Sarcoma Patients EuroNet

Chondrosarcoma

SPAEN Conference Milan 2/2/20

Kenneth Rankin

Consultant Orthopaedic Surgeon

North of England Bone and Soft Tissue Tumour Service

Newcastle upon Tyne, U.K.

The Newcastle upon Tyne Hospitals NHS

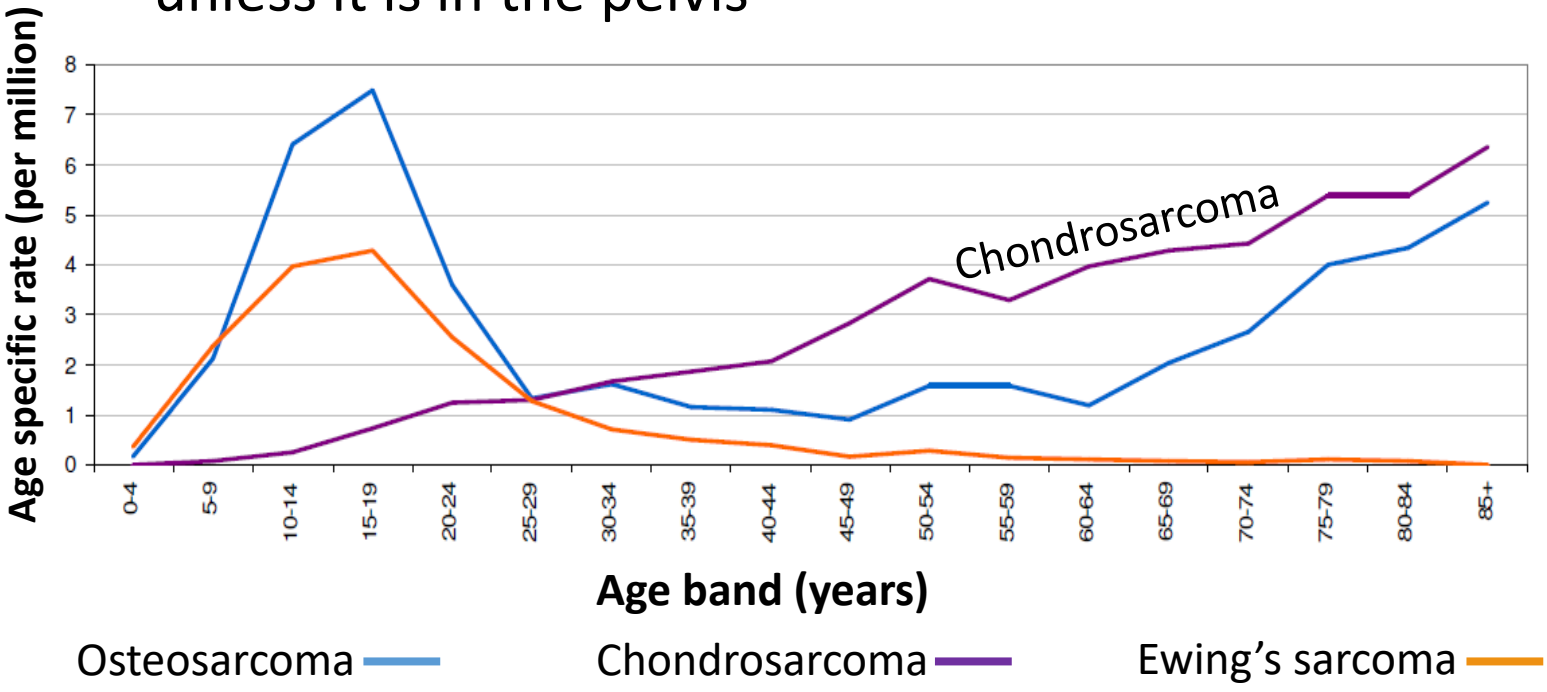
NHS Foundation Trust

Overview

- How common is chondrosarcoma?
- Types
- What causes it?
- What does it look like?
- Diagnosis and staging
- Grading
- Treatment options
- Patient outcomes
- Research and future therapies

How common is chondrosarcoma

- Most common bone sarcoma
  - If all grades are counted
  - Grade 1 is now termed atypical cartilage tumour (ACT) unless it is in the pelvis



Bone sarcomas

- Osteosarcoma (35%)
- Chondrosarcoma (25%)
  - Does not include ACT/grade 1 chondrosarcoma
- Ewing's sarcoma (16%)
- Rarer types make up the rest

Types

- Central
  - Cartilage cells left inside the bone that turn cancerous
  - Grade 1 to 3
  - Dedifferentiated chondrosarcoma
  - Clear cell
- Surface
  - Osteochondromas: bony lump with a cartilage cap that turns cancerous
  - Periosteal chondrosarcoma

What causes it?

- Cartilage cells that turn cancerous
- Not fully understood
- The IDH 1&2 gene mutations are involved in ‘central’ chondrosarcoma

Syndromes

- People with lots of cartilage tumours have higher chance of one of them becoming cancerous
- Multiple osteochondromas aka
  - Hereditary multiple exostoses (HME)
  - EXT gene mutations
  - Risk of transformation to chondrosarcoma up to 8.3%
- Multiple enchondromatosis
  - Ollier’s
  - Maffucci’s

Grading and rarer types

- Enchondroma
- Low grade (grade 1)
  - Atypical cartilage tumour unless in the pelvis
- Grade 2
- Grade 3
- Dedifferentiated chondrosarcoma
- Clear cell chondrosarcoma
- Extraskeletal myxoid chondrosarcoma

Enchondroma

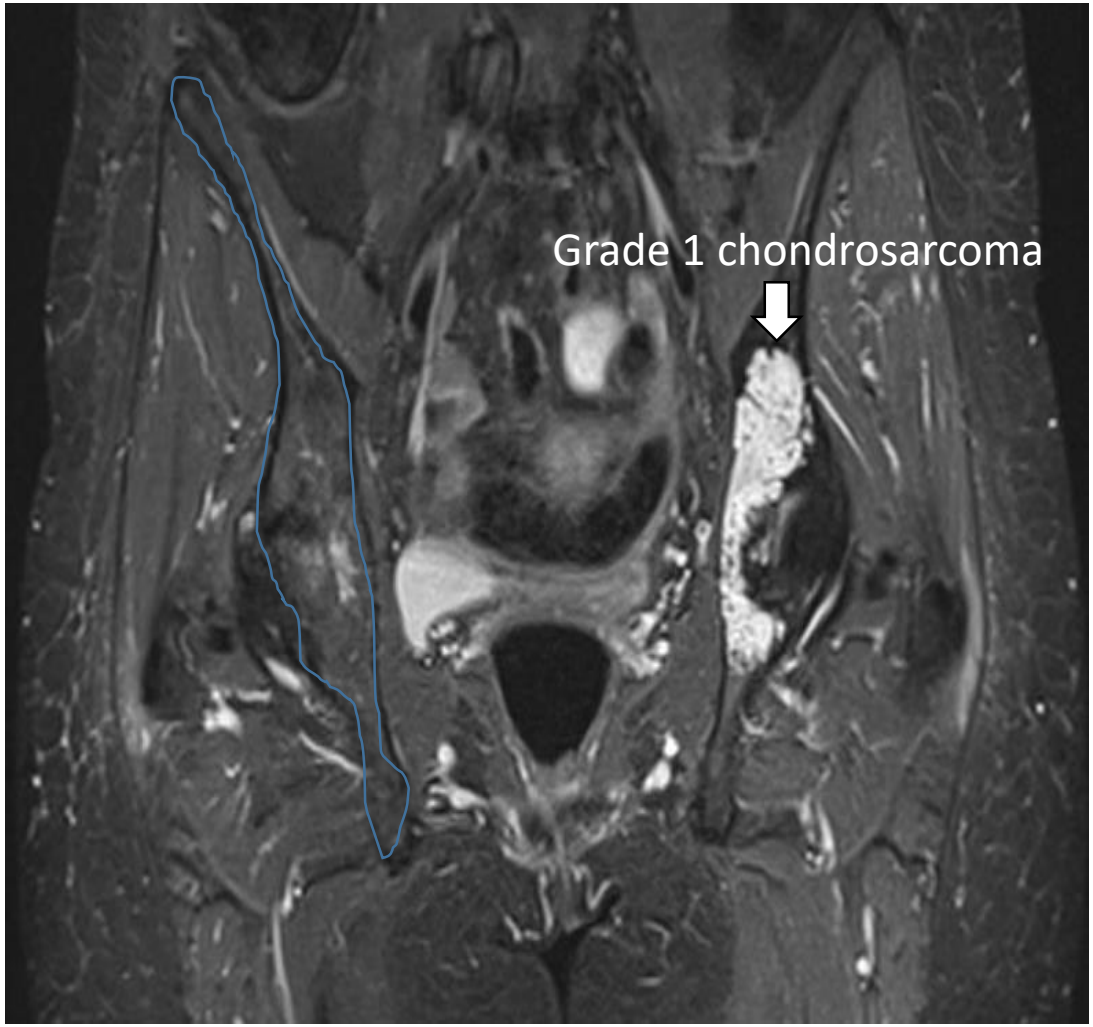
Treatment options

- Any concerns about a cartilage tumour then it is time for a biopsy
  - Increasing pain
  - Changes on x-rays or scans
- ACT/low grade chondrosarcoma
  - Curettage
- High grade chondrosarcoma
  - Wide excision i.e. remove the whole of the chondrosarcoma with a covering of normal tissue
- Radiotherapy
  - Skull base chondrosarcoma
- Chemotherapy
  - For patients with metastatic disease

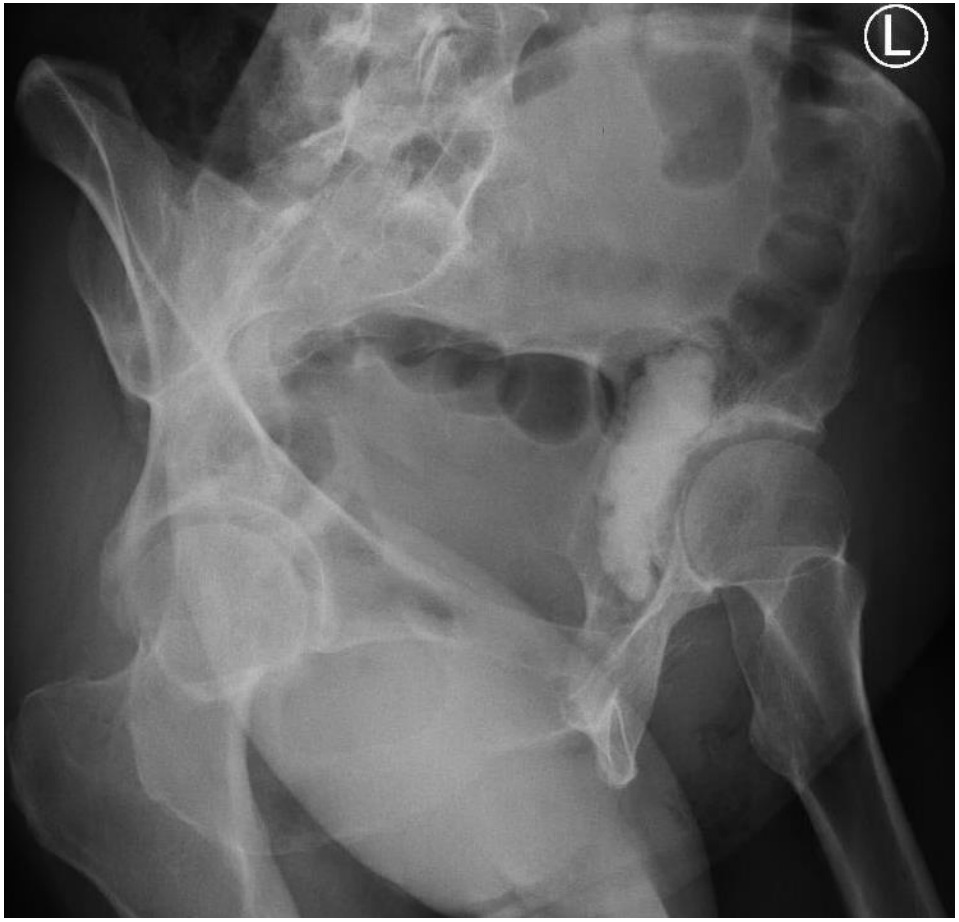
Warning!

