

Radiotherapy in Osteosarcoma

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Dr Beatrice Seddon, Sarcoma Unit, University College Hospital

Role of radiotherapy in osteosarcoma

- Local control of the primary tumour is essential for long-term survival
- Local therapy in osteosarcoma ideally is surgery as the most effective local therapy
- Post-operative radiotherapy is not routinely given
- Indications for post-operative radiotherapy are not well understood:
 - Close/positive surgical margins?
 - Poor histological response to neoadjuvant chemotherapy?
 - Pathological fracture?

Definitive radiotherapy in osteosarcoma

- Radiotherapy may be given as definitive local therapy if surgery is not possible, or is declined by the patient:
 - Usually sacral or pelvic tumours
- Osteosarcoma is radio-resistant, requiring high radiotherapy doses of >70Gy
- In the past, local control rates have been poor with definitive photon radiotherapy due to limitations in doses that could be delivered with existing techniques
 - Ozaki et al (JCO, 21: 334-341, 2003): 16/17 patients with pelvic osteosarcoma treated with photon RT alone (median dose 61Gy) failed locally

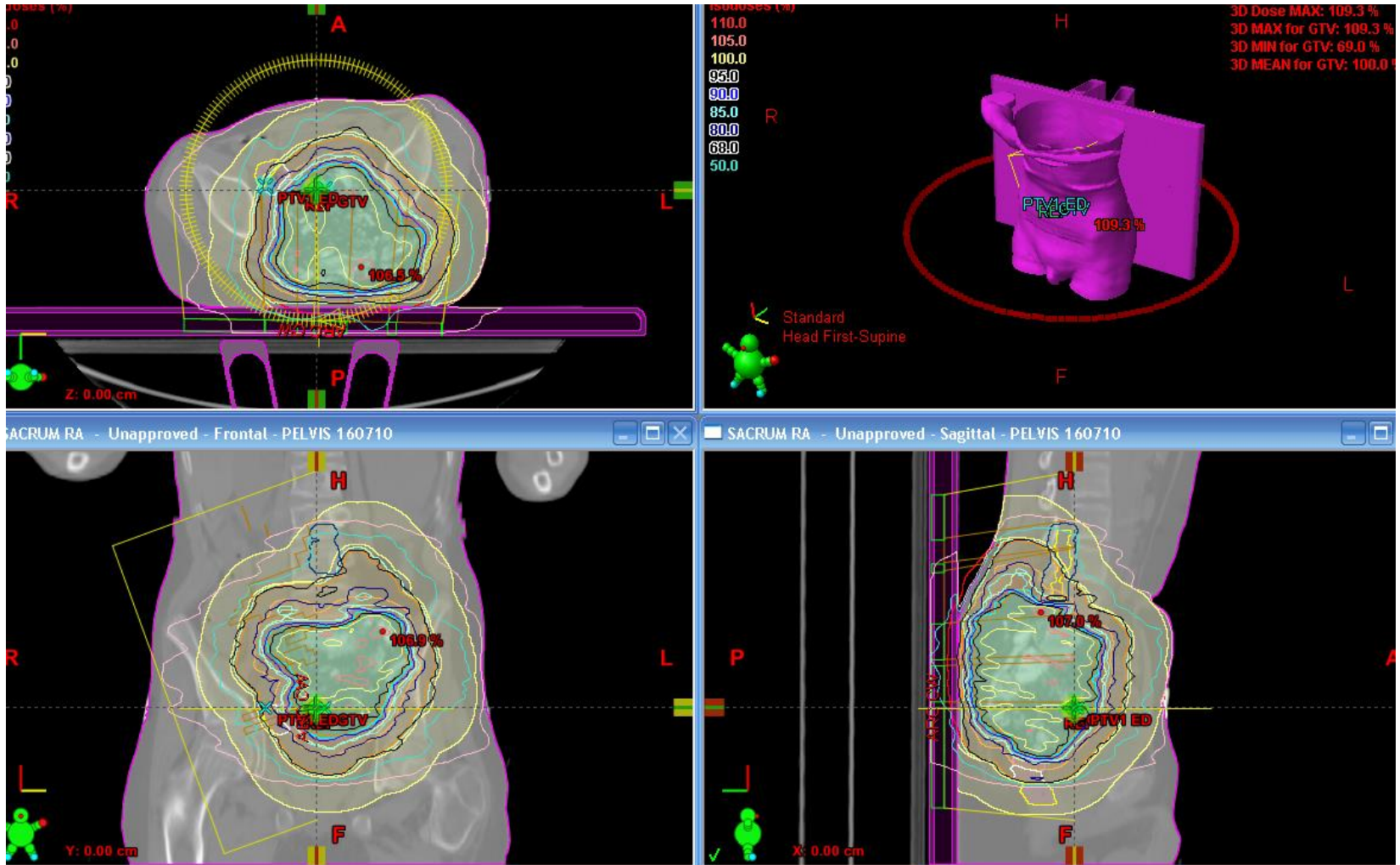
Definitive radiotherapy in osteosarcoma

- More recently, technical advances have improved the outcomes for these patients:
 - Photon radiotherapy delivered by intensity modulated radiotherapy (IMRT) to allow dose escalation
 - Particle radiotherapy to allow dose escalation:
 - Proton beam therapy
 - Carbon ion therapy

Intensity modulated radiotherapy

- Offers the opportunity to:
 - Conform better to the planning target volume (PTV)
 - Treat with greater homogeneity within PTV
 - Vary dose within PTV ('dose painting' concept)
 - Spare normal tissues – soft tissues and bone
 - Reduce normal tissue acute and late toxicity
- Allows dose escalation, aiming to improved local control, survival

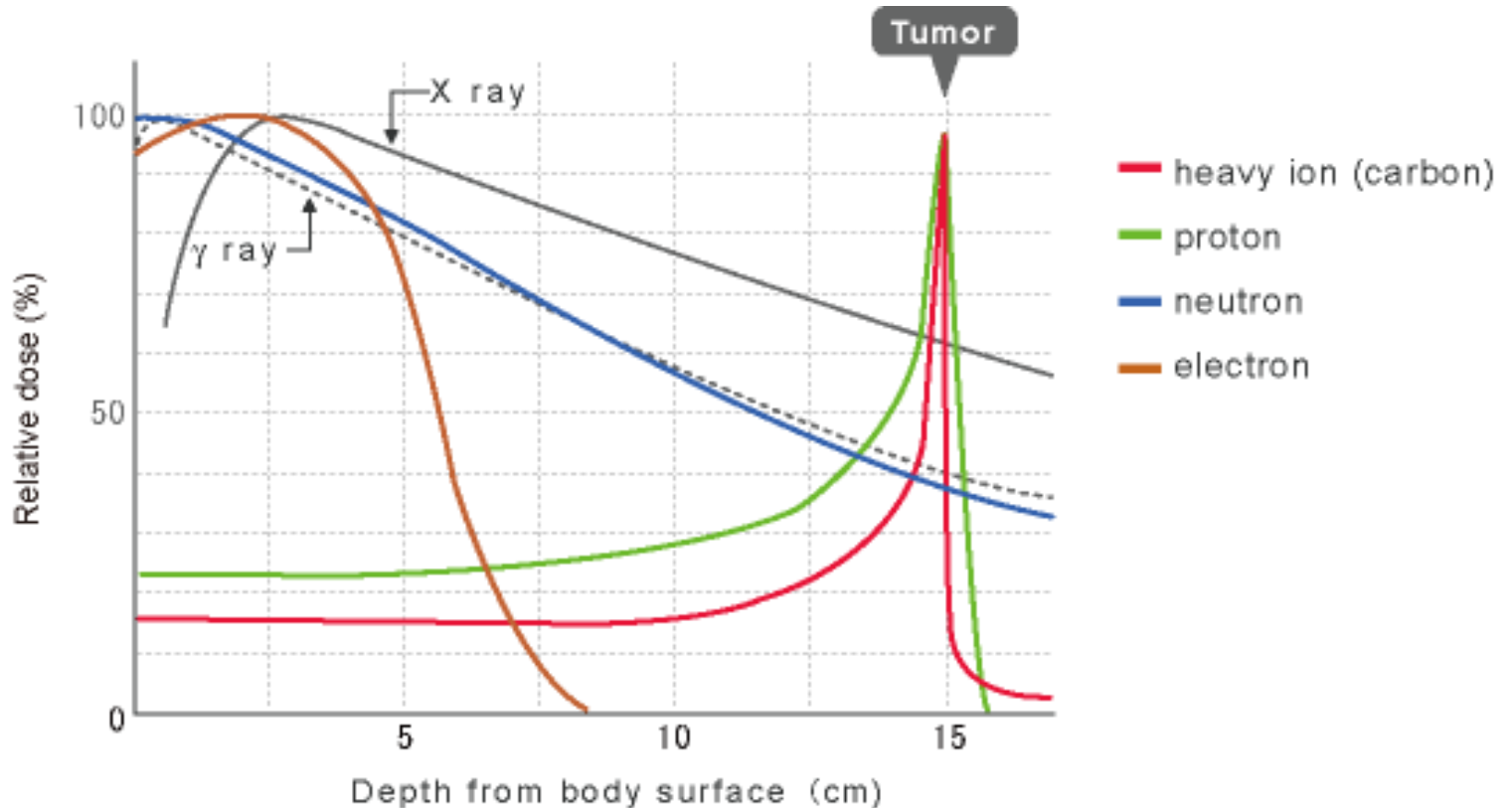
Osteosarcoma sacrum: 70 Gy in 35 fractions



