APPLIED RADIATION ONCOLOGY™
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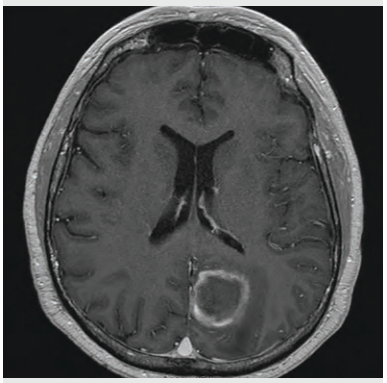
SA-CME CREDIT

The safety and efficacy of combined immunotherapy and radiation therapy
S Manjunath, JE Shabason, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA

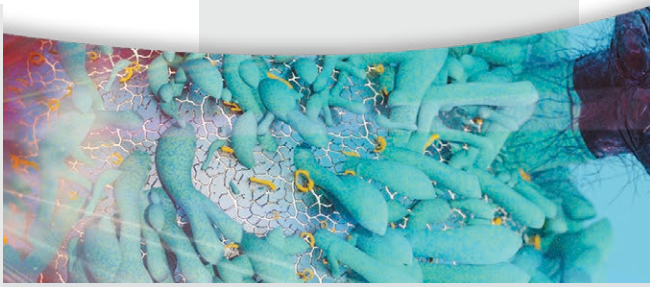
Combining immunotherapy with radiation therapy to induce the abscopal effect: What variables matter?
J Liu, Penn State College of Medicine, Hershey, PA; HB Mackley, Penn State Milton S. Hershey Medical Center, Hershey, PA

Initial report of a simulation-based medical education curriculum for radiation therapy planning
MK Rooney, College of Medicine, University of Illinois at Chicago; JM Melotek, CJ Stepaniak, SJ Chmura, DW Golden, University of Chicago, IL

Distribution of dedicated stereotactic radiosurgery systems in the United States
MK Dean, AA Ahmed, P Johnson, N Elsayyad, University of Miami Sylvester Comprehensive Cancer Center and Jackson Memorial Hospital, Miami, FL



Radiation Oncology Case
Scalp seeding after resection and stereotactic radiosurgery for solid tumor brain metastases



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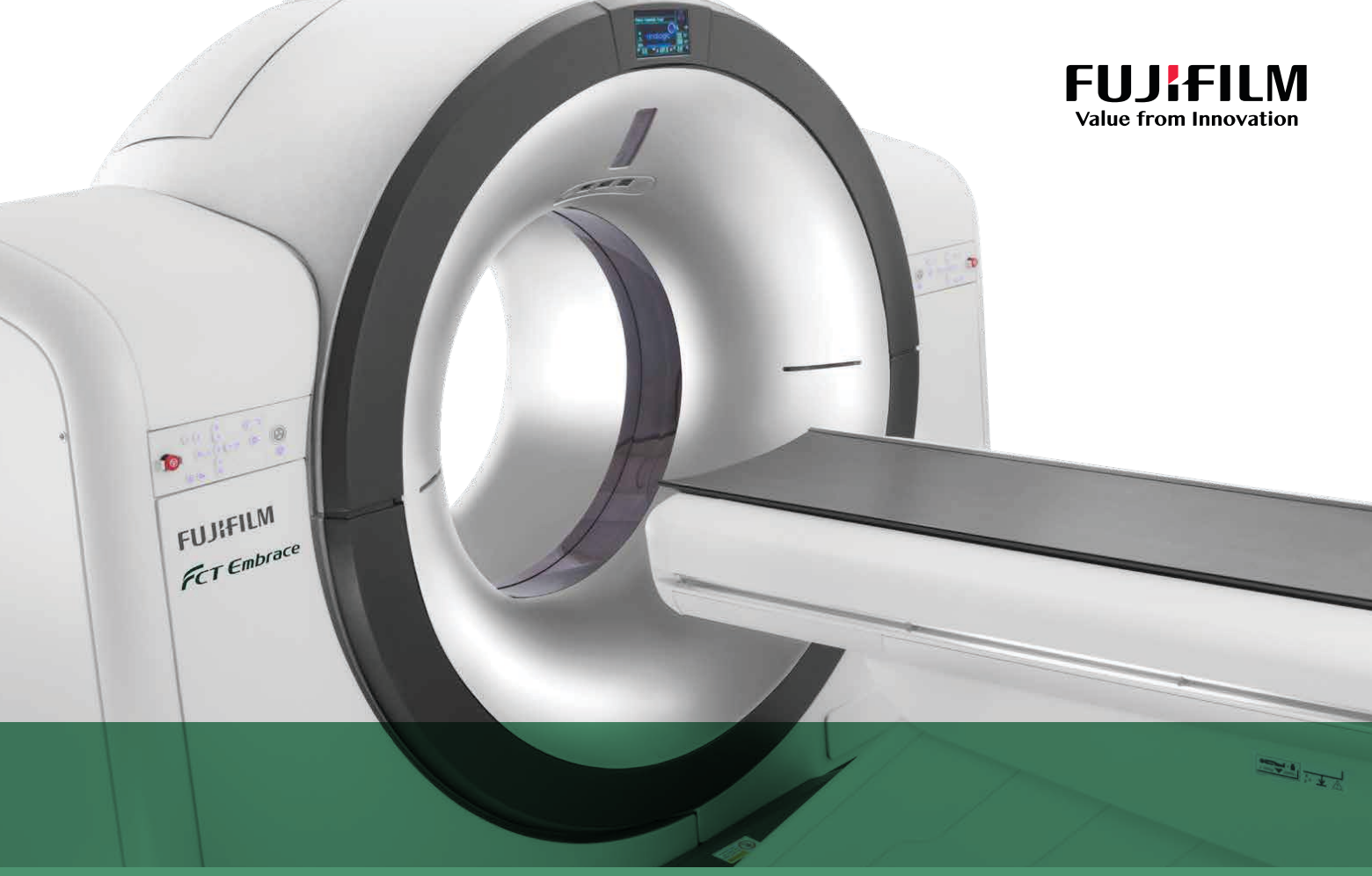

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March 2019
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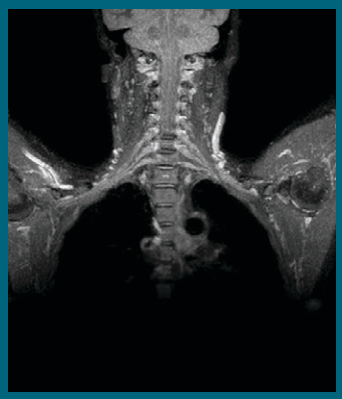

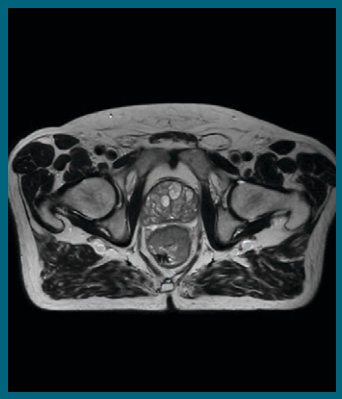

Captured on Elekta Unity during 2018 imaging studies

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EDITORIAL

Doubling down with radioimmunotherapy

John Suh, MD, FASTRO, FACR
Editor-in-Chief

Anticipated as one of the most promising areas of cancer research, immunotherapy is commanding attention and strengthening hope as the front runner in cancer therapeutics. In particular, radioimmunotherapy—the combination of immunotherapy and radiation therapy—is hailed as a breakthrough treatment for cancers such as non-Hodgkin lymphoma. Not surprisingly, this field is generating excitement, as well as many questions, as it rapidly advances clinically and commercially.[1] We are excited to feature radioimmunotherapy as the March focus, with two review articles offering free SA-CME credit.

The first review, *The safety and efficacy of combined immunotherapy and radiation therapy,* examines the rationale for employing radioimmunotherapy and better quantifying its toxicities. With a general focus on stereotactic body radiation therapy, this thoughtful article describes preliminary evidence on the efficacy of treating patients on immune checkpoint inhibitors with this combination approach.

The second review, *Combining immunotherapy with radiation therapy to induce the abscopal response: What clinical and treatment variables matter?,* provides a timely update on demographic, clinical, and treatment factors associated with the abscopal response and improved outcomes for metastatic disease. This article provides an overview of how radioimmunotherapy may have an encouraging role in inducing this rare clinical event.

This month's Technology Trends article further examines trials regarding radioimmunotherapy, as well as its potential in personalized medicine and beyond.

As always, we are also pleased to showcase a variety of original research articles, case reports and editorials in the issue, the latter of which impart terrific advice while shredding the taboo of failing, or fear of failing, when pursuing research as a resident (see Resident Voice) or beginning your first real job after residency (see Viewpoint).

Since this is our first issue of the year, I would again like to congratulate the winners of *ARO*'s 2018 Article of the Year contests:

Review Article winner: *Improving the therapeutic index for nonoperable esophageal cancer patients with modern radiation technologies*, Michael D. Chuong, MD, Miami Cancer Institute, et al

Research Article winner: *Postprostatectomy radiation therapy for biochemically recurrent prostate cancer*, Michael Schloss, MS-III, Alabama College of Osteopathic Medicine, et al

Case Report winner: *Severe contact dermatitis secondary to metal contaminants in radiation therapy paint pens*, Islam Younes, MD, MD Anderson Cancer Center, et al

We are excited to offer the articles of the year contest again in 2019, with awards up to $1,000. For details, please see https://appliedradiationoncology.com/contests.

Thank you for your continued engagement, ideas and contributions as we enter our eighth year of serving the radiation oncology community! We look forward to another exciting year ahead.

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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RESIDENT VOICE

"Failure is the mother of success," and other advice on resident research

Fumiko Chino, MD

Fumiko Chino, MD

Earlier this year, I found this sage advice at the end of my meal: "Failure is the mother of success." I don't often subscribe to the fortune cookie school of thought, but the words resonated with me. Failure is an expected complication of a successful career; and in research, it's basically required.

Research is now standard for radiation oncology residents, with most producing at least one first-author publication.[1] More than 90% of chief residents have done retrospective research, half have pursued basic science or translational projects, and 1 in 5 have conducted resident-led prospective clinical trials.[2] Small and large failures lead to all this success. Research often doesn't work; experiments fail, IRBs reject ideas, or trials don't accrue. Research is always two steps forward, one step back.

So, with failure in mind, here is my advice on resident research:

1. **Find a Good Mentor, Find Several.** Mentors should be available and generous. They should be able to meet on a semi-regular basis and allow you to take ownership of projects. As more than half of rad onc applicants already have publications,[3] many residents are walking in the door with mentors. A good mentor is your mentor for life; a bad mentor (even one with a famous name) may not be worth maintaining. Working with a variety of mentors broadens your skillset, and lifts pressure if a specific relationship or project goes sideways.

2. **Ask Questions That Matter (to You and to Patients).** I always think: How can this information eventually improve cancer care for my patients? Meaningful research generates passion and enthusiasm; this is the fire that drives you to continue when you cannot look at one more spreadsheet, gel, or DVH. If your research doesn't "spark joy," it's time to thank your mentor for their time and find a new project.

3. **Ask Questions That Can Be Answered.** I keep a list of interesting clinical questions waiting for answers. Some require large datasets, others need new data acquisition. Knowing which questions can be answered how and which resources are available to you is vital.

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***Dr. Chino** is chief resident at Duke University Radiation Oncology, Durham, NC.*

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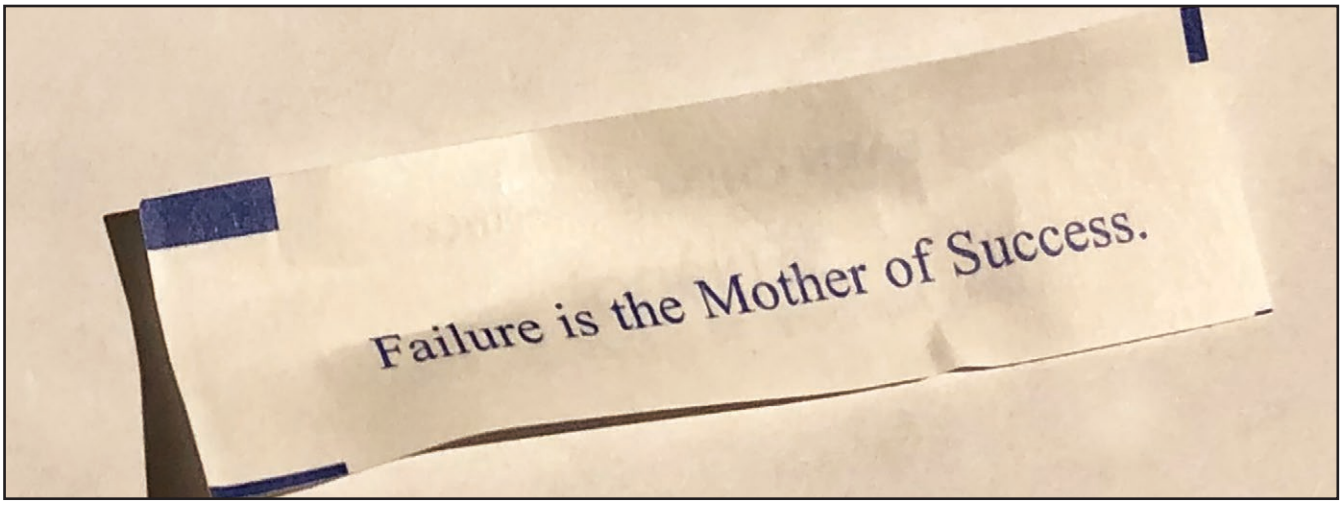

4. **Make Sure Your Work is New.** The first thing I start when thinking of a research idea is the "References" section. I collect the prior work on the topic to assess the novelty of the idea and the previous methods used to explore it. This saves work in the end and allows you to shape the project to truly fill the unmet need.

5. **Aim High (and Expect to Miss).** I often joke about how many times I have "donated" $60 to the *Journal of Clinical Oncology*. Desk rejects sting. My first 5 grant applications failed. I started my dedicated research time with the lofty goal of 10 accepted first-author publications in 12 months; I fully expected to fail but told all my research mentors my plans in order to set the bar high. It was amazing how much support I got for my ridiculous goal. Five original research articles, 2 case reports, 1 review article, a commentary, and a book chapter later I realized I never would have been this productive if I hadn't had this insane expectation. Of note: Missing the mark ("What only 7 manuscripts?") would also have clearly been acceptable.

I started residency knowing I wanted to do clinical research. For the past 5 years, I've worked hard to carve a niche for myself studying financial toxicity and how out-of-pocket costs can have real world effects on quality of life and quality of care.[4] I set high goals and failed more times than I can count. And I've often wondered if we wouldn't all do better—have less burnout, be happier residents, have more genuine success—if we *embraced* failure.

Failure *is* an option. Just fail forward.

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SA–CME Information

THE SAFETY AND EFFICACY OF COMBINED IMMUNOTHERAPY AND RADIATION THERAPY

Description
To date, there is little consensus on how to best combine radiation and immune checkpoint blockade (ICB) to maximize therapeutic gains while minimizing the potential for serious overlapping toxicities. This review summarizes relevant clinical data related to both safety and efficacy of the combination of ICB and radiation.

Learning Objectives
After completing this activity, participants will be able to:

1. Better quantify the risk of toxicity when using combined immunotherapy and radiation based on current published studies.
2. Put into practice the rationale for recommending combined immunotherapy and radiation.

Authors
Shwetha Manjunath, MD, is a resident, and **Jacob E. Shabason, MD, MTR,** is an assistant professor, both in the Department of Radiation Oncology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA.

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As part of this CME activity, the reader should reflect on how it will impact his or her personal practice and discuss its content with colleagues.

SA-CME (see page 7)

The safety and efficacy of combined immunotherapy and radiation therapy

Shwetha Manjunath, MD; Jacob E. Shabason, MD, MTR

Evasion of the host immune system is critical to the development and spread of cancer. Through aberrant activation of immune checkpoints, tumor cells have identified a potent strategy of immune escape.[1] When activated by foreign antigens, T-cells upregulate inhibitory receptors such as cytotoxic T-cell lymphocyte antigen 4 (CTLA-4) and programmed cell death protein 1 (PD-1). These immune checkpoints normally serve as protective homeostatic mechanisms to quell the immune response, thereby limiting immunopathology and promoting self-tolerance.[2] However, chronic antigenic stimulation without antigen clearance can drive effector T-cells into an abnormal state known as exhaustion. T-cell exhaustion mediated via the PD-1 pathway is one hypothesized mechanism by which the immune system fails to eradicate tumor cells.[3]

Inhibiting immune checkpoints has emerged as a promising anti-neoplastic therapy, reshaping treatment paradigms in oncology. The enthusiasm around immune checkpoint blockade (ICB) appears threefold. First, ICB has displayed superior survival in phase III trials over conventional therapies, making previously elusive outcomes now possible.[4-6] Second, responses achieved by ICB are durable. Third, ICB can be implemented across a wide range of heterogeneous cancer types. In a 2010 pivotal phase III trial of patients with metastatic melanoma, ipilimumab (antibody targeting CTLA-4) resulted in unprecedented long-term overall survival (OS) of 20% and, subsequently, became the first checkpoint inhibitor approved for clinical use in oncology.[4] A pooled analysis of several trials conducted in patients with metastatic melanoma validated durable long-term survival in 20% of ipilimumab-treated patients.[7] Furthermore, antibodies targeting the PD-1/PD-L1 axis, specifically nivolumab and pembrolizumab, have also demonstrated groundbreaking responses in 35% to 40% of patients with metastatic melanoma.[8,9] In addition to the success in melanoma, ICB, most notably anti-PD-1/PD-L1 therapies, have demonstrated activity in numerous other malignancies.[5,10-23]

Despite the clinical success of anti-CTLA-4 and anti-PD-1/ PD-L1 antibodies, only a minority of patients respond to immune checkpoint inhibitors. As such, novel strategies to enhance the efficacy and durability of ICB are needed. One such strategy is to utilize radiation therapy to augment the anti-tumor immune response. The immune-modulatory effects of radiation remain poorly understood and are summarized elsewhere.[24] The ability of radiation to specifically improve response to ICB was identified in early mice studies when Demaria and colleagues added radiation to CTLA-4 inhibition and witnessed regression of both irradiated and un-irradiated ("abscopal") tumors,[25] a phenomenon that has been replicated by other investigators.[26-28] This phenomenon of an abscopal response with combination radiation and ICB was later noted in several patient case reports in a variety of malignancies, revealing radiation's immune stimulatory properties and capacity to aid in systemic anti-tumor effects.[29-31] Perhaps the most compelling evidence of the synergy of radiation and ICB comes from the retrospective analysis of patients on KEYNOTE-001, a phase 1 trial of pembrolizumab in patients with metastatic non-small cell lung cancer (NSCLC). Specifically, in the subset of patients in this trial treated at the University of California, Los Angeles (UCLA) ($n = 97$), those who had radiation at some point in their oncological care appeared to have improved OS and progression-free survival (PFS) compared with those who never received radiation.[32] Overall, the combination of exciting preclinical data and intriguing

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SA-CME (see page 7)

case reports of the synergy of radiation and immunotherapy has led to dozens of ongoing clinical trials examining the combination of radiation and ICB in a variety of malignancies in the definitive, adjuvant and metastatic setting. This review aims to bridge the gap by highlighting our current clinical experience with radiation and ICB combination in regard to toxicity and efficacy in the treatment of solid tumors.

