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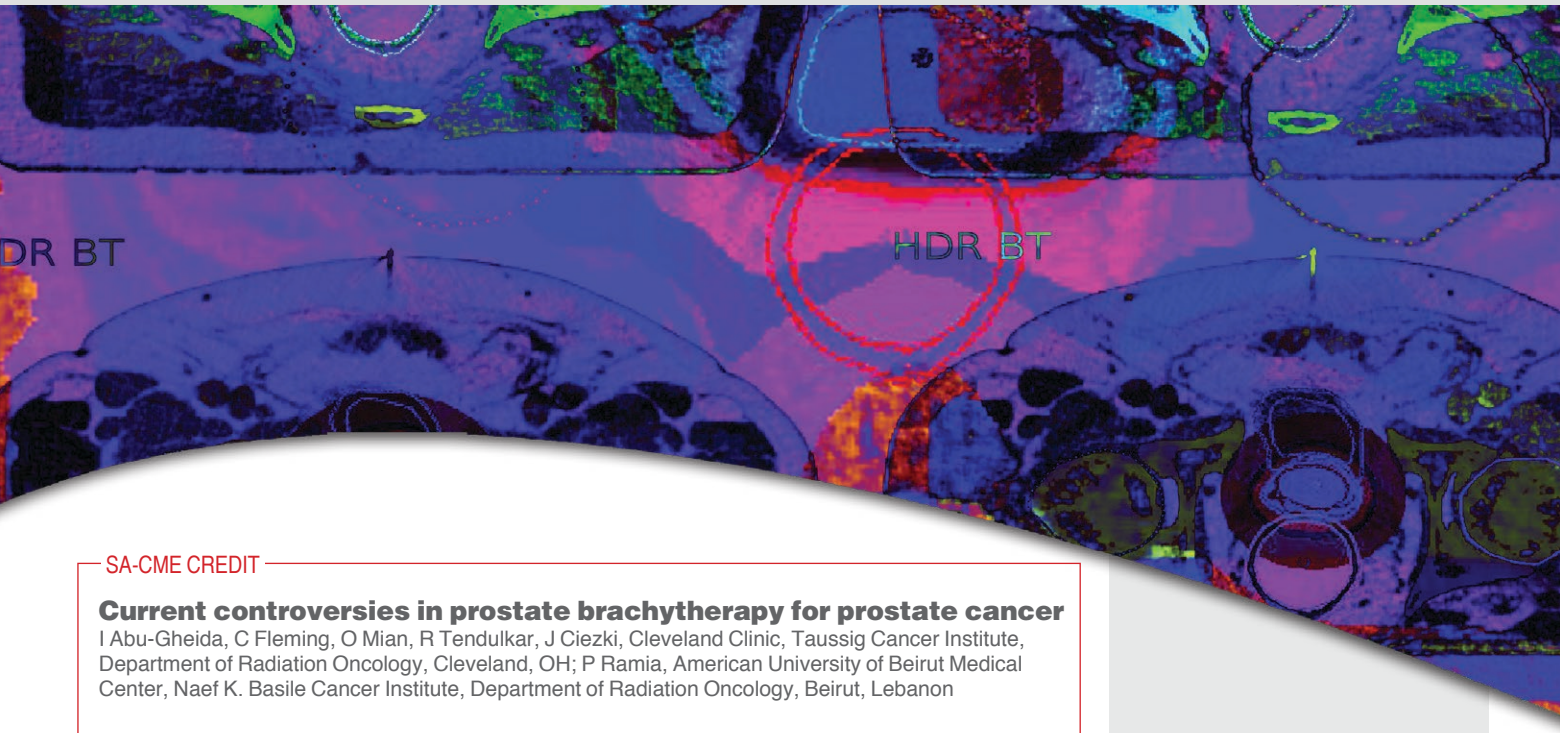

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Current controversies in prostate brachytherapy for prostate cancer

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High dose rate brachytherapy for prostate cancer: Current techniques and applications to varying disease presentations

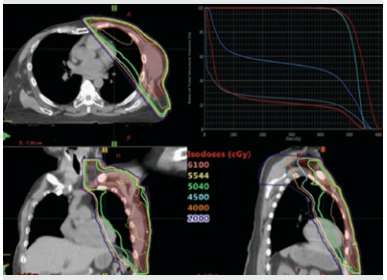
DJ Krauss, Oakland University William Beaumont School of Medicine, Royal Oak, MI

Daily image guidance as a noninvasive technique of rectal emptying in postprostatectomy radiation

DA Elliott, University of Toledo, Department of Radiation Medicine, Toledo, OH; N Nabavizadeh, JA Tanyi, AY Hung, Oregon Health & Science University, Knight Cancer Institute, Department of Radiation Medicine, Portland, OR

Technology Trends: Protons for prostate cancer—Bragging points, trials and treatment optimization

MB Massat



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PROSTATE CANCER FOCUS

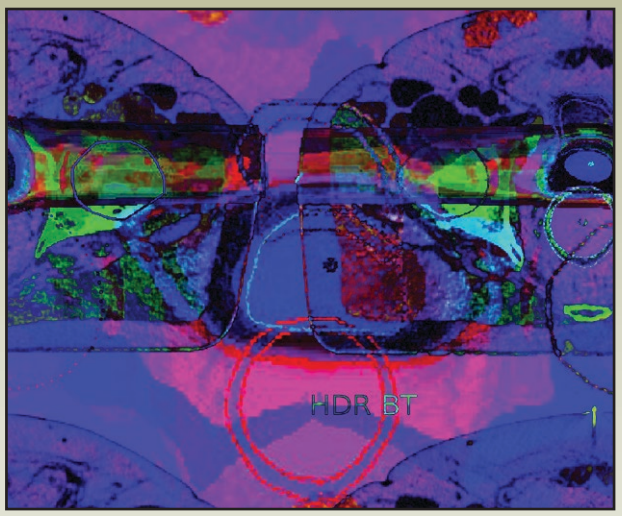
SA-CME CREDITS

RADIATION ONCOLOGY RESEARCH

Erratum

The SA-CME Information in the June 2017 issue (Vol 6 No 2, p. 5) should have listed the following dates for the Non-melanomatous skin cancer and Head and neck mycosis fungoides articles: June 1, 2017 (release and review date); May 31, 2019 (expiration date).

The June 2017 Technology Trends article (Electronic brachytherapy for skin cancer: Problems and progress Vol 6 No 2, p. 24-25), stated that the "University of California, Irvine, is conducting a multicenter study comparing electronic brachytherapy with Mohs micrographic surgery." The study was not initiated due to terminated funding.



EDITORIAL

TECHNOLOGY TRENDS

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EDITORIAL

Prostate brachytherapy: Pro-seeding forward

John Suh, MD, FASTRO
Editor-in-Chief

Welcome to the September issue of *Applied Radiation Oncology*, which focuses on prostate cancer, the most common cancer in men after skin cancer. Although the overall use of radiation modalities for prostate cancer has declined significantly since 2004,[1] it remains a very important treatment for this malignancy.

The two review articles featured this month, both of which offer SA-CME credit, examine key issues and approaches surrounding prostate brachytherapy, a very effective and efficient but underutilized treatment option for prostate cancer. *Current controversies in prostate brachytherapy for prostate cancer* is an insightful article exploring indications for low dose rate (LDR) brachytherapy, evolving guidelines, and criteria for patient selection. It also tackles the value of LDR brachytherapy in high-risk prostate cancer patients based on recent trials and retrospective studies, and provides a dosimetric analysis comparing LDR brachytherapy with external-beam radiation therapy (EBRT).

A second review article, *High dose rate brachytherapy for prostate cancer: current techniques and applications to varying disease presentations,* offers a comprehensive look at patient selection, use of HDR in conjunction with EBRT, and HDR brachytherapy as monotherapy. The article also assesses the logistics, advantages, and disadvantages associated with various HDR treatment planning approaches, and analyzes dosimetric goals and constraints.

We are also pleased to showcase the research findings in *Daily image guidance as a noninvasive technique of rectal emptying in postprostatectomy radiation*. This study discusses how rectal emptying serves as an easy intervention when rectal filling is noted on daily cone-beam computed tomography prior to radiation treatment—a practice linked to lower radiation dose to the rectum and potential decreased toxicity.

A final focus article is *Protons for prostate cancer: Bragging points, trials and treatment optimization*. This Technology Trends piece provides an update on controversies, clinical investigations, contraindications, and issues of uncertainty and motion associated with the modality.

Two case reports are featured this month as well: *Volumetric-modulated arc therapy improved heart and lung sparing for a left-sided chest wall and regional nodal irradiation case* is a well-written summary of how VMAT was the treatment of choice to spare the heart and lung without sacrificing target coverage, while outweighing the risk of secondary cancer. The second case, *An abscopal effect in a case of neuroendocrine atypical carcinoid lung cancer*, describes the first reported abscopal effect account of its kind in a 67-year-old never-smoker.

We hope you enjoy our prostate cancer issue and greatly look forward to the 59th Annual ASTRO Meeting, Sept. 24-27. Safe travels, and see you soon in San Diego!

Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

Reference

1. Malouff T, Mathy NW, Marsh S, et al. Trends in the use of radiation therapy for stage IIA prostate cancer from 2004 to 2013: a retrospective analysis using the National Cancer Database. *Prostate Cancer Prostatic Dis.* 2017;20(3):334-338. doi:10.1038/pcan.2017.15.

SA–CME Information

CONTROVERSIES IN LOW DOSE RATE PROSTATE BRACHYTHERAPY (page 6)

Description: Indications for low dose rate prostate brachytherapy (LDR-BT) monotherapy for high-risk or unfavorable intermediate-risk prostate cancer are currently not based on level I evidence. Guidelines discussing brachytherapy indications do not highlight the important RTOG 0232 interim analysis regarding the role of LDR monotherapy and toxicity profile advantage, nor do guidelines highlight the dosimetric value of brachytherapy. This article summarizes the role of LDR-BT in managing prostate cancer and examines patient selection.

Learning Objectives:

After completing this activity, participants will be able to:

1. Summarize the role of LDR-BT in prostate cancer management.
2. Discuss patient selection for LDR-BT.
3. Understand dosimetric analysis comparison of LDR-BT and external beam.

Authors: Ibrahim Abu-Gheida, MD, is a radiation oncology fellow, **Christopher Fleming, MD**, is a resident, **Omar Mian, MD, PhD,** is associate staff, **Rahul Tendulkar, MD**, is the clinical director and residency program director, and **Jay Ciezki, MD**, is a staff physician, Cleveland Clinic, Taussig Cancer Institute, Department of Radiation Oncology, Cleveland, Ohio. **Paul Ramia, MD**, is a resident at the American University of Beirut Medical Center, Naef K. Basile Cancer Institute, Department of Radiation Oncology, Beirut, Lebanon.

HIGH DOSE RATE BRACHYTHERAPY FOR PROSTATE CANCER (page 12)

Description: No direct clinical evidence supports the superiority of high-dose rate brachytherapy (HDR-BT) over low dose rate brachytherapy (LDR-BT), or vice versa, in terms of improved tumor control or reduced toxicity in patients with prostate cancer. This review fosters understanding of patient selection and technical description, examining HDR-BT in conjunction with external beam, and HDR-BT as monotherapy.

Learning Objectives:

After completing this activity, participants will be able to:

1. Understand clinical and technical factors for HDR prostate brachytherapy patient selection.
2. Understand logistics, pros and cons of approaches to HDR treatment planning (ie, CT vs. TRUS vs. MRI-based dosimetry).
3. Determine which patients are suited for definitive HDR-BT (monotherapy) vs. HDR-BT combined with external beam.
4. Understand dosimetric goals/constraints.
5. Understand dosing regimens (and evidence) for HDR-BT as monotherapy and boost.

Author: Daniel J. Krauss, MD, is an associate professor of radiation oncology, Oakland University William Beaumont School of Medicine, Royal Oak, Michigan

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Date of release and review: September 1, 2017
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SA-CME (see page 5)

Current controversies in prostate brachytherapy for prostate cancer

Ibrahim Abu-Gheida, MD; Christopher Fleming, MD; Paul Ramia, MD; Omar Mian, MD PhD; Rahul Tendulkar, MD; and Jay Ciezki, MD

Prostate cancer remains the most commonly diagnosed malignancy in men. An estimated 161,360 new cases will be diagnosed in 2017 in the United States, accounting for 19% of male cancer diagnoses and 8% of cancer mortality in men.[1] Localized prostate cancer management represents a challenge for clinicians as several definitive treatment options exist including surgical resection, external-beam radiation therapy (EBRT) +/- brachytherapy boost, high dose rate brachytherapy (HDR-BT), and low dose rate brachytherapy (LDR-BT). Treatment recommendations and decisions are often based on patient age, comorbidities, risk stratification, as well as patient preference. LDR-BT is an attractive option for many patients, either as monotherapy or in combination with EBRT. Brachytherapy techniques have continued to evolve over the past several decades with new data supporting technical innovation and revised treatment indications. The purpose of this review is to summarize the role of LDR-BT in managing prostate cancer and to discuss patient selection in a contemporary context.

Dr. Abu-Gheida *is a radiation oncology fellow,* ***Dr. Fleming*** *is a first-year resident,* ***Dr. Mian*** *is associate staff,* ***Dr. Tendulkar*** *is the clinical director and residency program director, and* ***Dr. Ciezki*** *is a staff physician, Cleveland Clinic, Taussig Cancer Institute, Department of Radiation Oncology, Cleveland, OH.* ***Dr. Ramia*** *is a second-year resident at the American University of Beirut Medical Center, Naef K. Basile Cancer Institute, Department of Radiation Oncology, Beirut, Lebanon.* *The authors would like to thank Chirag Shah, MD, and Salim Balik, PhD, for their contributions.*

History of Brachytherapy and Modern Techniques

Prostate LDR-BT dates back approximately 100 years, when radium was used to deliver radiation for enlarged prostates and prostate cancer.[2,3] Given the poor efficacy and significant toxicity associated with radium, this isotope was abandoned in favor of radioactive gold isotopes (^{198}Au).[4] Iodine-125 (^{125}I) and other isotopes largely replaced ^{198}Au due to radiobiological and physical advantages.[5] Modern techniques with template and transrectal ultrasound (TRUS) guidance have been used for 30 years with excellent treatment tolerance and long-term control.[5-7] The two most widely used radioactive sources in prostate LDR-BT are ^{125}I and palladium-103 (^{103}Pd) (**Table 1**). Peschel et al studied 272 patients treated with ^{125}I or ^{103}Pd and found no difference in biochemical disease-free survival.[8] However, complication rates appeared to be higher for ^{125}I, which is consistent with its radiobiological characteristics.[8] Given their excellent disease control rates, ^{125}I, ^{103}Pd and, more recently, radioactive cesium (cesium-131) are now preferred options for LDR-BT in patients who meet modern eligibility and indications criteria.[9-11]

Classic Selection Guidelines

Indications for prostate LDR-BT have been continuously evolving over the past decade. The 1999 American Brachytherapy Society (ABS) recommendations by Nag et al initially suggested prostate brachytherapy as a monotherapy only for patients with low-risk disease defined per the D'Amico criteria[12] as T1-T2a, Gleason sum < 6, and PSA < 10 ng/ml,[13] respectively. The ABS guidelines were subsequently updated to include prostate LDR monotherapy as an option for both low-risk and selected patients with intermediate-risk prostate cancer.[14] Currently, the National Comprehensive Cancer Network (NCCN) recommends brachytherapy

SA-CME (see page 5)

Table 1. Characteristics of the Two Most Common Prostate LDR-BT Radionuclides

	Iodine-125	Palladium-103
Half Life	60 days	17 days
Dose Rate	Slower	Faster
Half Value Layer in Lead (mm)	0.02	0.01
Average Photon Energy (MeV)	0.028	0.021
Dose-Monotherapy (Gy)	145	125
Dose-Boost (Gy)	110	90-100

Key: Gy: Gray, EBRT: external-beam radiation therapy

monotherapy for very low, low, and low-volume-intermediate-risk prostate cancer patients.[15] Contraindications for brachytherapy have also been changing; previous ABS guidelines used a prostate volume of > 60 cc as a cutoff to recommend against brachytherapy,[13,14] while more recent NCCN guidelines consider only "very large" gland size as a relative contraindication for brachytherapy without specifying a cutoff value.[15] A summary of the current guidelines is provided in **Table 2**.