IMRiS: Intensity Modulated Radiotherapy bone sarcomas

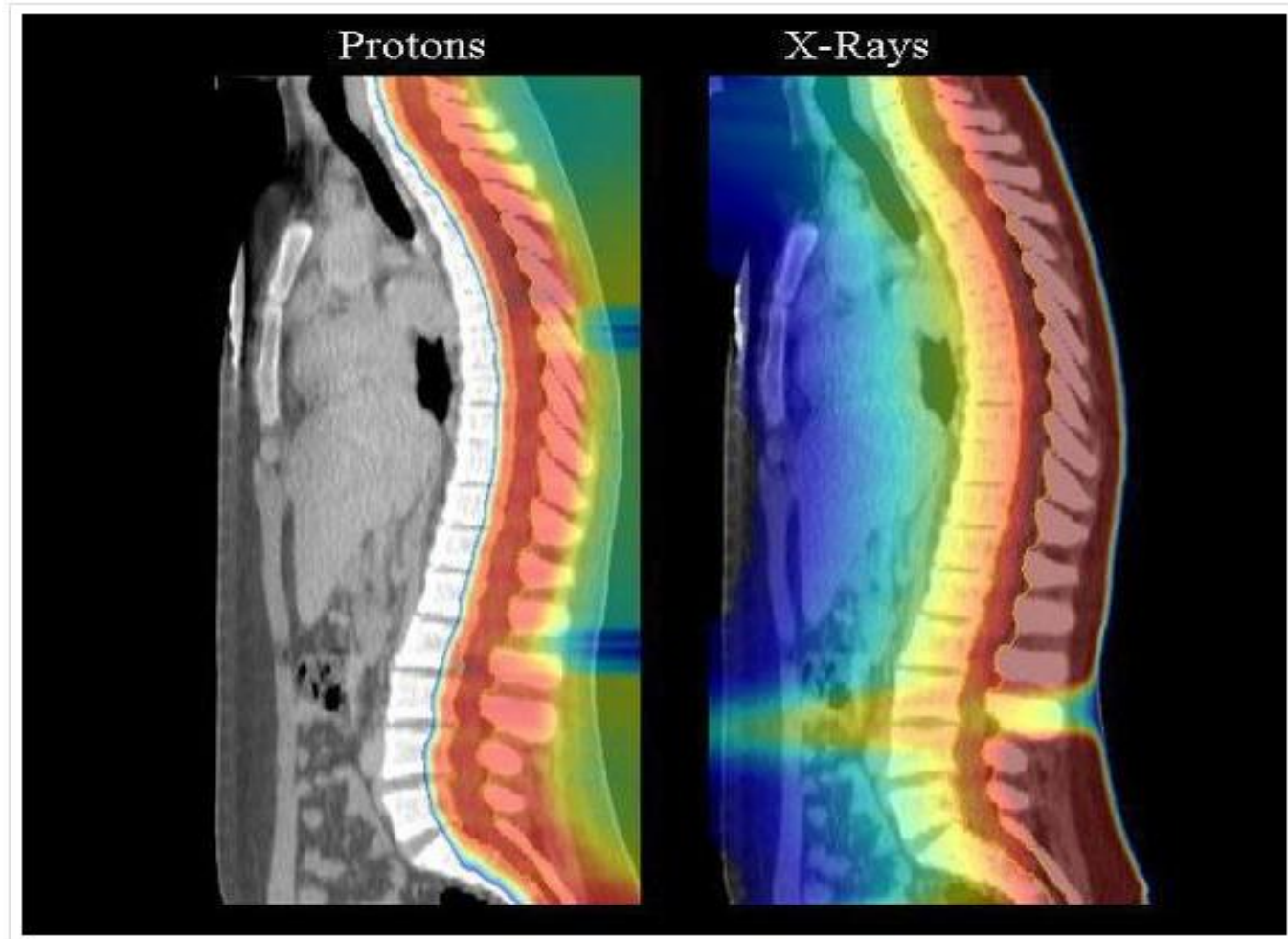
- Prospective phase II cohort study running nationally in UK
- BCRT funded research fellow, trial funded by CRUK
- Three cohorts:
 - Cohort 1: limb soft tissue sarcoma
 - Cohort 2: Ewing's sarcoma pelvis and spine
 - Cohort 3: Primary non-Ewing's sarcomas of pelvis and spine (osteosarcoma, chondrosarcoma, chordoma, spindle cell sarcoma of bone)
- Questions:
 - Can IMRT be used to deliver higher radiotherapy doses than a standard 3D-conformal radiotherapy plan?
 - Can we deliver doses of >70Gy?
 - Can we achieve durable local tumour control?
- Recruitment ongoing

