

# An update on Bone Sarcomas

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[www.londonsarcoma.org](http://www.londonsarcoma.org)

- Introduction/Overview  
Scenarios
- How collaborative research works  
Outlook
- +/- Giant cell tumours

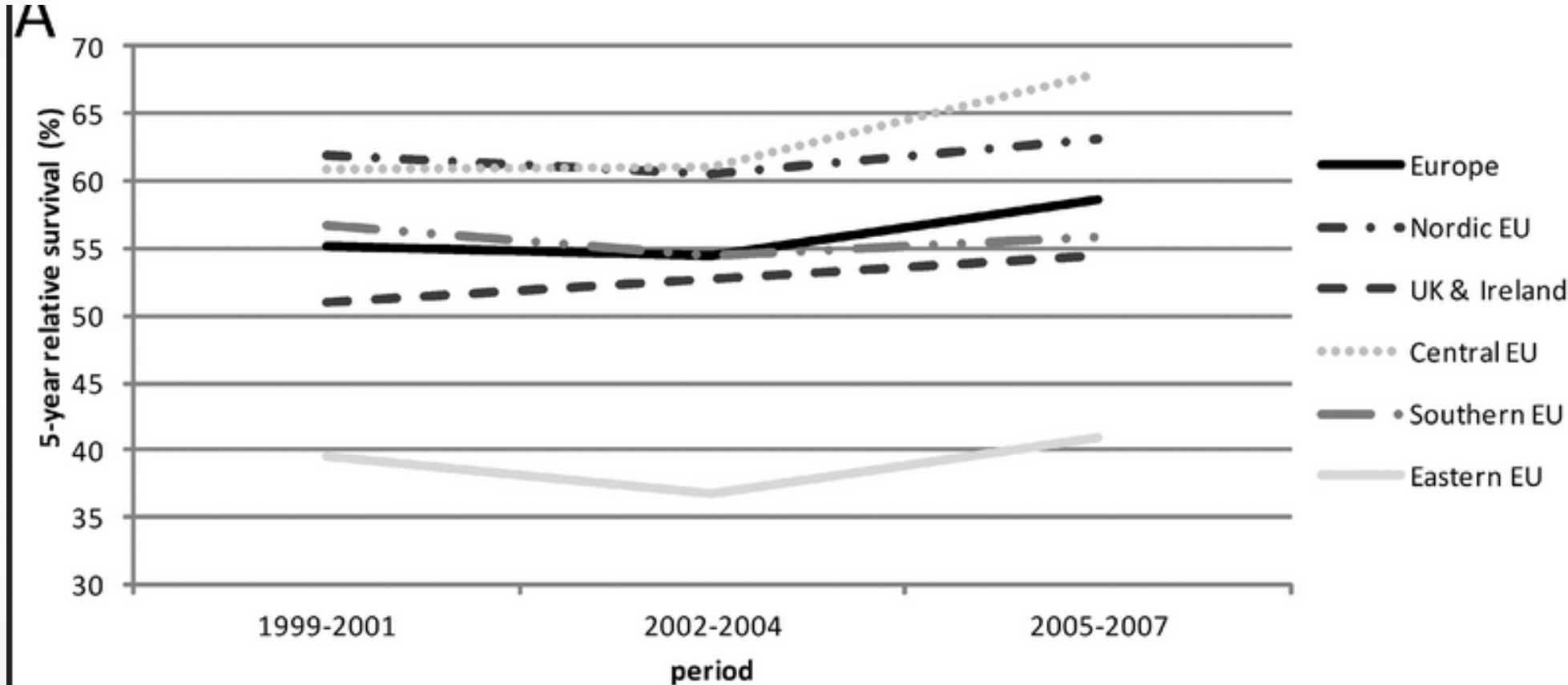
# What is in a name?

- Bone sarcoma, bone cancer, bone tumour
- Osteosarcoma, Ewing sarcoma, PNET, chondrosarcoma, spindle cell sarcoma of bone
- Low grade chondral tumour, enchondroma, osteochondroma, chondrosarcoma, high grade, low grade, dedifferentiated
- Leiomyosarcoma, angiosarcoma, fibrosarcoma
- Radiation-induced sarcoma
- Non-mesenchymal primary bone tumours
- Giant cell tumour of bone,
- Secondary bone cancer

# What is different or distinct about bone sarcoma

- Curable cancer of children and young people
- Curable sarcoma in older patients
- Rare
- Prolonged time to diagnosis, debilitating symptom constellations
- Standard of care is multidisciplinary & for many intensive multi-modality treatment
- Complex highly specialised (orthopaedic) surgery
- Lifelong morbidity
- Difficult biology
- Strong clinical trial record especially in OS and ES
- 'survival hasn't improved'
- Record for development of new treatments disheartening
- Overlapping 'bone tumour' communities
- Several areas of clinical uncertainty

# Bone Cancer Survival in Europe



Time trends in age-standardised [relative survival](#) for adult patients with [bone and cartilage cancer](#) across European regions.

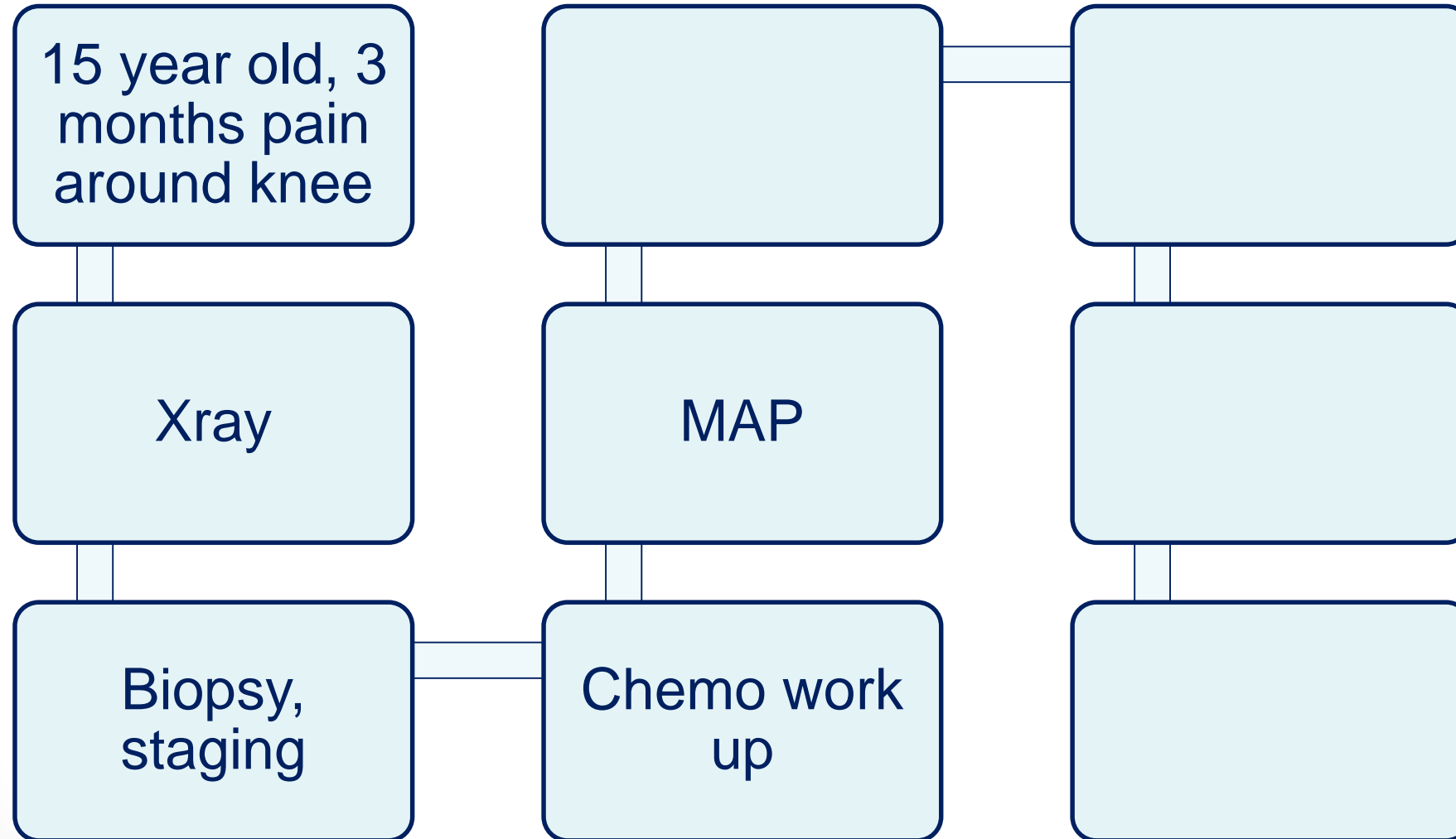
Stiller et al Cancer Epidem 2018;56:146



# Osteosarcoma, proximal tibia



# Osteosarcoma





# EURAMOS-1 Trial

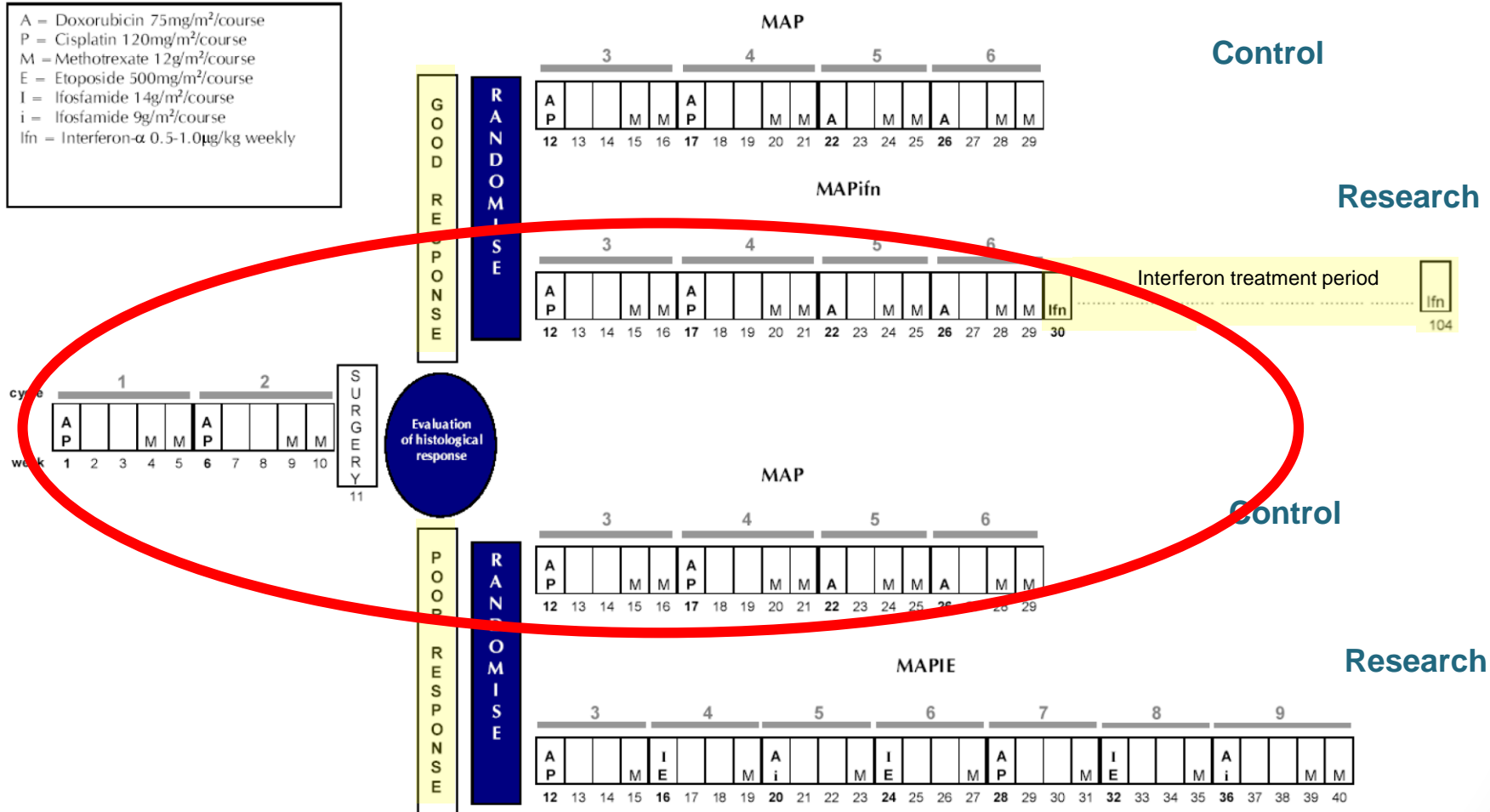


ID: EURAMOS-1, MRC BO08, AOST0331  
ClinicalTrials.gov: NCT00134030  
ISRCTN.com: 67613327  
EudraCT: 2004-000242-20

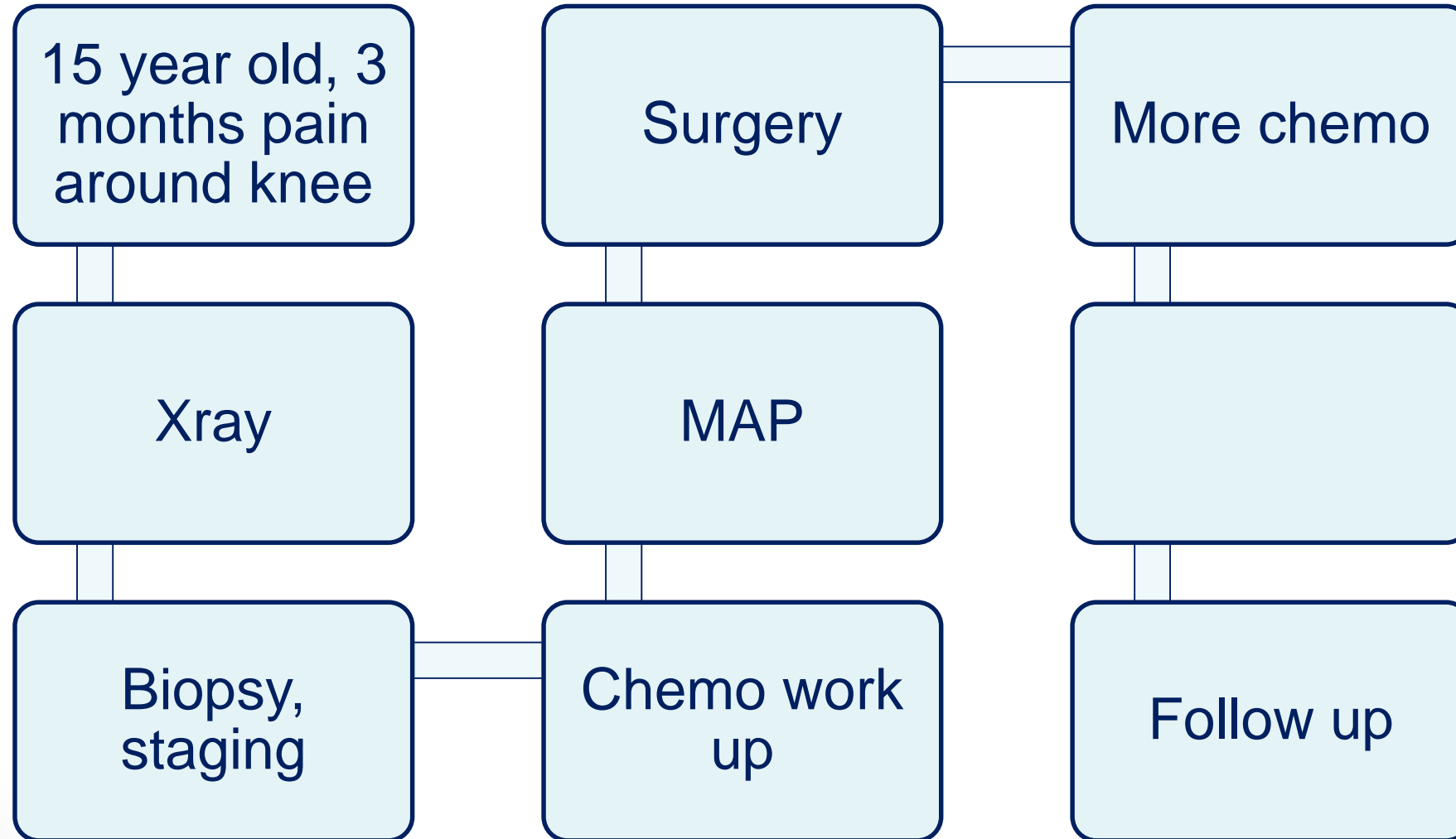
Chief Investigators: M Bernstein (Canada), S Bielack (Germany), Katie Janeway (USA), N Marina (USA), S Smeland (Norway), J Whelan (UK)  
Statisticians: M Sydes (CTU), F Ingleby (CTU), M Krailo (COG), J Gerß (COSS)  
Central Trial Management: K Sanders (CTU), B Popoola (CTU)

# EURAMOS-1 Trial schema

A = Doxorubicin 75mg/m<sup>2</sup>/course  
 P = Cisplatin 120mg/m<sup>2</sup>/course  
 M = Methotrexate 12g/m<sup>2</sup>/course  
 E = Etoposide 500mg/m<sup>2</sup>/course  
 I = Ifosfamide 14g/m<sup>2</sup>/course  
 i = Ifosfamide 9g/m<sup>2</sup>/course  
 Ifn = Interferon- $\alpha$  0.5-1.0 $\mu$ g/kg weekly

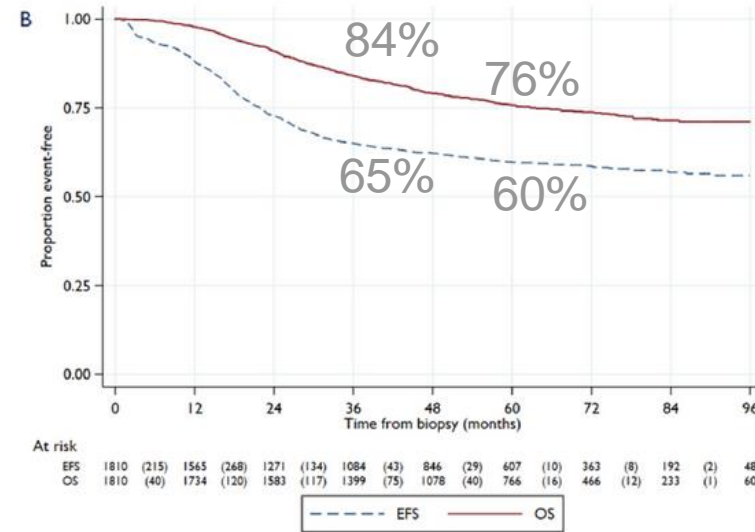
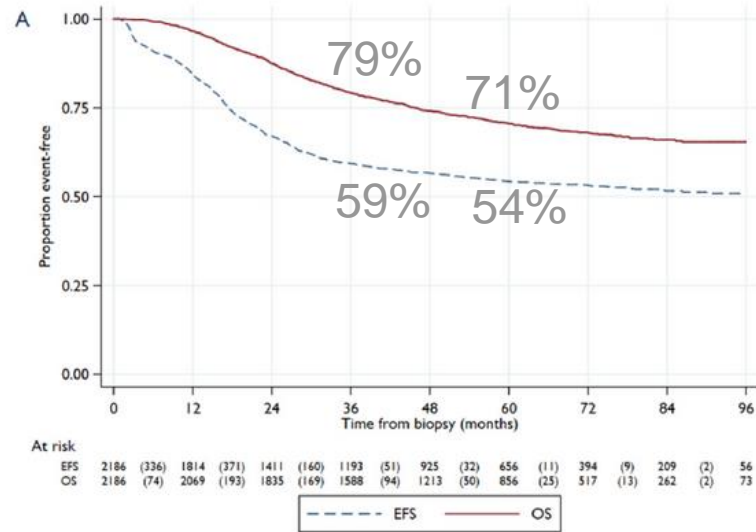


