Radiotherapy for Prostate Cancer

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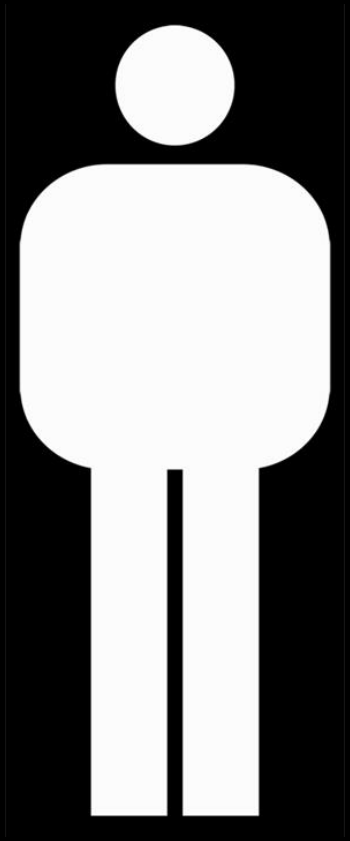
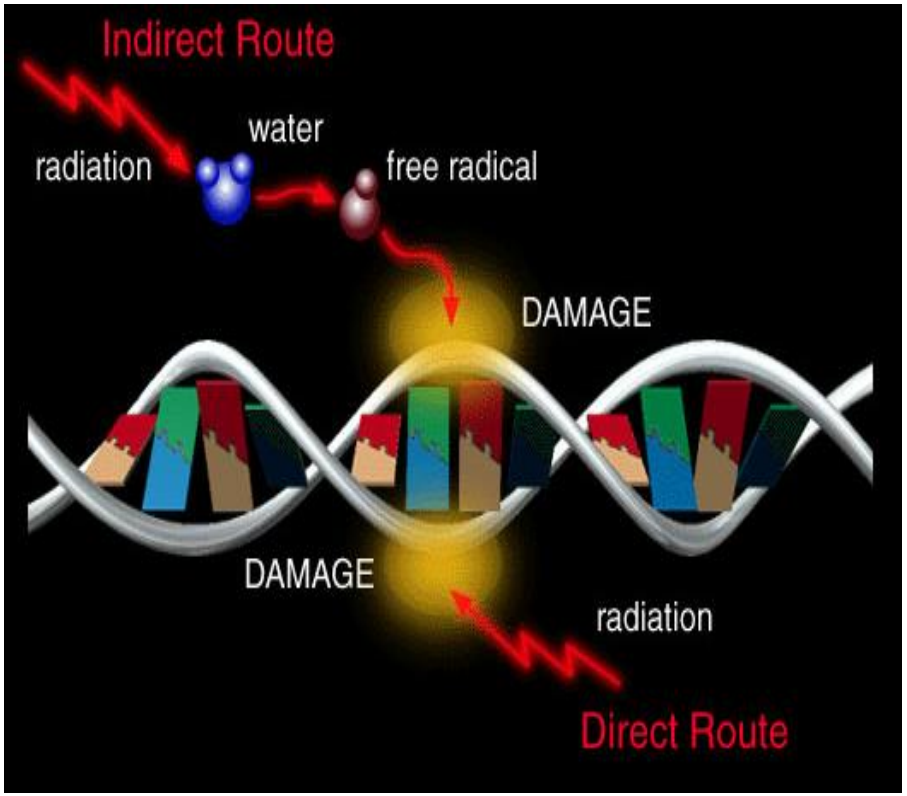
What would you most like to learn about?

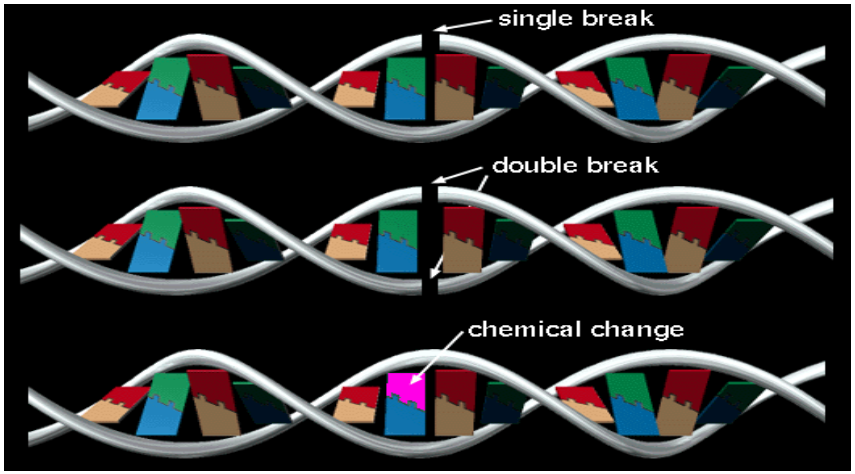
What are the challenges in practice when talking about Radiotherapy?

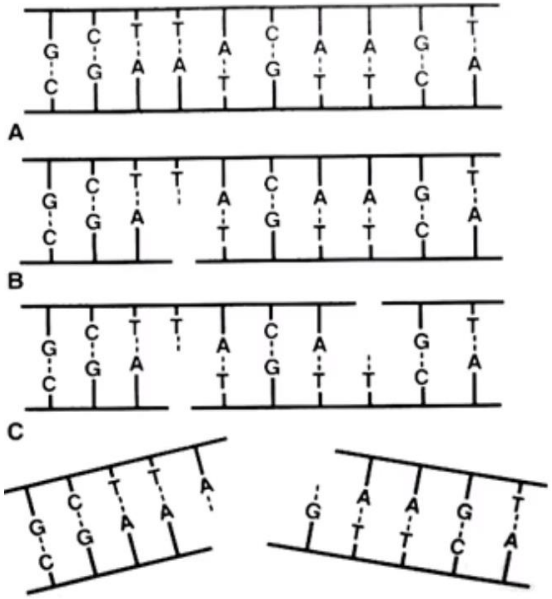
What are the challenges when supporting patients who have received Radiotherapy?



What is it and how does it work?







A: normal

B: SSB easily repaired

C: SSB easily repaired if well spaced

D: DSB usually lethal

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Types of radiotherapy

- External Beam Radiotherapy
- Brachytherapy
- Radionuclide therapy

- **All used to treat prostate cancer**

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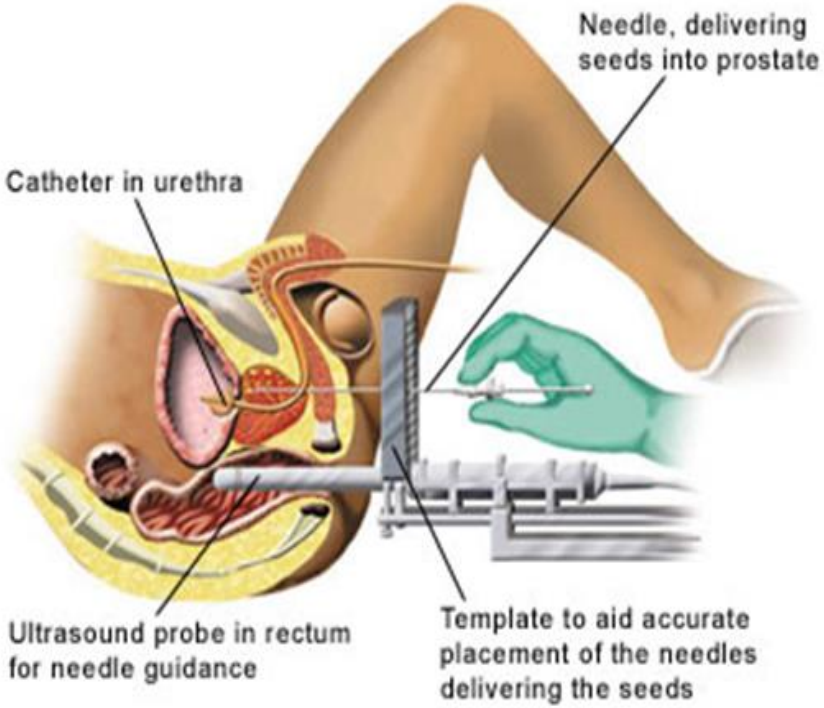
Most commonly



