June 2023
Volume 12, Number 2

Applied Radiation Oncology

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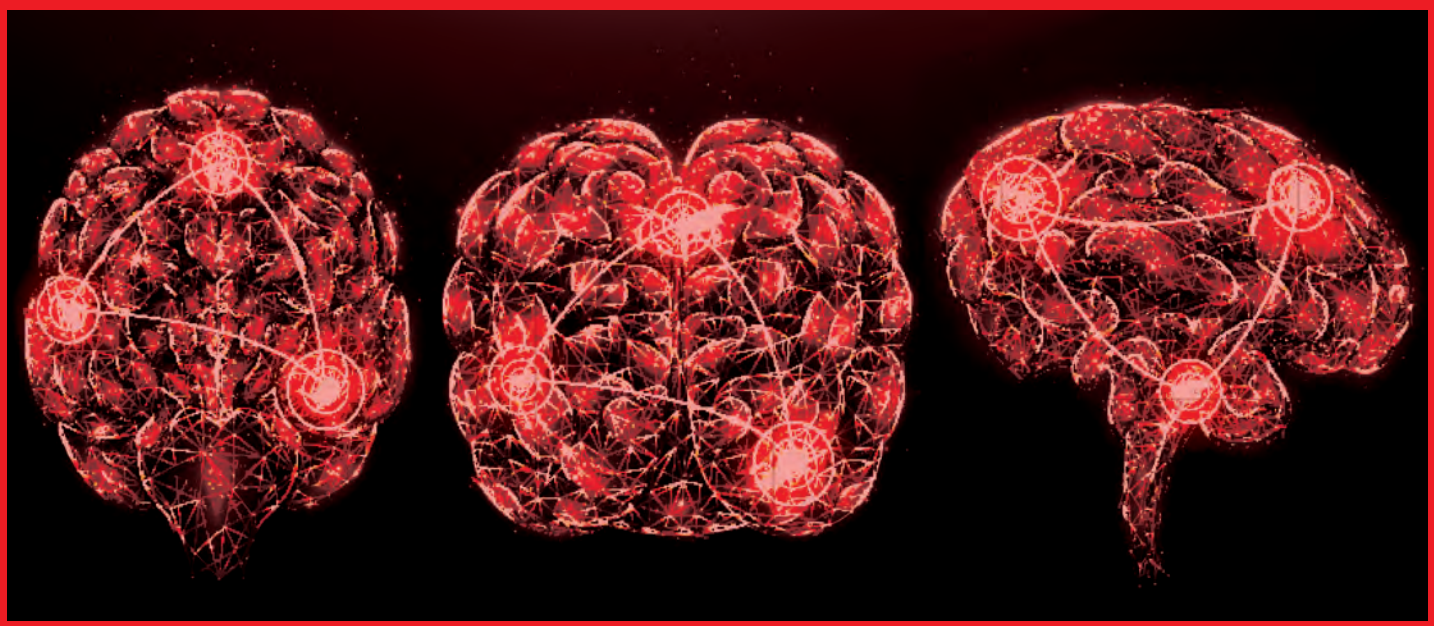

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ESSN: 2334-5446 (online)

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Applied Radiation Oncology™

June 2023, Vol 12, No 2

Applied Radiation Oncology (ISSN: 2334-5446) is published quarterly by Anderson Publishing, Ltd.,180 Glenside Avenue, Scotch Plains, NJ 07076. Subscription is free of charge to all medical professionals. To update your subscription preferences, visit appliedradiationoncology.com/subscribe. Complaints concerning non-receipt of this journal should be made via email to our publisher, Kieran Anderson at kieran@appliedrradiology.com.

Milestones and Master Plans

John Suh, MD, FASTRO, FACR

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.

Speeches, diplomas, and flowing seas of caps and gowns occur in late spring as medical students around the world celebrate commencement. For those who matched into radiation oncology, we welcome this next generation of radiation oncologists who will build their knowledge and expertise during training and play a vital role in moving this dynamic field forward.

Given *ARO*'s commitment to education, in particular medical students, we had 14 graduating medical students who worked with *ARO*'s four Medical Student Committees over the past year, developing skills, building connections, and creating learning opportunities for many. I would like to sincerely thank them for their valuable contributions! Page 32 lists details of where these medical students are headed next.

Speaking of achievement, this month's Resident Voice editorial, *Opportunities Are Knocking, Are You Listening?* reminds us how traversing new trails is not just personally empowering but professionally rewarding. From advocacy to sustainability to mountain climbing in the name of global health, options for meaningful growth abound, beyond what you might imagine. We hope you enjoy this terrific dose of inspiration by Vanderbilt's Kyra N. McComas, MD, who I am thrilled to also welcome as a regular *ARO Insights* blogger. You'll find her latest blog, *Suit Up, We're Going to Capitol Hill,* at https://appliedradiationoncology.com/aro-blog.

Our June issue also features the CME-accredited review article, *Stereotactic Radiosurgery for Brain Metastases: Review of Existing Data and Future Directions*, a comprehensive summary of current controversies and active areas of investigation highlighting multiple ongoing clinical trials. A second review, titled *Stanford Experience with Commissioning, Quality Assurance and IMRT/SBRT Treatment of the First Biology-Guided Radiation Therapy Machine,* offers a valuable look at the RefleXion X1 PET-based BgRT machine during its first 2 years of clinical use. The article examines advances in the clinical implementation of IMRT/SBRT technologies facilitated by the system's introduction, and highlights challenges in improving workflow efficiency and validating tracking accuracy.

Among research articles in the issue, *Whole-Lung IMRT in Children and Adults with Synovial Sarcoma and Lung Metastases: Single-Institution Prospective Clinical Trial* describes a useful study evaluating toxicity and clinical outcomes after cardiac-sparing, whole-lung IMRT in this patient population. In addition, *Evaluating the Utility of Webinars on the Radiation Oncology Residency Application Process in the COVID-19 Era* presents preliminary outcomes from an ACRO-led webinar series on educating medical students about residency application. The authors explain the usefulness of such a program, particularly amid challenges surrounding the residency application and match process.

Lastly, we present the interesting case report, *A Case of Vision Loss From Radiation-Induced Optic Neuropathy Resulting in Charles Bonnet Syndrome,* which underscores the need for clinicians to counsel patients about potential late effects of radiation and suggest routine surveillance following treatment.

On the operational front, we are pleased to announce our move this spring to an automated manuscript submission and peer review system, Editorial Manager, to streamline workflow on the front- and back-end of the publishing process. Details are in our Submission Guidelines online, and we look forward to your submissions.

We hope you enjoy the issue and wish you and recent graduates a wonderful summer, one filled with memories and opportunities for personal and professional growth!

Stereotactic Radiosurgery for Brain Metastases: Review of Existing Data and Future Directions

Description

The growing use of stereotactic radiosurgery (SRS) for brain metastases has exposed several unknowns, which are under investigation. This review aims to discuss the existing data that support SRS use and can provide the reader with a basis for making judgements in clinical situations in need of answers. The article also discusses various major pending clinical trials.

Learning Objectives

Upon completing this activity:

- Clinicians will understand the data that support use of SRS over WBRT and limitations of that data, as well as current clinical trials aimed at evaluating WBRT techniques in certain clinical scenarios.
- Clinicians will be able to prescribe generally appropriate SRS and multifractionated regimens for brain metastases based on size.
- Clinicians will be able to identify clinical scenarios that may benefit from preoperative SRS and/or enrollment on the open NRG clinical trial.

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Target Audience

- Radiation Oncologists
- Related Oncology Professionals

Commerical Support

None

Accreditation/Designation Statement

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1 hour

Date of release and review:
June 1, 2023

Expiration date:
May 31, 2024

Disclosures

Dr. Soltys discloses relationships with the following ineligible companies:

Novocure, research funding

Zap Surgical, Inc., speaker's honorarium

Accuray, Inc., advisory board honoraria

Dr. Rahimy reports no relationships with ineligible companies.

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Stereotactic Radiosurgery for Brain Metastases: Review of Existing Data and Future Directions

Elham Rahimy, MD;* Scott G. Soltys, MD

Abstract

Stereotactic radiosurgery (SRS) has become the standard of care for limited brain metastases to defer toxicities associated with whole-brain radiation therapy (WBRT). While WBRT decreases the appearance of new distant brain metastases, this is at the expense of worse cognitive decline without an overall survival benefit. However, the definition of limited brain metastases continues to be controversial and variably interpreted. Randomized trials are pending to evaluate whether contemporary WBRT techniques utilizing neuroprotective strategies such as hippocampal avoidance and memantine are more appropriate than SRS in specific clinical scenarios. The emerging use of SRS has also led to other discussions regarding postoperative cavity contouring, utility of preoperative SRS, and optimization of dose regimens, with growing support for fractionation of large tumors. In this narrative review, we will discuss the existing data and rationale supporting the predominance of SRS for brain metastases, and the evolving data for unanswered questions.

Keywords: radiosurgery, SRS, fractionated stereotactic radiation therapy, FSRT, radiation, radiation therapy, brain metastases, intracranial metastases

Survival of patients with metastatic cancer has markedly improved in recent years with development of better systemic therapies and surgical techniques, identification of targetable molecular mutations, and realization that aggressive treatment in patients with low volume (ie, oligometastatic) disease can be beneficial. With improved extracranial control and prognosis in many patients, optimizing intracranial control while minimizing late neurotoxicity has become paramount. Herein lies the appeal of stereotactic radiosurgery (SRS), which has supplanted whole-brain radiation therapy (WBRT) as the standard of care for limited brain metastases as supported by international guidelines[1,2] and consistent with more recent systematic and narrative reviews.[3-8] Practice patterns demonstrate a doubling of SRS use in the community from 2010 to 2015 with concomitant decline in WBRT.[9] The numerical threshold of "limited" remains controversial but continues to be expanded with increasingly narrower indications for WBRT. SRS allows for dose escalation for increased local tumor control while sparing normal brain tissue to minimize toxicities, which can significantly impact quality of life. The growth of SRS has led to several clinical questions that are still being fleshed out, a few of which we discuss in this review: Is there a limit in the number/volume of metastases appropriate for SRS over WBRT techniques? What is the best sequencing of surgery and SRS? And, what is the optimal SRS dose/fractionation? **Table 1** summarizes the active/recruiting trials aimed at elucidating some of these questions.

Methods

The PubMed database was searched using the terms *brain metastases*, *cavity*, and *stereotactic radiosurgery*, with article type selected for clinical trials, randomized controlled

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Disclosures: Dr. Rahimy reports none; Dr. Soltys reports research funding from Novocure, speaker's honorarium from Zap Surgical, Inc., and advisory board honoraria from Accuray, Inc. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Table 1. Notable Active/Recruiting Randomized Clinical Trials Evaluating Nuances of SRS Treatment for Limited Brain Metastases

Clinical trial	Trial number	Trial design	Eligibility	Interventions	Primary[α]
CCTG CE.7	NCT03550391	Phase III	5-15 brain metastases, total volume < 30 cc, largest < 2.5 cm maximal diameter	SRS vs HA-WBRT+memantine	OS, neurocognitive PFS
NRG BN009	NCT04588246	Phase III	BMV since upfront SRS ≥ 4 brain metastases/year	Salvage SRS vs HA-WBRT+memantine	Time to neurologic death[β]
HIPPORAD	DRKS00004598	Phase II	≥ 4 brain metastases, not exceeding 10 metastases ≥ 5 mm; none in or within 7 mm of hippocampus	HA-WBRT+SIB vs WBRT+SIB	Neurocognitive function at 3 months' post-radiation
CC009	NCT04804644	Phase III	≤ 10 SCLC brain metastases	SRS vs HA-WBRT+memantine	Time to neurocognitive failure
NRG BN012	NCT05438212	Phase III	1-4 brain metastases, 1 requiring resection	Preoperative vs postoperative SRS	Time to CAE (LF, nMD, or RN)
Alliance A071801	NCT04114981	Phase III	One grossly resected brain metastasis cavity 2-5 cm maximal diameter, with 0-3 unresected brain metastases < 4 cm	Single vs multifraction postoperative SRS (3 or 5 daily fractions)	Surgical bed recurrence-free survival

Abbreviations: *SRS, stereotactic radiosurgery; NCT, National Clinical Trial; HA-WBRT, hippocampal avoidance whole-brain radiation; OS, overall survival; PFS, progression-free survival; BMV, brain metastasis velocity; DRKS, Deutsches Register Klinischer Studien (German Clinical Trials Register); SIB, simultaneous integrated boost; CAE, Composite Adverse Endpoint; LF, local failure; nMD, nodular meningeal disease; RN, radiation necrosis*
[α]*Although not individually detailed here, it is important to note that the definition of neurocognitive failure, and cognitive test(s) and timepoints utilized, differs among the trials.*
[β]*Definition: From randomization until progressive neurologic decline at time of death, irrespective of status of extracranial disease, or death from intercurrent disease in patients with severe neurologic dysfunction, assessed up to 3 years*

trials, meta-analyses, reviews, and systematic reviews.

