



Pride and Prostatectomy Seeds and Sensibility

5-year outcomes following ^{125}I odine
prostate brachytherapy in B.C.

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Prostate brachytherapy at BCCA

- History
- ~~■ Procedures~~
- An analysis of 5 year outcomes
 - Define the cohort
 - Define the outcomes
 - Display the results
- Closing remarks

History

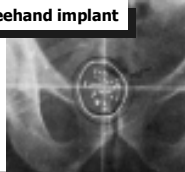


- After the failure of the MSSK freehand, retro-pubic approach, Dr. Charyulu of the Miami School of Medicine described a new technique that incorporated ([IJROBP 6:1261-1266, 1980](#)):
 - a percutaneous transperineal approach
 - real-time TRUS-guidance
 - integrated needle template
- Technique further developed and used to treat patients first by H H Holm at Copenhagen's Herlev Hospital. Unfortunately in doses too low to be effective. ([J. Urol 130:283-286, 1983](#))



History

MSSK freehand implant



BCCA U/S guided implant



- 1987 – Blasko, Grimm and Ragde adopted the technique ↑ the dose to 160 Gy (equivalent to 144 Gy by ICRU TG43 protocol)
- By 1994 results from Seattle → RFS superior to conventional doses of EBRT
- 1994 - first program in Canada (Jean Roy in Quebec City)
- January 1998 – first program in English Canada TSRCC (Gerard Morton, Neil Fleshner, and others)

BCCA Program



- Founded Nov. 1997
- First implants done July 20, 1998
- All cases have used 'pre-plan' Seattle technique
- All cases have used ^{125}I Iodine in the form of stranded or loose Oncura sources of ~ 0.33 mCi/source
- Manual planning algorithm used was developed and refined at VCC





BCCA program today



- Largest in Canada with nearly 1600 implants
- Usually 6 cases per week
- 10 Radiation Oncologists are qualified in the procedure
- All four BCCA centres have the trained staff and equipment to do all parts of the procedure



BCCA program



- 8 papers
- >60 abstracts, presentations and posters
 - Prospective databases and outcome audits
 - ED, AUR, other urinary toxicity and rectal toxicity often seeking correlations with post implant dosimetry
- There are two ongoing RCTs and a third to open soon
- National brachytherapy database [2005-07 ACURA grant]
- Research into advanced imaging, robotics and real time dosimetry [2006-09 NIH grant]



Analysis of 5 year outcomes

- Define the cohort
- Define the outcomes
- Display the results



Defining the Cohort



- The cohort reported here is comprised of the first 506 consecutive patients [all those implanted between July 20, 1998 and Aug. 31, 2001]
- Disease status updated Nov. 15, 2005
- Median FU 56 months

Defining the Cohort:



- Eligibility criteria:
 - Low risk = T1-2, GS \leq 6, iPSA \leq 10
 - 'Low tier' intermediate risk = T1-2 and
 - GS = 7 with iPSA \leq 10
 - or*
 - iPSA up to 15 with GS \leq 6
 - Fit for general or spinal anesthetic
 - U/S prostate volume of \leq 40 cc for the first 100 cases and \leq 50 cc thereafter

Defining the Cohort



- Clinical Stage: [UICC 1997]
 - T1c 218 (43%)
 - T2a 218 (43%)
 - T2b 70 (14%)
- Gleason sum:
 - 4 20 (4%)
 - 5 56 (11%)
 - 6 349 (69%)
 - 7 82 (16%)



Defining the Cohort



- iPSA:

Median 6.55 ng·ml⁻¹ (mean = 5.9, range 0.3-19)

- ≤ 4 ng·ml⁻¹ 99 (20%)
- 4-10 ng·ml⁻¹ 329 (65%)
- >10 ng·ml⁻¹ 82 (15%)

- Canadian Consensus Risk Group:

- Low 303 (60%)
- Intermediate 203 (40%)



Treatment protocol

- Low risk → ¹²⁵I implant
- 'Low tier' intermediate risk → 3/12 HT
→ ¹²⁵I implant → 3/12 HT
- HT was also used to achieve volume reduction
- Some low risk patients were placed on hormone therapy by the referring Urologist



