An overview of sarcoma

Dr Robin Jones
Consultant Medical Oncologist and Head of the Sarcoma Unit
Educational Objectives

– Provide an overview of the challenges of diagnosing + treating sarcomas

– Outline the management of localised disease

– Outline the management of advanced metastatic disease
Plan

– Introduction
  – Clinical overview
  – Diagnosis
  – Histopathology + staging

– Management localized disease
  – Surgery
  – Radiation
  – Chemotherapy

– Management advanced disease

– Case Studies
Introduction
Sarcoma

- Malignancies of connective tissue
  - Rare
  - Heterogeneous
  - Anatomic location
- Difficult to diagnose
- Multidisciplinary Team
Sarcoma

- One of the main families of “rare cancers”
- Individually each histological subtype extremely rare
- European study
  - 27,908 new cases/ year
  - 84% soft tissue
  - 15% bone

Stiller CA et al, Eur J Cancer 49; 684-695: 2013
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>EUROCARE-4 mean</th>
<th>US SEER-13 registries</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Survival</td>
<td>95%CI</td>
</tr>
<tr>
<td>Testicular</td>
<td>97.3 [96.4–98.2]</td>
<td></td>
</tr>
<tr>
<td>Skin melanoma</td>
<td>86.1 [84.3–88.0]</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>83.2 [80.9–85.6]</td>
<td></td>
</tr>
<tr>
<td>Hodgkin's disease</td>
<td>81.4 [78.9–84.1]</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>79 [78.1–80.0]</td>
<td></td>
</tr>
<tr>
<td>Corpus uteri</td>
<td>78 [76.2–80.0]</td>
<td></td>
</tr>
<tr>
<td>Prostate</td>
<td>77.5 [76.5–78.6]</td>
<td></td>
</tr>
<tr>
<td>Soft-tissue</td>
<td>61.2 [58.3–64.2]</td>
<td></td>
</tr>
<tr>
<td>Cervix</td>
<td>60.4 [57.7–63.2]</td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>56.2 [55.3–57.2]</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>55.7 [53.6–58.0]</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td>54.6 [52.7–56.6]</td>
<td></td>
</tr>
<tr>
<td>CM leukaemia</td>
<td>32.2 [29.0–35.7]</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>24.9 [23.7–26.2]</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>10.9 [10.5–11.4]</td>
<td></td>
</tr>
<tr>
<td>All cancer Men</td>
<td>47.3 [46.8–47.8]</td>
<td></td>
</tr>
<tr>
<td>All cancer Women</td>
<td>55.8 [55.3–56.2]</td>
<td></td>
</tr>
</tbody>
</table>

Table 1-2. Age-adjusted 5-year relative survival for different cancers, period analysis 2000–02

Verdecchia A et al, Lancet Oncol 8; 784-96: 2007
Fig. 1. Period analysis – 5-year relative survival (%) by sarcoma entities.
# Sarcoma histological subtypes

<table>
<thead>
<tr>
<th>Histological subtype</th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIST</td>
<td>135 (18%)</td>
</tr>
<tr>
<td>Pleomorphic/ unclassified</td>
<td>117 (16%)</td>
</tr>
<tr>
<td>Liposarcoma</td>
<td>112 (15%)</td>
</tr>
<tr>
<td>Leiomyosarcoma</td>
<td>85 (11%)</td>
</tr>
<tr>
<td>Dermatofibrosarcoma</td>
<td>38 (5%)</td>
</tr>
<tr>
<td>Other</td>
<td>261 (35%)</td>
</tr>
</tbody>
</table>

Ducimetiere F, Lurkin A et al, Plos One, 6; 2011
Leiomyosarcoma

- One of the most common subtypes
- Many different diseases:
  - Cutaneous
  - Uterine
  - Extremity
  - Vascular
  - Retroperitoneal
  - Bone

Sarcomas - biological groups

- Specific translocations generating fusion oncogenes
- Multiple complex genetic alterations
- Specific kinase mutations (GIST)
- Gene inactivation (NF1 in MPNST, INI1 in rhabdoid tumours, APC in desmoid)
- Simple genetic alterations (amplifications – mdm2+/cdk4 in well- / dedifferentiated liposarcoma)
## Translocation related Sarcomas

