Pelvic insufficiency fractures following radiation therapy for gynaecological cancers: Current knowledge.

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Introduction

- Advances in cancer continue worldwide:
  - estimated 18 million cancer survivors by 2022
  - at risk for developing treatment-related complications
  - increased fracture risk from treatment-induced bone loss in many sites and many patients
- Gynaecological cancers: third most diagnosed cancers in women in Australia
- Between 1982 -1986 and 2007- 2011:
  - 5-year relative survival from gynaecological cancers improved from 59% to 68%

Hui et al, 2015. Journal of Cancer. 6(1): 66-69.

AIHW, Cancer Australia 2012. Gynaecological cancers in Australia: an overview. Cancer series no. 70. Cat. no. CAN 66. Canberra: AIHW.

Gynaecological patients

- Radiation therapy indicated for:
  - 60% of cervical cancer patients
  - 45% of endometrial cancer patients
  - 5% of patients with ovarian cancer
- Cervix cancer: most common female malignancy in developed world
  - one of the most curable
- Various late effects of radiation therapy
  - impact quality of life
- Pelvic insufficiency fracture (PIF) may be a late effect of radiation therapy to the female pelvis

Ferlay, J. et al. (2013) Globocan 2012 v1,0. International Agency for Research on Cancer.
Ikushima et al (2006). Gynecologic Oncology: 103:1100-1104.

Pelvic insufficiency fractures (PIF) Predisposing conditions in women

- Bones with deficient elastic resistance
  - reduced BMD
- Osteoporosis
- Postmenopausal women
- Reduced body weight
- High doses of steroids
- Prolonged biphosphonate use
- Rheumatoid arthritis
- **Exposure to radiation therapy**

Dongryul & Seung (2014). Radiation Oncology Journal. 32(4):213-220

Ha et al (2010). Clinical Orthopaedics and Related Research . 468(12): 3393-3398

Treatment/Patient Factors in Radiation-Induced PIF

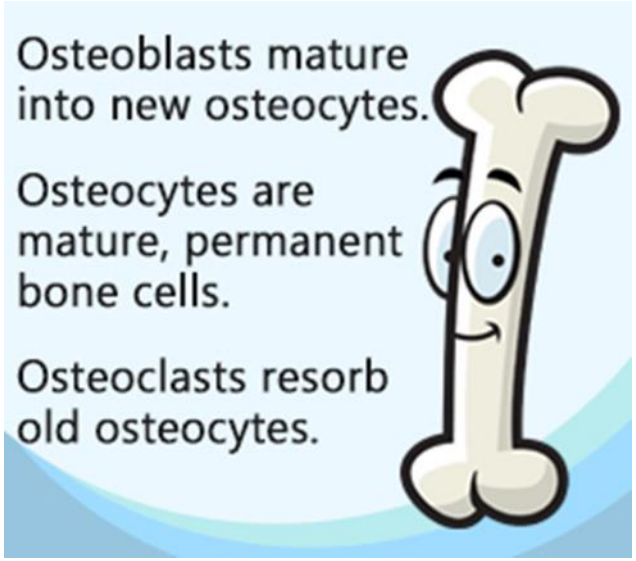
- Radiation therapy (RT) volume
  - RT to the area encompassing tumour
- RT dose per fraction
  - daily dose eg 2Gy
- Total dose
  - complete prescription
- RT technique
  - eg Intensity Modulated Radiation Therapy (IMRT) or conventional RT
- Chemotherapy

Dongryul et al. (2008) Int J Radiation Oncology Biol Phys 70(4)

Radiation therapy techniques

- Conventional RT: the gantry and treatment table may rotate to deliver radiation beams from one or more directions
- IMRT conforms the radiation dose more precisely to the three-dimensional (3-D) shape of the tumour by modulating—or controlling—the intensity of the radiation beam in multiple small volumes
- IMRT also allows higher radiation doses to be focused to regions within the tumour while minimising the dose to surrounding normal critical structures

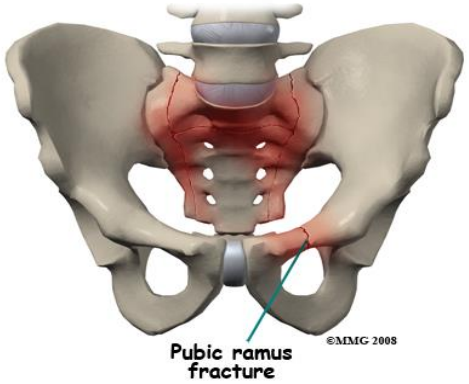
Pathogenesis of PIF



- Radiation: if dose high enough:
  - directly affects production of osteoblasts, osteoclasts, osteocytes
  - results in net reduction in bone matrix production
- A series of pathological changes
  - either delayed or acute
  - mild inflammation to neoplasia
  - microvascular occlusion
    - further compromises osteoblast function