SRS vs WBRT

We will first summarize the seminal data that support the routine use of SRS instead of WBRT, and the clinical scenarios when WBRT may be more appropriate. While WBRT decreases the appearance of new distant brain metastases (dBM), defined as development of new brain metastases different than the initial site,[10] this is at the expense of worse cognitive decline without an overall survival benefit.[11-18] WBRT originated in the 2D era when targeted irradiation of brain metastases was not possible and median survival of patients with metastases was only 2 to 4 months,[19-21] such that treatment durability (up to ~6 months with WBRT[12]) and late toxicity were not as relevant. Neurocognitive impairment (NCI) is markedly worse with conventional WBRT, especially in the domains of memory, learning, and executive function.[13-15,17,18,22-25] Alliance N0574 trial reported 3 month NCI of 64% with SRS vs 92% with SRS plus WBRT, which persisted at 6 and 12 months, indicating it is not a reversible toxicity.[25] Similarly, JCOG0504 reported a 2 times worse grade 2-4 NCI at 3 months post-WBRT vs salvage SRS (16 vs 8%, $P = 0.048$).[14] Beyond NCI, other toxicities include fatigue, temporary alopecia, stroke, hearing loss, endocrinopathies, dry eye/mouth, and even retinopathy,[26] all of which can impact quality of life.[24,27] The 1-year rate of new brain metastases with SRS is approximately 50% (although dependent on systemic therapy), and WBRT bestows an absolute dBM reduction of approximately 20% to 30% (with most studies using 30 Gy in 10 fractions).[11-14] A notable exception is melanoma, with no improvement in dBM, likely because of the radioresistant histology.[18] Despite this general improvement in intracranial control, no data suggest an overall survival benefit (although no trial has been powered for overall survival); the rationale is that overall survival is driven by extracranial disease control, which is dictated by systemic therapy response.[20] In addition, salvage SRS can often be done at the time of dBM without compromising outcomes (especially in patients with close follow-up and early salvage).[24,28,29] Apart from overall survival, another endpoint of interest is cognitive decline, which can be secondary to treatment itself vs tumor progression. Several studies have used the somewhat ambiguous endpoint of *neurologic death*, essentially defined as progressive neurological decline at the time of death (regardless of systemic status).[10] It is unknown whether WBRT

improves the neurological death rate, as results from limited studies have been mixed,[11,12,17,18,30] and it is difficult to define endpoint to begin with. However, several studies show that NCI is worse with WBRT rather than disease progression.[13-15,23,24]

The data above support the use of SRS instead of WBRT in patients with limited brain metastases and discourage the routine use of adjuvant WBRT after SRS. However, there is no universal consensus for defining limited. The initial SRS trials referenced above enrolled patients with less than 5 brain metastases. The large prospective observation study JLGK0901 then expanded that definition to up to 10, given no difference in overall survival when treated with SRS alone.[31] Other studies followed in suit supporting greater than 10 brain metastases;[32-34] however, given limitations in sample size/study design, controversy remains for greater than 10 and especially greater than 20 brain metastases.[1,2] While high-level evidence for these specific clinical scenarios is lacking, many argue that one can extrapolate from the consistent conclusions in the aforementioned studies, and use salvage SRS to postpone WBRT toxicities for as long as possible. In their institutional experience of SRS for multiple brain metastases (range, 1-85 metastases; mean of 7; and median of 3), Yamamoto et al report that 85% of patients died of causes other than brain disease progression, regardless of brain metastasis number,[35] again supporting the notion that overall survival is often not dictated by intracranial disease. Perhaps a more relevant proxy of intracranial tumor burden is not the number, but the volume of brain metastases.[2,31,36] Again, the threshold above which overall survival favors a WBRT technique has not been established. One of the higher proposed cutoffs is 30 cc, used in the Canadian phase III CE.7 comparing SRS vs hippocampal avoidance (HA) WBRT plus memantine for 5 to 15 brain metastases (NCT03550391). Another potentially relevant parameter is brain metastasis velocity. Several studies have shown worse overall survival and neurocognitive death for first/second intracranial relapse in patients with high brain metastasis velocity.[37,38] One proposed cutoff that may predict patients at high risk for neurologic death after SRS is greater than or equal to 4 metastases per year.[37] This cutoff is being used in the phase III NRG Oncology BN009 study evaluating salvage HA-WBRT plus SRS vs SRS in patients with high brain metastasis velocity after upfront SRS (NCT04588246).

The above CE.7 and BN009 studies remind us that there are contemporary alternatives to the 2D-era WBRT, further complicating the discussion surrounding HA-WBRT with/without memantine with/without SRS boost. With neuroprotective strategies such as HA and memantine, and dose escalation with integrated SRS, WBRT may be more beneficial in a select subset of patients who may have poorer oncologic outcomes with repeated salvage SRS courses. HIPPORAD is an accruing phase II German trial evaluating HA-WBRT plus simultaneous integrated boost (SIB),[39] with the hypothesis of improved tumor control with acceptable toxicity[40] and less NCI than standard WBRT. The durability of WBRT 30 Gy is poor with 0% local control (LC) by 14 months for any size nonbreast adenocarcinoma and squamous cell carcinoma,[41] in contrast to greater than 75% to 90% for SRS, even of large metastases greater than 2 cm.[42-44] It should be noted that the aforementioned neuroprotective strategies help to reduce, but not eliminate, NCI after WBRT. In NRG CC001, even with the 26% relative risk reduction of NCI with the addition of HA to WBRT with memantine, the rates of neurocognitive toxicity remained over 50%, with a significant cognitive decline between 2 and 4 months following radiation.[22] Similarly, even with the 22% relative risk reduction of NCI upon adding memantine to WBRT in RTOG 0614, the difference was not statistically significant ($P = 0.59$) given the likely insufficient statistical power from approximately 70% of patients dying by 6 months.[45] And as with any drug, there are side effects that patients may not tolerate, such as fatigue, headache, nausea, body aches, and gastrointestinal disturbances.[46]

Even the topics of leptomeningeal disease (LMD) and certain histologies such as small cell lung cancer (SCLC), which are believed to have an increased rate of micrometastatic intracranial involvement, have garnered support for SRS in certain scenarios. Retrospective data support SRS for focal LMD to delay WBRT.[47] While LMD is most commonly widely disseminated, if it is radiologically and symptomatically focal, SRS may be done for potentially faster symptom relief and to postpone WBRT toxicity while minimizing time off systemic therapy (vs buying time to test the intracranial efficacy of a new systemic therapy). SCLC was excluded from the aforementioned seminal SRS trials given the traditional thought that disease is micrometastatic at onset. While SRS is controversial in patients with SCLC, there is growing evidence supporting its use with no overall survival detriment and dBM rates similar to non-SCLC, including FIRE-SCLC and a systematic review and meta-analysis of approximately 18,000 patients.[48,49] CC009 is evaluating SRS vs HA-WBRT for less than or equal to 10 SCLC brain metastases (NCT04804644). Given the frequent use of WBRT in extensive stage SCLC, a move toward carefully selecting patients for SRS may save a large portion of patients from WBRT toxicities (due to adequate intracranial control with SRS or competing risk of non-neurologic death).

As mentioned above, the dBM failure rate with SRS is approximately 50% but dependent on systemic therapy. The development of more

effective systemic therapies with intracranial efficacy, such as newer generation targeted therapies and immune checkpoint inhibitors (ICI) often used in non-small cell lung cancer (NSCLC), melanoma, and renal cell carcinoma, may subdue the high dBM rate. The decision to defer SRS for systemic therapy should be carefully considered, taking into account systemic therapy factors such as estimated time to response, response rate (partial vs complete), durability of response, and toxicity/compliance concerns, as well as patient/tumor factors such as symptoms, size, and distance from eloquent structures. Consider a patient with newly diagnosed EGFR-mutated NSCLC with innumerable punctate brain metastases and two 2-cm metastases, especially if symptomatic or near eloquent structures (but with sufficient distance to meet SRS constraints for organs at risk). It may be optimal to pursue upfront SRS to these 2 metastases with initiation of osimertinib, and a 6-week interval MRI (median time to response on osimertinib[50]) to re-evaluate the nonirradiated metastases. For melanoma brain metastases, the trial CheckMate 204 demonstrated that nivolumab/ipilimumab can be an effective treatment with durable response in neurologically asymptomatic patients;[51] however, median time to response is approximately 2 months, and efficacy is poor in neurologically symptomatic patients (22% response rate).[51,52] Given the small sample size, it is unclear if this poor response is due to corticosteroid use vs disease burden/rapid progression, but it does highlight utility of local treatment (SRS vs resection) for large/symptomatic metastases.[52] Other nuances of systemic therapy include sequencing and timing with SRS, with unclear interactions that may lead to synergy vs toxicity (radionecrosis).[53] Promising studies suggest a potential overall survival benefit when SRS is administered concurrently with ICI (defined as within 4 weeks, given the long half-life of many ICIs) without increasing the risk of radionecrosis,[54-56] although prospective data are needed.

In conclusion, SRS has become the standard of care for limited brain metastases, although that definition is variably interpreted and there may be select scenarios whereby WBRT techniques are more appropriate (currently under investigation). While awaiting those open trials, one should consider clinical factors such as prognosis/extracranial disease burden, systemic therapy options with anticipated intracranial efficacy, and intracranial tumor burden, with brain metastasis number, size, and volume likely all having relevance for clinical decision-making (ie, 100 punctate brain metastases may favor WBRT techniques vs starting a systemic therapy if anticipated to have good intracranial efficacy, while two 2-cm to 3-cm metastases would favor SRS given the limited number of metastases and desire for dose escalation given poor durable LC with WBRT[41]).

Perioperative SRS

For large brain metastases (not well-defined but typically > 2-4 cm), resection is often considered upfront, especially in patients with good performance status and limited/single brain metastases in surgically accessible locations. More important than an arbitrary size cutoff is the presence of symptoms from tumor/vasogenic edema, especially if not well-controlled with steroids or if systemic therapy initiation (ie, immunotherapy) is delayed by steroid use. As we will discuss below, tumor control with definitive SRS decreases with increasing tumor size, which historically has favored upfront resection. Even with a gross total resection (GTR), 1-year local failure rate is high at approximately 50% to 65%, and at least halved with adjuvant radiation.[11,30,57] Patients who will start a systemic therapy with good intracranial efficacy (ie, targeted therapies like epidermal growth factor receptor [EGFR] inhibitors in NSCLC or dual immunotherapy in melanoma) arguably benefit less, and the decision for adjuvant radiation should be made on case-by-case basis. The Alliance N107c trial established cavity SRS as the standard of care over postoperative WBRT for the same reasons as discussed above.[23,24] It should be noted that with contemporary studies, LC with cavity SRS is improved compared with historic rates referenced above (including N107c), now exceeding 90%.[58] A variety of reasons could explain this observation: improved recognition of radionecrosis that may have historically been mistaken for local failure;[59] learning curve of accurate target/cavity delineation, especially with improved MRI techniques; and use of higher equivalent dose/fractionated regimens (see SRS dose/fractionation section).

Regarding target delineation, cavity SRS contouring can vary considerably.[60] Blood products and inflammation can make delineation of the cavity difficult.[60] A decision must be made on whether to include a 1-2 mm cavity margin (essentially a less conformal SRS plan to account for uncertainty in cavity delineation),[61] and whether to include the surgical corridor.[60,62] While consensus contouring guidelines exist,[60] these recommendations are based on expert opinion and not necessarily high-level evidence. Other nuances in cavity contouring include covering the preoperative extent of tumor contact with dura/falx/tentorium/venous sinus with or without additional margin.[60] All these additional expansions may variably increase LC, but at the expense of increasing radionecrosis risk, and thus should be carefully considered. For example, it may be institutionally/individually decided to use a margin for small cavities less than 2 to 3 cm, especially if the cavity is not well-defined on imaging, and to include the surgical corridor if the cavity is

superficially seated (ie, less than 1 cm) from the brain surface.

Another issue with the practical transition from WBRT to cavity SRS is the emergence of a new pattern of progression, which we will term *nodular meningeal disease* (nMD). This phenomenon is due to cerebrospinal fluid spread of tumor cells from surgery (which would have been irradiated with WBRT), and is likely underreported and mistaken for hematogeneous spread.[63-65] Incidence of nMD after cavity SRS is approximately 10%,[62,65] similar to the rates of classical LMD (cLMD). Unlike the "sugar coating" of cLMD, which is usually disseminated and associated with poor prognosis, nMD is typically focal nodules from iatrogenic spread.[66] It most often presents on the pachymeninges (ie, dural-based nodules plus/minus a hypervascular tail akin to meningiomas[64]), although leptomeningeal nodules are also possible, and the two are not mutually exclusive. Given that nMD often behaves similarly to new parenchymal metastasis with no overall survival benefit of WBRT, SRS is reasonable treatment for when it occurs.[66]

These disadvantages of cavity SRS have fueled interest in preoperative SRS. This trend is similar to other disease sites such as rectal/esophageal cancer and soft-tissue sarcoma, whereby preoperative radiation is favored for simpler target delineation, smaller radiation field (for lower toxicity risk), and to avoid postoperative tumor hypoxia, which may contribute to radioresistance. In addition, preoperative SRS could potentially "sterilize" tumor cells to circumvent the nMD phenomenon. Preoperative SRS can be logistically difficult, especially for multifraction regimens, as typically resection is being considered for urgent decompression of large symptomatic metastases.

The multicenter cohort study Preoperative Radiosurgery for Brain Metastases (PROPS-B) is the largest cohort study to date (n = 242) evaluating outcomes of patients undergoing preoperative SRS for brain metastases. It demonstrated low rates of meningeal disease (~8% at 2 years, only one-third being cMD vs cLMD) and radionecrosis (~7% at 2 years, half of which were symptomatic), with low postoperative surgical complications (4% of grade ≥ 3, similar to that expected for upfront resection).[67] Only 2 patients (0.8%) had nonmetastatic brain lesions (primary brain tumors), which emphasizes the importance of pathologic proven metastatic disease in patients being considered for preoperative SRS. LC was reasonable for a single fraction with a median dose of 15 Gy (1-year local progression of 15%, and 2-year progression of 18%; median tumor size ~10 cc, which correlates with ~2.7 cm tumor diameter). SRS was delivered a median of 1 day before surgery (interquartile range of 1-3 days). Refer to the SRS dose/fractionation section below for further discussion of preoperative SRS dosing.

