

## SUPPLEMENTARY MATERIAL

### SUPPLEMENTARY TABLES

Supplementary Table 1. Centre of Evidence-Based Medicine, levels of evidence of therapeutic studies. <http://www.cebm.net>

1A	Systematic review (with homogeneity) of RCTs
1B	Individual RCT (with narrow confidence intervals)
1C	All or none study
2A	Systematic review (with homogeneity) of cohort studies
2B	Individual Cohort study (including low quality RCT, e.g. <80% follow-up)
2C	“Outcomes” research; Ecological studies
3A	Systematic review (with homogeneity) of case-control studies
3B	Individual Case-control study
4	Case series and poor quality cohort and case-control study
5	Expert opinion without explicit critical appraisal or based on physiology bench research or “first principles”

Supplementary Table 2. NCCN Categories of evidence.

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1	Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2A	Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
2B	Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
3	Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

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Note: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Supplementary Table 3. EBRT for prostate cancer: treatment characteristics and outcomes

Study / location	Author, years of articles	Ref(s)	Era/Trial evaluating	RT type	n	total dose (Gy)	total fractions	Gy/fraction	FFBF def.	Risk group n			5-year FFBF (%)			5-year patient outcomes (%)			RTOG late Grade 3-4 toxicity		
										L	I	H	L	I	H	OS	CSM	DM	GU	GI	
MDACC	Kuban, 2008	7	CFRT escalation	3D	151	78	39	2	P	30	68	53	100	86	69	90	71	1	5.5	6.6	
				3D	150	70	35	2	P	31	71	48	88	83	54	83	76	5	7.1	1.3	
Dutch CKVO 96-10	Al-Mamgani, 2008	8	CFRT escalation	3D	333	78	39	2	P	63	90	180	N/A	70	N/A	82	80	4	13	6	
				3D	331	68	34	2	P	56	89	185	N/A	60	N/A	83	77	3	12	4	
PROG 9509	Zietman, 2010	9	CFRT escalation	3D	195	79	44	1.8	P	116	72	7	95	79	N/A	96	83	N/A	1.5	1	
				3D	197	70	39	1.8	P	111	76	10	75	68	N/A	97	78	N/A	2	0	
MRC RT01	Dearnaley, 2007	10	CFRT escalation	3D	422	74	37	2	P	99	127	184	71	71	N/A	88	N/A	7	4	10	
				3D	421	64	32	2	P	95	137	175	60	60	N/A	89	N/A	9	2	6	
RTOG 9406	Michalski, 2010, 2012	11 12	CFRT escalation	3D	108	68	38	1.8	P	55	37	69	68	70	42	90	70	N/A	2	2	
				3D	300	74	41	1.8	P	91	75	39	73	62	62	87	66	N/A	3	0	
				3D	167	79	44	1.8	P	85	54	36	67	70	70	88	76	N/A	4	2	
				3D	256	74	37	2	P	92	109	40	84	74	54	89	70	N/A	4.5	2.5	
				3D	220	78	39	2	P	80	109	32	80	69	67	88	69	N/A	5.5	5.5	
GETUG	Beckendorf, 2011	13	CFRT escalation	3D	153	70	35	2	P	-	153	-	-	68	-	92	N/A	1.9	2.6	1.9	
				3D	153	80	40	2	P	-	153	-	-	74	-	92	N/A	5.2	1.9	5.9	
RTOG 0126	Michalski, 2014	14	CFRT escalation; 3D-(CRT vs. IMRT subset)	3D+ IMRT	748	79	44	1.8	P	-	748	-	-	75	-	88	67	2	N/A	N/A	
				3D+ IMRT	751	70	39	1.8	P	-	751	-	-	60	-	89	66	3	N/A	N/A	
				3D	(491)	N/A	N/A	N/A	P	30	68	53	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.9	5.1
				IMRT	(257)	N/A	N/A	N/A	P	31	71	48	N/A	N/A	N/A	N/A	N/A	N/A	N/A	0.9	2.6
NCI Canada	Lukka, 2005	15	CFRT vs HFRT	3D	470	66	33	2	A	-	470	-	N/A	53	N/A	85	4	N/A	2.6	1.9	
				3D	466	52	20	2.63	A	-	466	-	N/A	60	N/A	88	3	N/A	4.1	1.9	
Australia	Yeoh, 2011	16	CFRT vs HFRT	3D	109	64	32	2	P	-	109	-	N/A	58	N/A	84	3	N/A	NR	NR	
				3D	108	55	20	2.75	P	-	108	-	N/A	69	N/A	86	1	N/A	NR	NR	
Italy	Arcangeli, 2012	17	CFRT vs HFRT	3D	85	80	40	2	P	-	-	85	N/A	N/A	79	82	8	10	0	0	
				3D	83	62	20	3.1	P	-	-	83	N/A	N/A	85	92	2	14	0	0	
FCCC	Pollack, 2013	18	CFRT vs HFRT	IMRT	152	76	38	2	P	-	101	51	N/A	86	86	90	2	4	3.3	2	
				IMRT	151	70	26	2.7	P	-	98	53	N/A	86	86	88	2	11	4	2	
MDACC	Kuban, 2010	19	CFRT vs HFRT	IMRT	102	76	42	1.8	P	30	1	1	96	96	N/A	N/A	N/A	N/A	0.9	1	
				IMRT	102	72	30	2.4	P	30	1	1	97	97	N/A	N/A	N/A	N/A	0	3	
21 <sup>st</sup> Century Oncology	Mantz, 2014	20	SBRT	Gantry	102	40	5	8.0	P	40	-	-	100	N/A	N/A	N/A	N/A	N/A	NR	NR	
Winthrop University	Katz, 2010, 2011	21, 22	SBRT	RA	304	35	5	7.0	P	211	81	12	99	93	75	N/A	N/A	N/A	1.7	0	
Genesis Healthcare	Fuller, 2014	23	SBRT	RA	60	38	4	9.5	P	40	39	-	100	92	N/A	N/A	N/A	N/A	6	0	

