Prostate Cancer

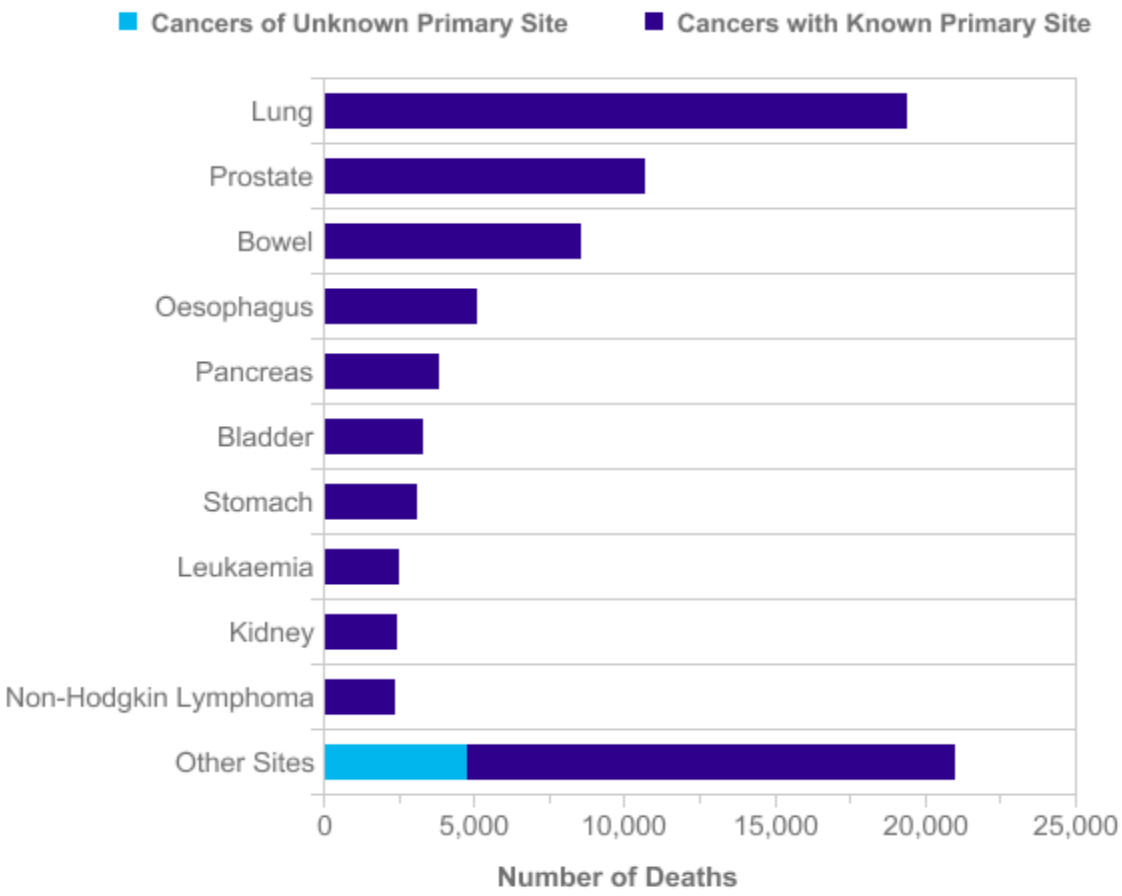
Dr Paula Wells
Consultant Clinical Oncologist

The Facts

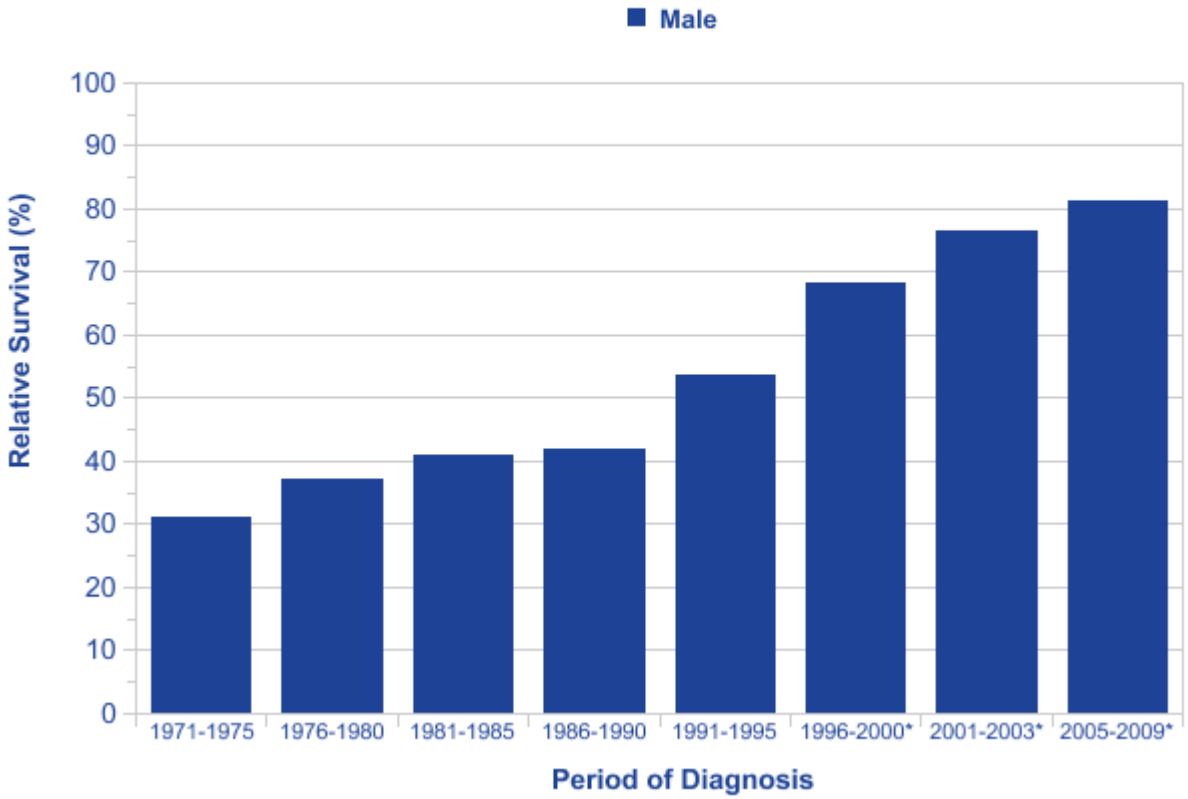
In UK:
Prostate cancer most common cancer in men
Second commonest cause of cancer death in men
Prostate cancer rates have tripled in 40 years
75% cases of prostate cancer over 65 years @ presentation
9/10 deaths from prostate cancer in men > 65 years

In 2010:
40975 men diagnosed with prostate cancer (112 per day)
10721 deaths from prostate cancer (29 per day)
2005-9 81.4% men in England survived their cancer > 5 yrs
Lifetime risk of developing prostate cancer is 1:8

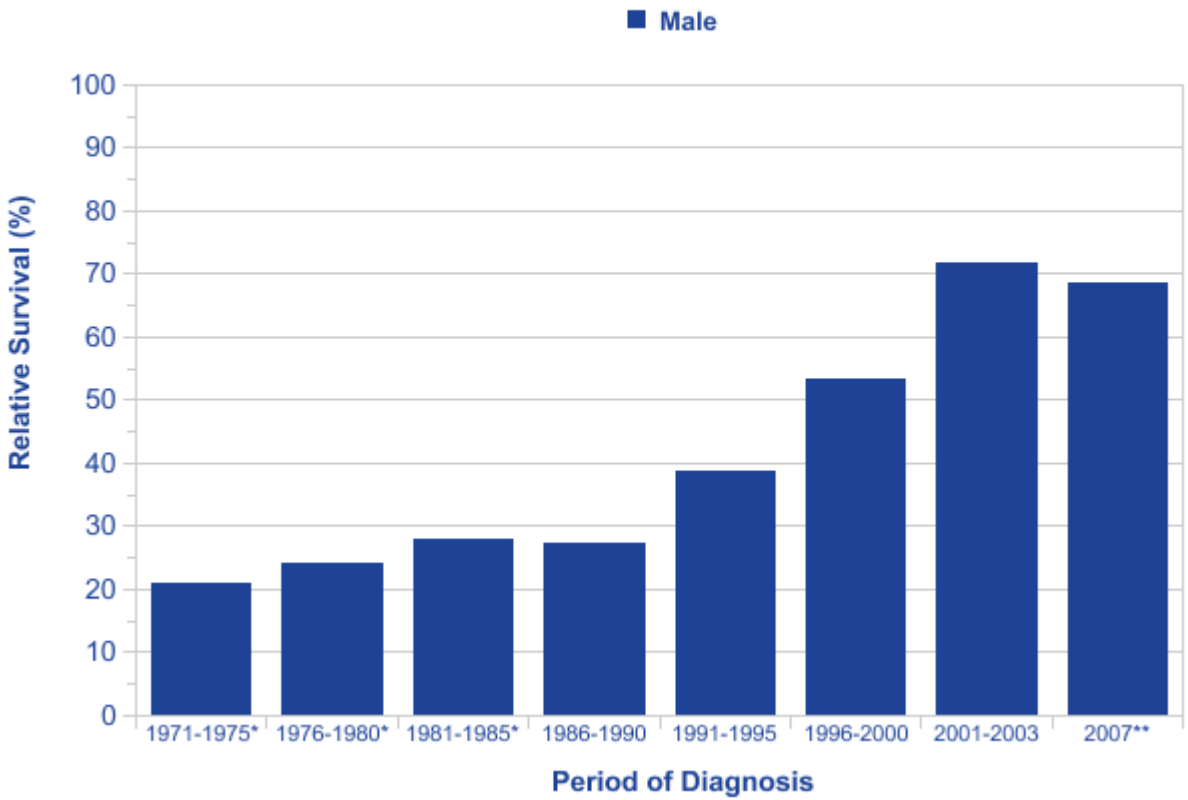
10 most common causes of cancer death – Males 2010



Survival over Time – 5year

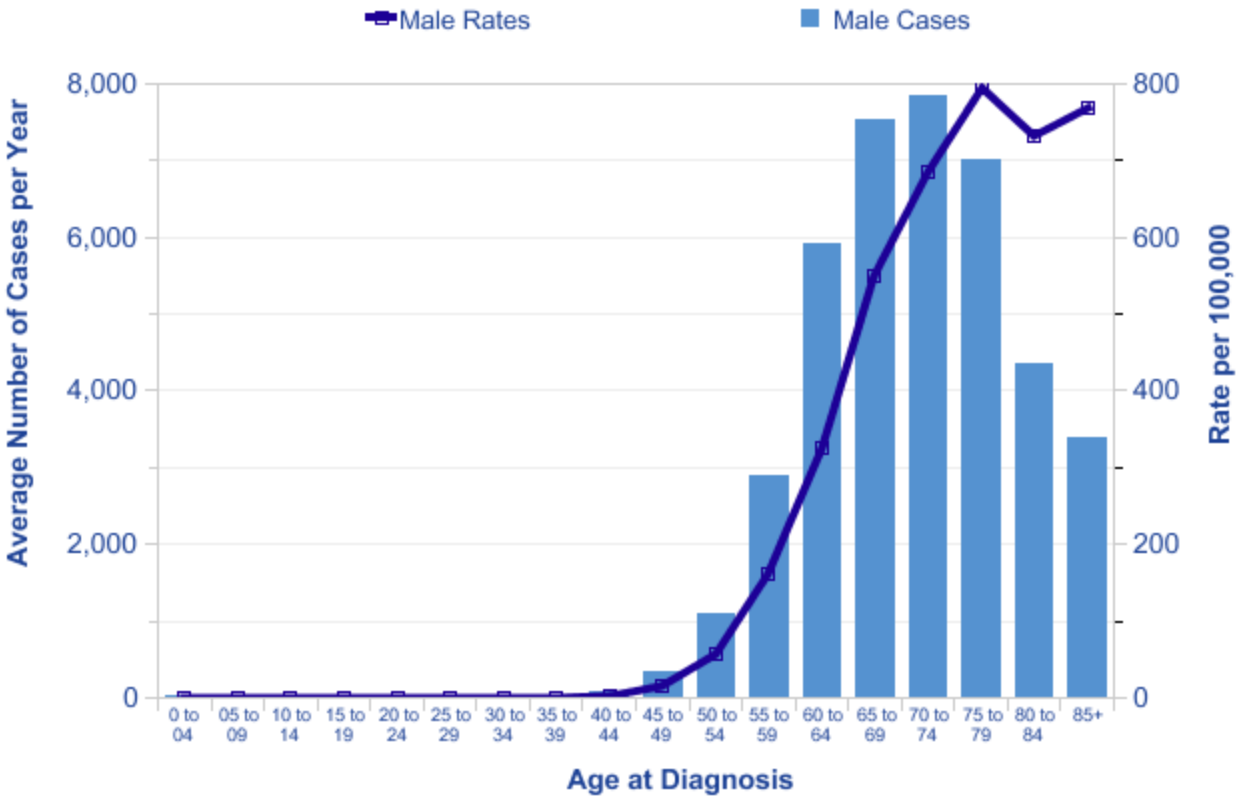


Survival over Time – 10 year



Aetiology

Age Low incidence under 50yrs



Aetiology

Family History
First degree relative increases risk by 120-150%
Highest risk when brother affected
When mother has breast cancer risk of prostate in son 19 - 24%

Breast cancer susceptibility gene BRCA2 – 7 x risk in men < 65yrs
5-9% prostate cancer linked to family history or genetic factors

Ethnicity
Increased in black men
Higher numbers of younger patients and diagnosed 3-5 years earlier than white men

Height
Increase in aggressive or fatal prostate cancer 12% for each 10cm above male average.

