

### BRACHYTHERAPY IN CARCINOMA PROSTATE

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- Indications and Rationale
- Types
- Monotherapy
- Combination with EBRT
- Evidence
- Technique
- Salvage



#### **Estimated New Cases**

			Males
Prostate	248,530	26%	
Lung & bronchus	119,100	12%	
Colon & rectum	79,520	8%	
Urinary bladder	64,280	7%	
Melanoma of the skin	62,260	6%	
Kidney & renal pelvis	48,780	5%	
Non-Hodgkin lymphoma	45,630	5%	
Oral cavity & pharynx	38,800	4%	
Leukemia	35,530	4%	
Pancreas	31,950	3%	
All Sites	970,250	100%	

#### **Estimated Deaths**

Males

Lung & bronchus	69,410	22%	
Prostate	34,130	11%	
Colon & rectum	28,520	9%	
Pancreas	25,270	8%	
Liver & intrahepatic bile duct	20,300	6%	
Leukemia	13,900	4%	
Esophagus	12,410	4%	
Urinary bladder	12,260	4%	
Non-Hodgkin lymphoma	12,170	4%	
Brain & other nervous system	10,500	3%	
All Sites	319,420	100%	

### Cancer Statistics, 2021

CA CANCER J CLIN 2021;71:7-33



INDIA – 9-10/100000 population





## Risk Stratification of Carcinoma Prostate

Table 1. Organizational pre-treatment prostate cancer risk stratification systems						
Institution/organization	Low risk	Intermediate risk	High risk			
Harvard (D'Amico) <sup>12</sup> AUA <sup>33</sup> EAU <sup>34</sup>	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10-20 not low-risk	≥T2c or PSA >20 or GS 8-10			
GUROC*3 NICE <sup>31</sup>	T1-T2a and GS ≤6 and PSA ≤10	T1-T2 and/or Gleason ≤7 and/or PSA ≤20 not low-risk	≥T3a or PSA >20 or GS 8-10			
CAPSURE*41	T1-T2a and GS ≤6 and PSA ≤10	T2b and/or GS =7 and/or PSA >10-20 not low-risk	T3-4 or PSA >20 or GS 8-10			
NCCN <sup>30</sup>	T1-T2a and GS 2-6 and PSA ≤10 not very low-risk AND very-low risk category: T1c and GS ≤6 and PSA <10 and Fewer than 3 biopsy cores positive and ≤50% cancer in each core	T2b or T2c and/or GS =7 and/or PSA >10-20 not low-risk	T3a or PSA >20 or GS 8-10 not very high risk AND very high-risk category: T3b-4			
ESMO <sup>32</sup>	T1-T2a and GS ≤6 and PSA <10	Not high risk and not low risk (the remainder)	T3-4 or PSA >20 or GS 8-10			

## **Risk Stratification**



Risk Group	Clinica <u>S</u>	al/Pathologic ee Staging (S	Features ST-1)			
Very low <sup>e</sup>	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate b cancer in each fragmer • PSA density <0.15 ng/m	Has all of the following: • cT1c • Grade Group 1 • PSA <10 ng/mL • Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core • PSA density <0.15 ng/mL/g				
Low <sup>e</sup>	Has all of the following but does not qualify for very low risk: • cT1–cT2a • Grade Group 1 • PSA <10 ng/mL					
	Has all of the following: • No high-risk group features • No very-high-risk group features	Favorable intermediate	Has all of the following: • 1 IRF • Grade Group 1 or 2 • <50% biopsy cores positive (eg, <6 of 12 cores) <sup>f</sup>			
Intermediate <sup>e</sup>	<ul> <li>Has one or more intermediate risk factors (IRFs):</li> <li>cT2b–cT2c</li> <li>Grade Group 2 or 3</li> <li>PSA 10–20 ng/mL</li> </ul>	Unfavorable intermediate	Has one or more of the following: • 2 or 3 IRFs • Grade Group 3 • ≥ 50% biopsy cores positive (eg, ≥ 6 of 12 cores) <sup>f</sup>			
High	Has no very-high-risk features and has exactly one high-risk feature: • cT3a OR • Grade Group 4 or Grade Group 5 OR • PSA >20 ng/mL					
Very high	Has at least one of the fo • cT3b–cT4 • Primary Gleason patter • 2 or 3 high-risk features • >4 cores with Grade Gr	llowing: n 5 oup 4 or 5	–NCCN Guidelines V			