Major knee pain- biopsy required

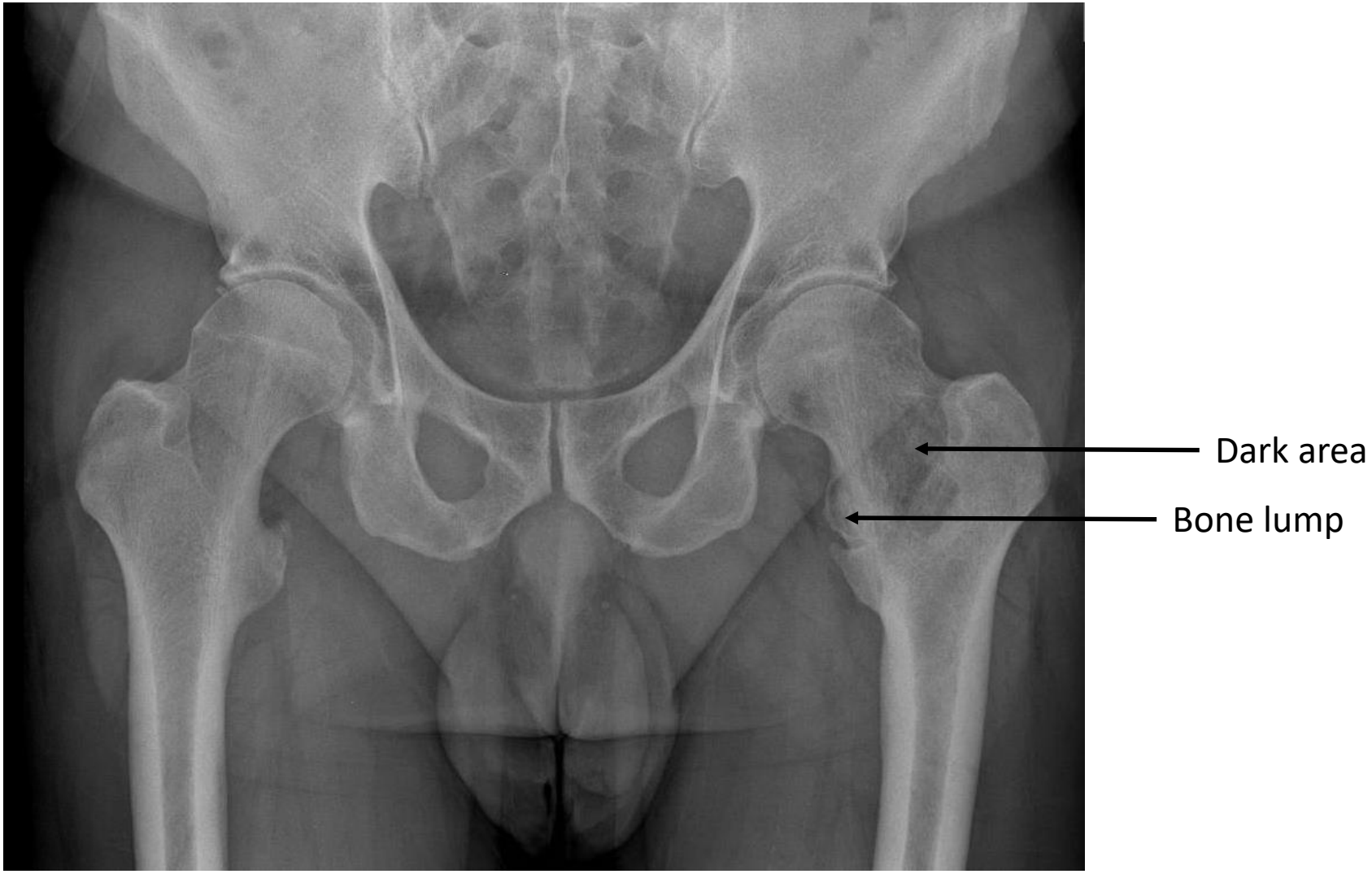
MRI for RIGHT hip pain- showed cartilage tumour in the LEFT side of the pelvis- biopsy required



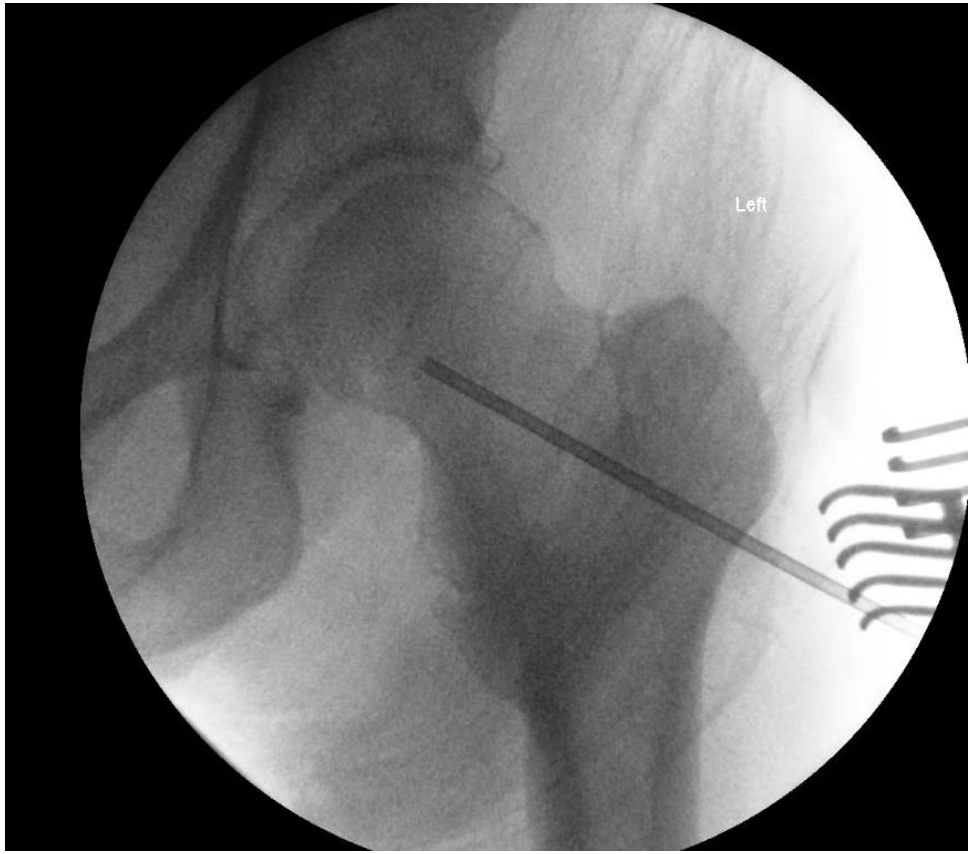
ACT in the pelvis= grade 1 chondrosarcoma


L

Grade 2/3 Chondrosarcoma



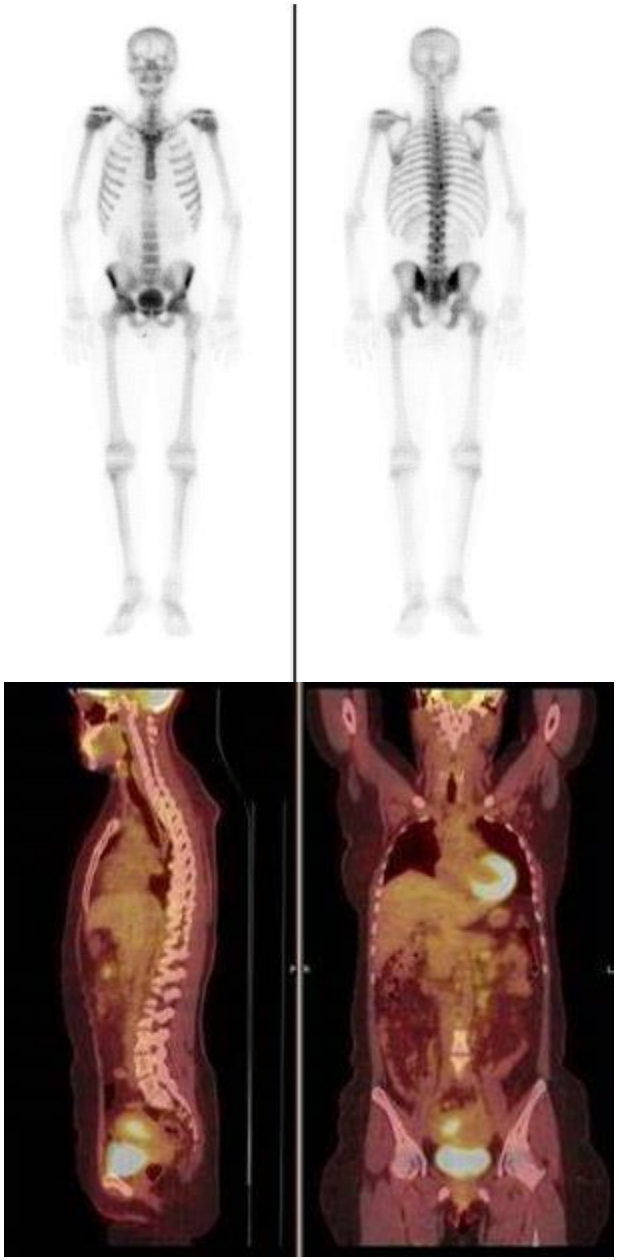
Bone biopsy



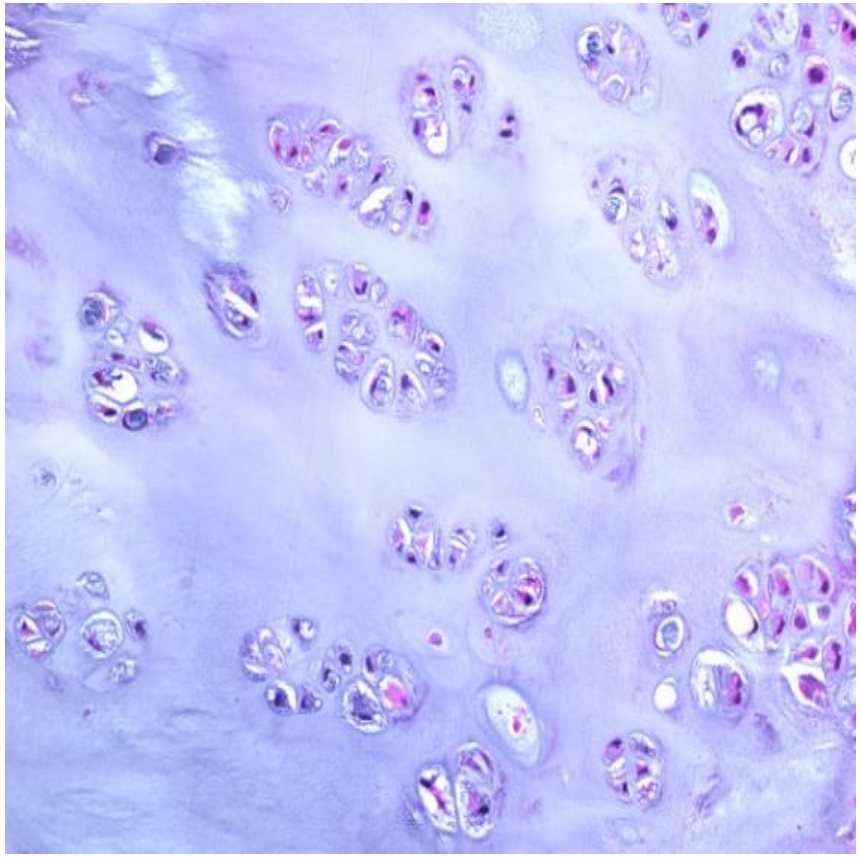
Grade 2
chondrosarcoma

Staging

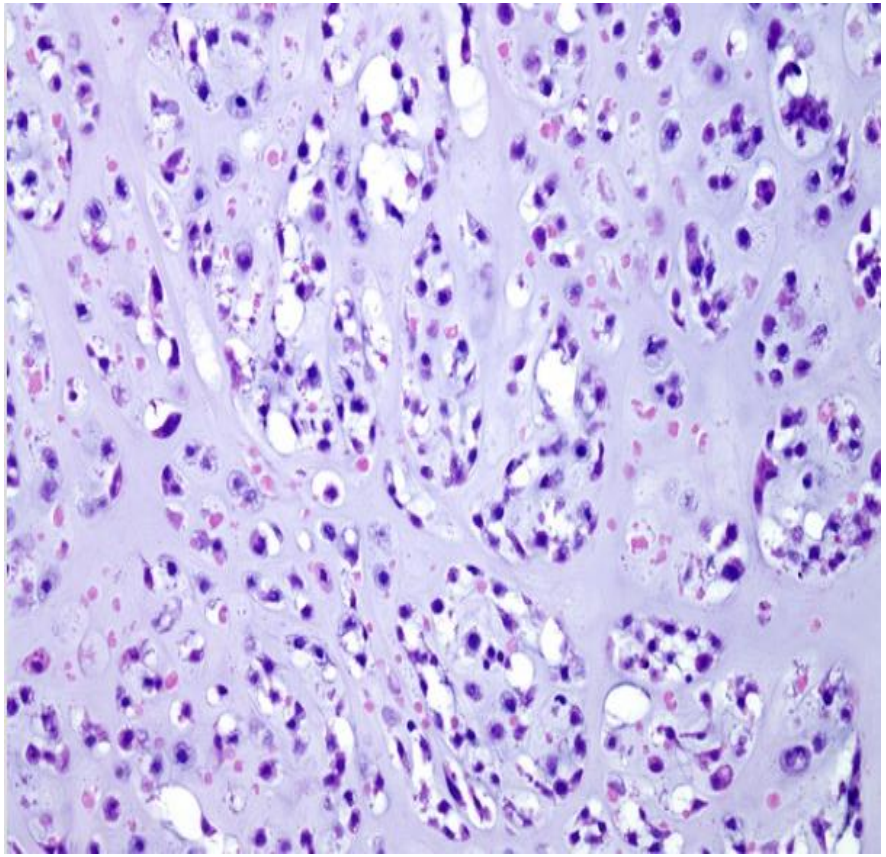
- Staging is simply- has it spread any where else?
  - Lungs
  - Other bones
- CT scan of the chest/abdomen and pelvis
- Nuclear bone scan
- CT/PET scan



