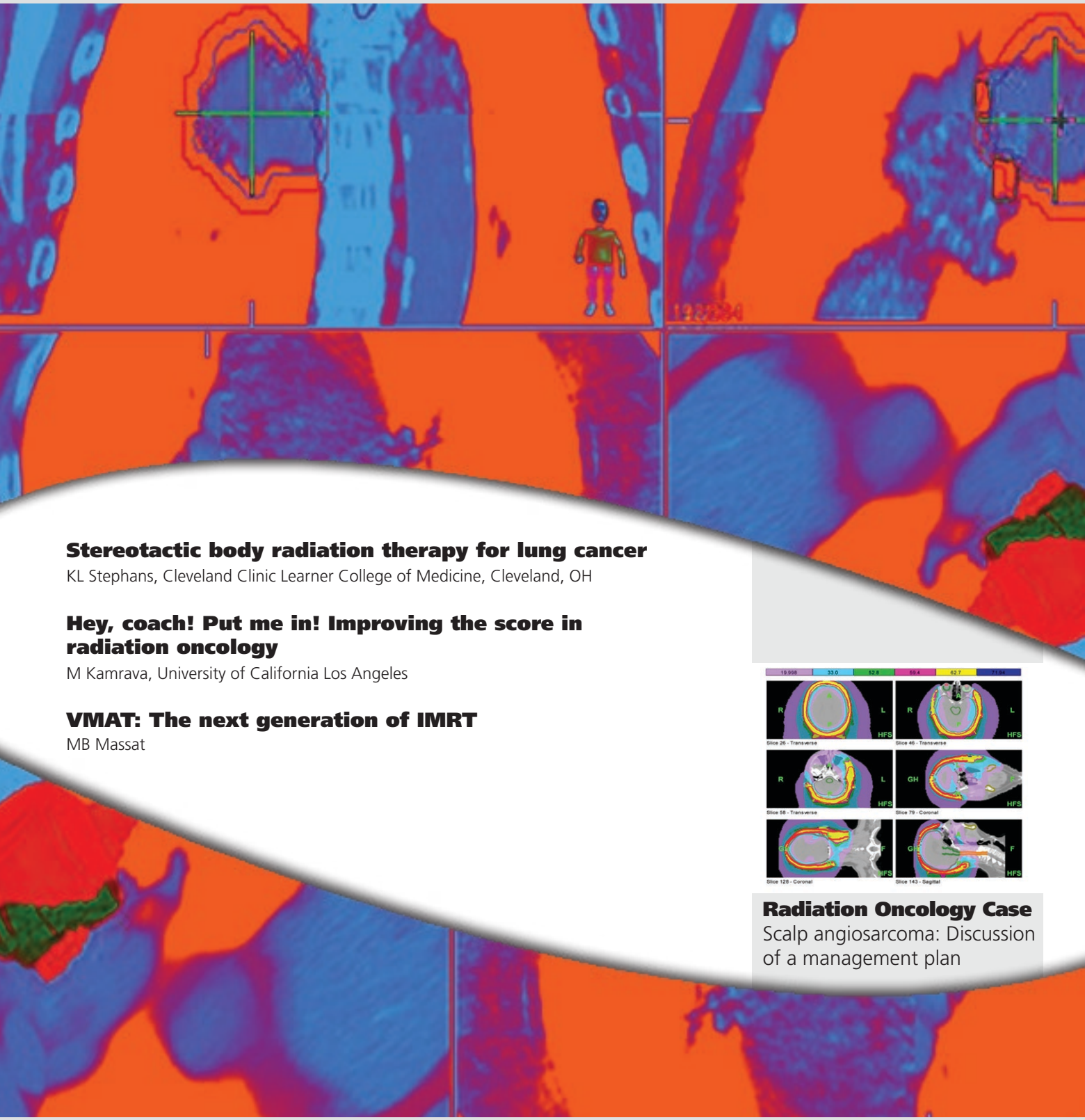
APPLIED RADIATION ONCOLOGY™
VOL 3 NO 3 SEPTEMBER 2014



Stereotactic body radiation therapy for lung cancer
KL Stephans, Cleveland Clinic Learner College of Medicine, Cleveland, OH

Hey, coach! Put me in! Improving the score in radiation oncology
M Kamrava, University of California Los Angeles

VMAT: The next generation of IMRT
MB Massat

Radiation Oncology Case
Scalp angiosarcoma: Discussion of a management plan

The World's Only Single Room Proton System – Now Treating.

MEVION
medical systems

Visit us at ASTRO 2014
Booth #728

LAD140331

APPLIED RADIATION ONCOLOGY™

Editor-in-Chief
John Suh, MD

Publisher
Kieran N. Anderson

Associate Publisher
Cristine Funke, RT(R)

Managing Editor
Sharon Breske

Art Director/Production
Barbara A. Shopiro

Circulation Director
Cindy Cardinal

TEL: 908-301-1995, FAX: 908-301-1997
info@appliedradiationoncology.com
www.appliedradiationoncology.com

CIRCULATION, COVERAGE and ADVERTISING RATES: Completed details of regarding circulation, coverage, advertising rates, space sizes, and similar information are available to prospective advertisers. Closing date is 30 days preceding date of issue. Click here to view our media planner.

EDITORIAL CONTRIBUTIONS: *Applied Radiation Oncology* accepts clinical-review articles and cases that pertain to radiation oncology and related oncologic imaging procedures that will be of interest to radiation oncologists. Manuscripts and cases may be sent electronically to Sharon Breske, Executive Editor for review with our Advisory Board. The opinions and recommendations expressed herein, in articles, columns and cases, are not necessarily those of the publisher. Every precaution is taken to ensure accuracy, but the publishers cannot accept responsibility for the correctness or accuracy of the information supplied or for any opinion expressed. Before using procedures or treatments discussed or suggested by authors, clinicians should evaluate their patients' conditions, compare the recommendations of other authorities, consider possible contraindications or dangers, and review applicable manufacturer's product information. Editorial closing date is the first day of the month 3 months prior to the issue date. Articles and cases should be geared to the practitioner and should reflect practical everyday clinical applications rather than research activity. Articles and cases may pertain to clinical management, administration, fiscal, technical, and medico-legal issues. Clinical review articles are also solicited by our Editorial Advisory Board. Any editorial submission should be original and unpublished, approximately 1500-2500 words and include the appropriate images, image captions and references. All submissions are to be submitted electronically by emailing a MS Word document, high resolution images, and selected DICOM image data sets to our Editor, Sharon Breske for review and approval. Authors will be notified by email of acceptance or rejection and of any major recommended revisions. Prior to publication, a PDF of your article or case will be emailed to you for final approval. Manuscripts and case should be emailed to Sharon Breske, at Sharon@appliedradiationoncology.com.

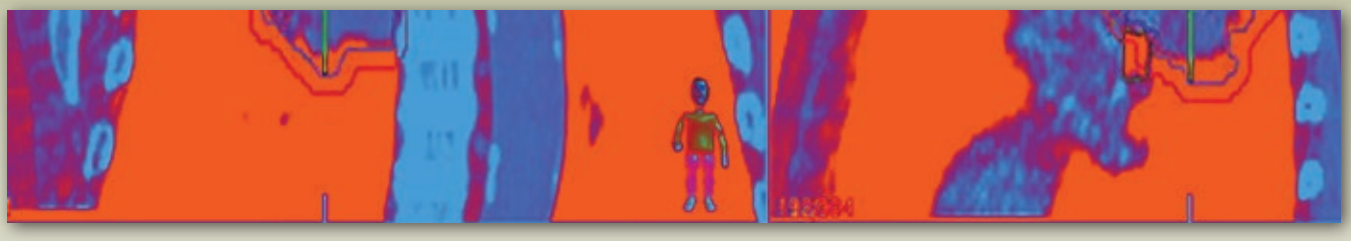
Anderson Publishing, Ltd
180 Glenside Avenue, Scotch Plains, NJ 07076
(908) 301-1995

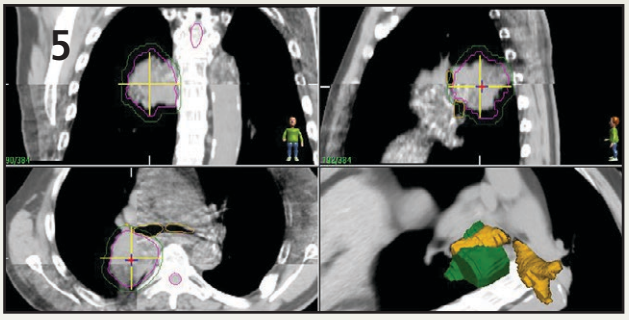
ISSN: 2334-5446 (Online)

Editorial Board

APPLIED RADIATION ONCOLOGY™

September 2014
Vol. 3, No. 3





DEPARTMENTS

Applied Radiation Oncology *(ISSN: 2334-5446 online) is electronically published quarterly by Anderson Publishing, Ltd.,180 Glenside Avenue, Scotch Plains, NJ 07076. Subscription is free of charge to all medical professionals and available by clicking here. Complaints concerning non-receipt of this e-journal must be made via email to our Publisher, Kieran Anderson at kieran@appliedradiationoncology.com.*

APPLIED RADIATION ONCOLOGY®

CLINICAL CASE CONTEST

Applied Radiation Oncology is pleased to offer our bimonthly clinical case review contest open to all physicians, radiation therapists, and physicists in the field of radiation oncology. Every two months we will feature the submitted cases on our website for review by you and your peers.

A rating system at the bottom of each accepted case will allow your peers to rate your case on a scale of 1-5 (5 being the best). The highest rated cases will be submitted for final review by the ARO Advisory Board, which will ultimately choose the "Best Presented and Most Interesting" case.

The contest will run through December 31, 2014.

You may enter as many different cases as you wish; however, please DO NOT enter the same case more than once.

A winning case will be chosen bimonthly and published in a future issue of ARO. The author of the winning case will receive an American Express Gift Card in the amount of $250.

Click here to see our contest information page!

Click here to view the guidelines and enter your case!

Click here to see a sample of a case accepted for publication!

Thank you for supporting ARO and we look forward to your participation in our Clinical Case Review Contest! Good Luck!

CLINICAL CASE CONTEST
GET PUBLISHED...WIN CASH!

VIEW GUIDELINES

EDITORIAL

ASTRO 2014: A golden gate to learning and improving

John Suh, MD, Editor-in-Chief

Every September, schools welcome eager students for another year of learning, studying, and test taking. In addition, another much-anticipated September event for the radiation oncology community occurs—the Annual Meeting of the American Society for Radiation Oncology (ASTRO). This year's 56th conference, held in San Francisco Sept. 14-17, is poised to not only break attendance records, but has received a record-breaking number of abstract submissions (2,870 plus) and posters (more than 1,850). You'll also find 360 oral scientific presentations, and 144 digital posters, the latter of which debut a new format and include touch screens, video and audio, as well an oral presentation by the author and longer viewing times (10-5 Sunday through Tuesday).

ASTRO will also discuss RO-ILS, the new patient safety initiative, and will unveil the second list of *"Five Things Physicians and Patients Should Question"* for Choosing Wisely, a campaign designed to help patients target care that's evidence-based, not duplicative, free from harm and truly necessary.

Furthermore, with more than 200 exhibitors vying for your attention, ASTRO provides a terrific opportunity to embrace new developments in radiation oncology, discuss them with your peers, and plan a better tomorrow for cancer treatment. As you explore the meeting's theme, "Targeting Cancer: Technology and Biology," be sure to make time for the 4 Plenary Sessions and 8 Clinical Trials, which feature the conference's most highly rated abstracts. Also, you should not miss the three keynote talks: "New Horizons in Oncologic Imaging: Unraveling Pathways to Synergy," "New Approaches to Targeting K-Ras," and "Human Error and Just Culture." You will learn innovative ways to incorporate many exciting changes as well as boost your knowledge.

Speaking of which, *ARO*'s September issue presents a new approach to improving adaptive planning through a creative basketball comparison in "Hey, coach! Put me in! Improving the score in radiation oncology." Even if you don't know that Lebron James decided to take his talents back to Cleveland, UCLA's Mitchell Kamrava, MD, breaks down the analogy of how watching the game in real time, calling time-outs as needed, making last minute changes, and shifting players, can ultimately lead to winning results in the radiation oncology arena.

This issue also describes how SBRT has evolved over the past 15 years and revolutionized the management of early stage NSCLC. Kevin L. Stephans, MD, a staff member of Cleveland Clinic, provides a great overview with his article "Stereotactic body radiation therapy (SBRT) for lung cancer." In addition, interesting case reports on rectosigmoid cancers and scalp angiosarcoma are also featured.

From these pages to ASTRO's vast opportunities, I hope you enjoy the educational offerings that abound this month—and the positive impact it will have on your practice.

As always, thank you for supporting *ARO*. See you in San Francisco!

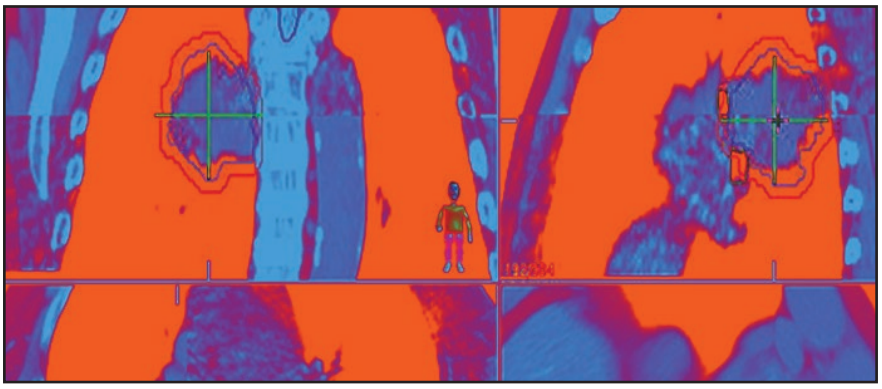
Dr. Suh is the Editor-in-Chief of Applied Radiation Oncology, *and Professor and Chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

Stereotactic body radiation therapy (SBRT) for lung cancer

Kevin L. Stephans, MD

Stereotactic body radiation therapy (SBRT) has evolved over the past 15 years and revolutionized the management of early stage non-small cell lung cancer (NSCLC). Compared to conventional radiation therapy, SBRT offers superior outcomes, lower costs and greater patient convenience.[1] SBRT likewise offers local control and cancer outcomes approaching surgical resection[2-8] with lower risk of treatment-related morbidity, making SBRT the treatment of choice for medically inoperable and many high-risk surgical candidates. Encouraging results in this population have led to the investigation of SBRT's role in operable stage I NSCLC, lung oligometastasis, stage I small cell lung cancer, and potentially as a boost to conventional radiation therapy for locally advanced NSCLC. The lessons learned in the lung SBRT experience also serve as a model for developing SBRT in other mobile soft-tissue sites, including the liver, pancreas, adrenal gland and prostate.

Dr. Stephans *is Associate Staff at the Cleveland Clinic Taussig Cancer Institute, Department of Radiation Oncology, Cleveland, OH, and Assistant Professor of Medicine (Radiation Oncology) at Cleveland Clinic Learner College of Medicine, Cleveland, OH.*



Technique

SBRT treatment planning begins with careful immobilization of the target with motion limited to <5-10 mm. This may be accomplished by abdominal compression (Figure 1), respiratory gating using either controlled breath-hold or external surrogates, or tumor tracking/respiratory modeling. Immobilization should be assessed by either fluoroscopy or 4DCT imaging at simulation, and verified by cone-beam CT (CBCT) or other imaging during treatment.