Aetiology

Insulin like growth factor 1 (IGF-1)
Men with high levels of IGF-1 38-83% increased risk

Previous cancers associated increased risk of prostate cancer
Renal cell carcinoma – 69%
Bladder cancer 14 -151%
Melanoma 15 - 50%
Lung Adenocarcinoma – 56%

Radiation

REDUCED prostate cancer risk in men with Diabetes

Symptoms and Diagnosis

LUTS

Dysuria rare for prostate cancer

Haematospermia rare for prostate cancer

Symptoms not specific to prostate cancer

BUT

These is addition to abnormal DRE and raised PSA for age should lead to referral

PSA vs Age

3 ng/ml or less is in normal range normal for a man under 60 years old

4 ng/ml or less is normal for a man aged 60 to 69

5 ng/ml or less is normal if you are aged over 70.

PSA not cancer specific

Prostate Cancer Screening

Prostate Lung Colorectal Ovary (PLCO) 2009 76,000 men
PSA yearly for six years
No survival benefit to screening @ PSA 4.0ng/ml @ 10 years

European Randomised Screening for Prostate Cancer (ERSPC) 182,000 men NEJM 2012
20% reduction in risk from Prostate Cancer death but high risk over diagnosis
PSA cut off 3.0ng/ml and screening interval four yearly

Overall
To prevent 1 death from prostate cancer over 11 years, 1055 men had to be screened with 37 cancers being detected

Management Algorithm

Assessment of risk – Roach formula

Estimated risk of lymph node involvement = 2/3 PSA + ([Gleason score -6] x10)

(For radical RT to prostate + SV should be less than 30%)

Biological Age

Hereditary

Co-morbidities

Patient choice

Very Low Risk Prostate Cancer

T1a-2a Gleason 3+3 adenocarcinoma pPSA < 10

Active surveillance

Radical Prostatectomy

Brachytherapy

Radical Radiotherapy (EBRT) alone

Very low risk Prostate Cancer

T1a
Disease specific progression – 5% @ 5 years
BUT ~ 50% progression at 10 years
Therefore offer therapy if life expectancy >15 years

T1b
Progression after 5 years

T1c
Up to 30% progression but look at other factors PSA dt, core positivity

T2a
30-35% progression @ 5 years

Active Surveillance Protocol

T1c to T2a

Gleason score 3+3 and PSA <10ng/ml

Or

Gleason 3+4 and PSA < 15 in men > 70y

FU median 8 years, OS 85%, DSS and met S 99%

PSA DT 7 years (42% >10years, 22% < 3years)

33% patients went on to have radical therapy:

22% PSA DT < 3 years

5% Gleason score progression at re biopsy

10% patient preference

Choo, Klotz et al 2001

Outcome of Deferred Treatment Prostate Cancer vs. Tumour Grade

% of patients (95% CI) surviving at 5 & 10 years.

Grade	**5 years (%)**	**10 years (%)**
Disease-specific survival		
Grade 1	98 (96-99)	87 (81-91)
Grade 2	97 (93-98)	87 (80-92)
Grade 3	67 (51-79)	34 (19-50)
Metastasis-free survival		
Grade 1	93 (90-95)	81 (75-86)
Grade 2	84 (79-89)	58 (49-66)
Grade 3	51 (36-64)	26 (13-41)

15-year risk of dying from Prostate Cancer vs. Gleason score @ diagnosis

(localised disease 55-74 years)

Gleason score	Risk of cancer death*	(%) Cancer-specific mortality † (%)
2-4	4-7	8
5	6-11	14
6	18-30	44
7	42-70	76
8-10	60-87	93

** The figures on the risk of cancer death differ for different age groups and represent the true risk*

Outcome of Scandinavian Prostate Cancer Group Study (SPCG-4)@ 12 years follow-up

(patients randomised between 1989 and 1999)

	RP (n 347) % (n)	WW (n 348) % (n)	Relative Risk (95% CI)	*p* value
DSS	12.5 (43)	17.9 (68)	0.65 (0.2-11.1)	0.03
MPD	19.3	26	0.65 (0.47-0.88)	0.006

(MPD – metastatic progressive disease)

Prostate Cancer Intervention Versus Observation Trial: VA/NCI/AHRQ Cooperative Studies Program #407 (PIVOT) 1994-2002 - ongoing analysis

Radical Prostatectomy

Guidelines and recommendations for Radical Prostatectomy	LE
Indications	
• **Low & intermediate risk localised** Prostate cancer (cT1b-T2 and Gleason score 2-7 and PSA< 20) and a life expectancy > 10 years.	1
Optional	
• T1a disease and a life expectancy > 15 years or Gleason score 7.	3
• Selected patients with **low-volume high-risk localised** Prostate Cancer (cT3a or Gleason score 8-10 or PSA >20).	3
• **Highly selected patients with very high-risk localised** Prostate Cancer (cT3b-T4 N0 or any T N1) in the context of multimodality treatment.	3
Recommendations	
• Short-term (three months) neo-adjuvant therapy with LHRH analogues is **not** recommended in the treatment of stage T1-T2 disease.	1
• Nerve-sparing surgery may be attempted in pre-operatively potent patients with low risk for extra-capsular disease (T1c, Gleason score < 7 and PSA < 10 ng/mL or see Partin tables/nomograms).	3
• Unilateral nerve-sparing procedures are an option in stage T2a disease	4

Complications of Radical Prostatectomy

Complication	Incidence (%)
• Peri-operative death	0.0-2.1
• Major bleeding	1.0-11.5
• Rectal injury	0.0-5.4
• Deep venous thrombosis	0.0-8.3
• Pulmonary embolism	0.8-7.7
• Lymphocoele	1.0-3.0
• Urine leak, fistula	0.3-15.4
• Slight stress incontinence	4.0-50.0
• Severe stress incontinence	0.0-15.4
• Impotence	29.0-100.0
• Bladder neck obstruction	0.5-14.6
• Ureteral obstruction	0.0-0.7
• Urethral stricture	2.0-9.0

Results of Organ Confined Prostatectomy

	Patient No	Mean FU (Mo)	5-yr PSA-free S (%)	10-yrPSA-free S (%)
Han (2001)	2404	75*	84	74
Catalona (1994)	925	28	78	65
Hull (2002)	1000	53	–	75
Trapasso(1994)	601	34	69	47
Zincke (1994)	3170	60	70	52

Radical EBRT

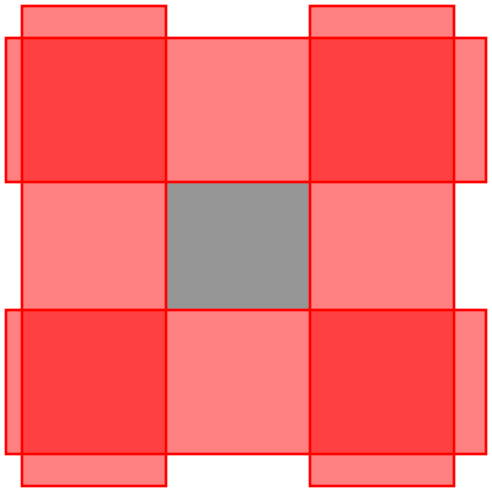
MD Anderson 2006
305 Stage T1-3 pPSA ~ 10ng/ml
70 vs 78 Gy
Increased risk of biochemical failure @ 70Gy

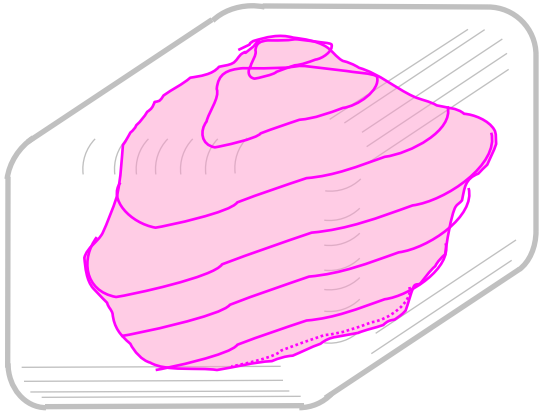
PROG 95-09 (2005)
395 T1b-T2b (75% Gl </= 6, pPSA </= 15)
Proton boost 18.8 Gy vs 28.8Gy + EBRT 50.4Gy
Increased biochemical control for higher dose arm

In practice – 74Gy is recommended

1980s

The Rectangular Era

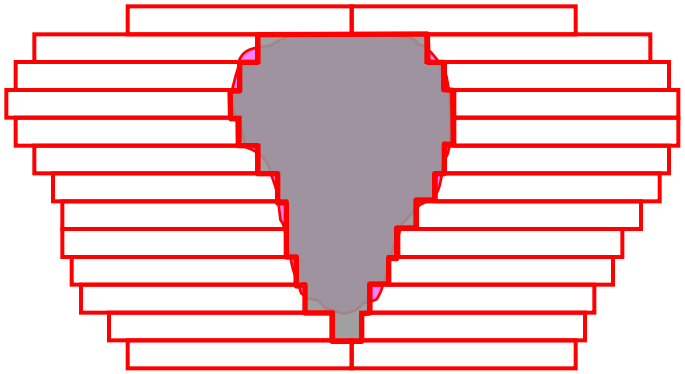


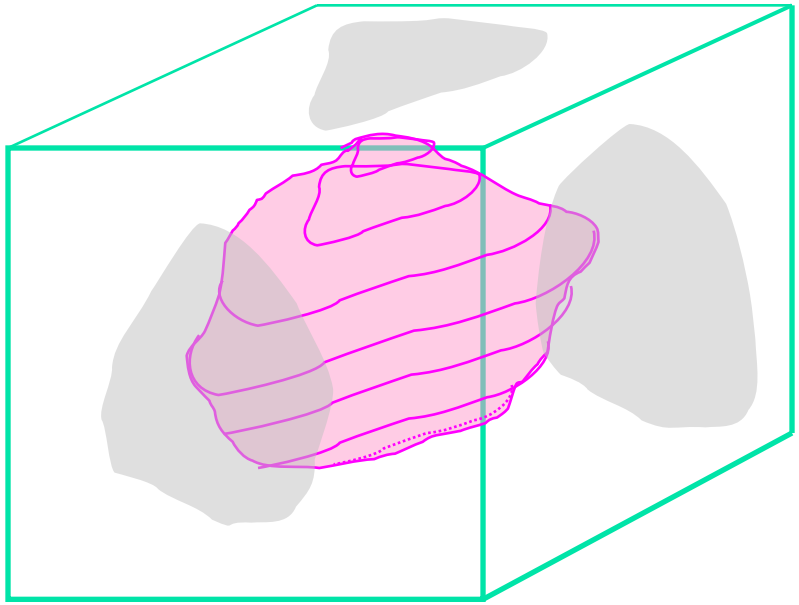


1990s

The Conformal Era

Blocks/MLC

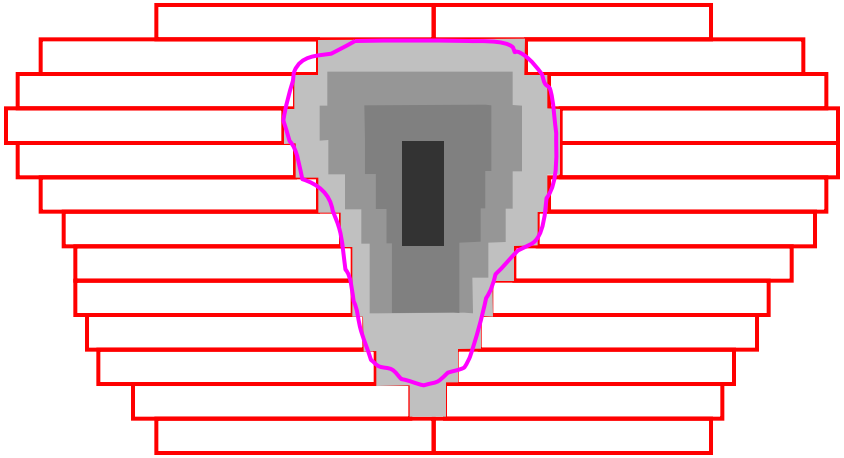




2000s

Intensity Modulation (IMRT)

Non-uniform fluence

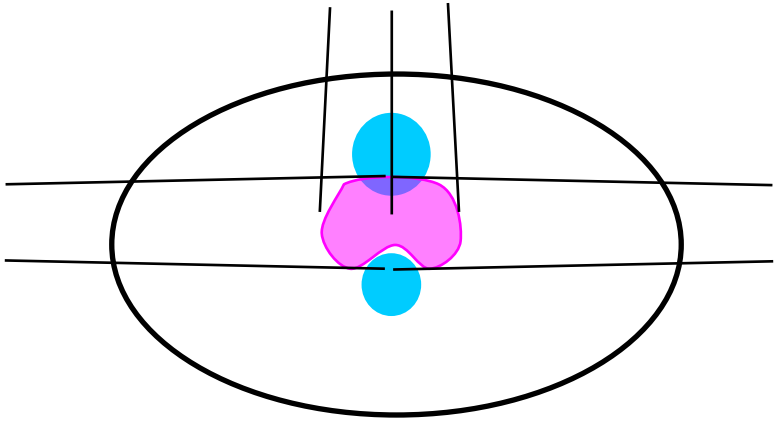


Forward Planning

Start with some beams

Adjust beam properties to achieve an *acceptable* dose distribution

energy
number of beams
direction
weight
wedges
shielding



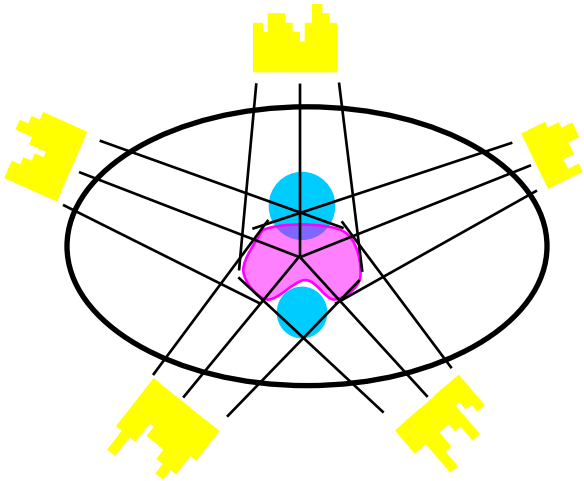
Inverse Planning

Outline PTVs and OARs

Set dose limits for PTV and OARs

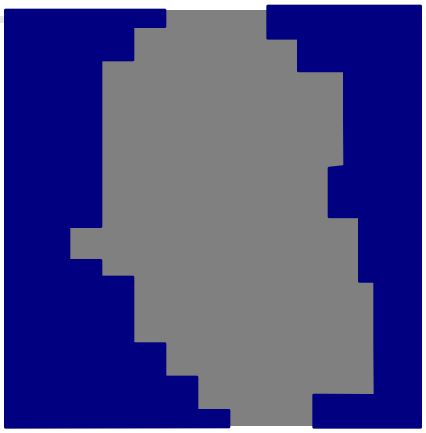
Select *energy*, *number of beams*, *directions*

