Closing the Loop – Clinical Research in Prostate Cancer Radiotherapy

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Clinical Research

- What is it?
- Why do we need it?
- Who does research?
- How does research impact on individuals?
- Where have we come from?
- Where are we going?

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What is it?

- In healthcare, a **clinical trial** (synonyms: clinical studies, research protocols, medical research) is the application of the scientific method to human health. Researchers use clinical trials to test hypotheses about the effect of a particular intervention upon a pathological disease condition. Well-run clinical trials use defined techniques and rigorous definitions to answer the researchers' questions as accurately as possible.

First ever clinical trial!

- James Lind 1747
- 12 sailors with scurvy divided into 6 groups
- Each group given a different treatment
- Results were that those given citrus fruits recovered
  - Other group who had some benefit were given cider!
- Results published in 1753 but virtually ignored

Why is it necessary?

- To have evidence what we do is ‘correct’
- To assess whether a new intervention is the same, better or worse than the current ‘standard’
- Evaluation of new drugs, medicines, interventions, medical devices

Different types of clinical research

- Prospective studies vs. retrospective studies
- Randomized control trials
  - Assess a particular intervention
- Observational studies
  - Cohort, Case control
  - Assess causation and correlation of disease with risk factors
- Phases of research trials
  - Pre-clinical data
  - Phase 0 – preliminary data
  - Phase I – safety and tolerability
  - Phase II – efficacy and safety
  - Phase III – comparison of new vs. standard
  - Phase IV – longer term safety after general release

How does research impact on individuals?

- Current standard of treatment is usually derived from the results of clinical research
- So almost everyone has been impacted by what others before them have done even when they have not directly been involved in a study

Regulations

- **Good Clinical Practice** is an international quality standard that is provided by International Conference on Harmonisation (ICH)
- Provides standards of practice and conduct of clinical trials
- Sets out the requirements of investigators and participants involved in human clinical studies
- The guidelines aim to ensure that the "rights, safety and well being of trial subjects are protected".

Who does research?

- Investigators usually health care professionals, associates
- And……..

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Benefits of taking part in studies

- Access to new treatments not widely available and if found to be beneficial…….
- “To help others who come after me”
- Trials rigorously regulated
  - NOT ‘experimental guinea pig’ but uncertainties involved
- Evidence to suggest just taking part in a trial actually improves outcome for individuals but probably related to strict adherence to protocol or guidelines

Not risk free……..

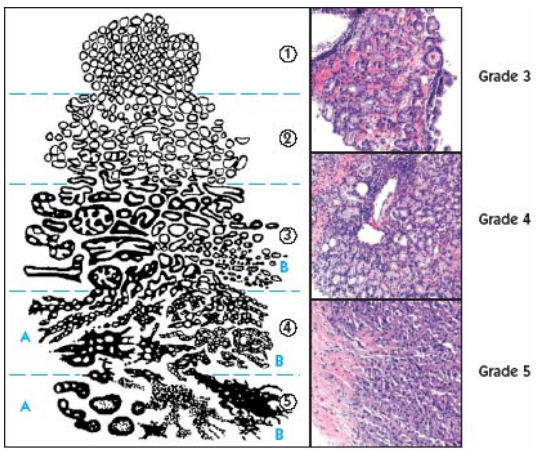
- New treatments may have both known and unknown risks
- New treatments may not be as effective as standard treatments
- The new treatment may not work for you
- Cannot choose which treatment (randomized trials)
- BUT not all trials have the same risks so it is important to understand what these are before participating or refusing to participate

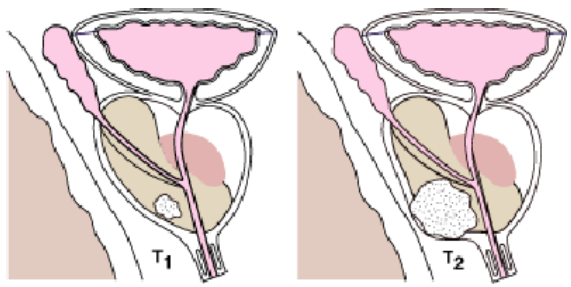
Prostate cancer

- Prostate cancer risk categorization
- Risk defines the type of treatment recommended
- Canadian consensus guidelines
    - Low risk
    - Intermediate risk
    - High risk

Low risk

- T1-2, Gleason score ≤6, PSA <10
- Approximately 60% disease free at 10 years
  - Traditional radiotherapy with doses up to 70 Gy delivered to the prostate





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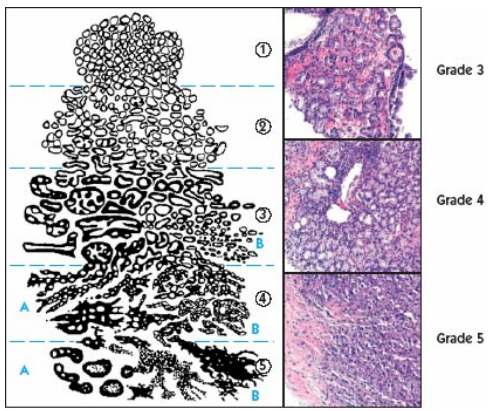
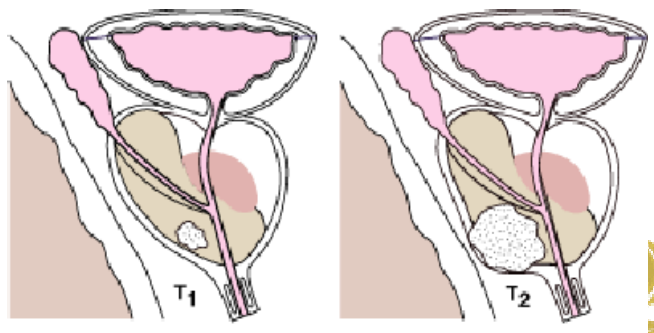
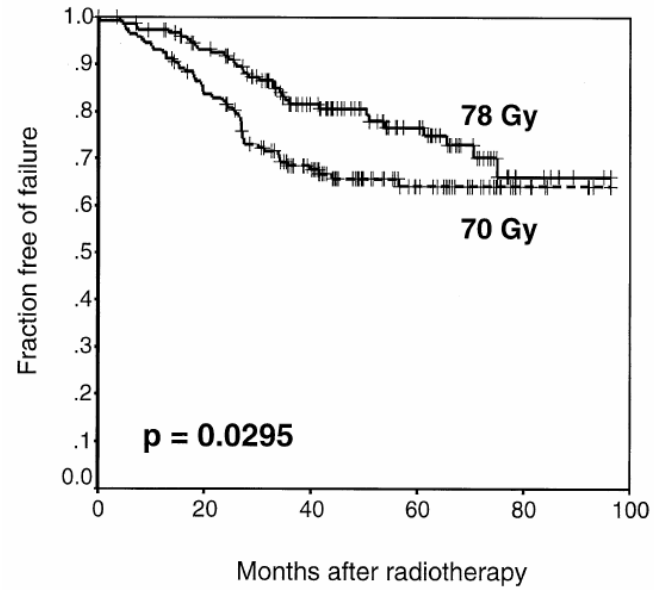
Intermediate risk

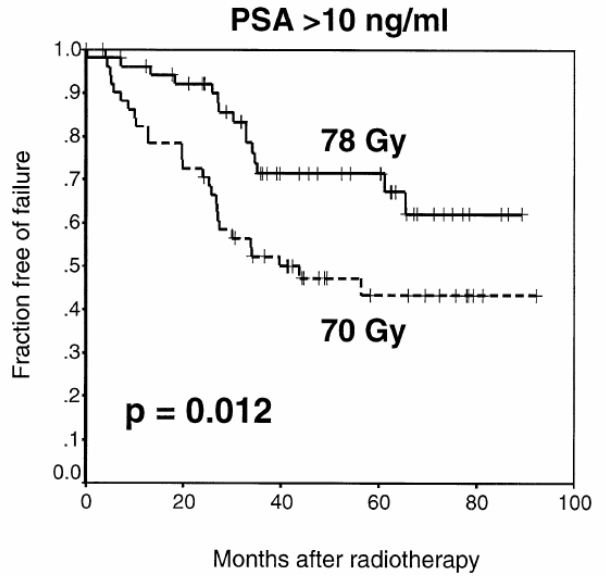
- T1-2, Gleason score $\leq$6, PSA 10 – 20
- T1-2, Gleason score 7, PSA < 20
- Approximately 40% disease free at 10 years
- Traditional radiotherapy with doses up to 70 Gy delivered to the prostate





Radiotherapy dose study





- 301 pts, low/intermediate risk
- 70 Gy v 78 Gy

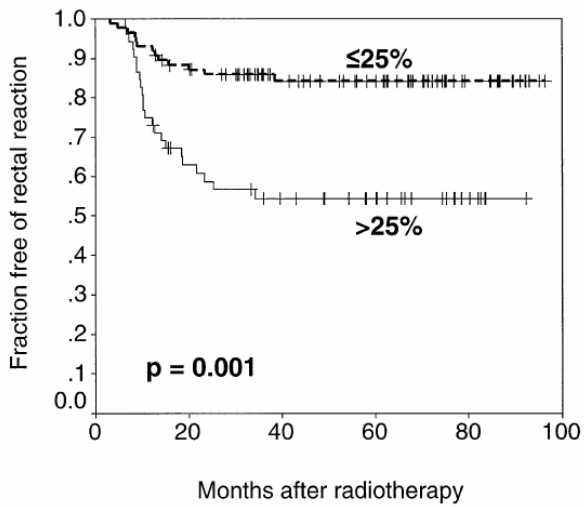


Fig. 5. Kaplan–Meier freedom from Grade 2 or higher late rectal complications by patients in whom ≤25% vs. >25% of the rectal volume received ≥70 Gy.