Historically, the planning target volume (PTV) was created from a fixed expansion (1 cm superior-inferior, 5 mm axially) of the contoured gross tumor volume (GTV),[7] although this can alternatively be derived from the union of multi-phasic CT GTV's (free-breathing, inhale, exhale) or 4DCT images into an internal target volume (ITV), which is then expanded uniformly by 5 mm yielding the PTV. Expanding the 4DCT ITV typically results in a smaller PTV, and likely more consistently represents the actual tumor motion, as well as center of mass.[9]

Beam arrangement may consist of 6 or more non-coplanar open beams, intensity-modulated radiation therapy (IMRT) beams, non-coplanar volumetric arcs (typically at least 3 arcs, each offset by 30-40 degrees), intensity-modulated arc therapy, or alternatively,

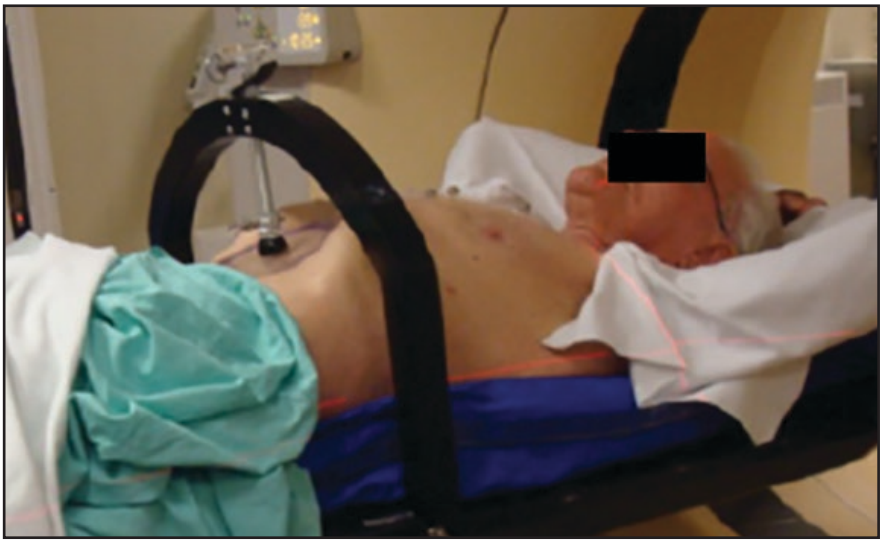


FIGURE 1. *Abdominal compression positioning for SBRT treatment.*

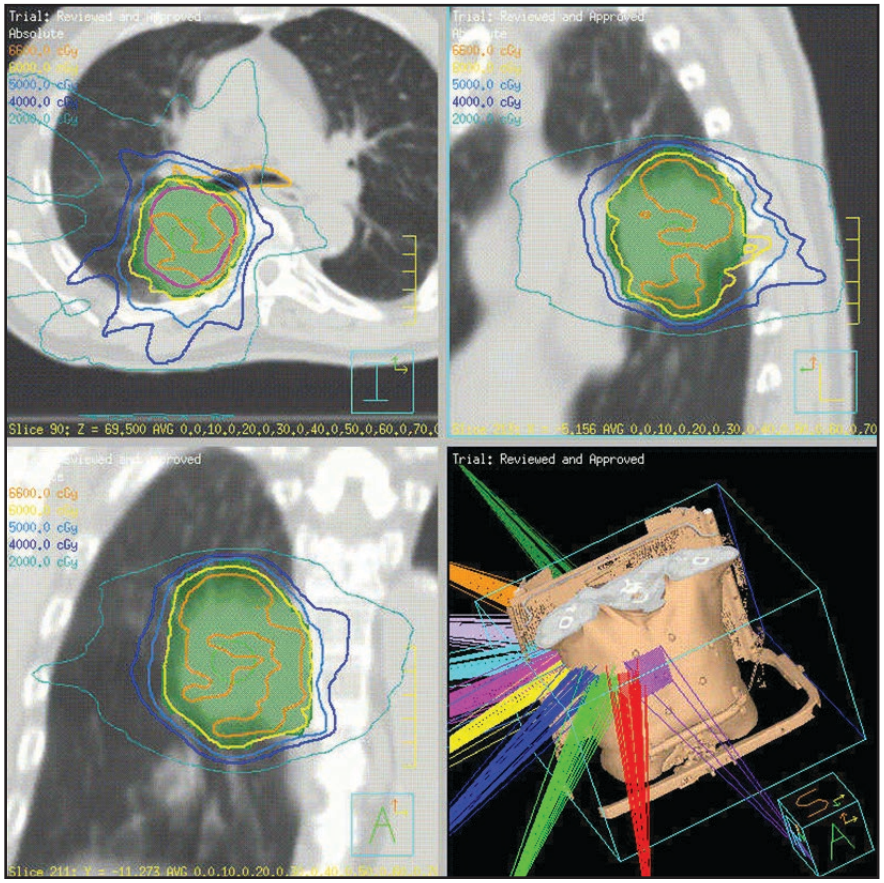
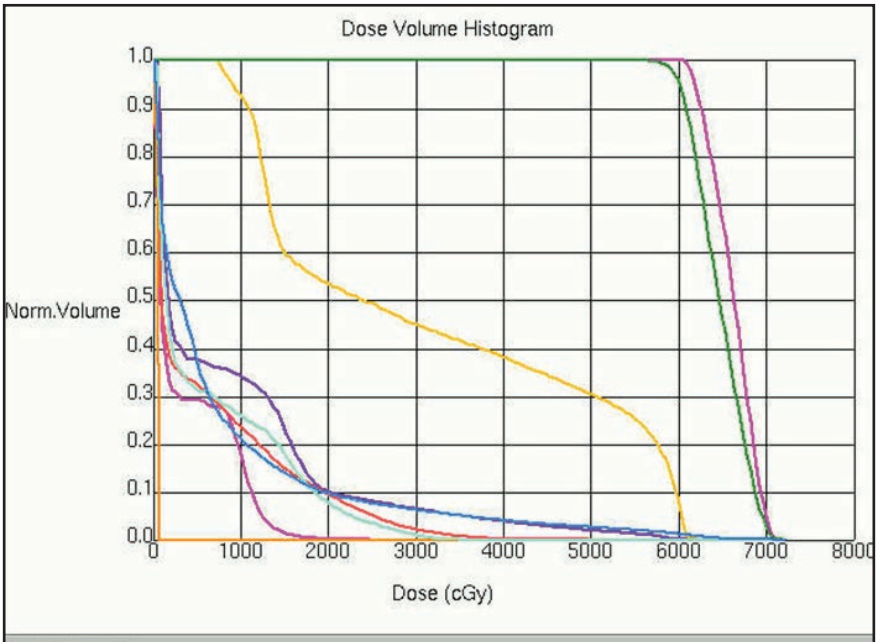


FIGURE 2. *Representative dose distribution for a central lesion. Proximal bronchial tree constraints were unable to be met for 50 Gy in 5 fractions, and the patient was thus treated to 60 Gy in 8 fractions based on a risk-adapted approach.*

particle-based therapy.[10,11] The use of IMRT in treating small moving lung targets is controversial due to concerns of potential underdosing, although IMRT is allowed by recent protocols such as RTOG 0813,[10] and reported outcomes with IMRT have been on par with other techniques.[12] Planning should utilize collapsed cone convolution or Monte Carlo algorithms, as there is a suggestion that pencil-beam algorithms may compromise tumor control due to more variable under-dosing.[13] Our institution uses the 4D-derived average CT as the planning image for the best estimate of density and tumor center-of-mass. Planning should focus on maximizing conformality and rapid dose fall-off. Heterogeneity is acceptable and may be desirable for purposes of faster fall-off, provided critical serial structures are not overexposed (Figures 2 and 3). Constraints should be based on appropriate protocols for the target being treated, such as RTOG 0236, 0813, 0915, or large institutional experiences.

Image guidance during treatment initially consisted of bony registration followed by port films, although modern approaches typically rely on CBCT (Figure 4). Free-breathing CT may not represent the true tumor center-of-mass due to respiratory motion, and a pitfall can be created by matching free breathing CT to a CBCT tumor at the time of treatment, potentially introducing a systematic error that occasionally exceeds the PTV expansion.[9] One should either use the average CT as the reference for matching, or otherwise localize only to bony anatomy if using a free-breathing image while verifying that the CBCT tumor falls within the ITV.

Patients should be routinely reimaged with CT after treatment for response assessment realizing that significant fibrotic reactions may occur (Figure 5).[14] Concerning features on CT include an enlarging mass-like density,



ROI Statistics

Line Type	ROI	Trial or Record	Min.	Max.	Mean	Std. Dev.
	ESOPHAGUS	Reviewed and Appro	46.9	6145.3	839.9	1191.1
	HEART	Reviewed and Appro	12.9	4969.6	577.4	850.2
	IPSI BP	Reviewed and Appro	17.6	68.3	44.8	14.0
	ITV	Reviewed and Appro	5948.3	7182.4	6611.0	252.2
	PBT	Reviewed and Appro	694.4	6235.0	3140.1	2008.8
	PTV Replan	Reviewed and Appro	5193.4	7182.4	6466.4	298.1
	TRACHEA	Reviewed and Appro	28.3	3495.7	594.3	791.1
	WHOLE LUNG	Reviewed and Appro	5.8	7098.3	749.3	1204.9

FIGURE 3. *Representative DVH for a central lesion. Proximal bronchial tree constraints were unable to be met for 50 Gy in 5 fractions, and the patient was thus treated to 60 Gy in 8 fractions based on a risk-adapted approach.*

as well as enlargement in the superior-inferior axis.[15] We typically reserve positron emission tomography (PET) scans for evaluating whether a lesion which appears suspicious on CT is recurrence vs. fibrosis. While no absolute standardized uptake value (SUV) cut-off exists, recurrence has been associated with SUV increases as well as residual SUV > 5 after SBRT.[15] Enlarging hypermetabolic lesions should undergo biopsy as there are occasional cases where high residual metabolism may be due to inflammation rather than recurrence.[16]

Cancer outcomes after SBRT for stage I NSCLC

Tumor control

Local control (LC) of the index lesion after lung SBRT is typically defined as the absence of tumor progression within 1 cm of the primary tumor site,[7] and has historically ranged from 90-98%,[2-8] consistent with a prospective surgical series showing an LRF rate of 5-7% for lobectomy, and 8-17% for sublobar resection.[17,18] Of note when comparing to surgical series, the terms lobar control (absence of failure within the treated lobe), and locoregional control (LRC, absence of local, lobar, or nodal recurrence) become relevant. RTOG 0236, a landmark prospective trial of SBRT using 60 Gy in 3 fractions (estimated 54 Gy in 3 fractions with heterogeneity corrections) for peripheral stage I NSCLC, demonstrated 3-year LC of 97.6%, lobar control of 90.6%, LRC of 87.2%, and a 22.1% rate of distant recurrence[7], consistent with other series.[2-8] Due in large part to the comorbidities of medically inoperable patients receiving SBRT, overall survival (OS) is typically lower in surgical series (48.3% at 3 years on RTOG 0236 for instance[7]), while cancer-specific survival is comparable.

There are no reported randomized trials comparing the outcomes of SBRT to surgical resection, and initial attempts have closed due to poor accrual, potentially reflecting differences between perceptions of the 2 treatments. Comparing outcomes in non-randomized series suffers from selection bias, and attempts at matched-pair or propensity-adjusted analysis are still likely influenced by SBRT series including older patients with more significant comorbidities, lower performance status, and lower pulmonary function than surgical series.[18] A matched-pair analysis between SBRT and wedge resection suggested improved LC with SBRT (96% vs. 80%), equivalent cause-specific survival, but better OS with surgery, attributed to differences in comorbidity.[20] Comparing lobectomy to SBRT, Robinson et al. found similar LC (98.7% v. 95.3%, p=0.088), regional control, and distant control with improved lobar control and survival in surgical patients,[21]

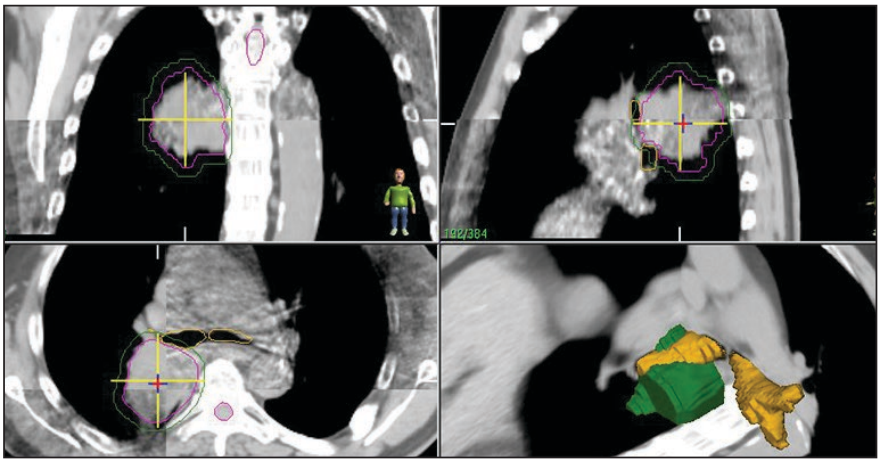


FIGURE 4. *Example of a CBCT image (upper left and lower right) at the time of treatment compared with a planning image from an average CT (lower left and upper right).*

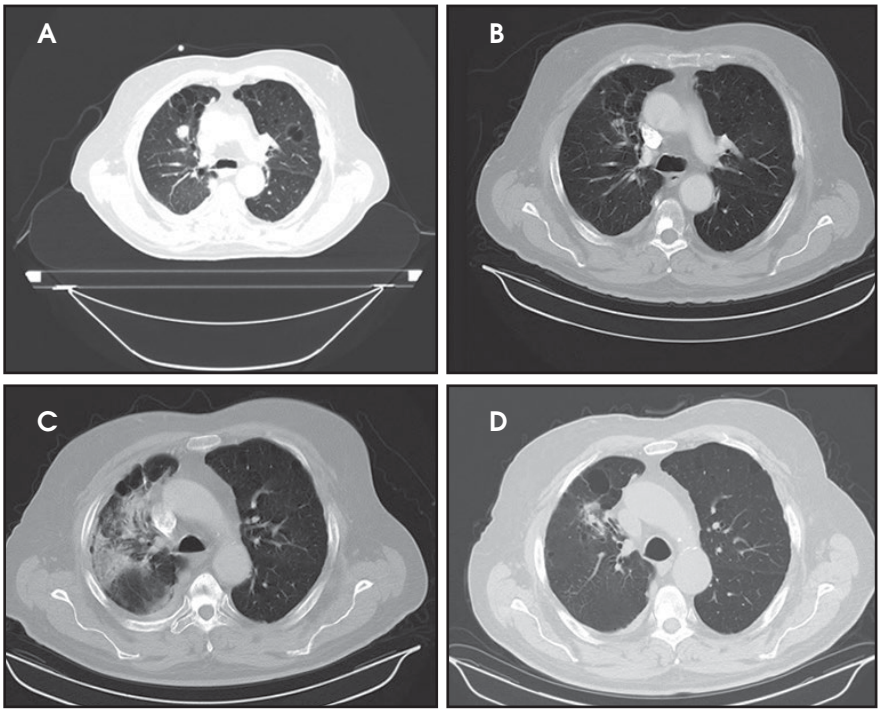


FIGURE 5. *Example of post-treatment imaging with initial tumor shrinkage, followed by inflammatory response, and long-term clearing of inflammatory response. A) Pre-SBRT, B) 4 months post-SBRT, C) 9 months post-SBRT, D) 24 months post-SBRT.*

with survival again perhaps related to selection. An earlier series from the same institution suggested improved local control and survival with surgical resection; however, after propensity matching, patient outcomes—including OS—came together.[19] Small series from Japan and the Netherlands reporting on SBRT for potentially operable patients also show LC and OS outcomes in line with surgical series.[4,5] A pooled meta-analysis of 40 SBRT studies totaling 4,850 patients and 23 surgical studies (lobar or sublobar resection, 7,071 patients total) likewise suggests no significant differences in LC between surgery and SBRT, and no effect of the percentage of potentially operable patients within SBRT series on LC.[8] The meta-analysis suggests better OS in a surgical series; however, within SBRT series, mean OS was correlated with reported percent operable patients, and a regression model using age and percent operability showed no significant OS differences between SBRT and surgery after correction.

