Emerging Trends and Future Directions in Prostate SBRT

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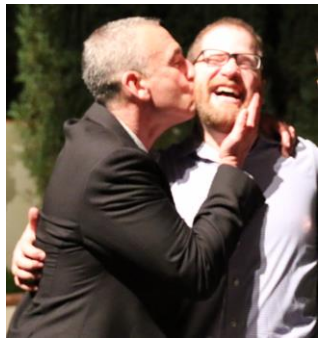
Chief Medical and Marketing Officer, Accuray, Inc.

Acknowledgment

Disclosures

- Financial:
  - Chief Medical and Marketing Officer, Accuray Inc.

- Other: Don’t ask don’t tell (and don’t ask Dr. Haas)



Early adopters

2014 Winthrop Hospital Prostate SBRT Team!

JOURNAL OF CLINICAL ONCOLOGY ORIGINAL REPORT

Stereotactic Body Radiation Therapy Versus Intensity-Modulated Radiation Therapy for Prostate Cancer: Comparison of Toxicity

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, Arnold L. Potosky, and Cary P. Gross

See accompanying editorial doi: 10.1200/JCO.2014.55.2380

James B. Yu, Laura D. Cramer, Jeph Herrin, Pamela R. Soulos, and Cary P. Gross, Yale School of Medicine; James B. Yu and Cary P. Gross, Yale Cancer Center, New Haven, CT; Jeph Herrin, Health Research and Educational Trust, Chicago, IL; and Arnold L. Potosky, Georgetown University School of Medicine, Washington, DC.

Published online ahead of print at www.jco.org on March 10, 2014.

Supported by Grant No. R01CA149045 from the National Cancer Institute, National Institutes of Health (NIH), by Clinical and Translational Science Award Program Grant No. KL2 RR024138 from the National Center for Advancing Translational Science (J.B.Y.), and by the NIH Roadmap for Medical Research.

The study sponsor (National Institutes of Health) did not play a role in the design of the study; the collection, analysis, or interpretation of the data; the writing of the manuscript; or the decision to submit the manuscript for publication. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Terms in blue are defined in the glossary, found at the end of this article.

ABSTRACT

Purpose
Stereotactic body radiation therapy (SBRT) is a technically demanding prostate cancer treatment that may be less expensive than intensity-modulated radiation therapy (IMRT). Because SBRT may deliver a greater biologic dose of radiation than IMRT, toxicity could be increased. Studies comparing treatment cost to the Medicare program and toxicity are needed.

Methods
We performed a retrospective study by using a national sample of Medicare beneficiaries age ≥ 66 years who received SBRT or IMRT as primary treatment for prostate cancer from 2008 to 2011. Each SBRT patient was matched to two IMRT patients with similar follow-up (6, 12, or 24 months). We calculated the cost of radiation therapy treatment to the Medicare program and toxicity as measured by Medicare claims; we used a random effects model to compare genitourinary (GU), GI, and other toxicity between matched patients.

Results
The study sample consisted of 1,335 SBRT patients matched to 2,670 IMRT patients. The mean treatment cost was $13,645 for SBRT versus $21,023 for IMRT. In the 6 months after treatment initiation, 15.6% of SBRT versus 12.6% of IMRT patients experienced GU toxicity (odds ratio [OR], 1.29; 95% CI, 1.05 to 1.53; $P = .009$). At 24 months after treatment initiation, 43.9% of SBRT versus 36.3% of IMRT patients had GU toxicity (OR, 1.38; 95% CI, 1.12 to 1.63; $P = .001$). The increase in GU toxicity was due to claims indicative of urethritis, urinary incontinence, and/or obstruction.

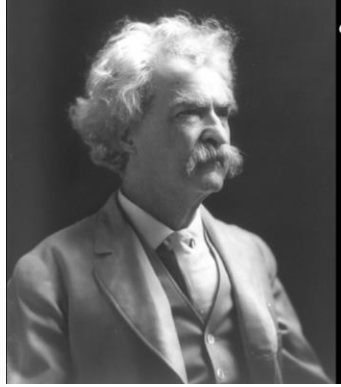
Conclusion
Although SBRT was associated with lower treatment costs, there appears to be a greater rate of GU toxicity for patients undergoing SBRT compared with IMRT, and prospective correlation with randomized trials is needed.

J Clin Oncol 32.

Yu JB, et al., J Clin Oncol. 2014 Apr 20;32(12):1195-201

Forbes

November, 2014



Prostate Cancer Advertising: Lies And The Damn Lies (Part 1)

Benjamin Davies Contributor ⓘ
Pharma & Healthcare
I cover urologic cancer & biotechnology.

The Sunday New York Times Magazine and The New Yorker are my two primary sources of (liberal) enlightened news. Unfortunately, last weekend both magazines had questionable prostate cancer advertising. This is my first of several columns to take apart some of the worst offenders I have seen over the years.

I have a rating system for prostate cancer advertisements based on two self-evident tenets. First, cancer advertising should be scrupulously true and evidence based. Second, cancer patients are uniquely vulnerable to "hopeful" advertising (or "hopeium") since often they face devastating odds of survival. We should all - collectively - shun advertisers that take advantage of these patients. I

Winthrop's Response To Criticism Of Prostate Cancer Advertising

Benjamin Davies Contributor ⓘ
Pharma & Healthcare
I cover urologic cancer & biotechnology.

I promised Winthrop University physicians a chance to respond to my earlier post. I think that is the honest approach. I have included the entire letter below.

Blacksburg Haas Reply

2014 Winthrop Hospital Prostate SBRT Team!

2014 Winthrop Hospital Prostate SBRT Team + SB?

SBRT PSA nadirs

Comparable to HDR, lower than EBRT

Hypofractionated SBRT versus conventionally fractionated EBRT for prostate cancer: comparison of PSA slope and nadir

Anwar *et al. Radiation Oncology* 2014, **9**:42
http://www.ro-journal.com/content/9/1/42

Mekhail Anwar*, Vivian Weinberg, Albert J Chang, I-Chow Hsu, Mack Roach III and Alexander Gottschalk

Matched pts w low-int risk dz @UCSF, CF-EBRT vs. SBRT

UCSF

Table 3 Results (all patients)

		SBRT	CF-EBRT	p-value
	Through year			
PSA Measurements #				
Mean (range)	1	3.9 (2 – 6)	4.1 (3 – 11)	
	2	5.8 (4 – 9)	5.6 (3 – 15)	
	3	7.6 (5 – 11)	7.3 (3 – 21)	
Nadir PSA (ng/mL)				
Median (range)	1	0.70 (0 – 2.5)	1.00 (0 – 8.5)	
	2	0.40 (0 – 1.4)	0.72 (0 – 2.7)	p = 0.0005*
	3	0.24 (0.1 – 1.4)	0.60 (0 – 2.2)	p = 0.002*
Time to Nadir PSA (mos.)				
Median (range)	1	12.0 (2.7 – 15.0)	11.5 (1.2 – 15.0)	
	2	21.0 (2.7 – 26.9)	18.0 (1.2 – 26.9)	
	3	32.3 (2.7 – 41.6)	28.6 (1.0 – 41.1)	p = 0.004^
Rate of PSA change: ng/mL/month				
Median slope (range)	1	−0.09 (−0.88, 0.04)	−0.09 (−0.60, 0.06)	
	2	−0.06 (−0.38, 0.01)	−0.04 (−0.65, 0.05)	p = 0.04*
	3	−0.05 (−0.19, 0.00)	−0.02 (−0.38, 0.04)	p = 0.006*

- Pts w SBRT experienced
  - lower PSA nadir
  - greater rate of decline in PSA 2/3yrs after tx
  - → c/w higher BED

Anwar et al, Radiat Oncol. 2014 Feb 2;9:42.

Original Report

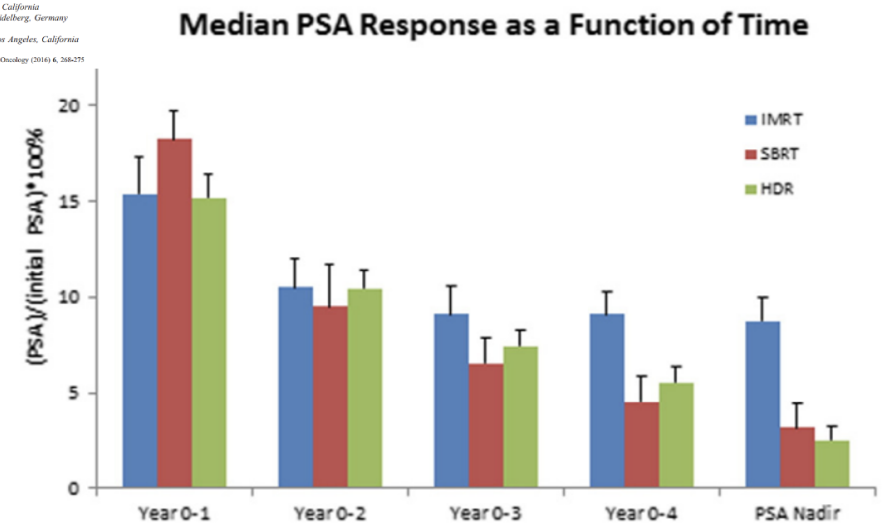
SBRT and HDR brachytherapy produce lower PSA nadirs and different PSA decay patterns than conventionally fractionated IMRT in patients with low- or intermediate-risk prostate cancer

Amar U. Kishan MD [a,*], Pin-Chieh Wang PhD [a], Shrinivasa K. Upadhyaya PhD [b], Henrik Hauswald MD [c], D. Jeffrey Demanes MD [a], Nicholas G. Nickols MD, PhD [a,d], Mitchell Kamrava MD [a], Ahmad Sadeghi MD [e], Patrick A. Kupelian MD [a], Michael L. Steinberg MD [a], Nicolas D. Prionas MD, PhD [d], Mark K. Buyyounouski MD, MS [d], Christopher R. King MD, PhD [a]

[a]Department of Radiation Oncology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California
[b]Department of Biological and Agricultural Engineering, University of California, Davis, Davis, California
[c]Department of Radiation Oncology and Radiation Therapy, Heidelberg University Hospital, Heidelberg, Germany
[d]Department of Radiation Oncology, Stanford University, Stanford, California
[e]Department of Radiation Oncology, Veteran Affairs Greater Los Angeles Healthcare System, Los Angeles, California

Received 1 August 2015; revised 30 October 2015; accepted 5 November 2015 Practical Radiation Oncology (2016) 6, 268-275

UCLA



Kishan et al, Pract Radiat Oncol. 2016 Jul-Aug;6(4):268-75

Like many, we keenly tracked the data

ADVANCES IN STEREOTACTIC RADIOSURGERY:

CLINICAL APPLICATIONS AND OUTCOMES

Overview

An alternative to surgery or conventional radiotherapy, stereotactic radiosurgery--including SRS and SBRT--is considered a standard of care treatment option for diseases involving the brain, spine, prostate, lung, liver, and pancreas. It has transformed the management of both malignant and benign lesions within all segments of the body and across a wide array of disease states. This symposium is designed to provide physicians with an understanding of standard therapeutic applications of stereotactic radiosurgery, as well as to highlight emerging indications and uses for the management of malignant and benign diseases.

Learning Objectives

At the end of this conference, participants should be able to:

- Describe the radiobiologic and physics-related rationale for employing stereotactic radiotherapy, as well as appreciate different modes of delivery
- Analyze candidates for prostate SBRT as well as expected outcomes related to biochemical control and toxicity
- Discuss future directions for the use of SBRT in the management of lung cancer, CNS lesions, breast cancer, gastrointestinal malignancies, and in the oligometastatic setting.

Target Audience

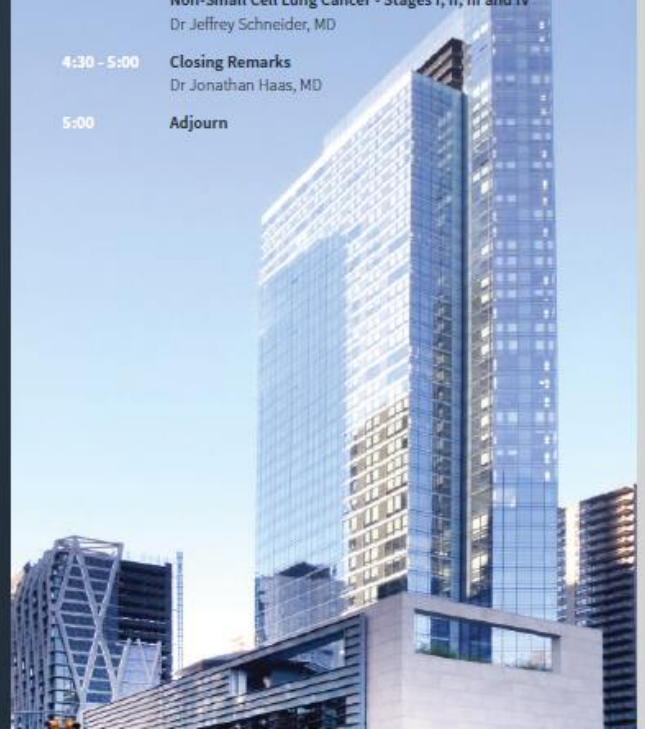
Radiation Oncologists
Urologists
Medical Oncologists
Primary Care Physicians
Medical Physicists
Neurosurgeons
Thoracic Surgeons
Breast Surgeons
General Surgeons
Pulmonologists

Accreditation

Winthrop-University Hospital is accredited with commendation by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians through 3/31/2019. Provider #0006392.

SCHEDULE

12:00 - 12:30	**Registration & Luncheon**
12:30- 12:50	**Welcome & Introduction** Dr Seth Blacksburg, MD
12:50 - 1:20	**Robotic Radiosurgery: Radiobiology & Physics** Dr Matthew Witten, MD
1:20 - 1:40	**Stereotactic Therapy for Benign CNS Conditions** Dr Jeffrey Brown, MD
1:40 - 2:00	**Malignant CNS Disease: SRS Applications** Dr Lee Tessler, MD
2:00 - 2:30	**Coffee Break & Exhibits**
2:30 - 3:00	**SBRT for Prostate Malignancy: The Urologist Perspective** Dr Aaron Katz, MD
3:00 - 3:30	**SBRT for Prostate Malignancy: The Radiation Oncologist Perspective** Dr Jonathan Haas, MD
3:30 - 4:00	**Keynote: Emerging Clinical Applications in Stereotactic Radiosurgery** Dr John Adler, MD
4:00- 4:30	**Stereotactic Body Radiotherapy in the Treatment of Non-Small Cell Lung Cancer - Stages I, II, III and IV** Dr Jeffrey Schneider, MD
4:30 - 5:00	**Closing Remarks** Dr Jonathan Haas, MD
5:00	**Adjourn**



ACTIVITY DIRECTORS

Jonathan Haas, MD
Chief, Division of Radiation Oncology
Winthrop-University Hospital
Associate Professor of Radiation Oncology
Stony Brook University School of Medicine

Seth Blacksburg, MD, MBA
Associate Director
Medical Director, NYCyberknife
Division of Radiation Oncology
Winthrop-University Hospital

KEYNOTE SPEAKER

John Adler, MD
Dorothy and Thye King Chan
Professor In Neurosurgery, Emeritus
Stanford University School of Medicine

Dr. Adler is the inventor of the Cyberknife radiosurgical linear accelerator, an image-guided radiosurgical robotic instrument that noninvasively ablates tumors and lesions throughout the body. In 2007, he was named the Dorothy and Thye King Chan Professor of Neurosurgery at Stanford University's School of Medicine. He was also the school's vice chair for innovation and technology. He is currently an Emeritus Professor of Neurosurgery.

COURSE FACULTY

Jeffrey Brown, MD
Attending Physician
Divisions of Neurosurgery and
Interventional Radiology

Aaron Katz, MD
Chairman
Department of Urology
Winthrop-University Hospital

Jeffrey Schneider, MD
Chief, Medical Oncology & Hematology
Winthrop-University Hospital
Associate Professor of Medicine
Stony Brook University School of Medicine

Matthew Witten, PhD
Chief Physicist
Director of Radiosurgery
Division of Radiation Oncology
Winthrop-University Hospital

Lee Eric Tessler, MD, FAANS, FACS
Executive Director and Co-Surgical Director
Long Island Brain Tumor Center
Assistant Professor, NYU Medical Center

2016

ADVANCES IN SBRT IN THE MANAGEMENT OF PROSTATE CANCER

NYU Winthrop Hospital™

DEPARTMENT OF RADIATION ONCOLOGY

WEDNESDAY, NOVEMBER 1ST, 2017
12PM - 5PM | RIO HOTEL, LAS VEGAS

SCHEDULE

12:00 pm	**Registration & Lunch**
12:30 - 12:35 pm	**Welcome & Introduction** *Moderator, Dr. Jonathan Haas*
12:35 - 12:55 pm	**History and Rationale of SBRT for Prostate Cancer** *Dr. Christopher King*
12:55 - 1:15 pm	**State of Science: Dose Escalation** *Dr. Debra Freeman*
1:15 - 1:30 pm	**5-year Outcomes from a Prospective Multi-Institutional Trial: Homogenous Dose Distribution** *Dr. Robert Meier*
1:30 - 1:45 pm	**HDR-Like Stereotactic Body Therapy for Post-Radiation Therapy Locally Recurrent Prostatic Carcinoma** *Dr. Donald Fuller*
1:45 - 2:00 pm	**Long Term Outcomes and Dose Response** *Dr. Alan Katz*
2:00 - 2:30 pm	**Is Prostate SBRT Proven? Did We Get It Right?** *Panel Discussion*
2:30 - 2:55 pm	**Break**
2:55 - 3:00 pm	**Welcome & Introduction** *Moderator, Dr. Seth Blacksburg*
3:00 - 3:20 pm	**Prostate Cancer Screening and Holistic Approaches in the Management of Prostate Cancer** *Dr. Aaron Katz*
3:20 - 3:40 pm	**Comparing Treatment Options for Prostate Cancer** *Dr. Seth Blacksburg*
3:40 - 4:00 pm	**Incorporating SBRT in the Management of Unfavorable-Intermediate and High Risk Prostate Cancer** *Dr. Michael Zelefsky*
4:00 - 4:20 pm	**Quality of Life & Minimizing Treatment Toxicity for SBRT Prostate Cancer** *Dr. Sean Collins*
4:20 - 4:40 pm	**How to Build a Successful CK Prostate Center** *Dr. Jonathan Haas*
4:40 - 5:00 pm	**What's the Future of Prostate SBRT?** *Panel Discussion*

SPEAKERS


Jonathan Haas, MD
Chair, Department of Radiation Oncology
NYU Winthrop


Seth Blacksburg, MD
Associate Director
Department of Radiation Oncology
Medical Director, NYCyberknife, NYU Winthrop


Christopher King, Ph.D.,M.D.
Chief
Genitourinary Radiation Oncology
UCLA School of Medicine