NRG BN012 is currently recruiting, comparing preoperative vs postoperative SRS in patients with 1-4 brain metastases, with 1 metastasis requiring resection (NCT05438212). With a calculated sample size of 224 patients, the primary hypothesis is that preoperative SRS will prolong time to a compositive adverse endpoint (CAE), defined as either local progression, radionecrosis, or nMD. Secondary endpoints include cognitive function and patient-reported outcomes. Doses are the same in both arms, 12-20 Gy in a single fraction; intact metastases are required to be less than 4 cm in diameter. Preoperative radiation is delivered within 7 days of surgery, while postoperative radiation is 10-30 days after surgery. Patients will be stratified by number of metastases (1 vs 2-4), breast cancer histology, cerebellar location, and whether targeted therapy/immunotherapy is used within 8 weeks of surgery or 4 weeks prior to registration. Type of surgical resection (piecemeal vs en bloc) will also be evaluated given unclear association with nMD.[68] Off trial, preoperative SRS may be pursued when logistically feasible and convenient for the patient, especially for colorectal cancer/breast histology or cerebellar location, which may have higher risk of nMD.[69]

SRS Dose/Fractionation

The most common late toxicity risk after SRS is radionecrosis, which typically occurs 3 months to a few years after SRS, and is symptomatic in approximately 33% to 50% of patients, requiring steroids or even resection.[70] Factors associated with radionecrosis include increasing tumor size,[71] increasing volume of normal brain irradiated (dictated by tumor size and gradient index),[72] certain systemic therapies (eg, trastuzumab emtansine),[73,74] and re-irradiation/repeat SRS.[75] In practice, radiosurgery doses/regimens are dictated in part by Radiation Therapy Oncology Group (RTOG) 9005,[71] with consideration for fractionation for large metastases (or metastases near critical structures like brainstem/optics) if logistically feasible. It is also influenced to a large degree by practitioner/institutional preference and certain patient factors (eg, prior radiation or future anticipated WBRT, and systemic therapy considerations). The most studied dosimetric parameters predictive of radionecrosis are V12 Gy or V14 Gy for single fraction (< 10-20 cc, perhaps < 30 cc for multiple targets).[72,76] Some institutions consider fractionation if V12-14 Gy exceeds a certain threshold, but it is important to not underdose the tumor to meet an arbitrary V12-14 Gy volume (increasing the risk of local failure and thus repeat SRS, which can double/triple the risk of radionecrosis).[72,75,77]

SRS doses were first established by RTOG 9005, a phase I/II dose escalation study that sought to determine the maximum tolerated dose (MTD) for single-fraction radiosurgery of recurrent previously irradiated primary brain tumors or brain metastases.[71]

Notably, all participants had received conventionally fractionated radiation greater than or equal to 3 months from study entry (36% were primary brain tumors with prior median 60 Gy, and 64% were brain metastases with prior median 30 Gy), and tumors located in the brainstem or greater than 4.0 cm were excluded. Starting doses were inversely proportional to maximum tumor diameter in any plane (ie, 12 Gy for the largest tumor size stratum of 3.1-4.0 cm), and increased by 3 Gy increments if grade 3-5 CNS toxicity (i.e., severe neurologic symptoms from radiation necrosis or cerebral edema) at 3 months was less than 20%. Chronic CNS toxicity, meaning after 3 months, was also recorded to determine MTD. Treatment was permitted with either the Gamma Knife (Elekta) or a linear accelerator (linac), and dose was prescribed to the 50% to 90% isodose line to the enhancing tumor without a margin. The final recommended doses were 24 Gy for a maximum tumor diameter less than or equal to 2.0 cm (median tumor volume in this group was 3.6 cc, which corresponds to 1.8 cm diameter), 18 Gy for 2.1-3.0 cm (dropped from 21 Gy because of unacceptable chronic CNS toxicity), and 15 Gy for 3.1-4.0 cm.

RTOG 9005 was the first radiosurgery study by the RTOG group, and it is important to emphasize it was not establishing doses based on efficacy (ie, LC) but on toxicity, given that SRS was initially being considered in patients with limited treatment options who had undergone prior radiation. Hence, recommended radiation dose from 9005 inversely correlates with tumor size. In addition, MTD was not actually met in the less than or equal to 2.0 cm stratum as investigators were unwilling to escalate beyond 24 Gy (27 Gy would equate to 54 Gy Dmax on the Gamma Knife).[71] In practice, how institutions dose the small metastases stratum varies significantly: Some follow 9005, quoting optimal balance of LC and radionecrosis,[42] others do not exceed 20-21 Gy,[42,78] while others further stratify the less than or equal to 2.0 cm group (ie, 24 Gy for < 1.0 cm, and 22 Gy for 1.0-2.0 cm, as is done on protocol in BN012). Of interest, 9005 reported that linac treatment was associated with higher local recurrence compared with the Gamma Knife, so initially it was thought that higher heterogeneity (the internal "hot spots" inherent to Gamma Knife planning given dose is prescribed to the 50% isodose line) yielded better LC. However, this observation was not seen in the subsequent RTOG 9508[79] or comparative studies, including a single-institutional randomized trial.[80] It may be that minimum dose (Dmin; akin to spinal metastases) and not maximum dose (Dmax) is more important for LC.[81,82] Regarding technique, a recently published international guideline thoughtfully discusses nuances regarding treatment planning of small brain metastases.[83] While planning margins were not used in 9005, clinical decision was based on the treatment platform and institutional/physician preference. For example, Gamma Knife, CyberKnife (Accuray Inc.), and the specialist linac Novalis (Varian) have submillimeter positional accuracy, yet for nonframe-based SRS some centers use no margin while others round up to 1 mm (seemingly innocuous, but it can double the irradiated volume and potentially increase the radionecrosis risk).[76,83] Differences in contouring due to partial volume effect on MRI can also unintentionally add/omit margin.[83]

Unlike the small metastases stratum, multiple series have shown that large metastases (> 2-2.5 cm) have poor LC with 9005 single-fraction dosing (1 year LC ~40%-50%).[43,78,84,85] Alluding to the principles of radiobiology, fractionated stereotactic radiation therapy (FSRT) has been employed to improve LC/radionecrosis risk. While randomized data do not yet exist, it is supported by comparative data and meta-analyses for intact and resected metastases.[86,87] With development of noninvasive frameless methods, hypofractionation can also be applied to the Gamma Knife.[88] Several comparative studies from Minniti et al support FSRT for large intact and resected metastases with 1-year LC improved to greater than 90% (even with a median intact metastases diameter of ~3.2 cm[44] and median cavity ~3.9 cm,[89] although intact melanoma may still have suboptimal LC),[44,89] and overall radionecrosis approximately halved to less than or equal to 10%.[44,89,90] The ideal multifraction regimen is not well established, although there is growing evidence for 27 Gy in 3 consecutive fractions (with better LC rates than 24 Gy, and less radionecrosis than 30 Gy)[44,89-92] and 30-35 Gy in 5 consecutive fractions.[8,93] There is an ongoing Italian randomized study evaluating 27 Gy in 3 fractions vs 35 Gy in 5 fractions for intact metastases.[94]

In addition, Alliance A071801 is currently comparing single-fraction SRS vs hypofractionated radiosurgery for resection cavities (NCT04114981), with fractionation of 27 Gy in 3 fractions for cavities less than 30 cc, or approximately 3.9-cm diameter, and 30 Gy in 5 fractions for greater than 30 cc. While awaiting these results, in practice some institutions utilize a volumetric cutoff to decide on 3 vs 5 fractions, similar to the Alliance A071801 study. Two separate institutional phase I/II dose studies reported MTD to be 27 Gy in 3 fractions (all cavities, MTD determined individually for 2-3 cm and 3-4 cm diameter cavities)[28,92] and 32.5 Gy in 5 fractions (20 of 25 were cavities; 3-6 cm diameter allowed, median 3.3-cm diameter).[95] Of note, these MTD and other dose finding studies often focus exclusively on cavity or intact metastases, and one must be cautious extrapolating for the other scenario. Logically it would seem that the risk of radionecrosis is higher for a similarly sized

cavity given surgical manipulation and a larger volume irradiated after including additional margins (which can potentially double the volume irradiated). Emory's phase I MTD 5-fraction study, for example, preliminarily reported toxicities exclusively in the cavity group.[95] In a similar vein, Minniti et al compared intact vs cavity FSRT with 27 Gy in 3 fractions, and reported similarly high 1-year LC (> 90%), although radionecrosis and meningeal disease were lower for the intact metastases (which also supports definitive SRS in cases whereby surgery is not required for rapid relief of neurological deficits).[90] Thus, in practice 30 Gy in 3 fractions or 35 Gy in 5 fractions are reasonable to consider (accepting potentially higher radionecrosis risk to optimize local control),[77] especially for intact metastases with radioresistant histologies such as colorectal cancer or possibly melanoma.[44]

It may even be that FSRT is beneficial for small intact or resected metastases less than or equal to 2.0 cm given radiobiologic properties. In the meantime, a large meta-analysis supports FSRT for cavities[87] (although most cavities are large and do not shrink significantly to be ≤ 2.0 cm for it to be a relevant issue). The Alliance A071801 and BN012 studies may be useful in answering this question for cavities.

Given the likely higher necrosis risks with cavity radiation, we return to the topic of preoperative SRS to discuss dosing. Initial studies had dose reduced from RTOG 9005 by approximately 10% to 20% and found unacceptably higher local failures;[67] this dose reduction attempt was likely driven by the fact that the vast majority of resections are GTR and postoperative hypoxia is not present. The PROPS-BM multicenter cohort study used a median 15-Gy SRS dose (SRS dose/fractionation was left to institutional protocol, although 99% were treated with a single fraction) and reported a low radionecrosis rate of 7% with median tumor size approximately 10 cc (which correlates with an approximate 2.7-cm tumor diameter). Subtotal resection, although infrequent (6%), was associated with worse local recurrence, which supports optimizing rather than reducing SRS dose. Notably, BN012 is a single-fraction study (as N107c utilized single fraction, and it was the landmark study to establish cavity SRS as the standard of care over WBRT) and does not dose reduce for the preoperative arm. Off trial, preoperative FSRT instead of SRS may alternatively be pursued for certain large metastases (eg, a 3-cm single colorectal cancer metastasis), assuming logistics and the urgency of surgery permits it (typically radiation is done 24-48 hours before resection).

Conclusion

While the increasing use of brain SRS in the last decade is logical given the accumulating high-level evidence reasserting its advantages over WBRT, many questions and uncertainties remain with regard to its application. The point at which patient-centric outcomes tip in favor of contemporary WBRT techniques over SRS is not clear, although several trials are evaluating promising metrics such as metastases volume and velocity. For large metastases, due to the variability of cavity contouring and identification of a new pattern of iatrogenic meningeal progression, preoperative SRS is currently under evaluation. In addition, large metastases not requiring surgical decompression are increasingly being treated by multifractionated regimens for potentially improved control and radionecrosis rates, although the optimal regimen is not clear. While awaiting answers from clinical trials, practice is influenced in part by institutional/individual preferences and interpretation/extrapolation of existing data.

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Stanford Experience With Commissioning, Quality Assurance and IMRT/SBRT Treatment of the First Biology-Guided Radiation Therapy Machine

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Abstract

Biology-guided radiation therapy (BgRT) is an emerging technology that integrates real-time PET imaging with radiation therapy to improve tumor targeting and treatment outcomes. This systematic review aims to summarize the Stanford experience on the current state of knowledge on machine commissioning, quality assurance, treatment planning, clinical applications, safety, and efficacy of BgRT in cancer treatment. The review underscores advancements in the clinical implementation of intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) technologies, facilitated by the introduction of the novel BgRT machine. It also highlights challenges related to improving workflow efficiency and validating tracking accuracy in real-world patient situations. This document serves as a valuable resource for researchers, clinicians, and decision-makers within the realm of radiation oncology, providing insights into the status of the PET-based BgRT machine and guiding the trajectory of future research.

Keywords: BgRT, Commissioning, QA

The RefleXion X1 system (RefleXion Medical, Inc.) is a novel PET-guided radiation therapy machine.[1-2] The X1 system consists of an 85-cm O-ring gantry linear accelerator (linac) rotating at 60 revolutions per minute (rpm), a fan-beam kilovoltage CT (kVCT) for image guidance of intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT), and PET for real-time tumor tracking for biology-guided radiation therapy (BgRT).[3] Major components of the system are shown in **Figure 1**. The linac consists of a 6-MV flattening filter-free (FFF) photon beam, a binary multileaf collimator (MLC) with 64 leaves, and 2 pairs of jaws located above and below the MLCs. The width of an MLC leaf is 6.25 mm at the isocenter (85 cm from the source). The maximum opening in the lateral direction formed by all MLC leaves retracted is 40 cm. The jaw pairs open 1 or 2 cm at the isocenter in the longitudinal direction. The nominal beam dose rate is 850 monitor units (MU)/min for the original IMRT/SBRT version of the machine. With the BgRT upgrade, the dose rate is 1000 MU/min. The kVCT scanner is located on a plane 61.4 cm superior to the room laser. The X1 machine consists of 2 symmetrically opposing 90-degree arcs of PET detectors incorporated into the architecture of a ring-gantry at the same plane to the linac 100 cm superior to the room laser.