Toxicity

SBRT is well-tolerated even in the medically inoperable population. Patients may experience fatigue for 4-6 weeks following treatment.[22] Pulmonary function is well-conserved[22-25] with generally <3% risk of radiation pneumonitis,[2-7,22-26] and even patients with extremely compromised pulmonary function exhibiting OS outcomes at or above the mean.[22,24] This suggests there is no lower limit to pulmonary function for SBRT, provided patients are medically stable. Neuropathic pain and rib fractures may occur with 10-15% of treatments of targets abutting the chest wall, although symptoms are generally modest and potentially less common than in surgical series.[27-29] Skin ulcers,[30] brachial plexopathy,[31] and bronchial[32] or esophageal fistulas[33] have been reported, but are extremely uncommon, and risk is modifiable during the planning process when identified.

Patient selection: Stage I NSCLC and the spectrum of operability

While there is no uniform definition of "medically inoperable," several surrogates and multiple predictive models of surgical morbidity are in use.[34] In practice, lung cancer patients fall on a spectrum from frankly unsuitable for surgery, to those at risk for surgical complications and mortality, to those at risk for quality of life changes with surgery and, finally, to patients in good health with minimal surgical risk. The first step in patient selection is for the multidisciplinary lung cancer team to stratify operative risk by considering the following:

Medically inoperable stage I NSCLC patients should receive SBRT, and not conventional radiation.[1]

Low-risk operable patients should proceed with surgical resection, which is the standard of care, and shown to be cost-effective relative to SBRT in modeling studies.[35,36] While early data for SBRT in operable patients is encouraging,[4,5] and OS between surgery and SBRT may be much closer after correction for age and comorbidities,[8,19] further data is needed before accepting SBRT as a first-line option for most operable patients.

As operative risk increases, SBRT rapidly becomes the treatment of choice. Modeling studies suggest a surgical risk threshold of between 3-4% above which the cost-effectiveness decisively swings in favor of SBRT,[35] a threshold consistent with treatment stratification in our clinic as well.

Some patients below this threshold may also choose SBRT due to better preservation of pulmonary function and to avoid oxygen requirements. In addition, a patient's advancing age (despite good health) and evolving priorities may prompt the decision of a more convenient and less invasive procedure.

Peripheral tumors

SBRT for peripheral tumors has demonstrated excellent long-term safety and efficacy as noted above. Areas of controversy include:

What degree of pre-treatment staging is required?

Historically, this has been PET-based (with brain imaging for stage IB or neurological symptoms). The development of less invasive mediastinal staging such as endobronchial ultrasound-guided sampling, and migration of healthier patients toward SBRT, has raised the question of whether more aggressive staging might improve outcomes. While 15-30% of clinical stage I NSCLC is upstaged by the finding of positive hilar nodes at surgery,[21,37] nodal failure rates appear paradoxically much lower after SBRT at 3-10%.[2-7] Without clear predictors of a high-risk subgroup for nodal failure,[38] the role of invasive staging remains controversial.

What is the ideal SBRT dose?

Excellent local control is seen with 60 Gy in 3 fractions as per RTOG 0236, although other regimens (48 Gy/4, 50 Gy/5, and 60 Gy/5) have similar outcomes without requiring as high of a biologically equivalent dose (BED). While regimens with BED > 100 Gy_{10} may saturate the dose response curve at low risk of toxicity,[6] perhaps some safety margin is helpful.

Simplifying treatment to single fraction regimens is also under investigation with RTOG 0915 recently suggesting similar outcomes between 48 Gy in 4 fractions and 34 Gy in 1 fraction,[11] while retrospective single fraction series continue to emerge.[39] The ideal fractionation for peripheral tumors remains controversial with a wide range of accepted fractionation schedules. As a result, more prospective data is needed.

Central tumors

While SBRT for peripheral stage I NSCLC has uniformly been associated with low risk, treatment of tumors within 2 cm of the trachea and proximal bronchial tree was associated with only a 50% freedom from grade 3 or higher toxicity after 60 Gy in 3 fractions in an Indiana University phase II report,[40] temporarily calling into question the safety of SBRT for central lung tumors. Of note, the early Japanese experiences using more moderate regimens such as 50 Gy in 5 fractions never discriminated between central or peripheral lesions without note of excessive toxicity in any subgroup.[6] Since then, additional reports of SBRT safety for central tumors have emerged using moderate dose regimens from 50-70 Gy in 4-10 fractions.[41-43] RTOG 0813, a multi-institutional dose escalation study for centrally located stage I NSCLC, also recently completed accrual escalating SBRT dose from 50 to 60 Gy in 5 fractions without protocol interruption from dose-limiting toxicity.[10] The early SBRT experiences employed few constraints focusing primarily on the maximization of conformality. Modern reports include a far more extensive set of normal tissue constraints, albeit still preliminary and only modestly validated. For patients presenting with larger central tumors, these constraints may not always be achievable. In this case, there is controversy over defaulting to conventionally fractionated radiation, although in my opinion, risk-adapted SBRT techniques such as the Dutch regimen of 60 Gy in 8 fractions maintain a BED > 100 Gy and are associated with excellent local control and safety.[42] While there is some inherent risk with SBRT for such large targets, failure to control these lesions often also leads to local morbidity.

Additional lung SBRT applications

Stage I small cell lung cancer (SCLC)

While SCLC is typically treated with concurrent chemoradiation, rare stage I presentations have been managed with success by surgery and adjuvant chemotherapy. By extension, 2 recent small series have explored SBRT followed by adjuvant chemotherapy in medically inoperable and poor risk stage I SCLC.[44,45] Prophylactic cranial irradiation in this setting is controversial.

Oligometastasis

SBRT may serve a role in managing lung oligometastasis with published series frequently treating up to 5 lung metastasis during SBRT, although in our practice it's typically limited to 1-2 oligometastatic sites. When treating oligometastasis, the intent of treatment must be clearly defined and balanced against the risks and cost of therapy.[46]

SBRT is most likely to add value in this setting with careful patient selection and with potential indications, including:

Curative intent treatment of patients with single lesions from metastatic colon or breast primaries based on extrapolation from surgical literature.

Newly diagnosed limited metastasis—ideally solitary—with a long interval from previous therapy, in which case SBRT might offer a delay in the need for potentially more toxic systemic therapy.

Isolated progression after a long interval of control on systemic therapy, possibly sterilizing isolated drug-resistant clones, best described in the anaplastic lymphoma kinase (ALK)- or epidermal growth factor receptor (EGFR)-mutated NSCLC setting.[47]

Limited residual disease after a long interval of control on systemic therapy with the intent of a break from systemic therapy.

SBRT as a boost for stage III NSCLC

While OS is not compromised, local control after chemoradiation for locally advanced NSCLC has been modest compared to surgical series with further dose escalation failing to improve outcomes.[48,49,33] SBRT is an alternative method of dose-intensification recently explored in 2 prospective series.[50,51] Feddock et al. reported the use of an SBRT boost of either 10 Gy x 2 for peripheral targets, or 6.5 Gy x 3 for central targets (per the RTOG 0813 definition) after 60 Gy conventional chemoradiation.[50] Treatment was well-tolerated (after modifications to the initial dose regimen for central tumors), and LC was a promising 83% at median 13 months. SBRT boost is a novel treatment approach with further investigation needed before widespread adoption.

Re-irradiation

Several series describe the use of SBRT for salvage of either isolated failure after conventional radiation for locally advanced disease,[52-56] or SBRT for early stage disease.[57-59] In both cases, patient selection is critical given modest progression-free survival and risk of toxicity. For local recurrences after prior EBRT, SBRT doses with BED > 100 Gy_{10} are associated with short-term LC ranging from 65-98%, although dyspnea and pneumonitis are common. Treatment of central or nodal recurrences is associated with a very high risk of toxicity.[56] SBRT for local recurrence after previous SBRT of peripheral recurrences <5 cm is associated with short-term LC of 33-60% after re-irradiation, while repeat SBRT for central tumors has been associated with significant toxicity and should be approached with extreme caution.

Conclusion

SBRT is an innovative treatment approach and represents the standard of care for medically inoperable stage I NSCLC. As results mature and techniques evolve, SBRT may be expanded to progressively healthier populations, while its role in locally advanced disease, recurrent disease, SCLC and oligometastasis continues to be explored.

References

1. Grutters JP, Kessels AG, Pijls-Johannesma M, et al. Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis. *Radiother Oncol.* 2010;95:32-40.
2. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. *Int J Radiat Oncol Biol Phys.* 2009;75:677-682.
3. Lagerwaard FJ, Haasbeek CJ, Smit EF, Slotman BJ, Senan S. Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2008;70:685-692.
4. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2012;83:348-353.
5. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? *Int J Radiat Oncol Biol Phys.* 2011;81:1352-1358.
6. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol.* 2007;2:S94-100.
7. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. *JAMA.* 2010;303:1070-1076.
8. Zheng X, Schipper M, Kidwell K, et al. Survival Outcome After Stereotactic Body Radiation Therapy and Surgery for Stage I Non-Small Cell Lung Cancer: A Meta-Analysis. *Int J Radiat Oncol Biol Phys.* 2014; S0360-3016(14)00706-8. doi: 10.1016/j.ijrobp.2014.05.055. [Epub ahead of print].
9. Wang L, Hayes S, Paskalev K, et al. Dosimetric comparison of stereotactic body radiotherapy using 4D CT and multiphase CT images for treatment planning of lung cancer: evaluation of the impact on daily dose coverage. *Radiother Oncol.* 2009;91:314-324.
10. RTOG 0813. (Accessed 07/25/14, at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0813.)
11. RTOG 0915. at http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=0915.)
12. Videtic GM, Stephans K, Reddy C, et al. Intensity-modulated radiotherapy-based stereotactic body radiotherapy for medically inoperable early-stage lung cancer: excellent local control. *Int J Radiat Oncol Biol Phys.* 2010;77:344-349.
13. Latifi K, Oliver J, Baker R, et al. Study of 201 non-small cell lung cancer patients given stereotactic ablative radiation therapy shows local control dependence on dose calculation algorithm. *Int J Radiat Oncol Biol Phys.* 2014;88:1108-1113.
14. Bradley J. Radiographic response and clinical toxicity following SBRT for stage I lung cancer. *J Thorac Oncol.* 2007;2:S118-124.
15. Huang K, Dahele M, Senan S, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR)—can we distinguish recurrence from fibrosis? A systematic review of the literature. *Radiother Oncol: J Eur Soc Ther Radiol Oncol.* 2012;102:335-342.
16. Henderson MA, Hoopes DJ, Fletcher JW, et al. A pilot trial of serial 18F-fluorodeoxyglucose positron emission tomography in patients with medically inoperable stage I non-small-cell lung cancer treated with hypofractionated stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;76:789-795.
17. Fernando HC, Landreneau RJ, Mandrekar SJ, et al. Impact of brachytherapy on local recurrence rates after sublobar resection: results from ACOSOG Z4032 (Alliance), a phase III randomized trial for high-risk operable non-small-cell lung cancer. *J Clin Oncol.* June 30, 2014, doi: 10.1200/JCO.2013.53.4115. [Epub ahead of print].
18. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. *Ann Thorac Surg.* 1995;60:615-622; discussion 22-3.
19. Crabtree TD, Denlinger CE, Meyers BF, et al. Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2010;140:377-386.
20. Grills IS, Mangona VS, Welsh R, et al. Outcomes after stereotactic lung radiotherapy or