**Abbreviations:** 3D-CRT: 3 dimensional conformal radiation therapy; CFRT: conventionally fractionated radiotherapy; CSM: cancer specific mortality; DM: distant metastasis; FCCC: Fox Chase Cancer Center; FFBF: freedom from biochemical failure; FU: follow-up; GETUG: French Groupe d' Étude des Tumeurs Uro-Génitales; GI: gastrointestinal; GU: genitourinary; H: high risk; HFRT: hypofractionated radiotherapy; I: intermediate risk; IMRT: intensity modulated radiation therapy; L: low risk; MDACC: MD Anderson Cancer Center; MRC: Medical Research Council; N/A not applicable; NCI: National Cancer Institute; OS: overall survival; PROG: Proton Radiation Oncology Group; RTOG: Radiation Therapy Oncology Group

**Note:** Studies are sorted by the RT fractionation scheme being tested. All studies evaluating CFRT escalation and CFRT vs. HFRT are phase II/III; those evaluating SBRT are controlled trials. The 5-year outcomes are rounded to nearest whole digit. The definition of FFBF (Phoenix, P; or ASTRO A) is listed.

Supplementary Table 4. BT boost and BT monotherapy for prostate cancer: outcomes and toxicity of prospective studies

Study	Ref.	Type	arms	n	Total BT dose (Gy)	Gy/fraction	Total EBRT dose (Gy)	median FU (y)	Actuarial FU (v)	FFBF def.	FFBF %			RTOG late Grade 3-4 toxicity %	
											L	I	H	GU (stricture)	GI
Demanes, 2005	<sup>24</sup>	Prospective	HDR-BT + EBRT	209	23	6	36	7.3	7.3	P	90	87	69	7.7 (6.7)	0
Hoskin, 2012	<sup>25</sup>	Phase III	EBRT	108	N/A	N/A	55	7.1	10	P	60	62	70	4 (2)	2
			HDR-BT + EBRT	110	17	8	36	7.1	10	P	100	89	80	11 (8)	0
Duchesne, 2007	<sup>26</sup>	Phase I/II	HDR-BT + EBRT	108	16-20	4-5	46	6.5	5	P	NR	NR	NR	4.5 (NR)	2.8
Demanes, 2009	<sup>27</sup>	Prospective	HDR-BT + EBRT	200	23	6	36	6.4	10	P	92	87	63	0 (0)	0
			HDR-BT + EBRT ADT	211	23	6	36	6.4	10	P	92	87	63	0 (0)	0
Galalae, 2006	<sup>28</sup>	Phase II	HDR-BT + EBRT	122	18	6	46-50	4.5	5	A	N/A	90	N/A	NR	NR
				25	18	6	46-50	5.5	5	A	N/A	N/A	68	NR	NR
				95	21	10	46-50	5.5	5	A	N/A	N/A	85	NR	NR
				23	18	6	46-50	6.5	5	A	N/A	N/A	N/A	NR	NR
				57	21	10	46-50	6.5	5	A	N/A	N/A	N/A	NR	NR
Hurwitz, 2011	<sup>30</sup>	Phase II	LDR-BT + EBRT + ADT	61	145	N/A	N/A	6.1		P	N/A	85	N/A	NR	NR
Kalkner, 2007	<sup>29</sup>	Phase I/II	HDR-BT + EBRT	154	20	10	50	6.1	5	P	97	83	83	5 (NR)	1
Lawton, 2007	<sup>31</sup>	Phase II	LDR-BT	101	145	N/A	None	5.3	5	P	94	N/A	N/A	NR	NR
Tang, 2006	<sup>32</sup>	Phase I/II	HDR-BT + EBRT	47	16	4	46	5	5	P	76	68	33	NR	NR
			HDR-BT + EBRT	41	20	5	46	5	5	P				NR	NR
			EBRT	104	N/A	N/A	66	4.7	5	A				NR	71
Galalae, 2004	<sup>33</sup>	Phase II	HDR-BT + EBRT	46	16-30	6-12	45.6-50	5	5	A	96	N/A	N/A	NR	NR
				188	16-30	6-12	45.6-50	5	5	A	N/A	88	N/A	NR	NR
				359	16-30	6-12	45.6-50	5	5	A	N/A	N/A	69	NR	NR