Why Particle Therapy?



Lower upstream dose
No downstream dose

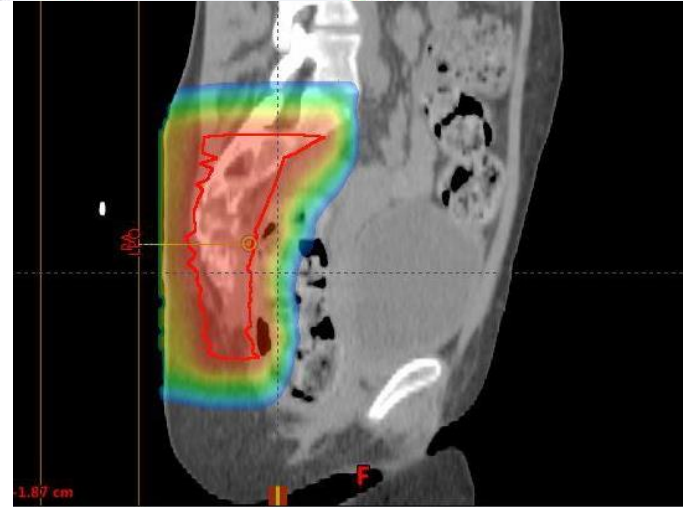
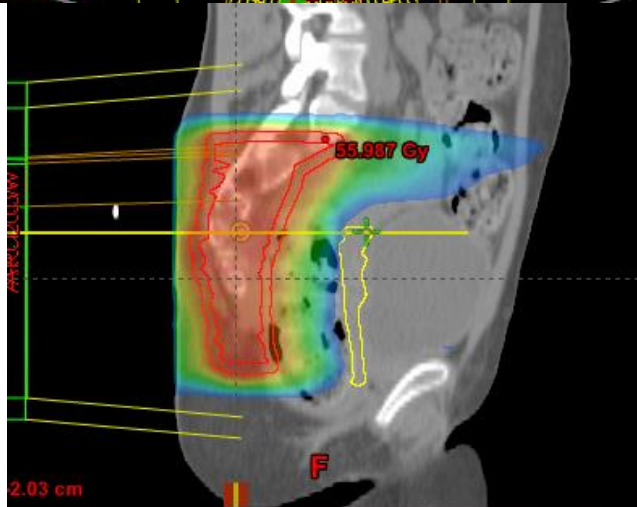
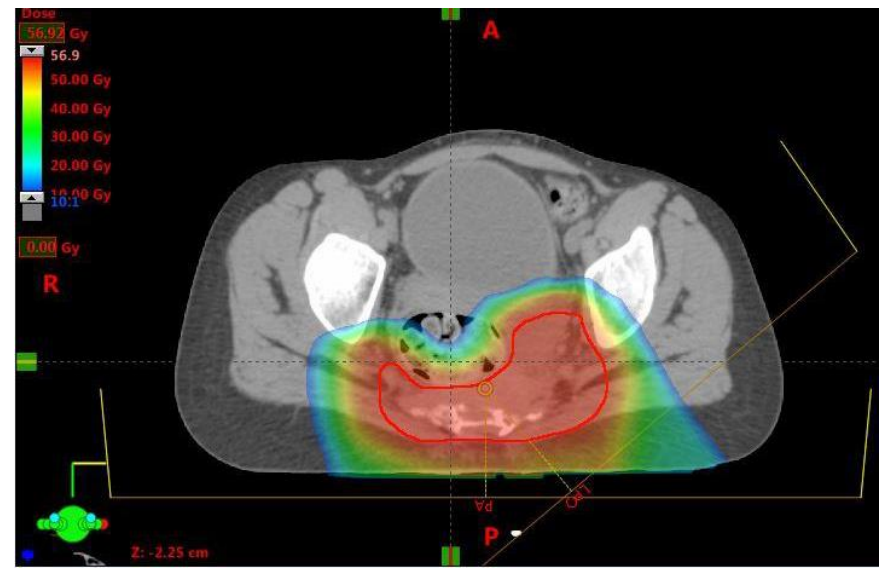
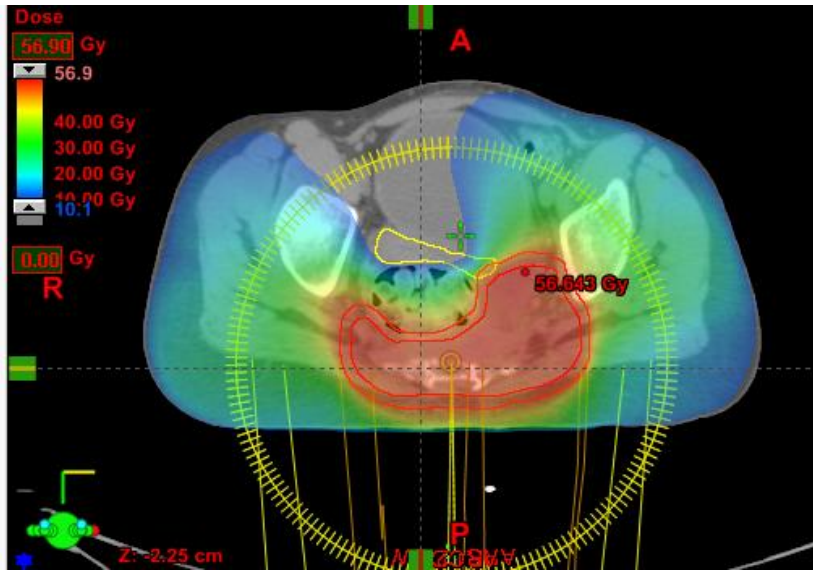
Comparing photons and protons