wedge resection for stage I non-small-cell lung cancer. *J Clin Oncol.* 2010;28:928-935.
21. Robinson CG, DeWees TA, El Naqa IM, et al. Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer. *J Thorac Oncol.* 2013;8:192-201.
22. Videtic GM, Reddy CA, Sorenson L. A prospective study of quality of life including fatigue and pulmonary function after stereotactic body radiotherapy for medically inoperable early-stage lung cancer. *Support Care Cancer.* 2013;21:211-218.
23. Henderson M, McGarry R, Yiannoutsos C, et al. Baseline pulmonary function as a predictor for survival and decline in pulmonary function over time in patients undergoing stereotactic body radiotherapy for the treatment of stage I non-small-cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2008;72:404-409.
24. Stanic S, Paulus R, Timmerman RD, et al. No clinically significant changes in pulmonary function following stereotactic body radiation therapy for early- stage peripheral non-small cell lung cancer: an analysis of RTOG 0236. *Int J Radiat Oncol Biol Phys.* 2014;88:1092-1099.
25. Stephans KL, Djemil T, Reddy CA, et al. Comprehensive analysis of pulmonary function Test (PFT) changes after stereotactic body radiotherapy (SBRT) for stage I lung cancer in medically inoperable patients. *J Thorac Oncol.* 2009;4:838-844.
26. Palma D, Lagerwaard F, Rodrigues G, Haasbeek C, Senan S. Curative treatment of Stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review. *Int J Radiat Oncol Biol Phys.* 2012;82:1149-1156.
27. Dunlap NE, Cai J, Biedermann GB, et al. Chest wall volume receiving >30 Gy predicts risk of severe pain and/or rib fracture after lung stereotactic body radiotherapy. *Int J Radiat Oncol Biol Phys.* 2010;76:796-801.
28. Stephans KL, Djemil T, Tendulkar RD, Robinson CG, Reddy CA, Videtic GM. Prediction of chest wall toxicity from lung stereotactic body radiotherapy (SBRT). *Int J Radiat Oncol Biol Phys.* 2012;82:974-980.
29. Voroney JP, Hope A, Dahele MR, et al. Chest wall pain and rib fracture after stereotactic radiotherapy for peripheral non-small cell lung cancer. *J Thorac Oncol.* 2009;4:1035-1037.
30. Hoppe BS, Laser B, Kowalski AV, et al. Acute skin toxicity following stereotactic body radiation therapy for stage I non-small-cell lung cancer: who's at risk? *Int J Radiat Oncol Biol Phys.* 2008;72:1283-1286.
31. Forquer JA, Fakiris AJ, Timmerman RD, et al. Brachial plexopathy from stereotactic body radiotherapy in early-stage NSCLC: dose-limiting toxicity in apical tumor sites. *Radiother Oncol.* 2009;93:408-413.
32. Corradetti MN, Haas AR, Rengan R. Central-airway necrosis after stereotactic body-radiation therapy. *New Eng J Med.* 2012;366:2327-2329.
33. Stephans KL, Djemil T, Diaconu C, et al. Esophageal Dose Tolerance to Hypofractionated Stereotactic Body Radiation Therapy: Risk Factors for Late Toxicity. *Int J Radiat Oncol Biol Phys.* 2014 Jul 8. pii: S0360-3016(14)00596-3. doi: 10.1016/j.ijrobp.2014.05.011. [Epub ahead of print].
34. Donington J, Ferguson M, Mazzone P, et al. American College of Chest Physicians and Society of Thoracic Surgeons consensus statement for evaluation and management for high-risk patients with stage I non-small cell lung cancer. *Chest.* 2012;142:1620-1635.
35. Louie AV, Rodrigues G, Hannouf M, et al. Stereotactic body radiotherapy versus surgery for medically operable Stage I non-small-cell lung cancer: a Markov model-based decision analysis. *Int J Radiat Oncol Biol Phys.* 2011;81:964-973.
36. Puri V, Crabtree TD, Kymes S, et al. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. *J Thorac Cardiovasc Surg.* 2012;143:428-436.
37. Sagawa M, Saitoh Y, Takahashi S, et al. Analysis of patients with resected small-size (less than or equal to 2 cm in diameter) peripheral type lung cancer lesions. *Nihon Kyobu Shikkan Gakkai Zasshi.* 1990;28:944-949.
38. Marwaha G, Reddy C, Stephans K, Videtic G. Lung SBRT: Regional nodal failure is not predicted by tumor size. *J Thorac oncol.* 2014;In Press.
39. Videtic GM, Stephans KL, Woody NM, et al. 30 Gy or 34 Gy? Comparing 2 single-fraction SBRT dose schedules for stage I medically inoperable non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2014 Jul 8. pii: S0360-3016(14)00615-4. doi: 10.1016/j.ijrobp.2014.05.017. [Epub ahead of print].
40. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. *J Clin Oncol.* 2006;24:4833-4839.
41. Chang JY, Li QQ, Xu QY, et al. Stereotactic ablative radiation therapy for centrally located early stage or isolated parenchymal recurrences of non-small cell lung cancer: how to fly in a "no fly zone." *Int J Radiat Oncol Biol Phys.* 2014;88:1120-1128.
42. Haasbeek CJ, Lagerwaard FJ, Slotman BJ, Senan S. Outcomes of stereotactic ablative radiotherapy for centrally located early-stage lung cancer. *J Thorac Oncol.* 2011;6:2036-2043.
43. Rowe BP, Boffa DJ, Wilson LD, Kim AW, Detterbeck FC, Decker RH. Stereotactic body radiotherapy for central lung tumors. *J Thorac Oncol.* Cancer 2012;7:1394-1399.
44. Shioyama Y, Nakamura K, Sasaki T, et al. Clinical results of stereotactic body radiotherapy for Stage I small-cell lung cancer: a single institutional experience. *J Radiat Res.* 2013;54:108-112.
45. Videtic GM, Stephans KL, Woody NM, et al. Stereotactic body radiation therapy-based treatment model for stage I medically inoperable small cell lung cancer. *Pract Radiat Oncol.* 2013;3:301-306.
46. Ashworth AB, Senan S, Palma DA, et al. An individual patient data metaanalysis of outcomes and prognostic factors after treatment of oligometastatic non-small-cell lung cancer. *Clin Lung Cancer.* 2014. Published Online: May 15, 2014 DOI: http://dx.doi.org/10.1016/j.cllc.2014.04.003.
47. Gan GN, Weickhardt AJ, Scheier B, et al. Stereotactic radiation therapy can safely and durably control sites of extra-central nervous system oligoprogressive disease in anaplastic lymphoma kinase-positive lung cancer patients receiving crizotinib. *Int J Radiat Oncol Biol Phys.* 2014;88:892-898.
48. Albain KS, Swann RS, Rusch VW, et al. Radiotherapy plus chemotherapy with or without surgical resection for stage III non-small-cell lung cancer: a phase III randomised controlled trial. *Lancet.* 2009;374:379-386.
49. Machtay M, Paulus R, Moughan J, et al. Defining local-regional control and its importance in locally advanced non-small cell lung carcinoma. *J Thorac Oncol.* 2012;7:716-22.
50. Feddock J, Arnold SM, Shelton BJ, et al. Stereotactic body radiation therapy can be used safely to boost residual disease in locally advanced non-small cell lung cancer: a prospective study. *Int J Radiat Oncol Biol Phys.* 2013;85:1325-1331.
51. Karam SD, Horne ZD, Hong RL, McRae D, Duhamel D, Nasr NM. Dose escalation with stereotactic body radiation therapy boost for locally advanced non small cell lung cancer. *Radiat Oncol.* 2013;8:179.
52. Liu H, Zhang X, Vinogradskiy YY, Swisher SG, Komaki R, Chang JY. Predicting radiation pneumonitis after stereotactic ablative radiation therapy in patients previously treated with conventional thoracic radiation therapy. *Int J Radiat Oncol Biol Phys.* 2012;84:1017-1023.
53. Parks J, Kloecker G, Woo S, Dunlap NE. Stereotactic body radiation therapy as salvage for intrathoracic recurrence in patients with previously irradiated locally advanced non-small cell lung cancer. *Am J Clin Oncol.* 2014, Jan 22. [Epub ahead of print].
54. Reyngold M, Wu AJ, McLane A, et al. Toxicity and outcomes of thoracic re-irradiation using stereotactic body radiation therapy (SBRT). *Radiat Oncol.* 2013;8:99.
55. Trakul N, Harris JP, Le QT, et al. Stereotactic ablative radiotherapy for reirradiation of locally recurrent lung tumors. *J Thorac Oncol.* 2012;7:1462-1465.
56. Trovo M, Minatel E, Durofil E, et al. Stereotactic body radiation therapy for re-irradiation of persistent or recurrent non-small cell lung cancer. *Int J Radiat Oncol Biol Phys.* 2014;88:1114-1119.
57. Hearn JW, Videtic GM, Djemil T, Stephans KL. Salvage stereotactic body radiation therapy (SBRT) for local failure after primary lung SBRT. *Int J Radiat Oncol Biol Phys.* 2014 Jul 10. pii: S0360-3016(14)00699-3. doi: 10.1016/j.ijrobp.2014.05.048. [Epub ahead of print].
58. Peulen H, Karlsson K, Lindberg K, et al. Toxicity after reirradiation of pulmonary tumours with stereotactic body radiotherapy. *Radiother Oncol.* 2011;101:260-266.
59. Valakh V, Miyamoto C, Micaily B, et al. Repeat stereotactic body radiation therapy for patients with pulmonary malignancies who had previously received SBRT to the same or an adjacent tumor site. *J Cancer Res Ther.* 2013;9:680-685.

Hey, coach! Put me in! Improving the score in radiation oncology

Mitchell Kamrava, MD

Imagine coaching a basketball game where you come up with a game plan but can't change it or check the score until the game is over. This is basically what we do in radiation oncology. We pick a dose, deliver it in its entirety, and then reimage to see how we've done.

Just as a coach constantly evaluates a game and calls time-outs when the strategy isn't working, we too must learn how to fittingly coach the game. To do this, we have to improve our understanding of the opponent, figure out how to best use our players, and check the score more often.

Scouting out the opponent

Our current approach to understanding our opponent typically involves figuring out how many players are on the team (ie, How big is the tumor?). In general, this has resulted in doses of 50-60 Gy for microscopic disease (a few players) and >70 Gy for gross disease (a lot of players). Our biggest advance in nuancing this has been defining different clinical target volume (CTV) dose levels and incorporating simultaneous integrated boosts. This development is essentially just an improvement in our ability to estimate the number of players on the team, but isn't a game changer in terms of treatment success.

Other efforts have focused on boosting areas of higher standard uptake value (SUV) (ie, more players) on positron emission tomography (PET)-based studies, demonstrating that these areas are at higher risk of local failure. Work from the University of Michigan on non-small-cell lung cancer (NSCLC) demonstrates that mid-treatment PET can be used to modify volumes and allow for tumor dose escalation and dose reduction to normal tissues.[1] This approach is being tested in clinical trials and will hopefully improve treatment outcomes, but still has a major weakness: It doesn't address the identity of the team's individual players and how this should impact treatment strategy. Isn't it important to know if LeBron James and Kobe Bryant are on the team vs. a team comprised of bench warmers (Figure 1)? Perhaps one could argue that if you deliver enough dose then you will win the game regardless. But the problem with this approach is there are plenty of games that we still lose and, in some cases, do so quite badly. Understanding more about what makes the LeBron James' of cancer so good—and how best to defend these top performers—is key to improving our winning percentage.

FIGURE 1. *On the left is a common starting lineup for the 2014 Milwaukee Bucks, who at the middle of the 2013-14 season, had the worst record in the NBA. On the right is the starting lineup for the 2014 Western Conference All-Star team. While each team has 5 players (ie, tumor size of 5 cm), one would clearly not play against these lineups the same way.*

Understanding the team

In short, dose and volume are our star players. Advances in treatment machines and daily imaging have bulked up and improved the skill sets of these stars, but haven't changed how best to use them. Generally, we push dose as

Dr. Kamrava *is a Radiation Oncologist at the Department of Radiation Oncology, University of California Los Angeles.*

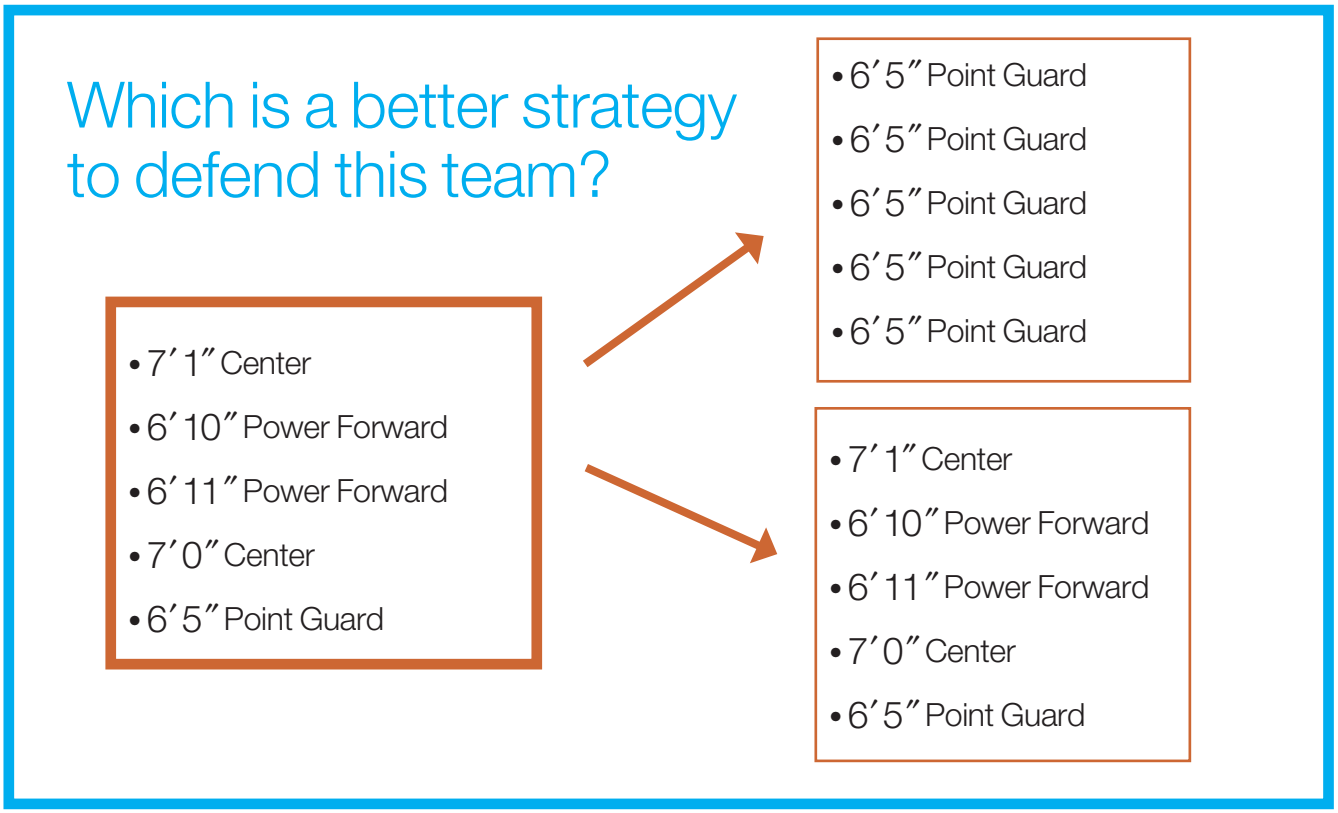


FIGURE 2. *If our goal is to guard the makeup of the team on the left (2 centers, 2 power forwards, and 1 point guard), it would make sense to build a team that could manage the makeup of this team (bottom right) rather than having a team made up of only point guards (top right).*

high as we can without hurting adjacent normal tissues. When we reach toxicity limits, we consider delivering higher doses only to subvolumes. While moving dose around to different volumes looks pretty on the treatment planning station, it's akin to watching the Harlem Globetrotters perform fancy tricks before they shoot a basket. It may be fun to watch, but it detracts from the game. We ultimately need to more adeptly use dose and volume. It's possible that hypofractionation (not related to adaptive planning) is better for defending only certain players, while a combination of standard fractionation and hypofractionation is best for others. In fact, using the maximal dose may not be the best strategy at all. Radiation results in significant genomic changes in tumors and can change the expression pattern of tumors to be more susceptible to certain pathway inhibitors. We must remember that multiple targeted agents (not adaptive strategies) are entering the draft each year and we need to recruit them to join our team. It's important to think about which of these players are superstars and will synergize with radiation, and which ones we don't need. As sexy new players like programmed cell death 1 inhibitors enter the draft, we must scrutinize their real value and not be wooed by the hype. In addition, we must determine how best to integrate our powerful roster of players with any newcomers (Figure 2).

HIV-positive oropharynx cancer presents an interesting example in that we are finding dose de-escalation may be a reasonable strategy. However, larger therapeutic gains might be possible with reductions/omission of systemic therapy in favor of targeted agents, rather than just pursuing modest reductions in radiation dose.

What's the score?

To improve our understanding of how we're doing, we must watch the game in real time (Figure 3). We need to adapt and learn during the game rather than reflect on why we lost after the game is over. MRI is an important component of helping us see the game, as it provides superior soft-tissue definition, functional information, and no additional radiation exposure to the patient. Integrating serial MRI scans and biopsy as tools to predict treatment response has been demonstrated in the investigation of serial studies to predict a therapeutic response with the imaging and molecular analysis (I-SPY) program in breast cancer. ISPY-1 was a collaboration between the National Cancer Institute Specialized Programs of Research Excellence (NCI SPOREs), the American College of Radiology Imaging Network (ACRIN), the Cancer and Leukemia Group B (CALGB), and

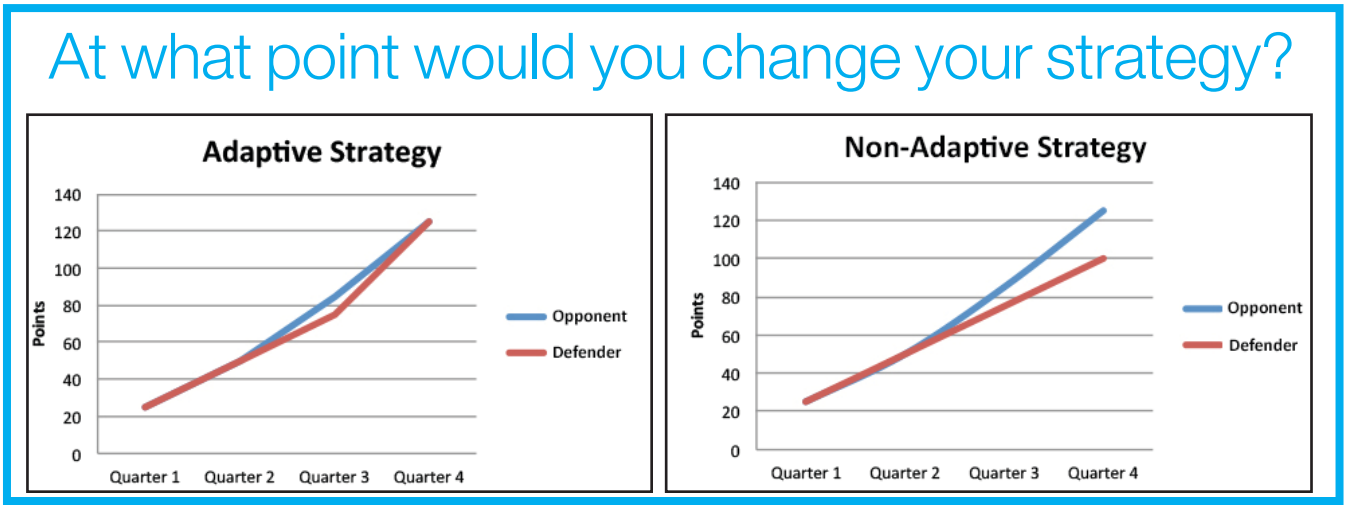


FIGURE 3. *On the right is a non-adaptive strategy where the score isn't checked until the end of the game. By quarter 3, the opponent starts to pull away but the defender maintains the same strategy and loses the game by quarter 4. On the left in an adaptive strategy, the defender recognizes that he's losing the game in quarter 3, but adapts and is even with the opponent by quarter 4.*

FIGURE 4. *The orange circles represent defenders, and the yellow are opponents. If one doesn't know where all the opponents are, the defenders must spread out to ensure coverage (left diagram), and may be unnecessarily outside the court. If the defenders know where all opponents are, they can use man-to-man coverage (right diagram).*

the NCI Center for Biomedical Informatics and Information Technology (CBIIT). It demonstrated that disparate disciplines could come together to integrate biomarkers and imaging data at multiple time points during treatment to help predict pathologic complete response after neoadjuvant chemotherapy in breast cancer.