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Dose study - protons

- 393 pts, low and intermediate risk
- 70.2 v 79.2 Gy
- Low rates of bladder and bowel side effects

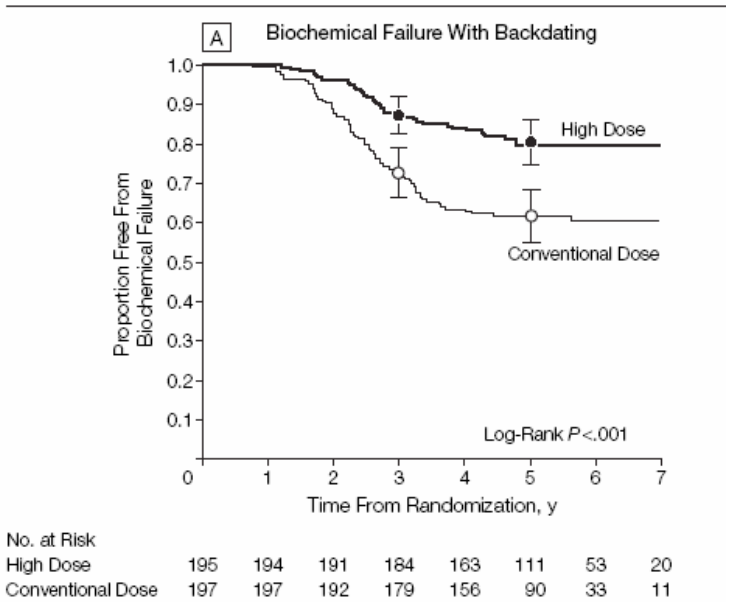

Table 2. Acute and Late Genitourinary and Gastrointestinal (Rectal) Morbidity, by Assigned Radiation Therapy Dose and Toxicity Grade

	No. (%)							
	70.2 GyE (n = 196*)				79.2 GyE (n = 195)			
Morbidity	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Acute								
GU	79 (40)	82 (42)	2 (1)	0	69 (35)	95 (49)	2 (1)	1 (1)
GI	62 (31)	81 (41)†	2 (1)	0	48 (25)	112 (57)†	0	0
Late								
GU	85 (43)	35 (18)	3 (2)	0	84 (43)	39 (20)	1 (1)	0
GI	71 (36)	15 (8)‡	1 (1)	0	84 (43)	33 (17)‡	1 (1)	0

Abbreviations: GI, gastrointestinal; GU, genitourinary.
*One patient underwent radical prostatectomy rather than radiation therapy because the bowel was too close to the prostate for safe administration of radiation. This patient was excluded from analysis of morbidity.
†$P = .004$ by χ^2 test.
‡$P = .005$ by χ^2 test.

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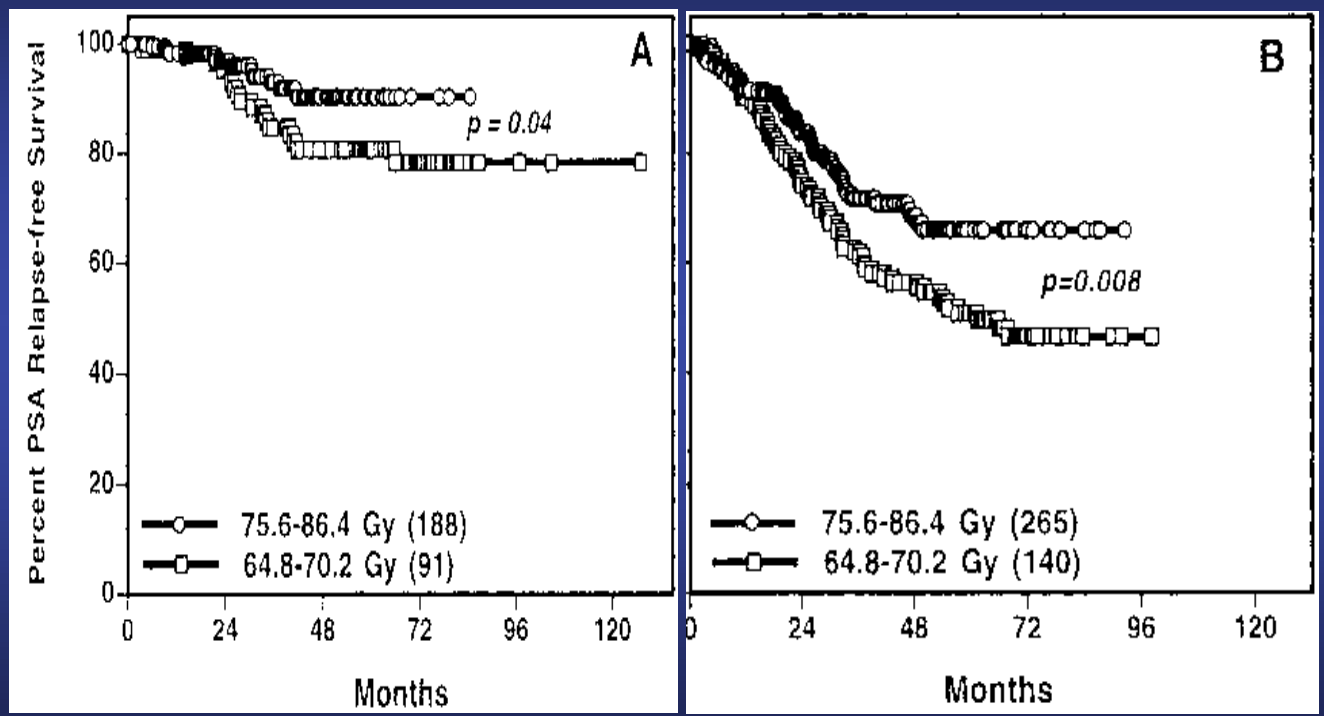
RT dose study

Clinical Examples: Improved results with dose escalation

Good risk

Intermediate risk



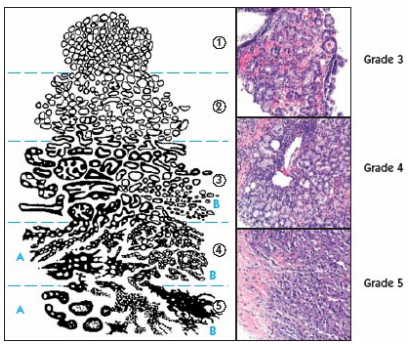
Zelefsky et al J Urol 2001

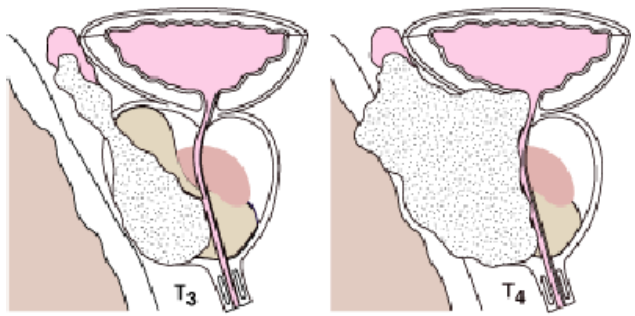
Ongoing trials results awaited

- RTOG 01-26
  - Intermediate risk, 70.2 vs 79.2 Gy
- Dutch
  - 669 pts, 68 Gy v 78 Gy
- French
  - 306 pts 70 Gy v 80 Gy, intermediate risk
- British
  - 803 pts 64 Gy v 74 Gy

High risk

- Any T, Any Gleason score, PSA >20
- Any T, Gleason score >7, Any PSA
- T3-4, Any Gleason score, Any PSA
- Approximately 20% disease free at 10 years
- Traditional radiotherapy with doses up to 70 Gy delivered to the prostate





High risk patients

- 415 pts
- RT alone vs RT + 3 yrs hormones

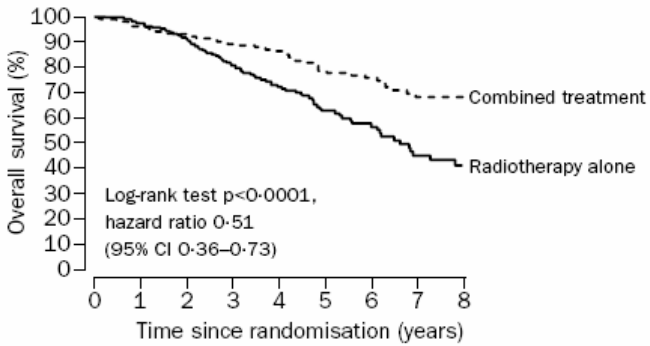


Figure 2: **Kaplan-Meier estimates of overall survival by treatment group**
O=number of deaths; N=number of patients.

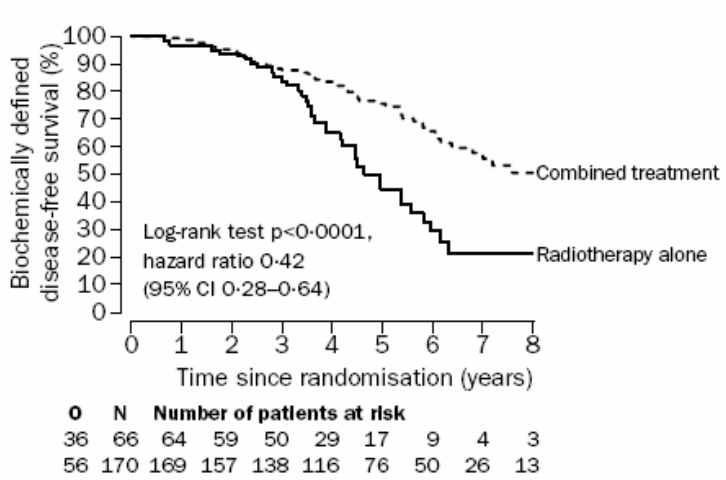


Figure 3: **Kaplan-Meier estimates of the biochemically defined disease-free survival**
O=number of failures; N=number of patients.