Table 2. Summary of Classical Prostate Brachytherapy Guidelines

		Nag 1999 ABS[13]	Davis 2012 ABS[14]	NCCN 2017 v2[15]
Indications	Monotherapy	< T2a Gleason sum < 6 PSA < 10 ng/ml	Low risk Int risk (optional)	Very low risk Low risk Int risk (low volume)
	With EBRT	T2b, T2c Gleason sum 8–10 PSA > 20 ng/ml *Other relative indications* PNI Multiple positive biopsies Bilateral disease Capsular penetration	Int risk (optional) High risk	Int risk High risk Very High risk
	Other indications	Not applicable	Not applicable	Salvage post definitive RT
	With ADT	Patients with large prostate (> 60 cc) High risk	Int risk (optional) Very High risk	High risk
	Contraindications to BT	***Relative*** Large median lobes History of pelvic RT High AUA score History of multiple pelvic surgeries Severe diabetes / healing problems Expected technical difficulties TURP Gland size > 60 cc Seminal vesicles involved ***Absolute*** Life expectancy < 5 years Large /unhealed TURP defect Unacceptable operative risks Metastatic disease	***Relative*** IPSS scores > 20 Small TURP defects History of pelvic RT IBD Large median lobes Gland size > 60cm^3 ***Absolute*** Limited life expectancy Ataxia-telangiectasia Distant metastases Unacceptable operative risks Absence of rectum Large TURP defects	***Only Relative ("not ideal")*** Very Large gland Very Small gland Bladder outlet obstruction/High IPSS score Previous TURP

Key: EBRT: external-beam radiation therapy; ADT: androgen deprivation therapy; PSA: prostate-specific antigen; PNI: perineural invasion; TURP: transurethral resection of prostate; AUA: American Urological Association; IPSS: International Prostate Symptom Score; Int Risk: intermediate risk.

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Table 3. Prospective LDR-BT Published Data

Trial	Risk Category	Treatment Arm	N=	Primary Endpoint bPFS			Significance	Grade III Toxicity	
				5 yr	7 yr	9 yr			
ASCENDE-RT[17,18]			398					Late	
	Intermediate (30.7%) High (69.3%)							GU	GI
		EBRT + LDR-BT	198	88.7 ±4.8	86.2 ± 5.4	83.3 ± 6.6	Log-rank P < 0.001	18%	8%
		DE-EBRT	200	83.8 ± 5.6	75.0 ± 7.2	62.4 ± 9.8		5%	3%
								SS	NSSD
RTOG 0232[16]			588	**5 yr PFS**				Overall Acute: 8% NSSD	
	Low-intermediate							Late GU	Late GI
		LDR-BT	292	86 (81,90)			P < 0.001 for futility	3%	2%
		EBRT +LDR-BT	287	85 (80,90)				7%	3%
								USSR	

Key: LDR-BT: low dose rate brachytherapy; EBRT: electron-beam radiation therapy; bPFS: biochemical progression-free survival; PFS: progression-free survival; SS: statistically significant; NSSD: not statistically significant difference; GU: genitourinary; GI: gastrointestinal; USSR: unknown statistical significance reported

Use of brachytherapy monotherapy or in combination with androgen deprivation therapy (ADT) for high-volume-intermediate-risk or high-risk prostate cancer patients remains an area of debate. Despite the absence of level-I evidence or randomized trials in this patient population, unfavorable intermediate-risk and high-risk men are generally not offered brachytherapy as monotherapy.

Modern Outcomes with Prostate LDR Brachytherapy

The initial report of the Nuclear Research and Consultancy Group (NRG) Oncology/Radiation Therapy Oncology Group (RTOG) 0232 comparing LDR-BT monotherapy to combined EBRT followed by an LDR-BT boost for intermediate-risk prostate cancer patients showed no difference in progression-free survival and overall survival with a median follow-up of 6.7 years. Moreover, there was no overall acute grade 3+ toxicity difference in both groups, but rather an overall grade 3+ late and grade 3+ GU toxicity profile favoring LDR monotherapy alone.[16] Another recent randomized trial, Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy (ASCENDE-RT), evaluated the role of LDR-BT in the management of intermediate- and high-risk prostate cancer and revealed a biochemical progression-free survival (bPFS) advantage favoring the addition of LDR-BT to EBRT for intermediate- and high-risk groups.[17] This trial did indicate a higher grade 3 GU toxicity at 5 years in the LDR-BT group, with half of those attributed to urethral strictures, while no other statistically significant differences in toxicity were found (**Table 3**).[18] These two trials, in addition to two previous prospective trials comparing EBRT alone to EBRT in combination with HDR-BT,[19,20] formed the basis for updated American Society of Clinical Oncology (ASCO) guidelines in 2017.[11] These guidelines support LDR-BT monotherapy as an option for low-intermediate-risk patients, and recommend a brachytherapy boost for intermediate- and high-risk patients treated with EBRT, conceding that there may be increased GU toxicity compared to EBRT alone.[11]

It is important to note that the recent ASCO guidelines did not address the impact of the interim analysis of the NRG oncology/RTOG 0232 study, which was originally designed to test for a 10% increase in the 5-year PFS for EBRT with LDR-BT boost.[16] The RTOG 0232 findings suggest LDR-BT monotherapy is at least as effective for patients with favorable intermediate-risk prostate cancer when compared to combined modality treatment.[16] Moreover, absent from the guidelines

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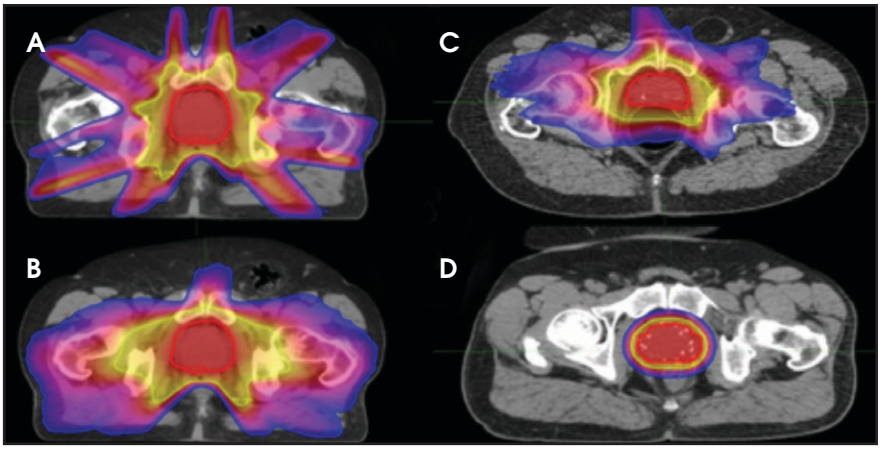

FIGURE 1. *Dosimetric comparison of (A) intensity-modulated radiation therapy (IMRT), (B) volumetric-modulated arc therapy (VMAT), (C) stereotactic body radiation therapy (SBRT), and (D) low dose rate brachytherapy (LDR-BT). Isodose lines correspond to 25% (blue), 50% (yellow), and 100% (red) of prescription dose.*

is an acknowledgement of the important finding that LDR-BT monotherapy had a better toxicity profile compared to combined modality therapy.[11,16] Similarly for high-risk prostate cancer patients, in the absence of randomized data comparing brachytherapy monotherapy (with or without ADT) against other treatment modalities, it seems worthwhile for the guidelines to incorporate two recent large retrospective series from the Cleveland Clinic and from the National Cancer Database.[21,22] These studies demonstrated a biochemical relapse-free survival (bRFS) and prostate-cancer-specific mortality (PCSM) advantage to LDR-BT monotherapy over radical prostatectomy and EBRT, respectively, in patients with high-risk prostate cancer.[21,22] Importantly, the toxicity profile in these retrospective studies again favored LDR-BT over EBRT or surgery when comparing an ^{125}I LDR-BT dose of 144 Gray (Gy) to an EBRT dose of at least 78 Gy or 70 Gy in 2 or 2.5 Gy per fraction, respectively, both with or without ADT, and radical prostatectomy followed by adjuvant or salvage EBRT to a median dose of 70 Gy in 2 Gy per fraction.[21] Finally, we believe that LDR-BT monotherapy is a sufficient treatment option for patients with localized intermediate-risk or high-risk prostate cancer. If combined modality radiation therapy was offered for these patients, we favor brachytherapy after EBRT. One reason is the uncertainty of calculating cumulative dose with external beam after the implant was placed and the potential for increased toxicity of delivering EBRT on top of an active implant. That said, we believe either could be reasonable depending on physician and institutional experience.

Dosimetric Differences Between Brachytherapy and EBRT

While available guidelines provide indications, outcome, toxicity, and, more recently, cost-effectiveness for prostate brachytherapy,[11-13] these guidelines seldom address the radiobiological and dosimetric advantage of brachytherapy. With EBRT it is necessary to account for setup error, patient (external) movement and organ (internal) movement, which are used to generate a planning target volume (PTV). The PTV typically ranges from 0.5 - 1 cm around the clinical target volume (CTV) depending on the method of immobilization and use of image-guided radiation therapy (IGRT).[23] Kneebone et al showed a reduction in the average deviations to 2.9 mm, 2.1 mm and 3.9 mm in the anteroposterior, right-left, and superoinferior directions, respectively, with the incorporation of rigid external immobilization.[24] Internal immobilization with endorectal balloon or spacers are used to further maximize treatment reproducibility, but may result in tissue deformation, increased anterior rectal wall contact to target, diminished patient compliance, increased costs, and possibly increased treatment failure.[25-28] Another challenge sometimes faced during EBRT treatment planning involves imaging artifacts associated with a hip prosthesis that can obscure pelvic anatomy and impair the ability of the treatment-planning system to accurately determine densities for dose modeling.[29] Finally, obese patients tend to be at a higher risk of interfraction setup errors resulting in a higher risk of relapse post EBRT.[30,31] Despite that, adequate EBRT coverage mandates that 3D-CRT or IMRT doses be normalized so that 98% of the PTV receive the prescription dose as per the current ongoing RTOG 0924 trial protocol.[32] For stereotactic body radiation therapy (SBRT) or hypofractionated radiation therapy cases, the dose is prescribed to cover at least 95% of the PTV[33] (**Figure 1A-C**).

On the other hand, for LDR-BT, optimal placement of sources is the key to achieving adequate dose to the prostate while minimizing toxicity to normal tissues (**Figure 1D**).[34] The photon decay characteristics of modern prostate brachytherapy sources result in highly local energy deposition, and generally yield a more conformal dose distribution.[35] Georg et al studied the dosimetric differences among modern radiation therapy techniques including volumetric-modulated arc therapy (VMAT), intensity-modulated proton therapy (IMPT), intensity-modulated carbon-ion therapy (IMIT), LDR-BT, and HDR-BT. All doses were clinically appropriate and were normalized to biologically equivalent fractionations. Brachytherapy was found to be superior

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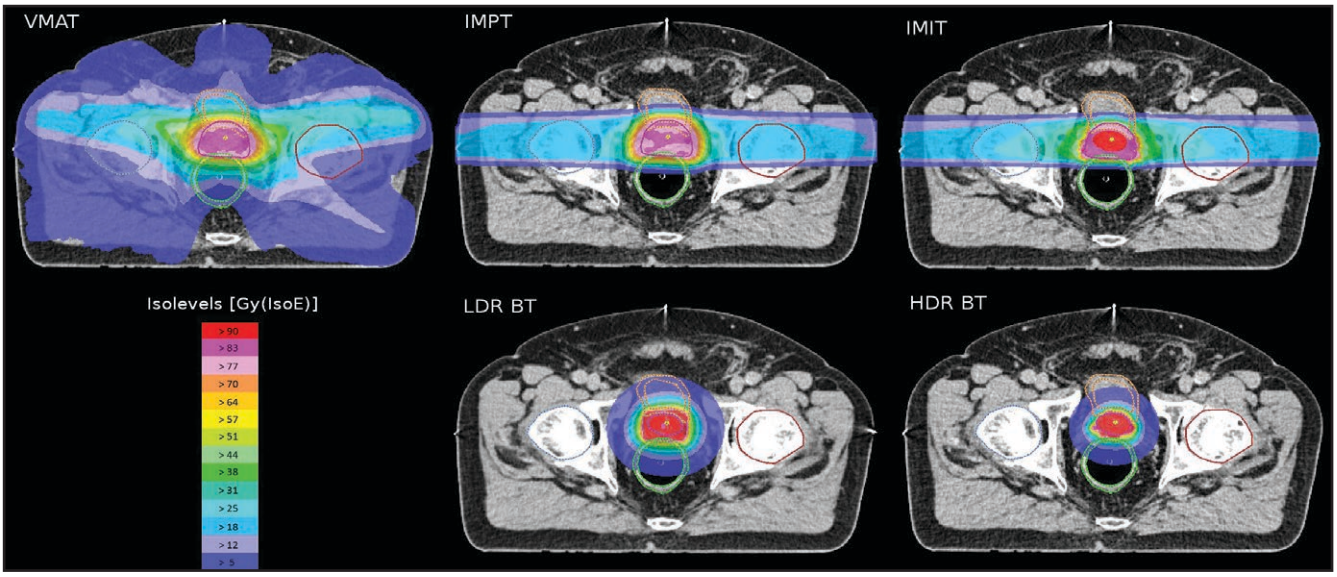

FIGURE 2. *Absolute dose distribution of different treatment modalities after radiobiological conversion (Cited from Georg D et al.* Int. J Radiat Oncol Biol Phys. *2014).*[36]

in sparing normal tissues (**Figure 2**).[36] Moreover, despite modern EBRT and IGRT techniques, given brachytherapy's significant inverse-square dose falloff advantage, intraprostate doses remain significantly higher with brachytherapy compared to EBRT.[37] This allows for dose escalation and increased biological effective dose, hence possibly explaining the improvement in PFS and PCSM, even in men with high-risk prostate cancer.[17,21,22]

Conclusion

In summary, prostate LDR-BT is a well-established treatment modality with excellent long-term outcomes for patients with localized prostate cancer, with similar outcomes between different radionuclides.[10,7] Appropriate patient selection remains a moving target in the modern era, and eligibility guidelines continue to evolve accordingly.[11-13] While brachytherapy as monotherapy is accepted as a standard for low-risk and low-volume-intermediate-risk prostate cancer patients, no randomized data show inferiority to combined treatment modalities in high-volume-intermediate-risk or high-risk prostate cancer patients. Recent multicenter randomized studies (RTOG 0232) have shown similar outcomes and favorable toxicity profiles for LDR-BT monotherapy compared to combined therapy with EBRT for patients with favorable intermediate-risk prostate cancer.[16] Retrospective data from the Cleveland Clinic and National Cancer Database have shown similar efficacy and toxicity results in high-risk patients.[21,22] These outcomes data are underpinned by the dosimetric advantage of brachytherapy over EBRT.[36] Prospective trials to evaluate the role of brachytherapy monotherapy in well-selected high-risk patients are needed to address gaps and shape future guidelines.