The follow-up ISPY-2 trial is an ambitious replacement trial that incorporates an adaptive clinical trial design.[2] It has two arms: one in which patients receive standard neoadjuvant chemotherapy, and one in which patients receive standard chemotherapy plus 1 of 5 new drugs. Patients will have 3 biopsies and 4 MRIs performed during the course of neoadjuvant chemotherapy (Time 0, 3 weeks, 12 weeks, and prior to surgery for the additional MRI). The primary endpoint of the study is pathologic complete response. Correlations between treatment response with imaging and biomarker changes will be made. Using the 4 MRIs and multiple biopsies will allow investigators to observe the game essentially every quarter.

While this model is appealing, the negative findings from the Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization (ALTTO) trial presented in June at the American Society of Clinical Oncology (ASCO) meeting in Chicago, call into question whether pathologic complete response is an appropriate marker. The combination of Lapatinib and Trastuzumab increased pathologic complete response in the neoadjuvant setting (NeoALTTO); however, these positive findings were not reproduced in the adjuvant setting.

While improvements in adaptive trial design are still needed, there are opportunities to develop such trials in radiation oncology. One example is a high-risk prostate cancer protocol that is open to accrual at the University of California Los Angeles (UCLA). As with the neoadjuvant chemotherapy model in breast cancer, high-risk patients receive neoadjuvant androgen deprivation therapy (ADT) for 2 months before initiating radiation therapy. Data

from the prostate literature suggests that a patient's initial response to neoadjuvant ADT as measured by the patient's prostate-specific antigen (PSA) before starting RT (ie, < 0.5), is ultimately predictive of patient outcome. This provides an early biomarker before the start of radiation therapy (RT), which could potentially stratify patients. Multiparametric MRI could be performed before starting ADT. Fiducial marker seeds could be placed in areas outside of MRI targets (to avoid interference on functional imaging) before starting ADT as well. During the placement of the marker seeds, an ultrasound/MRI fusion technique could be used to take a couple cores from the index lesion as determined from the MRI. The patient could then have his PSA measured again in 2 months with another multiparametric MRI exam before starting a brachytherapy implant as a boost.

At the time of brachytherapy, another biopsy could be performed in the operating room on the index lesion. The information gleaned from such a study could identify MRI and/or genomic features that could predict which men are not likely to achieve a low PSA value prior to starting radiation treatment. These men could be identified to perhaps try newer anti-androgen therapies or dose escalation to the dominant site of disease. Alternatively, for patients who do achieve a low PSA nadir, we may find that they are ultimately not destined to develop metastatic disease, and perhaps could avoid prolonged androgen deprivation.

Where is everyone on the court?

When we treat patients, we place a margin around our target to ensure we don't miss secondary to set-up error and/or organ motion. These margins are analogous to placing defenders in areas that are out of bounds (Figure 4). Daily image guidance has improved our ability to tighten these margins and minimizes how much area outside the line we are defending. Aside from not defending areas unnecessarily, you also want to know where the players are that you're defending on the court—a distribution that changes over the course of the game. Daily MRI imaging allows one to see how the initial distribution (ie, a 5 cm tumor) is changing over the course of treatment, as well as providing the opportunity to shrink the field, if appropriate. Ultimately, determining "appropriate" changes in treatment fields must be investigated using prospective adaptive trials, since over-adapting is also possible and could increase failures. If all players are initially spread out and occupy all the space from the baseline to the half-court line, but then all players move to between the baseline and the free-throw line, you would want to know this and move players accordingly. Two choices come with this decision: real time on-line adaptive planning and off-line adaptive planning. With the former, the defensive players can tell where the offensive players are and move to cover them. With off-line adaptive planning, the defensive players can't tell where the offensive players are, but the coach can see changes, call a time out and rearrange the defense quickly. The problem with this approach is time-outs are limited, so you must take them at the right times.

The other component of this is deciding whether to play man-to-man defense or zone. We typically play a zone defense in which we cover a large area (planning target volume). The problem is that our zone coverage isn't set up right. To ensure you don't surrender easy points and limit "points in the paint," teams often have 2 players at the free-throw line and 3 closer to the basket. Our standard approach is to have a homogeneous distribution throughout the whole target. This doesn't make sense when you need to cover higher risk areas on the court. With functional MRI imaging, you may be able to determine if LeBron James is moving around during the course of treatment. Maybe at the beginning he's at the free-throw line, but toward the middle of treatment he moves behind the 3-point line. Depending on the situation, you may also want to double team LeBron James while covering the rest of the court by a zone. To make this call, you must see what's happening.

Final thoughts

To truly adapt a treatment plan, one must understand what is going on and how the patient is responding. Advances in MRI imaging and MRI treatment planning will allow us to image a patient daily and help us accomplish these goals.

We must stop coaching with our eyes shut. If we watch the game as it unfolds, we can potentially call a time out when needed, and put the right players in to turn the game around. The ViewRay (Oakwood Village, Ohio) MRI-guided radiation therapy system presents an exciting new frontier toward this end. The ability to view a patient's anatomy using MRI imaging in real-time during treatment is a major step forward. This treatment platform allows us to pursue adaptive planning in a way we could only have dreamed of a decade ago. The first patient using the ViewRay system was treated this year, and we are excited to start adapting this technology for winning results.

References

1. Feng M, Kong FM, Gross M et al. Using fluorodeoxyglucose positron emission tomorgraphy to assess tumor volume during radiotherapy for non-small-cell lung cancer and its potential impact on adaptive dose escalation and normal tissue sparing. *Int J Radiat Oncol Biol Phys.* 2009;15;73(4):1228-34.
2. Barker AD, Sigman CC, Kellof GJ et al. I-SPY 2: an adaptive breast cancer trial design in the setting of neoadjuvant chemotherapy. *Clin Pharmacol Ther.* 2009;86(1):97-100.

TECHNOLOGY TRENDS

VMAT: The next generation of IMRT

Mary Beth Massat

For the past two decades, cancer death rates have steadily dropped, resulting in a 20% plunge in the risk of dying from cancer, according to the American Cancer Society.[1] Greater access to cancer prevention, early detection and treatment have played a key role in this decline. However, incidence rates over the last 5 years have essentially remained flat—falling just 0.6% for men and remaining stable in women—calling for the continued development of new and novel treatment strategies.

One such advance is volumetric-modulated arc therapy (VMAT). Originally proposed as intensity-modulated arc therapy (IMAT) in 1995 as an alternative to tomotherapy, the idea of VMAT is to optimize the treatment plan in many angles, and then sequence it into stacks of apertures at every angle, followed by delivery of the beam with multiple connected arcs.[2] VMAT delivers radiation with a multileaf collimator in a continuous dynamic mode during a single (or multiple) rotation of the gantry.

The early days

Varian Medical Systems (Palo Alto, California) commercialized VMAT in 2008 with the introduction of RapidArc, a single arc solution, followed by Elekta (Atlanta, Georgia), which developed a single and multiple arc solution. Philips Healthcare (Andover, Massachusetts) provides a treatment planning solution, SmartArc, while Siemens Healthcare (Malvern, Pennsylvania) offers a single and multiple arc planning solution, called Prowess. Sun Nuclear Corp. (Melbourne, Florida) also provides QA and dosimetry tools for VMAT treatment plans.

Mary Beth Massat is a freelance healthcare writer based in Crystal Lake, IL.

Initially, a key hindrance to VMAT's clinical adoption was optimizing the treatment plan, explains Kevin Brown, global vice president of Scientific Research at Elekta. "In the early days of VMAT, the dose distributions were not as good as IMRT," he explains. "Now that the optimizers have improved, there is no fundamental reason why the dose distributions should not be as good as IMRT."

In fact, one thing Brown and his researchers learned through their clinical collaborators was the importance of varying dose rate as treatment progressed. That's when Elekta began referring to IMAT as VMAT, says Brown. Most of the early clinical work on VMAT was for large concave targets, since these cannot be adequately treated with static beams. But for most targets today, clinicians can develop plans with an equivalent dose distribution with IMRT and VMAT.

"The difference is that VMAT will deliver the treatment faster," says Brown. "Today, it's a question of why not, rather than why."

Accelerated treatment, enhanced focus

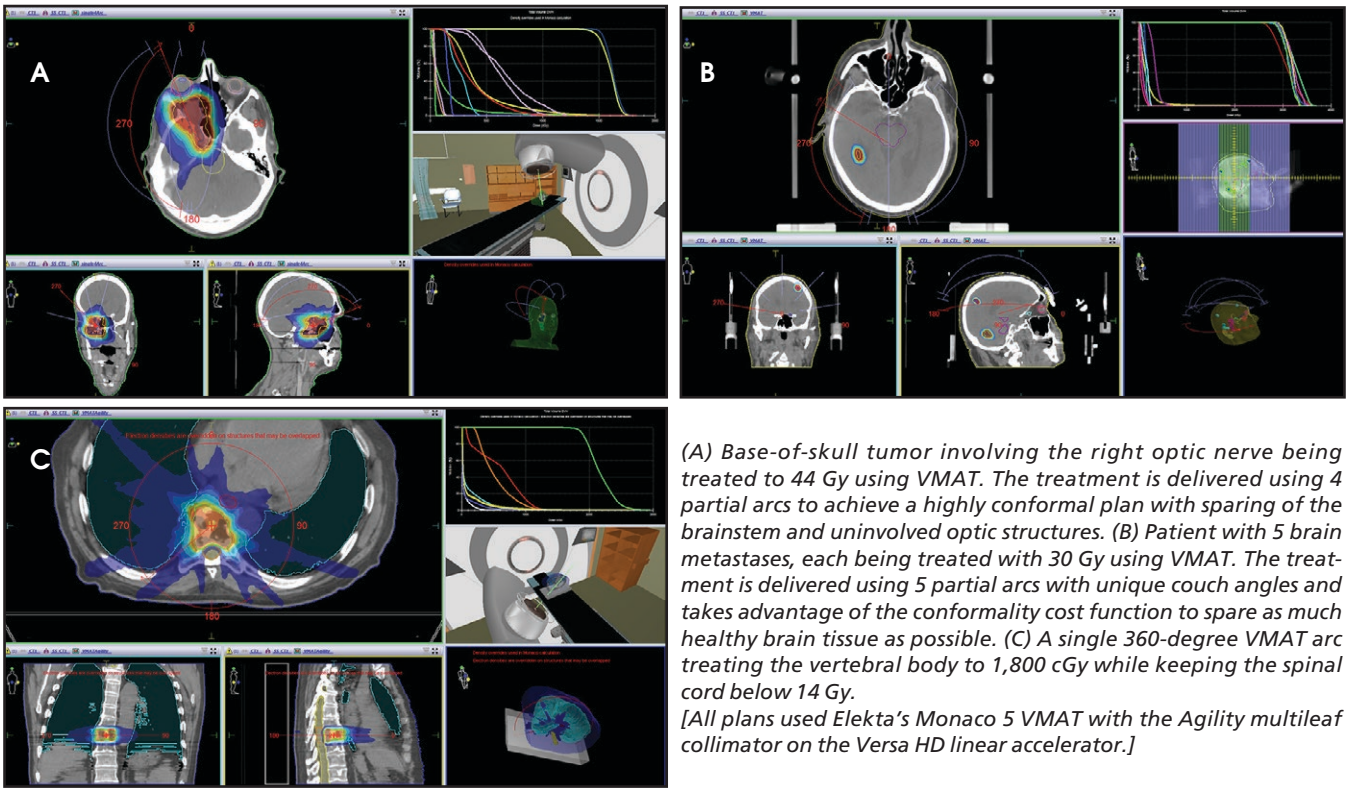
At the Swedish Cancer Institute in Seattle, Washington, Vivek K. Mehta, MD, a radiation oncologist and director for the Center for Advanced Targeted Radiotherapies, says that in addition to faster treatments, VMAT offers better treatment plans. "With more angles, we can be more focused on the tumor and less on the surrounding healthy tissue."

In his center, the first in North America to deliver VMAT plans with an Elekta linac, an initial comparison of IMRT to VMAT plans in 100 patients found that 95% were superior with VMAT across all disease types. "As we gained more experience, we re-planned those 100 patients and looked at the 5 where IMRT was better," says Dr. Mehta.

The result: Today 99% of VMAT plans are superior to IMRT at Swedish Cancer Institute. "There [are fewer] monitor units, better conformality, and it takes less time," he says.

"VMAT is the next generation of IMRT," adds Abhi Chakrabarti, PhD, director of Global Marketing for Philips Radiation Oncology Systems. "With VMAT, the technology allows treatments to be given in a shorter time; and therefore, the likelihood of patient movement decreases. The more clinicians can control something that is potentially damaging to healthy tissue—radiation—the more they can use it for the good."

Dr. Chakrabarti also has seen several centers outside the United States make the leap to VMAT from 3D conformal therapy, without implementing IMRT. "IMRT is more complex with more quality assurance (QA), but does not provide the time benefit," he says. With VMAT, the quality and time benefits exist, particularly for centers that have



(A) Base-of-skull tumor involving the right optic nerve being treated to 44 Gy using VMAT. The treatment is delivered using 4 partial arcs to achieve a highly conformal plan with sparing of the brainstem and uninvolved optic structures. (B) Patient with 5 brain metastases, each being treated with 30 Gy using VMAT. The treatment is delivered using 5 partial arcs with unique couch angles and takes advantage of the conformality cost function to spare as much healthy brain tissue as possible. (C) A single 360-degree VMAT arc treating the vertebral body to 1,800 cGy while keeping the spinal cord below 14 Gy.
[All plans used Elekta's Monaco 5 VMAT with the Agility multileaf collimator on the Versa HD linear accelerator.]

a large population base, whether in mature markets or emerging markets.

At Lewis Gale Regional Cancer Center in Pulaski, Virginia, James Nunn, MS, CHP, DABR, senior medical physicist, has seen firsthand the efficiency and speed of treatment with VMAT. Treatment times for patients receiving 7 to 14 individual beams with IMRT, especially if utilizing split beams, can take 30 minutes, he explains. VMAT can help lower a delivery from several minutes with IMRT down to 1 to 2 minutes per arc. That efficiency, and the potential to treat more patients without extending the clinic's hours, makes VMAT an economically attractive solution for busy facilities.