# Osteosarcoma



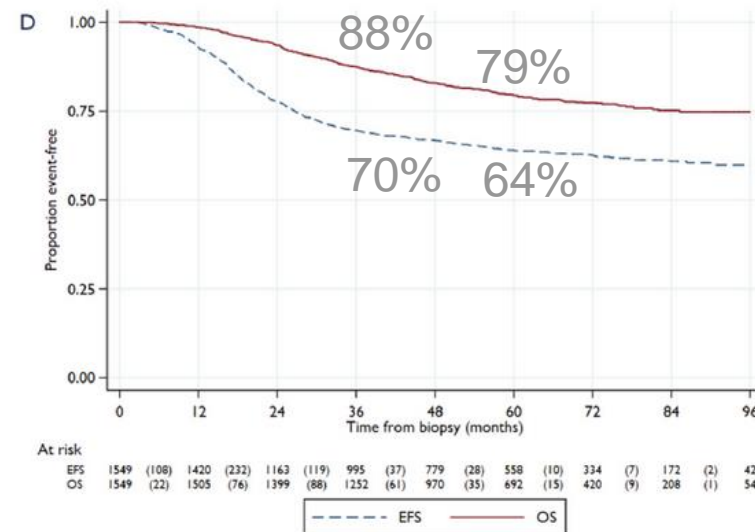
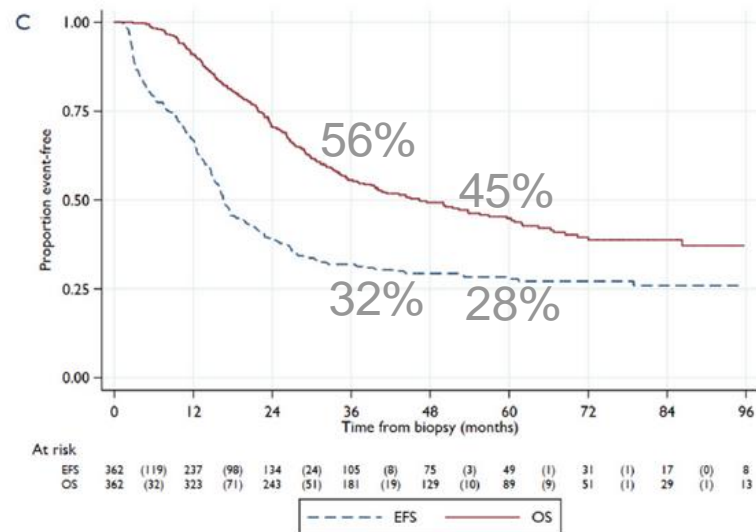
# EURAMOS-1 Outcomes