Defining the Cohort

- Hormone Therapy:
 - Yes 351 (70%)
 - No 155 (30%)



Defining the Cohort

- Just over 95% of all implants in this cohort were done by five Radiation Oncologists
- Three other ROs are recorded as surgeon-in-charge in at least one case
- Although BCCA now exclusively uses stranded sources, almost all of this cohort received loose sources



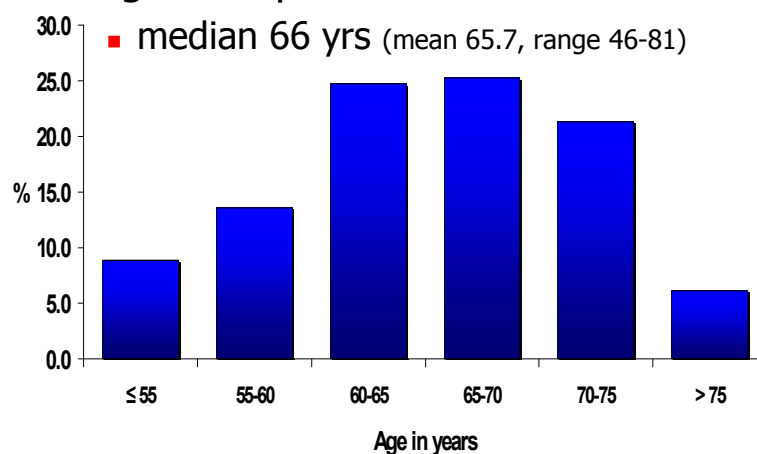
Defining the Cohort

- No patient received supplemental external beam radiation therapy (EBRT)
- No patient received a supplemental or revision implant
- No patient was continued on androgen suppression and none had HT restarted except in the case of disease recurrence



Defining the Cohort

- Age at implant:





Defining the Outcomes

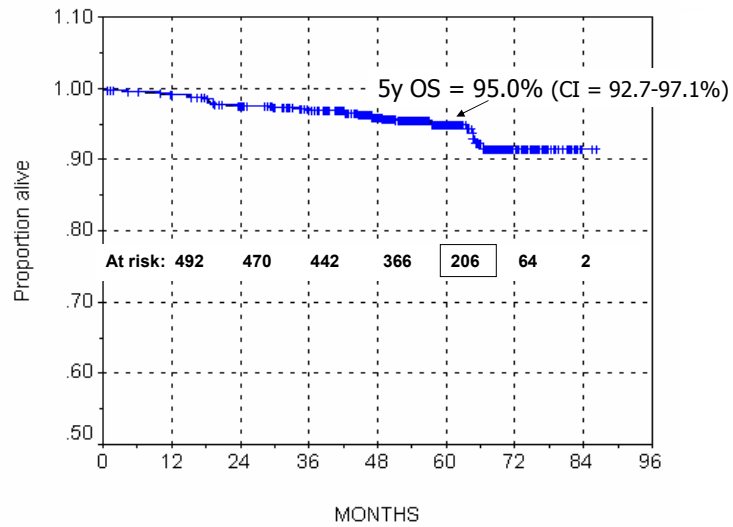
- Overall survival
- Relapse free survival
 - Clinical or radiological evidence of local tumour progression, lymphatic or haematogenous metastases
 - Or*
 - PSA failure by the Houston definition



Overall survival

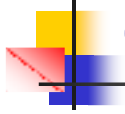
- N = 506, median FU = 56 months
(mean 54.1, range 0.73 – 86.3)
- 27 deaths have occurred
- 1 from metastatic prostate cancer
- Remaining 26 deaths → no clinical or biochemical evidence of persistent or recurrent disease at the time of death
- There were no treatment related deaths

