Radiotherapy for Treatment of Adult Granulosa Cell Ovarian Tumours

Dr Alexandra Taylor
Royal Marsden Hospital

Introduction: My role

Consultant in Clinical Oncology

Responsible for care of women with gynaecological cancer

- Radiotherapy
- Chemotherapy
- Ongoing review

Service development and research

How I came to specialise in the treatment of gynaecological cancers

- My first medical job was in oncology
- 4 years later, started specialist training in Clinical Oncology
- At St Bartholomew's Hospital, covered maternity leave – rapid learning curve about gynaecology cancer!
- After completing specialist training, undertook research project developing new radiotherapy techniques for treatment of cervical cancer
- Since this time, my focus has been to improve care for women with gynaecological cancer

Dr Melanie Powell

Prof Andrea Rockall

Background

- Standard options for treating recurrent granulosa cell tumours include
  - Surgery
  - Hormone therapy
  - Chemotherapy

- Very limited information on the role of radiotherapy

Royal Marsden Gynaecology Multi-disciplinary Team

WHAT IS RADIOTHERAPY?

Radiotherapy

- Nearly two thirds of all patients with cancer receive radiotherapy
- Uses high energy X rays
- Aim to kill all cancer cells within a specific region
- Treatment usually delivered on a linear accelerator

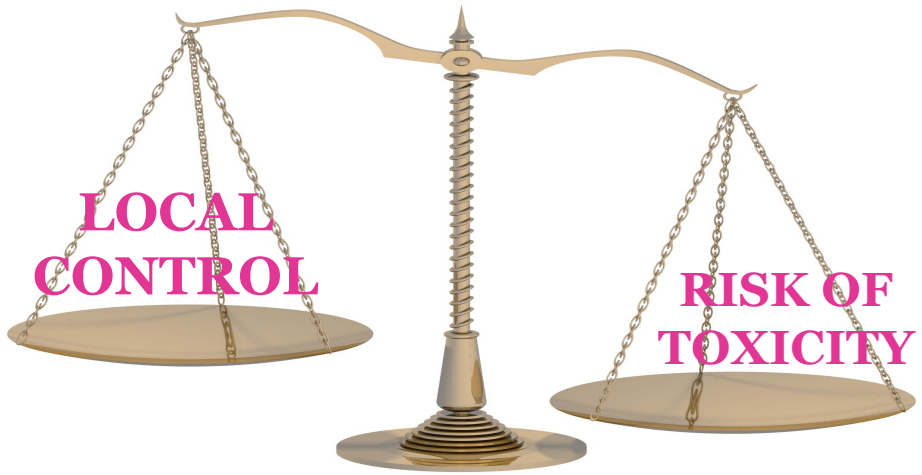
Radiotherapy principles

Definition

Use of ionising radiation for therapeutic purposes

Aim

–To deliver sufficient dose to kill all malignant cells within a target volume whilst sparing the surrounding normal structures



History of Radiotherapy

1895 Roentgen discovered X-Rays

1896 First use of X-Rays for diagnosis

1897 First used for treatment (a hairy mole)

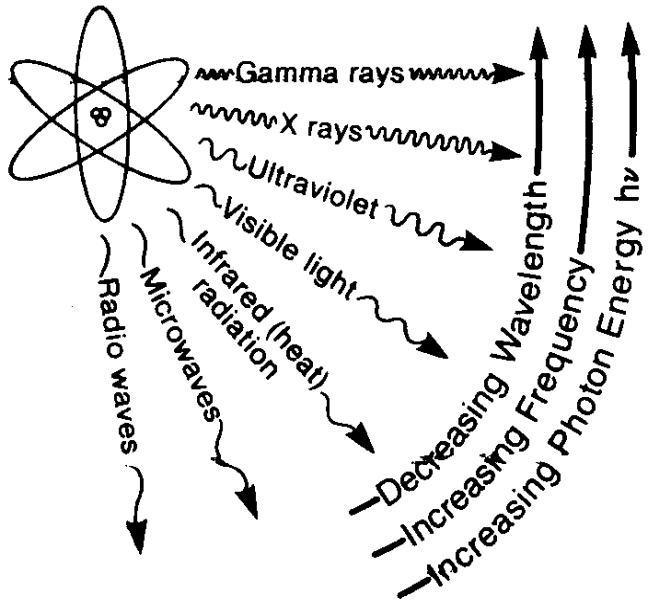
→ **EXTERNAL BEAM RADIOTHERAPY**

1898 Radium isolated by Marie and Pierre Curie

1905 Cervical tumour treated with radium

→ **BRACHYTHERAPY**

The Electromagnetic Spectrum

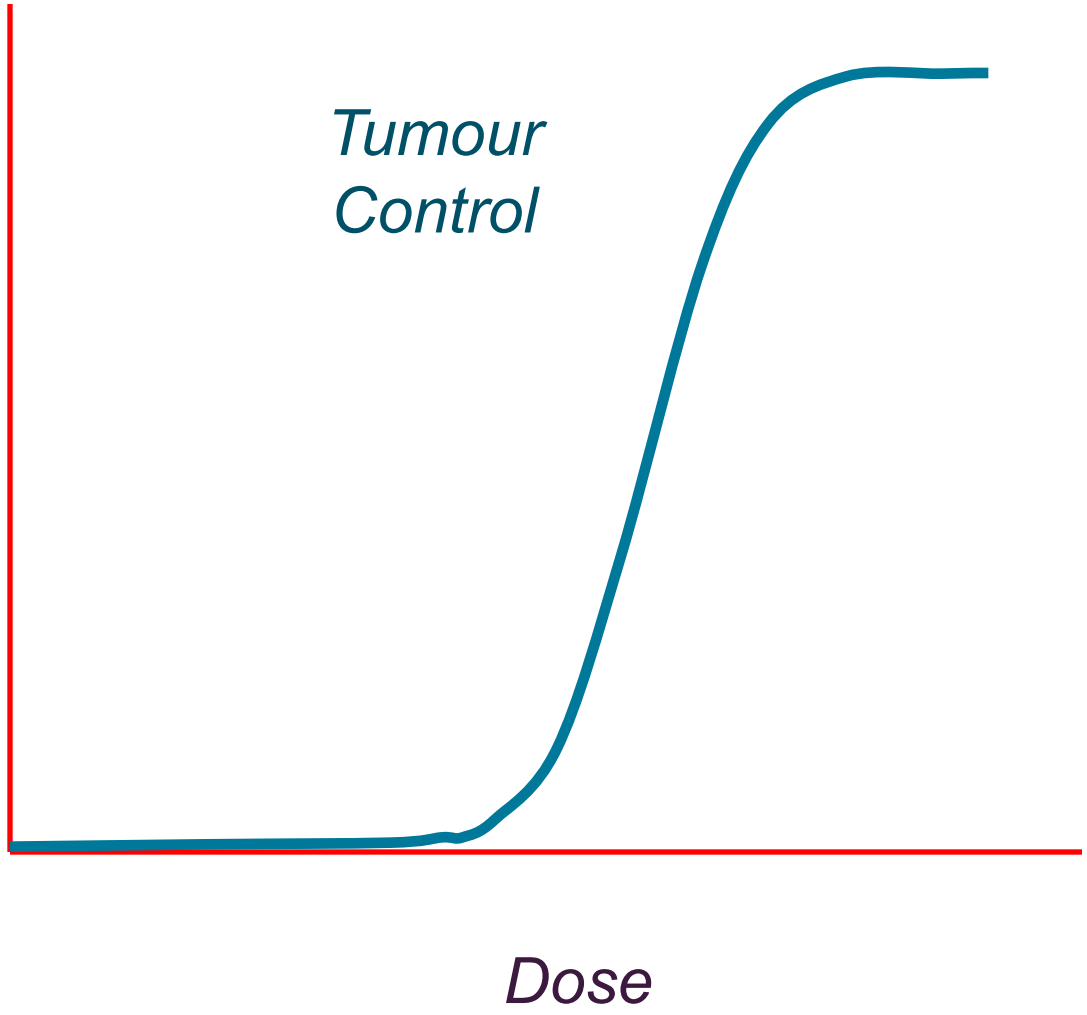


- Beams used in radiotherapy are **x-rays or gamma rays** (also called photons)
- High energies are sufficient to break chemical bonds
- Create free radicals which damage DNA
- Causes cell death only when the cell tries to grow
- This may be days, weeks or months later

