APPLIED RADIATION ONCOLOGY™
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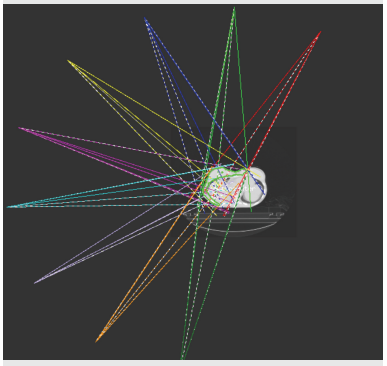

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FOCUS: STEREOTACTIC BODY RADIATION THERAPY

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EDITORIAL

Springing forward: Additions, contests, and SBRT updates

John Suh, MD, FASTRO
Editor-in-Chief

Welcome to the March issue of *Applied Radiation Oncology!* As we advance into spring, a season defined by vitality and change, we are excited to announce new growth of our own with the expansion of the *ARO* editorial advisory board. Over the last several months, we have welcomed the following new members:

- **May Abdel-Wahab, MD, PhD, FASTRO**, FACR, Director, Division of Human Health, International Atomic Energy Agency, Vienna, Austria
- **Sarah Hoffe, MD,** Section Head, GI Radiation Oncology, Moffitt Cancer Center, Tampa, FL
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- **Kristina Demas Woodhouse, MD,** Assistant Professor, Department of Radiation Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX

Serving as the journal's backbone, the advisory board plays an instrumental role in determining *ARO's* overall direction and objectives. We are indebted to their dedication and guidance in honing issue topics, recommending contributors, critiquing submissions, forming liaisons, and strengthening the journal's content and practical application, issue after issue. For a full list of advisory board members, please visit http://appliedradiationoncology.com/about-us.

The board also judges several ARO editorial contests, which we are excited to offer again this year. Details about the 2018 Research, Review and Case Report Articles of the Year (with $500 to $1,000 prizes), are available at http://appliedradiationoncology.com/contests. All articles accepted for publication are automatically entered.

In the Issue

This month, we focus on the burgeoning area of stereotactic body radiation therapy (SBRT). Two review articles, which offer free SA-CME credit, discuss important updates and considerations in the treatment of liver tumors and early stage non-small cell lung cancer (NSCLC), respectively. We also present survey results of SBRT for large node-negative NSCLC, provide an interesting analysis on stereotactic radiosurgery for spine sarcoma, and feature a timely Technology Trends piece on breast SBRT.

Also timely is this month's Resident Voice editorial, *Society for Women in Radiation Oncology: A resident perspective on #MeToo and the founding of SWRO*. This excellent contribution discusses professional misconduct and the gender gap in male-dominated fields such as radiation oncology.

We hope our issue, which also features case reports and a review of patient education in radiation oncology, fosters dialogue to enrich and continually improve collaboration and advancement across the field, clinic to clinic and colleague to colleague.

As always, thank you for your continued support. Happy spring!

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.*

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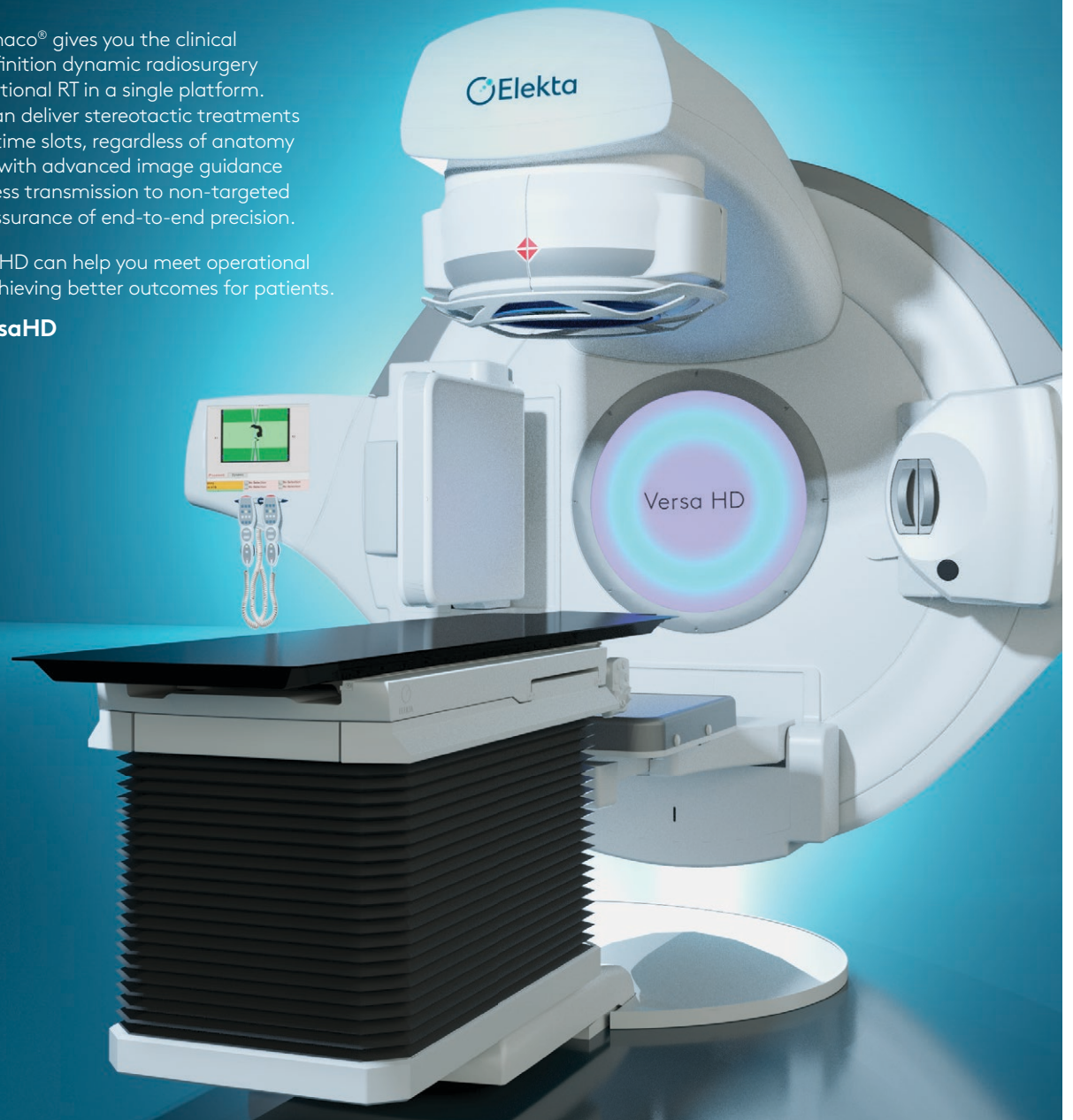

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RESIDENT VOICE

Society for Women in Radiation Oncology: Residents' perspectives on #MeToo and the founding of SWRO

Virginia Wedell Osborn, MD; Anna Lee, MD, MPH; Genevieve Maquilan, MD; Laura Dover, MD; Adrianna Henson Masters, MD, PhD; Lindsay Puckett, MD; Ashley Albert, MD; Courtney Hentz, MD; Kaleigh Doke, MD; Parul Barry, MD

Virginia Wedell Osborn, MD

***Dr. Wedell Osborn** is chief resident and **Dr. Lee** is a resident at SUNY Downstate Medical Center, Brooklyn, NY. **Dr. Maquilan** is a fellow at Massachusetts General Hospital, Boston, MA. **Dr. Dover** is a resident at University of Alabama at Birmingham. **Dr. Masters** is a resident at Wake Forest Medical Center, Winston-Salem, NC. **Dr. Puckett** is chief resident at Northwell Health System, New Hyde Park, NY. **Dr. Albert** is a resident at University of Mississippi Medical Center, Jackson, MS. **Dr. Hentz** is a resident at Loyola University Medical Center, Maywood, IL. **Dr. Doke** is a resident at University of Kansas Cancer Center, Kansas City, KS. **Dr. Barry** is an assistant professor at Rush University Medical Center, Chicago, IL.*

The #MeToo movement has unearthed many disturbing abuses of power, leaving almost no workplace unscathed. In her recent acknowledgement of such experiences within the medical community, Reshma Jagsi, MD, DPhil, a prominent radiation oncologist and researcher on gender equity in academic medicine, has initiated a dialogue inviting physicians to join the conversation.[1]

This conversation is especially germane to women in certain medical specialties, such as radiation oncology, which are predominantly male. Within our field, women continue to represent less than one-third of resident physicians. Our residents, in turn, train under a similarly low proportion of female attending physicians, and only a handful of female department chairs.[2] Three of the current authors have experienced at one point being the only female physician or physician in training in the entire department, and an additional two of us have been the only female resident.

When considering writing on the topic of #MeToo, many of the authors were hesitant to document even minor negative experiences due to fear of unforeseen repercussions. Some have received advice from well-intentioned colleagues to avoid the label "troublemaker" and to remember that we "still need to get a job" within a small field where everyone seems to know everyone else. While fortunately none of the authors have experienced assault within our field, we have both witnessed and experienced sexual harassment within our training and during professional meetings. As a group of women, with doctorate-level training and professional leadership roles, we were warned that speaking up may be professionally deleterious. This sentiment in and of itself is telling.

Our purpose is not to imply wrongdoings by our male colleagues with whom we have had the honor of working throughout our training. Many of us have had incredibly supportive male mentors and role models. Rather, we hope to highlight the degree of censorship that those without established careers or accessible female mentors still experience even after the opening of the #MeToo floodgates. We laud Dr. Jagsi and all the other women who have spoken publicly about experiences with harassment. We encourage our male and female colleagues to continue this dialogue, recognizing that it is an important issue within the medical field and does not solely occur outside of medicine. As trainees, however, we know that our career trajectories are still heavily reliant upon the sponsorship of those senior to us—the majority of whom, again, are men. We remain particularly vulnerable not only to harassment but, importantly, to the negative implications of having taken things "too seriously" whenever harassment experiences are brought to light.

Left to right: Anna Lee, MD, MPH; Genevieve Maquilan, MD; Kaleigh Doke, MD; Chelsea Miller, MD; Courtney Hentz, MD; Ashley Albert, MD; Virginia Osborn, MD; and Laura Dover, MD, at the 2017 ASTRO Annual Meeting, San Diego, California

The Society for Women in Radiation Oncology (SWRO) (www.societywomenradiationoncology.com) was founded in early 2017 by women residents who noticed our minority presence within the field and sought opportunities to connect with others having similar experiences. Although the distribution of medical trainees overall is now split between men and women, decreasing numbers of women have been entering radiation oncology residencies, and a survey is forthcoming to explore potential barriers that may be fueling this trend.[2] Within SWRO, we are working together with female and male attending physicians to facilitate networking and mentorship. While we remain hesitant to initiate our #MeToo conversations publicly, at least we can start to have them with each other, while we work together toward improving experiences of future residents.

References

1. Jagsi R. Sexual harassment in medicine — #MeToo. *New Engl J Med.* 2018;378:209-211.
2, Ahmed AA, Hwang WT, Holliday EB, et al. Female representation in the academic oncology physician workforce: radiation oncology losing ground to hematology oncology. *Int J Radiat Oncol Biol Phys.* 2017;98:31-33.

SA–CME Information

STEREOTACTIC BODY RADIATION THERAPY IN EARLY STAGE NON-SMALL CELL LUNG CANCER: A BRIEF PRIMER FOR THE MULTIDISCIPLINARY TUMOR BOARD

Description: Multidisciplinary team members treating lung cancers may not be aware of the complexity and coordination required for delivery of stereotactic body radiation therapy (SBRT) to lung masses. Shifts in practice have occurred in management of early stage non-small cell lung cancer (NSCLC), particularly with regard to the role of the specialized pulmonologist (interventional pulmonology), which involves different staging techniques than traditional mediastinoscopy. This review provides key information to foster a deeper understanding and appreciation for patient selection, work up, behind-the-scenes critical quality assurance tasks, and clinical pearls for stereotactic radiation therapy for lung cancer.

Learning Objectives:

After completing this activity, participants will be able to:

1. Identify appropriate candidates for stereotactic body radiation therapy in early stage non-small cell lung cancer.
2. Apply radiation dose guidelines and constraints, and potentially challenging scenarios.
3. Adopt the roles of the interventional pulmonologist and advanced bronchoscopist.
4. Implement physicist roles in treating this patient population with stereotactic body radiation therapy.

Authors: Andrew Kennedy, MD, is physician-in-chief, Radiation Oncology, Sarah Cannon, Nashville, TN. **Susan Garwood, MD,** is physician leader, Pulmonology, Sarah Cannon, Nashville, TN. **Allison Grow, MD, PhD,** is physician leader, Radiation Oncology, Sarah Cannon, Nashville, TN; and North Florida Radiation Oncology, Gainesville, FL. **Ryan Lipscomb, MS,** is medical physics leader, Sarah Cannon, Nashville, TN.

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Stereotactic body radiation therapy in early stage non-small cell lung cancer: A brief primer for the multidisciplinary tumor board

Andrew Kennedy, MD; Susan Garwood, MD; Allison Grow, MD, PhD; Ryan Lipscomb, MS

While the gold standard for curative treatment of stage I non-small cell lung cancer (NSCLC) is lobectomy,[1,2] year-over-year increased use of stereotactic body radiation therapy (SBRT), also known as stereotactic ablative radiation therapy (SABR), is growing exponentially.[3] During multidisciplinary tumor board discussions regarding prospective management of stage I NSCLC patients, a knowledge gap is often realized. Relatively new techniques (over the last 10 years) of SBRT and interventional pulmonology (IP) have advanced rapidly into the mainstream practice and affect the time interval to treatment. These techniques involve a higher complexity, cost and number of experts required for success compared to standard conformal radiation therapy for NSCLC. This report attempts to provide, in brief fashion, key information that may foster a deeper understanding and appreciation for patient selection, workup, behind-the-scenes critical quality assurance tasks, and clinical pearls for stereotactic radiation therapy for lung cancer.

Dr. Kennedy *is physician-in-chief, Radiation Oncology, Sarah Cannon, Nashville, TN.* ***Dr. Garwood*** *is physician leader, Pulmonology, Sarah Cannon.* ***Dr. Grow*** *is physician leader, Radiation Oncology, Sarah Cannon; and North Florida Radiation Oncology, Gainesville, FL.* ***Mr. Lipscomb*** *is medical physics leader, Sarah Cannon.*

Disclosure: Dr. Garwood is a consultant to Medtronic, Minneapolis, MN. The remaining authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Patient Selection

Recent evidence-based guidelines from the American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), and European Society for Radiotherapy and Oncology (ESTRO) provide excellent information on a variety of challenging topics in choosing which patients to offer SBRT.[4-6] The classic candidate for lung SBRT given with curative intent is medically inoperable, has a peripheral tumor < 5 cm in diameter, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, and a life expectancy of at least 2 years with respect to comorbidities.[5,7-10] Central tumors, tumors > 5 cm, and those near the chest wall will be further discussed below. Consultations with pulmonology and thoracic surgery are important to establish whether a patient is medically inoperable. Pulmonary function testing should be completed prior to intervention, and a split-function lung scan may be helpful in borderline candidates for lobectomy. In the era of minimally invasive thoracic surgery, some surgeons may offer video-assisted thoracoscopic surgery (VATS) wedge resection to patients who are borderline medically inoperable. In this setting, it is important for patients to understand that the data are evolving, and ongoing clinical trials will help establish efficacy of one approach over another.[11]

SBRT is appropriate for patients with biopsy-proven T1/T2, N0M0 non-small cell carcinomas. Ideally, patients will be thoroughly evaluated with computed tomography (CT) and positron emission tomography (PET)-CT for staging, augmented by IP sampling of suspicious hilar/mediastinal nodes.

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Oxygen dependence and very poor pulmonary function tests (PFTs) need not contraindicate SBRT in and of themselves, as long as the patient meets criteria for performance status and life expectancy. We typically do not offer treatment for such patients who have required two or more hospitalizations for chronic obstructive pulmonary disease (COPD)-related issues in the past year. In treating such a patient, we often set tighter constraints on lung parenchymal dose (addressed below).

SBRT is generally not appropriate for patients with transmural invasion into airways or the esophagus, even for small tumors; endoscopy may be required to rule it out when imaging is equivocal.

Pathologic confirmation of malignancy should be sought; in a few cases, this may be technically infeasible for reasons such as a high risk for pneumothorax or inaccessibility to both percutaneous and bronchoscopic approaches (eg, some apical tumors). In this setting, treatment may be offered if the patient meets clinical and radiographic criteria for malignancy (PET-positive lesion with progression on serial imaging, tobacco history).[12] In addition, in accordance with ASTRO and ASCO guidance, shared decision making with the patient, and the patient's family is important.[4,5]

Finally, patients with prior thoracic radiation therapy may obviously pose difficulty, but depending on tumor size and location, treatment is often technically feasible, with appropriate attention to composite normal tissue doses.[13]

Radiation Dose Guidelines and Constraints

For peripheral tumors (at least 2 cm from the central airways), published dosing guidelines include 30 to 34 Gy in a single fraction[10,14] and 54 to 60 Gy in 3 fractions.[7,9] We most frequently use the 3-fraction regimen. Recent phase II data show equivalent outcomes for the single-fraction regimen;[10] in the absence of phase III data, we suggest limiting its use to T1 tumors and to squamous histology. For tumors extensively contacting the chest wall, we occasionally use 4- and 5-fraction regimens, using the chest wall dose constraint discussed below.

For central tumors (within 2 cm of central airways), published dosing schemes include 48 to 52 Gy in 4 fractions and 50 Gy in 5 fractions. We typically employ 4-fraction regimens except in the case of larger tumors (> 5 cm) or difficulty meeting normal tissue constraints.[15-17]

Regarding normal tissue dose constraints, Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC)[18] and American Association of Physicists in Medicine (AAPM) Task Group (TG) 101[19] are good places to start and serve as the primary references for our physics staff. The relevant organs at risk (OARs) include normal lung parenchyma, esophagus, spinal cord, heart/left ventricle/coronary arteries, great vessels, trachea and major airways, brachial plexus, chest wall, and occasionally the stomach. In our opinion, many published dose constraints have two drawbacks: 1) They are based on lifetime organ tolerance doses, taking no account of possible future need for another course of thoracic radiation therapy. 2) They often prescribe point dose maxima, which in our opinion are not meaningful if appropriate volume-based constraints are met, and if taken too literally may preclude adequate coverage of a primary tumor adjacent to an OAR.

The gross tumor volume (GTV) is contoured on lung windows; for T1a tumors we typically include spiculations. We add 6 to 10 mm for clinical target volume (CTV)/planning target volume (PTV) margin, using greater margins for well-differentiated adenocarcinomas based on the expectation of disease extent being partially occult on CT.[20]

For the normal lung parenchyma, we subtract the PTV volume and then require V12 Gy < 15%. If the 50% conformality index (volume of 50% prescription dose volume /PTV volume) is > 3, we typically also require V7 Gy < 20% and V20 Gy < 10%. Tighter constraints may be set when PFTs are very poor (forced expiratory volume in 1 second [FEV1] or diffusing capacity of the lungs for carbon monoxide [DLCO] < 30% predicted); V12 Gy < 10% to 12% is reasonable to try.

For the spinal cord, we typically require that most of the cord receive < 8 Gy/12 Gy/15 Gy for 1-fraction, 3- or 4-fraction, and 5-fraction regimens, respectively. We then allow small volumes to receive more if needed to cover the PTV, up to and including 0.25 cc to 0.5 cc allowed to exceed the prescription dose. We typically write a series of 3 to 5 constraints with progressively smaller volumes allowed to receive more than various progressively increasing doses, effectively forcing the dose-volume histogram (DVH) into an acceptable form. The above values allow for reirradiation, should the need arise.

We take a similar approach to the remaining listed OARs. The esophagus in particular is clearly a "series" organ and when treating a tumor abutting the esophagus, we endeavor to avoid circumferential high dose. We may contour separate volumes for the adjacent and opposite sides of the esophagus at the level of the tumor, and set a point maximum constraint on the opposite side volume while simultaneously applying a set of volume constraints on the adjacent side. This maneuver is aided by having the patient swallow dilute barium sulfate at the time of simulation.

If there is difficulty meeting dose constraints, a few measures may be essayed. PTV margins may be reduced, either symmetrically or asymmetrically on the side adjacent to the problematic normal organ. Dose may be reduced; in our opinion a dose less than the equivalent of 8 Gy x 5 is probably

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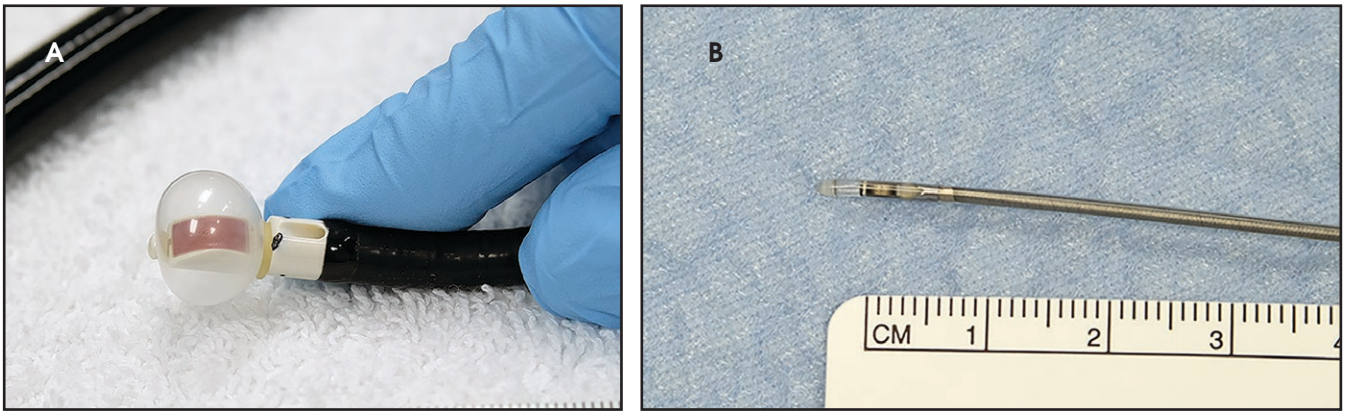

FIGURE 1. *(A) Convex endobronchial ultrasound (C-EBUS), and (B) radial ultra-miniature ultrasound probe (R-EBUS).*

not meaningful in the definitive setting. Fractionation may be increased with single- or 3-fraction regimens converted to 3, 4 or 5; the European SBRT literature is notable for 8-fraction regimens, which we have occasionally used. Finally, the relevant dose constraints may be judiciously relaxed.

It is important to note that, in general, tumor doses are underestimated with use of more naïve dose calculation algorithms such as ray tracing.[21] Due to the many tissue density interfaces inherent in treating lung and spinal cord lesions, we use a Monte Carlo dose calculation algorithm for these sites.

Difficult Scenarios

For tumors > 5 cm, we treat according to the above guidelines if the relevant normal tissue constraints can be met. We do not consider these tumors appropriate for single-fraction treatment until further data is available.

For tumors abutting the heart, we contour the myocardium and the left anterior descending artery (LAD) (or other adjacent major coronary vessel) and set a series of dose/volume constraints as described above. It is again important to note that, in many cases, a small volume (on the order of 0.5 to 1 cc) of the cardiac OARs must be allowed in the prescription dose volume to cover the tumor. Also, excellent, reliable motion compensation is needed to establish confidence regarding accurate dose delivery. Single-fraction treatment is not appropriate in this setting.

For tumors abutting the chest wall, we typically use 4 or 5 fractions and set a constraint of V30 Gy = 30 cc or less.[22] Patients should be counseled at consultation and at follow-up regarding the symptoms of postradiation myositis and risk of rib fracture, with the former relatively common (20% to 25% of patients with such tumors) and the latter relatively rare (< 2%) in our experience.