Patro et al (2015). Journal of Evolution of Medical and Dental Sciences 4(35): 6077-6080
http://www.slideshare.net/kanhucpatro/pelvic-insufficiency-fracture

Pelvic insufficiency fracture



- Direct effect of radiation on mature bone:
  - tolerance of 65-70Gy
  - most gynae radiation doses less per course
- Indirect effect associated with vascular changes
  - injury to the microvasculature of mature bone
  - microcirculation occlusion results in injury to
    - periostic vasculature
    - osteoblastic function
    - osteopenia: by decreased collagen production
- RT reduces bone mineralisation
- Stress on weight-bearing atrophic bones = IF

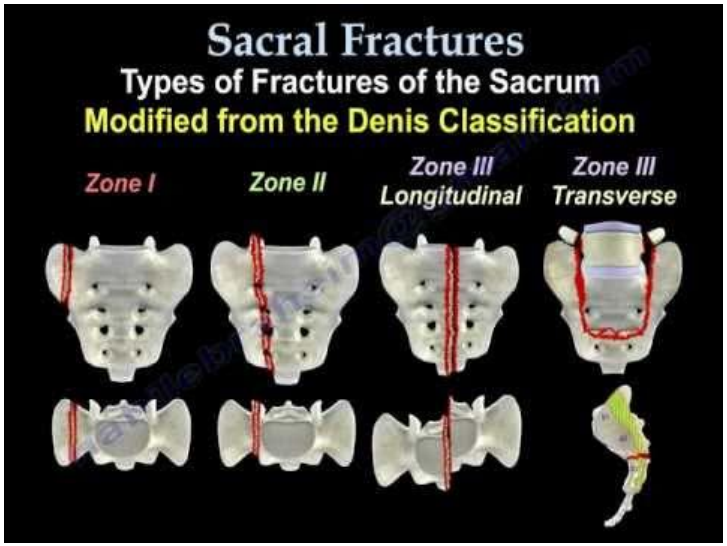
Connor TJ & Cole PA (2014). Geriatric Orthopaedic Surgery and Rehabilitation. 5(4): 178-190
Ikushima et al (2006). Gynecology Oncology, 103: 1100-1104

Symptoms

- Most common symptoms:
  - pelvic and low back pain
  - reduction in mobility
- Some women may find it difficult to see
  - regional and rural
- May relate to existing comorbidities
  - arthritis
  - osteoporosis
  - getting older
- Anxiety about cancer recurrence or metastatic disease

Dongryul et al. (2008) Int J Radiation Oncology Biol Phys 70(4).

PIF effect

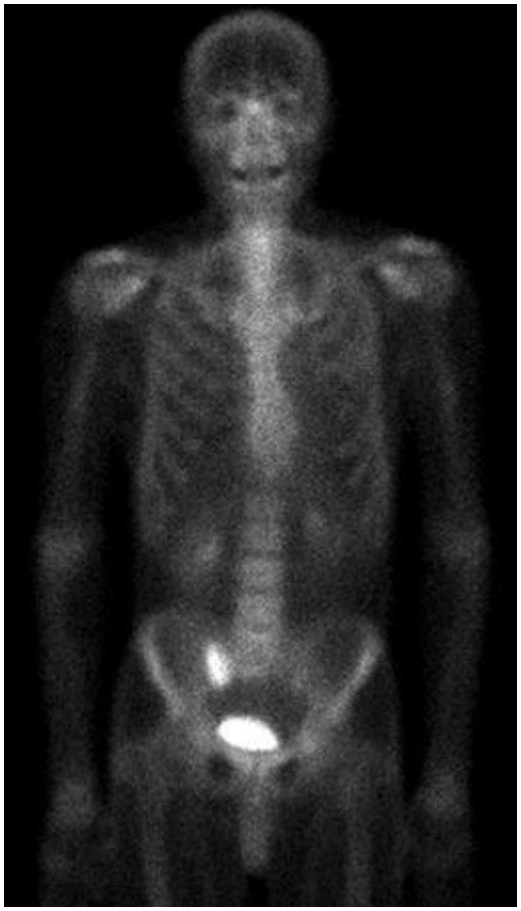


- Morbidity may be high
  - lack of mobility
  - considerable pain
  - possible time away from work
- Some patients need admission to hospital for assessment and pain control
  - reduced health-related QOL in physical / functional domains impacting on general well-being
- Pelvic pain may increase anxiety about recurrence or metastatic disease
- PIF picked up on imaging may be misdiagnosed as malignancy and unnecessarily treated

Dongryul & Huh (2014). Radiation Oncology Journal 32(4):213-220

Diagnosis

- X-ray may not pick up changes
- CT scan may be definitive:
  - typical fracture lines on sacral ala parallel to sacroiliac joint
  - sclerosis at adjacent area
  - may be multiple sites
- Magnetic Resonance Imaging (MRI) is highly sensitive
  - unable to be used with patients with pacemaker may be a limitation in this population of older persons
- Bone scan is highly sensitive