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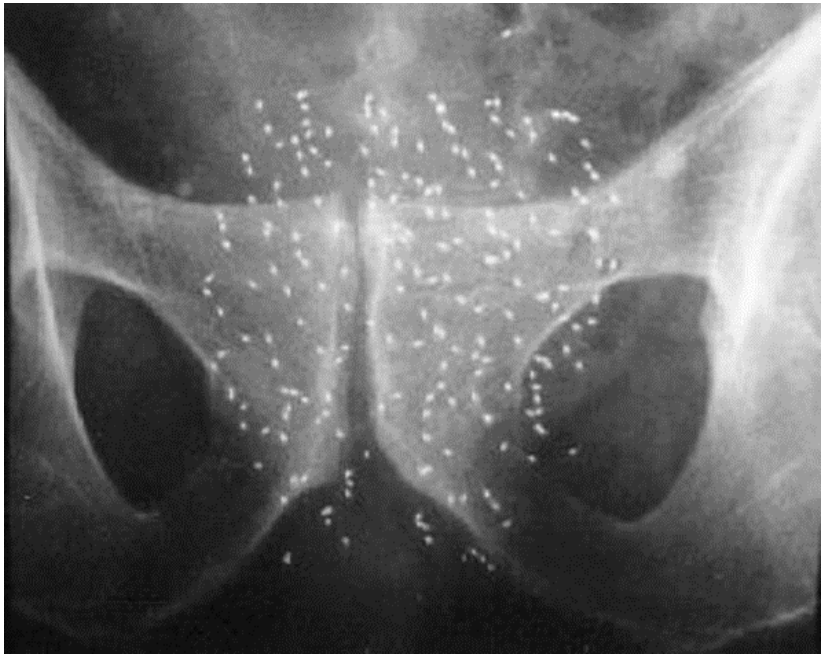
Brachytherapy: two methods of delivery

Iodine 125 LDR



Iridium 192 HDR

Low and intermediate risk disease – monotherapy
High risk/locally advanced disease – EBRT + BT*

*May be more effective than EBRT alone (equivalent dose typically 88.7Gy)

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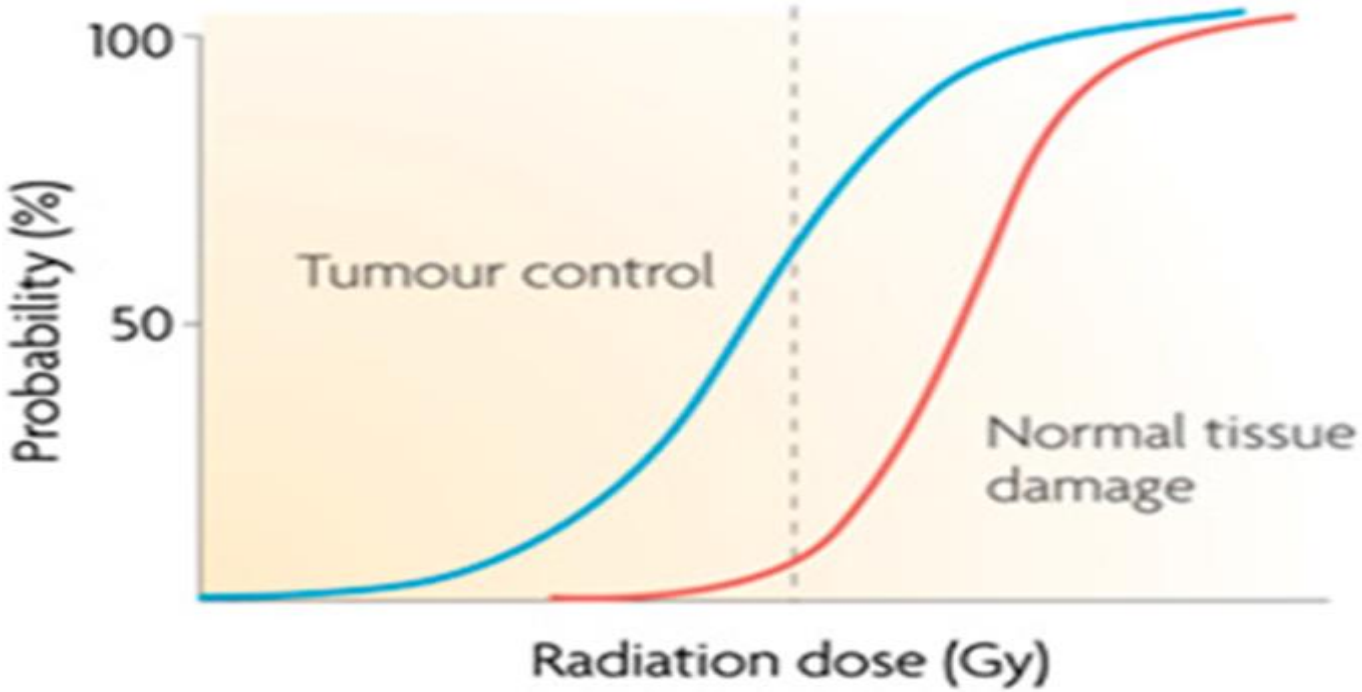
Goals of radiotherapy



- Critical structures in prostate radiotherapy = rectum and bladder

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Role of radiotherapy for prostate cancer

- Radiotherapy can be used at **all stages** of the disease

- **<u>Key message</u>**
- A large proportion of men with prostate cancer will have received radiotherapy, in some form

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Localised prostate cancer

Low risk	Intermediate risk	High risk
A primary treatment ‘option’ alongside radical prostatectomy *(if active surveillance not elected)*	A primary treatment ‘option’ alongside radical prostatectomy	Main treatment of choice *(some men may still choose to have radical prostatectomy)*
Radiotherapy to the whole prostate only	Radiotherapy to the whole prostate and part of the seminal vesicles	Radiotherapy to the whole prostate, seminal vesicles +/- pelvic lymph nodes
External Beam Radiotherapy OR Brachytherapy	External Beam Radiotherapy OR Brachytherapy	External Beam Radiotherapy OR External Beam Radiotherapy AND Brachytherapy combined
(Neo)-adjuvant treatment unlikely	Neo-adjuvant short course of ADT	Neo-adjuvant ADT continuing a minimum 2-3 years post radiotherapy

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Locally advanced prostate cancer

- **Primary radiotherapy is the recommended treatment of choice with neo-adjuvant long term ADT a minimum 2-3 years post radiotherapy**
- Similar approach to high risk, localised disease
- Radical prostatectomy may still be given as an option to some men with T3 disease
- Adjuvant or salvage radiotherapy after surgery may be required
  - Positive resection margins
  - Positive seminal vesicles
  - Positive lymph node involvement
- Debate and research ongoing regarding timing of radiotherapy after surgery

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Metastatic prostate cancer

- When metastatic disease is widespread, external beam radiotherapy will be used to **palliate symptoms** e.g. due to bone metastases.

- Radium-223 (radionuclide therapy) is also an effective treatment for treating the symptoms of bone metastases but it also offers a disease control/survival advantage as well (ALSYMPCA trial).

- **Active treatment** to control the disease may also still be used at this stage.

- Results from the STAMPEDE trial have demonstrated the benefit of local radiotherapy to the prostate and surrounding area (similar to high risk/locally advanced RT) for patients with a low metastatic burden

- High dose, ablative radiotherapy may also be used to treat focused sites of oligo-metastases or solitary metastases

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As an ‘option’ - factors considered

- **Disease control / survival**
- The 10 year follow up data from the ProtecT study of 1643 men demonstrated no significant difference in prostate cancer specific mortality between the surgery and radiotherapy groups.

- **Toxicity**
- Bowel side effects with external beam radiotherapy.
- ED statistics suggest slightly less men are affected following radiotherapy – but not that straightforward!
- Urinary side effects – similar between surgery and radiotherapy (certainly in the longer term)

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Cont….

