How can we best use HDR brachytherapy to escalate dose in intermediate and high risk disease?

Gerard Morton
Associate Professor

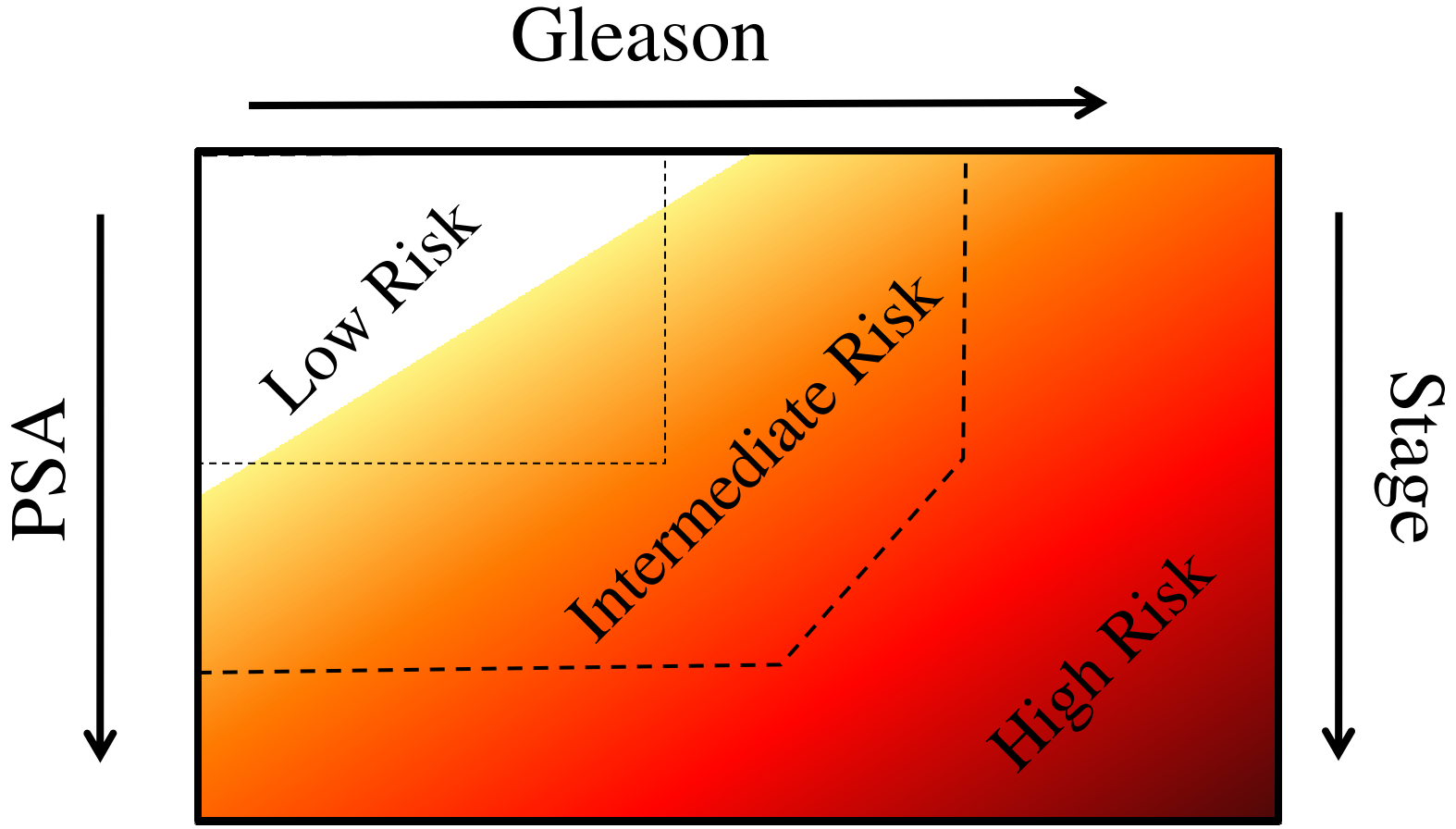
University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Objectives

- Why should we escalate dose?
- What HDR dose and fractionation should we use?
- What's the best HDR technique?
- Ongoing questions:
  - EBRT + BT vs. BT alone?
  - Role of ADT?
  - Elective nodal irradiation?

Prostate Risk Stratification



Radiation dose is important..

- Randomized EBRT dose escalation studies

Randomized EBRT Studies

Author	n	Dose Arms
MD Anderson	301	70 Gy vs 78 Gy
GETUG	306	70 Gy vs 80 Gy
Dutch Multicenter	669	68 Gy vs 78 Gy
Royal Marsden	126	64 Gy vs 74 Gy**
MGH/Loma Linda	393	70.2 Gy vs 79.2 Gy*
MRC RT01	843	64 Gy vs 74 Gy**

*proton boost

**neoadjuvant ADT x 3-6 mos

Randomized EBRT Studies

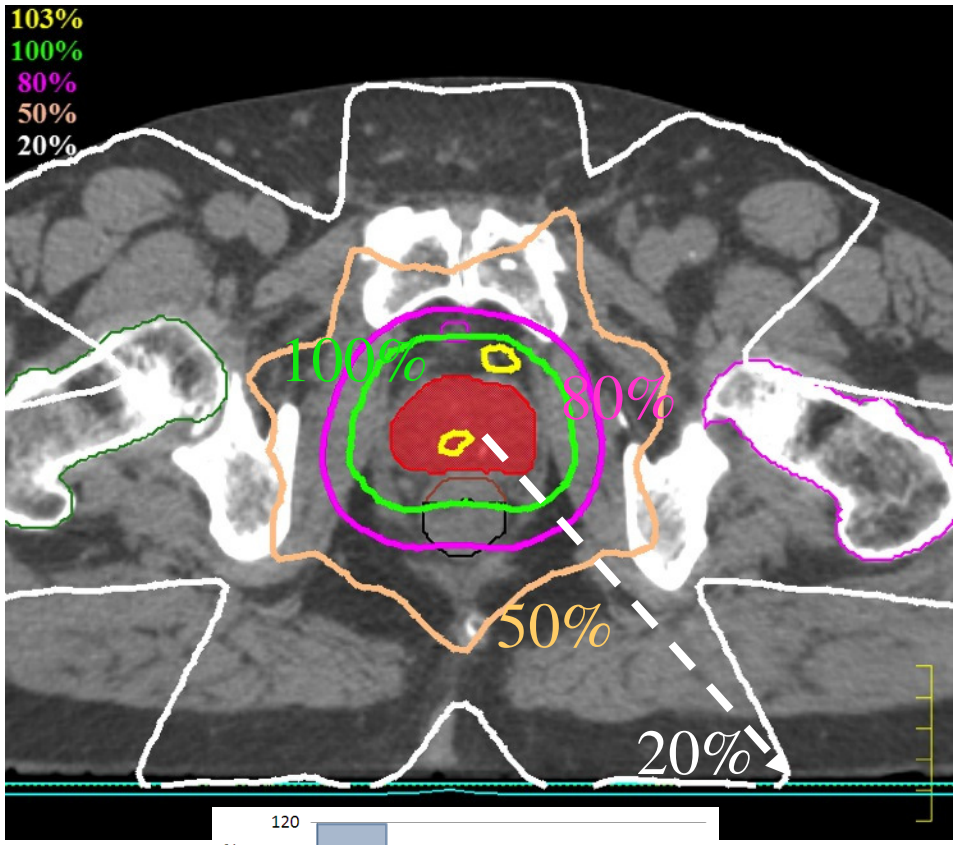
Author	Eligibility	Median Follow-up
MD Anderson	T1-T3	8.7 yrs
GETUG	T1-T3, PSA <50	61 months
Dutch Multicenter	T1-T4, PSA <60	70 months
Royal Marsden	T1-T3b	74 months
MGH/ Loma Linda	T1-T2b, PSA < 15	66 months
MRC RT01	T1-T3, PSA < 50	64 months

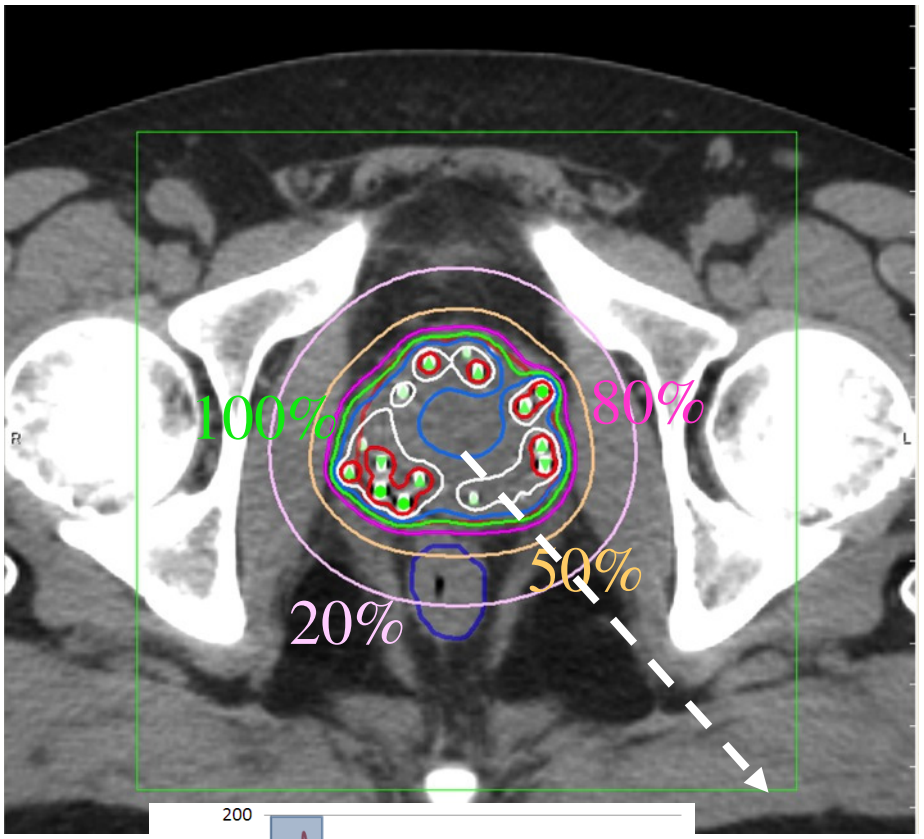
Randomized EBRT Studies

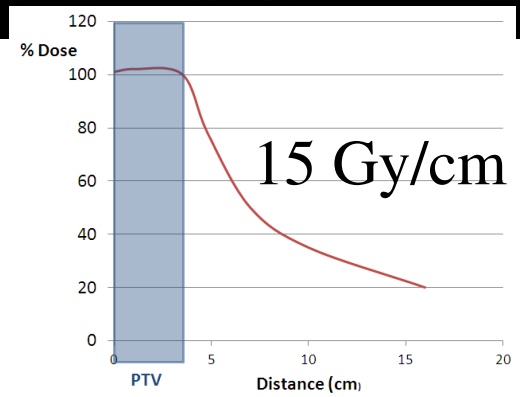
	bDFS		
Author	**Standard**	**High Dose**	**Time**
MD Anderson	59%	78%	8 years
GETUG	68%	77%	5 years
Dutch Multicenter	45%	56%	7 years
Royal Marsden	59%	71%	5 years
MGH/ Loma Linda	79%	91%	5 years
MRC RT01	60%	71%	5 years