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High dose rate brachytherapy for prostate cancer: Current techniques and applications to varying disease presentations

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High dose rate (HDR) brachytherapy has been an option for managing localized prostate cancer since the early 1990s. Several features of this treatment approach make it attractive to both patients and clinicians. First, the convenience of brachytherapy in general—namely, the potential to significantly shorten or eliminate the need for daily external-beam radiation therapy (EBRT) treatment visits that may extend up to 2 months—holds appeal to many younger, healthy, active patients looking to definitively address their disease with minimal disruption to their daily routine. Prostate brachytherapy options include permanent prostate seed implant, or low dose rate (LDR), brachytherapy and temporary prostate implant, more commonly called HDR brachytherapy. Both types of brachytherapy are safe and effective across a range of clinical presentations of prostate cancer and have been applied relatively consistently. Each may be used as definitive therapy, as is commonly the case for men with more indolent prostate cancers, or in conjunction with an abbreviated course of pelvic EBRT for men with more aggressive disease presentations.

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Relative to LDR, or permanent seed, brachytherapy, HDR offers several advantages including: no patient-specific radiation precautions having to be implemented as patients are not radioactive following treatment completion; decreased radiation exposure to clinical staff and the general public; increased clinical control over dose administration; and exploitation of the perceived sensitivity of prostate cancer to large, individual fractional doses[1,2] of radiation in contrast to the gradual deposition of dose over many months, as is the case with permanent seed implants. Each of these factors holds potential appeal to clinicians and patients and has contributed to heightened implementation of HDR brachytherapy over the past 20-plus years.

No direct clinical evidence exists supporting HDR brachytherapy's superiority over LDR (or vice versa) in terms of improved tumor control or reduced toxicity as there has never been a prospective, randomized comparison between the approaches. There are, however, several disadvantages to prostate HDR brachytherapy that may make it less appealing to practitioners depending on a given practice infrastructure, personnel availability, and time constraints. First, LDR procedures use low-energy radiation sources, most commonly iodine 125 (^{125}I) or palladium 103 (^{103}Pd). As such, these procedures require minimal source shielding, can be handled directly by clinical staff, and may be placed in a standard operating room. Iridium 192 (^{192}Ir), the most common HDR brachytherapy source, is high energy and requires a shielded vault for treatment. Logistically, this necessitates that interstitial implant procedures be performed in a shielded operating room and, if not available, that the interstitial implant will be left in the patient while he is moved for treatment planning and administration procedures.

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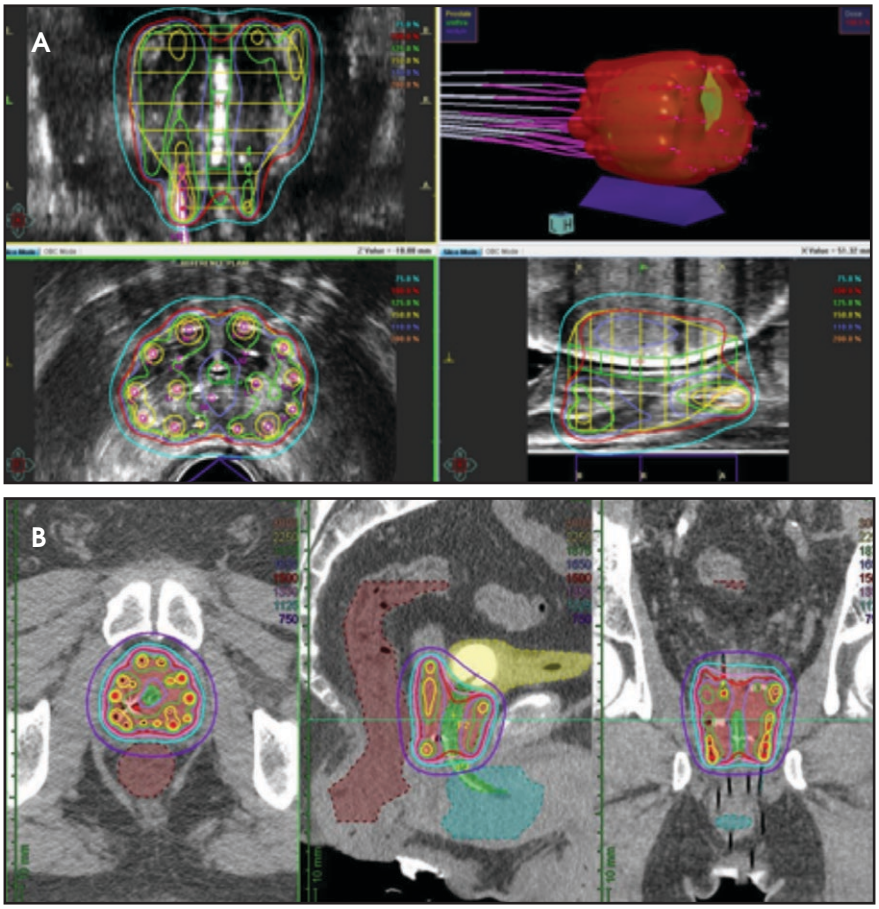

FIGURE 1. *Clinical dosimetry of ultrasound-based (A) and CT-based (B) high dose rate (HDR) brachytherapy planning.*

This increases time demands on physicians and ancillary clinical staff, and poses additional workflow challenges regarding anesthesia and quality assurance steps to minimize risks of implant displacement as patients are moved. Lastly is the Nuclear Regulatory Commission requirement that the treating radiation oncologist be physically present for treatment administration, which further increases the physician's time commitment.

Despite logistical challenges, the clinical advantages have held sufficient appeal to physicians and patients, such that it is becoming increasingly offered to patients as a viable treatment option for prostate cancer. Its safety and efficacy have been documented in multiple large prospective and retrospective institutional series, and ongoing investigation continues to streamline treatment approaches, bolstering convenience for radiation oncology departments and improving patient accessibility.

Patient Selection and Technical Description

Successful implementation of HDR brachytherapy for prostate cancer begins with appropriate patient selection. Anatomic factors lending to successful HDR treatment are as follows: prostate volume of approximately 20-60 cc (glands outside this range may still be considered for treatment); a central/straight urethral position that can be adequately avoided during transperineal needle implant; absence of significant benign prostatic hypertrophy/median lobe or transurethral resection of the prostate (TURP) defect at the prostate base; adequate spacing between the prostate and rectum; and adequate pubic arch width to avoid interference with needle placement. Clinical factors include general risks of both anesthesia and elective surgical procedures (the latter of which include comorbidities such as diabetes, cardiopulmonary factors, coagulopathy, etc.). Careful attention must be paid to baseline urinary function. Brachytherapy is not a good treatment option for patients with significant baseline obstructive uropathy. Risks for significant obstructive complications of brachytherapy increase substantially in such patients, and our practice typically will exclude patients with a baseline American Urologic Association (AUA) symptom score > 15 if already on medication, or > 20 if previously untreated for obstructive symptoms.[3] Any of these factors are relative contraindications to performing HDR brachytherapy and the treating physician should consider them on a patient-by-patient basis, weighing risks and benefits.

HDR brachytherapy procedures all begin with a transrectal ultrasound-guided transperineal implant of the prostate gland. A typical implant will consist of 15-20 needles placed symmetrically throughout the prostate, after which image-based dosimetric planning will be performed. Dosimetry may be calculated by images acquired directly on the transrectal ultrasonography (TRUS) unit used for needle implantation, computed tomography (CT) scan, or even MRI. Ideally, coverage of the prostate gland with the prescription isodose should exceed 95% of its volume (V100 > 95%). Typical dose heterogeneity tolerances are as follows:

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volume of prostate receiving 125% and 150% of the prescription dose (V125 and V150, respectively) should be < 60% and < 30%, respectively. Ideally, efforts should be made to avoid "hot spots" in the urethra, typically keeping < 5% of the urethra under 110% of the prescribed dose. Maximum dose to 1 cc of the rectum dose should not exceed 75% of the dose prescribed. Although typically not quantified for ultrasound-planned cases, a similar bladder constraint of ≤ 1 cc receiving 75% of the prescription dose is typically applied for CT-based dosimetry. **Figure 1** shows representations of an ultrasound- and CT-planned case.

Advantages and disadvantages are associated with each approach, and none have been shown to be clinically superior. Advantages to ultrasound-based planning include precise visualization of the prostate capsule and, should the infrastructure exist for a shielded operating room, the potential to complete an entire brachytherapy treatment administration without having to move the patient from the time of needle placement to dose delivery. CT-based dosimetry affords the opportunity for more precise anatomic quantification of bladder and rectal doses but requires that patients be moved multiple times to complete imaging studies and then returned to the shielded treatment room for treatment delivery. MRI is being used for dose planning in selected centers and, while providing unequivocally the highest image quality for dose planning, presents additional challenges regarding MR compatibility of the prostate implant and any necessary anesthesia equipment needed while the implant is in place.[4,5]

Once treatment planning is complete, the interstitial needles are connected to a remote afterloader that will deliver the radiation dose through each needle via an ^{192}Ir source. Depending on prostate size, dose prescribed, activity of the source, etc., treatment delivery is usually completed in 15-25 minutes. The implant may then be removed from the patient if the treatment given is the final prescribed fraction or secured for delivery of subsequent treatment fractions. Interfraction treatment interval should generally exceed a minimum of 6 hours.

HDR in Conjunction with External Beam

When first used for prostate cancer, HDR brachytherapy was predominantly implemented to boost the prostate as an adjunct to pelvic EBRT. This was considered particularly advantageous when first being used given the contemporary EBRT doses of 66-70 Gy that were considered standard at the time. Several single-institution experiences reported on the safety and efficacy of such treatment, and a prospective, randomized trial published by Hoskin et al[6] demonstrated superior biochemical control in patients receiving HDR brachytherapy boost treatment relative to those patients treated with EBRT alone.

Biological analyses of responses to changes in HDR dosing/fractionation suggested a high sensitivity of prostate cancer cells to increasing fractional doses. That is, prostate cancer has a low alpha-beta ratio, and biologically equivalent dose (BED), it was found, could be dramatically increased through relatively small increases in HDR fraction size. In fact, evidence of dose response in terms of enhanced biochemical control was demonstrated across a range of HDR fractionation regimens increasing progressively from as low as 550 cGy x 3 fractions up to 1150 cGy x 2 fractions.[7] More recently, HDR boost regimens given in a single fraction of 1500 cGy (usually in the context of ~45 Gy given to the pelvis via EBRT)[8,9] has gained favor and is the recommended dosing in the most recent open Radiation Therapy Oncology Group protocol (RTOG 0924) to allow HDR brachytherapy as a boost.

Despite the randomized evidence from Hoskin et al, a lack of evidence remains that conclusively supports the benefits of the combined approach of EBRT with HDR brachytherapy over contemporary, dose-escalated EBRT alone. Namely, a significant criticism of the Hoskin randomized trial has been, and remains, that the EBRT dose (55 Gy in 20 fractions) would be considered substandard in light of multiple randomized trials demonstrating biochemical control advantages for EBRT doses of 78-80 Gy.[10-12] Nonetheless, outcomes from that study revealed significantly improved median time to relapse of 116 months vs. 74 months favoring the group receiving HDR brachytherapy; this was despite a relatively modest HDR boost dose level of 8.5 Gy x 2.

Just recently, however, the ASCENDE-RT (Androgen Suppression Combined with Elective Nodal and Dose Escalated Radiation Therapy) prospective randomized trial has delivered corroborating evidence that adding LDR brachytherapy to pelvic EBRT improves biochemical control compared to men receiving 78 Gy EBRT alone for men with intermediate- or high-risk prostate cancer.[13] In that study, patients receiving EBRT alone were twice as likely to experience biochemical failure as those receiving an LDR brachytherapy boost (9-year biochemical control 83% vs. 62%; $p < 0.001$). The improvement in biochemical control did, however, come at a cost of increased toxicity. Five-year rates of grade 3 genitourinary (GU) toxicity were 18.4% for the brachytherapy patients compared to 5.2% for the dose-escalated EBRT patients, and 5-year grade 3 GI toxicity rates were 8.1% vs. 3.2%, respectively, for the brachytherapy boost vs. EBRT alone patients.[14]

No prospective, randomized comparisons support a biochemical or clinical disease control advantage for patients receiving HDR brachytherapy over contemporary, dose-escalated EBRT. However, single-institution experiences have reported favorable disease control rates comparable to those in the

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Table 1. Biological Equivalence Doses to 2 Gy Fraction Sizes (BED^{2Gy}) for Variable αα/βαRatio Assumptions

Fractionation	α/βα= 1.5 Gy	α/βα= 3.0 Gy	αα/βα= 5 Gy
7.25 Gy × 6	108.8 Gy	89.0 Gy	76.1 Gy
9.5 Gy × 4	119.4 Gy	94.8 Gy	78.7 Gy
12 Gy × 2	92.6 Gy	71.9 Gy	58.3 Gy
13.5 Gy × 2	115.7 Gy	89.1	71.4 Gy
19 Gy × 1	111.3 Gy	83.6	65.1 Gy
21 Gy × 1	135.0 Gy	100.8	78.0 Gy

Based on the formula: $BED_{2Gy} = D \times (1+d (\alpha/\beta)) / (1+2 / (\alpha/\beta))$; D = total dose; d = dose per fraction.

ASCENDE-RT trial with more favorable toxicity profiles. In a series of 832 intermediate- and high-risk disease patients treated with variable doses of HDR brachytherapy boost in conjunction with EBRT, Vigneault et al reported chronic grade 3 GU toxicity rates of 1.9-4.7% based on the dose levels to which patients were treated, and there was no reported acute or chronic grade 3 GI toxicity.[15] Biochemical control was approximately 95%. Martinez et al reported on the benefits of dose escalation using HDR brachytherapy as a boost. For the 472 patients described, chronic grade 3 GU toxicity rates were approximately 1% while reporting favorable 10-year biochemical control of approximately 81% for patients treated to high dose levels.[7] Yaxley et al reported 10-year biochemical control rates of 87% and 56% for intermediate- and high-risk patients, respectively, while showing that urethral stricture rate can be markedly reduced through careful attention to dose heterogeneity constraints, control for needle displacement prior to HDR treatment, and tighter inferior PTV margins during the EBRT portion of therapy.[16]

Finally, although a detailed discussion of androgen suppression is beyond the scope of this review, it should be mentioned that despite the aggressive disease presentations addressed with HDR boost therapy, the benefits of androgen suppression in the context of such treatment appears to be minimized or even absent.[17,18] To be clear, the role for androgen suppression has never been tested in prospective randomized fashion for HDR boost patients as it has for patients receiving EBRT treatment. Although this issue warrants additional consideration going forward, current standard practice, in this author's opinion, includes the administration of androgen suppression with HDR boost for patients with high-risk disease features.