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High risk patients

- 977 pts, cT3/pT3 and N+
- RT alone v RT + hormones

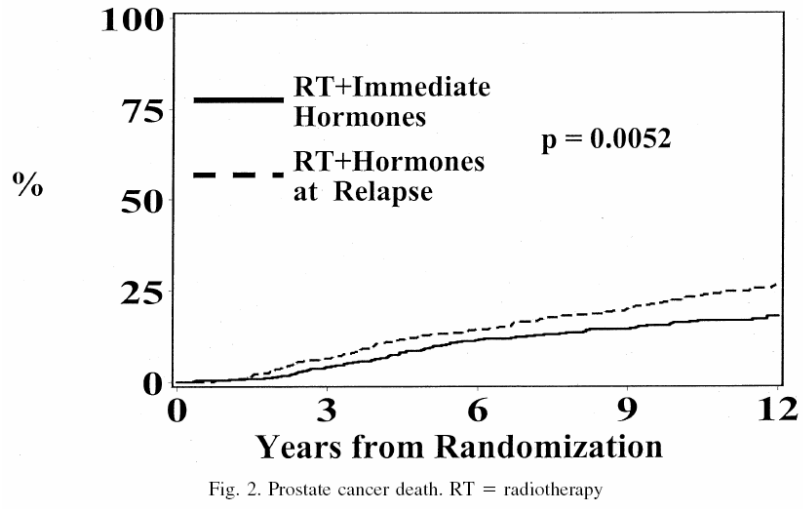

Fig. 2. Prostate cancer death. RT = radiotherapy

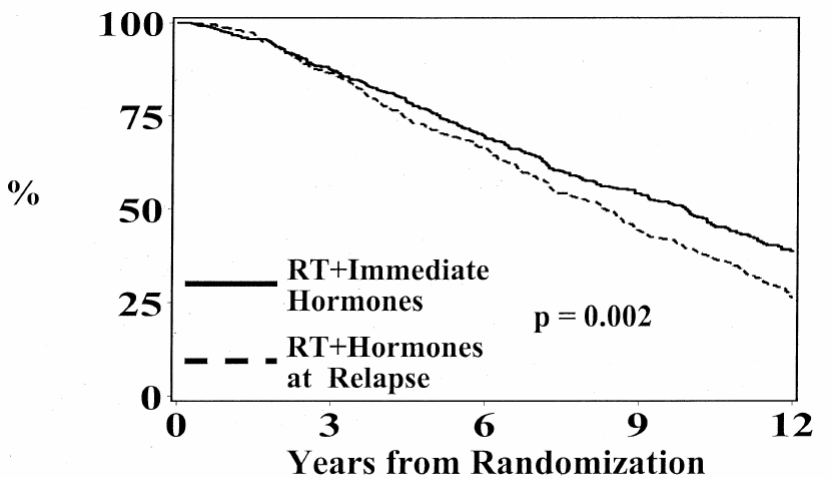

Fig. 1. Absolute survival. RT = radiotherapy.

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Radiotherapy after prostatectomy

- 1005 pts, pT2 positive margins/pT3
- RT within 4 months of surgery vs observation

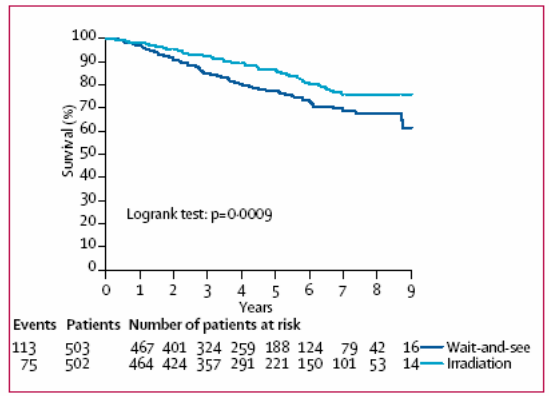

Figure 3: Clinical progression-free survival

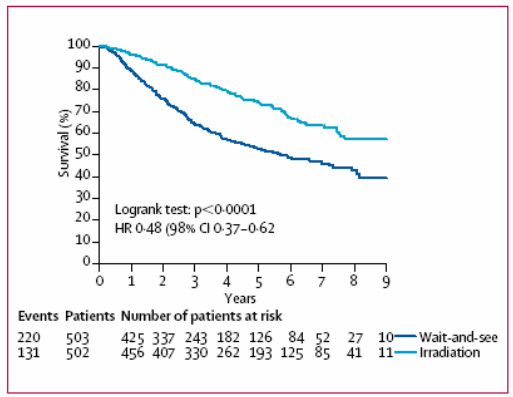

Figure 2: Biochemical progression-free survival

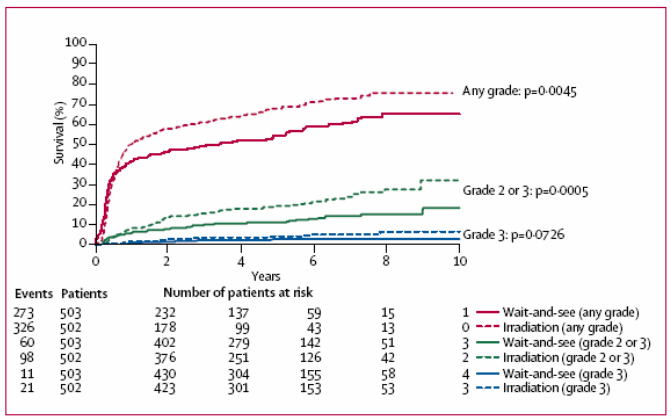

Figure 5: Cumulative incidence of late complications
p values indicate comparison of wait-and-see with irradiation groups.

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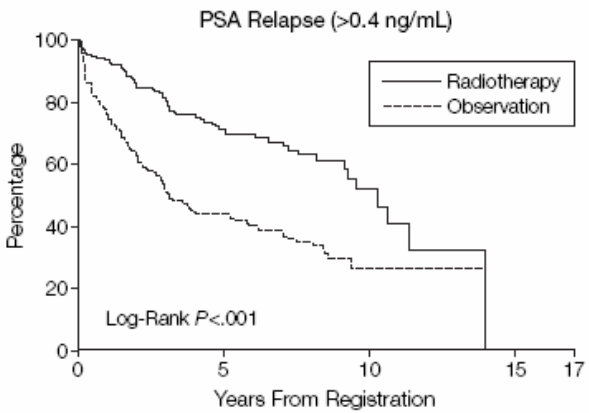
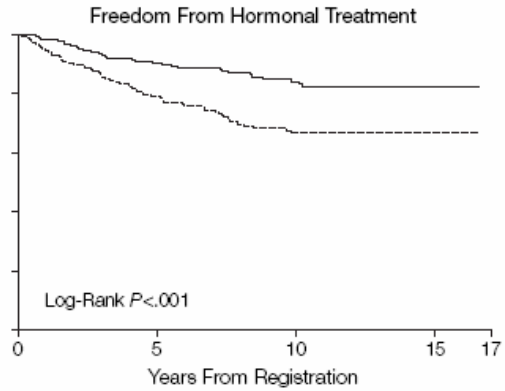
Radiotherapy after prostatectomy

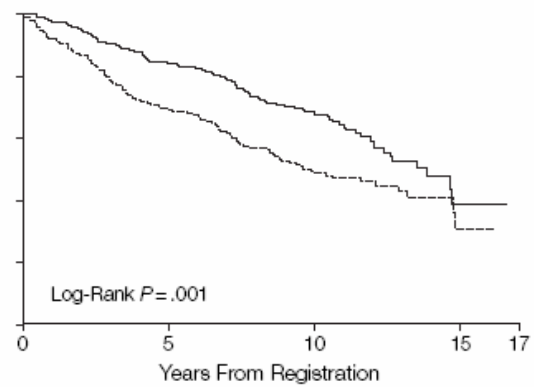
- 473 pts, pT2 positive margins, pT3
- RT vs observation



No. at Risk				
Radiotherapy	172	86	11	
Observation	175	63	10	



214	171	94	9
211	148	68	4



214	176	101	9
211	142	70	4

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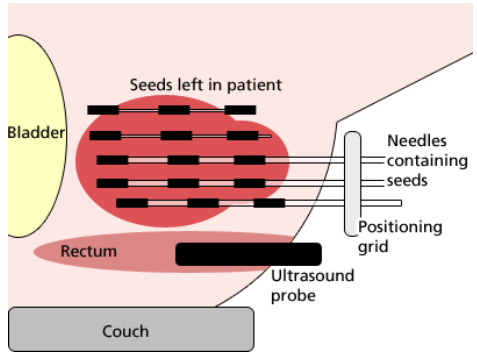
Brachytherapy



- Ontario
  - T1c-T2a, Gleason score ≤6, PSA <10
  - Prostate size <50cc
- Randomized study of brachytherapy alone vs surgery closed due to poor accrual
- External RT + brachytherapy

Radiotherapy at PMH

- Low risk patients
  - Brachytherapy
- Low and intermediate risk patients
  - Radiotherapy alone, no hormones.
  - Dose escalation
  - Intensity modulated radiation therapy
  - Image guidance for accuracy
- High risk patients
  - Radiotherapy + hormones

We know some answers but……

- Each clinical study produces many questions
- Answering these requires more research

Examples

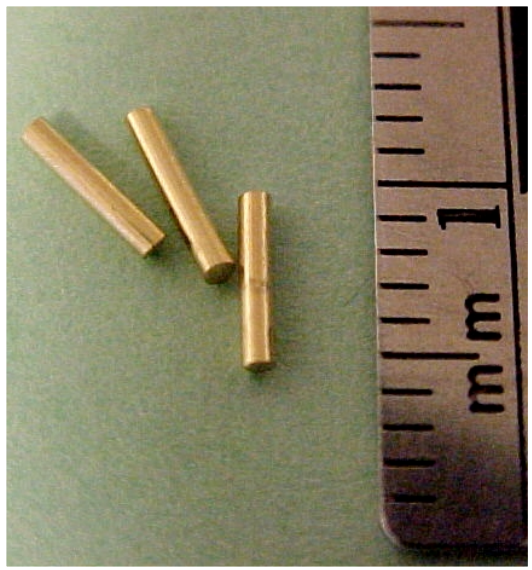
- Dose escalation studies
  - Can we reduce side effects from radiotherapy?
- High risk studies
  - How long should hormones be given?
  - Can chemotherapy be combined into treatment?
- Post prostatectomy studies
  - Can we reduce side effects
  - When should hormone therapy be used
- How do we integrate new treatments into the mix?