All patients  
n = 2186



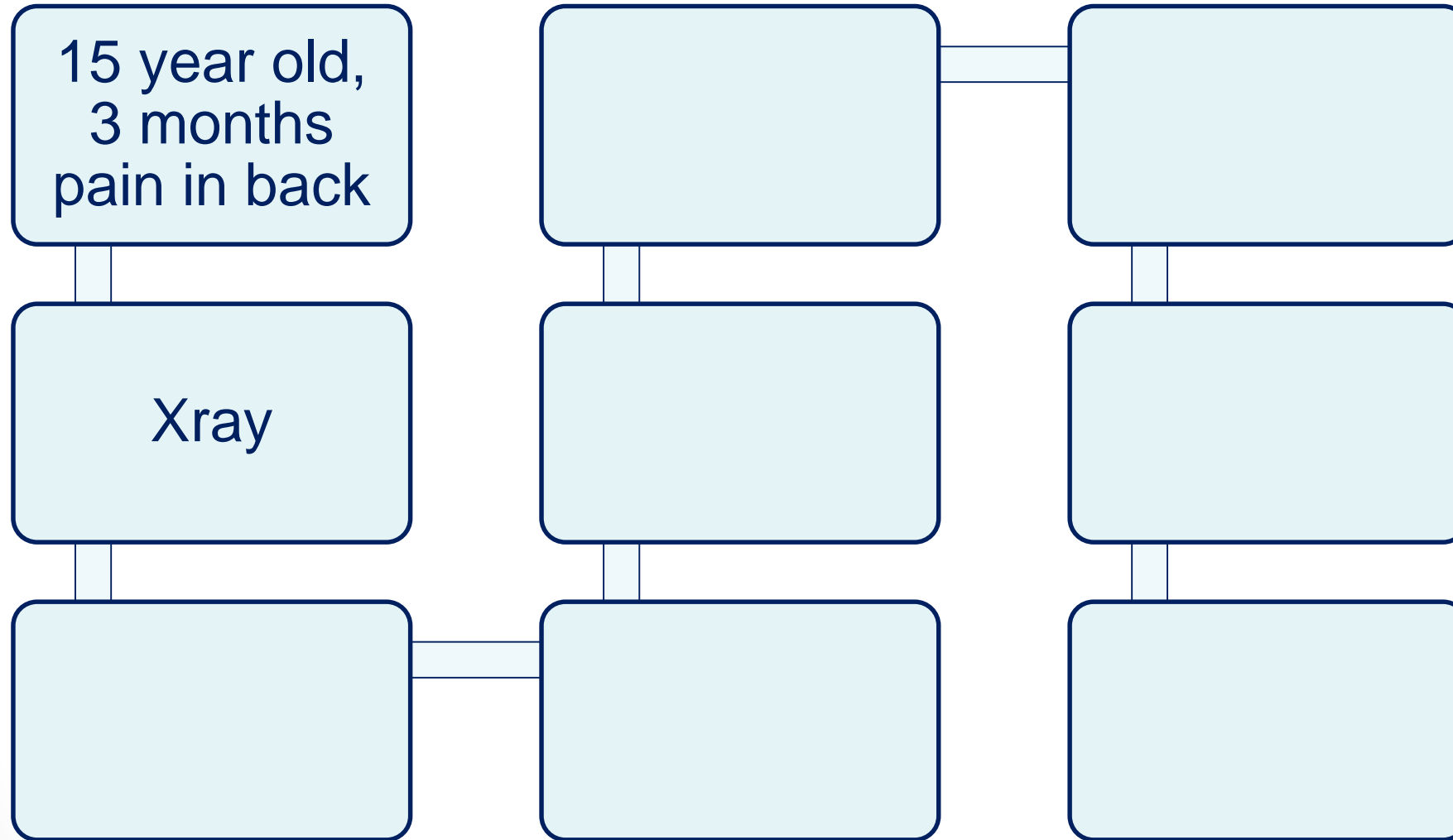
M0  
n = 1810

M1  
n=362

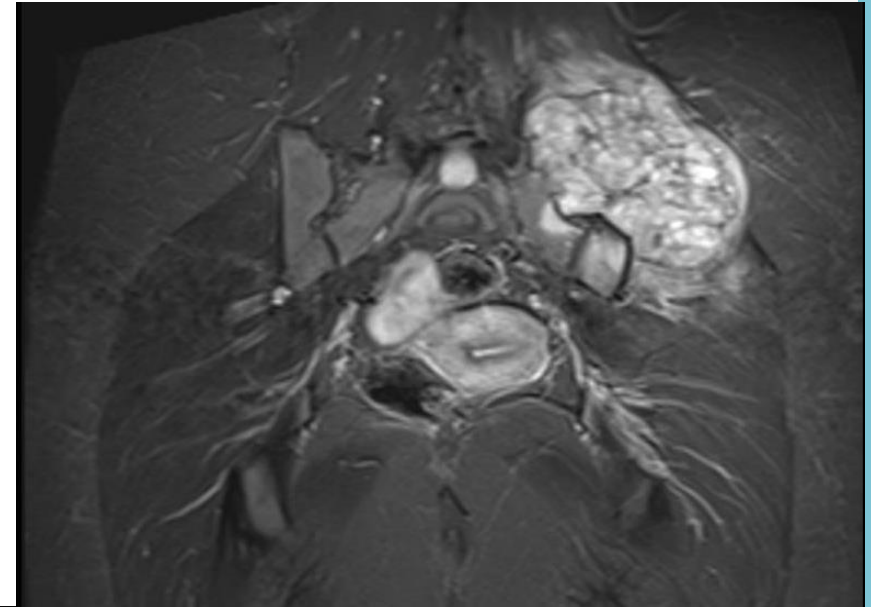


M0 CSR  
N=1549

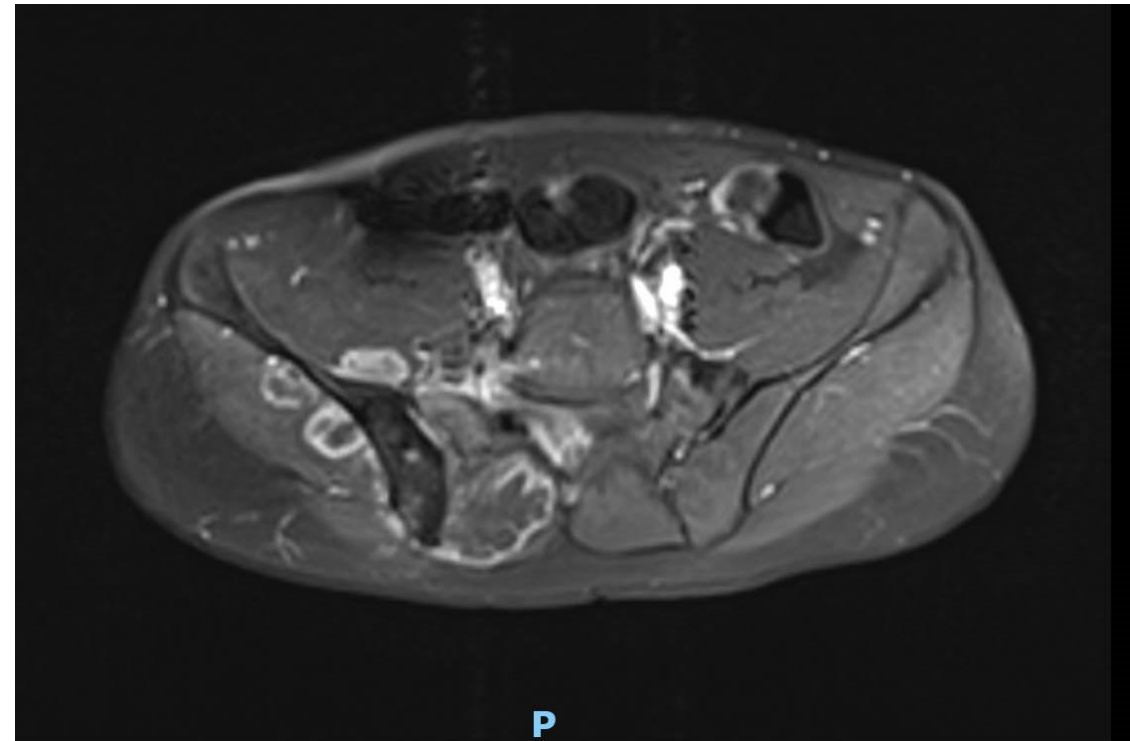
# Osteosarcoma



# Pelvic osteosarcoma

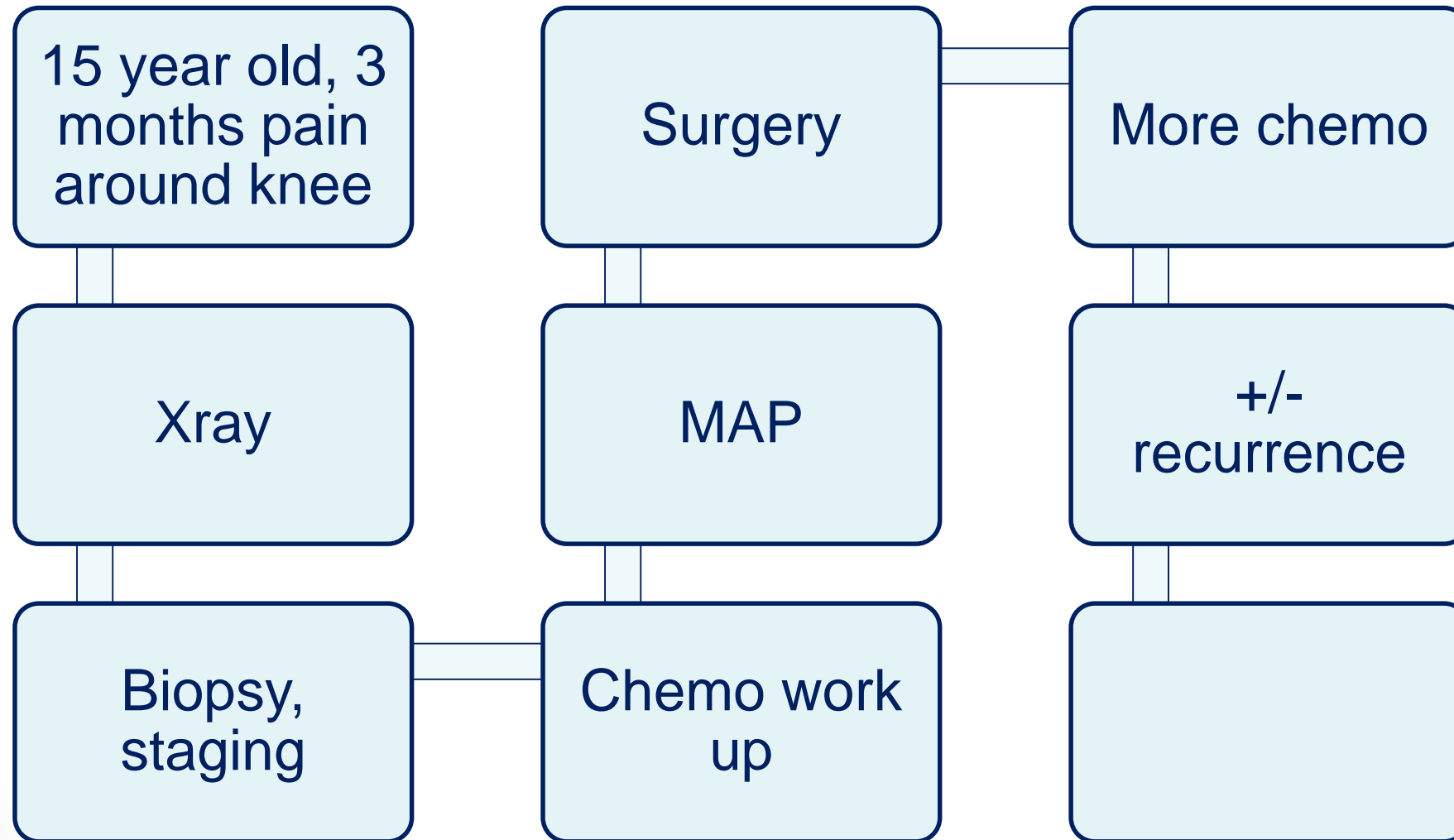


# Pelvic osteosarcoma

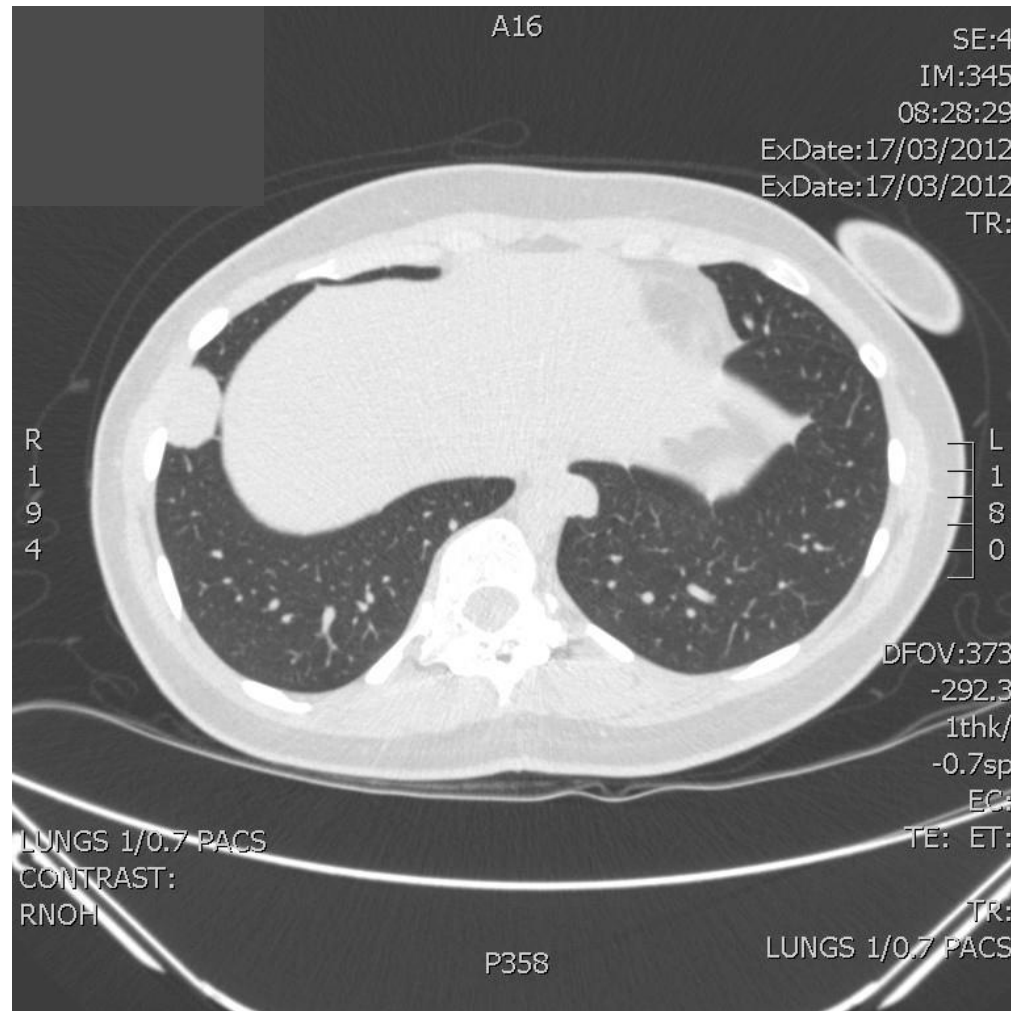




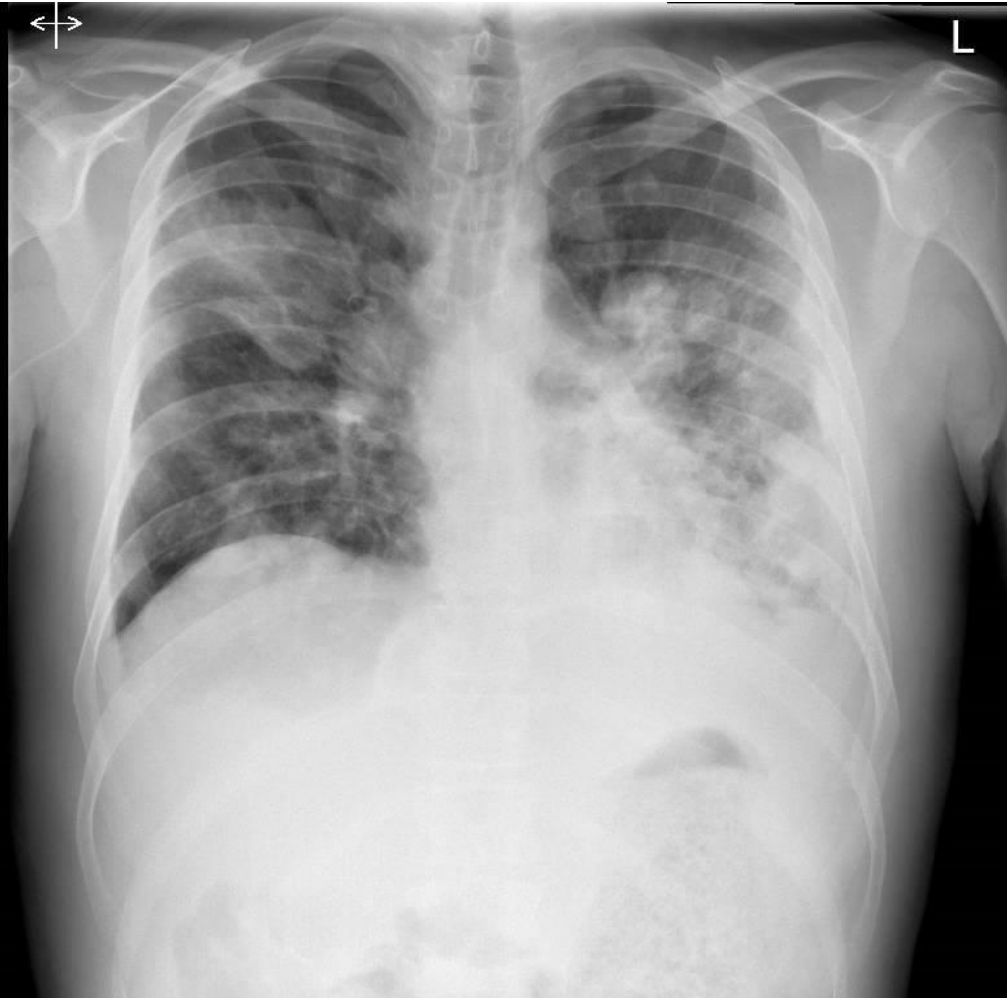
# Osteosarcoma







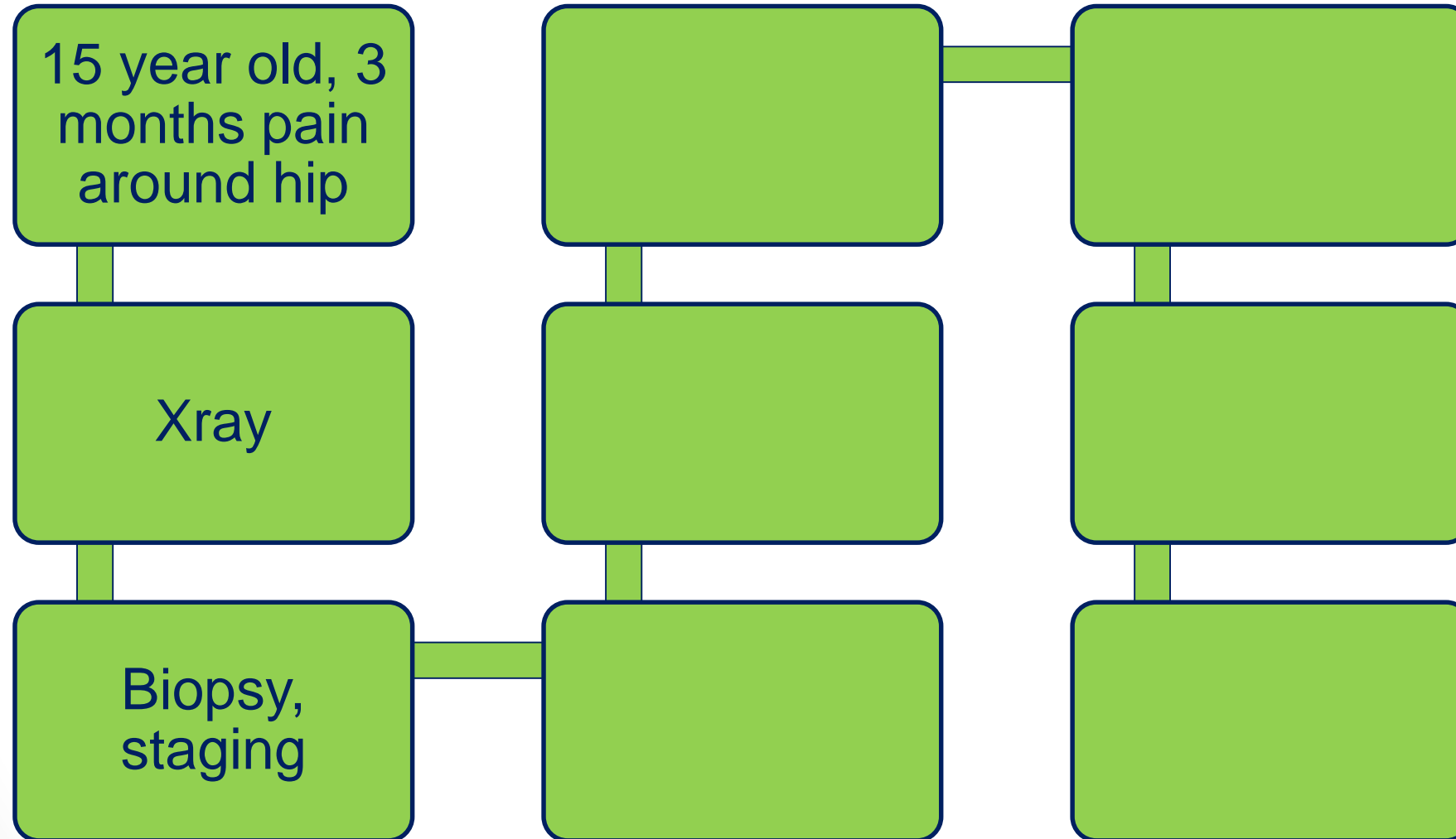
SULLIVAN, Samuel Mr (Mr),41498187  
Acc: 60091252  
Study Desc: Chest AP/PA  
Series Desc: W033 Chest p.a.  
2 - 1 (ALL)  
Lossy (1:23)



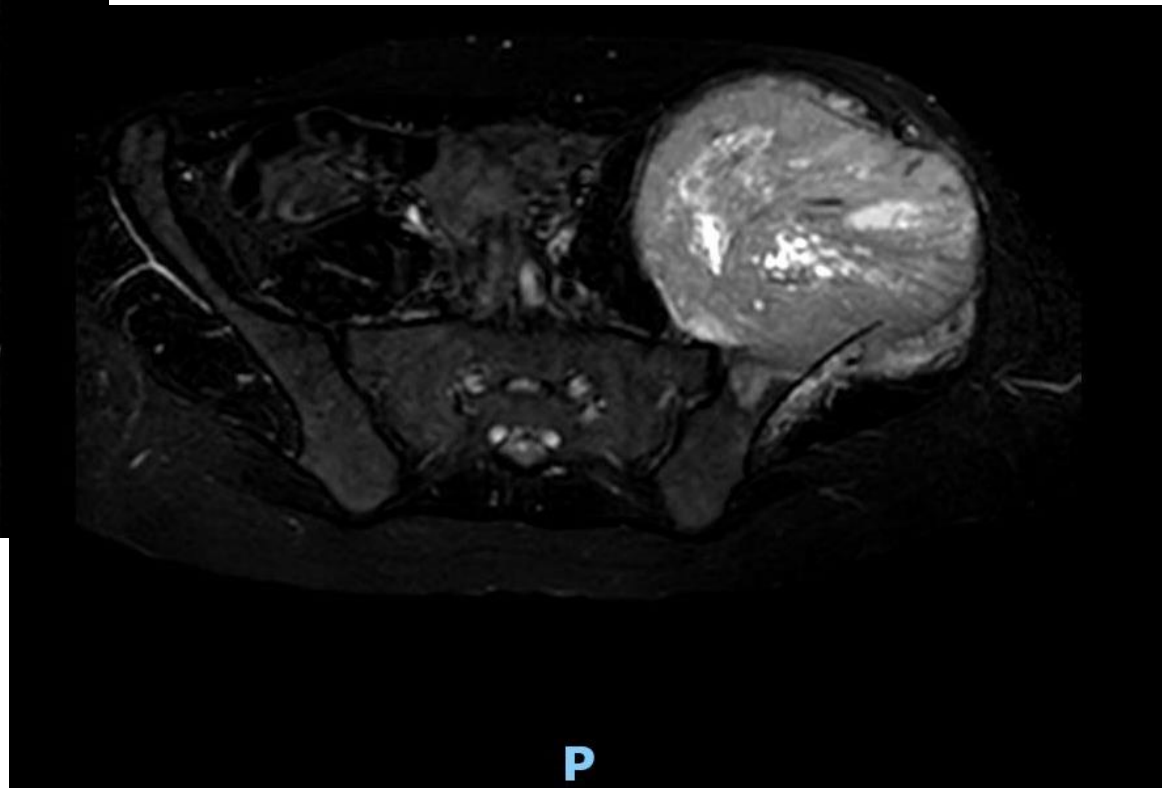
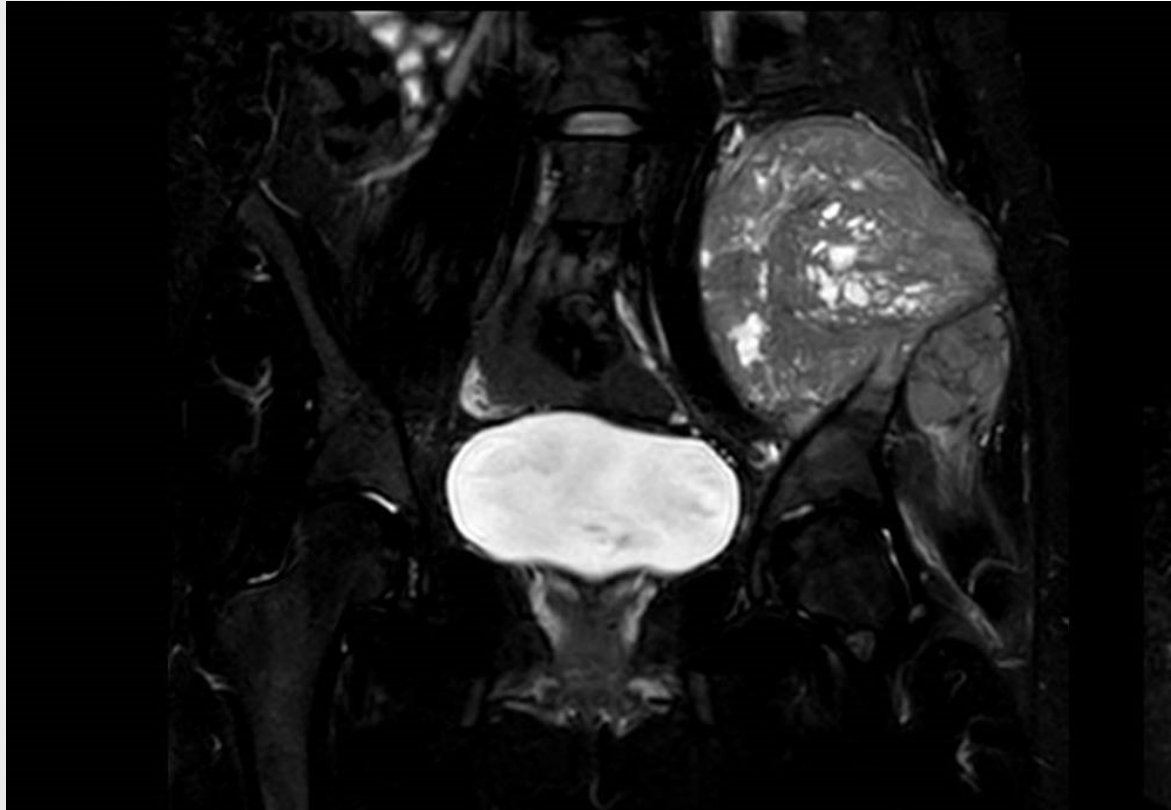
22 May 2018 15:10:17  
University College Hospital  
C:1722 W:3284  
Zoom: 27%