HDR Brachytherapy as Monotherapy

For patients with more favorable presenting disease characteristics, HDR brachytherapy alone (no EBRT) may be used as definitive local therapy for men with low- or favorable intermediate-risk disease. This treatment approach holds great appeal as treatment may be completed typically in 1 or, at most, 2 minimally invasive, outpatient procedures with no daily attendance requirement for external beam administration. Recent updates of large, single-institution experiences have revealed highly favorable disease control rates across a range of treatment techniques and fractionation regimens. Additionally, toxicity rates have proven highly favorable and, most notably, with optimal techniques and the elimination of supplementary EBRT, rectal toxicity rates grade ≥ 2 are remarkably low. Using HDR as monotherapy for favorable and intermediate-risk prostate cancer requires a greater level of technical/planning expertise to ensure adequate target coverage relative to its use as a boost adjunct to pelvic external beam treatment. As such, HDR used as monotherapy has been considered investigational in published guidelines by both the American Brachytherapy Society[19] and the Groupe Européen de Curiethérapie (GEC) and the European Society for Radiotherapy & Oncology (ESTRO).[20] The most recent publication of these guidelines, however, are 4-5 years old, and since that time, multiple large, single-institution experiences have described highly favorable outcomes for this approach. As such, it has gained favor in the hands of experienced practitioners as a standard option for patients with favorable or intermediate-risk prostate cancer.

A variety of dosing/fractionation regimens have been explored and reported on previously: 950 cGy x 4, 1200 cGy x 2, 1350 cGy x 2, 700 cGy x 6, 725 cGy x 6, 6 Gy x 8, 6 Gy x 9, and 6.5 Gy x 7 with similarly high biological equivalence to standard 2-Gy treatment fractions as shown in **Table 1**. William Beaumont Hospital compared treatment toxicity and outcomes of 494 low- and intermediate-risk patients treated with 1 of 3 dosing regimens: 950 cGy x 4, 1200 cGy x 2, and 1350 cGy x 2. Five-year biochemical control rates were 97%, 87%, and 93%, respectively, with no statistically significant differences appreciated between the treatment arms.[21] Of note, a significantly higher percentage of patients treated with the 950 cGy x 4 fractions regimen was considered NCCN (National Comprehensive Cancer Network) low-risk relative to

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the 2-fraction dosing regimens examined. Chronic grade 3 urinary toxicity rates were < 1% for all patients, and no chronic grade ≥ 3 GI toxicities were reported. UCLA recently reported on a similar cohort of 460 low- (64%) and intermediate-risk (36%) prostate cancer patients treated with HDR brachytherapy as monotherapy treated with doses of 42-43.5 Gy delivered in 6 treatment fractions over 2 implant procedures. Kaplan-Meier estimates of biochemical control rates were excellent at 98.9% for low-risk and 95.2% for intermediate-risk patients at 10 years.[22] No grade ≥ 3 rectal toxicity was reported, and chronic grade ≥ 3 urinary toxicity was < 1%. Additionally, Yoshioka et al reported out of Japan favorable outcomes in a series of 190 patients with intermediate- (n = 79) and high-risk (n = 111) prostate cancer treated with combination androgen suppression and HDR brachytherapy without the addition of EBRT. Historically, such patients would be offered HDR in combination with EBRT, yet reported outcomes were highly favorable. Using variable multifraction dosing regimens (6 Gy x 8; 6 Gy x 9; or 6.5 Gy x 7) given over 4-5 days, biochemical control rates reported at 8 years were 91% and 77%, respectively, for the intermediate- and high-risk patient subsets.[23] Similar to the previously described series, late severe toxicity was rare. Four grade 3 toxicity events in the series were reported: 2 urinary (1 incidence of hematuria and 1 urinary tract obstruction) and 2 GI (sigmoid colon perforation and urethrorectal fistula).

As clinicians have grown more comfortable with administering HDR brachytherapy in definitive fashion for prostate cancer, the management trend has been to increase fractional doses and decrease overall treatment fractions. This has been evident as common practice has trended from 4-6 fraction regimens down to 2. More recently, this has been taken to the extreme with several series reporting outcomes of patients treated entirely in a single HDR brachytherapy treatment fraction. Hoskin et al was the first to report outcomes of patients treated with doses of 19 Gy or 20 Gy in a single fraction.[24] Despite relatively favorable toxicity rates in this series, an increased rate of catheter usage was noted in the patients receiving 20 Gy as compared to those receiving 19 Gy. In a subsequent publication, patients with more aggressive prostate cancers (74% to 87% receiving supplemental androgen suppression) receiving single-fraction HDR brachytherapy as monotherapy were found to have similar long-term toxicity and biochemical control rates compared to patients treated using a 2- or 3-fraction regimen (13 Gy x 2; 10.5 Gy x 3).[25] A series of 60 patients treated with a single 19 Gy HDR fraction reported by Prada et al yielded highly favorable toxicity rates with no acute or chronic ≥ grade 2 urinary toxicity reported.[26] No significant rectal toxicity was encountered either, but unfavorable 6-year biochemical control rates of 66% and 60% for low- and intermediate-risk patients, respectively, must be considered. William Beaumont Hospital reported on a series of 58 patients treated with 19 Gy in a single fraction. Again, toxicity rates were highly favorable with chronic grade 2 GU toxicity of 12% and no grade 3 GU toxicity recorded. Aside from an isolated incidence of late grade 3 diarrhea requiring hospitalization, no grade ≥ 2 GI toxicity was observed. Preliminary biochemical control (3 years) was reported at 93%.[27] The highly favorable toxicity profile and tolerability of single-fraction HDR monotherapy have been corroborated in a prospective randomized comparison demonstrating no significant increase in complication risks relative to a multifraction regimen of 13.5 Gy x 2. In fact, urinary toxicity was slightly increased in the multifraction arm during year 1, and single-fraction treatment was associated with a lower occurrence of ≥ grade 2 erectile dysfunction.[28]

Despite promising initial results in the single-fraction experience, such treatment remains investigational, and the optimal single-fraction dosing regimen continues to be investigated. Specifically, the 19 Gy single-fraction dose was predicated on the assumption of the extremely low alpha-beta ratio for prostate cancer (1.2-1.5 Gy). Evidence shows that radioresponsiveness of prostate cancer may be heterogeneous and that certain cancers may, in fact, have alpha-beta ratios that are higher.[28] For such tumors, 19 Gy may prove to be an insufficient dose (see **Table 1**), and continued evaluation of the optimal single-fraction HDR treatment approach is necessary.

Summary

HDR brachytherapy for prostate cancer is an excellent treatment option for selected patients seeking definitive radiotherapeutic management. Use of HDR as a boost for patients with aggressive prostate cancer has been associated with high disease control rates and favorable toxicity profiles. Based on evidence, favored dosing regimens would be either: HDR brachytherapy 21 Gy in 2 fractions (10.5 Gy per fraction) or single fraction 15 Gy, typically combined with 45-50 Gy in 1.8-2.0 Gy fractions using external beam to the prostate and seminal vesicles +/- pelvic lymph nodes. Although not specifically tested against dose-escalated EBRT alone, potential advantages of brachytherapy added to EBRT in general are strongly suggested by the results of the ASCENDE-RT trial. Use of HDR as monotherapy for patients with low- or intermediate-risk prostate cancer is supported by numerous large, single-institution series reporting favorable long-term biochemical control rates with highly favorable toxicity profiles and should be considered a standard treatment option for such patients. As

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described, many dosing regimens would be acceptable, with the current standard approach at William Beaumont Hospital being 27 Gy delivered in 2 fractions (13.5 Gy per fraction), generally delivered 2 weeks apart. Caution should be exercised in omitting EBRT from the management of patients with high-risk disease features, as HDR monotherapy data for this patient cohort is limited. Single-fraction HDR brachytherapy as monotherapy should be considered investigational at this point and not offered outside the context of a clinical trial as long-term outcome data are lacking and little empiric evidence regarding optimal single-fraction doses exists.

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Daily image guidance as a noninvasive technique of rectal emptying in postprostatectomy radiation

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Abstract

Objective: To present a novel approach of rectal emptying with image-guidance in prostate bed radiation therapy.

Methods and Materials: From July 2011 to December 2012, 86 consecutively treated postprostatectomy prostate cancer patients with no evidence of metastatic disease received adjuvant/salvage radiation to 70 Gy in 35 fractions with volumetric-modulated arc radiation therapy. Prior to simulation, an enema was performed to optimize rectal anatomy for treatment planning. Daily treatment protocol consisted of a cone-beam computed tomography (CBCT) for patient setup utilizing the most caudal surgical clip and bony anatomy; if the daily rectal volume overlapped the planning target volume (PTV) by $\geq$1 cm in any axial plane on CBCT, treatment was held and the patient was asked to empty his rectum. Repeat CBCT was obtained after voiding and prior to treatment delivery. Occasionally, patients were required to undergo repeated rounds of bowel emptying and CBCT. Each day a patient was required to void, all CBCTs taken on that day were contoured over the same cranio-caudal dimensions as the primary treatment plan. The contours were transferred to the original treatment planning CT, allowing us to compare the dose-volume histogram (DVH) of the distended rectum to the actual treated rectal contours.

Results: Twenty-nine (33.7%) of 86 patients had at least 1 fraction within their course of therapy in which the rectal volume overlapped the PTV by 1 cm. An average of 2.9 (8.3%) interventions were performed among the 29 patients. Rectal volumes and average cross-sectional area (CSA) after intervention demonstrate an almost 50% reduction in volume, and CSA of the rectum with reduced rectal V70 in each case.

Conclusions: Rectal emptying when rectal filling is noted on daily CBCT prior to radiation treatment is an easy intervention to implement. This practice is associated with reduced radiation dose to the rectum and may potentially decrease rectal toxicity.

Rectal toxicity is a common complication of prostatic bed radiation, resulting in symptoms such as diarrhea and rectal urgency and, less commonly, bleeding, ulceration, incontinence and rectovesical fistula. Interventions, including endorectal balloons, have been shown to reduce rectal toxicity but are invasive and often not well-tolerated by patients.[1] Rectal emptying techniques such as laxatives, daily enemas, changes in fiber intake and antiflatulent agents have been employed to produce consistent rectal anatomy.[2-14] Image-guided radiation therapy (IGRT) has enabled

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Table 1. DVH Analysis

The number of interventions performed for each patient during the treatment course. Results of the averaged rectum V70 pre- and postemptying with the planned values listed for comparison.

Pt	Interventions	V70 Plan	V70 Pre	V70 Post
1	5	0.01	20.7	4.0
2	4	0.11	21.9	0.1
3	12	0.00	19.0	6.0
4	8	0.94	18.1	3.6
5	6	0.02	22.7	3.5

Abbreviation: Pt = patient

determination of shifts in patient position to accurately target the proper internal anatomy. Often, the treatment day anatomy, and specifically the planning target volume (PTV) and organs at risk (OAR), are positioned differently from what were originally planned, prompting efforts at adaptive radiation treatment planning, which involve substantial effort and resources.[15]

We present a novel approach using daily IGRT, which has been successful at our institution.

Table 2. Simulation and Mean Rectal Volumes Pre- and Postemptying

Pt	Plan Volume (cc)	Preintervention Volume (cc)	SD	Postintervention Volume (cc)	SD
1	30.1	61.2	9.2	32.4	4.8
2	32	63.4	14.0	32.5	0.9
3	58	119.9	21.5	72.0	10.6
4	41.1	59.4	10.7	43.0	2.5
5	18.6	36.4	8.5	20.2	3.3

Abbreviations: Pt = patient; SD = standard deviation

Table 3. Simulation and Mean Rectal Average Cross-Sectional Area Pre- and Postemptying

Pt	Simulation CSA (cm^2)	Preintervention CSA	SD	Postintervention CSA	SD
1	5.47	11.13	1.68	5.89	0.88
2	6.27	12.42	2.75	6.38	0.17
3	10.18	21.04	21.04	12.63	1.86
4	7.21	10.41	1.87	7.55	0.43
5	4.43	8.67	2.01	4.81	0.78

Abbreviations: Pt = patient; : CSA = cross-sectional area ; SD = standard deviation

Table 4. Bladder averaged V65 for the pre- and postintervention, and a comparison of bladder volumes

Pt	V65 Plan	V65 Pre	V65 Post	Plan Volume (cc)	Pre Volume (cc)	SD	Post-intervention Volume (cc)	SD
1	82.3	88.0	90.6	37.0	34.4	5.7	36.76	8.5
2	11.1	6.93	44.6	193.9	76.1	30.6	53.5	44.5
3	44.7	41.0	59.4	35.7	39.7	12.9	44.5	12.9
4	88.6	46.3	89.0	33.5	83.4	81.0	45.6	30.1
5	48.8	43.9	46.6	49.1	53.2	39.4	48.8	20.7

Abbreviations: Pt = patient; SD = standard deviation

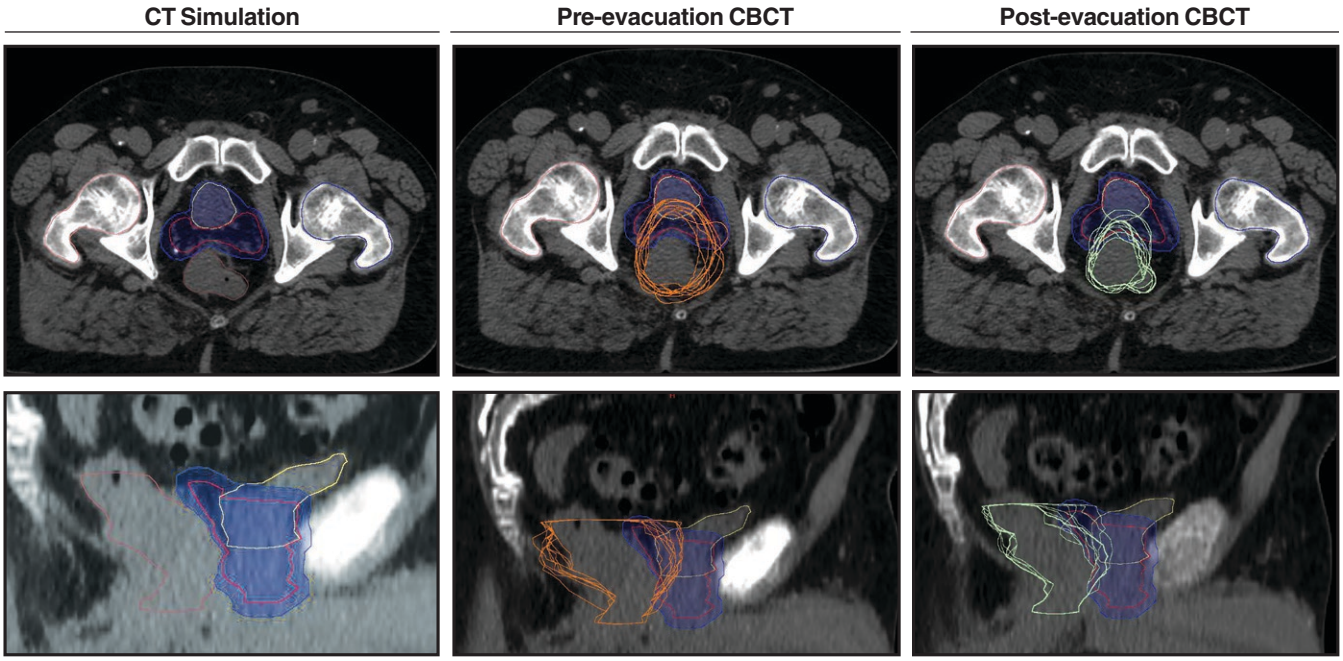

FIGURE 1. *Sample patient with axial and sagittal views of the simulation, with each intervention demonstrated with the associated contours for pre-evacuation CBCT (orange rectum) and the postevacuation CBCT (green rectum). Abbreviation: CBCT = cone-beam computed tomography*

Methods and Materials:

From July 2011 to December 2012, 86 consecutive patients were treated at our institution with prostate bed radiation therapy to 70 Gy in 35 fractions with volumetric modulated arc radiation therapy. All patients were instructed to have a full bladder for simulation, and an enema was performed to minimize rectal volume. Institutional protocol for treating the prostate bed includes use of daily cone-beam computed tomography (CBCT) for final patient positioning using bony anatomy and the most caudal surgical clips. If the visualized rectal volume overlapped the PTV by ≥ 1 cm in any axial plane, treatment was held and the patient was asked to empty his rectal contents, gas or feces, while continuing to drink fluids to maintain maximum bladder volume. Generally, the patient was asked to use the lavatory and attempt to walk for 20-30 minutes to assist in bowel emptying prior to proceeding. The patient was then repositioned and reimaged with CBCT to verify appropriate rectal positioning relative to the PTV. Occasionally, patients required multiple cycles of bowel emptying before adequate rectal volumes (ie, < 1 cm overlap into the PTV) was achieved.