Clinical Experience

Retrospective Studies

A variety of retrospective studies have evaluated the combination of radiation and anti-CTLA-4 and anti-PD-1 therapy. Overall the combination appears to be safe with no significant increase in toxicity compared with monotherapy. Many of these studies have assessed the combination of ICB with stereotactic radiosurgery (SRS) for brain metastases. In 2015, Memorial Sloan Kettering Cancer Center published a retrospective study examining outcomes of combined SRS and ipilimumab ($n = 46$).[33] Patients were treated with a single fraction of 15 to 24 Gy and divided into 3 groups: SRS prior to, concurrent with, or after ipilimumab. Patients treated with SRS prior to or concurrently with ipilimumab had an apparent survival advantage and lower regional recurrence rates compared with patients treated with SRS after ipilimumab (1-year OS 65% vs 56% vs 40%, $p = 0.008$; 1-year regional recurrence 69% vs 64% vs 92%, $p = 0.003$). The treatment was overall well tolerated, where 20% of patients developed grade 3 to 4 adverse events (AEs), none of which prevented the therapy completion. Typical systemic immune-related AEs (irAEs) associated with ipilimumab remained unaffected by SRS. Seven patients (15%) experienced central nervous system (CNS)-specific grade 3 to 4 AEs, and these were slightly more frequent in those receiving concurrent therapy. These findings demonstrate that combined SRS and ipilimumab is relatively safe with a possible immune stimulatory effect of concurrent SRS.

A similar retrospective analysis conducted at the University of Virginia evaluated 46 patients with metastatic melanoma with brain metastases who received ipilimumab and SRS to a median dose of 20 Gy. Patients were divided into 2 groups: 1) SRS with concurrent ipilimumab or ipilimumab following SRS; and 2) SRS after completion of ipilimumab. Group 1 had substantially improved local tumor control at 1 year (54.4% vs 16.5%, $p = 0.005$) and a nonstatistically significant improvement in survival (59% vs 33%, $p = 0.118$) compared with group 2. However, the authors reported a higher incidence of radiation necrosis in group 1 (19.4% vs 9.7%, $p = 0.066$), calling into question the safety of concurrent ipilimumab and SRS.[34]

In a retrospective study between Yale and MD Anderson, patients ($n = 99$) with metastatic melanoma who received SRS within 5.5 months after their ipilimumab therapy had significantly better intracranial disease control than those who received SRS later (HR 2.07, $p = 0.041$). This benefit was more prominent in patients with higher baseline lymphocyte count (>1000/μL). Intriguingly, the 1-year intracranial control rate for the early SRS group was nearly 50%, a rate nearing that achieved by SRS plus whole-brain irradiation (WBRT), whereas the intracranial control rate for the late-SRS group was 20% to 30%, similar to the historical rate achieved by SRS alone. The toxicities were not reported in this study.[35]

In another retrospective analysis, Chen et al examined the safety and efficacy of concurrent ICB (ipilimumab, nivolumab, or pembrolizumab) and radiation in patients with metastatic NSCLC, melanoma, and RCC who had brain metastases treated with SRS without prior WBRT. Patients were treated with SRS ($n = 181$), SRS with nonconcurrent ICB ($n = 51$), or SRS with concurrent ICB ($n = 28$). Among patients who received ICB, no grade 4 irAEs were reported, and there was no significant difference in rates of irAEs among those who received concurrent (ie, within 2 weeks) vs. noncurrent ICB with SRS. Furthermore, with a median SRS dose of 20 Gy, there were no differences in any grade acute CNS toxicity or in the rate of pathologically confirmed radionecrosis (3% total) across groups. In addition to its demonstrated safety, concurrent ICB with SRS predicted for a decreased likelihood of the development of ≥ 3 new brain metastases after SRS (OR 0.337, $p = 0.045$). Median OS for patients treated with SRS, SRS with nonconcurrent ICB, and SRS with concurrent ICB was 12.9 months, 14.5 months, and 24.7 months, respectively. Furthermore, SRS with concurrent ICB had improved OS compared with SRS alone (HR 2.69, $p = 0.002$) and SRS with nonconcurrent ICB (HR 2.40, $p = 0.006$). The OS benefit of concurrent SRS and ICB was significant in comparison with patients treated with SRS before (HR 3.82, $p = 0.002$) or after ICB (HR 2.64, $p = 0.02$).[36]

A large retrospective review from MD Anderson Cancer Center was conducted of 137 patients with metastatic melanoma with brain metastases to predict the risk of radiation necrosis after SRS and ICB. Patients received ipilimumab (87%), pembrolizumab (9%), or both (4%). The crude rate of radionecrosis was 27% with a median time to radiation necrosis of 6 months. In those who received ipilimumab, pembrolizumab, or both, the respective radionecrosis rates were 13%, 7%, and 27%. On multivariate analysis, the authors found immunotherapy type and timing of immunotherapy to SRS (whether administered within 3, 6, or 12 months before or after) was not clearly associated with a differing radiation necrosis risk.[37]

SA-CME (see page 7)

Martin et al recently published the largest series of patients treated with SRS with or without ICB to help define the risk or radiation necrosis with combination therapy. Specifically, this study retrospectively assessed 480 patients with brain metastases from melanoma, RCC, and NSCLC. The authors found that those who received ICB and SRS had higher rates of symptomatic radiation necrosis than those who received SRS alone (20% vs 7%, HR 2.56, p = 0.004). Their results also indicated that patients with metastatic melanoma were prone to increased rates of symptomatic radiation necrosis (HR 4.70, $p = 0.01$).[38]

Given numerous retrospective studies of SRS and ICB, there have been recent attempts to consolidate data. Lehrer et al published a meta-analysis to better elucidate the safety and efficacy of SRS with ICB. They reported an overall radiation necrosis rate of 5.3%, which was more notable in patients receiving ipilimumab over pembrolizumab or nivolumab. Their analysis indicated a 1-year OS of 64.6% vs 51.6% for concurrent (ie, SRS and ICB within 4 weeks of each other) and nonconcurrent therapy, respectively ($p < 0.001$).[39]

Taken together, these retrospective analyses of brain-directed radiation and ICB show that the combination is generally safe with a possible increase in risk of symptomatic radiation necrosis, and there are enticing signs of synergy between the two therapies. Other retrospective studies also indicate that the combination of ipilimumab and radiation to extracranial sites is overall well tolerated.[40-41]

Prospective Data

In addition to the plethora of the retrospective studies, in recent years prospective data has emerged evaluating the safety and efficacy of combined radiation and ICB. A number of these trials have evaluated the combination of radiation with ipilimumab. Investigators at the University of Pennsylvania completed a phase I trial of 22 patients with metastatic melanoma combining stereotactic body radiation (SBRT) with 4 cycles of adjuvant ipilimumab. The trial was designed with multiple dose levels. Liver and subcutaneous lesions were treated with 6 Gy x 2 or 3 fractions while lung and bone lesions were treated with 8 Gy x 2 or 3 fractions. Importantly, no dose-limiting toxicities (DLTs), defined as grade ≥ 4 irAEs or grade ≥ 3 non-irAEs, were observed. In fact, the observed toxicities were no different than one would expect from ipilimumab monotherapy, indicating radiation can safely be added to ipilimumab. Unirradiated lesions were assessed for an abscopal response; 18% of patients had a partial response (PR), 18% had stable disease (SD), and 64% had progressive disease (PD). With a median follow-up of 18 months, the median PFS was 3.8 months and median OS was 10.7 months.[26] Similar to preclinical studies, tumor PD-L1 expression correlated with inferior responses, suggesting that dual checkpoint blockade may enhance outcomes. Furthermore, results from another phase I trial in 35 patients with metastatic solid malignancies also demonstrated the combination of hypofractionated radiation (50 Gy in 4 fraction or 60 Gy in 10 fractions) and ipilimumab was safe.[42] Specifically, 34% of patients developed grade 3 toxicity (most frequently colitis) and there were 2 DLTs in those treated with liver-directed radiation. In terms of efficacy, 23% of patients derived a clinical benefit in abscopal tumors.[42] In addition, Williams et al recently published a phase I trial of 16 patients with metastatic melanoma and brain metastases with ipilimumab combined with SRS or whole-brain radiation. The combination was safe with no DLTs. Only one patient experienced a grade 3 neurotoxicity, but this occurred prior to administration of ipilimumab.[43] Furthermore, a phase I/II trial of patients with metastatic prostate cancer ($n = 71$) treated with ipilimumab with or without bone-directed radiation (8 Gy in 1 fraction) revealed that the combination was tolerable, and there were no increased toxicities in those who received radiation.[44] Similar safety results were seen in a phase III study comparing radiation with or without ipilimumab.[45]

Analogous to the combination of radiation and ipilimumab, phase I studies evaluating the combination of radiation and PD-1 blockade have demonstrated safety with signs of clinical efficacy. First, investigators from the University of Chicago conducted a phase I study evaluating the safety of pembrolizumab with multisite SBRT in patients with metastatic solid tumors ($n = 73$). At least 2 sites of metastatic disease were targeted with radiation. Radiation fractionation schedules for this trial included 30 Gy in 3 fractions for osseous disease, 50 Gy in 5 fractions for central lung tumors and mediastinal disease, and 45 Gy in 3 fractions for other sites. The therapy was overall well tolerated, but 6 out of 62 patients experienced grade 3 toxicities, corresponding to a DLT rate of 9.7%. When toxicity occurred, it tended to occur at the site of radiation. This trial also demonstrated possible synergism of radiation and pembrolizumab. The abscopal response rate was 13.2% in a population of heavily pre-treated patients. This population was unselected for PD-L1 expression and was enriched for histologies not associated with a significant response rate to pembrolizumab. Furthermore, the authors found that the expression of interferon-γ-associated genes from post-SBRT tumor biopsies significantly correlated with nonirradiated tumor response, albeit in a small sample size.[46]

Similarly, investigators from the University of Pennsylvania recently reported the initial results of a phase I trial combining SBRT and pembrolizumab for patients with metastatic solid tumors ($n = 24$). This trial included a cohort of patients who progressed on prior PD-1 blockade to better delineate

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the synergistic role of radiation therapy with ICB vs the effect of ICB alone. The investigators hypothesized that if patients demonstrated tumor shrinkage despite prior progression, this effect was likely due to the immune stimulatory effects of radiation. Overall, the trial had 2 stratums: 1) patients with melanoma or NSCLC who progressed on prior anti-PD-1 therapy and 2) patients with diverse solid malignancies that were anti-PD-1/PD-L1 therapy naïve. Every patient received 6 cycles of pembrolizumab, starting 1 week before radiation. Each group was evenly split to receive either 8 Gy x 3 fractions or 17 Gy x 1 fraction to the index lesion. All treatment-related toxicities were grade 1 and 2, suggesting that either fractionation with pembrolizumab was well-tolerated. Furthermore, this trial demonstrated signals of possible synergy. Within stratum 1 (n = 12), 2 patients (16.7%) who progressed on prior PD-1 inhibition demonstrated prolonged responses of 9.2 and 28.1 months. Within stratum 2 (n = 12), 1 patient achieved a complete response (CR) and 2 patients experienced prolonged SD of approximately 7 months. Interestingly, 2 irAEs (hypothyroidism and pneumonitis) occurred following radiation to a lung metastasis in the same patient who achieved a CR.[47]

As discussed, several single-arm phase I trials have been published establishing the safety of combined radiation and ICB, with encouraging signs of efficacy. However, to date no randomized or comparative trials combining ICB with or without radiation have been published, and to our knowledge only 3 such trials have been reported in abstract form. These trials have all combined anti-PD-1 therapy with or without radiation therapy in the metastatic setting and thus far have failed to show a definitive benefit of adding radiation therapy to anti-PD-1 therapy. At the 2018 American Society of Clinical Oncology (ASCO) annual meeting, Theelen et al reported on a multicenter trial randomizing 74 patients with metastatic NSCLC to pembrolizumab vs SBRT (8 Gy x 3 fractions) plus pembrolizumab. Although no results met statistical significance, there are encouraging signs of efficacy. Particularly in the combination arm, there was an increased objective response rate (39% vs 21%, p = 0.28), improvement in median PFS (7.1 vs 2.8 months) with a hazard ratio of 0.61 (95% CI 0.35-1.06, p = 0.08), and improvement in median OS (19.2 vs 7.6 months) with a hazard ratio of 0.58 (95% CI 0.31-1.1, p = 0.1). Importantly, the combination regimen was safe and there were no grade 3 or higher toxicities related to the addition of SBRT.[48] Furthermore, although not randomized, at the 2018 World Conference on Lung Cancer, Moreno et al presented comparative data of the anti-PD-1 antibody cemiplimab with or without SBRT (9 Gy × 3 fractions) in metastatic NSCLC. This study was a comparison of two phase 1 expansion cohorts, one with cemiplimab alone (n = 20) and the other in combination with SBRT (n = 33). Although, the combination arm had a similar safety profile, there did not appear to be any benefit of adding SBRT to cemiplimab.[49] Lastly, at the 2018 ASCO annual meeting McBride et al presented results from a phase II trial randomizing patients with metastatic head and neck squamous cell carcinoma (n = 53) to nivolumab with or without SBRT (9 Gy x 3). Although, the addition of radiation therapy did not increase the rate of ≥ grade 3 toxicities, SBRT did not enhance the efficacy of nivolumab with comparable objective response rates in the monotherapy vs combination arm (26.9% vs 22.2 %, p = 0.94).[50]

Importantly, the practice changing PACIFIC trial also provides unique insight into the safety of fractionated thoracic radiation with concurrent chemotherapy followed by ICB. Specifically, this trial, which randomized patients (n = 713) with stage III NSCLC to standard chemoradiation with or without adjuvant durvalumab (PD-L1 inhibitor), demonstrated a significant PFS and OS benefit with the addition of adjuvant durvalumab. The overall toxicity profile was similar between the durvalumab and placebo group with similar rates of any grade 3 to 4 AE (30% vs 26%).[51]

Conclusion

Based on promising preclinical data and enticing clinical case reports, there are more than 100 accruing clinical trials combining radiation therapy with various forms of immune checkpoint inhibitors. These trials span numerous malignancies in a variety of disease circumstances (metastatic, adjuvant, neoadjuvant or definitive) using different radiation doses, fractionation schedules, targets, and timing of ICB and radiation. These studies, along with ongoing and future basic and translational laboratory research, will undoubtedly provide more insight underlying the interaction of radiation and immunotherapy, and better define its safety and efficacy.

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SA–CME Information

COMBINING IMMUNOTHERAPY WITH RADIATION THERAPY TO INDUCE THE ABSCOPAL RESPONSE: WHAT CLINICAL AND TREATMENT VARIABLES MATTER?

Description

This review article identifies demographic, clinical, and treatment variables associated with the abscopal effect—the phenomenon in which radiation induces a regression of tumor cells outside the field of irradiation. Authors describe the current state of knowledge regarding these variables and examine research on the influence of tumor type, patient's immune system, overall tumor burden, and radiation therapy parameters on the abscopal effect.

Learning Objectives

After completing this activity, participants will be able to:

1. Understand the general mechanism of the abscopal effect and why combining radiation with immunotherapy may be beneficial.
2. Understand the types of cancers that are more immunogenic and could benefit from combining radiation with immunotherapy.
3. Update practices based on current literature regarding the optimal radiation dose, fractionation schedule, and timing in relation to immunotherapy associated with improved outcomes.

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Combining immunotherapy with radiation therapy to induce the abscopal response: What clinical and treatment variables matter?

Jason Liu, BS; Heath B. Mackley MD, FACRO

Ionizing radiation has been used for over a century to treat cancer. Historically, radiation was only thought to improve the local control of cancer. However, a growing body of evidence shows that radiation may induce a regression of tumor cells outside the field of irradiation, a phenomenon known as the abscopal effect. This phenomenon was first described by R.H. Mole in 1953.[1] While the mechanism remains unclear, the systemic effect of radiation therapy is believed to be immune related.[2-5] It is believed that the radiation damage induced in the tumor cell causes the release of damage-associated molecular patterns (DAMPs) that serve to immunize the host.[6-10] This can result in the widespread activation of immune effector cells, which can then attack tumor cells distant to the irradiated target.[11-15]

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While the number of case reports documenting the abscopal response is growing, the abscopal response remains rare and difficult to reproduce clinically with radiation therapy alone. Combining immunotherapy with radiation therapy, however, seems promising for bringing out this rare clinical event. Immunotherapy bolsters the host's immune system, examples of which include cytokine therapy, adoptive cell transfer, and the new generation of immune checkpoint inhibitors (ICIs). The two major classes of ICIs include PD-1–PD-L1 inhibitors (pembrolizumab, nivolumab, atezolizumab, avelumab, and durvalumab) and CTLA-4 inhibitors (ipilimumab and tremelimumab).

An exciting area of research in radioimmunotherapy is identifying what demographic, clinical, and treatment variables are associated with the abscopal response. Here, we review the current state of knowledge regarding these variables and identify areas requiring further investigation.

Abscopal Response Defined

In the literature, an abscopal effect is defined as a phenomenon in which localized treatment of a tumor causes shrinking not only of the treated tumor, but also of tumors outside the scope of the localized treatment. An abscopal effect may be either partial or complete. For purposes of our review, we define an abscopal *response* as a complete response resulting from the abscopal *effect*.

It is difficult to know whether a complete response after radiation and immunotherapy is due to the abscopal response or due to the activity of immunotherapy alone. However, there is evidence that the complete response rate is higher with radiation and immunotherapy than immunotherapy alone, which suggests that a complete response is due to the abscopal effect in patients treated

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with both radiation and immunotherapy.[16-21] A prospective trial in patients with metastatic melanoma treated with radiation and anti-CTLA-4 found the complete response rate to be 13.6%[18] compared to a 1.5% complete response rate for patients with metastatic melanoma treated with anti-CTLA-4 only.[22] While a fraction of complete responses in patients treated with radiation and immunotherapy may be attributed to immunotherapy alone, the majority of complete responses appear related to the abscopal effect.