The treatment delivery with the X1 system is achieved axially with the couch advancing at discrete intervals of 2.1 mm, making 1 or 4 passes through the treated region

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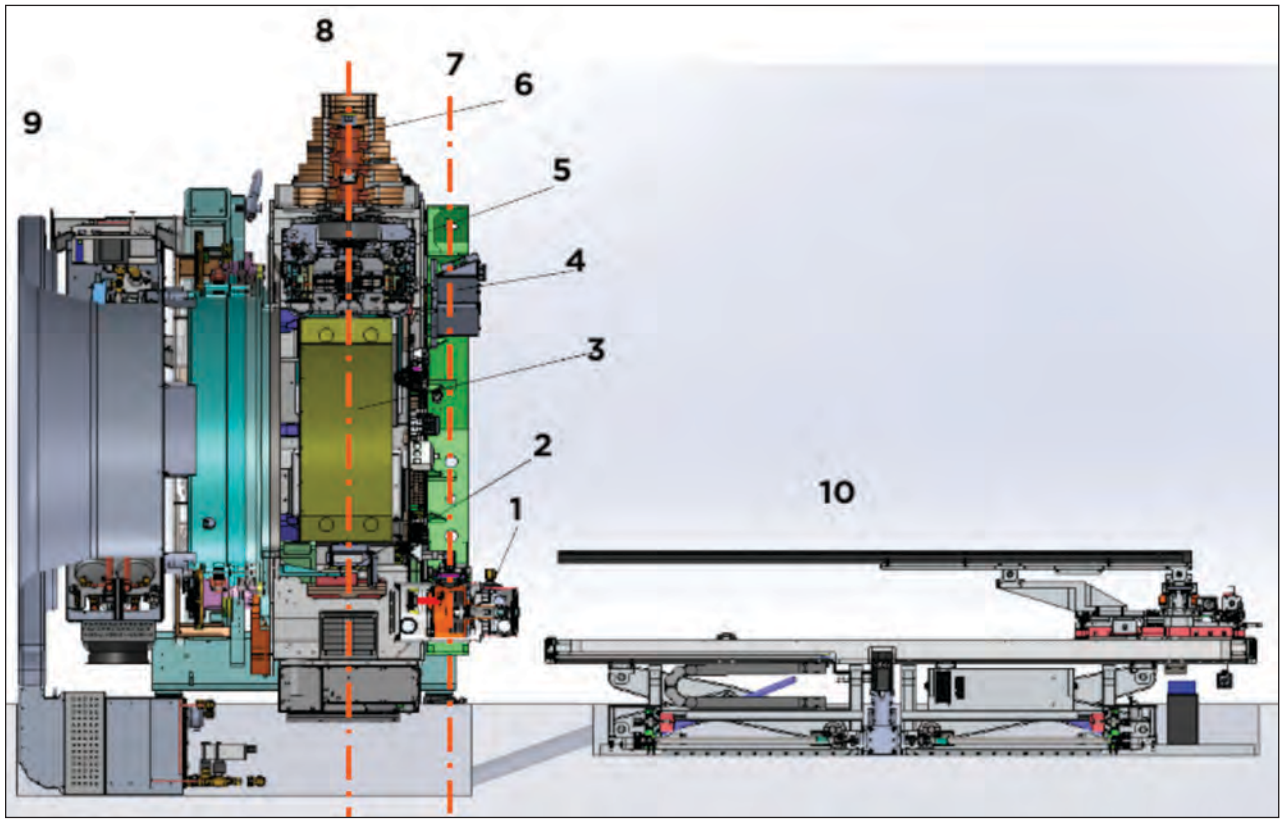
Disclosures: Dr. Han reports grants from RefleXion and ViewRay. Dr. Kovalchuk reports grants/contracts from RefleXion. Dr. Gensheimer reports grants/contracts from Varian and XRad Therapeutics. Dr. Vitzthum reports research funding from RefleXion. Dr. Xing reports no disclosures of interest. Dr. Surucu reports a Master Research Agreement with RefleXion Medical Inc. and honoraria from RefleXion for two invited lectures. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.

Figure 1. Section view of the RefleXion X1 linac with components: 1) kilovoltage CT (kVCT) x-ray tube; 2) MV electronic portal imaging device (EPID); 3) PET detectors; 4) kVCT detector; 5) primary collimators; 6) 6-MV linac; 7) kVCT plane; 8) MV and PET plane; 9) cooling system; and 10) couch. Figure reproduced from reference 4, with permission.



for IMRT/SBRT and BgRT. Detailed introductions of the X1 system can be found in these publications.[4-7] Given the similarities between the X1 and tomotherapy machines, the commissioning processes share much in common. However, the process for the X1 additionally includes small-field measurements and a more extensive imaging system commissioning.

The RefleXion X1 system received FDA clearance for conventional kVCT-guided treatment for IMRT/SBRT in March 2020. As of February 2023, the BgRT modality has been FDA-cleared for treating patients with lung and bone tumors, expanding the applications of the system to motion management via PET tracking. Our department was the first to install and commission the RefleXion X1 system for IMRT/SBRT in 2020, utilizing it to treat more than 100 patients since May 2021; we will be the first to upgrade the system to enable BgRT in June 2023. In this report, we present a comprehensive review of the X1 system during its first 2 years of clinical use, including commissioning, quality assurance, treatment planning, machine performance, and initial BgRT clinical trial results.

Commissioning the Machine

The mechanical and dosimetric aspects of the commissioning tests were performed[4] according to the AAPM Protocol Task Group 148.[8] The imaging system[3] and the treatment planning system (TPS) were also assessed.[7]

Mechanical Commissioning

The mechanical alignments of the radiation source, y-jaw, and MLC were verified using film and ion chambers. A center alignment check in the y-direction was conducted with a 0.3-mm misalignment tolerance. A 2-mm y-jaw opening and ion chamber measurements helped determine source misalignment, with an actual misalignment of 0.049 mm. The x-direction source position was checked against the MLC using a tongue-and-groove test, with transverse profiles measured in a water tank. The out-of-focus value was 0.66%, within the acceptable range. Y-jaw alignment with the beam plane was checked to ensure proper beam intersection and symmetry. Film tests showed y-jaw divergence and twist met tolerance levels of 0.5 mm and 0.5°. Off-axis clinical treatment fields were tested, with center variations within the acceptable range of 0.5 mm. MLC lateral alignment was assessed using a film at the isocenter, and the MLC offset and twist were within tolerances of 1.5 mm and 0.5°. The accuracy

of both the couch and laser positioning was verified. A starshot test was conducted to ensure the radiation beams converge accurately at a common isocenter during gantry rotation, yielding a result in which the minimum radius of the tangent circle was 0.7 mm.

Dosimetry Commissioning

Percentage depth dose (PDD) and profile scans were conducted for various field sizes using a diode detector in a compact 3D water tank. The agreement between measurement and TPS calculation was analyzed with 1D gamma analysis. The PDD10 differences were within 1%, with a mean of 0.3% for all fields, and the mean gamma (1%, 1 mm) pass rate beyond Dmax depth was 94.9%. Lateral profiles were measured at various depths, and the measured and TPS modeled transverse profile differences in the field core showed excellent agreement. For all measured fields, the mean profile differences in the field core were -0.3% ± 1.0% and -0.3% ± 1.2% for 2 cm and 1 cm jaw fields, respectively. Longitudinal profiles for fields were measured and compared with the TPS calculation. For all measured fields, the mean and max full-width at half-maximum (FWHM) differences were 0.3 and 0.4 mm for 2 cm jaw fields, and -0.3 and 0.5 mm for 1 cm jaw fields.

Dose-rate fluctuations at different gantry angles were monitored using a TomoDose (Sun Nuclear) diode array, with output constancy at 0.21% and profile constancy within the suggested tolerance. Rotational output constancy was verified with a 0.7% variation using an ion chamber. A synchronicity plan assessed accurate beam transmission through the MLC in clinical step-and-shoot mode with a gantry rotating at 60 RPM and the couch advancing 2.1 mm per step. The film result showed the maximum delivery offset and angular deviations at 0.26 mm and 0.17°, respectively. To assess complex integrated IMRT plan delivery accuracy, the AAPM TG119[9] head and neck (HN) and prostate plans were measured using the ArcCHECK (Sun Nuclear) diode array system. The measurement results were compared with TPS calculations via gamma analysis (3%, 2 mm) with the pass rates of 98.2% for the HN plan and 93.4% for the prostate plan.

RefleXion X1's clinical beams use small beamlets formed by MLC leaves (6.25-mm thick) and narrow y-jaw openings (10 or 20 mm), creating a lack of charged particle equilibrium and making accurate small-field dosimetry crucial. Shi et al[6] reported measurements and Monte Carlo (MC) model validation for the first clinical RefleXion unit, covering various small-field sizes. Diode detectors, a W2 scintillator detector, and films were used to acquire PDDs, beam profiles, and relative output factors. Results showed good agreement between diode, film, and MC simulations for output factors, profile penumbra, and FWHM. Averaged beam profile consistency between diode- and film-measured profiles among different depths was within 1.72%. The MC model of the linac, including pre-MLC beam sources and detailed MLC and lower y-jaw structures, was validated using BEAMnrc and GATE simulation codes. The study highlights the importance of ensuring small-field dosimetry accuracy for RefleXion systems, with results demonstrating acceptable consistency and agreement between measurement methods and MC simulations.

Imaging Commissioning

The imaging system, including the kVCT imager and PET imager, were also commissioned and reported. Han et al[10] reported on the commissioning of the fan-beam kVCT imaging system for the first clinical BgRT machine, focusing on positioning accuracy, image quality, and dose commissioning. The helical fan-beam kVCT subsystem features a 120-kV x-ray tube and a 16-row gadolinium oxysulfide (GOS) ceramic scintillator detector. A ball-cube phantom was utilized to assess the kVCT subsystem's positioning accuracy. The Catphan504 phantom (Phantom Laboratory) was imaged to evaluate the kVCT image quality of the BgRT system. The system demonstrated comparable spatial resolution to regular CT simulators through modulation transfer function test results. The evaluation demonstrates the kVCT characteristics of the innovative BgRT system, which features an architecture designed to accommodate CT, PET, and a linac. The image quality and HU (Hounsfield unit) constancy are comparable to traditional CT simulators, making the system a valuable tool for online adaptive radiation therapy.

Hu et al[3] evaluated the RefleXion X1 machine's PET subsystem performance using the National Electrical Manufacturers Association (NEMA) NU-2 2018 standard. The X1 machine integrates PET detectors into a ring-gantry linear accelerator, guiding radiation beam delivery. The PET subsystem was assessed based on sensitivity, spatial resolution, count-loss performance, image quality, and daily system checks. Spatial resolution and image contrast were comparable to typical diagnostic imaging systems for larger spheres. Image-quality contrast values were 29.6%, 64.9%, 66.5%, 81.8%, and 81.2%, with background variability of 14.8%, 12.4%, 10.3%, 8.8%, and 8.3% for sphere sizes of 13, 17, 22, 28, and 37 mm, respectively. However, sensitivity and count rate were lower due to the smaller PET detector area in the X1 system. The clinical efficacy of the X1 system in BgRT remains to be validated after it is officially released for clinical use. Overall, the X1 PET subsystem performance is comparable to typical diagnostic PET systems in terms of spatial resolution and image contrast for spheres larger than 13 mm in diameter.

Treatment Planning System Commissioning

The RefleXion X1's TPS commissioning results, reported by Simiele et al,[7] were assessed using multiple phantoms, comparisons with other TPS systems, and representative clinical IMRT and SBRT cases. Dosimetric parameters, output factors, and agreement between TPS and measurements for various clinical plans were analyzed. End-to-end testing with anthropomorphic head and lung phantoms showed total targeting errors of 0.8 mm for isocentric treatments and 1.1 mm for off-axis treatments. Overall, the RefleXion X1 TPS commissioning results were within the tolerances specified by AAPM TG 53, MPPG 5.a, TG 119, and TG 148 for targets greater than a 1.5-cm diameter located less than 15 cm from the treatment isocenter. A subset of the commissioning tests has been identified as baseline data for an ongoing quality assurance (QA) program.

Quality Assurance

A robust QA program is essential for the RefleXion X1, a complex treatment delivery system, to ensure the safety of treatment delivery. Han et al[11] reported the annual, monthly, and daily QA measurement results of the first clinical RefleXion X1 machine following the TG-148 guidelines. The daily QA was performed using TomoDose to verify the laser and kVCT alignment, as well as beam output. The daily MV beam output constancy result demonstrated that the machine was stable over a year of operation with a standard deviation (SD) of 1.1%. The mechanical accuracy of the laser, couch shift, kVCT imaging, and MV beam center were all within 1 mm. More comprehensive parameters, including output, beam quality, and profile consistency, were measured monthly using TomoDose and an ion chamber. Monthly TG-51 calibration was conducted, and the machine output was adjusted twice during the first year of operation to maintain the output SD below 0.6%. The monthly mechanical test concluded that the SD from the laser center to the imaging center was 0.64 mm. The kVCT image quality was tested monthly using a Catphan phantom, and the resolution, contrast, uniformity, noise, linearity, HU constancy, and slice thickness of the kVCT remained stable compared with the commissioning image qualities. Dynamic plan deliveries were tested using film, confirming that the deviation from the kVCT imaging center to the MV beam center was within 1mm. The first annual QA included mechanical centering, alignment, and divergence of the source, MLC, and y-jaws. The beam quality and profiles were measured using a 3D water phantom and diodes. All mechanical, dosimetry, and imaging tests in the annual QA passed the tolerance suggested by the TG-148. The QA results of the clinical BgRT system provide a valuable reference for future studies on machine stability and operational limits.