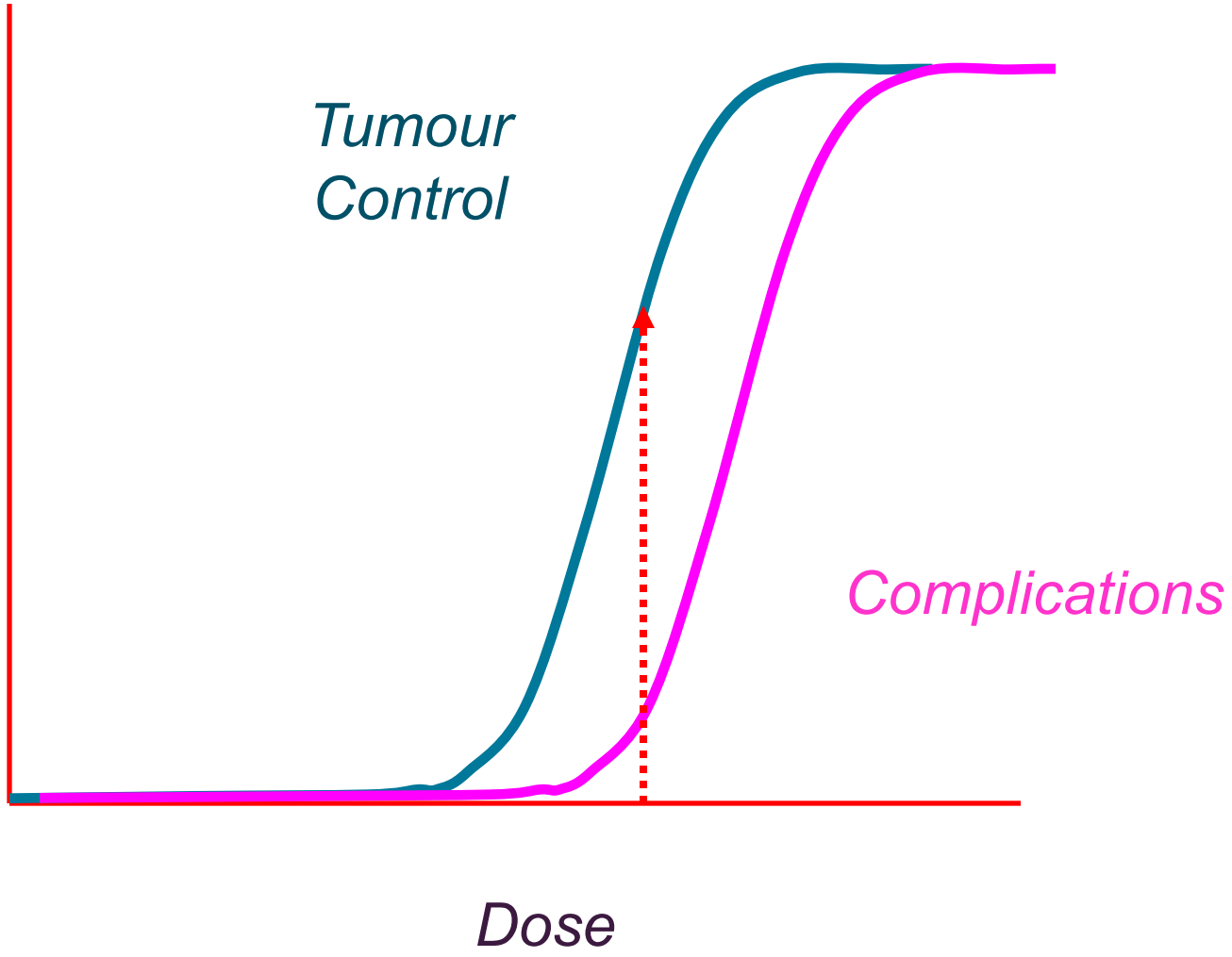
Fractionation

- Tumours have defective DNA repair mechanisms
- Using multiple small fractions allows normal cells to repair themselves
- This enables a higher total dose to be given to the tumour
- Standard radiotherapy is given daily Monday to Friday