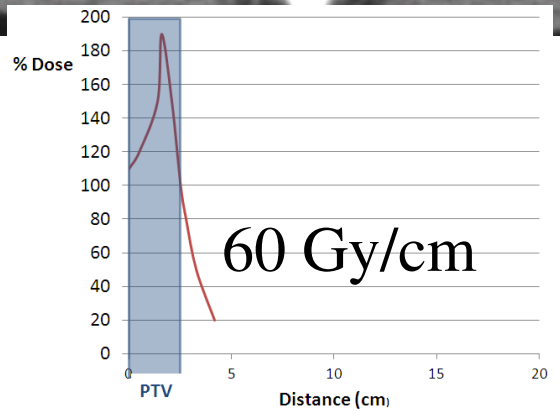
A 10% increase in EBRT dose is associated with a 10% increase in bDFS

EBRT vs. Brachytherapy









Role of Brachytherapy

- Prostate brachytherapy allows dose escalation beyond that achievable by any form of external beam
- Brachytherapy allows greater conformality
- Brachytherapy allows greater sparing of surrounding tissues
- Higher efficacy, less toxicity, less risk of second malignancy

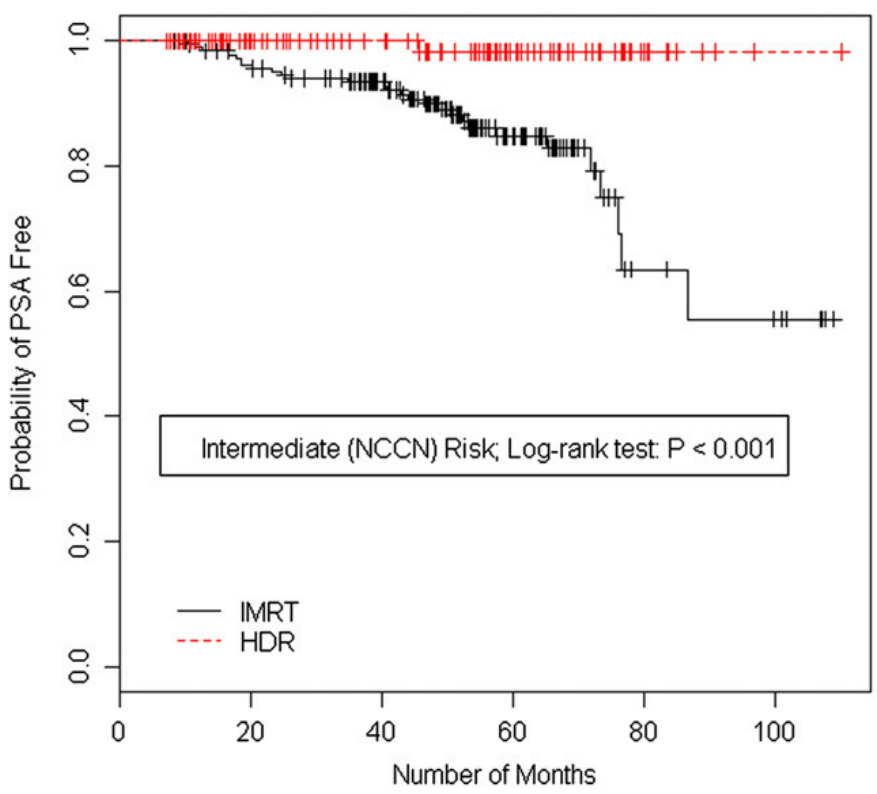
HDR + EBRT DFS

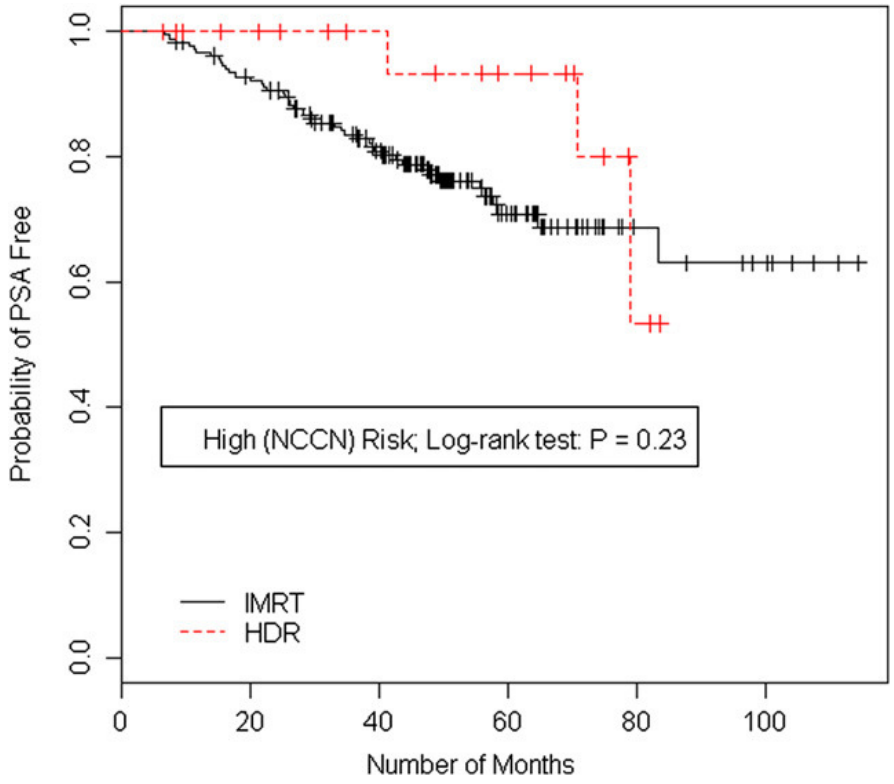
Study	FU (mo)	Overall	Intermediate	High Risk
Galalae (2004)	60	77%	88%	69%
Astrom (2005)	48	82%	88%	61%
Flynn (2007)	44	90%	92%	72%
Phan (2007)	59	86%	90%	78%
Ghilezan (2007)	70	82% (10 yr)	88%	74%
Hasan (2007)	68	81% (10 yr)	92%	71%
Bachand (2009)	44	96%	96%	96%
Deutsch (2010)	47	96%	98%	93%
Cury (2011)	65	91%	91%	
Morton (2011)	72	98%	98%	

ELSEVIER Brachytherapy 9 (2010) 313e 318

Comparison of PSA relapse-free survival in patients treated with ultra-high-dose IMRT versus combination HDR brachytherapy and IMRT

Israel Deutsch[1], Michael J. Zelefsky[1], Zhigang Zhang[2], Qianxing Mo[2], Marco Zaider[3], Gil'ad Cohen[3], Oren Cahlon[1], Yoshiya Yamada[1,*]





HDR + EBRT vs. 86.4 Gy IMRT

University of Toronto

Sunnybrook ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

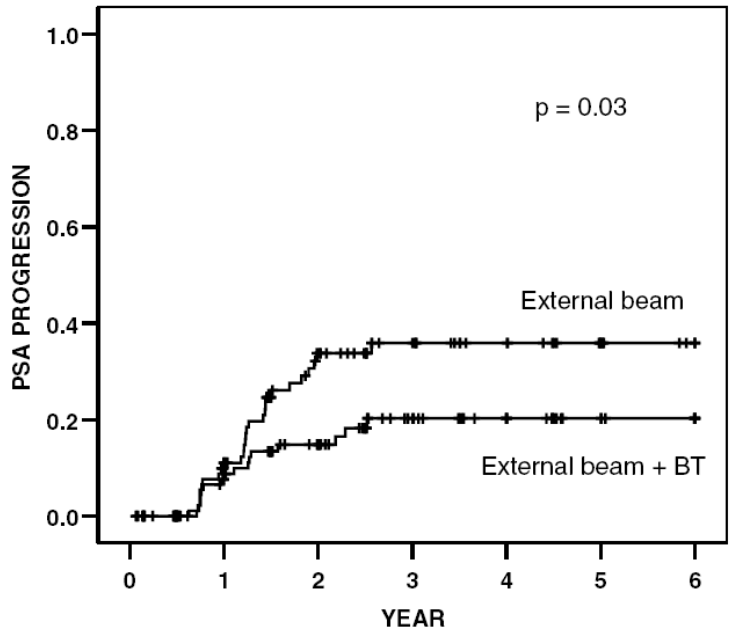
HDR + EBRT vs. EBRT alone

- Hoskin Randomised Trial

EBRT (35.75 Gy/13f) + HDR (8.5 Gy x 2)

vs.

EBRT (55 Gy/20f)



31% reduction in risk of recurrence

No difference in late toxicity

Hoskin et al. Radiother Oncol 84(2007):114-120
Hoskin et al. Radiother Oncol 2012

Conclusion

- HDR + EBRT provides higher disease-free survival than EBRT alone
- But what dose to use?

What Dose and Fractionation?

6.3 Gy x 5

4 Gy x 4

4 Gy x 4

4.75 Gy x 4

5 Gy x 4

5.5 Gy x 4

5.5 Gy x 4

5.5 Gy x 4

6 Gy x 4

6 Gy x 4

6.5 Gy x 4

5.5 Gy x 3

5.5 Gy x 3

6 Gy x 3

6 Gy x 3

7 Gy x 3

7.5 Gy x 2

8.5 Gy x 2

9 Gy x 2

9.5 Gy x 2

9.5 Gy x 2

10 Gy x 2

10 Gy x 2

11.5 Gy x 2

15 Gy x 2

9 Gy x 1

10 Gy x 1

15 Gy x 1

ELSEVIER

Brachytherapy 11 (2012) 20e 32

BRACHYTHERAPY

American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy

Yoshiya Yamada[1,*], Leland Rogers[2], D. Jeffrey Demanes[3], Gerard Morton[4], Bradley R. Prestidge[5], Jean Pouliot[6], Gil'ad N. Cohen[7], Marco Zaider[7], Mihai Ghilezan[8], I-Chow Hsu[6]

"Given the heterogeneity of prescription doses described in the literature, all reporting similar excellent outcomes in terms of toxicity and disease control, no particular dose fractionation schedule can be recommended."