Clinical Applications

Treatment Planning Studies

The RefleXion X1 treatment planning retrospective study was conducted by Pham et al[5] to evaluate the IMRT/SBRT plan quality and delivery efficiency. A total of 42 patient plans across 6 cancer sites, including conventionally fractionated lung, head and neck, anus, prostate, brain, and lung SBRT, were analyzed. These cases, originally planned with the Eclipse TPS (Varian) and treated with a C-arm linear accelerator, were selected for this retrospective study. For each Eclipse VMAT plan, corresponding plans with different jaw settings were generated on the X1 TPS using the same planning constraints. All clinically relevant metrics, such as planning target volume (PTV) D95%, PTV D2%, conformity index (CI), R50, organs-at-risk (OAR) constraints, and beam-on time were analyzed and compared between 126 volumetric-modulated arc therapy (VMAT) and X1 plans using paired t-tests. All but 3 planning metrics were either equivalent or superior for the X1 10 mm-jaw plans compared with the Eclipse VMAT plans across all planning sites investigated. The Eclipse VMAT and X1 10-mm jaw plans generally achieved superior plan quality and sharper dose fall-off superior/inferior to targets compared with the X1 20-mm jaw plans. However, the X1 20-mm jaw plans were still considered acceptable for treatment. On average, the required beam-on time increased by a factor of 1.6 across all sites for 10-mm jaw plans compared to 20-mm jaw plans and a factor of 5 to 10 compared with VMAT deliveries. The most recent upgrade to 1000 MU/min dose rate can further decrease the beam-on time and the gap between the VMAT and X1 treatment times. The study demonstrated that clinically acceptable IMRT/SBRT treatment plans were generated with the X1 TPS. This indicates that the X1 system can effectively produce high-quality treatment plans for various cancer sites, offering a promising alternative to traditional linac-based treatment planning systems.

IGRT and SBRT Treatment Delivery

The first X1 unit was installed and operated in IMRT/SBRT mode for more than a year. Shi et al[12] presented the first-year experience of treating patients in a clinical setting with this system. From May 2021 to May 2022, 78 patients were treated on the X1 system. Clinical and technical data, including treatment sites, number of pretreatment kVCT scans, beam-on time, patient setup time, and imaging time, were collected and analyzed. The most commonly treated site was head and neck (63%), followed by pelvis (23%), abdomen (8%), and thorax (6%). Except for 5 pelvis patients

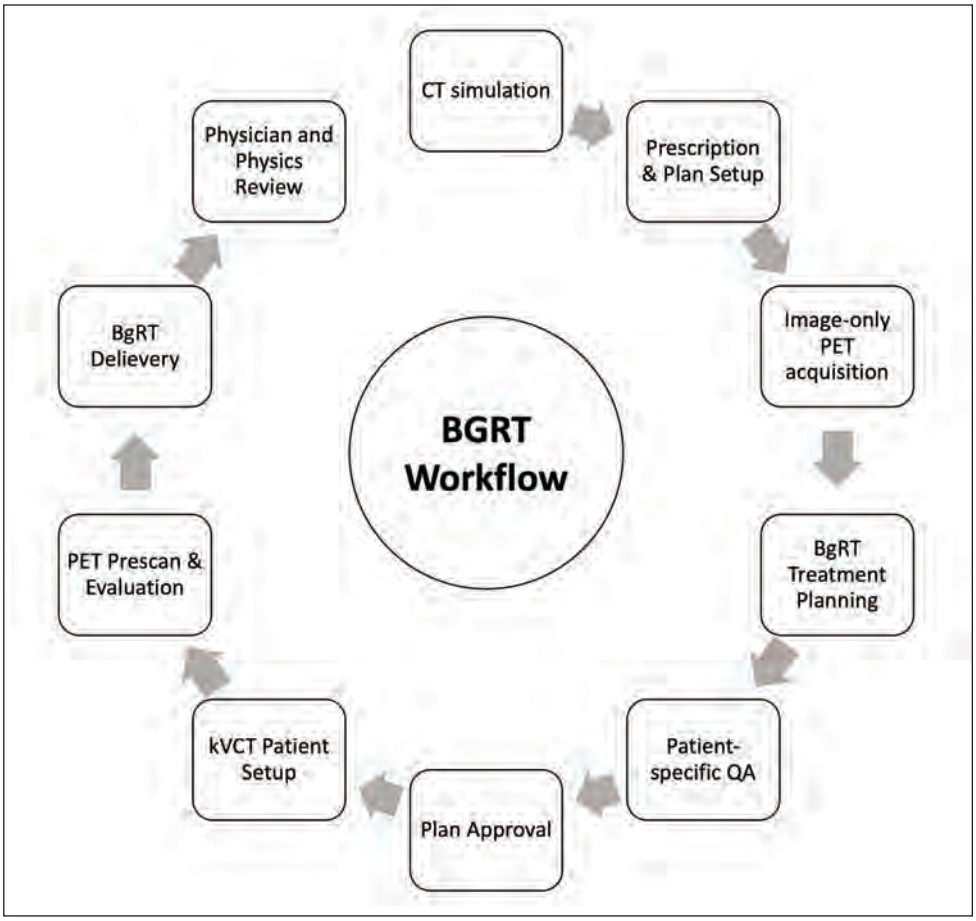


Figure 2. Clinical workflow diagram for biology-guided radiation therapy (BgRT) using the RefleXion X1 machine.

(6%) who received SBRT treatments for bony metastases, all treatments were conventionally fractionated IMRT. The average number of kVCT scans per fraction was 1.2 ± 0.5. The beam-on time averaged 9.2 ± 3.5 minutes, while the patient setup time and imaging time per kVCT were 4.8 ± 2.6 minutes and 4.6 ± 1.5 minutes, respectively. Patient-specific QA results and machine performance were also collected and reported. The patient QA had a passing rate of 97.4 ± 2.8% 3% and 2-mm gamma criteria. The machine uptime was 92% of the total treatment time. The user-satisfaction survey was conducted among 5 radiation oncology physicians, 5 medical physicists, 5 dosimetrists, and 4 radiation therapists to gather feedback on their experience with the X1 system. The kVCT image quality and daily QA process received the highest level of satisfaction, while the treatment workflow for therapists received the lowest level of satisfaction.

Simiele et al[13] successfully applied Six Sigma methodology and Failure Modes and Effects Analysis (FMEA) to mitigate errors in IMRT and SBRT treatment planning. The approach consisted of 5 phases: Define-Measure-Analyze-Improve-Control. The multidisciplinary team outlined the workflow process and identified/ranked the failure modes associated with the plan check items using AAPM TG-100[14] recommendations. Items with the highest average risk priority numbers (RPN) and severity greater than or equal to 7 were prioritized for automation using the Eclipse Scripting API (ESAPI). The Improve phase consisted of developing ESAPI scripts prior to clinical launch of X1 to improve efficiency and safety. In the Control phase, the FMEA ranking was re-evaluated 1-year post clinical launch. Overall, 100 plan check items were identified where the RPN values ranged from 10.2 to 429.0. Fifty of these items (50%) were suitable for automation within ESAPI. Of the 10 highest-risk items, 8 were suitable for automation. Based on the results of the FMEA, 2 scripts were developed: Planning Assistant used by the planner during preparation for planning, and the Automated Plan Check used by the planner and the plan checker during plan preparation for treatment. After 12 months of clinical use of the X1 and developed scripts, only 3 errors were reported. The average RPN pre-scripts was 138.0 compared with average post-scripts RPN of 47.8 ($P < 0.05$), signifying a safer process.

BgRT and Clinical Trials

In the first-in-human, multi-institutional clinical trial[15] of BgRT, called BIOGUIDE-X, a total of 15 patients

were enrolled with the objective of assessing the safety and performance of BgRT. Cohort I aimed to determine whether BgRT plans could be successfully created. Cohort II was designed to assess the deliverability of the BgRT plans on the RefleXion X1 and to further appraise the system's performance. This was accomplished by obtaining 2 more PET images during the first and last regular SBRT treatment days. The results of this detailed clinical trial will be summarized in future publications. The BgRT workflow steps and time requirements were also assessed in the clinical trial. **Figure 2** shows the BgRT process including CT simulation, contouring, imaging-only PET acquisition, BgRT planning, patient-specific QA, plan approval, and delivery. The workflow was assessed by recording time intervals between various steps. The new processes introduced by BgRT were found clinically feasible, but improvements are underway to shorten the time required for each step and increase patient comfort ahead of clinical implementation.

Although the current workflow requires F-18 fluorodeoxyglucose (FDG) administration daily before each BgRT fraction, the recent preclinical evaluation of a PET tracer with a longer decay time, ^{89}Zr-panitumumab (^{89}Zr-Pan)—an antibody PET tracer with a half-life of 78 hours that can be imaged for up to 9 days using PET—was conducted by our group.[16] Based on the study analysis translated from mice to humans, BgRT may be feasible for 5 consecutive days after a single 740-MBq injection of ^{89}Zr.

Conclusion

With the recent FDA clearance of BgRT, the department is preparing to treat patients using PET guidance through a new product release, which will improve the current IGRT workflow by increasing the dose rate and decreasing treatment time, improving efficiency of the treatment delivery by providing automated IGRT image matching and enabling re-imaging after large shifts, etc. This 2-year experience with the RefleXion X1 system demonstrates its effectiveness in a clinical setting, offering a promising treatment option for various cancer sites. As the system continues to evolve and incorporate new capabilities such as BgRT, it is expected to further improve patient outcomes and streamline the treatment process.

In conclusion, this review has highlighted the key advancements and findings in the clinical applications of the new FDA-cleared BgRT RefleXion linac. The synthesis of the reviewed studies demonstrates the growing understanding of the complex commissioning, QA, and treatment planning processes. Despite progress, several gaps and limitations in the current literature have been identified, such as optimizing the BgRT workflow and verifying the BgRT tracking accuracy in real patients. To address these issues, future research should focus on PET tracking accuracy, particularly for multitarget treatment. Understanding these aspects will not only advance the widespread use of BgRT, but also broaden its indications for radiation therapy in the treatment of metastatic cancer. Ultimately, continued investigation into PET-based BgRT is crucial for the advancement of radiation oncology as a whole.

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Whole-Lung IMRT in Children and Adults With Synovial Sarcoma and Lung Metastases: Single-Institution Prospective Clinical Trial

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Abstract

Objective: To evaluate the toxicity and feasibility of whole-lung irradiation (WLI) in children and adult patients with synovial sarcoma and pulmonary metastases.

Methods and Materials: After completing standard therapy, 14 patients with synovial sarcoma and lung metastases (ages 12-52, mean 30 years) were treated with WLI in (n = 10) or as per (n = 4) a prospective trial with cardiac sparing intensity-modulated radiation therapy (IMRT) to 1500 cGy in 150 cGy per fraction. The primary objective was to assess the overall toxicity rate at 1 year after radiation, with a secondary objective to assess the pulmonary failure-free survival (PFFS).

Results: Median follow-up among all patients was 33 months from time of IMRT (range, 3-69 months). At the time of IMRT, 13 of 14 patients had residual or recurrent gross disease in the lungs. At 18 months, the PFFS was 14.3%, with a median time to pulmonary failure of 6.2 months from IMRT. All acute toxicities from IMRT were grade 1, including fatigue (n = 9), esophagitis (n = 4) cough (n = 2), dermatitis (n = 2), nausea (n = 3), and dysphagia (n = 1). Late toxicities from IMRT at 1 year were minimal, including low-grade dyspnea and mild cough.

Conclusion: Whole-lung IMRT for patients with synovial sarcoma and lung metastases is feasible with minimal acute and late toxicity. However, long-term durable pulmonary control was not achieved in our cohort of patients with residual/recurrent gross pulmonary disease. Low-dose IMRT with 1500 cGy should be further explored as part of consolidation therapy (rather than in the setting of recurrent/residual disease) as is the standard for Ewing sarcoma and rhabdomyosarcoma.

Keywords: Synovial sarcoma, whole-lung irradiation, pulmonary metastases, consolidative therapy

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Disclosure: Dr. Casey serves on the editorial advisory board of *Applied Radiation Oncology*. The authors have no other conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere.
Data-availability statement: All data generated and analyzed during this study is included in this published article.

Synovial sarcoma accounts for approximately 5% to 10% of all sarcomas[1-3] and is frequently observed in young adults, with a mean age of 39.[4] In addition, synovial sarcoma is the most common non-rhabdomyosarcoma sarcoma in children.[5] Pulmonary metastases represent the most common site of metastases and is the leading cause of death in patients with synovial sarcoma.[1,4]

In patients with other radiosensitive pediatric sarcomas such as rhabdomyosarcoma (RMS) and Ewing sarcoma, whole-lung irradiation (WLI) is the standard of care as part of consolidation at the completion of planned therapy for patients with lung metastases.[6-8] In this setting, WLI is well tolerated[9] and associated with reduced pulmonary relapses and improved event-free survival (EFS).[10] However, for patients with lung metastases and synovial sarcoma, WLI is not part of the treatment mainstay, despite the frequency of pulmonary metastases and potential oncologic benefit. Additionally, like RMS and Ewing sarcoma, synovial sarcoma is a radiosensitive histology.[11,12] In this trial, we sought to evaluate the toxicity and clinical outcomes after cardiac-sparing, whole-lung intensity-modulated radiation therapy (IMRT) in patients with synovial sarcoma and lung metastases.

Methods

Patients

This was a single-institution prospective clinical trial of patients with synovial sarcoma and lung metastases at Memorial Sloan Kettering Cancer Center (MSKCC) treated between September 2014 and June 2022. Fourteen patients were treated with WLI in (n = 10) or as per (n = 4) the prospective trial. Patients completed standard therapy as determined by the primary management team (eg, surgery +/- radiation to the primary site and any adjuvant chemotherapy, most commonly Adriamycin + Ifosphamide + MESNA [AIM]) and were eligible for enrollment if they had lung metastases at diagnosis and/or developed lung metastases during the course of therapy. All patients had CT chest imaging prior to the start of WLI to serve as a baseline for follow-up scans and were recommended as per protocol to have a baseline echocardiogram and pulmonary function tests (PFTs) prior to starting radiation treatment. The study was approved by the MSKCC Institutional Review Board/Privacy Board (IRB 14-075).