Interventional Pulmonology

The role of the interventional pulmonologist and advanced bronchoscopist has changed significantly in the past 10 years in lung cancer evaluation.[23] The yield of tissue for diagnosis in peripheral nodules < 2 cm with traditional fiberoptic bronchoscopy is < 14% leaving little diagnostic role for the pulmonologist for many years.[24] For this reason, computed tomography (CT)-guided biopsy had been the mainstay for peripheral lesions due to its high sensitivity of 90% in malignant disease,[25] but came with the cost of pneumothorax in up to 20% to 40%.[26] CT-guided biopsy also remains an incomplete procedure, not allowing simultaneous access to the mediastinum and hilum, or ability to provide advanced treatment planning with fiducial marker placement in one setting.

Staging of lung cancer has also been a struggle with reliance on CT and PET. The sensitivity and specificity of CT scanning for identifying mediastinal lymph node metastases is approximately 55% and 81%, respectively, which confirms that CT scanning has limited ability to either rule in or exclude mediastinal metastasis. For PET scanning, estimates of sensitivity and specificity for identifying mediastinal metastasis are approximately 77% and 86%.[23] Tissue biopsy remains essential to confirm radiographic findings. Prior to 2013, mediastinoscopy had remained the gold standard for mediastinal evaluation by the American College of Clinical Pharmacy (ACCP) guidelines.[27] Much like CT-guided biopsy, it has a high sensitivity but remains an incomplete procedure with no access to the hilum, which is essential for complete staging prior to SBRT and carries risk of morbidity.[28]

Due to the complex nature of this evaluation, patients require multiple specialty visits for diagnosis, staging and planning prior to their first treatment, which can easily lead to fragmented care and long delays in treatment time. Recent advances in image-guided biopsies have changed the paradigm to allow streamlined evaluation for diagnosis, staging and treatment planning all in one procedure under the direction of an interventional pulmonologist or advanced bronchoscopist.

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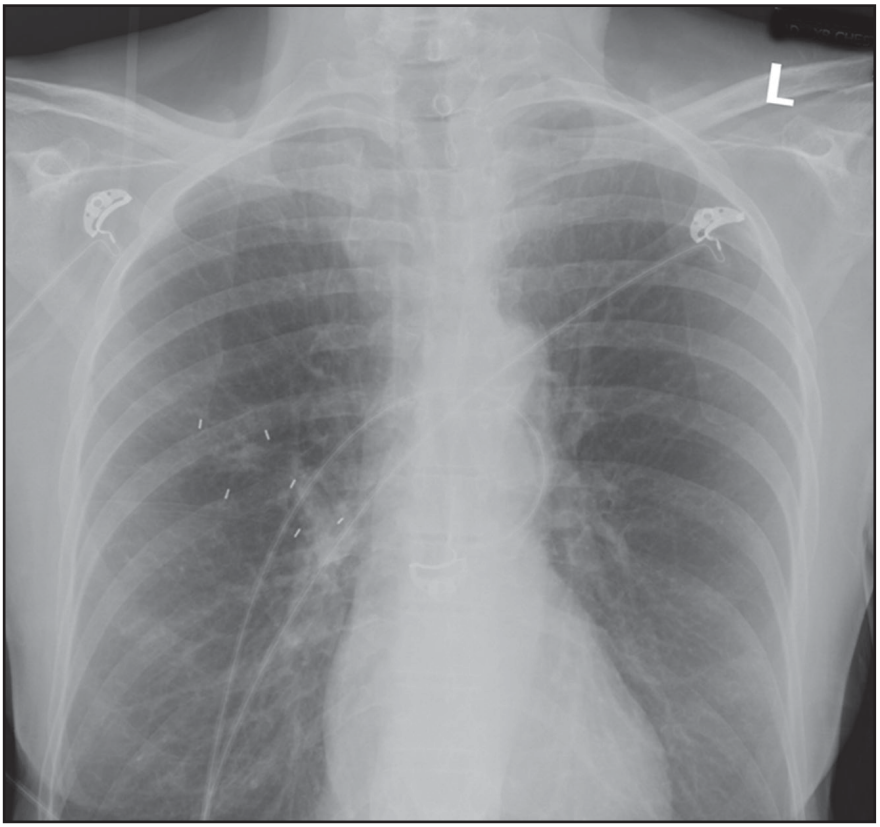

***FIGURE 2**. Anteroposterior (AP) radiograph of a patient with two right lung tumors, each with three fiducials.*

The two most important modalities are endobronchial ultrasound (EBUS) and electromagnetic navigational bronchoscopy (ENB).

Endobronchial ultrasound allows visualization of the underlying pulmonary structures around central airways and in peripheral lung tissue. EBUS comes in two main forms: convex EBUS (C-EBUS) and radial probe EBUS (R-EBUS), (**Figure 1**). C-EBUS is ideally suited for central lesions or nodal evaluation in the mediastinum and hilum except for subaortic, para-aortic and paraesophageal nodes (level 5, 6 and 8, 9) which are not reachable by this method. C-EBUS is equipped with a 7.5-MHz, saline inflatable balloon attached to the tip of the bronchoscope, and includes flow capability to evaluate for vascularity or cystic nature of lesions. It has a depth of penetration of 4 cm. Overall there is a median sensitivity of 89%, and a median negative predictive value of 91% in NSCLC staging.[23]

Radial probe (R-EBUS) comes in two main forms: a mini probe with balloon, and an ultra-thin probe ideally suited to complement navigational bronchoscopy (**Figure 2**). Yields with radial probe alone or in combination with electromagnetic navigation (EMN) vary widely depending on lesion size, technology used, presence or absence of a bronchus sign, and whether the ultrasonographic image reveals a concentric or eccentric image of the nodule or mass.[29-31]

Electromagnetic navigational bronchoscopy is a DICOM image-guided technique that uses a navigational system to guide instruments through the airways to target a lesion for biopsy. Thin-slice CT images (< 2 mm) in the planning phase create a virtual 3-dimensional (3D) tree of the airway to use as a roadmap. CT formatting is essential for accurate navigation and parameters differ per scanner. ENB uses an electromagnetic field board placed under the patient's thorax to enable real-time tracking of instruments. Tissue sampling success with ENB alone varies widely but averages 65% per attempt, and improved rates of successful biopsies are seen in upper and middle lobe lesions, positive bronchus signs, and greater experience by the user to overcome the learning curve.[32] Angulated 45- to 130-degree catheters can assist in entering hard-to-maneuver airways such as the superior segment of the lower lobe and apical medial portion of the upper lobe. Biopsy of lower lobe peripheral lesions can also be challenging due to respiratory motion and increasing atelectasis as procedure length expands. We strongly recommend review of anatomic restrictions with thoracic, surgical and pulmonary colleagues to understand where the highest chance of success for biopsy and fiducial placement exists.

An added advantage with ENB is the ability to approximate distance from the center of the lesion to allow ideal fiducial placement per radiation oncology protocols. A novel approach using ENB is a fiducial marker placement guidance system (FPGS). The system leads to less migration of fiducials and a greater number of patients who had 6D motion tracking vs 3D.[33] Further improvements may eventually decrease CTV to PTV margins. Selection of fiducial type and placement preferences may differ by radiation therapy delivery device and facility. Open conversation is encouraged between proceduralists and radiation oncologists to establish best practices based on resources, experience and equipment availability.

We note increased success in multiple key metrics identified in a pilot in our hospital system in which streamlined patient intake for initial evaluation of possible stage I NSCLC is performed

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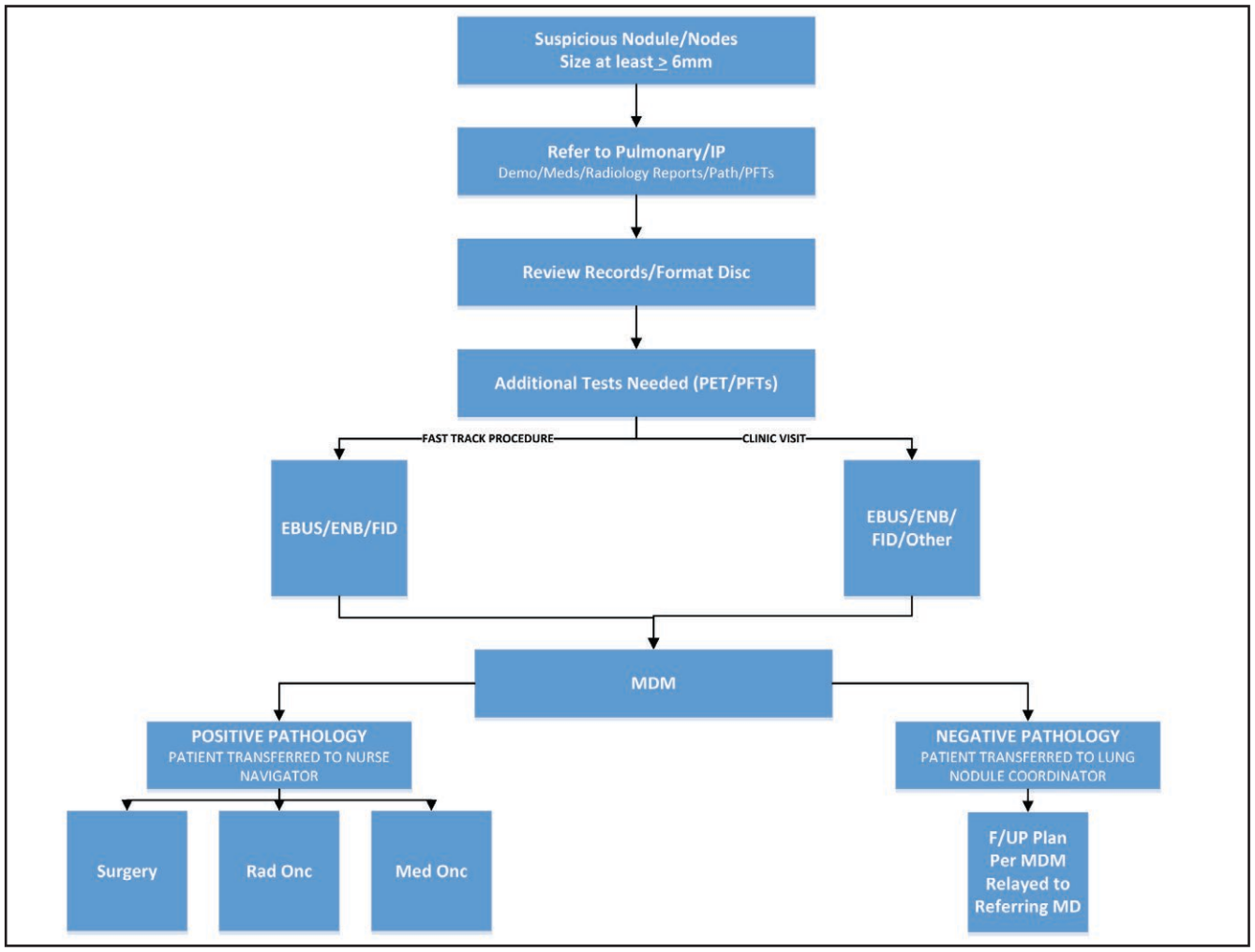

***FIGURE 3**. Sarah Cannon clinical pathway for assessment and multidisciplinary evaluation of suspicious lung nodules.*

by the interventional pulmonologist/advanced bronchoscopist as their first point of contact. While this requires increased upfront work for the proceduralist, outcomes noted to date are more timely evaluation, a single-setting biopsy and fiducial placement in the majority of patients. (**Figure 3**). This includes a real-time multidisciplinary discussion of each patient, use of specialist nurse navigators, and lung nodule coordinators to assist patients with care coordination and improve patient retention.

Radiation Oncology Medical Physics

Probably because so few physicists routinely attend multidisciplinary tumor boards, the multidisciplinary team members are unaware of the critical and time-consuming contributions physicists make to ensure high-quality SBRT treatments. Clinical medical physicists responsible for SBRT programs have several diverse key responsibilities. Both ASTRO and AAPM have worked to outline this scope in a concise manner.[8,34]

Five key physicist roles for SBRT are:

1. Quality control (QC) and quality assurance (QA): Implement and maintain both initial and ongoing periodic QA/QC for all aspects of the treatment simulation (CT/PET/magnetic resonance imaging [MRI]), treatment planning, and treatment delivery processes.
2. Perform or supervise the treatment planning process with the radiation oncologist.
3. Verify that the final approved treatment plan satisfies the radiation oncologist's prescription.
4. Implement comprehensive checklists for the entire treatment delivery process.
5. Provide direct supervision for all treatment delivery sessions.

Entire books are devoted to clinical medical physics as it relates to lung SBRT treatments. In the interest of

SA-CME (Release date: March 1, 2018; Expiration date: April 30, 2020)

brevity, our comments are restricted in scope to gantry-based linear accelerators and not robotic and tomotherapy linacs. Modern gantry-based linear accelerators have sufficient precision and redundancy to allow the use of stereotactic techniques broadly across community hospitals. Periodically, the physicist tests the precision and accuracy of all systems to ensure that they persist throughout the life of the program and are within acceptable tolerance for every SBRT treatment. A program needs adequate physics staffing, equipment, and a well-documented QA program. The AAPM has, in the form of TG 101 and 142,[35,36] published extensive recommendations for the QA of those machines, and the systems built around enlisting them in an SBRT program. We direct the interested reader to those reports for further reading. Practically, the main objectives are to ensure the planned delivery satisfies the prescription, set the patient into position within the acceptable uncertainty, utilize imaging to fine-tune and confirm patient positioning prior to treatment, and monitor patient positioning during treatment to ensure successful delivery geometry. All aspects of the physicists' key responsibilities reflect these treatment objectives.

Several methods are commonly used for managing and monitoring patient motion during lung SBRT treatments. There is target motion, which is expected and planned for, and then there is unacceptable and unplanned motion of the target. Generally, the planned motion is due to respiratory motion during the portion of the respiratory cycle in which we want to treat the tumor. This can be, and most often is, the entire cycle. This motion is accounted for in the PTV using the information from the 4D-planning CT. This target volume plus the uncertainty of the treatment delivery system as a whole defines the final target volume (PTV). This PTV can usefully define the line dividing acceptable and unacceptable intrafraction patient motion. The most common ways to monitor that motion for lung SBRT are through either a surrogate or x-ray imaging. Two surrogates are commonly used: an infrared-visible cube reproducibly positioned on the patient's body, or a system that monitors a region of interest of the patients' skin surface itself. The main assumption with these systems is that tumor and general patient motion are well represented by the motion of the body surface. Alternatively, it is common to use periodic x-ray imaging of fiducial markers placed in proximity to the target to guide initial patient setup and monitor intrafraction motion.

The literature contains extensive comparisons of fiducial markers and relative merits. For patient positioning alone, an ideal marker would be as small as is consistent with reliable low-dose x-ray imaging, artifact free when acquiring cone-beam CTs (CBCTs) for initial positioning, low cost, and free from tendencies to migrate between planning CT and treatment delivery. Fiducial markers tend to excel with some, but not all, of these characteristics. It is important to work as a multidisciplinary team (consisting of pulmonology, radiation oncology, and medical physics experts, etc.) when evaluating which marker(s) to incorporate into the lung SBRT program.

In summary, the highest-quality physics programs supporting lung SBRT share a set of characteristics: a) adequate physics and dosimetry staffing in line with industry recommendations (ASTRO, ACR are relevant examples); b) thorough documentation of the QA program and results; c) adequate equipment to support the QA program; d) a lung SBRT-specific patient positioning system; e) a system to monitor patient motion during SBRT treatments; and f) most importantly, team-based collaboration between all disciplines involved in the safe implementation of SBRT to periodically review all aspects of the program to ensure it evolves as these techniques advance.

Final Thoughts

Delivery of a few high-dose fractions to a small target carries with it one of the highest risk/reward scenarios in clinical radiation oncology. Although it does take longer for a patient to start treatment compared to nonstereotactic radiation therapy for lung cancer, it is helpful for the multidisciplinary team to understand this in context of the unique circumstances of fiducial placement, SBRT plan complexity, risks, adaptive constraints, and "behind-the-scenes" critical quality assurance tasks, to deliver safe, effective, best practice ablative radiation therapy.

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SA-CME (Release date: March 1, 2018; Expiration date: April 30, 2020)

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SA–CME Information

STEREOTACTIC ABLATIVE RADIATION THERAPY IN THE TREATMENT OF LIVER TUMORS

Description: This review article discusses the major indications for stereotactic ablative radiation therapy for liver cancer, as well as the technologies available and/or necessary for safe treatment delivery. Specific areas discussed include hepatocellular carcinoma, intrahepatic cholangiocarcinoma, dose, image guidance and respiratory management, emerging techniques, and radiation-induced liver disease.

Learning Objectives:

After completing this activity, participants will be able to:

1. Learn the three most common indications for stereotactic ablative radiotherapy in the liver.
2. Apply the control and significant toxicity rates associated with liver SABR treatment.
3. Adopt the rationale for high-quality image guidance and respiratory management in liver SABR.

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SA-CME (Release date: March 1, 2018; Expiration date: April 30, 2020)

Stereotactic ablative radiation therapy in the treatment of liver tumors

Benjamin O. Spieler, MD; Lorraine Portelance, MD; Eric A. Mellon, MD, PhD

Liver cancer-related death rates continue to accelerate worldwide.[1,2] Numerous local techniques are evolving to address the growing burden of disease. These techniques include surgery (partial liver resection or liver transplant), ablation (radiofrequency, microwave, ethanol, cryoablation), and intra-arterial injections (chemoembolization, radioembolization, bland embolization). Systemic treatments, such as sorafenib, regorafenib, or nivolumab, are also expanding. An additional option is stereotactic ablative radiation therapy (SABR). SABR has harnessed innovations in external-beam radiation therapy delivery and toxicity modeling to safely and noninvasively deliver high radiation therapy doses to liver tumors in only 1 to 5 treatments. Here we review the indications, efficacy, toxicity and methods for SABR in liver tumors. While prospective comparative data is lacking between SABR and other local techniques, we suggest that SABR offers high local control, low toxicity, and ability to treat a range of tumor volumes and locations in a precise, noninvasive manner. While choice of local liver tumor therapy is currently institution-specific, future utilization of liver SABR promises to increase with experience and recognition.

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SABR in the Treatment of Primary Liver Cancer

Hepatocellular Carcinoma (HCC)

HCC is the most common primary liver cancer in the world, with a fourfold increase in incidence over the last 40 years in the United States.[3] Partial liver resection or orthotopic liver transplant (OLT) remain the accepted first-line treatments for eligible patients.[4,5]

Patients waiting for OLT are at risk for disease progression. Clinical series demonstrate that SABR can prevent HCC progression prior to transplant. Sapisochin et al compared SABR (n = 36) with transcatheter arterial chemoembolization (TACE) (n = 99) and radiofrequency ablation (RFA) (n = 244) as bridges to OLT. They found that drop-out rate, post-transplant survival and HCC recurrence were similar for all techniques, despite SABR treating a greater tumor burden than RFA: an average of 2 lesions to 1, 4.5 cm diameter to 2.5 cm, and a higher mean Model of End-stage Liver Disease (MELD) score.[6]

In the United States, 70% to 90% of all HCC cases occur with cirrhosis, and many patients are unsuitable for resection.[7] For patients unable to undergo definitive resection, **Table 1** summarizes studies demonstrating that SABR is an excellent option for tumor control with limited toxicity. No randomized data exist to prove superiority of SABR compared to other techniques. Nevertheless, a 2016 retrospective study from the University of Michigan compared SABR (n = 63 treated with 27 to 60 Gy in 3 to 5 fractions) to RFA (n = 161), showing they are equally effective for treating inoperable HCC < 2 cm, but

SA-CME (Release date: March 1, 2018; Expiration date: April 30, 2020)

Table 1. SABR HCC Series Outcomes

First Author, Year	Patients/ Tumors *Liver function*	Median Diameter	Study Design	Dose/ Fractions (BED for α/β=10)	Local Control % (1y/2y/3y)	Overall Survival % (1y/2y/3y)	Toxicity % ≥ Grade 3
Sapir, 2018[9]	125/173 CTP A & B	2.4 cm	Retrospective, SABR vs TACE	42-50 Gy/3-5 (BED_{10} 100)	97/91/---	74/35/---	8
Sapisochin, 2017[6]	36/72 22 CTP A, 14 CTP B	4.5 cm	Retrospective: SABR vs TACE vs RFA, Bridge to OLT	36 Gy (30-40)/6 (median BED_{10} 58)	Drop-out rate before OLT = 16.7%	83/---/61, 61% 5-year survival	Before OLT = 0
Wahl, 2016[8]	63/83 57 CTP A, 24 CTP B, 2 CTP C	2.2 cm	Retrospective, SABR vs RFA	27-60 Gy/3-5 (median BED_{10} 100)	97/84/---	74/46/---	8
Huertas, 2015[46]	77/97 66 CTP A, 11 CTP B	2.4 cm	Retrospective	45 Gy/3 (BED_{10} 113)	99/99/---	82/57/---	5.2
Sanuki, 2014[47]	185 158 CTP A, 27 CTP B	2.5 cm	Retrospective	35-40 Gy/5 (BED_{10} 60-72)	99/93/91	95/83/70	3
Yoon, 2013[48]	93/103 69 CTP A, 2 4 CTP B	2.0 cm	Retrospective	30-60 Gy/3 (BED_{10} 60-180)	95/---/92	86/54/---	6.5
Bibault, 2013[49]	75/96 67 CTP A, 8 CTP B	3.7 cm	Retrospective	40-50 Gy/3 (BED_{10} 60-131)	90/90/---	79/50/---	8
Bujold, 2013[50]	102/164 102 CTP A	7.2 cm	Phase I/II Trial	36 Gy (30-54)/6 (median BED_{10} 58)	87/---/---	55/34/---	36
Andolino, 2011[51]	60/71 36 CTP A, 24 CTP B	3.2 cm	Retrospective	30-48 Gy/3-5 (BED_{10} 60-72)	---/90/---	---/67/---	35
O'Connor, 2012[52]	10/11 7 CTP A, 2 CTP B, 1 CTP C	3.4 cm	Retrospective: Bridge to OLT	51 Gy/3 (BED^{10} 138)	Drop-out rate before OLT= 0 %	100% 5-year survival	Before OLT = 0
Cárdenes, 2010[53]	17/25 6 CTP A, 1 1 CTP B	4 cm	Phase I Trial	40-48 Gy/3-5 (BED_{10} 72-125)	100/100/---	75/60/---	18

Key: CTP = Child-Turcotte-Pugh, SABR = stereotactic ablative radiation therapy, TACE = transarterial chemoembolization, RFA = radiofrequency ablation, BED = biologically equivalent dose

that SABR provides better local control (LC) than RFA for lesions ≥ 2 cm.[8] A second retrospective investigation compared SABR and TACE, with 2-year LC significantly better for SABR, 91.3% to 22.9%, respectively, and no significant difference in overall survival (OS).[9]

An advantage of SABR compared with other local techniques is that lesions can be treated that are difficult to access by RFA, embolization or surgery (eg, large volume tumors; disease complicated by portal thrombus;[10] and lesions near the liver capsule, major vessels or diaphragm).