What dose and fractionation?

- Effective
- Low toxicity
- Resource utilisation/ cost
- Convenience

What dose and fractionation?

Hypothesis

15 Gy HDR + 37.5 Gy EBRT in 15 fractions

would be equivalent to

10 Gy x 2 HDR + 45 Gy EBRT in 25 fractions

for disease control and late effects

Int J Radiat Oncol Biol Phys 77:811-7, 2010
Int J Radiat Oncol Biol Phys 80:1299-1305, 2011
Radiother Oncol 100:463-467, 2011

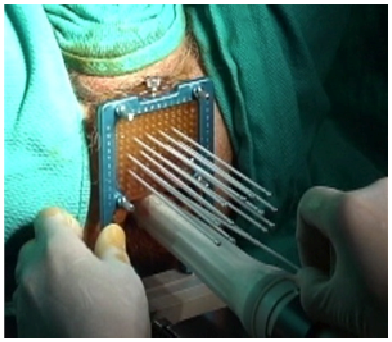
Materials and Methods

- Two Sequential Phase II Clinical Trials
- Stage T1c-T2c
  - Gleason 7, PSA < 20 ng/ml
  - Gleason 6, PSA 10-20 ng/ml
- No androgen deprivation therapy
- Prostate Volume < 60 cc
- No prior TURP

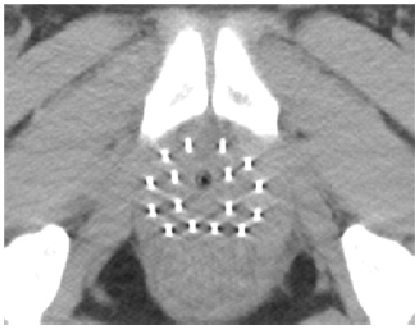
Materials and Methods

10 Gy x 2; Outpatient, 1 week apart + 45 Gy/25 fractions

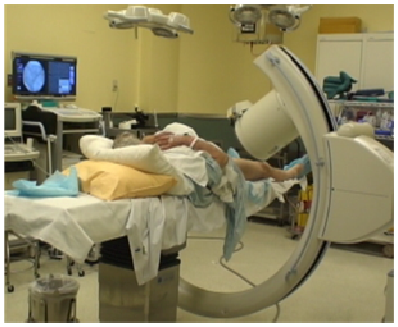
15 Gy x 1; Outpatient + 37.5 Gy/15 fractions



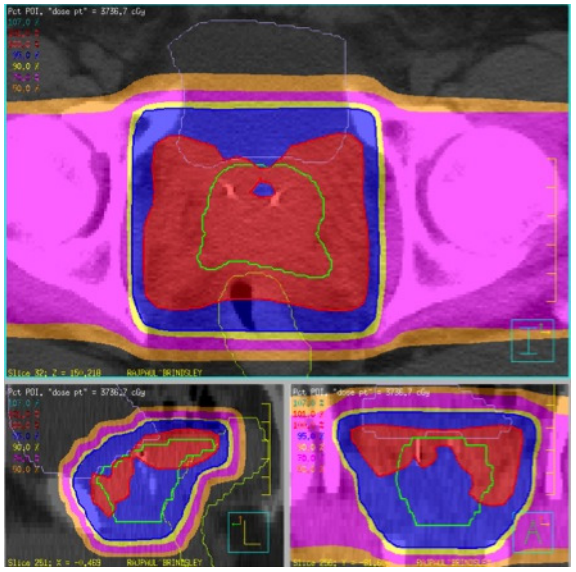
Catheter Insertion

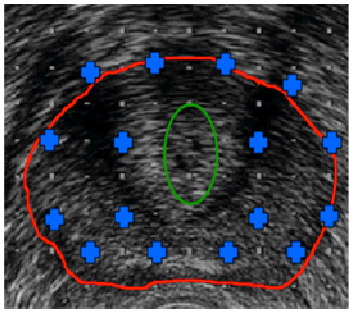


CT Planning



QA and Treatment





Dose Optimisation

University of Toronto

Sunnybrook ODETTE CANCER CENTRE

A Cancer Care Ontario Partner

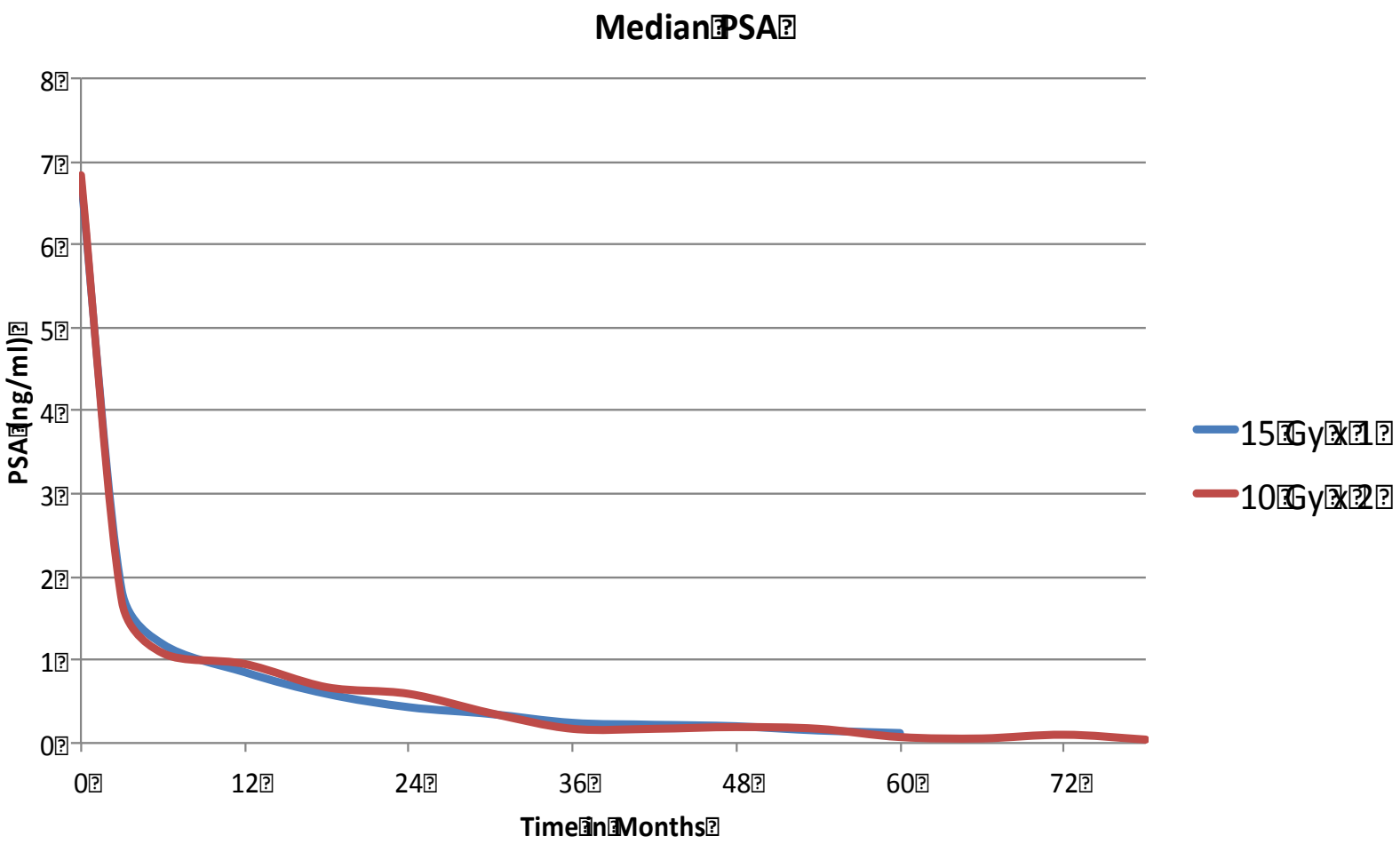
Materials and Methods

Parameter	15 Gy x 1	10 Gy x 2
N	125	60
Age	65.8 (45-79 yrs)	67.8 (51-83 yrs)
PSA	6.76 (2.0-18.6)	6.83 (1.2-17.9)
Gleason 7: Gleason 6	93%:7%	80%:20%
Stage T1c:T2	62%:38%	53%:47%
Follow-up	4 yrs (20-65 mos)	6 yrs (24-84 mos)

Materials and Methods

- Efficacy: PSA, DRE, Biopsy at 2 years
- Toxicity: CTCAE v3.0
- PRO: EPIC, IIEF, IPSS