Aaron Katz, MD
Chair
Department of Urology
NYU Winthrop


Alan Katz, MD
Radiation Oncology
FROS Cyberknife Center


Robert Meier, MD
Radiation Oncology
Swedish Medical Center


Debra Freeman, MD
Radiation Oncology
WellSpring Oncology

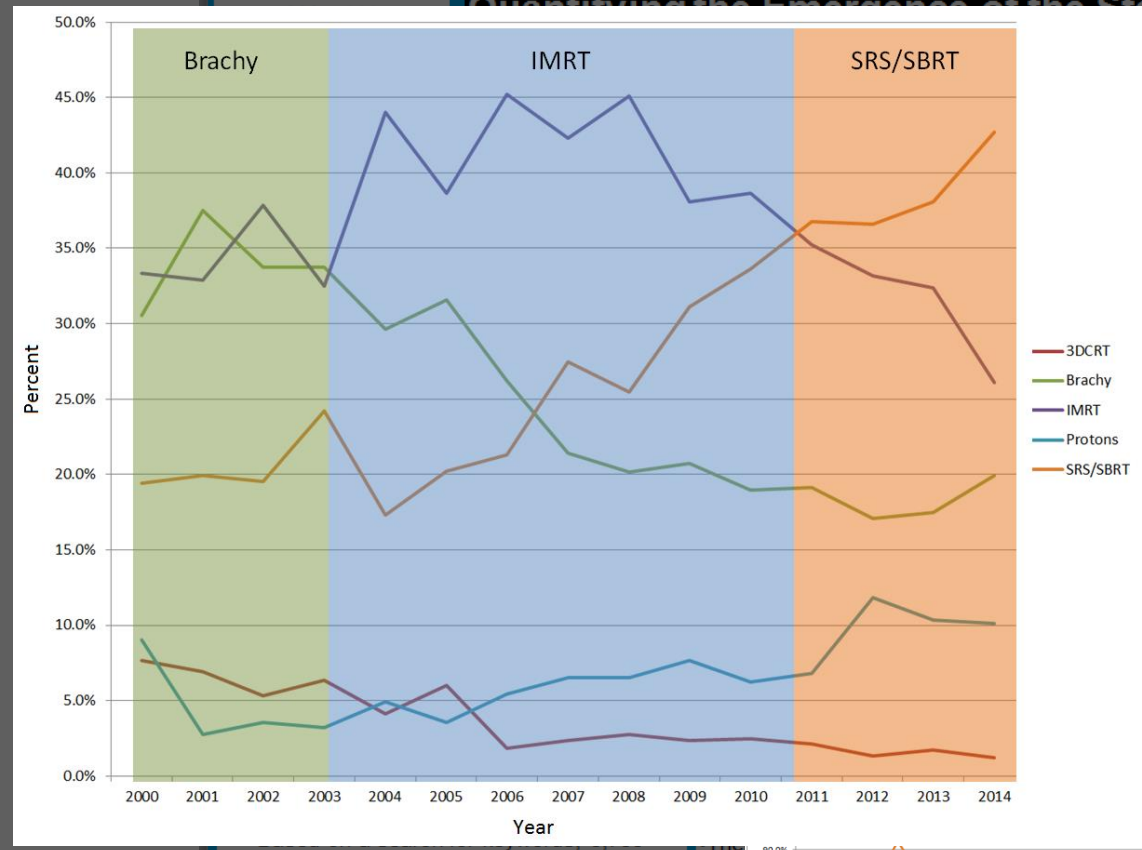

Sean Collins, MD
Director, CyberKnife Prostate Program
MedStar Georgetown University Hospital


Michael Zelefsky, MD
Vice Chair, Department of Radiation Oncology
Memorial Sloan Kettering Cancer Center


Donald Fuller, MD
Radiation Oncology
Scripps Coastal Medical Center


Awais Mirza
Activity Director
NYU Winthrop

2017
RSS



ereotactic Era: A Fifteen
Presentations, 2000-2014

ven Clancey, Ph.D., Allison R. Powers, M.Sc.,

sponding author: sblacksburg@winthrop.org

Figure 2: Abstracts by Treatment Technique

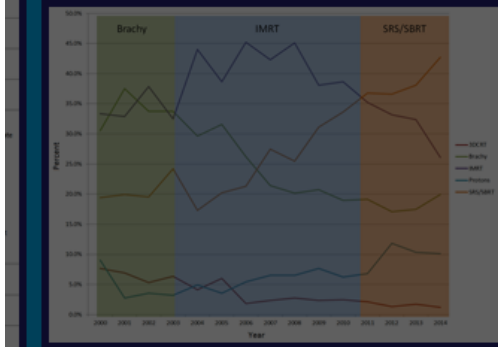


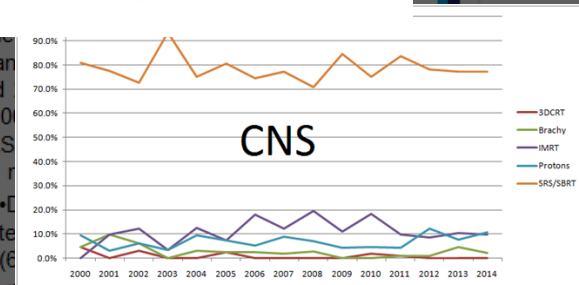
Figure 3: Treatment Technique by Disease

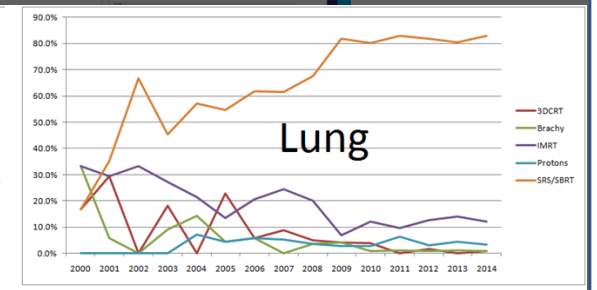
abstracts were also assigned a treatment technique.

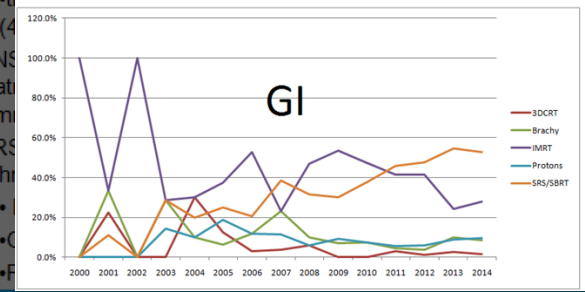
- The median number of authors per abstract was 7 ± 2.7 (range 1, 22).
- The median number of accepted abstracts per year was 1339 (range 522, 2253).
- Fisher's Exact Test and Multinomial Logistic Regression were utilized to characterize trends during this period.

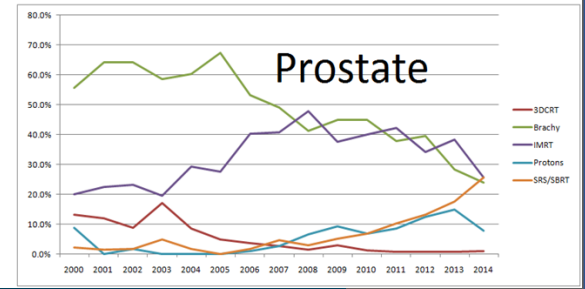
Results:

- The number of accepted abstracts increased during the course of inquiry, with 6,794 from 2000-2007 and 13,082 from 2008-2014.
- There was an increase in presentations related to Gastrointestinal (8.4% vs. 10.7%, p<.0001) and Lung malignancy (9.2% vs. 12.6%, p<.0001) and a decrease in presentations related to Prostate cancer









NYU Winthrop Hospital

DEPARTMENT OF RADIATION ONCOLOGY

ADVANCES IN SBRT IN THE MANAGEMENT OF PROSTATE CANCER

SATELLITE SYMPOSIUM AT THE AMERICAN SOCIETY FOR RADIATION ONCOLOGY (ASTRO) 2018 ANNUAL MEETING

OCTOBER 21, 2018

MARRIOTT RIVERWALK IN ALAMO BALLROOM C
San Antonio, Texas

Accredited by NYU Winthrop Hospital for 2.75 CME Credits

AGENDA

6:15p	**Light Dinner Buffet**
6:30p	**Introduction and Welcome** Jonathan Haas, MD
6:35p	**Rationale and Radiobiology of SBRT: Comparing Treatment Platforms** Jonathan Haas, MD
6:50p	**The History of SBRT for Prostate Cancer: The NYU Winthrop Hospital Experience** Seth Blacksburg, MD, MBA
7:10p	**5-7 Year Outcomes from a Prospective Multi-Institutional Trial: Homogenous Dose Distribution** Robert M. Meier, MD
7:30p	**Challenging Cases Utilizing SBRT for Prostate Cancer: The MSKCC Experience** Michael Zelefsky, MD
7:50p	**Break**
8:00p	**SBRT: The Urologists Perspective** Aaron E. Katz, MD, FACS
8:20p	**SBRT as a Salvage Option for Localized Recurrent Disease** Donald B. Fuller, MD
8:40p	**KEYNOTE ADDRESS** **State of the Science: Dose Escalation in SABR for Prostate Cancer** Robert D. Timmerman, MD
9:00p	**Panel Discussion Q & A** Jonathan Haas, MD and Seth Blacksburg, MD, MBA

FACULTY

Jonathan Haas, MD*
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Michael Zelefsky, MD
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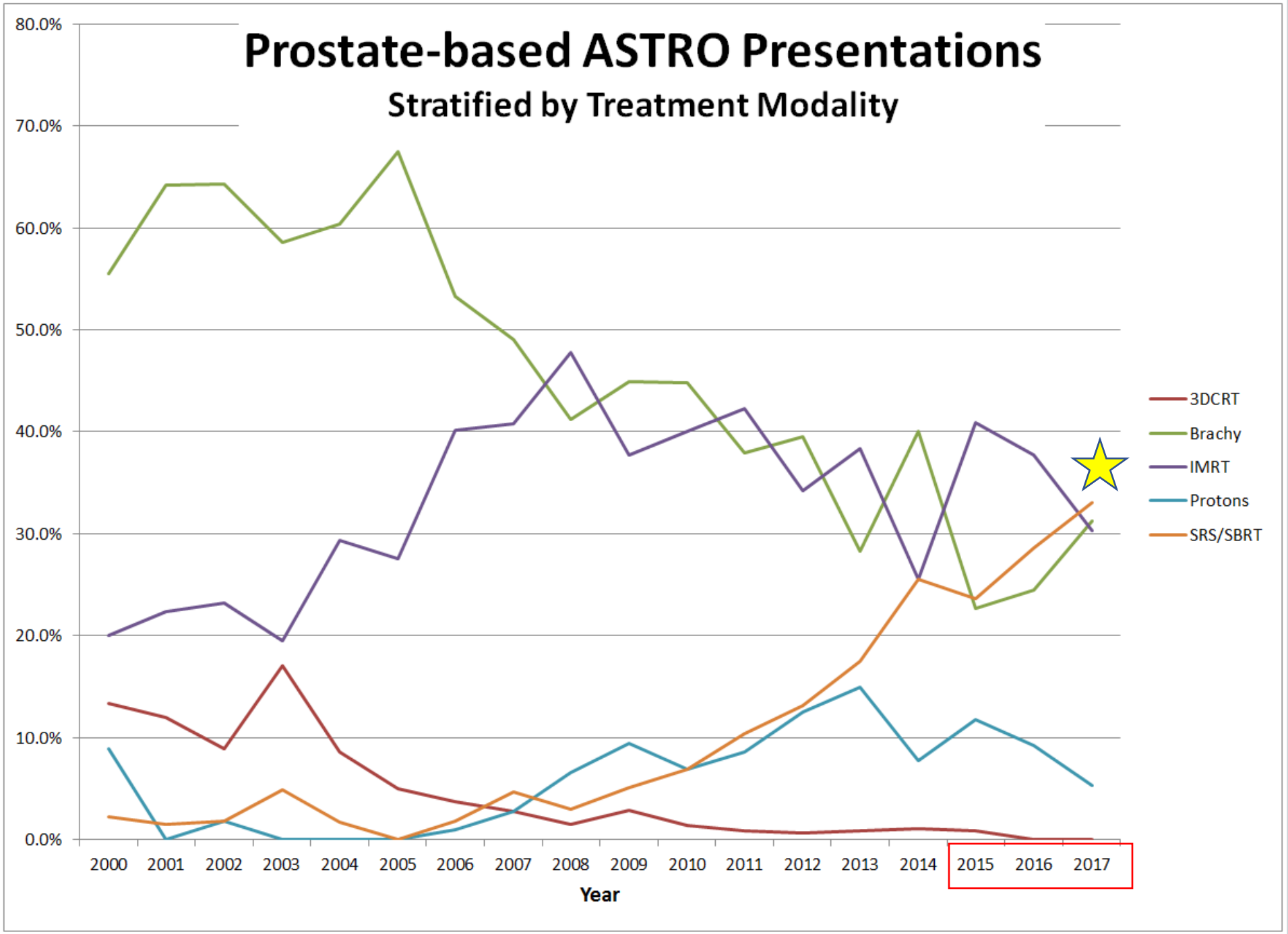
Chief, Brachytherapy Service
Memorial Sloan Kettering Cancer Center
New York, NY

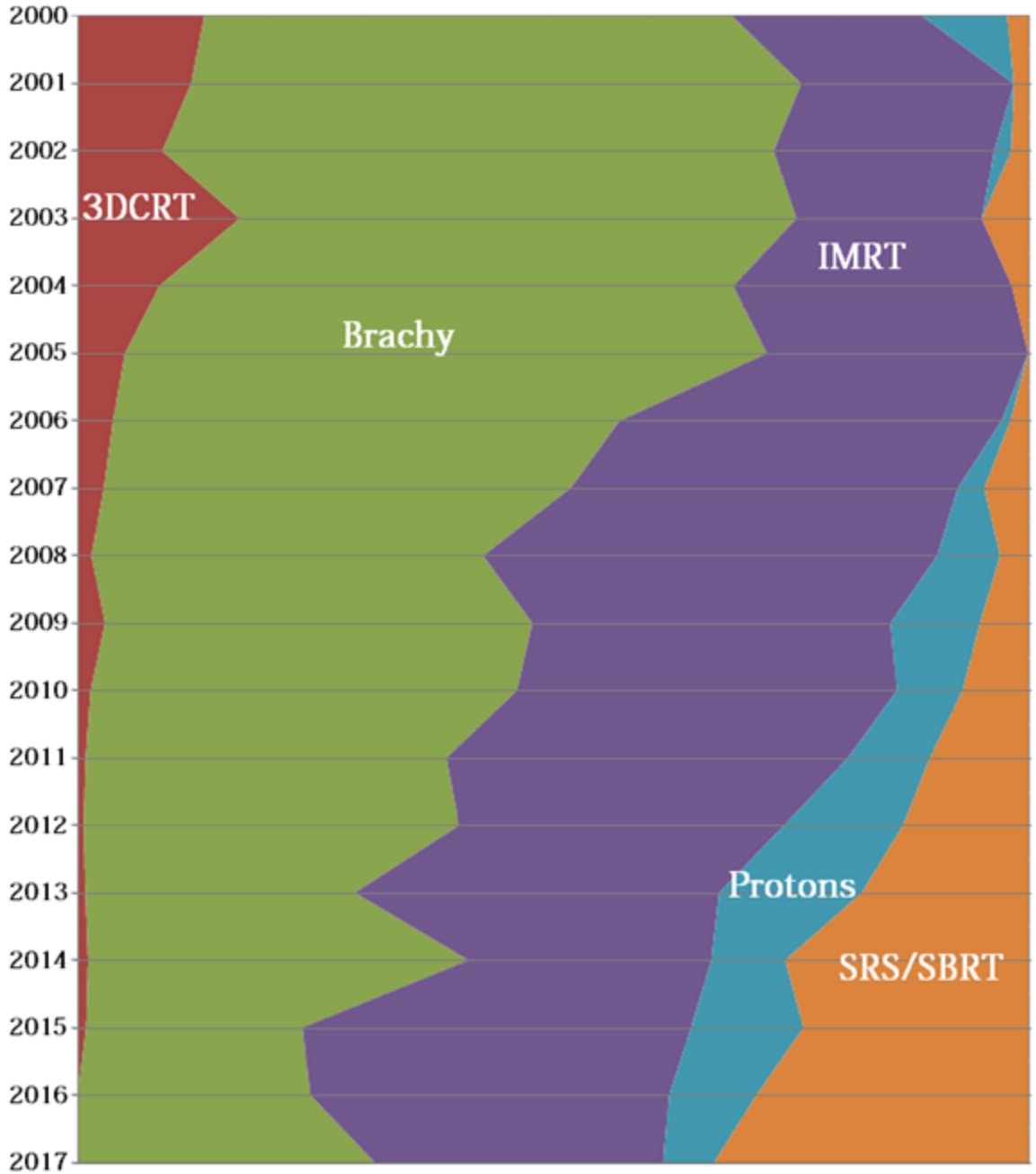
2018 ASTRO, San Antonio



Blacksburg S et al, ASTRO 2019

Histomap of Prostate Modalities Reflected at ASTRO

18year history of Prostate presentations



Blacksburg S et al, ASTRO 2019


HE'S DOING SBRT!

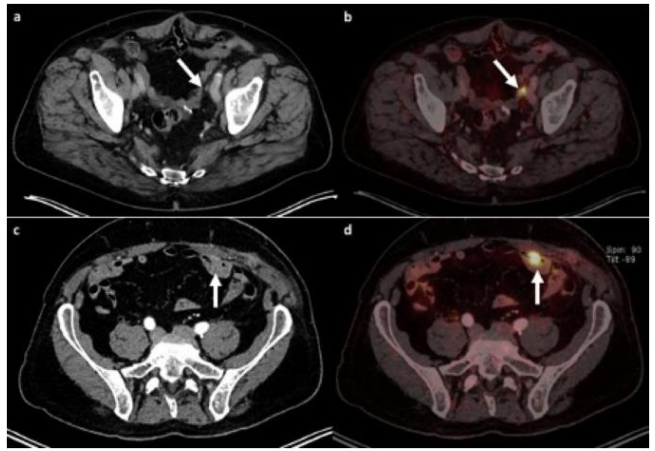
Prostate SBRT – The New Standard

SBRT already established as the standard of care by the NCCN at all stages of prostate cancer from localized, post-operative, and advanced metastatic disease

EBRT Regimen										Post-RT	Advanced Disease: Primary Tumor	Advanced Disease: Metastases
										sRT	mCSPC M0 CRPC mCRPC	MDT
Conventional									☼		☼	
											☼	
Moderate Hypofractionation										☼	☼	☼
									☼	☼	✓	☼
Ultra Hypofractionation (SBRT)										✓	✓	✓
												✓
	6.2–6.4 Gy x 5 fx								☼			
EBRT Boost Techniques												
EBRT with simultaneous integrated boost	See footnote b.		☼	✓	✓	☼	☼		☼	☼	☼	
EBRT with sequential SBRT boost	*Prostate:* 1.8 Gy x 23–28 fx *Boost:* 6 Gy x 3 fx 9.5 Gy x 2 fx			☼	☼	☼						

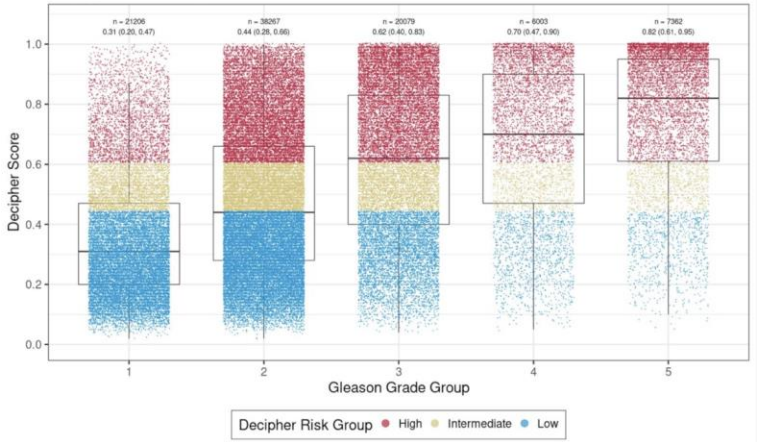
(✓ Preferred; ☼ Acceptable based on clinical and medical need; Regimens shaded gray are not recommended)

The Future is Now…What Next?