Data acquisition

All interventions were identified by chart review. The pre-emptying and postemptying CBCTs were coregistered with rigid registration, using bony anatomy and the most apical surgical clips. In the setting of multiple interventions to achieve appropriate rectal volumes, the last CBCT was considered the postemptying CBCT. Each CBCT rectum was physician contoured over the same cranio-caudal dimensions as the primary treatment plan. Institutional rectal volumes were followed, in which the rectum contour extends 3 mm superior and inferior to the PTV. The co-registered CBCTs from each daily treatment were then fused to the planning CT in the treatment planning software, Eclipse Treatment Planning System volume 8.9 (Varian Medical Systems, Palo Alto, California), using bony anatomy and the most caudal surgical clip.

Data analysis

To minimize the effect of outliers on the dose-volume histogram (DVH) analysis, patients requiring > 3 interventions throughout their treatment course were identified and reviewed. Rectal volumes and an average cross-sectional area (CSA) were calculated on the pre- and postemptying CBCTs. Average CSA was calculated by dividing the rectal volume by the cranio-caudal length of the rectum.

Results

Twenty-nine of the 86 treated patients underwent at least 1 intervention of rectal voiding during their course of treatment. For each patient, this occurred an average of 2.9 (8.3%) times. Five patients had > 3 interventions; these patients were reviewed for DVH comparison and had an average of 7 interventions (range 4 to 12); the results of the rectal DVH analysis are shown in **Table 1.** The pre-emptying

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V70 for each patient is close to or > 20 percent, the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) threshold for 10% grade 3+ toxicity.[16] The rectal volumes and calculated average CSA for pre- and postemptying as well as treatment planning volumes are shown in **Table 2** and **Table 3**, and by both measures reduce volume and CSA of the rectum by almost 50%. Also, a comparison of bladder DVH and volumes are shown in **Table 4.**

For a single patient, axial and sagittal views of the CT simulation were created for visual representation of the interventions (**Figure 1**). Each intervention was demonstrated with the associated contours for pre-evacuation CBCT, and postevacuation CBCT contours shown as a compilation on the treatment planning CT.

Discussion

Daily changes in rectal anatomy are a concern during prostate bed radiation therapy; attempts to overcome these changes have included invasive procedures such as daily pretreatment enemas or endorectal balloons, as well as multiple dietary and pharmacologic interventions.[2-14] We proposed the use of daily CBCT to minimize rectal distortion into the PTV. If the rectum distends into the PTV $\geq$ 1 cm on any axial image, asking patients to empty their rectal contents while continuing to drink fluids to maintain maximum bladder volume is a simple, noninvasive and infrequent intervention to incorporate into clinical practice.

Previous investigators have reported daily interfraction motion and filling increases the overall radiation dose to the rectum when compared to the expected dose during treatment planning,[17] while others have also reported more biochemical and local failures from variations in rectal distension.[18-19] Numerous prospective studies have evaluated interventions to control daily rectal distension including: diet intervention, bowel relaxants, laxatives, rectal emptying via enema, self-evacuation with finger and rectal tubes.[2-14] A systematic review of numerous rectal distension interventions was unable to find a superior intervention; however, techniques employing rectal emptying before treatment were shown to be effective in decreasing rectal volumes and prostate motion.[20]

Although the use of various techniques are employed to limit rectal distension, our technique reveals that it may not be necessary in all patients, as only 33% of patients required a single rectal emptying intervention following daily CBCT review of the rectum. However, in patients requiring the intervention, there is a dramatic effect on reducing rectal volumes to near treatment-planning volumes with minimal effect on the bladder. This has a potential effect on target coverage as rectal distension has been reported to cause distortions in both anterior-posterior (AP) and superior-inferior (SI) motion[21-25] and this has also been seen in prostate bed patients.[26] With this protocol, the target is covered more reliably, potentially improving control while reducing toxicity, a classic win-win situation.

The intervention of daily CBCT with rectal voiding if necessary may also have a behavioral effect on patients. Patients who have required multiple interventions have endeavored to cooperate with timing their bowel movements before their scheduled treatments. This change in behavior as well as an increase in bowel movement frequency during radiation therapy may reduce the need for interventions in the latter half of treatment.

We also considered drawing just the rectal wall instead of the entire rectal volume. Contouring the rectal wall increases relative dose; an absolute point dose would unlikely be helpful in this scenario as well. Contouring the complete volume to include feces and gas is more comparable to routine plan review and constraints seen in QUANTEC.[16] When considering the artificial increase in relative dose due to decreased contour volume, it is also imperative to consider our institution protocol of contouring the rectal volume short in the cranio-caudal dimension; a small volume magnifies the relative dose-volume. With the challenges in comparing relative dose, we also reported CSA in attempts to decrease this variability and allow comparisons to historical data.

Conclusions

We have successfully implemented in our department a noninvasive approach to managing rectal filling during prostate bed radiation therapy using daily IGRT with CBCT. If IGRT with daily CBCT is to be utilized for prostatic bed IMRT, thought should be taken to review internal anatomy for abnormalities that could be easily augmented to parallel treatment planning volumes.

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Protons for prostate cancer: Bragging points, trials and treatment optimization

Mary Beth Massat

In patients with prostate cancer, advances in photon beam therapy such as 3-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) have helped spare surrounding normal organs and reduce gastrointestinal side effects. Unfortunately, the entrance and exit dose associated with photons results in a significant volume of normal tissue receiving low to moderate radiation doses.[1]

Enter proton therapy's "bragging" rights. Under the Bragg peak phenomenon inherent in proton therapy, the radiation beam halts when it hits its target rather than traversing through the patient's body. In prostate cancer treatment, this spares radiation to outlying areas such as the bladder and rectum, and has helped fuel proton therapy's growth for this patient population. Nonetheless, some debate—namely regarding expense—surrounds its use.

"What is fueling the controversy is that it costs more," says Jason A. Efstathiou, MD, DPhil, director of the Genitourinary Division, Department of Radiation Oncology, and clinical co-director of The Claire and John Bertucci Center for Genitourinary Cancers Multidisciplinary Clinic at Massachusetts General Hospital (MGH) in Boston, one of the first hospitals to establish a proton therapy center.

***Ms. Massat** is a freelance healthcare writer based in Crystal Lake, IL.*

PARTIQol trial

Dr. Efstathiou is also the principal investigator for PARTIQol (Prostate Advanced Radiation Technologies Investigating Quality of Life), a multicenter randomized phase III clinical trial comparing IMRT to proton beam therapy (PBT) to determine which therapy best minimizes treatment side effects and improves quality of life using patient-reported outcomes.[2] Trial results should also help reveal whether proton therapy is worth its high price tag, especially given the plethora of management options for prostate cancer, including active surveillance, brachytherapy, prostatectomy and external-beam radiation therapy.

"This is an important question for physicians, patients, policymakers and payers—everyone has a stake in it, and that's what really led us to open this randomized trial," says Dr. Efstathiou. "We assume that if we treat to the same biologically equivalent dose, then we can achieve the same cure rates (between PBT and IMRT). So, the brunt of this is quality of life: Can protons deliver fewer bowel effects, less fatigue, less second cancers and improved quality of life?"

The open trial has a goal of 400 patients; 230 were enrolled as of press time, and Dr. Efstathiou expects to finish patient accrual by the end of 2019. In addition to MGH, 11 other U.S. centers are participating: Case Western Reserve University (Cleveland, OH); Mayo Clinic (Rochester, MN); Memorial Sloan Kettering Cancer Center (New York, NY); Northwestern Medicine Chicago Proton Center (Chicago, IL); Princeton ProCure/CentraState Medical Center (Somerset, NJ / Freehold, NJ); Provision Proton Therapy Center (Knoxville, TN); Rutgers Cancer Institute of New Jersey (New Brunswick, NJ); University of Maryland (College Park, MD); University of Pennsylvania (Philadelphia, PA); University of Washington (Seattle, WA); and Washington University (St. Louis, MO). University of Florida will join in late 2017.

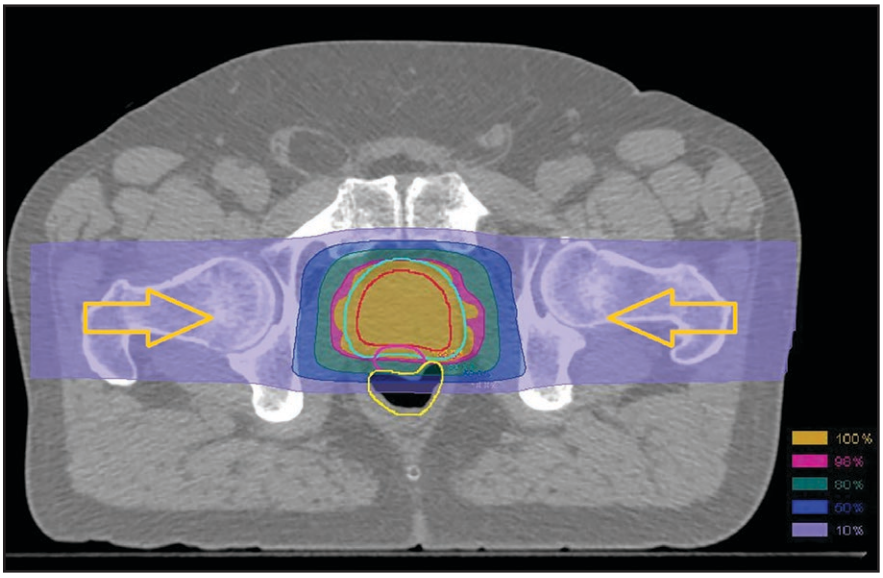

FIGURE 1. *Dose distribution for a patient receiving proton treatment by pencil-beam scanning. The yellow arrows indicate the direction of the two lateral beams. The prostate volume is shown in red, planning target volume in cyan, spacer in magenta and rectum in yellow. Isodose lines and areas are shown at 10%, 50%, 80%, 98%, 100% dose levels.*

The trial allows the use of rectal spacers and moderate hypofractionation, and pencil-beam PBT (**Figure 1**) is encouraged. "We want the best of the best for each therapy, and to evolve as practice changes," says Dr. Efstathiou. "We don't want to be outdated." He adds that over 10 papers have been published on the physics behind PBT for prostate cancer and biospecimens are also being collected to help identify biomarkers for preferential response.

"Proton therapy has some real potential benefits; [the question is] how to best harness that. At the same time, we need to evaluate it against the best standard of care we have today—IMRT—to see if it's any better," says Dr. Efstathiou. "We need to develop the requisite evidence, and simultaneously work to decrease the cost. PBT might be better than IMRT or it may not. But we do need to look at how to make this treatment more cost-effective."

Lack of insurance coverage for PBT, including participation in PBT trials such as PARTIQol, is another limiting factor. In a 2016 *Lancet Oncology* commentary, Dr. Efstathiou discussed how the "high frequency of coverage denial severely hinders participant accrual and timely completion of trials, which increases trial costs and skews the study population toward older patients who have Medicare coverage for proton therapy. Thus, despite calls from diverse stakeholders, including patients, physicians, policymakers, and payers, the generation of evidence for proton therapy is being greatly slowed."[3]

Patients pay a price as well. If insurance doesn't cover PBT, many will opt out. "Often, the use of proton beam therapy is dictated by whether a patient's medical insurance plan covers proton beam therapy or not," says C. Richard Choo, MD, professor in the Department of Radiation Oncology, Mayo Clinic, Rochester, Minnesota. Launched in 2015, the Mayo Clinic proton beam facility features 4 treatment rooms equipped with pencil-beam scanning and a large proton-beam-generating synchrotron. It features intensity-modulated PBT that uses spot scanning to deposit streams of protons back and forth through a tumor, closely targeting the tumor and sparing healthy tissue.

Contraindications

Contraindications must also be considered, and may rule out PBT as an appropriate treatment option for prostate cancer. Having a bilateral hip prosthesis is a primary contraindication, says Dr. Choo, although patients with a unilateral hip prosthesis can be evaluated on a case-by-case basis. Other contraindications include having an implanted cardiac pacemaker, defibrillator or deep brain stimulator that would be unsafe if turned off; inflammatory bowel disease with active bowel symptoms or inflammation; and prior pelvic radiation therapy causing a field overlap.

"Proton therapy is primarily used when the clinical target volume is limited to the prostate, plus or minus the seminal vessels," Dr. Choo adds, noting that it is not routine in cases where the clinical volume includes the pelvic lymph nodes and the prostate/seminal vessels.

Addressing uncertainty

In prostate proton therapy, range and position uncertainties, including stopping power, can be accounted for by creating plans using robust optimization. At the Mayo Clinic, Thomas J. Whitaker, PhD, assistant professor, Department of Radiation Oncology, says they review dose volume histogram (DVH) and dose distributions for the nominal plan plus each uncertainty plan. Their standard uncertainties in planning are +/- 3 mm in x, y, and z directions and +/- 3% range uncertainty (variation in stopping power).

Proximity of the rectum to the prostate target volume has always been the primary challenge for prostate radiation therapy by external beams. Hsiao-Ming Lu, PhD, director of clinical physics and associate professor, Department of Radiation Oncology at MGH, has had some success with the use of a rec-

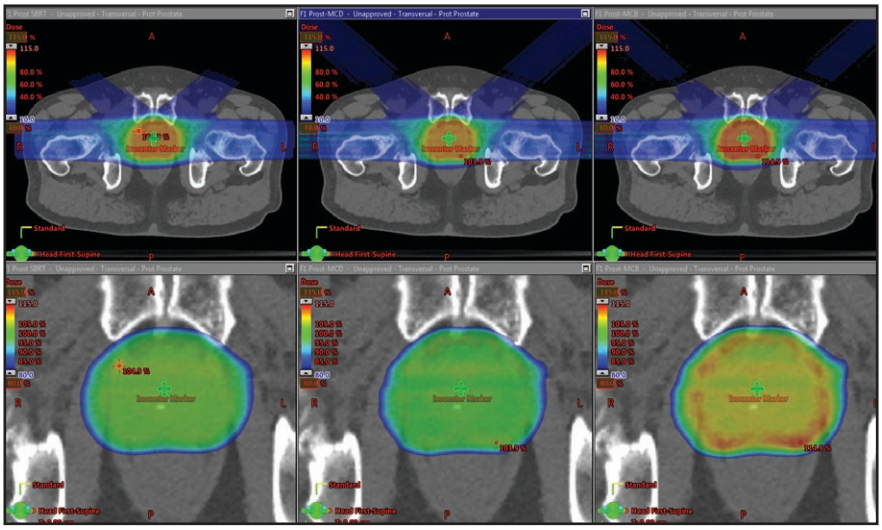

FIGURE 2. *Treatment planning dose, next to the Monte Carlo dose, next to the Monte Carlo biologic dose, used for evaluation.*

tal spacer, a type of gel injected in the space between the prostate and the rectum that helps separate the areas by 0.5 cm or 1 cm. The gel is absorbed within 6 months and no adverse reactions have been reported.