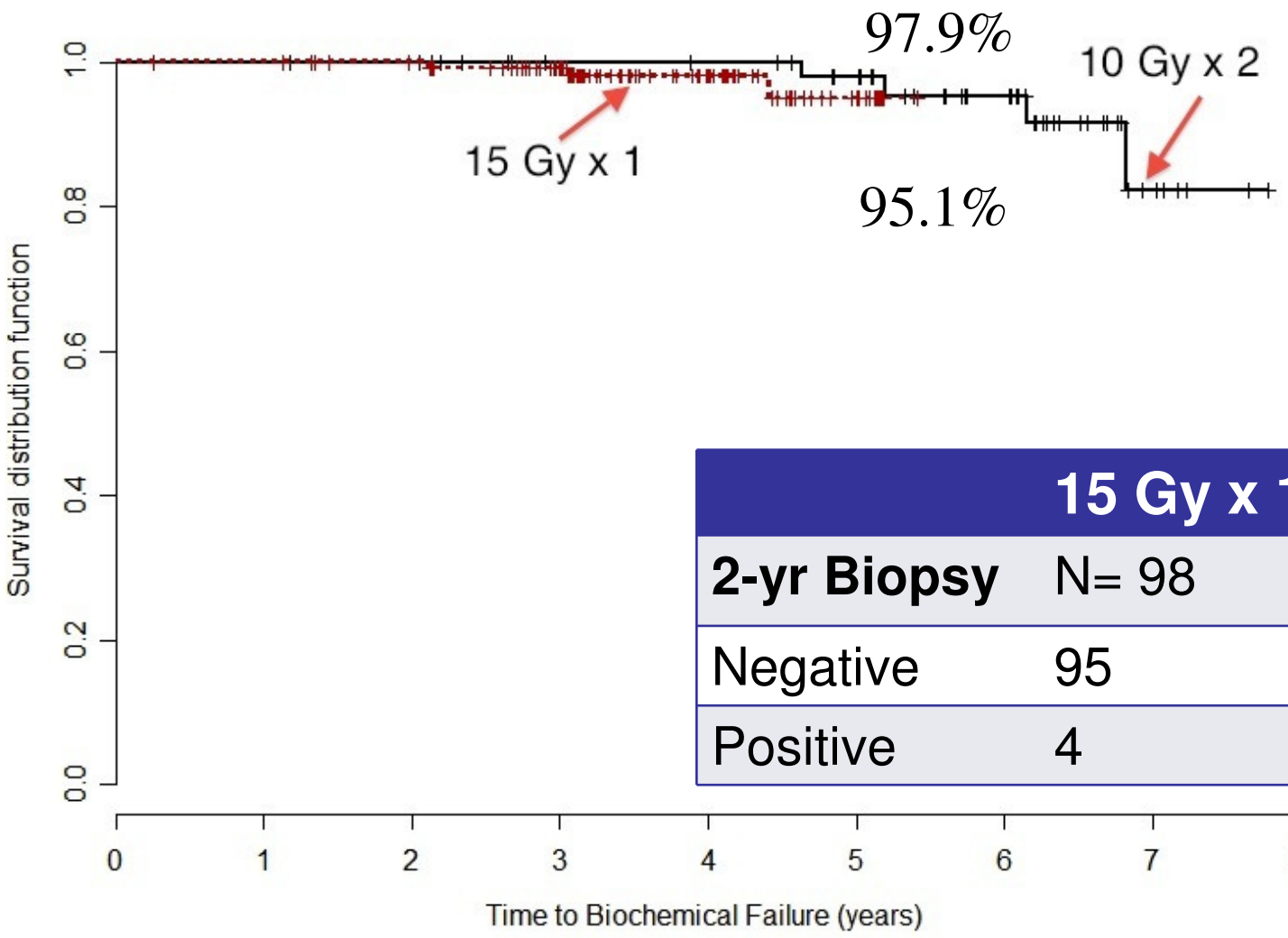
PSA Response



University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Biochemical DFS



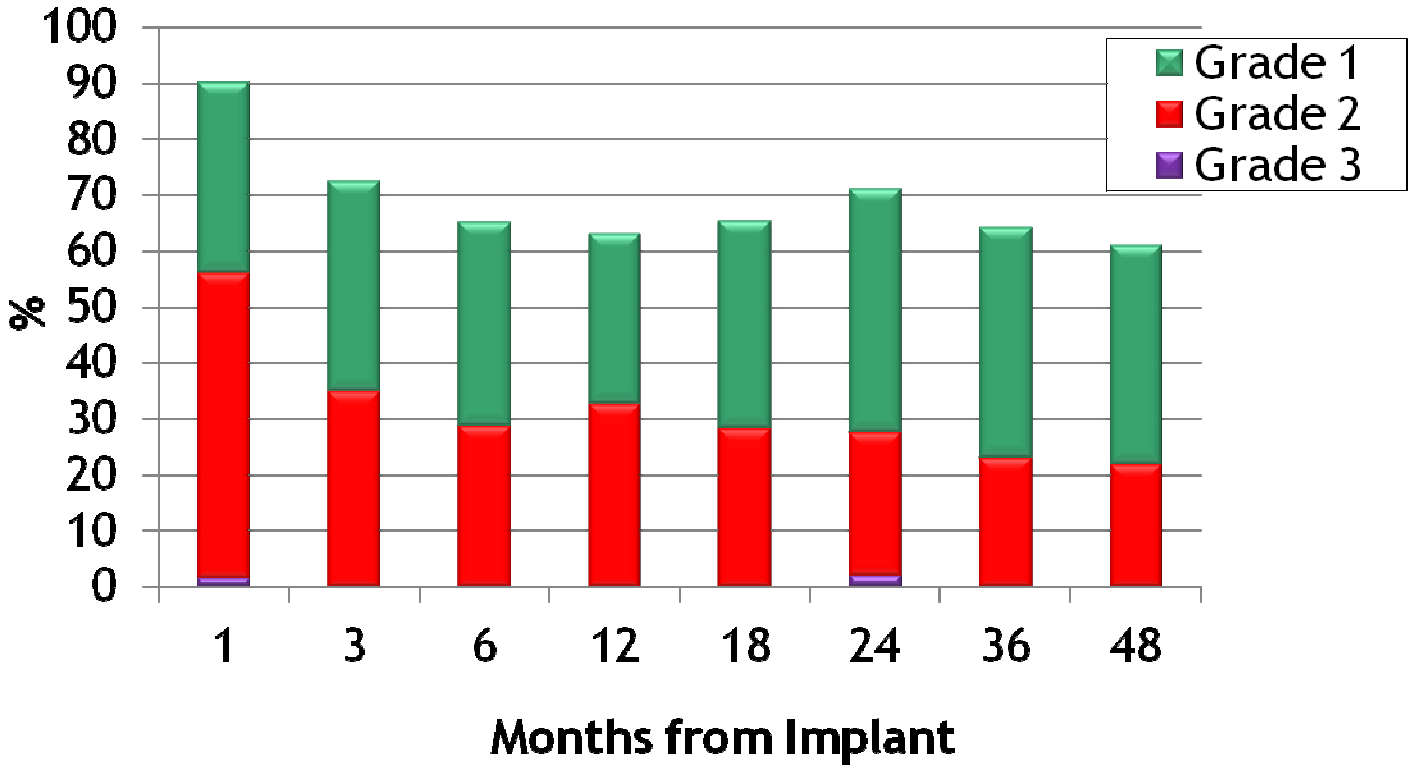
	15 Gy x 1	10 Gy x 2
2-yr Biopsy	N= 98	N = 49
Negative	95	45
Positive	4	4