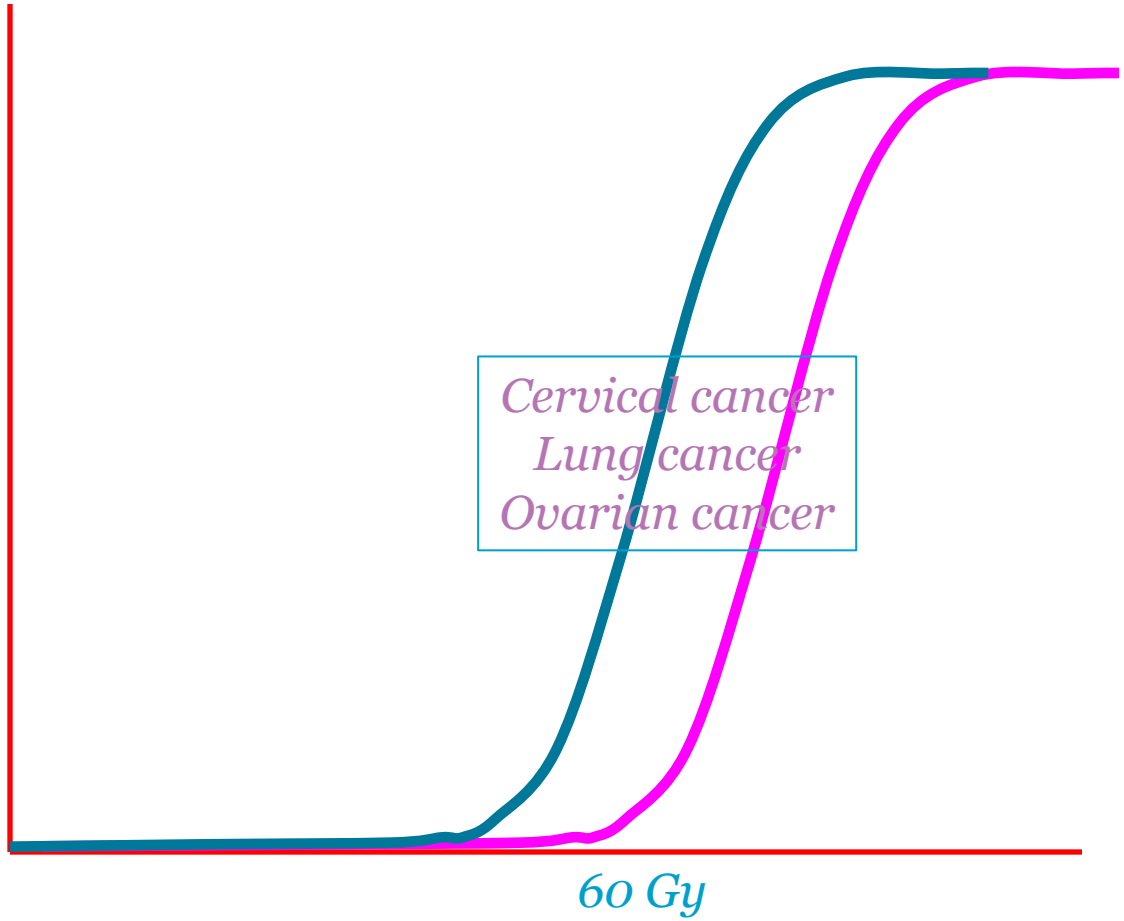
Radiotherapy Principles



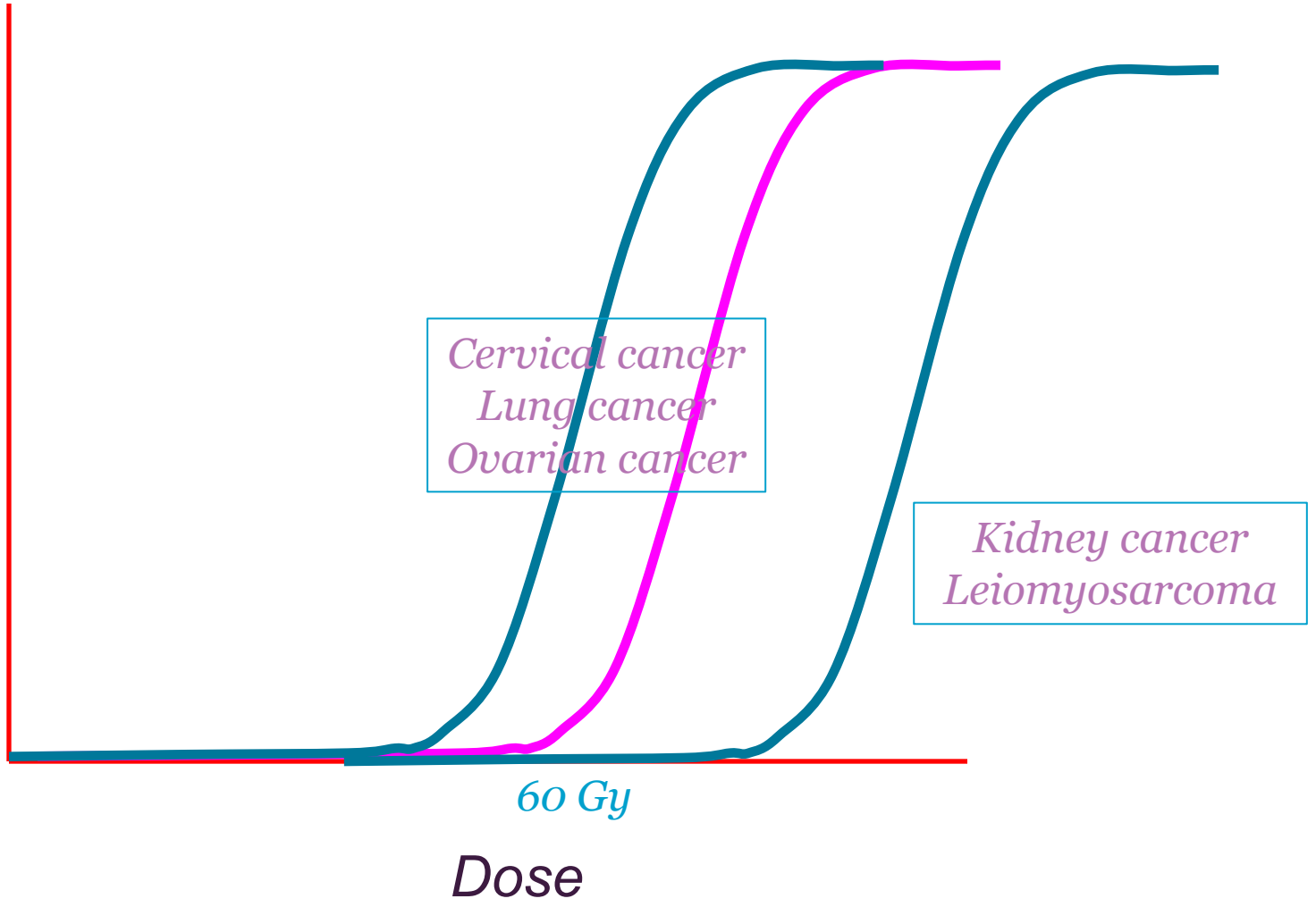
Radiotherapy Principles



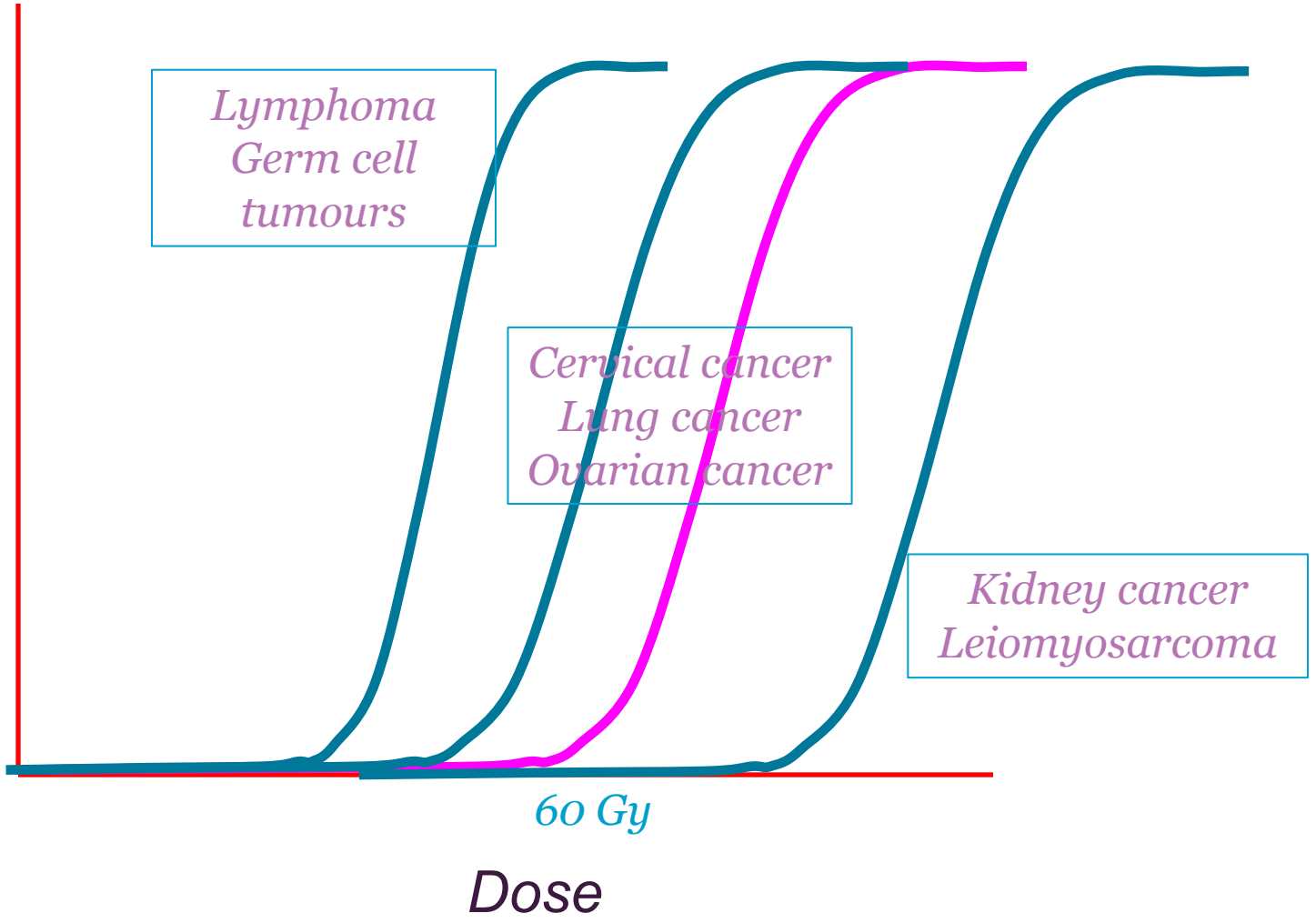
Radiotherapy Principles



Radiotherapy Principles



Radiotherapy Principles



Normal Tissue Toxicity - Risk Factors

–Radiotherapy dose: total dose and dose per fraction

–Radiotherapy volume

– *Other factors*

- Previous surgery
- Diabetes
- Concurrent drugs: e.g. chemotherapy
- Performance status
- Genetic predisposition

Acute toxicity: side effects that occur during treatment

Mechanism: Radiotherapy damages rapidly proliferating normal cells

- Diarrhoea and abdominal cramps
- Urinary frequency and pain passing urine
- Skin reaction