Pathology

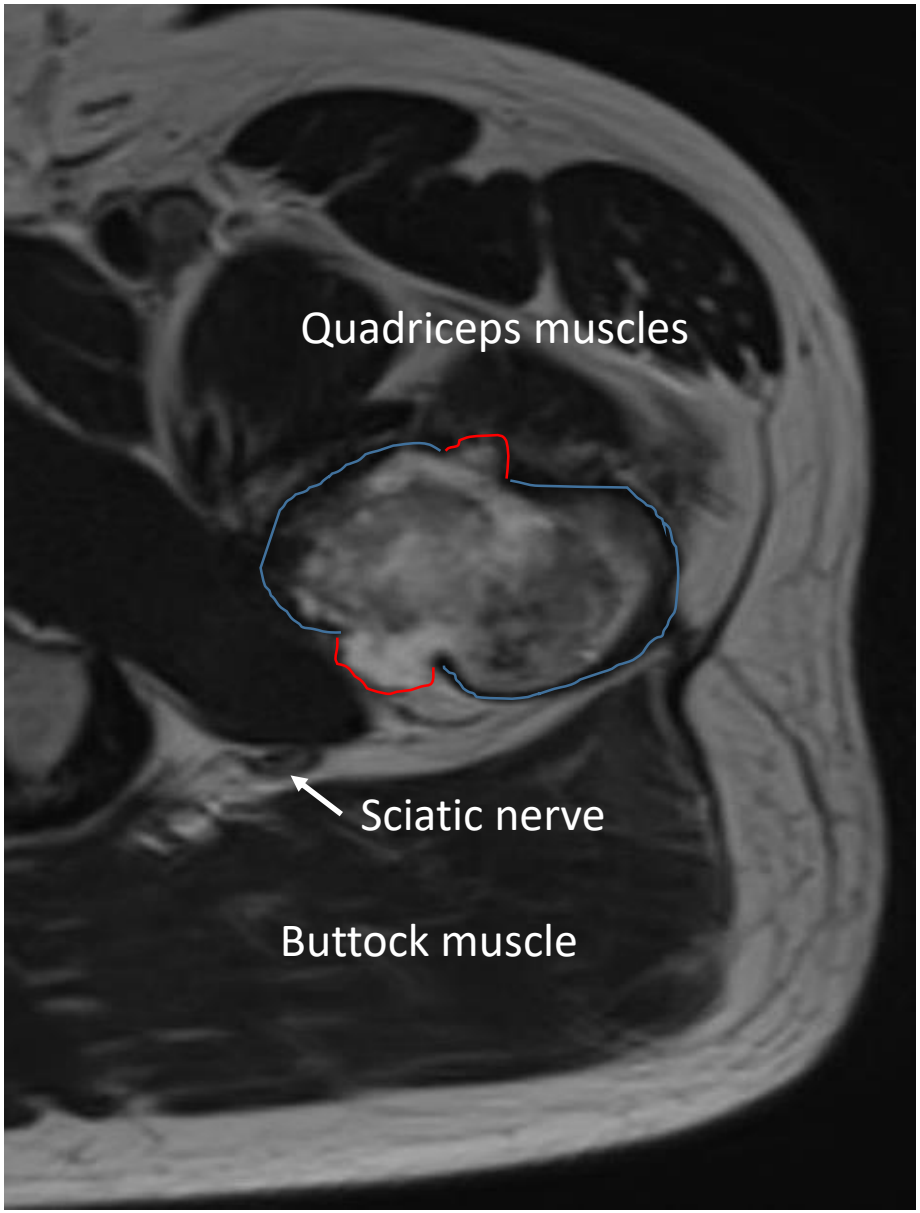


Grade 1



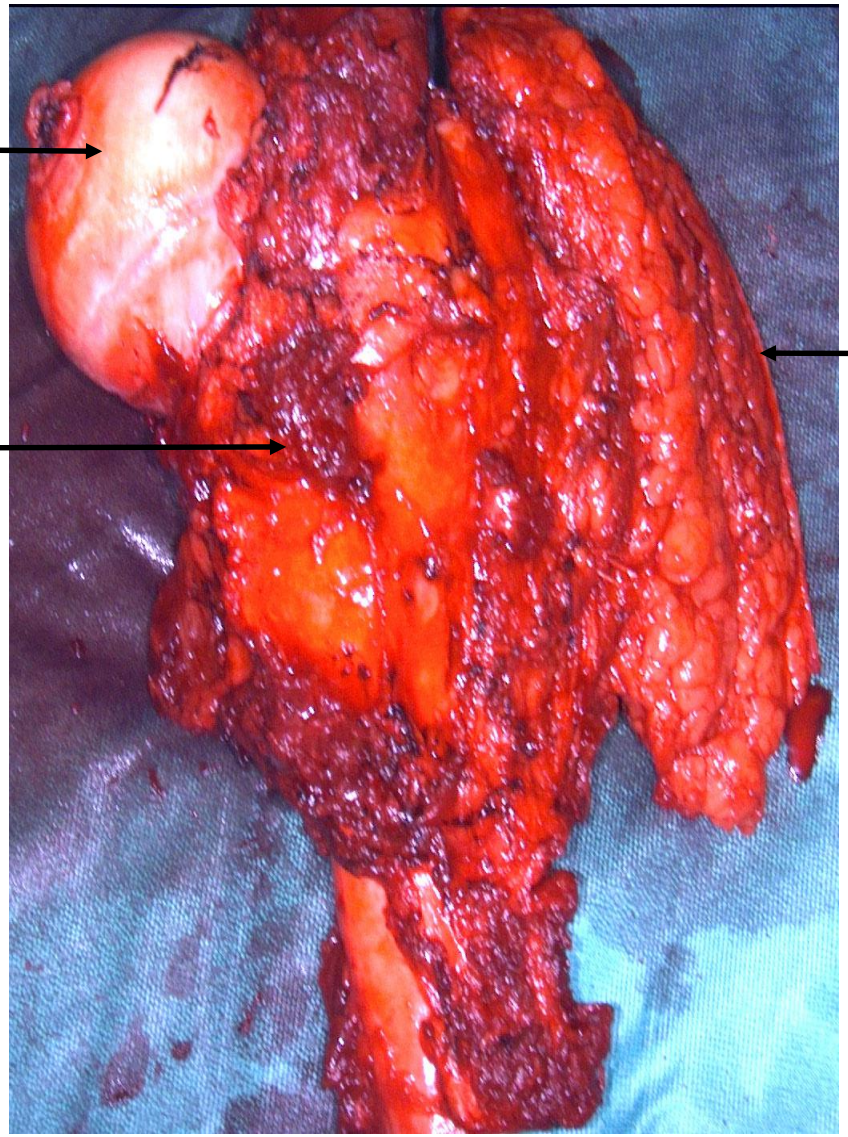
Grade 2/3- lots more cells

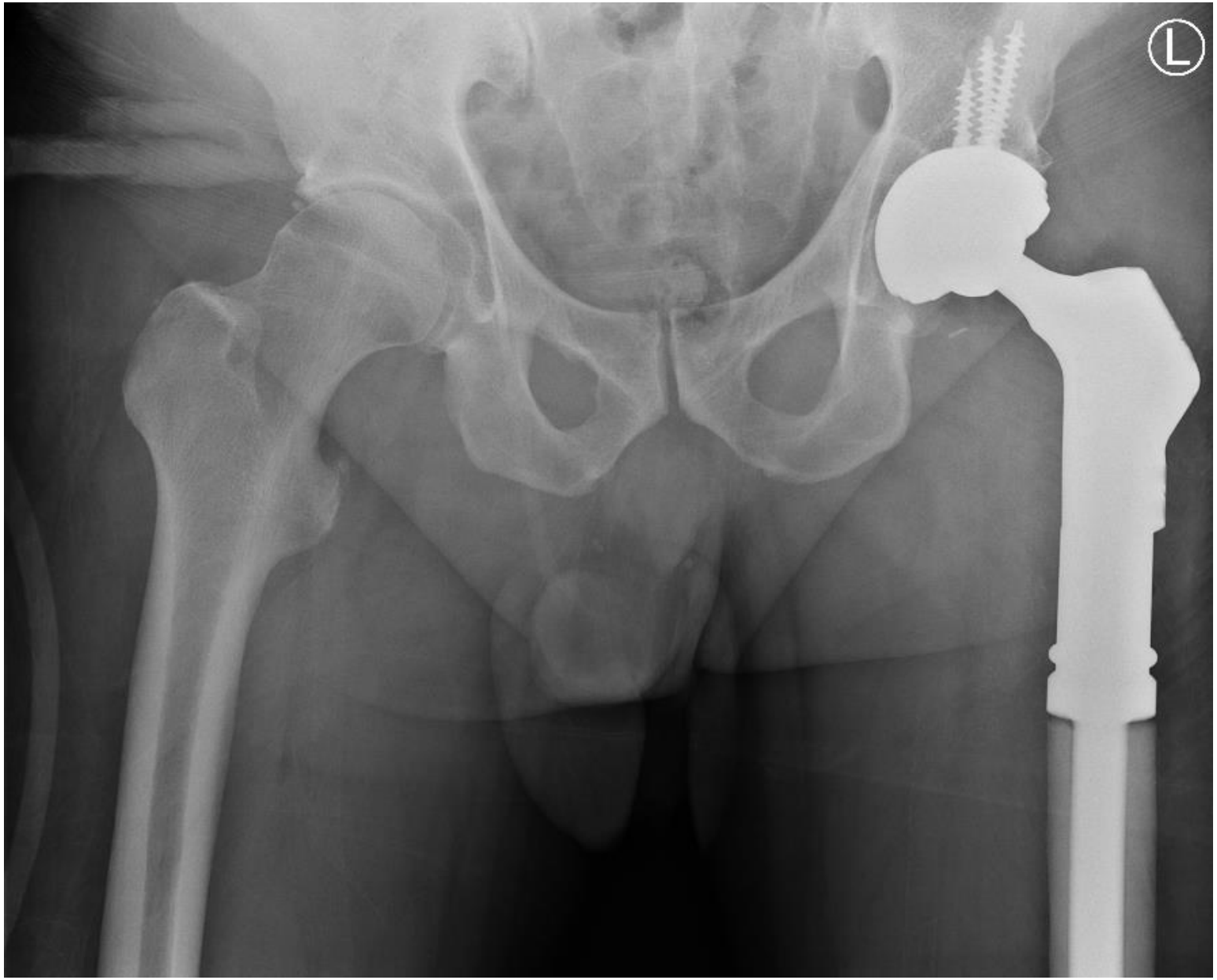
Front



Back

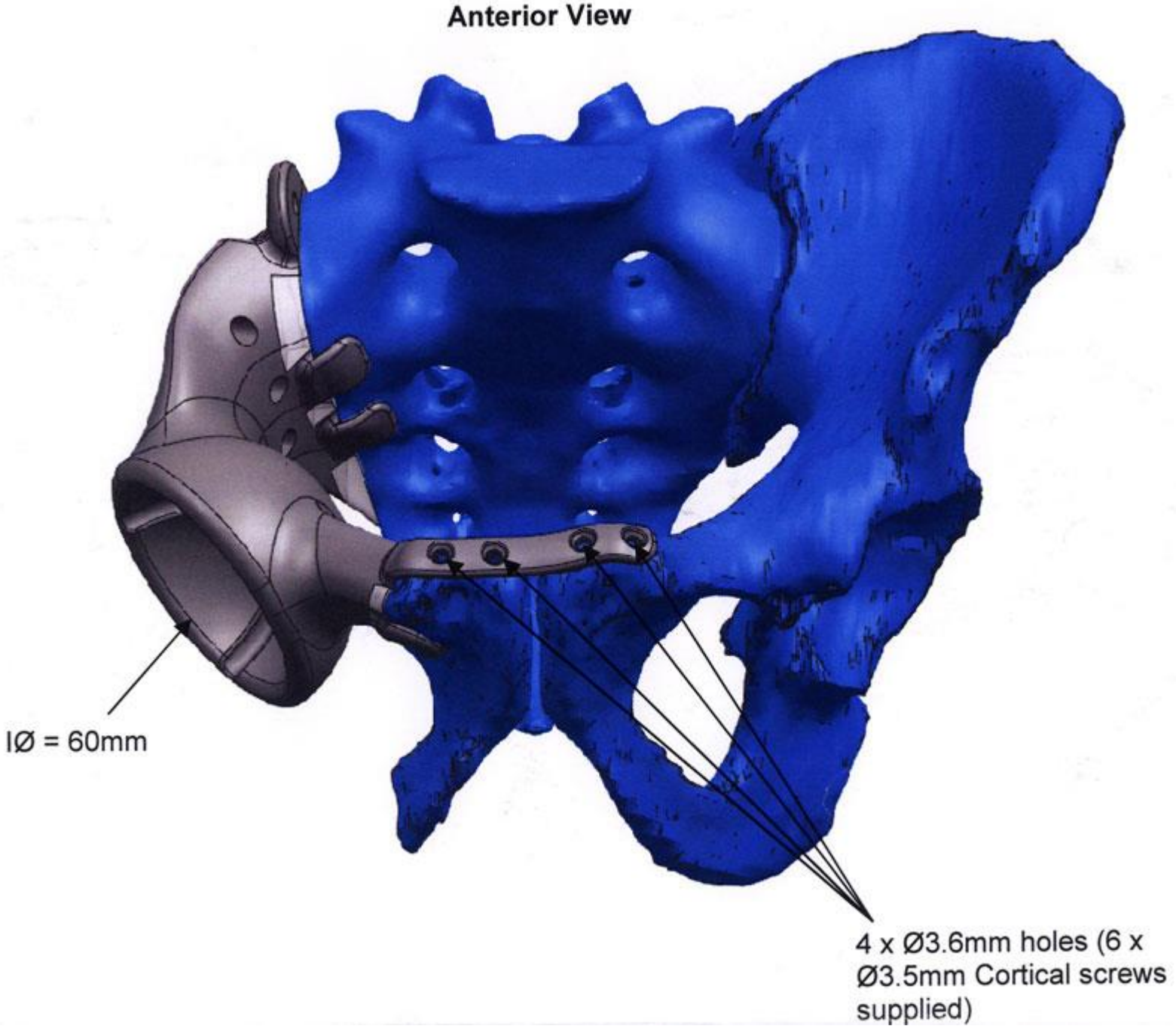
Upgraded to 3 when whole specimen was assessed