External Beam Radiotherapy

- Radiotherapy planning
  - Insertion of prostate markers (fiducials)
  - CT scan for planning
  - Individualized radiotherapy plan
- Radiotherapy delivery
  - Daily image guidance to ensure accuracy
    - Electronic portal imager
    - Conebeam CT

Prostate markers

- 24k gold
- 1 x 5mm
- Inserted in medical imaging department via ultrasound



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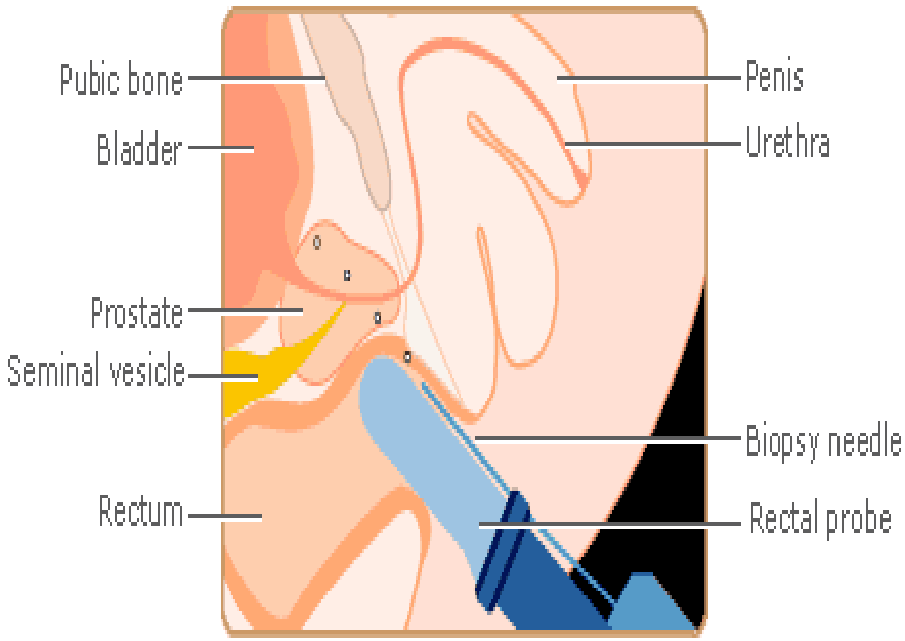
Prostate markers

- Transrectal ultrasound
- 3 markers inserted into base, mid-portion and apex of prostate



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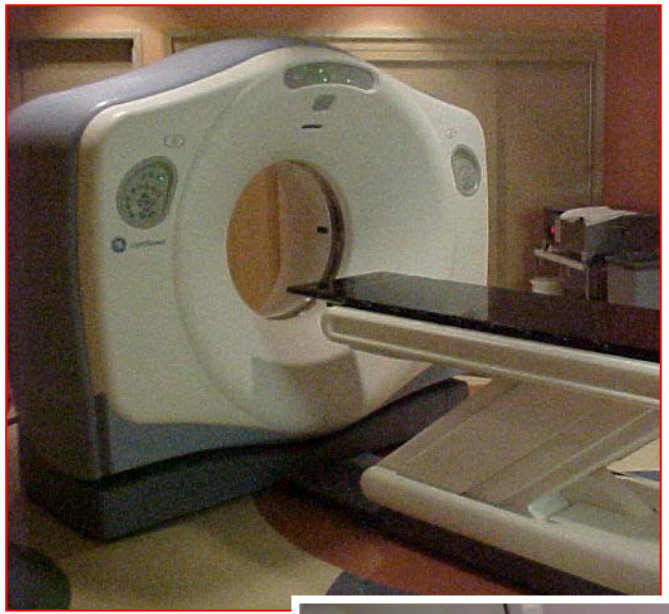
CT simulation



- Specific CT scanner designed for radiotherapy planning
- Visualize soft tissue within the pelvis as well as bone
- Immobilization device for daily setup

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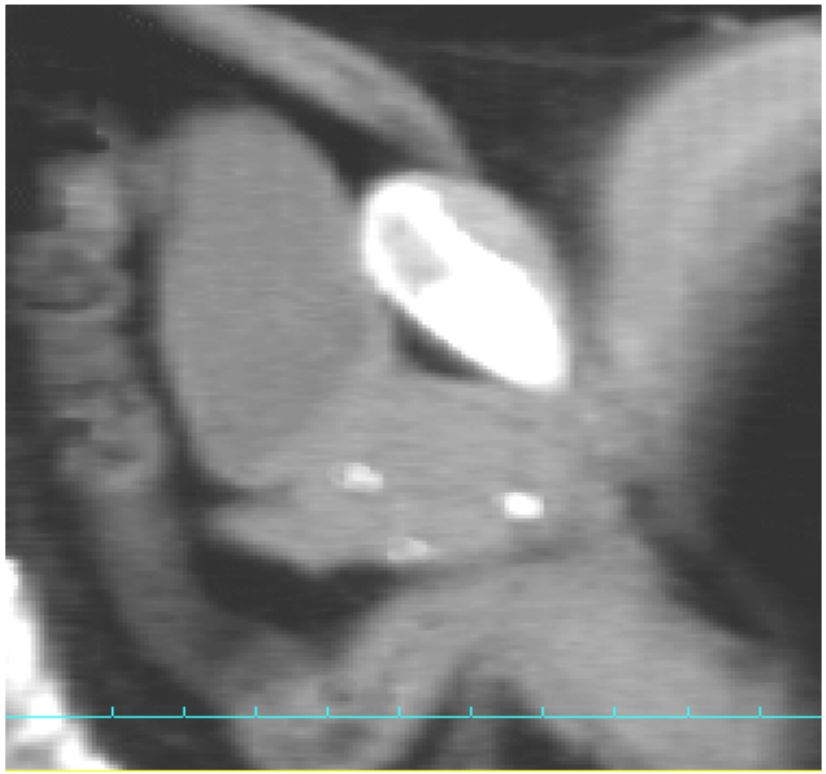
- CT slices used to outline position of prostate (2mm thick)
- Radiotherapy plan generated based on CT
- However day to day variation of prostate position



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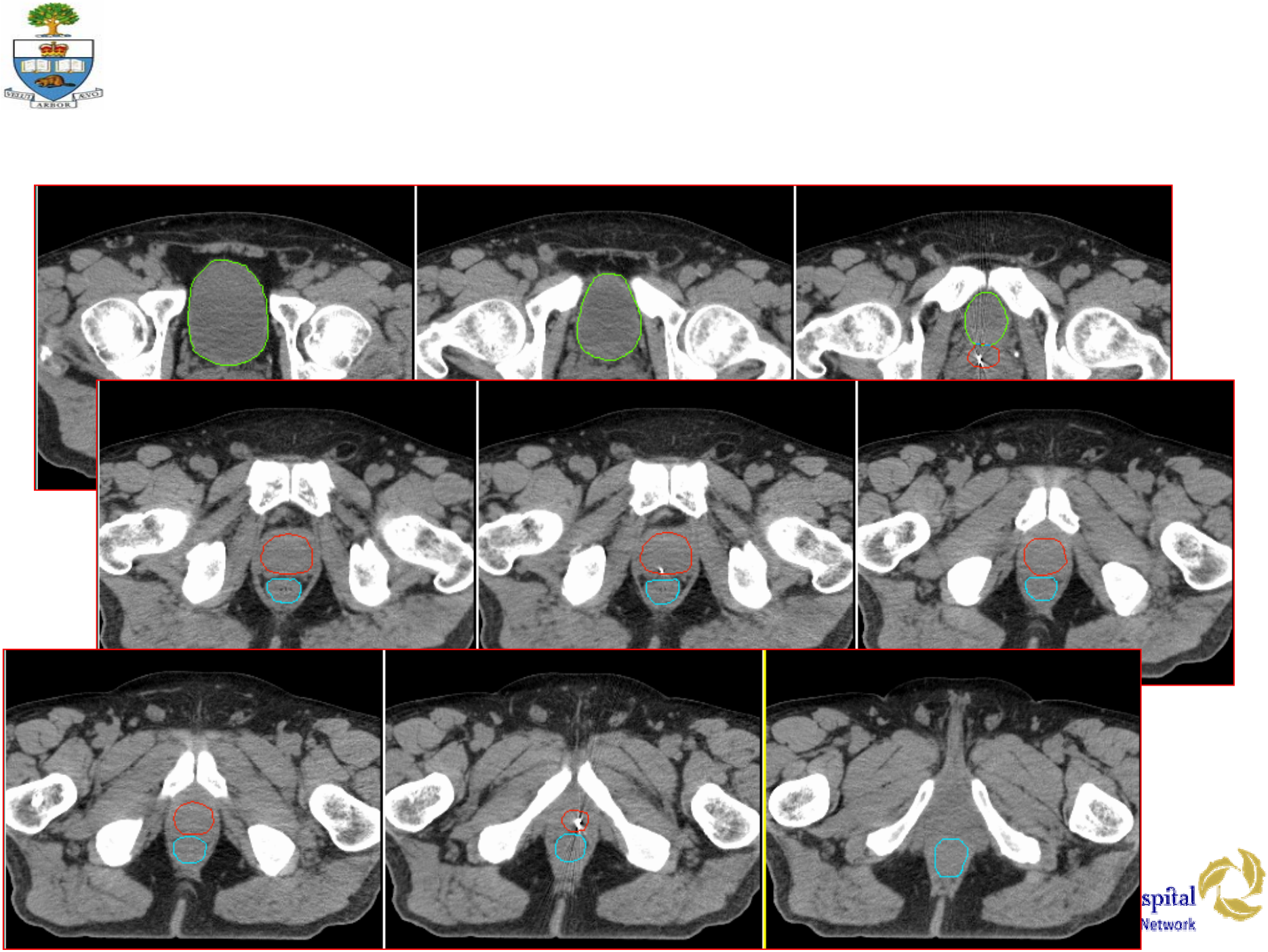