- **Patient preferences / concerns**
- Removal of a cancer form the body
- Risk of surgery
- Treatment duration for external beam radiotherapy
- Support during radiotherapy
- Addition of ADT with radiotherapy but may only be short term
- Disease monitoring post treatment / PSA bounce
- Treatment availability (an issue with Brachytherapy)

- **Clinical contra-indications for RT** (especially external beam)
- Other co-morbidities e.g. Chrons / inflammatory bowel disease
- Previous pelvic radiotherapy
- Large prostate volume >50cc (may rule out Brachytherapy)

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Image-guidance and improved dose targeting

- Improvements in pre-treatment imaging

  = **improved delineation of the target volume and organs at risk**
- Advances in radiotherapy delivery

  = **high dose radiation beams 'shaped' more precisely to the target**
- Improvements in imaging during treatment

  = increased accuracy in treatment delivery

- All of the above has led to increases in the dose prescribed

  = **improved disease control**
- All of the above has led to decreases in the doses delivered to organs at risk

  = reduced toxicity

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CT localisation (delineation of target and OAR)

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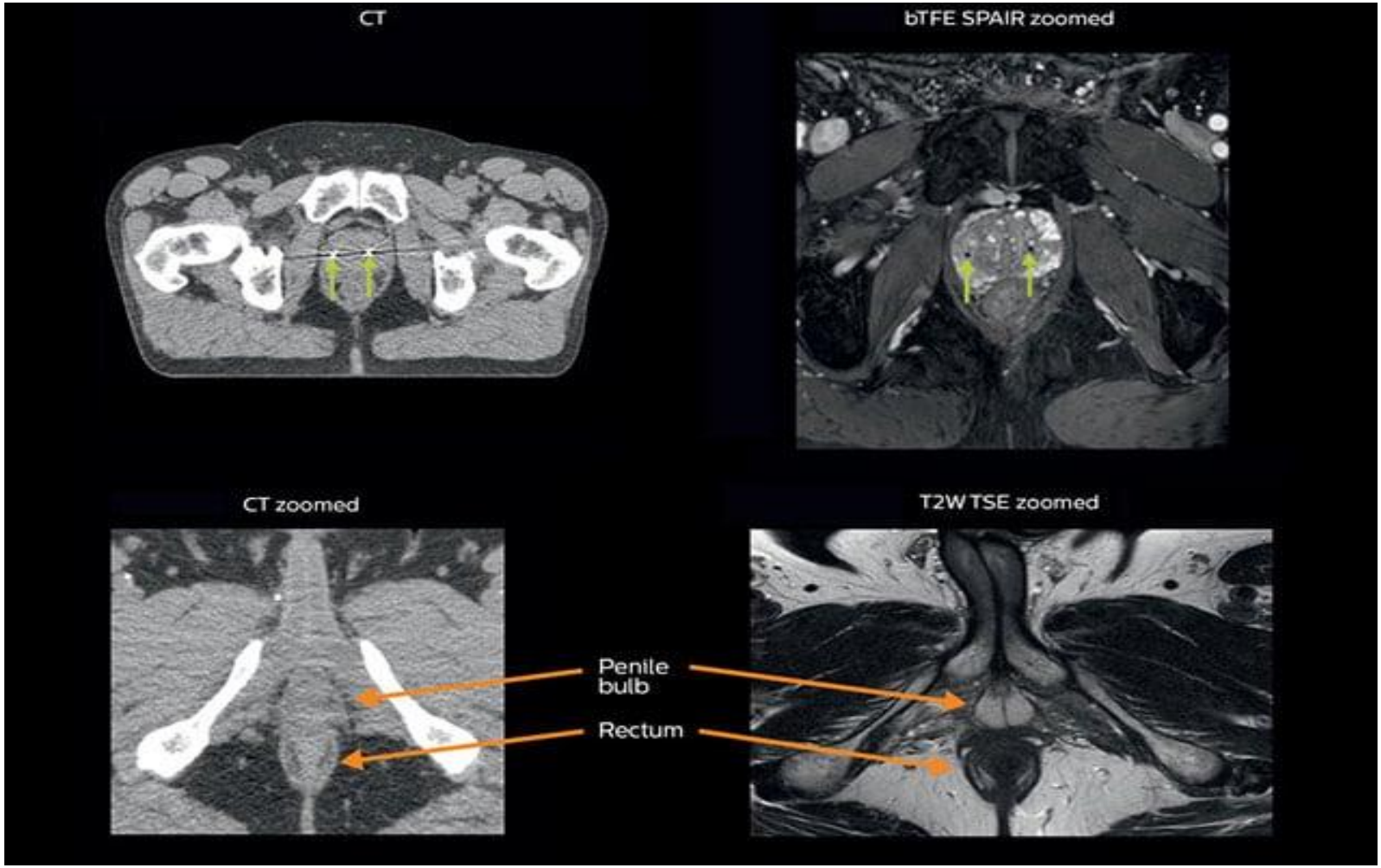
MRI – improved visualisation



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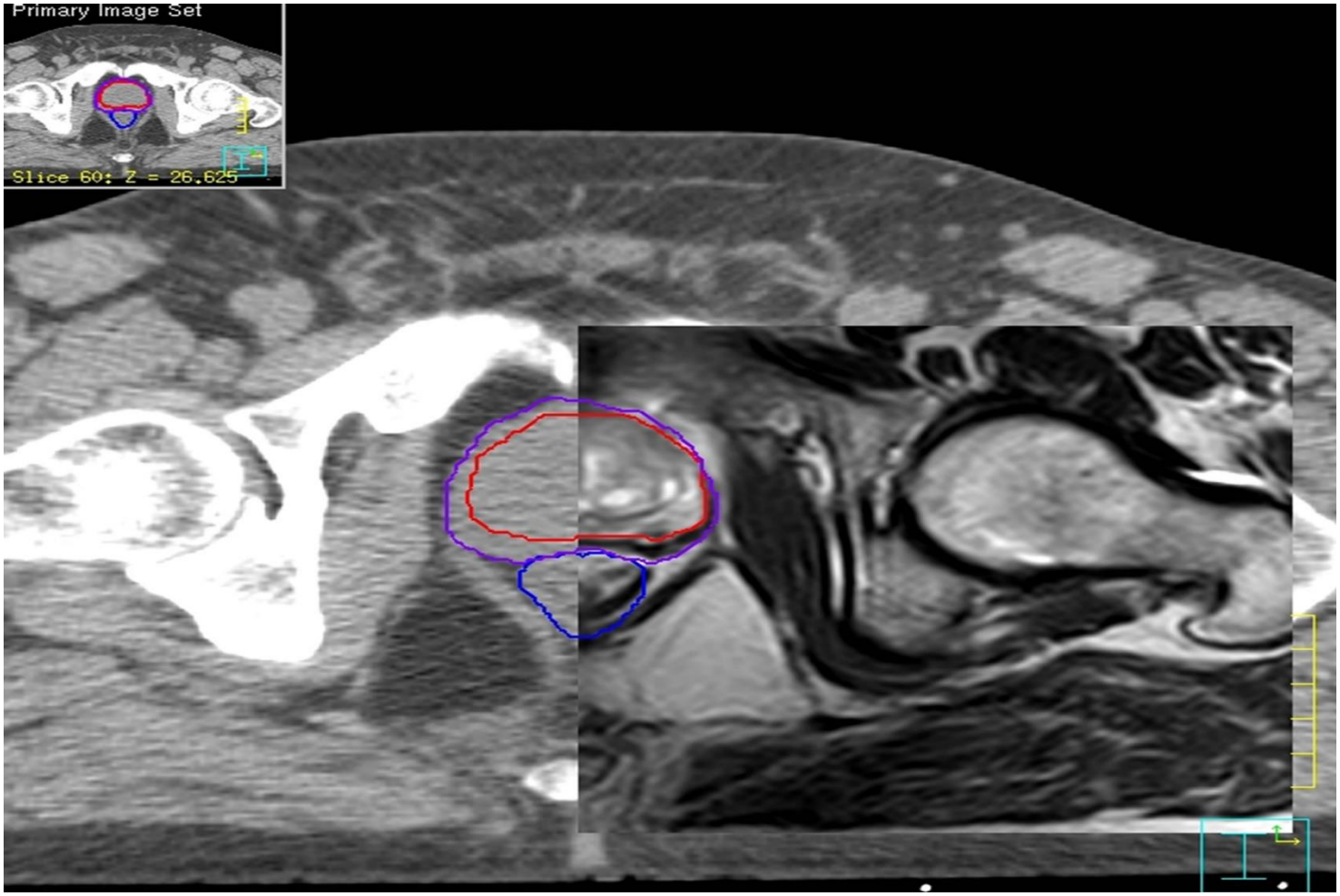
CT-MR fusion