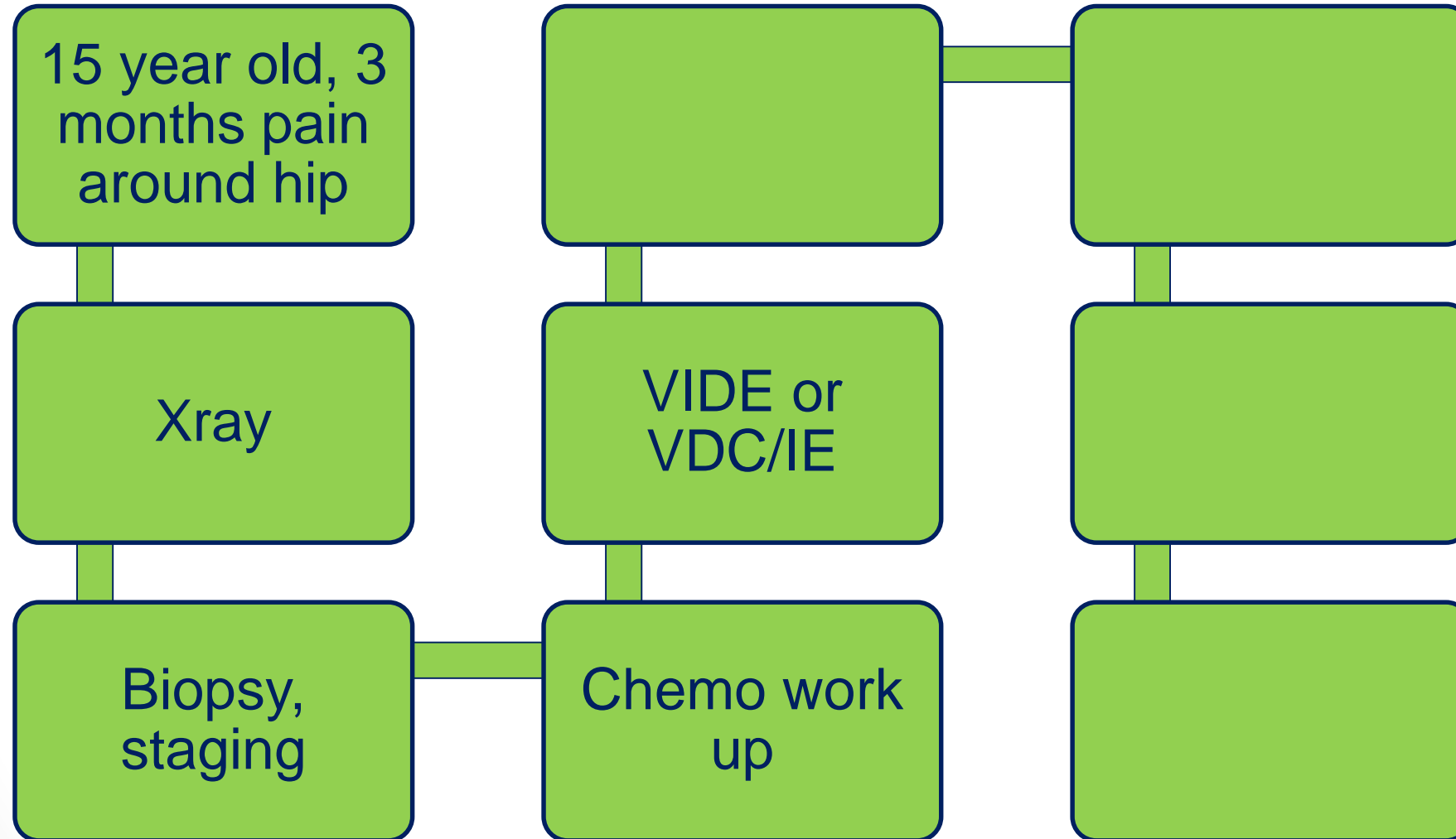
# Ewing sarcoma



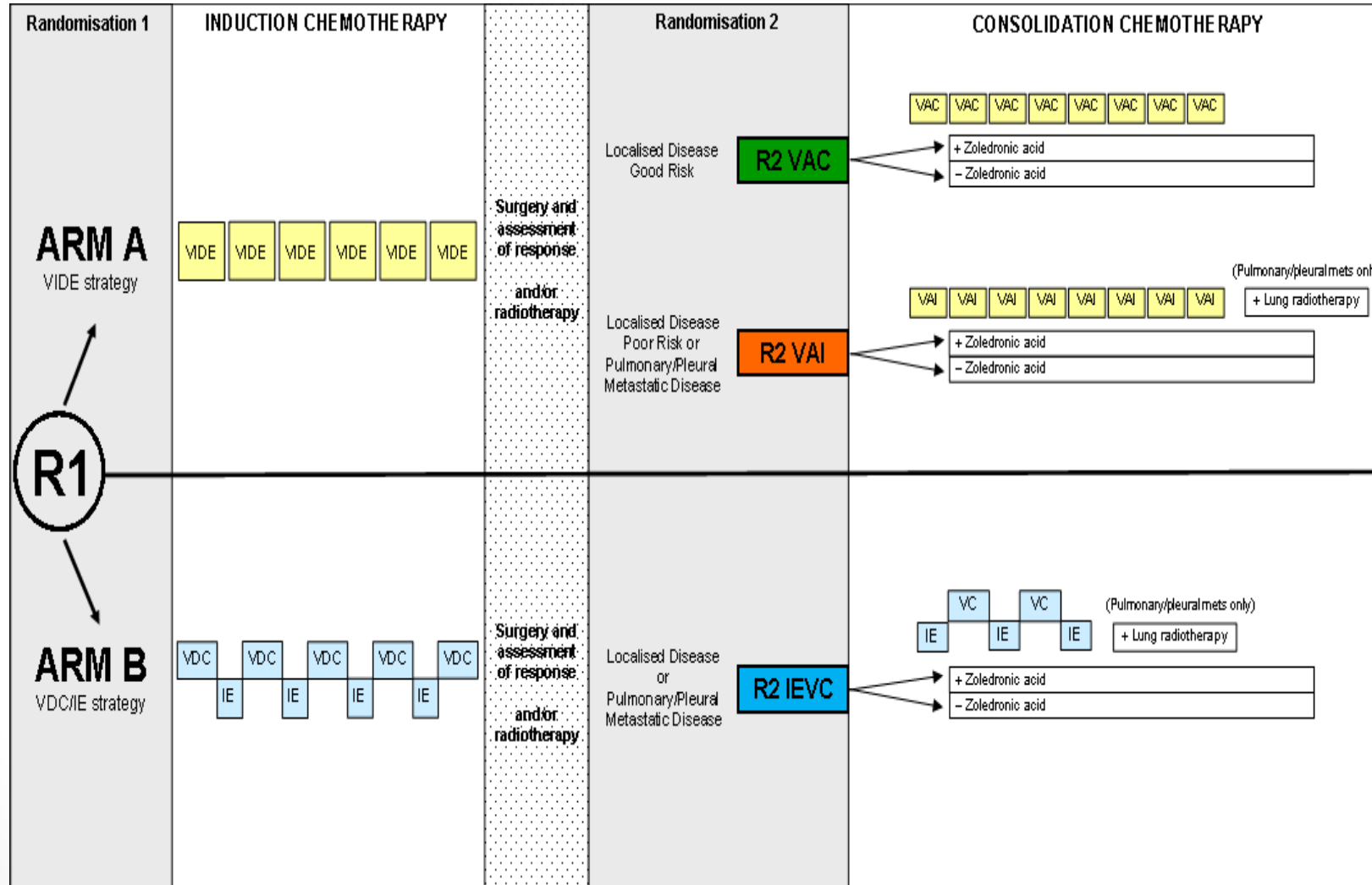
# Ewing sarcoma



# Ewing sarcoma



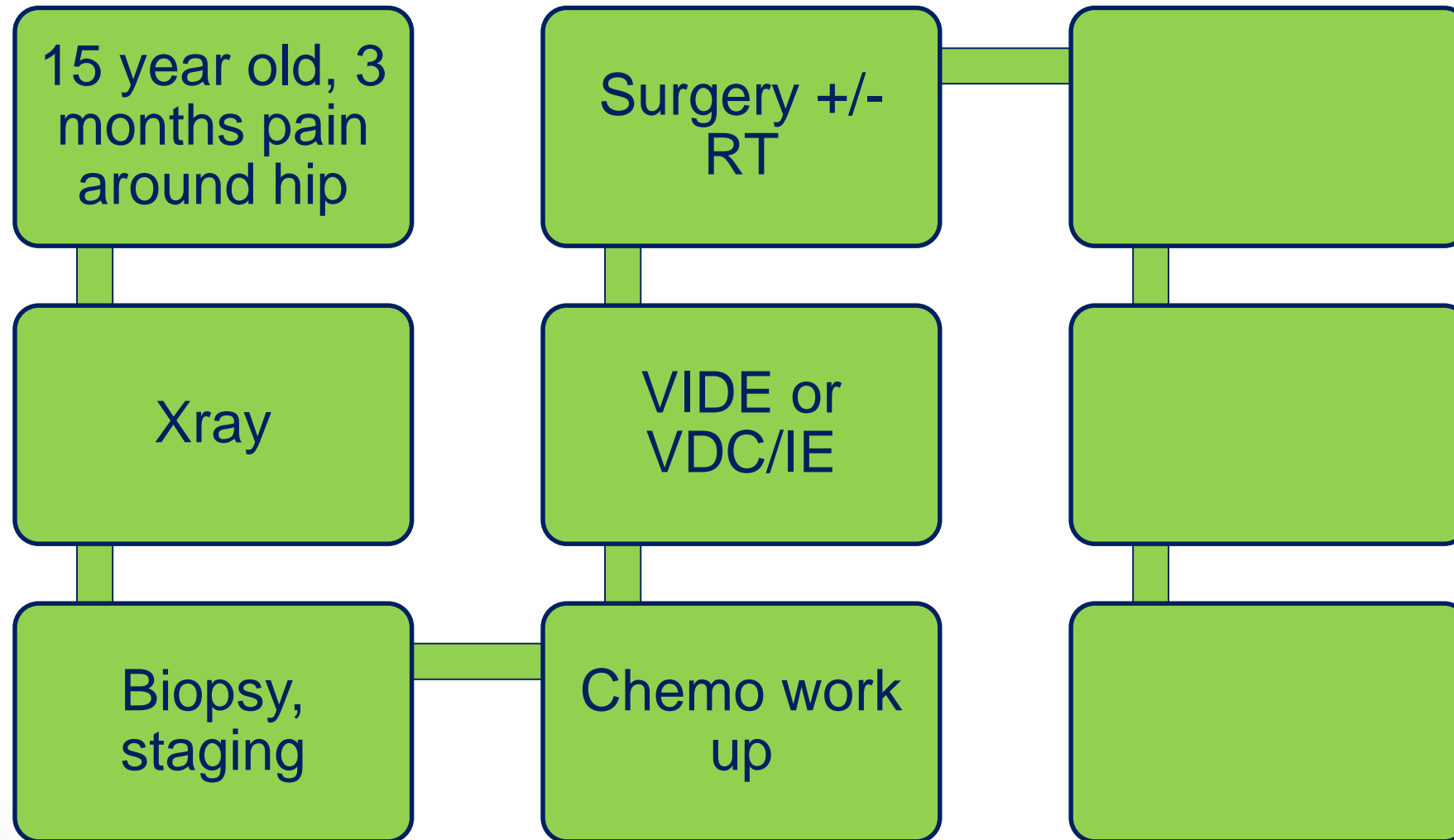
# EURO EWING 2012



**VDE** Vincristine, Ifosfamide, Doxorubicin, Etoposide  
**VDC** Vincristine, Doxorubicin, Cyclophosphamide  
**IE** Ifosfamide, Etoposide

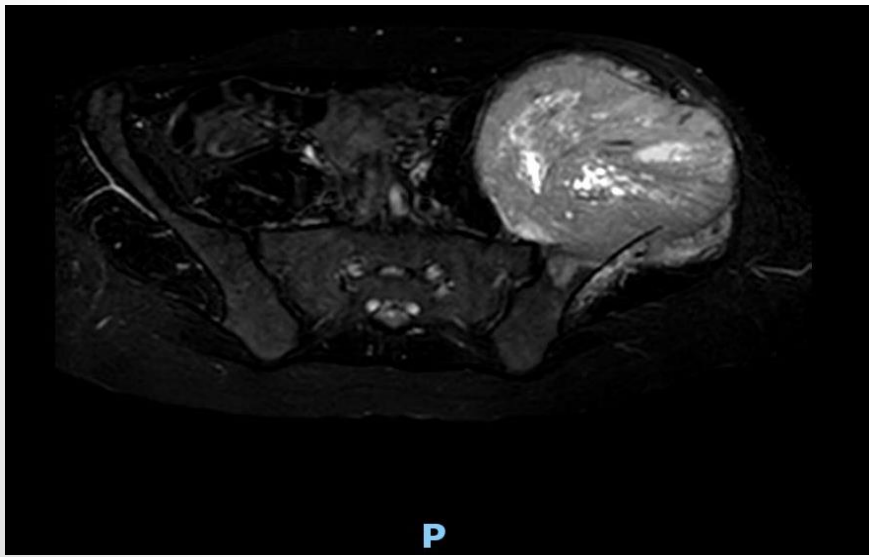
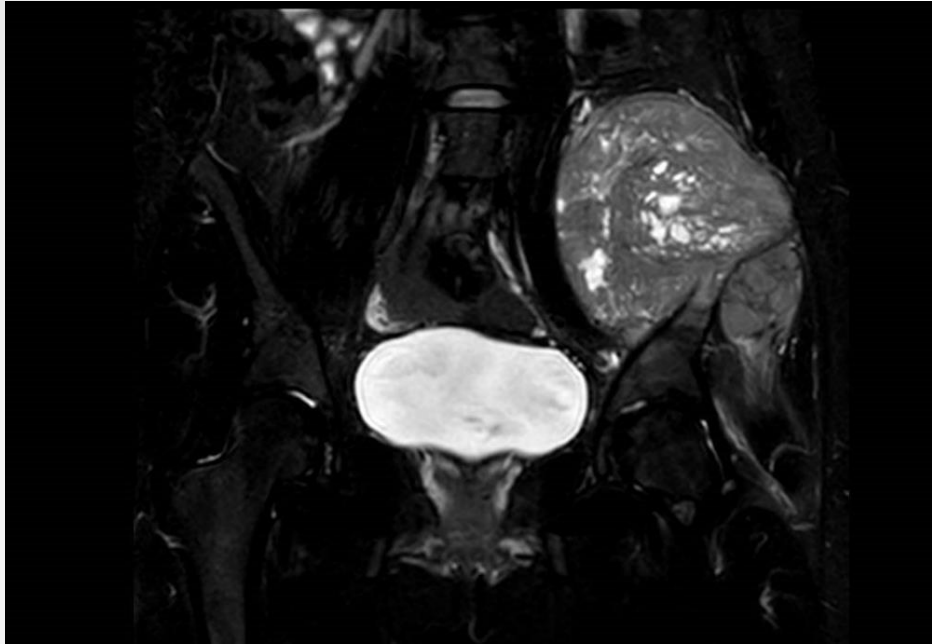
**VAI** Vincristine, Actinomycin D, Ifosfamide  
**VAC** Vincristine, Actinomycin D, Cyclophosphamide  
**IE** Ifosfamide, Etoposide  
**VC** Vincristine, Cyclophosphamide

# Ewing sarcoma

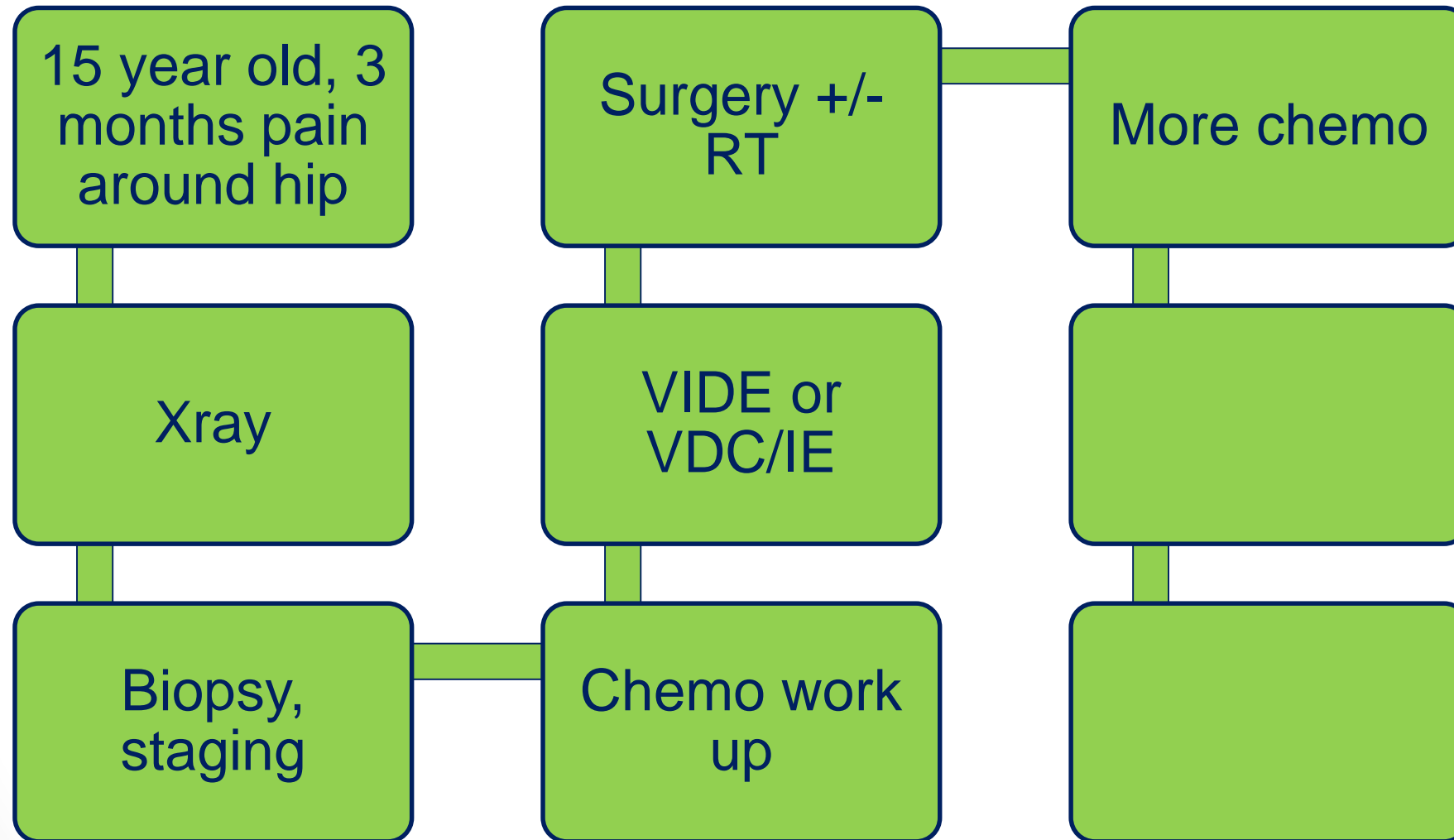




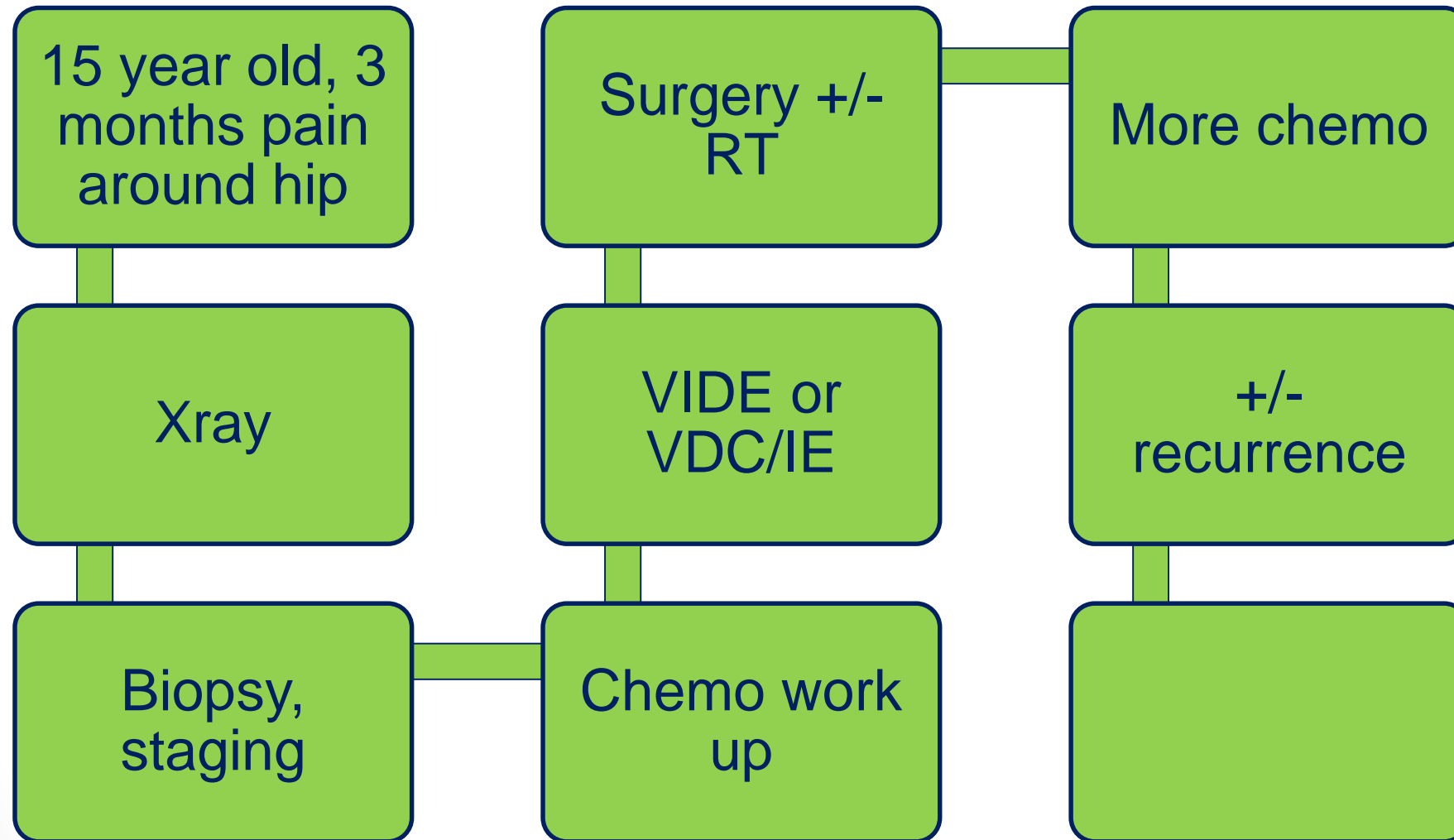
# Ewing sarcoma, pelvis



# Ewing sarcoma



# Ewing sarcoma





# rEECCur

The London Sarcoma Service



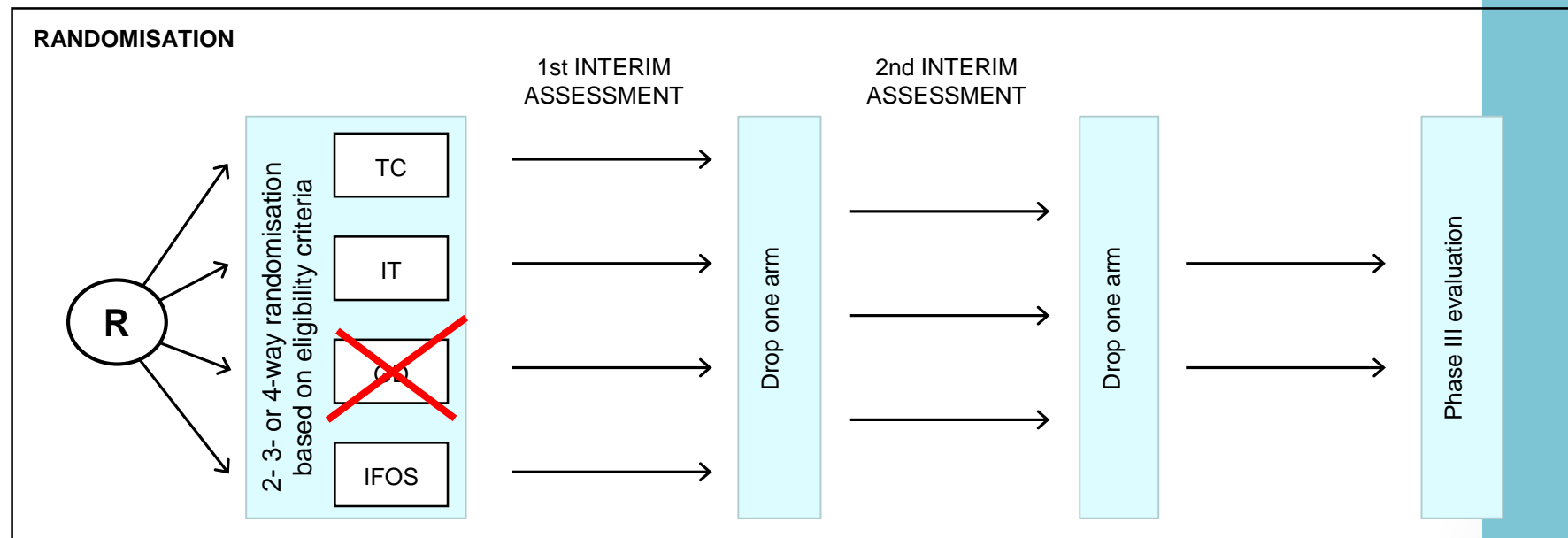
## International Randomised Controlled Trial of Chemotherapy for the Treatment of Recurrent and Primary Refractory Ewing Sarcoma