Overall survival

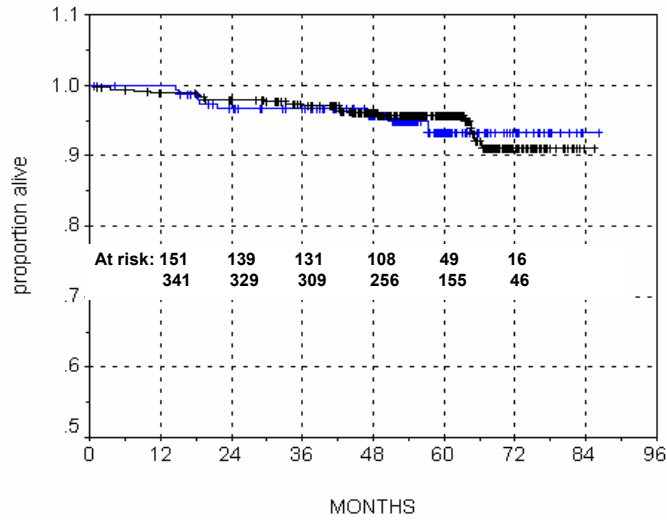


Cox regression for overall survival

Covariate	P value
Age	0.144
Order of implant	0.217
Use of HT	0.298
Log iPSA	0.117
Gleason score	0.331
Clinical T stage	0.241
BCCA Risk group	0.753
CC Risk group	0.486



Overall survival by use of HT



Overall survival by use of HT

Group	Number of patients	Median FU	Number of events	K-M 5 year OS	95% CI	Log Rank P value
No HT	155	53.7	8	93.3%	88.7-98.1%	0.9024
HT	351	57.1	19	95.7%	93.4-98.0%	



Defining the Outcomes

- Overall survival
- Relapse free survival
 - Clinical local tumour progression, X-ray/CT or bone scan evidence of lymphatic or haematogenous metastases
 - Or*
 - PSA failure by the Houston definition



Relapse free survival and the Houston definition

- Defined as the date when a follow-up PSA value $\geq 2.0 \text{ ng}\cdot\text{ml}^{-1}$ above nadir
 - Best +/- predictive value in several large, long-term databases
 - Valid in patients who receive neo-adjuvant or concomitant androgen suppression (as opposed to ASTRO)
 - Does not produce false plateaus (as opposed to ASTRO)
 - Equally valid in patients receiving brachytherapy or EBRT



Houston definition

- Surgical definition is usually taken to be the date when the PSA is $> 0.2 \text{ ng}\cdot\text{ml}^{-1}$
- This is 10 times lower
- How can we compare our data to surgical series?



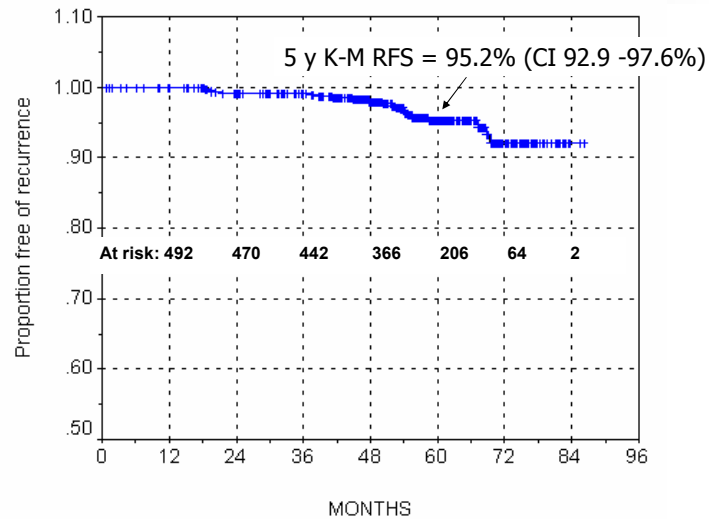
Houston definition

- I will not make any comparisons with surgical series, but I welcome you to make your own comparisons
- Mature datasets yield the same results regardless of definition
- The validity of the data and conclusions I will present are not sensitive to the definition of PSA failure