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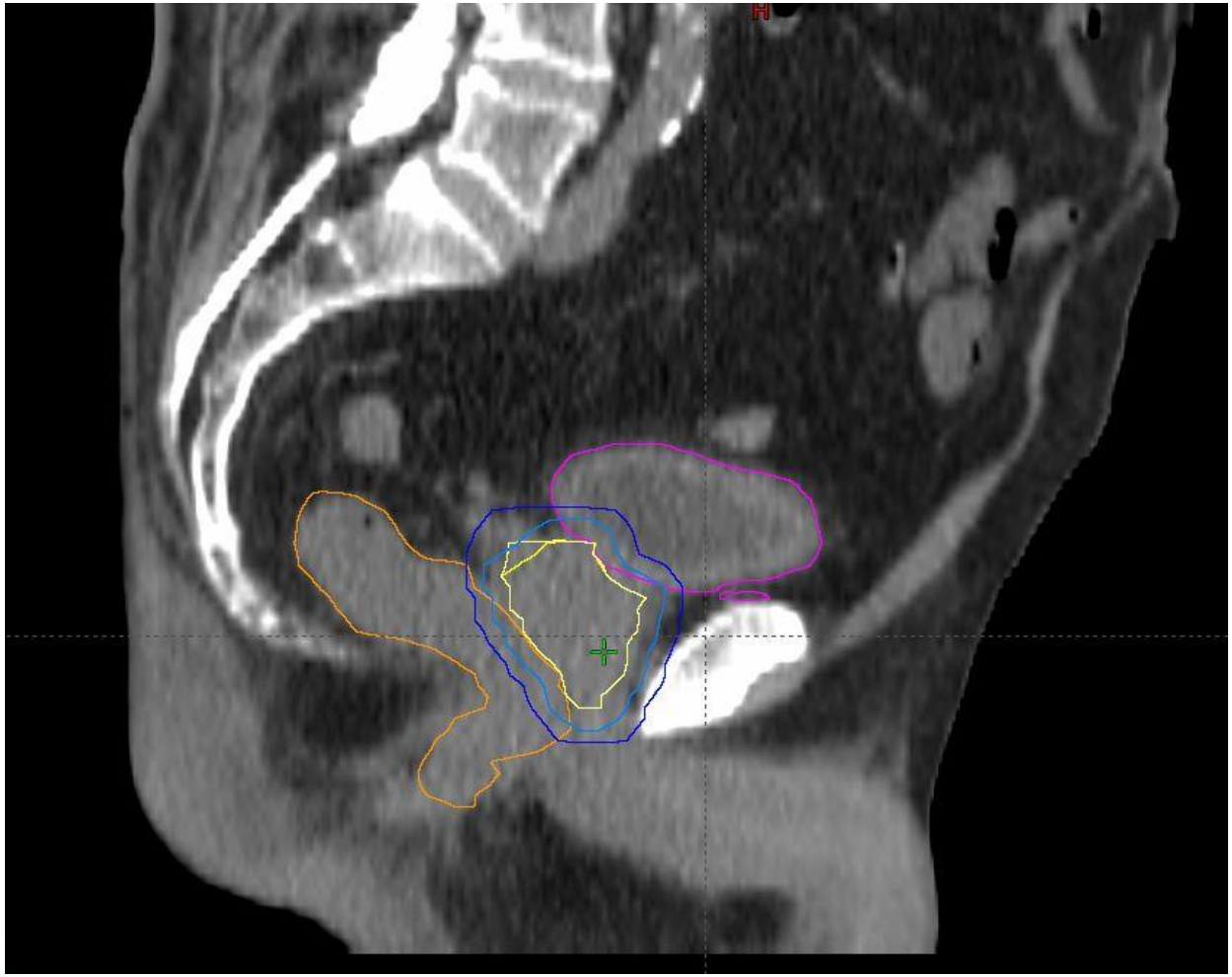
Target and OAR delineation (example)



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EBRT ‘prostate’ dose prescribed

- Conventional treatment is delivered in a series of daily doses (called fractions #), usually Monday to Friday, until the prescribed total dose is reached.

- It is well documented that EBRT as a definitive/primary treatment should deliver a minimum dose (or biological equivalent) of 74Gy in 37 # to the prostate.

- Hypo-fractionated regimes are becoming standard practice for prostate cancer 60Gy in 20# to the prostate.

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Conventional or Hypo-fractionated High Dose Intensity Modulated Radiotherapy (CHHiP) trial

T1B - T3A N0 M0

Risk of SV involv ≤30%

PSA ≤30ng/ml

Conventional
74Gy 37F 7.5 wks

Hypofractionation Schedule 1:
57Gy 19F 3.8 wks

Hypofractionation Schedule 2:
60Gy 20F 4.0 wks

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Stereotactic Ablative Radiotherapy (SABR)

- Currently being researched for localised, low-intermediate risk prostate cancer
- PACE trial – SABR vs. surgery and SABR vs. conventional RT
- SABR involves the delivery of large, ablative doses per fraction. For example: 36.25Gy in 5#
- A very high degree of accuracy is required.

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Planning and delivery method

- With 3D planning techniques, the whole target volume can be viewed in all directions and radiation beams can be created that closely match it’s size and shape.

- Intensity Modulated Radiotherapy (IMRT) is a more advanced 3D planning technique which varies the radiation intensity across each beam, and in turn can shape the high dose delivered even more precisely to the target.

- Types of IMRT – Fixed field IMRT, Volumetric Modulated Arc Therapy (VMAT) and Tomotherapy

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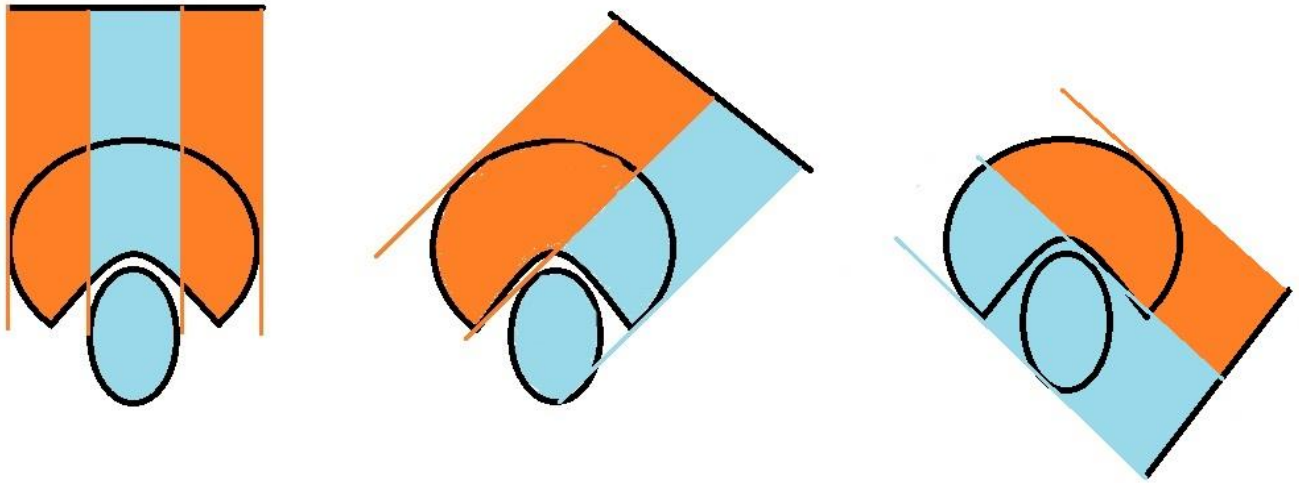
IMRT basic illustration: varying beam intensities build up the dose to the prostate, as the machine moves around the patient. Intensity is lowest (blue) in the path of the rectum.