To compare four chemotherapy regimens in recurrent/ refractory ES to identify the best for use as a *backbone* in future treatment with respect to:

*Efficacy*

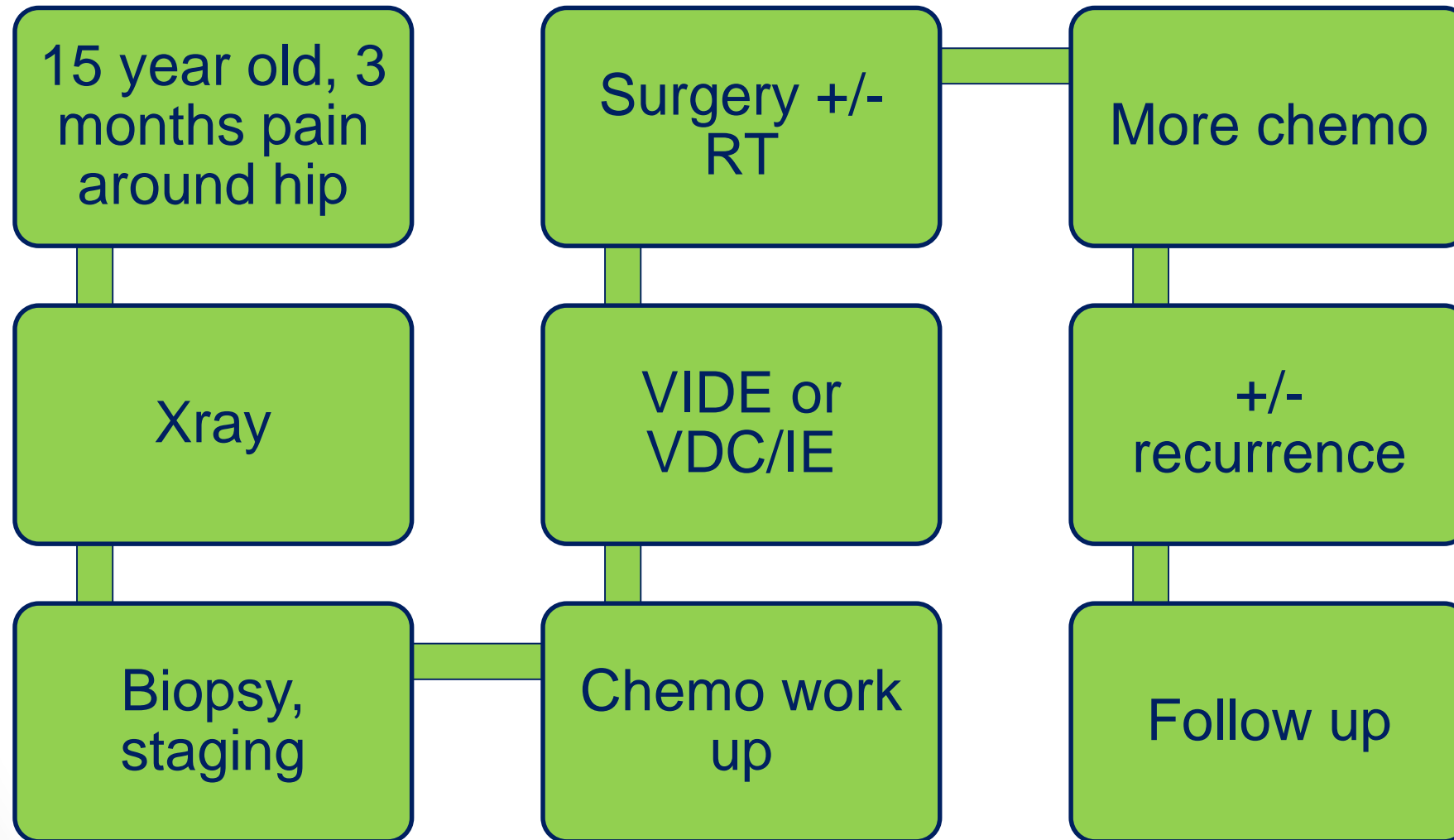
*Toxicity*

*Acceptability to patients*



- Recruitment
- Phase II – at minimum of 275 patients
- Phase III – a target of at least 400 patients
- 525 patients in total

# Ewing sarcoma





# Other bone sarcoma scenarios

- Different ages
- Different sites

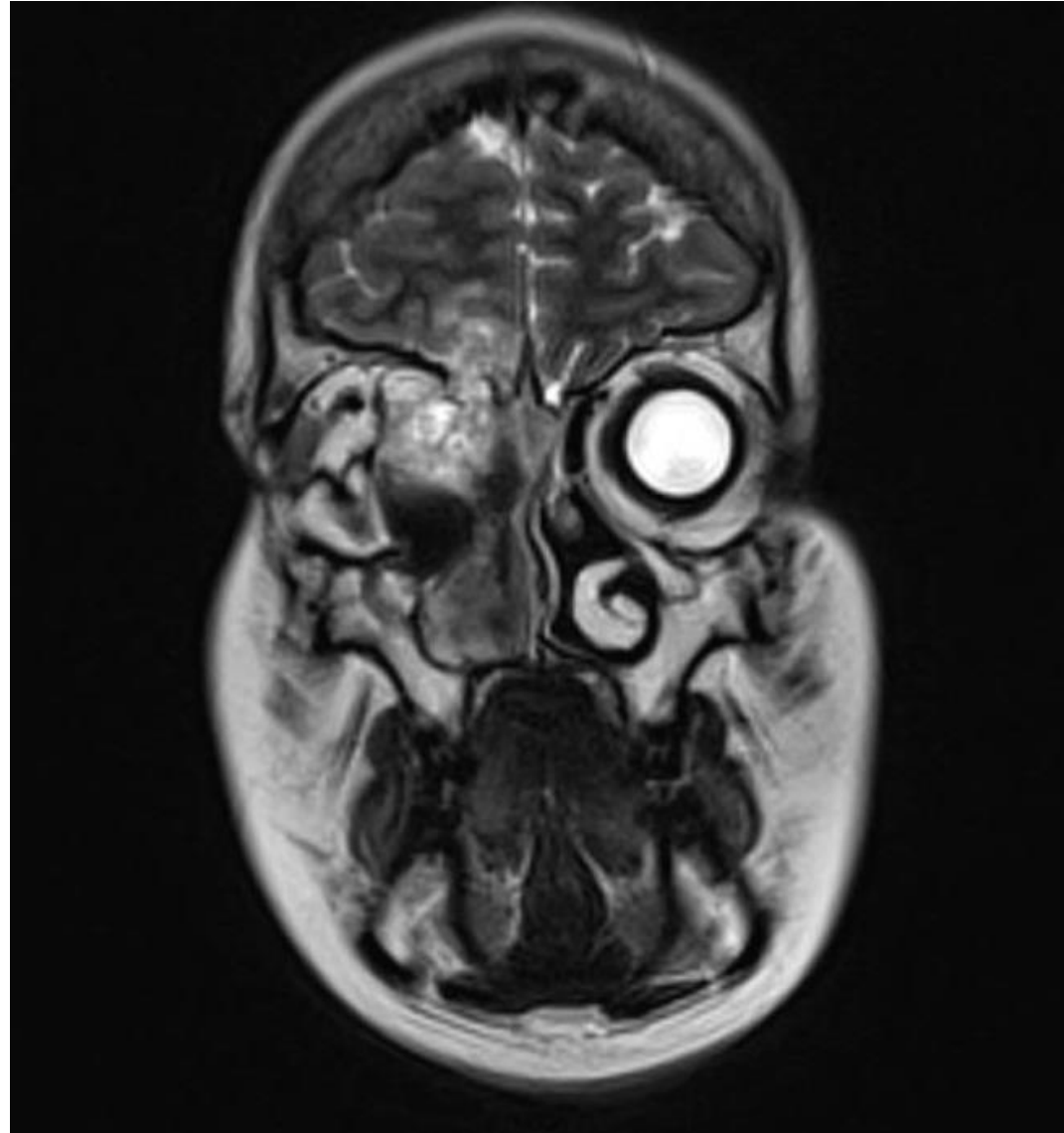






# Other things

- Different ages
- Different sites
- Secondary osteosarcoma

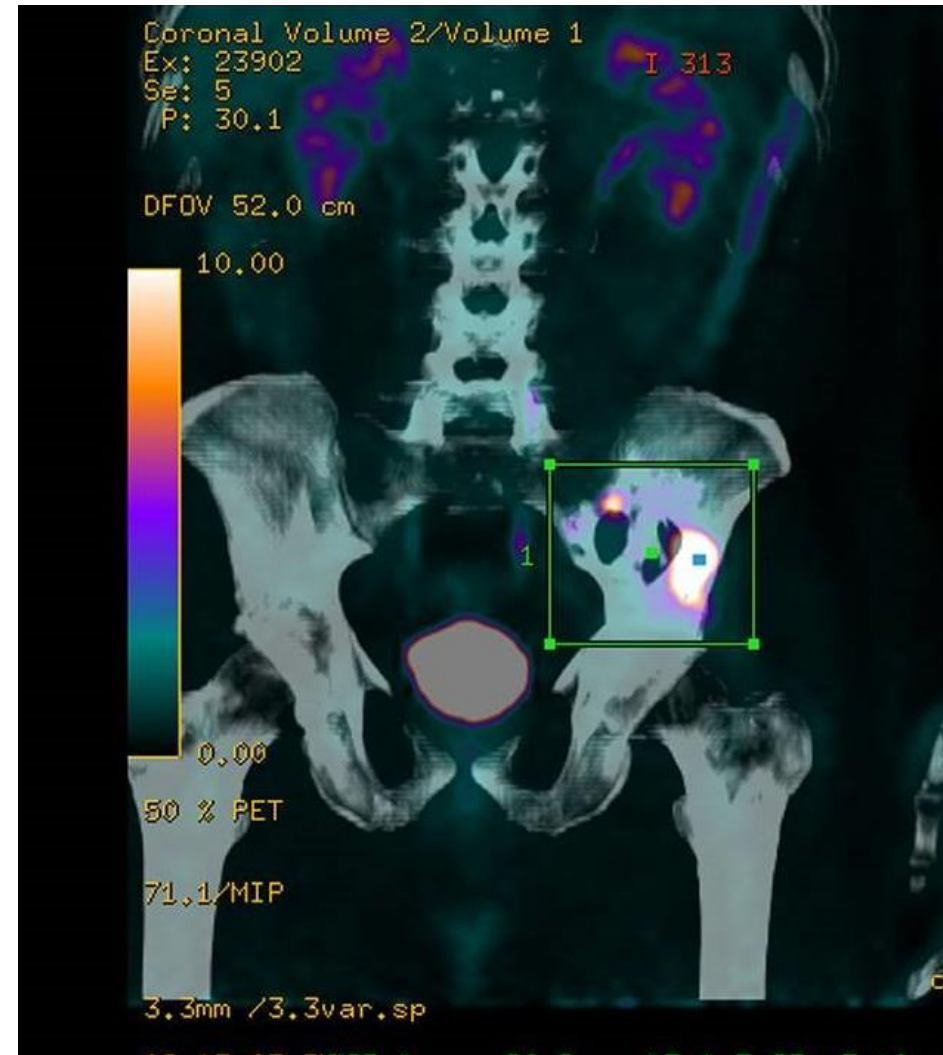


# Other things

- Different ages
- Different sites
- Secondary osteosarcoma
- Approaches to surgery
- Approaches to radiotherapy

# Other things

- Different ages
- Different sites
- Secondary osteosarcoma
- Approaches to surgery
- Approaches to radiotherapy
- PET



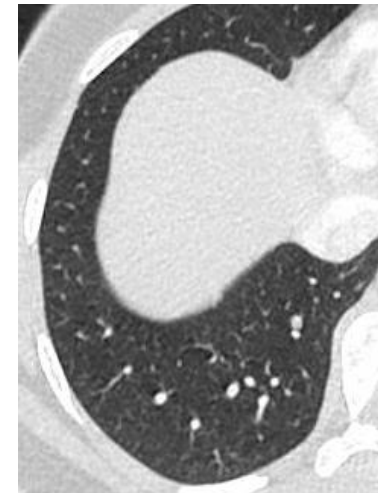
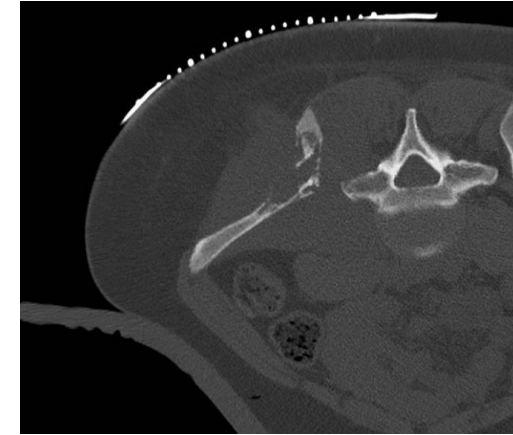
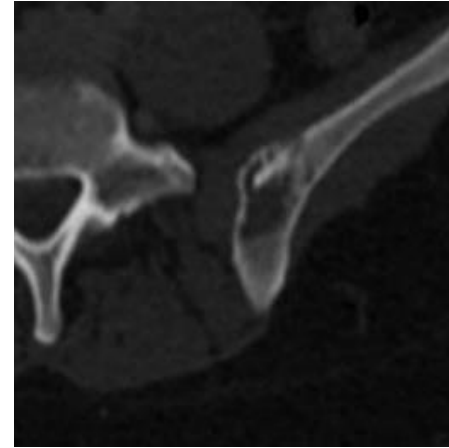
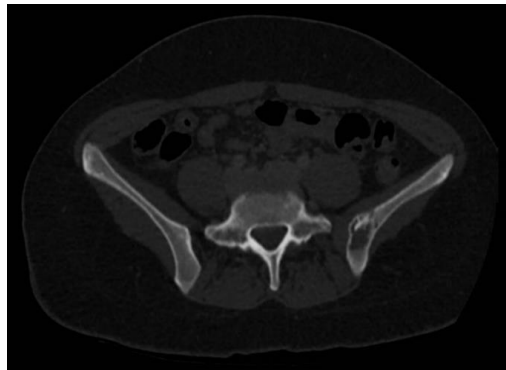
# Other things

- Different ages
- Different sites
- Secondary osteosarcoma
- Approaches to surgery
- Approaches to radiotherapy
- PET
- High dose chemotherapy

# Other things

- Different ages
- Different sites
- Secondary osteosarcoma
- Approaches to surgery
- Approaches to radiotherapy
- PET
- Time to diagnosis

Ewing sarcoma left ilium – symptoms for 1 year. Episode of pyelonephritis 8.5 months before diagnosis



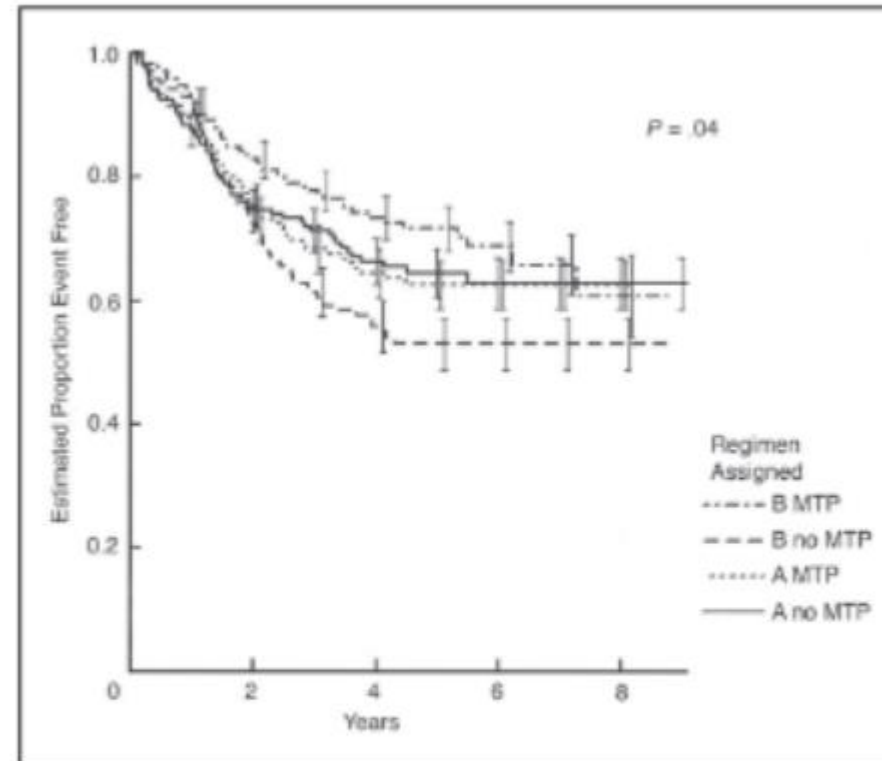
# Other things

- Different ages
- Different sites
- Secondary osteosarcoma
- Approaches to surgery
- Approaches to radiotherapy
- PET
- Time to diagnosis
- Second malignancies