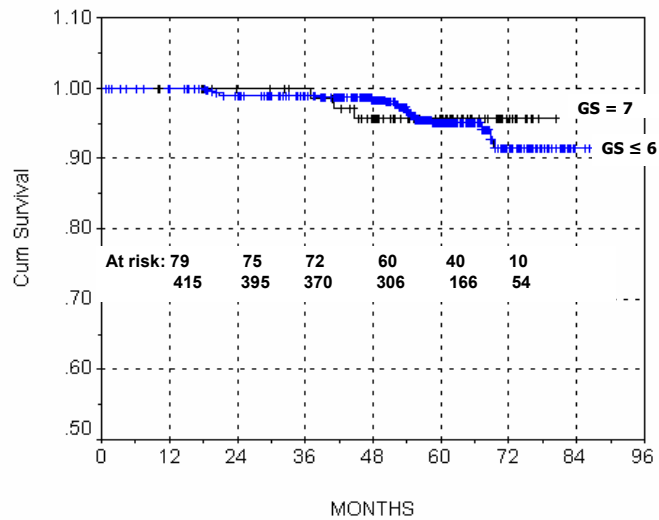
Relapse free survival

- There have been 20 recurrences including one death from prostate cancer
 - 4 local 2 nodal
 - 3 distant 11 PSA only
- All patients with clinical or radiological evidence of local, regional or distant failure also had simultaneous or prior PSA failure by the Houston definition

Relapse free survival



Relapse free survival: GS = 7 versus ≤ 6

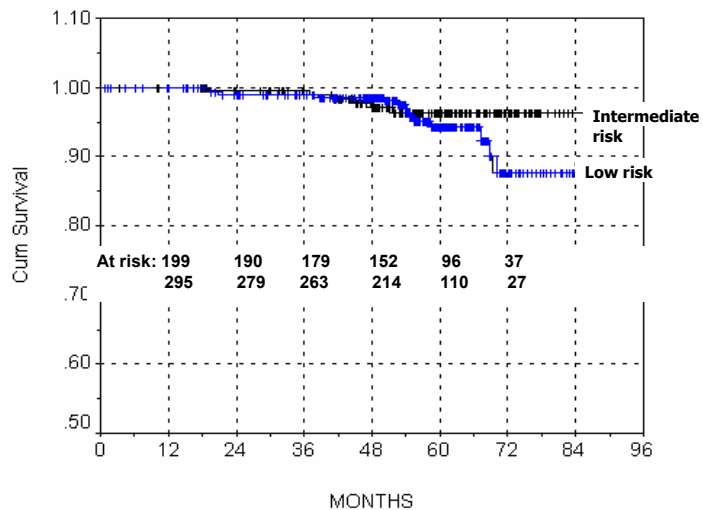


Relapse free survival: GS = 7 versus ≤ 6



Group	Number of patients	Median FU	Number of events	K-M 5 year RFS	95% CI	Log Rank P value
GS =7	82	59.4	3	95.7%	90.9-100	0.8353
GS \leq 6	424	55.4	17	95.1%	92.4-97.7	

Relapse free survival: Low risk versus intermediate risk



Relapse free survival: Low risk versus intermediate risk

Group	Number of patients	Median FU	Number of events	K-M 5 year RFS	95% CI	Log Rank P value
Low risk	303	54.7	14	94.3%	90.8-97.8	0.2136
Intermediate risk	203	58.6	6	96.4%	93.5-99.3	

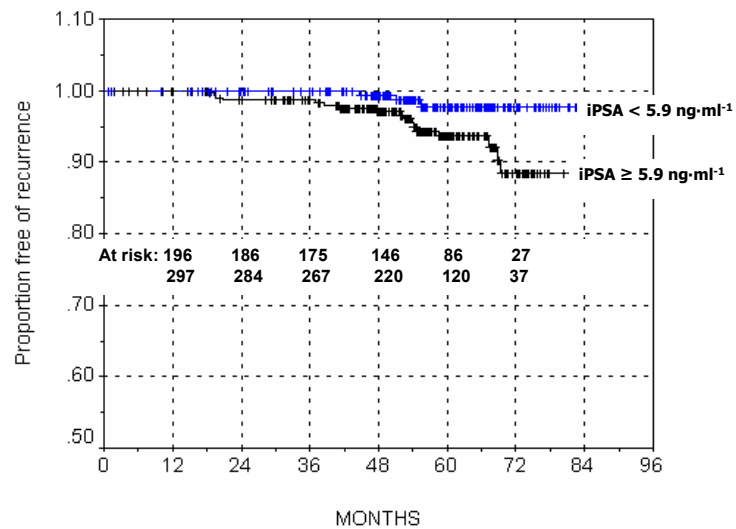


Cox regression for RFS

Covariate	P value
Age	0.134
Order of implant	0.865
Use of HT	0.666
Log iPSA	0.012
Gleason score	0.666
Clinical T stage	0.577
BCCA Risk group	0.826
CC Risk group	0.349