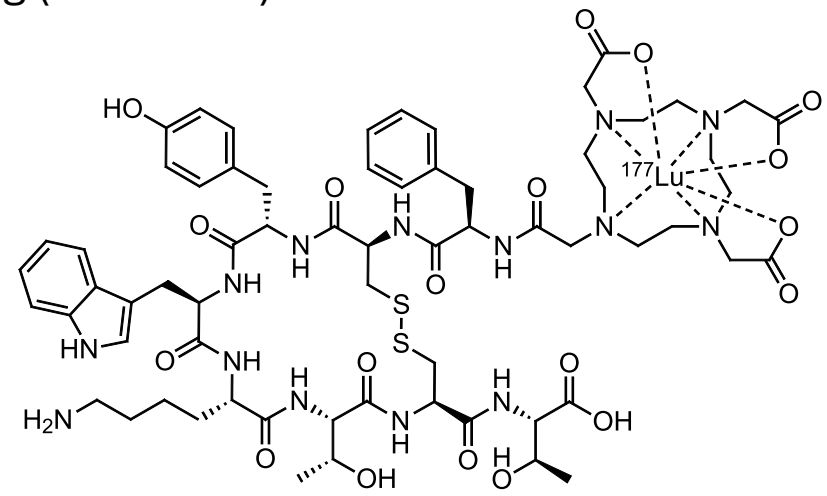


- Imaging (PSMA PET)

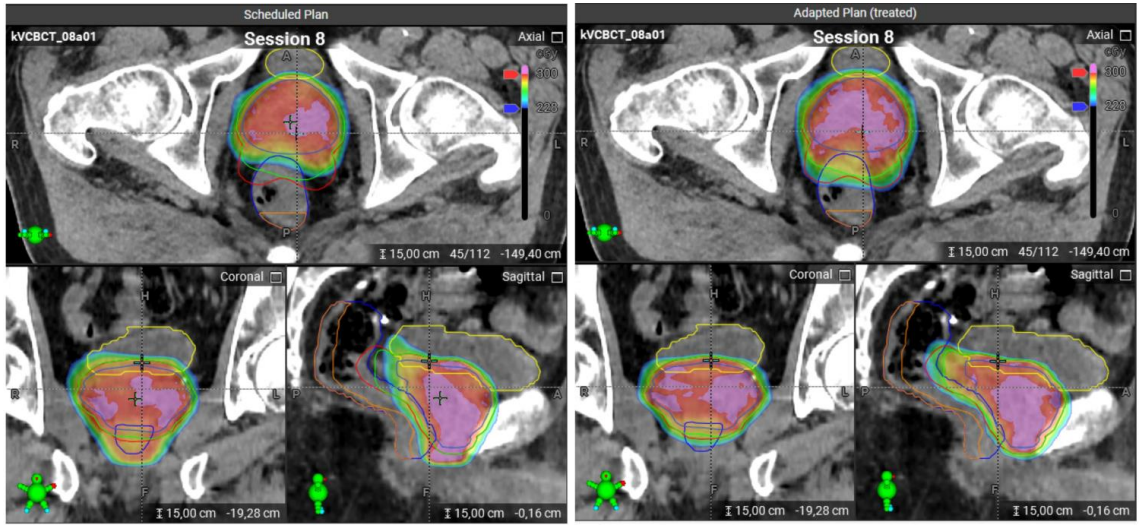
- Biology



- Technology



- Novel Therapeutics (Lutetium-177)



- Adaptive Radiotherapy

Agenda: Emerging Trends, Future Directions

- PSMA PET in staging and treatment planning
  - Novel combinations w radiopharmaceuticals and systemic agents
- Biomarker-driven personalization of SBRT
  - Molecular-Based Imaging Redefining the Disease Landscape
- Focal boosting, adaptive therapy, and ultra-short fractionation
- Oligometastatic Disease

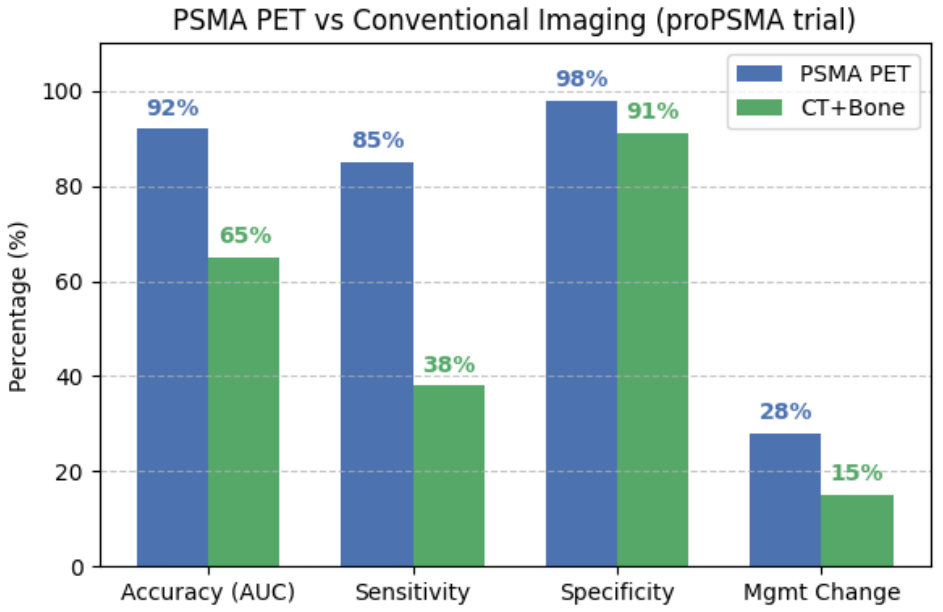
Agenda: Emerging Trends, Future Directions

- PSMA PET in staging and treatment planning
  - Novel combinations w radiopharmaceuticals and systemic agents
- Biomarker-driven personalization of SBRT
  - Molecular-Based Imaging Redefining the Disease Landscape
- Focal boosting, adaptive therapy, and ultra-short fractionation
- Oligometastatic Disease

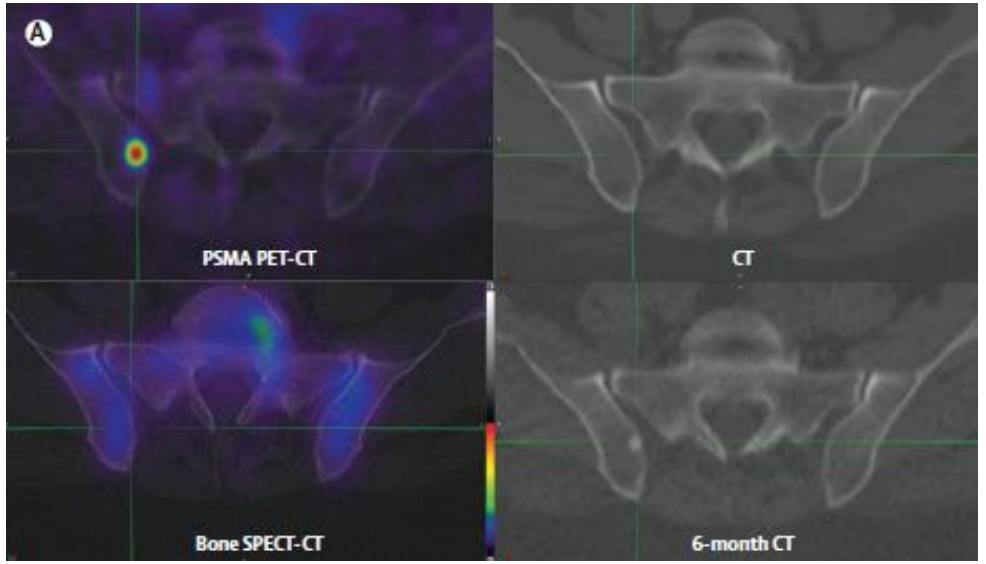
PSMA/PET= Precision Imaging

Prostate-specific membrane antigen PET-CT in patients with high-risk prostate cancer before curative-intent surgery or radiotherapy (proPSMA): a prospective, randomised, multicentre study

*Michael S Hofman, Nathan Lawrentschuk, Roslyn J Francis, Colin Tang, Ian Vela, Paul Thomas, Natalie Rutherford, Jarad M Martin, Mark Frydenberg, Ramdave Shakher, Lih-Ming Wong, Kim Taubman, Sze Ting Lee, Edward Hsiao, Paul Roach, Michelle Nottage, Ian Kirkwood, Dickon Hayne, Emma Link, Petra Marusic, Anetta Matera, Alan Herschtal, Amir Iravani, Rodney J Hicks, Scott Williams, Declan G Murphy, for the proPSMA Study Group Collaborators**



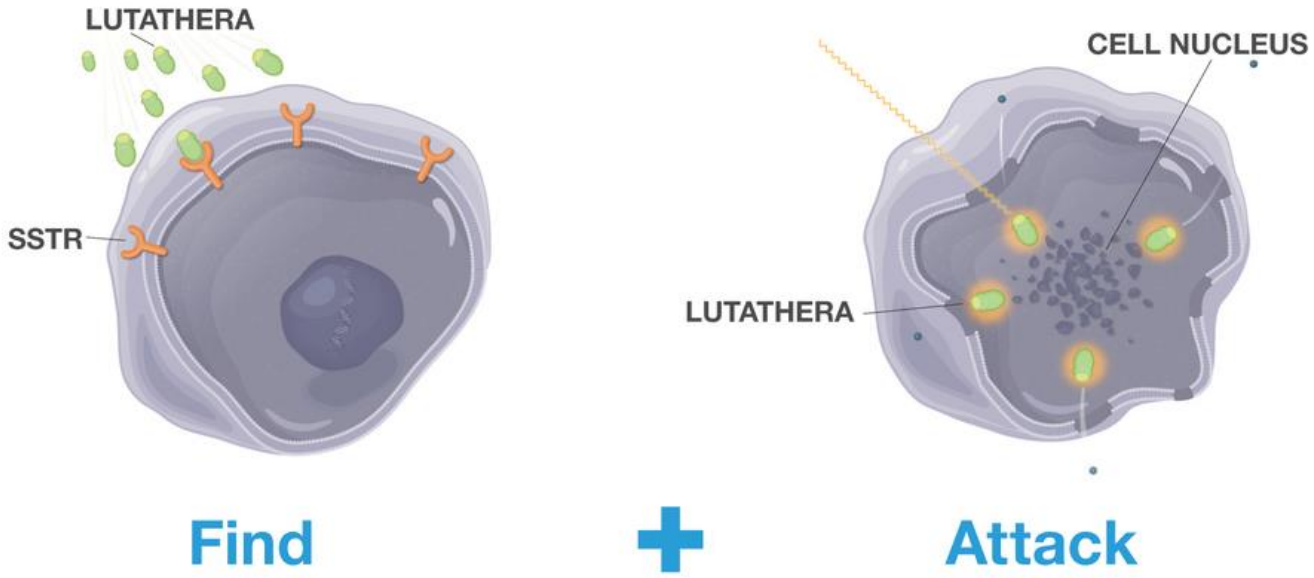
- NCCN-endorsed alternative for initial staging
  - UIR, HR, VHR
- Impact on RT planning, in combination with MRI
  - nodal coverage and DIL identification
- Growing role in recurrence detection and response monitoring
  - High sensitivity of PSMA PET→ early detection of “targetable” disease at low PSA
  - SBRT for early oligoprogressive disease can delay initiation of ADT and/or other systemic therapies



Hoffman et al. Lancet. 2020 Apr 11;395(10231):1208-1216.

Radiopharmaceuticals and SBRT

- SBRT is excellent at controlling visible tumors (whether in the prostate or metastases)
- 177Lu-PSMA delivers beta-particle radiation selectively to PSMA-expressing prostate cancer cells throughout the body, even to tiny deposits below imaging thresholds

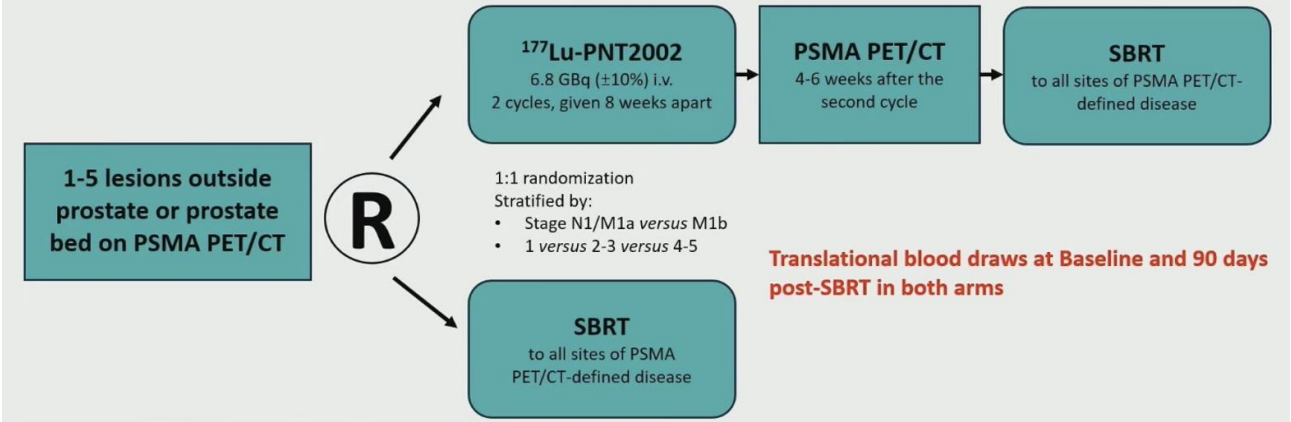


REDISCOVERING RADIATION MEDICINE AND EXPLORING NEW INDICATIONS

ASTRO 67TH ANNUAL MEETING
September 27 – October 1, 2025
Moscone Center | San Francisco

^{177}Lutetium-PSMA Neoadjuvant to Ablative Radiotherapy for Oligorecurrent Prostate Cancer: Primary Endpoint Analysis of the Phase II LUNAR Randomized Trial

- Hypothesis: Adding PSMA-based radioligand therapy with 177Lu-PNT2002 to metastasis-directed SBRT in men with oligorecurrent prostate cancer will prolong PFS by acting on occult micrometastatic disease



Original Reports | Genitourinary Cancer

^{177}Lu-Prostate-Specific Membrane Antigen Neoadjuvant to Stereotactic Ablative Radiotherapy for Oligorecurrent Prostate Cancer (LUNAR): An Open-Label, Randomized, Controlled, Phase II Study

Amar U. Kishan, MD[1,2]; Luca F. Valle, MD[1,3]; Holly Wilhalme, MS[4]; Carol Felix, BS[1]; Rejah Nabong, BS[5]; Jesus E. Juarez-Casillas, MS, BS[1]; Kevin Flores, BS[1]; T. Martin Ma, MD, PhD[6]; Vinicius Ludwig, MD[5]; Mariko Nakayama, MD[5,7]; Zachary Ells, BS[5]; Magnus Dahlbom, PhD[5]; Michael Lauria, PhD[1]; Catherine Meyer, PhD[5]; Minsong Cao, PhD[8]; Joanne B. Weidhaas, MD, PhD[1]; Donatello Telesca, PhD[9]; Kristen McGreevy, PhD[9]; Nicholas G. Nickols, MD, PhD[1,3]; Danielle Karasik, BS[1]; Sophia Parmisano, BS[1]; T. Vincent Basehart, BS[1]; Wayne Brisbane, MD[2]; Leonard Marks, MD[2]; Matthew B. Rettig, MD[3,10]; Robert E. Reiter, MD[2]; Paul C. Boutros, PhD[2,11]; Martin Allen-Auerbach, MD[5]; Johannes Czernin, MD[5]; Michael L. Steinberg, MD[1]; and Jeremie Calais, MD, PhD[5]

Toxicity

- No significant increase in toxicity with ^{177}Lu-PNT2002

	SBRT only (N=42)	^{177}Lu+SBRT (N=45)	p-value
Anemia			0.3
Grade 1	9 (21.4%)	14 (31.1%)	
Lymphopenia			0.08
Grade 1	6 (14.3%)	14 (31.1%)	
Grade 2	4 (9.5%)	8 (17.8%)	
Grade 3	2 (4.8%)	3 (6.7%)	
Neutropenia			0.4
Grade 1	1 (2.4%)	4 (8.9%)	
Grade 2	0 (0.0%)	1 (2.2%)	
Thrombocytopenia			0.7
Grade 1	4 (9.5%)	6 (13.3%)	
Transaminitis			
Grade 1	1 (2.4%)	0 (0.0%)	0.5
Renal Failure			1.0
Grade 1	0 (0.0%)	0 (0.0%)	
Grade 2	1 (2.4%)	0 (0.0%)	
Fatigue			0.4
Grade 1	26 (76.5%)	27 (64.3%)	
Grade 2	0 (0.0%)	2 (4.8%)	
Dry Mouth			1.0
Grade 1	2 (5.6%)	3 (6.8%)	
Dry Eyes			0.5
Grade 1	0 (0.0%)	2 (4.4%)	
Nausea			
Grade 1	5 (14.3%)	4 (8.9%)	0.4
Grade 2	1 (2.9%)	0 (0%)	0.4

Kishan AU, et al., J Clin Oncol. 2025 Dec 20;43(36):3812-3821.