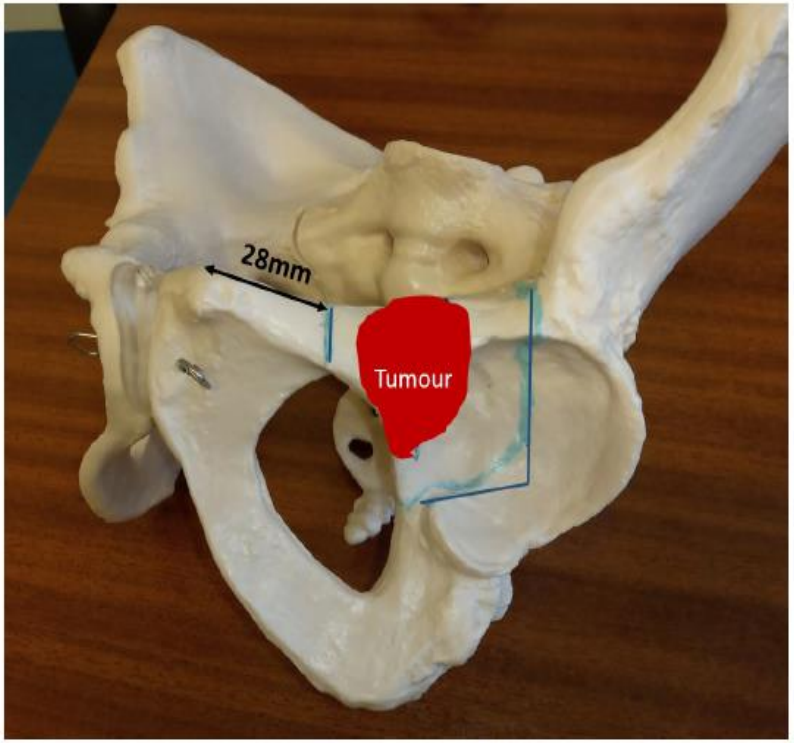

L

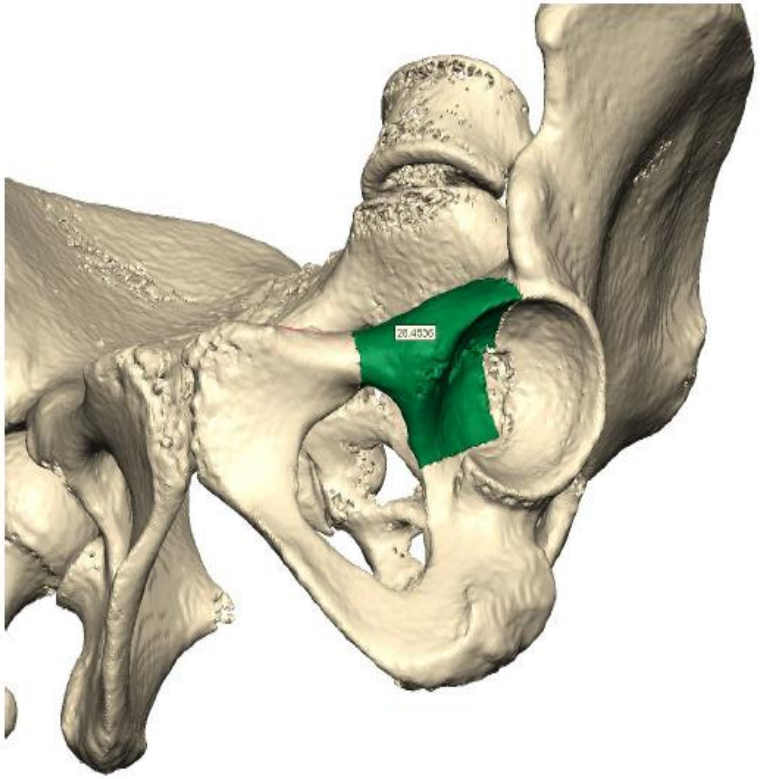
Prox femur replacement

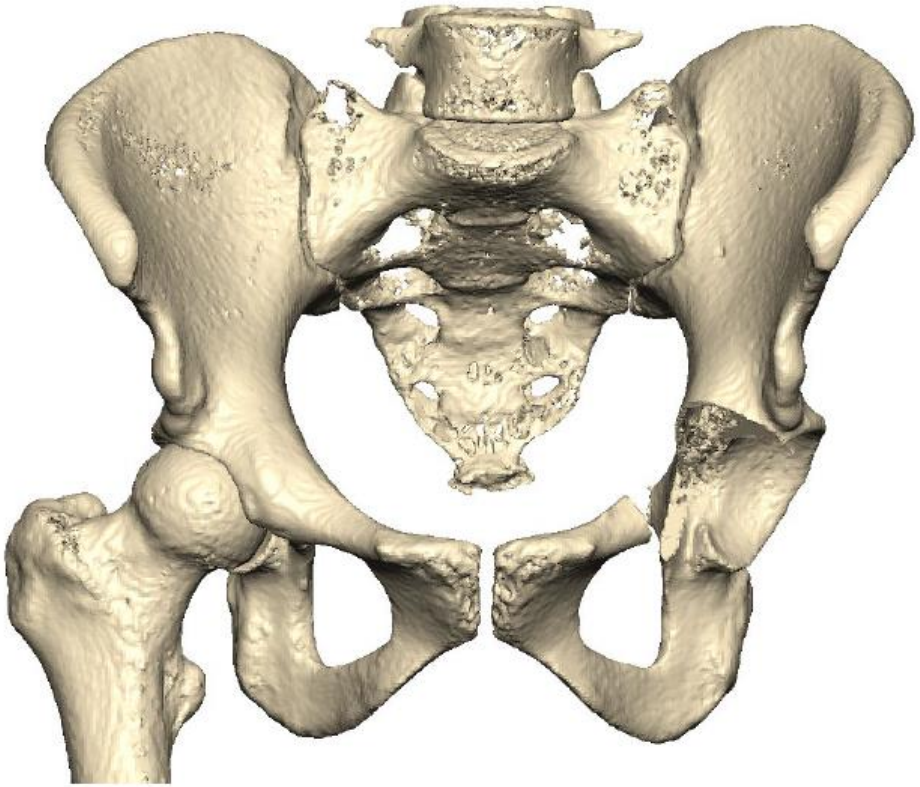
- Variable outcomes
- Majority of patients walk comfortably
- Most use at least one crutch or a stick


Anterior View
IØ = 60mm
4 x Ø3.6mm holes (6 x Ø3.5mm Cortical screws supplied)

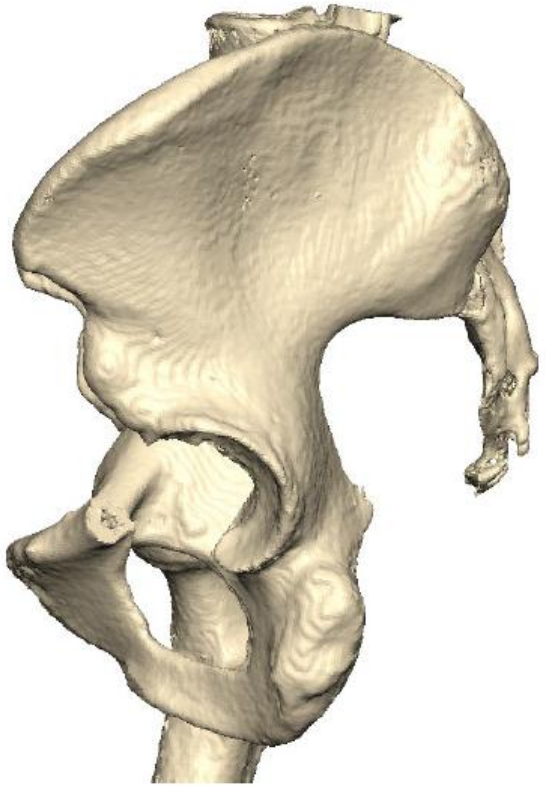
L
R


28mm
Tumour

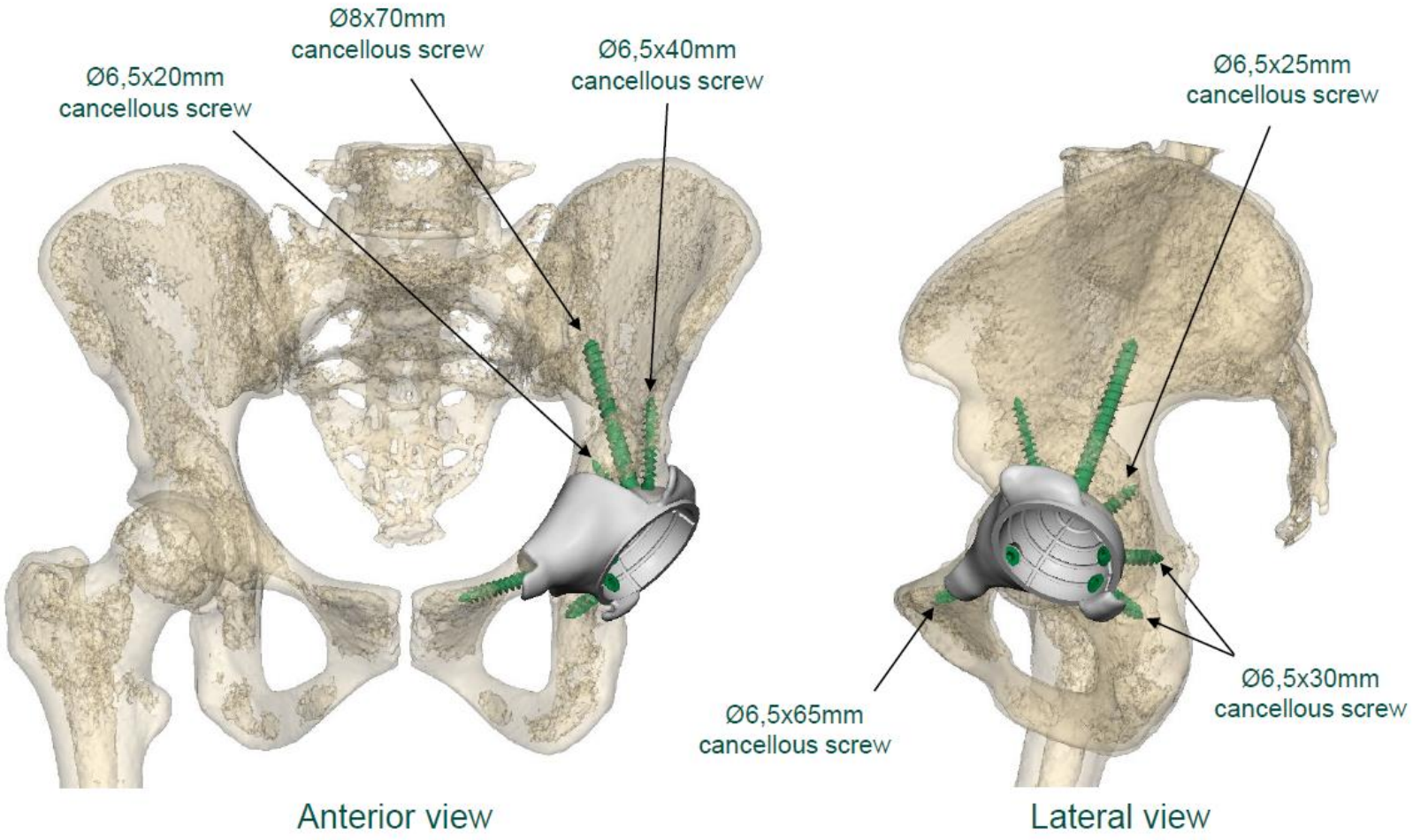

20.4636



Anterior view



Lateral view

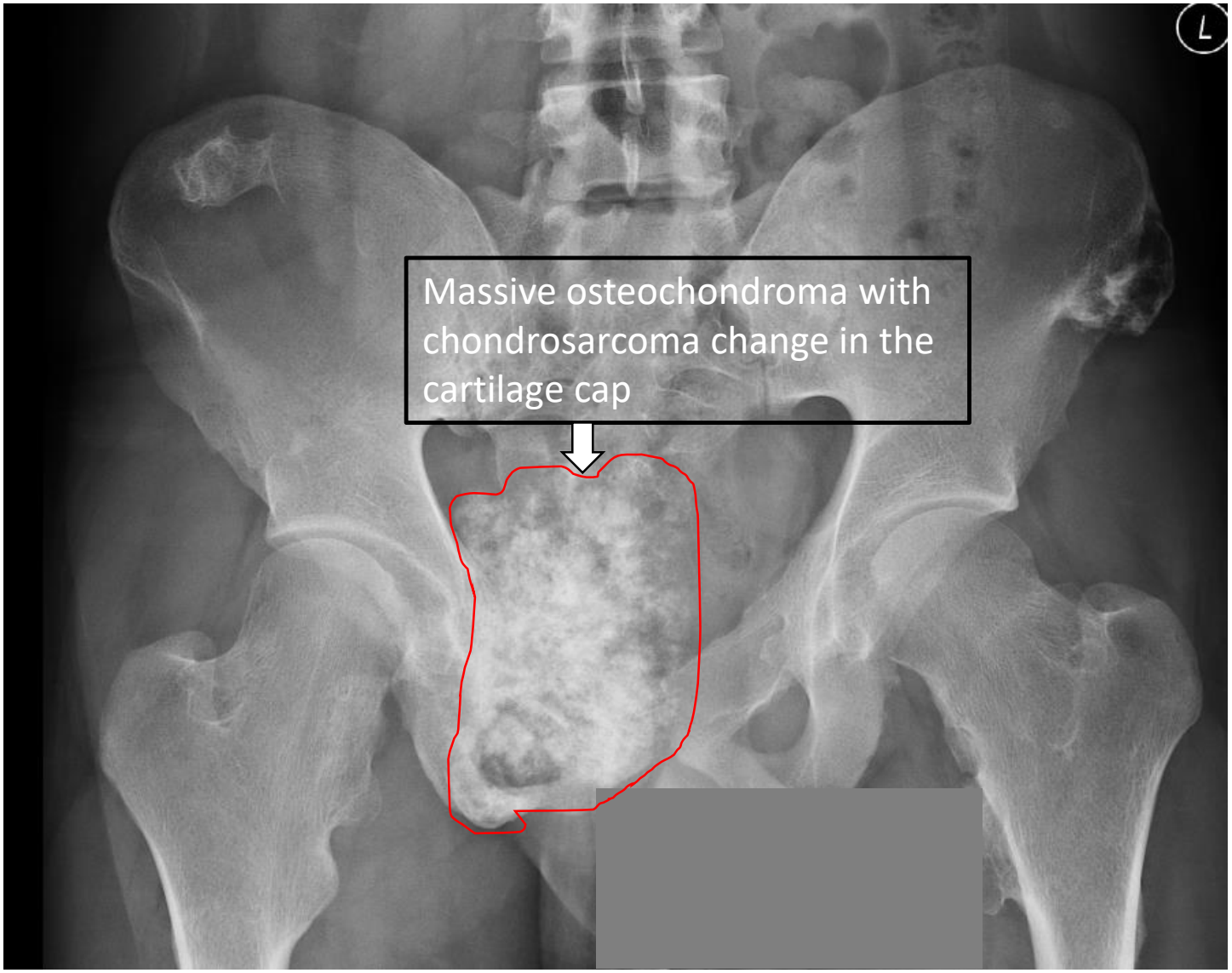

Ø8x70mm
cancellous screw
Ø6,5x40mm
cancellous screw
Ø6,5x20mm
cancellous screw
Anterior view
Ø6,5x25mm
cancellous screw
Ø6,5x65mm
cancellous screw
Ø6,5x30mm
cancellous screw
Lateral view