Influence of Tumor Type

Tumors are complex environments that contain cancer cells as well as stromal and immune infiltrates. Tumor-infiltrating cells can demonstrate either tumor-suppressive or tumor-promoting effects depending on cell type. Regulatory T-cells and tumor-associated macrophages have been associated with pro-tumor functions, whereas $CD8^+$ T-cells have been associated with anti-tumor functions.[23-27]A review of case reports reveals a striking feature of the abscopal response in tumor types infiltrated preferentially by $CD8^+$ T-cells.[27]A pan-cancer analysis of tumors showed that renal cell carcinoma, lung adenocarcinoma, and melanoma had the highest aggregate T-cell infiltration scores.[28] Other cancer types with high aggregate T-cell infiltration scores include head and neck squamous cell carcinoma, cervical and endocervical cancer, colon and rectum adenocarcinoma, and lung squamous cell carcinoma.This suggests that an abscopal response would be more likely in one of these cancer types treated with radioimmunotherapy.

Influence of Patient Immune System

Factors that affect a patient's ability to have an abscopal response include degree of myelosuppression, neutrophil to lymphocyte ratio, and prior exposure to radiation therapy and chemotherapy.[29] The ability to have an abscopal response depends on the patient's ability to mount an immune response. Therefore, patients with decreased lymphocyte counts due to cytotoxic chemotherapy or bone marrow infiltration by tumor are less likely to have an abscopal response. Similarly, patients receiving prolonged fractionation regimens of 30 to 40 fractions are less likely to have an abscopal response due to the decreased availability of effector and memory cells.[30] T-cells are highly sensitive to radiation, with a D90 of 0.5 Gy.[31] Even with smaller, more conformal radiation therapy fields, protracted radiation therapy regimens may deliver lymphotoxic doses and exhaust T-cells, hindering their ability to produce an abscopal response.[32]

Although protracted radiation therapy regimens might reduce the incidence of an abscopal response, this does not preclude immunotherapy from being beneficial after fractionated radiation therapy. In the PACIFIC trial, patients with stage III non-small cell lung cancer who received definitive chemoradiation achieved a further response and survival benefit with durvalumab.[33] Whether the benefit of the durvalumab was enhanced by the previous chemoradiation because of an abscopal effect, or in in spite of chemoradiation's temporarily deleterious immune effects, is unknown, but certainly is an ongoing area of interest to researchers.

Influence of Overall Tumor Burden

Patients with significant tumor burden are less likely to achieve an abscopal response than patients with limited disease burden. For example, Kwon and colleagues found that patients with significant metastatic burden from prostate cancer did not benefit from CTLA-4 blockade and radiation therapy, whereas patients with limited disease burden did.[34] Similarly, Hiniker and colleagues found that patients with metastatic melanoma treated with anti-CTLA-4 and radiation therapy were more likely to achieve an abscopal response if they had a smaller volume of disease at baseline.[18] The 3 patients in their study with an abscopal response had a baseline unirradiated sum of product diameter (SPD) of 4.3 cm^2, 8.0 cm^2, and 22.8 cm^2 compared with a median value of 15.2 cm^2 in patients without an abscopal response. Other useful ways of assessing tumor burden in trials include tumor volume, tumor diameter, and number of metastatic areas.

Influence of Radiation Therapy Parameters

Radiation delivery can be altered by changes in dose, fractionation, and duration. Currently, there is no consensus on optimal radiation therapy parameters to induce an abscopal response, and pre-clinical studies have produced conflicting results. Some data suggest that single-fraction radiation is better than multiple fractions. Shen and colleagues, for instance, found that mice bearing B16 melanoma responded more favorably to 800 cGy once a week compared to 200 cGy 5 times a week.[35] However, Schaue and colleagues found that mice bearing B16 melanoma had better tumor control and immunity when treated with 2 radiation doses of 7.5 Gy compared to a single dose of 15 Gy.[36] Similarly, Dewan and colleagues found that mouse breast carcinoma cells were more likely to respond to 24 Gy in 3 fractions and 30 Gy in 5 fractions than a single fraction of 20 Gy.[37] Some studies also report similar results for both single-fraction and multiple fraction radiation.[38-40] The variability of these results may be attributed to other factors, including tumor type and radiation techniques.

Regarding the optimal sequencing of radiation therapy with immunotherapy, it is difficult to generalize. For ipilimumab, it is believed that delivering radiation therapy concurrently with immunotherapy is the best approach. Preclinical studies have shown that administering radiation therapy before

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Table 1. Ongoing Clinical Trials Examining Radiation Therapy Parameters Associated with the Abscopal Response in Patients with Metastatic Disease

Identifier*	Details	Intervention	Outcomes of Interest
NCT02710253	MD Anderson Cancer Center, metastatic cancer, phase II, n = 130	Patients randomized to receive either 50 Gy in 4 fractions using stereotactic radiation or 60-70 Gy in 10 fractions, 20-30 Gy in 5 fractions, or 30-45 Gy in 10-15 fractions using conventional external-beam radiation	Systemic disease control, treatment-related toxicities, frequency of systemic disease control
NCT02406183	Radiotherapie, metastatic melanoma, phase I, n = 13	Patients randomized to receive ipilimumab and 24 Gy in 8 fractions using stereotactic radiation or 30 Gy in 10 fractions or 36 Gy in 12 fractions using conventional external-beam radiation	Maximum tolerated dose, overall survival, progression free survival, absolute lymphocyte count, frequency of Foxp3+ Treg cells, functional analysis looking at shifts in Th1/Th2/Th17, plasmacytoid dendritic cells, myeloid-derived suppressor cells, IDO expression
NCT01896271	University of Texas Southwestern Medical Center, metastatic renal cancer, phase II, n = 26	Patients randomized to receive high dose IL-2 and stereotactic ablative RT from 8-20 Gy in 1-3 fractions	Overall survival, progression free survival, time to progression, median response duration, local control rate, tumor-specific immune response, treatment-related toxicities, health-related quality of life
NCT01862900	Providence Health and Services, metastatic breast cancer, Phase I/II, n =1 3	Patients randomized to receive anti-OX40 mAb and a single radiation dose of 15, 20, or 25 Gy to their liver or lung metastases	Maximum tolerated dose, response rate, immune response to anti-OX40 and radiation based on the number of circulating CD4+ and CD8+ T-cells
NCT02826564	Ghent University Hospital, metastatic urothelial cancer, phase I, n = 20	Patients randomized to receive stereotactic body RT prior to or concurrent with pembrolizumab therapy	Treatment-related toxicities, tumor response, immunologic response using peripheral blood samples, analyzed with FACS phenotyping, functional testing, and ELISA

* = www.clinicaltrials.gov.
Key: FACS: fluorescence-activated cell sorting, ELISA = enzyme-linked immunosorbent assay

immunotherapy results in inferior outcomes, supporting the use of concurrent delivery.[37] However, other agents such as durvalumab have been effective if administered after chemoradiation.[33] Further study is warranted regarding optimal timing of radiation therapy and immunotherapy for each type of immunotherapy agent and cancer type.

One of the few studies examining the relationship between radiation therapy parameters and the abscopal response was a retrospective review of patients with metastatic melanoma treated with radiation therapy and anti-CTLA-4.[41] The total dose, number of fractions, dose per fraction, biological equivalent dose (BED), target location, and timing of radiation therapy in relation to immunotherapy were analyzed to determine if they were associated with an abscopal response. It was found in the bivariate analysis that only a higher BED was significantly associated with an abscopal response. The target location seemed to have some effect, but the sample size for each location was not large enough for results to be significant.This potential relationship between BED and abscopal responses was supported by Marconi and colleagues, who reported in a meta-analysis that the occurrence rate of abscopal responses in pre-clinical models increased with BED.[42]

Additionally, a smaller treatment field is believed to be associated with an abscopal response. Larger treatment fields expose a larger volume of T-cells to radiation, causing them to

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Table 2. Treatment-related Toxicities for Patients Receiving Immunotherapy and Radiation Therapy

Anti-CTLA-4 and Radiation Therapy

	Comparison	Disease	N	Results
Kiess et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	15	No increase in toxicity compared to ipilimumab alone (n = 3 pruritis, n = 1 diarrhea)
Patel et al	Ipilimumab + RT vs. RT alone	Metastatic melanoma	20	Higher rate of radiation necrosis compared to RT alone (30% vs. 21%)
Qin et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	44	No increase in toxicity compared to ipilimumab alone (37 toxicities for ipilimumab vs. 33 toxicities for ipilimumab + RT)
Silk et al	Ipilimumab + RT vs. RT alone	Metastatic melanoma	5	No increase in toxicity compared to RT alone (12.5% for RT vs. 3.9% for ipilimumab + RT)
Tazi et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	10	No increase in toxicity compared to ipilimumab alone (n = 2 diarrhea)
Koller et al	Ipilimumab + RT vs. ipilimumab alone	Metastatic melanoma	70	No increase in toxicity compared to ipilimumab alone for main toxicities colitis and hypophysitis

Anti-PD-1–PD-L1 and Radiation Therapy

	Agent	Disease	N	Results
Shaverdian et al	Pembrolizumab + RT vs. pembrolizumab alone	Non-small cell lung cancer	98	Higher rate of treatment-related pulmonary toxicity compared to pembrolizumab alone (13% vs. 1%)
Ahmed et al	Nivolumab + RT vs. nivolumab alone	Metastatic melanoma	26	No increase in toxicity compared to nivolumab alone
Antonia et al	Durvalumab + chemoRT vs. chemoRT alone	Non-small cell lung cancer	475	No increase in total grade 3 toxicities compared to chemoradiation alone (29.9% vs. 26.1%)

Key: RT = radiation therapy

be exhausted and unable to mount an immune response. Proposed strategies to lower radiation-therapy-induced lymphopenia include hypofractionation, reduced treatment field size (from the elimination of elective nodal coverage or with highly conformal techniques such as stereotactic body radiation therapy or stereotactic radiosurgery), and shortening beam-on treatment times.[43]

Effect of Radiation Therapy Parameters on the Abscopal Response: Ongoing Trials

Most trials studying the combination of immunotherapy and radiation therapy are examining safety and efficacy. For the purposes of our review, we are focusing on trials studying the specific radiation therapy parameters associated with an abscopal response. We identified 5 trials examining the role of radiation dose, fractionation, and timing on the abscopal response (**Table 1**). Four of the trials are studying effects of the dose and fractionation on the abscopal response, and one is studying the effect of timing of radiation therapy in relation to immunotherapy on the abscopal response.

A trial by the MD Anderson Cancer Center (NCT02710253) is examining the response rates of patients with metastatic cancer treated with salvage radiation after progression on systemic immunotherapy. The study is recruiting any patient with at least one site of metastatic disease who has been treated with immunotherapy within the last 6 months. Patients will be treated with standard doses of 50 Gy in 4 fractions with stereotactic radiation or 60 to 70 Gy in 10 fractions, 20 to 30 Gy in 5 fractions, 20 to 30 Gy in 5 fractions, or 30 to 45 Gy in 10 to 15 fractions with conventional external-beam radiation to one or more sites of disease amenable to radiation.

A trial by Radiotherapie (NCT02406183) seeks to examine the response rates and maximum tolerated dose of patients with metastatic melanoma treated with anti-CTLA-4 and stereotactic body radiation. Patients are eligible if more than 28 days have passed since their last treatment with anti-CTLA-4 therapy and they have at least 3 extracranial metastatic lesions. Patients will be treated with doses of 24 Gy in 8 fractions, 30 Gy in 10 fractions, or 36 Gy in 12 fractions to one area of disease with concurrent anti-CTLA-4 therapy.

A trial by the University of Texas Southwestern Medical Center

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(NCT01896271) seeks to examine the response rates of patients with metastatic renal cancer treated with high-dose IL-2 and stereotactic ablative body radiation. The study is currently active for any patient with clear cell renal cell carcinoma and up to 6 sites of metastatic disease with more than one lesion > 1.5 cm. Patients will be treated with stereotactic ablative radiation, with doses varying from 8 to 20 Gy in 1 to 3 fractions followed by high-dose IL-2 treatment.

A trial by Providence Health and Services (NCT01862900) seeks to examine the response rates and maximum tolerated dose of patients with metastatic breast cancer to the liver or lung treated with stereotactic body radiation and an anti-OX40 mAb. Eligible patients have at least one lesion in either the lung or liver, with one site of disease that will not receive radiation. Patients will receive a single dose of 15 Gy, 20 Gy, or 25 Gy to the liver or lung metastasis with concurrent anti-OX40 treatment.

A trial by the Ghent University Hospital (NCT02826564) seeks to examine the response rates of patients with metastatic urothelial cancer receiving stereotactic body radiation with pembrolizumab. The study is active for patients with urothelial cancer and at least one area of metastatic disease, with one site of disease that will not receive radiation. Patients will be treated with stereotactic body radiation prior to or concurrent with systemic pembrolizumab treatment.

To gauge the immunologic response, four of the studies are using biologic correlates, which include absolute lymphocyte count, frequency of Foxp3^{+}Treg cells, shifts in Th1/Th2/Th17, number of plasmacytoid dendritic cells, number of myeloid derived suppressor cells, and IDO expression. The abscopal effect is often considered a medical spectacle without a unifying model, and its exact mechanisms have yet to be elucidated.[20] Studying these biologic correlates may shed light on the possible mechanism of the abscopal effect.

Radioimmunotherapy Toxicities

There is some concern that combining immunotherapy with radiation therapy will increase toxicities. **Table 2** summarizes the toxicity reports from 6 retrospective studies[44-49] for patients treated with ipilimumab and radiation therapy; one retrospective study[50] for patients treated with pembrolizumab and radiation therapy; one retrospective study[51] for patients treated with nivolumab and radiation therapy; and one retrospective study[33] for patients treated with durvalumab and chemoradiation. In general, for patients treated with combined immunotherapy and radiation therapy, there does not seem to be a significant increase in toxicity compared to treatment with immunotherapy alone or radiation therapy alone.

Conclusion

The combination of immunotherapy and radiation therapy is a very promising treatment regimen suggested to increase the occurrence of the previously rare abscopal response. Much uncertainty remains regarding how to best enhance the abscopal response clinically. Understanding the variables that may predict an abscopal response may help determine the necessary steps to unlock a more efficient long-term immune response after radiation therapy and convert this rare phenomenon to an everyday clinical benefit.

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Initial report of a simulation-based medical education curriculum for treatment planning

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Abstract

Purpose/Objective(s): Varying degrees of treatment planning education are provided across radiation oncology residency programs. The specific aim of this project was to implement and evaluate a self-directed simulation-based treatment planning curriculum developed to teach residents key treatment planning concepts in a series of interactive, "hands-on" modules.

Methods/Methods: A curriculum was developed consisting of 3 treatment planning modules including anteroposterior/posteroanterior (AP/PA) spine, 3-field breast, and intensity-modulated radiation therapy (IMRT). Participants completed anonymous evaluations after completing each module assessing their treatment planning proficiency using Likert-type scales (1 = "not at all" to 5 = "extremely"; reported as median [interquartile range]). Nonparametric statistical tests were used.

Results: Eleven residents in their postgraduate year (PGY-2 to PGY-5) at a single academic medical center completed the curriculum during the 2014-15 academic year. Completion of the modules was associated with improved resident comfort with AP/PA treatment planning ($p = 0.03$), 3-field breast treatment planning ($p < 0.01$), and IMRT planning ($p = 0.03$). Resident self-reported understanding of the following treatment planning concepts was significantly improved after completing the modules: dose grid ($p < 0.01$); beam energy selection ($p = 0.03$); calculation point ($p = 0.04$); iterations ($p = 0.01$); segments ($p = 0.02$); optimization ($p < 0.01$); and ring structure ($p < 0.01$).

Conclusion: Radiation oncology residents experience significantly improved comfort with treatment planning and understanding of treatment planning concepts after completion of self-directed treatment planning modules. Development of additional modules as part of a formal treatment planning curriculum is warranted.

In the era of highly conformal and image-guided radiation therapy, optimal therapeutic response requires accurate delineation of target volumes and adequate dose coverage of those volumes while sparing normal tissues. However, review of plans submitted for multi-institutional clinical trials reveals that many plans fail to adequately cover the target volume or exceed normal dose constraints resulting in minor or major deviations. Such variability has been shown to lead to worse clinical outcomes including decreased overall survival and increased normal tissue toxicity.[1,2]

As members of an interprofessional team, radiation oncologists must understand fundamental principles of treatment planning. However, radiation oncology residents experience varying degrees of formal treatment planning education.[3,4] Furthermore, there is minimal literature describing effective educational methods or interventions for teaching treatment planning during residency.[5] Inconsistent training may contribute to the larger problem of treatment planning and dosimetric variability observed between centers in multi-institutional randomized trials.

Simulation-based medical education (SBME) is an increasingly recognized form of effective and easily disseminated educational intervention across multiple medical fields including radiation oncology.[6] The primary objective of this project was to develop, implement, and evaluate a novel self-directed SBME treatment planning curriculum to teach

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Table 1. Goals and Objectives for the Anteroposterior/Posteroanterior (AP/PA) Spine Module

General goal	Specific educational objectives
Develop the skills to create an AP/PA treatment plan	The learner will demonstrate the ability to _____ by the end of the workshop. 1. open a treatment plan 2. contour a target 3. create a PTV using an expansion 4. set a treatment isocenter 5. create a treatment field 6. set beam borders 7. prescribe a dose and number of fractions 8. turn on isodose lines 9. evaluate a basic dose-volume histogram 10. change a beam energy 11. copy and oppose a treatment field
Understand concepts related to an AP/PA treatment plan	The learner will understand the concept of _____by the end of the workshop. 1. depth-dose curves 2. dose-volume histograms 3. different beam energy and the effect on maximum dose 4. GTV to PTV expansion and the significant increase in volume with a small PTV expansion 5. single versus opposed beams and the effect on maximum dose The learner will rate himself or herself as more comfortable with basic radiation treatment planning.