# Research networks and collaborations

# Catalysts to collaborative efforts in osteosarcoma

- Survival not improving
- Study groups at an impasse

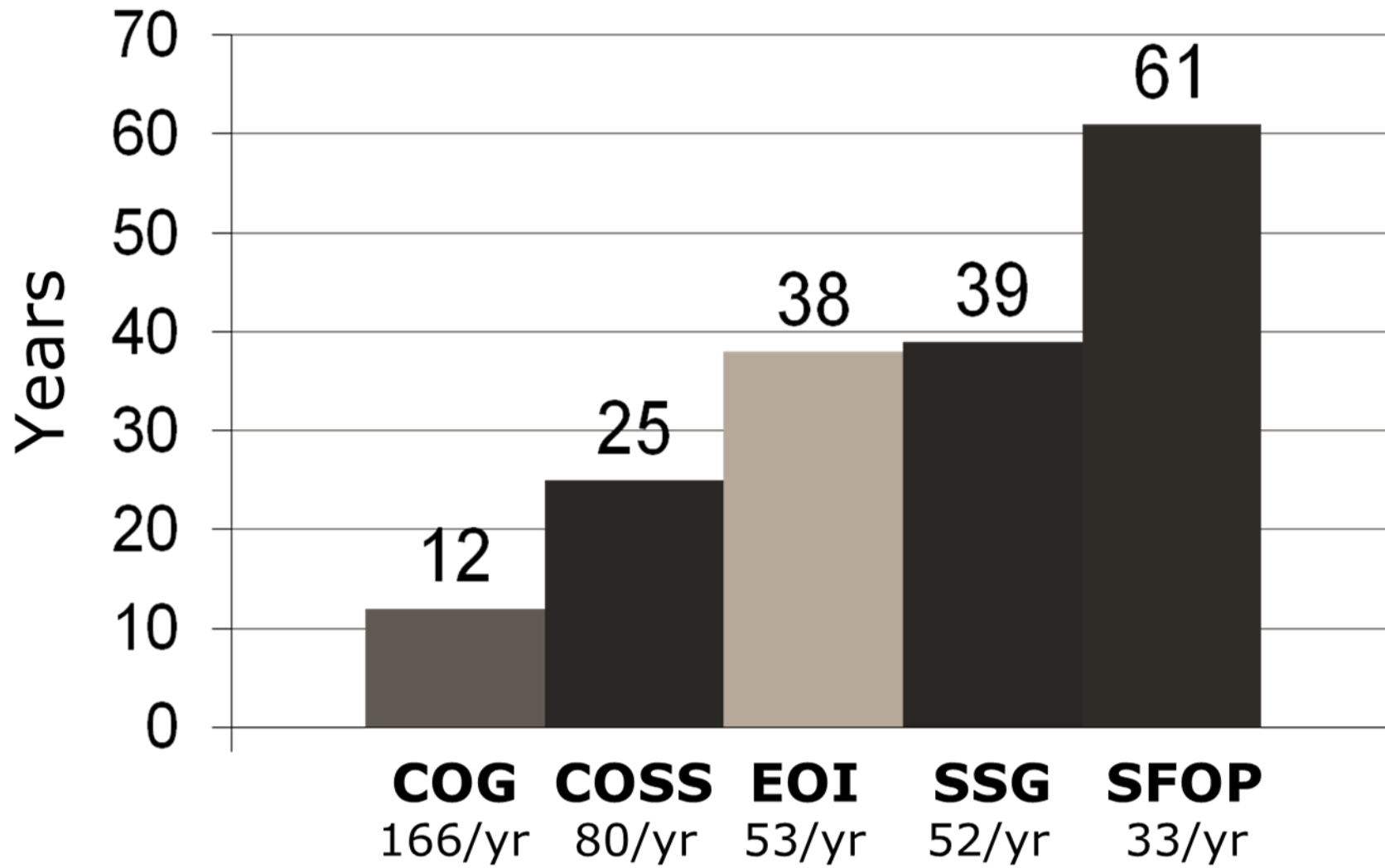


**Fig 4.** Event-free survival for patients according to treatment arm. Regimen A consisting of cisplatin, doxorubicin, and high-dose methotrexate was the standard arm of this study. Regimen B included the same agents with the addition of ifosfamide. Regimens A+ and B+ also included the investigational agent muramyl tripeptide (MTP). Overall trend for difference was significant ( $P = .04$ ).



# Accrual to 2,000 pts at previous rates

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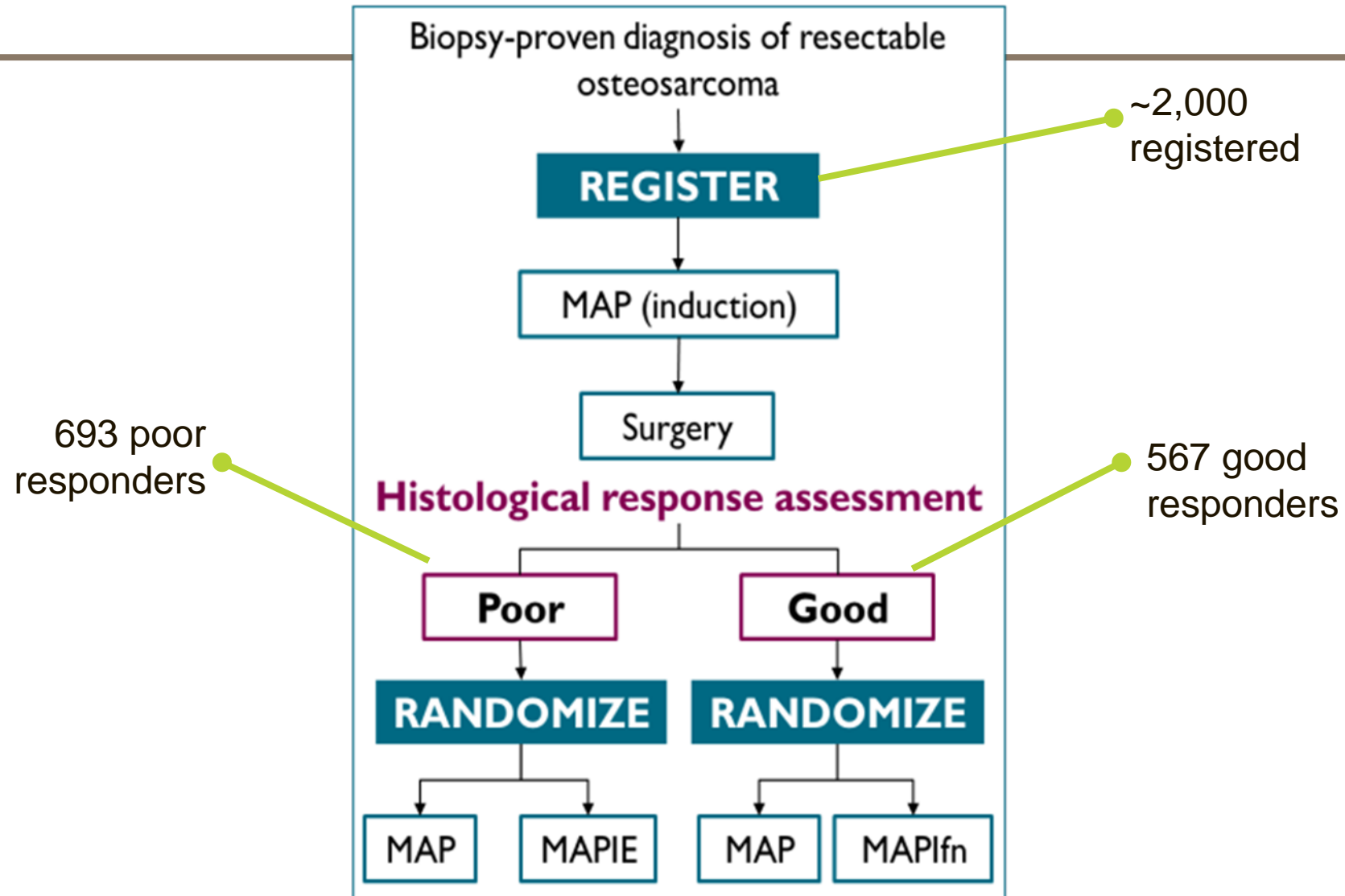


# European and American Osteosarcoma Study Group

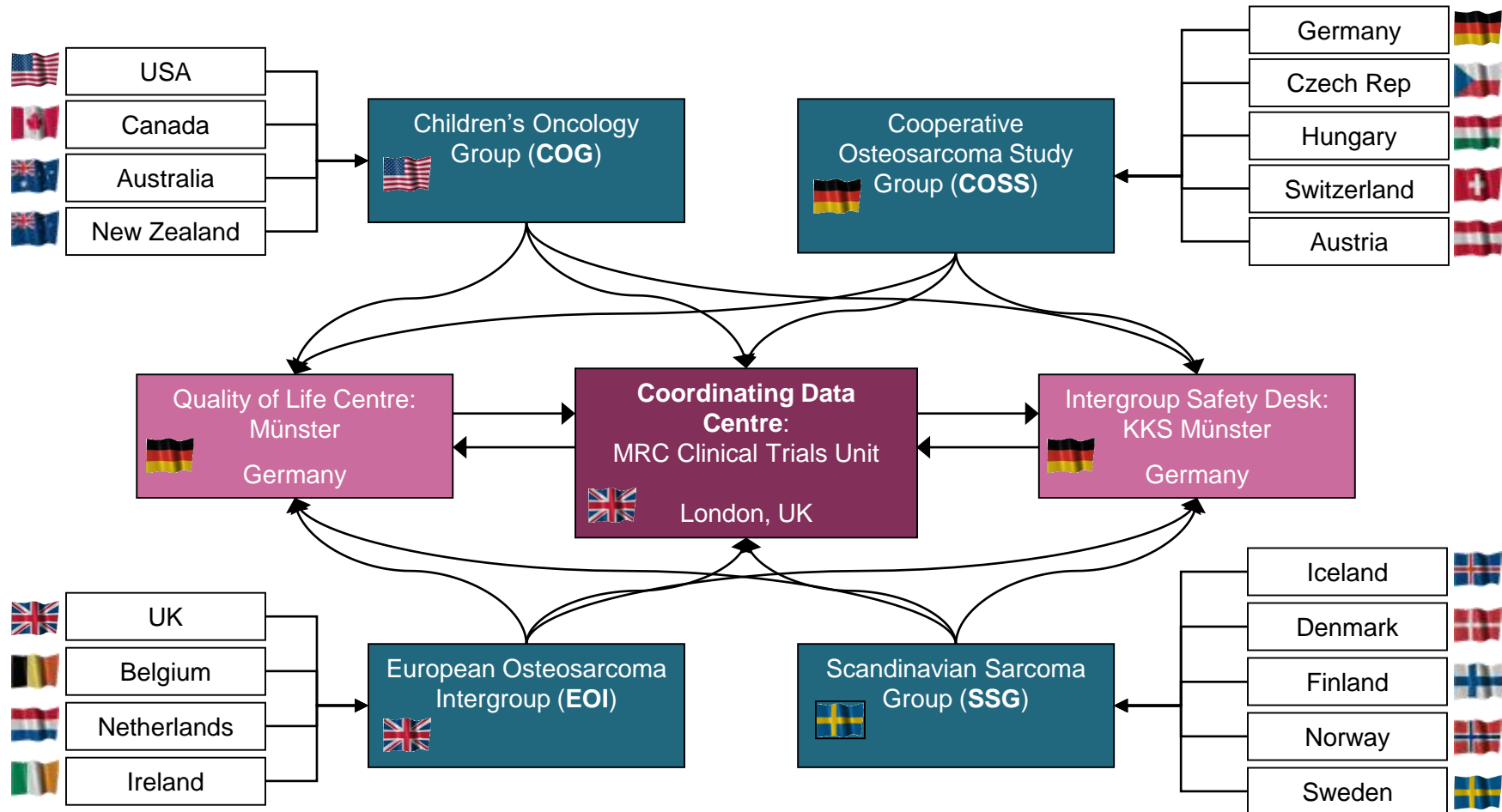
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- **Established Oct 2001**
- **Participating groups - COSS, COG, EOI, SSG**
- ***Aim***
  - **to improve survival from OS**
- ***Objectives***
  - **to carry out large international randomised trials**
  - **to facilitate biological research**
  - **to seek new therapeutic approaches**
  - **to develop common understanding and methodologies for staging, pathology etc.**

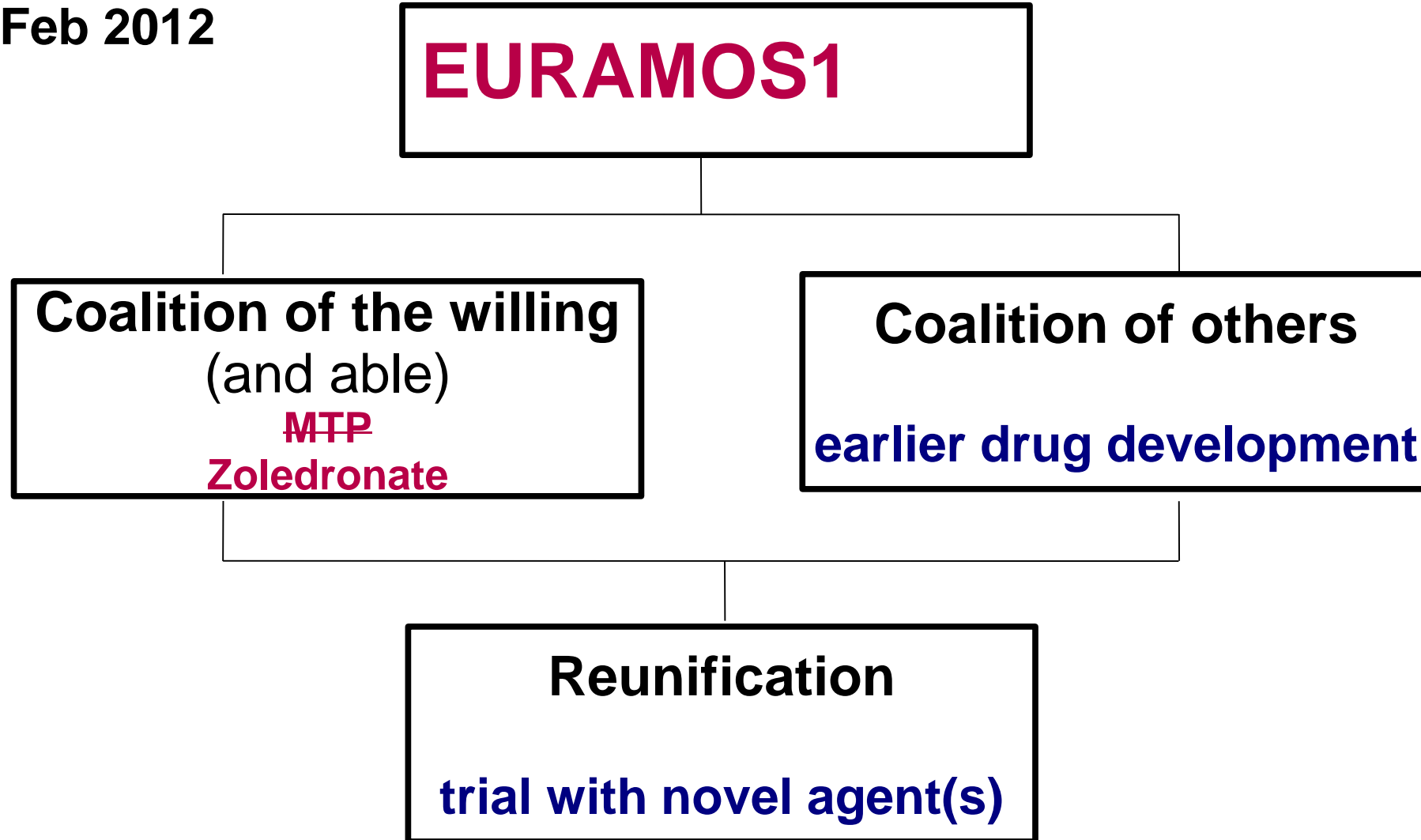
# EURAMOS-1 Trial Design



# Trial set-up



**2nd International Meeting on Future Clinical Trials  
for the Adjuvant Treatment of Osteosarcoma:  
Creating a Strategic Consensus** **London**  
**Feb 2012**



## Challenges to collaboration

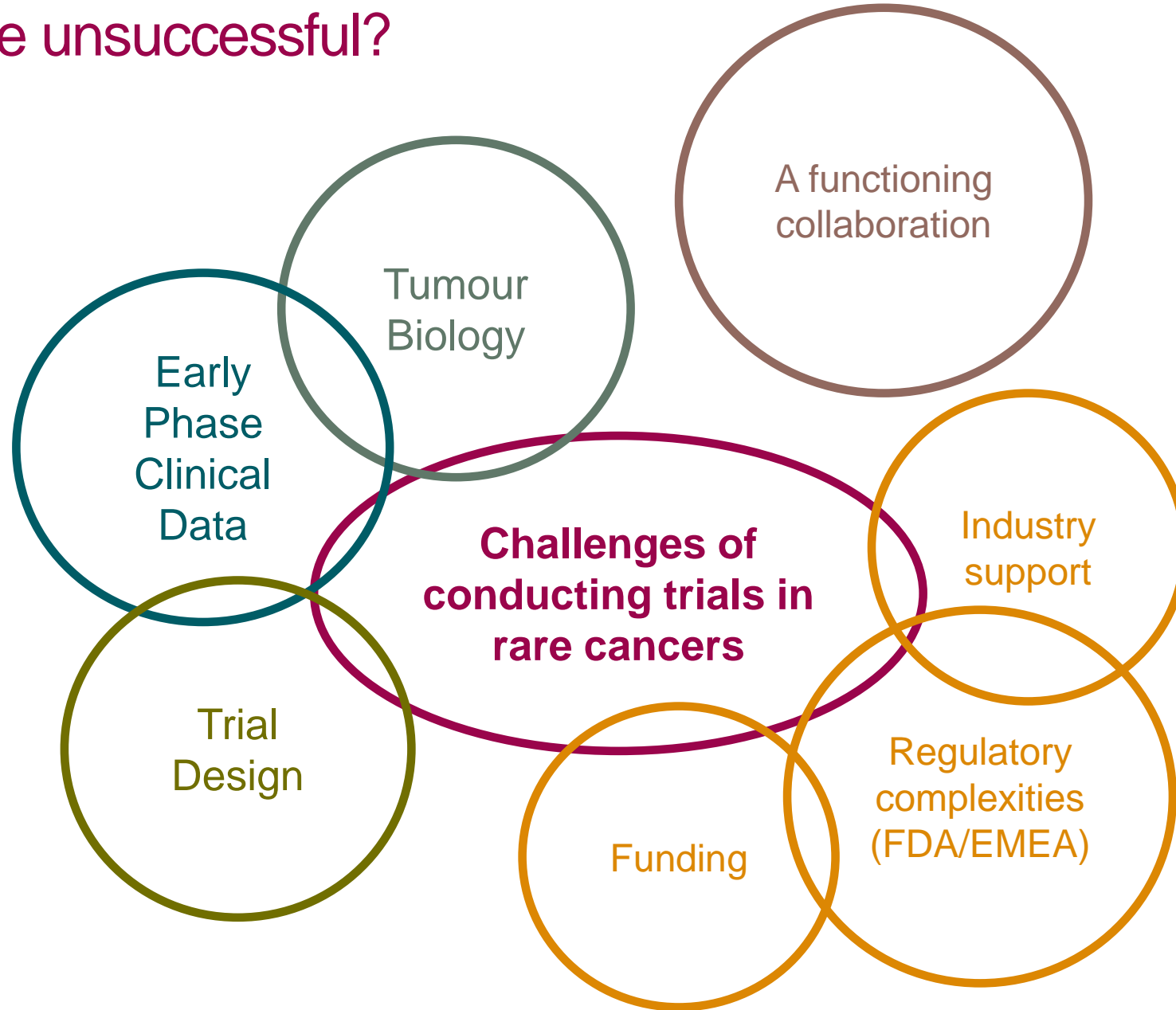
### **Clinical and personal**

- Differing practices: pragmatism and compromise
- Buy-in and ownership
- Less recognition for principal investigators