Original Reports | Genitourinary Cancer

^{177}Lu-Prostate-Specific Membrane Antigen Neoadjuvant to Stereotactic Ablative Radiotherapy for Oligorecurrent Prostate Cancer (LUNAR): An Open-Label, Randomized, Controlled, Phase II Study

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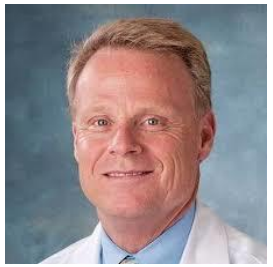
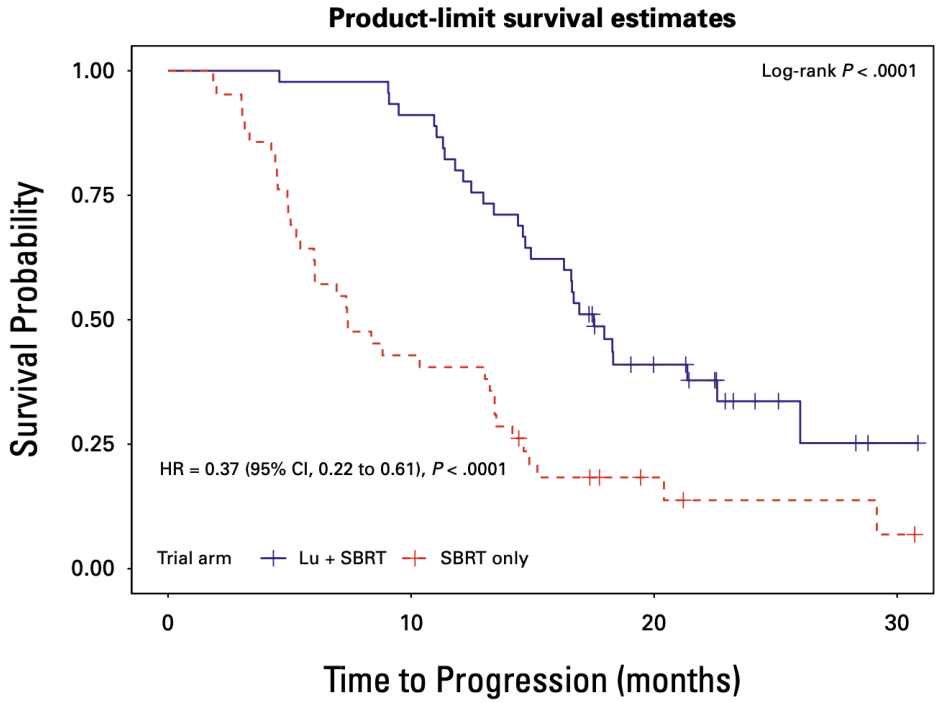
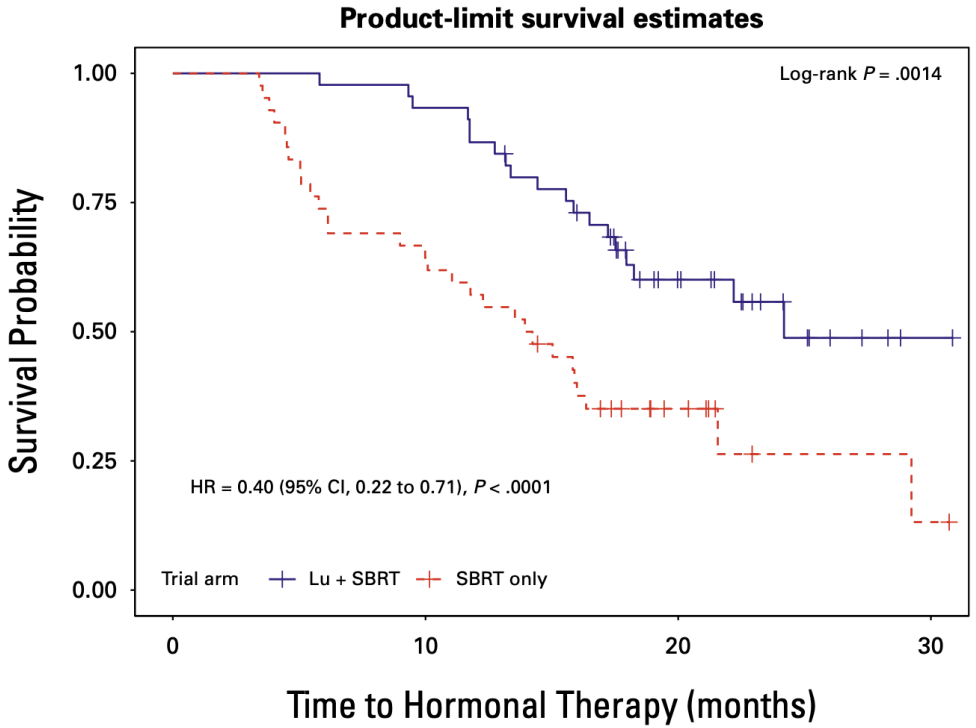




- Median PFS increased 7.4mos to 17.6mos



- Median HT free survival increased from 14.1mos to 24.3mos
- Repeat MDT without HT was delivered in 17/64 patients (27%) w new lesions

Kishan AU, et al., J Clin Oncol. 2025 Dec 20;43(36):3812-3821.

Original Reports | Genitourinary Cancer

^{177}Lu-Prostate-Specific Membrane Antigen Neoadjuvant to Stereotactic Ablative Radiotherapy for Oligorecurrent Prostate Cancer (LUNAR): An Open-Label, Randomized, Controlled, Phase II Study

Amar U. Kishan, MD[1,2]; Luca F. Valle, MD[1,3]; Holly Wilhalme, MS[4]; Carol Felix, BS[1]; Rejah Nabong, BS[5]; Jesus E. Juarez-Casillas, MS, BS[1]; Kevin Flores, BS[1]; T. Martin Ma, MD, PhD[6]; Vinicius Ludwig, MD[5]; Mariko Nakayama, MD[5,7]; Zachary Ells, BS[5]; Magnus Dahlbom, PhD[5]; Michael Lauria, PhD[1]; Catherine Meyer, PhD[5]; Minsong Cao, PhD[8]; Joanne B. Weidhaas, MD, PhD[1]; Donatello Telesca, PhD[9]; Kristen McGreevy, PhD[9]; Nicholas G. Nickols, MD, PhD[1,3]; Danielle Karasik, BS[1]; Sophia Parmisano, BS[1]; T. Vincent Basehart, BS[1]; Wayne Brisbane, MD[2]; Leonard Marks, MD[2]; Matthew B. Rettig, MD[3,10]; Robert E. Reiter, MD[2]; Paul C. Boutros, PhD[2,11]; Martin Allen-Auerbach, MD[5]; Johannes Czernin, MD[5]; Michael L. Steinberg, MD[1]; and Jeremie Calais, MD, PhD[5]

Conclusions and Future Directions

- Adding two cycles of ^{177}Lu-PNT2002 to SBRT significantly improved PFS in men with oligorecurrent prostate cancer, presumably by action against occult metastatic disease, without attendant increase in toxicity
  - PFS was defined based on PSMA PET/CT-based progression, which may not carry the prognostic impact of progression on conventional imaging but is a highly pragmatic endpoint
- Increased TCR productive rearrangements at 90 days was prognostic, and a biomarker based on germline variants in genes largely related to immune response and DNA repair was identified
- 64% of patients on the ^{177}Lu-PNT2002+SBRT arm still progressed, suggesting that further optimization is possible

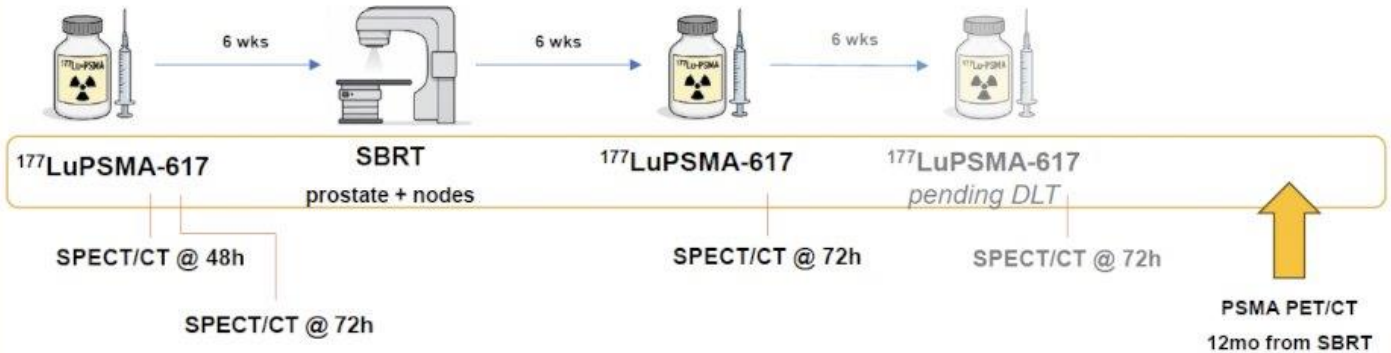
Kishan AU, et al., J Clin Oncol. 2025 Dec 20;43(36):3812-3821.

STARLiT: STereotActic body Radiotherapy and ^{177}Lutetium PSMA in Locally advanced prostate cancer: A Phase I/II Trial

Key Eligibility
n=45

- Newly diagnosed very-high risk, defined has ≥2 of:
  - cT3
  - ≥ GG4
  - PSA ≥ 40ng/mL

  and / or
  - cN1
- PSMA PET positive disease
  - SUVmax ≥ 10
- M0



1° endpoint:

Ph1: Maximally tolerated dose of Lu-PSMA when administered with prostate SBRT
Ph2: 3-yr ADT-free survival

NCT06574880

2° endpoints:
- Overall survival
- Cumulative incidence of distant metastases and prostate cancer-specific survival
- Patient reported quality of life
- Time to salvage therapy

Correlative science:
- AI histopathology
- Radiomics
- DNA, RNA, and circulating biomarkers

- Trial activated February 2025 – does early radioligand therapy in the intact setting add to SBRT in patients with high-risk prostate cancer?
- Phase I/II single-arm, open-label trial enrolling 45 locally advanced (high-risk) prostate cancer patients to determine MTD of Lu-177 with SBRT (phase I) and evaluate 3-year ADT-free survival (phase II)

Agenda: Emerging Trends, Future Directions

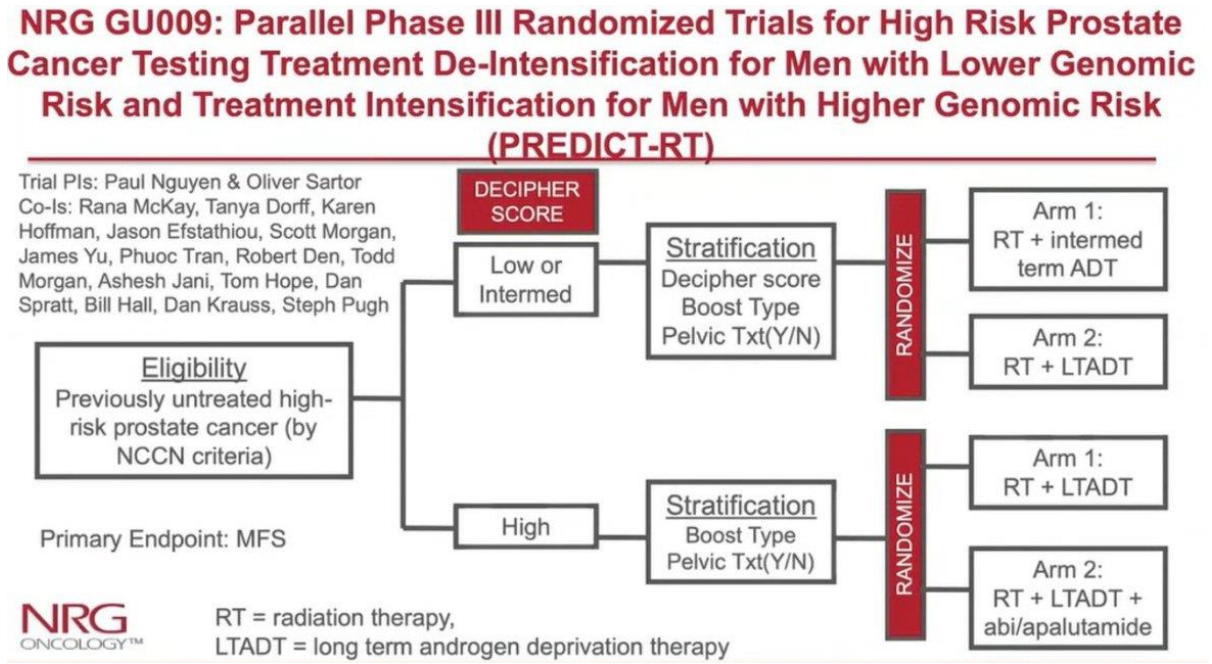
- PSMA PET in staging and treatment planning
  - Novel combinations w radiopharmaceuticals and systemic agents
- Biomarker-driven personalization of SBRT
  - Molecular-Based Imaging Redefining the Disease Landscape
- Focal boosting, adaptive therapy, and ultra-short fractionation
- Oligometastatic Disease

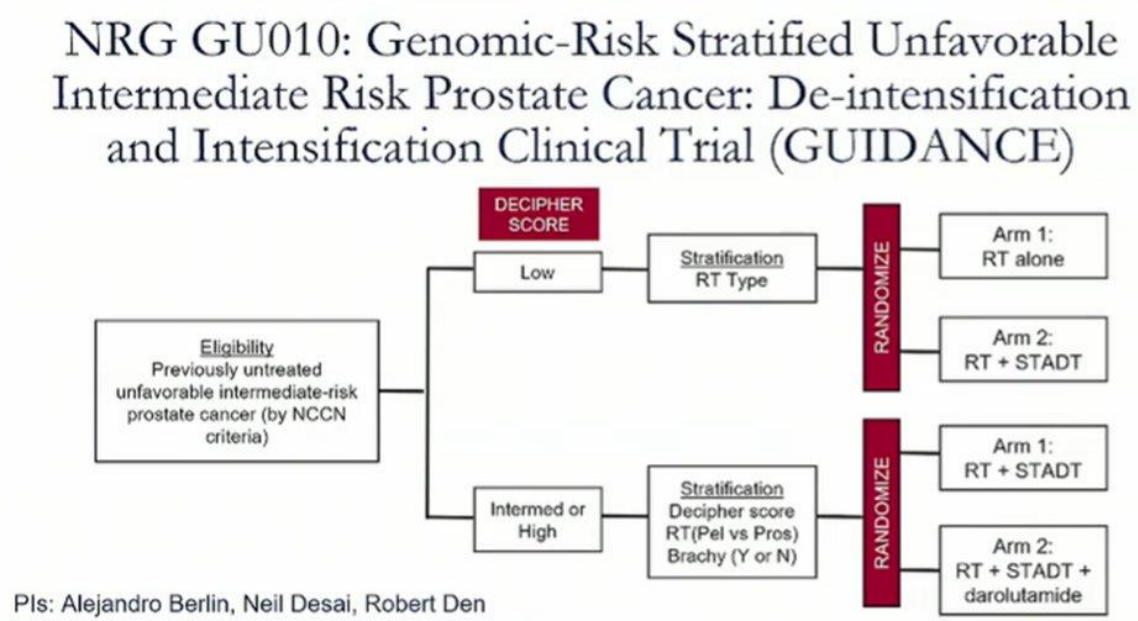
Biomarkers and Genetic Stratification

- Molecular biomarkers are increasingly used to guide critical decisions in prostate cancer radiotherapy
  - Decipher – High-risk RT ± ADT and salvage RT ± ADT
  - PAM50 – Salvage RT+ADT only benefits luminal B subtype (NRG GU006 – BALANCE trial)
  - ArteraAI – AI algorithm that helps predict if ADT would provide significant benefit
  - Prolaris– genomic test that helps inform active surveillance vs. treatment
  - PORTOS – Predicts risk of G2 or higher adverse events with dose-escalated RT (79.2 Gy)
  - PROSTOX – Predicts risk of severe late GU toxicity from SBRT

- Reshaping decision-making in prostate RT, guiding ADT choices, toxicity considerations, and refining risk stratification
- Growing body of literature examining *genetic factors contributing to radiosensitivity* enabling even more tailored therapeutic approaches

Biomarkers and Genetic Stratification





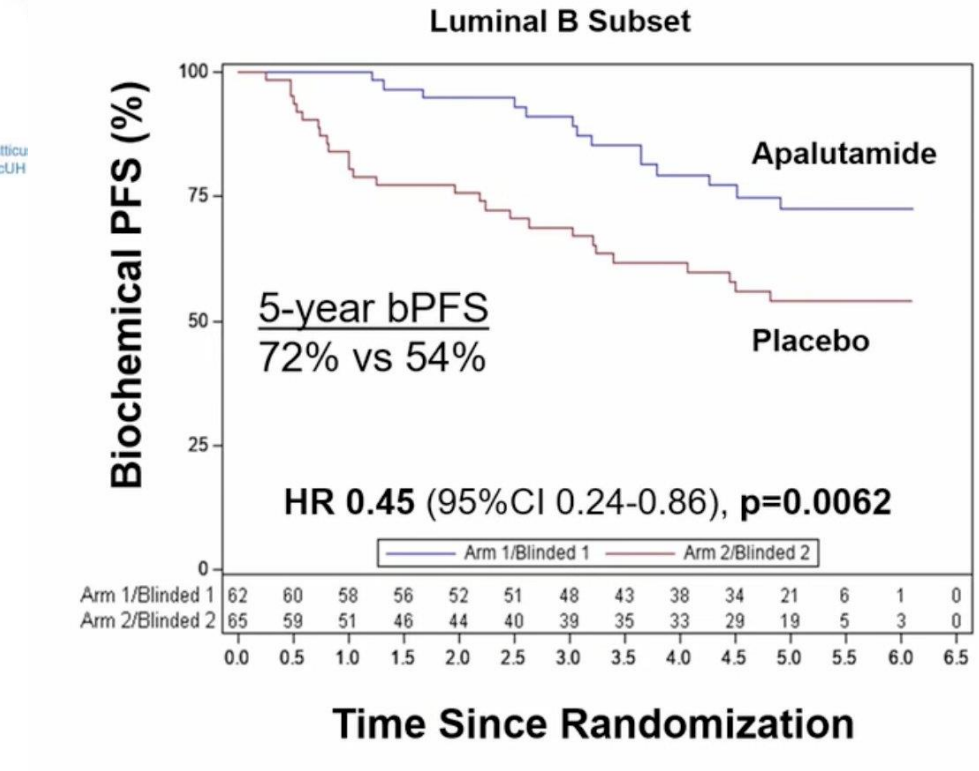
- 2,478pt accrued, approx. 2yrs earlier than anticipated accrual date

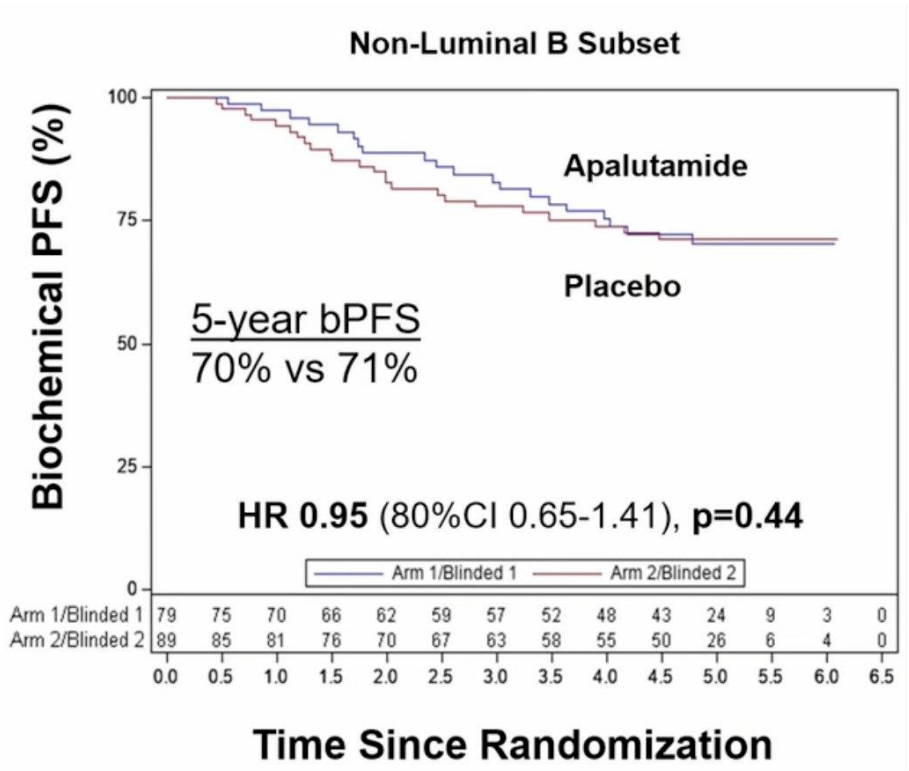
NRG ONCOLOGY

Advancing Research. Improving Lives.