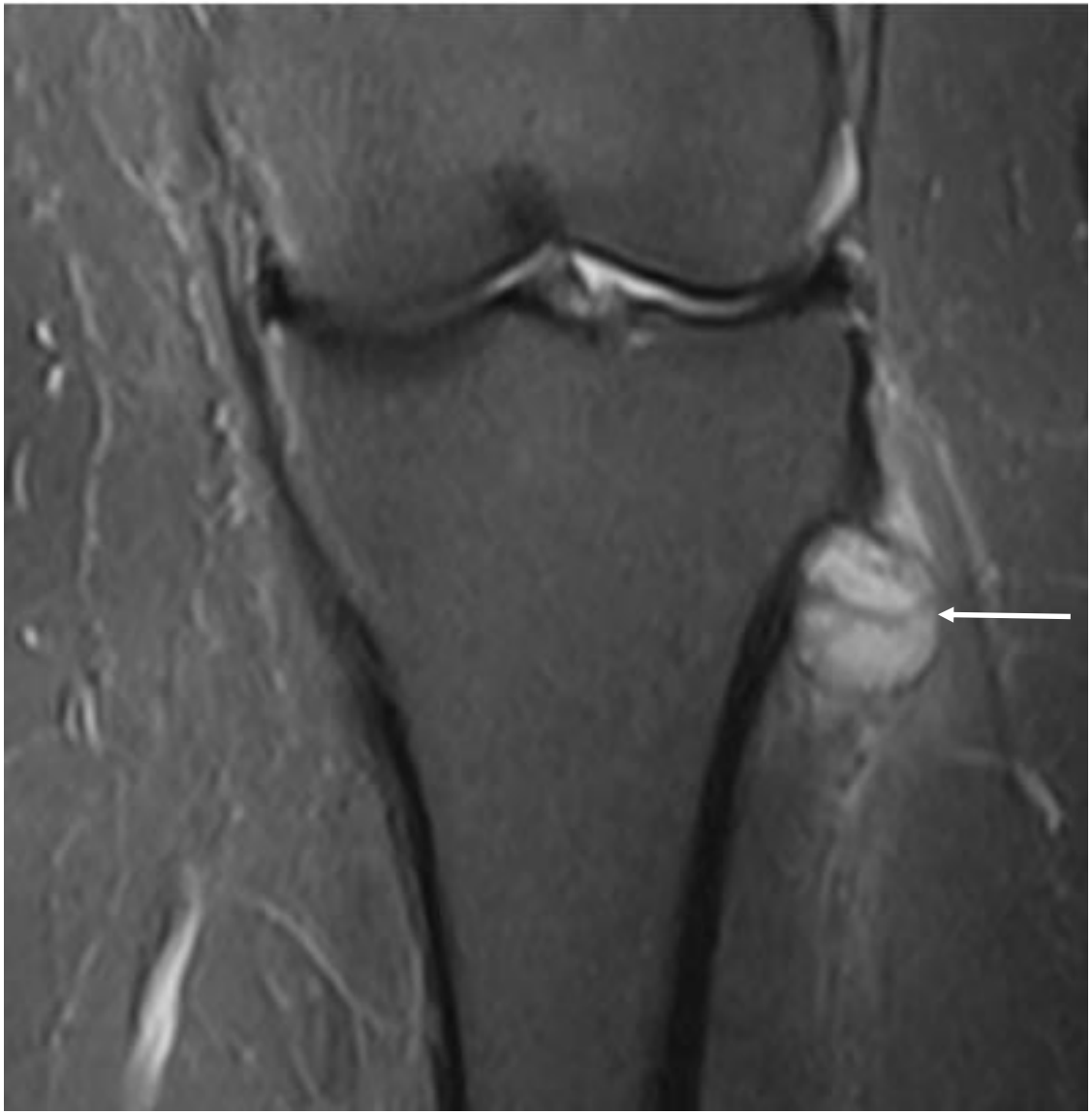
3D custom implant

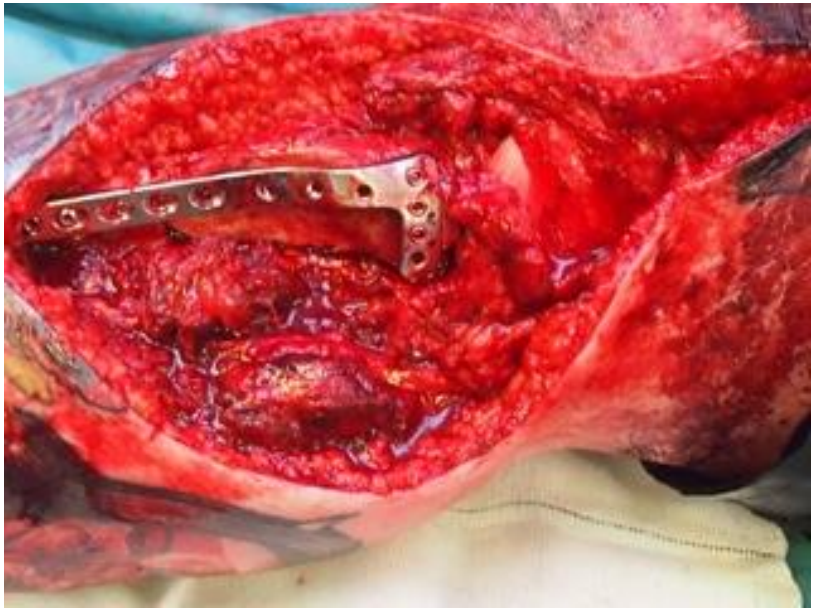
- High infection risk
- Very good function
  - Equal leg lengths
  - Walk without any sticks/crutches

Surface chondrosarcomas

- Can occur on the cartilage cap of an osteochondroma
- Periosteal chondrosarcoma
  - Extremely rare


Massive osteochondroma with chondrosarcoma change in the cartilage cap


Periosteal chondrosarcoma



Perarticular resection

- Good tumour clearance
- Knee joint saved
- Late instability
- Patient still needs 1x crutch

Has had metastatic chondrosarcoma to lung and 2x low grade chondrosarcomas

Patient outcomes

- Varies depending on
  - The stage i.e. if metastases are present survival is lower
  - The grade: nearly 100% five year survival for ACT/low grade chondrosarcoma versus 32% at best for dedifferentiated chondrosarcoma
  - The level of surgery

Research, trials and future therapies

- Research
  - Genomics via the ICGC: IDH mutations highlighted
  - Cell surface targets
  - Image guided surgery
- Trials
  - London chondrosarcoma study
  - IDH mutations in blood samples correlate with chondrosarcoma grade
  - IDH inhibitors are in clinical trials

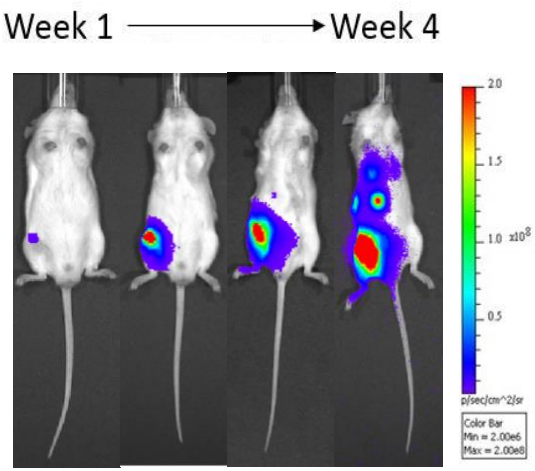
Newcastle University
Northern Institute for Cancer Research

DEDIFFERENTIATED CHONDROSARCOMA MOUSE MODEL- Zak Gamie PhD

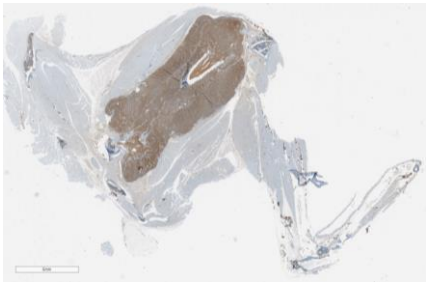
In vivo mouse orthotopic model of dedifferentiated chondrosarcoma