Iteratively calculate intensity modulated beams

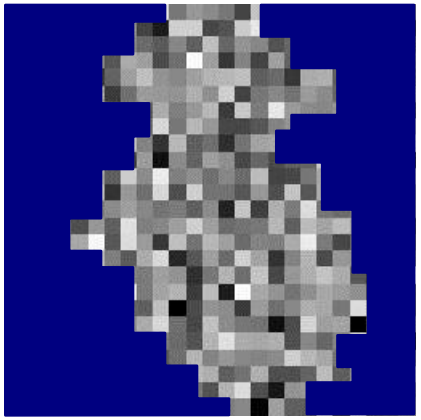


Inverse Planning

Forward planning optimises the weights of a few beams

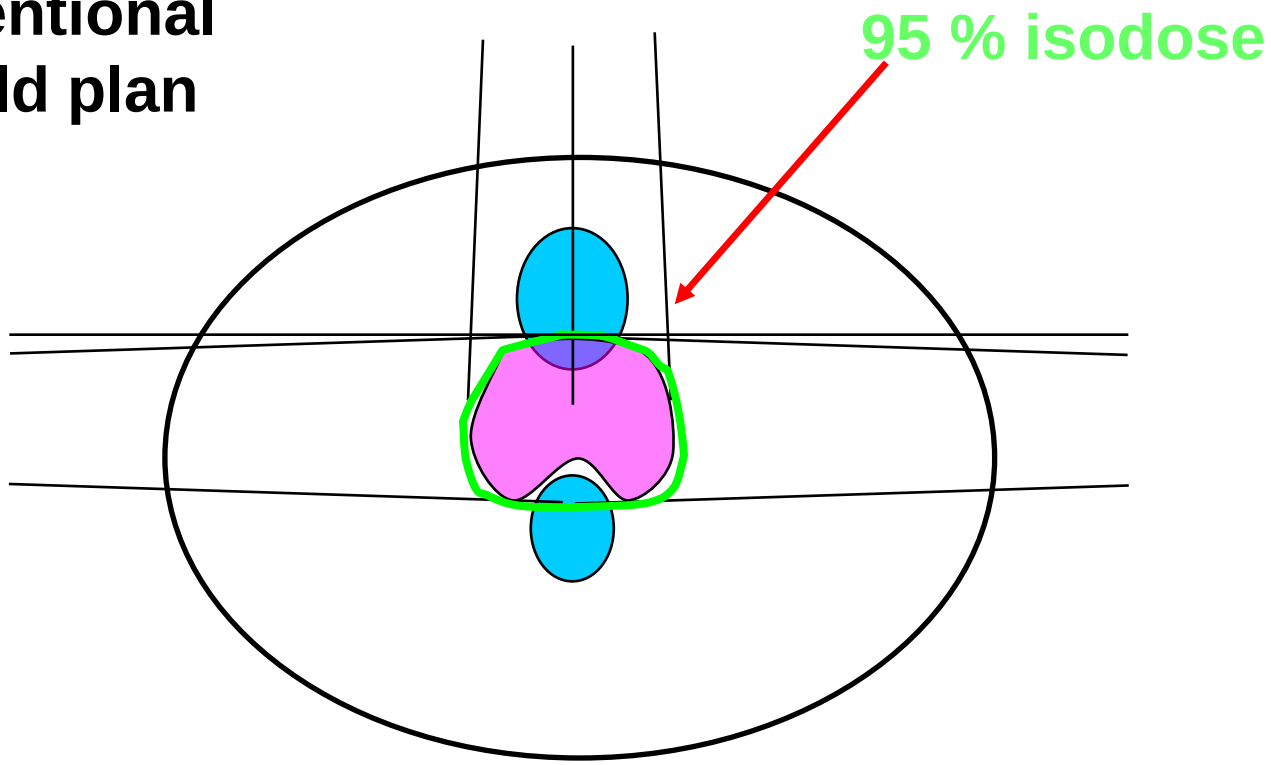


Inverse planning optimises the weight of thousands of beamlets for each treatment field



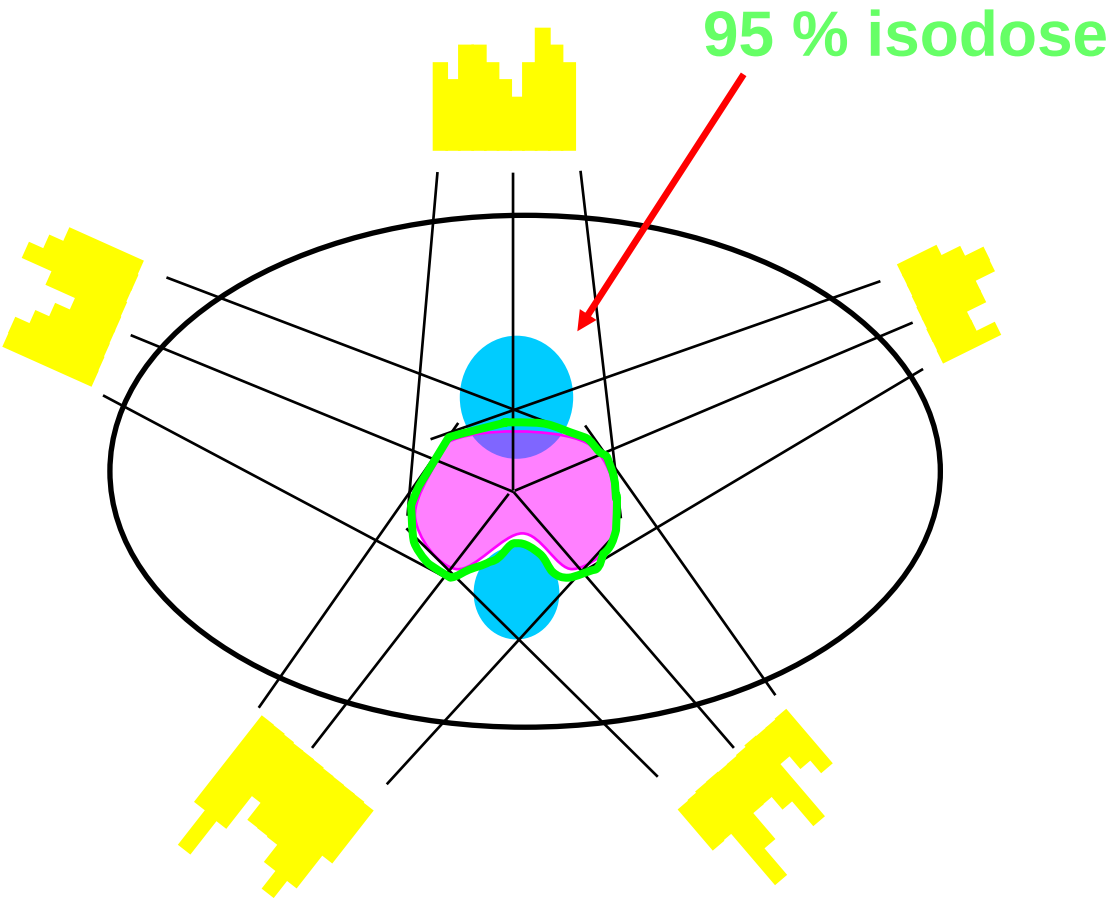
3D-CRT: What can it do?

Conventional 3 field plan

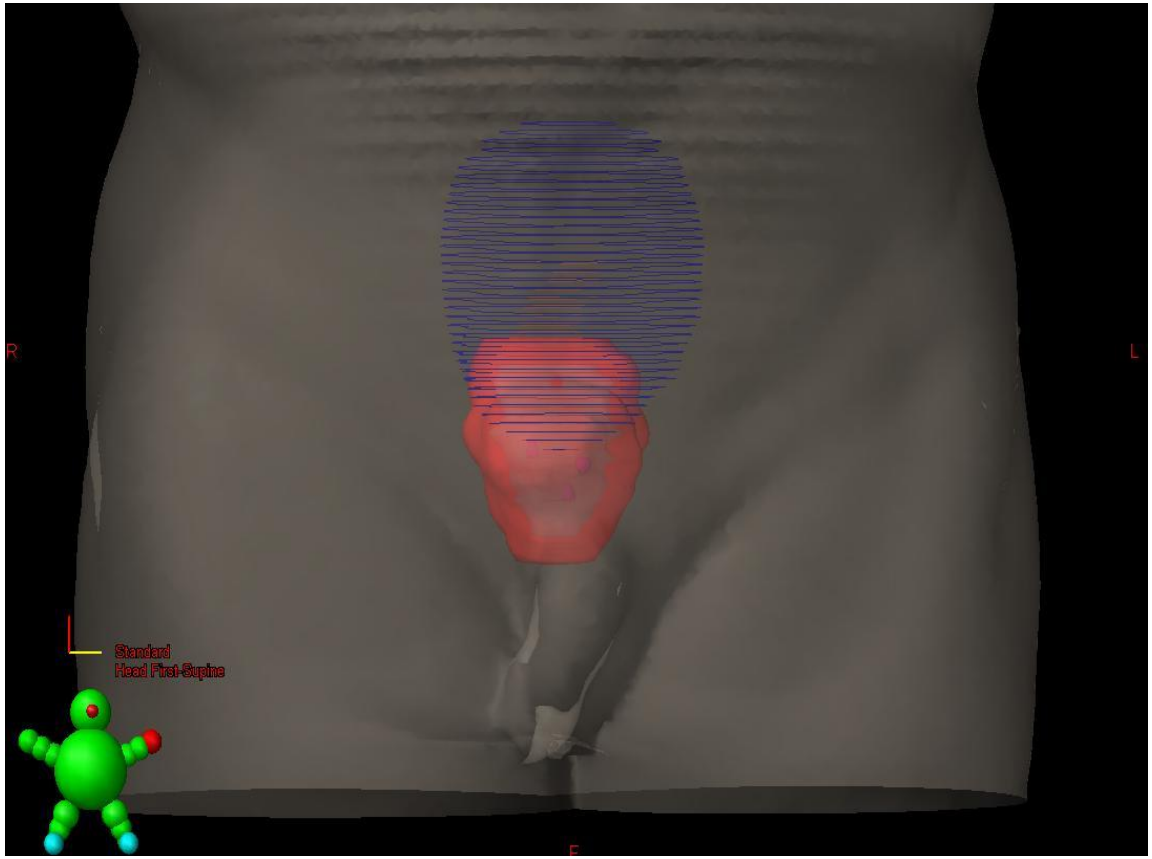


IMRT: What can it do?