Key: PTV = planning target volume, GTV = gross tumor volume

Table 2. Goals and Objectives for the 3-field Breast Module

General goal	Specific educational objectives
Develop the skills to set up a 3-field breast plan using a 2-isocenter and monoisocentric technique	The learner will demonstrate the ability to _____ by the end of the workshop. 1. set 2 isocenters for the tangent fields and supraclavicular fields 2. select tangent beam angles 3. set the jaws for tangent and supraclavicular beams 4. match the tangent beams and supraclavicular fields in a 2-isocenter plan 5. create a second treatment planning trial 6. set the isocenter for a monoisocentric treatment plan 7. compare 2 planning trials
Understand concepts related to a 3-field breast plan	The learner will understand the concept of _____by the end of the workshop. 1. half-beam blocks 2. field matching 3. calculation points 4. calculating the angle of beam divergence The learner will rate himself or herself as more comfortable with basic radiation treatment planning.

residents fundamental radiation treatment planning concepts in a series of interactive, hands-on modules. With improved treatment planning knowledge, radiation oncology residents will function more effectively as members of an interprofessional radiation therapy team.

Methods and Materials

Development of the Intervention

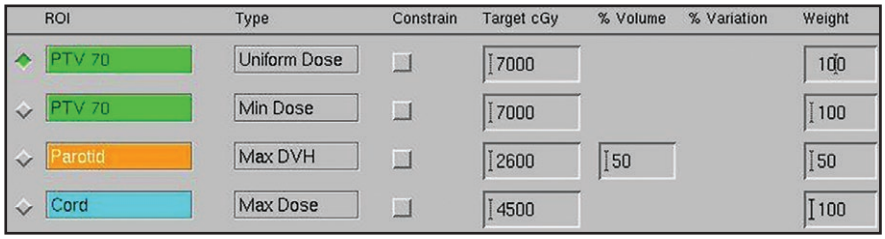
A pilot curriculum was developed consisting of 3 treatment planning modules that could be completed independently or in small groups using the Pinnacle treatment planning system (Philips Healthcare, Andover, Massachusetts).[7] The modules are self-directed and each take approximately 1 hour to complete. Since these workshops teach basic treatment planning concepts and skills, they are completed in order: first anteroposterior/posteroanterior (AP/PA) spine, then 3-field breast, and finally intensity-modulated radiation therapy (IMRT). Specific goals and educational objectives of each module are described in **Tables 1, 2, and 3**. A screenshot sample from the IMRT module is provided in **Figure 1.** The modules can be downloaded at https://www.mededportal.org/publication/9297/.

Curriculum Implementation

During the 2014-15 academic year, 11 residents (postgraduate year PGY-2 to PGY-5) from a single institution participated in the pilot curriculum. Participants were exposed to various aspects of treatment planning, including plan design, dose prescription, and plan evaluation. Participants were asked to complete evaluations before and after completing the modules assessing their treatment planning proficiency using Likert-type scales (1 = "not at all," 2 = "somewhat," 3 = "moderately," 4 = "quite," 5 = "extremely"; reported as median [interquartile range]). Free responses were also collected for qualitative analysis. Study data were collected and managed using REDCap (Research

Table 3. Goals and Objectives for the Intensity-modulated Radiation Treatment (IMRT) Module

General goal	Specific educational objectives
Develop the skills to run a basic IMRT optimization	The learner will demonstrate the ability to _____ by the end of the workshop. 1. set IMRT optimization parameters 2. set planning objectives for the target volume and organs at risk 3. use a ring structure to constrain the high dose region of an IMRT plan 4. compare two IMRT trials
Understand concepts related to IMRT treatment planning	The learner will understand the concept of _____by the end of the workshop. 1. targets and organs at risk 2. optimization parameters 3. planning objectives 4. IMRT segments The learner will rate himself or herself as more comfortable with basic radiation treatment planning.



Set planning objectives for OAR's

1. Click "Add Objective": Change the ROI to "Cord". For "Type" choose "Max Dose". What is the dose constraint for the cord? Enter this for the max dose cGy. Set the weight to 100 since we are not willing to accept any dose above our constraint.
2. Click "Add Objective": Change the ROI to "Parotid". For "Type" choose "Max DVH". What is the dose constraint for the parotid gland? Enter this for the target cGy and % Volume. Set the weight to 50 since we are willing to accept some dose above this constraint.

FIGURE 1. *Screenshot excerpt from the intensity-modulated radiation therapy (IMRT) module. To access the complete IMRT module, visit https://www.mededportal.org/publication/9297/.*

Electronic Data Capture) electronic data capture tools hosted at the https://redcap.uchicago.edu/.[8] REDCap is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources. The Wilcoxon rank-sum statistical test was used to compare pre- and post-workshop evaluation scores. Qualitative responses were analyzed for common themes. This study was approved as exempt by the University of Chicago Institutional Review Board.

Results

All 11 residents completed the treatment planning modules and submitted anonymous evaluations. Pre- and postmodule ratings are summarized in **Table 4.** Module completion was associated with improved resident comfort with AP/PA treatment planning (pre 3 [2-3] vs post 4 [3-4], $p = 0.03$), 3-field breast treatment planning (pre 3 [2-3] vs post 4 [3-4], $p < 0.01$), and IMRT planning (pre 3 [2- 4] vs post 4 [3-4], $p = 0.03$). Resident self-reported understanding of the following treatment planning concepts significantly improved after completing the modules: dose grid (pre 2 [2-3] vs post 4 [3-4], $p < 0.01$); beam energy selection (pre 3 [2-4] vs post 4 [3-4], $p = 0.03$); calculation point (pre 2 [1-3] vs post 4 [3-5], $p = 0.04$); iterations (pre 1 [1-3] vs post 4 [3-4], $p = 0.01$); segments (pre 3 [2-4] vs post 4 [3-4], $p = 0.02$); optimization (pre 2 [2-3] vs post 4 [4-4], $p = 0.01$); and ring structure (pre 2 [1-3] vs post 3 [3-4], $p < 0.01$).

In the qualitative analysis, residents described acquiring important skills and knowledge through the modules. Additionally, they gave feedback regarding module strengths as educational tools and suggested future curriculum improvements. Learning the basics of treatment planning software and functionality (6/11), practicing beam setup and modification (6/11), understanding the treatment planning dose grid (4/11), and evaluating treatment plans (2/11) were cited as important treatment planning concepts taught in the modules. The most commonly described curriculum strength was the explicit step-by-step instructions that guided learners through the modules and allowed for future reference and practice (3/11). Suggested improvements included providing the curriculum earlier in the academic year, particularly for junior residents (2/11), and creating more complex cases as additional learning opportunities (1/11).

Discussion

Formal treatment planning education during training varies significantly across US residency programs.[3,4] Given the importance of optimal treatment planning in the delivery of highly conformal radiation therapy, residency

Table 4. Self-reported Resident Comfort with Treatment Planning and Dosimetry Concepts Before and After Completion of Modules. Reported as Median [Interquartile range].

	Premodule rating	Postmodule rating	*p* value
Treatment planning comfort			
AP/PA	3 [2-3]	4 [3-4]	0.03
3-field breast	3 [2-3]	4 [3-4]	<0.01
IMRT	3 [2-4]	4 [3-4]	0.03
Treatment planning concept understanding			
Dose grid	2 [2-3]	4 [3-4]	<0.01
Beam energy selection	3 [2-4]	4 [3-4]	0.03
Calculation point	2 [1-3]	4 [3-5]	0.04
Iterations	1 [1-3]	4 [3-4]	0.01
Segments	3 [2-4]	4 [3-4]	0.02
Optimization	2 [2-3]	4 [4-4]	<0.01
Ring structure	2 [1-3]	3 [3-4]	<0.01

programs should work to implement a formalized treatment planning curriculum for residents in training. This study reports the pilot implementation of a self-directed SBME curriculum designed to teach fundamental treatment planning and dosimetry concepts to radiation oncology residents. Completion of the SBME modules was associated with positive learning outcomes and increased self-reported competence for multiple predetermined educational objectives. This report provides evidence that self-directed modules can be effective tools to teach foundational treatment planning concepts to residents at varying stages of training (PGY-2 through PGY-5).

SBME is increasingly recognized as an effective form of educational intervention for teaching a wide variety of skillsets across numerous medical specialties including radiation oncology.[6,9,10] This pilot curriculum is an example of radiation oncology SBME designed to teach treatment planning and dosimetry concepts to residents. Through a simulated treatment planning environment and screen-based simulator, residents can experiment and learn with real-time performance feedback. Importantly, SBME allows for acquisition and practice of new skills with no potential patient harm. This contrasts with traditional apprenticeship-based education in radiation oncology, which often involves practicing skills such as contouring and treatment planning on real patients, leading to inconsistent exposure to treatment planning concepts along with the potential risk of patient harm.

Online and self-directed teaching modules offer advantages compared to traditional didactic approaches. As an experiential form of learning, this pilot hands-on treatment planning curriculum allows residents to experience, reflect, think, and act in a recursive manner based on Kolb's experiential model to effectively assimilate knowledge and master new concepts.[11] Importantly, because these modules are self-directed, learners can complete them at their own optimal pace. Lecture-based didactics are designed to teach groups of students and, therefore, are not as adaptable for individual variations in background knowledge or skill sets. The pilot treatment planning curriculum also allows learners to tailor their experience to address specific knowledge gaps without focusing on already mastered topics. Lastly, residents can complete individual self-directed learning modules more efficiently in noncontinuous intervals, allowing a more personalized schedule.

While this investigation provides evidence that the self-directed treatment planning modules are effective teaching tools for residents in training, in their current form these modules are not independently sufficient for ensuring an integrated and fully contextualized understanding of radiation therapy treatment planning. Individual variation in patient anatomy and treatment systems can significantly impact treatment planning and delivery. Learning the idiosyncrasies of treatment planning on a case-by-case basis is difficult to teach in general self-directed modules. This type of knowledge might better be acquired through communication and apprenticeship-based teaching approaches in which mentor expertise guides learning. Therefore, the present curriculum is not intended to replace, but rather to complement, other educational methods. As an example, the self-directed modules might be used to teach fundamental principles of treatment planning to residents while practical application of that knowledge can be honed under the tutelage of an experienced teacher.

Potential drawbacks to this treatment planning curriculum must also be recognized. The most important obstacle to self-directed learning is the potential for lack of individualized feedback and communication between learner and educator. As described above, in traditional lecture-based didactics, learners can ask questions on knowledge gaps and receive personalized feedback from experts. However, self-directed learning limits this interchange, and thus may be less efficient for teaching challenging concepts that would be better communicated through educator-learner dialogue. One potential method to mitigate this is to pair a senior resident (PGY4-5) with a junior resident (PGY2-3) to work through each module in a near-peer mentor

dyad.[12] The junior resident "drives" the treatment planning system while the senior resident provides instruction and feedback. For example, at our institution one junior resident described how "working together in pairs, especially with a senior resident, was particularly helpful … and put the case into clinical context." Another potential disadvantage of this curriculum is that successful teaching is predicated upon residents taking responsibility for educating themselves without protected time to do so. Given the high demands of residency training, it may be difficult for residents to thoroughly complete the entire curriculum and they may miss important opportunities to learn. Our program, therefore, protects time after clinic every 2 to 3 months to complete each module

The findings of this study may be limited by several factors related to the experimental design. First, this study was conducted with a sample of only 11 residents at a single institution. Ideally, the curriculum will be evaluated in the setting of a randomized controlled trial, which would increase the statistical power and limit biases, making findings more generalizable. While the results met statistical significance despite limited power, the findings may not be applicable to all residency programs or individual residents. Further investigation will characterize the efficacy of these modules when implemented in a larger and more diverse setting. Another limitation is the difficulty in interpreting self-reported competence as an educational end point. For example, it is possible for learners to feel more confident with a particular skill set after an educational intervention even though an objective performance evaluation may not indicate improvement. While objective measures of learner performance (eg, impact on patient outcomes) would be the ideal educational endpoints to assess the efficacy of any medical education curriculum, such evaluation is outside the scope of this initial pilot study. Given the promising results of our institutional implementation of the modules, expansion and objective evaluation of this and similar SBME curricula is a logical and important future direction of this work.

Given the public availability of the modules, this curriculum and future similar self-directed SBME treatment planning modules can be adopted for widespread use by radiation oncology training programs. Importantly, dissemination of the curriculum may lead to more consistent treatment planning education for radiation oncology residents on a large scale. This might help address the issue of inter-observer treatment planning variability described earlier and potentially improve clinical outcomes for patients. Additionally, given the positive pilot data for the self-directed modules in this study, further development of similar curricula to offer residents more in-depth and comprehensive exposure to treatment planning concepts is warranted. Finally, expansion of these modules to cover more advanced treatment planning material and other radiation oncology skill sets may enhance the continuing medical education of practicing radiation oncologists.

Conclusion

This study reports the pilot implementation of a self-directed SBME treatment planning curriculum for radiation oncology residents. Successful completion of the curriculum was associated with significant increases in self-reported learner competence in multiple predetermined educational objectives relating to fundamental treatment planning concepts. Further development and evaluation of similar curricula is warranted given the discrepancies in formal treatment planning educational methods across radiation oncology training programs.

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Distribution of dedicated stereotactic radiosurgery systems in the United States

Mary K. Dean, MD; Awad A. Ahmed, MD; Perry Johnson, PhD; Nagy Elsayyad, MD

Abstract

Objective: The use of stereotactic radiosurgery (SRS) is increasing in the United States (US). There are three major photon-based systems available: Gamma Knife (GK), CyberKnife (CK), and gantry-based linear accelerator (linac) systems. We sought to provide a recent description of the US distribution of these systems.

Methods/Materials: Analysis of the respective manufacturer websites for each system allowed for the compilation of a database by location. Several demographic variables were collected including county population, physician distribution, median household income, and academic affiliation. Machines were mapped by type and by state distribution. Multinomial logistic regression assessed for correlations between covariables and the endpoint of having a certain type of SRS system. Data collection and analysis was completed in 2017.

Results: There are 428 dedicated SRS systems in the United States, with linac-based systems the most common (39%), followed by CK (35%) and GK (26%). Relative to GK, CK (odds ratio [OR]: 0.39; 95% confidence interval [CI]: 0.33-0.45) and linac-based systems (OR: 0.71; 95% CI: 0.60-0.85) were less likely to be associated with academic centers. Areas of higher median household incomes were associated with CK (OR: 1.01; 95% CI: 1.01-1.02), and higher populated regions were associated with linac-based machines (OR: 1.03; 95% CI: 1.00-1.06). The distribution of total SRS systems per capita varies between states, with Montana, Alaska, and Oklahoma having the highest, and South Dakota, Vermont, and Wyoming having the lowest.

Conclusions: The US distribution of SRS systems varies geographically and demographically, which may lead to unequal accessibility for certain populations, and requires further research.

Stereotactic radiosurgery (SRS) is commonly used to treat malignant intracranial tumors but also can be used to treat benign entities as well as extracranial tumors. This treatment modality employs the use of multiple noncoplanar beams to provide a highly conformal dose distribution with a very rapid falloff beyond the periphery of the target.[1] SRS was first employed by Lars Leksell in 1967 using the Gamma Knife. Subsequently, different platforms for SRS delivery were developed, with three distinct major photon-based systems available today: Gamma Knife (Elekta, Stockholm, Sweden), CyberKnife (Accuray, Sunnyvale, California), and gantry-based linear accelerator (linac) systems including Novalis Tx (Varian [Palo Alto, California] and BrainLAB [Munich, Germany]) and Edge (Varian). Each machine has technical advantages and disadvantages, and no randomized data demonstrate superiority of any one system in terms of efficacy and/or toxicity.

Recent data described increasing SRS utilization in the United States and identified multiple disparities, including less utilization at nonacademic facilities and among patients residing in lower-income

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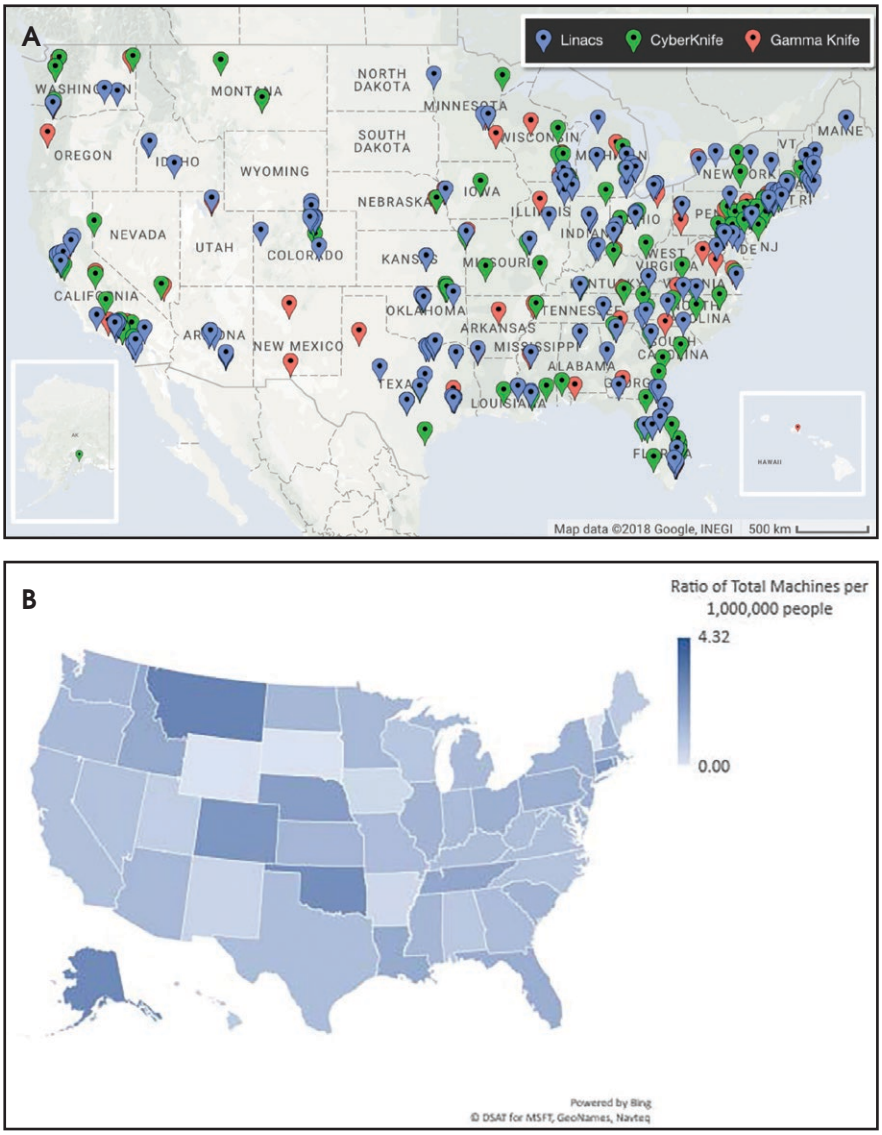

FIGURE 1. *(A) Distribution of SRS systems by machine type in the United States, (B) Geographic distribution of SRS machines per 1,000,000 people by state.*

regions.[2] To our knowledge, there is no current literature describing the geographic distribution of SRS systems in the United States. In this report, we construct a database of SRS systems in the United States, determine the overall distribution by state, and examine select demographic features for each system type.