Intrafemoral injection of 5000 HT1080 Luc+ cells

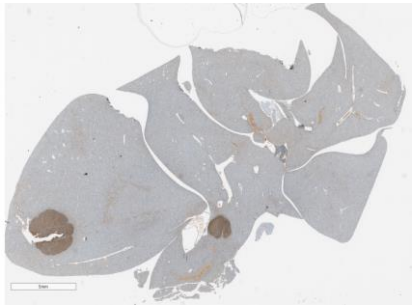
IVIS



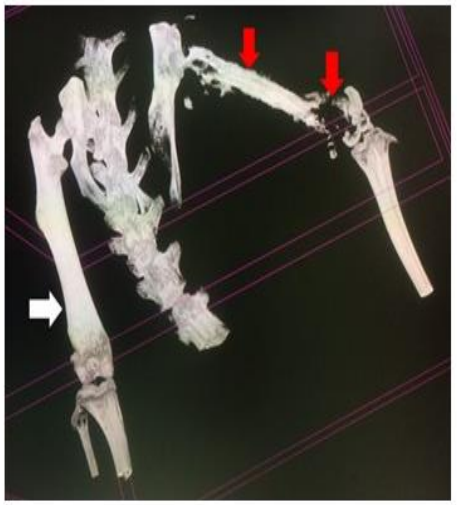
HISTOLOGY



Whole Leg

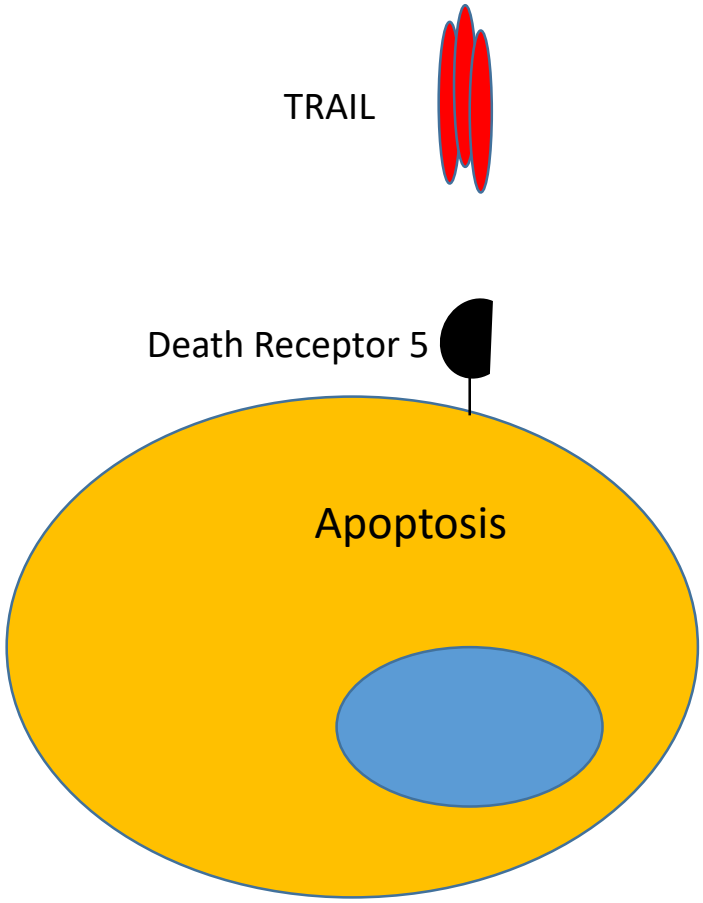


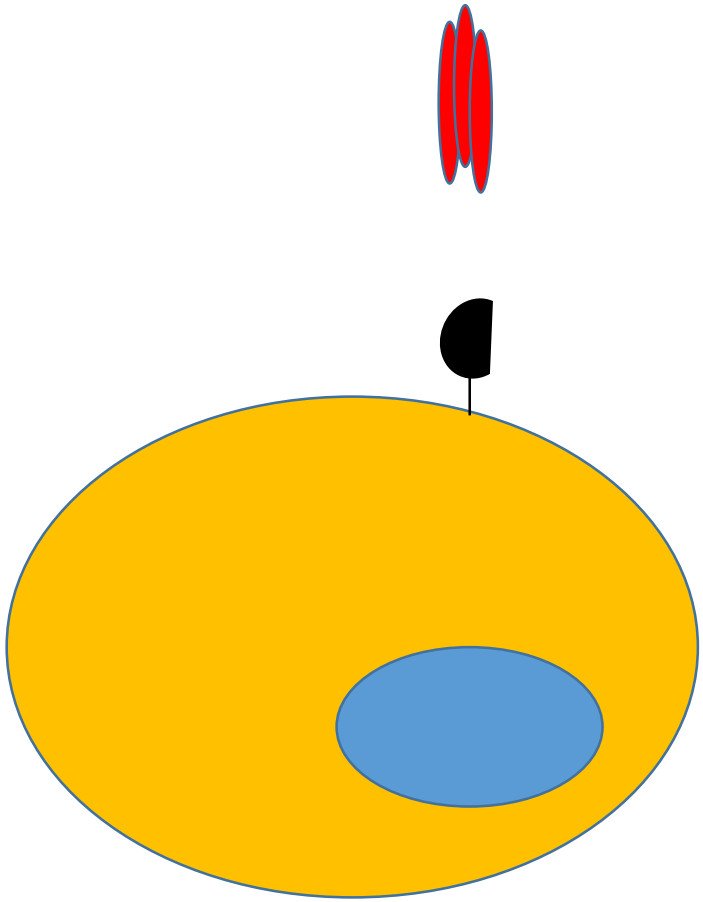
Lung

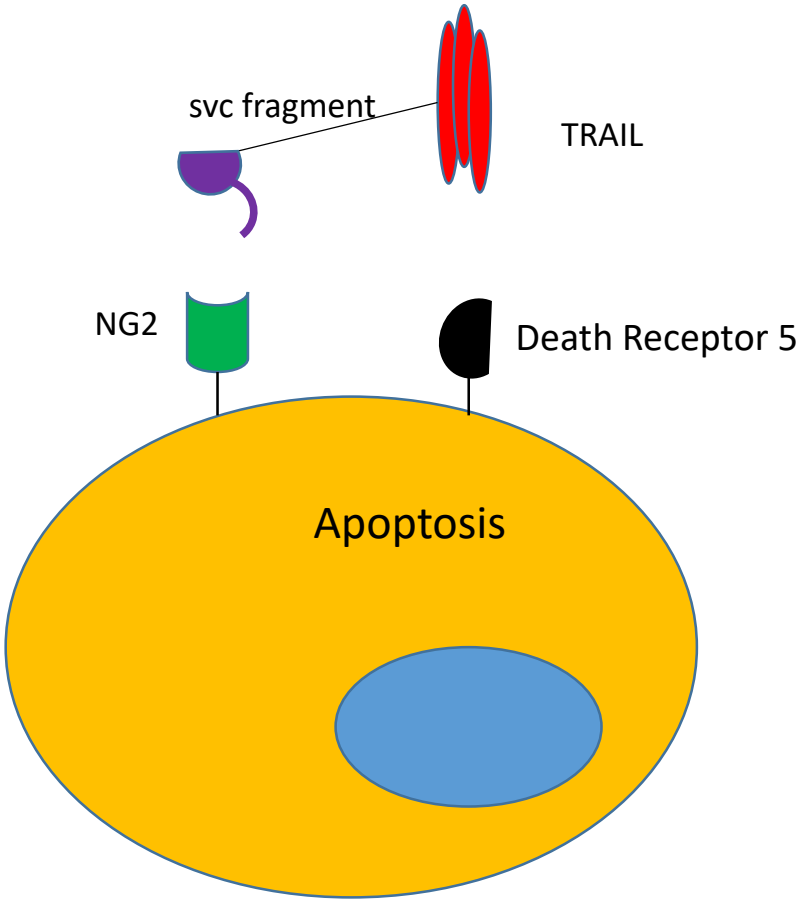


Recapitulation of human disease

orthopaedic research UK


TRAIL
Death Receptor 5
Apoptosis

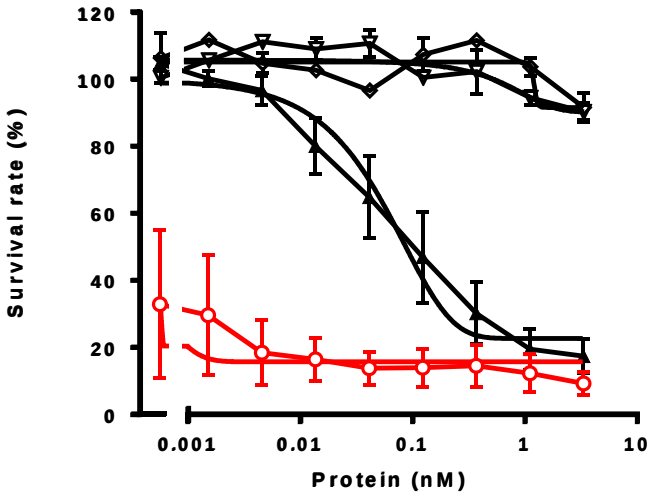



svc fragment
TRAIL
NG2
Death Receptor 5
Apoptosis

Using ScFv(NG2)-Fc-TRAIL in sarcoma cell lines

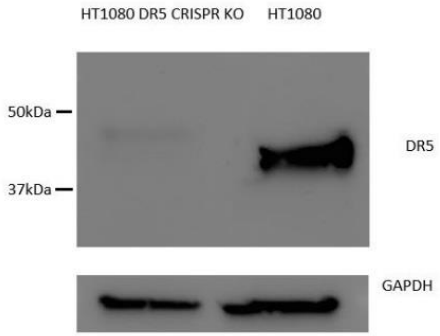
Newcastle University
Northern Institute for Cancer Research

DR5+ve/NG2+ve



DR5+ve/NG2-ve

CRISPR DR5 KO

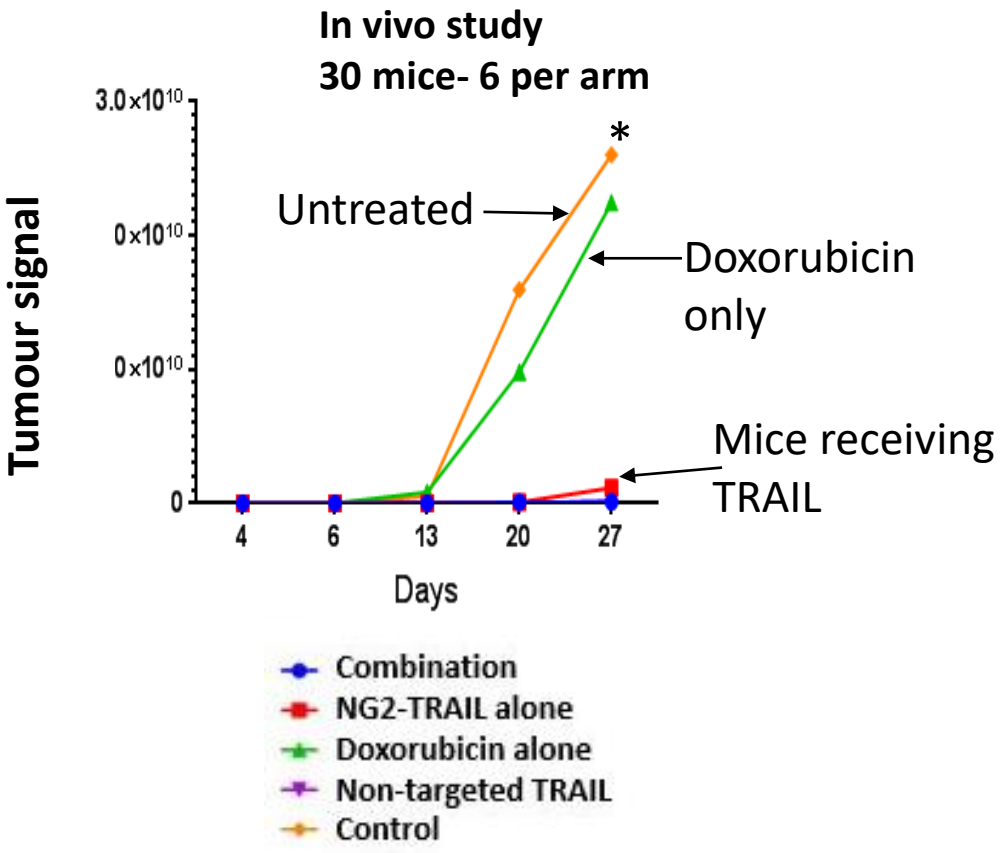


NG2 targeted TRAIL (HT1080)
Non-targeted TRAIL (HT1080)
NG2 targeted TRAIL (HT1080 CRISPR DR5-ve)
Non-targeted (HT1080 CRISPR DR5-ve)

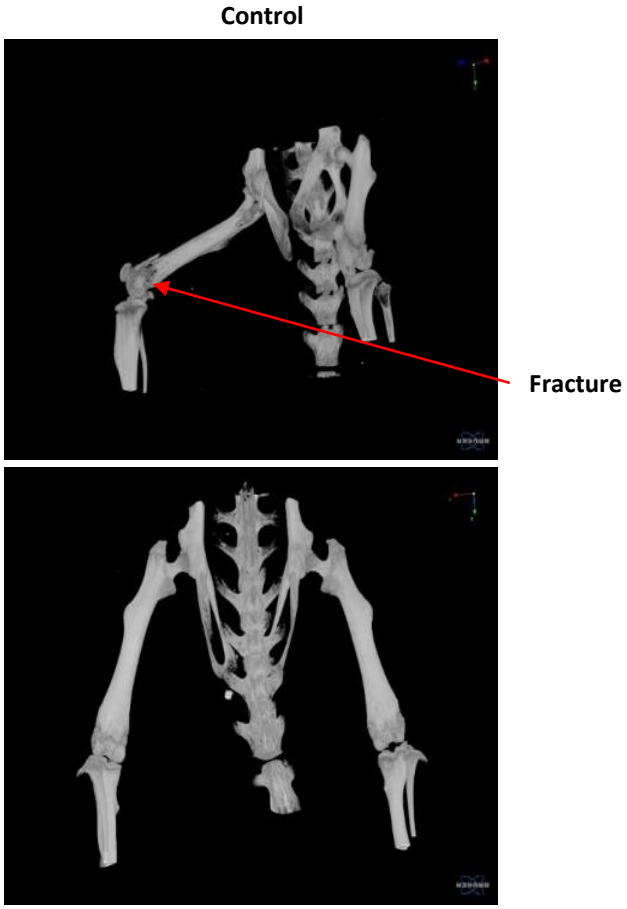
orthopaedic research UK

ScFv(NG2)-Fc-TRAIL is a potent therapeutic in an *in vivo* mouse model for dedifferentiated chrondosarcoma

Newcastle University
Northern Institute for Cancer Research



*= $p<0.05$ using Two-way ANOVA analysis between control and groups



Summary

- Promising laboratory data
- Need to assess DR5/NG2 expression levels in chondrosarcomas from previous patients
- Need to bring this therapeutic to the clinic
- Potential for treatment before surgery to try and kill off the chondrosarcoma

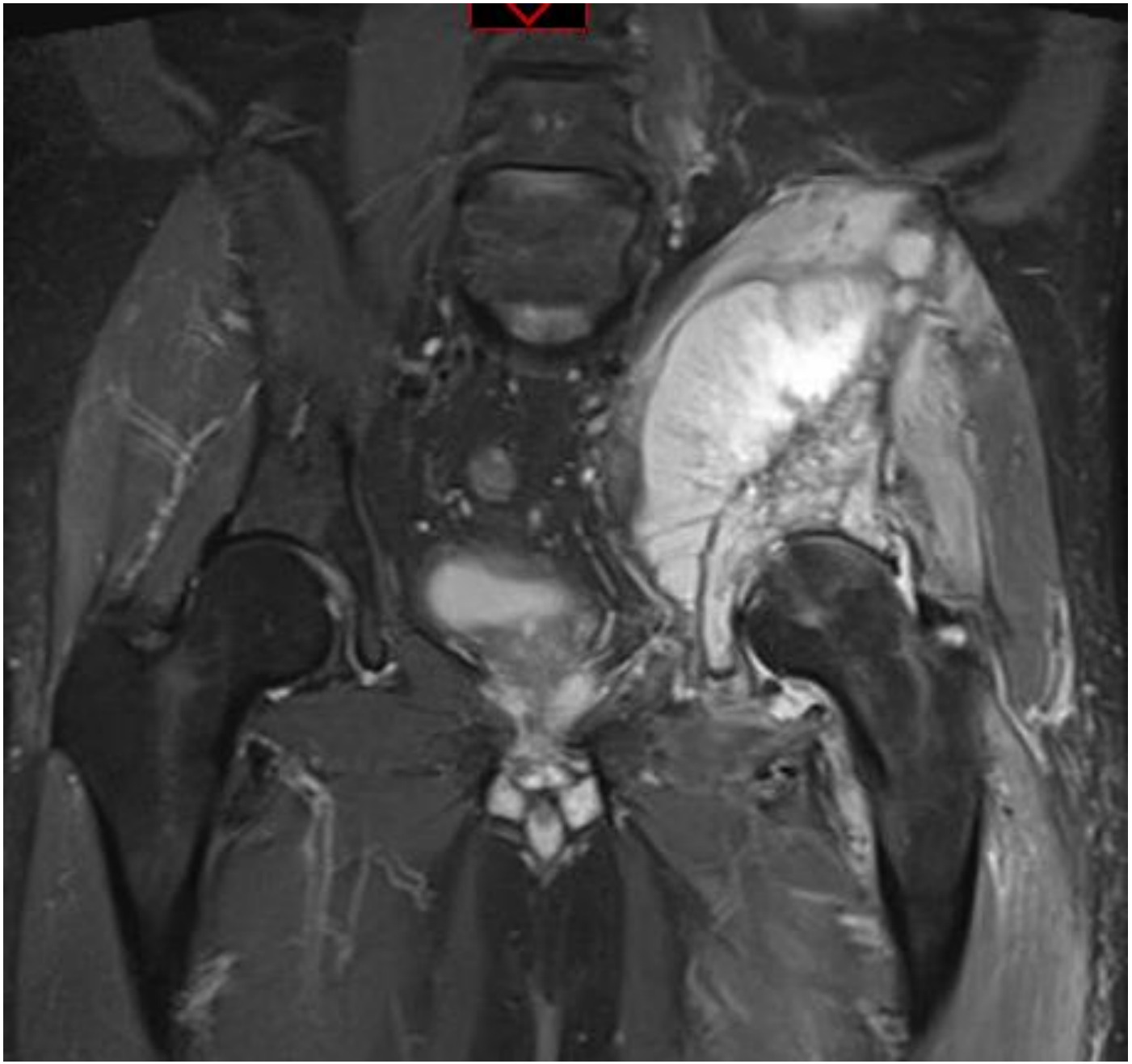
Imaging guidance for open sarcoma surgery?

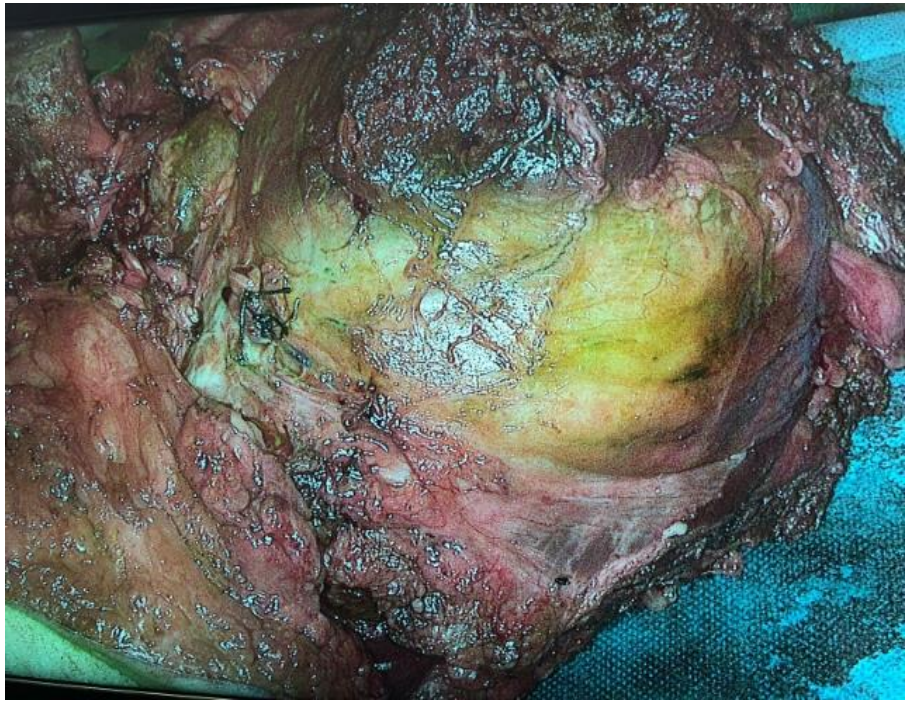
Indocyanine Green

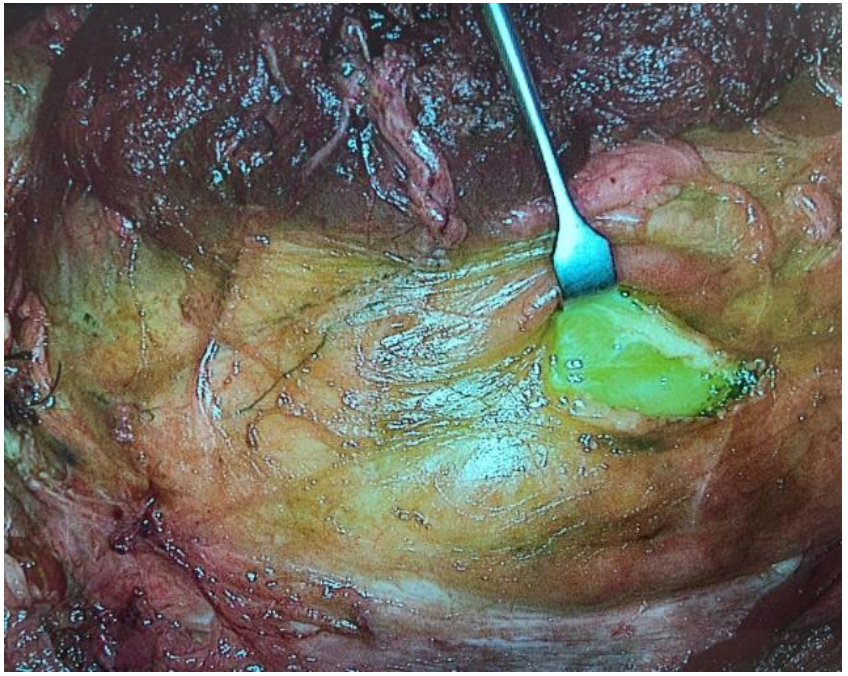
Fluorescence camera for open surgery e.g. Stryker SPY-PHI