The question of integral dose

In addition to shrinking treatment times, another VMAT advantage is that it allows the clinician to shape the dose more conformally to the target's location, says Deepak Khuntia, MD, a radiation oncologist at the Targeted Radiation Institute, Pleasanton, California, and vice president of Medical Affairs with Varian Medical Systems. "While we can get more conformal plans than before, the integral dose—the total dose of radiation absorbed by the body—is more spread out than it would be with conventional IMRT and 3D techniques," he says, "and we must pay close attention to that."

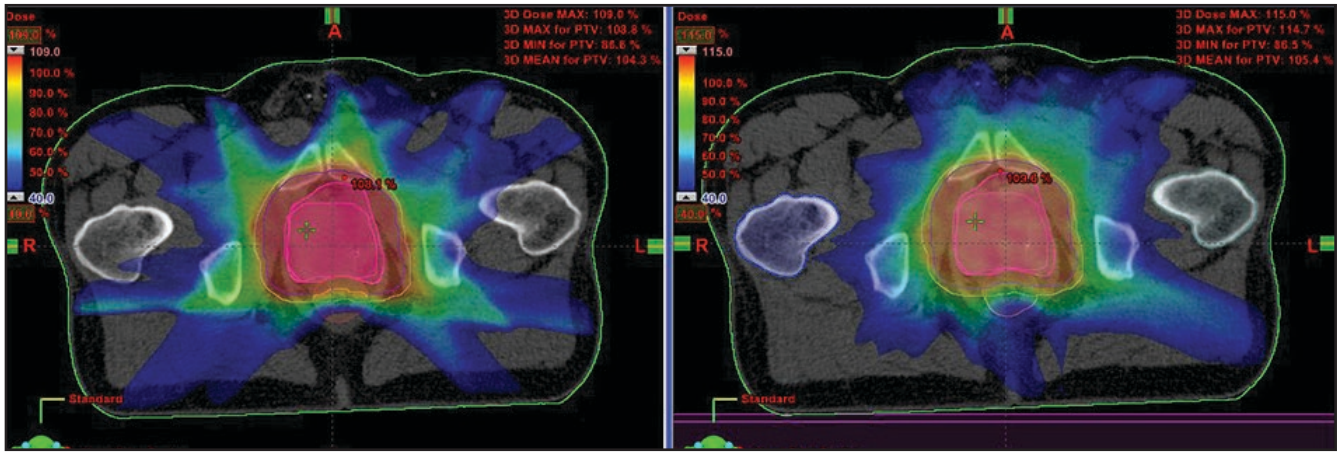
While there is limited evidence that higher integral dose impacts patient outcomes, clinicians should review this consideration on a case-by-case basis to ensure doses to normal structures are low enough to meet practice standards.

Nunn agrees that integral dose is an important consideration when developing treatment plans with modulated arcs. With a traditional IMRT treatment using 5 to 7 beams, some areas in the body receive little radiation. As such, the integral dose is very low. With VMAT, however, the arc is continually moving as the multileaf collimator (MLC) modulates dose. As a result, some areas receive a radiation dose that they otherwise would not with traditional IMRT techniques.

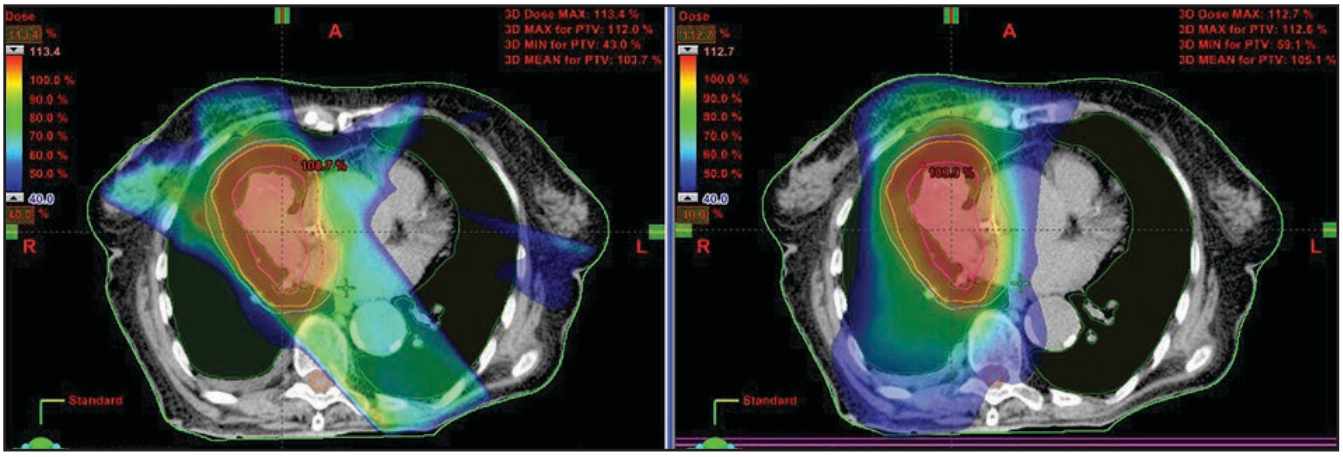
"With VMAT, we have dose going through the body at 360°, so integral dose becomes a more important factor in areas with critical structures," explains Nunn. "This is why in our facility we haven't switched everything over to VMAT. In some instances the integral dose to critical structures can be higher with VMAT than IMRT; consequently, in those cases we use traditional IMRT."

However, Dr. Mehta cautions that the issue of integral dose depends on how you look at low dose. In some cases, dose can be less with VMAT compared to IMRT. For example, since VMAT is delivering dose at every angle, each angle is delivering less dose than if the dose were

TECHNOLOGY TRENDS



Images from an IMRT (left) and Varian RapidArc radiotherapy (right) treatment plan for prostate cancer. The RapidArc treatment required 804 monitor units and took 1.5 minutes to deliver (vs. 1,147 monitor units for the IMRT plan, which took 5.5 minutes to deliver).



Images from an IMRT (left) and Varian RapidArc radiotherapy (right) treatment plan for lung cancer. The treatment required 399 monitor units and took 75 seconds to deliver (vs. 1,327 monitor units for the IMRT plan, which took 5.5 minutes to deliver).

delivered only across 4 angles. Determining which option is better for patients depends on the particulars. If a patient is being re-treated, then the ability to disburse the dose across more angles may be better than using fewer, fixed angles. On the flip side, if a certain path should be avoided due to a critical structure, then a fixed field makes more sense.

Dr. Mehta also notes that with IMRT, a small amount of low-dose radiation leakage occurs when the machine is ramped up in dose and then brought back down to zero. "With VMAT, we turn the machine on one time, so there is less [leakage] of the radiation," he explains. "For young patients, we really don't want any of that low dose leakage."

VMAT at work

At Lewis Gale Regional Cancer Center, approximately 40 to 60 patients a day receive external-beam radiation therapy (EBRT). Before implementing VMAT, most patients at the clinic received 3D conformal and step-and-shoot IMRT, notes Nunn. Currently, however, VMAT is most often used for treating cancers centrally located in the body, such as the esophagus, prostate, lung and brain.

Nunn adds that with traditional IMRT QA, the accelerator gantry can be held stationary and the plan delivered to a phantom, or chamber array. "You have to be more careful in correcting for how the beam enters your QA device," he says. "Your QA device placement is, therefore, more critical."

While the QA process may be more complex, Nunn says VMAT is easier today than when he first used it in 2009. From solutions that check rotational plans, to second-check software with 3D analysis, to new planning software and more advanced computers, Nunn has witnessed several improvements in speed and capability.

"It doesn't take us too much time to plan arc treatments with today's computing power, so for some cases we do two plans—IMRT and VMAT," Nunn explains. "We can then compare target coverage and integral dose, and our physicians can choose the most

appropriate plan to meet their treatment objectives…Our learning method was to take our existing IMRT treatment planning knowledge, and extend and modify these techniques to arc treatments."

A bigger challenge for Nunn was interconnecting devices from various vendors to perform VMAT. While single-vendor solutions are currently available, that wasn't the case when his facility began acquiring modules to perform VMAT. Nunn had to ensure his second-check software was compatible with arcs, his record-and-verify software could sequence to the linac, and the couch top was properly characterized in the planning software.

For Elekta users, the company's digital linac helps streamline the move to VMAT. "If our customers have a modern Elekta linac purchased within the last 8 to 10 years, then it is capable of being upgraded to deliver VMAT treatments," Brown explains. This upgrade is limited to the dose-rate control, and the treatment planning software—the main component. Monaco 5, Elekta's latest release, features both VMAT and IMRT algorithms.

Elekta's next generation linac, Versa HD, is further optimized for VMAT treatments. It incorporates the Agility multileaf collimator and the new high-dose-rate mode. According to the company, Agility provides integrated digital control of leaves and leaf guides, combined with unique Rubicon optical leaf positioning for an accurate and reliable beam-shaping solution. Coupled with leaf transmission of less than 0.5 percent, Agility enhances treatment delivery while reducing integral dose.

In 2013, Varian received clearance for RapidPlan, a knowledge-based treatment planning system tool that helps clinics leverage shared clinical best practices from leading institutions, or a center's own best practices to create a model treatment plan. RapidPlan uses dose and patient anatomy information from existing plans to help clinicians estimate dose distributions in new patients. With RapidPlan, facilities can further decrease variance in the quality of plans, and increase efficiency in the planning process, particularly for complex cases, according to the company. This is not a template, but rather a personalized treatment plan utilizing knowledge obtained from what physicians deem the best plans of the past.

At the American Association of Physicists in Medicine (AAPM) annual meeting in July, Philips introduced Pinnacle^3 Auto-Planning, which accelerates both IMRT and VMAT planning and makes the process more consistent and reproducible. The solution reduces time and effort to create a plan, and eliminates manual data entry.

"Clinicians are not only burdened with more patients as volumes increase, but they also want consistency in treatments," says Dr. Chakrabarti. "We expect variations in skill sets across different centers, and products like this are designed to help elevate the level of the plan for all centers—improving the access and quality of health care for everyone."

VMAT today and tomorrow

Dr. Mehta and his colleagues have begun using VMAT for stereotactic body radiation therapy (SBRT), and he finds the VMAT plans are comparable to traditional SBRT plans. However, SBRT treatments can take several hours to complete, while VMAT can take several minutes, as in the case of external-beam therapies. This can have a significant impact on lung cancer patients, who often lack good lung capacity and have difficulty holding their breath.

Lung cancer patients can also benefit from triggered imaging, a process that can be used during a VMAT treatment using Varian technology to enhance targeting accuracy during treatment delivery in most disease sites, including the lung. With gold markers implanted into the lung tumor, the patient is imaged at specific points of the respiratory cycle during the VMAT treatment. If the patient moves, the operator can pause the beam and arc until the patient is back in position. The imaging is done in near real time, which enables clinicians to better ensure that radiation is being delivered to the right place at the right time, says Dr. Khuntia.

"The imaging, treatment plan and motion interfaces are all put together in a harmonic way to allow the operator to analyze each component at once and prevent mistreatment," he says.

Looking to the future, Nunn expects to see more VMAT treatment techniques used for stereotactic ablative radiotherapy (SABR) treatments. Another prediction is that VMAT will replace most IMRT plans in the United States, says Dr. Mehta.

"Many centers will find the leap to VMAT from IMRT is not that hard… Once they have the skill set for IMRT, they can use that same exact skill set for VMAT," he says. "It's an evolution, a continuation and improvement to IMRT."

As automation increases, Brown also predicts greater VMAT adoption. "As we make the entire delivery process more automatic, that will make the process even more efficient, reproducible and safer," he says. "Clinicians will be looking for the most efficient way to deliver good quality treatments to every patient. VMAT represents, for the vast majority, the most efficient way to deliver treatment."

References

1. Siegel R, Ma J, Zou Z et al. Cancer statistics, 2014. *CA: Cancer J Clin*, 2014; DOI: 10.3322/caac.21208.

2. Yu CX. VMAT and the tradeoff between treatment time and dose conformality. http://vimeo.com/77145182. Paper presented at: American Association of Physicists in Medicine 52nd annual meeting and exhibition, Philadelphia,July 18-20, 2010.

RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for September 2014!

Scalp angiosarcoma: Discussion of a management plan

Stephanie Rice, MD, Kevin R. Kozak, MD, PhD, and Pranshu Mohindra, MD

CASE SUMMARY

A 60-year-old male presented with a 3-month history of a lump on the left vertex of his scalp. On examination, the lesion appeared erythematous with a central clearing. Initial biopsy demonstrated epithelioid angiosarcoma. No other skip lesions were noted during a mapping procedure with 8-punch biopsies. Wide local excision with a sentinel lymph-node biopsy demonstrated extensive dermal and subcutaneous fat infiltration from angiosarcoma extending to the deep aspect of the right margin, and a distinct soft-tissue deposit with a focus of angiosarcoma without any obvious association with lymph nodal tissue within the sentinel biopsy specimen. Re-excision, with accompanying split thickness skin grafting, was performed to obtain negative margins.

With a high risk of distant and locoregional recurrence postsurgery, the patient elected to receive adjuvant chemotherapy with weekly paclitaxel (80 mg/m^2) for 12 cycles. After completing chemotherapy, the patient received adjuvant radiotherapy (RT). The radiation treatment isodose distribution and the corresponding dose-volume histogram (DVH) are noted in Figures 1 and 2, respectively. The treatment plan was 66 Gy in 33 fractions delivered with helical tomotherapy without bolus and a 5 mm planning target volume (PTV) expansion. This technique is described by Orton, et al.[1] Time for delivery of 1 fraction (2 Gy) was 797.2 seconds. Ultimately the patient received 60 Gy in 30 fractions out of concern for viability of his split thickness skin graft. The benefits of using helical tomotherapy on this patient include the ability to treat nodes on the left side of the neck, to avoid field matching issues that can lead to hot and cold spots in the treatment field, and daily megavoltage CT (MVCT) imaging to ensure proper patient setup and accurate dose delivery.

IMAGING FINDINGS AND DIFFERENTIAL DIAGNOSIS

Preoperative magnetic resonance imaging (MRI) of the brain demonstrated a 1.1 × 2.1 × 0.9-cm enhancing lesion in the left anterosuperior parietal scalp with extension to the overlying skin surface. No findings demonstrated intracranial spread. An incidental 6-mm lesion in the right internal-auditory canal likely representing a vestibular schwannoma was noted. Work-up was negative for regional or distant metastatic disease.

Differential diagnosis includes angiosarcoma, basal cell carcinoma, squamous cell carcinoma, Kaposi's sarcoma, hemangioma, actinic keratosis, and contusion.