"That separation helps reduce the dose to the rectum, whether [it originates from a] proton beam or IMRT," Dr. Lu says. Based on initial use in a limited number of patients, Dr. Lu says that with IMRT a much smaller dose is hitting the rectum, and with PBT there is virtually no dose to the posterior portion of the rectum.

Since the gel features a water-like density, it is implanted under ultrasound-guidance, and must be identified for treatment planning using MR scans, which requires coordination with radiology and MR scheduling. But despite increased workflow requirements, Dr. Lu is fairly confident that MGH will increase use of the rectal spacer.

The spacer may also help with patients who are contraindicated for EBT or PBT due to inflammatory bowel disease or kidney transplants. "With arc-based EBT, there is usually some dose posteriorly," says Dr. Efstathiou. "If we use laterally based proton beams with the spacer, there may be minimal dose to the rectum, and we may help avoid an inflammatory disease bowel flair."

At the Mayo Clinic, two anterior oblique fields and two opposed lateral fields are used on patients with rectal spacers, notes Dr. Choo. "When using the 4-field approach, we only treat two fields daily, one lateral and one anterior oblique field," he says. "Then we alternate the laterality daily."

An advantage of the anterior oblique fields is reduced radiation to the femoral heads. "In patients with a rectal spacer, anterior oblique fields can be applied more readily because the concern about a higher RBE [relative biological effectiveness] at the end of range landing onto the anterior rectum is lessened, given that a rectal spacer allows a greater separation, ie, distance, between the prostate and the rectum," he says.

A treatment planning study at MGH investigated anterior-oriented proton beams for prostate cancer and found that it could provide adequate target coverage with dose to the rectum significantly reduced.[4] Additionally, a 2015 multi-institution study examined the feasibility of anterior-oriented proton beams for prostate cancer patients with a single or bilateral prosthesis (for whom the standard technique of using only lateral beams was not an option), and found that it provided adequate target coverage and had favorable and acceptable toxicity.[5] While the use of spacers would help with anterior oblique beams, it doesn't necessarily eliminate the problem of end of range uncertainty, says Dr. Lu.

Dr. Efstathiou adds that MGH is exploring the use of anterior and anterior-based oblique proton beams, and says that studies suggest that with a rectal spacer it may be feasible.

RBE throughout the spread out Bragg peak (SOBP) is another area of uncertainty—a "problem that no one really handles well," says Dr. Whitaker, noting that Mayo uses a Monte Carlo calculation engine that provides a physical dose and a linear energy transfer (LET) distribution (**Figure 2**). "It is well-established that RBE is proportional to LET, but it is just not well-established what the proportions are," he says. "We have our own biologic dose calculation created by weighting the physical dose by the LET distribution. This allows us to see potential biologic hot spots and to move away from critical structures."

RBE uncertainty, especially a higher RBE at the end of the range, is an important factor in determining beam direction and arrangement (lateral beam vs. anterior oblique), adds Dr. Choo, especially in the absence of a rectal spacer.

"Our current practice assumes RBE of 1.1 throughout the entire SOBP," says Dr. Lu. "There is no clinical data yet, but some clinicians think it could increase to 1.2 near the end of the SOBP, which is substantial. How that will affect the treatment, however, is hard to know at this point."

Motion matters

While image guidance on traditional EBRT systems has migrated to 3D imaging primarily via cone-beam CT, many PBT systems still rely on 2D orthogonal x-ray imaging. As a result, many sites

such as MGH and the Mayo Clinic use implanted fiducial markers as well as rectal water balloons. Preliminary indications are promising in patients with a prostate spacer and in which rectal water balloons are no longer used, but it is not yet clear if the prostate is as stable without the balloons.

"Once we determine our technique with using the spacers, then we'll look at this closer to see if the spacers help reduce motion," says Dr. Lu.

The next step in image guidance for proton therapy is cone-beam CT. MGH has purchased a cone-beam x-ray for installation on the PBT system, which may help address beam range uncertainty. "There are efforts now to explore the possibility of using cone-beam CT to evaluate variations of the beam path to control one source of the beam range uncertainty," says Dr. Lu.

At Mayo, prostate cancer patients have 4 carbon fiducial markers implanted in the prostate prior to treatment. Using on-board 2D orthogonal imaging, the markers are imaged before treatment to confirm setup and account for intra-fraction motion. Dr. Choo says that 3D imaging is also available with the center's CT on rails for volumetric confirmation of target coverage.

Future study needs

While the PARTIQol trial is expected to make research inroads regarding PBT for prostate cancer, additional investigation is needed. In particular, says Dr. Choo, is the need to compare toxicity and efficacy of PBT vs. photon-based RT, and to evaluate hypofractionation regimens, which can improve PBT cost-effectiveness.

"We also need more radiobiology studies with regard to proton beam—for example, to address issues such as RBE uncertainty," he adds, and "a need for implantable sensors to accurately and continuously pinpoint the location of tumors in real-time while PBT is being delivered, such as with the Calypso Beacon system (Varian Medical Systems, Palo Alto, California) in a photon therapy setting."

Ideally, more studies and technological advances will continue to improve PBT, cost-wise and in the clinic, for prostate cancer and additional disease sites.

"Proton beam therapy … has been around a long time [and] is evolving as a technology," says Dr. Efstathiou. "Yes, it is expensive to build cyclotrons, but we will continue to see smaller and less expensive solutions over time, just as we've seen with other technologies like smartphones and computers."

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RADIATION ONCOLOGY CASE

Volumetric-modulated arc therapy improved heart and lung sparing for a left-sided chest wall and regional nodal irradiation case

Vishruta A. Dumane, PhD; Nisha Ohri, MD; Sheryl Green, MD

CASE SUMMARY

A 56-year-old postmenopausal woman initially presented in October 2013 with complaints of intermittent left breast pain, redness and a left axillary mass for several months. Clinical examination was notable for an edematous and erythematous left breast with peau d'orange and a palpable underlying 6-cm mass with bulky axillary lymphadenopathy. Core biopsies of the left breast and left axilla demonstrated poorly differentiated ductal carcinoma, ER-/PR-/Her2-. Skin biopsy was negative. Workup was negative for metastatic disease, and the cancer was staged IIIB cT4d N2a M0. Beginning in December 2013, the patient was treated with neoadjuvant chemotherapy consisting of 4 cycles of dose dense Adriamycin and cyclophosphamide (AC) followed by Taxol and carboplatin (TC), which consisted of 12 cycles of Taxol and 3 cycles of carboplatin (the last dose of carboplatin was held due to electrolyte wasting). Genetic testing was positive for BRCA2 mutation. The patient subsequently developed an Adriamycin-related cardiomyopathy in which her ventricular ejection fraction dropped from 65% to 45% and did not recover. The patient underwent left modified radical mastectomy and prophylactic right mastectomy in June 2014. There was no residual carcinoma in the left breast. Four of 16 axillary lymph nodes contained metastatic disease. The patient then presented in July 2014 for post-mastectomy radiation therapy (PMRT).

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IMAGING, PATHOLOGY FINDINGS

A bilateral mammography in October 2013 showed bulky left axillary adenopathy, some of which was associated with heterogeneous microcalcifications, extensive skin thickening, and a 2-cm area of pleomorphic calcifications in the upper outer quadrant of the breast corresponding to the marked palpable abnormality. On ultrasound, diffuse skin thickening was seen throughout the left breast. There were large confluent areas of irregular marginated hypoechoic tissue in the upper outer quadrant and multiple abnormal axillary lymph nodes containing calcification. The patient underwent ultrasound-guided biopsy of the left breast lesion in the 2:30 axis and 7 cm from the nipple, and of an enlarged left axillary lymph node. Pathology from the left breast demonstrated infiltrating poorly differentiated ductal carcinoma and focal intermediate grade ductal carcinoma in situ (DCIS), solid type, ER-/PR-/Her2-. The left axillary lymph node contained poorly differentiated infiltrating ductal carcinoma with associated necrosis and calcifications. Punch biopsy of the skin showed chronic inflammation of the dermis. Bilateral breast MRI was performed in November 2013 before initiating neoadjuvant chemotherapy. In the left breast, there was generalized skin thickening, an irregular heterogeneously enhancing mass

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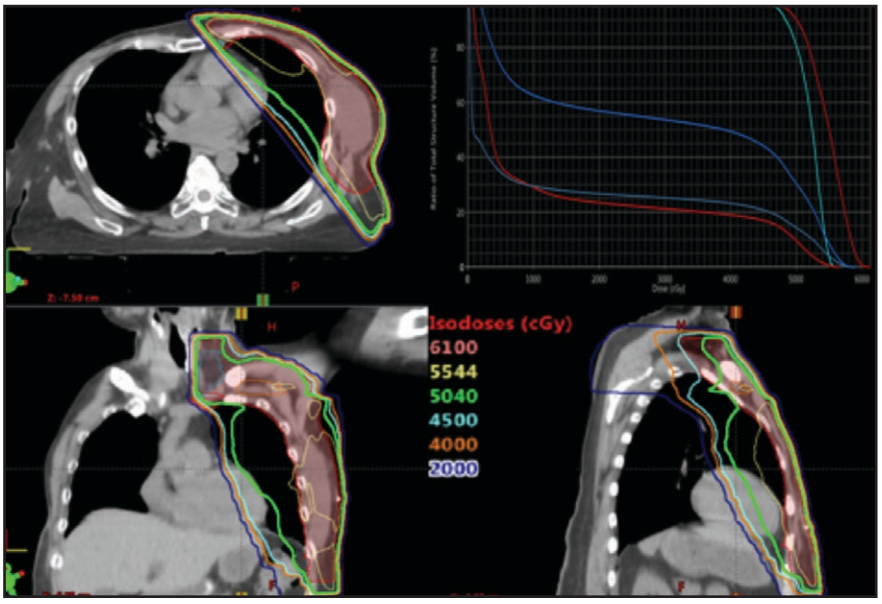

FIGURE 1. *Dose distribution with PWT in the axial, coronal and sagittal planes. DVHs are indicated for the PTV (red), IMNs (cyan), ipsilateral lung (blue), heart (red) and total lung (pale blue). Abbreviations: PWT = partially wide tangents, DVH = dose-volume histogram, PTV = planning target volume, IMN = internal mammary nodes*

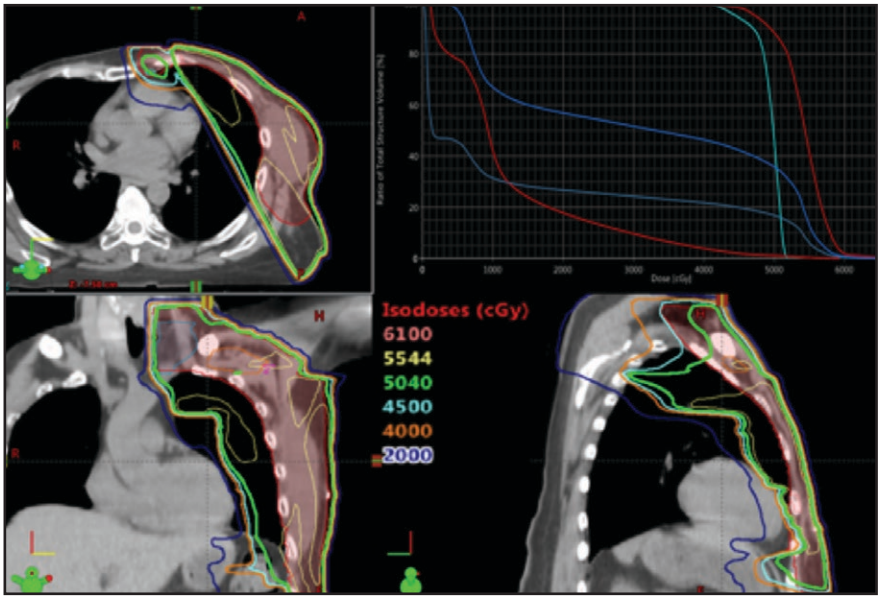

FIGURE 2. *Dose distribution with 20/80 photon/electron mix in the axial, coronal and sagittal planes. DVHs are indicated for the PTV (red), IMNs (cyan), ipsilateral lung (blue), heart (red) and total lung (pale blue). Abbreviations: DVH = dose-volume histogram, PTV = planning target volume, IMN = internal mammary nodes*

and nonmass enhancement throughout the entire lateral breast (10 x 10 x 6.4 cm) extending into the pectoralis muscle, with associated tethering and irregularity of the pectoralis fascia (no enhancement of pectoralis muscle), an abnormal subpectoral lymph node (1.5 cm), and bulky left axillary adenopathy with the largest lymph node (4 x 2.5 x 2.5 cm in diameter). No adenopathy of the internal mammary nodes (IMNs) was seen. Following chemotherapy, a bilateral breast MRI (May 2014) demonstrated near-complete resolution of the extensive enhancement in the left breast and complete resolution of left axillary adenopathy. No suspicious findings were noted in the right breast. Bilateral mammogram and ultrasound in May 2014 demonstrated in the left breast 2 new groups of suspicious pleomorphic microcalcifications in the upper outer quadrant. Biopsy of these microcalcifications was not performed as the patient elected to proceed with bilateral mastectomy.

The patient underwent left modified radical mastectomy and prophylactic right mastectomy. Pathology of the left mastectomy specimen demonstrated no residual carcinoma in the left breast. There was lobular carcinoma in situ with atypical lobular hyperplasia, florid duct hyperplasia, radial scar, fibrocystic changes and associated calcifications. Skin, nipple and deep margin were negative. Residual carcinoma was identified in 4 out of 16 left axillary lymph nodes with therapy-related changes, the largest measuring 1 cm, without extracapsular extension, ER-/PR-/Her2- on immunohistochemistry and fluorescence in situ hybridization.

DIAGNOSIS

The patient presented with inflammatory breast cancer (IBC) and the diagnosis was based on the initial clinical breast examination, which is defined by erythema, edema and peau d'orange. The patient was clinically staged IIIB (cT4d N2a M0); morphology of infiltrating poorly differentiated ductal carcinoma, ER-/PR-/Her2-. She underwent neoadjuvant chemotherapy with a partial radiographic and pathologic response. However, there was residual disease in the axilla (macrometastases). Given her age, pathologic findings, and the aggressive nature of triple negative inflammatory breast cancer, postmastectomy radiation treatment was clearly indicated.