Prostate Cancer

## Why brachytherapy?



- Practical -
  - Existing source, afterloading
  - No Organ motion
  - Short treatment times
- Physical
  - Greater implant volume including seminal vesicles and extracapsular coverage
  - Optimization allows highly conformal dose delivery
  - Dose sculpting around OARs
- Biological
  - Low  $\alpha/\beta$  tumour 1.5
  - Dose escalation greater than EBRT
  - Hypofractionation
- Radioprotection
  - Minimum isolation
  - No radioactivity within the patient
- Significantly reduced cost

## **BRACHYTHERAPY - TYPES**





- TEMPORARY- HDR BRACHYTHERAPY
- Iridium 192



- PERMANENT –SEEDS
   LDR
- iodine 125
- palladium 103
- Caesium 131



### HIGH DOSE-RATE AFTERLOADING <sup>192</sup>IRIDIUM PROSTATE BRACHYTHERAPY: FEASIBILITY REPORT

TIMOTHY P. MATE, Int. J. Radiation Oncology Biol. Phys., Vol. 41, No. 3, pp. 525-533, 1998





			Shankara CANCER HOSPITAL & RESEARCH CENTRI				
Regimen	Preferred Dose/Fractionation	Very Low and Low	Favorable Intermediate	Unfavorable Intermediate	High and Very High	Regional N1	Low Volume M1 <sup>a</sup>
EBRT							
Moderate Hypofractionation (Preferred)	3 Gy x 20 fx 2.7 Gy x 26 fx 2.5 Gy x 28 fx	~	~	~	~	~	
	2.75 Gy x 20 fx						~
Conventional Fractionation	1.8–2 Gy x 37–45 fx	~	~	~	~	~	
Ultra-Hypofractionation	7.25–8 Gy x 5 fx 6.1 Gy x 7 fx	~	~	~	~		
	6 Gy x 6 fx						~
Brachytherapy Monotherap	ру						
LDR Iodine 125 Palladium 103 Cesium 131	145 Gy 125 Gy 115 Gy	~	~				
HDR Iridium-192	13.5 Gy x 2 implants 9.5 Gy BID x 2 implants	~	~				
EBRT and Brachytherapy (	combined with 45–50.4 Gy x 25	-28 fx or 37.	5 Gy x 15 fx)				
LDR Iodine 125 Palladium 103 Cesium 131	110–115 Gy 90–100 Gy 85 Gy			~	√		
HDR Iridium-192	15 Gy x 1 fx 10.75 Gy x 2 fx			~	~		

#### NCCN Guidelines Version 4.2022 Prostate Cancer

/ Sri



# Indications for Bracytherapy

### MONOTHERAPY

Very Low

low

Favourable Intermediate

**BOOST** after EBRT

Unfavouable Intermediate High Risk

Very High Risk

# Contraindications



### ABSOLUTE

- M1 disease
- Medically unfit for anaesthesia
- Pre existing rectal fistula
- No proof of malignancy
- Ataxia telengectasia

### RELATIVE

- Gland > 60 cc
  - Preimplant cytoreduction can be achieved with ADT +- 5αreductase inhibitor
- Pubic arch interference
- TURP last 3 months or large TURP defect
- Obstructive urinary symptoms IPSS > 15
- Peak flow rate <10ml/sec or post void residual >100cc
- Inflammatory bowel disease
- Prior rectal Surgery

# TURP



- With accurate U/S identification, a TURP defect <25% the total prostate volume and at least 1cm margin around the defect, there is a low impact on urinary function post implant
- Defect >2cc has been correlated to increase urinary morbidity compared to patients with a defect <2cc</li>
- If a TURP is needed, it is preferably done before brachytherapy with a 3month gap before implant.





# Brachytherapy: Where Has It Gone?

Daniel G. Petereit Journal of Clinical Oncology, Vol 33, No 9 (March 20), 2015: pp 980-982

The decline of prostate brachytherapy with its comparable outcomes, low morbidity, and comparative cost-effectiveness poses immediate concerns related to patient choice, economic costs, and health policy. An analysis by Hayes et al<sup>16</sup> examined the cost of observation

- Increase in number of robotic prostatectomies
- Increase in technical sophistication of EBRT – IMRT, SBRT, Proton
- Reimbursement for IMRT higher
- Negative press
- Suboptimal training



#### % of Non-academic Practices by Case Volume



Percentage	Number of cases
73.7%	<12 cases
24.8%	13-53 cases
1.5%	>53 cases

Volume 96 • Number 3 • 2016

IJORBP

Prostate brachytherapy case volumes and residency training

### ADVANTAGES OF BRACHYTHERAPY OVER IMRT

- Reduced treatment time
- Even best form of IMRT is still an XRT only.
- Radiobiologically superior
- Clinically and financially more relevant to Indian conditions

## BRACHYTHERAPY





Dosimetric comparison of (A) IMRT (B) VMAT (C) (SBRT), and (D) (LDR-BT). Isodose lines correspond to 25% (blue), 50% (yellow), and 100% (red) of prescription dose.