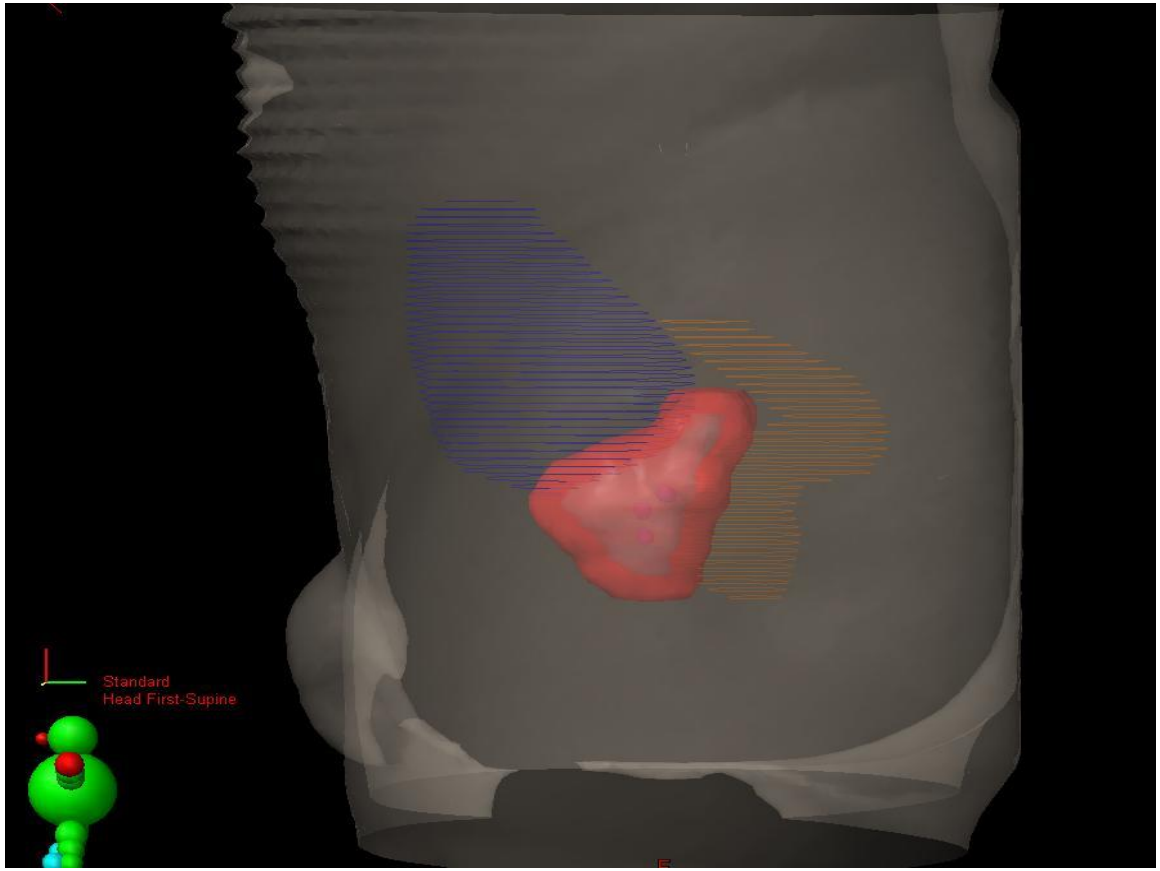
IMRT plan



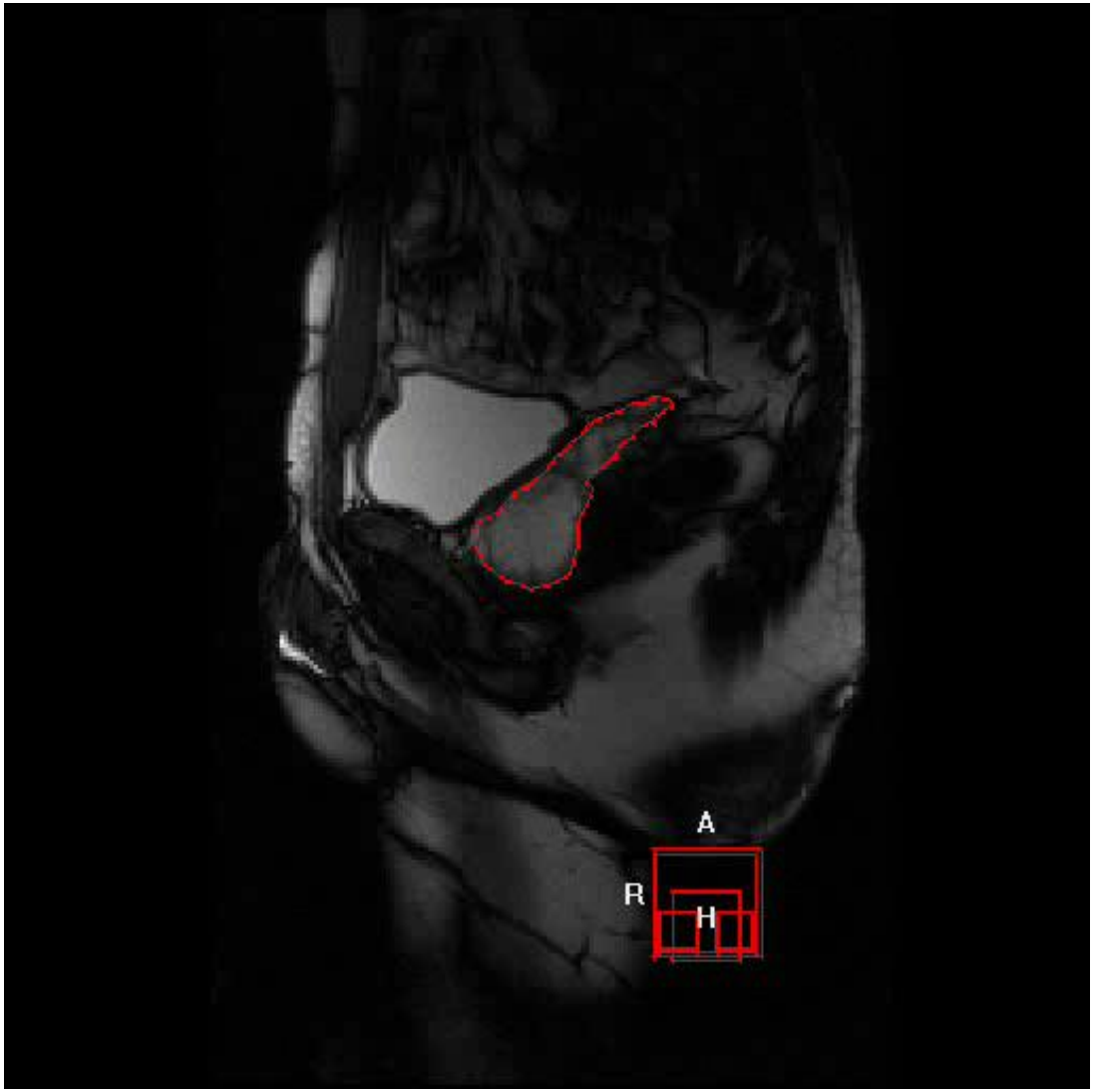
Prostate PTV and OAR



Prostate PTV and OAR

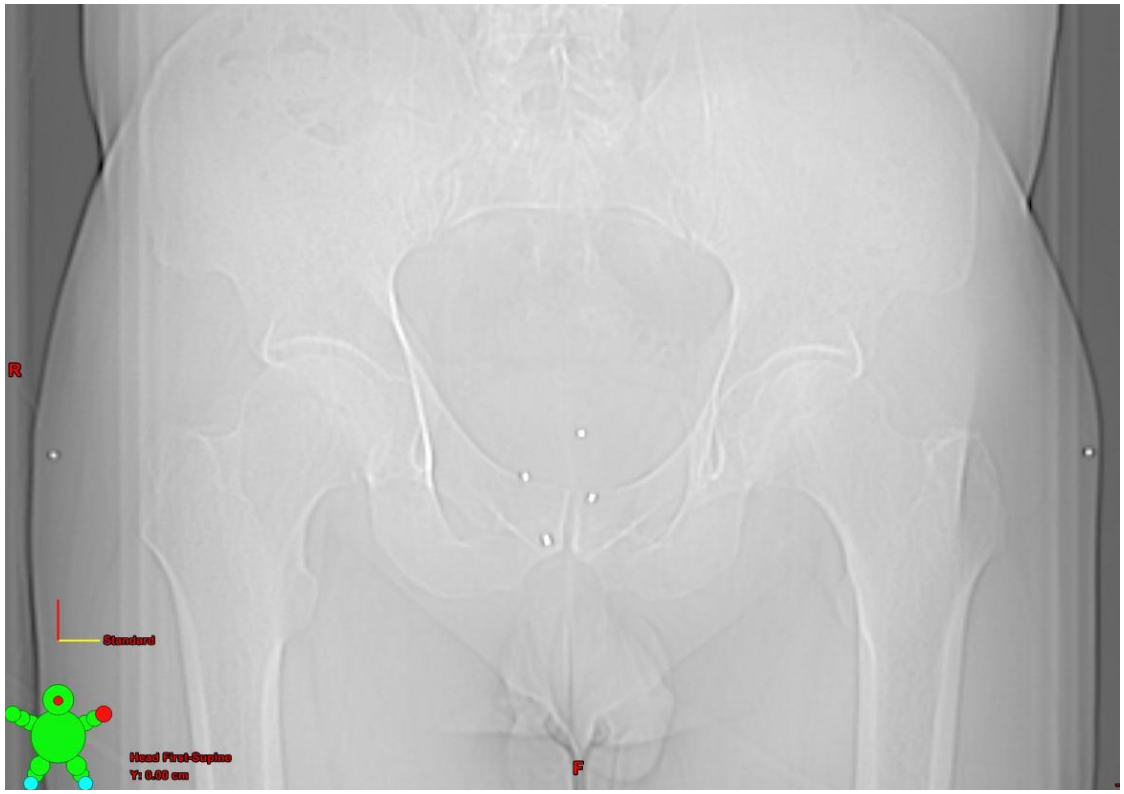


Prostate Movement Over an 8 Minute Period

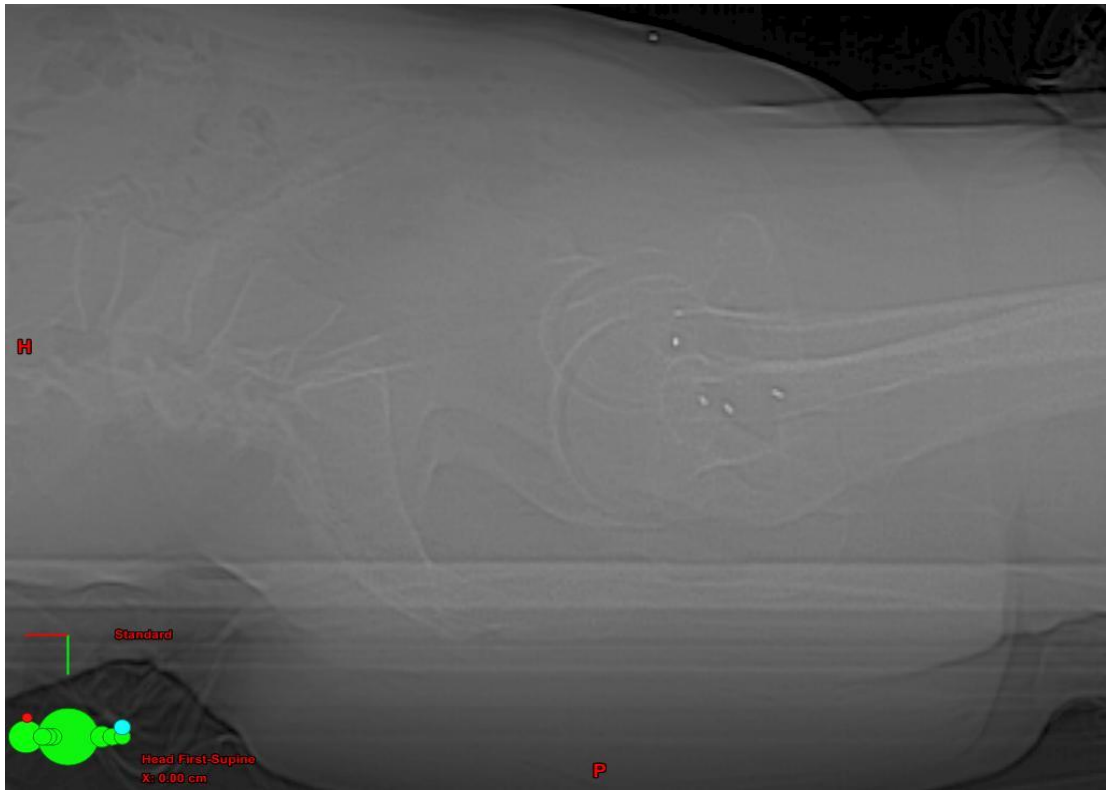


Target verification using KV imaging

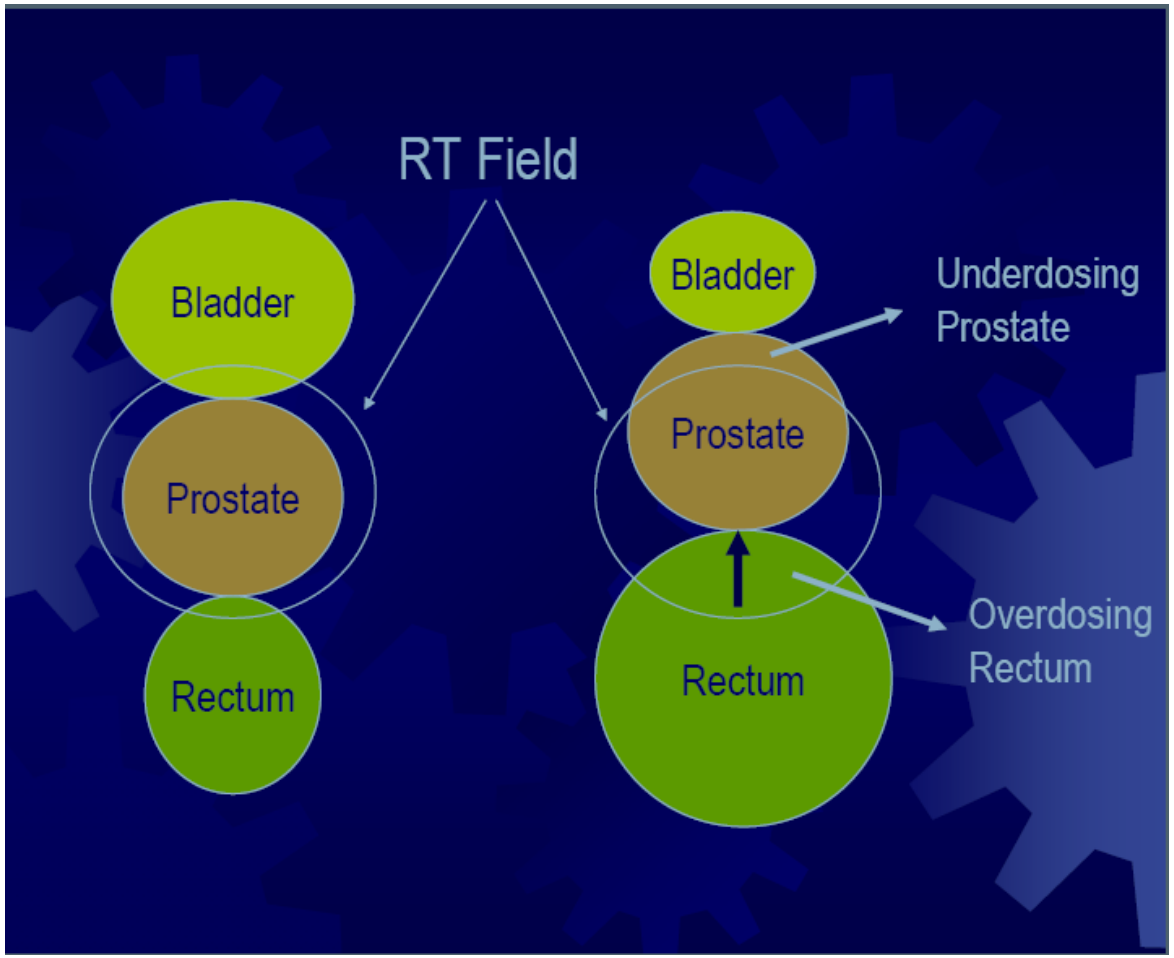
Gold seeds - IGRT



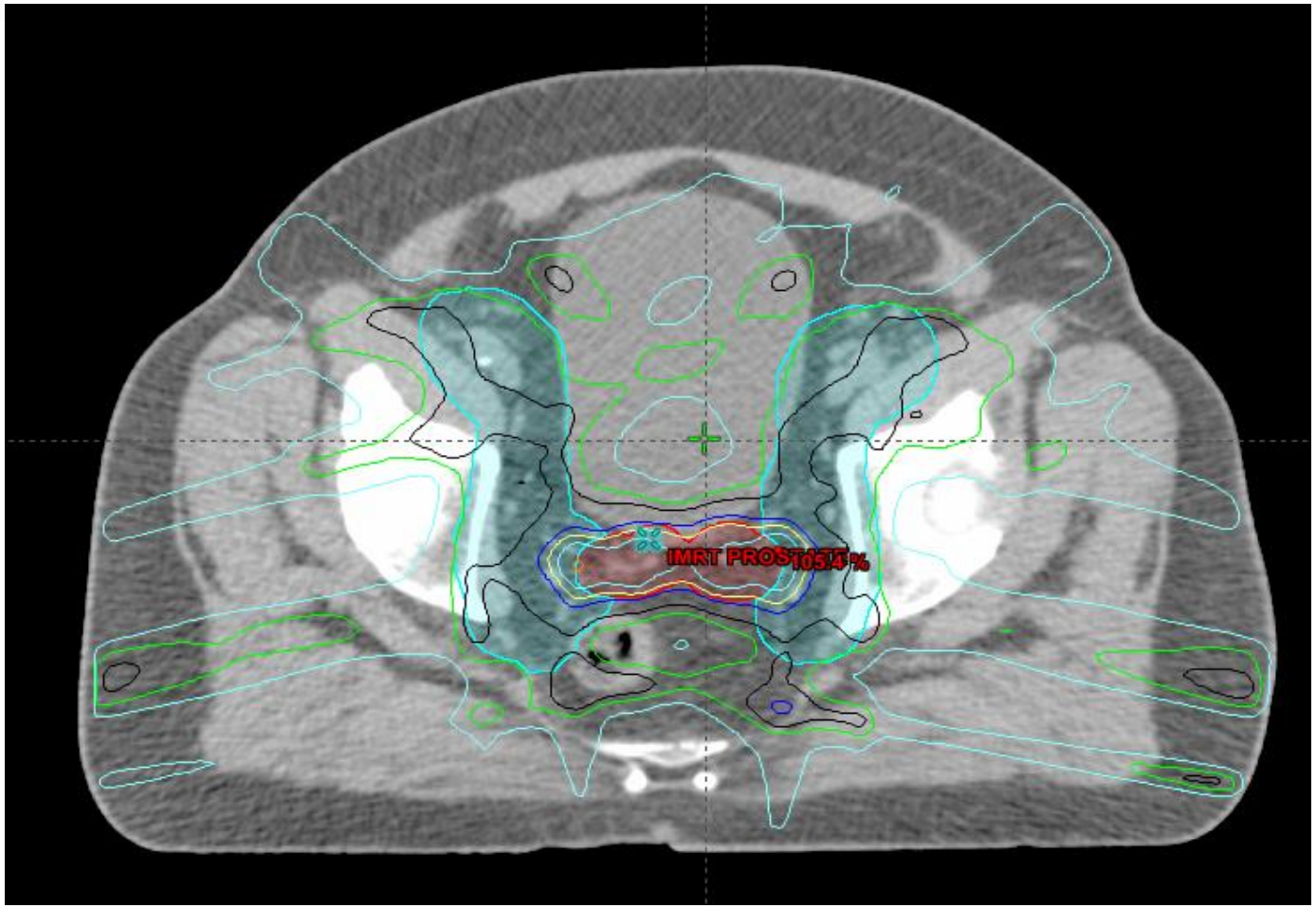
Gold seeds - IGRT



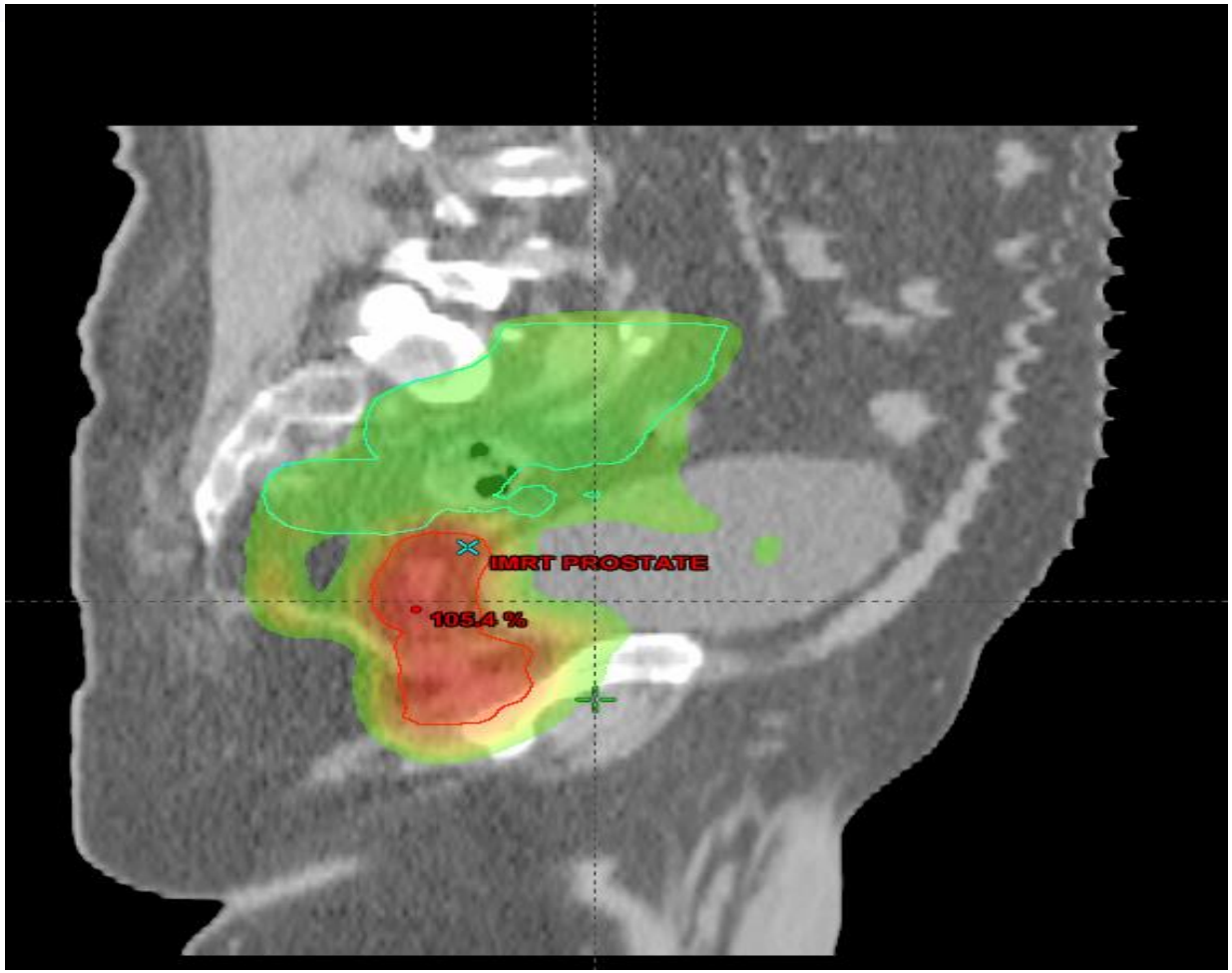
Gold seeds - IGRT



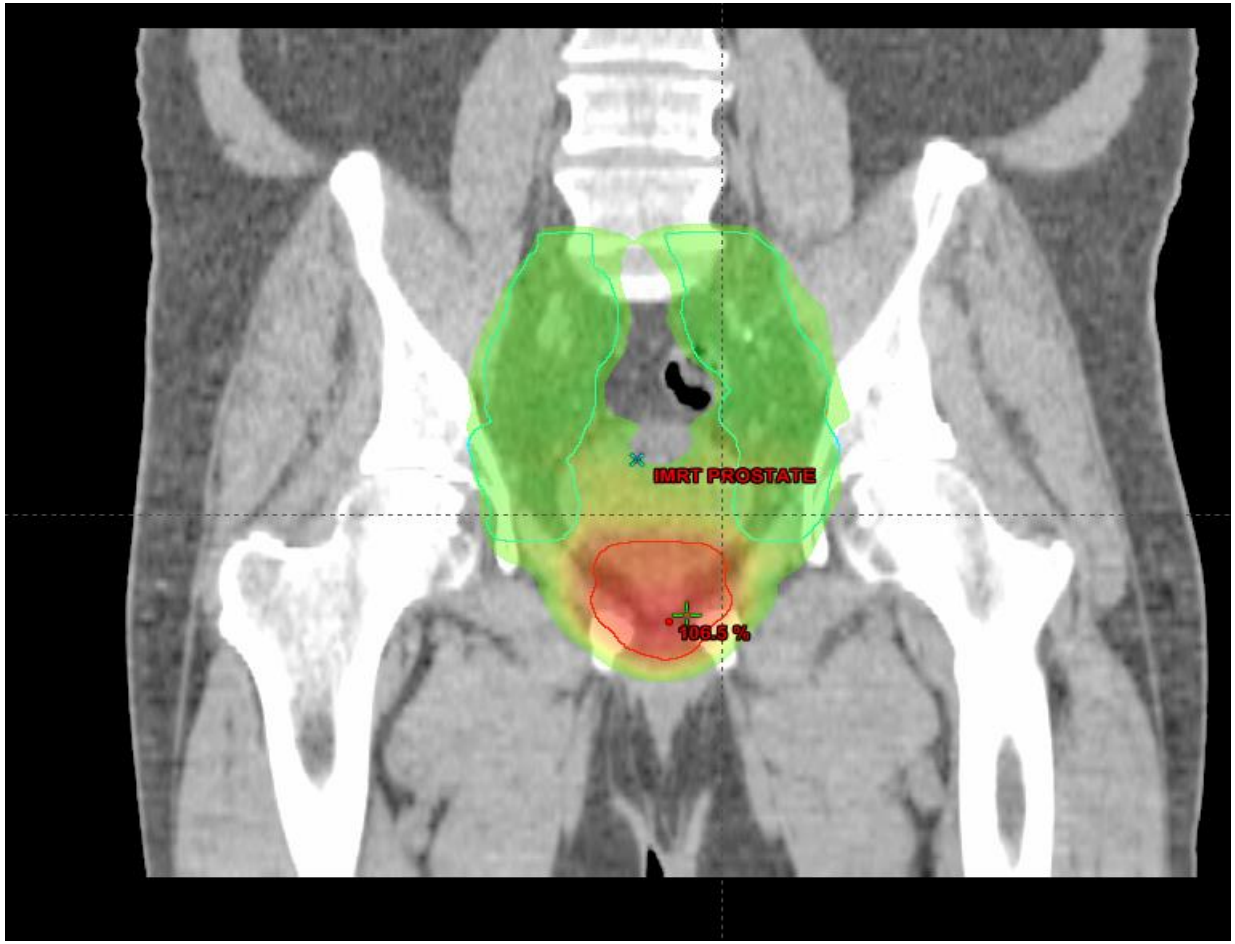
Prostate EBRT – IMRT plan



Colour wash image - sagittal



Colour wash image - coronal



Radiotherapy Overview

In daily practice, a minimum dose of > 74Gy is recommended with short-term androgen deprivation therapy (ADT) (based on the results of a phase III RCT).

Higher Dose RT provide a significant increase in 5-year freedom from clinical or biochemical failure for patients in an intermediate-risk group:

- Dutch Trial :68Gy with 78Gy
- MRC RT01 study: 64Gy with 74Gy
- MD Anderson study especially in high risk group

Where we are now?