- Fatigue

Typically resolves within 4-6 weeks of completing treatment

Does not predict for long term toxicity

Late toxicity: occurs months or years after treatment

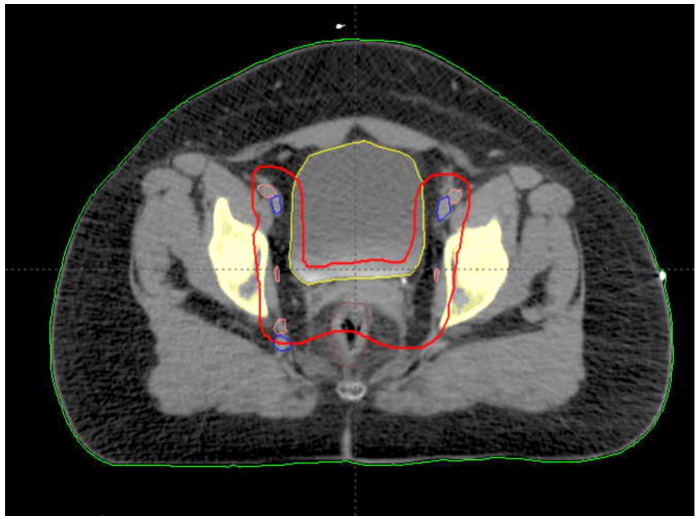
- ***Mechanism:*** complex multi-factorial pathway resulting in chronic loss of stem cells, vascular changes and fibrosis

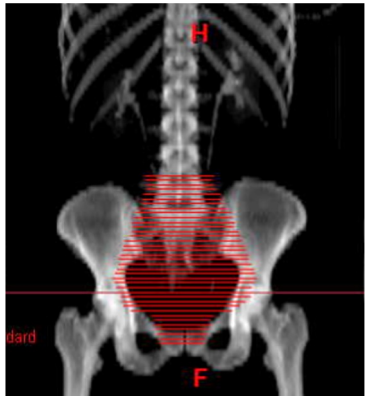
- This impairs healing and regeneration of normal tissues

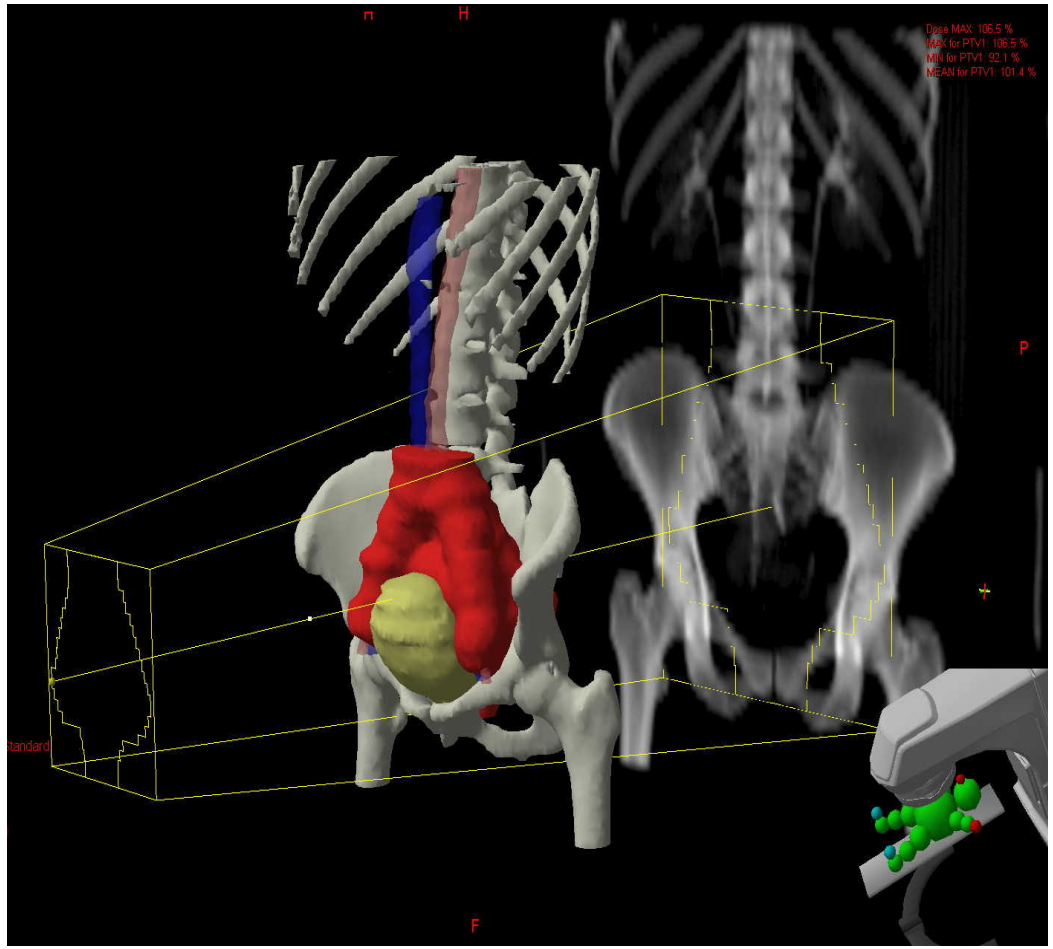
- Effects can be permanent

- Symptoms arise as a result of physiological deficits

Designing a radiotherapy treatment







Treatment planning

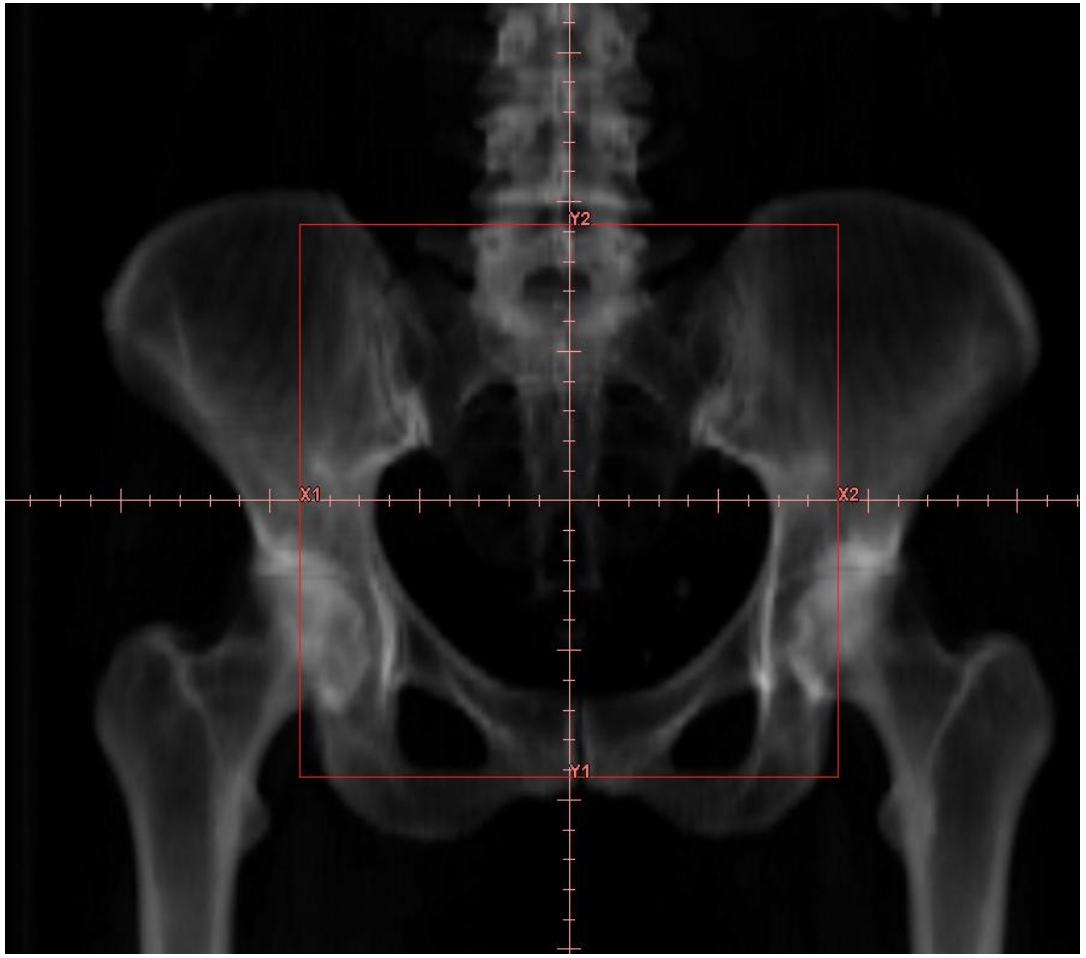
1. Define the target volumes on the planning CT scan