University of Toronto

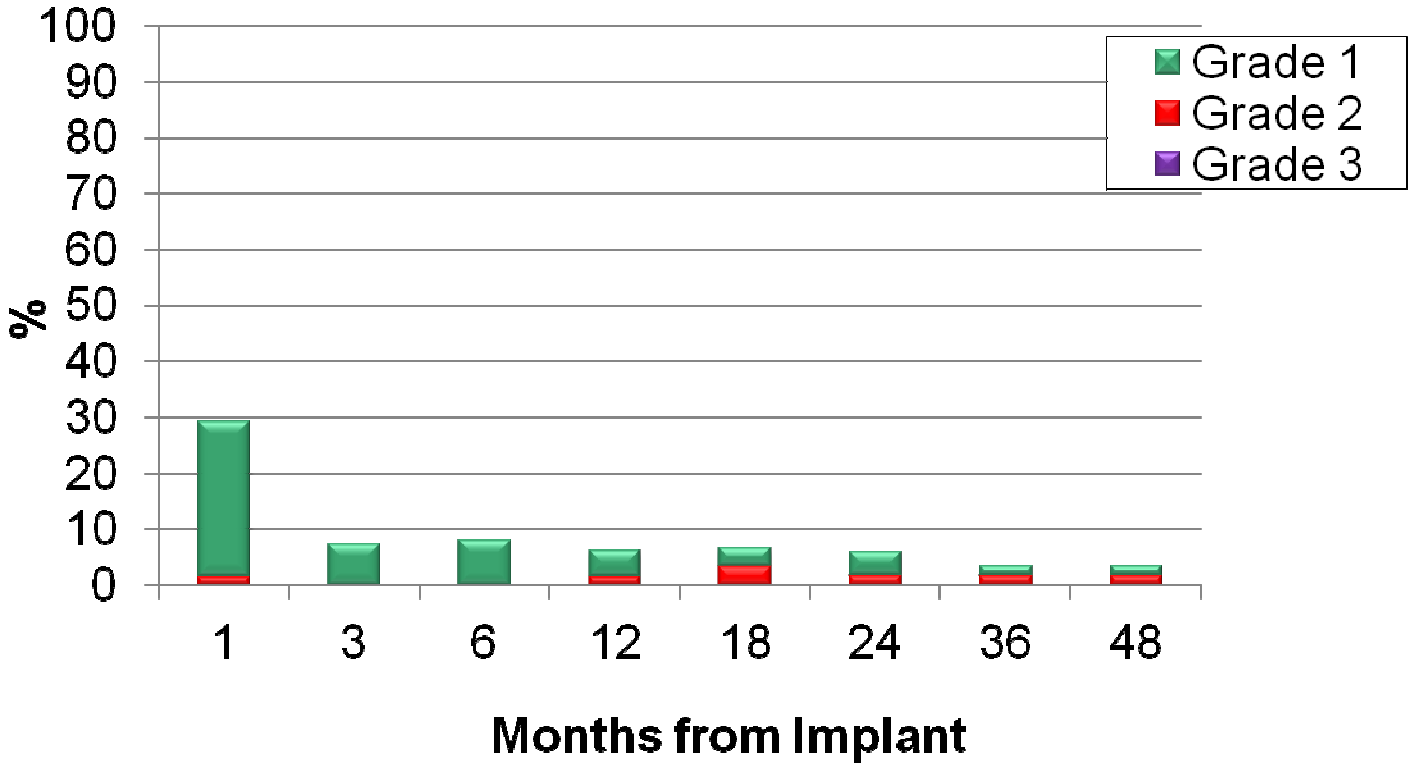
Radiother Oncol 100:463-467, 2011

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

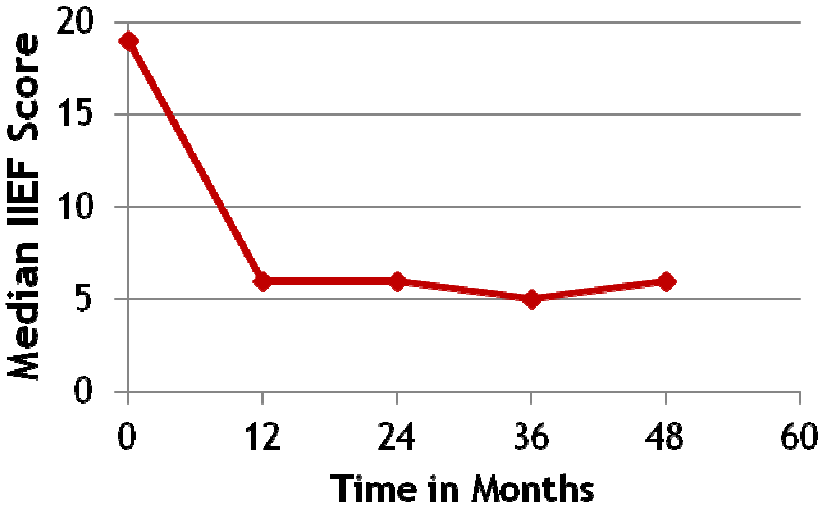
Toxicity 15 Gy x 1: GU

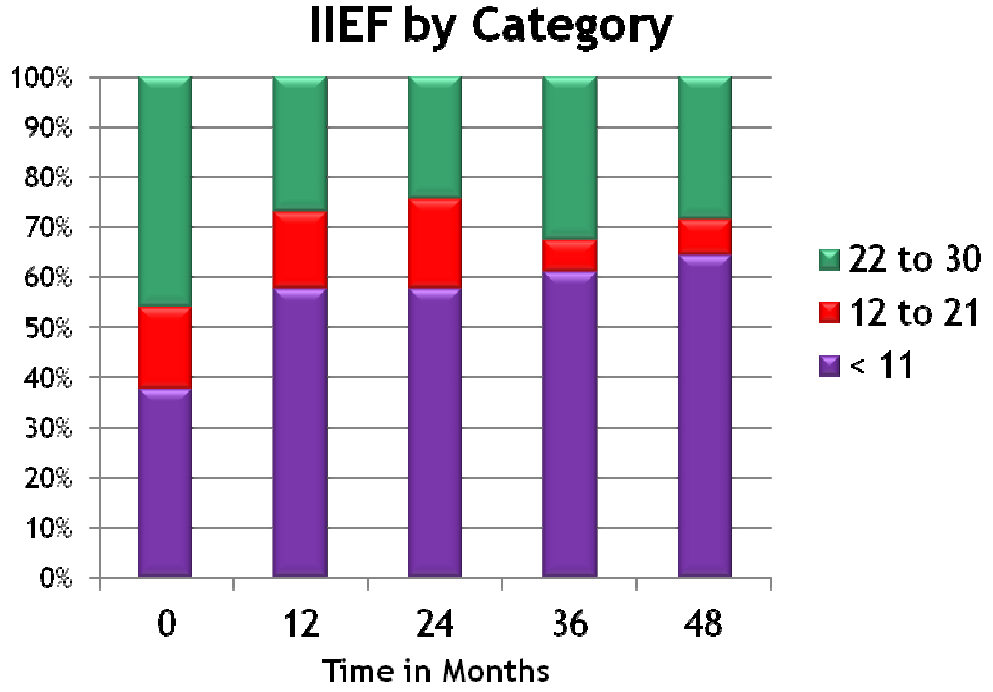


Toxicity 15 Gy x 1: GI



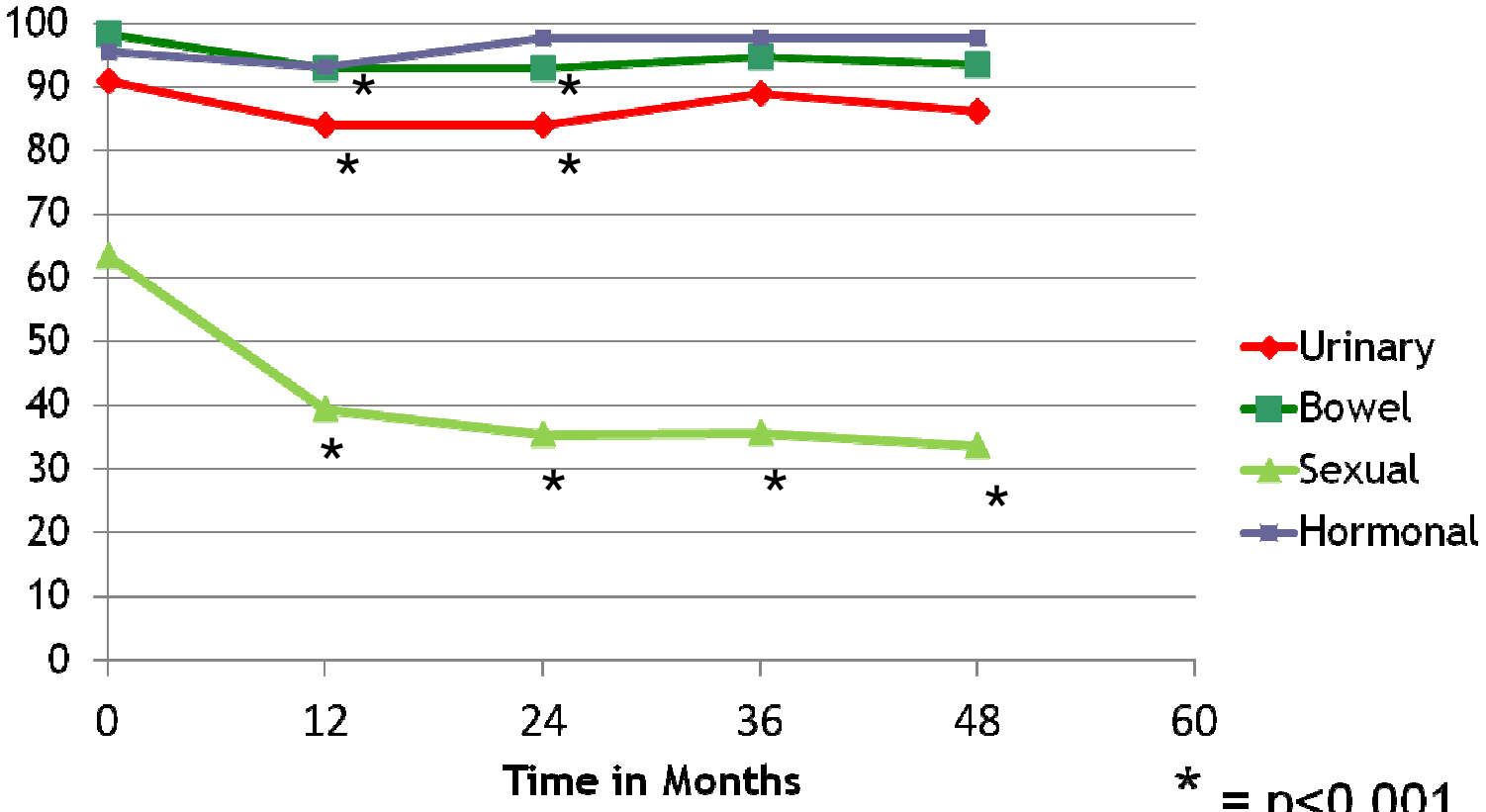
Toxicity 15 Gy x 1: Erectile Function





30% develop mild/moderate and 20% develop severe erectile dysfunction

15 Gy x 1: Median EPIC Domain Scores



University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

15 Gy x 1 vs. 10 Gy x 2

Parameter	Difference
Acute GU Toxicity	Less with single fraction, p 0.0126
Late Toxicity	No difference
Health Related QOL	No difference
2-yr biopsy results	No difference
Recurrence	No difference

Lessons from Dosimetry

- Acute urinary toxicity associated with prostate V200 (p .0141) and baseline IPSS (p.0125)
- Late urinary function and bother associated with dose to urethra (p.0168), threshold D10 =120%
- Erectile Dysfunction associated with larger volume of CTV