Particle therapy in osteosarcoma

- Proton beam therapy
 - Beam characteristics allow dose escalation, potentially achieving long term local control
 - Unclear if it is superior to high quality IMRT, as similar doses can be delivered, and RBE similar to photons (RBE 1.1)
 - PBT in the UK:
 - Christie PBT facility now opening and in ramp-up
 - UCH PBT facility go-live July 2020

Osteosarcoma of sacrum: IMRT vs IMPT



Osteosarcoma: Proton beam therapy

Proton-Based Radiotherapy for Unresectable or Incompletely Resected Osteosarcoma

- For inoperable or incompletely resected tumours (R1 and R2)
- Proton (56%) and mixed proton-photon (44%) plans
- 55 patients treated 1983 – 2009, median age 29 years
- Median dose 68.4Gy (SD 5.4Gy)
- Site – head and neck, spine, pelvis, rib/chest wall (only 2 limbs)
- 5 year local control **72%** (58% patients had surgery)

Particle therapy in osteosarcoma

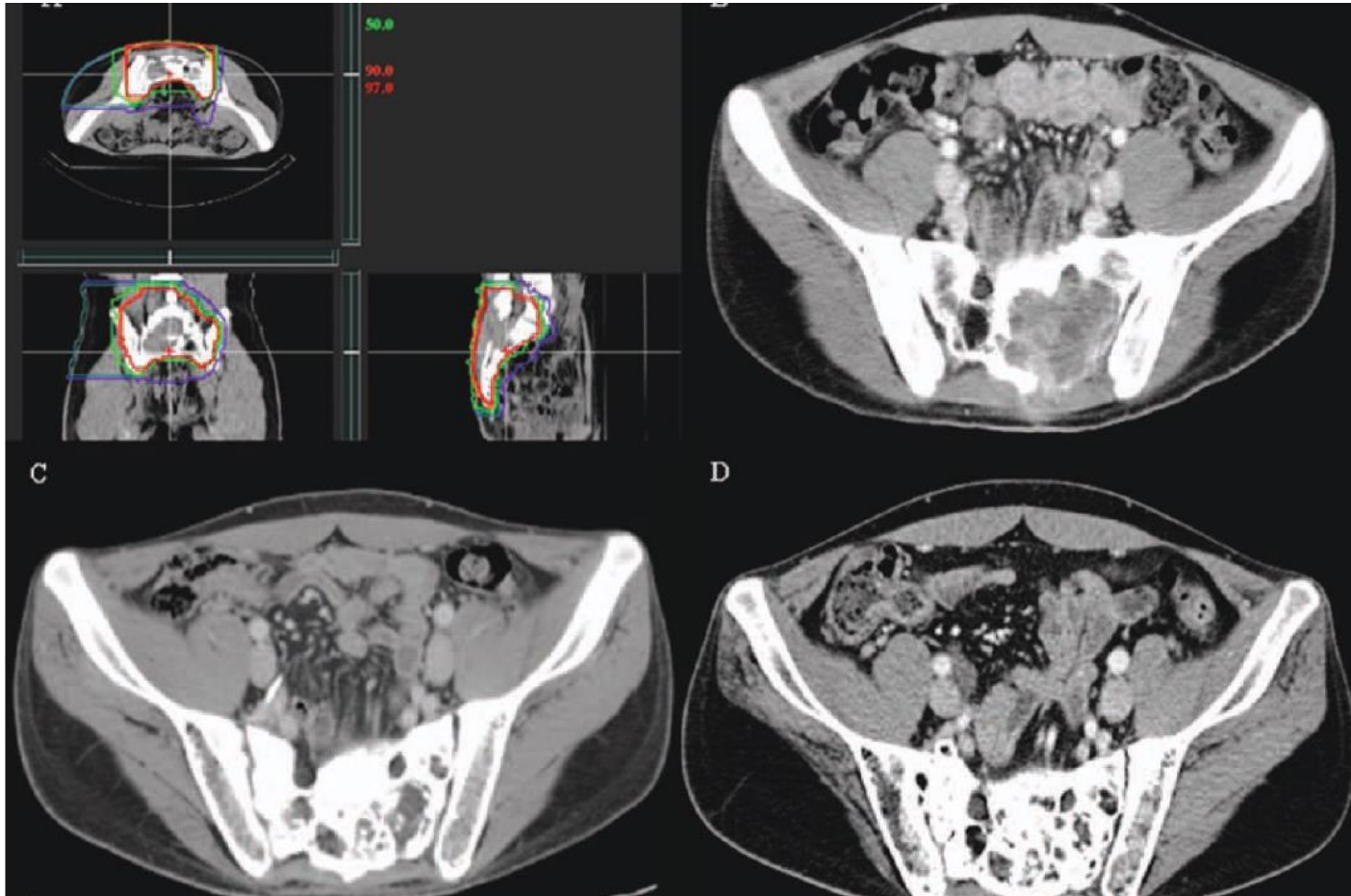
- Carbon ion therapy
 - Beam characteristics allow dose escalation, potentially achieving long term local control
 - RBE 3.0 – higher than proton beam therapy or photons, making carbon ions potentially more effective
 - Carbon ion facilities much less common than PBT:
 - Many centres in Japan
 - Europe – Heidelberg, Germany and CNAO, Italy

Osteosarcoma: Carbon ion radiotherapy