2. Dose prescription
   - Total dose to each volume
   - Number of fractions

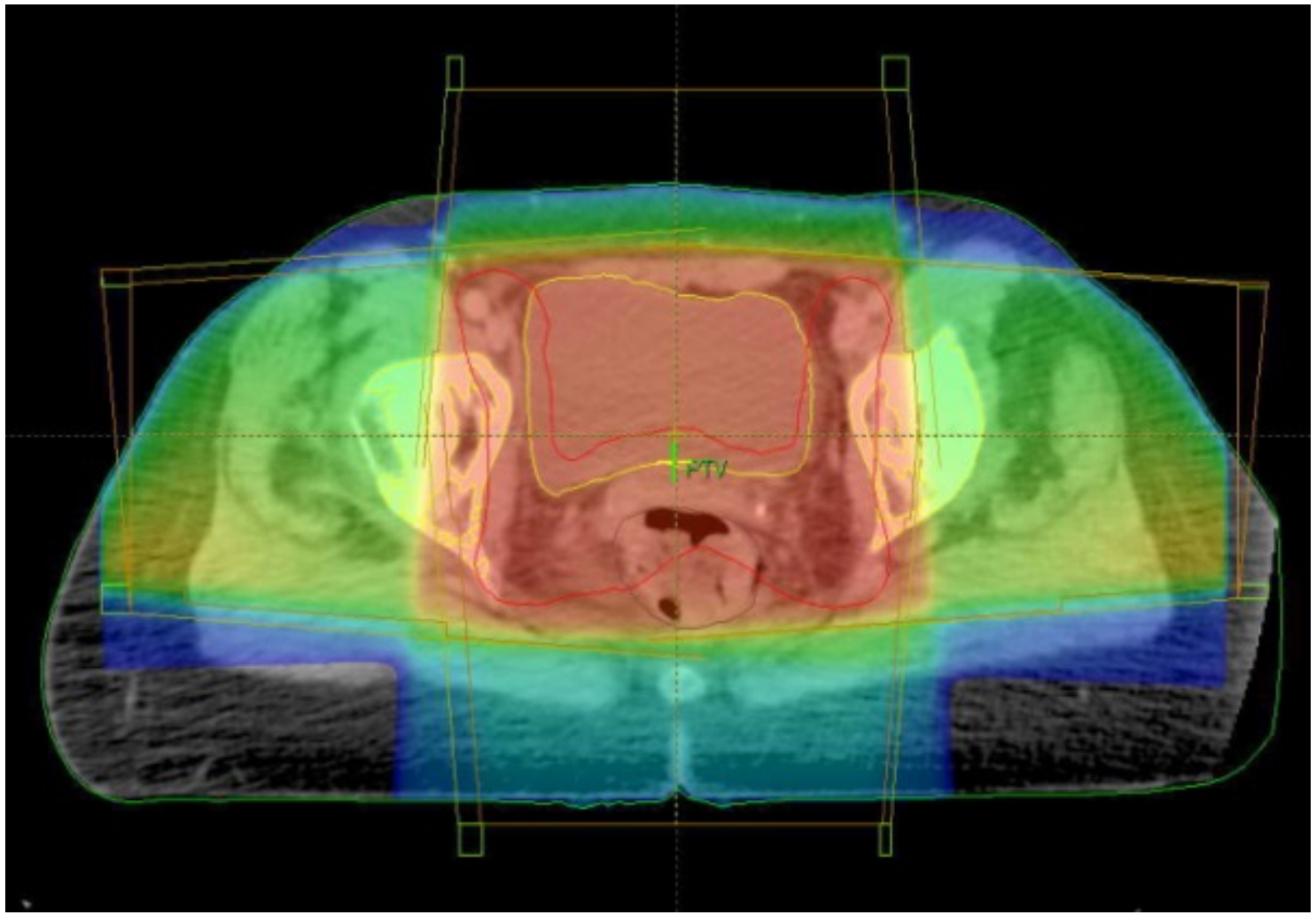
3. Specify dose limits for organs at risk (normal structures)