DIAGNOSIS

Scalp angiosarcoma

DISCUSSION

As a result of this entity's rarity, standardized treatment recommendations are primarily based on (A) retrospective institutional series spanning multiple decades that are subject to inherent selection biases and patient/treatment heterogeneity, and (B) extrapolation from treatment algorithms for other soft-tissue sarcoma histologies.[2] Complete tumor resection appears to be an important prognostic factor in patients with head-and-neck angiosarcoma. Admittedly, this improved outcome could be due to selection bias of lesions amenable to resection without evidence of spread elsewhere. Additionally, size < 5 cm

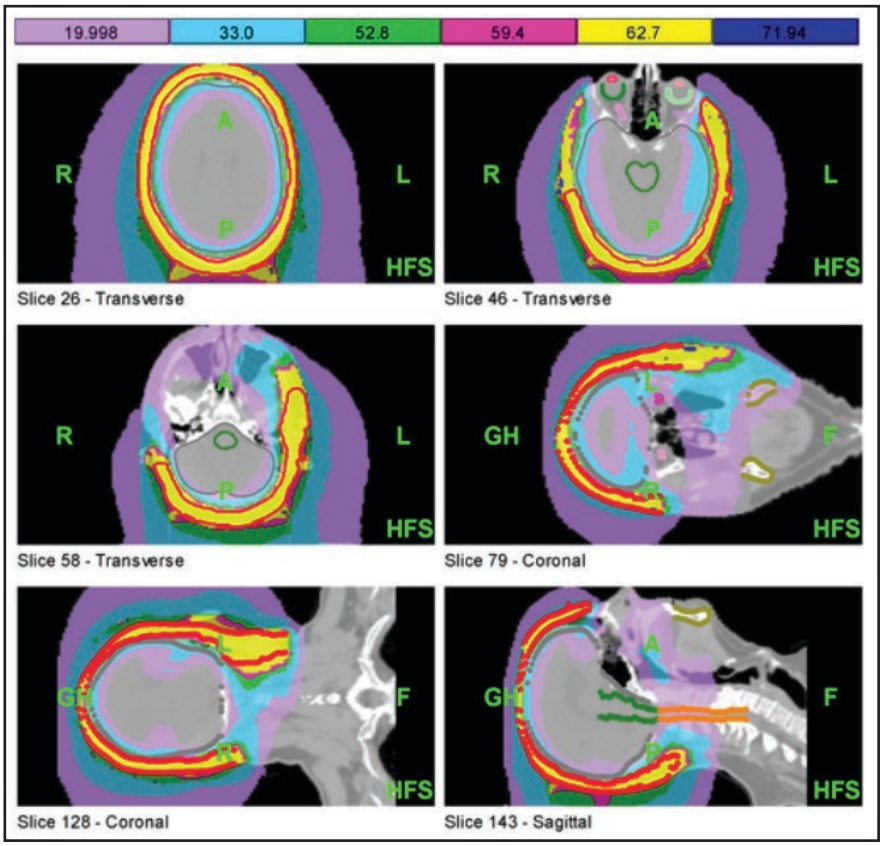


FIGURE 1. *Axial, coronal and sagittal images of the planning CT with super-imposed isodose distribution. Given that a focus of angiosarcoma was identified in the left parotid region, irradiated volumes included the entire scalp and the periparotid region. We used helical tomotherapy to allow coverage of the entire scalp, left parotid region, and left neck nodal volume, and delivered 60 Gy homogenously to this volume.*

corresponds with better overall survival and lower locoregional recurrence.[3,4] Emerging data suggests that epithelioid morphology is an adverse prognostic factor.[3]

Scalp angiosarcoma is an aggressive form of angiosarcoma, with high propensity for early metastatic spread and local recurrence. Because of this, field design typically includes total scalp irradiation with large margins and consideration of regional lymphatic treatment.[5] The margin size and total coverage area is significantly larger than used to treat other head and neck cancers due to the high rates of local recurrence at the edge of the RT field as well as distant failure. In a Surveillance, Epidemiology and End Results (SEER) database analysis (1973-2007), 5- and 10-year overall survival (OS) rates were noted to be 34% and 14%, respectively.[6] Local recurrence rates as noted in different series range from 53% to 100%, while distant metastatic disease in these series ranged from 28% to 64%.[7-10] Cutaneous angiosarcomas are the most common subtype of angiosarcoma, and tend to occur in patients ages 65 to 70 with a male predominance.[11,12] Angiosarcomas make up 15% of all head-and-neck sarcomas, and approximately 1-2% of all soft-tissue sarcomas.[13,14]

A wide variety of systemic therapies have been evaluated in angiosarcoma. A phase II study evaluated paclitaxel given as a 60-minute infusion of 80 mg/m^2 on days 1, 8, and 15 of a 4-week cycle in metastatic or unresectable angiosarcoma patients. The overall response rate (ORR) at 6 months was 19% with a progression-free survival (PFS) rate at 2 and 4 months of 74% and 45%, respectively. The median overall survival was 8 months.[15] Memorial Sloan Kettering Cancer Center (MSKCC), New York, retrospectively evaluated paclitaxel response in 9 scalp angiosarcoma patients, and demonstrated an 89% response rate (4 partial, 4 complete).[16] The median duration of response was 5 months (range 2-13 months). These data support the long-held impression that scalp angiosarcomas may be more paclitaxel-responsive than other angiosarcomas (eg, visceral). Activity of pegylated-liposomal doxorubicin in angiosarcoma (all sites) was demonstrated in a series reported from the University of Minnesota, Minneapolis, with 3/6 patients developing a PR lasting 6, 19 and > 20 months.[17] Docetaxel resulted in a ORR of 67% (22% complete response [CR]) in a series of 9 cutaneous angiosarcomas.[18] A phase II study of bevacizumab in metastatic or locally advanced angiosarcoma and epithelioid hemangioendothelioma demonstrated 4/30 (13%) patients with a partial response (PR), 15/30 (50%) with stable disease, and a mean time to progression of 26 weeks.[19] Sorafenib has been shown to have ORR of 14% in angiosarcoma with a median PFS of 3.8 months and median OS of 14.9 months.[20] In addition, an Italian retrospective study documented ORR of 68% with gemcitabine in advanced angiosarcoma with a median PFS of 7 months, and OS of 17 months.[21]

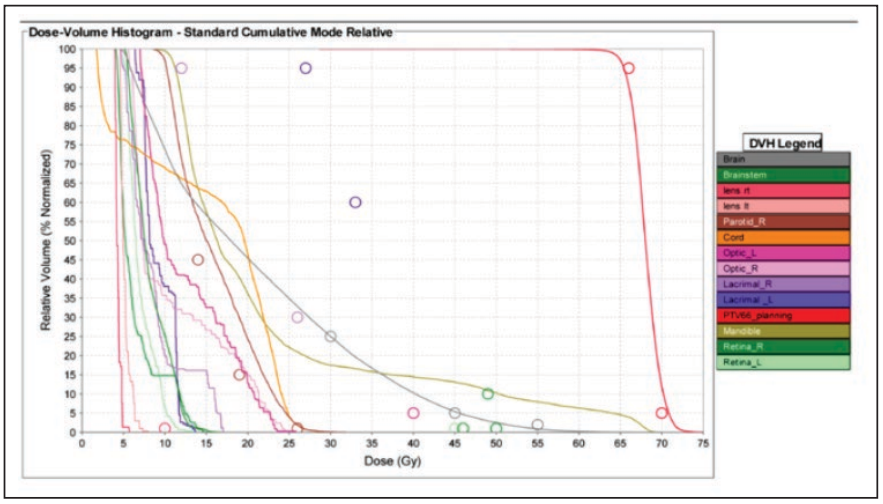


FIGURE 2. *DVH of the radiation plan approved for treatment. The treatment was initially planned for a total dose of 66 Gy, but was subsequently scaled down to 60 Gy to maximize the probability of skin graft integrity.*

In general, due to a dearth of data, radiation treatment principles for scalp angiosarcoma are extrapolated from the larger soft-tissue sarcoma experience. Routinely used postoperative doses range from 60 to 66 Gy in 1.8 to 2 Gy fractions, with higher doses used when gross disease is present (limited by normal tissue tolerance). A study of 70 patients with nonmetastatic angiosarcoma of the face and scalp found that patients treated with surgery and RT (vs. surgery alone or RT alone) had improved 5-year OS (68% vs. 40% vs. 22%, p = 0.01), disease-specific survival (DSS) (76% vs. 43% vs. 22%, p = 0.006), and better local control (84% vs. 25% vs. 22%, p = 0.0003).[10] The benefit of combined modality local therapy remained significant on multivariate analysis (p = 0.0003). This study also found that local recurrence correlated with the development of distant metastatic disease. The University of Florida angiosarcoma experience demonstrated improved outcomes with hyperfractionated (3 times daily) schemes. Non-scalp primary lesions were associated with better outcomes. Improved outcomes were also observed in patients receiving 70 Gy or more, suggesting better outcomes with higher doses of radiation therapy.[22] Better outcomes with combined modality therapy have been demonstrated in other studies as well.[8,11] Interestingly, Guadagnolo and colleagues found that positive surgical margins did not portend a poorer prognosis, suggesting that aggressive resections that may compromise delivery of timely adjuvant radiation therapy may not be necessary.[10] In general, re-excision to obtain negative margins could be beneficial if timely healing is expected, and it is not anticipated to significantly increase morbidity or cosmetic deformity.

For RT delivery, the 3 most commonly used techniques include opposed electron-photon fields, brachytherapy, and intensity-modulated radiation therapy (IMRT). A description of opposed electron-photon fields for scalp irradiation was reported by Akazawa and colleagues,[23] and subsequently optimized by investigators at MD Anderson Cancer Center.[24] Field matching is done with 6 MV photons and 6 MeV electrons with 2 pairs of lateral electron and photons fields. The electrons treat most of the lateral scalp while photons are used on the superior scalp with a central block to protect underlying brain tissue. Bolus is employed to ensure adequate dose to surface tissues. Due to concerns regarding underdosing at the junction of the photon-electron fields, as originally described, a 3 to 4-mm overlap of the electron and photon fields has been recommended to improve dosimetric homogeneity.

Another technique for scalp irradiation is surface-mold brachytherapy. Ozyar et al. described a technique using remote-controlled afterloading high-dose-rate (HDR) brachytherapy in a patient with multifocal basal cell carcinoma.[25] Catheters traversing the entire scalp were placed parallel at 10 to 12-mm spacing. HDR microselection equipment with an Ir-192 source was used. A total dose of 4,050 cGy at 0.5-cm skin depth was given over 3 weeks. The patient remained without evidence of disease through 6 years with no late complications from the radiation. No *in vivo* dosimetric verification was reported. Advantages of this technique include homogeneous dose distribution with steeper dose fall-off beyond the target, and simpler setup compared to IMRT or opposed photon-electron fields.

A third radiotherapy approach is total scalp irradiation using IMRT.[1,26,27] Among the most commonly reported IMRT techniques used is helical tomotherapy. Orton and colleagues have shown that helical tomotherapy has the ability to deliver beamlets tangential to the scalp while avoiding field-matching problems, and only requires the use of one modality. Tangential beamlets available from a tomotherapy unit enhance the dose to superficial tissues, eliminating the need for bolus. Dosimetric verifications of superficial dose were performed on the surface of an anthropomorphic phantom with gafchromic EBT radiochromic film, Kodak EDR2 film, and a skin solid-state dosimeter known as MO*Skin*. The time for setup, MVCT, shifts and treatment is about

25 minutes, comparable to the time for treatment on a conventional linear accelerator.[27] A helical-treatment delivery approach also avoids field-matching problems and allows simultaneous treatment of regional nodal volumes, as was required in our case.

Hadziahmetovic and colleagues recently described a bolus technique called scalp uniform bolus application (SCUBA). Due to concern about daily reproducibility of conventional wax or superflab bolus, they used airtight scalp uniform bolus with 2 wetsuit diving hoods that were equivalent to a 5-mm bolus without air gaps. Optically stimulated luminescent dosimeters (OSLDs) were used to measure dose to the scalp on the head-phantom with either 20-field IMRT or opposed 6 MV photons and 6 MeV electrons. This proves inexpensive, effective, and easily reproducible as an option for uniform bolus for either opposed photon-electron or IMRT plans.[28]

CONCLUSION

Scalp angiosarcoma is a rare entity with little data to guide treatment decisions. Retrospective studies are difficult to interpret due to heterogeneities in patient selection, disease burden and treatment techniques. For resectable lesions, resection is generally considered the first line of treatment. Given the high propensity for local recurrence, adjuvant radiation therapy is warranted. We have described a variety of radiation approaches to consider, including opposed electron-photon fields, brachytherapy and IMRT, each with advantages and disadvantages. Use of adjuvant chemotherapy also merits consideration in view of the risk for distant recurrences.

REFERENCES

1. Orton N, Jaradat H, Welsh J, et al. Total scalp irradiation using helical tomotherapy. *Med Dosim.* 2005;30:162-168.
2. Young RJ, Brown NJ, Reed MW, et al. Angiosarcoma. *Lancet Oncol. 2010*;11:983-991.
3. Lahat G, Dhuka AR, Hallevi H, et al. Angiosarcoma: clinical and molecular insights. *Ann Surg. 2010*;251:1098-1106.
4. Buehler D, Rice SR, Moody JS, et al. Angiosarcoma outcomes and prognostic factors: a 25-year single institution experience. *Am J Clin Oncol;* 2013. [Epub ahead of print]
5. Mendenhall WM, Mendenhall CM, Werning JW, et al. Cutaneous Angiosarcoma. *Am J Clin Oncol.* 2006;29:524-528.
6. Albores-Saavedra J, Schwartz AM, Henson DE, et al. Cutaneous angiosarcoma. Analysis of 434 cases from the Surveillance, Epidemiology, and End Results Program, 1973-2007. *Ann Diagn Pathol.* 2011;15:93-97.
7. Maddox JC, Evans HL. Angiosarcoma of skin and soft tissue: a study of forty-four cases. *Cancer.* 1981;48:1907-1921.
8. Pawlik TM, Paulino AF, McGinn CJ, et al. Cutaneous angiosarcoma of the scalp: A multidisciplinary approach. *Cancer.* 2003;98:1716-1726.
9. Sasaki R, Soejima T, Kishi K, et al. Angiosarcoma treated with radiotherapy: impact of tumor type and size on outcome. *Int J Radiat Oncol Biol Phys.* 2002;52:1032-1040.
10. Guadagnolo BA, Zagars GK, Araujo D, et al. Outcomes after definitive treatment for cutaneous angiosarcoma of the face and scalp. *Head Neck.* 2011;33:661-667.
11. Mark RJ, Tran LM, Sercarz J, et al. Angiosarcoma of the head and neck. The UCLA experience 1955 through 1990. *Arch Otolaryngol Head Neck Surg.* 1993;119:973-978.
12. Lydiatt WM, Shaha AR, Shah JP. Angiosarcoma of the head and neck. *Am J Surg.* 1994;168:451-454.
13. Wanebo HJ, Koness RJ, MacFarlane JK, et al. Head and neck sarcoma: Report of the Head and Neck Sarcoma Registry. Society of Head and Neck Surgeons Committee on Research. *Head Neck.* 1992; 14:1-7.
14. Freedman AM, Reiman HM, Woods JE. Soft-tissue sarcomas of the head and neck. *Am J Surg.* 1989;158:367-372.
15. Penel N, Bui BN, Bay JO, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: the ANGIOTAX Study. *J Clin Oncol. 2008*;26: 5269-5274.
16. Fata F, O'Reilly E, Ilson D, et al. Paclitaxel in the treatment of patients with angiosarcoma of the scalp or face. *Cancer. 1999*;86:2034-207.
17. Skubitz KM, Haddad PA. Paclitaxel and pegylated-liposomal doxorubicin are both active in angiosarcoma. *Cancer.* 2005;104:361-366.
18. Nagano T, Yamada Y, Ikeda T, et al. Docetaxel: a therapeutic option in the treatment of cutaneous angiosarcoma: report of 9 patients. *Cancer. 2007*;110:648-651.
19. Agulnik M, Yarber JL, Okuno SH, et al. An open-label, multicenter, phase II study of bevacizumab for the treatment of angiosarcoma and epithelioid hemangioendotheliomas. *Ann Oncol. 2013*;24:257-263.
20. Maki RG, D'Adamo DR, Keohan ML, et al. Phase II study of sorafenib in patients with metastatic or recurrent sarcomas. *J Clin Oncol. 2009*;27:3133-3140.
21. Stacchiotti S, Palassini E, Sanfilippo R, et al. Gemcitabine in advanced angiosarcoma: a retrospective case series analysis from the Italian Rare Cancer Network. *Ann Oncol.* 2012;23:501-508.
22. Scott MT, Portnow LH, Morris CG, et al. Radiation therapy for angiosarcoma The 35-year University of Florida Experience. *Am J Clin Oncol.* 2013;36:174-180.
23. Akazawa C. Treatment of the scalp using photon and electron beams. *Med Dosim.* 1989;14:129-131.
24. Tung SS, Shiu AS, Starkschall G, et al. Dosimetric evaluation of total scalp irradiation using a lateral electron-photon technique. *Int J Radiat Oncol Biol Phys.* 1993;27:153-160.
25. Ozyar E, Gurdalli S. Mold brachytherapy can be an optional technique for total scalp irradiation. *Int J Radiat Oncol Biol Phys.* 2002;54:1286.
26. Bedford JL, Childs PJ, Hansen VN, et al. Treatment of extensive scalp lesions with segmental intensity-modulated photon therapy. *Int J Radiat Oncol Biol Phys.* 2005;62: 1549-1558.
27. Hardcastle N, Soisson E, Metcalfe P, et al. Dosimetric verification of helical tomotherapy for total scalp irradiation. *Med Phys.* 2008;35:5061-5068.
28. Hadziahmetovic M, Weldon S, Pearson M, et al. Scalp uniform bolus application (SCUBA) technique for homogeneous scalp and regional nodal irradiation. *Pract Radiat Oncol.* 2014; 4:95-99·

Prepared by Dr. Rice, a Transitional Year Resident at Aurora St. Luke's Medical Center, Milwaukee, WI; Dr. Kozak, Director of Radiation Oncology at Mercy Regional Cancer Center, Janesville, WI, and Chief Medical Officer of Co-D Therapeutics, Inc. Madison, WI; and Dr. Mohindra, Assistant Professor at University of Maryland School of Medicine, Baltimore, MD. The patient described in the clinical case was treated at the University of Wisconsin Hospital and Clinics, Madison, WI, which is the former institutional affiliation for all three authors at the time the case was treated and the report written.