SA-CME (Release date: March 1, 2018; Expiration date: April 30, 2020)

Table 2. SABR Liver Metastases Series Outcomes

First Author, Year	Patients/ Tumors	Tumor Diameter	Study Design	Dose/ Fractions (BED for α/β=10)	Tumor Response % (CR/PR/SD/PD)	Local Control % (1y/2y/3y)	Overall Survival % (1y/2y/3y)	Toxicity % ≥ Grade 3
Meyer, 2016[54]	14/17	3.2 cm	Phase I	35-40 Gy/1 (BED_{10} 157.5)	69/31/0/0	100/100/---	85/78/---	0
Scorsetti, 2014[18]	42/52	3.5 cm	Phase II	75 Gy/3 (BED_{10} 262.5)	43/17/9/31	95/91/85	81/65/---	0
Fode, 2015[20]	225	---	Retrospective	45-68 Gy/3 (BED_{10} 112.5-228)	---	91/87/---	At 1/3/5/7.5 years: 80/39/23/12	4.8
Comito, 2014[17]	42/52	< 6 cm	Phase II	75 Gy/3 (BED_{10} 262.5)	43/32/15/10	95/90/85	85/65/43	0
Stintzing, 2013[22]	30/35	3.3 cm	Retrospective: Matched study, SABR vs RFA	24-26 Gy/1 (BED_{10} 87.5)	---	85/80/---	Median OS: 34.4 months	0
Goodman, 2010[55]	19/33	4.2 cm	Phase I	18-30 Gy/1 (BED_{10} 50.4-120)	---	77/---/---	62/49/---	10.5
Lee, 2009[56]	68	5.2 cm	Phase I	41.4 (27-60) Gy/6 (BED_{10} 71.4)	6/43/30/21	71/---/---	63/---/---	10.3
Rusthoven, 2009[19]	47/63	2.7 cm	Phase I/II	36-60 Gy/3 (BED_{10} 79.2-180)	---	95/92/---	77/30/---	2.1

Key: SABR = stereotactic ablative radiation therapy, RFA = radiofrequency ablation, BED = biologically equivalent dose, CR = complete response, PR = partial response, SD = stable disease, PD = progression of disease

Intrahepatic Cholangiocarcinoma

Intrahepatic cholangiocarcinoma (ICC) is the second-most common primary liver cancer worldwide, representing 10% to 20% of liver cancer diagnoses. Surgery is the only curative treatment for local disease, but up to 70% of ICC is unresectable.[11]

In 2016, physicians from MD Anderson Cancer Center and Harvard analyzed outcomes from a series of unresectable ICC patients who received chemotherapy followed by moderately hypofractionated radiation therapy and identified a survival advantage with dose escalation.[12] Patients treated to a biologically equivalent dose (BED) > 80.5 Gy had almost double the 3-year survival of those treated to lower doses (73% to 38%, respectively).

Princess Margaret Hospital conducted the first phase I trial using SABR to treat inoperable ICC. Ten patients were treated to a median dose of 36 Gy in 6 fractions, with 1-year LC of 65% and median OS of 15 months, an improvement over historic controls. There were no cases of radiation-induced liver disease (RILD), and toxicities were grade 3 or less.[13]

SABR in the Teatment of Liver Metastases

Each year, 30 000 patients with colorectal cancer (CRC) are found to have oligometastatic disease (OMD) limited to the liver either on presentation or at recurrence.[2,14,15] In 2016, the European Society for Medical Oncology recommended the use of SABR in combination with systemic agents to treat unresectable colorectal OMD.[16] In the last decade, several phase I and II studies using SABR to treat hepatic OMD from favorable primaries have reported 2-year LC rates > 90%, and median OS significantly higher than historical controls treated with systemic therapy alone (29 to 32 months vs. 24 months for chemotherapy).[17-19] In a large retrospective series studying outcomes from SABR treatment of mainly hepatic OMD, Fode et al identified 5 factors associated with favorable survival: World Health Organization (WHO) performance status 0-1, solitary metastasis, size ≤ 3 cm, metachronous metastases and pre-SBRT systemic therapy. BED_{10} > 100 Gy correlated with low local recurrence rates.[20]

The recent CLOCC trial (chemotherapy + local ablation vs chemotherapy) randomized 119 patients with liver-only colorectal unresectable metastatic disease to systemic therapy alone vs systemic therapy with RFA and surgical resection (when possible),

SA-CME (Release date: March 1, 2018; Expiration date: April 30, 2020)

and demonstrated a median OS benefit with local therapy (45.6 months vs 40.5 months).[21] While no local ablative technique has demonstrated superiority compared to another local ablative technique in a randomized trial, Stintzing et al performed a matched comparative analysis of 60 patients with unresectable colorectal liver metastases, divided between SABR (24 to 26 Gy in 1 fraction) and RFA. One-year LC favored SABR (85%) compared to RFA (65%).[22] This suggests that SABR could further enhance survival benefits for unresectable liver metastases compared to RFA.

SABR also provides excellent control of oligometastatic liver disease from noncolorectal primaries. A 2016 series demonstrated 100% 2-year LC rates for 58 noncolorectal liver metastases.[23] Additional studies of SABR for liver metastases are summarized in **Table 2.**

SABR Technique

Dose

In practice, the authors of this manuscript generally follow the isotoxicity approach initially proposed by Dawson et al and adapted into the Radiation Therapy Oncology Group (RTOG) 1112 trial (NCT01730937) protocol.[24,25]. In RTOG 1112, 5-fraction SABR is prescribed to Child-Turcotte-Pugh class (CTP) A HCC, and the mean liver dose (MLD, defined as liver minus gross tumor volume [GTV]) determines the prescription dose based on an expected 5% incidence of RILD. If the MLD in the achieved plan is less than 13 Gy, the dose is 50 Gy over 5 fractions; however, the dose is reduced as MLD increases. Caution must be employed for dose to adjacent stomach and bowel, and additional dose constraints are also provided within the RTOG 1112 protocol.

Logically, this schema can also be applied to CTP A patients with liver metastases or cholangiocarcinoma, as BED_{10} = 100 Gy (50 Gy in 5 fractions) correlates with good tumor control.[12,20] For patients with limited liver metastatic disease without underlying liver dysfunction, 60 Gy in 5 fractions (BED_{10} = 132 Gy) can be considered. Conversely, caution must be used in CTP B patients. A phase I/II trial reported 38% grade 3 or higher toxicities for CTP B HCC patients treated with SABR.[26] The use of dose escalation in this fragile population requires careful patient selection. For CTP C patients, hospice should be considered.

Image Guidance and Respiratory Management

Since increasing MLD correlates with increasing rates of RILD and limits prescription dose and anticipated tumor control, attempts should be made to reduce the MLD.[27,28] Custom immobilization, image guidance and respiratory management allow reduction of the planning target volume (PTV) margin to about 5 mm.

Patients with limited respiratory motion assessed by fluoroscopy, 4-dimensional computed tomography (4D-CT), or cine magnetic resonance imaging (MRI) could be treated with an internal target volume (ITV) encompassing the respiratory excursion plus PTV expansion for setup uncertainty. However, craniocaudal and anterior-posterior excursions of liver tumors of 2 to 3 cm have been reported with limited motion reduction by abdominal compression.[29] Therefore, appropriate motion management techniques must be available to treat patients with large respiratory motions. Example strategies include respiratory gating, breath-hold and active tracking.[30-32] Such systems include the Cyberknife Synchrony (Accuray, Sunnyvale, California) and Varian Real-Time Position Management (Varian, Palo Alto, California) systems, which use cameras during therapy to track markers placed on the body's surface that are correlated to the internal tumor position. A common alternative is Elekta's Active Breathing Coordinator (Elekta, Stockholm, Sweden), which tracks and assists reproducible lung filling during treatment.

These systems require internal calibration of the target position to the tracking system using fluoroscopy or breath-hold cone-beam CT at the beginning of each treatment. For these x-ray-based image guidance techniques, we strongly recommend target localization with radiopaque fiducials placed prior to simulation.[33] This has been shown to lower the maximum setup error from 12 mm (based on diaphragm position and bony landmarks) to 2 mm.[34] Residual Lipiodal (Guerbet, Villepinte, France) injected from prior TACE treatments can also be used.[35]

Definition of the target requires intravenous (IV) contrast at the time of simulation and/or careful fusion to diagnostic scans. If gating or breath-hold is employed, simulation must include images for planning in that respiratory phase.

Emerging Techniques

Recently, an MRI-guided radiation therapy system has become available for treatment of liver tumors.[36,37] MRI simplifies the SABR procedure since it enables direct tumor visualization for planning and daily setup as well as near real-time imaging during treatment. An example of MRI-guided treatment is shown in **Figure 1**. Real-time visualization of liver targets can be further enhanced by use of gadoxetate MRI contrast.[38]

In some settings, proton SABR could enhance normal liver sparing compared to conventional photon treatments given the reduced exit dose from the Bragg peak, reducing MLD and increasing the size or dose of treatment.[39,40] Nevertheless, respiratory motion offers more complications in

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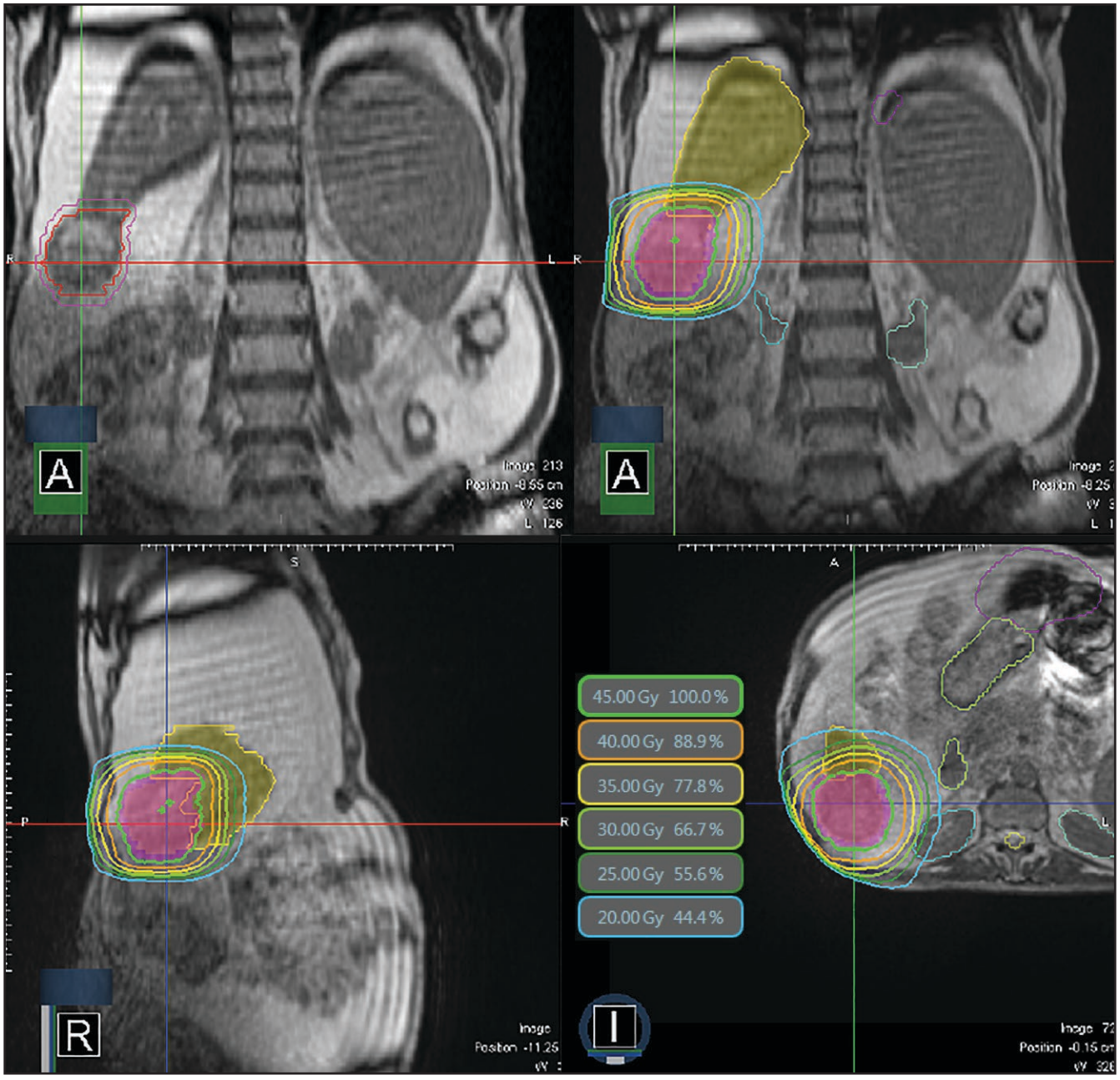

FIGURE 1. *Example of liver stereotactic ablative radiation therapy (SABR) treatment with MR-guided radiation therapy. A 62-year-old woman with hepatocellular carcinoma, CTP class B, underwent 45 Gy in 5 fractions of SABR to an exophytic liver mass. Top left demonstrates a coronal view of the gross tumor volume (GTV, red) expanded 5 mm to planning tumor volume (PTV, purple). The images shown were acquired in 2 minutes on the Co-60 radiation therapy device at time of simulation, and the same quality 2-minute images are obtained each day for patient setup. Tumor within the red contour is seen as hyperintense compared to the liver. The top right image demonstrates the same tumor in coronal view with PTV in color-wash purple, the liver in color-wash yellow, and the planned dose distribution extending from the center (45 Gy, green-blue line) to the outside (20 Gy, light blue line). The bottom images demonstrate the target and dose distribution for sagittal (bottom left) and axial (bottom right) views. The kidneys (light blue and light green), duodenum (dark green), spinal cord (yellow), and stomach with expansion (purple) are also contoured. During treatment, sagittal images are obtained of the GTV at a rate of 4 times per second with near real time automated target tracking and gating. If the GTV moves outside of the 5-mm tracking box, treatment is paused within milliseconds. Treatment is then resumed within milliseconds when the target returns within the tracking box.*

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proton than photon treatment due to derangement of the Bragg peak location caused by target depth variability. Use of proton SABR has been limited historically because few proton therapy centers were equipped with respiratory gating; however, the number of capable centers is increasing.[41,42]

Radiation-induced Liver Disease

Recognition of the liver's parallel functional structure, reinforced by surgical experience and refined through advances in Normal Tissue Complication Probability (NTCP) modeling, provides the physiologic justification for partial-liver irradiation.[43] When one-third of the normal liver parenchyma (standardized to 700 cc of tissue) is protected from doses > 15 Gy in 3-5 fractions, the risk of RILD is < 5% for patients with baseline CTP A hepatic function.[44]

RILD is the most common dose-limiting toxicity for radiation therapy of liver tumors with time-to-onset ranging from 2 weeks to 8 months post-treatment. Classical RILD is characterized by fatigue, anicteric ascites, elevation of alkaline phosphatase out of proportion to other live enzymes, abdominal pain, and hepatomegaly. Nonclassical RILD patients present with jaundice and elevated serum transaminase. Given the overlap with liver failure of other causes, such as hepatitis, it is often difficult to directly ascribe to radiation therapy. Management is supportive, similar to management of other types of liver injury.

In practice, patients generally report transient loss of appetite and increased fatigue resolving by 3 months following SABR, with pretreatment quality of life maintained through 1 year.[45]

Conclusion

Numerous studies support SABR for the treatment of liver tumors such as unresectable hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and liver metastases. Careful consideration of image guidance and respiratory management allows for minimization of normal liver treated, improving the safety, effectiveness, and size and number of tumors that can be treated successfully. Comparative studies to other techniques, improving radiation therapy delivery technologies, and expanding indications, such as bridge to transplant in HCC or oligometastatic liver disease, may increase future utilization of liver SABR.

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Stereotactic radiosurgery for primary and metastatic sarcomas of the spine

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Abstract

Purpose: The goal of this institutional analysis was to evaluate the role of stereotactic radiosurgery (SRS) in primary and metastatic spinal and paraspinal sarcomas.

Methods: Patients with pathologically confirmed sarcomas who received spine SRS at our institution between June 2001 and December 2013 were retrospectively reviewed in this analysis, which was approved by the institutional review board. Electronic medical records of clinical exams, and computed tomography (CT)/magnetic resonance imaging (MRI) were evaluated. Post-treatment pain control, neurological improvement, and radiographic tumor control were the primary endpoints of this study.

Results: A total of 23 patients (78 vertebral bodies, 53 tumors) were included. The average age of the cohort was 57 years. The median surgical dose was 18 Gy in a single fraction (range, 10 to 20) prescribed to the 90% isodose line. Median follow-up time was 14 months. Fourteen patients were deceased, with a median survival of 15.5 months. The average tumor volume was 53.12 cc (range: 2.02 to 207.25 cc). Overall pain response was 75% (25% partial and 50% complete relief). Pain was stable in 25% of the patients, and no pain progression was observed. Total neurological response was 67% (0% complete, 67% partial). The remaining 33% of the patients were neurologically stable after treatment. In 1 patient, a new neurological deficit was observed after SRS. Total radiographic response was 67% (0% complete, 29% partial, 38% stable). Local tumor progression was observed in 33% of the patients. One patient initially had a partial radiographic response that progressed after 10 months. Another patient was initially stable but experienced radiographic progression after 3 months. Eight vertebral compression fractures (VCFs) were noted, 2 of which may be attributed to SRS. No other adverse effects were observed.

Conclusions: A total of 23 patients and 78 spinal levels were treated with SRS, resulting in fairly good response rates for pain relief, neurologic improvement, and radiographic tumor response (75%, 67%, and 67%, respectively). Our results indicate that SRS has a role in the treatment of primary and metastatic sarcomas of the spine.

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Unlike the majority of cancers that originate from epithelial tissues, sarcomas are rare tumors that arise from embryonic mesenchymal cells. Due to this origin, sarcomas tend to follow a distinct biologic pattern, causing them to grow radially away from the center.[1-5] Managing sarcomas in the spinal and paraspinal region often comes with a difficult choice: using aggressive treatment to achieve optimal local tumor control or a more conservative approach to minimize the risk of severe toxicity. Poor local control (LC) for sarcoma patients correlates with a significant decrease in overall survival (OS).[6] Thus, it is crucial to find the appropriate balance between LC and toxicities for these patients to achieve the best possible outcomes.

Complete surgical resection, the favored method of achieving LC for most spine sarcomas,[6-11] is effective but difficult to accomplish without harming the spinal cord and other intricate tissues such as the surrounding muscles, tendons, nerves and bone. Resection of these tissues often necessitates extensive reconstruction and complex stabilization, which can result in functional/neurological deficits[10] as well as the need for lengthy postoperative rehabilitation. Sarcoma response to conventional external-beam radiation therapy (EBRT) varies with histologic subtype.[12] This group of tumors requires radiation doses of 50 to 66 Gy delivered in 2 Gy per fraction to achieve local control. These doses exceed the spinal cord tolerance of 46 to 50 Gy, resulting in a high risk of radiation-induced myelopathy.[13-17] Another potential option for these patients is stereotactic radiosurgery (SRS), which is increasingly being used as an effective treatment for spine lesions of varied histologies. It delivers a high biologically effective dose (BED) of radiation to treatment targets, while minimizing the amount that reaches healthy tissue. This makes SRS an appealing option for spine sarcomas.

Previous reports on the use of SRS to treat spine sarcomas have found that SRS appears to control pain in up to 93.8% of symptomatic lesions,[17] and provides durable tumor control in up to 87.9% of lesions, resulting in a better chance of increased OS.[18] Other reports found SRS to be effective in treating primary sarcomas but not metastases.[17] These findings are encouraging, but since there are few reports on this topic, this patient population remains poorly understood. Our study presents a cohort of patients treated at a single institution, under a uniform dose/fractionation scheme. The goal of this institutional analysis is to evaluate the role of SRS in primary and metastatic spinal and paraspinal sarcomas.

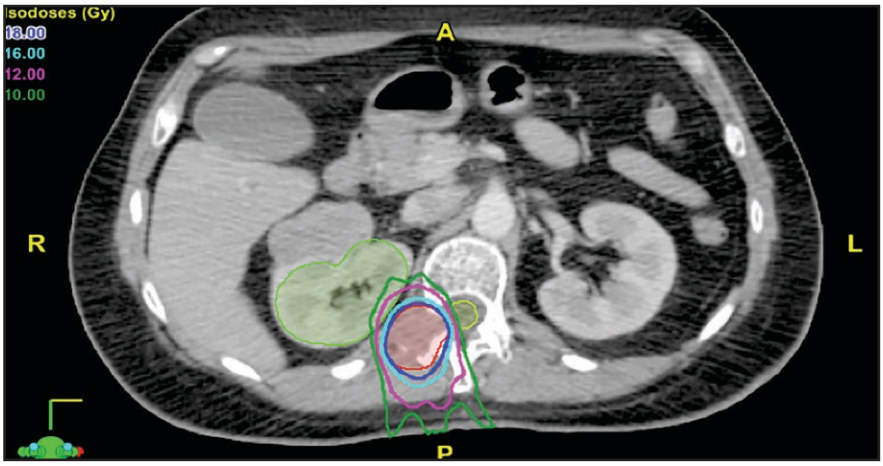

FIGURE 1. *Axial view of the treatment planning images obtained from a 48-year-old woman with a paraspinal uterine leiomyosarcoma metastasis centered at the right L1 lamina with an epidural component and mild indentation of the thecal sac. Isodose lines demonstrating 18 Gy in a single fraction delivered to the planning target volume (PTV) are shown in red; yellow represents the dose delivered to the cord.*

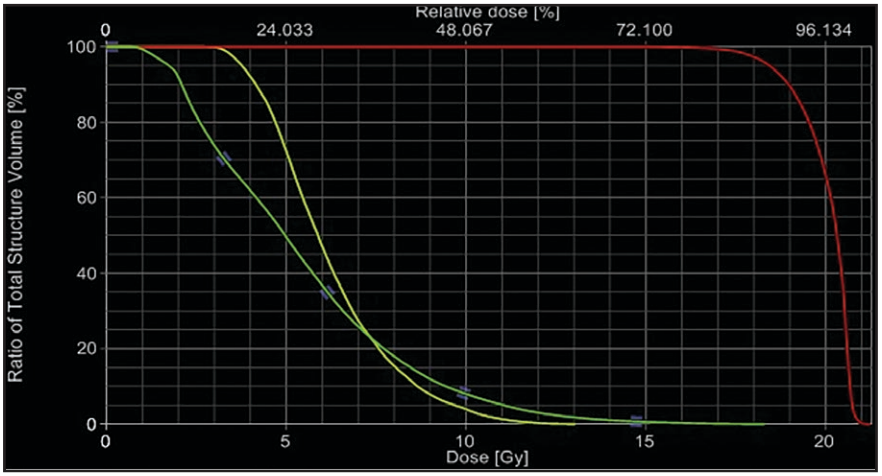

FIGURE 2. *Dose-volume histogram of the same patient. Red represents the dose delivered to the PTV, green is the dose delivered to the organ at risk.*

Methods

Patients with pathologically confirmed sarcomas who received spine SRS at a single institution between June 2001 and December 2013 were retrospectively reviewed after obtaining institutional review board approval. A total of 23 patients treated to 78 vertebral levels were included. Electronic medical records of clinical exams, computed tomography (CT), and magnetic resonance imaging (MRI) were evaluated.

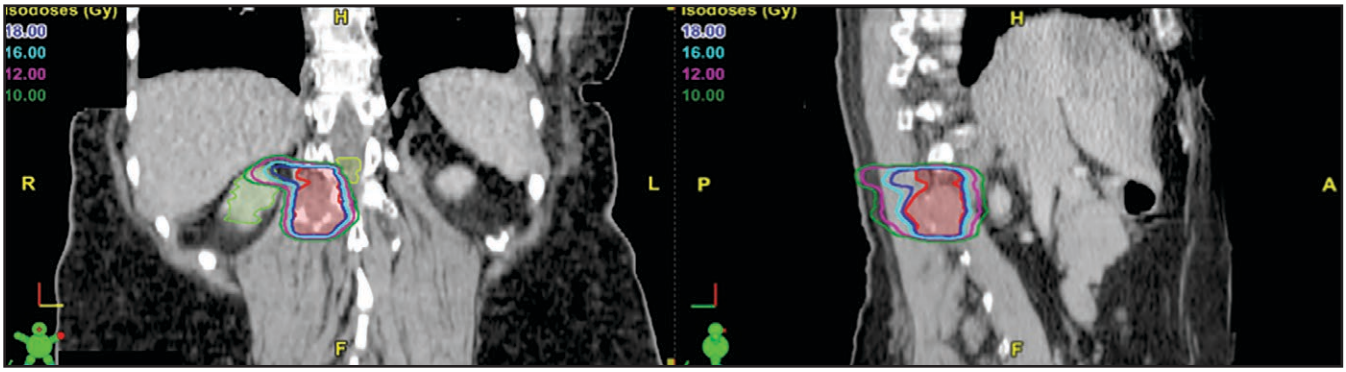

FIGURE 3. Frontal view of the same patient (left). Sagittal view of the same patient (right).

Table 1. Patient Characteristics

Patients, no.	23
Sex, no. (%)	
Males	11 (48%)
Females	12 (52%)
Age, years	
Median (range)	57 (21-92)
Ethnicity, no. (%)	
African American	6 (26%)
Caucasian	14 (61%)
Unspecified	3 (13%)
Treatment	
# Sites/Tumors Treated	53
Total # VBs Treated	78

Key: VBs = vertebral bodies

Post-treatment pain control, neurological improvement, and radiographic tumor control were the primary endpoints of this study. Although not a primary endpoint, occurrence and progression of toxicities, including vertebral compression fractures (VCF), were also recorded.