Int J Radiat Oncol Biol Phys 80:1299-1305, 2011

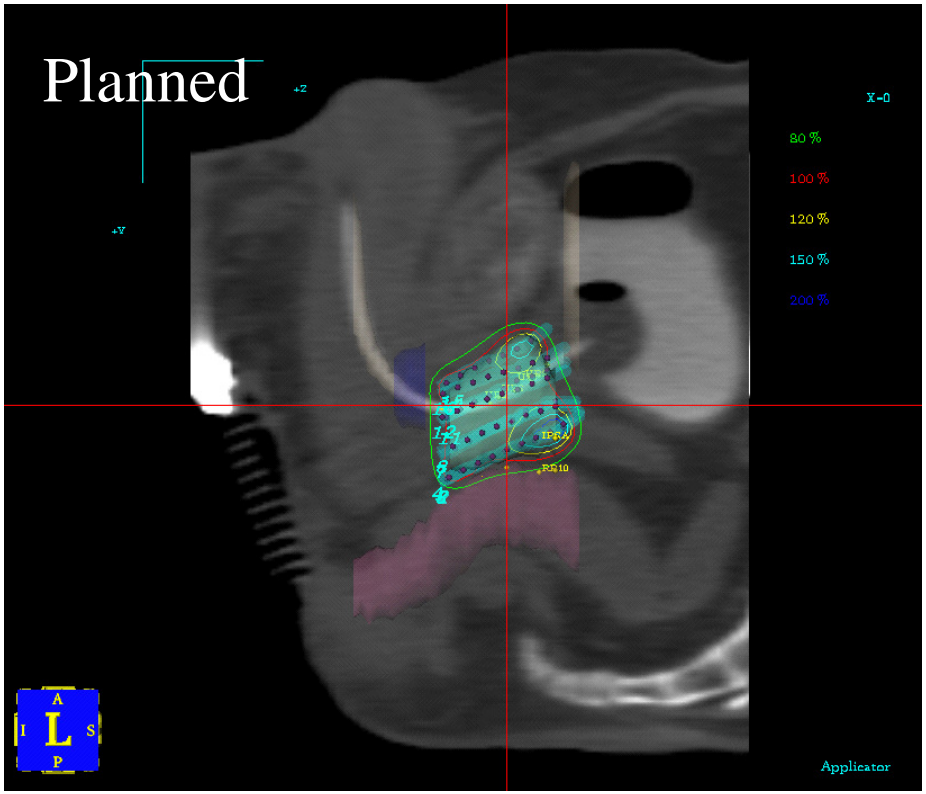
Conclusion

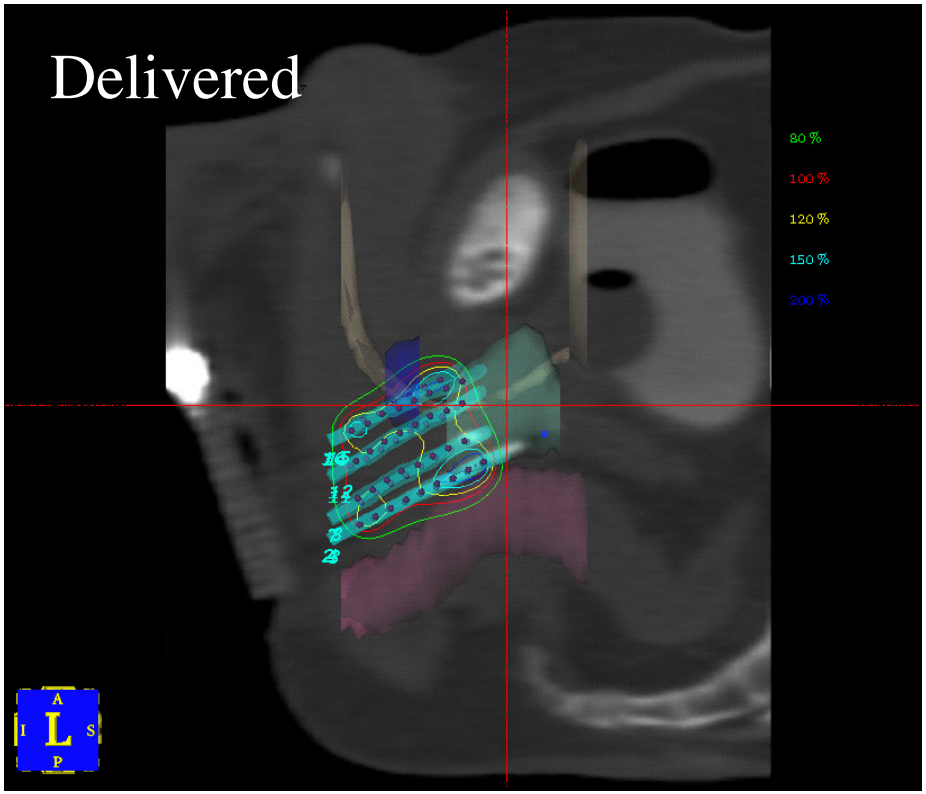
- Single 15 Gy HDR has become standard fractionation in most Canadian centres
- Potential to further reduce toxicity with improved technique

What Technique?

- Limitations of CT based Technique
- Advantages of real-time intra-operative planning

CT-Based Technique and Catheter Displacement





University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

CT-Based Technique and Catheter Displacement

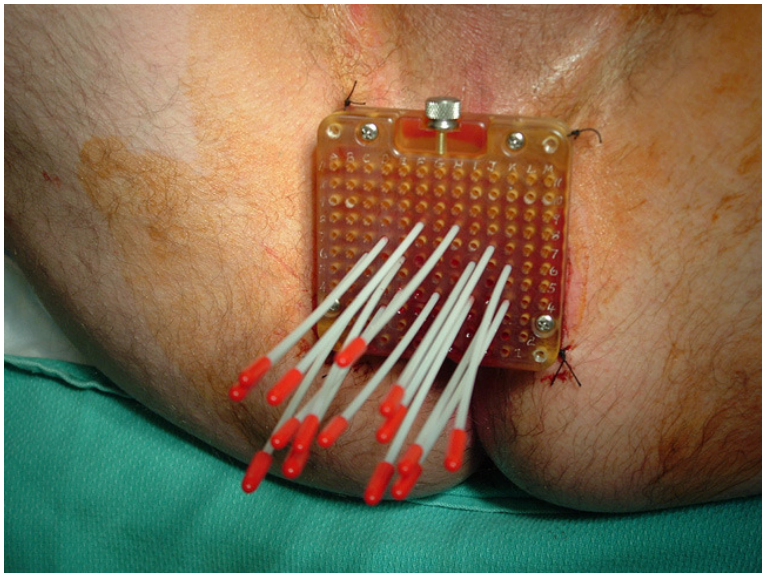


Fig. 1. Flexible afterloading catheters are fixed to a 7 × 7 cm template by means of a locking screw. The template is sutured securely to the perineum at all four corners.

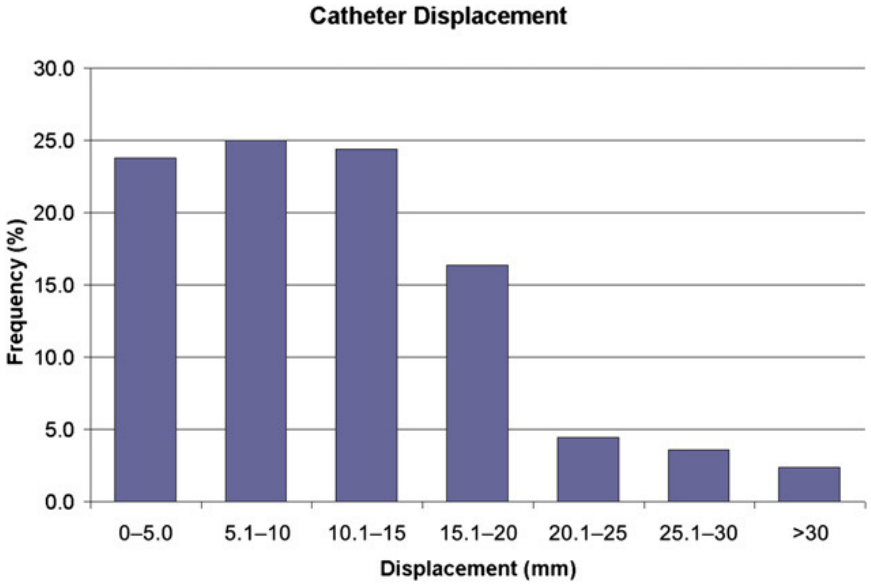


Fig. 3. Displacement of individual catheters ($n = 336$) between time of CT planning and treatment delivery as measured by coregistered kilovoltage cone-beam CT images in the treatment room.

Brachytherapy 10(4):299-305, 2011

University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

CT-Based Technique and Catheter Displacement

Table 1
Mean dosimetric parameters as planned based on initial CT scan and as determined from image coregistration with initial (unadjusted) and final kilovoltage cone-beam CT before treatment delivery

	Mean, % (range, %)		
Parameter	Planned	Unadjusted	Final
Prostate V_{100}	97.6 (95.3–99.4)	77.3 (47.2–96.8); $p < 0.0001$	90.2 (81.1–96.8); $p = 0.0002$
Prostate D_{90}	110.5 (103.7–116.4)	72.9 (33.1–110.2); $p < 0.0001$	97.4 (79.0–110.2); $p = 0.0023$
Urethra V_{120}	8.3 (0.9–17.0)	21.2 (1.4–58.2); $p = 0.0046$	22.2 (7.3–65.8); $p = 0.0471$
Urethra D_{10}	118 (101–125)	125 (107–140); $p = 0.0094$	126 (119–140); $p = 0.0324$

V_{100} = percent of volume receiving 100% of prescription dose; D_{90} = percent of prescribed dose to 90% of volume; V_{120} = percent of volume receiving 120% of prescription dose; D_{10} = percent of prescribed dose to 10% of volume.

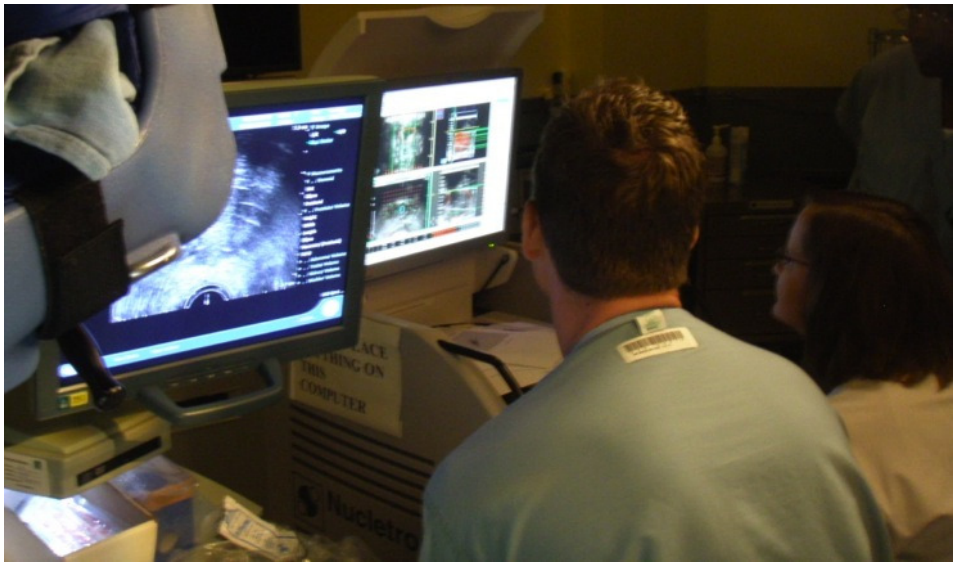
p Value indicates difference from planned parameter.

Brachytherapy 10(4):299-305, 2011

University of Toronto

Sunnybrook ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Intra-Operative 3D US Based Planning



Catheter Insertion and Treatment Delivery Without Moving Patient

University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Intra-Operative 3D US Based Planning

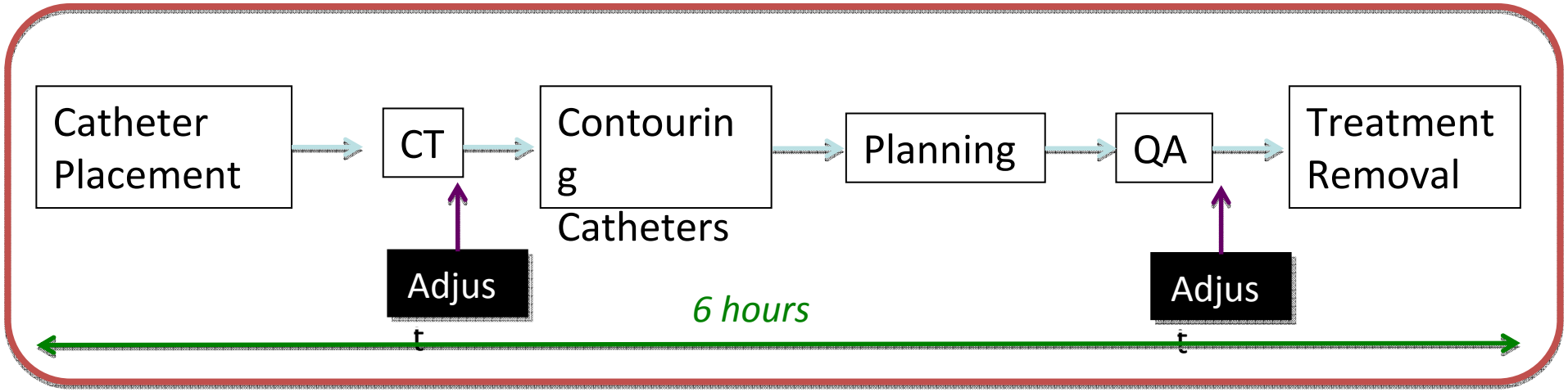
- More consistent dosimetry than IPSA
  - V200, Urethral Dose