It also enables us to <u>simultaneously</u> deliver different dose prescriptions, to different defined volumes e.g. PTV1 - prostate only; PTV2 - prostate + SV; PTV3 - prostate, SV + LN.



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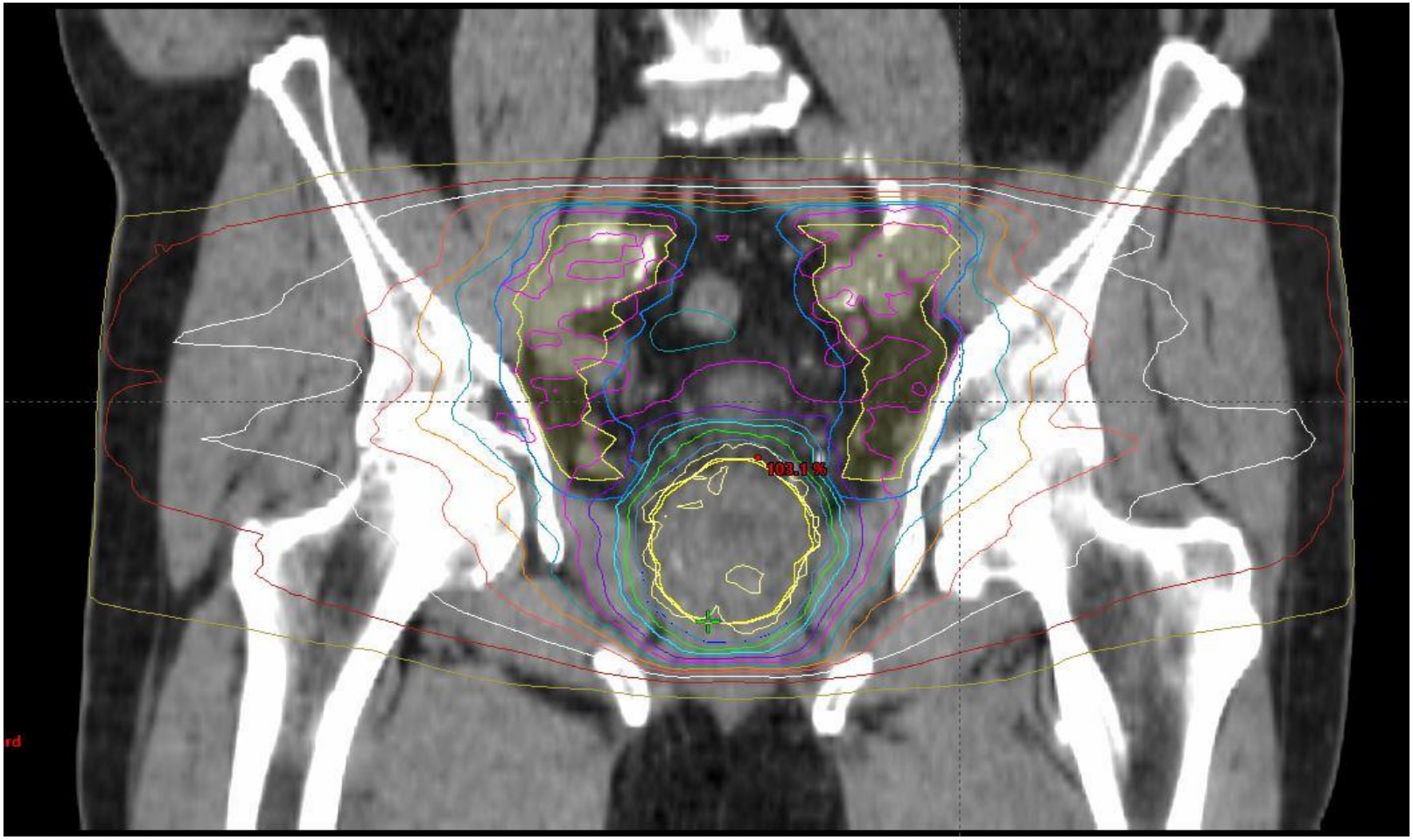
Prostate, SV and nodes plan



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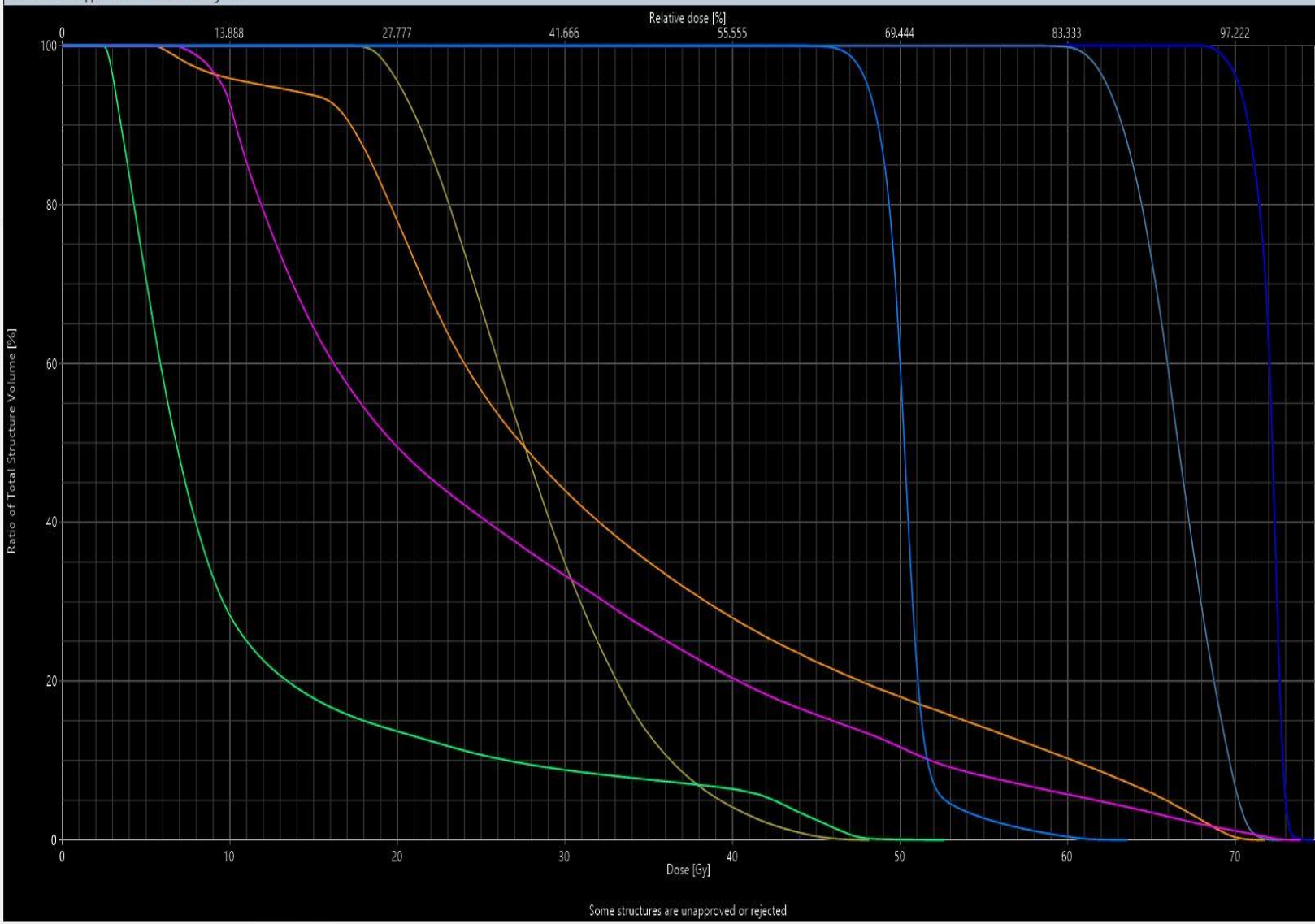
zzt0068
1
Prostate and Nodes 72Gy/32#
TrtProstate7
TrtProstate8
Prostate and Pelvis Nodes 72Gy/32#
TrtProstate7
TrtProstate8