### **Practical**

- Sponsorship
- Infrastructure requirements
- Differing regulations by jurisdiction
  - Knowledge
  - Local processes and national regulations
- Funding support
- Indemnity

# Why were we unsuccessful?





The primary goal of the EURO EWING consortium is to improve survival and other key patient outcomes from ewing sarcoma

**Through:**

- **Clinical trials**
- **Collaborative research**
- **Patient and carer advocacy**

48

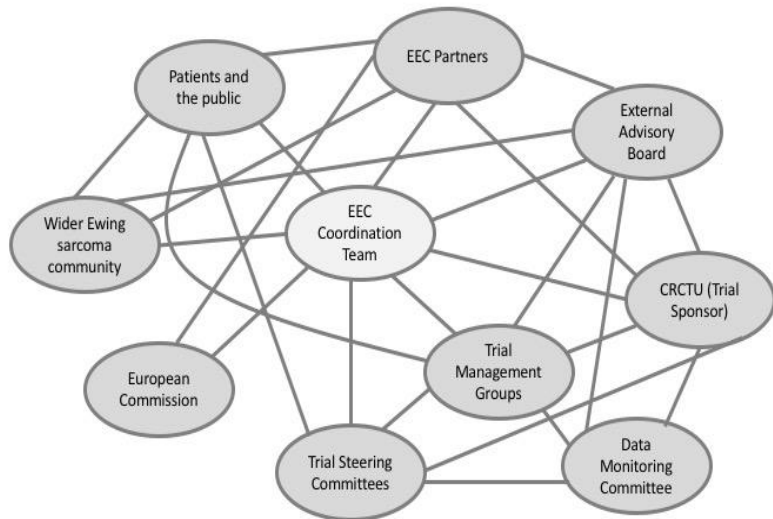
*This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602856.*



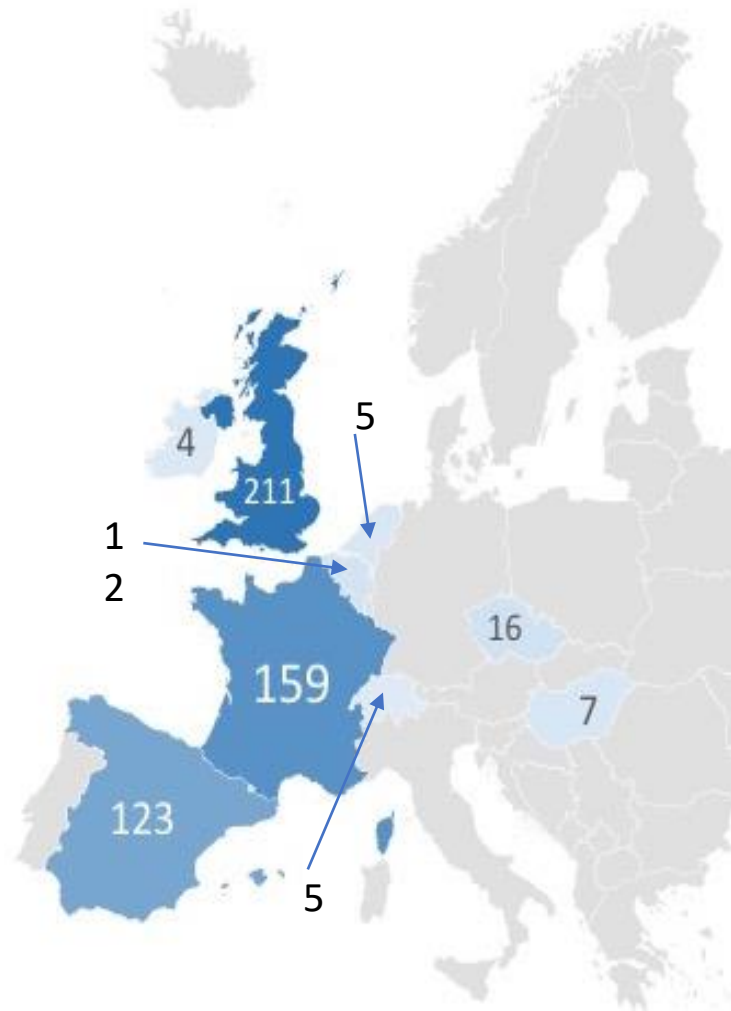
# EURO EWING CONSORTIUM

- FP7-HEALTH-2013-INNOVATION-1 Collaborative Project
- 2.4.1-1: Investigator-driven treatment trials to combat or prevent metastases in patients with solid cancer
- Total value €5.7 million over 5 years
- 20 Partner organisations across 9 European countries



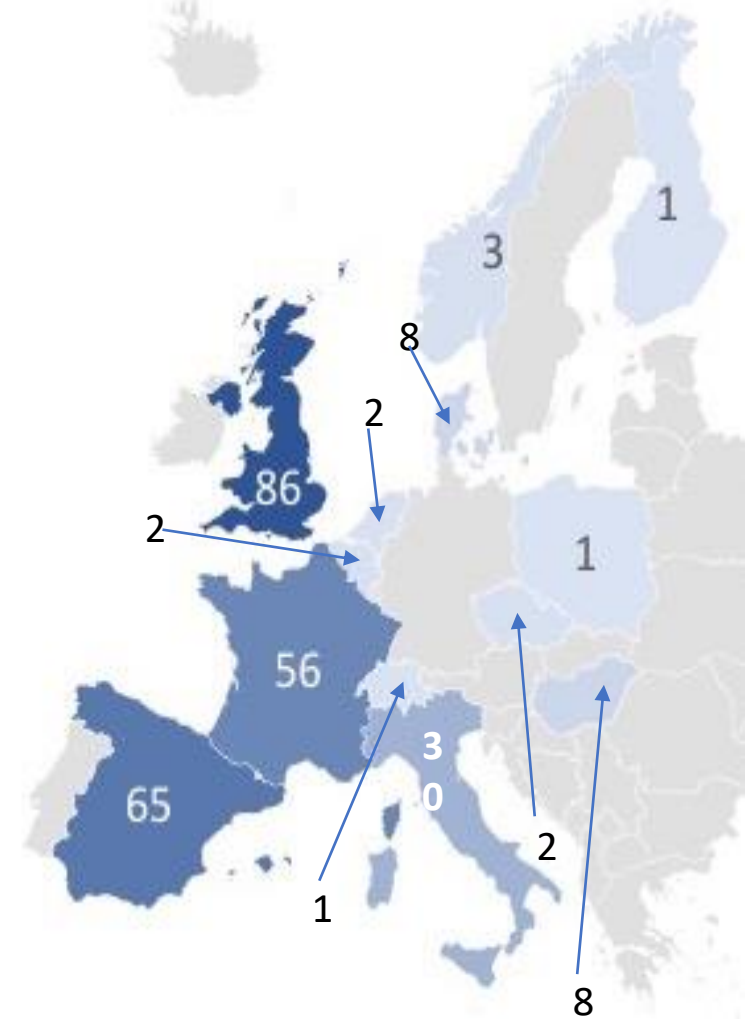






## EURO EWING 2012

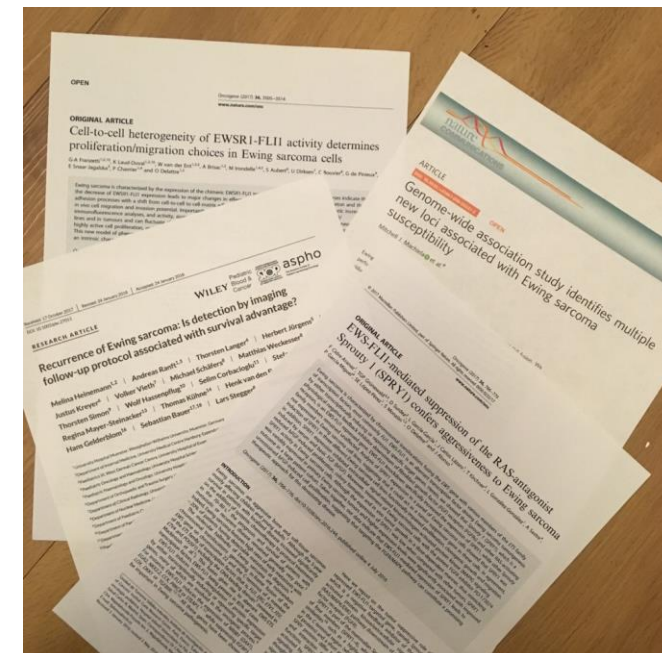


## rEECur

~ 900 randomised patients in 5 years



Biospecimen type	Number of samples/ TMAs
Fresh frozen tumour 	102
Formalin-fixed paraffin-embedded tumour 	237
Blood 	311
Tissue Microarray (TMA) 	106 cases on 3 TMAs







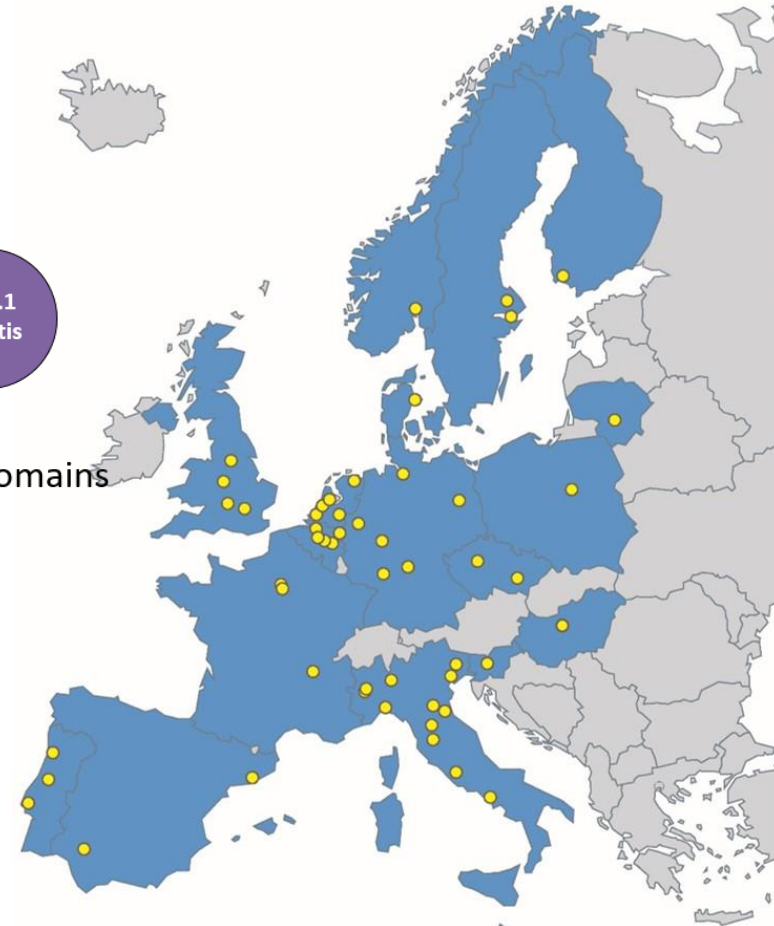
# European Reference Network

for rare or low prevalence complex diseases

Network  
Adult Cancers  
(ERN EURACAN)

Coordinator  
Centre Léon Bérard  
France

# ERN EURACAN



17 European countries

## RARE ADULT SOLID CANCERS

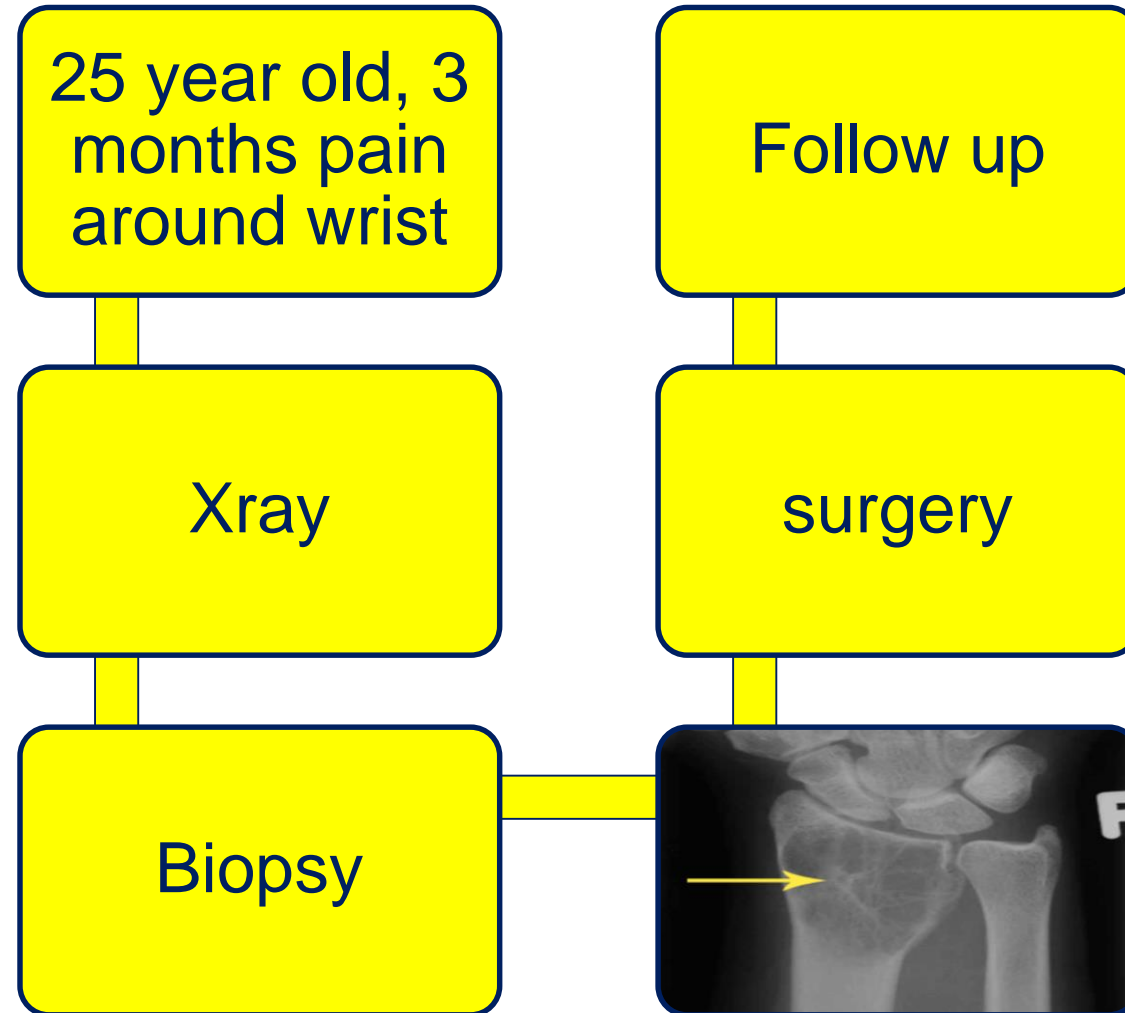
# Bone sarcomas – a summary

- Varied group of diseases, morbid in all, curable in some
- Uncommon
- Affect patients of all ages
- Complex treatments
- Specialist care essential
- Limited progress on improving standard of care
- Emerging new therapies – especially TKIs in OS and ES

# Questions?

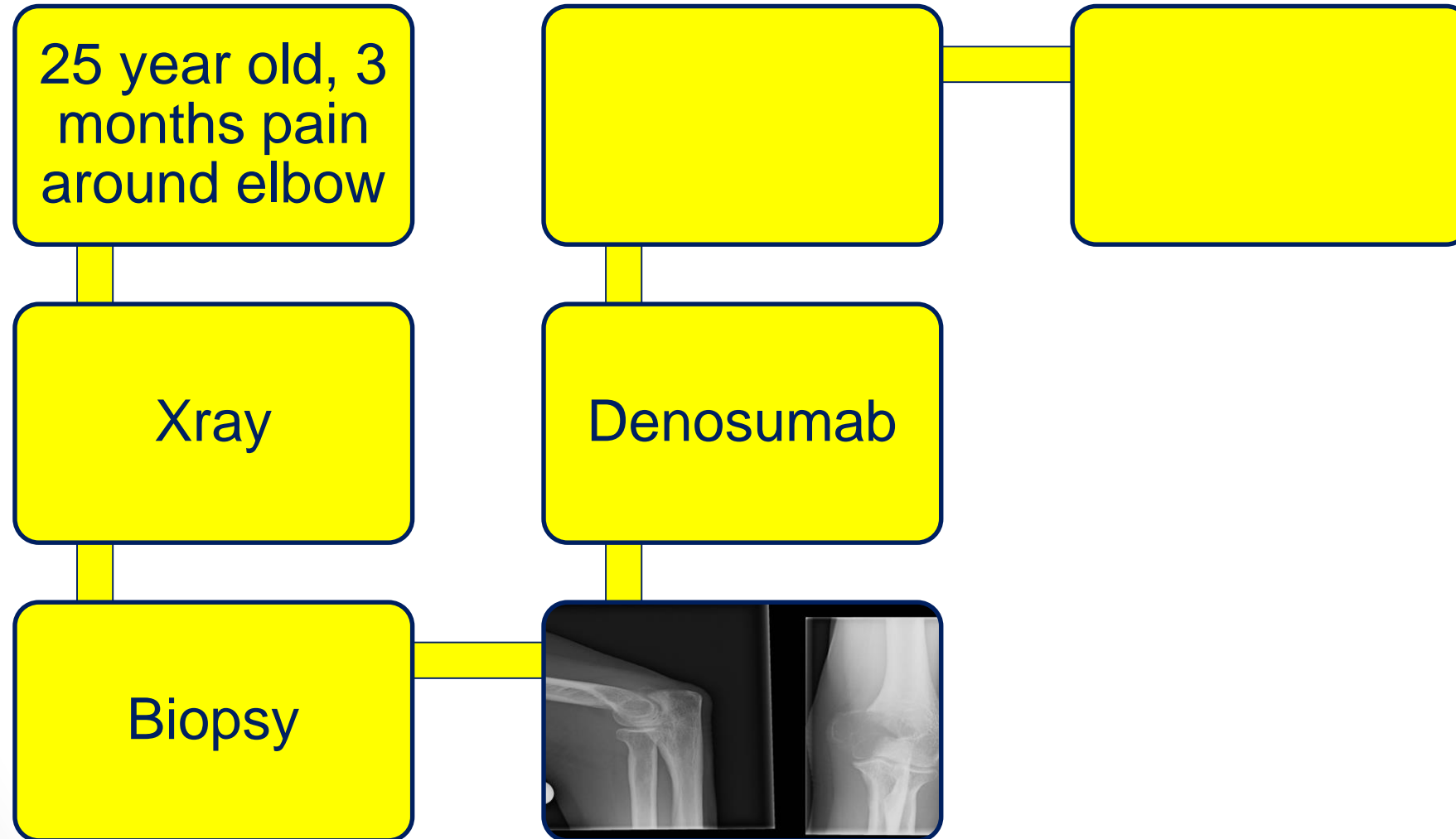
[Jeremy.Whelan@nhs.net](mailto:Jeremy.Whelan@nhs.net)