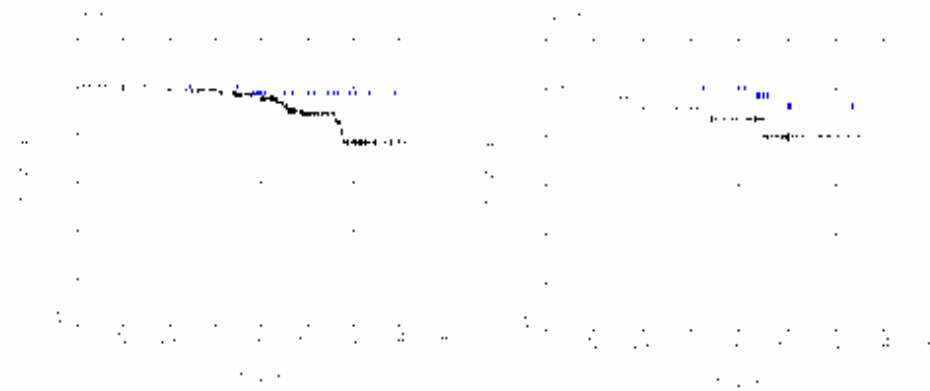
RFS for patients above and below the mean iPSA of 5.9 ng·ml⁻¹



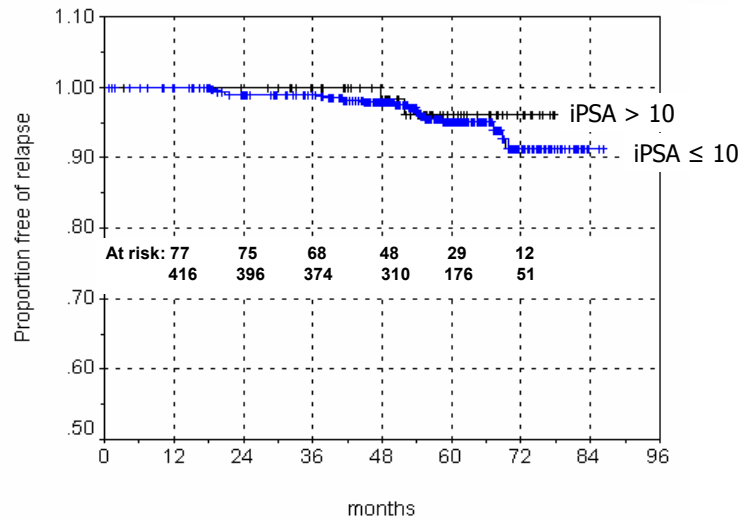
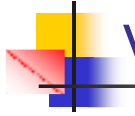
RFS for patients above and below the mean iPSA of 5.9 ng·ml⁻¹

Group	Number of patients	Median FU	Number of events	K-M 5 year RFS	95% CI	Log Rank P value
iPSA < 5.9	200	56.0	3	97.7%	95.0-100	0.0198
iPSA ≥ 5.9	306	55.2	17	93.6%	90.2-97.2	

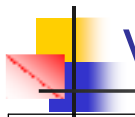
RFS for patients above and below the mean iPSA of 5.9 ng·ml⁻¹



RFS for patients $\leq 10 \text{ ng}\cdot\text{ml}^{-1}$ versus $> 10 \text{ ng}\cdot\text{ml}^{-1}$



RFS for patients $\leq 10 \text{ ng}\cdot\text{ml}^{-1}$ versus $> 10 \text{ ng}\cdot\text{ml}^{-1}$



Group	Number of patients	Median FU	Number of events	K-M 5 year RFS	95% CI	Log Rank P value
iPSA > 10	78	55.4	2	96.1%	90.7-100	0.4821
iPSA ≤ 10	416	55.6	18	95.0%	90.7-97.9	