Image guided surgery for sarcoma

Patient	Age	Sex	Location	Max tumour dimension (mm)	Histology	Margins	Tumour Grade	Fluorescent	Guided the surgery?
1	65	M	Pelvis	125	**Chondrosarcoma**	R0	3	YES	**NO**
2	73	F	Upper Limb	80	Myxofibrosarcoma	R0	3	YES	YES
3	78	M	Lower limb/groin	130	Pleomorphic sarcoma	R0	3	YES	YES
4	63	F	Upper limb	55	Leiomyosarcoma	R0	2	YES	NO
5	75	F	Lower Limb	27	Myxofibrosarcoma	R1	3	YES	NO
6	26	M	Chest wall	105	Synovial sarcoma	R0	3	YES	NO
7	53	F	Lower Limb	114	Osteosarcoma	R0	High	NO (due to >90% necrosis)	NO
8	79	F	Upper Limb	45	Myxofibrosarcoma	R1	1	YES	NO
9	46	M	Lower Limb	75	Myxofibrosarcoma	R0	1	NO	NO
10	68	M	Lower Limb	38	Myxofibrosarcoma	R0	3	YES	NO
11	55	F	Upper limb	98	Pleomorphic rhabdomyosarcoma	R0	3	YES	YES
12	56	M	Proximal femur	105	**Chondrosarcoma**	R0	3	YES	**YES**

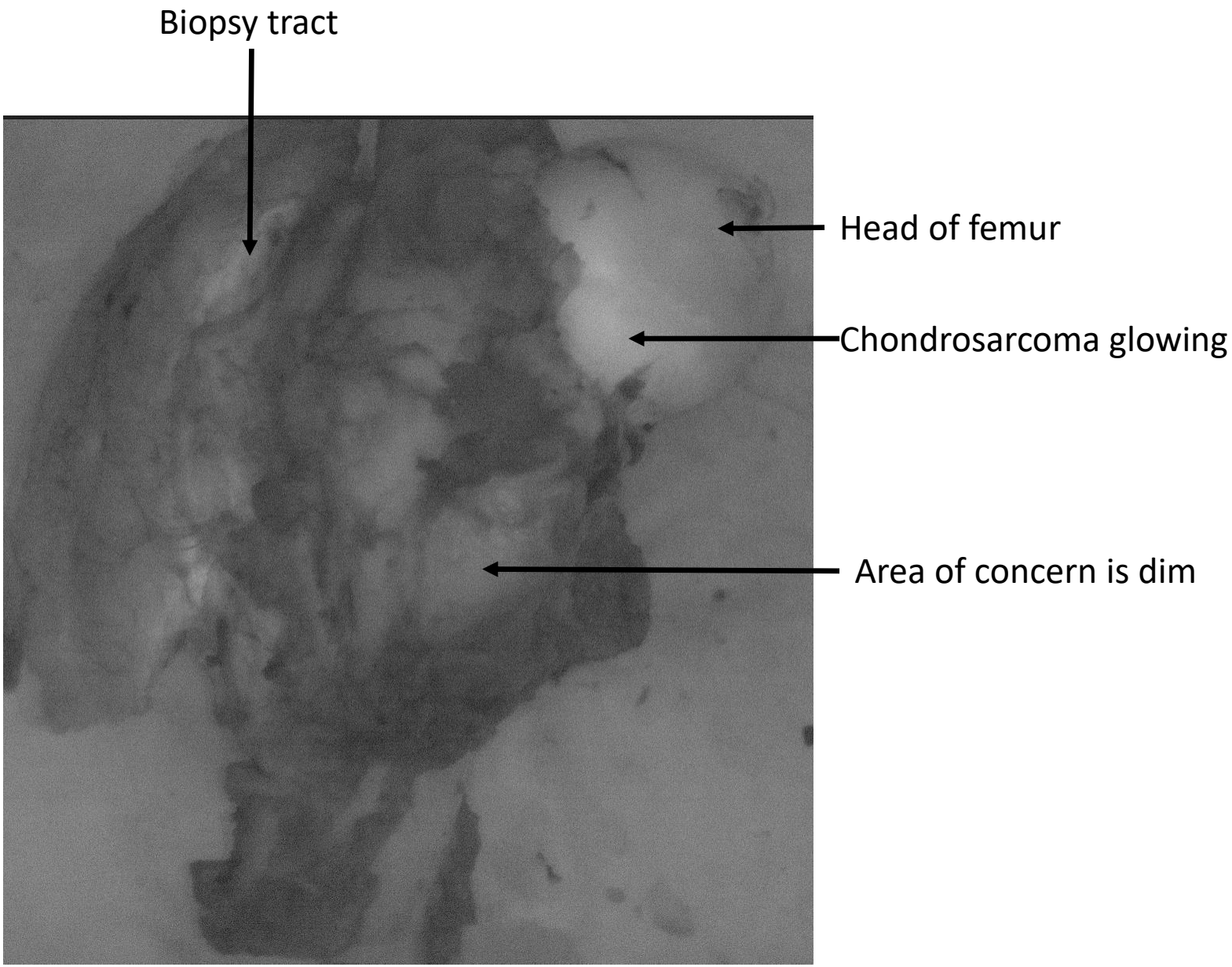






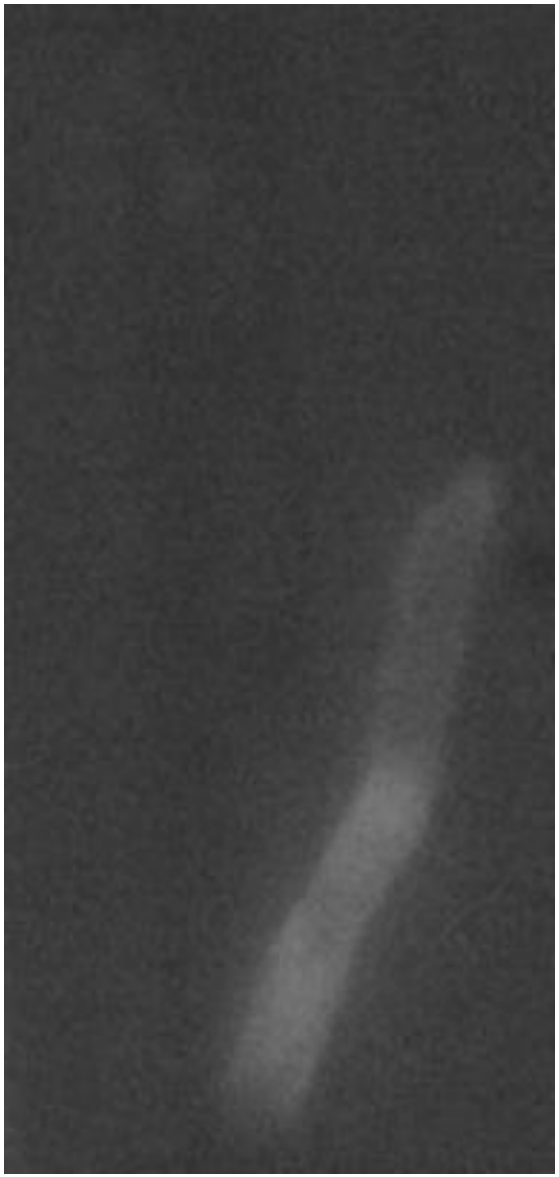
Hindquarter amputation

- Wheelchair bound
- Outcome relates to attitude of the patient


Biopsy tract
Head of femur
Chondrosarcoma glowing
Area of concern is dim

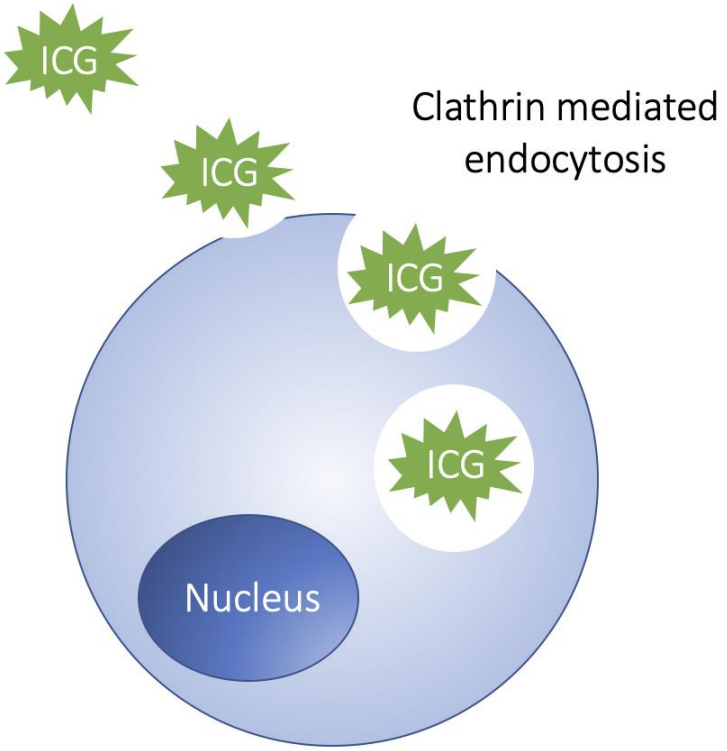
Chondrosarcoma bone cores

‘Green mode’

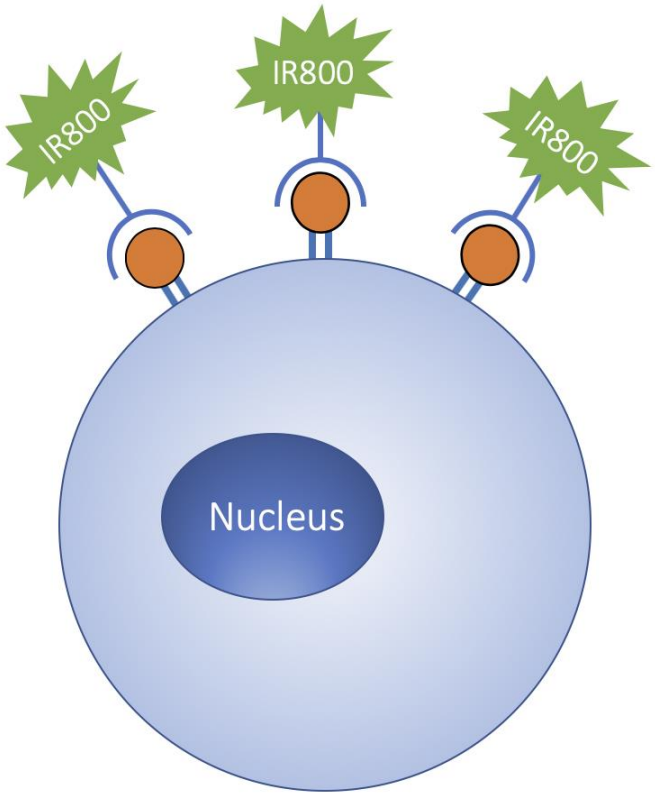


‘Black and white SPY mode’