# Giant cell tumour of bone





# Giant cell tumour of bone





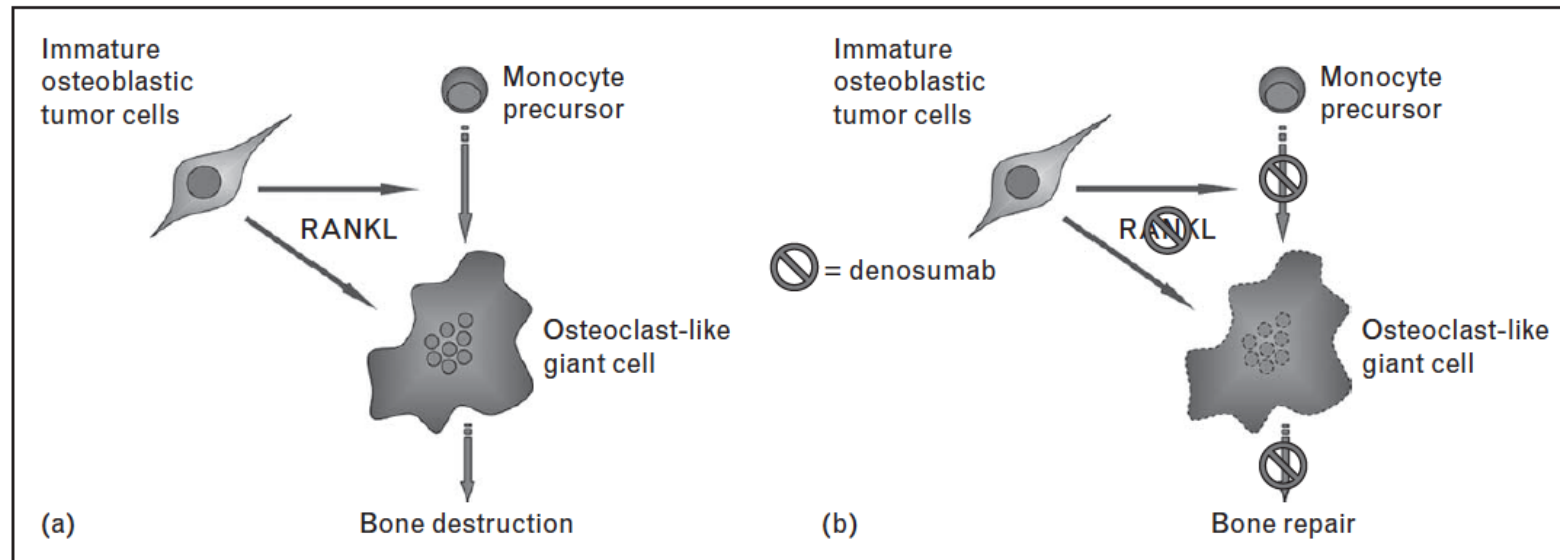
# Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study

Sant Chawla, Robert Henshaw, Leanne Seeger, Edwin Choy, Jean-Yves Blay, Stefano Ferrari, Judith Kroep, Robert Grimer, Peter Reichardt, Piotr Rutkowski, Scott Schuetze, Keith Skubitz, Arthur Staddon, David Thomas, Yi Qian, Ira Jacobs

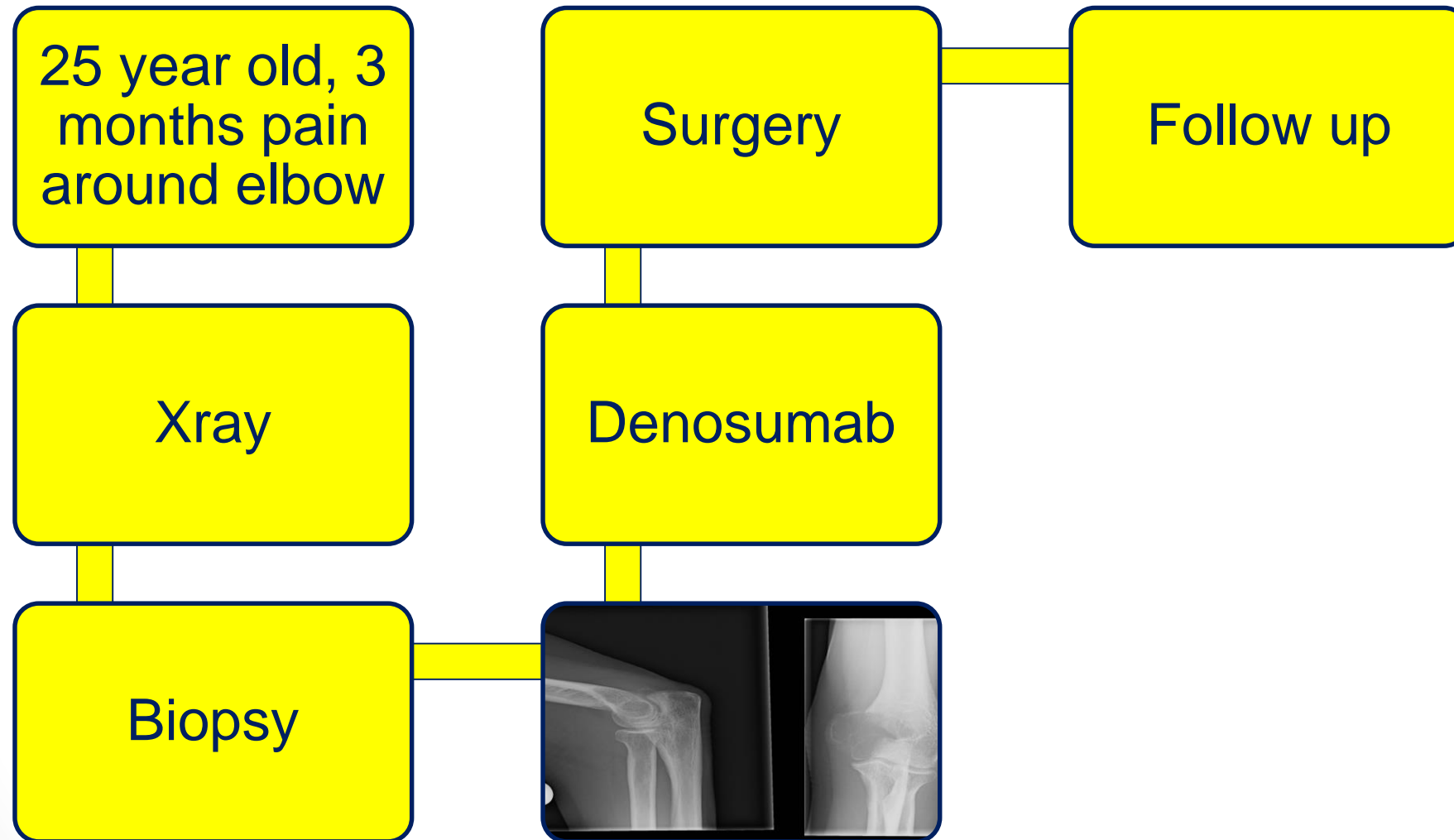
## Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study



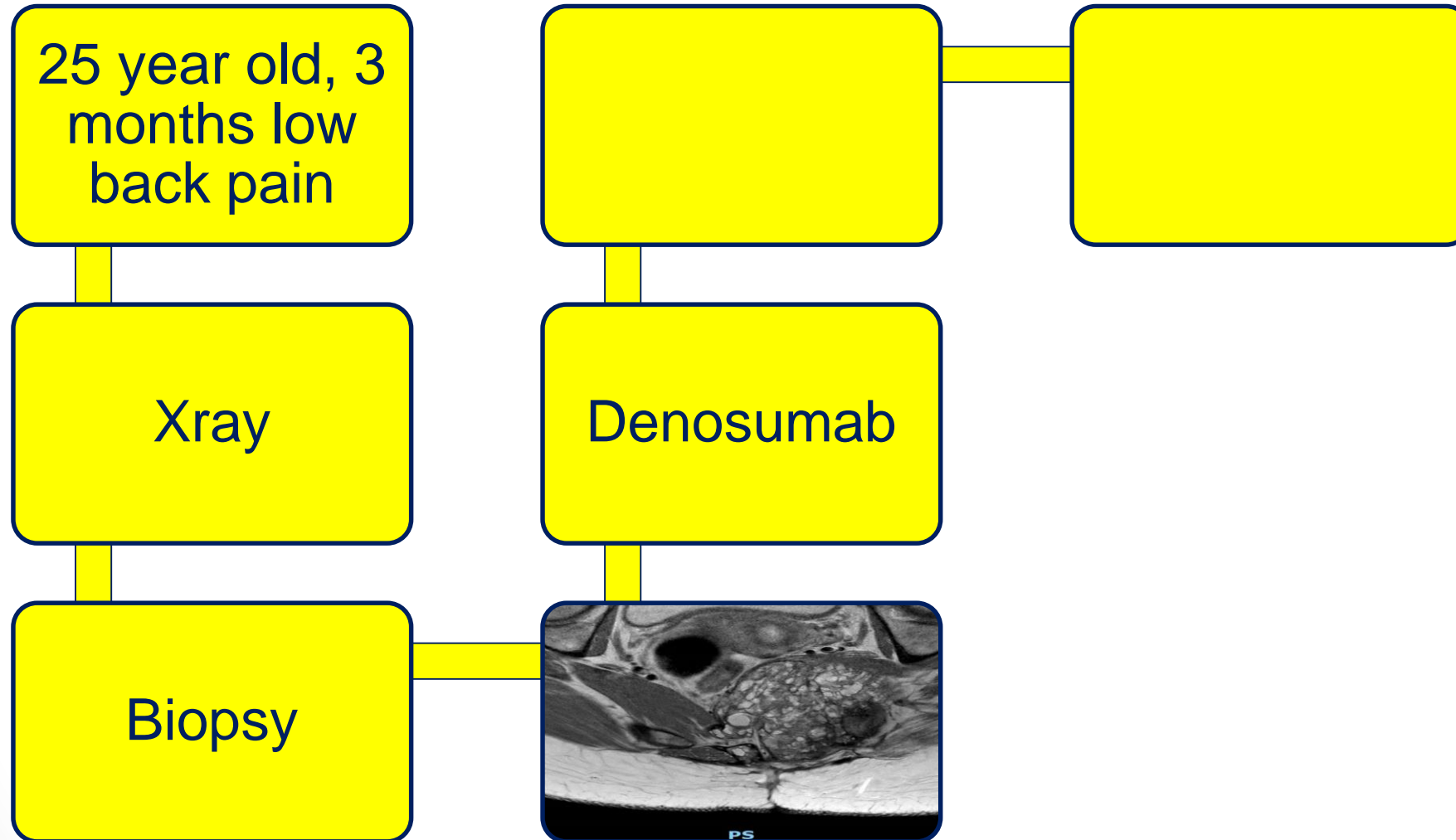
David Thomas, Robert Henshaw, Keith Skubitz, Sant Chawla, Arthur Staddon, Jean-Yves Blay, Martine Roudier, Judy Smith, Zhishen Ye, Winnie Sohn, Roger Dansey, Susie Jun



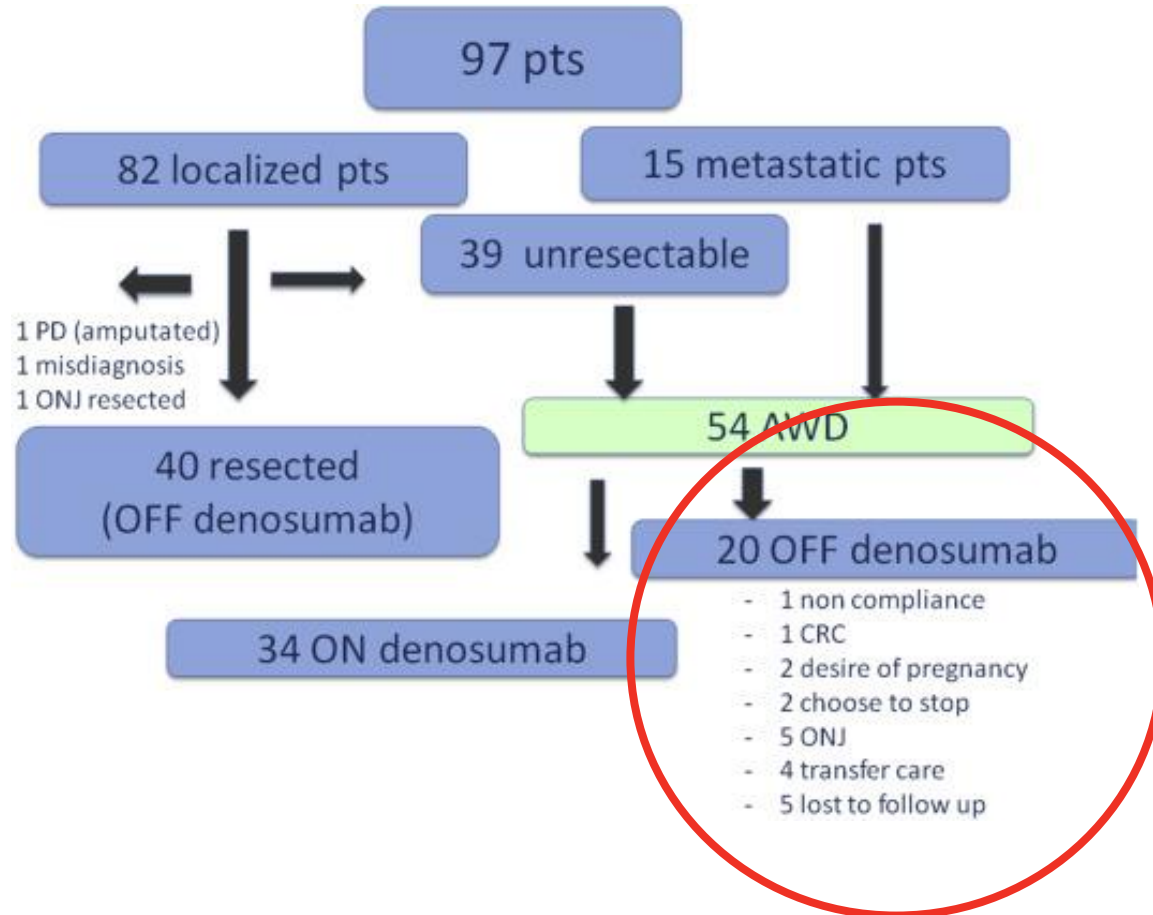
# Giant cell tumour of bone



# Giant cell tumour of bone

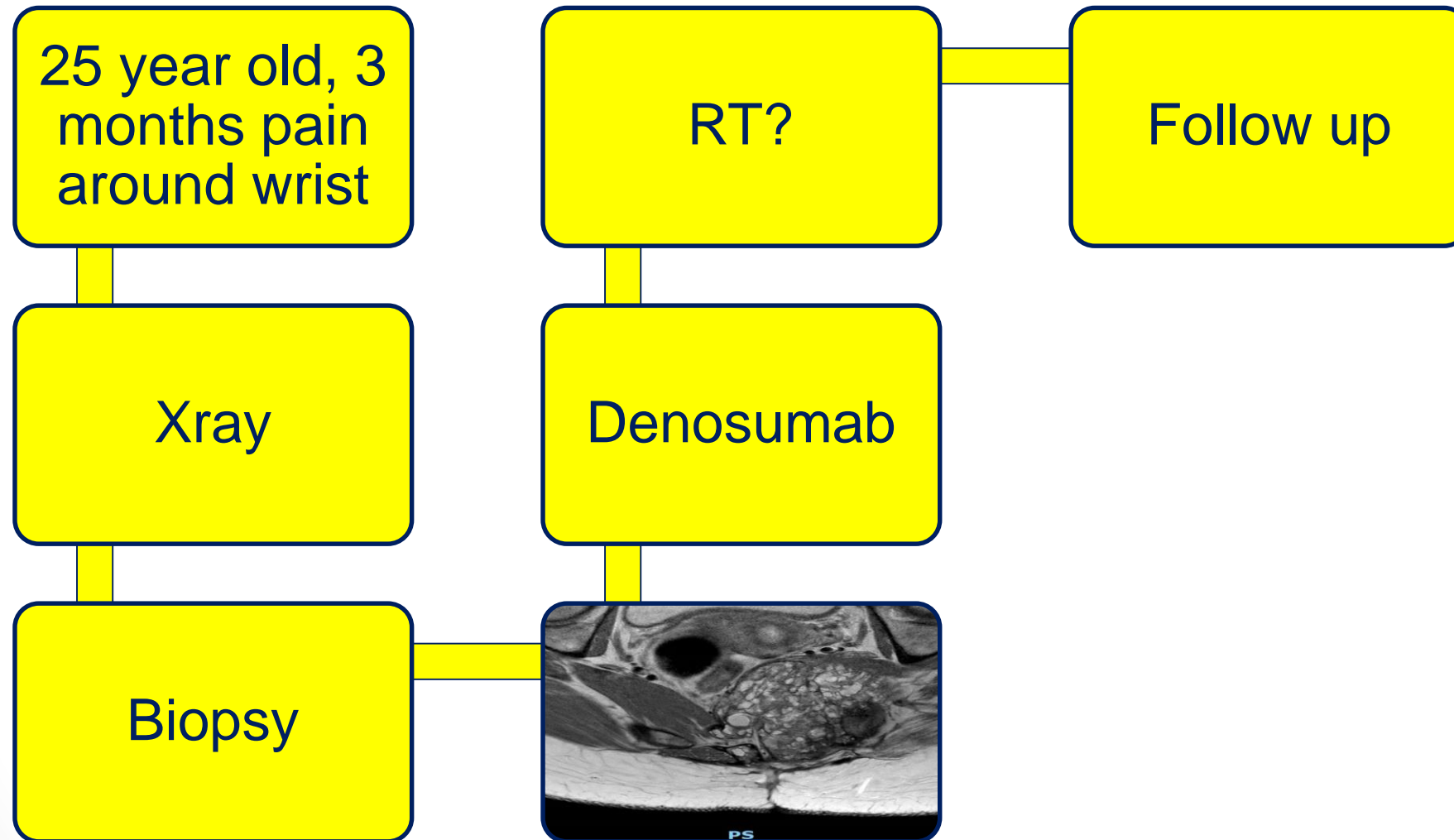


# Longer term use of denosumab for GCTB



Outcome known for n = 10  
 4/10 PD  
 after median 8 months  
 (range 7-15 months)

# Giant cell tumour of bone



# Giant cell tumour of bone