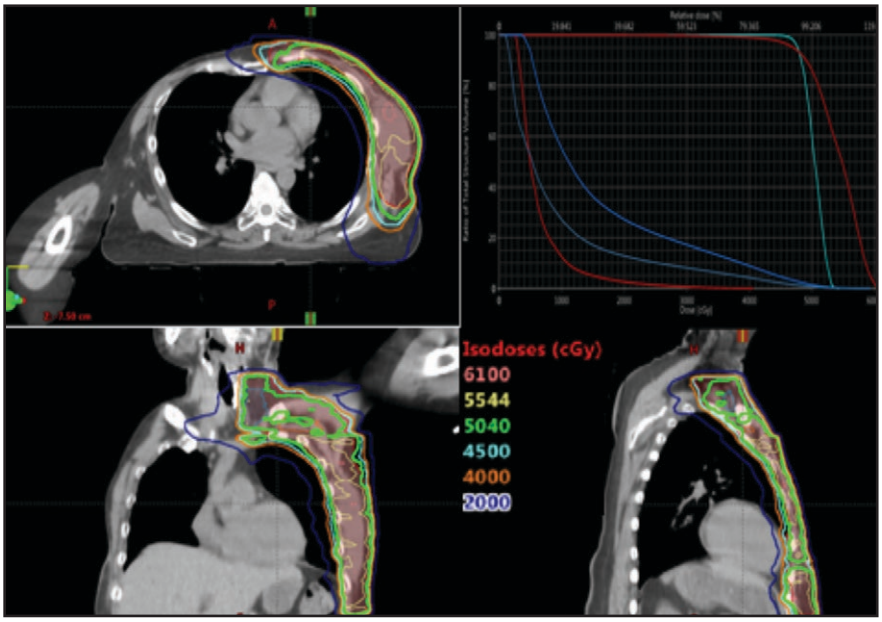

FIGURE 3. *Dose distribution with VMAT in the axial, coronal and sagittal planes. DVHs are indicated for the PTV (red), IMNs (cyan), ipsilateral lung (blue), heart (red) and total lung (pale blue). Abbreviations: VMAT = volumetric-modulated arc therapy, DVH = dose-volume histogram, PTV = planning target volume, IMN = internal mammary nodes.*

LITERATURE REVIEW

A retrospective analysis of 316 patients with IBC who received trimodality therapy consisting of neoadjuvant chemotherapy, modified radical mastectomy and postmastectomy radiation to the chest wall and regional lymph nodes, has shown that of all 4 subtypes of breast cancer ($ER^+/PR^+/HER2^+$, $ER^+/PR^+/HER2^-$, $ER^-/PR^-/HER2^+$, $ER^-/PR^-/HER2^-$), triple negative (TN/ $ER^-/PR^-/HER2^-$) breast cancer is associated with higher rates of distant relapse (DR), locoregional recurrence (LRR) and worse overall survival (OS).[1] The median OS time was 40 months for the $ER^+/PR^+/HER2^+$ subtype, 38 months for ER^+, 29 months for $HER2^+$ and 24 months for the TN subtype. The median time to LRR was 35 months for the $ER^+/PR^+/HER2^+$ subtype, 36 months for ER^+, 26 months for $HER2^+$ and 19 months for the TN subtype. The median time to DR was 31 months for $ER^+/PR^+/HER2^+$, 34 months for ER^+, 22 months for the $HER2^+$ group and 19 months for the TN subtype, which, therefore, remains a therapeutic challenge.

The risk of LRR is a greater concern in patients with IBC especially in the triple negative (TN) subtype.[1] Patients with IBC undergoing trimodality therapy who received neoadjuvant therapy were more likely to have residual disease in the axilla increasing their risk for locoregional recurrence, further emphasizing the need for optimal regional nodal management.[2] Moreover, a large percentage of locoregional failures had a regional component.[2] A nonrandomized study found that accelerated hyperfractionated radiation therapy (RT) to a total dose of 66 Gy at 1.5 Gy per fraction delivered twice daily [vs.] 60 Gy at 2 Gy per fraction delivered once daily had better local control for IBC.[3] The study also showed that among patients who were treated twice a day to a total dose of 66 Gy vs. 60 Gy, the locoregional control (LRC) at 5 years was 84.3% vs. 57.8%, and at 10 years was 77% vs. 57.8%. A 3- to 5-mm thick bolus (tissue equivalent material) was used to increase dose to the skin/superficial tissue for every fraction during the first week, followed by only the first fraction of the day for the second week, and then as needed for the remaining treatment. However, as shown by a study from MD Anderson, this accelerated hyperfractionation regimen increased skin toxicity.[4] The LRR rate in patients treated after 1994 (when taxanes were introduced as adjuvant therapy) was 8% for a total dose of 66 Gy. Bolus of 3-5 mm thickness was placed on the chest wall with the same frequency described earlier.[3] The rate of late skin toxicity among patients treated to a total dose of 66 Gy was almost twice as large at 29% compared to 15% among those treated to a total dose of 60 Gy.[4] This study led to the recommendation that escalation of postmastectomy radiation dose to 66 Gy appeared to only benefit patients with poor response to chemotherapy and those who were < 45 years old. Patients > 45 years old and who had achieved good response to neoadjuvant chemotherapy should be treated with conventional fractionation. In this respect, a later study from Memorial Sloan Kettering Cancer Center (MSKCC) reported that in patients treated to a total dose of 50 Gy to the chest wall and regional lymph nodes in daily fractions of 1.8 Gy or 2 Gy with skin bolus of thickness 0.5 cm – 1 cm applied over the chest wall for each fraction, had a LRR rate of 13%,[5] which is slightly higher than that reported from MD Anderson.[4] These patients were treated after 1995, had received taxanes as part of their combined modality therapy and the majority of them (89%) did not receive a scar boost. In our case, our patient was > 45 years of age, had received a taxane and had no residual disease in the breast following neoadjuvant chemotherapy. However, since she had 4 out of 16 axillary lymph nodes containing

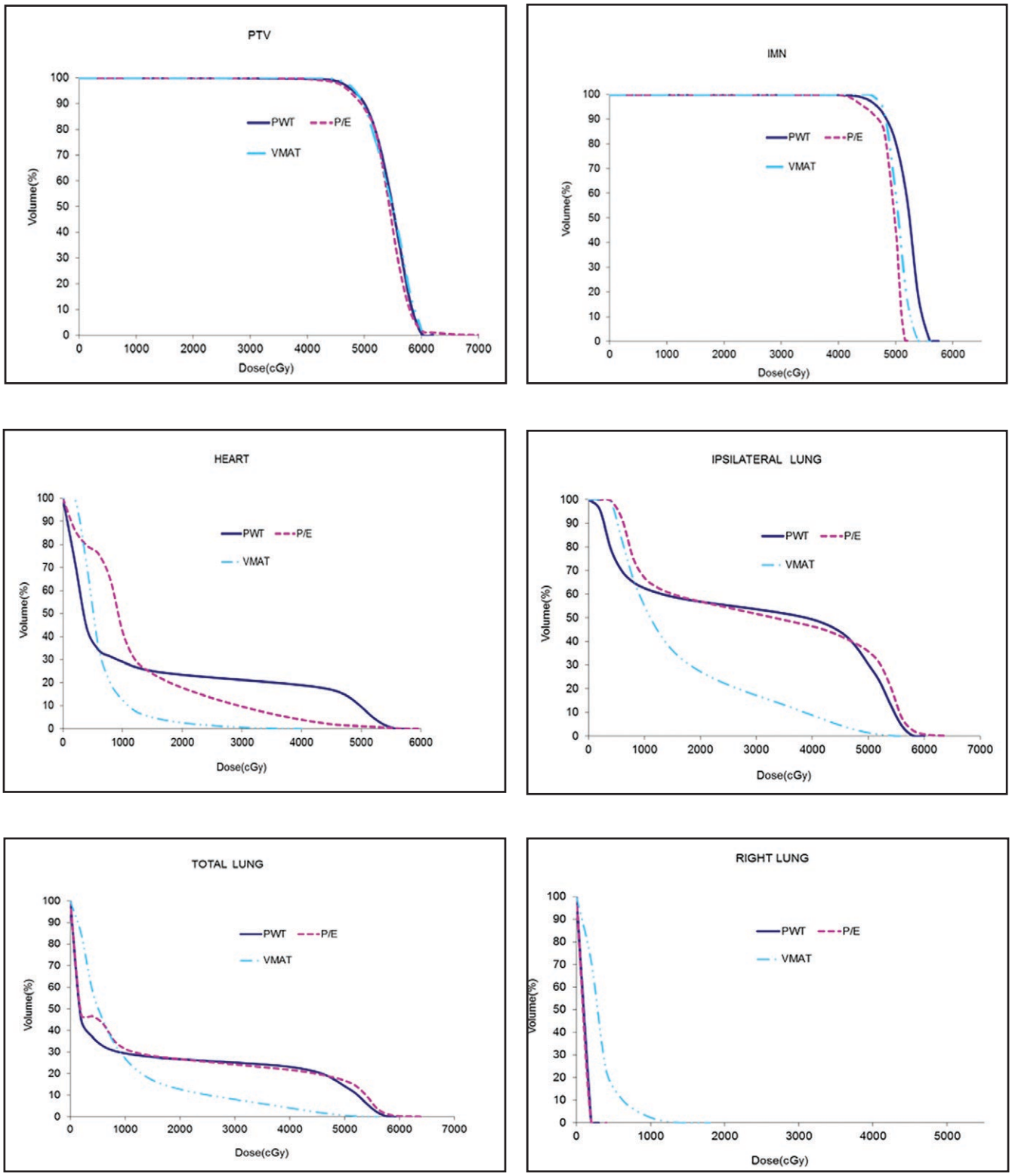

FIGURE 4. *Comparison of DVHs for the PTV, IMNs, heart, ipsilateral lung, total lung and contralateral lung with PWT, 20/80 P/E mix and VMAT. Abbreviations: DVH = dose-volume histogram, PTV = planning target volume, IMN = internal mammary nodes, PWT = partially wide tangents, P/E = photon/electron, VMAT = volumetric-modulated arc therapy*

Table. 1. Dosimetric comparison of parameters for PTV coverage, IMN coverage and critical organs for PWT, 20/80 P/E mix and VMAT

Structure	Parameter	PWT	20/80 P/E mix	VMAT
PTV	D95 (%)	95.2	93.7	96
	V95 (%)	95.2	93.7	96.2
	D05 (%)	116.9	116.7	117.7
	Dmax (Gy)	60.5	66.7	61.2
	HI*	0.2	0.3	0.2
	CI†	2.2	2.4	1.5
IMN	Mean (Gy)	51.8	49.3	50.4
	D95 (%)	92.9	88.3	94.7
	V95 (%)	92.1	85.9	93.8
Heart	Mean (Gy)	13.6	12.4	6.4
	V25 Gy (%)	22.2	13.3	1.3
	V15 Gy (%)	25	24	5
	V5 Gy (%)	36.9	77.8	49.1
Ipsilateral Lung	Mean (Gy)	29.8	31.2	16.3
	V20 Gy (%)	56.9	56.9	27.1
	V10 Gy (%)	62.5	67.1	55.3
	V5 Gy (%)	73.6	96.8	92.6
Total Lung	Mean (Gy)	14.3	15.1	9.4
	V20 Gy (%)	26.7	26.7	12.8
	V10 Gy (%)	29.4	31.4	27
	V5 Gy (%)	34.6	45.6	51.4
Contralateral Lung	Mean (Gy)	0.5	0.7	3.3
	V10 Gy (%)	0	0	2.3
	V5 Gy (%)	0	0	15.8

*HI = (D2%-D98%)/D50%;
†CI = (volume of PTV x volume of prescription isodose)/(volume of PTV within prescription isodose)2
Abbreviations: HI = homogeneity index, CI = conformity index, PTV = planning target volume, IMN = internal mammary nodes, PWT = partially wide tangents, P/E = photon/electron, VMAT = volumetric-modulated arc therapy.

metastatic disease, adequate coverage of the regional lymph nodes was essential.[2] Therefore, a course of adjuvant postmastectomy radiation therapy to the left chest wall, axilla, supraclavicular fossa, and internal mammary nodes (IMNs) was recommended to 50.4 Gy in 1.8 Gy fractions delivered once daily along with a 5-mm thick bolus covering the chest wall for each fraction.

Including IMNs during irradiation of the left breast is known to increase dose exposure to the underlying normal tissue such as the heart and lung. This patient had exposure to Adriamycin and she suffered from cardiomyopathy having a left ventricular ejection fraction of 45%. Cyclophosphamide is known to cause pulmonary toxicity by local inflammation in the lung parenchyma affecting gas exchange,[6] potentially exacerbating lung injury caused by RT. The risk of radiation pneumonitis (RP) post RT in patients who have received chemotherapy with taxanes is also a concern.[7] Given this patient's risk factors for cardiopulmonary toxicities, the heart and the lung dose had to be minimized as much as possible while providing adequate radiation dose to the left chest wall and regional lymph nodes.

TREATMENT PLANNING TECHNIQUES

The partially wide tangents (PWT) technique is considered the most appropriate balance of target coverage and normal tissue sparing[8,9] and was initially used to plan this case. Details on patient simulation and contouring have been described earlier.[10,11] The dose distribution with the PWT plan is shown in **Figure 1**. The amount of lung incorporated with this technique was > 3 cm, the resulting mean heart dose (MHD) was 13.6 Gy, and the ipsilateral lung V20 Gy was 56.9%. Darby et al have shown that the rate of a major coronary event increases linearly by 7.4% per Gy of MHD.[12] Moreover, women with preexisting cardiac risk factors have a higher increase in the absolute risk than women without these factors. Therefore, there was a need to reduce the MHD for this case to as low as can be achieved. Short-term pulmonary side effects in breast cancer patients after adjuvant RT showed no cases of RP in patients whose ipsilateral lung V20 Gy was kept at < 30%,[13] while exceeding this constraint increased the likelihood of pulmonary complications.[14] Since cardiopulmonary toxicity was a concern

in this case, given the dosimetric parameters, the PWT technique was unable to provide a viable plan for treatment.

The depth of heart and lung included in the tangential fields can impact the volumetric doses and, therefore, it has been shown that a combination of photons and electrons can reduce the heart and lung doses, especially over the use of tangential fields when the depth of the lung treated is > 3 cm.[15] Two photon/electron (P/E) techniques were then planned, namely the 20/80 photon/electron mix and the 30/70 photon/electron mix[8,15] with 6 MV photons and 12 MeV electrons. The MHD was comparable with both P/E techniques (12.4 Gy vs. 12.1 Gy, respectively); however, the MILD with the former was slightly lower at 31.2 Gy compared to 32.7 Gy, as was the V20 Gy (56.8% vs. 60.8%). **Figure 2** displays the dose distribution for the 20/80 photon/electron mix. Although the MHD was comparable among the two techniques, no benefit was seen with the 20/80 photon/electron mix in reducing dose to the ipsilateral lung over PWT.