A Double-Blinded Placebo-Controlled Biomarker Stratified Randomized Trial of Apalutamide (APA) and Radiotherapy for Recurrent Prostate Cancer (NRG GU006, BALANCE)

Daniel E Spratt, MD, Theodore Karrison, PhD, Howard M Sandler, MD, Edwin M Posadas, MD, Ronald Chen, MD, MPH, Robert E Wallace, PhD, James I Monroe, PhD , Leonard Gomella, MD, Robert T Dess, MD, Andrew Vassil, MD, Annie Ebacher, MD,





- NRG GU006, BALANCE trial: ph II biomarker stratified randomized trial of patients receiving salvage radiotherapy (SRT) with or without APA

Spratt et al. Int J Radiat Oncol Biol Phys. 2025;123(4):P1197-P1198.

https://doi.org/10.4143/crt.2020.1247

Cancer Res Treat. 2022;54(1):54-64

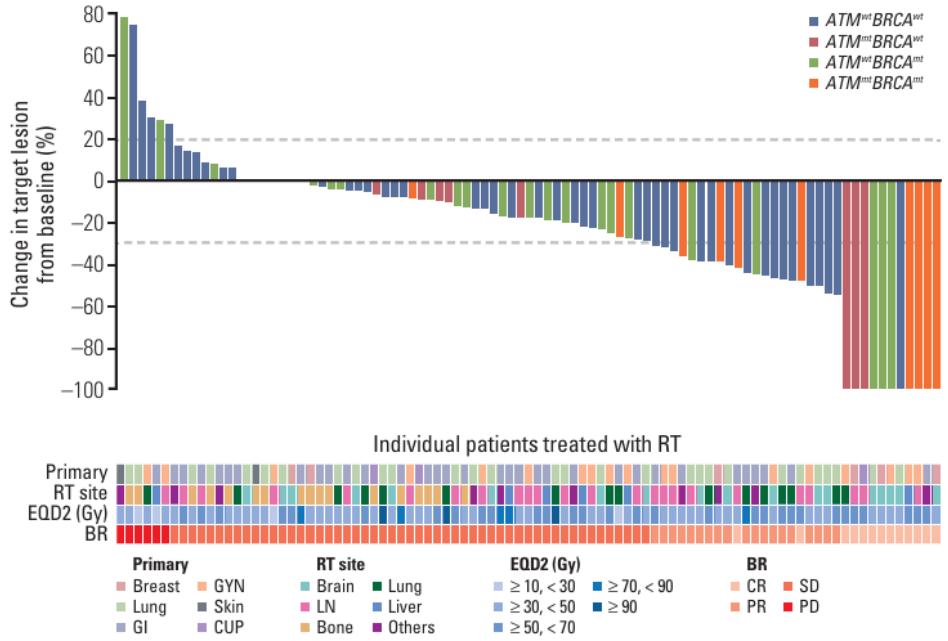
Original Article

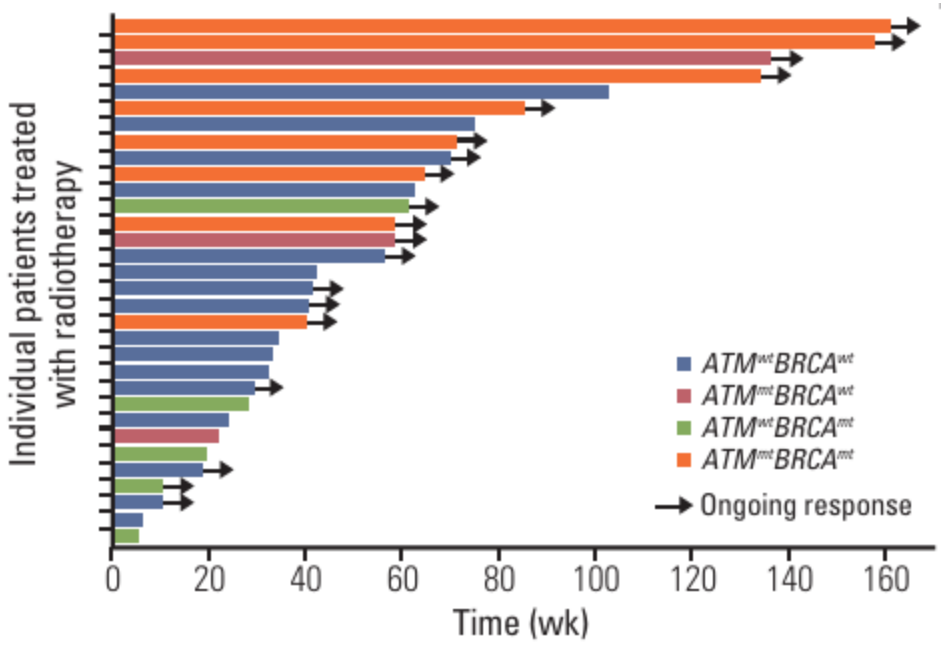
Increased Radiosensitivity of Solid Tumors Harboring *ATM* and *BRCA1/2* Mutations

Kyung Hwan Kim[1], Han Sang Kim[2], Seung-seob Kim[3], Hyo Sup Shim[4], Andrew Jihoon Yang[1], Jason Joon Bock Lee[1], Hong In Yoon[1], Joong Bae Ahn[2], Jee Suk Chang[1]

Kim et al. Cancer Res Treat. 2022;54(1):54-65.

- Clinical study evaluating somatic ATM and BRCA1/2 mutations in solid tumors and their differential radiosensitivity based on mutation profile



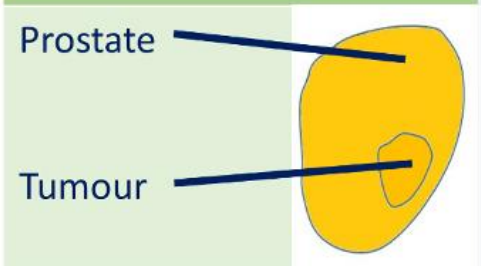
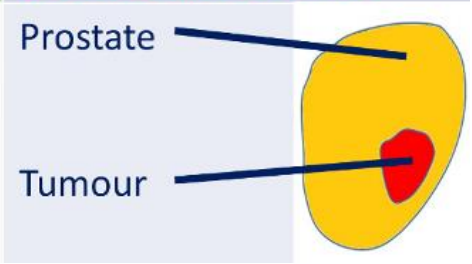


- Waterfall plot showing % change in tx'd lesions with tumors exhibiting ATM and/or BRCA mutations exhibiting the greatest treatment response
- The panel on the right shows a swimmer plot representing duration of response in patients that exhibited an objective respons e

Agenda: Emerging Trends, Future Directions

- PSMA PET in staging and treatment planning
  - Novel combinations w radiopharmaceuticals and systemic agents
- Biomarker-driven personalization of SBRT
  - Molecular-Based Imaging Redefining the Disease Landscape
- Focal boosting, adaptive therapy, and ultra-short fractionation
- Oligometastatic Disease

Dose and Fractionation Strategies

Standard treatment	FLAME (NCT01168479; phase III)
OTT = 7-8 weeks	OTT = 7 weeks
35-40 fractions, 5x/week	35 fractions, 5x/week
Whole gland irradiation	Whole gland irradiation ± focal tumour boost
	

- FLAME→ improved bDFS utilizing a focal boost of macroscopically visible tumor in the setting of standard fractionation (77 Gy/35 fx with DIL boost up to 95 Gy) compared to no boost

Dose and Fractionation Strategies

	FLAME			Hypo-FLAME
	Standard	DIL Boost	p-value	SBRT-DIL Boost
5-year bDFS	85%	92%	p<0.001	93%
Late G2+ GI	23%	28%	NS	12%
Late G2+ GU	12%	13%	NS	4%

Kerkmeijer et al. J Clin Oncol. 2021 Mar 1;39(7):787-796.
Guricova et al. J Clin Oncol. 2025 Oct;43(28):3065-3069.
Draulans et al. Radiother Oncol. 2024 Dec:201:110568.

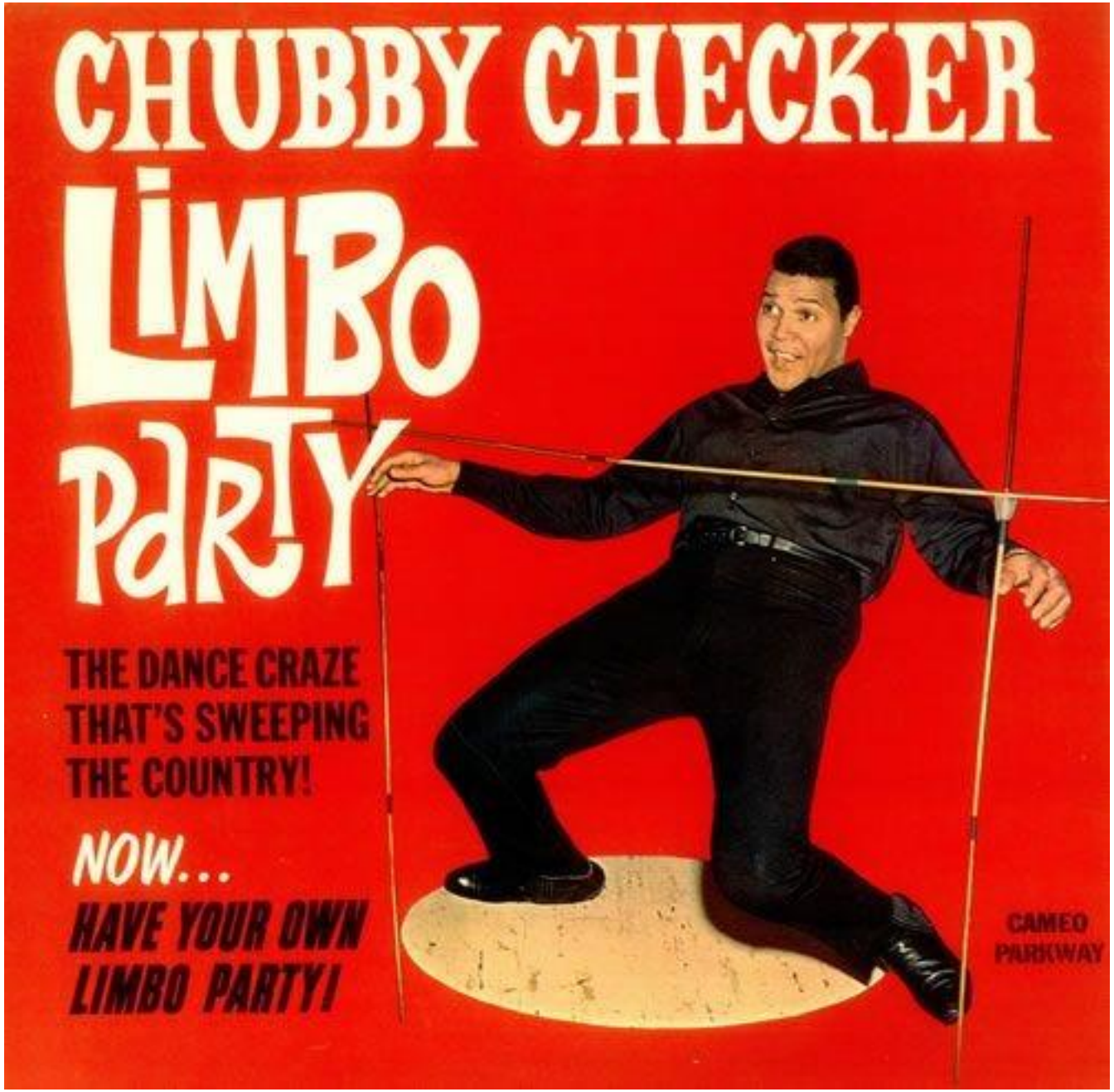
Prostate SBRT – The New Standard

SBRT already established as the standard of care by the NCCN at all stages of prostate cancer from localized, post-operative, and advanced metastatic disease

EBRT Regimen										ent RT	Advanced Disease	
										Post-RT	Primary Tumor	Metastases
										sRT	mCSPC M0 CRPC mCRPC	MDT
Conventional											☼	
											☼	
Moderate Hypofractionation										☼	☼	☼
										☼	✓	☼
Ultra Hypofractionation (SBRT)										✓	✓	✓
												✓
	6.2–6.4 Gy x 5 fx								☼			
EBRT Boost Techniques												
EBRT with simultaneous integrated boost	See footnote b.		☼	✓	✓	☼	☼		☼	☼	☼	
EBRT with sequential SBRT boost	*Prostate:* 1.8 Gy x 23–28 fx *Boost:* 6 Gy x 3 fx 9.5 Gy x 2 fx			☼	☼	☼						

(✓ Preferred; ☼ Acceptable based on clinical and medical need; Regimens shaded gray are not recommended)

Ultra Hypofractionation (SBRT)	9.5 Gy x 4 fx 7.25–8 Gy x 5 fx 6 Gy x 6 fx 6.1 Gy x 7 fx	☼	✓	✓	✓	☼	☼
	9–10 Gy x 3 fx 12 Gy x 2 fx 16–24 Gy x 1 fx						
	6.2–6.4 Gy x 5 fx						



Ultra Hypofractionation (SBRT)	9.5 Gy x 4 fx 7.25–8 Gy x 5 fx 6 Gy x 6 fx 6.1 Gy x 7 fx	☼	✓	✓	✓	☼	☼
	9–10 Gy x 3 fx 12 Gy x 2 fx 16–24 Gy x 1 fx						
	6.2–6.4 Gy x 5 fx						

Dose and Fractionation Strategies

- Ultra-extreme hypofractionation appears to be well-tolerated overall but data are preliminary with longer follow-up needed
  - 2-fraction SBRT single-arm (2STAR, SMART PRO) – 26 Gy/2 fx
  - 2-fraction SBRT with DIL boost single-arm (2SMART) – 26 Gy/2 fx (GTV boost to 32 Gy)
  - 5 fraction vs. 2-fraction SBRT (HERMES) – 36.25/5 fx vs. 24 Gy/2 fx (GTV boost to 27 Gy)
  - 1-fraction SBRT single-arm (ONE SHOT) – 19 Gy/1 fx (17 Gy to urethra)
  - 5 fraction vs. 1-fraction SBRT (PROSINT) – 40 Gy/5 fx vs. 24 Gy/1 fx

- Alayed et al. Radiother Oncol. 2019 Jun;135:86-90.
- Zenda et al. BMJ Open. 2024 Aug 25;14(8):e082899.
- Ong et al. Radiother Oncol. 2023 Apr;181:109503.
- Cooper et al. Int J Radiat Oncol Biol Phys. 2025 Nov 1;123(3):773-782.
- Zilli et al. Radiother Oncol. 2024 May;194:110181.
- Greco et al. JAMA Oncol. 2021 May 1;7(5):700-708.

EUROPEAN UROLOGY ONCOLOGY 8 (2025) 763–773

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journal homepage: euoncology.europeanurology.com

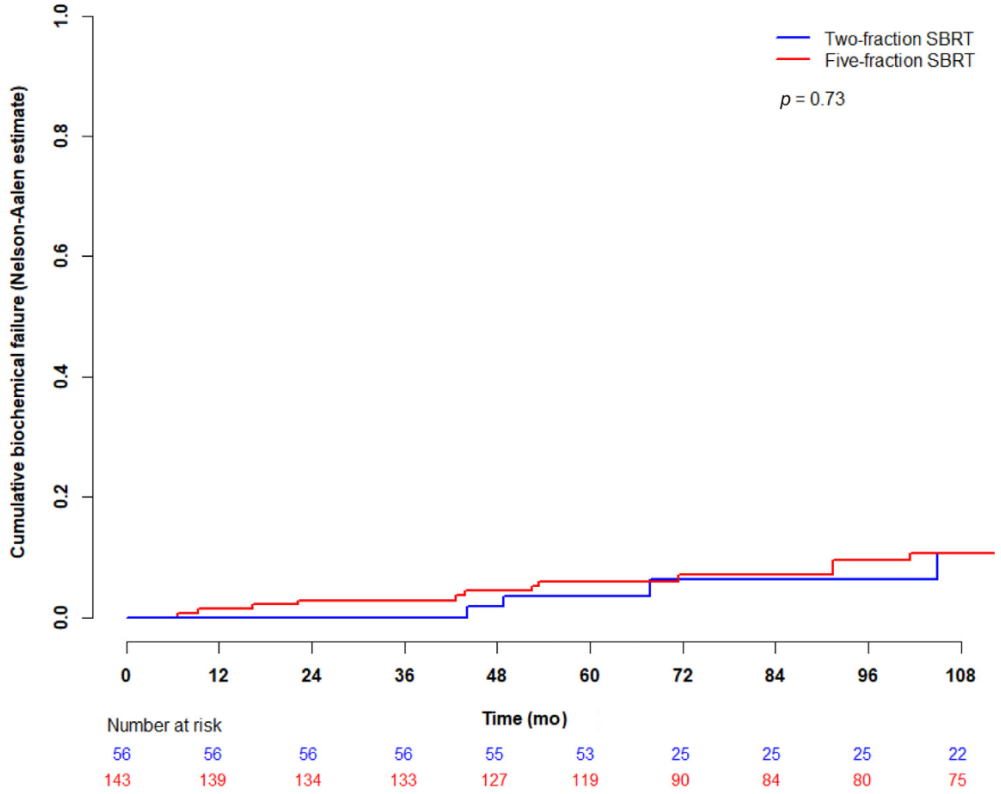
European Association of Urology

Original articles

Two-fraction Versus Five-fraction Stereotactic Body Radiotherapy for Intermediate-risk Prostate Cancer: The TOFFEE Meta-analysis of Individual Patient Data from Four Prospective Trials

Cristian Udovicich [a,b], Patrick Cheung [a,b], William Chu [a,b], Hans Chung [a,b], Jay Detsky [a,b], Stanley Liu [a,b], Gerard Morton [a,b], Ewa Szumacher [a,b], Chia-Lin Tseng [a,b], Danny Vesprini [a,b], Wee Loon Ong [a,b,c], Thomas Kennedy [a,b], Melanie Davidson [a,b], Ananth Ravi [b], Merrylee McGuffin [a,b], Liying Zhang [a], Alexandre Mamedov [a], Andrea Deabreu [a], Meghan Kulasingham-Poon [a], Andrew Loblaw [a,b,d,]*

[a] *Odette Cancer Centre, Sunnybrook Health Sciences Centre, Toronto, Canada;* [b] *Department of Radiation Oncology, University of Toronto, Toronto, Canada;* [c] *Alfred Health Radiation Oncology, School of Translational Medicine, Monash University, Melbourne, Australia;* [d] *Department of Health Policy, Measurement and Evaluation, University of Toronto, Toronto, Canada*