<table>
<thead>
<tr>
<th>Disease</th>
<th>Chromosomal Change</th>
<th>Fusion Gene</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ewing’s/PNET</td>
<td>t(11;22) or t(21;22)</td>
<td>EWS-FLI1, EWS-ERG</td>
<td>85%, 5-10%</td>
</tr>
<tr>
<td>Synovial sarcoma</td>
<td>t(x;18)</td>
<td>SYT-SSX</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Myxoid liposarcoma</td>
<td>t(12;16)</td>
<td>CHOP-TLS</td>
<td>&gt; 75%</td>
</tr>
<tr>
<td>Alveolar rhabdomyosarcoma</td>
<td>t(2;13) or t(1;13)</td>
<td>PAX3-FKHR, PAX7-FKHR</td>
<td>70%, 15%</td>
</tr>
<tr>
<td>Clear cell sarcoma</td>
<td>t(12;22)</td>
<td>EWS-ATF1</td>
<td>&gt; 75%</td>
</tr>
<tr>
<td>Desmoplastic small round cell tumor</td>
<td>t(11;22)</td>
<td>EWS-WT1</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>
## Distribution by Site

<table>
<thead>
<tr>
<th>Site</th>
<th>Incidence (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower extremity</td>
<td>40</td>
</tr>
<tr>
<td>Upper extremity</td>
<td>20</td>
</tr>
<tr>
<td>Retroperitoneal and intraperitoneal**</td>
<td>20</td>
</tr>
<tr>
<td>Trunk</td>
<td>10</td>
</tr>
<tr>
<td>Head and neck</td>
<td>10</td>
</tr>
</tbody>
</table>

*Percentages are approximate.

**These sites include GIST tumors

Clark MA et al. NEJM 2005;353:701-11
Distribution by Age

- Age as a factor in histopathology
  - Embryonal rhabdomyosarcoma
    - Childhood
  - Alveolar rhabdomyosarcoma/ Synovial sarcoma
    - Adolescents and young adults
  - Pleomorphic rhabdomyosarcoma/ liposarcomas
    - Older population
Aetiology and Risk factors

- Unknown in most cases
- Radiation-associated
- Lymphoedema
- Genetic predisposition
- Chemical exposure
- Immunodeficiency
- Trauma??
Diagnosis
Clinical Criteria for Referral

– Mass > 5 cm in size
– Mass deep to the fascia/fixed/immobile
– Mass increasing in size
– Pain
Diagnosis

Clinical
- Patients present with a gradually enlarging mass
- Pain develops when mass compresses nerves or other structures
- Can be mistaken for benign lesions

Physical Exam
- Assess size of mass and its relationship to neurovascular and bony structures
Diagnosis: Imaging

- X-ray
- MRI
  - Extremity
  - Head and neck
  - Chest wall
- CT
  - Abdomen and pelvis
  - Chest: evaluate for metastatic disease
  - Bone
Typical lower limb soft tissue sarcoma
Retroperitoneal Sarcoma: CT appearance of well- / dedifferentiated Liposarcoma
Ewing Sarcoma

Radiographs show “onion skin” periosteal reaction views of distal femur

MRI view of pelvic Ewing Sarcoma
Diagnosis: Biopsy

Biopsy
- In an adult
  - Any soft tissue mass that is symptomatic or enlarging
  - Any mass that is larger than 5 cm
  - Any new mass that persists beyond 4 weeks should be sampled
- Improperly performed biopsies can alter outcome.

Diagnosis: Biopsy

- Radiological guided biopsy

- Core or incisional biopsy
  - Extremity masses should be biopsied through a small *longitudinal* incision

- Entire biopsy tract can be excised at the time of resection
Pattern of growth and spread

- Direct local extension infiltrating adjacent tissues and structures

- Lymph node spread rare
  - Except in epithelioid, rhabdomyosarcoma, vascular sarcomas

- Distant metastasis at presentation uncommon
  - Lung is first site in 70-80%
Histopathology + Staging
Histopathology

- Histological grade predicts risk of
  - Distant metastasis
  - Overall survival

- Grade is of no prognostic value in certain subtypes
  - Malignant Peripheral Nerve Sheath Tumour
  - Extraskeletal myxoid chondrosarcoma

- Others are always considered high grade
  - Angiosarcoma
  - Ewing sarcoma
Staging

- Challenging
  - Anatomy
  - Histological subtype

- Soft Tissue Sarcoma
  - Derived from data on extremity tumors
  - Several staging systems
  - AJCC 8th Edition

- Bone Sarcoma Staging Systems
  - Enneking
  - AJCC
Management
Localised Disease
- Surgical resection with **clear margins** offers the best chance of cure in the absence of metastatic disease.