Registered Images
ClinicianApprove
12345
Bladder
Bladder_H64
Bladder_Opt
Body
Bowel_H50
Bowel_Opt
BowelBag
CouchInterior
CouchSurface
CTVe_50
CTVp_72
CTVpsv_64
Femoral_Heads
PTV_Total
PTVe_50
PTVe_50Crop
PTVp_72
PTVpsv_64
PTVpsv_64Crop
Rectum
Rectum_0.2
Rectum_H64
Rectum_Opt
TotalBowel
TotalBowel_0.3
User Origin
Reference Points

TrtProstate7 - Unapproved - Dose Volume Histogram

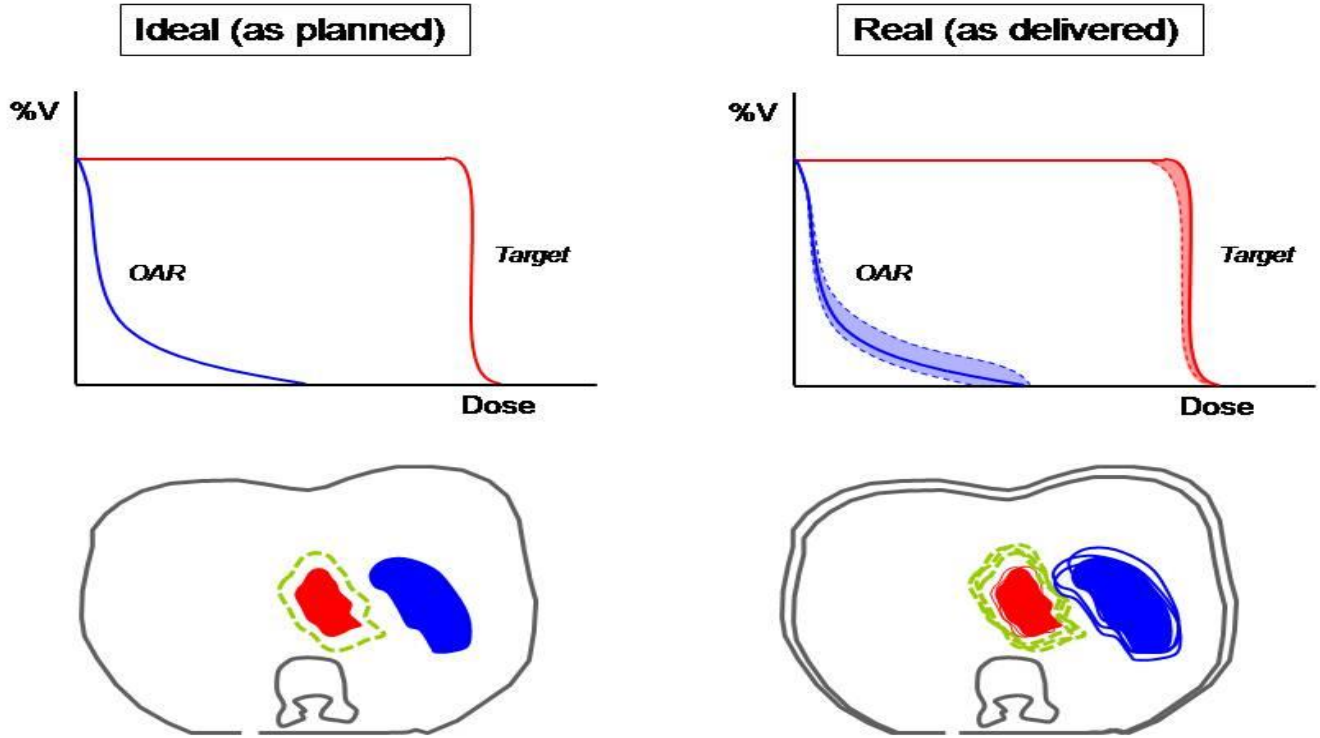


Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

Show DVH	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [Gy]	Max Dose [Gy]	Mean Dose [Gy]
☑	Bladder	Unapproved	TrtProstate7	1	371.5	100.0	100.0	6.591	73.958	26.104
☑	Femoral_Heads	Unapproved	TrtProstate7	1	152.1	100.0	100.0	17.143	48.189	28.280
☑	Rectum	Unapproved	TrtProstate7	1	76.7	100.0	100.0	5.355	71.793	32.625
☑	TotalBowel	Unapproved	TrtProstate7	1	352.4	100.0	100.0	2.352	52.640	10.953
☑	PTVp_72	Unapproved	TrtProstate7	1	113.8	100.0	100.0	67.541	74.737	72.000
☑	PTVpsv_64	Unapproved	TrtProstate7	1	105.8	100.0	100.0	56.335	72.808	66.511
☑	PTVe_50	Unapproved	TrtProstate7	1	558.4	100.0	100.0	42.180	63.597	50.359
☐	Body	Unapproved	TrtProstate7	1	21851.1	100.0	100.0	0.000	74.737	14.255