Dosimetry parameters

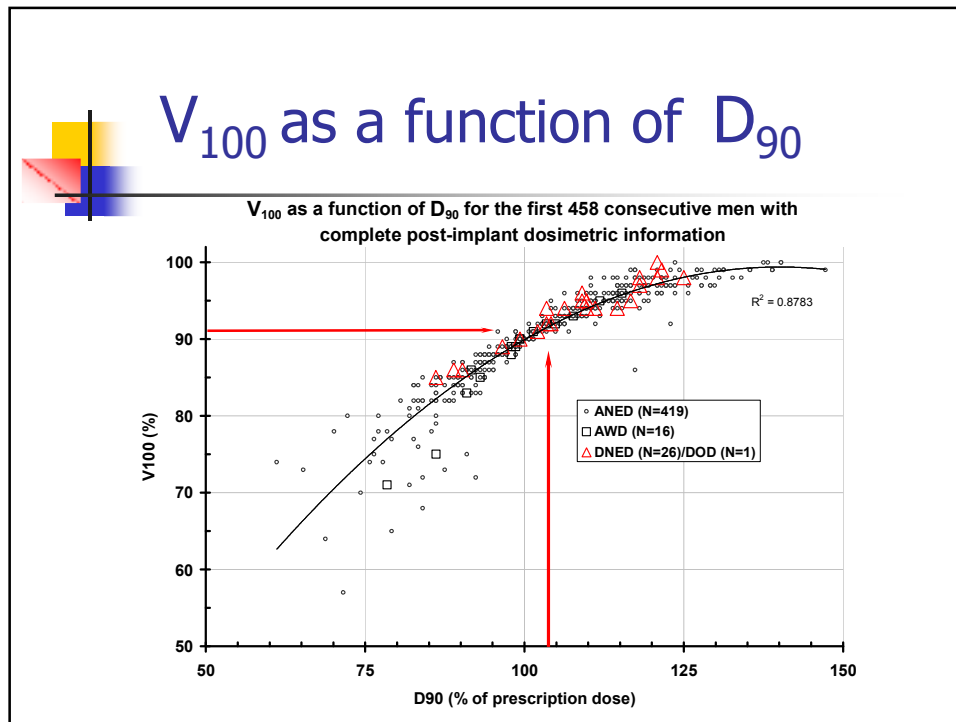
- Median V₁₀₀ 92% [mean 90.6%, range 57- >99%]
 - Median V₁₅₀ 57% [mean 56%, range 17- 89%]
 - Median D_{90%} 104% [mean 104%, range 61-147%]
 - Median D₉₀ 150 Gy [mean 150Gy, range 88 – 212Gy]
- Post implant dosimetric data are available on 458 of these 506 men (90.5%); among these patients there have been 17 recurrence events.



Cox regression for RFS including only patients with post-implant dosimetry

Covariate	P value
Age	0.045
Order of implant	0.709
Use of HT	0.543
Log iPSA	0.006
Gleason score	0.408
Clinical T stage	0.691
D90	0.732
V100	0.686
BCCA Risk group	0.418
CC Risk group	0.576

V_{100} as a function of D_{90}



Complications

- There were no treatment related deaths in the cohort
- 3% of men had prolonged urinary obstruction (requiring catheter diversion for > 21 days)
- 8 men have required TUPR for benign stricture
- 1 man has a local recurrence causing outlet obstruction and will require palliative TUPR
- No implants needed to be abandoned because of pubic arch interference
- No patient has required permanent urinary or fecal diversion as a result of radiation injury



Summary of results

- 506 consecutive low risk and 'low-tier' intermediate risk patients treated with permanent, U/S-guided ^{125}I interstitial brachytherapy at BCCA
- Consists of all patients treated between July 20, 1998, and Aug. 31, 2001
- As of November 15, 2005 patients were assigned disease status as follows:
 - ANED = 460 AWD = 19
 - DNED = 26 DOD = 1
- Crude RFS $[(\text{ANED} + \text{DNED}) / 506 \times 100] = 96\%$