- **Function-preserving limb conservation** is the goal
  - Marginal excision, wide local excision,
  - margins usually defined by adjacent vital structures, e.g. vessels
  - compartmental resection: taking subtype/biology into account

- Amputation is rarely necessary < 5%

- **Radiotherapy** is indicated high grade deep seated tumours
Management

– Surgery +/- radiation

– Patients with high grade tumors
  – Approximately 50% develop recurrent disease

– Metastatic disease
  – Median overall survival about 12 - 18 months
Referral to Specialist Centres

– Canadian study:
  – Limb STS patients referred to centre within 3 months Dx
    – Improved OS
    – Reduced risk amputation

– Swedish study:
  – Limb/ trunk STS referred to centre before surgery improved
    – Disease Specific Survival (but not OS)

– Five studies (1 UK, 1 France, 3 Sweden) compared surgical margins
  – 4 found adequate margins more likely specialist centres

– Consistent evidence of reduced risk of local recurrence at specialist centres
Amputation versus Limb Sparing Surgery

- Randomized prospective study by NCI:
- Limb sparing surgery + post operative RT vs. amputation
- n=44 (both arms included post operative chemotherapy)
- Median follow-up 9 years
- Higher local recurrence for limb-sparing group (19%) versus amputation group (13%)
- Overall survival 70% limb-sparing group; 71% amputation group (p=0.97)

Adjuvant Radiation

- Randomized trial
  - Extremity soft tissue sarcoma
  - High grade

- Median follow-up 9.6 years

- Local recurrence
  - Significantly higher in no radiation arm
  - p=0.003

- Overall Survival
  - NO significant difference

- Consider adjuvant radiation
  - High grade tumors >5 cm
  - Resection margin <1 cm

Neoadjuvant Radiation

- Randomized trial
  - Neoadjuvant versus adjuvant radiation
  - Neoadjuvant: Overall survival slightly better

- Neoadjuvant radiation
  - Lower dose
  - Smaller field size
  - Reduced fibrosis
  - Reduced oedema
  - Increased wound complication (35% versus 17%)

Adjuvant systemic therapy: benefit

- **Embryonal rhabdomyosarcoma**
  - VAC (vincristine, actinomycin-D, cyclophosphamide)

- **Ewing sarcoma**
  - Vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide

- **Osteosarcoma**
  - MAP (Methotrexate, doxorubicin, cisplatin)

- **Gastro intestinal stromal tumor (GIST)**
  - Imatinib
Adjuvant therapy in other subtypes: No clear survival benefit

- Small patient numbers

- Heterogeneous histological subtypes

- Sub optimal chemotherapy schedules
  - 1997: meta analysis
    - Only 1 trial included doxorubicin + ifosfamide
    - Low dose both drugs
  - Clear dose response relationship in metastatic setting

ISG – STS 1001

- histology-tailored chemo x 3
  - MLPS: Trabectedin
  - LMS: GEM + DTIC
  - UPS: GEM + TAX
  - Synovial Sa: HD-IFX
  - MPNST: IFX + ETO

  $\rightarrow$ Surgery + RT

- epiADM+IFX x 3

  $\rightarrow$ Surgery ± RT

- high grade
- deeply seated
- $\geq$5 cm
Relapse Free Survival

Table 2. EUROSARC: RFS - Cox’s univariate HR and its 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Treatment ARM</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>1 (ref.)</td>
<td>-</td>
<td>0.007</td>
</tr>
<tr>
<td>Tailored</td>
<td>1.955</td>
<td>1.119-3.190</td>
<td>0.38</td>
</tr>
</tbody>
</table>
Table 4. EUROSARC: OS - Cox’s univariate HR and its 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Treatment ARM</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard</td>
<td>1 (ref.)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Tailored</td>
<td>2.687</td>
<td>1.104 - 6.937</td>
<td>0.034</td>
</tr>
</tbody>
</table>