Ibrahim Abu-Gheida

ARO ,September 21, 2017





Representative dose distributions for a selected patient for all 5 treatment techniques after radiobiological conversion.

Georg et al.

IJORBPVolume 88 • Number 3 • 2014



NATURE REVIEWS | UROLOGY VOLUME 14 | JULY 2017



# Sequencing





## Pre- requisites

- TRUS and HDR under one roof
- Dedicated systems available but expensive

- Pre op laxatives/enema
- 3 way catheter
- TRUS in the OT- Side firing probe
- SA/EA





## Procedure





• SYED- NEBLETT TEMPLATE





























Courtesy : Dr Sanjiv Sharma – Manipal Hospital

# DOSE



Y. Yamada et al. / Brachytherapy 11 (2012) 20-32

Table 3Current dose fractionation schedules

Institution	Dose fractionation	Bladder	Urethra	Rectum
MSKCC	Boost 7Gyx3		<120% prescription	$D_{2 cc} < 70\%$
	Mono 9.5Gyx4			
	Salvage 8Gyx4			
UCSF	Boost 15Gyx1	$V_{75} < 1 \text{ cc}$	$V_{125} < 1 \text{ cc}, V_{150} = 0 \text{ cc}$	$V_{75} < 1 \text{ cc}$
	Mono 10.5Gyx3			
	Salvage 8Gyx4*		*(dose tunnel whenever possible)	
WBH	Boost 10.5Gyx2	No constraint	$V_{100} < 90\%$ of prescription	$V_{75} < 1\%$ of prescription
	Mono $4 \times 9.5$ Gy (historical)	(intra-op TRUS-based dosi)	$V_{115} < 1\%$ of prescription	
	12-13.5Gyx2 (current)			
	Salvage 7Gyx4 combined with hyperthermia			
TCC	Boost 6Gyx2	<80% of Rx	<125% of prescription	<80% of Rx to outer wall
	×2 implants			
GW	Boost 6.5Gyx3	<100% prescription	<110% prescription	mucosa <60%, outer wall <100%
	Mono two sessions of 6.5Gyx3			
Toronto	Boost 15Gyx1	n/a	$D_{10} < 118\%$	$V_{80} < 0.5 \text{ cc}$
			Max < 125%	
UCLA-CET	Boost 6Gyx4	90-100% wall	120% combo	Rectal wall 80%
	Mono7.25Gyx6	80% balloon	105% any TUR	Rectal wall 80-85%
			110% mono	

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GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update



Peter J. Hoskin<sup>a,\*,1</sup>, Alessandro Colombo<sup>b,1</sup>, Ann Henry<sup>c,1</sup>, Peter Niehoff<sup>d,1</sup>, Taran Paulsen Hellebust<sup>e,1</sup>,

Radiotherapy and Oncology 107 (2013) 325-332

#### EBRT SCHEDULES

- 45 Gy in 25 fractions over 5 weeks.
- 46 Gy in 23 fractions over 4.5 weeks.
- 35.7 Gy in 13 fractions over 2.5 weeks.
- 37.5.Gy in 15 fractions over 3 weeks.

#### HDR BOOST

#### HDR MONOTHERAPY

- 15 Gy in 3 fractions.
- 11-22 Gy in 2 fractions.
- 12–15 Gy in 1 fraction.

34 Gy in 4 fractions.36–38 Gy in 4 fractions.31.5 Gy in 3 fractions.26 Gy in 2 fractions.

GEC/ESTRO recommendations on high dose rate afterloading brachytherapy for localised prostate cancer: An update



Peter J. Hoskin<sup>a,\*,1</sup>, Alessandro Colombo<sup>b,1</sup>, Ann Henry<sup>c,1</sup>, Peter Niehoff<sup>d,1</sup>, Taran Paulsen Hellebust<sup>e,1</sup>,

Radiotherapy and Oncology 107 (2013) 325-332

### OAR CONSTRAINTS

- Rectum: D2 cc  $\leq$  75 Gy EQD<sub>2</sub>
- Urethra:
  - o D0.1 cc =  $\leq 120$  Gy EQD<sub>2</sub>
  - $o \quad D10 \leqslant 120 \text{ Gy EQD}_2$
  - $o \quad D30 \leqslant 105 \; Gy \; EQD_2$

### **RECURRENT PROSTATE**

36 Gy in 6 fractions [44]. 21 Gy in 3 fractions [45]. 30 Gy in 2 fractions to peripheral zone after 30–40 Gy external beam [46].