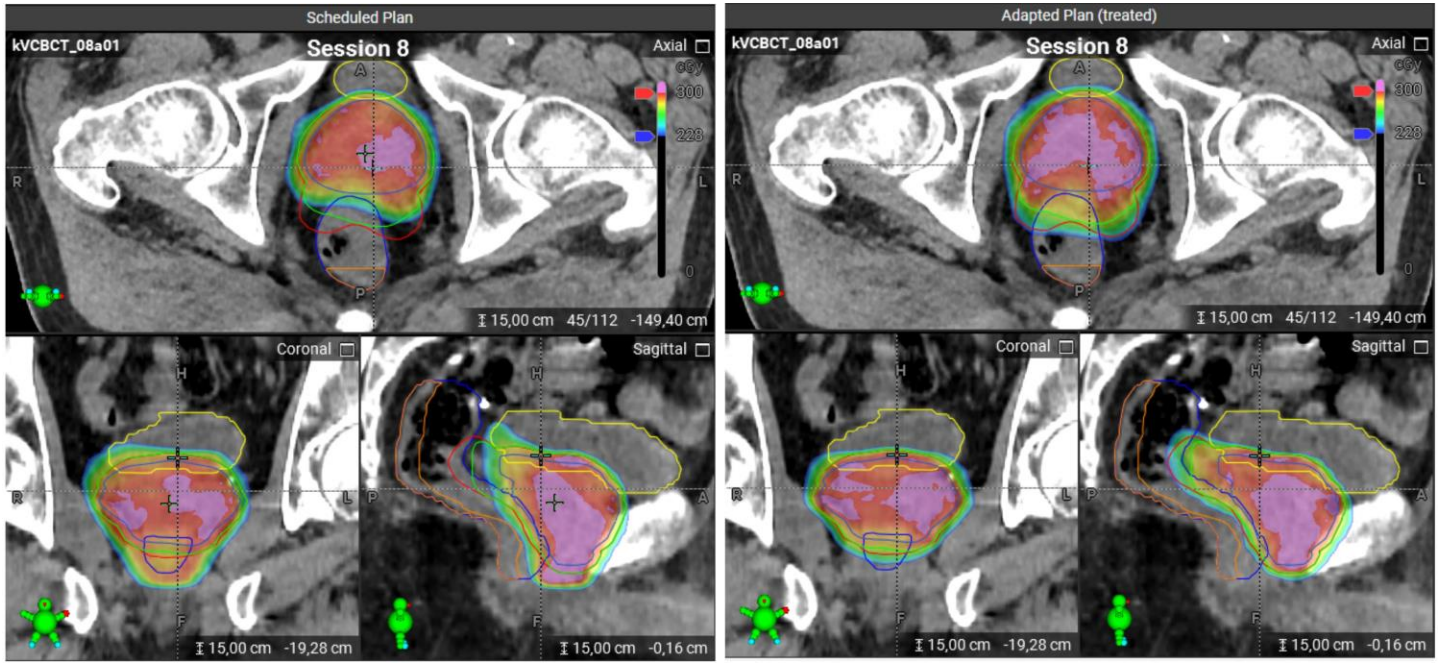


- meta-analysis of individual patient data evaluated IR-PC from four prospective trials of prostate SBRT (two trials each of 2F- and 5F-SBRT).
- Median f/u 9.4yrs.
- no significant diff in 5yr BCF or DM; no sig diff in acute or late urinary or bowel QoL

Udovicich C, et al., Eur Urol Oncol. 2025 Jun;8(3):763-773

Adaptive SBRT

- Given the high dose per fraction, SBRT magnifies geometric uncertainties and risk
  - Growing adoption of adaptive radiotherapy (ART) for prostate cancer due to known variabilities in daily anatomy as well as both inter- and intra-fraction motion
  - Lack of strong clinical trial data to quantify benefit over standard SBRT



3-7 May 2024

Glasgow, UK

ESTRO 2024

Daily adaptive radiotherapy is pushed by manufacturers instead of clinical evidence

Chair: Carsten Brink, *Denmark*; **Chair:** Lorenzo Placidi, *Italy*

Overview: Daily adaptive radiotherapy (DART) has recently been supported by relevant technological innovations, and we are now approaching the era of daily adaptation of treatment plans based on a patient's evolving anatomy. While manufacturers advocate widespread adoption of DART, some critics argue that this push is driven by commercial interests rather than robust clinical evidence. In addition, the benefits of the DART should also be assessed while maintaining at least the same quality standards. Potential critical issues for discussion include the challenges of technology implementation, regulatory oversight and the need for guidance. This discussion aims to explore the motivations behind manufacturers' promotion of DART and to review the existing clinical evidence to support its widespread adoption

Session Code: 2130 Session Type: Debate Track: Physics

Research

JAMA Oncology | Original Investigation

Magnetic Resonance Imaging–Guided vs Computed Tomography–Guided Stereotactic Body Radiotherapy for Prostate Cancer

The MIRAGE Randomized Clinical Trial

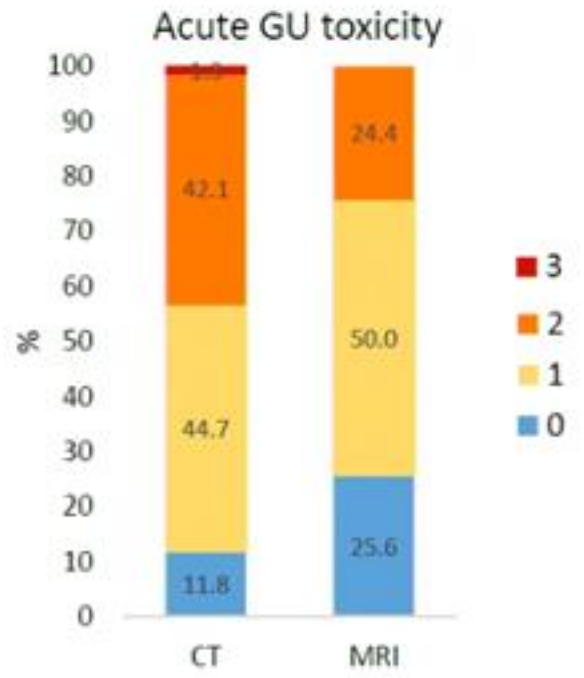
Amar U. Kishan, MD; Ting Martin Ma, MD, PhD; James M. Lamb, PhD; Maria Casado, BS; Holly Wilhalme, MSc; Daniel A. Low, PhD; Ke Sheng, PhD; Sahil Sharma, BS; Nicholas G. Nickols, MD, PhD; Jonathan Pham, PhD; Yingli Yang, PhD; Yu Gao, PhD; John Neylon, PhD; Vincent Basehart, BS; Minsong Cao, PhD; Michael L. Steinberg, MD

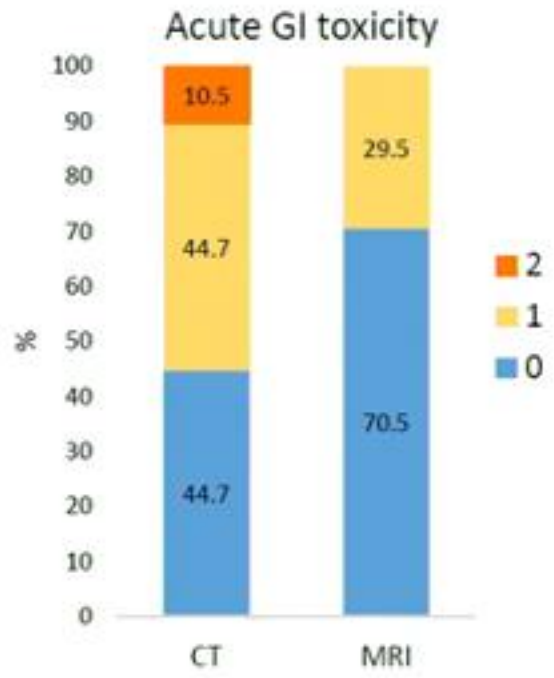
IMPORTANCE Magnetic resonance imaging (MRI) guidance offers multiple theoretical advantages in the context of stereotactic body radiotherapy (SBRT) for prostate cancer. However, to our knowledge, these advantages have yet to be demonstrated in a randomized clinical trial.

OBJECTIVE To determine whether aggressive margin reduction with MRI guidance significantly reduces acute grade 2 or greater genitourinary (GU) toxic effects after prostate SBRT compared with computed tomography (CT) guidance.

DESIGN, SETTING, AND PARTICIPANTS This phase 3 randomized clinical trial (MRI-Guided Stereotactic Body Radiotherapy for Prostate Cancer [MIRAGE]) enrolled men aged 18 years or older who were receiving SBRT for clinically localized prostate adenocarcinoma at a single center between May 5, 2020, and October 1, 2021. Data were analyzed from January 15, 2021, through May 15, 2022. All patients had 3 months or more of follow-up.

Visual Abstract
Invited Commentary page 373
Supplemental content





- Phase 3 RCT comparing SBRT(40Gy/5fx's) with CT (4mm margins) vs. MRI (2mm margins)- guidance for localized prostate cancer
  - **If >10% of the prostate area moved outside of a 3-mm gating boundary, an automatic beam hold was initiated.**
  - **Daily recontouring/online adaptive not performed**
- Acute grade 2+ GU toxicity was lower with MRI (2mm margins) than with CT (4mm margins) guidance (24.4% vs 43.4%, P = .01), as was acute grade 2+ GI toxicity (0.0% vs 10.5%, P = .003)
  - Biochemical outcomes and long-term toxicity pending
  - 32% HR/VHR, 8% cN1

Kishan AU, et al, JAMA Oncol. 2023 Mar 1;9(3):365-373

Radiotherapy and Oncology 167 (2022) 203–210

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

Dosimetric impact of interfraction prostate and seminal vesicle volume changes and rotation: A post-hoc analysis of a phase III randomized trial of MRI-guided versus CT-guided stereotactic body radiotherapy

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- Post-hoc analysis from MIRAGE showed interfraction changes in target volume and prostate dimensions
  - all patients experienced isotropic prostate volume increase during SBRT ($p = 0.0016$).
- Despite volumetric changes, prostate dosimetry remained favorable with a 2 mm margin, though proximal SV dosimetry was more sensitive.
- Conclusion: Online adaptive therapy *may occasionally* be needed to address prostatic swelling and proximal SV rotations.

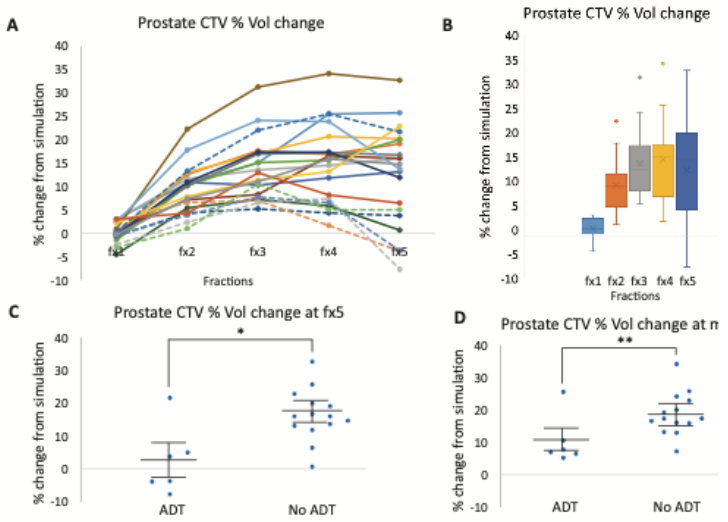

Table 1
Dosimetry of prostate and proximal SV CTV.

	Prostate CTV				Proximal SV CTV			
	V100%	V95%	D_{mean}	D95%	V100%	V95%	D_{mean}	D95%
Mean	96.1	98.9	41.4	40.0	83.9	91.3	40.6	37.0
Median	97.5	99.9	41.4	40.3	87.1	96.3	41.2	38.5
Minimum	82.4	90.4	40.4	34.3	9.1	14.1	26.6	15.2
Maximum	100.0	100.0	41.8	41.0	100.0	100.0	42.2	41.2
Q1	94.7	98.8	41.3	40.0	78.6	89.7	40.6	36.7
Q3	98.5	100.0	41.6	40.5	96.9	99.9	41.4	40.3
Frequency of ≥100% (%)	n/a	n/a	40.0	29.2	n/a	n/a	34.4	13.2
Frequency of ≥95% (%)	73	94	40.0	37.6	33	59	38.0	23.6
Frequency of ≥90% (%)	91	100	40.0	39.2	44	74	38.8	31.6

V100% and V95% are expressed in % volume of the respective target; D_{mean} and D95% are expressed in Gy. CTV, clinical target volume; Q1, quartile 1; Q3, quartile 3; SV, seminal vesicle.

- In 94% of fractions, at least 95% of the target volume received at least 95% of the prescribed dose for the prostate
- compared to only 59% for the proximal SV.

Ma TM, et al, Radiother Oncol. 2022;167:203-210.

Journal of *Personalized Medicine*

MDPI

Article

1.5T MR-Guided Daily-Adaptive SBRT for Prostate Cancer: Preliminary Report of Toxicity and Quality of Life of the First 100 Patients

Filippo Alongi [1,2], Michele Rigo [1], Vanessa Figlia [1], Luca Nicosia [1], Rosario Mazzola [1], Niccolò Giaj Levra [1], Francesco Ricchetti [1], Giovanna Trapani [1], Giorgio Attinà [1], Claudio Vitale [1], Edoardo Pastorello [1], Antonio De Simone [1], Davide Gurrera [1], Stefania Naccarato [1], Gianluisa Sicignano [1], Ruggero Ruggieri [1] and Francesco Cuccia [1,*]

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Alongi F, et al., J Pers Med. December 2022; 2022, 19(12):2192.

Current Oncology

MDPI

Article

Online Adaptive MR-Guided Ultrahypofractionated Radiotherapy of Prostate Cancer on a 1.5 T MR-Linac: Clinical Experience and Prospective Evaluation

Vlatko Potkrajcic [1,*], Cihan Gani [1], Stefan Georg Fischer [2], Simon Boeke [1], Maximilian Niyazi [1], Daniela Thorwarth [1,3], Otilia Voigt [1,3], Moritz Schneider [1,3], David Mönnich [1,3], Sarah Kübler [1], Jessica Boldt [1], Elgin Hoffmann [1], Frank Paulsen [1], Arndt-Christian Mueller [4] and Daniel Wegener [1,5]

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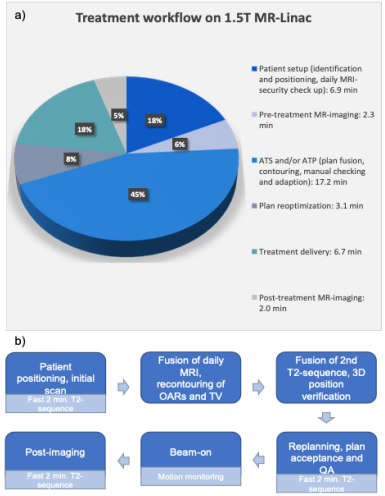
Pokrajac V, et al, Curr Oncol. May 2024; 2024, 31(9):2679-2688.



Clinical and Translational Radiation Oncology 46 (2024) 100771

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Stereotactic ultrahypofractionated MR-guided radiotherapy for localized prostate cancer – Acute toxicity and patient-reported outcomes in the prospective, multicenter *SMILE* phase II trial

C.A. Fink [a,1,*], J. Ristau [a,b,1], C. Buchele [a], S. Klüter [a], J. Liermann [a], P. Hoegen-Saßmannshausen [a], E. Sandrini [a], A. Lentz-Hommertgen [a], L. Baumann [c], N. Andratschke [d], M. Baumgartl [d], M. Li [e], M. Reiner [e], S. Corradini [e], J. Hörner-Rieber [a], D. Bonekamp [f], H.-P. Schlemmer [f], C. Belka [e], M. Guckenberger [d], J. Debus [a], S.A. Koerber [a,g]

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Table 2
Highest-grade physician-reported GU and GI toxicity up to and at the 12-week follow-up visit.

		RTOG			CTCAE		
	Highest Grade Toxicity	GU	GI	GU and/or GI	GU	GI	GU and/or GI
up to 12 weeks	I	37 (54%)	14 (20%)	32 (46%)	6 (9%)	9 (13%)	8 (12%)
	II	10 (14%)	12 (17%)	19 (28%)	12 (17%)	6 (9%)	16 (23%)
	III	1 (1%)	3 (4%)	3 (4%)	-	-	-
at 12 weeks	I	21 (31%)	8 (12%)	22 (33%)	1(1%)	-	1 (1%)
	II	-	4 (6%)	4 (6%)	-	1 (1%)	1 (1%)

- 69 patients with low/intermediate-risk (4% high-risk) localized prostate cancer underwent MRgSBRT with online adaptive therapy.
  - 37.5Gy/5fx's to PTV, 40Gy to DIL
- Modest acute toxicity with no grade 3+ events at 12-week follow-up.
  - No residual grade 2+ GU toxicity at 12 weeks.
- Direct comparison with MIRAGE or PACE not feasible due to different doses/prescriptions, but observed rates of acute gastrointestinal and genitourinary toxicity are encouraging.
- Patient-reported outcomes indicate minimal impact on quality of life post-radiotherapy.
  - Pending long-term oncologic and QOL outcomes

Fink CA, et al, Clin Transl Radiat Oncol. 2024;46:100771.

Physics and Imaging in Radiation Oncology 29 (2024) 100562

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Original Research Article

Impact of daily plan adaptation on accumulated doses in ultra-hypofractionated magnetic resonance-guided radiation therapy of prostate cancer

Yuqing Xiong [a], Moritz Rabe [a], Carolin Rippke [b], Maria Kawula [a], Lukas Nierer [a], Sebastian Klüter [b,c], Claus Belka [a,d,e], Maximilian Niyazi [a], Juliane Hörner-Rieber [b,c,f,g,h], Stefanie Corradini [a], Guillaume Landry [a], Christopher Kurz [a,*]

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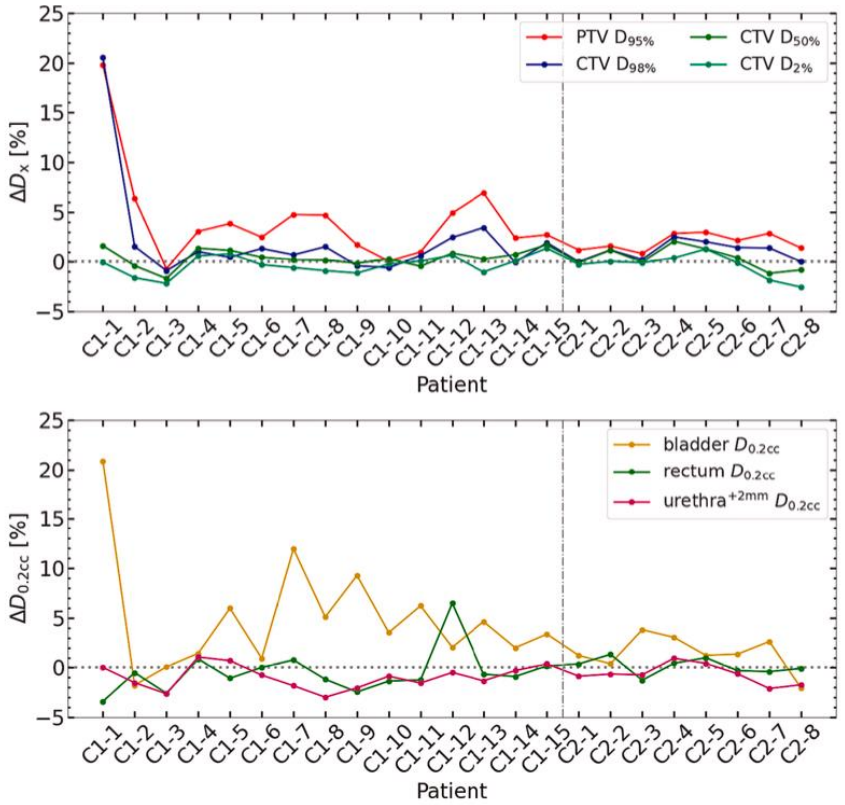

- Measurement of accumulated dose from 23pts with PCa treated with MRg adaptive SBRT (7.5Gy x 5)
  - Each fraction's MR images were deformably registered to the planning MR image.
  - Both non-adapted and adapted fraction doses were accumulated
- Improved Target coverage with mixed OAR sparing
  - PTV* D95% increased significantly by 2.7 %
    - CTV* D98% by 1.2 %
  - Bladder D0.2cc decreased by 0.4 %, urethra+2mm D0.2cc by 0.8 %
  - Rectum D0.2cc ***increased*** by 2.6 %
    - though rectum D0.2cc still below the clinical constraint.