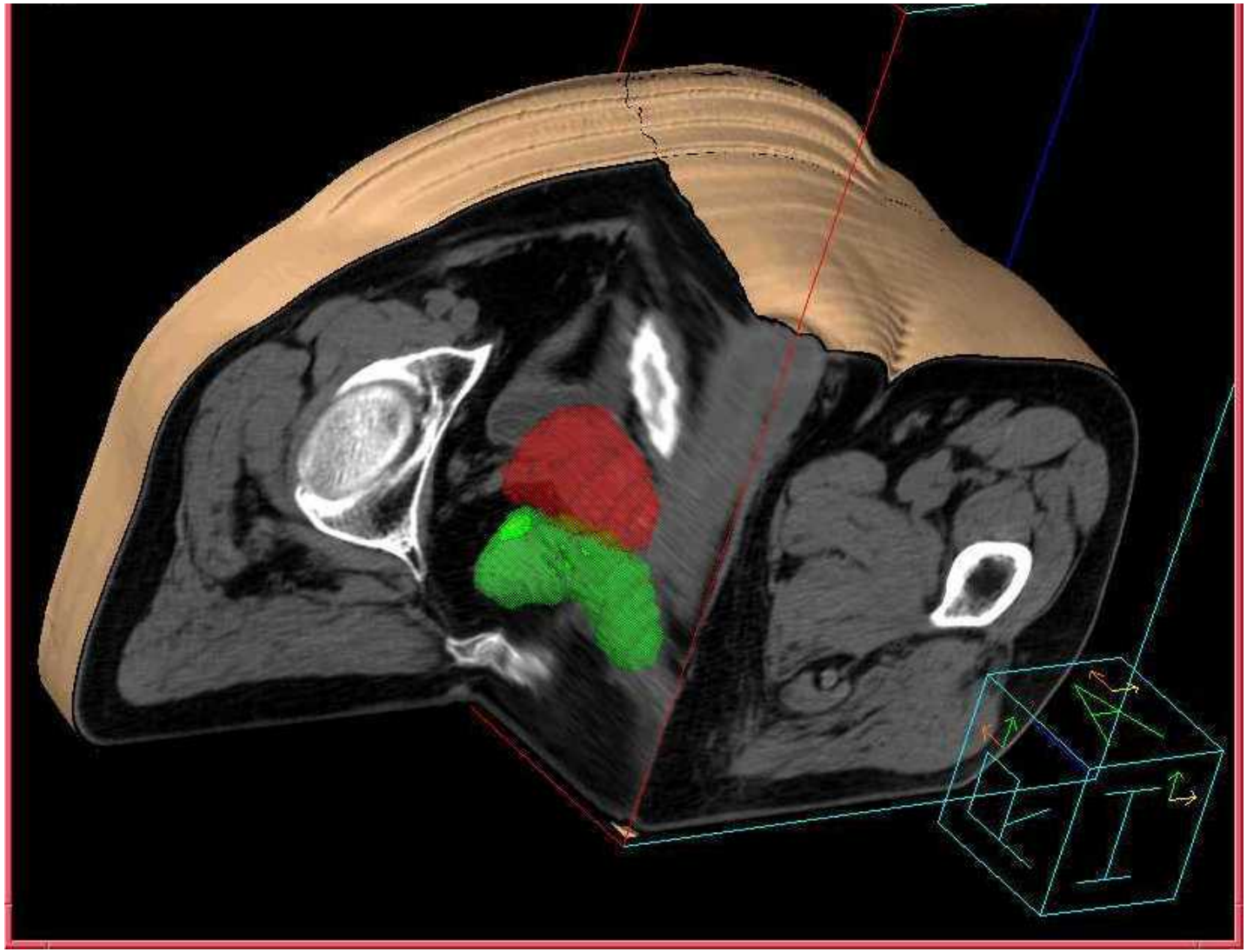

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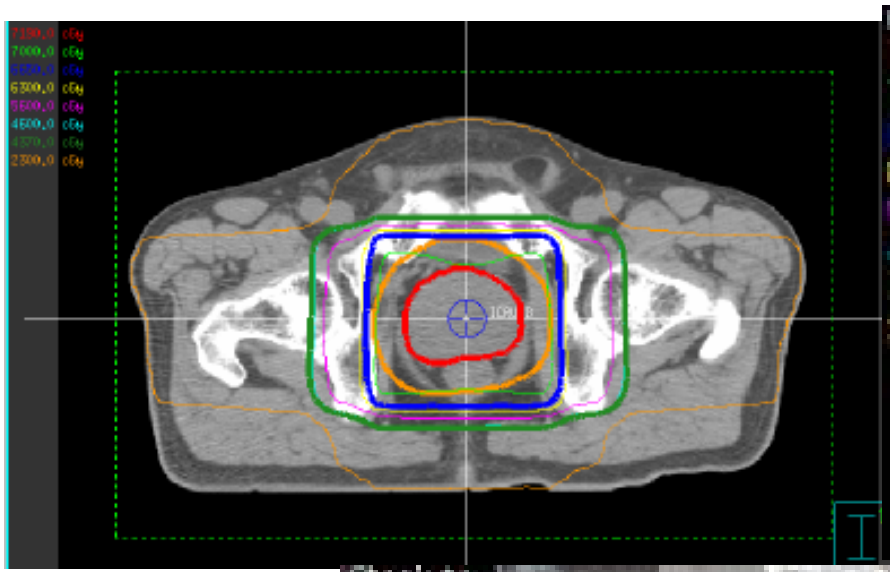
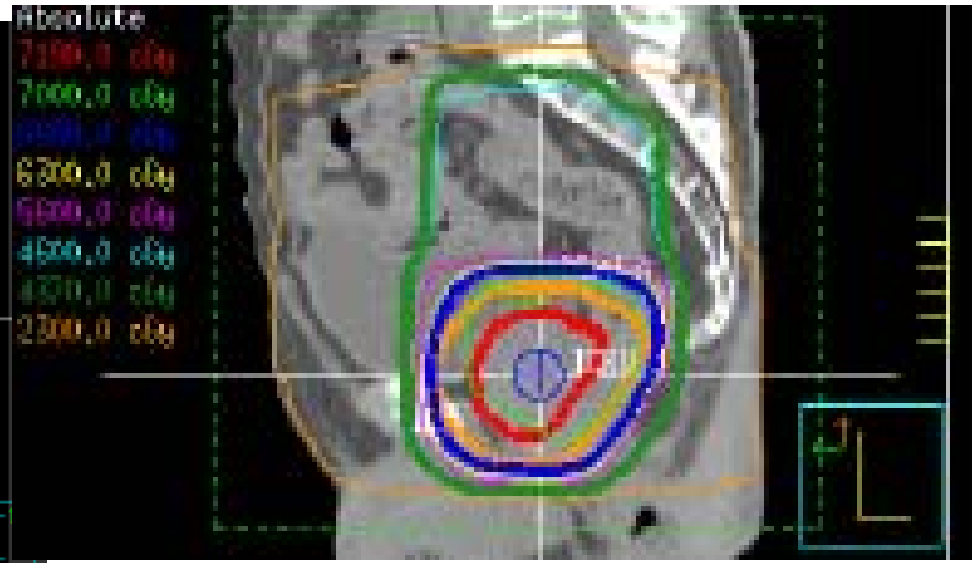
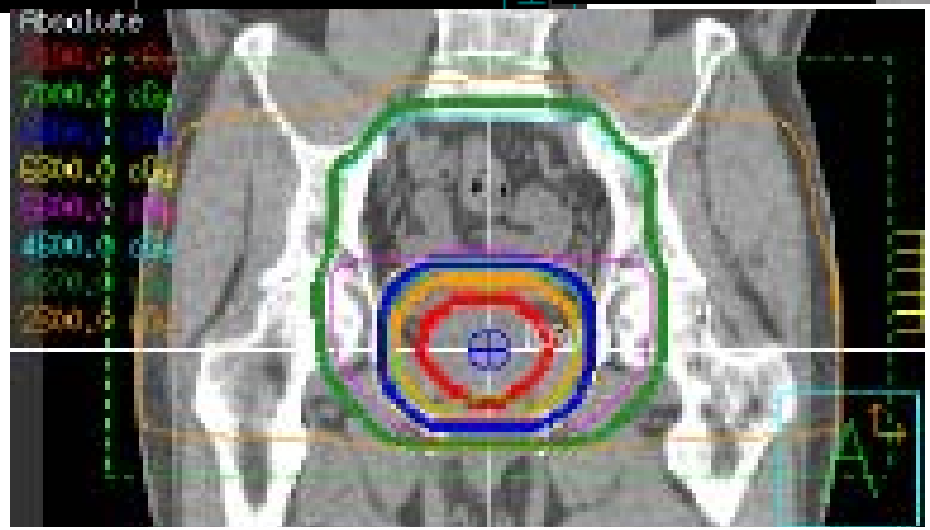
Intensity Modulated Radiation Therapy (IMRT)