ICG + Cancer cells

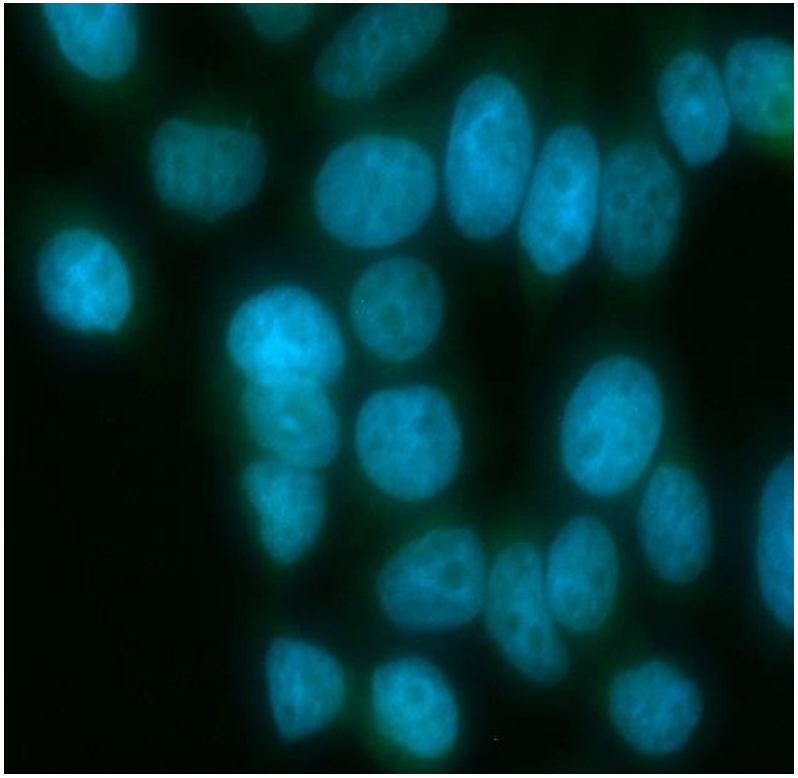


Cancer subtype specific: mab + IR800

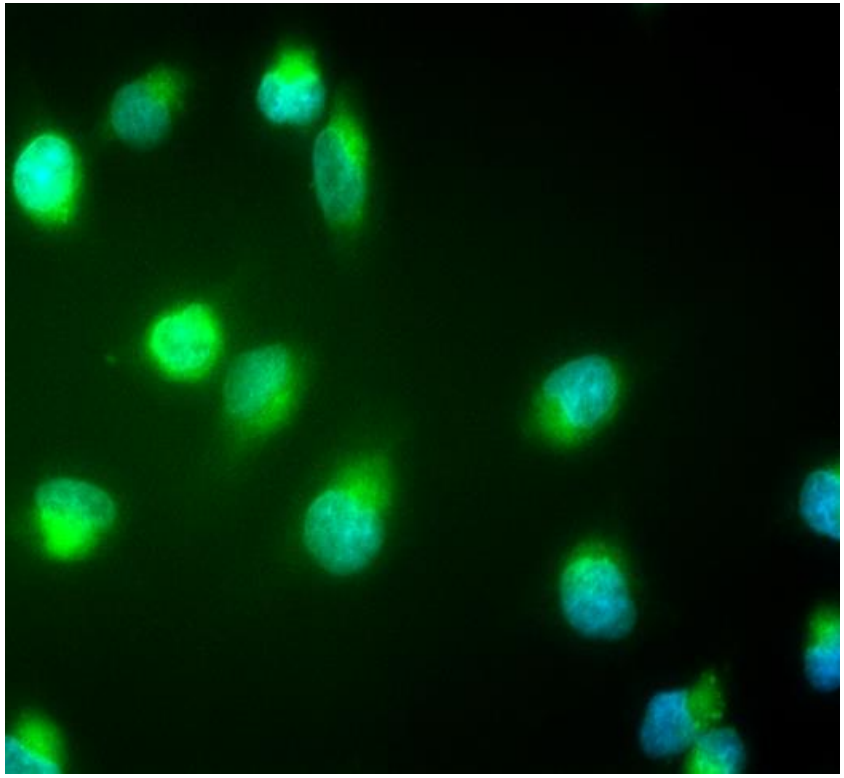


ICG 25µM
OVERNIGHT INCUBATION

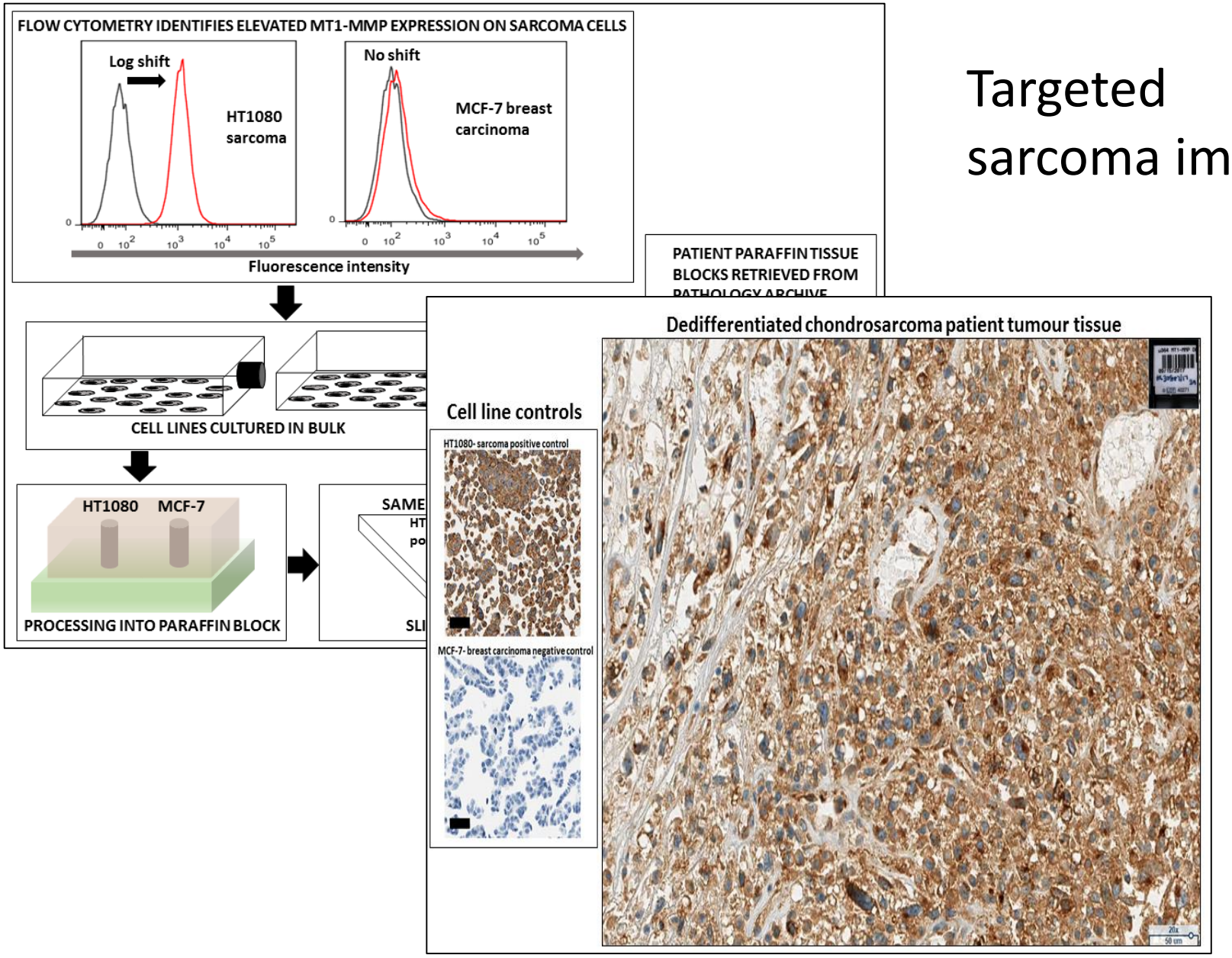
MCF-7 breast carcinoma

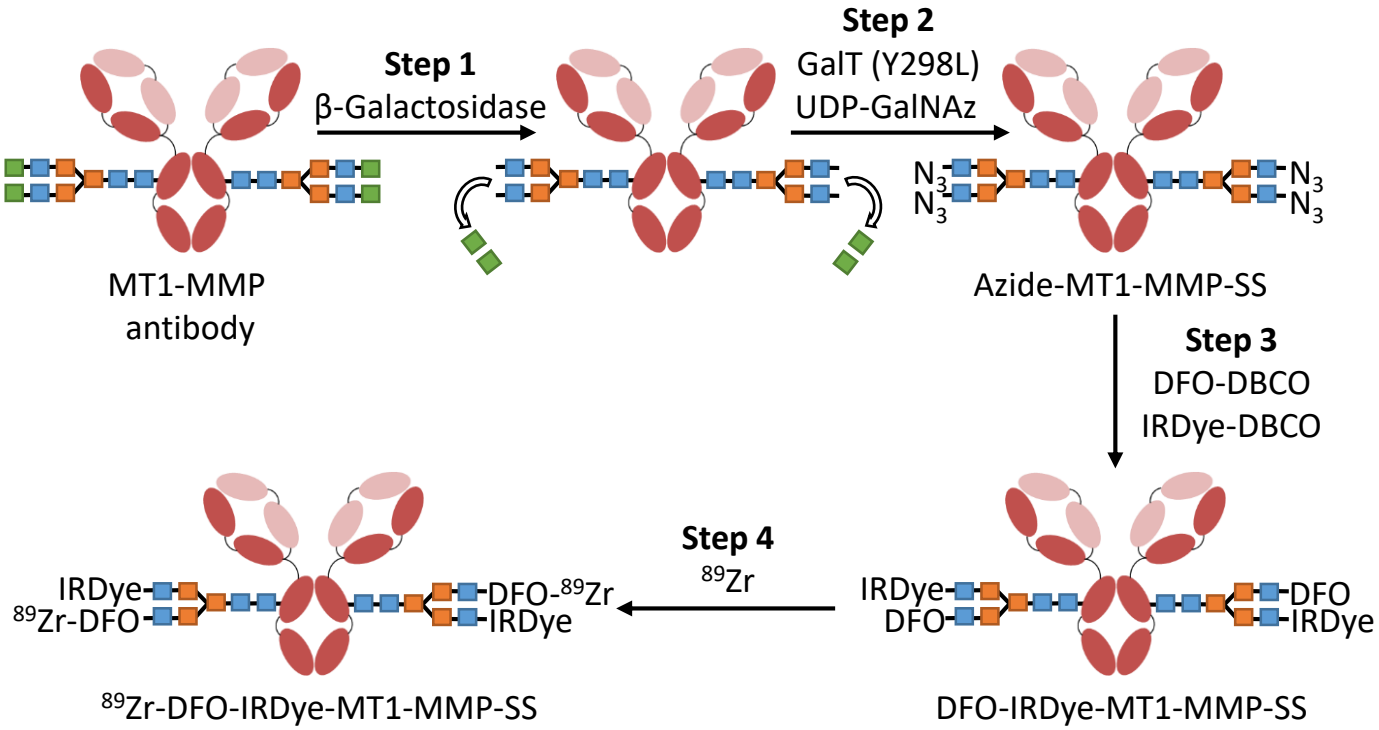


HT1080 dedifferentiated chondrosarcoma

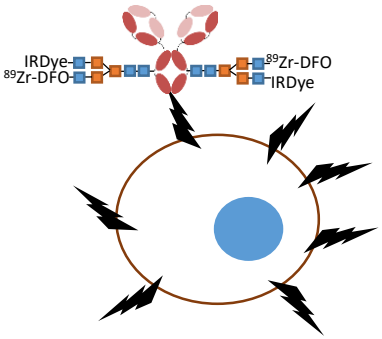


Targeted sarcoma imaging

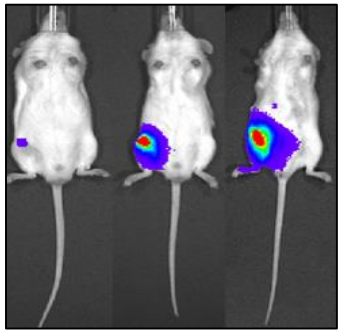




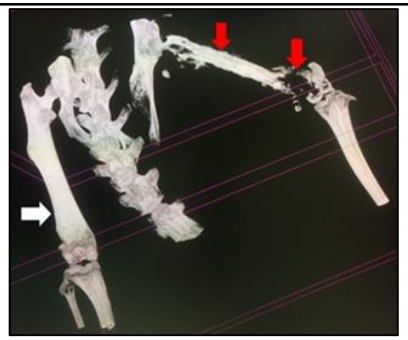
Site-selective chemoenzymatic synthesis of dual modality MT1-MMP imaging agent



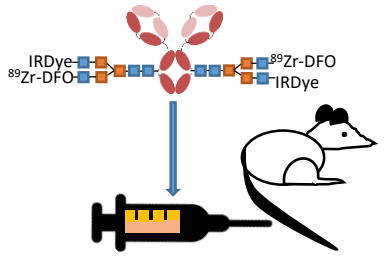
In vitro cell binding assays



IVIS to track tumour formation

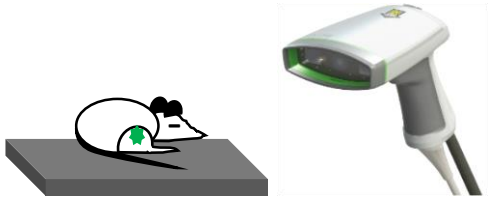


CT to monitor bone destruction



Injection of conjugated monoclonal antibody at week 3

ORTHOTOPIC MOUSE MODEL

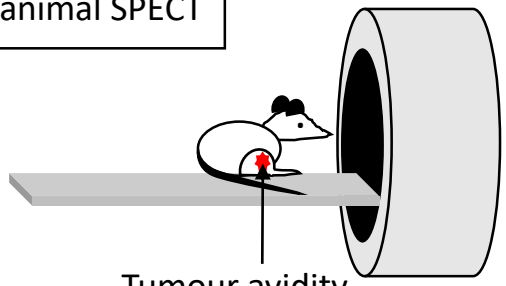


Near infrared handheld camera

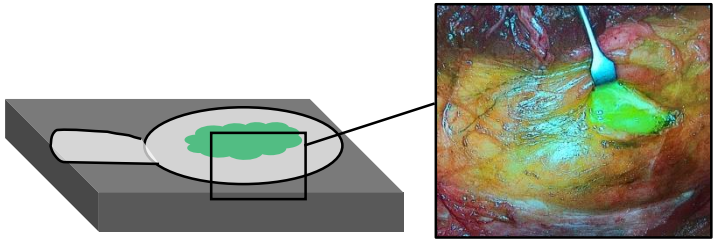
Fluorescence guided surgery

orthopaedic research UK

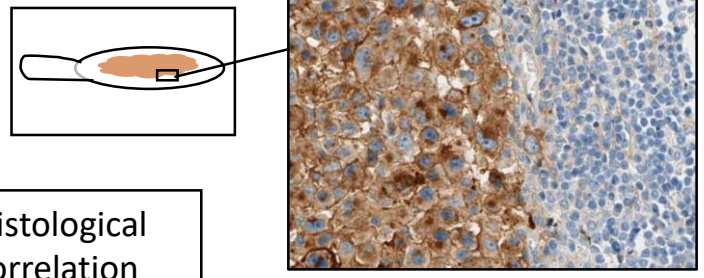
Small animal SPECT



Tumour avidity



Ex vivo specimen analysis



Histological correlation

Overall conclusions

- Chondrosarcoma is still treated mainly with surgery alone
- Clinical trials are becoming available for patients with spread (metastases)
- Image guided surgery is promising
- IDH mutations can be picked up on blood tests
  - May catch relapse earlier
- Therapeutics for cell surface targets/Immunotherapy showing promise

Acknowledgements

Charity support

orthopaedic research UK

Sarcoma Patients EuroNet

Our patients