Randomised studies of RT – Doses 76Gy-81Gy (Kupelian P 2005, Zeitman 2005, Zelefsky 1998)

3 Randomised trials advantage to neo-adjuvant HT (Pilepich 2001, Porter 2000, Laverdiere 2000, Roach 2000, (Overview)).

MRC study 64Gy vs 74Gy + Neo HT 11% increase biochemical DFS
Neoadjuvant HT - 13% increase in OS (D'Amico 2008)

Conventrional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate cancer - CHHiP

Dose escalation / hypofractionation
Alpha/beta ? ~ 1.5Gy for prostate cancer

Toxicity of EBRT – EORTC 22863 (Ataman 2004)

Toxicity	Grade 2		Grade 3		Grade 4		Any significant toxicity (≥ grade 2)	
	No.	%	No.	%	No.	%	No.	%
Cystitis	18	4.7	2	0.5	0	0	20	5.3
Haematuria	18	4.7	0	0	0	0	18	4.7
Urinary stricture	18	4.7	5	1.3	4	1	27	7.1
Urinary incontinence	18	4.7	2	0.5	0	0	20	5.3
Overall GU toxicity	**47**	**12.4**	**9**	**2.3**	**4†**	**1†**	**60**	**15.9**
Proctitis	31	8.2	0	0	0	0	31	8.2
Chronic diarrhoea	14	3.7	0	0	0	0	14	3.7
Small bowel obstruction	1	0.2	1	0.2	0	0	2	0.5
Overall GI toxicity	**36**	**9.5**	**1**	**0.2**	**0**	**0**	**37**	**9.8**
Leg oedema	**6**	**1.5**	**0**	**0**	**0**	**0**	**6**	**1.5**
Overall toxicity*	**72**	**19.0**	**10**	**2.7**	**4**	**1**	**86**	**22.8**

Salvage Treatment After Radiotherapy

	BRFS(5 yrs)	Complications
• Salvage Surgery	44-65%	Incontinence 40% Stricture 25%
• Cryotherapy	58%	Incontinence 15% fistula 10% rectal and perineal pain35%
• HIFU	10-50%	Stricture 11%, rectal fistula up to66%
• Brachytherapy	34 -75% (LDR)	Incontinence 6%, GU (G3-4)17% 89% (2 yrs for HDR) GI 7%

Prostate Brachytherapy

Treatment of early-stage prostate cancer by permanent implant of Iodine seeds

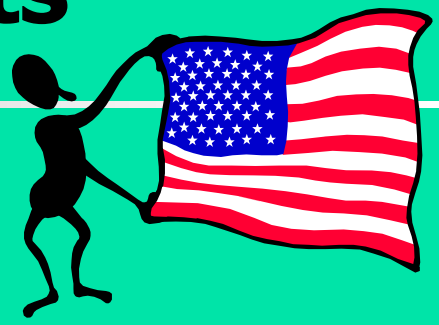
Low dose rate

Bulk of dose delivered within year ($T_{1/2}$ 59.4 days)

Low risk: T1c-T2a, PSA<10, prostate vol<50cc
i.e. low risk of extra-capsular spread

Established treatment option in UK & US

Brachytherapy: results



US

Seattle (late 1980s)

Stock & Stone (1990) – 96% 10yr DFS (low risk)

Potters (1992) – 93% 12yr DFS

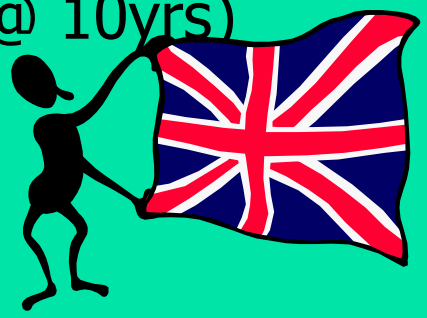
UK

Leeds (1995) DFS and OS (85% and 95% @ 10yrs)

Guildford (1999)

Guy's & St Thomas' (2003)

Barts (2008)



Iodine-125 seeds

Emissions:	27-35 keV photons (γ and X rays)
Half value layer:	0.02 mm lead
	1.7 mm tissue
Half-life:	59.4 days
Typical AKS:	0.533 µGyh-1 @1m
Size:	4.5mm x 0.8mm
Number used:	60 to 100 per implant

Sealed-sources - no radiation contamination from seeds

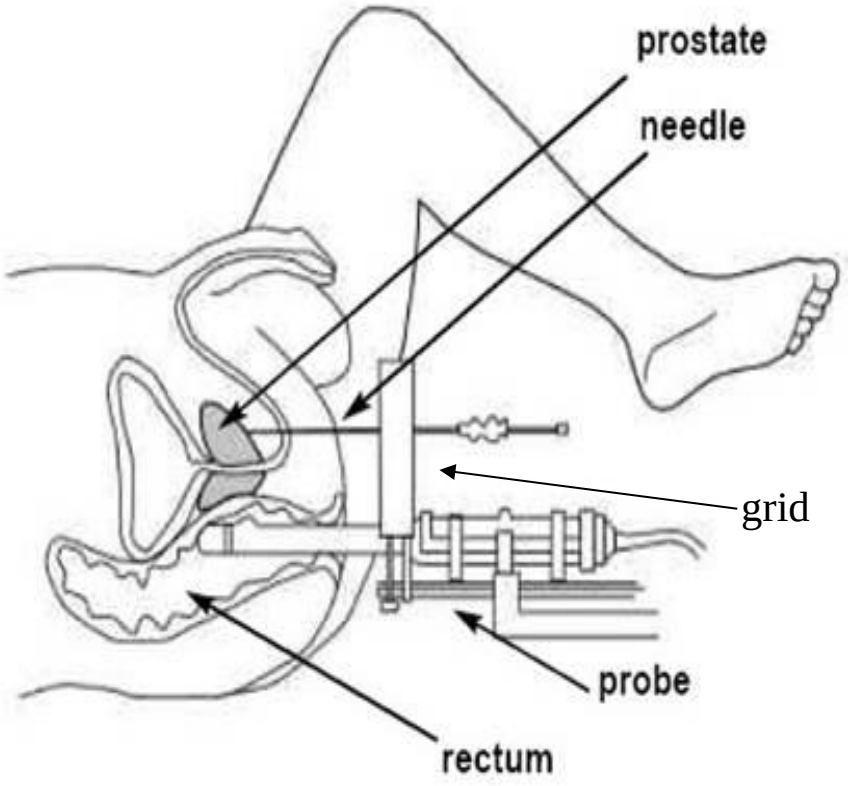
Implant Technique

Single-stage interactive dose feedback ('dynamic')

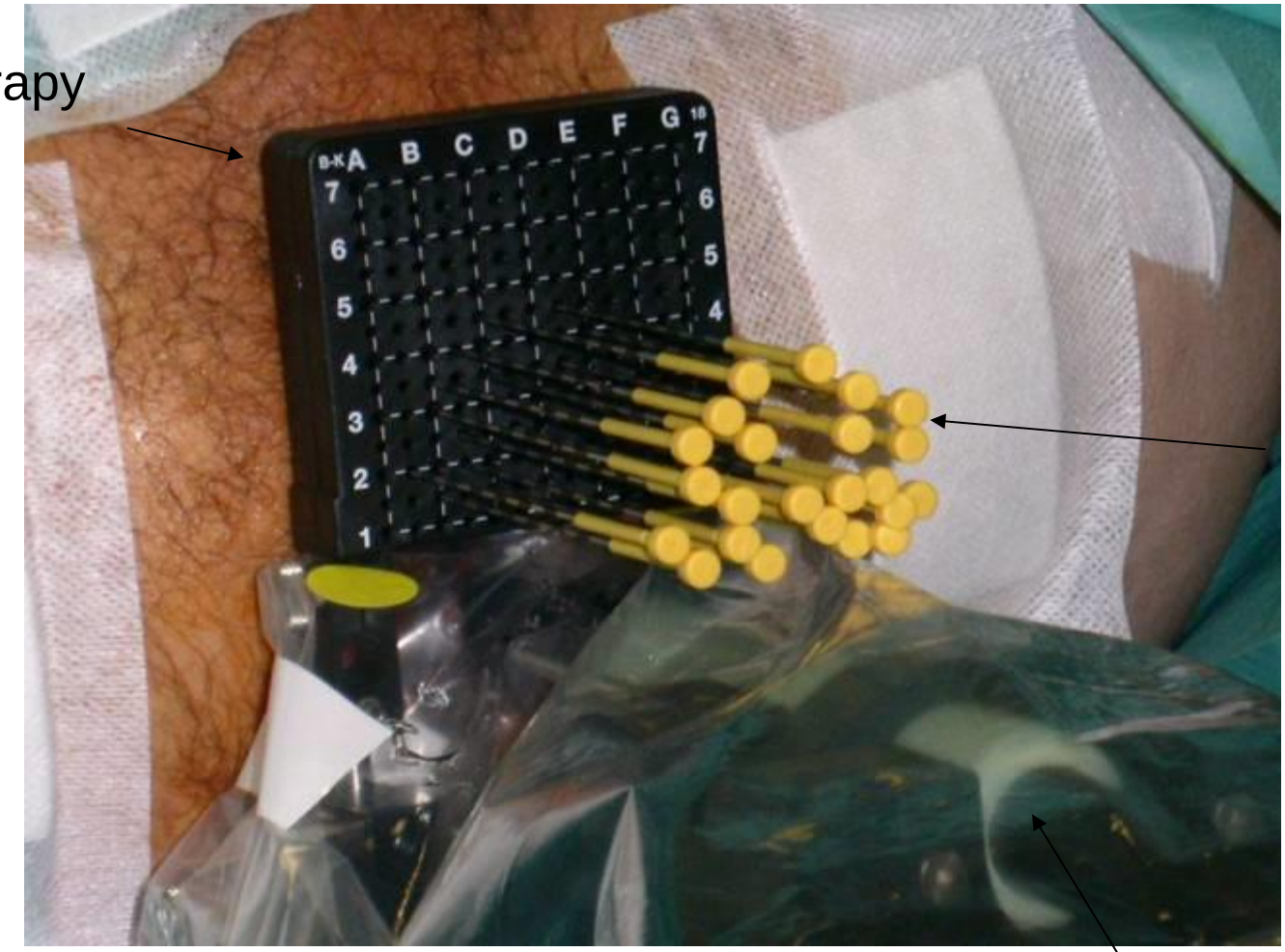
Day case; GA

Patient in extended Lithotomy position

Trans-rectal ultrasound probe



Needles implanted



Implanting seeds

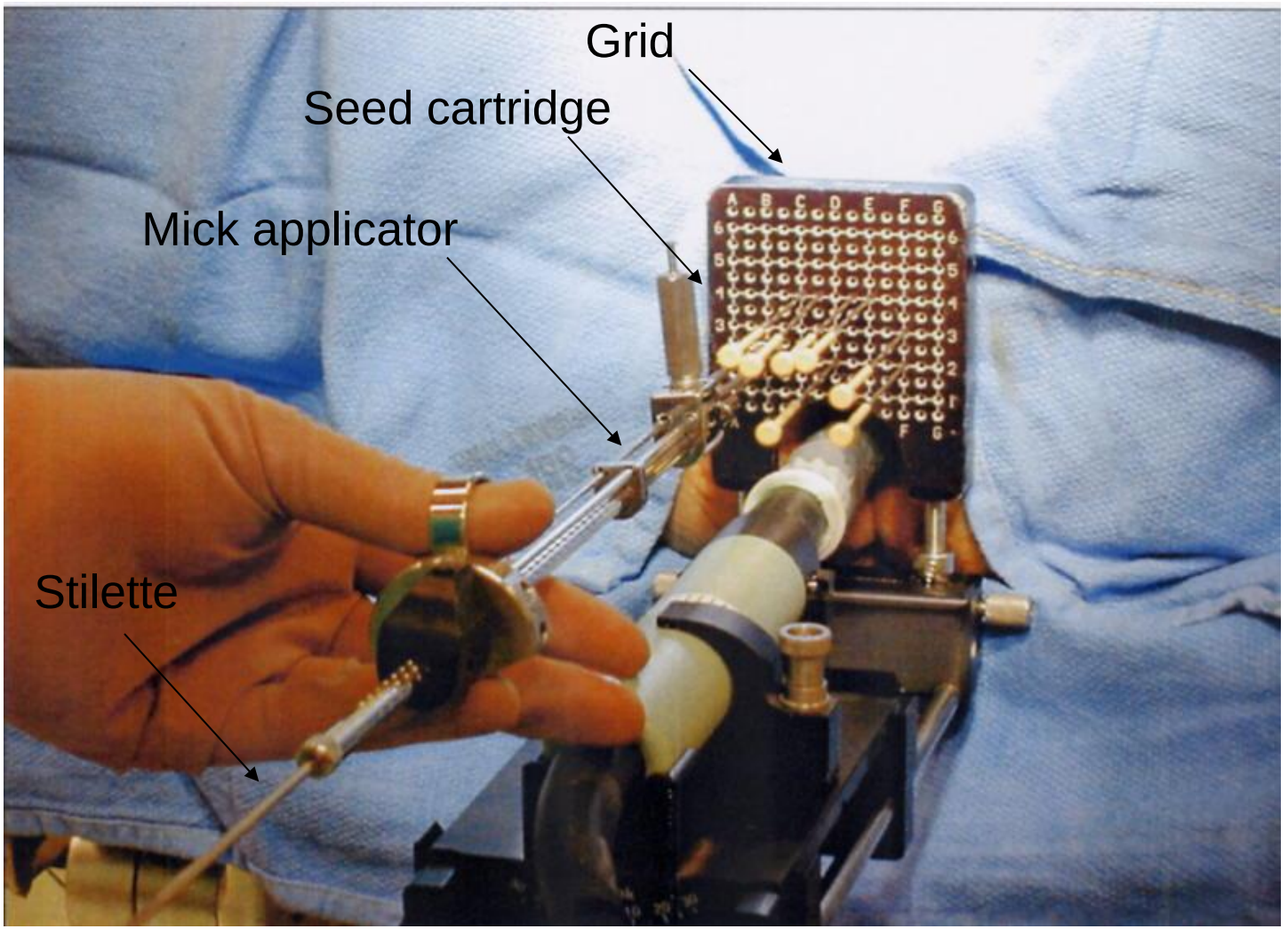
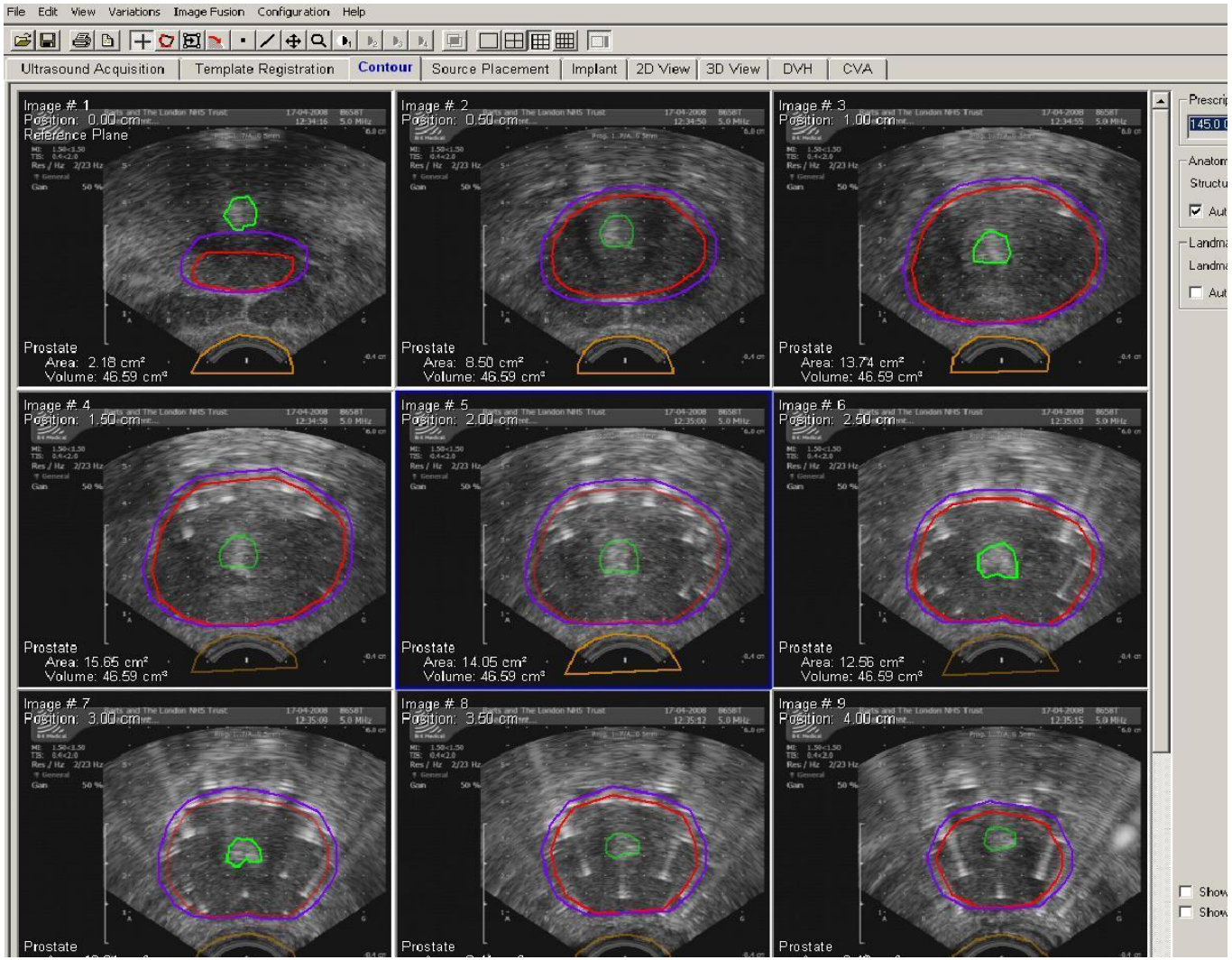