- Modern way of shaping radiation beam and dose to closely match shape of the prostate in 3D
- Advantage of delivering high dose to the prostate and lower doses to the surrounding normal tissue
- Eradicate disease + minimum side effects

‘Four field box’







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Four field box

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Intensity Modulated Radiation Therapy (IMRT)

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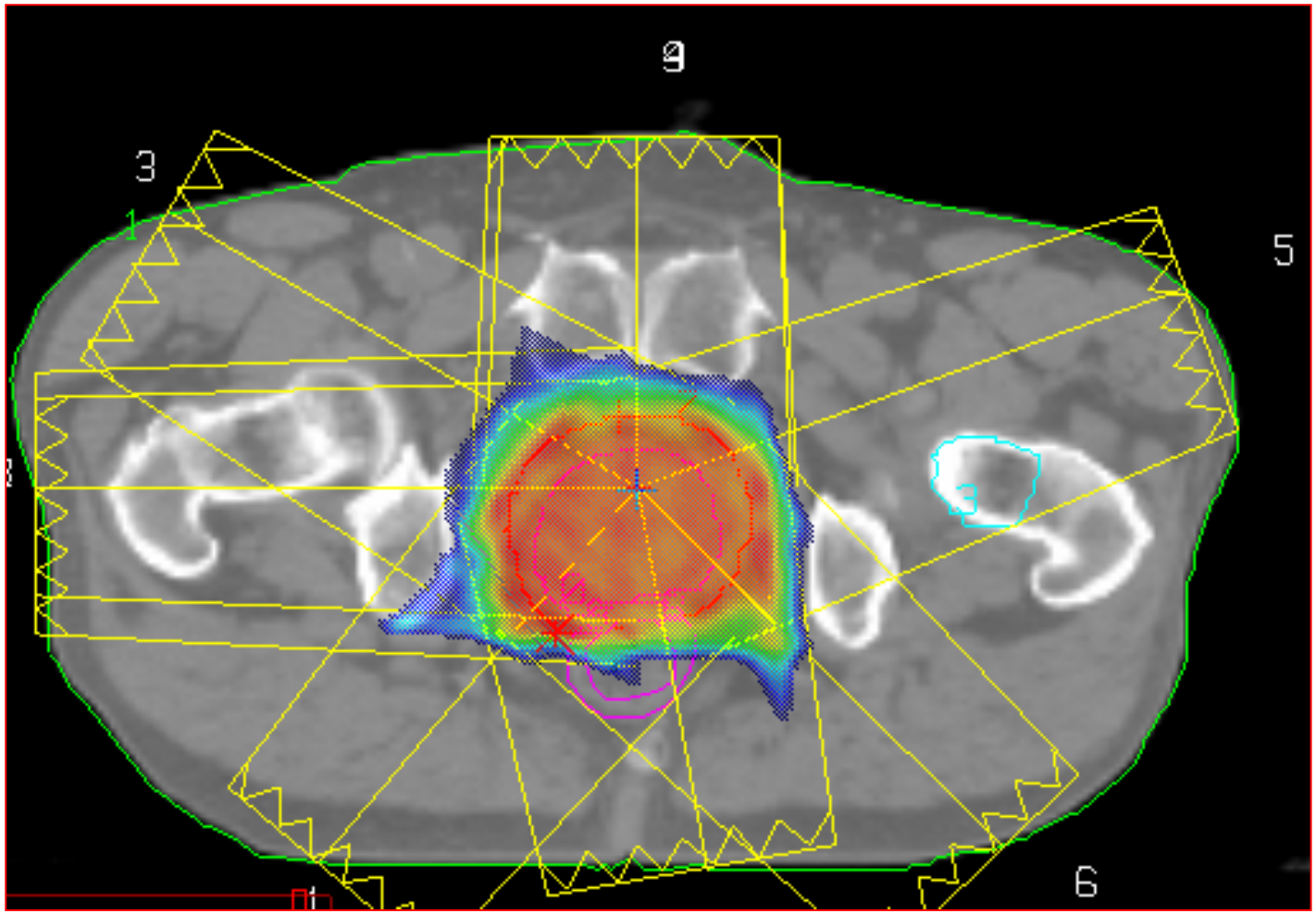

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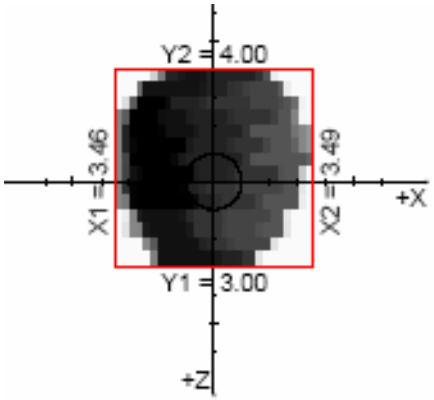

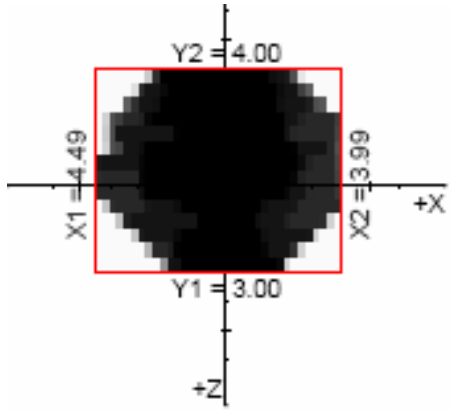

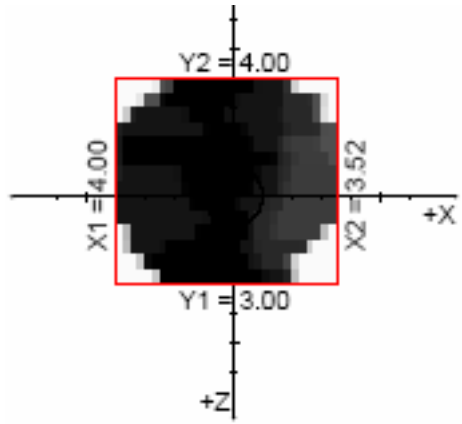

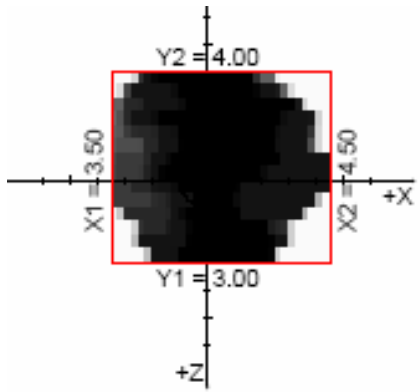

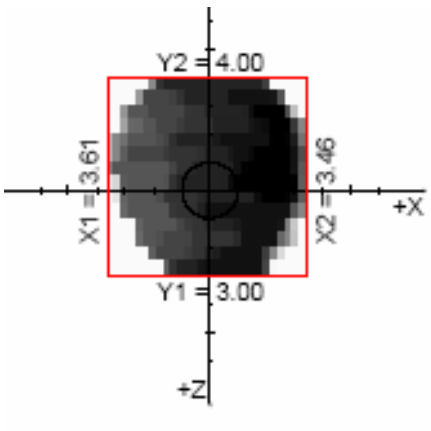

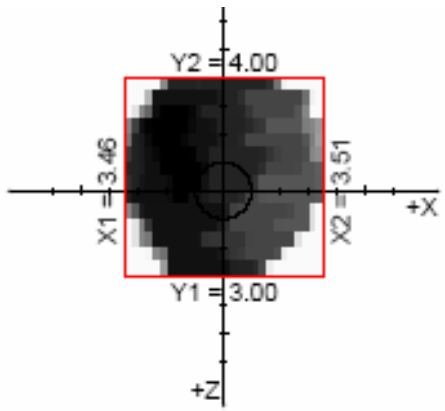

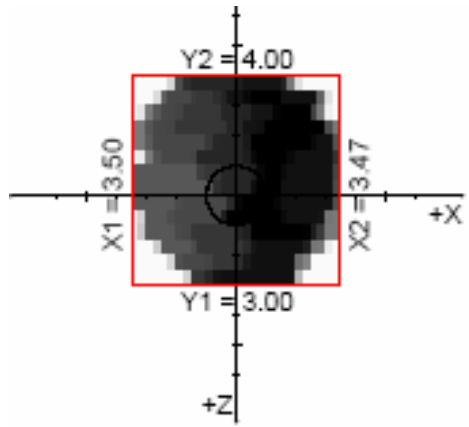

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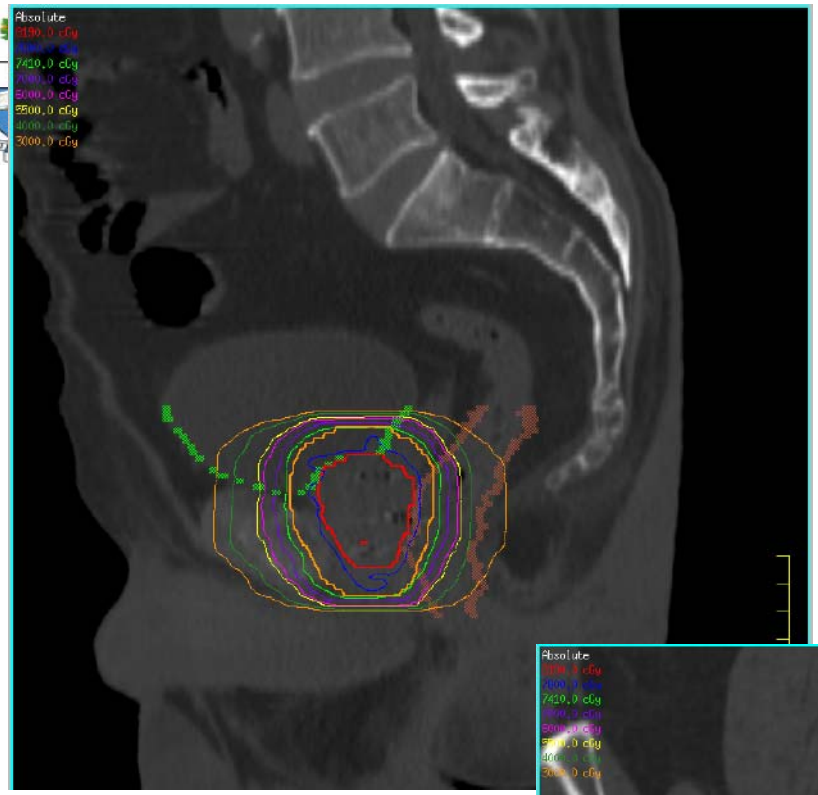