Ovary	10 Gy	50%
Bowel	45 Gy	5%
Rectum	60 Gy	5%
Bladder	65 Gy	5%

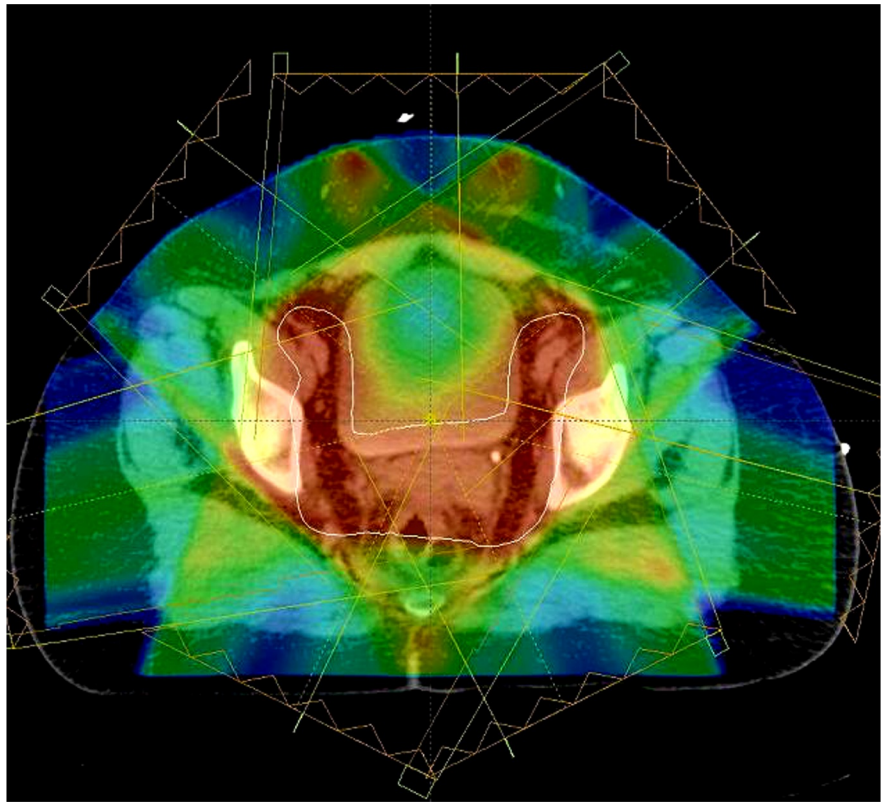
Radiotherapy techniques
Conventional

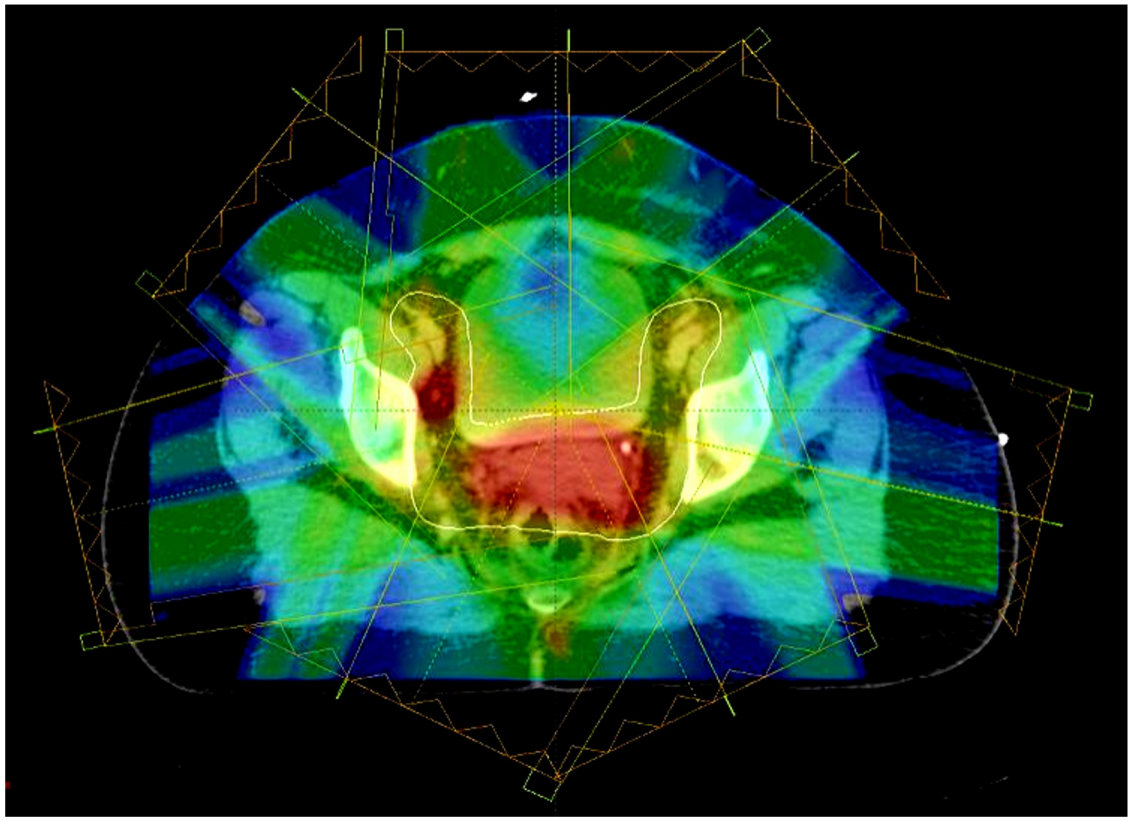


Radiotherapy techniques
Virtual simulation and conformal



Radiotherapy techniques
Intensity modulated radiotherapy

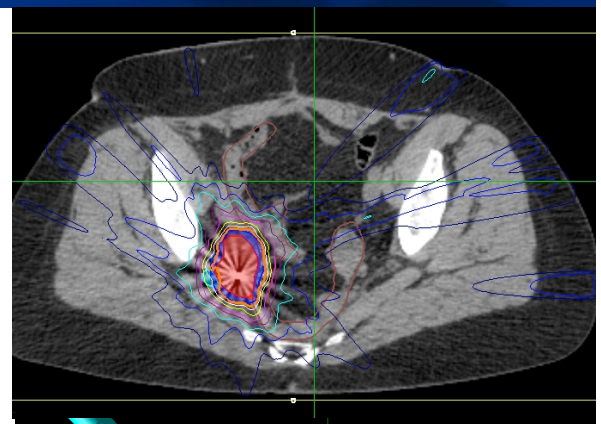


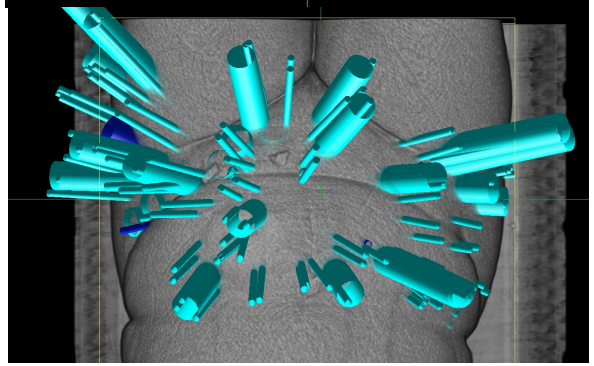


Stereotactic radiotherapy Cyberknife

- Imaging
  - Real-time imaging with X-rays
  - Can track implanted gold markers, lung lesion or bone

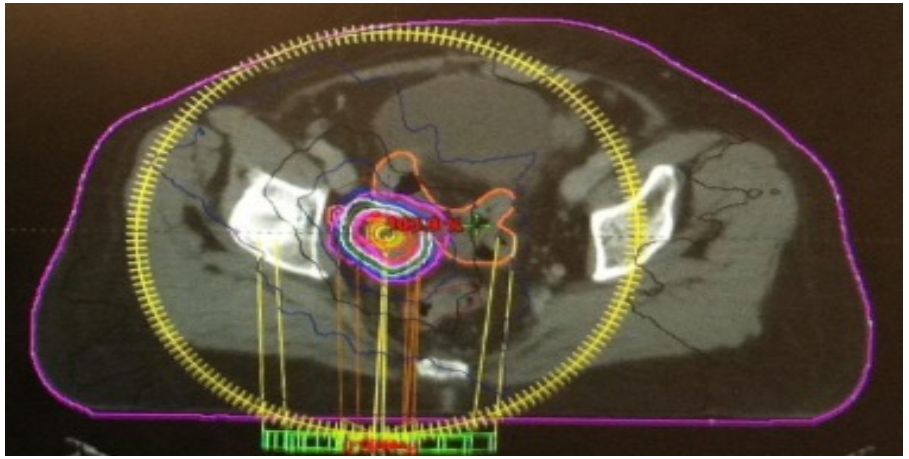
- Treatment
  - 100-150 non-coplanar beams
  - Takes 30-60 minutes per fraction





Stereotactic radiotherapy
Linear accelerator

- Imaging
  - Cone beam CT image
  - Soft tissue matching and couch shifts
- Treatment time quicker
- May be preferable for pelvic treatments



Treatment options

Low dose	To stop bleeding, reduction in tumour to help pain Simple treatment, starts quickly
Medium dose	To achieve local control, unlikely to have permanent effect, often other sites of disease
High dose	To treat single site of disease. Higher risk of long term toxicity.

RADIOTHERAPY FOR OVARIAN CANCER

Radiotherapy for ovarian cancer
Post-operative whole abdominal radiotherapy

- Whole abdominal radiotherapy following surgery for ovarian cancer was used as standard treatment before chemotherapy became available
- Radiotherapy caused higher risk of bowel complications than chemotherapy
- Nowadays not used in this setting

Radiotherapy for ovarian cancer
Recurrent disease

Involved field radiotherapy

- Can achieve good control for small volume recurrence
- Can now achieve higher doses with IMRT

Stereotactic radiotherapy

Increasingly being used for single site of recurrence: lung, lymph node, liver

Well tolerated, local control 80%

British Gynaecological Cancer Society recommendations

- There is no role for whole abdominal radiotherapy as post-operative treatment of ovarian cancer
- Definitive treatment using IMRT or stereotactic radiotherapy may be considered for loco-regional recurrence or oligometastatic disease
- Palliative radiotherapy should be considered for symptomatic disease including vaginal bleeding and pain

RADIOTHERAPY FOR GRANULOSA CELL TUMOURS

Historical data
Post-operative radiotherapy

First report of radiotherapy being used for GCT was in 1959

- 12 women treated from 1936-1957

Hauspy *et al, IJROBP 2011*

- 103 patients with GCT, 31 received post-operative radiotherapy
- 39 of 103 had recurrence
- Median survival 251 months with RT versus 112 months without RT

Other studies have not shown any benefit for RT

No longer consider RT for post-operative treatment in ovarian cancer

Historical data
Radiotherapy for advanced and recurrent disease

Wolf *et al*, 1999

- 14 patients: 10 treated with whole abdominal radiotherapy, 4 pelvic radiotherapy
- 6 out of 14 had a complete response, 3 remained alive without disease 10-21 years after treatment

Savage *et al*, 1998

8 patients received 20-60 Gy

Clinical response in 4 (50%) - duration >4 years in 3 patients

Radiotherapy for recurrent disease

Cohan *et al, 2006 presented* 3 case reports

- 7 x 10 cm pelvic mass treated with 55 Gy in 30 fractions

  Reduced in size to 4 x 2.5 cm. Response 13 months

- Multiple abdominal recurrences. Whole abdominal RT 30 Gy in 20 fractions

  Mass shrank from 13 x 17 cm to 5 x 6.6 cm Response 5 months

- 20 cm mass in abdomen treated with 45 Gy in 25 fractions. Reduced to 3.7 x 2.5 cm. Ongoing response at 21 months

Radiotherapy for granulosa cell tumours
Royal Marsden experience

- Reviewed outcomes for women treated with radiotherapy for recurrent GCT between 2012-2022
- Examined clinical information, radiotherapy details and imaging
- Project approved by research and ethics board

Radiotherapy for recurrent GCT
Results

- 13 patients received radiotherapy, 26 sites of disease
- Average age 48 years old
- Average time from diagnosis to recurrence was 58 months (6-169 months)
- All patients had initially had surgery with complete removal of disease
- 12/13 women had surgery at least once for relapse

Radiotherapy for recurrent GCT
Previous Systemic therapy

Chemotherapy

No chemotherapy	4
1 course	4
2 courses	2
4+ lines	3

Hormonal therapy

11/13 patients

Sites of recurrence

Multiple sites in 7 patients

Location

- Pelvic 38%
- Abdomen 43%
- Lymph node 14%
- Lung 5%

Size of tumour

- Majority had large tumours (> 5 cm)
- Range from 5 - 5943 cm^3

Radiotherapy details

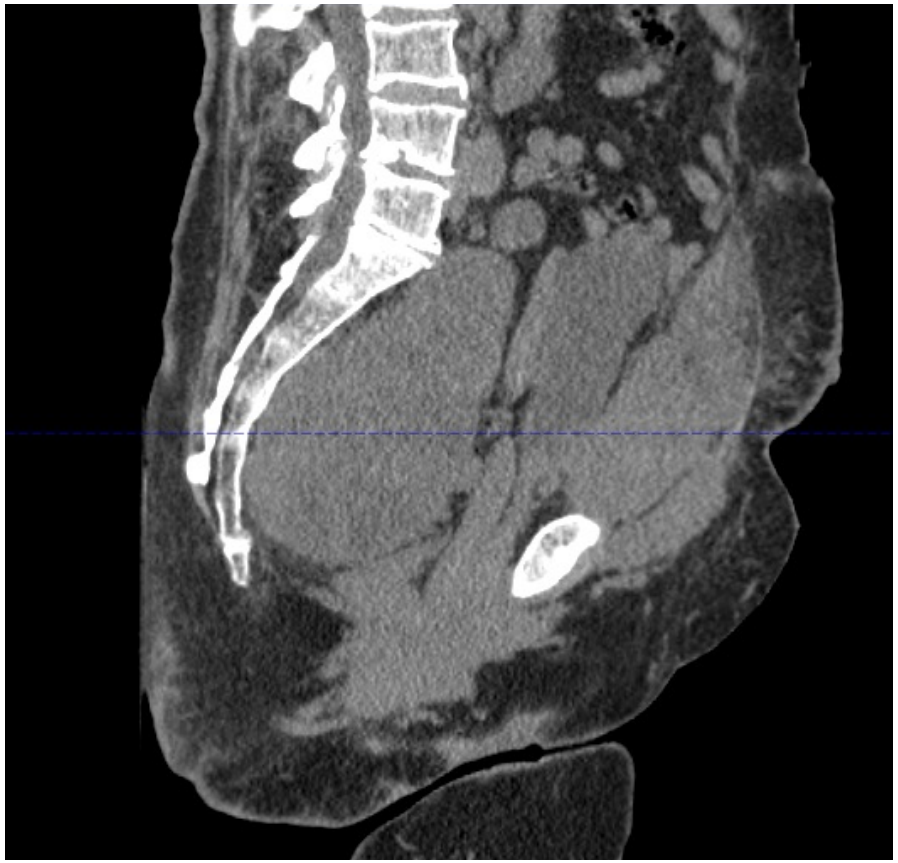
- In total, 26 sites were treated
- Eight of the 13 women had multiple courses of treatment
- Included re-irradiation of 3 sites
- One was post-operative with no measurable disease