Radiation

All patients received cardiac-sparing IMRT to 1500 cGy in 10 fractions of 150 cGy per fraction, 1 fraction per day, in accordance with the protocol after metastatectomy and after or concurrent with chemotherapy. No patient received radiation therapy to the lungs prior to treatment. In general, patients were simulated in a supine position with an alpha cradle and without abdominal compression. The clinical target volume (CTV) was the bilateral lung volume, including all pleural recesses and bilateral hila. The internal target volume (ITV) included an expansion on the CTV to encompass the bilateral lungs on all phases of the respiratory cycle (as defined by the 4DCT). The planning target volume (PTV) was a 1-cm expansion in all directions on the ITV, to account for spatial uncertainties in patient positioning and treatment delivery. Further descriptions on the cardiac-sparing WLI and details on constraints can be found in previously published work.[13] Three patients had an additional stereotactic body radiation therapy (SBRT) boost (25-30 Gy in 5 fractions) after WLI for treatment of gross disease.

Protocol Follow-up

Following completion of therapy, patients were to undergo CT chest imaging and toxicity assessments at 3, 6, 12, 18, and 24 months; an echocardiogram at 6, 12, and 24 months; and PFTs at 6 and 24 months.

Statistical Analysis

The primary objective of the study was to assess the safety of whole-lung IMRT following standard treatment in patients with synovial sarcoma and lung metastases. Secondary objectives were to determine rates of pulmonary failure-free survival (PFFS) and overall survival (OS) after completion of whole-lung IMRT. The safety endpoint included both acute (< 3 months from completion of WLI) and late toxicities (1 year from completion of WLI). The Common Terminology Criteria for Adverse Events, version 4.0, was used to grade acute and late toxicities. The PFFS was defined as survival with no progressive disease in the lungs from the initiation of IMRT, and OS was calculated as the time from initiation of IMRT to death, no matter the cause. Living patients at the time of analysis were censored at the time of the last follow-up visit. The Kaplan-Meier method was used to assess the PFFS and OS.

Results

Patient, Tumor, and Dosimetric Characteristics

The median patient age at WLI was 38 years (range, 13-55 years), with 10 male patients and 4 female patients (**Table 1**). Six patients presented with lung metastases at diagnosis, while the other 8 patients developed lung metastases at a median time of 25 months from diagnosis (range, 9-39 months), after initial treatment failed (**Table 2).** All patients were treated with chemotherapy prior to or concurrent with lung RT. Ten patients underwent metastatectomies prior to the initiation of RT. Median follow-up among all patients was 33

Table 1. Baseline Patient and Tumor Characteristics

VARIABLE	NUMBER	(%)
Total number of patients	**14**	
Sex		
Male	10	71
Female	4	29
Age at diagnosis, years		
< 18	3	21
18-35	7	50
> 35	4	29
Race		
Non-White	3	21
White	11	79
Mono/biphasic		
Monophasic	8	57
Biphasic	3	24
Unknown	3	21
SYT-SSX1 translocation		
Translocation positive	11	79
Translocation negative	0	0
Unknown	3	21
Primary site		
Extremity	12	86
Abdomen wall	1	7
Neck	1	7
Primary tumor size, cm		
≤ 5	12	86
> 5	2	14
Metastatic at diagnosis		
To the lung	6	43
To site other than lung	0	0
No	8	57

Table 2. Characteristics of Metastatic Pulmonary Disease at IMRT Start

TIME TO LUNG METASTASES, MONTHS	NUMBER	(%)
At diagnosis	6	43
< 12 mo	2	14
12-24 mo	3	21
> 24 mo	3	21
Previous metastectomy in lungs		
Yes	10	71
No	4	29
Gross disease at IMRT start		
Yes	13	93
No	1	7
Number of lung metastases at IMRT start		
0	1	7
< 5	6	43
5-10	2	14
> 10	5	36
Size of largest lung metastases at IMRT start		
< 0.5	2	15
0.5-1.0	7	54
1.0-2.0	2	15
> 2.0	1	8
Unknown	1	8

Abbreviations: IMRT, intensity-modulated radiation therapy; mo, month

months from time of IMRT (range, 3-69 months). At the time of WLI, 13 of 14 patients had residual or recurrent gross disease in the lungs, as determined by imaging prior to the start of RT. The median number of lung metastases at the start of RT was 4 (range, 1-10 metastases), with the average size of the largest metastasis being 1.0 cm (range, 0.3-3.2 cm). The average mean cardiac dose of all patients was 1058 cGy (range, 870-1286 cGy).

Clinical Outcomes

Twelve of 13 patients with pulmonary gross disease at the time of IMRT progressed at an initial pulmonary disease site after completion of IMRT. One patient never progressed in the lung after completion of chemotherapy and WLI, and has remained disease free for 30 months. The 1 patient with no gross disease at time of IMRT relapsed after 8 months at a new site of disease in the lungs.

At 18 months, the PFFS was 14.3% (**Figure 1**). Two of 3 patients treated with SBRT for their pulmonary relapse experienced subsequent local pulmonary control. The OS at 18 and

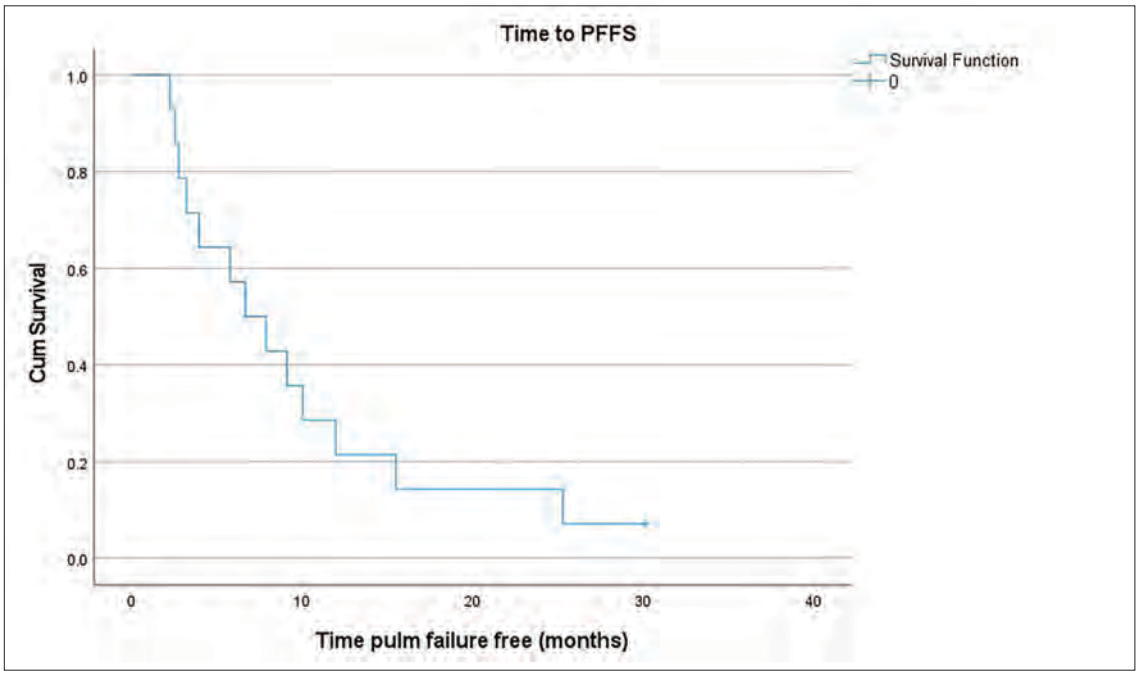

Figure 1. Kaplan-Meier survival curve for pulmonary failure-free survival (PFFS) of the patient cohort.

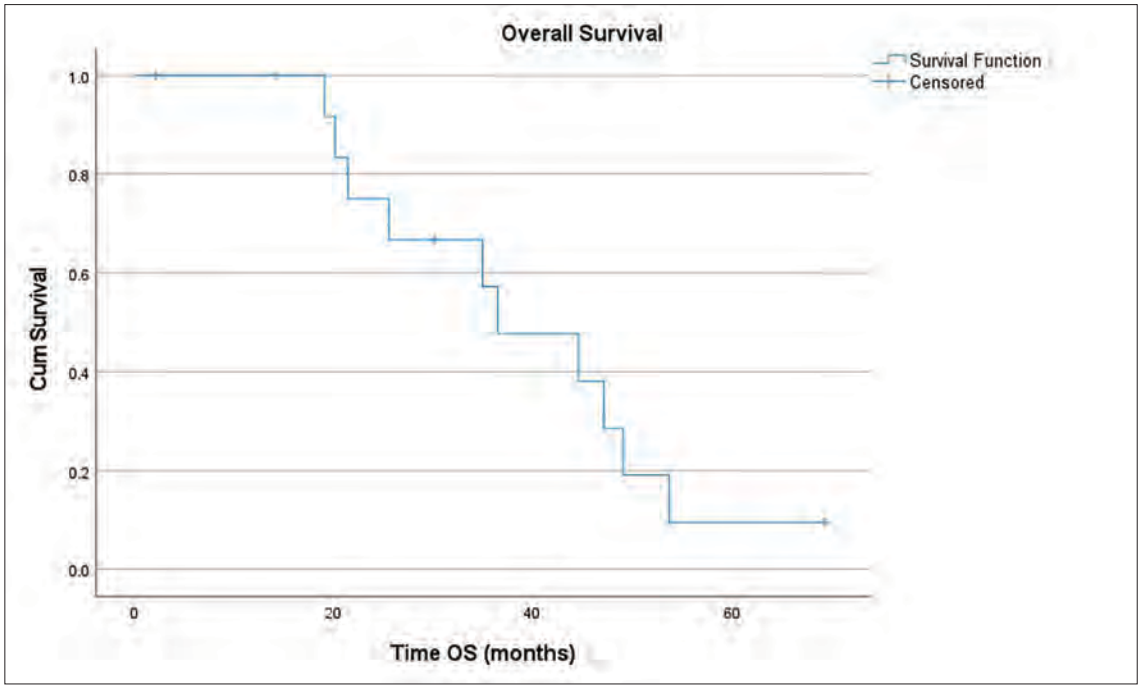

Figure 2. Kaplan-Meier survival curve for the overall survival of the patient cohort.

36 months from IMRT was 100% and 57.1%, respectively (**Figure 2**). All patients had pulmonary disease at the time of death.

Toxicities

All acute toxicities from IMRT were grade 1, including fatigue (n = 9), esophagitis (n = 4) cough (n = 2), dermatitis (n = 2), nausea (n = 3), and dysphagia (n = 1). Late toxicities from IMRT at 1 year were minimal, including low-grade dyspnea and mild cough, although the etiology of these findings is likely multifactorial due to tumor burden, surgery, chemotherapy, and radiation therapy. No patients experienced an impairment in their daily functioning as a result of treatment. No significant decline in cardiac function as measured by echo (ejection fraction [EF] mean decline by 1.6%, $P = 0.74$), or pulmonary function as measured by PFTs

(forced expiratory volume [FEV] mean decline 0.6%, $P = 0.91$; forced vital capacity [FVC] mean decline 1.0%, $P = 0.99$; diffusing capacity of the lungs for carbon monoxide [DLCO] mean decline 7.0%, $P = 0.52$) was seen at 1-year follow-up.

Discussion

Overall, whole-lung, cardiac-sparing IMRT is feasible for patients with synovial sarcoma metastatic to the lung and with minimal acute and late toxicities. However, in our patient cohort in which 93% of patients had residual gross disease in the lungs at the time of radiation, long-term pulmonary control was not achieved.

A dosimetry study comparing WLI using an anteroposterior-posteroanterior technique vs cardiac-sparing IMRT (CS-IMRT) showed the volume of the left ventricle, right ventricle, myocardium, and coronary arteries received a significantly lower radiation dose in the CS-IMRT plans as compared to the anteroposterior-posteroanterior plans.[14] There has since been a multi-institutional protocol investigating the feasibility of cardiac-sparing whole-lung IMRT in children and young adults with a diagnosis of Wilms tumor, Ewing sarcoma or RMS, and lung metastases showing minimal long-term cardiac morbidity. In our study utilizing WLI IMRT for patients with synovial sarcoma, we were able to achieve a mean heart dose of 1058 cGy, and no difference in cardiac functioning as measured by echo was observed.

Regarding pulmonary toxicity following WLI delivered with IMRT, on a prospective trial including 20 patients with Wilms, RMS, and Ewing sarcoma, only 1 patient developed pulmonary restrictive disease.[13] In studies that examine patients treated with low-dose WLI using conventional techniques, there are often mild reductions in pulmonary function abnormalities with low rates of clinically symptomatic moderate or severe pulmonary symptoms on follow-up.[9,15,16] These results indicate that while pulmonary function test abnormalities are often seen after WLI, the incidence of clinically significant pulmonary toxicity is low, particularly at low doses of 15 Gy, the dose used in this study. In our study, there were no significant declines in cardiac or in pulmonary function as measured by PFTs, and no patients experienced toxicities impeding their daily activities at 1 year. Overall, WLI is widely tolerated among patients with synovial sarcoma as it is for patients with Ewing sarcoma and RMS.

Long-term durable pulmonary control was not achieved in our cohort of patients with residual/recurrent gross disease in the lungs at the time of radiation. The target population of this study was patients who initially presented with synovial sarcoma metastatic to the lungs, and who completed standard therapy without gross residual disease in the lungs at the time of radiation therapy. However, 8 of 14 patients had relapsed pulmonary disease during or after initial treatment, and 13 of 14 patients presented with gross residual disease in the lungs at the start of radiation therapy. Thus, our study included an unfavorable cohort of patients with progressive, bulky disease in the lungs at the time of WLI, unlike those typically treated with WLI as part of consolidation for RMS and Ewing sarcoma. Furthermore, the majority of these patients did not receive a boost or additional treatment to their gross pulmonary disease.