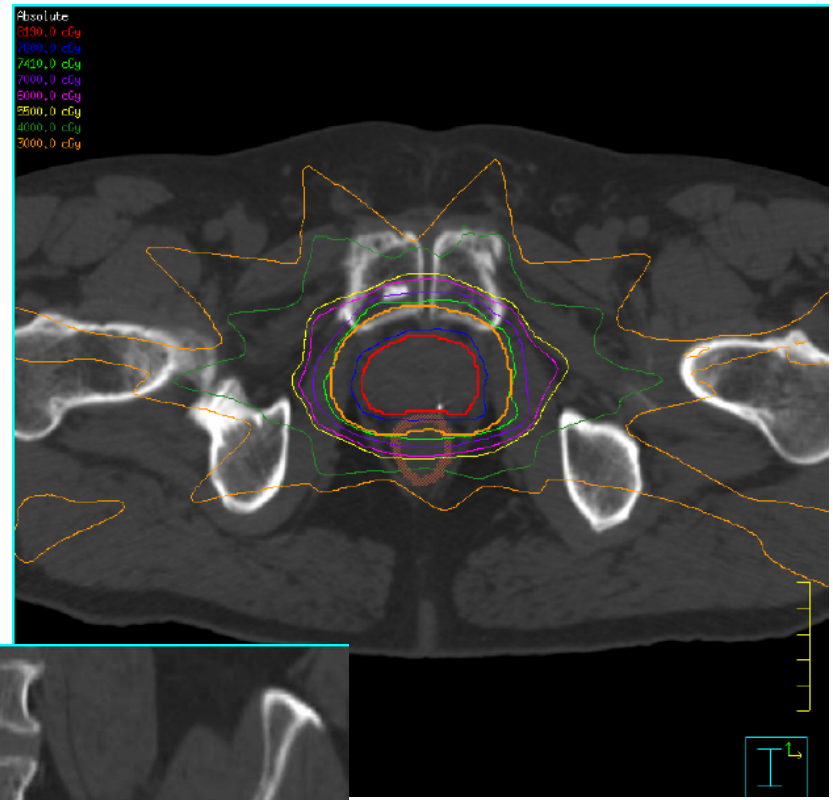

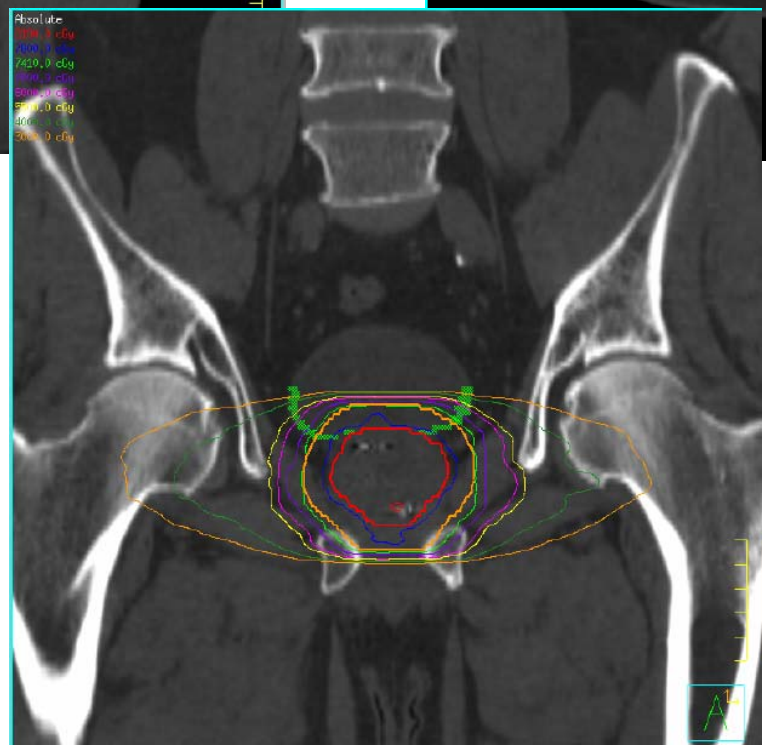

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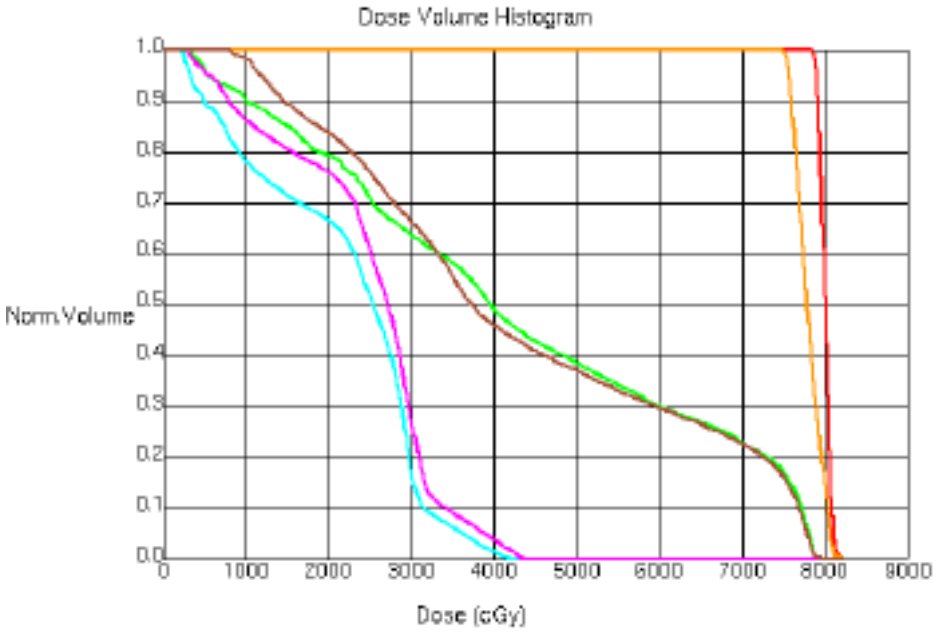

DVH Calculation
- Cumulative
- Differential

Dose Axis Display
- Normalized Dose
- Absolute Dose
- Auto-Compute Max
- Specify Max Dose

Volume Axis Display
- Normalized Volume
- Absolute Volume

Tabular DVH...

ROI Statistics

Line Type	ROI	Trial	Min.	Max.	Mean	Std. Dev.	% Outside Grid	% > Max	Generalized EUD
	BW	0.Trial_1	333.5	7929.4	4266.1	2417.9	0.00 %	0.00 %	4268.84
	CTV	0.Trial_1	7786.2	8217.4	8001.6	98.1	0.00 %	0.00 %	8002.06
	LF	0.Trial_1	200.3	4177.3	2175.2	1034.2	0.00 %	0.00 %	2174.54
	PTV10-7	0.Trial_1	7405.2	8217.4	7797.7	159.4	0.00 %	0.00 %	7798.49
	RF	0.Trial_1	254.7	4337.3	2444.9	953.6	0.00 %	0.00 %	2444.81
	RW	0.Trial_1	792.6	7957.8	4338.7	2247.2	0.00 %	0.00 %	4338.64

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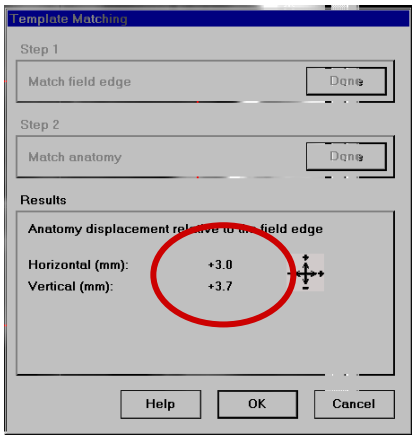