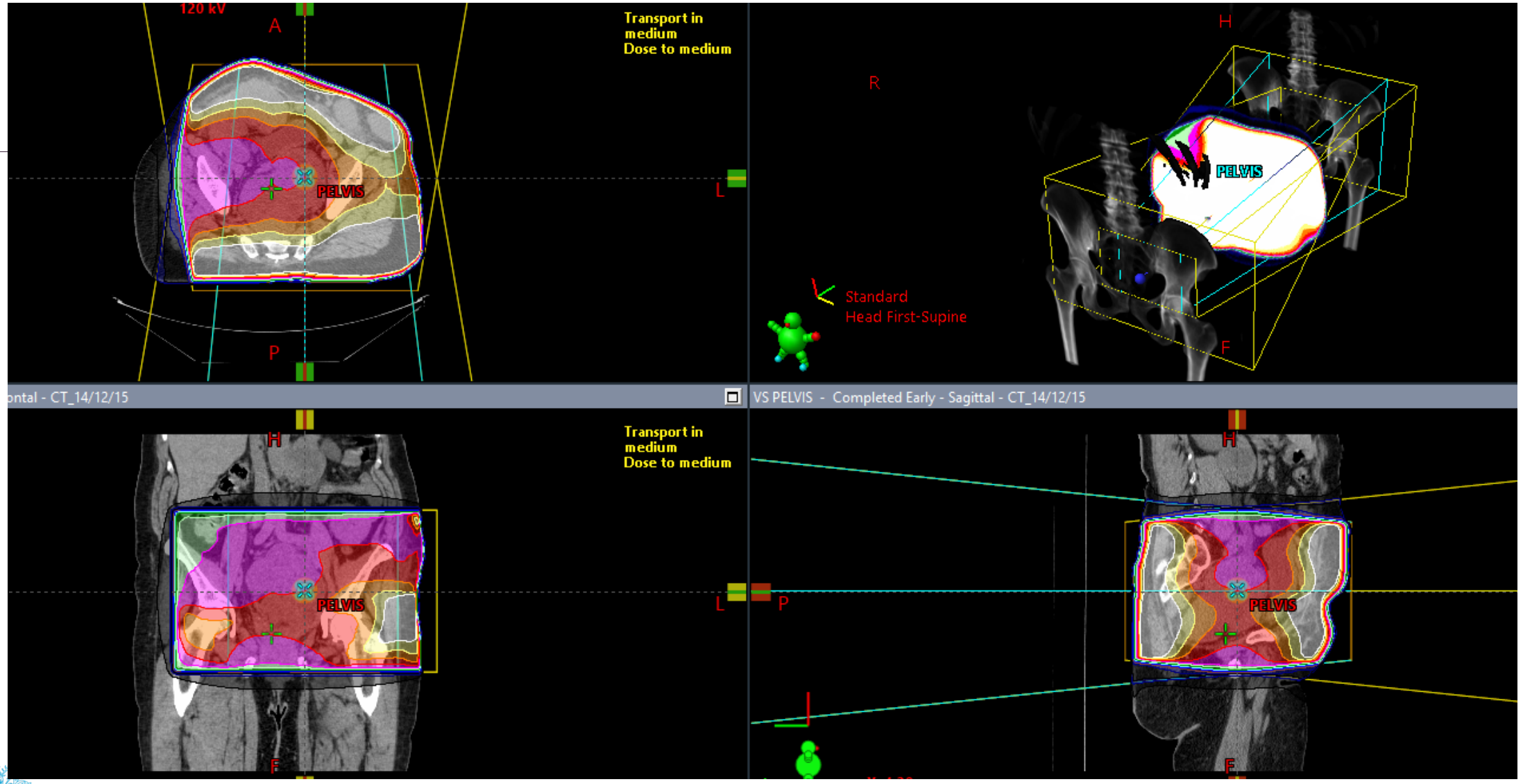
Technique

– Stereotactic radiotherapy	4
– IMRT	16
– Large volume fields	6

Dose 20-45 Gy in 5 – 20 fractions

Large field radiotherapy

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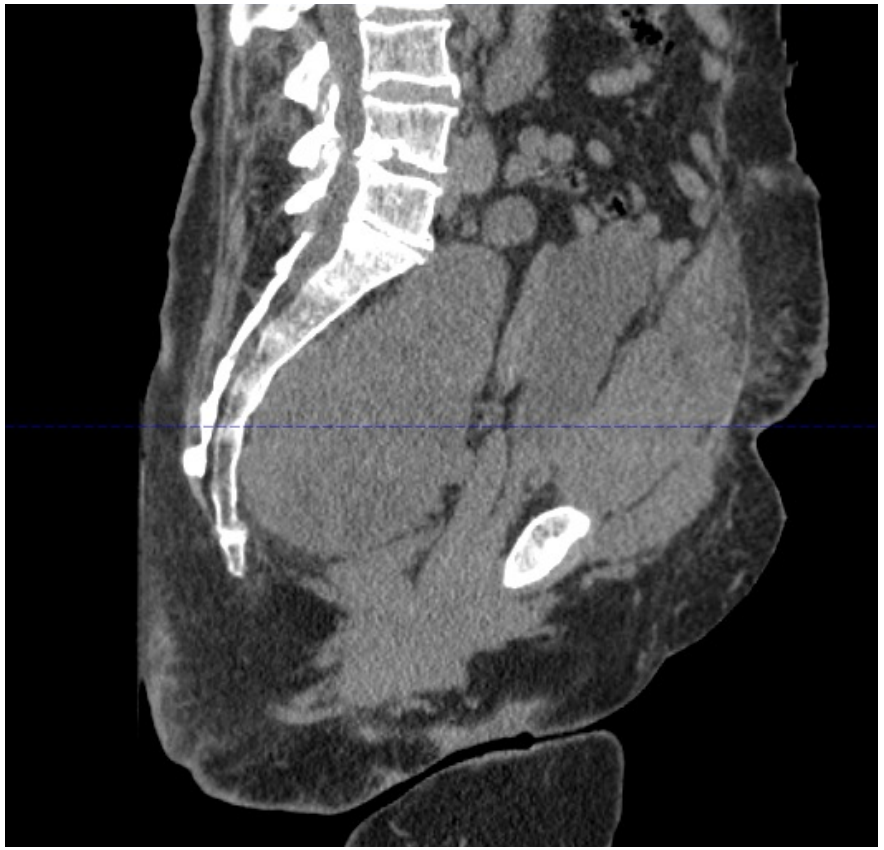
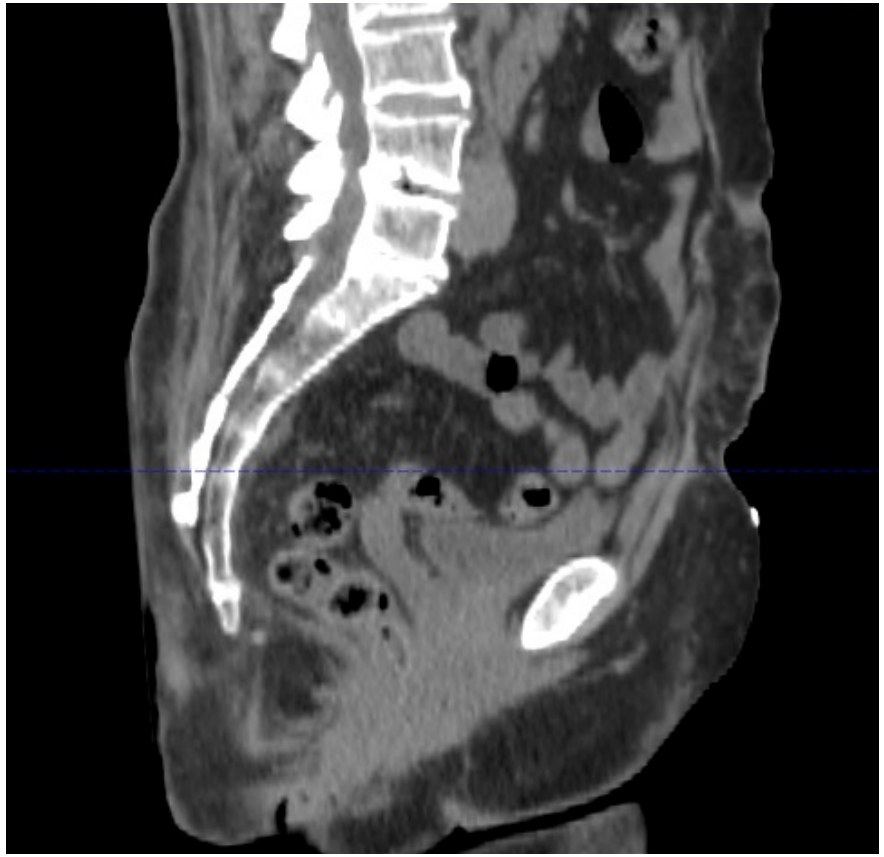
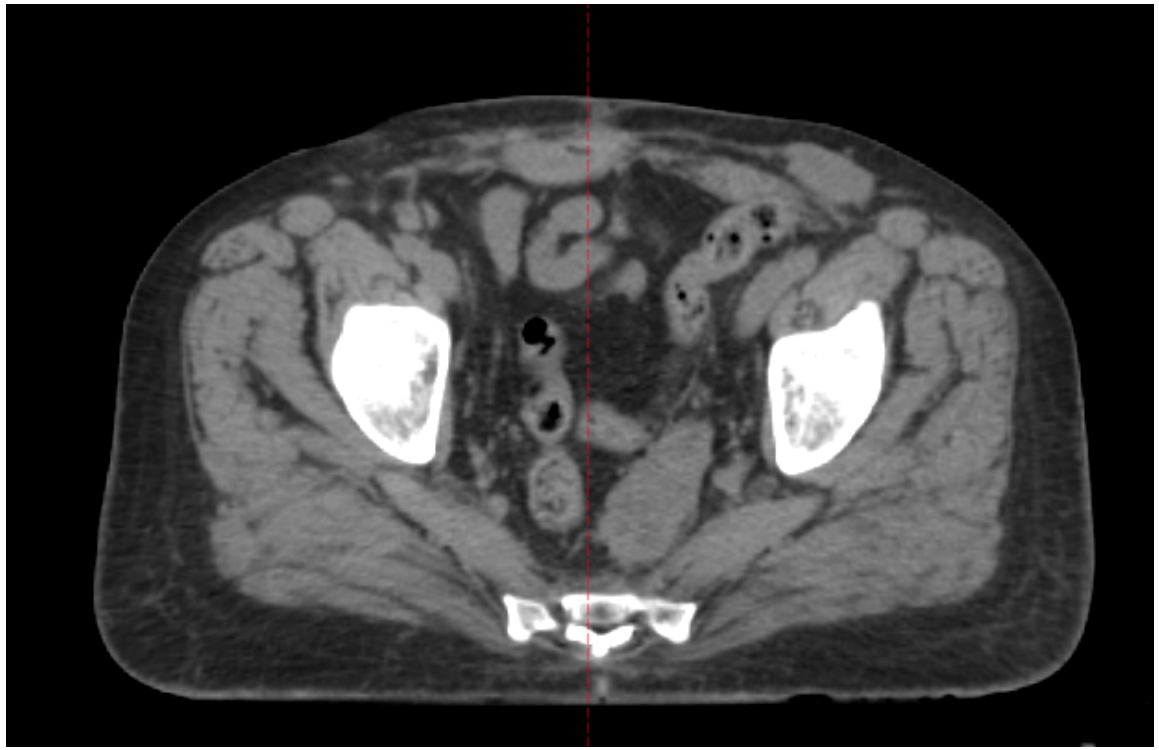
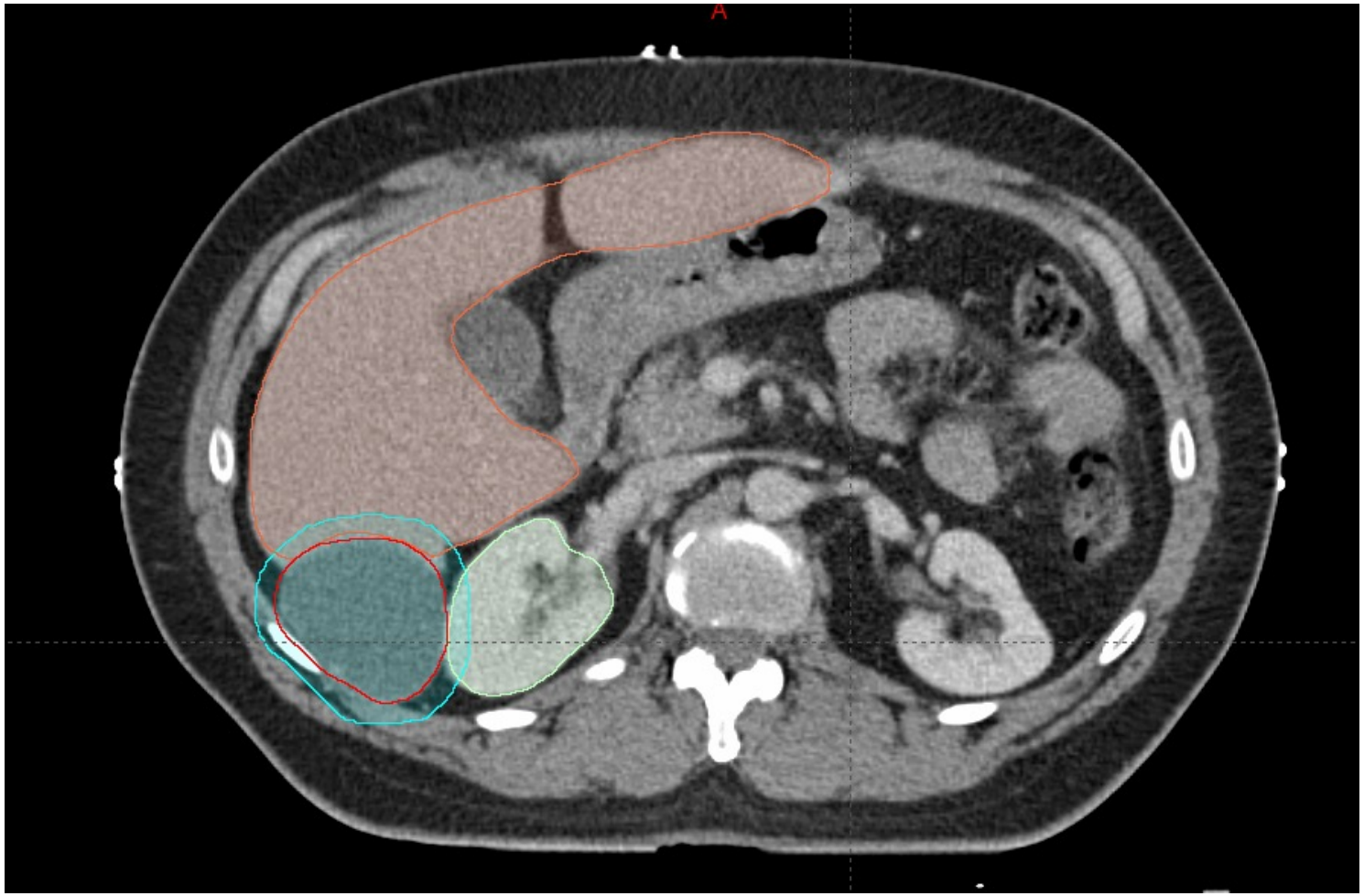
Response to radiotherapy