  Batchelar et al, Brachytherapy 10:3s27, 2011
- Minimal Catheter Displacement: we deliver what we plan
  - Median shift 0.7 mm with US vs. 10.5 mm with CT

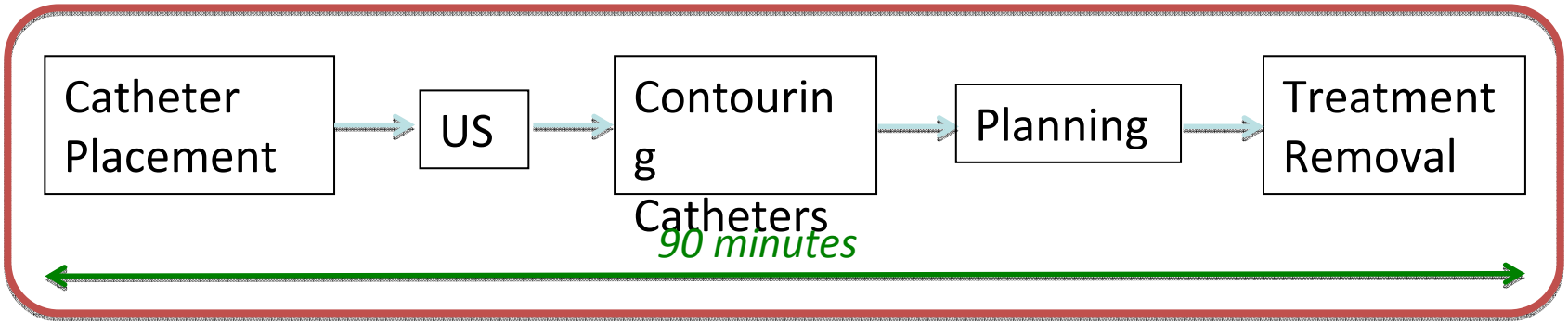
  Batchelar et al, Brachytherapy 10:3s92, 2011
- Volume of CTV 30% smaller than on CT

CT vs. US

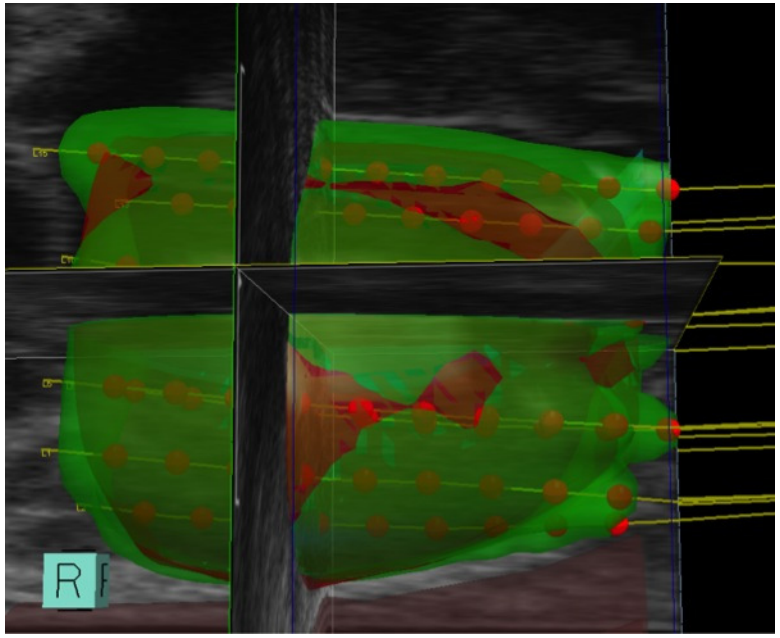
CT Technique

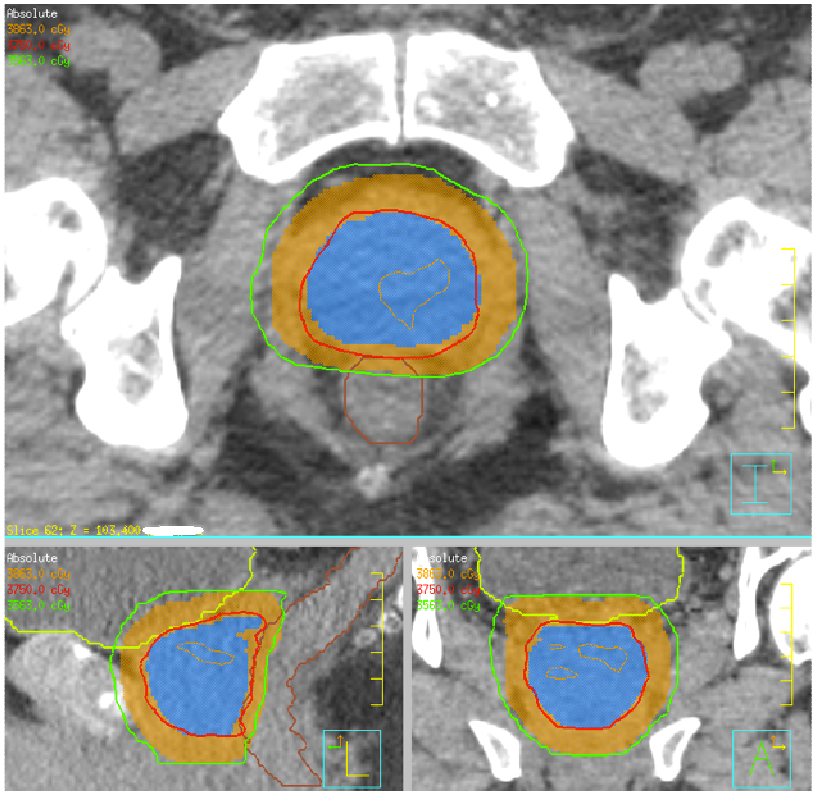


US Technique



Current Protocol





15 Gy x 1 HDR
Real Time 3D TRUS Planning

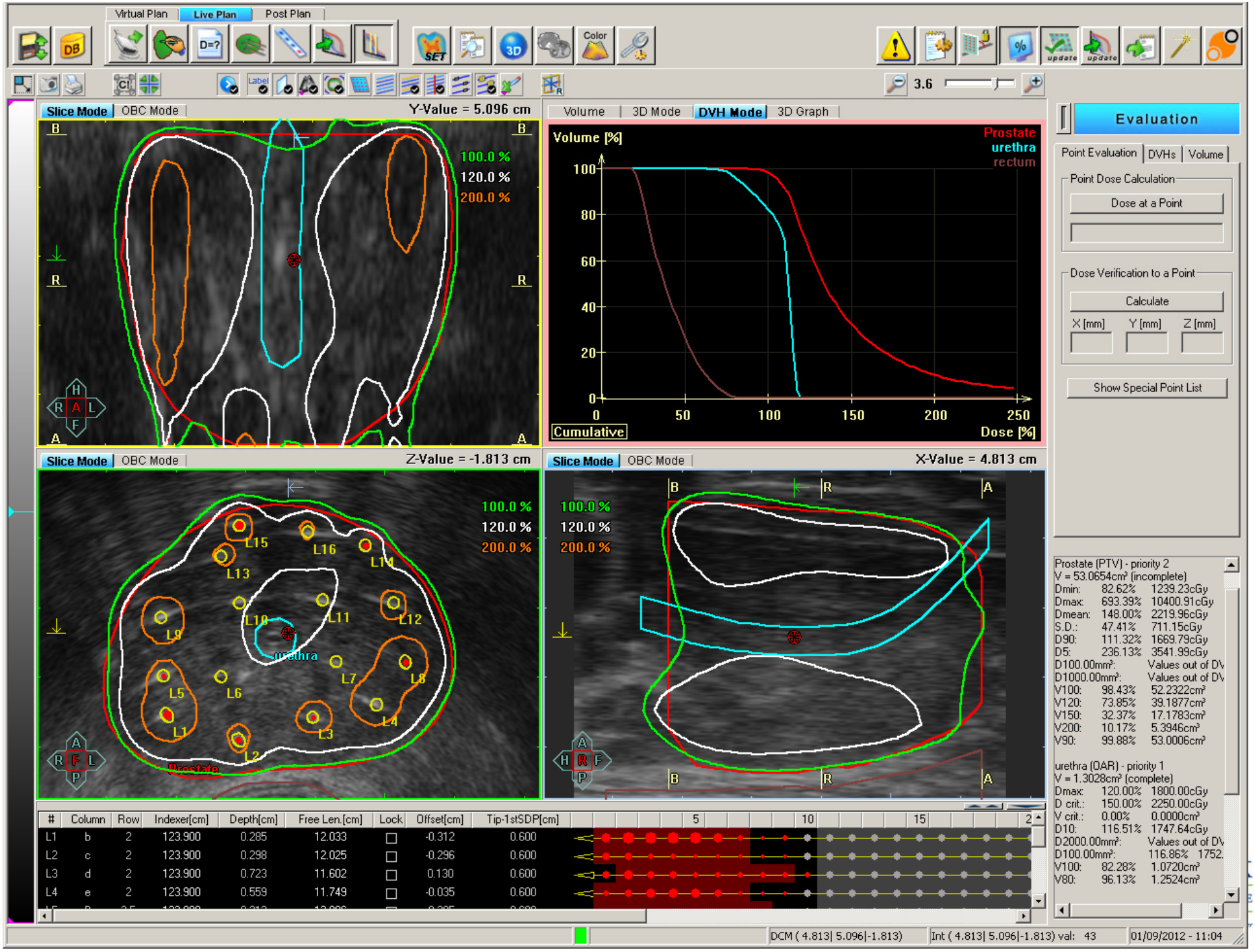
37.5 Gy/15 fractions
IMRT or VMAT

University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Interactive Process

Radiation Oncologist
Radiation Therapist
Medical Physicist
Nurse, Anaesthetist


Virtual Plan
Live Plan
Post Plan
Slice Mode
OBC Mode
Y-Value = 5.096 cm
100.0 %
120.0 %
200.0 %
Volume
3D Mode
DVH Mode
3D Graph
Volume [%]
Prostate
urethra
rectum
Cumulative
Dose [%]
Z-Value = -1.813 cm
X-Value = 4.813 cm
Evaluation
Point Evaluation
DVHs
Volume
Point Dose Calculation
Dose at a Point
Dose Verification to a Point
Calculate
X [mm]
Y [mm]
Z [mm]
Show Special Point List
Prostate (PTV) - priority 2
V = 53.0654cm³ (incomplete)
urethra (OAR) - priority 1
V = 1.3028cm³ (complete)
DCM (4.813| 5.096|-1.813)
Int (4.813| 5.096|-1.813) val: 43
01/09/2012 - 11:04

3DUS based planning

- Introduced June 2009
- 462 patients treated since then
  - Acute urinary retention 2%
  - 1 urethral stricture
- Less decline in urinary function and bother at 1 year
- Less decline in bowel function and bother at 1 year

For discussion…

- Ongoing questions:
  - EBRT + BT vs. BT alone?
  - Role of ADT?
  - Elective nodal irradiation?