The Novalis system (Brainlab, Munich, Germany) was used for spine SRS. Patient immobilization was achieved with the aid of vacuum bags. A contrast-enhanced simulation CT scan with a slice thickness of 3 mm was performed with infrared fiducial markers (ExacTrac, BrainLAB). These images were fused with diagnostic T1- and T2-weighted MRIs in the treatment planning system to define the target volume. No expansion margin was added to the gross tumor and, thus, the gross tumor volume (GTV) was equal to the planning target volume (PTV). T2-weighted MRIs were used to delineate the spinal cord 6 mm above and 6 mm below the defined GTV. A spinal cord planning organ at risk volume was not constructed. Multiple coplanar intensity-modulated radiation beams were used to optimize the radiation dose to the target volume and minimize the dose to surrounding tissue. Single doses of 10 to 20 Gy (median 18 Gy) were delivered. All doses were delivered in a single fraction and were prescribed to the 90% isodose line. The primary dose constraint for plan selection was to achieve the objective of 10 Gy to 10% of the partial volume of the spinal cord and a maximum point dose of 14 Gy. The aim for target volume coverage was to deliver 95% of the dose to 95% of the volume. However, preference was given to spinal cord dose-sparing constraints and, in cases where this was not achievable, a slight underdosage to the target volume was accepted. Prescribed dose did not vary based on tumor histology. This procedure has been detailed in previous reports.[19-21] Treatment planning images are shown in **Figures 1-3**.

Clinical follow-up consisted of periodic clinical examinations in which pain and neurologic responses were assessed. The 0-10 Numerical Rating Pain Scale was used to quantify pain response. Several methods were used to assess neurologic response, including the 0-5 point Medical Research Council scale for motor strength, the pinprick test for numbness, the Romberg evaluation for balance, as well as testing of the cranial nerves.[2]

As a secondary endpoint, occurrence and progression of potentially SRS-induced spinal instability (in the form of vertebral compression fractures [VCF], or impending VCFs that required surgical stabilization beyond 1 week after SRS) were evaluated with follow-up imaging. Cases of spinal instability at vertebral levels not treated with SRS, those that received surgical stabilization prior to SRS, and those that occurred with concurrent tumor progression were not attributed to SRS in our analysis. Our methods for evaluating VCFs have been detailed in a previous report.[21]

Results

A total of 23 patients and 78 treated vertebral levels were included. The average age of the cohort was 57 years (**Table 1**). The median radiosurgical dose was 18 Gy (range: 10 to 20 Gy) in a single fraction prescribed to the 90% isodose line (**Table 2**). Eleven patients had received prior radiation therapy (RT) to the spine and 10 patients underwent prior surgical resection of their tumor. Follow-up was available for 48 (62%) vertebral bodies, with a median follow-up time of 14 months. Fourteen patients were deceased, with a median survival of 15.5 months (**Table 2**). Leiomyosarcoma was the most common histologic subtype among the cohort with 9 patients (**Table 2**). The average tumor volume was 53.12 cc (range: 2.02 to 207.25 cc) (**Table 2**).

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Table 2. Tumor and Stereotactic Radiosurgery Characteristics

Tumor Location, Number of Tumors	
Cervical	11
Thoracic	17
Lumbar	20
Sacral	5
Median Tumor Volume (range), cm^3	53.12 (2.02 – 207.3)
Median Radiosurgery Doses (range), Gy	18 (10-20)
Other Treatments	
Radiation Therapy	11
Surgical Resection	10
Histology, number of Pts	
Leiomyosarcoma	9
Ewing's Sarcoma	3
Osteosarcoma	2
Neurofibrosarcoma	2
Liposarcoma	2
Chondrosarcoma	1
Hemangiopericytoma	1
Rhabdomyoblastic anaplastic Sarcoma	1
Spindle Cell Sarcoma	1
Unspecified	1
Follow-Up (clinical, radiographic, or both)	
Number of Patients (%)	11 (48%)
Median Duration (range)	14 m
Survival	
Deceased at Time of Study, no. (%)	14 (61%)
Median Survival (range)	15.5 m (26 d – 6.2 y)

Key: VBs = vertebral bodies; Pts = patients; m = month; d = days; y = years

Table 3. Stereotactic Radiosurgery Response Rates

Response	Total Favorable Response	Complete (CR)	Partial (PR)	Stable	Progressed
Radiographic	67% (CR+PR + Stable)	0%	29%	38%	33%
Neurologic	67% (CR+PR)	0%	67%	33%	0%
Pain	75% (CR+PR)	50%	25%	25%	0%

Overall pain response was 75% (25% partial and 50% complete relief). Pain was stable in 25% of the patients, and no pain progression was observed (**Table 3**). Total neurological response was 67% (0% complete, 67% partial). All remaining patients were neurologically stable after treatment. In 1 patient, a new neurological deficit was observed after SRS. This patient suffered from decreased grip strength on the left after receiving SRS 16 Gy/1fx to C1-C2 and C4-C5. Total radiographic response was 67% (0% complete, 29% partial, 38% stable). Local tumor progression was observed in 33% of the patients (**Table 3**). One patient initially had a partial radiographic response that progressed after 10 months. Another patient was initially stable but experienced radiographic progression after 3 months. Eight VCFs were noted, 2 of which may be attributed to SRS. No other adverse effects were observed.

Discussion

The standard methods of achieving LC in spine sarcomas are limited. SRS, an alternative method of achieving LC, has shown efficacy in preliminary studies, and our results corroborate this. In our study, 23 patients and 78 spinal levels were treated with SRS, resulting in fair response rates for pain relief, neurologic improvement, and radiographic tumor response. Our sample size is comparable to those of the previous published reports on spine sarcoma SRS, and when taken in conjunction with the results of the prior reports, our series allows for a better understanding of SRS treatment of spine sarcomas.

Although sarcomas are sometimes characterized as painless masses, pain is common when they occur in certain areas of the body such as the spine. An important goal of radiosurgical treatment of spine sarcomas is pain alleviation. Levine et al produced the first report on spine sarcoma SRS evaluating 24 patients (30 lesions) treated with 30 Gy in 3 fractions. Fourteen patients had primary spine sarcomas: 7 received SRS as definitive treatment, and 7 received SRS adjuvant to surgery; 10 patients had spine sarcoma metastases and received SRS with or without prior radiation therapy. In their series, pain response results were reported for 23 out of the 30 treated lesions; out of these 23 lesions, 22 experienced pain relief (7 out of 7 primary lesions, and 15 out of 16 metastases).[17] At 75%, our pain response was also relatively high, with a rate comparable to that of a report by Chang et al of the Korea Cancer Center Hospital (KCCH), whose observed pain control rates at 6 months, 1 year, and 2 years were 89.3% (25/28), 68.2% (15/22), and 61.5% (8/13) respectively. Their series found that small tumor volume correlated with post-SRS pain control.[16] Brown et al only observed pain relief in patients treated palliatively.[22] **Table 4** summarizes the largest spine sarcoma SRS series.[16-18,23-26]

Besides pain control, preservation of neurological function and improvement of any neurological deficits is an important treatment goal. Our series is one of the few to report on this endpoint, with 4 out of the 6 patients in our cohort who presented with neurologic deficits experiencing a decrease in their symptoms. The series by Levine et al—the only other sarcoma SRS series that observed neurological responses—reported that 2 of their patients presented with neurological symptoms. One experienced complete relief after SRS, and the other experienced partial relief.[17] Neurological function outcome data after EBRT is also limited. However, it is plausible that deficits may be able to be maintained or possibly improved by EBRT alone in the few radiosensitive histologic subtypes such as Ewing's sarcoma. Functional status following surgical resection of spine sarcomas is more extensively reported on and, therefore, better understood. Bilsky and colleagues (n = 59) reported improvement in function after resection in 13% of patients, and maintenance of function in 79%.[8] Another report noted similar rates with functional improvement observed in 14% (vs 67% in the present series) of the 110 spinal sarcomas resected, and maintenance of pre-treatment function in 83%.[9] In this series, outcome correlated with histologic subtype; chondrosarcoma histology was predictive of better postsurgical functional status, and osteosarcoma histology was associated with worse postsurgical functional status.[9]

LC was the only endpoint evaluated in all of the previously reported series as well as our own. Therefore, the efficacy of spine SRS in achieving LC in sarcomas is the most well understood endpoint. A report by Folkert et al found that in comparison to hypofractionated SRS, single-fraction SRS was associated with improved LC.[18] Levine et al determined that in metastases, however, LC is difficult to evaluate due to the high mortality of these patients.[17] The Mayo Clinic series reported on the response of spine sarcomas combined with sarcomas of other anatomical locations with an LC of 85% at 2 years for patients treated definitively/curatively. This series did not analyze local control for patients treated palliatively since these patients did not have routine imaging.[22] In the series by Chang et al, young age was found predictive of favorable local progression-free survival. Their series also found a correlation between dose and LC with patients receiving above 22 Gy experiencing better LC at 2 years compared with those below 22 Gy.[16] A study on sarcoma response to conventional RT such as Kepka's found the sarcoma response rate to be 22% when < 63 Gy was delivered; however; the rates rose to 60% when doses above 63 Gy were used.[13] Our institution delivered a mean surgical dose of 18 Gy and our LC was 67%. Although LC was moderate in our series, symptom control was achieved and maintained even in cases with radiographic progression, which highlights the palliative utility of SRS.

Although there is reason to believe that the precision of SRS minimizes potential toxicities, they do occur in certain patients. In our series, one non-VCF toxicity was observed. A patient experienced a new neurological deficit of decreased grip strength in the left hand after EBRT of 51 Gy/17 fx to the entire cervical spine, with an SRS boost of 16 Gy/1 fx to C4-C5 2 weeks prior to the EBRT, and a boost of 16 Gy/1 fx to C1-C2 1 week after EBRT. Pertinent spine imaging was not available to evaluate the potential contribution of radiation toward this patient's symptoms. The patient also had metastatic disease within the left radius corresponding to the time of symptom presentation. Even though this may have been the cause, the potential effects of radiation cannot be eliminated as a contributing factor to the development of the deficit. With 1 patient experiencing a non-VCF toxicity, our toxicity rate was relatively low; however, our median follow-up of 14 months may have precluded the observance of late toxicities. Complications/toxicities in the report by Levine et al include delayed transient radiculopathy and dysesthesias in 2 patients and a rectal tumor cavity fistula in 1 patient.[17] In Folkert's study at Memorial Sloan Kettering Cancer Center, complications included 1 case of grade 3 fatigue, 1 case of grade 3 postoperative wound complication, and 2 cases of grade 3 tracheoesophageal fistulae.[18] In the Mayo clinic series, late toxicities occurred in 2 spine patients, 1 of which was treated to a recurrent sacral lesion and experienced grade 3 neuropathy. Prior to SRS, this patient received conventional RT (59.4 Gy/33 fx) to the same region. The other patient who experienced a toxicity in his or her cohort was treated to T11 and experienced myelodysplastic syndrome (MDS); this toxicity developed 3 years after treatment.[22] It is worth noting that the primary histology in this series was Ewing's sarcoma; this histologic subtype is typically considered to be radio-responsive, and is known to affect relatively young patients, which may be why late toxicities were observed in their cohort.

In Brown's series, most of the patients (3 out of 4) with long-term follow up had Ewing's sarcoma demonstrating how histologic subtype likely plays an important role in the disease sequalae. Due to the varied radiation responses of the different sarcoma histologic subtypes, it is difficult to directly compare the previous studies with our own. Leiomyosarcoma was the predominant histology in our cohort, accounting for approximately 39% of the patients. There is little existing literature on the radio-responsiveness of leiomyosarcomas. The little that is known is drawn from literature on conventional RT in the treatment of leiomyosarcomas of the uterus where it most frequently occurs.[12] As with other sarcomas, surgery is the recommended treatment and, when indicated, adjuvant RT. A University of Michigan institutional analysis (n = 8)

Table 4: Spine Sarcoma SRS Series

Study	Total Patients	Total Tumors	Median Dose/ Fraction (Gy) [range]	Median FU (months) [range]	Median Overall Survival (months)
AM Levine et al SHB 2009	24	30 total	30/various [20-35]	NR	NR
		Primary definitive SRS – 7	30 [24-35]	33 [20–49]	NR
		Primary adjuvant SRS – 7	30 [25-30]	NR	NR
		Metastases - 16	30 [20-30]	NR	11.1 (mean)
UK Chang et al KCCH 2012	27	32	21.6/1 [15.2–28.9]	22 [4-68]	29
MR Folkert et al MSKCC 2014*	88	120	Single Fx: 24 Hypo Fx: 28.5	12.3 [1-80.7]	16.9
JE Leeman et al MSKCC 2016*	88	120	24/1	14.4 [0.6-88.9]	18.9
DE Spratt et al MSKCC 2016	9	12	24/1 [24/1- 30/3]	11.2	NR
JA Miller et al CCLCM 2017	18	40	16/1 [10/1 - 25/5]	Radio - 9 [1-86] Clinical 15 [2-95]	16
AJ Bishop et al MDACC & Keck SOM 2017	48	66	NR	19	17 [1-121]
Current Series	23	53 (78 VBs)	18/1 [10/1-20/1]	14	15.5 [0.8-6.2]

*Studies are from the same cohort of patients; CCLCM – Cleveland Clinic Lerner College of Medicine ; CR–complete response ; FU– follow-up ; MSKCC – Memorial Sloan Kettering Cancer Center; NR – not reported ; PR – partial response ; SHB - Sinai Hospital of Baltimore;

Predominant Histologies	Neuro Response	Radio Response	Pain Response	Toxicities
Leiomyo – 29% Chondro – 21% Angio – 13%	NR	75% (18/24)	NR	6 cases
--	100% (1 CR & 1 PR out of 2)	71% (2 CR, 3 PR out of 7)	100% (7/7)	1 case nausea, 1 case malaise 1 case skin irritation, 1 rectal cavity fistula
--	NR	57% (4 CR out of 7)	NR	2 pts w delayed transient radiculopathy, dysesthesia, partial motor loss w resolution of symptoms
--	NR	90% (9 stable out 10) at >3 mo	94% (15/16)	None
Osteo – 40.6% Malignant fibrous histiocytoma – 13% Synovial – 13%	NR	At 6 m - 96.7% (29/30) At 1 yr - 78.3% (18/23) At 2 yr - 76.9% (10/13)	At 6 m - 89.3% (25/28) At 1 yr - 68.2% (15/22) At 2 yr - 61.5% (8/13)	NR
Leiomyo – 30% Hemangiopericytoma - 15.8% Lipo – 14.2%	NR	At 12 m - 87.9% At 24 m - 77.4%	NR	2 (2.3%) VCFs, 1 case (1% of Pts) Gr 3 acute dermatitis, 4 cases of chronic tox above Gr 3 (1 case of fatigue, 1 case of postop wound complication, 2 cases tracheoesophageal fistulae)
Leiomyo – 30% Hemangiopericytoma - 15.8% Lipo – 14.2%	NR	At 1 yr actuarial LFFS - 85.9% At 1 yr actuarial rate of freedom from any failure within the spine - 57.7%	NR	NR
Leiomyo - 50% Hemangiopericytoma - 17% Myxoid Fibro- 17%	NR	92%	NR	NR
Leiomyo - 32% Chondro - 17% Spindle cell - 17%	86%	At 6 m - 63% At 12 m - 51%	Adjusted at 6 m – 35% Unadjusted at 6 m – 77%	3 (8%) VCFs 4 (10%) Pain flare 1 case Gr 3 foot drop
Leiomyo - 42% Epithelioid - 14% Malignant fibrous histiocytoma/unclassified pleomorphic sarcoma - 13%	NR	At 1 yr - 81% At 3 yrs - 61%	NR	Most common acute toxicities were fatigue 15 cases (23%), esophagitis 6 cases & nausea 6 cases Chronic toxicities included 4 (6%) insufficiency fractures, & 3 neuropathies (none were Gr 3 or 4)
Leiomyo – 39% Ewing's Sarcoma - 13% Osteosarcoma – 9% Neurofibrosarcoma – 9% Liposarcoma – 9%	25%	67%	75%	2 (3%) VCFs 1 case of progressive decrease in L hand grip strength

Gr – grade; KCCH – Korea Cancer Center Hospital; LFFS – local failure free survival ; M – months ; MDACC – MD Anderson Cancer Center ; SOM - School of Medicine ; Tox - toxicity; VBs – vertebral bodies ; VCF – vertebral compression fracture; Y- years

reported on the intra-lesional resection of spine leiomyosarcomas in which they observed excellent clinical response rates; however, recurrence occurred in 63% of patients.[27] In our series, 6 of the leiomyosarcoma tumors that were painful at presentation were evaluable for follow-up. Pain remained stable in 1 site and relief was experienced in 5 (complete – 3, partial – 2). Five of the tumors/treatment sites associated with neurological deficits at presentation were evaluable for neurological follow-up, and functioning remained stable in all 5 sites. Local control was achieved in 3 out of the 5 sites (stable – 2, partial – 1) evaluable for radiographic follow-up, and tumor progression was observed in 2 of the sites. The radiographic progressions were asymptomatic, and a complete and durable pain response was achieved in 1 of the treatment sites even though it progressed radiographically. Our response rates for leiomyosarcomas and the overall LC rate for the cohort may suggest that when en bloc surgical resection/negative margins are not possible, SRS efficacy may be similar to that of surgery. Since SRS is delivered in as little as 1 fraction, treatment time is significantly shortened, and the need for postsurgical rehabilitation is eliminated; as a result, SRS is convenient and does not interfere with concurrent chemotherapy schedules. However, given the small size of our cohort, this is speculative and larger studies are needed to better understand the treatment responses in these patients.

Limitations of this study include those inherent in retrospective analyses, and our inclusion of subjective endpoints such as pain and neurological response. Despite this subjectivity, the clinical responses were observed throughout the 12 years included in this analysis, at a single institution by a single physician, resulting in increased uniformity. Another limitation is the small sample size of our cohort, which precludes us from making definitive statements on SRS efficacy for spine sarcomas. Although larger studies are needed, when our results are taken in conjunction with the previously reported series, the role of SRS in the treatment of spine sarcomas can be better understood. Additionally, our cohort had a relatively diverse representation of ethnicities.

When presented with the difficulty of choosing between local control and safety, in addition to the standard treatment options, SRS should be considered. With 75% of our patients experiencing pain relief, 67% experiencing neurologic improvement, and 67% experiencing radiographic tumor control, our results suggest that SRS has a role in treating primary and metastatic sarcomas of the spine. Further studies that are larger, histology specific, and geared toward determining the optimal dose are needed to create more conclusive guidelines on treating spine sarcomas with SRS.

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Stereotactic body radiation therapy for ≥ 5 cm node-negative non-small cell lung cancer: Survey of U.S. academic thoracic radiation oncologists

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Abstract

Purpose: Large (≥ 5 cm) node-negative non-small cell lung cancer (NSCLC) is relatively uncommon; efficacy and toxicities of stereotactic body radiation therapy (SBRT) in this unique population have been under-evaluated.

Methods and Materials: We surveyed U.S. academic thoracic radiation oncologists regarding SBRT practice patterns in node-negative ≥ 5 cm NSCLC and assessed factors necessitating changes in SBRT management. A 25-question survey of demographics and practice patterns, including 5 clinical cases, was sent to 107 radiation oncologists who self-identified as thoracic/lung cancer specialists.

Results: Response rate was 34% (36/107). Among respondents, two-thirds had at least 6 years of work experience following residency; 67% and 67% annually treated > 60 lung cancer and > 25 lung SBRT cases, respectively. Nearly all (97%) routinely offered SBRT for ≥ 5 cm NSCLC, and 55% used a SBRT treatment of 50-60 Gy in 5 fractions, with fractions delivered every other day in 60%. Dosing/fractionation were most commonly altered for central disease (77%). Sixty percent would offer additional chemotherapy; chemotherapy was strongly considered for patients with good performance status (74%), younger age (69%), and larger tumor size (68%). The 5 clinical cases revealed significant practice variability in dose, fractionation, treatment timing, and chemotherapy use.

Conclusions: Practice patterns of SBRT for ≥ 5 cm NSCLC display substantial heterogeneity. Five-fraction regimens with biologically effective dose ≥100 Gy were most commonly performed, with common endorsement of every other day delivery and chemotherapy.

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Non-small cell lung cancer (NSCLC) is the most common cause of cancer death in the world.[1,2] Early stage NSCLC is commonly treated with lobectomy, with stereotactic body radiation therapy (SBRT) being the standard of care for inoperable early stage NSCLC.[2-12] Initial studies of SBRT have demonstrated excellent local control rates of ≥ 90%, but these large cohort studies have consisted primarily of small (≤ 4 cm) primary tumors, with node-negative NSCLC tumors ≥ 5 cm being vastly under-represented.[12] Owing to the uncommon nature of these large node-negative NSCLC tumors, data-driven recommendations regarding this patient population are largely lacking.[12-15] Hence, the National Comprehensive Cancer Network (NCCN) does not offer concrete guidelines on treatment of node-negative ≥ 5 cm NSCLC.[3]

Because of this limited data and lack of consensus, there is great heterogeneity in how these cases are treated in clinical practice, and many questions remain regarding practicality of several SBRT schemes in this population. Hence, we

Table 1. Demographics of the Surveyed Population (n = 36 Respondents)

Parameter	Respondents (Percent*)
Gender	
Male	30 (83.3%)
Female	6 (16.7%)
Median (range) age, years	46 (31-64)
Postresidency experience*	
0-5 years	12 (33.3%)
6-10 years	7 (19.4%)
11-20 years	10 (27.8%)
21-30 years	7 (19.4%)
>30 years	0 (0.0%)
Location of practice*	
Urban	28 (77.8%)
Suburban	6 (16.7%)
Rural	2 (5.6%)
Geographic region*	
Northeast	12 (33.3%)
Midwest	10 (27.8%)
South	7 (19.4%)
West	7 (19.4%)
Number of co-radiation oncologists in practice*	
1	0 (0%)
2-9	12 (33.3%)
10-25	17 (47.2%)
>25	7 (19.4%)
Percent of practice involving lung cancer	
0-25%	8 (22.2%)
26-50%	11 (30.6%)
>50%	17 (47.2%)
Total lung cancer cases seen per year	
0-30	4 (11.1%)
31-60	8 (22.2%)
61-90	6 (16.7%)
>90	18 (50.0%)
Total cases treated with lung SBRT per year	
0-10	4 (11.1%)
11-25	8 (22.2%)
26-50	11 (30.6%)
51-75	4 (11.1%)
>75	9 (25.0%)
Total ≥ 5 cm NSCLC cases treated with SBRT per year*	
0	5 (13.9%)
1-2	10 (27.8%)
3-5	10 (27.8%)
6-10	5 (13.9%)
>10	6 (16.7%)
Participation in lung cancer cooperative group trials	
Yes	34 (94.4%)
No	2 (5.6%)

*Percentages may not add up to 100% due to rounding. Abbreviations: SBRT, stereotactic body radiation therapy; NSCLC, non-small cell lung cancer.

surveyed U.S. academic thoracic radiation oncologists to assess current practice patterns, and to determine which clinical parameters significantly altered their therapeutic decision-making for the treatment of large, node-negative NSCLC.

Methods and Materials

We asked 107 thoracic radiation oncologists from 71 U.S. academic institutions to participate in a 25-question survey. All invited participants self-identified as specializing in thoracic and/or lung radiation oncology. A single thoracic/lung radiation oncologist was invited per institution in most cases; however, multiple radiation oncologists were invited for select larger institutions in which multiple providers specifically focus their clinical practice on lung cancer. The invitation contained instructions for participation and information regarding the study. The first invitation was sent on June 29, 2016. Participants who requested not to be contacted in the future were immediately removed from the database. The remaining respondents were contacted with a reminder email on July 12, 2016, to maximize response rate. No further communication with participants ensued.