Methods and Materials

We acquired the active US locations for the Gamma Knife (GK), CyberKnife (CK), Novalis Tx and Edge systems using the respective manufacturer websites[3-6] during 2017. Novalis Tx locations were recorded only from the Novalis Tx website to avoid any potential overlap with the Varian website; therefore, the Varian website was only utilized to extract information on Edge locations. The Novalis Tx and Edge locations were grouped together to represent dedicated linac-based systems. Although other general-purpose linacs have SRS capability, it was not possible to accurately determine if they were being used for SRS based on the manufacturer website. Additionally, such systems are not always capable of treating the entire range of targets traditionally covered by SRS. As a result of these factors, our study focused on dedicated SRS systems only.

We searched by state and then recorded the city, state, zip code, and facility name for each location. We then used the US census data to determine

Table 1. Demographics for Each SRS system

	Gamma Knife	CyberKnife	Linac-based	p value ANOVA
Urbanization				$p=0.53$
Urbanized Area	93	115	135	
Urban Cluster	20	34	31	
Median Household Income (mean)	$50,939	$57,035	$52,775	$p=0.06$
Facility Affiliation				$p<0.001$
Academic	43	14	41	
Non-academic	70	135	125	
Population by County (mean)	607,412	458,862	783,209	$p=0.12$
Number of Physicians in County (mean)	4334	3777	3790	$p=0.57$

Table 2. Multinomial Model Examining System Type as a Three Level Endpoint

	CyberKnife (Gamma Knife as reference)		Linac-based (Gamma Knife as reference)	
	Odds Ratio (95% CI)	*p* value	Odds Ratio (95% CI)	*p* value
County Population (per 100,000 capita)	1.01 (0.98-1.04)	$p = 0.52$	1.03 (1.00-1.06)	$p < 0.03$
Median Household Income (per $1,000)	1.01 (1.01-1.02)	$p < 0.001$	0.99 (0.99-1.01)	$p = 0.85$
Urbanization				
Urban area (reference)	—		—	
Urban cluster	1.16 (1.00-1.34)	$p = 0.05$	0.91 (0.79-1.04)	$p = 0.16$
Affiliation				
Academic (reference)	—		—	
Non-academic	0.39 (0.33-0.45)	$p < 0.0001$	0.71 (0.60-0.85)	$p < 0.001$
Number of Physicians in County	1.00 (1.00-1.00)	$p = 0.99$	0.99 (1.00-1.00)	$p = 0.16$

the county population (2016 estimate), which we used as a rough indicator of population density, and the median household income (in 2016 dollars).[7] Using the US Census Bureau definitions, we noted whether the location was an "urbanized area" (50,000+), "urban cluster" (2500 to 49,999), or "rural area" (< 2500). We also recorded the location as nonacademic or academic if it had a radiation oncology residency program accredited by the Accreditation Council for Graduate Medical Education (ACGME).[8] Data on county physician distribution was recorded from the American Medical Association (AMA) publication[9] for 2015 (reflecting 2013 data), the most recent year data was available.

A one-way analysis of variance (ANOVA) examined statistically significant differences between means of independent groups. A multinomial logistic regression was used to model the three-level outcome variable of machine type with GK as the reference level, and outcomes modeled as a linear combination of the independent covariables. A two-tailed Wald Z-test was used to assess the significance of coefficients with a p value ≤ 0.05 used as the threshold for statistical significance. Odds ratios (OR) and 95% confidence intervals (CI) are reported. All statistical analysis was performed using R-version 3.2.2.

To test the quality of data collected on machine distribution, 20 locations were randomly selected using a random number generator and called to confirm their existence. All 20 (100%) were confirmed as SRS sites, and all 20 (100%) sites were verified to have been correctly classified as GK, CK or linac-based.

To determine relative local distribution of SRS, we compared the total number of machines to the total US population as well as the number in each state to that state's population (2017 estimate).[10] All machines were mapped appropriately to their respective cities and zip codes using BatchGeo mapping software (Copyright © 2018, BatchGeo LLC), and the state distribution ratios were mapped using GeoNames via Microsoft Excel (Copyright © 2018, DSAT for MSFT, GeoNames, Navteq).

Results

A total of 428 SRS systems in the US were included in the database: 166 linac-based (39%), 149 CK (35%), and 113 GK (26%). **Figure 1A** shows a geographic depiction of the database by machine type. Most machines were in urbanized areas, and none were in rural areas. GK had the largest number of locations in academic centers (38%), while CK had the lowest (9%) ($p < 0.001$). CK comprised the largest proportion of machines in urban clusters (23%) and was associated with the highest median household income on average ($57,035), although neither of these demographic categories revealed any statistically significant differences among the SRS systems ($p = 0.06$) on unadjusted analysis. **Table 1** contains the full results for the demographics of each system. Only 14 centers had at least 2 types of SRS systems, 7 of which were academic centers.

On multinomial regression (see **Table 2**), going from a nonacademic to academic setting showed a decrease in the likelihood of having a CK (OR 0.39; 95% CI: 0.33 to 0.45) or a linac-based system (OR 0.71; 95% CI: 0.60 to 0.85) compared with a GK. Areas of higher median household incomes were associated with CK machines with an odds ratio of 1.01 (95% CI: 1.01 to 1.02) for every increase in median household income by $1,000. Higher populated regions were associated with linac-based machines with an odds ratio of 1.03 (95% CI: 1.00 to 1.06) per 100,000 capita.

The total ratio of number of available SRS machines per 1,000,000 people in

Table 3. Distribution of Dedicated SRS Systems by State and Population

	Total Number of SRS machines	Population Estimate 2017	Ratio of Total Machines per 1,000,000 people
United States	428	325719178	1.31
Alabama	4	4874747	0.82
Alaska	2	739795	2.70
Arizona	9	7016270	1.28
Arkansas	1	3004279	0.33
California	42	39536653	1.06
Colorado	13	5607154	2.32
Connecticut	8	3588184	2.23
Delaware	1	961939	1.04
District of Columbia	3	693972	4.32
Florida	34	20984400	1.62
Georgia	12	10429379	1.15
Hawaii	1	1427538	0.70
Idaho	3	1716943	1.75
Illinois	18	12802023	1.41
Indiana	8	6666818	1.20
Iowa	1	3145711	0.32
Kansas	4	2913123	1.37
Kentucky	5	4454189	1.12
Louisiana	8	4684333	1.71
Maine	1	1335907	0.75
Maryland	9	6052177	1.49
Massachusetts	10	6859819	1.46
Michigan	12	9962311	1.20
Minnesota	7	5576606	1.26
Mississippi	4	2984100	1.34
Missouri	7	6113532	1.15
Montana	3	1050493	2.86
Nebraska	4	1920076	2.08
Nevada	3	2998039	1.00
New Hampshire	2	1342795	1.49
New Jersey	14	9005644	1.55
New Mexico	1	2088070	0.48
New York	29	19849399	1.46
North Carolina	10	10273419	0.97
North Dakota	1	755393	1.32
Ohio	18	11658609	1.54
Oklahoma	10	3930864	2.54
Oregon	5	4142776	1.21
Pennsylvania	20	12805537	1.56
Rhode Island	2	1059639	1.89
South Carolina	7	5024369	1.39
South Dakota	0	869666	0.00
Tennessee	12	6715984	1.79
Texas	32	28304596	1.13
Utah	2	3101833	0.64
Vermont	0	623657	0.00
Virginia	9	8470020	1.06
Washington	10	7405743	1.35
West Virginia	2	1815857	1.10
Wisconsin	5	5795483	0.86
Wyoming	0	579315	0.00

the United States was 1.31. The states with the lowest ratios of SRS machines per 1,000,000 people were South Dakota, Vermont, and Wyoming (all with ratios of 0). The states with the highest ratios (excluding District of Columbia) were Montana (2.86), Alaska (2.70), and Oklahoma (2.54). **Figure 1B** geographically depicts this variation in distribution by state. **Table 3** lists the ratios for all states.

Discussion

Our results show an increase in the number of SRS systems compared to historic values and suggest a nationwide growth of SRS utilization overall. In 2003, approximately 160 dedicated radiosurgery units were reported.[11] Since then, the number of radiosurgery units has increased by 268%.

Our analysis found a shift in the prevalence of machine types. GK was the first SRS system to enter the US market in the 1980s, and in 2005 there were about twice as many GK systems as CK or Novalis.[11] Our data show that linac-based SRS has surpassed GK (135 vs 93) and is now the most commonly utilized SRS system. Additionally, multinomial regression showed that more populated regions were more likely to use linac-based SRS. While the exact reasons for increased utilization of linac-based SRS are unclear and warrant further investigation, it may be related to easier implementation with shorter treatment times and decreased labor intensity.[12]

The demographics were fairly similar between machine types. Our data showed that GK systems had the largest percentage of locations in academic centers. Multiple factors could explain this association including cost, need for ancillary support, and the historical evolution of SRS within such centers, but this requires further investigation for quantification. Nonacademic centers and regions of higher household income were associated with CK systems on multinomial regression. Although a

cost analysis is beyond the scope of this paper, this association may stem from differences in billing, reimbursement and/or marketing for this SRS system.

Compared to the total distribution of SRS machines in the United States, several states had low distribution ratios. Although its utilization is increasing,[2] the demand for SRS systems is not well-defined. Based on the 2017 Leksell Gamma Knife Treatment Statistics Report, brain metastases accounted for the largest percentage of cases (47%), followed by meningioma (17%) and vestibular schwannoma (12%).[13] As more studies show high local control and low normal tissue complications with SRS for brain metastases,[14,15] the demand for SRS may rise. Additionally, with advances in oncologic therapy and improved imaging techniques, the utilization of SRS to treat intracranial metastases may further increase. Our aim is to provide a snapshot of the distribution of SRS equipment in the United States, although further investigation into potential disparities in access to SRS care may be warranted.

Additional limitations of our study include a potential lag time between the installation or decommission of an SRS system and the associated update on the respective manufacturer website. The random telephone-call sampling did confirm the existence and types of the SRS systems, although a couple had been modified or upgraded. This analysis did not consider general-purpose linacs that can potentially deliver SRS or less common SRS systems. Therefore, the degree to which linac-based SRS is utilized relative to GK and CK may be more pronounced, and we acknowledge that the number of procedures performed on nondedicated systems may be higher than those performed on dedicated systems.

Our database (available at appliedradiationonlcology.com/articles/SRS-in-the-US) is the most recent and comprehensive list of dedicated SRS systems in the United States of which we are aware and potentially identifies areas that may be in need of such technology. It can provide patients with a resource for the multiple types of SRS systems available by location and perhaps decrease institutional limitations that restrict patients to one specific type of system. Additionally, it allows physicians and managers to visualize and understand the current distribution of SRS systems in their market and in the United States, which may guide future decisions when purchasing new equipment. This database can also serve to motivate future analyses that could further explore potential discrepancies in accessibility.

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VIEWPOINT

First-year fears and fundamentals: An open letter to new radiation oncologists

Stuart E. Samuels, MD, PhD

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To all new graduates of a radiation oncology residency: The first year as an attending can be the most challenging year in a medical career. This is no truer than in radiation oncology. You have just graduated residency and now you must manage your first real job. For the first time in your medical career, what you do matters, and the buck stops with you. Additionally, you are likely in a new environment with new people and technology that is different from where you trained. You are also probably moving into a new home in a new neighborhood. In short, everything is new, and pressure is high. And did I mention the board exam is less than 10 months away? Feeling the stress?

Before we delve into a myriad of topics, some quick advice:

Take a breath. You made it. You have completed 9 to 13 years of training, have finally graduated, and you have a job—so congratulations, and relax for a minute.

Remind yourself that you have prepared for this. Being an attending is significantly more stressful than being a resident. You will agonize over small details in plans and second guess yourself constantly. Remind yourself, there is nothing coming at you that you cannot handle.

Trust your training. You will see a lot of variations in how to treat every disease site. You may or may not decide to incorporate other ideas into your treatment algorithms, but no matter what you do, be able to justify it to yourself. Never treat in a way you are uncomfortable with, even if others think you should.

You have a lot to learn. You are at the beginning of your career. Everyone you meet in the department has more experience than you. Be open to learning from them.

Be ready to work hard. At least initially while getting familiar with your new environment, you may be working more hours than you did during residency. It will take time to feel comfortable in your new position and work out the kinks in the workflow. Things will get harder before they get easier.

I am not a mental health professional or life coach. I am just a colleague who has been through this journey and hopes to impart some advice based on my and other's experience that I wish someone had given me. Below are topics and challenges experienced by first-year attendings—a list by no means exhaustive.

Attitude

As with most things, it is important to have a good attitude when entering your first job. Be optimistic that this could be a long-term position and take roadblocks in stride. Try not to let minor problems derail your attitude. Most roadblocks are really just opportunities for improvement. As the newest person to the practice, you may be given a schedule that is not ideal, asked to cover for others more than you expected, be told you need to take call on holidays, or find that your time off is limited because of others' vacation. This may feel like abuse or "hazing," and you may feel obligated to comply with all requests out of concern for job security. You should realize that most of these fears are unwarranted and are a relic of feelings and expectations acquired during medical

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school, internship and residency. While there is some hierarchy in any practice, most physicians understand that new attendings are partners in the practice and do not want to create a hostile work environment. Some of us have a people pleasing personality and say yes to everything. Others may feel the need to say no to protect themselves. Neither way is ideal. My suggestion is to become the "yes, and" person. Be willing to say yes and, while saying yes, be sure to voice requests and ask about compensation for extra effort. Be flexible and accommodating but not foolish. If you take call one holiday, make sure you get the next two off. If you cover for someone, make sure to say that you will look for a time they can cover for you. In this way you can help out but not feel taken advantage of.

Finally, and probably most importantly, you should voice concerns of unfair treatment or division of responsibilities. If you feel you cannot express yourself, or are not being heard, you may need to look for another job.

Loneliness

The first year of practice is very lonely. Until now you have been constantly surrounded by friends and colleagues. In medical school, internship and residency, there were always others going through the same thing who you could talk to and empathize with. In short, you had a support group, a community. In addition, you had supervisors you could trust because there was always a dean, program director or mentor who was invested in you and who you generally felt had your best interests in mind. Additionally, at your training center, you were slowly oriented to the clinic and introduced by others to all the necessary people and items to be successful at your job. By the end of your training you knew all the radiation staff, all the referring doctors by name, and generally how to navigate your hospital. All this changes with your first job.

You are likely to be the only new person hired to your institution and need to figure things out yourself. You may not be introduced to anyone. Except for teaching you how to use the electronic medical record (EMR), no one in your office is likely to train you on how to do anything. You will have a boss, but no one is supervising you directly and no one is invested in your career anymore. This freedom is liberating, but it is also terrifying and lonely.

Additionally, you will spend a lot more time by yourself at work than you ever have. Until now, you have been constantly surrounded by other medical students, residents and attendings. Even when you did work by yourself, when you finished you had to interact and speak to another resident, attending or someone about your work. As an attending, you may spend hours writing notes, contouring volumes and responding to emails, and you may not see another individual all day.

My advice is this: First, do not be discouraged. Everyone feels lonely in the beginning and it will pass as you acclimate to your new work environment. Second, make some friends because you are not and cannot function as an island. You may want to sponsor a breakfast at your clinic (donuts and coffee are cheap) as you introduce yourself to the staff. You should also make a conscious effort to learn everyone's name. This may seem obvious, but for many people it is not. Also, when you first start and when the clinic is not busy, you may want to schedule time with your administrators, dosimetrists and physicists to talk about their jobs and how you can smoothly transition into the clinic. I also recommend finding a work friend such as another physician in your group—someone you can trust—to become your ally. Finding a work friend takes time and effort but will make your life at work much more enjoyable. Finally, attempt to participate in your practice's social events as this will build social capital and help integrate you into the group more quickly while staving off loneliness.

If you are experiencing severe depression or adjustment disorder that does not improve after several months, see a medical professional.

Support Staff

Communication with your support staff, and by this I mean your administrators and schedulers, is essential. Discuss how you would like your clinic run. Discuss how many new patients, and how many follow-ups you want to see. Discuss what day will you see the on-treatment visits and make sure there are fewer slots for consults and follow-ups. In the beginning, I would recommend no more than 2 new patients (1-hour slots) per 4-hour clinic and fill the rest with follow-ups (30-minute slots). Your clinic will not be busy in the beginning (unless you inherit a service) and you should use your time to study for the board exam.

Nursing

Remember that you are the new person and you are being inserted into a clinic that already functions in a particular way with its own unique culture. Nurses may have different roles in different clinics. Discuss with the nurses in your clinic how they function and what to expect, how long they take with each patient, and how long for a patient to be roomed. Some nurses take vitals only while others do a complete intake of the history. My suggestion is, at least in the beginning, not to make big changes in the nursing protocols until you have more experience in the clinic. Saying things like, "During my training, nurses were involved in consenting patients and scheduling treatments," in a clinic where that is not the norm will prompt an eye roll and a negative interaction.

Simulation

Discuss with the simulation therapist the immobilization devices that are available. Often the simulation capabil-

ities you trained with are not available. For example, many computed tomography (CT) simulators cannot give contrast. In that case, you should register a diagnostic CT. Some simulators do not have breath-hold, in which case you may want to consider prone for left-sided breast treatments and larger clinical target volumes (CTVs) for free-breathing lung treatments. If they do not have what you are familiar with, discuss the alternatives. Do not get bogged down with devices, as they are only tools. Do not think that if you do not have a vacuum-locked bag you cannot do spine stereotactic body radiation therapy (SBRT). The purpose of the bag is to create reproducibility. If you can get this with a compliant patient on a simple mat and can verify it with a cone-beam CT, SBRT is safe. Think about how you want to immobilize the patient and then ask the therapists what they suggest. It is important to be flexible and thoughtful.

You will need to place a simulation order for each patient describing the setup you want. For the first several patients, I suggest you ask the simulation therapist to call you after the patient is immobilized but before the CT to confirm you like the setup. You may realize that you were not clear in the instructions or that the therapist misinterpreted your order. This is the time to clarify what you want and how they should proceed in the future. Once you have confidence with the immobilizations and that the therapist is following the simulation orders as you request them, then you do not need to see the setup before the CT. As with being called to the linac, as described later, when you are called to the simulator, you should go ASAP, even if it means interrupting another encounter.