Demanes, 2011	<sup>34</sup>	Prospective	HDR-BT	157	42	7	None	5.2	8	P	97	97	N/A	NR	NR
			HDR-BT	141	38	9.5	None				P	97	97	N/A	NR

Abbreviations: ADT: androgen deprivation therapy; EBRT: external beam radiation therapy; FFBF: freedom from biochemical failure; FU: follow-up; GI: gastrointestinal; GU: genitourinary; H: high-risk; HDR-BTb: high dose rate brachytherapy boost; I: intermediate risk; L: low risk; N/A: not applicable; NR: not reported; RTOG: Radiation Therapy Oncology Group;

Note: Gy rounded to whole numbers. Studies sorted by longest median FU time.









## **SUPPLEMENTARY MATERIAL - FIGURES**

### **Sup Figure 1.**

Title: Characteristic PSA curves after treatment.

Legend: Different RT modalities have different trends in post-treatment PSA. The Phoenix definition (i.e. nadir + 2 ng/mL -- circled on the right) following treatment is preferred in defining BF. EBRT typically induces a slow and inconsistent decrease in PSA to levels that are typically still detectable. After EBRT, PSA may still be detectable. After LDR-BT, PSA has been noted to decrease to < 0.3 ng/mL in most men with localized disease. After HDR-BT, there is typically a very low PSA nadir (e.g. < 0.05 ng/mL). All RT modalities may induce a PSA bounce (i.e. a temporary elevation in PSA without disease recurrence -- circled on the left). For EBRT, this occurs within 3 years after RT; bounces will normalize within about one year. It is important to understand that PSA bounces after RT are common and do not automatically represent cancer recurrence.

Abbreviations: BT: brachytherapy; EBRT: external beam radiation therapy; HDR: high dose rate; LDR: low dose rate; PSA: prostate specific antigen; RT: radiation therapy

### **Sup Figure 2.**

Title: Timeline of RT evolution.

Legend: The timeline for the development of EBRT and BT for prostate cancer. The shift from 3D conformal radiation therapy to IMRT (with MLCs) during the 1990s, theoretical radiobiological models from 2001 (which support the use of high doses per fraction, such as those in HFRT, SBRT, and HDR-BT), development of HDR-BT (to use in place of LDR-BT) in the 1980s, and advances in image guided radiation therapy (IGRT) for EBRT since the 1980s

have influenced the evolution of RT modalities, including HFRT, SBRT, HDR-BT, and particle beam therapy (e.g. protons).

Abbreviations: BT: brachytherapy; CFRT: conventionally fractionated radiation therapy; EBRT: external beam radiation therapy; HDR: high dose rate; HFRT: hypofractionated radiation therapy; IGRT: image guided radiation therapy; LDR: low dose rate; IMPT: intensity modulated proton therapy; MLC: multi leaf collimator; PSA: prostate specific antigen; RALS: remote afterloading system; RT: radiation therapy; SBRT: stereotactic body radiation therapy;