Responses were anonymous and were recorded with Google (N = 34) or Word documents (N = 2). The complete survey **(Supplemental Figure 1)** was divided into demographic questions, clinical scenarios in which respondents commented on typical treatment preferences, and 5 clinical cases to assess dose/fractionation of SBRT and chemotherapy administration. Demographic questions addressed clinical experience, the nature of the clinician's practice, and patient volume. Next, preferences on mediastinal staging modalities, chemotherapy use and timing, and practical/technical aspects of SBRT were recorded. Subsequently, various clinical scenarios were presented to assess whether each respondent would change management. Respondents selected from a list of several potential reasons for adding chemotherapy in addition

Table 2. Practice Patterns of the Surveyed Population (n = 35 Respondents)*

Parameter	Respondents (Percent)
Mediastinal staging modality used in patients with ≥ 5 cm NSCLC and negative mediastinal nodes on CT	
PET scan only	4 (11.4%)
EBUS and/or mediastinoscopy plus PET scan	31 (88.6%)
SBRT dose (in Gy)/fractionation (number of fractions) used most routinely for ≥ 5 cm NSCLC**	
50-60/5	21 (55.3%)
54-60/3	7 (18.4%)
48-50/4	3 (7.9%)
60/8	3 (7.9%)
70/10	3 (7.9%)
Other	1 (2.6%)
SBRT timing scheme of ≥ 5 cm NSCLC	
Daily	14 (40.0%)
Every other day	21 (60.0%)
SBRT delivery preference	
Fixed-beam 3D (forward planning)	1 (2.9%)
Fixed-beam IMRT (inverse planning)	4 (11.4%)
Dynamic arc therapy (forward planning)	4 (11.4%)
VMAT (inverse planning)	22 (62.9%)
No preference	4 (11.4%)
Increased patient age factoring into changing dose/fractionation scheme	
Yes	2 (5.7%)
No	33 (94.3%)
Poor performance status factoring into changing dose/fractionation scheme	
Yes	8 (22.9%)
No	27 (77.1%)
Central tumor location factoring into changing dose/fractionation scheme	
Yes	25 (71.4%)
No	10 (28.6%)
Administration of chemotherapy for patients with ≥ 5 cm NSCLC being definitively treated with SBRT	
Yes	21 (60.0%)
No	14 (40.0%)
Preferred timing of chemotherapy***	
Prior to SBRT	4 (19.0%)
After SBRT	17 (81.0%)
Concurrent with SBRT	0 (0%)
Concurrent with SBRT with additional chemotherapy before or after SBRT	0 (0%)
Factors in ≥ 5 cm NSCLC considered to administer chemotherapy	
Good performance status	26 (74.3%)
Younger age	24 (68.6%)
Larger size of tumor	24 (68.6%)
Chest wall invasion	15 (42.9%)
Central tumor location	12 (34.3%)
Poor tumor differentiation on biopsy	12 (34.3%)
No pathologic mediastinal staging performed	9 (25.7%)
Adenocarcinoma histology	7 (20.0%)
Visceral pleural involvement	7 (20.0%)
Not consider chemotherapy with these factors	5 (14.3%)

*One of the 36 respondents stated that they do not treat ≥ 5 cm NSCLC. The responses in this table, therefore, are based on the 35 respondents who completed these questions. **Three respondents gave 2 answers each. ***Chemotherapy timing question is out of 21 respondents who stated they would administer chemotherapy for patients with ≥ 5 cm NSCLC being definitively treated with SBRT.
Abbreviations: SBRT, stereotactic body radiation therapy; NSCLC, non-small cell lung cancer; PET, positron emission tomography; EBUS, endobronchial ultrasonography; IMRT, intensity-modulated radiation therapy; VMAT, volumetric-modulated arc therapy

Table 3. Dose/Fractionation Schemes in Respondents Opting to Change Such with Central Lesions (n = 25)

SBRT dose (in Gy)/ fractionation scheme (number of fractions) used for central tumors	
50-60/5	9 (36.0%)
60/15	8 (32.0%)
60/8	3 (12.0%)
70/10	2 (8.0%)
Other	3 (12.0%)

to SBRT. Lastly, 5 clinical cases were presented that holistically addressed the previously mentioned parameters; respondents were asked to comment on their chosen dose, fractionation, and timing, as well as adjuvant chemotherapy usage. At the end of the survey period, responses were collated and tabulated.

Results

Demographics

The overall response rate was 34% (36/107). **Table 1** illustrates respondent demographics. Thirty-three percent had 0-5 years of work experience after residency, 19% had 6 to 10 years, 28% had 11 to 20 years, and 19% had > 20 years. Most respondents practiced in an urban location (78%), and they most commonly worked in the Northeast (33%) and Midwest (28%). Forty-seven percent were partners in a radiation oncology practice of 10 to 25 radiation oncologists, whereas 33% were in a practice of 2 to 9 physicians.

Lung cancer patients comprised over half of the practitioner's patient volume for approximately half (47%) of respondents, with lung cancer patients constituting 26% to 50% of the practice in an additional 31% of respondents. Half of the surveyed population saw > 90 lung cancer cases per year. Two-thirds of respondents (67%) delivered SBRT to at least 26 patients annually, with high volume providers (> 75 cases per year) accounting for 25% of total respondents. Most respondents (86.1%) had significant experience delivering SBRT to NSCLC tumors ≥ 5 cm, with 28% treating 1 to 2 cases per year, 28% treating 3 to 5 cases per year, 14% treating 6 to 10 cases per year, and 17% treating >10 cases per year. Of those surveyed, 94% participated in lung cancer cooperative group trials.

Practice Patterns

Table 2 highlights the collective responses to the survey's practice pattern questions. Eighty-nine percent used endobronchial ultrasound (EBUS) and/or mediastinoscopy in addition to positron emission tomography (PET) scanning as part of the initial staging workup. One respondent did not treat any NSCLC ≥ 5 cm with SBRT. Among respondents, 55% most typically treated ≥ 5 cm NSCLC with 50 to 60 Gy in 5 fractions, with 18% using 48 to 54 Gy in 3 fractions, and 8% each preferring 48 to 50 Gy in 4 fractions, 60 Gy in 8 fractions, and 70 Gy in 10 fractions. Sixty percent of respondents would deliver fractions every other day, whereas 40% would deliver fractions daily.

Inverse planning with volumetric-modulated arc therapy (VMAT) was the preferred SBRT delivery technique for 63% of respondents, with the remainder generally split between inverse planning with fixed-beam intensity-modulated radiation therapy (IMRT), forward planning with dynamic arcs, and having no preference (11% each). Increasing patient age did not change dose and fractionation scheme for 94% of the surveyed population. Poor performance status, however, altered 23% of respondents' dosing and fractionation schemes. With poor performance status, 3 advocated 5-fraction regimens (45-50 Gy/5 fractions), 3 supported modestly hypofractionated schemes (60 Gy/20 fractions, 60 Gy/15 fractions, 50 Gy/10 fractions), and 2 supported palliative-type regimens (45 Gy/15 fractions, 30 Gy/10 fractions). Central tumor location altered treatment dosing/fractionation for 71% of respondents, with treatment modifications listed in **Table 3**.

Sixty percent of respondents recommended chemotherapy use in ≥ 5 cm NSCLC patients being definitively treated with SBRT, with 81% and 19% preferring chemotherapy administration following and prior to SBRT, respectively. The factors most commonly reported as leading to consideration of chemotherapy included good performance status (74%), larger tumor size (69%), and younger age (69%). The responses to several other pertinent clinical factors influencing chemotherapy use are recorded in **Table 2**. Twenty-six percent would consider chemotherapy if no pathologic mediastinal staging was performed, and 20% would consider chemotherapy if there was visceral pleural involvement or adenocarcinoma histology. Five respondents (14%) would not consider chemotherapy regardless of any of the above-mentioned factors.

Cases

The results of the surveyed clinicians' recommended dosing and fractionation schemes in 5 clinical cases are shown in **Table 4**. Respondents offered SBRT for all cases with the exception of 2 respondents who refrained from using SBRT in case 2, the case in which the largest tumor size (7.5 cm) was depicted.

Discussion

Although ≥ 5 cm NSCLC cases are relatively uncommon thoracic malignancies, there is no consensus recommendation for this patient population.[3] Additionally, in regard to the utility and efficacy of SBRT in large node-negative NSCLC, guidelines regarding dose and fractionation are lacking. As such, there is no consensus among providers regarding patient stratification and adjusting management accordingly based on various patient and tumor characteristics. Thus, our survey was designed to evaluate the diverse opinions of

Table 4. Clinical Cases (n = 35 Respondents)

Case	Respondents (Percent)
59 y/o patient, ECOG 1, with 5.0-cm poorly differentiated peripheral NSCLC, no nodes on PET, presenting for SBRT	
Dose (in Gy)/Fractionation Scheme (number of fractions)	
54-60/3	10 (28.6%)
48-50/4	7 (20.0%)
50-60/5	16 (45.7%)
60/8	0 (0.0%)
70/10	2 (5.7%)
60/15	0 (0.0%)
Conventional fractionation	0 (0.0%)
Other	0 (0.0%)
Frequency/Chemotherapy	
Fractions given daily WITH chemotherapy	4 (11.4%)
Fractions given every other day WITH chemotherapy	5 (14.3%)
Fractions given daily WITHOUT chemotherapy	11 (31.4%)
Fractions given every other day WITHOUT chemotherapy	15 (42.9%)
75 y/o patient, ECOG 0, with 7.5-cm well-differentiated peripheral NSCLC, no nodes on EBUS, presenting for SBRT	
Dose/Fractionation Scheme*	
54-60/3	1 (2.9%)
48-50/4	0 (0.0%)
50-60/5	16 (45.7%)
60/8	5 (14.3%)
70/10	1 (2.9%)
60/15	3 (8.6%)
Conventional fractionation	5 (14.3%)
Other (66/3, 60-72/4)	2 (5.7%)
No SBRT	2 (5.7%)
Frequency/Chemotherapy	
Fractions given daily WITH chemotherapy	9 (25.7%)
Fractions given every other day WITH chemotherapy	5 (14.3%)
Fractions given daily WITHOUT chemotherapy	8 (22.9%)
Fractions given every other day WITHOUT chemotherapy	13 (37.1%)
64 y/o patient, ECOG 1, with 5.6-cm poorly differentiated central NSCLC, no nodes on PET, presenting for SBRT	
Dose/Fractionation Scheme*	
54-60/3	0 (0.0%)
48-50/4	1 (2.9%)
50-60/5	22 (62.9%)
60/8	4 (11.4%)
70/10	1 (2.9%)
60/15	4 (11.4%)
Conventional fractionation	2 (5.7%)
Other (50/10)	1 (2.9%)
Frequency/Chemotherapy	
Fractions given daily WITH chemotherapy	5 (14.3%)
Fractions given every other day WITH chemotherapy	6 (17.1%)
Fractions given daily WITHOUT chemotherapy	15 (42.9%)
Fractions given every other day WITHOUT chemotherapy	9 (25.7%)

Table 4 continues on the next page

Table 4. Clinical Cases (n = 35 Respondents)

Continued from previous page

70 y/o patient, ECOG 2, with 5.4-cm poorly differentiated peripheral NSCLC with lymphovascular invasion, no nodes on mediastinoscopy, presenting for SBRT	
Dose/Fractionation Scheme*	
54-60/3	7 (20.0%)
48-50/4	5 (14.3%)
50-60/5	19 (54.3%)
60/8	0 (0.0%)
70/10	1 (2.9%)
60/15	2 (5.7%)
Conventional fractionation	0 (0.0%)
Other (34/1)	1 (2.9%)
Frequency/Chemotherapy	
Fractions given daily WITH chemotherapy	5 (14.3%)
Fractions given every other day WITH chemotherapy	2 (5.7%)
Fractions given daily WITHOUT chemotherapy	11 (31.4%)
Fractions given every other day WITHOUT chemotherapy	17 (48.6%)
62 y/o patient, ECOG 0, with 6.3-cm moderately differentiated central NSCLC, no nodes on EBUS, presenting for SBRT	
Dose/Fractionation Scheme*	
54-60/3	0 (0.0%)
48-50/4	1 (2.9%)
50-60/5	16 (45.7%)
60/8	5 (14.3%)
70/10	1 (2.9%)
60/15	5 (14.3%)
Conventional fractionation	4 (11.4%)
Other (70/2, 60/4, 70/10)	3 (8.6%)
Frequency/Chemotherapy	
Fractions given daily WITH chemotherapy	11 (31.4%)
Fractions given every other day WITH chemotherapy	4 (11.4%)
Fractions given daily WITHOUT chemotherapy	10 (28.6%)
Fractions given every other day WITHOUT chemotherapy	10 (28.6%)

*Percentages may not add to 100% due to rounding. Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; PET, positron emission tomography; SBRT, stereotactic body radiation therapy; EBUS, endobronchial ultrasonography.

U.S.-based academic practitioners. Furthermore, large-volume retrospective and prospective studies assessing optimal SBRT fractionation/timing, the role of chemotherapy, and the outcomes and toxicity of SBRT in this unique patient population did not exist when the survey was administered; however, a few recently published studies have begun to provide clinical data for this patient population.[16-20]

A vast majority (88%) of respondents preferred the addition of EBUS or mediastinoscopy in addition to PET scanning for staging, despite little evidence to support that lymph node sampling improves outcomes in stage I-IIIA NSCLC.[21,22] However, it must be recognized that large tumors, especially central ones, have notably higher risks of occult nodal involvement,[23] likely explaining why respondents preferred lymph node sampling in this higher risk patient population. Despite this increased risk, a recent multi-institutional retrospective analysis revealed no improvement in tumor control (local, regional and distant) or survival with the addition of mediastinal lymph node sampling.[24] Analysis to determine which subgroup(s) of patients with larger lesions that benefit the most from pathologic mediastinal evaluation is warranted.

The most common dosing and fractionation scheme among respondents was 50 to 60 Gy in 5 fractions (55%), which is consistent with the most commonly utilized regimens in recently published data.[16-18] Respondents also supported delivering treatments every other day (60%); however, there was considerable variation in this regard. Some studies have shown decreased toxicity with fractions delivered every other day, and that spacing out SBRT

treatments in other neoplasms can also reduce toxicities.[25,26] Decreased toxicity with every other day vs daily treatment has been reported for this patient population.[17] Moreover, inverse planning with VMAT was preferred (63%). This might reflect the recent increased use of VMAT and its advantage of reducing treatment times and potentially improving conformity of dose coverage. However, there are conflicting dosimetric data comparing IMRT and VMAT as means for SBRT delivery,[27-29] and the significance of dynamic motion effects during VMAT is currently not well defined for tumors ≥ 5 cm.[30]

Among age, performance status and central tumor location, the latter was most commonly associated (71%) with a change in management by the surveyed population. Of the 24 respondents who would change management, 11 (46%) switched from a classic SBRT scheme of ≤ 5 fractions to > 5 fractions. Given that prior reports of SBRT for lesions < 5 cm have demonstrated increased toxicity when treating centrally located lesions,[31] and that treating larger tumors presumably has higher risks of toxicities than smaller tumors, this finding of switching fractionation schemes for central tumors is not unanticipated. Higher rates of toxicities have been reported for central lesions;[16] however, more recent data suggest no toxicity differences based on tumor location.[18] Additional clinical outcomes data are needed to determine whether SBRT of larger tumors is associated with higher rates of toxicities than for < 5 cm tumors, and if toxicity rates are higher in central lesions despite more widespread adoption of modern SBRT techniques.

The addition of chemotherapy to SBRT was endorsed by 60% of respondents, of whom 81% preferred chemotherapy to be sequenced after SBRT. Despite this preference, only 2 studies have shown an overall survival (OS) improvement with the addition of adjuvant chemotherapy to SBRT.[32,33] In the current survey, chemotherapy was more commonly considered in patients with good performance status (74%), younger age (69%), and larger tumor size (69%). These characteristics highlight that the perceived ability to tolerate chemotherapy, rather than specific tumor characteristics, is a common guiding rationale behind recommending chemotherapy in this high-risk population. Interestingly, 74% and 57% of respondents chose not to offer chemotherapy in cases 1 and 5, which depicted younger patients with a good performance score. Regardless, with distant failure occurring in 19% to 33% of patients,[16-20] studies that assess the exact clinical benefit of adjuvant chemotherapy are greatly needed, and novel approaches of trialing SBRT and immunotherapy for this patient population may also prove beneficial.[34]

Responses to the 5 clinical cases further identified which clinical parameters altered SBRT treatment regimens and chemotherapy usage. SBRT regimens > 5 fractions were prescribed most commonly in case 5 (46%) and case 2 (40%), which presented a 6.2-cm central tumor and a 7.5-cm peripheral tumor, respectively. Regarding treatment timing, although 60% advocated this in the initial question, in no clinical case did > 60% of respondents endorse every other day fractionation. Administration of SBRT fractions every other day was highest in case 1 (57%), presenting a 5.0-cm peripheral tumor. In fact, the 2 cases with central disease showed the lowest proportion of respondents recommending every other day fractionation (43% and 40%), although these were least likely to receive 5-fraction regimens to begin with. Of note, a 3-fraction regimen was most common in case 1 (29%), a patient with a 5.0-cm peripheral tumor, and in case 4 (20%), a patient with a 5.4-cm peripheral tumor. Case 4 also displayed the lowest rate of chemotherapy administration (20%). In contrast, chemotherapy was recommended most commonly in case 5 (43%), which depicted a 62-year-old patient with good performance status and a 6.3-cm moderately differentiated central lesion. The responses to the cases differed from the generic practice patterns questions, clarifying that each treatment plan was indeed created on a case-by-case basis.

SBRT for large node-negative NSCLC has many challenges, notably increased risks of toxicities and poorer tumor control, but its efficacy and toxicity have been reported in several recent studies. Significant (grade ≥ 3) toxicities have been reported in 5% to 30% of patients, and local control rates of 85% to 95% are nearly comparable to SBRT data for smaller lesions.[16-20] Despite the efficacy and safety of SBRT for large NSCLC, toxicity minimization is of the utmost importance in this population. The use of proton therapy could be a promising alternative to photon-based SBRT, wherein physical properties of the heavier proton particle that limits irradiation to normal adjacent tissues may translate into reduced toxicities to organs at risk, as well as potentially allow for dose escalation to improve local control. Intensity-modulated proton therapy, although in limited use, could further reduce toxicities.[35-37]

Respiratory gating, which propagates radiation delivery only at designated phases of the respiratory cycle, most commonly at the end of expiration, can further reduce dose to OARs. Inverse plan optimization of gating using patient specific data (ie, 4-dimensional computed tomography [4D-CT] and individual breathing patterns), as compared to traditional gating methods, has been shown to significantly reduce irradiation doses to the heart, esophagus and spinal cord.[38] Lastly, increased use of PET imaging for radiation treatment planning[39] and improvements in MRI-guided SBRT may allow for better delineation of the tumor from healthy tissue, leading to sharper planning treatment volumes.[40]

Although this is the first survey of its kind assessing practice patterns for patients with large, node-negative non-small

cell lung cancer, there are several limitations to this work. First, analysis is based on a limited number of respondents (n = 36). We limited the survey to academic thoracic radiation oncologists who self-identified as specialists in lung cancer to target a study population of providers who are most experienced in treating large node-negative NSCLC with SBRT. Fortunately, we do note a considerably high response rate among the total population surveyed (34%). Additionally, participation bias likely exists, as providers with more experience treating large tumors may have been more likely to complete the survey. As such, our results may not be representative of the practice patterns of SBRT in this unique patient population among the radiation oncology workforce outside of U.S. academia. Also, as in all surveys, wording of questions and limited space to offer a comprehensive clinical vignette or response options provided in the survey may have inappropriately simplified the complex nature of treatment planning in this challenging patient population. For instance, to simplify the wording of the survey, we did not acquire each respondent's dose/fractionation SBRT scheme simultaneously with dosing frequency, as we did for the clinical cases, and we instead used 2 separate questions to obtain this information. Lastly, when we assessed for chemotherapy usage in the cases, it was presented in a binary manner, which may have influenced respondents to not choose chemotherapy if they could not also dictate when it would be administered in relation to SBRT.

Conclusion

There are no current recommendations regarding SBRT for ≥ 5 cm node-negative NSCLC. Most commonly, respondents advocated treatment with 50 to 60 Gy in 5 fractions using VMAT, with fractions delivered every other day. However, substantial variability existed across treatment parameters. Central tumor location prompted most respondents to adjust their SBRT management, with roughly half adopting a > 5 fraction regimen. Chemotherapy was recommended more often in patients with good performance status, younger age and larger tumor size.

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Supplemental Figure 1. Complete Survey Sent to Academic Thoracic Radiation Oncologists

DEMOGRAPHICS

1. What is your gender?
   a. Male
   b. Female

2. What is your age?
   _____

3. Which one of the following best describes your clinical/work experience since completing residency training?
   a. 0-5 years
   b. 6-10 years
   c. 11-20 years
   d. 21-30 years
   e. > 30 years

4. Please describe your current practice location.
   a. Urban
   b. Suburban
   c. Rural

5. In which geographic region do you practice?
   a. Northeast
   b. Midwest
   c. South
   d. West

6. How many radiation oncologists are in your practice?
   a. 1
   b. 2-9
   c. 10-25
   d. > 25

7. What percentage of your practice involves lung cancer patients?
   a. 0-25%
   b. 26-50%
   c. > 50%

8. Which one of the following best describes the number of TOTAL lung cancer cases you see per year?
   a. 0-30 cases/year
   b. 31-60 cases/year
   c. 61-90 cases/year
   d. > 90 cases/year

9. Which one of the following best describes the number of patients with whom you treat lung SBRT per year?
   a. 0-10 patients/year
   b. 11-25 patients/year
   c. 26-50 patients/year
   d. 50-75 patients/year
   e. >75 patients/year

10. Which one of the following best describes the number of cases of ≥ 5 cm NSCLC you treat with SBRT per year?
    a. 0 cases/year
    b. 1-2 cases/year
    c. 3-5 cases/year
    d. 6-10 cases/year
    e. > 10 cases/year

11. Do you participate in lung cancer cooperative group trials?
    a. Yes
    b. No

QUESTIONNAIRE

1. As part of workup for a patient with ≥ 5 cm NSCLC with negative mediastinal nodes on CT scan, which of the following would you recommend for mediastinal staging (if tolerated)?
   a. PET scan only
   b. EBUS and/or mediastinoscopy plus PET scan

2. What is the SBRT dose and fractionation scheme that you most typically prescribe for ≥ 5 cm NSCLC?
   _____ Gy in _____ fractions

3. Which of the following best describes your SBRT timing scheme of ≥ 5 cm NSCLC?
   a. Daily
   b. Every other day
   c. Other

4. Which of the following is your preference, if any, regarding technique of SBRT delivery in these patients?
   a. Fixed-beam 3D (forward planning)
   b. Fixed-beam IMRT (inverse planning)
   c. Dynamic arc therapy (forward planning)
   d. VMAT (inverse planning)
   e. No preference

Supplemental Figure 1 continues on the next page

Supplemental Figure 1. Complete Survey Sent to Academic Thoracic Radiation Oncologists

Continued from the previous page

5. Would increasing patient age lead you to change the dose/fractionation scheme?
   a. Yes
   b. No

6. If yes, what would be your preferred dose and fractionation for elderly patients?
   _____ Gy in _____ fractions

7. Would poor performance status lead you to change the dose/fractionation scheme?
   a. Yes
   b. No

8. If yes, what would be your preferred dose and fractionation for patients with poor performance status?
   _____ Gy in _____ fractions

9. Would a central location of the tumor lead you to change the dose/fractionation scheme?
   a. Yes
   b. No

10. If yes, what would be your preferred dose and fractionation for centrally located tumors?
    _____ Gy in _____ fractions

11. Would you advocate administration of chemotherapy for patients with ≥5 cm NSCLC being definitively treated with SBRT?
    a. Yes
    b. No

12. If yes, what would be your preferred timing of chemotherapy?
    a. Prior to SBRT
    b. After SBRT
    c. Concurrent with SBRT
    d. Concurrent with SBRT with additional chemotherapy prior to, or after, SBRT

13. Which factor(s) in ≥ 5 cm NSCLC patients would lead you to consider chemotherapy? Please select all that apply.
    a. Younger age
    b. Good performance status
    c. No pathologic mediastinal staging performed
    d. Larger size of tumor
    e. Central tumor location
    f. Poor tumor differentiation on biopsy
    g. Visceral pleural involvement
    h. Chest wall invasion
    i. Adenocarcinoma histology
    j. I would not consider chemotherapy in any of these circumstances.