Image capture & contouring



Producing the plan

Automatic source placement
Source activity; seed number

Run optimisation routine, user-defined dose rules (constraints)*:

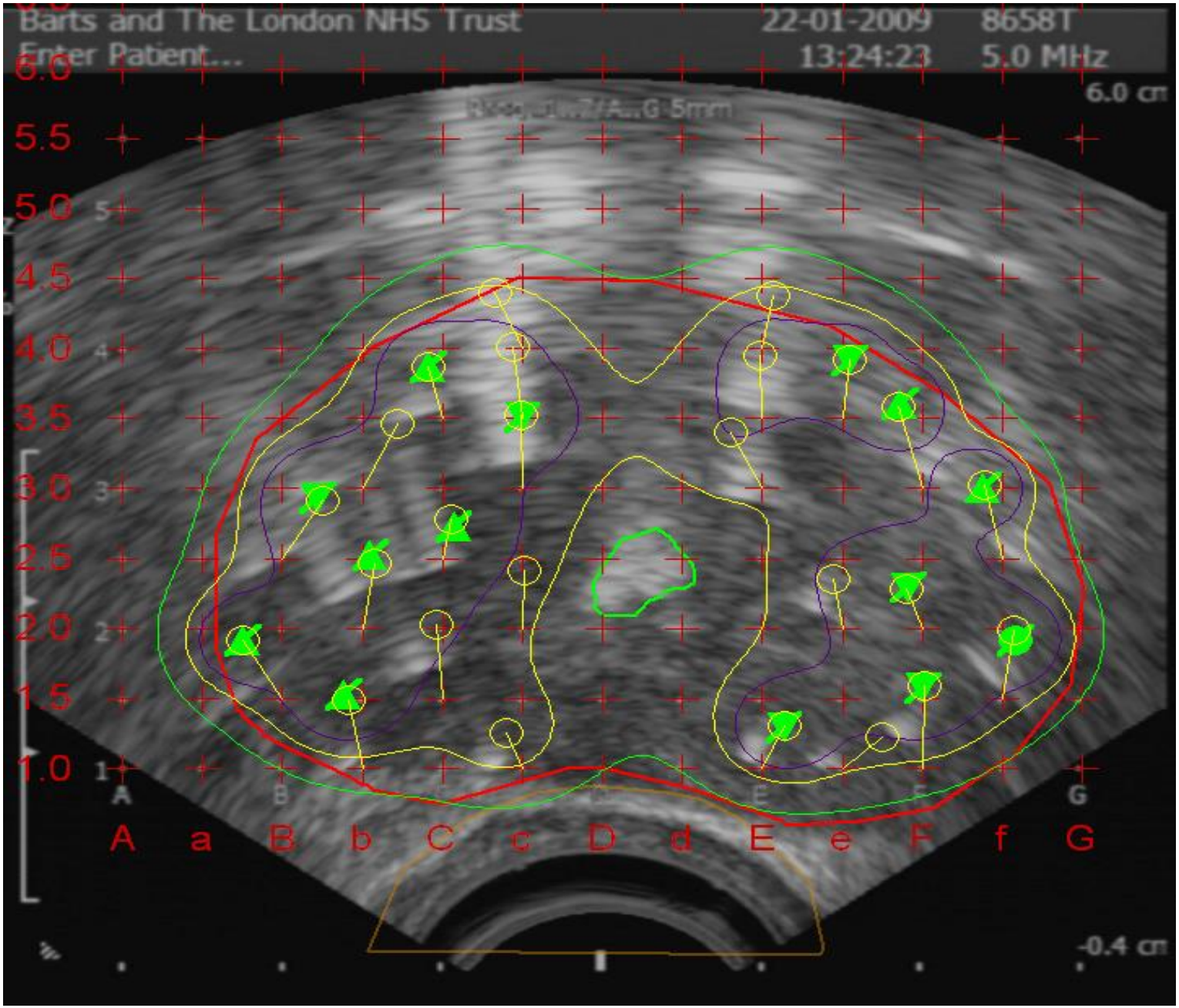
- 100% prostate + margin vol to be above 100% prescribed dose
- 75% prostate + margin vol to be below 200% prescribed dose
- 90% urethra vol to be below 140% prescribed dose
- 95% rectum surface to be below 150% prescribed dose
- 50% of prostate+margin vol to be below 150%

** Potters et al Brachytherapy 2 2003 & GEC Estro Guidelines 2007*

Quality alerts

D90 = dose received by 90% of the prostate must be greater than 100% of prescription dose i.e. dose coverage

V200 = volume of prostate receiving more than 200% of prescription dose must be less than 30% i.e. plan not too hot


Barts and The London NHS Trust
Enter Patient...
22-01-2009
13:24:23
8658T
5.0 MHz
6.0 cm
-0.4 cm
A a B b C c D d E e F f G

Late effects of Brachytherapy

Urinary retention 1.5-22% (SBH 1/110)

Post implant TURP – up to 8.6%

Incontinence 0-19%

Chronic urinary morbidity in up to 20%

Gd 2-3 proctitis 5-21%

ED up to 40%

Cyberknife

Cyberknife is a frameless robotic radiosurgery system

Three main elements :

Radiation is produced from a small linear accelerator.

Has a robotic arm which allows the energy to be directed at any part of the body from any direction

Image guidance system: X-ray imaging cameras to obtain instantaneous x-ray images

Intermediate Risk Prostate Cancer

cT2b-T2c (T3a) or Gleason score 7 or PSA 10-20
Roach score >15-30% risk SV involvement

Prostatectomy +/_ RT (RADICALS trial)
EBRT + Neoadjuvant hormone therapy
(Hormone therapy)
(AS)

TTP T2 disease 6-10 years
T2b (> half lobe) – T2c 70% progression @ 5 years

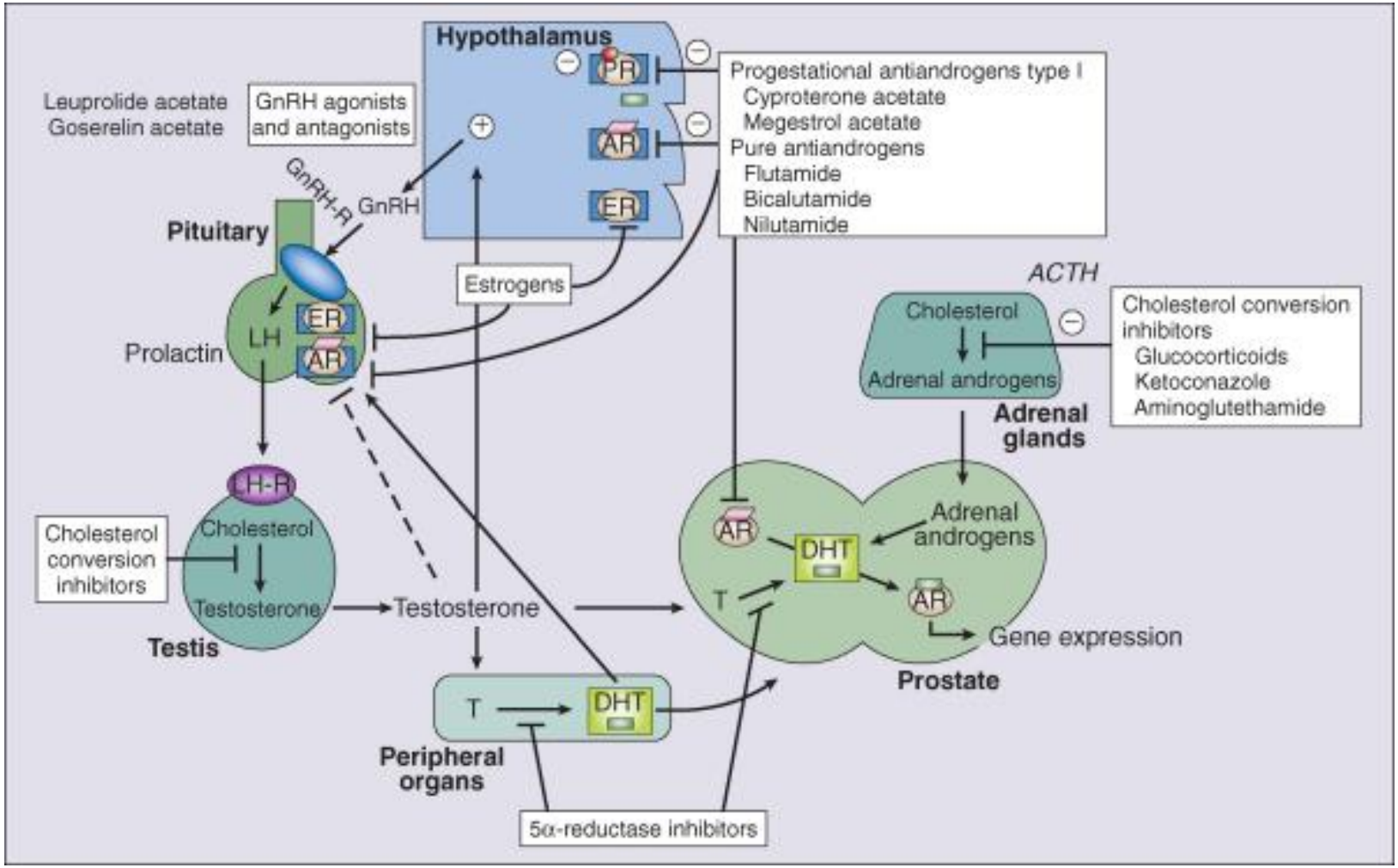
Cochrane review
Neoadjuvant hormone therapy + RP no improvement in OS DFS
BUT improves local pathological variables eg + margins and organ confined rates
Adjuvant HT + RP – trend to OS but stat significant DFS

RADICALS trial

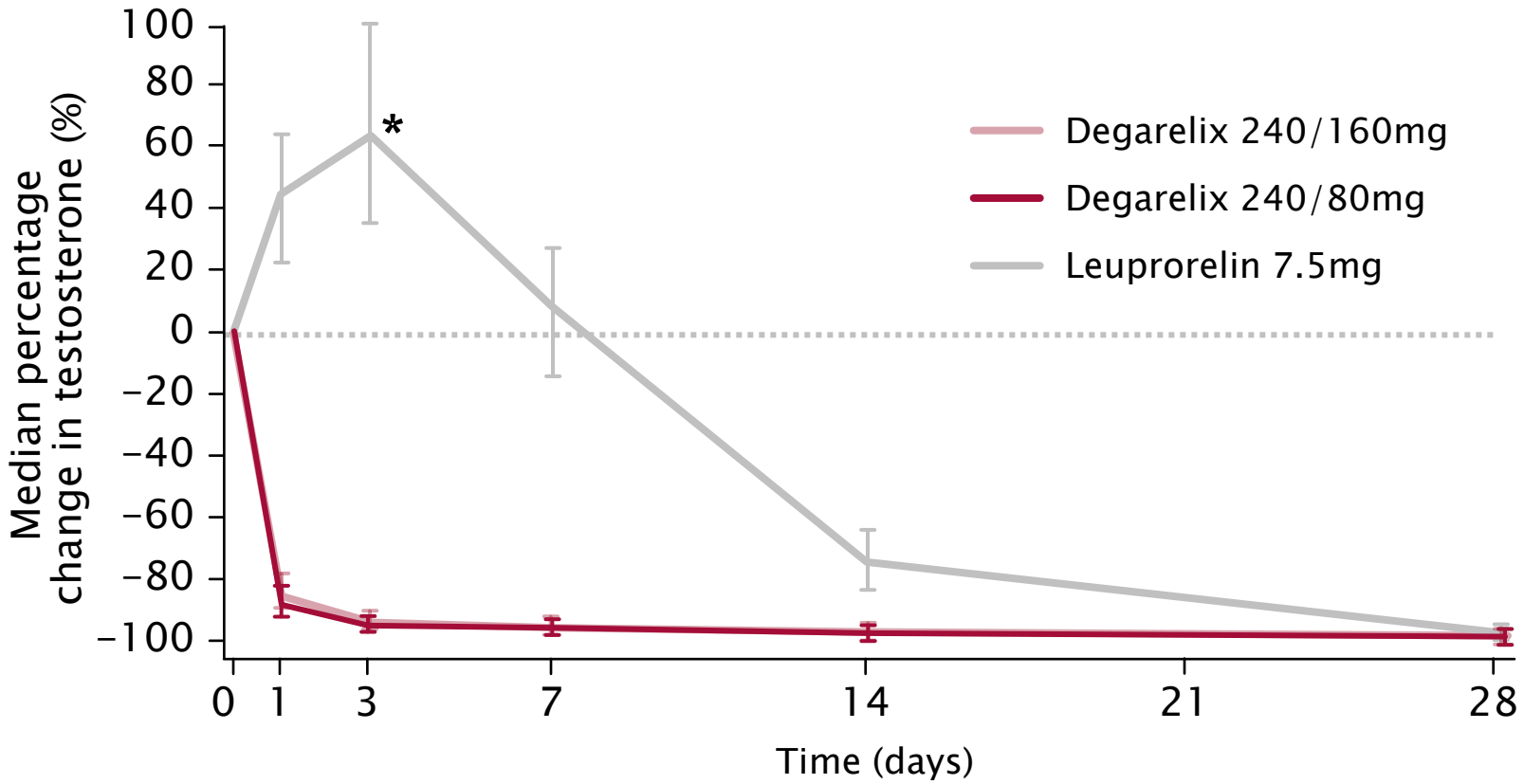
Management of Advanced Disease

- LHRHa (eg Zoladex)
- Bicalutamide (Casodex)
- Dexamethasone
- Docetaxel (Taxotere)
- Stilboestrol
- Strontium