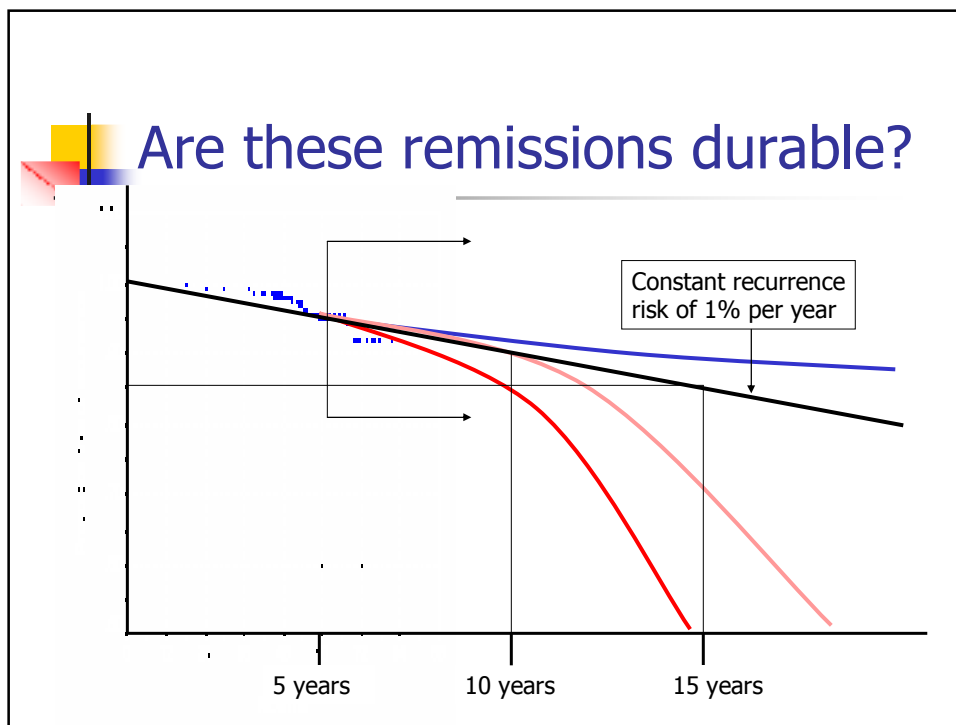


Summary of results

- 5 y Actuarial RFS is 95.2%
 - 95% CI is 92.9% to 97.6%
- No clear correlations tie the 5 year outcomes to prognostic factors
 - Paucity of recurrence events
 - Narrowly defined eligibility criteria
 - Apparently adequate, if not always perfect, dosimetry from the start the program

Closing remarks

- Are the remissions durable?
- BCCA trials in brachytherapy
- Perspectives on the Surgery versus Brachytherapy question





Are these remissions durable?

- The median PSA at latest FU is 0.04 ng·ml⁻¹
- In a subgroup of 348 men with ≥ 48 mths FU who are scored ANED:
 - 8 (2.3%) have a PSA > 0.5 ng·ml⁻¹
 - 31 (8.9%) have a PSA > 0.2 ng·ml⁻¹
 - 143 (41%) have an undetectable PSA
- Men with PSA values of < 0.5 ng·ml⁻¹ at ≥ 5 years post EBRT have a less than 10% risk of PSA or clinical recurrence in the subsequent five years



The Trials: ASCENDE-RT

- **A**ndrogen **S**uppression **C**ombined with **E**lective **N**odal and **D**ose **E**scalated **R**adiation **T**herapy
- Investigator driven, industry sponsored sequential phase II-III RCT:
 - Supported by unrestricted educational grants from Oncura and Sanofi-Aventis



ASCENDE-RT

- Intermediate and high risk localised PCa with iPSA \leq 40, and Clinical Stage \leq T3a
- ARM-1
 - AS - 8/12 neo-adjuvant + 4/12 concomitant/adjuvant
 - EPNI 46Gy in 23#
 - 2 phase HD 3-d conformal EBRT boost = 32Gy in 16#s
- ARM-2
 - AS - 8/12 neo-adjuvant + 4/12 concomitant/adjuvant
 - EPNI 46Gy in 23#
 - 125 Iodine brachytherapy boost = 115Gy