Volume Contouring

At this point in your career, you should be fairly comfortable with contouring as this is where we spend the most time training during residency. For a comprehensive site-specific review, see Chhabra et al 2018.[1] You must give yourself time to do the contours as this is the most essential part of treatment planning. In fact, as a new attending, you may need extra time to contour or to look at atlases (I continue to look at atlases often). Additionally, some disease sites by the very nature of their complexity, like head and neck, require prolonged contouring regardless of skill. Even after a few years of treating head and neck cancer, it still takes me an hour to complete volumes. Review your clinic schedule and make sure you have enough time for this task. My suggestion is to have at least 2 half days during the week, one in the beginning of the week and one at the end, when you know you can get volumes done. This is often not possible in busy clinical practices where you see patients every day. If that is the case, you may need to contour after hours. You should try to get the volumes done within 3 days of the simulation to avoid treatment delays.

It is appropriate to ask a dosimetrist for help, especially for contouring normal structures. In many institutions, dosimetrists contour most or even all the normal structures. If they do, be sure to review them prior to treatment planning. Small changes in an organ at risk (OAR) can have large consequences on the dose-volume histogram (DVH).

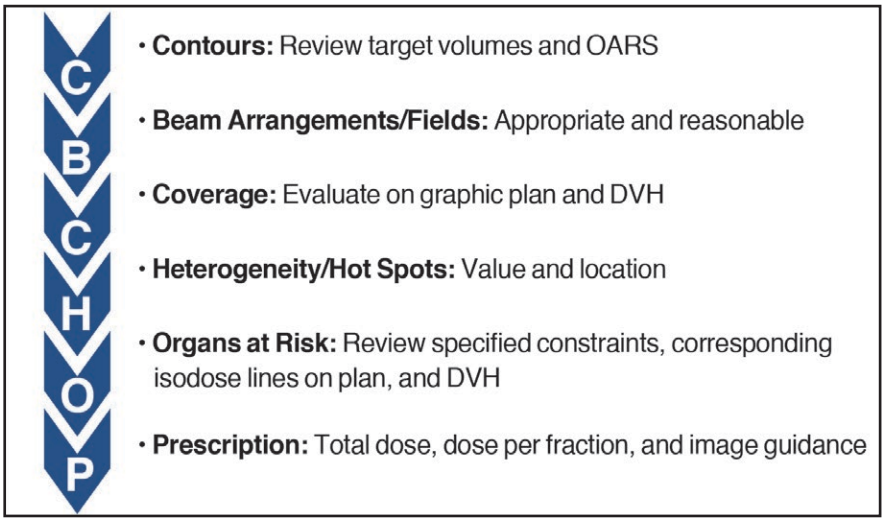

***FIGURE 1**. Flowchart diagram summarizing the CB-CHOP acronym and components of plan quality.[8] Key: OAR = organs at risk, DVH = dose-volume histogram. Reprinted with permission from the authors.*

Regarding planning target volumes (PTVs), a review of relevant literature[2-7] and a discussion with your physicists about the immobilization devices and machine capabilities will help you determine a safe PTV for each disease site you treat. You should try to treat with standard PTVs of 0.5 cm for most sites and a 0.3 cm PTV when using an Aquaplast mask and cone-beam CT (CBCT). Small variations are acceptable.

Dosimetry

This group is often the most experienced and will be your greatest teachers. There is nothing better than an experienced dosimetrist who knows exactly how to plan. Alternatively, there is nothing more frustrating than a bad dosimetrist who struggles to make decent plans. It is important to tread carefully in this arena because often dosimetrists are used to doing things a certain way and do not like variations. That being said, there is no such thing as a perfect plan. We are spoiled in residency with excellent dosimetrists who have been working with the same physicians for years who produce excellent plans on the first try. This is not often the case in practice.

Trust your training, and know it is often necessary to teach the dosimetrists how you like plans done, what priorities you place on different OARs, and what techniques you suggest they employ. Also, you must consider the deviations you are willing to accept and how many plan revisions are worth the effort. After finishing volumes, it is often beneficial to have a brief conversation with the dosimetrist about your priorities and how you want the patient planned. Even if these are in the prescription or treatment planning note, a direct conversation is often worthwhile. There is no such thing as over-communicating. However, be kind and tread carefully.

For plan review, a recent publication in *Applied Radiation Oncology*[8] suggests using the mnemonic CB-CHOP (**Figure 1**) to remember the components: contours, beam arrangements/fields, coverage, heterogeneity/hot spots, organs at risk, and prescription. Please refer to that publication for details. Even as you become more experienced, it is a good habit to review it in every plan to avoid errors.

If after several plans it appears the dosimetrist is just not getting it, kindly suggest that another dosimetrist, preferably one with more experience, look at it. Also, feel free to contact the dosimetrists you trust at your training program for quick suggestions that may save a lot of time.

Finally, you will occasionally remember something after the plan is made that will require a re-plan. DO IT! Don't worry about the wasted time or the eye rolls. Apologize, and try not to make it a habit.

Image Review

A task rarely performed by residents but required by attendings is daily image review. This tedious task needs to be completed after every treatment and before the patient's next treatment. You will need to carve out time at the day's beginning or end to do this. As with treatment plans, there is no such thing as a perfectly reproduced setup. You will need to decide whether each image is acceptable or unacceptable. This can be difficult but my general rule is this: If the deviation from the digitally reconstructed radiograph (DRR) to the daily image is less than or equal to the PTV, I accept it. After all, this is why we put on PTVs, ie, to account for the daily set-up error. Also, it can be frustrating for the therapists to adjust for 1 to 2 mm.

You will be asked to come to the treatment machines to review the setup for a treatment start. This is often called a simple simulation or sim 2. Please be prompt and go ASAP. If you need to interrupt a consult, so be it. Keeping treatment machines on time is an essential part of the clinic.

Sometimes during this simple simulation you will see difficult-to-assess images, such as MV imaging of the spine for a palliative treatment. Perhaps the therapists think they are aligned but you cannot tell. Trust that if you cannot see it well, neither can the therapists. Ask them to show what they are matching to. If it seems reasonable, then proceed. If not, check the patient setup in the room, and perhaps ask them to take another angle (like an oblique) or a KV image, or even a CBCT. It is much better to take longer and ensure the patient is in the correct setup than to rush through the approval process.

Therapists

Talk to the therapists about how you like setups, what you feel is reasonable and when you should be called to the machine. When called to a treatment machine, a physician should interrupt any other activity and go to the machine as soon as possible. This includes other patient encounters including consults and follow-ups. Politely apologize for the momentary interruption and go to the machine. A patient may not be tolerating the treatment or there may be a clinical issue to attend to. While the therapists are good at their jobs, remember they have no clinical training whatsoever and so cannot assess patients. Additionally, delays on the treatment machine should be avoided as much as possible. Therapists also look favorably upon doctors who are prompt and do not cause delays. You want to be that doctor.

Chart Rounds

The purpose of this conference is to do a clinical peer review at the beginning of all treatments to ensure safety. This conference often takes quite a while and it is important to vet the chart efficiently and quickly. This is also where your treatment approaches will be critically appraised by your more experienced peers and your treatments will be criticized or corrected. Think of yourself as a sixth-year resident in this conference. You have a lot to learn, and this learning is hands on. You *will* make errors and you *will* be corrected. That is a good thing and it will make you a better doctor. Most errors will be minor or simply a variation of a standard practice and will not require any change in the plan. Some may be serious enough to require a change in the treatment plan. If so, change it. I learned more in the chart rounds my first year as an attending than I ever did as a resident. As a resident I was focused on the presentation and whether I would be "pimped" on the disease. As an attending you quickly get past the presentation and can focus on the volumes and think more generally about the treatment approach. Best not to have an ego for this part. If you feel attacked, it is because the other doctors do not know how to communicate effectively. Hopefully you will be with experienced physicians who will help you become a better doctor.

You will also find that many colleagues are treating patients in a nonstandard way. You may feel that some practices are unethical (eg, long palliative courses or use of intensity-modulated radiation therapy [IMRT] when

not indicated to make extra money), or potentially even harmful (undertreatment because of excessive or unreasonable concern for OAR limits, or overly aggressive treatment that compromises OAR limits). It is challenging to give feedback to more senior attendings. However, trust your training and if you think an error has occurred, express your concern. Be diplomatic. Instead of attacking the other physician, it is perfectly appropriate to say, "I am not familiar with how you are treating this patient, what literature is it based on?" If the colleague can justify the treatment, then great. You can also say, "Based on how I trained, I might suggest…" and then give one or two suggestions in a nonthreatening way. If I find several things to be unusual in a treatment plan, I might only pick one or two to mention at the conference, specifically those that make the plan unsafe. Remember, there are many ways to treat and just because it is not your way, does not make it wrong. Learn to appreciate others' approaches.

It is often a good idea to sit down with your new boss and other attendings in your group to discuss general approaches to cancer treatment. A good institution will allow you to treat how you prefer as long as you can justify it, but some places have specific preferences. Generally speaking, you should give considerable weight to the way cancer has been treated at your new institution even if you are not familiar with it. First, you may learn something new. Second, it is very difficult to change a practice as the new person. If you find yourself constantly at odds with your colleagues about the way to treat patients, you may not have found the right job.

Finally, and importantly, own up to mistakes. Do not defend or hide them. If you make a serious error that harms or potentially harms a patient, be upfront and contact risk management. You are a professional in charge of peoples' lives and must take responsibility for your actions. This is also the best way to avoid losing your license.

You have a lot to learn, and this learning is hands on. You will make errors and you will be corrected. That is a good thing and it will make you a better doctor.

Clinical Mentorship

Especially in the first year, it is common to have uncertainties even about the simplest cases. There is no shame in asking for help. As discussed above, you may feel alone and do not want to ask your new colleagues for help for fear of appearing incompetent. I think this is a mistake. Humility and honesty are not weaknesses, but strengths. You should try and find a mentor at your new institution from whom you can solicit advice and trust.

If you absolutely feel there is no one at your institution to ask, remember you still have resources from your training institution. Do not hesitate to contact mentors from residency about difficult cases or to use them as a sounding board for thoughts. I found that as I gained experience and confidence I reached out less, but it was comforting to know that expert opinions were in easy reach.

Documentation

You are required to document everything you do in the clinic. My suggestion is to make templates (I modified mine from residency). Also, you should ask colleagues how they document. Frequently, radiation-specific notes are created and stored in Aria (Varian, Palo Alto, California) or other patient-tracking programs. Work with your IT team on streamlining the documentation process.

Billing and Productivity

This is a topic never mentioned in my residency. You need to stay productive to prove you are worth the investment to the practice. Everything you do in the clinic is given a relative value unit (RVU). Therefore, you can look at your RVUs and determine your productivity. Make sure to clarify how your practice accounts for professional codes (patient encounters) and technical codes (treatment planning and delivery). Discuss with your new boss your productivity expectations and what happens if you either exceed or fail to meet those goals. Most practices realize that the year after graduation consists of practice building and studying for the board exam and do not have high productivity expectations.

I would suggest reviewing the American Society for Radiation Oncology (ASTRO) coding guidelines found at https://www.astro.org/Daily-Practice/Coding/Coding-Guidance. Even a cursory understanding of billing and coding will help maximize your productivity. If you think coding is dense and complicated, remind yourself that you passed neuroanatomy in medical school and it can't be more complicated than that.

Talk to your billing department and ask what documentation is required for a level 3, 4, and 5 consult and follow-up. Ask what documentation is allowed for different procedures and where the documentation needs to go. Two physicians with the same clinical load may have different RVUs depending on how each documents and bills.

In general, consults are billed based on complexity and amount of time required for the consultation. Most radiation oncology consults are going to be billed as level 5 because cancer patients have complex disease processes and complex coordination of care. Simple consults like keloids, heterotopic ossification, eye plaques and other sites where there is relatively little complexity can be billed as level 3 or 4.

Follow-ups are also billed based on complexity and I use a similar algorithm as consults. Level 3 follow-ups are simple follow-ups such as breast cancer that require little coordination. Level 4 follow-ups are those with new imaging or pathology to review or moderate coordination of care. Finally, level 5 follow-ups involve patients with disease progression who require more treatment.

For those who cover hospitals, inpatient consults only have 3 levels, 1, 2, and 3 and I use the same algorithm as above. Generally speaking, most inpatient consults are complex and I almost always bill a level 3.

Referring Physicians

In my practice, I interact with referring oncologists and surgeons more than my fellow rad onc colleagues. Ask the other members of your practice who your referring providers are and reach out to them. Tumor boards, if you have them, are a great place to introduce yourself. You can always find office numbers on the internet and you can usually manage to locate an email address or a cell phone. Give out your cell number to all referring providers and let them know you are available any time to discuss or see a patient. You want your referring physicians to know you are available, even on short notice, and are willing to overbook your clinic to accommodate requests. All things equal, referrers are more likely to send patients to someone who will see them quickly. This is probably the most important aspect of building a practice. I also recommend a follow-up call or email to the referring provider after a consultation or follow-up, even if you are sending them your clinic note. It helps maintain the relationship.

Board Studying

While learning a new system and building a practice, you'll feel a gnawing thought in the back of your mind: preparing for the boards! Thankfully you do not need to worry about the boards until the second half of the year so I would not even pick up a book until at least January. Take the first 6 months and just adjust to the clinic and the new work environment. Starting in January I would find a study group (your co-residents or other new attendings) and start systematically covering all the disease sites on a weekly or biweekly schedule until April, and then spend the next few weeks practicing the templates and algorithms and memorizing the details of each site. Board study is a much longer topic that will not be addressed here. Suffice it to say, it can wait until after the new year.

Moving On

Many of us don't know what kind of job we really want (although we think we do) and we are thrilled to have any job upon graduation. There may be moments of disillusionment when you think this is not what you expected and you are unhappy. Feelings of depression and "burnout" are common in our field.[9,10] When you graduate residency, there is no magic that takes the stress out of life; there are just new stresses. Unfortunately, there is no pot of gold at the end of the rainbow; there is no perfect job.

Because the beginning is so tough, I would suggest giving your job at least 2 years before deciding to leave. You need to time to adjust and you do not want to change jobs while preparing for the board exam. However, if you feel you have a hostile work environment or overall disappointment and efforts to improve the situation have failed, you should consider finding a new job. I would simply suggest examining all the angles before quitting, as the proverbial grass is not always greener.

First Patient Anecdote

My very first patient as an attending must have sensed my anxiety (and perhaps I look young) because she asked the one question every new attending dreads: "How long have you been doing this?" Without hesitating, I said, "Five years," because I included internship and residency. After all, I am not new to medicine or radiation. I am well trained, and she should know she is in good hands.

I am sure I have missed many topics, but hopefully these experiences and tips will help you prepare for a successful first year and navigate the exciting, sometimes daunting, but ultimately rewarding road ahead.

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The outlook and potential of combined radiation therapy and immunotherapy

Mary Beth Massat

The field of immunotherapy has progressed rapidly since the approval of the CLTA-4 blocking antibody ipilimumab for metastatic melanoma in 2011. Immunotherapy uses substances made by the body or in a laboratory to boost the body's natural immune system function to fight cancer. It includes monoclonal antibodies and tumor-agnostic therapies, T-cell therapy, nonspecific immunotherapies, oncolytic virus therapy, and vaccines.[1]

Excitement is also mounting for the potential to use immunotherapy in conjunction with radiation therapy (RT). This interest, says Ralph R. Weichselbaum, MD, chair of the Department of Radiation and Cellular Oncology at The University of Chicago Medicine, is partially due to the use of immunotherapy in patients who likely would have died from their disease, but instead had prolonged survival or have been cured.

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"A healthy immune system is likely to be important for radiation therapy to be successful," Dr. Weichselbaum says. "This knowledge comes to us from animal models and some clinical observation. Whether radiation therapy and immunotherapy have a successful interaction in the context that a lot of people, including myself, think it might, is still open to question."

Much of the clinical data is preliminary and many confounding variables make interpretation difficult. However, initial experimental and human data in the context of case reports or small trials are impressive.

Although data are limited thus far, an array of clinical trials are examining combinations of RT and immunotherapy across different clinical settings, such as metastatic or locally advanced cancers, as well as in various types of cancers.

"Ultimately, what we need are hypothesis-driven studies that scientifically look at each aspect of the combinations to really understand the mechanisms by which there is synergy between radiation therapy and immunotherapy," says Abhishek Solanki, MD, an assistant professor with clinical expertise in radiation oncology at Loyola University Medical Center in Maywood, Illinois.

Trials to Watch, Trails to Forge

Jonathan D. Schoenfeld, MD, MPH, associate professor of radiation oncology at Harvard Medical School, and radiation oncology director of the Melanoma Disease Center at the Dana-Farber Cancer Institute in Boston, is leading a phase II multi-institution trial sponsored by the National Cancer Institute (NCI). The trial is evaluating the immunologic effects of RT and the impact of combining radiation with durvalumab and tremelimumab in patients with metastatic colorectal or non-small cell lung cancer (NSCLC). He

Perhaps debulking the tumor with stereotactic radiation decreases the T-cell exhaustion and this could be one mechanism by which radiation therapy may help immunotherapy be more active.

Abhishek Solanki, MD

also believes that the most impactful studies will examine the use of radiation in patients for whom immunotherapy either hasn't worked or where only a minority of patients have responded.[2]

"We want to take these novel agents and then test in a step-wise fashion the addition of radiation therapy," Dr. Schoenfeld says. The study is comparing patients who receive immunotherapy alone against those who receive combined immunotherapy and RT.

Patients are randomized to three groups: group A receives only durvalumab and tremelimumab immunotherapy; group B receives immunotherapy and high-dose RT; and group C receives immunotherapy and low-dose RT.[2]

"We are collecting blood and tissue samples from these patients and looking before and after radiation therapy to look for changes in blood and the tumor that we don't see in the group receiving immunotherapy alone," Dr. Schoenfeld explains. "With biopsy and blood samples, we hope to understand what radiation therapy is adding to the immunotherapy or what the immunotherapy is adding to radiation therapy."

This potential synergistic relationship between RT and immunotherapy is a key research theme. Dr. Weichselbaum has been involved in numerous studies assessing the combination of immunotherapy and radiation therapy. In 2018, a group from the University of Chicago examined the safety and toxicity of pembrolizumab and multisite stereotactic body radiation therapy (SBRT) in patients with metastatic solid tumors. While the combined treatments were well tolerated with acceptable toxicity in the phase I study, additional studies are needed to further examine the clinical benefit and predictive biomarkers.

"The use of combined immunotherapy and radiation therapy looks relatively safe—that's what these phase I trials will tell us," Dr. Weichselbaum says. "We also need to work out the timing, at least in terms of checkpoint inhibitors. How much do we treat with radiation? Is it a local or systemic effect, such as the abscopal effect?"

