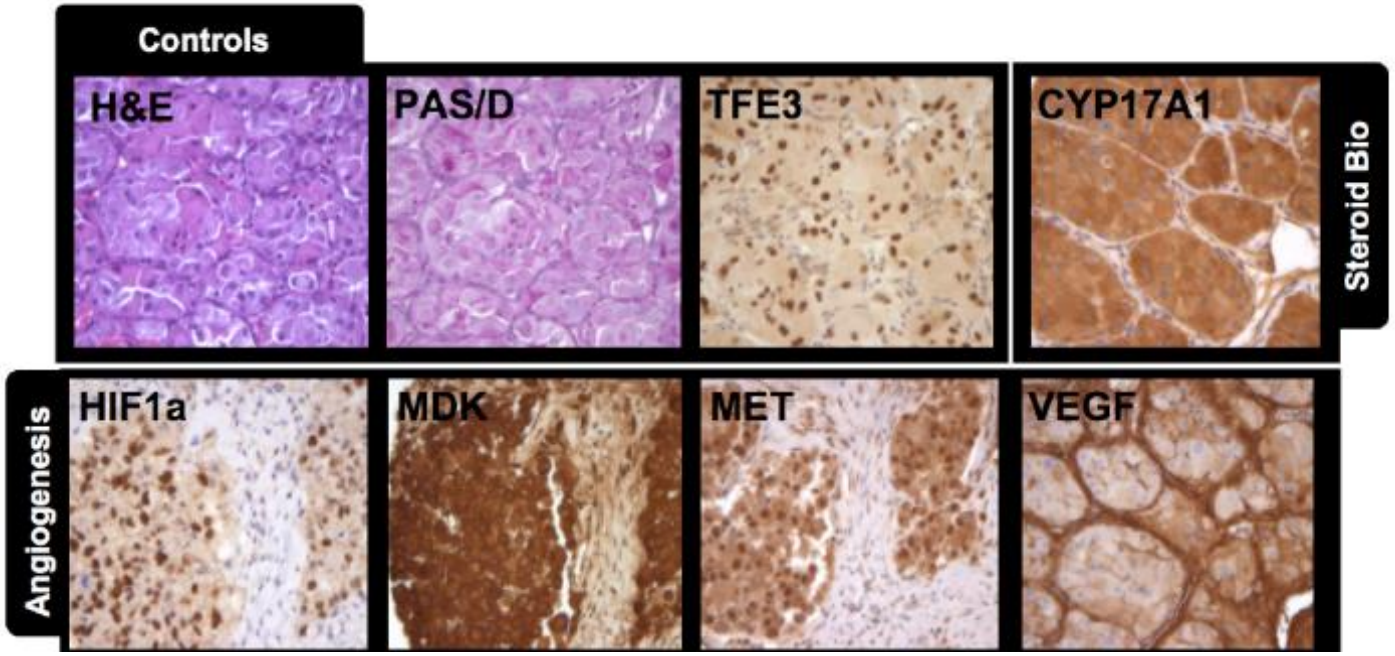
- Incidence: approx 0.5-1/100,000
- Adolescents/Young adults
  - Female>male
  - Natural history variable,
    - High metastatic rate,
    - Often to atypical sites (brain, bone, soft tissue)
    - But metastases often indolent in their behavior,
      - Multiple surgical resections may be appropriate.
    - Can grow to a certain size, and then remain indolent.
    - Therefore Patient's Natural History very important

Alveolar Soft Part Sarcoma

- Median survival with metastatic disease approx 36 months cf metastatic STS

- Characterised by an unbalanced translocation t(X;17)(p11:p25) which results in the fusion of the ASPL and TFE3 genes.
- Resulting in unregulated transcription of TFE3 controlled genes.
- Strong expression of angiogenic factors

Expression in ASPS



Stockwin et al. (2009) *BMC Cancer*

VEGF inhibition in ASPS: Initial "anecdotes"

Sunitinib: 4 evaluable patients on compassionate use protocol

- 2 Partial Responses, 1 SD, 1 PD

(Stacchiotti et al. (2009) *Clinical Cancer Research)*

Cediranib: 7 patients on two Phase I studies

- 4 Partial Responses, 2 Minor Responses, 1SD

CASPS: A phase II trial of Cediranib in the treatment of patients with ASPS

- To confirm the ability of cediranib to halt disease progression in patients with metastatic ASPS at 24 weeks after randomisation & to produce objective response according to RECIST criteria.
- Randomised 2:1 to receive cediranib or placebo;
  - At 24 weeks, Rx will be unblinded after which all pts on placebo will be given cediranib.
- Primary endpoint week 24 percentage change in the sum of target marker lesions from randomisation.
- Led by Ian Judson (ICR): global collaboration including 2 sites in Australia

Conclusions

- Increasing number of very rare sarcoma subtypes with distinct biology, clinical behaviour
- Diagnostic accuracy critically important
- Clinical guidance critically important
- Given the impact on that patient
- International sarcoma network leading the way for other rare cancers/rare subtypes
  - Help provide diagnostic and clinical guidance
  - Conduct appropriate clinical trials