WLI is considered standard at the end of therapy for patients with Ewing sarcoma and RMS with lung metastases. For both tumors, studies have shown an improvement in progression-free survival after consolidative WLI.[6,9] Data indicate that local control of pulmonary metastases is associated with improved survival as well.[10] Similar to RMS and Ewing sarcoma, synovial sarcoma is a radiosensitive histology[11] that may benefit from such an approach. In addition, given the consistent pattern of pulmonary failure at a pre-existing site of gross disease, consideration of high-dose radiation such as SBRT after WLI to gross residual disease should be considered for optimal control of pulmonary metastases from synovial sarcoma, as is now done for patients with Ewing sarcoma and RMS.[17] In our series, 2 of 3 patients treated with subsequent SBRT for pulmonary relapse obtained local pulmonary control. A series from the University of Rochester using SBRT for pulmonary metastases from soft-tissue sarcomas showed an 82% rate of local control at 3 years and an improvement in OS from 0.6 years to 2.1 years with the use of SBRT.[18]

Conclusion

In conclusion, our study shows that 15 Gy WLI with cardiac-sparing IMRT is feasible and well tolerated in patients with synovial sarcoma. However, this approach was not sufficient for treatment of patients with relapsed, gross residual disease in the lungs (13 of 14 patients included). Overall, we recommend that 15 Gy WLI with IMRT should be explored further (with consideration of an SBRT boost for gross disease) for patients with synovial sarcoma and lung metastases at the completion of initial therapy as part of consolidation therapy, rather than in the setting of recurrent/residual disease.

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Evaluating the Utility of Webinars on the Radiation Oncology Residency Application Process in the COVID-19 Era

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Abstract

Objective: Since the start of the COVID-19 pandemic, the number of digital resources available for medical students interested in radiation oncology (RO) has increased. Here, we evaluated the utility of webinars focused on educating medical students about the RO residency application process.

Materials and Methods: The American College of Radiation Oncology (ACRO) Resident Committee hosted webinars in 2021 and 2022 prior to the Electronic Residency Application Service (ERAS) application deadline. For each webinar, program directors gave short presentations about the ERAS application, interviews, and program ranking, and concluded with a question-and-answer session. Participant demographics were collected using live poll questions, and understanding was assessed using a Likert scale (range, 1-4). Recordings were available online for asynchronous viewing. Differences between groups were assessed using Chi-square statistics.

Results: Between both webinars, there were a total of 69 participants and 340 asynchronous views. A total of 86% and 71% of participants answered the demographics and understanding questions, respectively. The majority attended medical school within the US (75%), were in their third/fourth year (70%), were graduating with an MD degree (88%), and planned to apply to RO residency (78%). In terms of baseline knowledge of the application process, 49% believed they knew "a lot," while 51% believed they knew "a little" or "nothing." Most participants noted that the webinar improved their understanding of the general application process (mean 3.80), the ERAS application (mean 3.65), and the interview process (mean 3.90). When stratified by baseline understanding (n = 39), participants who knew "a little" about the application process reported higher scores than participants that knew "a lot." However, these differences were not statistically significant.

Conclusions: Webinars can improve medical student understanding of the RO residency application process. Given the recent decline in applications to RO, engaging with medical students through dedicated webinars is a unique strategy worth continued utilization.

Keywords: radiation oncology, residency, education, webinar

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Disclosures: The authors have no conflicts of interest to disclose. The American College of Radiation Oncology (ACRO) funded this study. None of the authors received funding for the production of this original manuscript and no part of this article has been previously published elsewhere with the exception of an abstract at the 6th Annual ROECSG Spring Symposium, May 5, 2023, Chicago.
Data availability statement: Data generated and analyzed for this study are included in the published article and fully available for reuse. For additional requests, please contact the corresponding author.
Acknowledgement: The authors thank Fraser Cobb and the team at the American College of Radiation Oncology for their administrative support. We also thank Drs. Rahul Tendulkar, Christina E. Henson, Ana P. Kiess, Ann C. Raldow, and Stephen Rosenberg for their participation.

Table 1. Baseline Characteristics of Webinar Participants

	TOTAL (N = 59)	2021 (N = 31)	2022 (N = 28)	P-VALUE
Current Training Level				
M1-2 Year	4 (6%)	4	0	0.05
M3-4 Year	41 (70%)	22	19	
Resident/Fellow in Another Specialty	7 (12%)	1	6	
Not a Current Student or Trainee	7 (12%)	4	3	
Location of Medical School				
Within US	44 (75%)	25	19	0.26
Outside US	15 (25%)	6	9	
Expected Degree				
MD	52 (88%)	28	24	0.50
DO	1 (2%)	1	0	
MD/PhD, DO/PhD	5 (8%)	2	3	
Other	1 (2%)	0	1	
Plans to Apply into Radiation Oncology				
Not Planning on Applying	1 (2%)	1	0	0.63
Considering Applying	12 (20%)	6	6	
Definitively Applying	46 (78%)	24	22	
Baseline Knowledge of Radiation Oncology Residency Application Process				
Nothing	4 (7%)	3	1	0.56
A little	26 (44%)	20	21	
A lot	29 (49%)	8	6	

Since the start of the COVID-19 pandemic, the number of webinars and virtual sessions dedicated to medical student education has increased. In radiation oncology (RO), virtual disease, site-specific educational sessions were shown to significantly improve medical students' understanding of the role of RO.[1] The utility of webinars to prepare medical students to apply to residency, however, is largely unexplored.[2,3] Here, we present the preliminary outcomes from a webinar series dedicated to educating medical students on the RO residency application process.

Methods

The American College of Radiation Oncology (ACRO) Resident Committee hosted webinars for RO residency applicants using the Zoom videoconferencing platform. Webinars were held in August of 2021 and 2022 prior to the initial submission deadline of the Electronic Residency Application Service (ERAS) application. Webinars were advertised by multiple methods including direct email to ACRO and the Association of Residents in Radiation Oncology (ARRO) listservs and social media (Twitter and Instagram). Emails and/or social media posts were performed weekly starting 1 month in advance of the sessions. Each webinar consisted of 2 resident moderators and a panel of 2 to 3 residency program directors. New moderators and program directors were used each year, representing 9 residency programs. For both webinars, program directors provided a general overview of the residency application process by presenting short lectures about the ERAS application, interview process, and residency program ranking. Sessions did not focus on the specifics of a particular residency program. The sessions concluded with an open question-and-answer segment. Each webinar lasted approximately 1 hour. Afterward, a recording of each webinar was posted to the ACRO YouTube channel for asynchronous viewing.

Baseline participant demographics were assessed using the questions listed in **Table 1**. These questions were presented as a live poll within the Zoom videoconferencing platform prior to the didactic presentations, and participants were given 2 minutes to respond. At the conclusion of the webinar, after the question-and-answer segment, participant perceptions were evaluated using a Likert scale ranging from 1 (No, not at all) to 4 (Yes, definitely). These questions were also presented as a live poll within the Zoom videoconferencing platform and participants were given 2 minutes to respond (**Table 2**). Both sets of questions were developed by consensus with the ACRO Resident Committee. Given the use of live polling, a limited number of demographics and perceptions questions (and choices for each question) were used. Results of both questionnaires were combined and reported using descriptive statistics. While the structure of each webinar was the same, comparisons between each year were performed to assess for changes in applicant demographics and perceptions. A subset analysis was also conducted to assess whether participants' baseline knowledge level of the residency application process impacted their perceptions of the webinar. Comparisons between groups were performed using the Chi-squared test in SAS (Carey, NC). A P value < 0.05 was considered statistically significant. The study was approved by the Wake Forest University School of Medicine institutional review board.

Results

Baseline Characteristics of Webinar Participants

The baseline characteristics of webinar participants are outlined in **Table 1**. Between the 2 webinars there were a total of 69 participants (36 in 2021 and 33 in 2022) and more than 340 asynchronous views online. Of all participants, 59 (86%) responded to the demographics questions (31 in 2021 and 28 in 2022). The majority of participants (70%) were in their third or fourth year of medical school, while nearly one quarter (24%) were either resident/fellows in another specialty or not currently students/trainees. When examined by year, there was a trend toward a significant increase in nonmedical student participation: 16% vs 32% of participants in 2021 and 2022, respectively (Chi-square, $P = 0.05$). Additionally, most participants attended medical school in the US (75%) and were planning to graduate with an MD degree (88%). While most participants were planning on applying to RO for residency (78%), baseline knowledge about the residency application process was relatively split: 44% identified as only knowing "a little" about the process, 49% identified as knowing "a lot" about the process, and only 7% identified as knowing "nothing" about the process. Other than training level, there were no statistically significant differences in baseline characteristics between each year.

Changes in Participant Understanding

Participant perceptions at the end of the webinar are outlined in **Table 2**. Of the 69 total webinar participants, 49 (71%) answered these questions (27 in 2021 and 22 in 2022). Overall, participants had favorable perceptions of the webinar with the majority noting a definitive improvement in their general understanding of the application process (82%) as well as their understanding of the ERAS application (69%) and interview process (89%). The webinar appeared to have the highest impact on participants' understanding of the interview process (mean 3.90), followed by general understanding of the application process (mean 3.80) and ERAS application (mean 3.65) (**Figure 1A**). However, these differences were not statistically significant (Chi-square, $P = 0.12$). For a subset of participants (n = 39), survey results were able to be stratified by a baseline understanding of the application process ("a little" vs "a lot"). Compared with participants who felt they knew "a lot" about the application process, those that knew "a little" about the process reported higher scores in general understanding (mean 3.80 vs 3.60), ERAS application (mean 3.72 vs 3.50), and interview process (mean 3.93 vs 3.8) at the end of the webinar (**Figure 1B**). These differences, however, were not statistically significant by the Chi-square test. Finally, at the end of the webinar, the majority (96%) of participants indicated they plan to apply to RO residency within the next 2 years.

Table 2. Perceptions and Application Plans of Webinar Participants

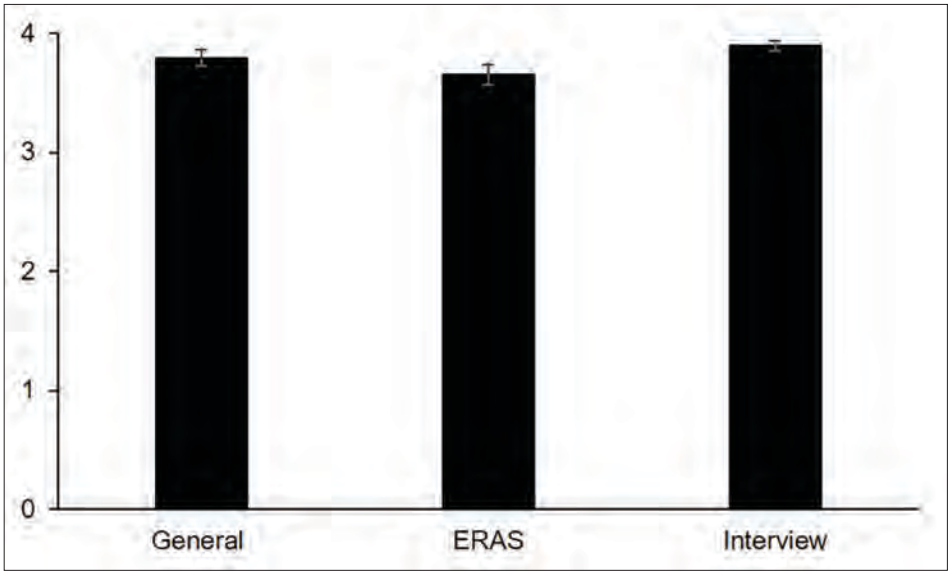
	TOTAL (N = 49)	2021 (N = 27)	2022 (N = 22)	P-VALUE
Webinar Improved My General Understanding of the Application Process for Radiation Oncology				
Yes, Definitively (4)	40 (82%)	21	19	0.27
Yes, Somewhat (3)	8 (16%)	6	2	
No, Not Really (2)	1 (2%)	0	1	
No, Not at All (1)	0 (0%)	0	0	
Webinar Improved My Understanding of the ERAS Application				
Yes, Definitively (4)	34 (69%)	20	14	0.78
Yes, Somewhat (3)	13 (27%)	6	7	
No, Not Really (2)	2 (4%)	1	1	
No, Not at All (1)	0 (0%)	0	0	
Webinar Improved My Understanding of the Radiation Oncology Interview Process				
Yes, Definitively (4)	44 (89%)	23	21	0.24
Yes, Somewhat (3)	5 (11%)	4	1	
No, Not Really (2)	0 (0%)	0	0	
No, Not at All (1)	0 (0%)	0	0	
Plans on Applying to Radiation Oncology				
Within the Next 2 Years	47 (96%)	25	22	0.19
Within 3-4 Years	2 (4%)	2	0	
Not Applying	0 (0%)	0	0	

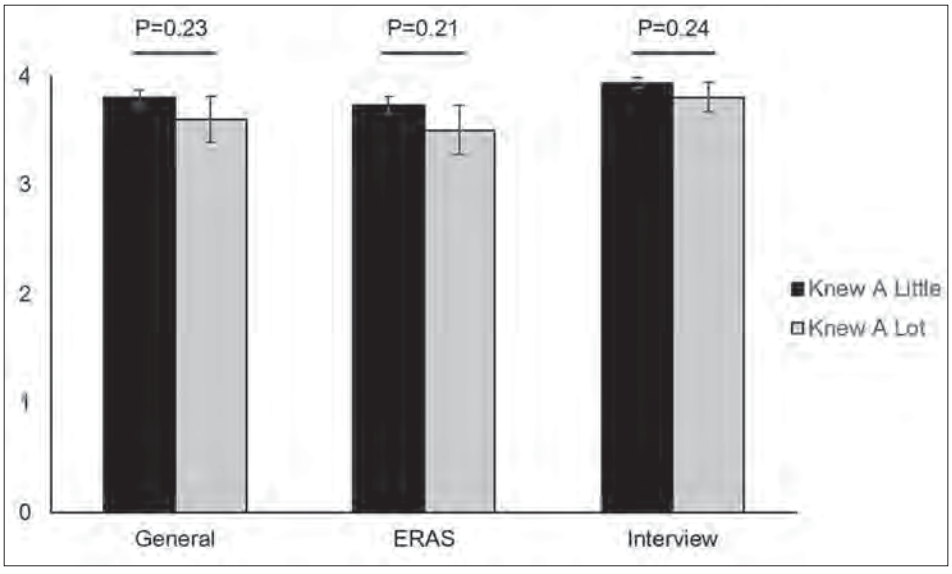
Abbreviation: ERAS, Electronic Residency Application Service

Discussion

Since the start of the COVID-19 pandemic there has been an increase in remote learning opportunities for RO trainees, including virtual clerkships,[4-7] online educational videos,[8,9] and webinar series.[1] Moreover, a recent systematic review identified 47 free digital educational resources specific to RO.[10] As the number of digital resources in RO increases, we must examine their utility and whether they meet the needs of their target audience.