The abscopal effect is a systemic immunologic response initiated by localized radiation that results in activating the immune system to kill cancer cells distant to the primary target. A systematic review of studies on the abscopal effect suggests that the effect seems to occur in the setting of radiation therapy with immunotherapy.[3]

The optimal RT target site to maximize immune-activation is also unknown. Dr. Solanki is the lead author in a review of published studies examining the combination of immunotherapy and RT in genitourinary malignancies. In the article, the authors note that in a phase I trial combining radiation with SBRT in patients with visceral metastases, irradiating the liver lesions led to a greater immunologic response than treating lung lesions.[4]

The PACIFIC Trial also examined the use of durvalumab after chemoradiotherapy in patients with locoregionally advanced NSCLC.[5] This study randomized patients with stage III lung cancer receiving standard chemoradiation and, if they didn't progress, patients were randomized to placebo or durvalumab immunotherapy. Patients receiving immunotherapy had significantly longer progression-free survival and overall survival in the group that received durvalumab.

"Perhaps debulking the tumor with stereotactic radiation decreases the T-cell exhaustion and this could be one mechanism by which radiation therapy may help immunotherapy be more active," Dr. Solanki says. "Or, treating multiple tumors may release different tumor antigens that are local to that tumor and the tumor microenvironment, so there may be a larger mileu of antigens for the immune system to work

Whether biomarkers can predict success of immunotherapy and radiation therapy combinations where neither were successful alone is a longer story and a harder question to answer.

Ralph R. Weichselbaum, MD

against. We don't yet know the right number of lesions or sites to treat with radiotherapy to augment immunotherapy."

There is also the question of how chemotherapy fits in with immunotherapy. Does it augment immunotherapy and radiation therapy or does it interfere or decrease the interaction between radiation and immunotherapy?

"In general, we don't know what additional modality will help immunotherapy the most," says Dr. Solanki. "We as a field need to find something that works."

Another area of investigation in the use of immunotherapy and radiation therapy is biomarker discovery. Current biomarkers for immunotherapy include PDL1 expression, T-cell type and characteristics, and tumor mutational burden, although Dr. Weichselbaum says some of these biomarkers remain under evaluation.

"Whether biomarkers can predict success of immunotherapy and radiation therapy combinations where neither were successful alone is a longer story and a harder question to answer," says Dr. Weichselbaum.

There is also interest in how radiation therapy changes inflammation in the blood and changes DNA damage in a way that stimulates the immune system, Dr. Schoenfeld explains. "Probably the most exciting work that's been done is investigating if radiation therapy wakes up the immune system to recognize parts of the tumor that weren't recognized before."

For example, T-cells may be recognizing more or different parts of the tumor after radiation when it is combined with immunotherapy. A recent study by Silvia Formenti, MD, et al, reported that radiation therapy in combination with a CTLA-4 blockade induced systemic anti-tumor T-cells in several chemo-refractory metastatic NSCLC cancer patients for whom the previous use of the anti-CTLA-4 antibodies by itself and with chemotherapy did not demonstrate significant efficacy.[6]

Toxicity is another area where data is unclear, although the combination of radiation therapy and immunotherapy appears to be relatively safe.

"We are not seeing high toxicity rates or unexpected toxicity developing in patients receiving combination treatments of radiation and immunotherapy," says Dr. Schoenfeld. However, he cautions that extended patient follow-up is needed to ensure that radiation doesn't increase long-term toxicity. Also, newer immunotherapy treatments will need to be carefully evaluated for both initial and late toxicity.

"Based on the data we have today, we know enough that for most patients who need palliative radiation therapy and could benefit from immunotherapy, it is probably safe to try those treatments either at the same time or close in time to each other," Dr. Schoenfeld adds.

The bottom line is, there is still much to learn about immunotherapy and what factors will help patients the most. Adding to the challenge are the many variables in cancer care—from the location of the primary disease and metastatic involvement to prior treatments and response. That's where personalized medicine, artificial intelligence (AI) and machine learning (ML) are poised to help.

Personalizing Care

"Radiation therapy may be a way to personalize immunotherapy, to use radiation as a personalized vaccine," says Dr. Schoenfeld. "That's a big subject of research, however, [and] we are still developing the capabilities to give radiation to a patient, targeting more than two to three areas at the same time. We are almost at the limit of what we can do with limited manpower and limited time to plan and deliver treatments. That's one area

Probably the most exciting work that's been done is investigating if radiation therapy wakes up the immune system to recognize parts of the tumor that weren't recognized before.

Jonathan D. Schoenfeld, MD, MPH

where artificial intelligence and machine learning can offer an opportunity to help us integrate all this information that gets increasingly complex and take it into account [for each patient]."

Personalized medicine, guided by AI and ML, could also be invaluable in helping identify patients who will benefit the most from immunoradiotherapy.

"Where AI and machine learning may be most useful is to help us with precision medicine to best select treatments that are most likely to help the patient in front of you," says Dr. Solanki. While the jury is still out regarding a synergy between radiation therapy and immunotherapy, Dr. Solanki believes immunotherapy will play a greater role in patients with localized disease who are receiving RT and, conversely, radiation will play a larger role in patients with stage 4 metastatic disease.

"It is possible that we will see a shift in the general radiation oncology clinic toward a higher volume of metastatic patients who we are treating with radiation, both potentially for synergy with immunotherapy but also in the setting of oligometastatic disease. There are increasing data showing that in the setting of oligometastatic disease, radiation or surgery as metastasis-directed therapy can help improve survival in patients with limited metastatic disease," Dr. Solanki adds.

Dr. Weichselbaum also notes that immunotherapy may be used earlier in the disease process to treat primary tumors and prevent metastases. Ideally, more organizations such as the National Institutes of Health and the American Society for Radiation Oncology (ASTRO) will fund more radioimmunotherapy research.

"We need skilled investigators looking at interactions," he says. This includes biomarker discovery—biomarkers that can indicate who will and who will not respond as well as biomarkers that may potentially block the combination effect of immunotherapy and radiation therapy.

"There is also the idea of personalized vaccines, where we can determine the antigenic peptides and develop a vaccine that could be combined with radiotherapy," adds Dr. Weichselbaum. "These are some of the ways we might be able to personalize future cancer treatments."

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Scalp seeding after resection and stereotactic radiosurgery for solid tumor brain metastases

Siobhra O'Sullivan; Maeve Keys; Ronan McDermott; David Fitzpatrick; John Armstrong, MD; Pierre Thirion, MD; Clare Faul

CASE SUMMARY

Following surgical resection of brain metastases from solid tumors, adjuvant stereotactic radiosurgery (SRS) is increasingly used instead of whole-brain radiation therapy (WBRT). We report 2 cases of subcutaneous recurrence along the surgical tract following craniotomy and SRS for solid tumor metastases, along with a review of the literature. There was no evidence of extracranial disease in either case.

Case 1

A 56-year-old man with a background history of transitional cell carcinoma (TCC) of the bladder had been treated with cysto-prostatectomy and adjuvant chemotherapy in 2017. He presented 1 year later with headaches, ataxia and visual disturbance. Examination revealed a right homonymous hemianopia. Contrast-enhanced magnetic resonance imaging (MRI) of the brain showed 2 enhancing lesions of the left occipital lobe (**Figure 1A**) and left cerebellum, measuring 2.5 cm and 2.6 cm, respectively. He underwent craniotomy with a postoperative brain MRI showing complete resection of the left occipital lesion (**Figure 1B**) and an 80% resection of the left cerebellar lesion. Pathology was consistent with metastases from TCC. He was treated with adjuvant SRS to the resection cavities to a dose of 24 Gy/3 fractions prescribed to the 80% isodose line with a 2-mm planning target volume (PTV) margin (**Figure 1C**). At a 3-month follow-up, the patient reported worsening ataxia and an increasing subcutaneous mass at the occiput. Investigation with contrast-enhanced CT showed multiple cystic metastases within the cerebellum as well as subcutaneous deposits along the surgical tract consistent with surgical tract recurrence (**Figure 1D**). He was treated with salvage WBRT to a dose of 30 Gy/10 fractions but died shortly after.

Case 2

An 80-year-old woman with a prior history of 2 primary malignancies: 1) a non-small cell lung cancer (NSCLC) (adenocarcinoma) treated with SBRT to the lung in early 2016 followed by chemoradiation for early mediastinal nodal progression the same year, and 2) a clear-cell renal carcinoma treated with nephrectomy in 2016. Two years later she presented to the emergency department with new onset confusion. Contrast-enhanced computed tomography (CT) and brain MRI revealed a solitary left frontal enhancing mass with surrounding vasogenic edema (**Figure 2A**). She underwent frontal craniotomy with gross total resection of the tumor (**Figure 2B**) and completed adjuvant SRS to the resection cavity to a dose of 30 Gy/5 fractions prescribed to the

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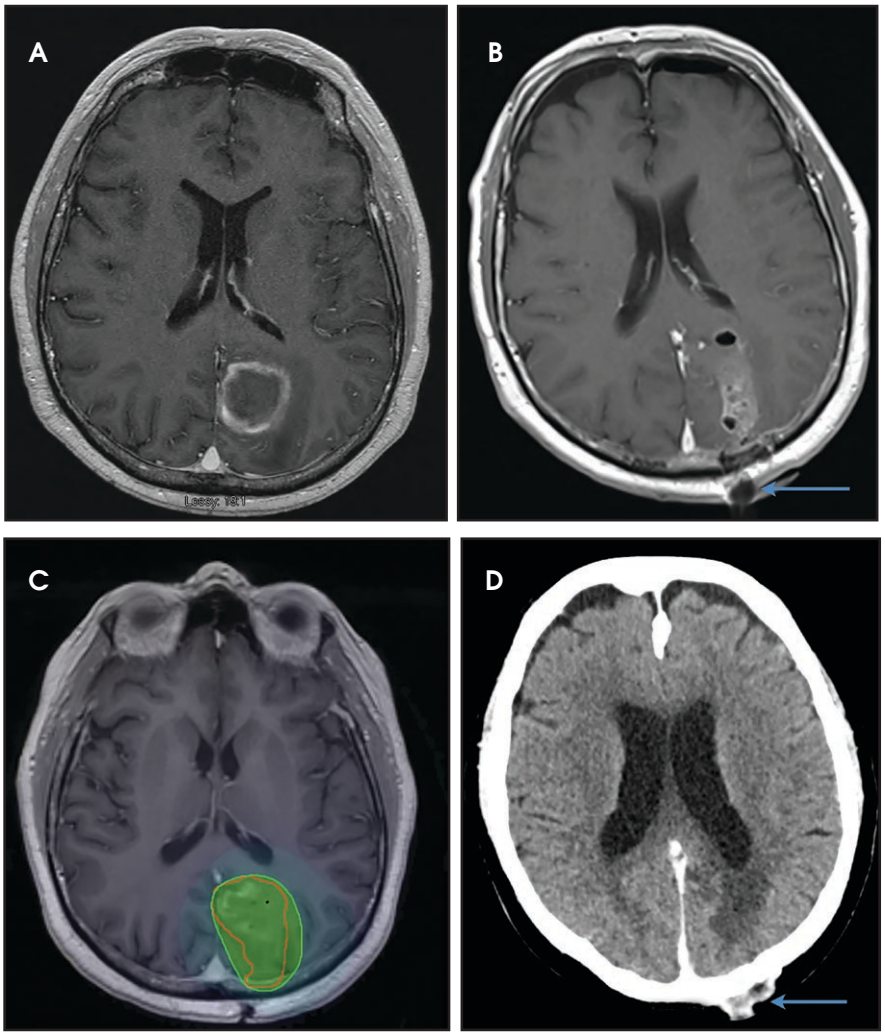

FIGURE 1. *(A) Preoperative MRI showing enhancing mass of the left occipital lobe. (B) MRI 48 hours postoperatively showing complete resection of the mass with surgical tract (arrow). (C) SRS plan showing the PTV (orange) and the prescription isodose line in green. Lower isodoses are represented by color wash. (Note there is a difference in slice angle of the planning scan compared to the diagnostic images.) (D) CT imaging at 3-month follow-up showing subcutaneous recurrence along the craniotomy tract (arrow). Key: MRI = magnetic resonance imaging, SRS = stereotactic radiosurgery, PTV = plannting target volume, CT = computed tomography.*

80% isodose line with a 2-mm PTV margin (**Figure 2C**). Pathology was consistent with a metastasis of lung origin. She presented 3 months later with an enlarging scalp lesion. Investigation with contrasted-enhanced CT and MRI confirmed subcutaneous disease along the craniotomy site (**Figure 2D**), with further intracranial parenchymal progression in both frontal lobes for which she was asymptomatic. There was no extra-cranial disease on positron emission tomography/CT (PET/CT). Biopsy of the scalp mass was thyroid transcription factor 1 (TTF-1) positive consistent with local recurrence of NSCLC following craniotomy. She was treated with salvage WBRT with bolus over the skin lesions to a dose of 30 Gy/12 fractions. She has stable disease on follow-up and is due to commence treatment with pembrolizumab.

DISCUSSION

Until recently, postoperative WBRT has been the standard of care for patients with resected brain metastases. This was based on 2 landmark trials by Patchell et al showing improved intracranial control and lower rates of neurologic death when compared with either modality alone.[1,2] With a WBRT technique, however, irradiation of large volumes of normal brain tissue results in deterioration in medium and long-term neurocognitive function and quality of life.[3-7] Postoperative surgical cavity SRS has the potential benefit of allowing delivery of high doses to the target and sparing healthy brain tissue. When compared to postoperative WBRT, surgical cavity SRS results in increased rates of distant intracranial recurrence (including leptomeningeal recurrence) and also unexpectedly worse local control in some studies,[7,8] yet the lack of an observed difference in survival has meant that adjuvant SRS alone has been adopted in many centers. The assumption is that patients will be offered salvage treatment at failure, thus deferring or potentially avoiding WBRT and its associated toxicities altogether. When considering treatment options, however, it should be remembered that intracranial disease progression is also an important cause of neurocognitive decline.[9] In addition, survival is often determined by systemic disease burden and so may not be the most relevant endpoint in assessing the impact of local therapies on intracranial disease. As patients are living longer with better systemic and targeted treatments, it becomes increasingly important to strive for both durable intracranial control and reduced treatment-associated cognitive toxicity.

With SRS delivering higher biological doses to the resection cavity compared to WBRT, it seems counterintuitive that local control could be worse with an SRS approach. One hypothesis is that the target definition

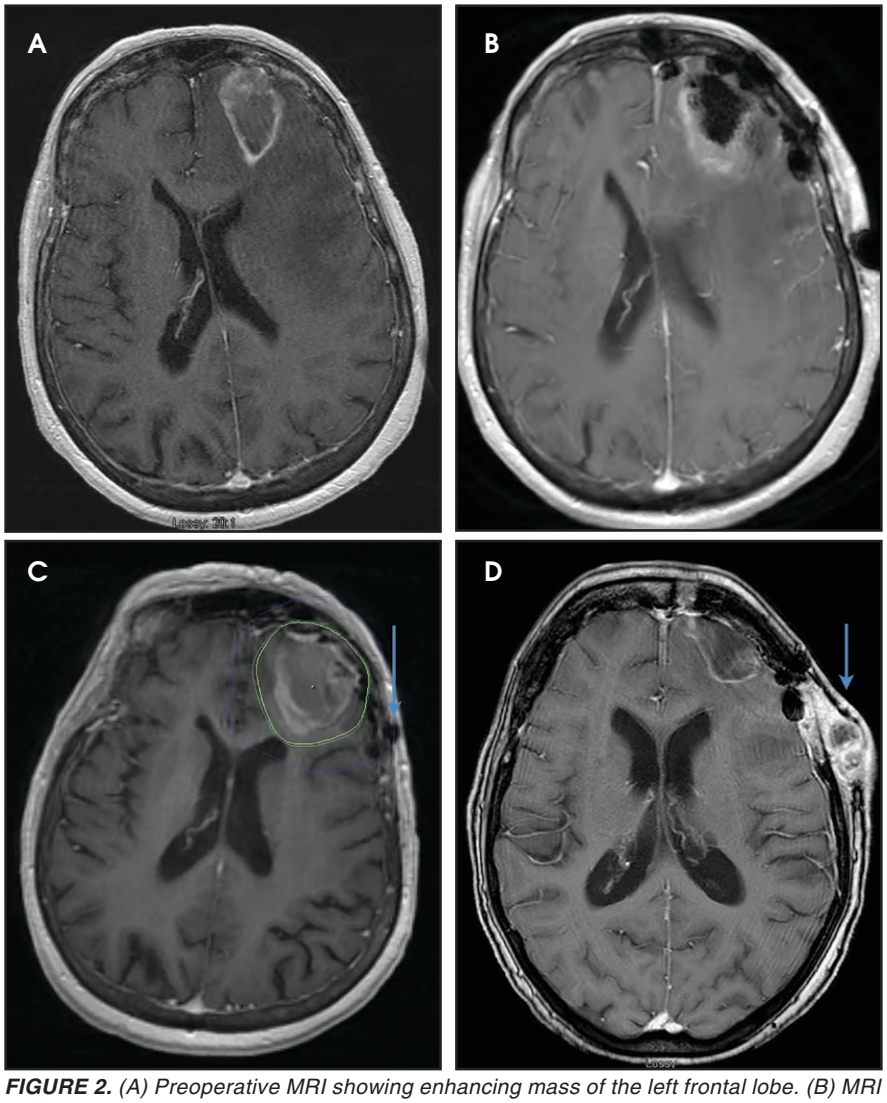

FIGURE 2. *(A) Preoperative MRI showing enhancing mass of the left frontal lobe. (B) MRI 48 hours postoperatively showing complete resection of the mass with contusion at the cavity. (C) SRS plan showing prescription isodose line in green, with craniotomy tract outside of the treatment volume (arrow). (D) 3-month follow-up MRI showing subcutaneous recurrence (arrow). Key: MRI = magnetic resonance imaging, SRS = stereotactic radiosurgery.*

of the cavity is complex with high rates of interobserver variability when compared to the targeting of intact brain metastases. To help standardize this, Soliman et al published a consensus contouring guideline for completely resected metastases earlier this year.[10] The study is an expert consensus and not based on patterns of failure analysis. The authors highlight the importance of including meningeal and venous sinus margins within the clinical target volume (CTV) when these structures were involved on preoperative imaging. They also advise that the surgical tract should be included for deep-seated tumors, but do not advise expanding this to include the tract within the skull and subcutaneous tissue.