"In conclusion, online adaptation in MRgRT was found to be advantageous in improving target coverage and OARs sparing, especially for patients experiencing strong anatomical changes. ***However, the average improvement was limited for most patients."***

Xiong Y, et al., Phys Imaging Radiat Oncol. 2024;29:100562.

Received: 3 June 2021 | Revised: 14 September 2021 | Accepted: 30 October 2021
DOI: 10.1002/acm2.13479
JOURNAL OF APPLIED CLINICAL MEDICAL PHYSICS
RADIATION ONCOLOGY PHYSICS

Varian ethos online adaptive radiotherapy for prostate cancer: Early results of contouring accuracy, treatment plan quality, and treatment time

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Abstract
The Varian Ethos system allows for online adaptive treatments through the utilization of artificial intelligence (AI) and deformable image registration which automates large parts of the anatomical contouring and plan optimization process. In this study, treatments of intact prostate and prostate bed, with and without nodes, were simulated for 182 online adaptive fractions, and then a further 184 clinical fractions were delivered on the Ethos system. Frequency and magnitude of contour edits were recorded, as well as a range of plan quality metrics. From the fractions analyzed, 11% of AI generated contours, known as influencer contours, required no change, and 81% required minor edits in any given fraction. The frequency of target and noninfluencer organs at risk (OAR) contour editing varied substantially between different targets and noninfluencer OARs, although across all targets 72% of cases required no edits. The adaptive plan was the preference in 95% of fractions. The adaptive plan met more goals than the scheduled plan in 78% of fractions, while in 15% of fractions the number of goals met was the same. The online adaptive recontouring and replanning process was carried out in 19 min on average. Significant improvements in dosimetry are possible with the Ethos online adaptive system in prostate radiotherapy.

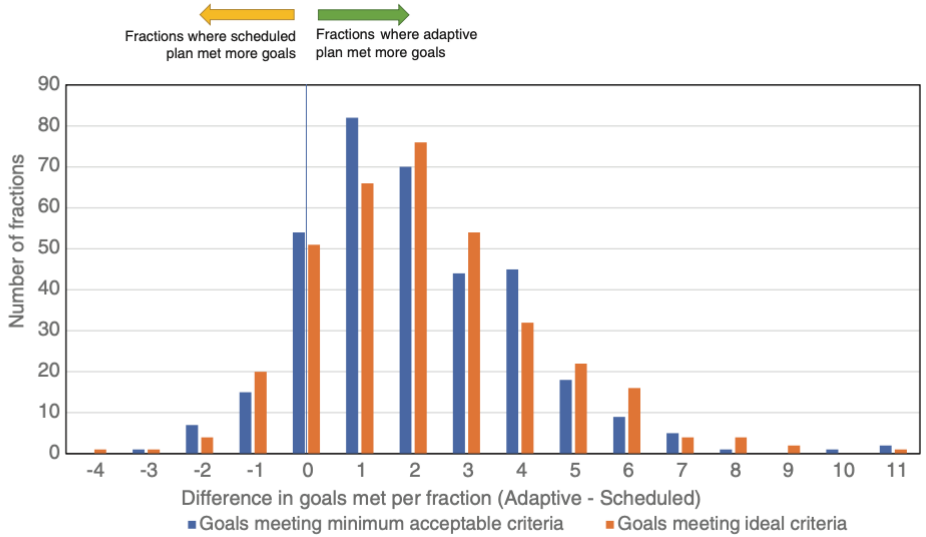


FIGURE 2 Histogram of differences in number of planning clinical goals met per fraction

- OART on 12 retrospective prostate/bed +/- LNs and 6 prospective patients
- The adaptive plan met more goals than the scheduled plan in 78% of fractions
  - In 15% of fractions the number of goals met was the same.

TABLE 2 Percentage of fractions that the adaptive plan was selected for treatment

Treatment site	Percentage that adapted plan was selected
Intact prostate	98.8%
Intact prostate and nodes	98.7%
Prostate bed and nodes	89.4%
All sites	95.3%

TABLE 4 Timing data for retrospective and clinical patient fractions

Treatment site	Retrospective data Adaptive time (average ± SD) (mm:ss)	Clinical data Adaptive time (average ± SD) (mm:ss)
Intact prostate	15:21 ± 03:18	33:57 ± 05:13
Intact prostate and nodes	19:30 ± 04:06	34:12 ± 06:23
Prostate bed and nodes	21:20 ± 03:55	34:17 ± 07:23
All sites	19:11 ± 04:29	34:11 ± 06:34

- Clinical Tx took, on avg, 34 mins
  - Does this include Global Time: Patient Setup, Acquisition of Verification Imaging, Image Analysis and Recontouring, Online Adaptation Time, Plan Approval, Patient-Specific QA, Technical Setup and Calibration, Treatment Delivery, Waiting for Radiation Oncologist and Medical Physicists.

Byrne M, et al, J Appl Clin Med Phys. October 2021.

Adaptive SBRT

- ASPIRE (NCT06825091)
  - Phase III RCT of adaptive SBRT vs. standard IG-SBRT for localized prostate cancer
    - Adaptive arm: Daily adaptive planning (both MR- and CT-based adaptive SBRT)
      - 36.25 Gy/5 fx (PACE-B) or 42.7 Gy/7 fx (HYPO-RT-PC)
      - Treatment EOD over 2-3 weeks
      - Goal of tightening margins
    - Standard arm: No plan modifications after initial CT simulation and planning
      - 36.25 Gy/5 fx (PACE-B) or 42.7 Gy/7 fx (HYPO-RT-PC)
      - Treatment EOD over 2-3 weeks
  - Primary outcome - urinary QOL (EPIC-26)
  - Started enrollment Spring 2025, Target accrual 320 patients
  - Trial estimated to close 2030

Agenda: Emerging Trends, Future Directions

- PSMA PET in staging and treatment planning
  - Novel combinations w radiopharmaceuticals and systemic agents
- Biomarker-driven personalization of SBRT
  - Molecular-Based Imaging Redefining the Disease Landscape
- Focal boosting, adaptive therapy, and ultra-short fractionation
- Oligometastatic Disease

SBRT metastatectomy

EDITORIAL

Oligometastases

CANCER TREATMENT is based on an often unstated paradigm of disease pathogenesis. Since 1894, when W.S. Halsted[1,2] clearly elucidated a mechanism of breast cancer spread and used it to design and support the radical mastectomy, surgical and radiotherapeutic approaches to most cancers have been based on this theory. The Halsted theory proposed that cancer spread is orderly, extending in a contiguous fashion from the primary tumor through the lymphatics to the lymph nodes and then to distant sites. Radical en bloc surgery, such as radical neck dissection in continuity with removal of the primary tumor, radical hysterectomy, and primary and regional irradiation for a variety of tumor sites are all based on this notion of cancer spread. More recently, another hypothesis has gained prominence, also first suggested with regard to breast cancer.[3-5] This systemic hypothesis proposes that clinically apparent cancer is a systemic disease. Small tumors are just an early manifestation of such systemic disease, which, if it is to metastasize, has already metastasized. Lymph node involvement is not orderly contiguous extension, but rather a marker of distant disease. Systemic metastases are multiple and widespread, and when subclinical are referred to as micrometastases. Under these circumstances, treatment of local or regional disease should not affect survival.

Both the contiguous and systemic theories of cancer pathogenesis are too restricting and do not consider what is now known about tumor progression during clinical evolution. A third paradigm, one that synthesizes the contiguous-systemic dialectic, has been suggested by one of us[6] to explain the natural history of breast cancer. This thesis argues that cancer comprises a biologic spectrum extending from a disease that remains localized to one that is systemic when first detectable but with many intermediate states. Metastases are a function of both tumor size and tumor progression.

While much tumor evolution occurs during the preclinical period, we suggest that there is a progression of malignancy during the clinical evolution of a cancer. There is some evidence to support this progression of clinical cancer because pathologic grade usually correlates with tumor size, with smaller tumors being of lower grade than large ones.[7-10] Although this may be owing in part to the more rapid growth of high-grade tumors, it is also consistent with tumor progression during the clinical evolution of the tumor. Such possible tumor progression with increasing metastatic capacity during the clinically apparent period is receiving increasing support as we learn more about the multistep nature of the development of malignancy.[11-13] Once tumors become invasive, they may gradually acquire the properties necessary for efficient and widespread metastatic spread.[14] Therefore the likelihood, number, and even sites of metastases may reflect the state of tumor development. This suggests that there are tumor states intermediate between purely localized lesions and those widely metastatic. Such clinical circumstances are not accounted for by either the contiguous or the systemic hypotheses. The systemic hypothesis is binary: metastases either do or do not exist. If present, even if microscopic, they are extensive and widespread. The contiguous hypothesis considers systemic metastases to occur only after nodal disease; but when they occur, they are also blood borne, extensive, and widespread.

From considerations of these theories of cancer dissemination, in the light of the emerging information on the multistep nature of cancer progression, we propose the existence of a clinical significant state of *oligometastases*. For certain tumors, the anatomy and physiology may limit or concentrate these metastases to a single or a limited number of organs. The likelihood of the oligometastatic state should correlate with the biology of tumor progression, rough clinical surrogates of which, for many tumors, might be primary tumor size and grade. Metastasizing cells may seed specific organs as a function of the seeding tumor cell number and characteristics as well as the receptivity of the host organ. The importance of "seed and soil" have been considered elsewhere[15,16] and will not be discussed further. Tumors early in the chain of progression may have metastases limited in number and location because the facility for metastatic growth has not been fully developed and the site for such growth is restricted (this is in contrast to micrometastases, which, although small in size, are extensive in number). With further progression, the tumor seeding efficiency increases and becomes less fastidious with regard to the location of metastatic growth. In addition to this progression of malignancy, the increasing primary tumor size and therefore cell number should also be correlated with the increasing number of cells seeding. Tumor size is the principal basis of tumor staging and, with histologic grade, correlates with the likelihood of metastases.[6,10,16] This, we suggest, is due to the number of tumor cells, the tumor vascularity, and malignant progression as tumors grow.

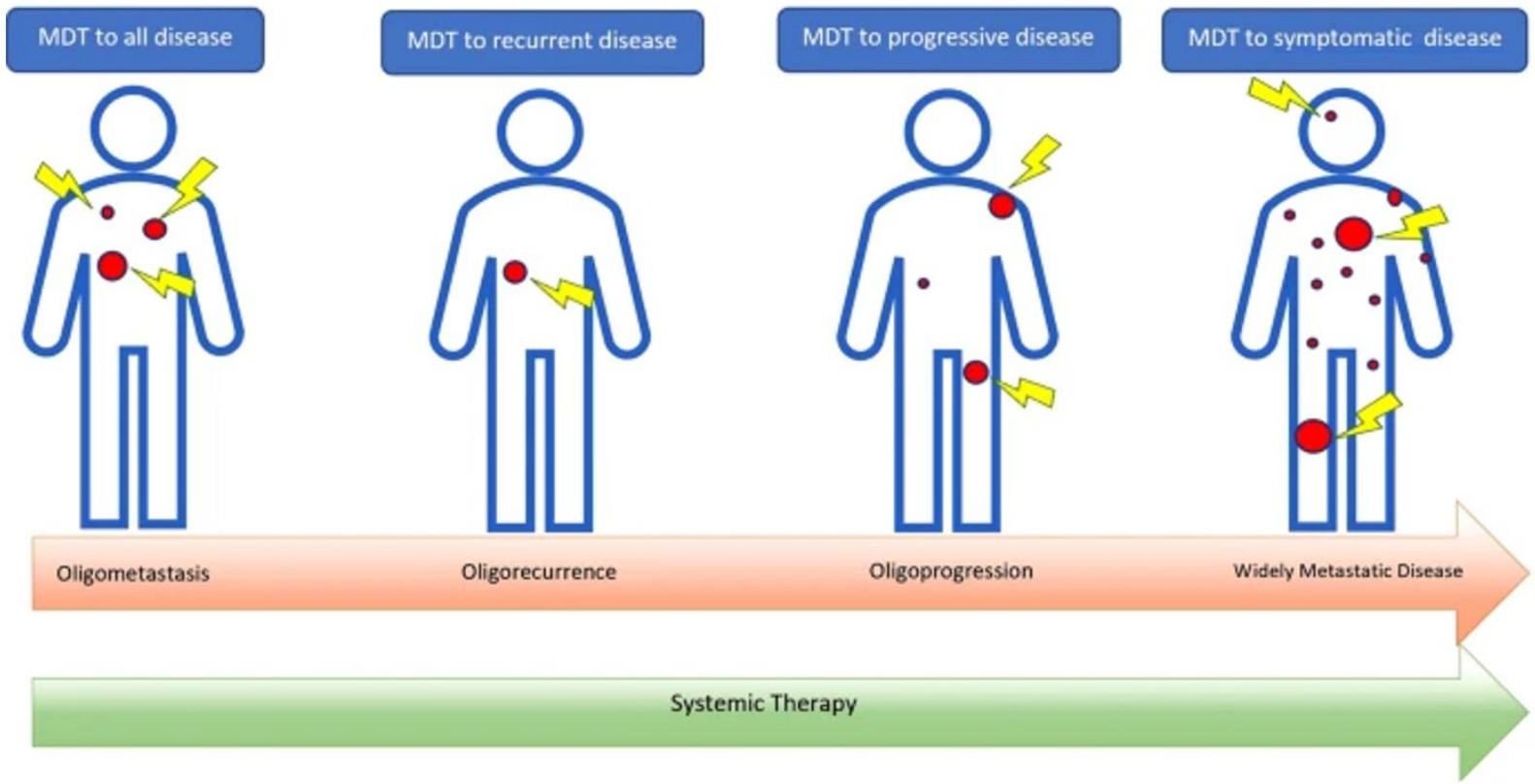
An attractive consequence of the presence of a clinically significant oligometastatic state is that some patients so affected should be amenable to a curative therapeutic strategy. The occasional success of surgical excision or

8 *Journal of Clinical Oncology*, Vol 13, No 1 (January), 1995: pp 8-10

Samuel Hellman
Ralph R. Weichselbaum
The University of Chicago
Chicago, IL

Hellman S, Weichselbaum RR. Oligometastases. *J Clin Oncol*. 1995;13(1):8-10

Oligo-something disease

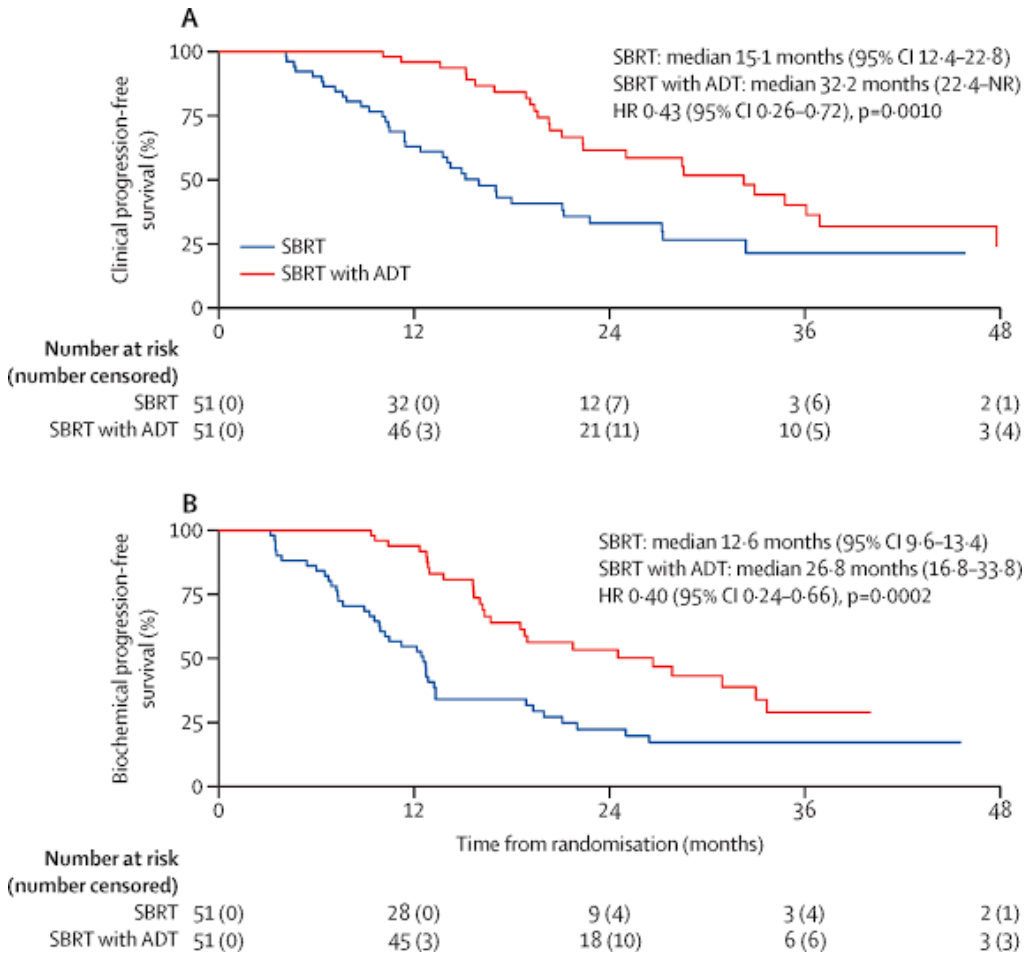


Beckham TH, Yang TJ, Gomez D, Tsai CJ. Metastasis-directed therapy for oligometastases and beyond. *Br J Cancer*. 2021;124(1):136-141. doi:10.1038/s41416-020-01128-5

ADT with SBRT versus SBRT alone for hormone-sensitive oligorecurrent prostate cancer (RADIOSA): a randomised, open-label, phase 2 clinical trial

Giulia Marvaso, Giulia Corrao*, Mattia Zaffaroni, Maria Giulia Vincini, Chiara Lorubbio, Sara Gandini, Cristiana Fodor, Sofia Netti, Dario Zerini, Stefano Luzzago, Francesco Alessandro Mistretta, Konstantinos Venetis, Giulia Cursano, Tiziana Burla, Ketti Mazzocco, Federica Cattani, Giuseppe Petralia, Nicola Fusco, Gabriella Pravettoni, Gennaro Musi, Ottavio De Cobelli, Chad Tang, Piet Ost, David A Palma, Roberto Orecchia, Barbara Alicja Jereczek-Fossa*

- Randomized phase II trial of SBRT alone vs. SBRT + ADT for hormone-sensitive oligorecurrent prostate cancer
  - RT dose to oligometastatic sites 30 Gy/3 fx EOD
  - ADT duration – 6 months
  - Primary outcome – clinical PFS
- Study met primary outcome of improved clinical PFS as well as biochemical PFS with the addition of 6-month short-term ADT



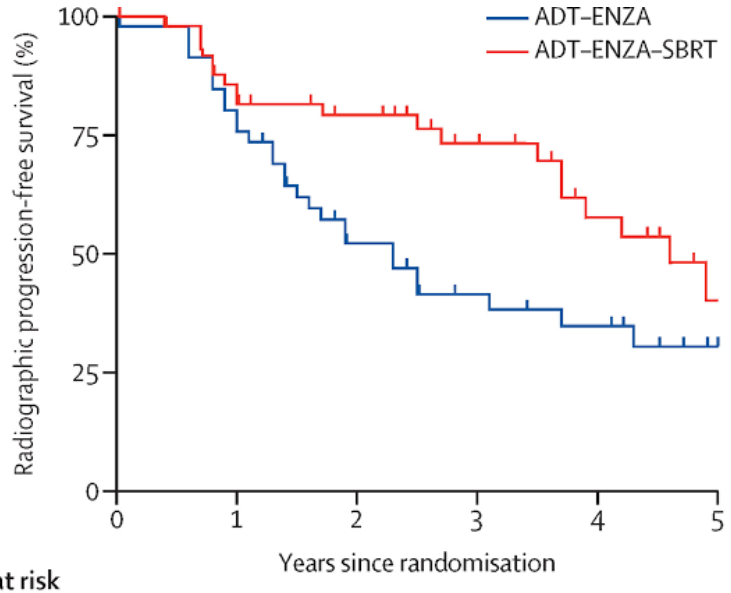
Marvaso et al. Lancet Oncol. 2025 Mar;26(3):300–311.