CASES

1. 59 yo patient, ECOG 1, with 5.0 cm poorly-differentiated peripheral NSCLC, no nodes on PET, presenting for SBRT.
   I would prescribe _____ Gy in _____ fractions given _____ and _____ chemotherapy.

2. 75 yo patient, ECOG 0, with 7.5 cm well-differentiated peripheral NSCLC, no nodes on EBUS, presenting for SBRT.
   I would prescribe _____ Gy in _____ fractions given _____ and _____ chemotherapy.

3. 64 yo patient, ECOG 1, with 5.6 cm poorly-differentiated central NSCLC, no nodes on PET, presenting for SBRT.
   I would prescribe _____ Gy in _____ fractions given _____ and _____ chemotherapy.

4. 70 yo patient, ECOG 2, with 5.4 cm poorly-differentiated peripheral NSCLC with lymphovascular invasion, no nodes on mediastinoscopy, presenting for SBRT.
   I would prescribe _____ Gy in _____ fractions given _____ and _____ chemotherapy.

5. 62 yo patient, ECOG 0, with 6.3 cm moderately-differentiated central NSCLC, no nodes on EBUS, presenting for SBRT.
   I would prescribe _____ Gy in _____ fractions given _____ and _____ chemotherapy.

Patient education in radiation oncology: Evolution and innovation

Nadia Saeed, BA

Patient education is a dynamic and evolving area of medicine, with important applications for patient care, compliance, and comprehension of health information. Improving patients' understanding of treatment nuances and intricacies can, in turn, potentially boost their adherence to treatment**.** There is also a significant emotional dimension to patient education, particularly in alleviating stress, uncertainty, and fear associated with treatment.[1] Patient education is also critical in encouraging active patient participation and shared decision-making.[2] Moreover, the role of patient education has become increasingly critical in the context of medicine's paradigm shift in decision-making, in which patients take a more active role in treatment decisions. Thus, adequate knowledge and an understanding of treatment complexities are necessary to ensure effective patient participation in this decision-making process.[3]

Radiation oncology is a particularly complex treatment modality, encompassing several components and extensive care coordination between different professionals.[4] Many patients present at first consultation with little knowledge and understanding of the role of radiation treatment in multimodal cancer therapy.[4] Moreover, misconceptions exist regarding radiation—including the belief that radiation causes, rather than treats, cancer—providing an additional role for education in this field.[5] Features of radiation treatment considered significant for incorporating into patient education material include technical information about radiation, side effects of treatment, emotional dimensions and self-care, follow-up, and design and implementation of a wellness plan.[6] Furthermore, adequate knowledge and understanding of radiation treatment is critical for effective patient participation in decision-making. In particular, information about the benefits and potential long-term side effects of radiation is considered essential for making well-informed decisions regarding treatment. Patient education is a vector to deliver such information, ultimately empowering patients to take an active role in their care.[7,8] This article will discuss the evolution of patient education in radiation oncology, examining education tools and practices, as well as new innovations and future directions.

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Background

In determining the most effective methods and tools for patient education in radiation oncology, one must consider how patients best learn. Attention to learning theories of education is helpful in this regard (**Figure 1**). The major traditional learning theories include constructivism, which emphasizes the construction of meaning from experience; cognitivism, which focuses on the acquisition and organization of information into internal mental structures; and behaviorism, which considers learning to be an observable change in frequency of behavior.[9] From a behaviorist perspective, patients will have exhibited adequate learning when they demonstrate changed patterns of behavior. In the context of radiation, this can be seen through changes in patient behaviors such as improved management of treatment side effects (eg, consistent use of a vaginal dilator in pelvic radiation), or greater adherence to treatment recommendations (eg, bladder or bowel emptying prior to daily radiation). The cognitivist theory of learning can help us understand how patients acquire and assimilate information presented through educational tools into their existing cognitive structures.

Moreover, newer theories of learning continue to emerge, including models that consider the growing influence of technology in people's lives. In particular, the cognitive theory of multimedia learning explains how people learn from words and pictures through information processing using two channels—one for verbal and one for pictorial material.[10] In this model, effective learning consists of proper cognitive processing, which includes attention to relevant information and organizing such information into a coherent cognitive structure. This also requires

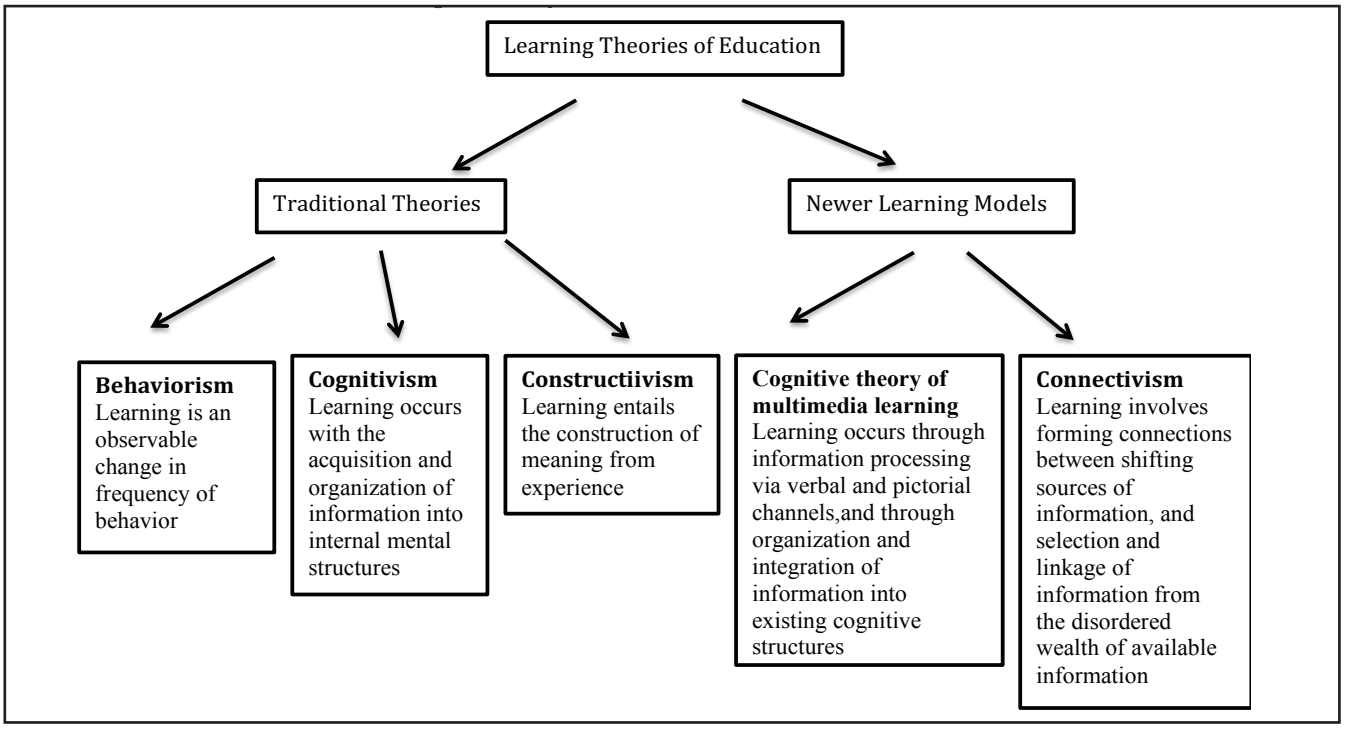

FIGURE 1. *Learning theories of education*

activating long-term memory by integrating new information with existing knowledge. Given the trend in radiation oncology toward more engaging patient educational tools that employ increasing visual components, this theory has significant applications to the design and implementation of patient education tools. In addition, online sources of information, including web pages and social media forums, are an emerging and increasingly significant form of patient education tools, as will be discussed. A newer learning theory of education—connectivism, which focuses on integrating knowledge and forming connections between shifting and evolving sources of information—helps one understand how these tools can shape learning.[11] Selecting and linking information into a network from the expansive, complex, and disordered wealth of information from which to draw—the *connection* of knowledge—is a key concept in this theory. In the context of patient education, this theory helps us understand how patients can learn from, and ultimately integrate information between, multiple and dynamic sources of information, some of which are nonhuman.

Patient education can also serve as a sign of quality care. The Centers for Medicare & Medicaid services (CMS) implement guidelines to ensure its recipients receive quality health care, defined by efficacy, safety, efficiency, patient-centeredness, equitability, and timeliness.[12] "Health Promotion and Education" is among the CMS-mandated quality metrics. Moreover, several other CMS quality care measures also incorporate education, such as through preventive health education, education for in-hospital stays, and discharge instructions, further highlighting its critical role in quality care. In radiation oncology, patient education can have important implications in defining high-quality care. It can serve as one indicator of provider time spent with the patient and the degree of patient-centeredness of a clinic visit. Furthermore, the use of educational tools in a clinical setting can be standardized with instruction to provide an objective criterion for equitable physician-patient communication. Robinson et al reviewed characteristics and measures of patient-centered care, reporting patient education, patient involvement in care, shared decision-making, and communication as critical components.[13] They found patient-centered interactions to be associated with increased adherence to treatment and physician recommendations, as well as improved health outcomes. Patient education also plays an important role in patient safety.[14]

Tools and Practices

Different forms of patient education tools have been utilized in the clinical setting, with varying degrees of efficacy in radiation therapy (**Table 1**). In addition to direct verbal education from providers, earlier tools have included pamphlets and printed materials. However, educational materials soon evolved to incorporate different modalities, engaging patients more actively and providing information more

Table 1. Tools and Practices in Patient Education for Radiation Oncology

Author, Year	Number of Patients (N)	Study Objective	Method/Intervention	Outcome
Hagopian, 1996[15]	75	Evaluate effect of informational audiotape in side-effect management in radiation patients	Intervention group – standard of care + informational audiotapes Control group – facility standard of care	Experimental group demonstrated more knowledge about radiation and side effects and improved self-care behaviors
Hahn et al, 2005[16]	53	Assess efficacy of educational video in meeting informational needs in radiation patients	All subjects completed baseline questionnaire, viewed educational video, and completed post-test (assessing patient satisfaction, emotional response, and opinion on intervention relevance)	Video rated as "highly relevant" by 77% of patients Subjects ≥ 58 yrs rated video more relevant than subjects < 58 years (55% vs 27%, p = 0.04) Subjects ≥ 58 yrs demonstrated more satisfaction with side effect information in video than subjects < 58 years (78% vs 41%, p = 0.006)
Laszewski et al, 2016[17]	58	Determine media preferences of patients receiving educational intervention on radiation dermatitis prevention (verbal, written, video)	All patients received education on skin care for preventing radiation dermatitis with verbal, video, and written methods before simulation. Reinforcement at weeks 1 and 3 of treatment, at which time patients could choose which modality they preferred for reinforcement.	Most patients chose verbal and video instruction over written instruction at both reinforcement time points
Rainey, 1985[1]	60	Assess the effects of preparatory education audiovisual program for patients undergoing radiation	Intervention group – viewed audiovisual program featuring procedural and sensory information about radiation prior to treatment Control group – standard of care without audiovisual program	Intervention group displayed significantly higher treatment-related knowledge at the beginning of treatment and significantly less emotional distress at the end of treatment
Dunn et al, 2004[18]	92	Assess effect of educational video on psychological stress, knowledge, and self-efficacy in patients undergoing radiation	Intervention group – viewed educational video about radiation therapy Control group – did not view radiation video Patients assessed with pre-test and post-test	No significant differences on any outcome variable between controls and intervention group High levels of satisfaction reported by the intervention group, despite lack of significant difference in outcomes
Dawdy, 2016[19]	60	Assess effect of multimedia education tools on CT planning preparation for patients undergoing intensity-modulated radiation therapy (IMRT) for prostate cancer	Controlled, randomized experimental group study Experimental group – received educational video and pamphlet discussing preparation for prostate IMRT Control group –received education pamphlet only	No statistically significant differences in patient preparedness or rescanning rate between experimental and control group Experimental group reported feeling more prepared after watching video

effectively. For example, a study assessing the potential benefit of educational audiotapes in patients undergoing radiation found that audiotapes discussing radiation treatment and the management of side effects resulted in improvements across several outcome measures compared to the facility's standard of care. These included demonstrated knowledge of radiation and its potential side effects, and the use of more beneficial self-care practices.[15]

With the regular use of computers during the patient visit, education videos became, and remain, a popular and effective tool for providing information about radiation treatment and improving patient comprehension. The use of these videos in a clinical setting has been associated with high patient satisfaction. For example, a prospective study evaluating the efficacy of an educational video in 53 radiation oncology patients reported that 77% of participants found the video to be highly relevant, and more than 90% were highly satisfied with video information describing simulation and radiation treatment.[16] Additionally, older patients reported greater satisfaction with the video compared to younger patients, indicating a potential additional benefit to audiovisual forms of education in this patient population. Many patients may prefer audiovisual education materials compared to verbal and/or written materials as well. In an analysis of patient preference for educational reinforcement concerning radiation dermatitis, Laszewski et al found that patients prefer video education tools and verbal reinforcement compared to written materials.[17] Moreover, some studies have found that audiovisual aids are more successful in helping patients better understand the complexities of radiation treatment compared to verbal and/or written materials alone. In a study by Rainey et al, patients who viewed an audiovisual program featuring procedural and sensory information about radiation prior to treatment displayed significantly higher treatment-related knowledge at the beginning of treatment, and significantly less emotional distress at the end, compared to patients who received standard of care without the audiovisual program.[1] Their results also highlight the critical emotional role of education in alleviating fear and uncertainty patients feel in anticipation of treatment.

It should be noted, however, that the literature is mixed regarding the efficacy of videos over more traditional forms of patient education materials in terms of improved objective response measures. Some studies have found that even when patients report satisfaction with videos, they may fail to show significantly increased knowledge or modification of behaviors targeted by the education materials than patients who receive pamphlets and handouts alone.[18,19] Nevertheless, given that the majority of these studies found significantly higher patient satisfaction and feelings of preparedness for treatment, there are clear benefits to audiovisual modality use even in the absence of strictly "educational" improvements—especially in the context of anxiety and uncertainty associated with radiation treatment.

Considering Online Sources of Information

In addition to educational resources presented in the clinical setting, patients now have access to a wealth of online information about radiation. A 2001 multi-institutional study assessing internet utilization by patients receiving radiation found that 42% of patients presenting at academic centers and 29% of patients presenting at community centers used the internet to find information about cancer, with 62% of patients treated at academic centers owning a computer in the home.[20] Additionally, a survey study evaluating the impact of media and internet on oncology patients and providers in Canada found that 50% of patients actively search for information related to their illness using the internet; additionally, access to the internet was one predictor of higher rates of information seeking. These percentages have likely increased substantially in recent years with the growing number of patients with direct internet and computer access.

There are clear benefits to patient internet use—particularly, in supplementing educational materials presented in clinic with additional information that cannot be provided during a short doctor's appointment. However, there are also concerns regarding the accuracy of online information, as well as patients' ability to understand and interpret such information as it relates to their illness and care. In Chen and Siu's analysis, most oncologists believe that patients have difficulty interpreting online medical information accurately.[21] YouTube has become a popular platform to access free educational and instructional videos in a variety of areas; medical treatment topics, including radiation therapy, are no exception. Prabhu et al assessed the quality of brachytherapy educational videos on YouTube by comparing the video content with respect to information provided in the brachytherapy informed consent guidelines.[22] Only 3.6% of videos met standards, while half were below standards. Moreover, only half of the videos were uploaded to the site by physicians, hospitals, or private practices. Given how frequently these videos were viewed (median views were 4482.5, with a range of 212 to 415 007), there is a critical need to ensure the accuracy and comprehensiveness of content in these easily accessible patient education tools.

It is important to note that a significant limitation of radiation oncology patient education materials involves the readability and complexity of terminology used, particularly in online materials.[23] An

evaluation published in 2016 of patient education materials from the websites of the American Society for Radiation Oncology (ASTRO), American Association of Physicists in Medicine (AAPM), American Brachytherapy Society (ABS), RadiologyInfo.org, and Radiation Therapy Oncology Group (RTOG) found nearly all articles to be written at an education level higher than that recommended by the National Institutes of Health (NIH) and American Medical Association (AMA).[24] The majority of the information in these materials, therefore, may not be fully understood by patients who read them.

New Innovations and Future Directions

New directions in patient education for radiation attempt to bypass the need for patients to conceptualize complex medical jargon and instead provide a virtual, 3-dimensional (3D) experience. Innovative multimodal patient education tools are being increasingly explored as new options for improving understanding and engaging patients undergoing radiation therapy (**Table 2**). This realm uses technology to engage a generation of patients with access to a host of devices and platforms, including virtual reality, social media and apps. In particular, interest is rapidly expanding in the use of virtual reality to foster understanding of complex aspects of radiation therapy and visualizing radiation treatment, which remains nebulous and difficult for many patients to picture.[25]

Williams et al demonstrated the potential benefits of incorporating 3D visualization into radiation oncology patient education tools.[26] In their survey analysis, patients were shown a video about the treatment process that included real footage and 3D animations before receiving their first fraction. The majority of patients (98%) found the video useful in meeting informational needs, and a third of patients reviewed the videos again, mostly to help explain radiation therapy to family/friends, indicating a potential use for visualization tools to expand education beyond the patient.

The 3D visualization applications of patient education have expanded to immerse patients in a full virtual reality system. The Virtual Environment for Radiotherapy Training system (VERT) is a simulation tool that utilizes virtual reality to help train radiation therapy practitioners; however, it has recently been used for patient education applications in several studies.[27] Jimenez et al studied VERT as part of an education program for breast cancer patients, which included content on radiation immobilization, computed tomography (CT) simulation, treatment planning, and treatment delivery.[27] The authors found high levels of patient satisfaction with the 3D features of VERT and with program comprehensiveness, highlighting the benefit of visualization in the tools used to convey information about radiation. Flockton also found benefits associated with VERT for patient education purposes.[28] In a study of patients with prostate cancer, VERT was used to simulate the delivery of radiation to the prostate, and to visually demonstrate the importance of a full bladder and empty rectum consistently during treatment. Participants found that VERT helped them better understand radiation therapy (including its technologies) and visualize the treatment process, ultimately improving feelings of preparedness for treatment. The patients also reported that VERT helped them better understand why a full bladder and empty rectum are required for treatment. This latter finding also highlights the significant implications that emerging patient education tools have for patient compliance in radiation oncology.[28]

The use of VERT also has important applications for better addressing the emotional dimensions of undergoing radiation therapy. Visual familiarity with the treatment process prior to receiving the first fraction can better prepare patients for what to expect, reducing fear of the unknown and anxiety associated with treatment. These benefits have already been demonstrated in studies using 3D visualization and/or VERT. In Williams et al's study, nearly half of all patients reported feeling less anxious and scared about treatment after watching the video with 3D animation.[26] Marquess et al found that in patients with prostate cancer who participated in VERT, anxiety significantly decreased, specifically about the in-treatment experience, daily x-rays, radiation dose to the prostate, movement of the accelerator close to the patient, and regarding overall treatment precision.[29]

Social media and apps are also potential innovative vehicles for patient education in radiation oncology, harnessing the growing influence of technology in everyday lives. For example, Twitter has been shown to be effective in providing education and support to patients with breast cancer.[30] In 206 patients with breast cancer who participated in the Breast Cancer Social Media Twitter support community, the majority of patients reported increased overall knowledge about breast cancer, metastatic disease, research and clinical trials, treatment options, imaging, radiation oncology, and more. Moreover, participation in this social media support group not only increased knowledge, but also changed behaviors and follow-up actions. For example, 31.2% of patients sought a second opinion or presented additional information to their providers following participation, while 71.9% stated they would now engage in outreach and advocacy for breast cancer. Moreover, 67% of patients reported decreased anxiety after participation, highlighting the emotional impact of social media tools in radiation oncology.

Apps have also been evaluated in the context of symptom management during radiation treatment, with potential applications for pre-treatment education. Langius-Eklof et al had patients under-

going radiation for prostate cancer report information about their symptoms daily using the Interaktor.[31] Most of the patients consistently used the app, describing it as easy to use. Given today's widespread app use and the apparent feasibility of treatment-related applications, apps can potentially enhance patient education in radiation oncology.

Contextual Considerations

It is important to note that these emerging education tools may not be the most suitable option for all patients. Age, among many factors, plays an important role. For example, in elderly patients perhaps less familiar with the technologies and online platforms of newer education tools, more traditional materials and methods may be more effective. Clotfelter reported successful outcomes with an educational video and accompanying booklet aimed at improving pain management in elderly patients with cancer.[32] Patients who received the educational intervention had significantly lower cancer pain intensity compared to controls. Similarly, Jewitt et al assessed the efficacy of an educational pamphlet on stereotactic body radiation therapy (SBRT) for elderly patients with lung cancer.[33] The pamphlet, specifically designed for elderly patients, was considered effective by 86% of the patients. Importantly, most of these patients preferred verbal or written forms of education materials (65% and 78%, respectively), to online information or educational classes. Moreover, attention must be given to the cognitive challenges in elderly cancer patients, which can be further compounded by chemotherapy-induced memory impairment and can impact treatment compliance.[34] Educational tools that also consider the cognitive capacities of the patient are ideal.

Age is not the only factor affecting the dynamics of patient education interventions. A variety of social, contextual, and cultural factors play a significant role in shaping the responses to patient education tools. These include culture, race, education, and health literacy, among others.

Illness, and its treatment, is a culturally embedded experience; priorities and expectations of care are shaped by patients' cultural values.[35] Provider-patient communication, including that involved in educational interventions, must take into account a patient's cultural background. One important component of these cultural dynamics is language barriers, which can pose significant challenges to health information accessibility. Inability to fully understand education materials has important implications for treatment compliance (a frequent target of patient education interventions) and patient satisfaction.[35,36] This is especially critical in a field such as radiation oncology, in which treatment is complex and patients, regardless of cultural background, often are unfamiliar with radiation therapy. Multimedia tools in different languages may aid intervention in this regard. For example, Valdez et al evaluated the efficacy of an education intervention for Latina women with cervical cancer using interactive, multimedia kiosks.[37] Patients who received the intervention demonstrated significantly improved knowledge about cervical cancer. Attention to cultural factors should be considered when designing education materials for patients undergoing radiation.

Race is another important factor in provider-patient communication, with implications for the development of and response to educational materials for patients.[38] Communication factors resulting in inadequate access to health information and lack of shared decision-making play a significant role in unequal health outcomes among racial group.[39] Evidence suggests that comprehensive interventions may be necessary to ensure greater equitability in communications and education across racial groups. Anderson et al conducted a pain education intervention in minority patients with cancer, using a culture-specific video and booklet.[40] However, there were no significant differences in quality of life, perceived pain control, or functional status between groups that did and did not receive the intervention, suggesting that more comprehensive educational interventions may be required to significantly change outcomes.

Education level and literacy are also important considerations when designing educational tools. Low health literacy has been significantly associated with poorer health outcomes.[41] Ensuring educational materials are accessible and understandable for patients with low health literacy is critical, particularly in radiation oncology, which requires strict adherence to daily treatment. Limiting educational objectives, focusing on behaviors, and presenting context initially can increase education material accessibility for patients with low health literacy.[42] In addition, the use of audiovisual aids may be particularly important in this patient population by engaging multiple senses in learning.

Conclusion

Radiation oncology remains one of the more misunderstood treatment modalities in cancer care. Many patients know much less about radiation than chemotherapy or surgery, and many have difficulties in comprehending the more complex aspects of treatment. Thus, there is a particularly significant role for patient education in this field, improving knowledge and comprehension, and potentially improving behaviors related to treatment. There is also a significant emotional dimension to patient education, which has the potential to alleviate anxiety, uncertainty, and fear associated with treatment. Traditional education materials have included pamphlets and other written materials; however, audiovisual materials such as videos have been associated with greater patient satisfaction. New considerations have emerged in the Internet Era with patients having widespread access to

a wealth of online education resources, many of which are not reviewed and approved by medical providers. Many of these resources are also written at a level beyond that recommended by the NIH and AMA. New tools in patient education attempt to bypass these issues by directly immersing the patient in a 3D virtual reality experience using VERT, helping patients better visualize the treatment process and understand the more complex aspects of radiation therapy at a visceral level. Future directions in patient education for radiation oncology are likely to continue exploring applications of innovative tools and technologies such as VERT, as well as social media platforms, to improve patient education.