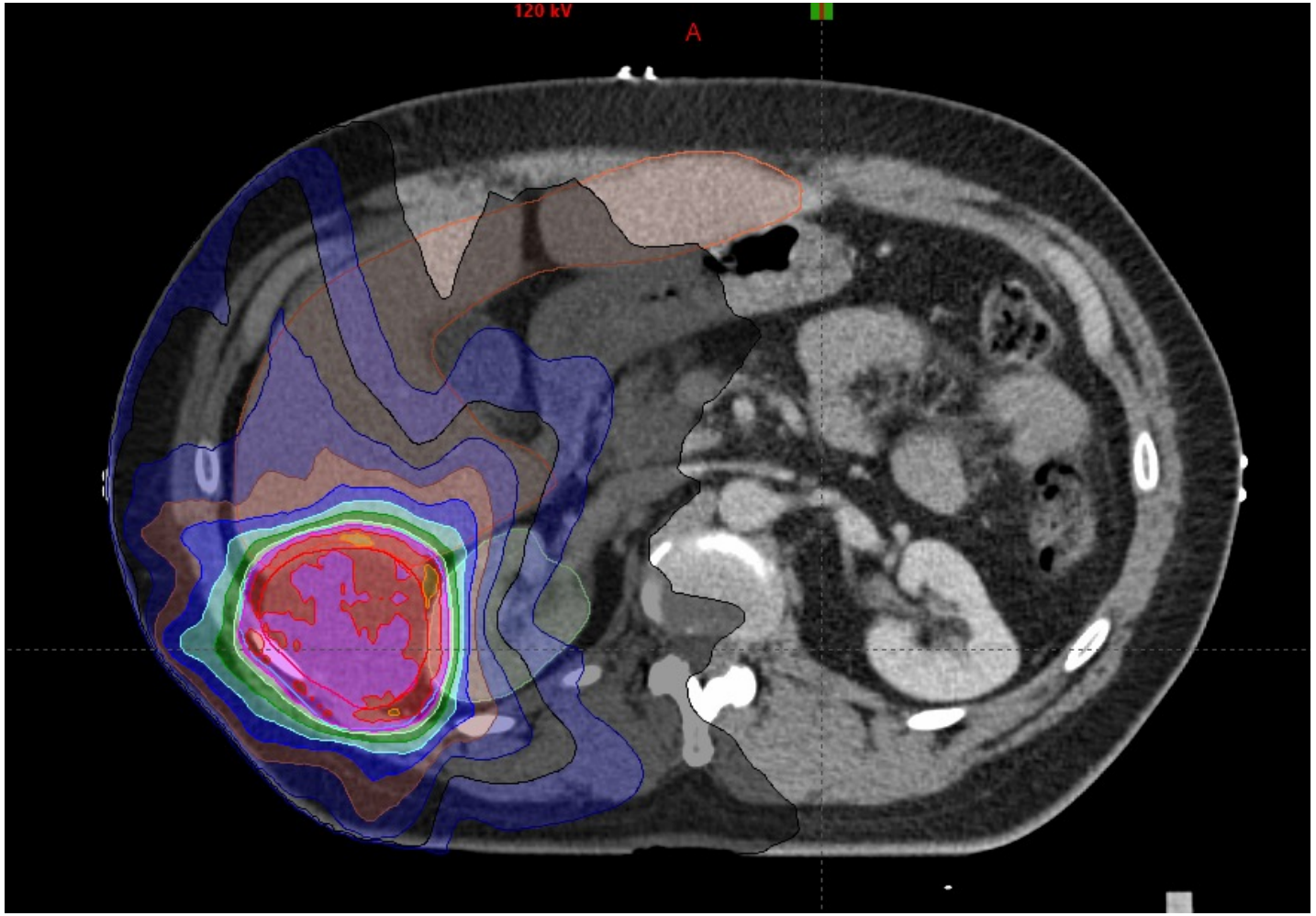




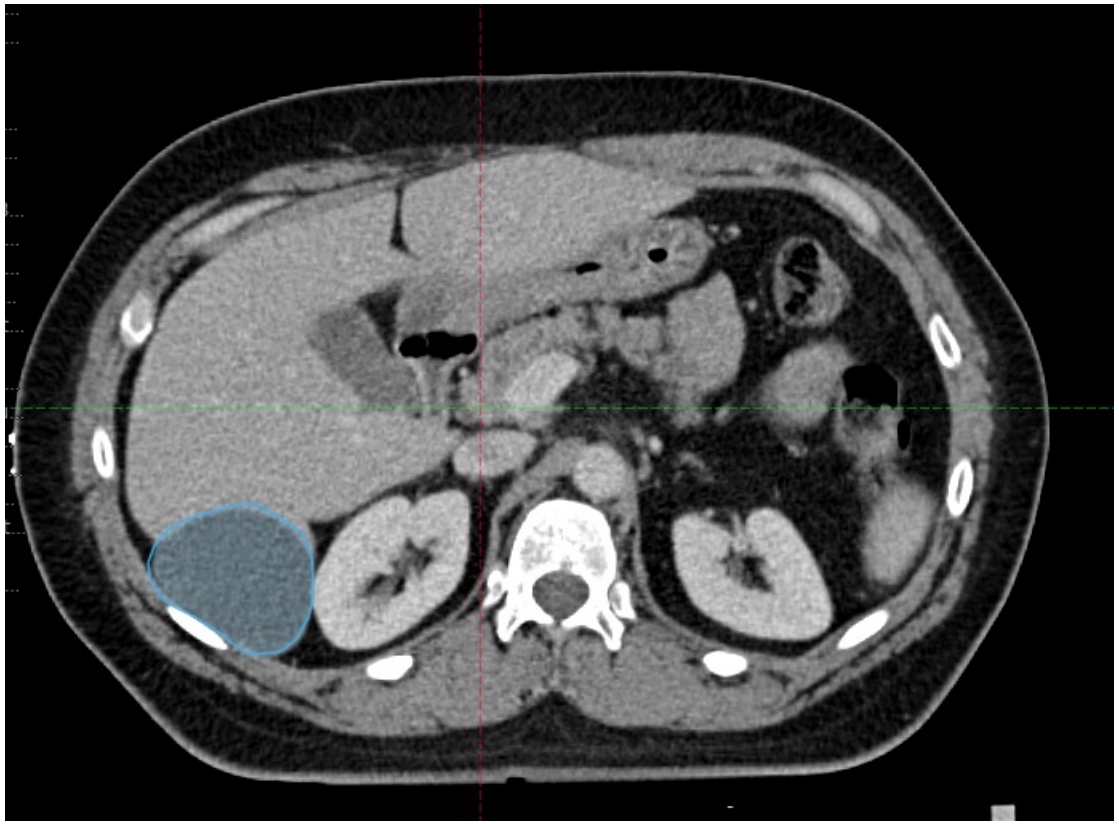
IMRT

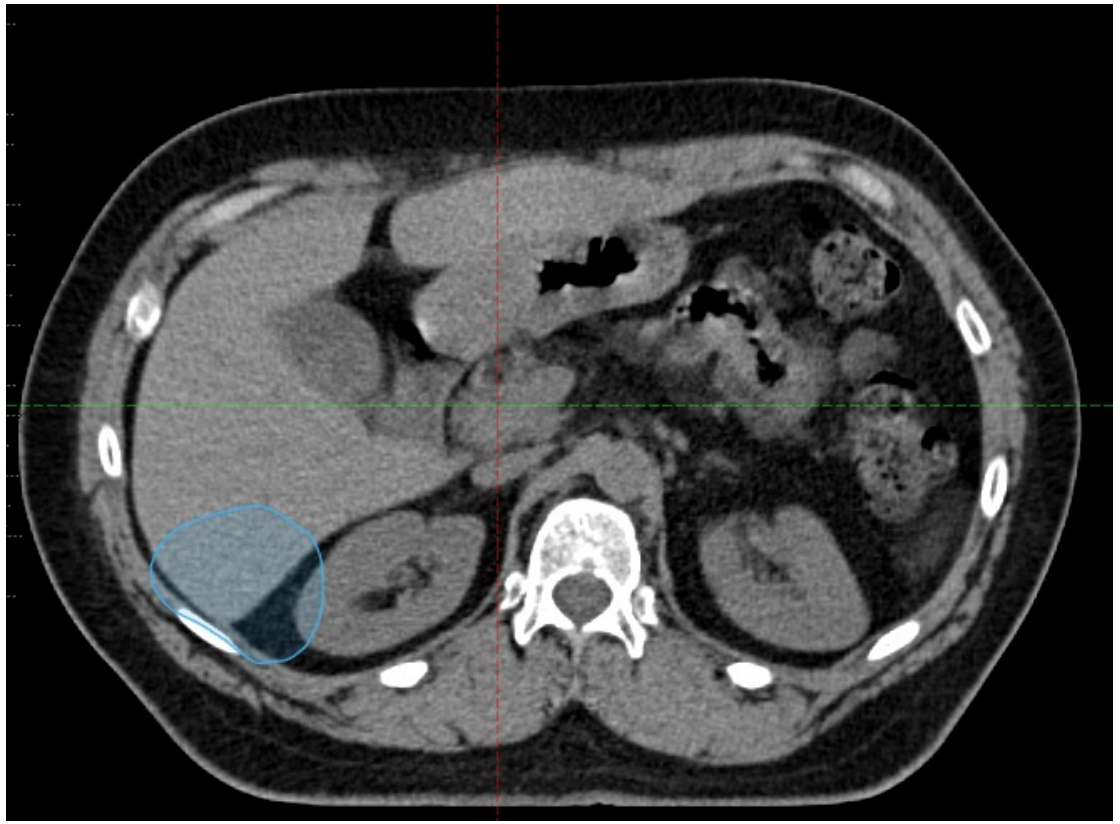


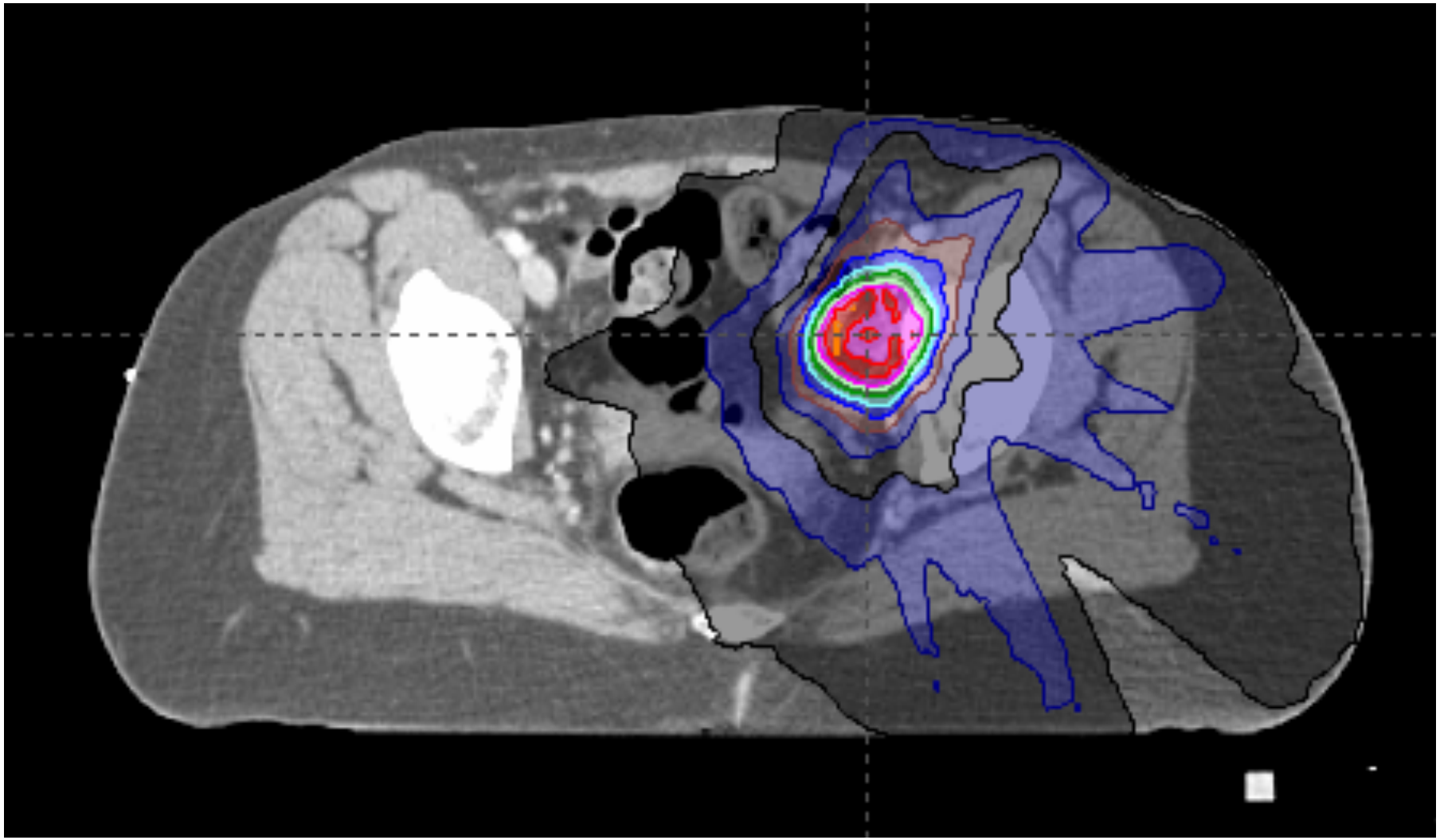
IMRT



Response







Response to radiotherapy

- Unable to assess response in 2 patients
- Reduction in tumour was seen in 100% of assessable sites

Median reduction in tumour volume:

79% (18-100%) at 3 months after RT

90% (24-100%) at 12 months

4/11 patients had a complete response and 2/11 had <1% residual

One patient relapsed in the irradiated site after 47 months

Overall local control 92% (median follow up 44 months)

Biochemical response

	Inhibin A	Inhibin B
Pre treatment	221	10297
3 months after RT	4	178
12 months after RT	3	48

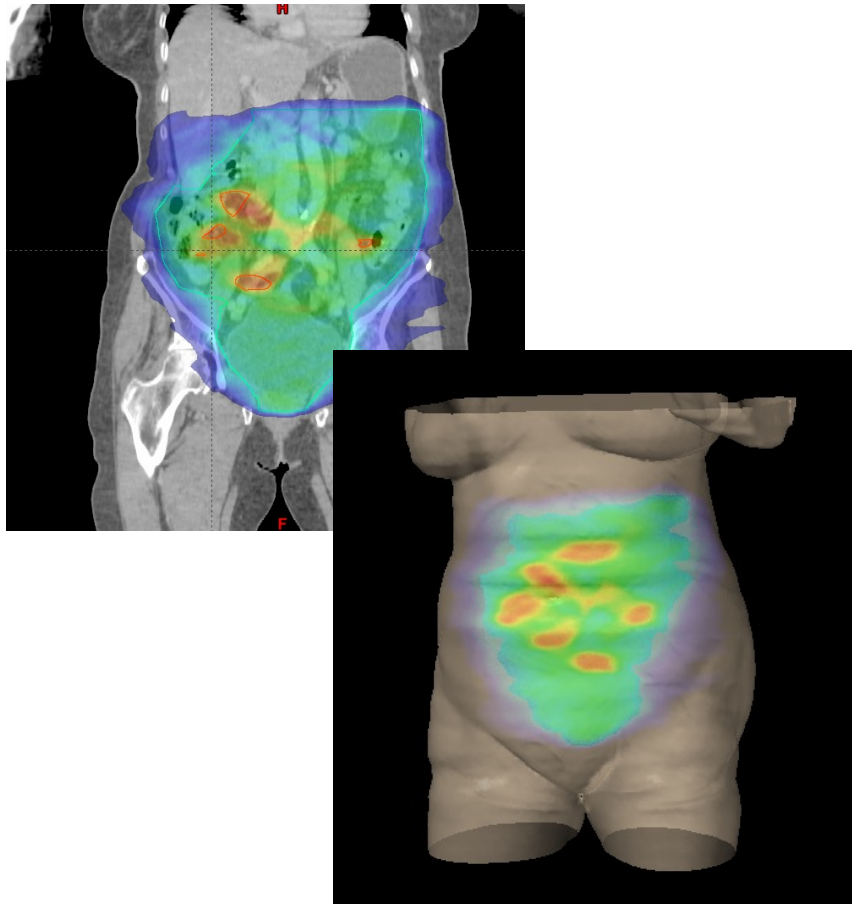
Conclusions

- Radiotherapy can be an effective treatment for recurrent granulosa cell tumours
- Selected cases and very limited data
- Have achieved durable responses even with lower radiotherapy doses suggesting these tumours may be very sensitive to treatment
- Radiotherapy response does not relate to response to chemotherapy

- Need further studies to determine optimal approaches
  - For localised disease
  - For more widespread disease

Future ideas

- Evaluate optimal dose response
- Explore whether alternative radiotherapy approaches are feasible
- Can we identify which tumours will respond?



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