EBRT + BT vs. BT alone

- HDR Monotherapy

6 Gy x 9	6 Gy x 6	7 Gy x 4	11.5 Gy x 3	13 Gy x 2
	6 Gy x 6	9 Gy x 4		13.5 Gy x 2
	6.5 Gy x 6	9.5 Gy x 4		
	7 Gy x 6	9.5 Gy x 4		
	7 Gy x 6			

- 85-99% bDFS for low/intermediate risk, 79-91% bDFS for high risk

EBRT + BT vs. BT alone

RTOG 0232

A PHASE III STUDY COMPARING COMBINED EXTERNAL BEAM RADIATION AND TRANSPERINEAL INTERSTITIAL PERMANENT BRACHYTHERAPY WITH BRACHYTHERAPY ALONE FOR SELECTED PATIENTS WITH INTERMEDIATE RISK PROSTATIC CARCINOMA

Study Chairs (9/6/11)

Radiation Oncology
Bradley R. Prestidge, M.D.
Memorial Hermann Southwest
Department of Radiation Oncology
7600 Beechnut Street
Houston, TX 77074
(713) 456-5622
FAX# (713) 456-4076
brad@prestidgemd.com

Urology
Martin Sanda, M.D.
(617) 667-2960
FAX# (617) 667-3013
msanda@bidmc.harvard.edu

Pathology
Mahul Amin, M.D.
(310) 423-6631
FAX# (310) 423-0170
aminm@cshs.org

Outcomes
Deborah Watkins Bruner, R.N., Ph.D.
(404) 712-9695
FAX# 404-727-8514
deborah.w.bruner@emory.edu

University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Role of ADT

RTOG 0815

A PHASE III PROSPECTIVE RANDOMIZED TRIAL OF DOSE-ESCALATED RADIOTHERAPY WITH OR WITHOUT SHORT-TERM ANDROGEN DEPRIVATION THERAPY FOR PATIENTS WITH INTERMEDIATE-RISK PROSTATE CANCER

Study Chairs

Principal Investigator/Radiation Oncology Alvaro A. Martinez, MD, FACR William Beaumont Hospital Department of Radiation Oncology 3601 W. Thirteen Mile Road Royal Oak, MI 48009 Phone: 248-551-7058/Fax: 248-551-0089 E-mail: amartinez@beaumont.edu	External Beam Radiotherapy Co-Chair Daniel J. Krauss, MD William Beaumont Hospital Department of Radiation Oncology 3601 W. Thirteen Mile Road Royal Oak, MI 48009 Phone: 248-551-3576/Fax: 248-551-0089 E-mail: dkrauss@beaumont.edu
High Dose Rate Brachytherapy Co-Chair I-Chow Hsu, MD UCSF, Department of Radiation Oncology 1600 Divisadero St. Suite H1031 San Francisco, CA 94143-1708 Phone: 415-353-7175/Fax: 415-353-9883 E-mail: ihsu@radonc.ucsf.edu	Low Dose Rate Brachytherapy Co-Chair Gerard Morton, MD Toronto-Sunnybrook Regional Cancer Center Department of Radiation Oncology 2075 Bayview Ave. Toronto, ON M4N 3M5 CANADA Phone: 416-480-6165/Fax: 416-217-1338 E-Mail: gerard.morton@sunnybrook.ca

University of Toronto

Sunnybrook ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Elective Nodal Irradiation

RTOG 0924

ANDROGEN DEPRIVATION THERAPY AND HIGH DOSE RADIOTHERAPY WITH OR WITHOUT WHOLE-PELVIC RADIOTHERAPY IN UNFAVORABLE INTERMEDIATE OR FAVORABLE HIGH RISK PROSTATE CANCER: A PHASE III RANDOMIZED TRIAL

Study Chairs

Principal Investigator/Radiation Oncology Mack Roach III, MD UCSF, Department of Radiation Oncology 1600 Divisadero Street San Francisco, CA 94143-1708 Phone: 415-353-7181/Fax: 415-353-7182 E-mail: mroach@radonc.ucsf.edu	High Dose Rate Brachytherapy Co-Chair I-Chow Hsu, MD UCSF, Department of Radiation Oncology 1600 Divisadero Street Suite H1031 San Francisco, CA 94143-1708 Phone: 415-353-7175/Fax: 415-353-9883 E-mail: ihsu@radonc.ucsf.edu
Intensity Modulated Radiotherapy Co-Chair Hans Chung, MD Toronto-Sunnybrook Regional Cancer Center Department of Radiation Oncology 2075 Bayview Avenue Toronto, ON M4N 3M5 CANADA Phone: 416-480-4834/Fax: 416-480-6002 E-mail: hans.chung@sunnybrook.ca	Low Dose Rate Brachytherapy Co-Chair Gerard Morton, MD Toronto-Sunnybrook Regional Cancer Center Department of Radiation Oncology 2075 Bayview Ave. Toronto, ON M4N 3M5 CANADA Phone: 416-480-6165/Fax: 416-217-1338 E-Mail: gerard.morton@sunnybrook.ca

University of Toronto

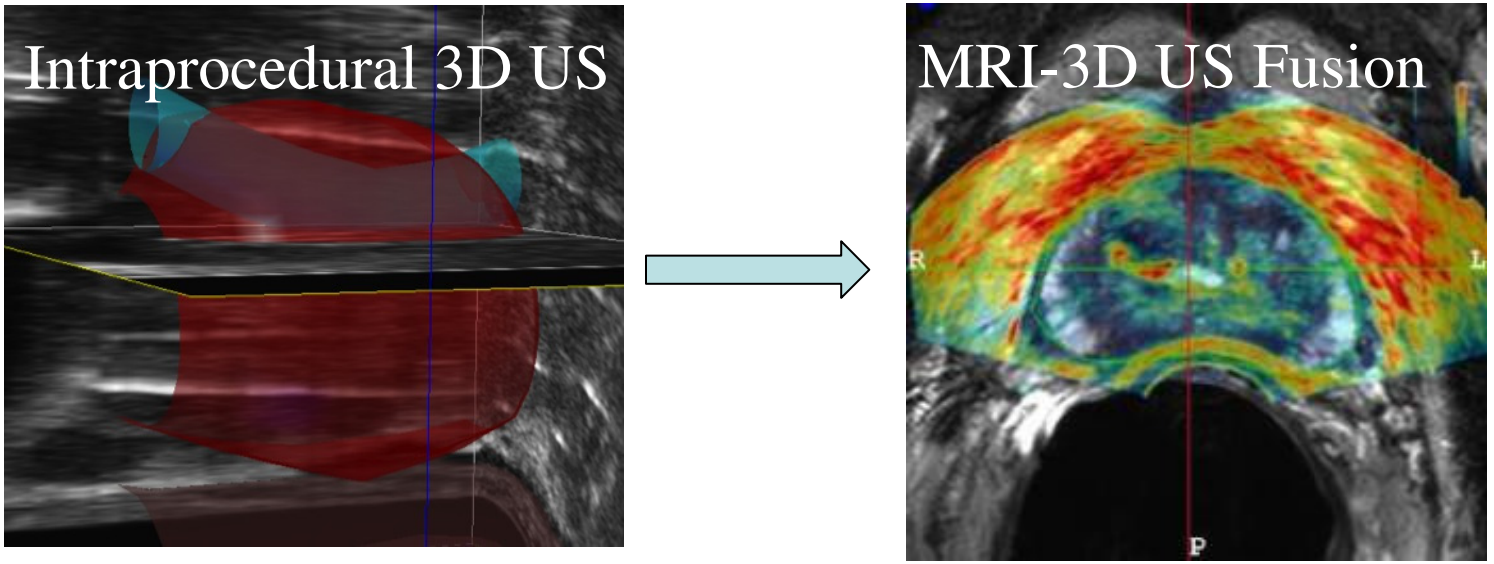
Sunnybrook ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Brachytherapy in Canada

Risk Group	Definition	Treatment	Expected 5 yr DFS
Low	T1c, G6, PSA <10	BT alone	90-95%
Intermediate	T1/T2, G6, PSA 10-20	BT alone	80-95%
	T1/T2, G7, PSA < 10	BT alone	80-95%
	T1/T2, G7, PSA 10-20 or bulk disease	BT + EBRT	80-95%
High	T3 or G8-10 or PSA > 20	BT + EBRT + ADT	65-90%

Further Refinements

- MRI-3DUS Image Fusion Platform



Summing it all up….

- HDR is an effective and well tolerated method of local boosting combined with EBRT
- HDR monotherapy very promising
- Rapidly evolving data on dose and technique

Acknowledgements

Radiation Oncology

Andrew Loblaw

Hans Chung

Ewa Szumacher

Patrick Cheung

Cyril Danjoux

Danny Vesprini

Will Chu

Medical Physics

Raxa Sankreacha

Deidre Batchelar

Ananth Ravi

Renee Korol

Collins Yeboah

Radiation Therapy

Niki Law

Thomas Cisecki

Cinical Trials

Andrea Deabreu

Liying Zhang

Alex Mamedov

University of Toronto

Sunnybrook
ODETTE CANCER CENTRE
A Cancer Care Ontario Partner

Acknowledgements

Abbott - Canadian Association of Radiation Oncologists Uro-Oncology (ACURA) Award

Motorcycle Ride for Dad