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Stereotactic body radiation therapy for breast cancer: Benefits, challenges and choices

Mary Beth Massat

Ongoing advances in the diagnosis and treatment of breast cancer have prompted a sharp decline in breast cancer mortality rates. Indeed, in October 2017, the American Cancer Society reported a 39% drop in these rates between 1989 and 2015 for women over 50. That's 322,600 lives saved in 26 years.[1]

Today, women have multiple treatment choices for breast cancer—from traditional surgery, chemotherapy and radiation therapy, to newer options in immunotherapy and targeted therapy. Yet, even conventional therapies are undergoing changes as researchers and clinicians investigate emerging technologies such as stereotactic body radiation therapy (SBRT).

One of the largest SBRT practices in the United States is at NYU Winthrop Hospital in Mineola, New York, under the direction of Jonathan A. Haas, MD, chairman, Department of Radiation Oncology. In 2011, Dr. Haas launched a study, which obtained internal review board (IRB) approval, to evaluate the treatment of early stage breast cancer with SBRT. He collaborated with Sandra S. Vermeulen, MD, executive director of the Swedish Radiosurgery Center at Swedish Medical Center, Seattle, Washington, and together they treated 65 breast cancer patients with the CyberKnife (Accuray, Sunnyvale, California) (**Figure 1**).

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Dr. Haas presented their data at ASTRO 2017 in San Diego, and reported a 98% control rate at the 5-year follow-up. "That's better than any other adjuvant treatment for breast cancer that's out there," he says, acknowledging that although one patient relapsed, it was in a different quadrant of her breast and possibly a different cancer.

His treatment protocol in the study is based on accelerated partial breast irradiation (APBI) guidelines by the Radiation Therapy Oncology Group (RTOG). Patient eligibility and selection is a critical component, consisting of women with a tumor < 3 cm, margins negative by > 2 mm, a surgical cavity distance of 5 to 7 cm from the skin line, no positive lymph nodes, and exclusion of patients with invasive lobular carcinoma.

"Compared to other accelerated partial breast treatments, the major advantage of SBRT is not inserting a catheter into the breast for treatment," Dr. Haas says. "As long as there is proper patient selection, I don't think there are any disadvantages for patients. It is less invasive, more comfortable and more convenient. Compared to 4 to 6 weeks of daily treatment for whole-breast radiation therapy, this is only 5 treatment days, which is a huge benefit for our patients."

In general, SBRT also is a more precise way to deliver radiation therapy, says Steven Feigenberg, MD, professor and vice chair of clinical research, and chief of thoracic radiation oncology at the Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine. In conventional radiation therapy planning, a margin of 5 to 10 mm is added to the target to account for intrafractional and interfractional setup uncertainties; however, SBRT typically can reduce those margins to 1 to 2 mm.

Dr. Feigenberg explains that SBRT in the United States typically involves 1 to 5 treatments, depending on tumor size and proximity to surrounding normal tissues. While most breast SBRT is performed following surgery, a group at Duke University School of Medicine led by Janet K. Horton, MD, has

FIGURE 1. *The Accuray CyberKnife*

examined preoperative single-fraction APBI in a phase 1 study.[2] The authors reported that the therapy was well tolerated and should continue clinical trial testing as it may also enable identification of radiation response biomarkers. Currently, they are accruing patients in a phase II study.

"A very interesting aspect of preoperative radiation therapy is the potential for improvement in cosmesis as compared to conventional 3-dimensional (3D) APBI," Dr. Feigenberg says. "The key to the benefits of preoperative therapy is the substantial reduction in normal breast being radiated, which theoretically improves cosmesis; makes more people eligible for 3D APBI; and decreases dose to all surrounding normal structures, reducing the morbidity of therapy."

SBRT is also a treatment that patients want, says Elizabeth Nichols, MD, assistant professor of radiation oncology, and clinical director of the Department of Radiation Oncology, University of Maryland School of Medicine (UMSOM). In addition to decreased toxicity to surrounding tissue and enhanced patient convenience with fewer treatments, SBRT may be more cost-effective for a health system.

"For every day that we deliver radiation therapy, there is a cost associated with that," Dr. Nichols explains. "Therapies with a longer course of treatment will cost more. However, we also believe there is the potential for decreased side effects with SBRT compared to whole-breast irradiation, so downstream there are potentially fewer costs."

Current Challenges

A significant hurdle to providing SBRT for breast cancer is lack of reimbursement—a key reason Dr. Haas opened his study. As the data matures and SBRT is viewed as safe and effective for early stage breast cancer—as well as more convenient and potentially more cost-effective—he is hopeful insurers will initiate coverage.

Dr. Nichols also notes that Medicare does not cover breast SBRT, due in part to a mismatch between what clinicians and insurers label as SBRT. "SBRT is a high dose per fraction, in just a few fractions, using image guidance with a very sharp dose gradient outside the tumor and in the surrounding tissue," she explains. Since breast SBRT is new and evolving, insurers may not be aware of the treatment efficacy and patient outcomes data from recent and ongoing clinical studies.

It would also be helpful for any type of SBRT procedure to have a real-time tumor tracking system, says Dr. Feigenberg. "A system that could do the tracking with a marker *inside* the tumor in real-time *during* treatment is the holy grail," he says. While several techniques use surrogate markers and rely on surface imaging to monitor tumor movement, they are not 100%, he adds.

Plus, placement of surrogate markers for image guidance can be difficult, says Dr. Haas. If these are inserted during a lumpectomy, the surgeon must place them in a way that facilitates their imaging. One of Dr. Haas' radiation therapists, Lauren Boone, devised a method to place the markers during computed tomography (CT) simulation in a 10-minute outpatient procedure with no anesthesia. The procedure has worked remarkably well at NYU Winthrop, says Dr. Haas, who has taught it to other physicians.

Also promising is real-time imaging with magnetic resonance (MR)-guided radiation therapy systems, notes Dr. Feigenberg. "It's not just doing volumetric imaging with cone-beam CT, which was a big improvement for visualizing the tumor before and after treatment, but having 3D image guidance *during* treatment," he says. "It's a very interesting development, especially to see exactly what dose is delivered."

Studies in the Works

Although Dr. Haas has not yet conducted a clinical trial that escalates the dose— "It's hard to argue with a 98% success rate," he says—his department will participate in a study with UT Southwestern Medical Center and Asal Rahimi, MD, MS, director of clinical research, to examine single-fraction SBRT treatment intraoperatively. After lumpectomy, eligible patients will be enrolled to evaluate a single 20 to 30 Gy dose delivered to the surgical cavity. While Dr. Haas is admittedly not a fan of delivering treatment without knowing the final pathology, "the data supports it as effective, and we know it can be done safely in intraoperative therapy." He adds that continued clinical studies of SBRT will likely examine further acceleration of the treatment regimen. In fact, Dr. Rahimi and colleagues recently published results of a phase 1 dose escalation trial for early stage breast cancer using 40 Gy in 5 fractions.[3] The results demonstrated minimal toxicity and invasiveness, and excellent local control rates and cosmesis.

At UMSOM, Dr. Nichols participated in a clinical study for preoperative partial breast radiation that used standard APBI dose fractionation. Results demonstrated a 15% pathologic complete response—meaning there was no viable cancer left behind or no cancer at all.[4] Other research in Europe found a similar 15% to 20% pathologic

FIGURE 2. *The Elekta Versa HD system*

complete response using nonablative doses of radiation.[5]

"Between those two studies, we think something is there that requires further investigation," Dr. Nichols says. "We can't make the direct jump from SBRT to no surgery, so one of our clinical trials is to deliver ablative doses of radiation followed by surgery with the hope that we can see similar results." The next step would be a trial examining SBRT without surgery.

Dr. Feigenberg is equally excited about the potential to successfully treat breast cancer with SBRT and avoid surgery. He notes that nearly all data comparing whole-breast with partial-breast radiation show no difference in local control except for trials that tested intraoperative radiation therapy. Specifically, two randomized trials had higher local failure rates of 3 to 10 times, suggesting that the target treated with intraoperative approaches may be suboptimal.[6,7] These higher failure rates open the window to using preoperative radiation to better cover the optimal target.[8]

However, as Dutta et al point out in their review of intraoperative radiation therapy—the TARGIT-A (Targeted Intraoperative Radiation Therapy) and the ELIOT trials that both reported higher rates of recurrence in the same breast—a major limitation was the lack of image guidance, resulting in the inability to document dose to the lumpectomy cavity and adjacent structures.[9]

TheTechnology Behind Breast SBRT

Several radiation therapy systems are available for breast SBRT. With the CyberKnife, the beam can be delivered from many different angles (noncoplanar treatment), minimizing dose to other parts of the body. "It is robotic and intelligent, with two imagers that track the movement of four fiducial markers placed around the cavity," says Dr. Haas. It also has a respiratory tracking system using leads placed on the chest and stomach, enabling accuracy of < 1 mm in tracking movement.

"CyberKnife remains the only robotic delivery system that detects submillimetric changes in the patient and target position, and automatically adjusts the aim of the linac to account for them throughout the treatment session," says Fabienne Hirigoyenberry-Lanson, PhD, vice president of Accuray's Global Medical and Scientific Affairs. "Coupled with by-design noncoplanar delivery of linac beams, the CyberKnife can deliver highly conformal beams with incredible accuracy." The result of this accuracy has reduced margins and dose to surrounding normal tissue.

Dr. Hirigoyenberry-Lanson adds that there are increased concerns regarding treating very low risk, small and localized lesions, and whether such lesions should even be treated. "This situation puts a premium on treatments that are noninvasive and have the last chance of altering a patient's quality of life. The CyberKnife system can, in most cases, deliver such a treatment."

The Versa HD system (Elekta, Stockholm, Sweden) (**Figure 2**) delivers highly conformal doses in hypofractionated settings in standard treatment slots and, according to John Christodouleas, MD, vice president of Elekta's Medical Affairs and Clinical Research, offers advantages in mitigating motion-related inaccuracies and increasing patient comfort by lessening on-table time.

"The large imaging and treatment field of view of Versa HD enables accurate and efficient treatment of more advanced indications where the lymphatic system needs to also be treated in addition to the primary target," says Dr. Christodouleas. Versa HD is also integrated with the company's Active Breathing Coordinator (ABC), which provides automated gating. This helps patients pause breathing at a specific tidal volume to maximize distance between the tumor and adjacent critical structures.

Addressing the growing awareness for integrating MRI into radiation therapy, Elekta's MR-linac, which is pending FDA approval, has the potential to address the movement of breast tissue as the patient breathes during the treatment cycle. Dr. Christodouleas explains that it integrates precision radiation dosing via a state-of-the-art linear accelerator with

FIGURE 3. The GammaPod by Xcision Medical Systems

imaging from a high-field, 1.5T MRI without compromising either system.

"It is the first system to achieve the technological feat of simultaneous radiation delivery and fast acquisition of high-quality, high-field MR images, providing the ability to 'see what you treat' during treatment and respond based on what is being seen," Dr. Christodouleas adds. In addition to the potential to provide precise tumor targeting and real-time adaptive treatments that may improve margin and fraction regimens, the MR-linac may enable a reduction in both the field size for treatment of nodes and the size of the boost field for treating the primary tumor.

Fresh off its clearance by the Food and Drug Administration (FDA) in December 2017, GammaPod (Xcision Medical Systems, Columbia, Maryland) (**Figure 3**) is designed specifically for SBRT treatments of the breast. Both Drs. Nichols and Feigenberg were involved in the clinical trial used in the FDA submission, as well as in evaluating dosimetric improvements of the device comparing APBI delivered by brachytherapy or intensity-modulated radiation therapy (IMRT).[10,11] With GammaPod, they demonstrated a substantial decrease in dose to the skin, and less heterogeneity of dose compared to brachytherapy, theoretically increasing patient eligibility for noninvasive treatment with a better side effect profile.

GammaPod delivers more conformal doses of radiation in less time, says Steve Rubenstein, vice president of marketing for Xcision. "GammaPod provides the first stereotactic radiotherapy system that has been optimized to noninvasively deliver a dose distribution to a target within the breast," he says. "We are unaware of other technologies that can noninvasively deliver conformal dose distributions with sharp falloff using a stereotactic localization and immobilization system for the breast. With highly conformal dose distributions, GammaPod treatments can lower dose to the heart, lungs and surrounding healthy breast tissue."

Unique to GammaPod is its noninvasive breast cup system that provides a secure immobilization to minimize motion during treatment and is imbedded with a fiducial wire for stereotactic target localization. Additionally, it delivers highly conformal dose distribution using dynamic dose painting.

"During treatment, the radiation sources and collimators rotate to deliver radiation from thousands of beam angles," Rubenstein explains. "An intense focal dose is created at the point where the beams converge. By moving the patient table during treatment along a dynamically traveling path, the target volume passes in and out of the focal spot so the dose is painted to the target."

Patients are imaged and treated with identical 3D setup geometry, adds Rubenstein, and all treatments are performed in the prone position, which has been shown to limit dose to the heart and lungs.

A look ahead

Xcision has established a consortium of academic institutions to lead the evidence development process, Rubenstein says. The group consists of the University of Maryland School of Medicine in Baltimore; UT Southwestern Medical Center in Dallas; Allegheny General Hospital in Pittsburgh; and The Ottawa Hospital in Ontario, Canada.

Dr. Christodouleas says that while hybrid CT-MR planning is more rapidly being used for precision breast treatments, "without having the same imaging horsepower available to assess anatomy at the time of treatment, it becomes more difficult to develop more aggressive treatments."

Elekta's MR-linac consortium of 12 centers features a research infrastructure in which physicians can develop a new breast SBRT paradigm that "adapts its target and total dose based on biologic responses assessed on quantitative MR

sequences, such as diffusion-weighted imaging (DWI)," he adds.

Birgit Fleurent, chief marketing officer at Accuray, points out that ASTRO, through its Choosing Wisely initiative, has recognized that, "equivalent tumor control and cosmetic outcome in specific patient populations can be achieved with shorter courses of therapy (approximately 4 weeks) vs 'conventionally fractionated' schedules delivered over 5 to 6 weeks, often followed by 1 to 2 weeks of boost therapy. Investigators at leading academic hospitals researching CyberKnife SBRT, following lumpectomy, are also seeing similar tumor control and cosmetic outcomes vs conventional therapy, but over the course of only 1 to 2 weeks."

With advanced technology such as Versa HD, CyberKnife, GammaPod and the potential for real-time MR-guided treatments, along with numerous clinical studies delivering data to guide treatment decisions, SBRT is emerging as a promising option for breast cancer treatment.

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RADIATION ONCOLOGY CASE

Esophageal adenocarcinoma presenting as gynecomastia

Chris Moser, BS; Steven H. Stokes, MD

CASE SUMMARY

Gynecomastia, enlargement of the male breast, is a common condition that affects infants, adolescents and middle-aged to older men. Of the latter group, the highest prevalence occurs in men aged 50-80, with as many as 24% to 65% being affected.[1]

Ectopic production of immunoreactive human chorionic gonadotropin (beta-hCG) has reportedly been found in a variety of nontrophoblastic neoplasms including large cell carcinomas of the lung, gastric carcinoma, renal cell carcinoma and hepatomas. We report an unusual case of a gonadotropin-producing sarcomatoid adenocarcinoma of the esophagus that manifested as gynecomastia.

A 69-year-old man presented to his primary care physician in December 2016 for evaluation of bilateral tender gynecomastia without any history of breast mass or injury. Examination did not show any focal masses. There was no history of dysphagia, weight loss or other constitutional symptoms, and no history of testicular swelling, pain or masses.

Mr. Moser *is a fourth-year medical student, and* ***Dr. Stokes*** *is a radiation oncologist, Southeast Alabama Medical Center, Dothan, AL.* *Disclosure: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.*

A testicular examination and ultrasound revealed no anatomic abnormalities. Prostate examination was normal. A thorough lab workup for gynecomastia revealed a beta-hCG level of 3520. The patient underwent a computed tomography (CT) scan of the chest, abdomen and pelvis, and distal esophageal wall thickening was seen along with adjacent adenopathy. A subsequent esophagogastroduodenoscopy (EGD) revealed Barrett's esophagus with an ulcerated lesion at the gastroesophageal junction. Biopsy of the lesion showed poorly differentiated adenocarcinoma with sarcomatoid features. Tumor cells were positive for cytokeratin-7 (CK7), pan keratin, and p40, and negative for CK5/6 and HER2. F-18 fluorodeoxyglucose (FDG) demonstrated paratracheal and paraesophageal lymph node involvement, a 1.3-cm left lower lobe metastasis, and a right upper lobe metastasis too small to characterize (**Figure 1**).

As there was no dysphagia, the patient underwent 4 cycles of cytotoxic chemotherapy with 5-fluorouracil and Cisplatin for his stage IV cancer. After 4 cycles of chemotherapy, follow-up positron emission tomography (PET) showed continued growth of the esophageal and lung lesions, and his beta-hCG had increased to 16 397. During chemotherapy the patient developed erythema and watering in his right eye, and was diagnosed with uveitis. He attempted a trial of steroids but did not improve. He underwent a fine-needle aspiration of his right eye in April, which showed atypical glandular cells, confirming metastases of the adenocarcinoma to his eye. A magnetic resonance imaging (MRI) exam of the brain was performed to rule out brain metastases and pituitary involvement and showed normal brain tissue, but areas of decreased signal in the right frontal and left parietal bones; these findings were not seen on CT or PET studies. He received laser cyclophotocoagulation, intraocular Avastin, and palliative radiation of 3060 cGy, which improved symptoms but caused blurred vision. This was appropriately correctable with a contact lens. A repeat EGD was performed, which demonstrated persistence of the nearly obstructing tumor. His chemotherapeutic regimen was switched to FOLFIRI (FOL = Leucovorin Calcium [Folinic Acid]; F = Fluorouracil; IRI = Irinotecan Hydrochloride) and he elected to undergo palliative radiation of his esophageal tumor. His beta-

FIGURE 1. *F-18 fluorodeoxyglucose (FDG) demonstrated paratracheal and paraesophageal lymph node involvement, a 1.3-cm left lower lobe metastasis, and a right upper lobe metastasis too small to characterize.*

hCG subsequently improved to 2031, but a follow-up PET-CT after the cycle showed progressive worsening of his pulmonary metastases. He was then started on Cyramza and Paclitaxel. His right eye became progressively painful and he elected to undergo enucleation in November, which revealed a recurrence of the cancer in his eye.

A sample of a lung lesion was taken and sent for genomic studies. At this time, the patient had developed progressively worsening dyspnea and his beta-hCG had regressed to 9490. He developed a malignant pleural effusion and received a pleural tube. The genomic studies showed amplification of ERBB2, BRCA1 rearrangement of intron 19 and tumor mutation burden of 16 muts/MB. The patient elected to undergo treatment with Pembrolizumab, but died a week following initiation of treatment, one year following his initial presentation.

DISCUSSION

This is an unusual manifestation of a paraneoplastic syndrome resulting from an esophageal sarcomatoid adenocarcinoma. Gynecomastia as the presenting symptom of this tumor type has not been reported in the literature. This case has unique features in both the initial presentation and the presence of ocular metastases. Histologic reports of beta-hCG producing Barrett's adenocarcinomas of the esophagus have been reported,[2] as well as gonadotropin-producing adenocarcinomas of the pancreas, stomach and prostate. Elevated levels of beta-hCG are usually a sign of aggressive disease and are strongly associated with a poor prognosis. Elevated beta-hCG production in some adenocarcinomas has been shown to increase expression of vascular endothelial growth factor and may contribute to the aggressiveness of these tumors. Elevated levels of beta-hCG can be observed in 45% to 60% of patients with biliary and pancreatic cancer[3] and 18% of gastric carcinomas. The prognosis of metastatic esophageal cancer in any form is poor and carries a 5-year relative survival rate of 4.5%.[4] A case of gonadotropin-secreting esophageal carcinoma containing an unusual histologic combination of adenocarcinoma and choriocarcinoma was also reported.[5] The patient in that case developed gynecomastia as well, but metastatic spread involved the choriocarcinoma and ultimately contributed to his demise.

CONCLUSION

There are very few reported cases of esophageal carcinoma with metastasis to the orbit. Survival rates have varied across studies, with mean survival time ranging 7.4 months to 1.3 years.[6] Metastases account for 7% of orbital tumors, with the breast and prostate as the most common primary sites.

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RADIATION ONCOLOGY CASE

Concomitant hyperthermia and intensity-modulated radiation therapy for a large-field chest wall re-irradiation

Zi Ouyang, PhD; Ping Xia, PhD; Nicky Vassil, BS; Kevin J. Yu; Jennifer S. Yu, MD, PhD

CASE SUMMARY

For patients with breast cancer, chest wall radiation therapy (RT) reduces the risk of local recurrence after surgery.[1] But even with adjuvant RT, 5% to 15% of the patients develop locoregional recurrences,[2] which are often inoperable and may cause significant problems such as bleeding, pain, ulceration, brachial plexopathy or arm edema, if untreated.[3,4] Hyperthermia (HT), a potent radiosensitizer, has been used along with RT for the treatment of locoregional recurrent breast cancer. A review and meta-analysis was published on 34 studies on HT-RT in locoregional recurrent breast cancers.[5] The complete response (CR) rate increased from 38% with RT alone to 60.1% with HT-RT. In a re-irradiation (ReRT) setting, single-arm studies reported a CR rate of 66.6% with a mean ReRT dose of 36.7 Gy (range, 29.4 to 50.5 Gy), delivered at an average dose per fraction of 2.7 Gy (range, 2 to 4 Gy).[5]

Treatment planning for chest wall RT and ReRT is challenging due to complex target geometry and large variations in target volumes. Over the past two decades, different radiation treatment techniques have been developed to address this issue,[1,6-10] including the use of wide tangential beams, mixed photon and electron beams, electron-beam-only technology, fixed-gantry intensity-modulated beams (static IMRT), and volumetric-modulated arc beams (VMAT).[11-14]

In this report, we describe a static IMRT treatment planning technique for a large-field recurrent chest wall irradiation with concurrent hyperthermia.