Impact of Carbon Ion Radiotherapy for Unresectable Osteosarcoma of the Trunk

- N = 78 patients treated 1996 – 2009
- Inoperable osteosarcoma of trunk (pelvis 61, spine and paraspinal 15, other sites 2)
- Median dose 70.4GyE in 16 fractions over 4 weeks
- Median follow-up 42 months
- 5 year local control rate **62%** (no patients had surgery)
- 5 year overall survival 33%

Osteosarcoma: Carbon ion radiotherapy



Research questions

- How does PBT compare to good quality IMRT photon radiotherapy delivering equivalent doses? Is it really better (as claimed)??
- How does carbon ion therapy compare with proton beam therapy – is there an advantage for osteosarcoma as a radio-resistant tumour?
- What is the role of post-operative radiotherapy in osteosarcoma to improve local tumour control (boring but important) ?

Research questions

- Current protocols:
 - IMRiS phase II study of IMRT (osteosarcoma cohort)
 - Phase I/II Therapy Trial to Determine the Safety and Efficacy of Heavy Ion Radiotherapy in Patients With Osteosarcoma (Heidelberg)
 - Recruitment 2010 – 2020 – aiming for 20 patients
- Challenges – how to investigate in a timely way in such a rare tumour, when radiotherapy is only used infrequently?
- How to ask randomised questions in such a rare tumour?
- What are the alternatives to randomised questions?