Rationale for image-guided delivery

Basic concept of radiotherapy: planning vs. delivery



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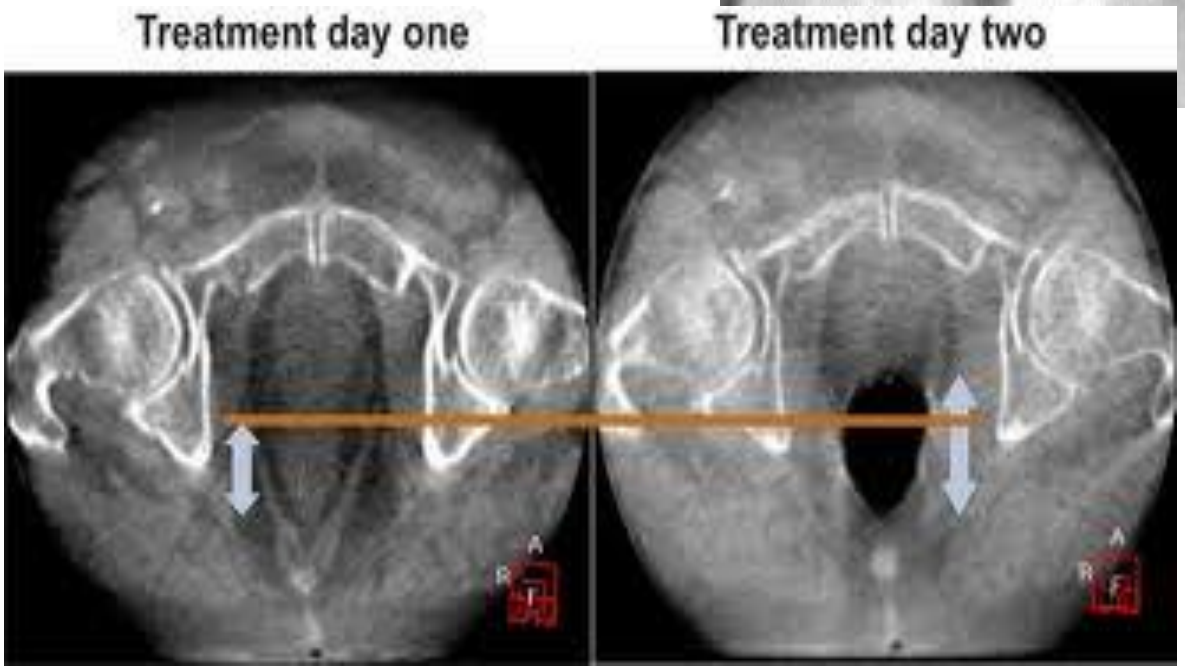
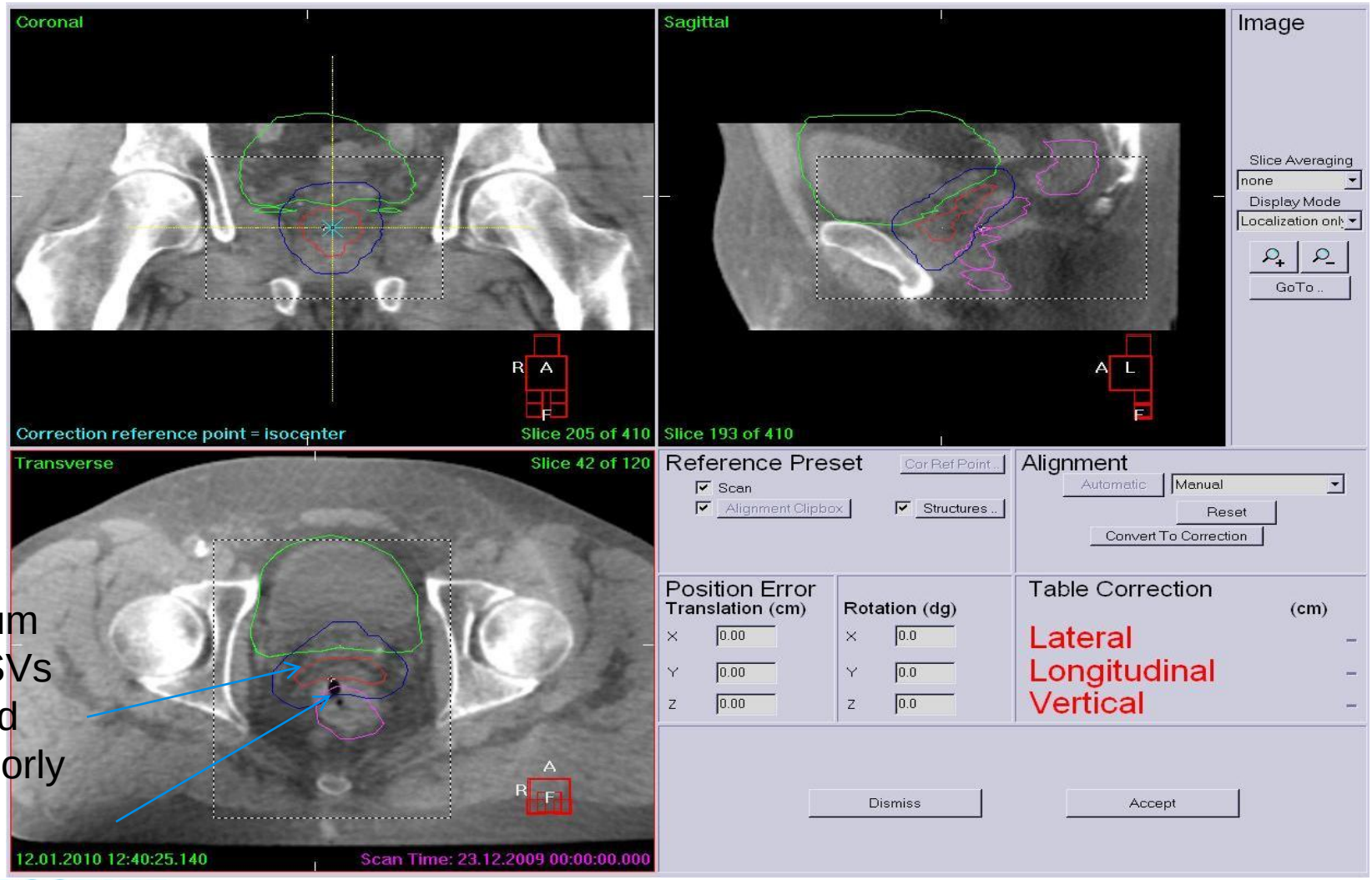


Methods of IGRT

Effect of an empty bladder (seen on cone beam CT images): the shift anteriorly would have moved the rectum into the higher dose region planned for the prostate/seminal vesicles (planned blue/red outlines) and the seminal vesicles into the lower dose region where the bladder originally was (planned green outline).



Rectum and SVs shifted anteriorly

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The ‘draw’ of new technology and devices

- How much more clinical benefit do they really offer?
- Implications for treatment counselling

- Cyberknife
- Protons
- MR guided treatment machines
- Rectal spacers
- Real time tracking / gating

The Christie said patients would "benefit hugely" from having the service in Manchester

A pioneering therapy to treat cancer will be used for the first time at an English hospital before Christmas.

The proton beam therapy, which targets tumours more precisely than current treatments, will be given at Manchester's The Christie.

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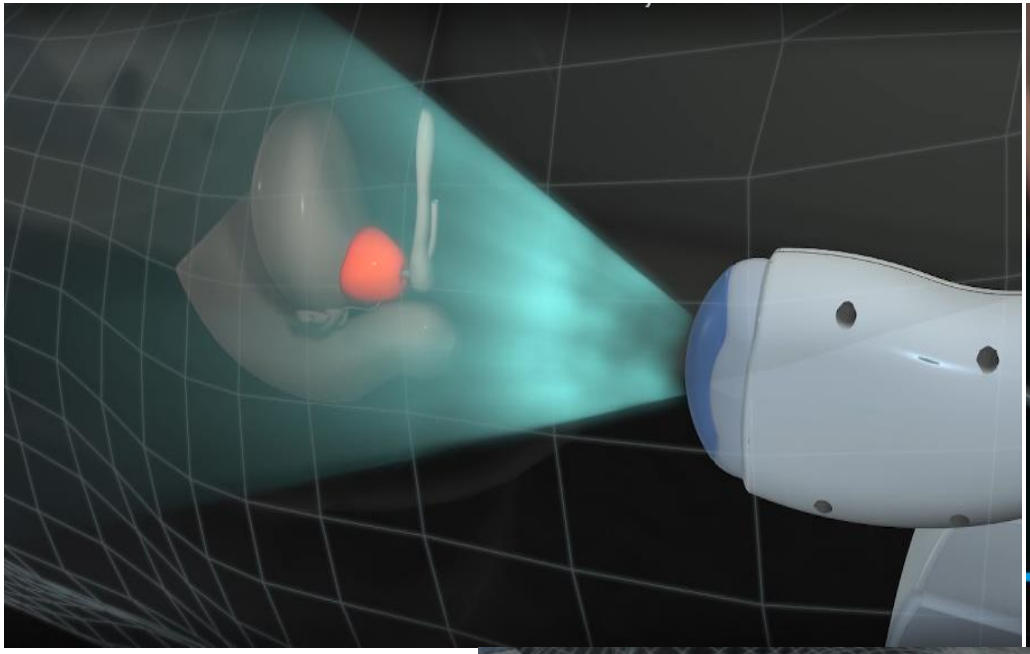
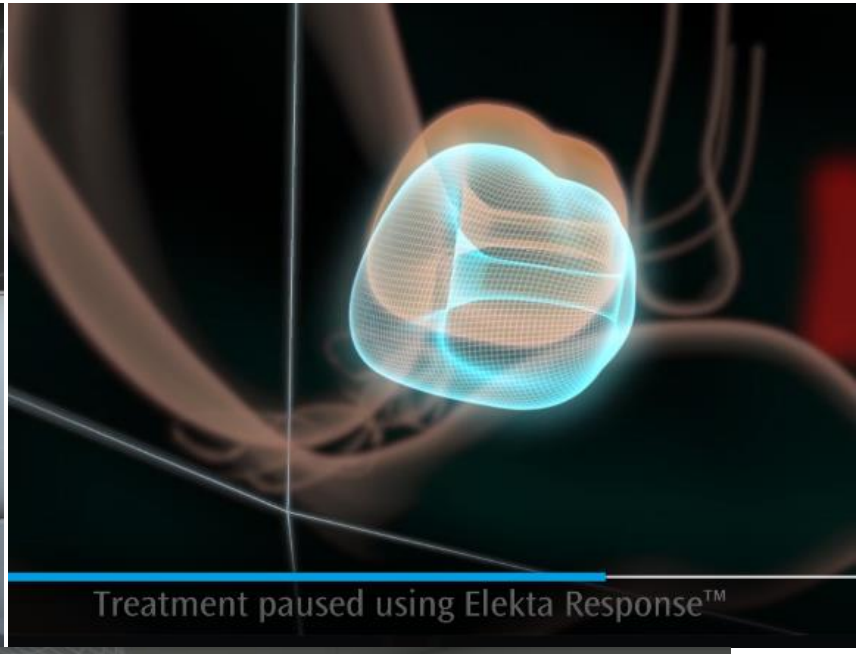
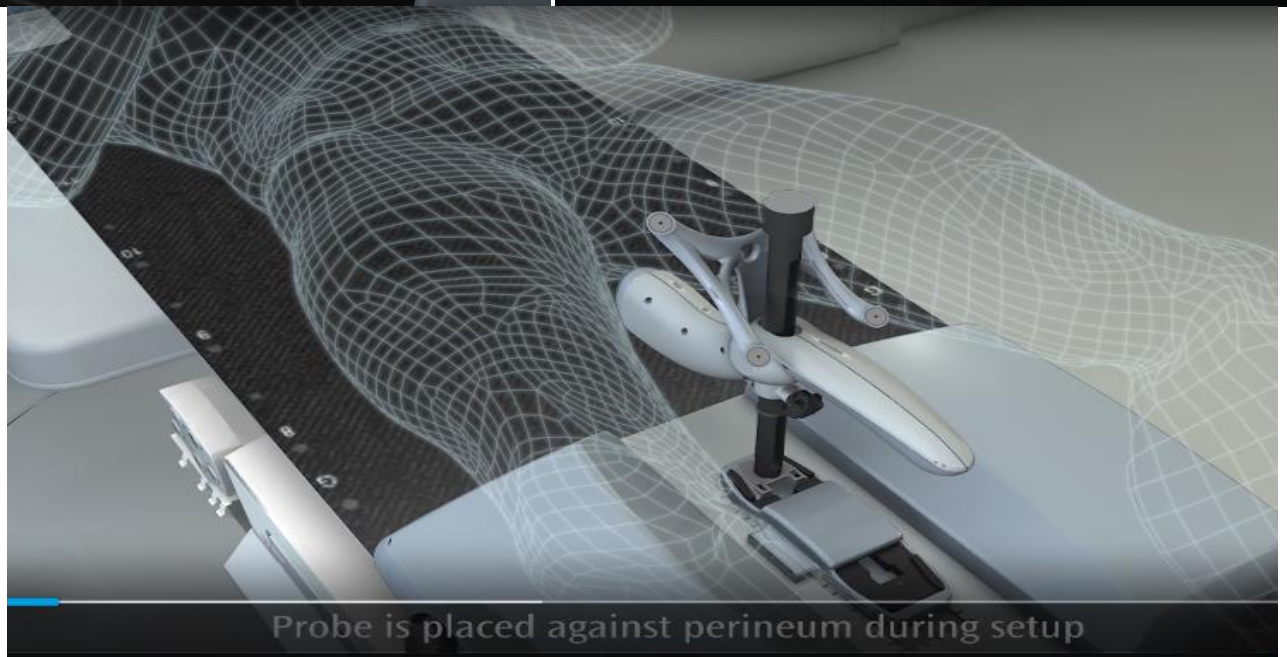
Clarity ultrasound system