RADIATION ONCOLOGY CASE

Pre-operative chemoradiation for rectosigmoid cancers: Where do we draw the line?

Nikhil Joshi MD, Neil M. Woody MD, May Abdel-Wahab MD, PhD

CASE SUMMARY

A 39-year-old male presented with a 6-month history of blood in his stools, accompanied by a persistent sensation of fullness and pain in his rectum. He was evaluated with blood work, a colonoscopy, a CT scan of his abdomen and pelvis, and an MRI scan. Serum carcinoembryonic antigen (CEA) was 1.3 ng/ml. The colonoscopy revealed a mass extending from 9 cm to 16 cm as measured from the anal verge. The mass was circumferential, constricting and friable with some bleeding. A biopsy revealed moderately differentiated adenocarcinoma. On clinical radiological correlation, the mass was found to extend into the sigmoid colon but was centered below the peritoneal reflection)Figure 1). He was treated with neoadjuvant chemoradiation to 50.40 Gy in 28 fractions and concurrent Capecitabine 825 mg/m^2 twice daily for 5 days a week during radiation (Figures 2 and 3). This was to be followed by total mesorectal excision after 4 to 6 weeks. The patient proceeded for sperm banking before initiating chemoradiation.

IMAGING FINDINGS

MRI of his pelvis revealed a mass located in the upper rectum extending into the sigmoid colon. The mass was noted to be circumferential and involving almost 95% of the luminal circumference (Figue 1). There was significant extra rectral spread noted along with a number of involved nodes throughout the mesorectum. A CT scan of the abdomen and pelvis was negative for liver metastases.

DIAGNOSIS

Locally advanced adenocarcinoma of the rectosigmoid (T3N2bM0, stage IIIC).

DISCUSSION

The current paradigm for treating locally advanced rectal cancer is neoadjuvant chemoradiotherapy followed by total mesorectal excision. A number of studies have shown that this approach for the treatment of advanced rectal cancers has a number of benefits, which include a possible increase in overall survival, a definite increase in the disease-free survival, an increase in local control, and an increase in the rate of sphincter salvage.[1]

Whether this paradigm also applies to high rectal or rectosigmoid cancers is not known. We describe a case of high rectal cancer that was treated with

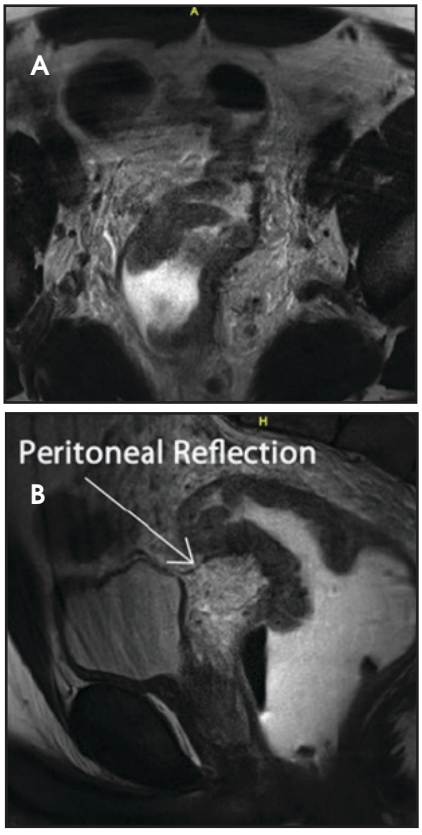


FIGURE 1. *Representative T2 MRI scans with intraluminal contrast depicted in (A) the axial section showing a near circumferential rectal mass, which is hypointense, and (B) the sagittal section showing the craniocaudal extent of the tumor and relationship with the peritoneal reflection.*

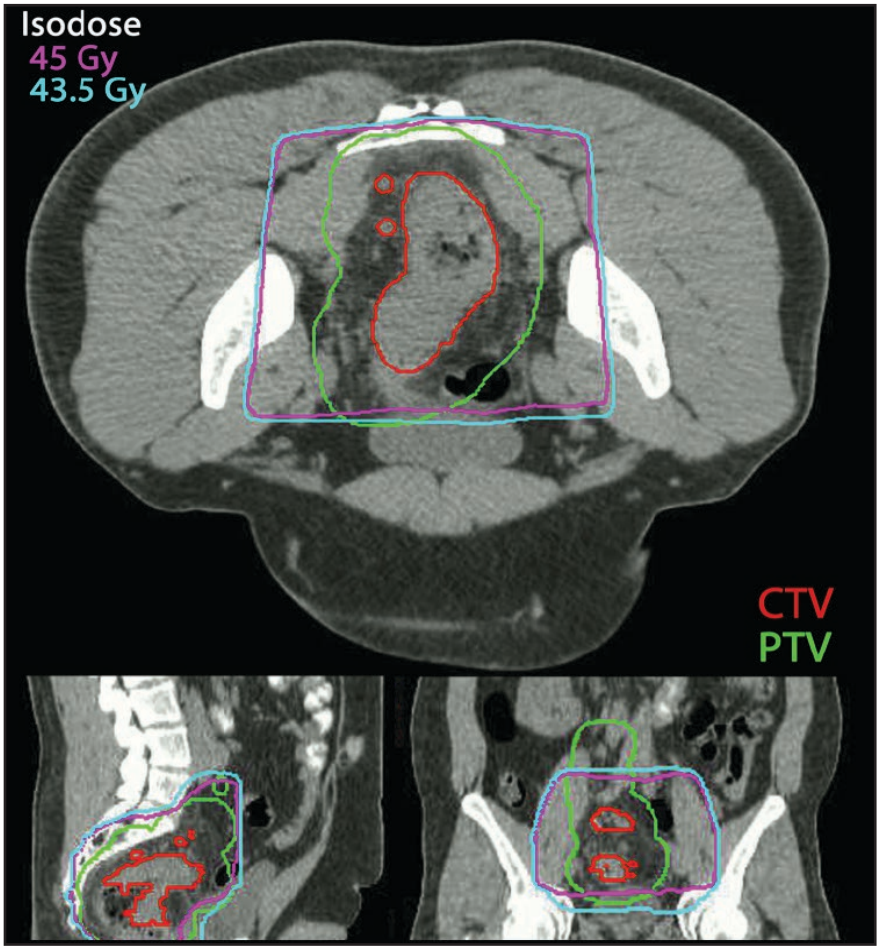


FIGURE 2. *Representative axial (top), sagittal (bottom left) and coronal (bottom right) CT slices showing dose coverage of CTV and PTV by the 45 Gy and 43.5 Gy isodose lines.*

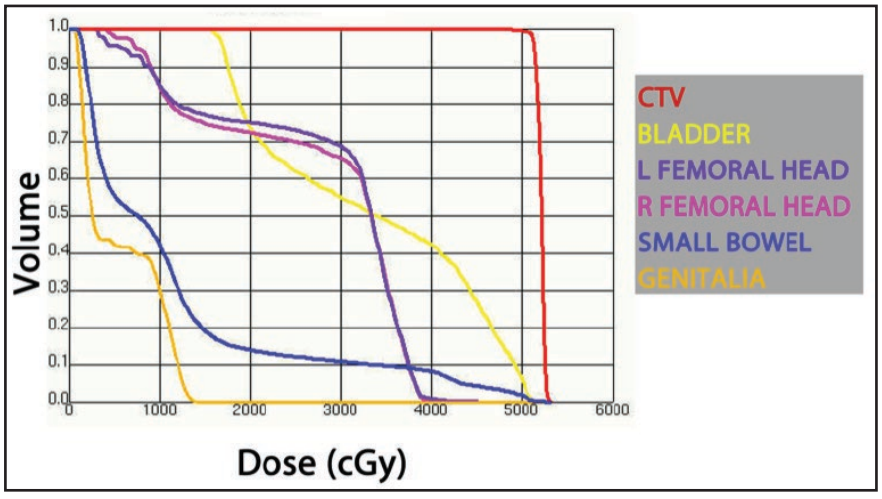


FIGURE 3. *Dose-volume histogram showing coverage of the CTV and dose received by organs at risk.*

neoadjuvant chemoradiotherapy, and explore the benefits of this approach.

The inclusion criteria for the German and Dutch trials studying neoadjuvant chemoradiation and neoadjuvant radiation, respectively, provide guidance in this respect. While the German trial included tumors up to 16 cm from the anal verge, the Dutch trial included tumors up to 15 cm from the anal verge and below S1-S2.[2] However, only 21% and 32% of patients included in the preoperative and postoperative chemoradiotherapy groups, respectively, for the German rectal cancer trial had tumors more than 10 cm from the anal verge.[1] In the Dutch trial, for patients with tumors located from 10 to 15 cm from the anal verge, the difference in local recurrence rate was not significantly different (3.8% for surgery alone vs. 1.3% for multimodality treatment).The Swedish rectal cancer trial included patients with tumors below the sacral promontory,[3] and the European Organization for the Research and Treatment of Cancer (EORTC) rectal cancer trial included patient with tumors up to 15 cm from the anal verge.[4] Notably, all 4 arms of the EORTC trial had less than 10% of patients with tumors > 10 cm from the anal verge. The National Comprehensive Cancer Network (NCCN) 2014 guidelines define true rectal cancers as those within 12 cm from the anal verge.[5] Hence, there is considerable debate as to what constitutes an upper rectal cancer vs. a true sigmoid colon cancer, and as to whether preoperative therapy benefits this subset of cancers or not. Mulcahy summarizes these observations as well.[6]

Measuring rectal tumors from the anal verge is difficult for high rectal/rectosigmoid cancer, as is correlation of these measurements with imaging findings. A useful anatomical landmark is the peritoneal reflection.

Tumors below the peritoneal reflection may be called rectal cancers, while those above may be called sigmoid cancers. MRI scans help define the peritoneal reflection and also have the ability to predict a negative radial margin.[7] Apart from the loco regional control benefit noted with preoperative therapy, the 2 main advantages of such therapy are to increase the rate of sphincter preservation, and optimally cytoreduce the disease, enabling easier and margin-negative resections. While the first reason is not an issue with high rectal cancers, the argument can be made that optimal preoperative therapy may help greatly in reducing R1 resections for locally advanced rectal cancers, as demonstrated in a retrospective review of T3-T4 high rectal cancers by O'Neill.[8]

Additionally, the latest analysis from the German rectal cancer trial reported superior disease-free survival and a decreased distant metastases rate for patients achieving high tumor regression after long-course preoperative chemoradiation, further underscoring the value of this treatment.[9] Lastly, there is increasing concern to limit the late effects of radiation to normal tissues, particularly the small bowel. We believe that a gentler chemoradiation fractionation (at 1.8 Gy per fraction instead of 5 Gy per fraction[3]) achieves reasonable cytoreduction of the tumor while avoiding considerable toxicity to the small bowel for high rectal tumors. This is even more so the case with techniques like 3D conformal therapy and intensity-modulated radiotherapy (IMRT).

CONCLUSION

While there is no clear consensus as to the management of high rectal/rectosigmoid cancers, the current approach for tumors located below the peritoneal reflection is a course of neoadjuvant chemoradiation, especially for locally advanced tumors encroaching upon the mesorectal fascia in which preoperative MRI suggests the possibility of an R1 resection. Tumors above the peritoneal reflection and truly sigmoid cancers may be treated as primary colon cancers with surgery and adjuvant systemic therapy per histology and stage.

REFERENCES

1. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol.* 2012;30:1926-1933.
2. Kapiteijn E, Marijnen C, Nagtegaal I, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med.* 2001;345:638-646.
3. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med.* 1997;336:980–987.
4. Bosset JF, Collette L, Calais G, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med.* 2006;355:1114–1123.
5. NCCN Clinical Practice Guidelines in Oncology, Rectal cancer, version 3.2014, http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf.
6. Mulcahy M. Radiotherapy for cancer of the rectum: which patients stand to benefit? *Gastrointest Cancer Res.* 2009;3(2):81-83.
7. Burton S1, Brown G, Daniels I, et al. MRI identified prognostic features of tumors in distal sigmoid, rectosigmoid, and upper rectum: treatment with radiotherapy and chemotherapy. *Int J Radiat Oncol Biol Phys.* 2006;65:445-451.
8. O'Neill B, Brown G, Wotherspoon A, et al. Successful downstaging of high rectal and recto-sigmoid cancer by neo-adjuvant chemo-radiotherapy. *Clin Med Oncol.* 2008;2:135-144.
9. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: updated results of the CAO/ARO/AIO-94 trial. *J Clin Oncol.* 2014; epub ahead of print.

Dr. Joshi *is a Clinical Fellow,* ***Dr. Woody*** *and* ***Dr. Abdel-Wahab*** *are Staff Physicians at the Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, OH.*

APPLIED RADIATION ONCOLOGY™

CALL FOR PAPERS

Applied Radiation Oncology e-Journal

A key resource for practical clinical information.

John Suh, MD

Dr. Suh is the Editor-in-Chief of *Applied Radiation Oncology,* and Professor and Chairman, Dept. Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.

Dear Colleagues:

We are pleased to let you know that our community of registered radiation oncologists has grown exponentially over the last few months. We appreciate your support and, as part of our mission to foster an online community where peers share practical solutions in the clinical setting, *Applied Radiation Oncology* is issuing a call for clinical cases and review articles.

We are looking for authors to write and submit clinical cases and review articles on topics that include (but are not limited to): imaging, contouring, target delineation, treatment planning, patient immobilization, organ tracking, safety and quality, and other timely topics essential to the discipline.

If you or your colleagues have an interesting case or review article for publication in *Applied Radiation Oncology,* please read our Author Guidelines, which can be found on our website. As a reference for the types of articles and cases published in *Applied Radiation Oncology*, visit our website and browse our archives.

We are also running a Case Contest with a cash prize for the next few months. See page 3 in this publication and visit our website for more information.

This is a wonderful opportunity to impart your knowledge to your peers by submitting a clinical case or review article to suhj@ccf.org.

Sincerely,
John Suh, MD
Editor-in-Chief, *Applied Radiation Oncology*

The World's Only Single Room Proton System – Now Treating.

MEVION
medical systems

Visit us at ASTRO 2014
Booth #728

LAD140331