Median FU: 12.34 months (IQ range: 25.45)

P=0.033
Management
Advanced
Disease
NCCN Guidelines for Metastatic Soft Tissue Sarcoma

Disseminated metastases or unresectable

Options:
- Observation, if asymptomatic.
- Chemotherapy
- Radiation
- Palliative surgery
- Best supportive care
- Ablation procedures
  - RFA
  - Cryotherapy
- Embolization procedures
Systemic therapy in Soft Tissue Sarcoma

- Chemotherapy is the mainstay of treatment for unresectable metastatic disease
- Previously “one size fits all” approach to therapy
  - Anthracyclines
  - Ifosfamide
  - Others (DTIC, navelbine, cisplatin)
- Gemcitabine and docetaxel
- Pazopanib
- Trabectedin
- Eribulin
Different drugs for different diseases

- Localized
  - Osteosarcoma: MAP
  - Ewing: VDC/ IE
  - Rhabdomyosarcoma: VAC
  - GIST: Imatinib

- Metastatic
  - Dermato fibrosarcoma protuberans: Imatinib
  - Giant cell tumor of bone: Denosumab
  - Alveolar soft part sarcoma: Cediranib/ sunitinib
  - Inflammatory myofibroblastic tumor: ALK inhibitors
  - PEComas: mTOR inhibitors
  - Endometrial stromal sarcoma: Aromatase inhibitors
  - Chordoma: Imatinib/ mTOR Inhibitors
  - Ewing/ Rhabdomyosarcoma: Cyclo/ topotecan
  - Ewing/ Rhabdomyosarcoma: Irinotecan/temozolamide
  - Solitary fibrous tumor: Anti angiogenic agents
Case Study 1

- 44 year old man
- Lower leg mass following energetic football match
- No past medical history
- On examination
  - >6 cm mass
  - Non tender
  - Appears fixed
What would be your management plan?

A. Surveillance
B. Refer for an ultrasound scan
C. Physiotherapy
D. Biopsy in GP surgery
Ultrasound Scan

“Solid mass: possible lipoma but sarcoma can NOT be excluded”
Next steps...

– Refer via ‘2 week wait pathway’

– First investigation at The Royal Marsden

Core needle biopsy and further imaging
MRI scan
Test results

- Biopsy confirms high grade sarcoma
- Staging CXR is normal
- Treatment:
  - Surgery
  - Radiotherapy
- Follow up
Case Study 2

- 68 year old man
- Presenting with upper GI bleed
- Hb 80g/dl, MCV 65
What would be your management?

A. Surveillance
B. Upper GI endoscopy
C. Abdominal ultrasound
Upper GI Endoscopy
CT scan
Biopsy: CD117
Gastrointestinal stromal tumour (GIST)
GIST treatment options:

- Surgery
- Potentially curative
- Drug treatment (Imatinib)
Case Study 3

- 49 year old woman

- No past medical history apart from
  - “Long-standing uterine fibroids”

- Increasing abdominal pain + bleeding
What would your management plan be?

A. Pain control and surveillance
B. Abdominal + pelvic imaging (+pain control)
C. Refer to on call surgeon
Case Study 3

- Presented as an emergency

- Surgery
  - Total abdominal hysterectomy
  - Bilateral salpingo oophorectomy
  - Infra colic omentectomy
  - Partial right hemicolecction
  - Ileal small bowel resection

- Pathology: undifferentiated uterine sarcoma
Conclusion

– Sarcomas challenging to diagnose
  – Rare
  – Heterogeneous
  – Wide distribution of anatomic sites

– Multi-disciplinary Team
  – Localised disease: Surgery +/- radiation

– Collaboration with GPs vital!
The Sarcoma Team at The Royal Marsden

Oncology Team

Prof Judson  Dr Benson  Dr Jones  Prof van der Graaf  Dr Miah  Dr Zaidi

Surgical Team

Mr Hayes  Mr Strauss  Mr Smith  Prof Oyen

Pathology Team

Dr Thway  Prof Fisher

Radiology

Dr Moskovic

Please see clinical information sheet in your packs for more information