### ACR Appropriateness Criteria high-dose-rate brachytherapy for prostate cancer

I-Chow Joe Hsu<sup>1,\*</sup>, Yoshiya Yamada<sup>2</sup>, Dean G. Assimos<sup>3</sup>, Anthony V. D'Amico<sup>4</sup>,

I.-C.J. Hsu et al. / Brachytherapy 13 (2014) 27-31

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Table 1Sixty-year-old man, stage T3b, Gleason score 7, adenocarcinoma

Treatment	Rating	Comments
EBRT 45 Gy + HDR brachytherapy $5.5-6.5$ Gy $\times 3$	7	
EBRT 45 Gy + HDR brachytherapy $8-11.5$ Gy $\times 2$	8	The panel felt the 2-fraction regimen has the best supporting evidence for this patient, who has a history of TURP and SV invasion.
EBRT 45 Gy + HDR brachytherapy $13-15$ Gy $\times 1$	5	

Table 2 Fifty-year-old man, stage T1c, Gleason score 3/3, adenocarcinoma

Treatment	Rating	Comments
HDR monotherapy 9.5 Gy $\times$ 4	7	Although there is a trend toward more hypofractionated monotherapy regimens, the panel felt the more fractionated regimens have a longer followup and stronger evidence for routine use.
HDR monotherapy 10.5 Gy $\times$ 3	5	
HDR monotherapy 13.5 Gy $\times$ 2	5	
HDR monotherapy 19 Gy $\times$ 1	3	



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

Yoshiya Yamada<sup>1,\*</sup>, Leland Rogers<sup>2</sup>, D. Jeffrey Demanes<sup>3</sup>, Gerard Morton<sup>4</sup>

Brachytherapy 11 (2012) 20-32

**RESULTS:** Despite a wide variation in doses and fractionation reported, HDR brachytherapy provides biochemical control rates of 85–100%, 81–100%, and 43–93% for low-, intermediate-, and high-risk prostate cancers, respectively. Severe toxicity is rare, with most authors reporting less than 5% Grade 3 or higher toxicity. Careful attention to patient evaluation for appropriate patient selec-

**CONCLUSION:** The clinical outcomes for HDR are excellent, with high rates of biochemical control, even for high-risk disease, with low morbidity. HDR monotherapy, both for primary treatment and salvage, are promising treatment modalities. © 2012 American Brachytherapy Society.



# BRACHYTHERAPY DOSE

## Monotherapy

- LDR
  - I-125 145Gy
  - Pd-103- 125Gy
  - Cs-131- 115Gy

## Monotherapy

HDR
Ir-192
13.5Gy x 2
9.5Gy BID x2



## **BRACHYTHERAPY DOSE**

### BOOST

### • LDR

- I-125 –100-115 Gy
- Pd-103- 90-100 Gy
- Cs131-85 Gy

### BOOST

- HDR
  - Ir-192
    - 15Gy x 1
    - 10-11Gy x2



# **Personal Practice**

- HDR 11.5Gy x 2 fractions
- EBRT 50 Gy /1.8 2.0 Gy / FRACTION
- Max. urethral dose </= 120% MPD
- MPD allowed to indent few mm anteriorly but still covered by 80% isodose
- Higher doses to posterolateral portions (anatomic rationale) 150-200%
- Rectal dose </= 75%

## RESULTS

#### Long-term outcomes of high-dose-rate brachytherapy for intermediate- and high-risk prostate cancer with a median follow-up of 10 years

John W. Yaxley<sup>\*,†</sup>, Kevin Lah<sup>†,‡</sup>, Julian P. Yaxley<sup>§</sup>, Robert A. Gardiner<sup>†,¶</sup>, Hema Samaratunga<sup>\*\*</sup> and James MacKean<sup>\*</sup>

BJU Int 2017; 120: 56-60

bNED	INTERMEDIAT	E RISK	HIGH RISK	
5 YEARS	93.3		74.3	
10 YEARS	86.9		56.1	
URETHRAL STRICTURE	4.2 %			
10yr actuarial cancer speci	fic survival	90.8 %		
Actuarial overall survival ra	ate	86.7 %		

Author	Number of patients	Free biochemical reccurence (%)	Cause specific survival (%)	Local control (%)	Years after diagnosis
Demanes et al. [63]	298	94	100	100	5
Ghilezan et al. [64]	95	98	100	100	5
Grills et al. [65]	65	98	_	_	3
Mark et al. [66]	206	89	_	_	5
Rogers et al. [67]	328	96 low risk 89 intermediate risk	100	—	3
Yoshioka et al. [68]	111	100 low risk 89 intermediate risk	—	100	3

TABLE 5: Clinical results after HDR brachytherapy alone for patients with low- and intermediate-risk prostate cancer.