In the cases presented here, both patients had limited intracranial disease with no evidence of extracranial disease and were treated as per current standard with surgical resection followed by cavity SRS. There were no identifiable postoperative complications (bleeding, infection, meningocoele) in either case. The CTV included the surgical cavity and tract out to the meninges and did not extend beyond the boundaries of the inner skull table. Following the publication by Choi et al in 2012,[11] we have used a 2-mm PTV margin for all postoperative cases in our center. **Figures 1C and 2C** show the SRS treatment plans with the prescription isodose line in green. The craniotomy tract also is visible on these images and is not included within the treatment volume.

Cutaneous metastases have been described for many solid malignancies and usually represent late disseminated disease. On the other hand, direct subcutaneous tumor seeding following craniotomy for solid tumor metastases is quite rare. We have identified only 3 case reports in the literature, all of which used SRS to treat the cavity.[12-14] This pattern of failure has not been described following postoperative WBRT. The patient in our second case had a history of NSCLC and renal cell carcinoma (RCC), and had a biopsy of the subcutaneous lesion confirming that this was most consistent with direct tumor recurrence of NSCLC after a craniotomy as opposed to cutaneous metastasis from RCC. It is worth highlighting that neither of our cases received systemic therapy following initial treatment of intracranial disease and it is possible that this may have reduced the risk or at least delayed the development of tumor recurrence at the scalp.

We agree with the consensus targeting guidelines by Soliman et al and are not advocating including the entire postsurgical changes within bone and subcutaneous tissue within the SRS target volume. We wish rather to highlight a pattern of failure that is rarely described in the literature, but which may become more commonly recognized as WBRT is increasingly omitted. As a radiation therapy community, we must acknowledge that despite current trends in clinical practice, the optimum treatment paradigm for patients with

resectable brain metastases is yet to be determined and questions remain, including: Are the rates of intracranial recurrence with adjuvant SRS alone too high and should we still consider WBRT in this cohort? Perhaps preoperative SRS would be a more favorable approach? This, in theory, reduces the risk of leptomeningeal and surgical tract seeding of viable tumor intraoperatively.[15,16] There is an ongoing phase 3 study comparing pre- vs postoperative cavity SRS with the primary outcome to determine a leptomeningeal disease-free rate.[17]

CONCLUSION

We present 2 cases of direct scalp seeding following craniotomy and cavity SRS for intracranial metastases from solid malignancies. This is a pattern of failure that has not been described following WBRT. The theme in both the clinic and trial settings is one of a local therapy approach, accepting the increased risk of intracranial and leptomeningeal failure, with delay or avoidance of WBRT. For patients with resected brain metastases, progress is being made with randomized trials and recently published consensus contouring guidelines, although there remains no consensus on the optimum treatment paradigm.

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Neoadjuvant chemoradiotherapy for laryngeal synovial sarcoma

Ella Mae Cruz-Lim, MD; Johanna Patricia Adevoso-Cañal, MD, MHA

CASE SUMMARY

Synovial cell sarcoma of the head and neck comprise less than 0.1% of all head and neck cancers.[1] The first case of head and neck synovial sarcoma was described in 1954 by Jernstrom. The larynx is the least common site of occurrence of synovial sarcomas, making laryngeal synovial sarcoma an extremely rare disease entity.

Due to the paucity of cases, the optimal treatment of laryngeal synovial sarcoma is yet to be established. Based on reports, wide local excision with or without adjuvant radiation therapy is usually the first treatment of choice. The role of chemotherapy remains controversial.

We present a patient diagnosed with unresectable laryngeal synovial sarcoma who underwent neoadjuvant radiation therapy with concurrent weekly chemotherapy.

The patient is a 22-year-old Filipino man, ECOG 0, with no known medical comorbidities or vices. He presented with a 7-month history of foreign body sensation in his throat. Thereafter, he developed hoarseness, pooling of saliva, and solid-food dysphagia. He then experienced difficulty breathing and sought consult.

The patient underwent tracheostomy, nasogastric tube insertion and simple supraglottic excisional biopsy for what was thought to be a benign process. Pathologic examination demonstrated a malignant spindle cell tumor **(Figure 1).**

Although a sarcomatoid squamous cell carcinoma was initially included in the histologic differential diagnosis, the patient's age and the characteristic appearance in the hematoxylin and eosin (H&E) stain favored the diagnosis of synovial sarcoma. Multiple immunostains were done for confirmation **(Table 1, Figure 2)**.

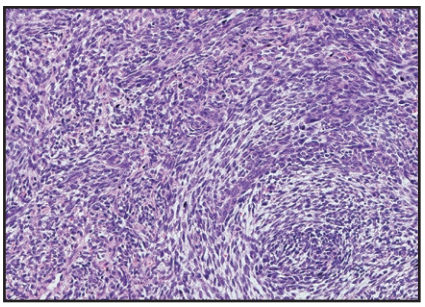

FIGURE 1. *Microscopically, the tumor was composed of spindle cells characteristic of monophasic spindle-cell type synovial sarcoma.*

Head and neck magnetic resonance imaging (MRI) with gadolinium revealed a complex 10.4 × 7.6 × 5.1 cm (CC × W × AP) mass occupying the posterior oral cavity, oropharynx and larynx **(Figure 3A)**. Few subcentimeter cervical lymph nodes were also seen. A 0.6-cm pulmonary nodule in the left upper lobe was noted on chest computed tomography (CT), deemed to be inflammatory.

Direct laryngoscopy under general anesthesia was then attempted. However,

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Table 1. Summary of Immunohistochemical (IHC) Stains

IHC Stain	Result
Cytokeratin	Focal and diffuse positivity
Vimentin	Focal and diffuse positivity
S-100	Nonreactive
CD99	Strongly and diffusely positive
BCL2	Strongly and diffusely positive
SMA	Nonreactive

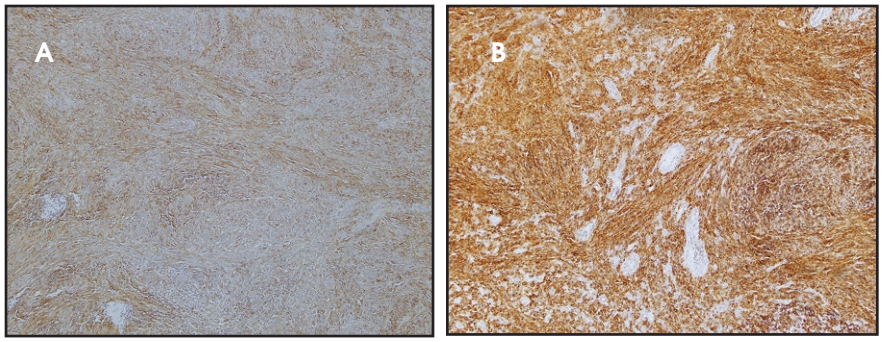

FIGURE 2. *Immunohistochemical staining shows that the tumor cells are positive for (A) CD99 and (B) BCL2, indicative of synovial sarcoma.*

during the procedure, profuse bleeding (~500 cc) from the mass was encountered. The procedure was terminated after achieving adequate hemostasis.

In light of the tumor's friability and propensity to bleed, and after careful review of the scarce literature regarding this rare malignancy, the head and neck tumor board decided to pursue neoadjuvant radiation therapy with concurrent chemotherapy consisting of 30 mg of weekly intravenous doxorubicin. Surgery was planned for after assessment of response to neoadjuvant treatment, should the sarcoma become resectable.

During initial consult with radiation oncology, a foul-smelling, fungating mass was visualized in the posterior oropharynx, while a subcentimeter cervical lymph node was palpable on the left submandibular area.

Three-dimensional conformal radiation therapy (3DCRT) was delivered using a linear accelerator with a 6-MV photon beam. The gross tumor volume (GTV) included all gross disease on physical examination and contrast-enhanced MRI. The clinical target volume (CTV) was generated by adding 2 cm to the GTV, shaving off bone and muscle. The planning target volume (PTV) was the CTV plus 0.5 cm. Bilateral neck levels 2 to 4 were electively covered due to the propensity of synovial sarcoma to metastasize to the lymphatics. The plan was to administer 200 cGy daily fractions for 7 weeks to a total dose of 7000 cGy to the PTV. However, by the sixth week, the patient developed excessive secretions that prevented him from lying supine for his radiation therapy treatment in spite of suctioning, anticholinergic medications and sedation. Treatment was stopped at 6 weeks, having delivered a total dose of 6000 cGy to the tumor and bilateral neck.

There was grade 3 radiation dermatitis, which eventually healed after local wound care. The chemotherapy course was unremarkable.

Six weeks after treatment, repeat MRI with gadolinium showed a decrease in the mass to $7.8 \times 4.5 \times 4.8$ cm (CC × W × AP) with interval resolution of its oropharyngeal, oral cavity and glottic extensions **(Figure 3B)**.

The planned stepwise surgical resection then commenced beginning with excision of the supraglottic mass via transoral approach (**Figure 4**). Completion laryngectomy was done 3 weeks after. No untoward events were noted intraoperatively or postoperatively. The final histopathology report showed monophasic synovial sarcoma, 4 cm in greatest dimension, with 60% tumor necrosis involving the left glottis and supraglottis. No lymphovascular space or perineural invasion was noted. All surgical margins were clear, ranging 0.7 to 2 cm. No further adjuvant treatment was warranted. Thereafter, close follow-up with clinical examination and imaging as per National Cancer Center Network (NCCN) guidelines will ensue.

DISCUSSION

Laryngeal synovial sarcoma is a rare head and neck malignancy with approximately 20 cases reported in the literature.[2] The most reported site of presentation is the parapharyngeal space, while the larynx is the least frequent site of occurrence.

The term "synovial" refers to the tumor's microscopic resemblance to the synovium, but these tumors do not in fact arise from synovial structures. Immunohistochemistry plays a major role in diagnosing synovial sarcoma, of which there are 2 main variants: monophasic and biphasic. Molecular testing can also be done, as synovial sarcoma harbors a specific chromosomal translocation, t(X:18) (p11.2; q11.2). This leads to fusion between the SYT gene on chromosome 18 and the SSX1 and SSX2 genes on the X chromosome.[3]

There is very limited literature on head and neck synovial sarcomas, with the majority being case reports and single-institution studies. The management of these rare tumors, and of head and neck sarcomas in general, has largely been extrapolated from studies on the more common extremity sarcomas.

The primary treatment modality for head and neck sarcomas is surgery, with

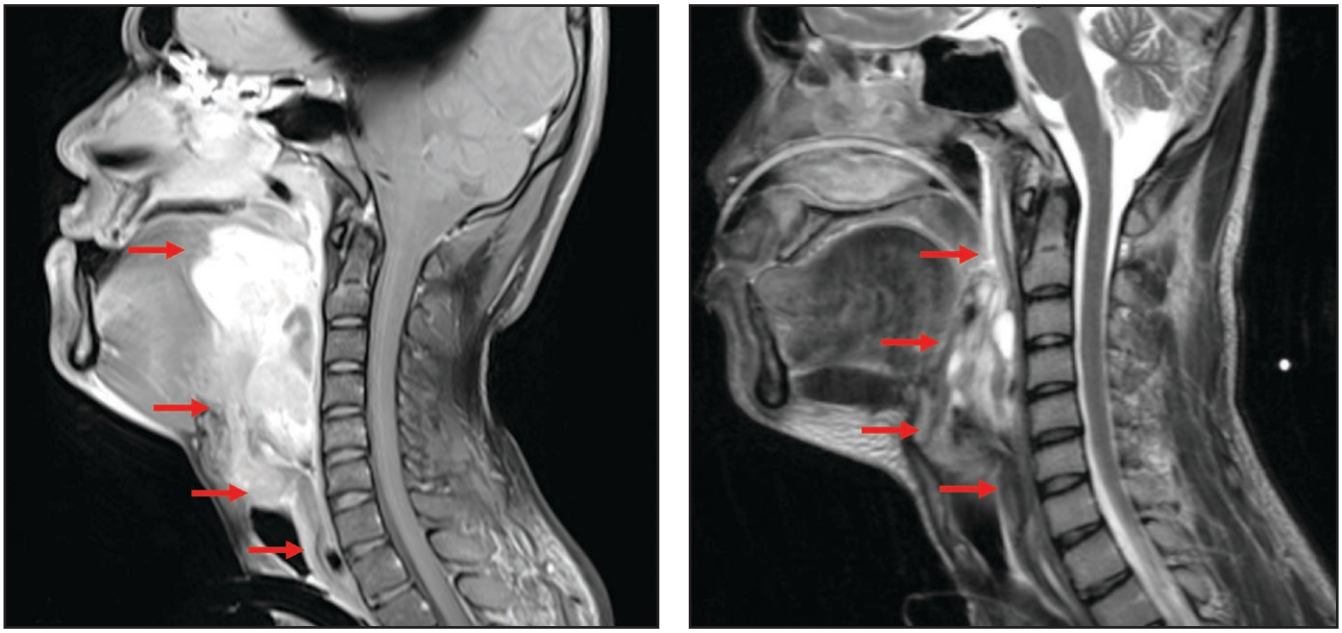

FIGURE 3. *(A) T1 with gadolinium MRI sagittal image showing a 10.4 × 7.6 × 5.1 cm (CC × W × AP) mass occupying the airway from the oropharynx to the glottis. (B) T2-MR sagittal image showing decrease of the mass to 7.8 × 4.5 × 4.8 cm (CC × W × AP) with clearing of the oropharynx, oral cavity and glottis.*

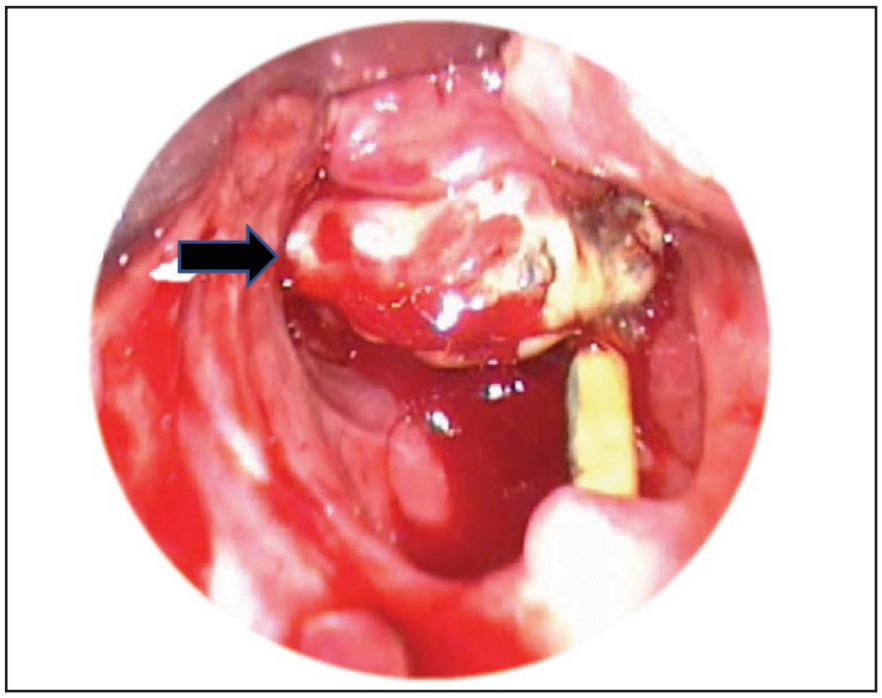

FIGURE 4*. Endoscopic view of the supraglottic mass (black arrow) seen posterior to the epiglottis.*

adjuvant radiation therapy reserved for large tumors, high-grade sarcomas and positive margins.[4] According to NCCN guidelines, the primary goal in oncologic resection of head and neck sarcomas is complete en bloc excision, while minimizing functional and aesthetic complications. There is no consensus regarding margin width, but on average, a 2-cm margin is considered acceptable.[5]

However, the unique anatomic considerations of the head and neck limit the ability to obtain negative surgical margins, which may explain the higher local recurrence rate and lower disease-specific survival of head and neck sarcomas.[6]

The role of radiation therapy in the treatment of head and neck sarcomas came out of the high rates of local recurrence following inadequate surgery. Adjuvant radiation therapy is usually given to patients with high-grade tumors of any size. Studies on preoperative vs postoperative radiation therapy for head and neck sarcomas are limited; thus, the optimal timing of radiation therapy is yet to be determined.[7]

Adjuvant radiation therapy has been shown to benefit R1 or R2 surgeries the most, with local control rates increasing from 25% to 54%.[8] Definitive radiation therapy alone has no role in primary treatment of head and neck sarcomas.[9] A report on 112 patients with unresectable

soft-tissue sarcomas who underwent radiation therapy, of which 3% were synovial sarcomas, used a median radiation dose of 64 Gy. Twenty percent of patients received chemotherapy. Five-year local control was 51% for tumors < 5 cm and 9% for tumors > 10 cm ($p < 0.001$). Doses of ≥ 63 Gy resulted in better local control, disease-free survival and overall survival compared to lesser doses, while doses of 68 Gy or more led to more complications.[10]

Although surgery followed by adjuvant radiation therapy is standard treatment for soft-tissue sarcomas, it is associated with high rates of local recurrence particularly in patients with head and neck sarcoma, incompletely resected sarcomas and large soft-tissue sarcomas. Hence, studies investigating treatment alternatives—including the addition of chemotherapy and concurrent chemoradiotherapy—have been pursued.

Patients with head and neck synovial sarcoma have a high likelihood of harboring distant metastasis; therefore, more effective systemic therapy is necessary. While synovial sarcomas are known to be chemosensitive tumors, the role and benefit of chemotherapy in the treatment of soft-tissue sarcomas in general is not as well defined as that of radiation therapy. There is even less literature concerning chemotherapy in head and neck sarcomas, more so the case for neoadjuvant chemoradiation for head and neck cancers. This approach aims to primarily improve local control without compromising function, and to abate micrometastatic disease early on.

A retrospective study of 29 cases of head and neck sarcoma, including synovial sarcoma, showed longer mean survival with chemoradiotherapy treatment (71.5 months) compared to without (42.3 months). Age was the only statistically significant survival predictor.[11]

Our patient with primary laryngeal synovial sarcoma represents a rare case that was treated with neoadjuvant chemoradiation therapy. This case demonstrated how neoadjuvant chemoradiation therapy successfully facilitated oncologic surgical resection of an initially unresectable laryngeal synovial sarcoma. Close patient follow-up will continue to monitor disease outcomes.

CONCLUSION

Head and neck synovial sarcoma is a rare disease entity posing several diagnostic and treatment challenges. Hence, a multidisciplinary team approach consisting of head and neck surgeons, radiation oncologists and medical oncologists is optimal. In the absence of evidence-based guidelines and randomized prospective studies, management decisions for head and neck synovial sarcoma should be individualized. Novel approaches to treatment should be investigated for their potential to improve patient outcomes.

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