Dr. Ouyang *is a physics resident,* ***Dr. Xia*** *is head of medical physics,* ***Ms. Vasil*** *is a dosimetrist, and* ***Dr. Jennifer Yu*** *is a radiation oncologist, all at Cleveland Clinic, Cleveland, OH.* ***Mr. Kevin Yu*** *is a student at Johns Hopkins University, Baltimore, MD.*

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METHODS AND MATERIALS

The patient was diagnosed at age 38 with stage III (at least cT3N1) moderately differentiated invasive ductal carcinoma (ER/PR/HER2+) of the right breast. After neoadjuvant chemotherapy with dose-dense doxorubicin and cyclophosphamide followed by docetaxel, the patient underwent a double mastectomy with reconstructions (ypT3, yN1mic, M0). In her initial radiation treatment, the patient received 50 Gy in 25 fractions to the right chest wall, 46 Gy in 23 fractions in the supraclavicular and axillary regions, and 10 Gy in 5 fractions to the scar. The patient completed 1 year on trastuzumab. She then underwent oophorectomy and completed 5 years on anastrozole. At age 44, the patient presented with a chest wall recurrence with widely metastatic disease involving her liver, retroperitoneal lymph nodes, brain and bones. To manage her metastatic disease, she received whole-brain RT (30 Gy in 10 fractions) and systemic treatment with pertuzumab, trastuzumab

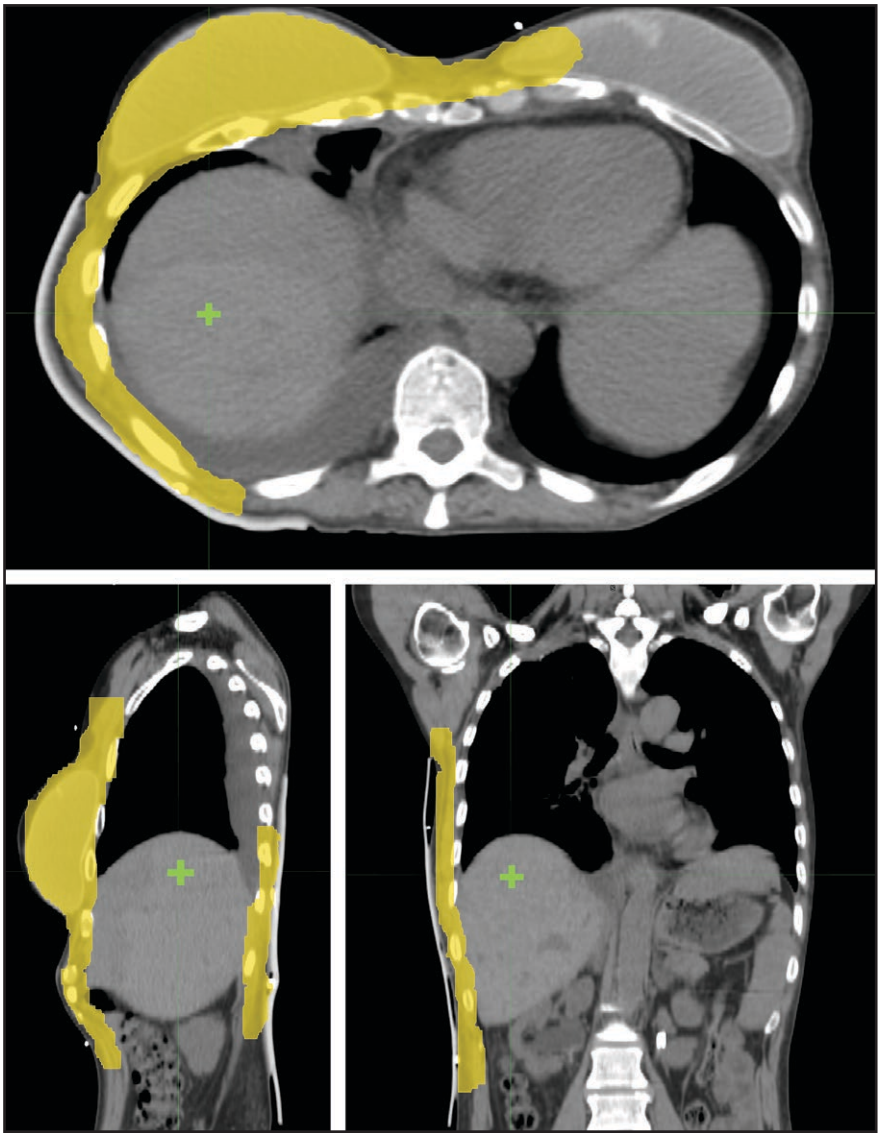

FIGURE 1. *Simulation computed tomography (CT) images at the isocenter slice. Planning target volume (PTV) is highlighted in yellow. The green cross marks the isocenter.*

and docetaxel. She responded well to systemic treatment and had only minimal disease in her visceral organs, but the chest wall recurrence continued to progress. She was then referred for palliative thermoradiotherapy to her chest wall disease. At this point, her right chest wall disease extended superiorly to the clavicle, laterally wrapped around her side to her back, and inferiorly involved the skin overlying her upper abdomen. Her IMRT radiation plan is described in this report. While she was receiving hyperthermia and radiation to her right chest wall, she developed an isolated recurrence in her left chest wall, which was treated with a separate electron field. During thermoradiotherapy, she stopped taking docetaxel, but continued with pertuzumab and trastuzumab.

IMRT TREATMENT PLANNING

Considering the large target volume and toxicity, the patient was prescribed with 46 Gy in 23 fractions for ReRT along with HT twice a week based on previous publications.[15] The planning target volume (PTV) included the right breast and chest wall with a total volume of 1711.42 cm^3 (**Figure 1**). Step-and-shoot IMRT was planned on an ARTISTE machine (Siemens Medical Solutions, Malvern, Pennsylvania) using Pinnacle^3 treatment planning system R9.6 (Philips, Andover, Massachusetts). As shown in **Figure 1**, the isocenter was placed at the right lobe of the liver. Nine 6-MV photon beams were set up at angles from 30° to 190° with 25° spacing in between (**Figure 2**). A 5-mm bolus was wrapped around the right side of the patient to ensure superficial target coverage.

The plan was optimized using the direct machine parameter optimization (DMPO) method with final optimization objectives listed in **Table 1**. For the Max equivalent uniform dose (EUD), the parameter *a* was set to 1, making the EUD equivalent to the target mean dose. The plan was done in a "warm start" fashion, meaning the planning objectives were added and adjusted in multiple trials without resetting beams in between. In **Table 1**, "Ring" represented a planning tuning structure, created by expanding the PTV by 1 cm and then subtracting the expansion from the external/patient body. The "5000 Hot Spot" represents a structure converted from the isodose line of 5000 cGy.

To cover the large field sizes and achieve an adequate level of intensity modulation, jaws were allowed to move during the treatment. The beams had 7 to 11 segments each, and **Figure 3** is an example beam's eye view with 6 segments (gantry angle 215° shown).

RESULTS

The plan had a total of 999 MUs per fraction with a delivery time (beam on time) of 25 minutes. As shown in the dose-volume histograms of the plan (**Figure 4**), volume of the PTV receiving the prescription dose was 95.65%.

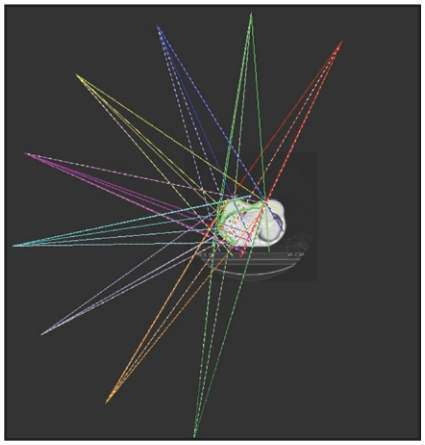

FIGURE 2. *Beam set-up for the large-field breast/chest wall intensity-modulated radiation therapy (IMRT) plan.*

Table 1. Final Planning Objectives with the Corresponding Weights

ROI	Objective Type	Dose (cGy)	% Volume	Weight (0–100)
PTV	Min Dose	4600		50
PTV	Uniform Dose	4600		75
Right Kidney	Max EUD	1000		5
PTV	Max Dose	5200		100
Lung	Max DVH	2000	25	10
Left Kidney	Max EUD	1000		0.5
Ring	Max Dose	2300		1
Right Kidney	Max Dose	2200		1
Right Lung	Max DVH	2000	35	90
5000 Hot Spot	Max Dose	4600		5
Liver	Max EUD	2000		20

Key: ROI = region of interest, PTV = planning target volume, EUD = equivalent uniform dose, DVH = dose-volume histogram

Table 2 summarizes the dosimetric endpoints to the critical structures, and **Figure 5** shows the isodose distributions.

Measures of homogeneity and conformity can differ in the literature.[15] In this report, the homogeneity index (*HI*) is calculated as follows,

$$HI = \frac{D_{\max(0.03cc)}}{D_{Rx}},$$

where, $D_{max(0.03cc)}$ is the maximum dose to a 0.03 cm^3 voxel, and D_{Rx} is the prescription dose. Based on this equation, the dose is calculated to be more homogeneous as the *HI* approaches 1.

To assess the plan conformity, the concept of conformity index (*CI*) was used:

$$CI = \frac{V_{Rx}}{TV}.$$

Here, *TV* is the target volume, V_{Rx} is the volume that receives the prescription dose. A *CI* close to 1 indicates good plan conformity. In this plan, the *HI* and *CI* for the PTV were calculated to be 1.12 and 1.09, respectively.

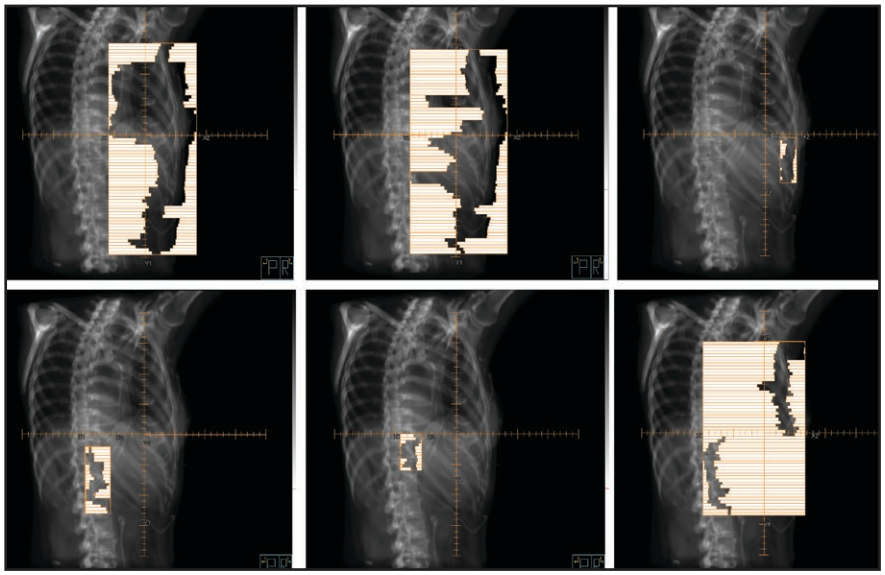

FIGURE 3. *Beam's eye views at gantry angle 215°.*

DISCUSSION

Treatment planning for chest wall ReRT, especially with a large-volume irradiation, can be challenging. Similar challenges exist in treatment planning for bilateral breast cancer and chest wall irradiation with the internal mammary nodal (IMN) involvement. Bechham et al reported their treatment planning technique using multiple static IMRT fields to treat the left breast and IMN with 50 Gy in 25 fractions.[11] Using a different treatment planning system from what we used in this report (Eclipse, Varian, Palo Alto, California), they found that 9 to 11 equally spaced IMRT beams within a 190° span were sufficient, resulting in better dose sparing of the heart and lung. They reported that the average V_{30Gy} to the heart was 1.7%, and V_{20Gy} to the left lung was 17.1%, compared to 12.5% to the heart and 26.6% to the left lung from the standard 3-dimensional (3D) plans. As a result of using multiple IMRT fields, however, more healthy tissue received low doses.

Kaidar-Person et al[16] described their clinical experience of using helical tomotherapy in 9 patients with bilateral breast cancer with regional nodal involvement. The prescription dose to breasts/chest wall ranged from 40 to 60 Gy. They reported that the average V_{20Gy} to both lungs was 29% and average mean dose to the heart

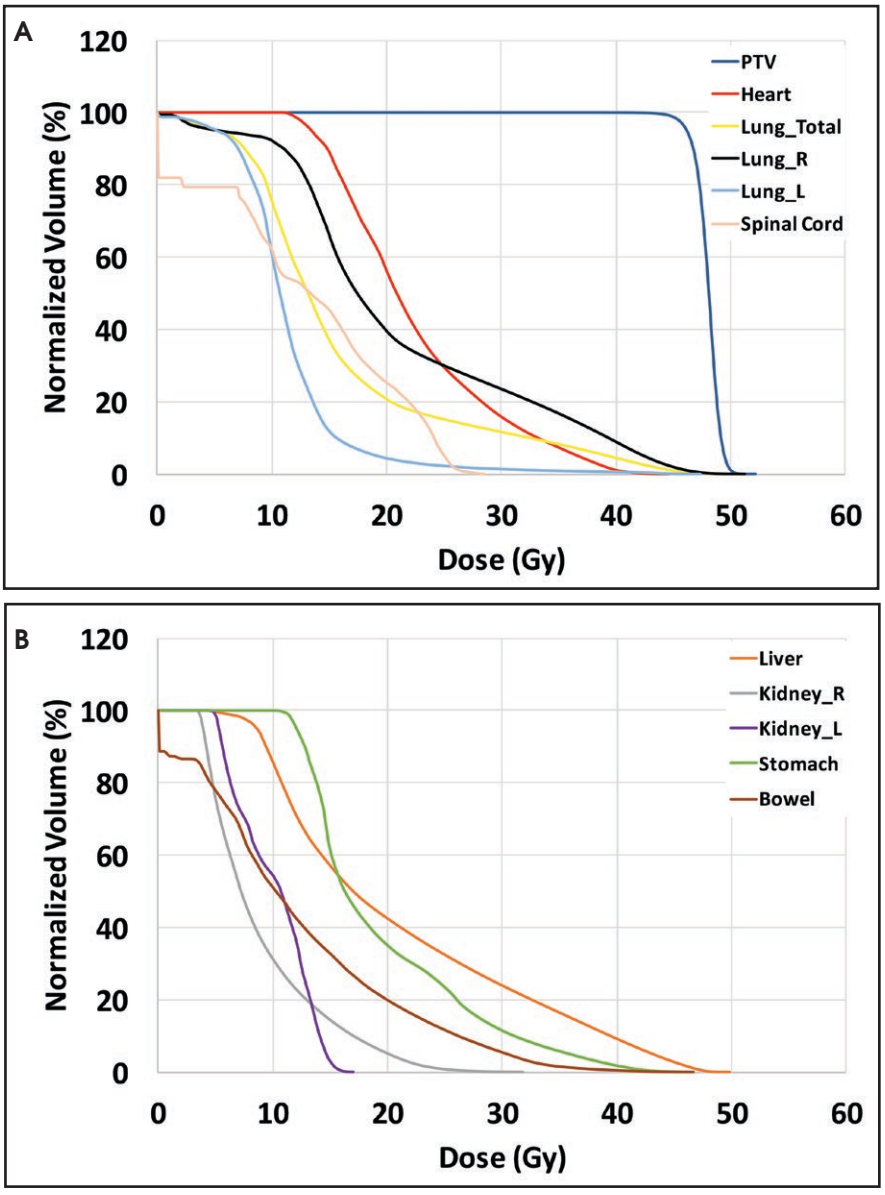

FIGURE 4. *Dose volume histograms (DVHs) of the planning target volume (PTV) and organs at risk (OARs) are listed in (A) and (B); 95% of the PTV is covered by the prescription dose.*

was 20 Gy. Clinically, they reported acute toxicity during radiation, including dysphagia (5/9), fatigue (4/9), nausea and weight loss (1/9), and skin desquamation (9/9). The authors speculated that these observed acute toxicities were likely related to the relatively high volume of normal tissue irradiated. Thus, they recommended conventional 3D techniques (such as bilateral tangents, matching electron fields) prior to the initiation of IMRT/VMAT/tomotherapy.

Dumane et al[17] recently reported on a case of using VMAT (50.4 Gy) for a left-side chest wall and regional nodal radiation, comparing the partially wide tangents technique (PWT) and the mixed photon and electron technique to the VMAT technique. Using the PWT plan, the mean heart dose was 13.6 Gy and the ipsilateral lung

Table 2. Dosimetric Evaluation of the Critical Structures

ROI	Endpoint
Heart	V_{30Gy} = 15.85%
Heart	D_{mean} = 22.41 Gy
Total Lung	V_{20Gy} = 20.64%
Total Lung	D_{mean} = 15.92 Gy
Liver	D_{mean} = 20.93 Gy
Total Kidney	D_{mean} = 9.58 Gy
Total Kidney	V_{20Gy} = 2.22%
Spinal Cord	D_{max} = 28.48 Gy
Bowel	D_{max} = 46.59 Gy
Bowel	D_{1cc} = 42.4 Gy
Stomach	D_{max} = 46.67 Gy

Key: ROI = region of interest

V_{20Gy} was 56.9%. Using the mixed photon and electron plans (20:80 or 30:70 photons to electrons), the mean heart dose was 12.1 to 12.4 Gy and the ipsilateral lung V_{20Gy} was 56.8% to 60.8%. Using the VMAT plan with 2 partial arcs of range 210° (from 300° to 150°), the mean heart dose was 6.4 Gy and the ipsilateral lung V_{20Gy} was 27.2%. Similar to Bechham's study,[11] Dumane et al reported that the volume of the total lung receiving low dose increased; in particular, V_{5Gy} to the contralateral lung increased from 0% to 15.8%.

Kirova et al[18] reported on a postmastectomy conformal electron-beam radiation therapy technique. In this technique, the chest wall and IMN were included in 1 electron field at a gantry angle of 20° to 30° from the vertical, with a prescription dose of 50 Gy and a photon boost up to 5 Gy to the IMN. Different bolus thicknesses were used to achieve adequate penetration and dose homogeneity. As reported by the same group,[6] for over 700 patients treated with this technique, the 5-year locoregional recurrence-free survival and overall survival were both over 90% with minimal short and long-term toxicity.

HT is a well-established radiosensitizer, which provides dosimetric advantages especially in ReRT settings. A published randomized trial[19]

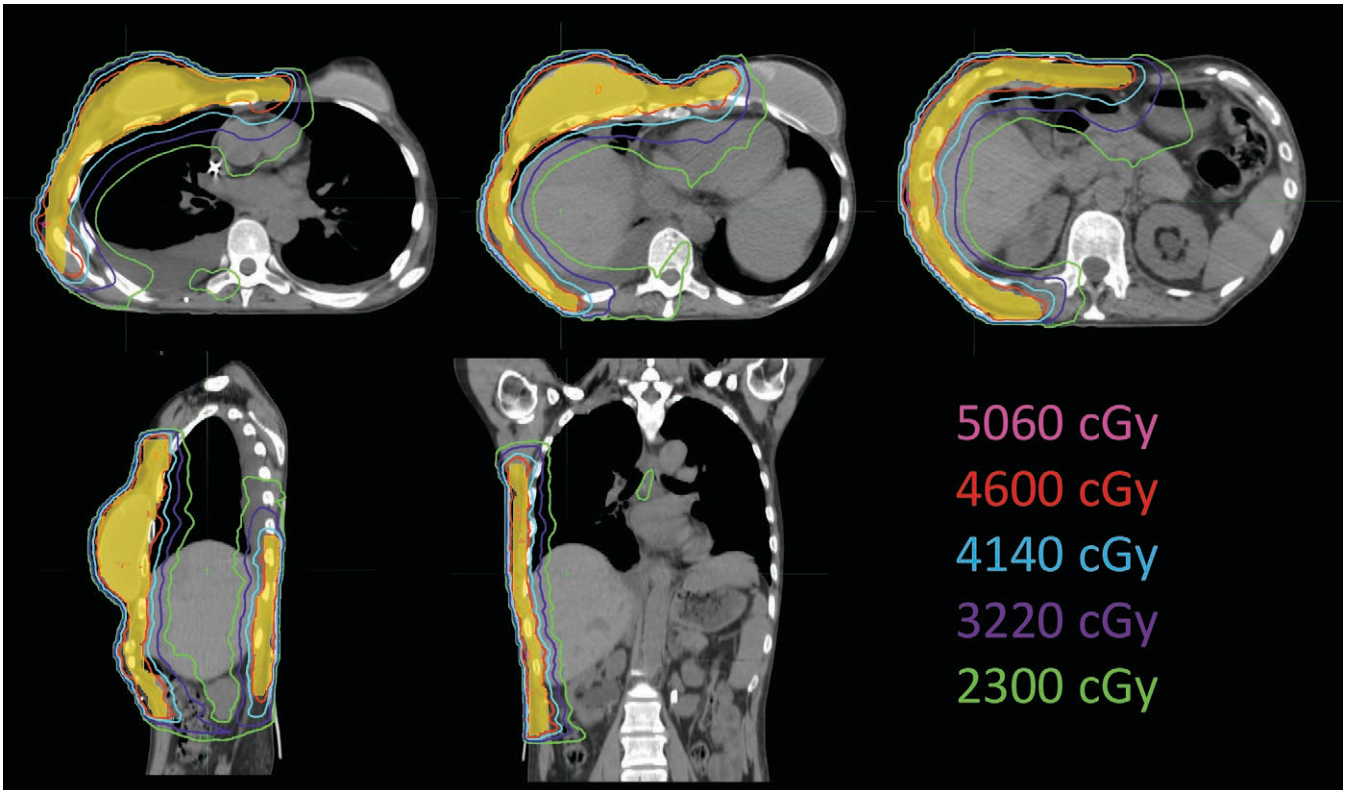

FIGURE 5. *Isodose distributions in the axial, sagittal and coronal views. Planning target volume (PTV) is highlighted in yellow; 110%, 100%, 90%, 70% and 50% isodose lines are displayed.*

showed that with a median dose of 41 Gy (range, 18 to 66 Gy) for patients with prior RT to superficial tumors, CR was 68% and 24% for HT and non-HT arms, respectively. Given the radiosensitization of HT, a lower prescription dose (46 Gy in 23 fractions) compared to other studies was prescribed for the patient described in this report. In our institute, hyperfractionation (1.2 Gy, twice a day-BID) is considered as an option to decrease side effects for patients who had bad reactions to their first course of RT. However, the benefits of hyperfractionated concurrent HT-RT are not clinically proven. For most patients, BID treatments are not practical. Therefore, as seen in this case, conventional fractionation is more common.

Unlike the typical volumes in chest wall and regional node irradiation, target volumes for recurrences in the chest wall are more irregular and variable. As shown in **Figure 1**, the target volume for this patient on the right side wrapped around her chest wall to the posterior, inferiorly extended beyond the kidney, and laterally crossed the median sternum. We used the electron beam to treat the isolated recurrence on the left chest wall. The more extensive tumor volume on the right chest wall was treated with 9 step-and-shoot IMRT fields concurrent with hyperthermia to boost tumor radiosensitivity. Dosimetrically, V_{30Gy} of the heart was 15.85% and the mean dose to heart was 22.41 Gy. V_{20Gy} of the total lung was 20.64% and the mean dose to the total lung was 15.92 Gy. For this patient, the main dose-limiting organ at risk (OAR) was the lung, along with other organs such the liver, kidney, stomach, small bowel and heart. According to the Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC) summary,[20] mean dose to the heart < 26 Gy and V_{30Gy} < 46% are associated with < 15% pericarditis, and mean dose to the lung < 20 Gy and V_{20Gy} < 30% are associated with < 20% symptomatic pneumonitis. The plan follows these recommendations to minimize acute heart and lung toxicity.

In this case, it was not practical to use matching electrons or tangential photon beams due to the large target volume. For this patient, we used the ARTISTE, a Siemens linear accelerator, for its large field size (40-by-40-cm modulated field) and 0.5-cm multileaf width. Similar static IMRT techniques can be applied to Varian and Elekta (Stockholm, Sweden) linear accelerators. Despite the VMAT capability on Varian and Elekta treatment machines, we believe that the static IMRT technique has advantages over VMAT technique for the following reasons. For this patient, the maximum tumor dimension projected from some beam angles exceeded the

maximum field width for non-TrueBeam Varian machines (29 cm width and 40 cm length). With the lower jaw (x jaw) fixed on 29 cm, a part of the tumor volume was only exposed to certain beams but not all beams. Therefore, static IMRT technique enhances the flexibility for optimization, increasing beam intensity modulations and beam weights for those beams that can encompass the entire tumor volume. Without jaw tracking capability on the non-TrueBeam Varian machines, the jaws for the VMAT plan remain open to the largest field size for the arc beams, increasing leakage from the MLC. When planning for large tumor volumes, even with Varian TrueBeam machines, we frequently encounter problems with the 15-cm distance limit between the MLC leaf separation from the same leaf bank, on the carriage motion limit. Moreover, the current implementation of VMAT delivery only allows 1 segment per beam angle, which requires a large arc length to increase the intensity modulation for a VMAT plan. For this patient, using a full arc could further increase the total lung dose and heart dose. For these reasons, static IMRT was preferred to VMAT despite possible extended treatment times/length.

FOLLOW-UP

The patient tolerated her hyperthermia and radiation well. She developed acute grade II radiation dermatitis that was treated with conservative measures. She had a complete response to hyperthermia and radiation within the treated area. She resumed hormone therapy. Six months after her hyperthermia and ReRT, she developed new dermal metastases outside of the irradiated area. She also progressed systemically and, therefore, went on to chemotherapy. She was ultimately enrolled in hospice care 2 years later.

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