Connor TJ & Cole PA (2014). Geriatric Orthopaedic Surgery and Rehabilitation. 5(4): 178-190

Reviews of impact of radiation therapy

- *Moreno et al (1999):* 8 patients with PIF post radiation therapy
  - average onset of symptoms 13.7 months
  - initial symptom: pain
  - abnormalities on bone scan:
    - sacroiliac joint in 8 and pubis in 3
  - initial diagnosis was bone metastases in 5
- *Hui et al (2010)*: pelvic radiation therapy significantly reduced BMD by 11.1% compared with 15.2% with chemotherapy, and 24% with chemotherapy/radiation therapy combined
  - changes were seen as early as 6 months post treatment
- *Higham & Faithfull (2015):* may be difficult to isolate specific factors post multimodality treatment.

Moreno et al (1999). Int J Radiation Oncology Biol. Phys. 44(1):61-66
Hui et al (2010) American Journal of Obstetrics and Gynaecology 353:e1
Higham, CE, Faithfull, S Clinical oncology 11/2015, Volume 27, Issue 11

Incidence of PIF – longitudinal study

- Tokumaru et al (2012) undertook longitudinal MRI at 3,6,12,18,and 24 months following radiation therapy for uterine cervical cancer:
  - 59 eligible patients
  - PIF was seen in 36.9%
  - Can occur as early as 2 months after radiation therapy but can develop 8 years and beyond
  - Median time between 6 and 20 months

Tokumaru et al (2012). International Journal of Radiation Oncol Biol Phys, 84(2).

Newer technologies

- *Ioffe et al (2014)* compared instances of PIF between IMRT and conventional radiation to the pelvic girdle
  - found significant decrease in post-treatment pelvic girdle complications in patients treated with IMRT.
- *Nama et al (2015)* reviewed 10 cases of PIF in gynaecological cancers treated with standard treatment
  - they recalculated the dose volume histogram based on IMRT protocols for patient with PIF
  - they found that none of the patients would have received any radiation at the fracture site with IMRT.

Ioffe et al (2014) Int J Gynecol Cancer 2014 May, 24(4):806-12
Nama et al (2015) Journal of Radiotherapy in Practice, 14(2).

Considerations

- Predictive factors + H/O radiation therapy
  - lifestyle factors:
    - smoking and alcohol excess
    - exercise, weight, and diet
  - postmenopausal
  - osteopososis
  - family history
  - biochemical assessment of Vit D
- Rural: If a patient presents with pelvic pain following pelvic radiation therapy then PIF should be considered
  - MRI or computed tomography should be undertaken

Prevention

- Baseline bone density measurement pre-treatment
- Serum Vit D
- Regular assessment
- Several factors to maintain healthy bones
  - exercise: prevention of osteoporosis
  - early diagnosis of PIF for symptom control
- *Higham & Faithfull (2015): 'there are no randomised controlled studies investigating the primary prevention of post-fracture management of RIPIFs'*

Hui et al (2010. American Journal of Obstetrics & Gynecology. 203: 353.e1-7. http://www.analcancerhelp.info/coping-with-side-effects/coping-with-pelvic-radiatio.htmlsupplementation- extra dietary calcium daily

Management

- Analgesia and gentle mobilisation is advised unless the fracture is unstable...
  - referral to an orthopaedic surgeon is advised
- Conservative: bedrest, gentle mobilisation, analgesia
  - resolution occurs between 3 and 30 months
- NSAIDS may be contraindicated *(Patro, 2015)* due to blockage of prostaglandin activity which play a significant role in bone healing
- All patients with a fragility fracture should have a serum Vit D measure
- Physiotherapy, heat, massage, TENS
- Conflicting evidence of the role of bisphosphonates *(Francis et al, 2015)*
- No evidence for HRT

Conclusion

- The incidence of PIF ranges from 11% - 89%
- Morbidity may result in reduced mobility, pain and time from work
- Some patients need admission for assessment and pain control
- There may be reduced health-related quality of life
- Pelvic pain may increase anxiety about recurrence or metastatic disease
- PIF seen on imaging may be misdiagnosed as malignancy and unnecessarily treated.

Finally……..

- Early diagnosis critical to maintain QOL and management of PIF
- IMRT may significantly reduce the risk of PIF
- Many countries may not have newer technologies:
  - some patients treated before IMRT and migrant patients may have residual PIF
- Patients in rural and regional areas may be misdiagnosed
  - if lower back pain not considered a possible late effect of previous radiation therapy
- Post-treatment strategies:
  - include information to prevent PIF
- Empower patients, GPs and HPs to recognise PIF


thank you