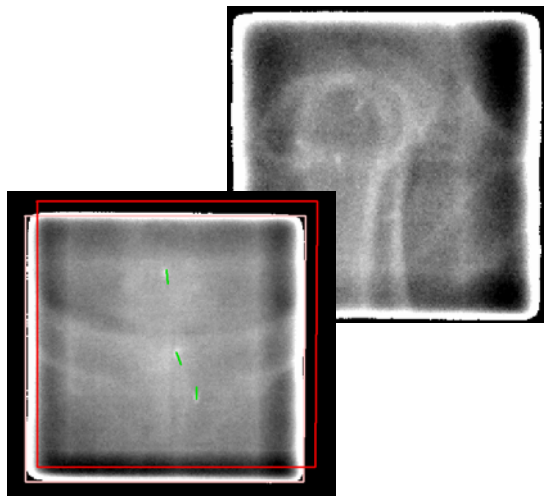

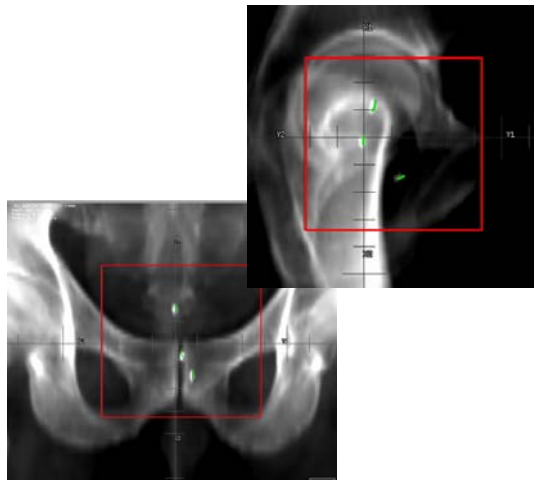

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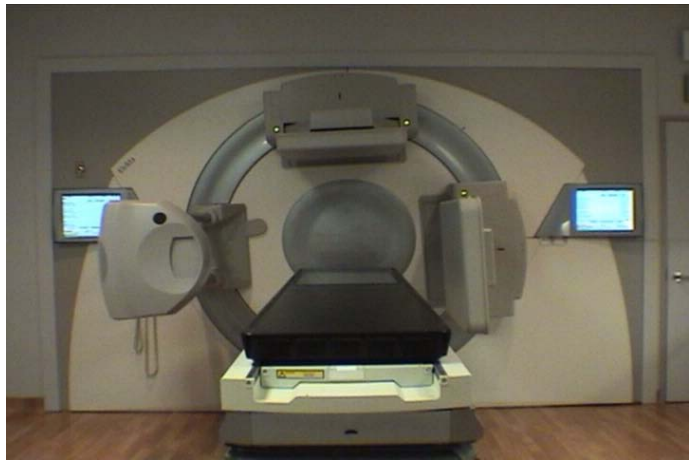

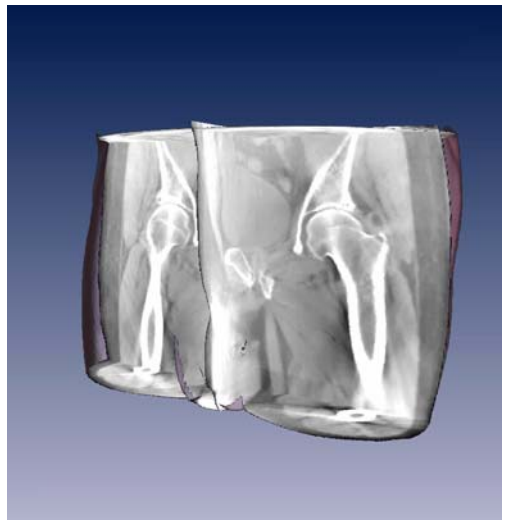

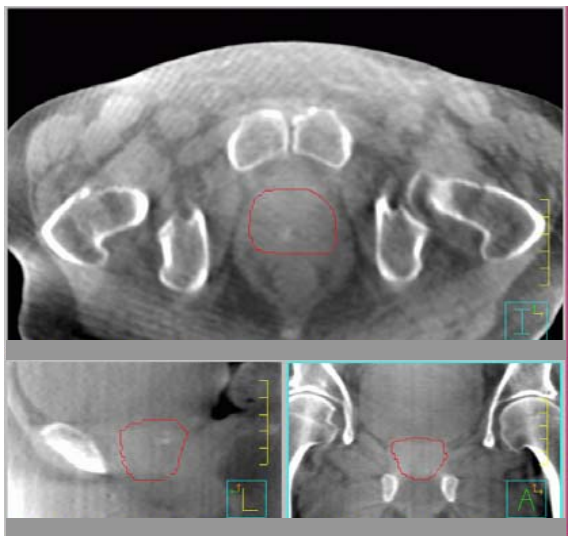

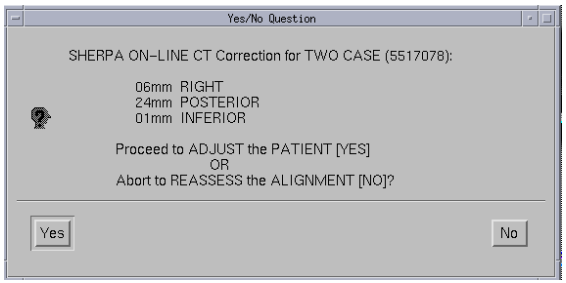

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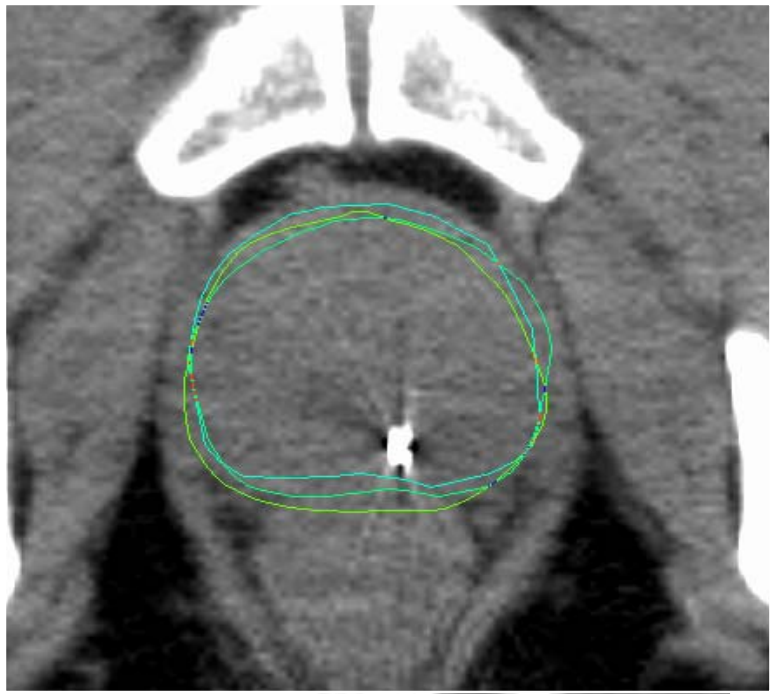
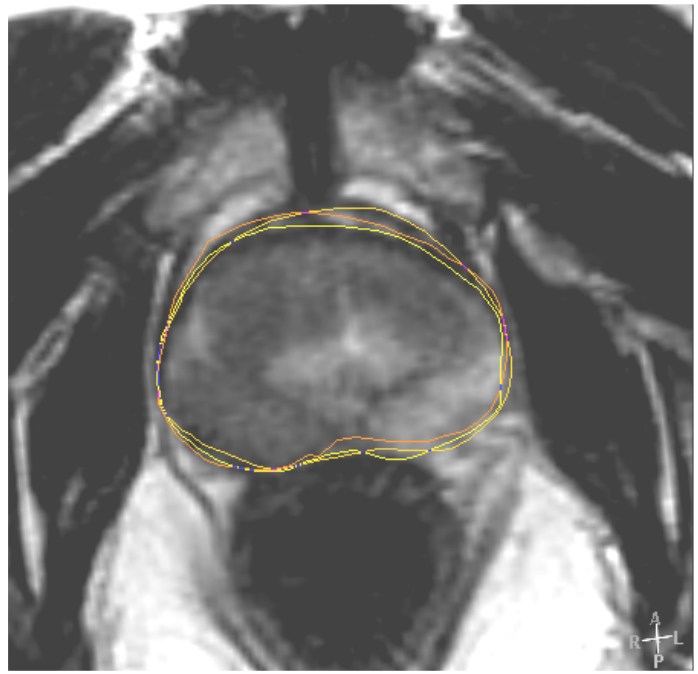
Clinical research trials at PMH

- At first consultation all the information presented can be overwhelming
- Always ask if there is anything suitable for your situation
- Broad range of applications depending on the situation
- Sometimes can be eligible for more than one study
- Occasionally there may be no trial that suits your needs

PROFIT study

- National study
- 1204 intermediate risk pts
- 4 weeks vs 8 weeks RT
- Goal is to show if the 2 dose schedules are the same





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Advanced imaging study

- Investigating the use of MRI for radiotherapy planning and cone beam CT for accurate guiding of radiotherapy
- 190 low/intermediate risk pts
- Goal is measure whether adding MRI and CBCT can help reduce side effects from radiotherapy and also whether MRI can be used to measure response to radiotherapy

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Magnetic Resonance Spectroscopy Study

- 20 pts
- Using MRS to study the metabolic activity in prostate cancer
- Involves biopsy and MRS during course of radiotherapy
- Might help to measure response to radiotherapy treatment

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MRI Guided biopsy study

- 50 pts previously treated with radiotherapy
- Using MRI to accurately locate prostate cancer within the gland after radiotherapy to guide biospy
- Goal is to develop new ways of identifying and targeting tumour within the prostate for local salvage therapy e.g. cryotherapy, microwave therapy, radiotherapy

Brachytherapy and External beam radiotherapy studies

- Intermediate and high risk pts (UBC)
  - 390 pts
  - External beam RT + brachytherapy boost vs. external beam + conformal boost
- Intermediate risk pts (RTOG)
  - 1520 pt
  - External beam + brachytherapy vs. brachytherapy alone
- Goal is to compare 2 treatments

Radiotherapy dose escalation study

- 60 high risk pts
- Measuring the feasibility and safety of increasing radiotherapy dose to the pelvic lymph nodes and prostate
- Goal is to test short and long term side effects

PROTEOMICS study

- 40 pts prostate cancer undergoing radiotherapy
- Feasibility of collecting blood and urine to measure proteins in patients
- Goal is to increase understanding of biomolecular changes that occur during radiotherapy with potential application of prediction of radiotherapy response and side effects

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Acknowledgments

- Radiation Oncology
  - A. Bayley, R. Bristow, C. Catton, J. Crook, M. Gospodarowicz, M. McLean, C. Menard, M. Milosevic, P. Warde
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  - T. Craig, J. Chow, A Damyanovich, Y. Cho, M. Heydarian
- Radiation Therapy
  - T. Rosewall, V. Kelly, V. Kong, Team 3 planners
  - Treatment Unit Therapists

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