ASCENDE-RT end points

- Primary: 5 year RFS by the Houston definition
- Secondary:
 - Overall survival
 - Metastasis-free survival
 - Pathological local control (24 month biopsy)
 - The incidence of acute and late side effects and complications associated with the treatment interventions
 - The effect of the planned interventions on QOL
 - Rate of testosterone recovery



ASCENDE-RT: Accrual

Phase of trial	Accrual dates	Accrual period	Total Registered
II	15/11/02 – 31/07/03	8.5 mths	41
III	20/08/04 - open	17 mths	116
Combined II and III	Non consecutive	25.5 mths	157



6X1 versus 2X3:

- VICC's Eric Berthelet is PI
 - Sponsored by Abbott
- RCT comparing 1 month depot Lupron x 6 versus 3 month depot Lupron X 2 for men requiring HT by protocol or for volume reduction before brachytherapy
- End points are time to testosterone recovery, QOL and sexual function

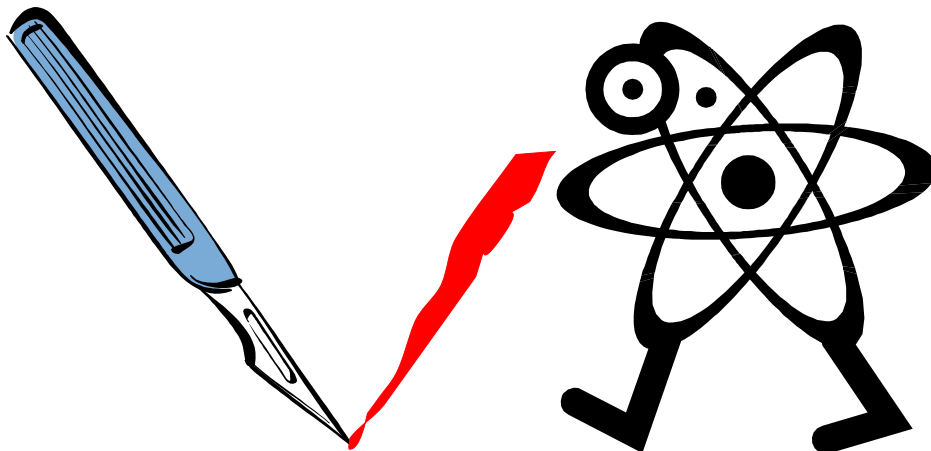


IMVI-RT

- **I**ntensity **M**odulated **V**ersus **I**nterstitial **R**adiation **T**herapy
- In planning and funding stage – could open as soon as 6 months from now.
 - IMRT purports to produce a similar low recurrence rate with fewer adverse urinary side effects



Surgery or Brachytherapy





Radical Prostatectomy

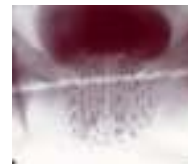


- Advantages
 - The definitive appeal of the knife
 - When you're over the worst of it, you're over the worst of it
- Disadvantage
 - 20-30% chance of needing adjuvant or salvage XRT
 - Much greater incidence of ED in the first 2-5 years

Great when it works
New technology and better techniques have kept surgery competitive



¹²⁵Iodine Brachytherapy



- Advantages
 - A day care procedure with a very low grade 3+ complication risk
 - Very low recurrence risk in the first 5 years
- Disadvantages
 - You can never be 100% certain that the worse is over
 - Concern that long term results will show accelerated rates of recurrence

Radiotherapy technique of choice
Competitive with any other treatment
Second cancers may reduce long term benefit

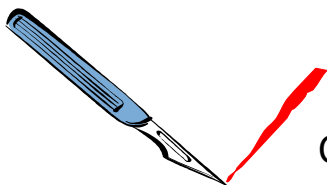


Surgery or Brachytherapy

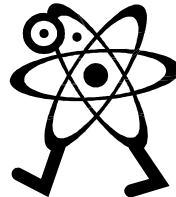
- Number of men who had brachytherapy last year without a surgeon's opinion?
- Zero
- Number of men who had radical surgery without a second opinion from a radiation oncologist?
- > 400



Surgery or Brachytherapy



Getting to
choose?



Priceless