The use of multibeam intensity-modulated radiation therapy (IMRT) or volumetric-modulated radiation therapy (VMAT) in such situations can help improve target coverage, conformity and homogeneity while sparing the heart and lung from doses ≥ 15 Gy.[16-18] This approach is known to carve out high-dose areas around the heart, specifically related to the coronary arteries. We then planned this case with VMAT using 2 partial coplanar arcs of range 210° (from 300° to 150°). Details of the field arrangement and planning have been published earlier[10] and we closely followed those described by Popescu et al.[18] Dose distribution for the VMAT plan is shown in **Figure 3**. The definition of homogeneity index (HI) and conformity index (CI) are the same as in our previous case report.[19] Compared to both 3DCRT planning techniques, the MHD with VMAT was reduced by almost 50% to 6.4 Gy. VMAT also reduced the mean ipsilateral lung dose (MILD) to 16.3 Gy and the V20 Gy to 27.2%. Comparison of the DVHs for the 3 plans is shown in **Figure 4**, which illustrates the superior heart and lung sparing and adequate coverage achieved with VMAT compared to PWT and 20/80 photon/electron mix techniques. **Table 1** shows a detailed dosimetric comparison of the various dosimetric parameters amongst the different planning techniques. Contouring of the chest wall clinical target volume (CTV) and the nodal CTV was done as per the Radiation Therapy Oncology Group (RTOG) breast cancer contouring atlas.[20] The planning target volume (PTV) was CTV + 5 mm margin and included the skin in the chest wall region. For a uniform basis of comparison, the PTV was kept the same in all plans.

DISCUSSION

Exposure of the heart to ionizing radiation during RT of the left breast/chest wall is unavoidable and depends on the patient's anatomy.[18] It is known to increase a patient's long-term risk of developing ischemic heart disease.[12] This increase is proportional to the MHD, and women with preexisting cardiac risk factors have an even greater absolute increase in risk from radiation. The absolute risk for a 56-year-old patient who received an MHD of 6 Gy with at least 1 existing cardiac risk factor of suffering from an acute coronary event (nonfatal or fatal major coronary event [MCE], or unstable angina) within the first 10 years after receiving radiation is 2% to 3.1%. The increase in rate of an MCE per Gy MHD for a patient with at least 1 cardiac risk factor is 19.6% in the first 4 years after exposure, and death rate from MCE per Gy MHD increases 13.6% in the first 4 years. Compared with 3-D conformal planning, VMAT reduced the MHD by as much as 7 Gy in this case. Therefore, the risk of having an MCE after RT for this patient was reduced with VMAT by as high as 137.2% compared to the 3D conformal plans, and the risk of death from ischemic heart disease (IHD) was reduced by as much as 95.2%.

A recent study investigated short-term pulmonary radiation pneumonitis (RP) using changes in pulmonary function tests (PFTs) after locoregional radiation therapy (LRRT)[13] in which regional nodal irradiation (RNI) included the IMNs. The constraint for the ipsilateral lung V20 Gy was < 30%. Chemotherapy included cyclophosphamide and taxanes and was concluded 3-4 weeks before initiating RT. By adhering to this constraint, incidence of symptomatic RP was ~6% (both grade 1 and 2) and no grade 3 or 4 pneumonitis was observed. In an earlier study by the same group, 475 patients with breast cancer who had received RT were followed for pulmonary complications at 1, 4 and 7 months post treatment.[14] Patients who received locoregional RT that included the IMNs while maintaining the ipsilateral lung V20 Gy around 30%, showed 5.5% grade 1 and 11% grade 2 complication rates. Patients for whom the V20 Gy was around 35% showed a 23% grade 1 and 11.5% grade 2 complication rate. Goldman et al[13] concluded that by reducing the V20 Gy to < 30% they could reduce the rates of short-term RP and changes in short-term pulmonary function compared to patients in the earlier study by Lind et al.[14] Varga et al[21] have shown that use of sequential taxane-based chemotherapy in treating patients for chest wall and regional nodes including IMNs with adjuvant RT showed no incidence of RP or lung fibrosis. In these patients, the V20 Gy on average was 29% ± 1.1%.[21] The risk of acute and chronic RT-induced lung morbidity is influenced by the irradiated lung volume, total dose and dose per fraction.[22,23] In this case, we could maintain the ipsilateral lung V20 Gy < 30% with

VMAT, but not with 3-dimensional conformal radiation therapy (3DCRT).

VMAT, however, increased the volume of the heart and the lung covered with low dose. For this case, the heart V5 Gy was 37% with PWT, 48% with VMAT and 78% with photon/electron mix technique. The influence of low dose—specifically the volume of the heart covered by 1 to 2 Gy with RT on heart disease—has been investigated in the literature.[24] No correlation was found between low dose and cardiac perfusion defects or function, and there was no worsening of these defects within a short-term follow-up (1 year) after exposure. However, the MHD for all patients in the Chung study was < 6.1 Gy (6.4 Gy in this case study). Hence, even though PWT best spared the volume of the heart covered with low dose, the MHD was more than double that with VMAT due to increased volume of the heart covered by higher doses with MHD. The study cautioned that a dose-response relationship in the short term might exist at higher doses. A combination of VMAT and deep inspiration breath hold (DIBH) can provide a cumulative benefit in further minimizing heart exposure for patients treated with locoregional RT of left-sided breast cancer.[25] Compared with VMAT alone, a combination of VMAT and DIBH can reduce the MHD on average by 2.9 Gy (1.5 Gy – 4.3 Gy).[26] The volume of the lungs receiving low dose is also increased with VMAT compared to standard 3D conformal techniques. However, no grade 3 or higher pneumonitis rates have been observed, even when the ipsilateral lung V5 Gy was 100%.[27] Moreover, incidence of secondary cancers after RT has a latency of onset ≥ 10 years after initial treatment,[28] and is unlikely to manifest in this case.

FOLLOW-UP

The patient developed progressive hyperpigmentation and erythema of the irradiated left chest wall, and dry desquamation was noted at a dose of 3420 cGy. On Sept. 2, 2014, the patient successfully completed RT as planned, and during the last week of treatment she developed patchy areas of moist desquamation (NCI CTCAE v4.0 Grade 2-3), most pronounced in the region of the mastectomy scar. The skin reaction was managed with topical emollients and petrolatum gauze dressings. Discomfort was managed effectively with over-the-counter analgesics, and she completed treatment without interruption.

At follow-up 2 months later (delayed due to interval surgery for prophylactic bilateral salpingo-oophorectomy), she reported feeling well overall. She denied any specific chest wall complaints other than a sensation of tightness in the left upper extremity and lateral chest wall. Physical examination was notable for mild residual hyperpigmentation of the left chest wall with no overt desquamation. The left chest wall skin and subcutaneous tissue appeared mildly thickened and indurated but without discrete palpable lesions. There was no upper extremity lymphedema. She was referred to physical therapy for management of the upper extremity symptoms, which improved with range of motion exercises. No evidence of lymphedema was noted in follow-up visits at 9, 12 and 15 months post treatment. At 9 months post treatment, she was diagnosed with metastatic disease (brain, bone and contralateral internal mammary nodes), and was treated with further chemotherapy and palliative irradiation of brain and osseous metastases. She returned for follow up in April 2016 and had no symptoms suggesting cardiovascular or respiratory compromise. No evidence of chest wall or ipsilateral regional nodal recurrence was present.

CONCLUSION

We present a case of a patient diagnosed with IBC of the TN subtype, which is an aggressive disease. Multimodality treatment included chemotherapy, surgery and radiation. The need to cover the chest wall and regional nodes combined with unfavorable anatomy required the use of advanced RT planning and delivery techniques other than standard 3D conformal methods. In this case, VMAT was able to best spare the heart and the lung without sacrificing target coverage, outweighing the risk of secondary cancer.

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RADIATION ONCOLOGY CASE

An abscopal effect in a case of neuroendocrine atypical carcinoid lung cancer

Amy L. Cummings, MD; Tania B. Kaprealian, MD; G. Peter Sarantopoulos, MD; Melody A. Mendenhall, NP; Jonathan W. Goldman, MD

CASE SUMMARY

A 67-year-old never-smoker without a significant past medical history presented with a tender, 1.5-cm subcutaneous mass in her right neck. Immunohistochemical staining from a punch biopsy suggested intermediate grade bronchial neuroendocrine carcinoma (atypical carcinoid) with strongly positive cytokeratin-7, neuron-specific enolase, moderate thyroid transcription factor-1, and 40% Ki-67 proliferation index. Baseline scans revealed right interlobar and inferior pulmonary lymphadenopathy, scattered pulmonary micronodules, and multiple peri-centimeter subcutaneous soft-tissue nodules. Approximately 1 year after diagnosis, she enrolled in a clinical trial of temozolomide and an oral poly ADP ribose polymerase (PARP) inhibitor. After 4 months on treatment, she was noted to have 25% growth in target and nontarget disease (**Figure 1 A, C, E**) and discontinued the trial. Three weeks later, she underwent palliative radiation with 30 Gy in 10 fractions targeted to a symptomatic calvarial metastasis. One month after radiation, she noted rapid improvement in her skin nodules. A repeat skin nodule biopsy revealed the tumor had been replaced by fat (**Figure 2**). Seven months after radiation, there was near complete response on imaging (**Figure 1 B, D, F**), and she received no further treatment. Updated imaging 18 months later confirmed a durable response.

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DISCUSSION

An abscopal effect is a rare event of tumor regression at a site distant from an irradiated field.[1] First postulated in the 1950s, the effect has been investigated via *in vitro* studies that suggest transferable soluble factors in the growth medium[2] and *in vivo* studies that report indirect T- and B-cell response in off-site organs in irradiated mice.[3] More recently, it has been hypothesized that the response is an immunogenic modification of the tumor and its microenvironment, leading to an atypical vascular network flush with inflammatory cytokines that trigger danger-associated molecular patterns (DAMPs), which lead to the maturation of dendritic cells and priming of tumor-specific CD8+ T cells.[4,5] Synergy with targeted immune treatment also has been suggested, which was described by Postow et al in a case of melanoma treated with ipilimumab and radiation therapy, which highlighted NY-ESO-1 as a potential antigen target heightened by radiation therapy.[6] Cases of abscopal effect have been reported in nonsmall cell lung adenocarcinoma, thyroid medullary carcinoma, Merkel cell carcinoma, lymphocytic leukemia, hepatocellular carcinoma, renal cell carcinoma, and cervical squamous cell carcinoma,[7] but clinical trials have yet to establish a consistent response in solid tumors.[8]

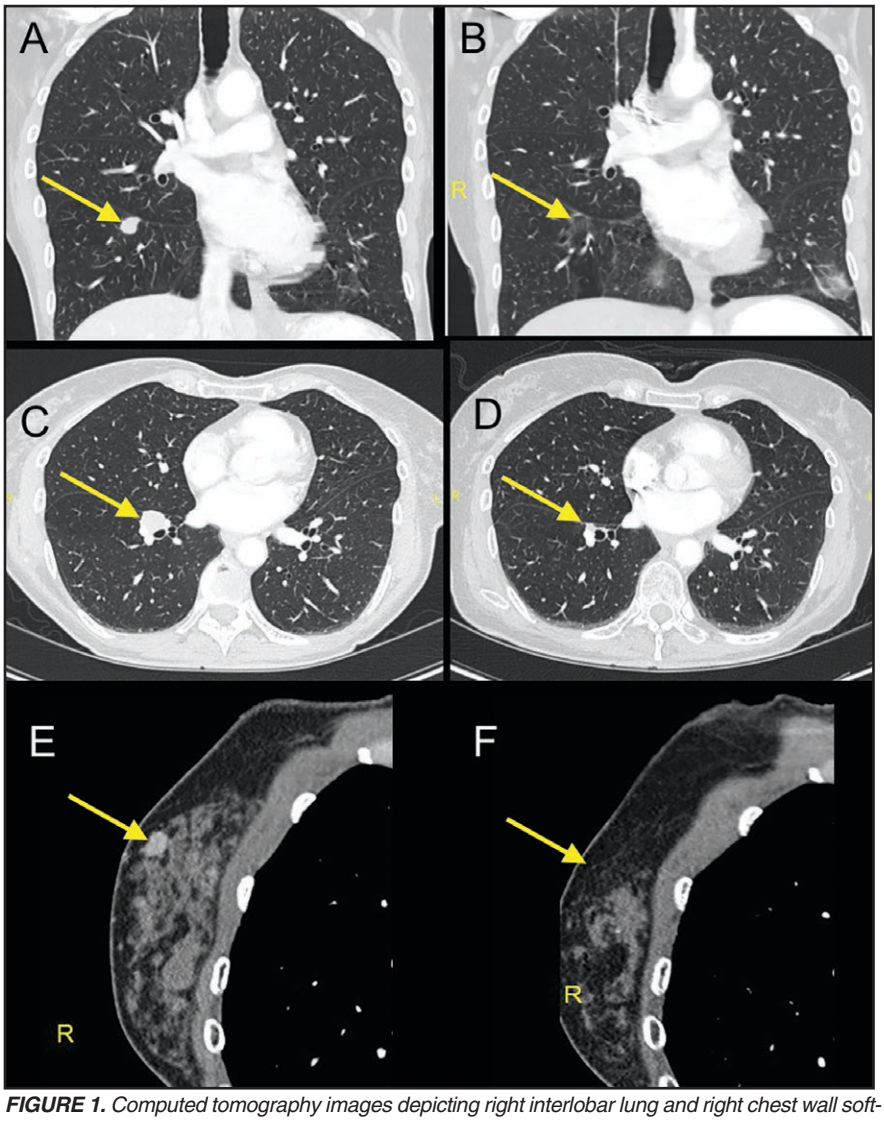

FIGURE 1. *Computed tomography images depicting right interlobar lung and right chest wall soft-tissue masses from scans prior to radiation (A, C, E) with interval resolution 7 months later (B, D, F).*

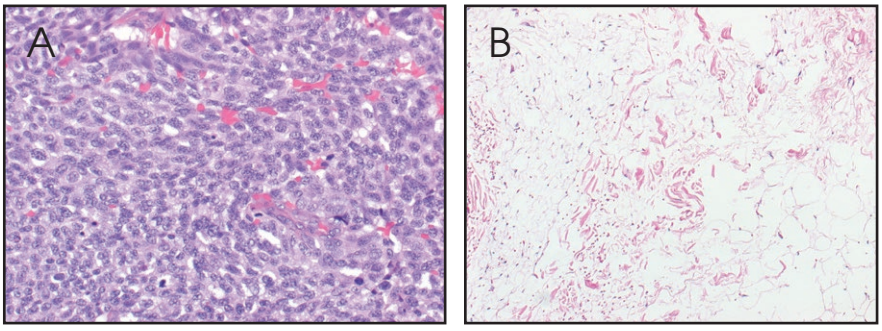

FIGURE 2. *(A) Histologic sections from a punch biopsy of a subcutaneous right neck mass show lobules and sheets of small-to-medium, uniform tumor cells with scant eosinophilic cytoplasm (Hematoxylin and eosin, H&E, x400). (B) Histologic sections from a punch biopsy in the region of the prior neck mass revealed well-differentiated fibroadipose tissue with extravasated erythrocytes within the subcutaneous region without identification of residual tumor (H&E, x100).*

Bronchial neuroendocrine atypical carcinoid is not typically radiation sensitive.[9] As such, the rapid and sustained response achieved by this patient suggests an immunogenic mechanism of an abscopal effect. It is assumed that the patient's prior treatment with temozolomide and an oral PARP inhibitor is unrelated to this response, as disease progression was noted during that treatment, and radiation occurred several weeks after the trial was discontinued.

CONCLUSION

Here we present the first case of abscopal effect in bronchial neuroendocrine carcinoma (atypical carcinoid) lung cancer. Additional studies regarding the mechanism by which an abscopal effect is elicited, especially in neuroendocrine tumors, is recommended.

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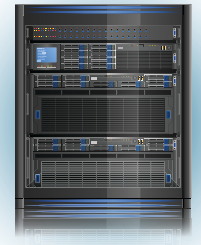

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