The Lancet Oncology
Volume 26, Issue 9, September 2025, Pages 1158-1167

Articles

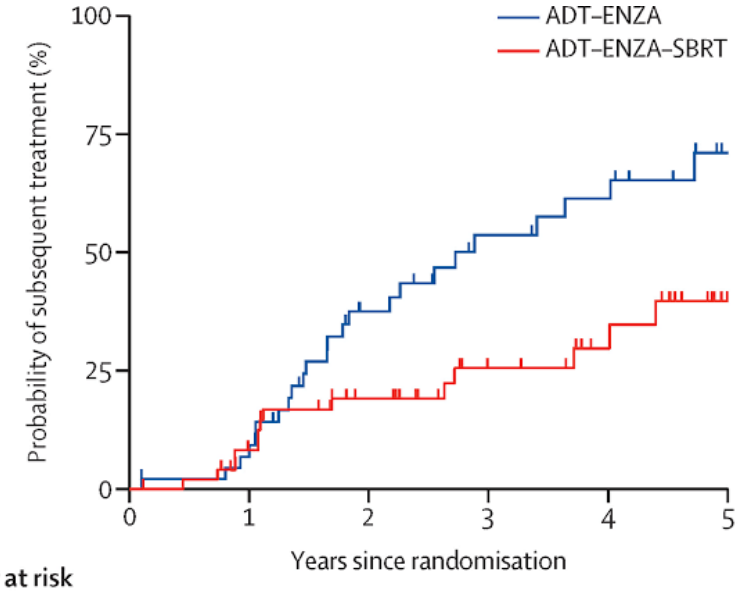
Metastases-directed therapy in addition to standard systemic therapy in oligometastatic castration-resistant prostate cancer in Canada (GROUQ-PCS 9): a multicentre, open-label, randomised, phase 2 trial

Tamim Niazi MD [a], Prof Fred Saad MD [b], Steven Tisseverasinghe MD [c], Rashmi Koul MD [d], Isabelle Thibault MD [e], Peter W M Chung MD [f], George Wakil MD [g], Michael Lock MD [h], Guila Delouya MD [b], Boris Bahoric MD [a], Andrew Feifer MD [i], Venkata Ramana Agnihotram MD [j,l], Theodoros Tsakiridis MD [k], Fabio L Cury MD [l], Rafika Dahmane MD [m], Nikhilesh Gajanan Patil MD [n], Scott Tyldesley MD [o]



Number at risk (censored)						
ADT–ENZA	48 (··)	37 (4)	20 (3)	13 (1)	10 (6)	2 (1)
ADT–ENZA–SBRT	52 (··)	42 (5)	33 (9)	22 (4)	15 (9)	2 (2)

- Randomized phase II trial of MDT in castrate-resistant prostate cancer
  - Randomization – ADT-enzalutamide ± SBRT to all oligometastatic sites (≤5 mets)
- SBRT significantly improved radiographic PFS 4.6 years vs. 2.3 years
- In the setting of advanced castrate-resistant prostate cancer, SBRT has a role in combination with ADT and AR inhibitors



Number at risk (censored)						
ADT–ENZA	48 (··)	39 (5)	21 (3)	13 (1)	10 (6)	2 (1)
ADT–ENZA–SBRT	52 (··)	43 (6)	32 (10)	20 (5)	14 (10)	2 (1)

Niazi et al. Lancet Oncol. 2025 Sept;26(9):1158-1167.

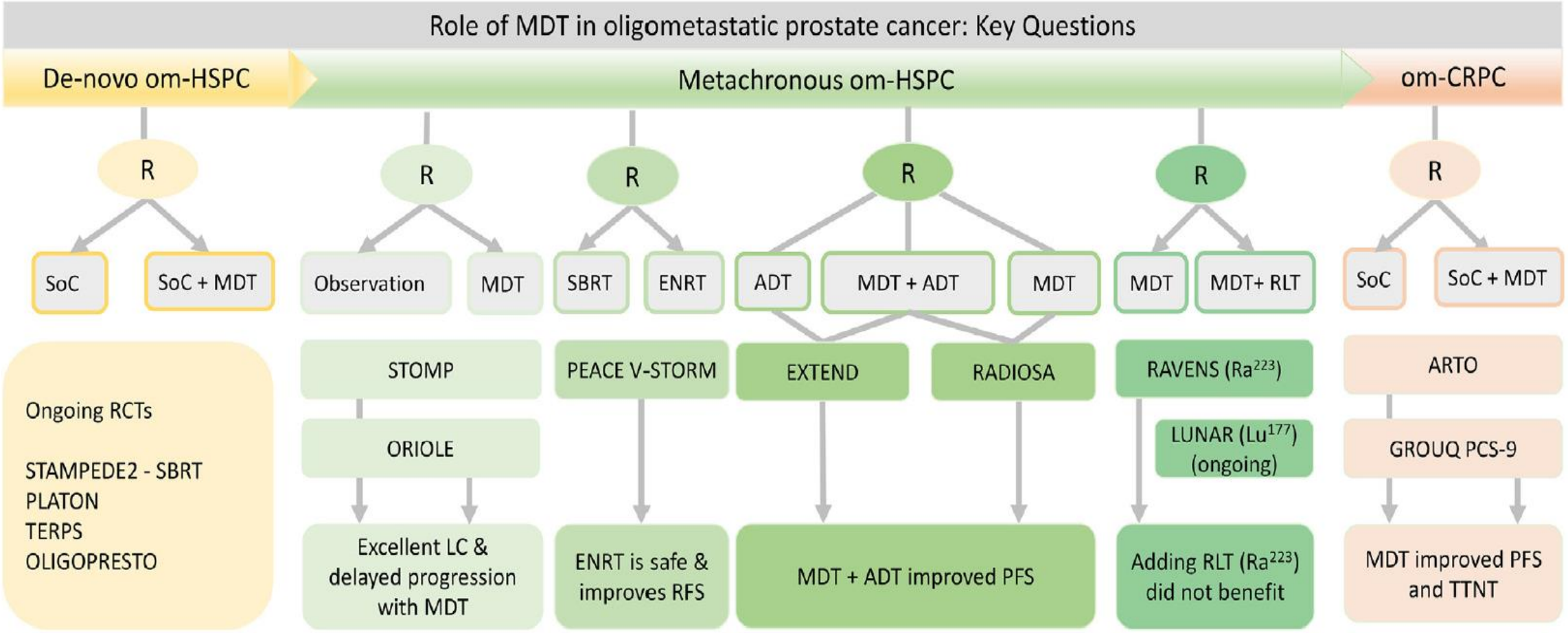
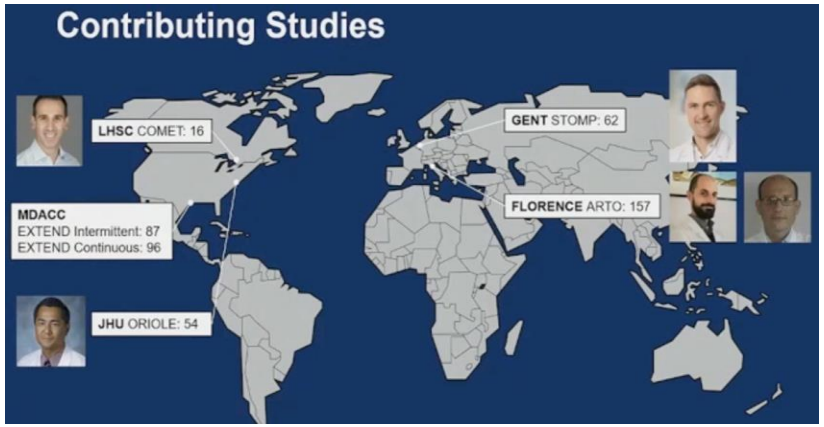


Table 1 Studies Incorporating MDT in De-Novo omHSPC

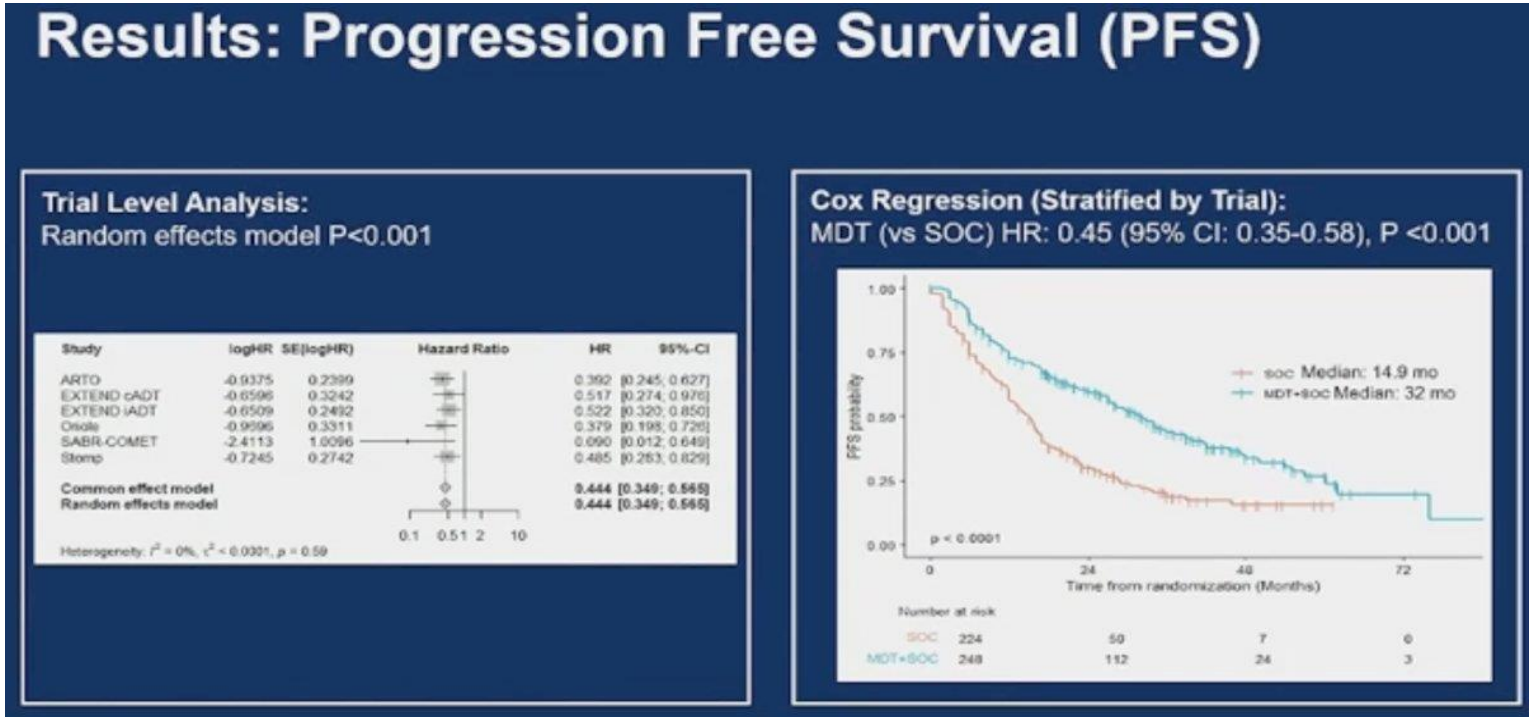
Published Studies Author	Setting (%)	Patients (n)	Type	Imaging	Intervention	Endpoint
Ongoing studies						
STAMPEDE 2: SABR trial (NCT06320067)	OMD (100%)	2476	Phase III RCT	CT/BS (1-5 lesions)	Standard Arm: SoC Test Arm: SoC + SBRT	Dual primary endpoints rPFS OS
PLATON trial (NCT03784755)	OMD ORD (stratification factor)	410	Two-arm phase II RCT	PSMA-PET CT/BS (stratification factor)	Standard Arm: Systemic therapy + Local treatment to prostate Test Arm: Systemic therapy + Local treatment to prostate and metastatic sites	FFS
TERPs trial (NCT05223803)	OMD (100%)	122	Phase II RCT	CT/BS (1-3 lesions) PSMA-PET (1-5 lesions)	Standard Arm: BST + RT to prostate Test Arm: BST + RT to prostate + SBRT	2 year FFS

Singh M, et al, Semin Radiat Oncol. 2025 Jul;35(3):423-432.

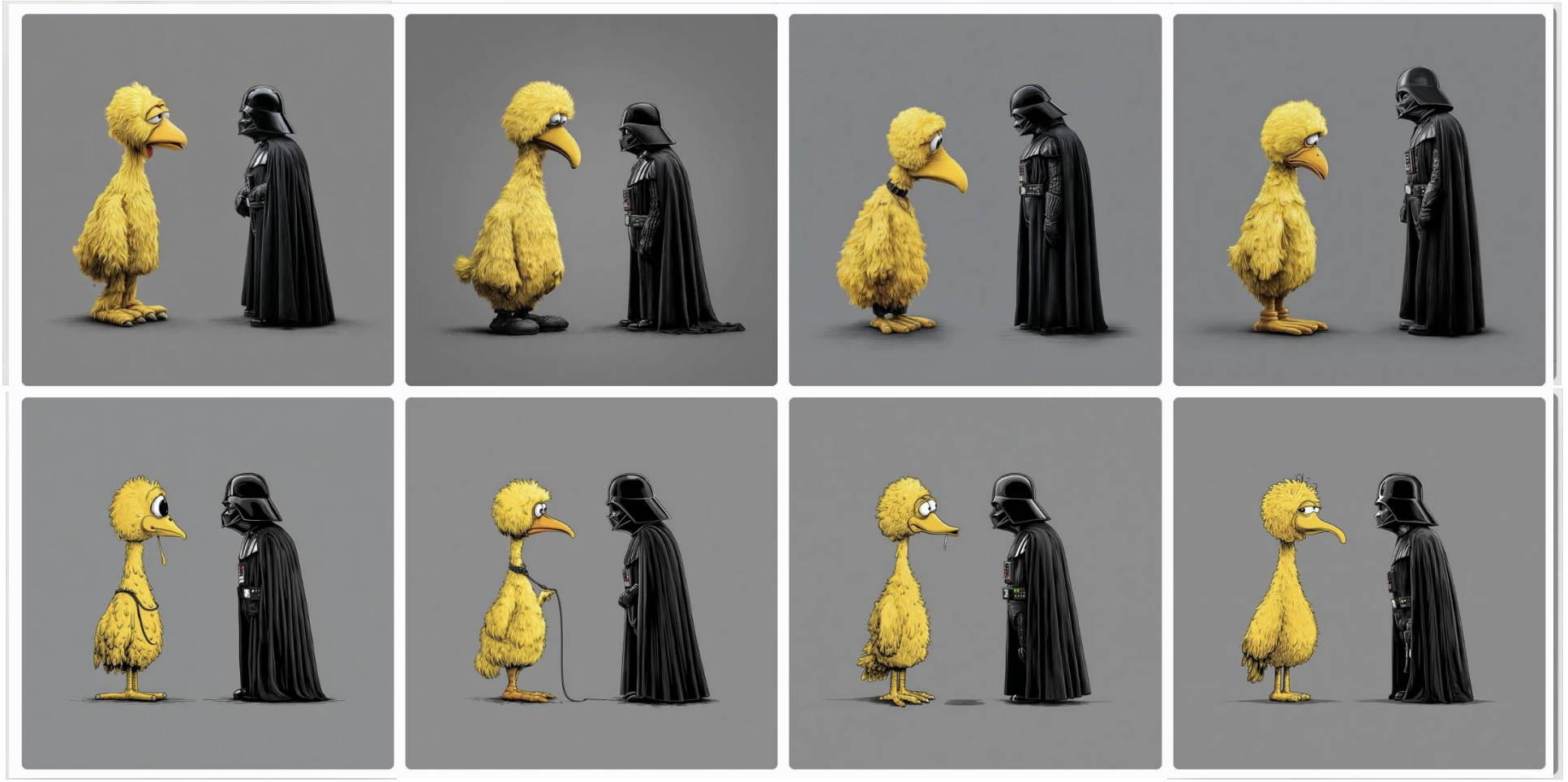
ASCO GU2025: WOLVERINE meta-analysis C. Tang et al



- Meta-analysis of 5 randomized trials on omPC (standard of care +/- MDT):
  - **improvements in PFS, rPFS, and castration resistance-free survival**
  - MDT improved overall survival with a p-value of 0.051
- MDT benefit was maintained **across all subgroups** including patients with untreated primaries, staging imaging, castration sensitive/resistance status, and treatment with/without ADT.



Thank you!



Systemic Therapy Combinations

- Combining SBRT with advanced systemic therapy approaches—including AR inhibition—offers a synergistic strategy to treat both visible and microscopic disease

- However, is it time to rethink the paradigm of ADT as the backbone of management of metastatic prostate cancer in the oligorecurrent setting?