Endocrine Basis of Prostate Cancer

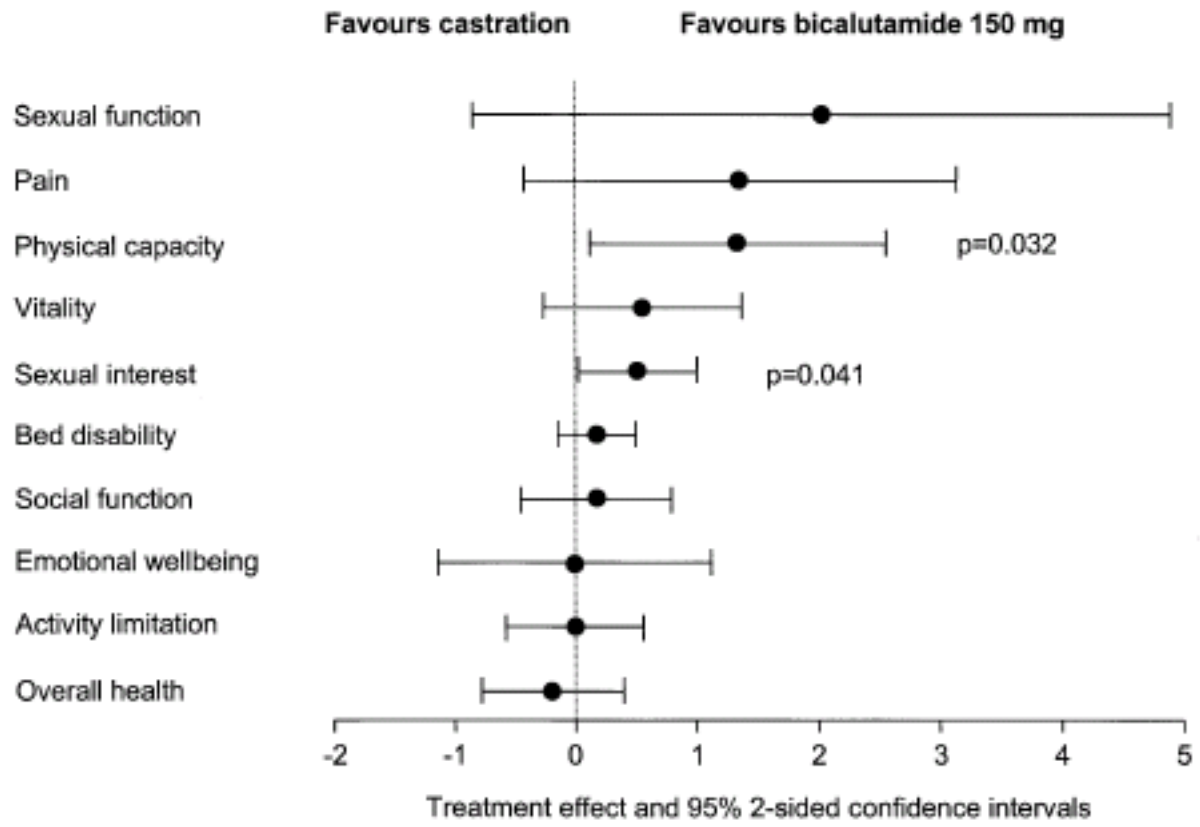


Testosterone response to LHRH agonist vs antagonist

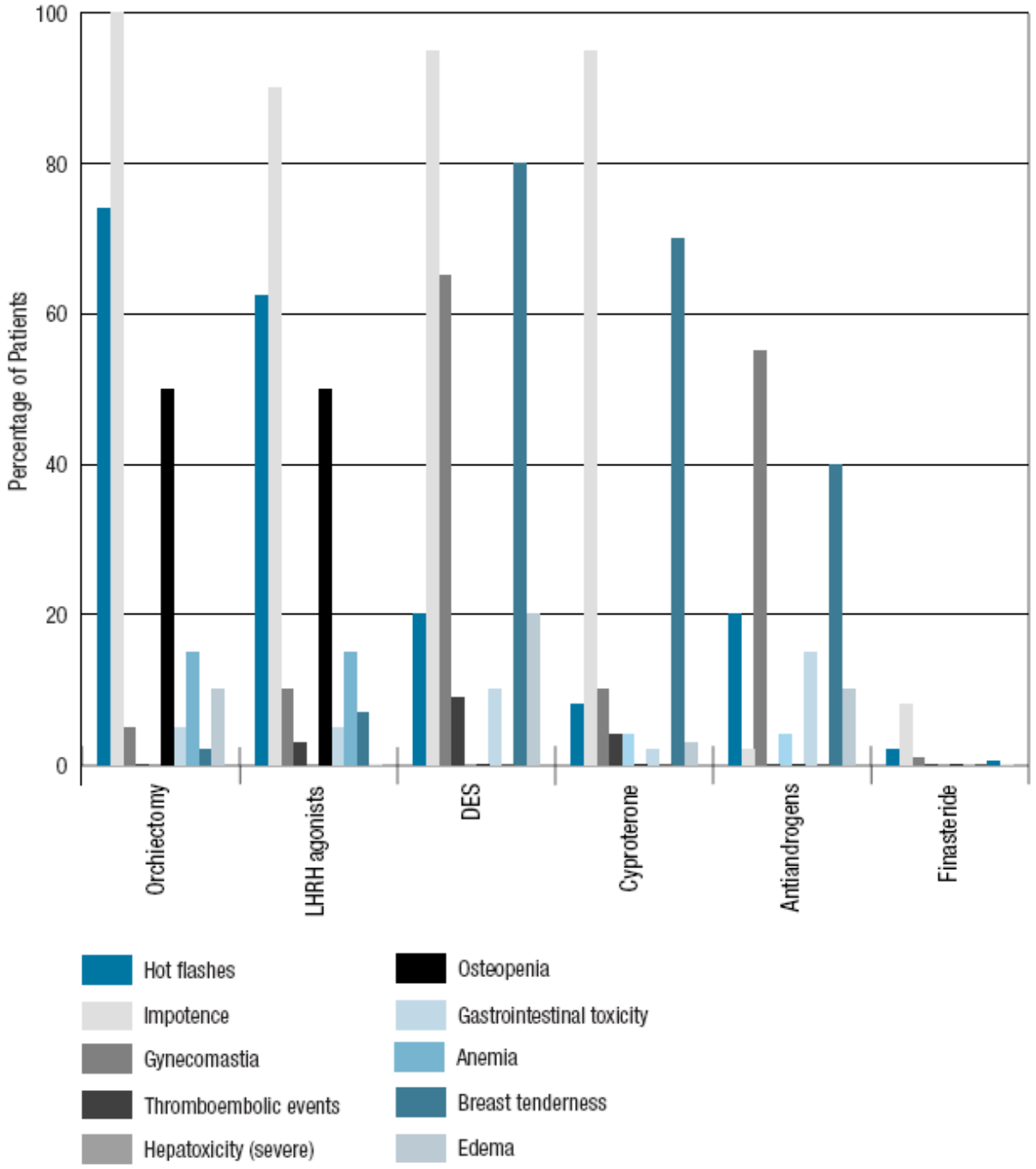


*p<0.001 degarelix (both doses) versus leuprorelin

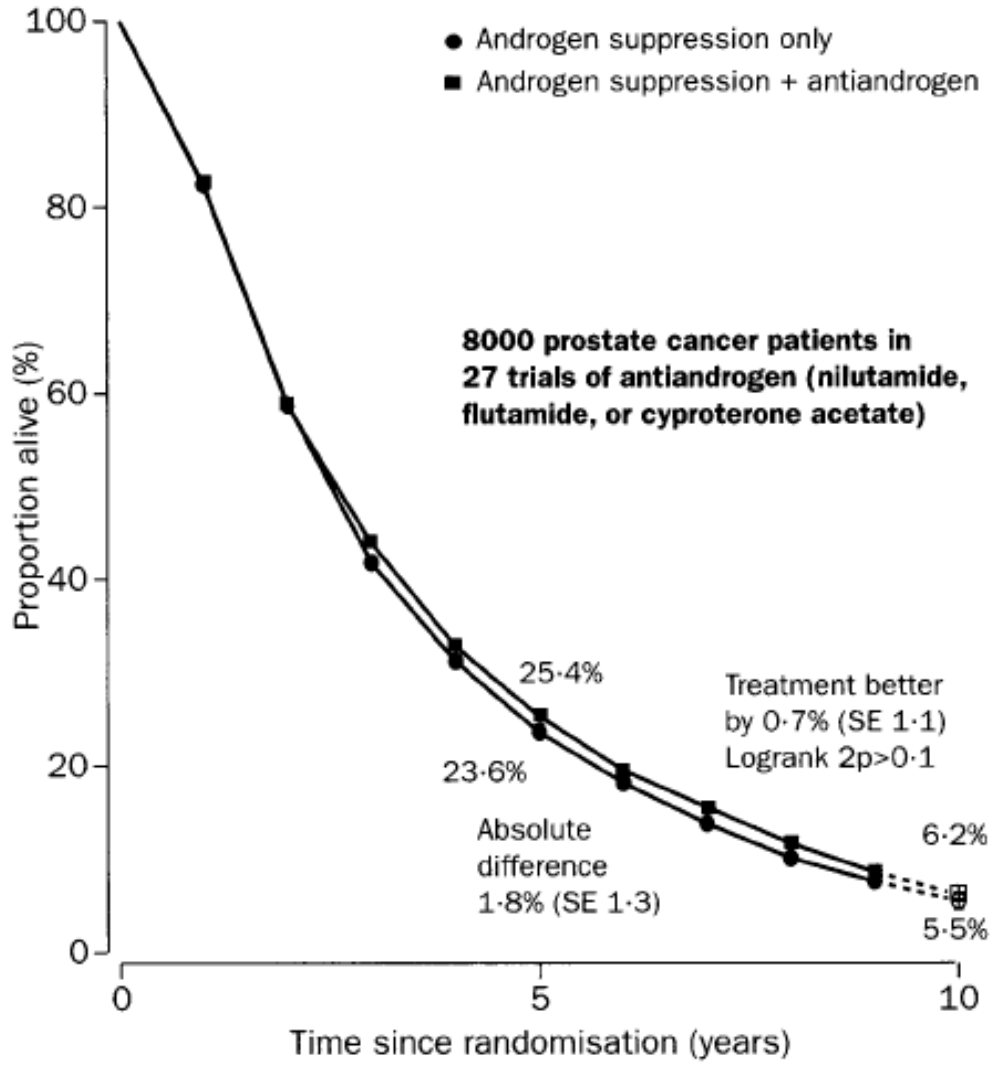
LHRH agonist vs Antiandrogen



Quality of life analysis of the effect of treatment with bicalutamide 150 mg or castration at 12 months in M1 patients. Reproduced
[7]


100
80
60
40
20
0
Percentage of Patients
Orchiectomy
LHRH agonists
DES
Cyproterone
Antiandrogens
Finasteride
Hot flashes
Impotence
Gynecomastia
Thromboembolic events
Hepatoxicity (severe)
Osteopenia
Gastrointestinal toxicity
Anemia
Breast tenderness
Edema

10-year Survival in the 27 Randomised Trials of MAB Versus Monotherapy



Continuous vs Intermittent Hormone therapy

Trial	n	Setting	Treatment	Results
De Leval et al Clin Pros Can (2002)	68	T3-4, N+, M+ Relapsed post RP Single centre Phase III	Goserelin + flutamide	Lower development of CRPC in intermittent arm
Tunn et al AUA 2007 (abstract only)	167	Rising PSA after RP Multi-centre phase III (RELAPSE trial)	Leuprolide + cyproterone cover	Similar progression to CRPC, improved QoL in intermittent arm
Miller et al ASCO 2007 (abstract only)	335	N+ M+ relapse post RP Multi-centre phase III	Goserelin + bicalutamide (over 50% time off Rx)	Similar time to progression, improved QoL
De Silva et al ASCO 2006 (abstract only)	626	T3-4 N+ M+	Triptorelin + cyproterone	Similar time to progression, improved QoL

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Conclusions

Significant treatment options now open to all patient groups

Different challenges in management depending on stage

Aggressive therapy where appropriate but increasing use of AS in early stage low risk cancer internationally

Advanced disease patients have two thirds of lifetime in hormone refractory phase