Advances in Urology Volume 2009, Article ID 327945, 11 pages

Group	No. of Pts	T-Stage (%)	PSA	Median Follow-up (months)	Biochemical Control (%)	Failure Definition	OS (%)
William Beaumont Hospital <sup>2</sup>	207	T1c-T3c	11.5 (Mean)	52.8	74	ASTRO Consensus Panel	91.6
Seattle Prostate Institute <sup>28</sup>	104	T1b-T3c	12.9 (Mean)	45	85	3 rises	NS
Kiel, Germany <sup>32</sup>	144	T1b-T2a (20) T2b-T3 (80)	25.6 (Mean)	96	74	3 rises all >1 ng/mL	71.5
California Endocurietherapy Cancer Center <sup>29</sup>	110	T1b-T3c	NS	36	85	>1.5 ng/ mL	NS
Goteburg, Sweden <sup>27</sup>	50	T1-T2 (74) T3 (26)	NS	45	78 T1 100	>1.0 ng/ mL	96
Berlin, Germany <sup>30</sup>	230	T2 (34.8) T3 (58.3)	12.8 (median)	40	T2 75 T3 60	ASTRO Consensus Panel	93 at 5 yr
Munich, Germany <sup>24</sup>	40	T2 (45) T3 (42.5)	40.7	74	79.5	Local Control	87.5
Lahey Clinic <sup>25</sup>	61	T1-T2 T1c (14)	10.4 (mean)	11.8	92.2	3 rises	98
Long Beach Memorial Medical Center <sup>23</sup>	200	T2a (32.5) T2b (32) T3a-b (21.5)	10	24	97	ASTRO Consensus Panel	97

Table 3. Published Studies on the Use of High-Dose Rate Brachytherapy in Locally Advanced Prostate Cancer–Patient Characteristics/Outcome

Seminars in Radiation Oncology, Vol 13, No 2 (April), 2003: pp 98-108

# TROG 03.04 RADAR Trial

David Joseph, Int J Radiation Oncol Biol Phys, Vol. 106, No. 4, pp. 693–702, 2020

High Risk – Brachytherapy Boost



HDR Brachy + AS – superior

HDR boost superior to dose escalation by EBRT

## Reirradiation

A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER)

EUROPEAN UROLOGY 80 (2021) 280-292

Modality	5y RFS	GU toxicity	GI toxicity
RP	53%	21%	1.5%
Cryo	57%	15%	0.9%
HIFU	46%	23%	0.8%
SBRT	56%	5.6%	0.0%
HDR	58%	9.6%	0.0%
LDR	53%	9.1%	2.1%

 Five-year RFS was similar across modalities on meta-regression, although differences in severe GU and GI toxicity appear to favor reirradiation, particularly HDR brachytherapy.



EUROPEAN UROLOGY 80 (2021) 280-292

# **Toxicity - Acute Symptoms**

- Dysuria
- Hematuria
- Perineal hematoma (< 3 %)</li>
- Obstruction- Urethral Stricture (5-12%)
- Perineal Pain (< 5%)
- Rectal urgency and frequency (< 10%)

# **Delayed Complications**

- Chronic cystitis (3-7 %)
- Incontinence (1% for non-TURP, 25-42% for TURP)
- Rectal ulceration (< 1 %)</li>
- Urethral necrosis (< 1 %)</li>
- Erectile dysfunction (> 70y/o, 20-25%;< 70y/o, 10-15%)</li>

### Table 1

### HDR monotherapy vs. <sup>103</sup>Pd monotherapy

Toxicities	HDR (%)	<sup>103</sup> Pd (%)	
Acute dysuria (Grades 1-3)	36	67	p <0.001
Acute urinary frequency/urgency	54	92	p < 0.001
Urethral stricture			
Chronic urinary frequency/urgency	32	56	p <0.001
Urethral stricture	8	3	
Three-year impotency rate	16	45	

Most of above toxicities were Grade 1.

No difference in chronic dysuria, incontinence retention, and hematuria.

## Conclusion

- Evidence strongly suggest that prostate BT can be used as definitive treatment or as a boost to external beam radiotherapy
- Associated with
  - excellent local control,
  - Biochemical disease-free survival,
  - excellent post-treatment health-related quality of life
- Mainstream therapeutic option for low- tointermediate risk disease

## THANK YOU