https://www.elekta.com/software-solutions/treatment-management/imaging/clarity/



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Radiobiology

- Doses delivered to organs at risk must be kept below their tolerance dose
- Going above this can cause serious damage and loss of function
- Tolerance and resulting toxicity are dependent on the dose received and the volume irradiated.
- Careful planning and delivery is vital
- Normal tissue and cancer cells have the capacity for repair and for re-population – hence why we fractionate our treatments
- Tissue type – early and late responding tissues
- Early responding tissues have a higher proliferation rate = they are more radiosensitive e.g. mucosal lining of the bladder and GI tract = acute side effects. Most affected by total dose. High alpha-beta ratio
- Late responding tissues have a slower proliferation e.g. connective tissues = damaging effects are seen months later. Most affected by dose delivered per fraction. Low alpha-beta ratio
- Prostate low ratio; bladder and bowel high ratio – hypo-fractionated regimes exploit these differences
- Patients will experience both acute and late / long term side effects
- They can also be exacerbated, or minimised, by other influential factors e.g. smoking, diet.

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Acute and late effects

- Effects are classed as either early or late depending on the time it takes for cell damage to become apparent
- Early effects occur due to:
  - An acute inflammatory response (release of cytokines = endothelial dilation and migration of inflammatory cells to the tissue)
  - Death of stem cells responsible for creating new tissue
- Late effects occur as a result of processes that take a longer time to develop:
  - Stem cells with a slower cell turnover
  - Continued cytokine signalling in endothelial tissue and chronic inflammatory response = fibrosis
  - Loss of endothelial cells = increased proliferation of surviving cells = constriction and fibrosis
  - Or cell loss can = large dilated capillaries with thin walls (due to insufficient epithelial lining) = telangectasia

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Urinary and Bowel side effects

- **Urinary**
- Acute inflammation = radiation induced cystitis
- Long term inflammation & fibrosis = cystitis, reduced ‘stretch’ = urge incontinence, telangiectasia

- **Bowel**
- Acute inflammation of small bowel = diarrhoea, urgency
- Acute inflammation of large bowel/rectum = proctitis = tenesmus, urgency, spasms
- Long term = similar symptoms, general change in bowel habit, urgency, mucus discharge, flatulence, peri-anal/rectal pain, loss of sensation between defecation and passing urine, telangiectasia, possible incontinence, possible fistula (rare nowadays)
- Other conditions:
  - Bile acid malabsorption (BAM)
  - Carbohydrate malabsorption e.g. lactose, or other disaccharide intolerance
  - Small intestinal bacterial overgrowth (SIBO)

- **Pelvic floor dysfunction**

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Sexual dysfunction

- Erectile dysfunction –due to the irradiation of the penile bulb and neuro-vasculature tissue surrounding the prostate
- Also reduced pelvic floor function
- Manifests as a late effect
- BUT…..
- As a result of damage to the cells during treatment
- Concern about ED may already be present
- Many patients are also on ADT
- Disease burden may be an impacting factor
- As with surgery, orgasmic dysfunction also possible (though less so) e.g. climacturia, dry orgasm/reduced volume, pain
- Loss of prostate sensation and rectal side effects may also be an issue for patients who enjoy anal sex

Treating erectile dysfunction after radical radiotherapy and androgen deprivation therapy (ADT) for prostate cancer

A quick guide for health professionals: supporting men with erectile dysfunction

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Holistic management

- Open questioning and enquiry / making every contact count
- May need specialist referral
- History taking
- Diagnostic investigations
- Medication
- Lifestyle interventions
  - Exercise – pelvic floor exercises
  - Fluid intake e.g. reduced/no caffeine
  - Smoking cessation
  - Toileting exercises
  - Dietary modification
- Other aids e.g. for incontinence
- Treatments e.g. surgical, hyperbaric oxygen or thermal therapy
- Psychological support and social support
  - Patient-centred approach (establish specific needs and impact)
  - Motivational interviewing style approaches
  - HOPE or similar (acceptance / normalising)
  - Specialist referral

Guidance:
The Practical Management of the Gastrointestinal Symptoms of Pelvic Radiation Disease

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Self-management and proactive intervention

- Patients need information about late / long term effects
- Support for self-managing them
- Information on what to look out for
- FU pathways that incorporate assessment of side effects as well as disease
- Monitoring and management of low grade toxicity, not just about the higher grade toxicities (RTOG GI example below)
- Baseline assessment useful in managing expectations
- Holistic needs assessment help to contextualise the symptoms

Grade 1	Grade 2
Increased frequency or change in quality of bowel habits not requiring medication/rectal discomfort not requiring analgesics	Diarrhoea requiring parasympatholytic drugs (e.g. Lomotil)/mucous discharge not necessitating sanitary pads/rectal or abdominal pain requiring analgesics

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Local pathways and initiatives?

What is your FU pathway for radiotherapy patients?

How well do you think it manages the long term effects of treatment?

Examples?