Figure 1. Impact of webinar on participant understanding. At the end of each webinar, participants identified whether the webinar improved their understanding in 3 domains (general application process, ERAS application, interview process) using a Likert scale from 1 (no, not at all) to 4 (yes, definitely). Displayed are A) the mean scores of all respondents (n = 49) and B) mean scores stratified by baseline knowledge level (n = 39). Error bars represent standard error of the mean.





Overall, our results suggest that a national webinar dedicated to the RO residency application process is both feasible and has utility, as most participants noted improved understanding of the general application process, the ERAS application, and the interview process. Since the webinar recordings were placed online, they have garnered more than 340 views. We believe a webinar is an ideal format to educate medical students about the RO residency application process because it utilizes both attending and resident physicians—two sources of information that medical students consider highly trustworthy for residency advice.[11] Additionally, webinars are an opportunity for active participation as medical students are able to ask program directors specific questions of interest.

While participant perceptions were similar each year, there was a greater proportion of non-medical student participants in 2022 than 2021 (32% vs 16%). This potentially reflects the ongoing changes in the educational and training backgrounds of RO applicants. For example, in the 2023 Main Residency Match, 24% of RO PGY2 positions were filled by international medical school graduates or non-US senior medical students.[12] While these webinars were intended to educate medical students, who comprise the majority of RO residency applicants, they can also be informative to applicants with other training backgrounds who are looking to become radiation oncologists in the US. Given that these webinars discussed the nuances of applying to RO, and not just the residency application process in general, this change in participant training background is unlikely to impact our study's assessment of participant perceptions.

Our preliminary findings are also in line with the results from other studies on residency application webinars. Within RO, for example, a 2016 webinar on medical student applications was noted to have "positive feedback" from participants.[13] Dedicated residency webinars also have had favorable results in other fields. In plastic surgery, Serebrakian et al[2] found that a webinar led by a single institution increased medical student confidence levels about matching into residency. Similarly, Fereydooni and colleagues[3] found that a webinar led by recently matched medical students improved participants' understanding of the vascular surgery application process (eg, number of applications needed). Thus, our findings add to the limited body of literature that demonstrates the utility of webinars

dedicated to the residency application process.

Our study is not without its limitations. For example, we used built-in poll questions during the webinar in place of postwebinar surveys to increase participation. While the response rate to the polls was high, particularly for the initial question set, it limited the number of demographic and understanding domains we could evaluate. Additionally, because perceptions were assessed at the end of the webinar, it is likely that some participants left before answering these questions. Because these webinars were held prior to ERAS application submission, we were unable to assess whether participants retained the knowledge they learned and applied it to the application process. Additionally, since postwebinar surveys were not conducted, we were unable to assess whether participants applied (or matched) into RO. In the future, detailed pre- and postwebinar questionnaires could be used to address these limitations. The Zoom live poll questions could also be distributed throughout the webinar, which could help increase response rate. In terms of accounting for participants' baseline knowledge, we did not find a difference in understanding when stratified by baseline knowledge due to the smaller number of participants who answered both sets of questions. Additionally, because the webinars were advertised digitally, it is possible that this self-selected for participants who proactively sought out information on residency applications and were already well informed about the process.

Conclusions

A national webinar with program directors and residents can improve medical students' understanding of the RO application process. This resource should continue to be offered for future applicants given the current landscape of the RO residency application and match process.

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Congratulations Medical Student Committee Graduates!

Applied Radiation Oncology would like to recognize and thank the first round of medical school graduates who served in one or more of our four Medical Student Committees launched last year (First Pass Peer Review Committee, Podcast & Webinar Committee, Social Media Committee, and Future Content Committee).

Amidst demanding schedules and workloads, these participants leveraged teamwork, organization, innovation, and drive to produce myriad accomplishments with *ARO* throughout the academic year. Among them: the new Beam On podcast series; a quarterly student enewsletter focused on radiation oncology; published articles; peer reviews of case reports, research papers and review articles; and social media growth across various platforms.

The following students have graduated and are off to the exciting world of residency/internship.

Congratulations and thank you for your hard work and achievements.

Best wishes for a rewarding future in radiation oncology!

Hanan Albenayyan
Podcast & Webinar Committee
Social Media Committee
Medical internship:
Saudi Arabia health system

Evrosina Irini Isaac
Podcast & Webinar Committee
Residency: Virginia Commonwealth University

Jana Kobeissi
Podcast & Webinar Committee
First Pass Peer Review Committee
Residency: Cleveland Clinic

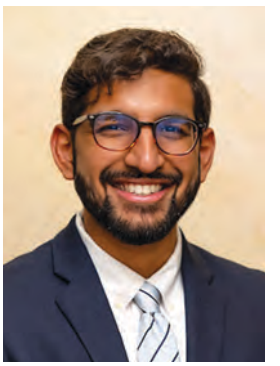
Emerson Lee
Future Content Committee
Residency: Harvard

Lauren Linkowski
Podcast & Webinar Committee
Social Media Committee
Future Content Committee
Residency: University of Pennsylvania

Hefei Liu
First Pass Peer Review Committee
Residency: University of Pennsylvania

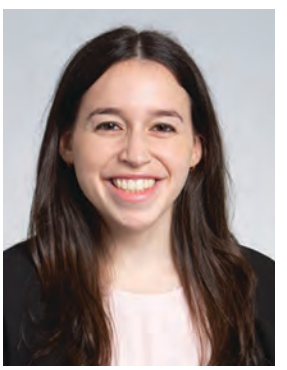
Karthik Meiyappan
First Pass Peer Review Committee
Social Media Committee
Residency: Emory

Townes "Alston" Mickel
First Pass Peer Review Committee
Future Content Committee
Residency: UT Southwestern

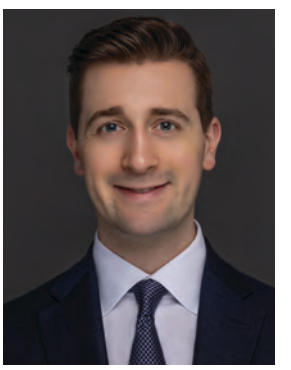


Akshat Patel
First Pass Peer Review Committee
Residency: UT Southwestern

Sidharth "Sid" Ramesh
Podcast & Webinar Committee
Residency: University of Pennsylvania



Shoshana Rosenzweig
First Pass Peer Review Committee
Social Media Committee
Residency: Memorial Sloan Kettering



Michael Schad
First Pass Peer Review Committee
Residency: University of Pennsylvania

Ellie Thompson
First Pass Peer Review Committee
Podcast & Webinar Committee
Transitional year: Lexington Medical Center
Residency: University of Florida, Shands

Tina Vaziri
First Pass Peer Review Committee
Residency: Johns Hopkins

A Case of Vision Loss From Radiation-Induced Optic Neuropathy Resulting in Charles Bonnet Syndrome

Susan K. Sandstrom, RN, MSN, APRN-NP, AOCN;[1*] David Bruce Mansur, MD;[1] Michael L. Morgan, MD, PhD;[2] Serah Choi, MD, PhD[1]

Abstract

Radiation-induced optic neuropathy (RION) is a rare late effect following radiation caused by damage to the optic nerves or chiasm. It is a profound and devastating complication of radiation therapy with no effective treatment and is irreversible. Charles Bonnet syndrome (CBS) is a rare phenomenon characterized by complex visual hallucinations that occur concurrently with visual field loss or visual acuity loss. This case describes a woman with a CNS WHO grade 2 meningioma who received conventionally fractionated radiation therapy with a proton beam to the residual tumor and resection cavity after near total resection. She subsequently developed RION with vision loss and hallucinations and was diagnosed with CBS. We recommend that even though the incidence of RION is rare, patients should be counseled by providers for potential late effects of radiation treatment with surveillance routinely after treatment.

Keywords: Radiation toxicity, radiation-induced optic neuropathy, Charles Bonnet syndrome, proton beam radiation therapy

Case Summary

A 60-year-old Black woman with a history of hypertension, long-term use of hydroxychloroquine sulfate use for rheumatoid arthritis, migraine headaches, and bilateral cataract extractions, presented to the emergency department with dizziness, headache, and vision changes consisting of photophobia and blurred vision. Of note, the patient had been seen for a routine ophthalmic examination the month prior with noted dry eyes, stable pseudophakia OU (oculus uterque or each eye) and myopia with astigmatism and presbyopia. She also had been on long-term use of hydroxychloroquine for 18+ years with no changes on examination. Visual acuity was OD 20/20 and OS 20/25+ with Ishihara color plates 11/11 in each eye and full visual fields. (See **Table 1** for a timeline of visual examinations and symptoms.) Brain MRI with and without contrast demonstrated a 3.5-cm extra-axial mass in the base of the skull arising in the right middle cranial fossa located medially in the para-cavernous region. The patient underwent a near total resection of the tumor and pathology showed a CNS WHO grade 2 meningioma. One month following surgery, she completed conventionally fractionated radiation therapy to the residual tumor and surrounding high-risk region using proton beam therapy to a total dose of 50.4 cobalt gray equivalents (CGE) in 28 fractions (1.8 CGE per fraction) **(Figure 1)**. In the absence of an established dose response and given the proximity of the optic apparatus and the emerging uncertainty about proton relative biological effectiveness (RBE) and radiation injury, a dose of 50.4 CGE was used. The maximum (to 0.03 cc volume) and mean doses to the optic nerves and chiasm were: right

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Disclosure/informed consent: The authors have no conflicts of interest to disclose. None of the authors received outside funding for the production of this original manuscript and no part of this article has been previously published elsewhere. The patient has provided informed consent for the publication of this case report.

Table 1. Timeline of Visual Examination and Visual Symptoms

DATE	VISUAL EXAMINATION
4/2018	Visual acuity was OD 20/20 and OS 20/25+ with Ishihara color plates 11/11 in each eye and full visual fields.
5/2018	Presents with headaches, dizziness, blurred vision and photophobia. Undergoes craniotomy for subtotal resection of CNS WHO grade 2 meningioma.
9/2018	Completion of proton beam radiation, 50.4 CGE in 28 fractions.
7/2019	Visual acuity was OD 20/25 and OS 20/25-2 with full visual fields.
9/2019	Visual acuity was OD hand motion and OS 20/40 with Ishihara color plates OD 0/11 and OS 5/11 with a right junctional scotoma with right eye generalized depression and left eye temporal depression on visual field examination. Patient presents with formed visual hallucinations.
5/2020	Vision loss progressed to acuity of OD with no light perception and OS 20/200 with inability to read Ishihara color plates and continued right junctional scotoma. Patient is having worsening visual hallucinations.

Figure 1. Postoperative, preradiation treatment brain MRI with contrast with the radiation prescription isodose lines. The red colorwash represents the prescription isodose line (50.4 CGE/28 fractions), yellow = 52 CGE, orange = 45 CGE, green = 25 CGE, and purple = 10 CGE.

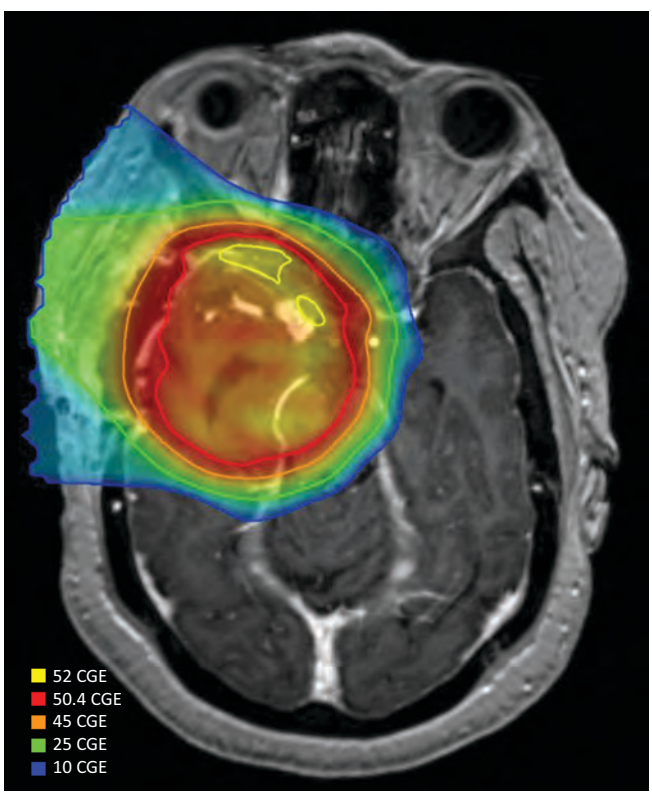
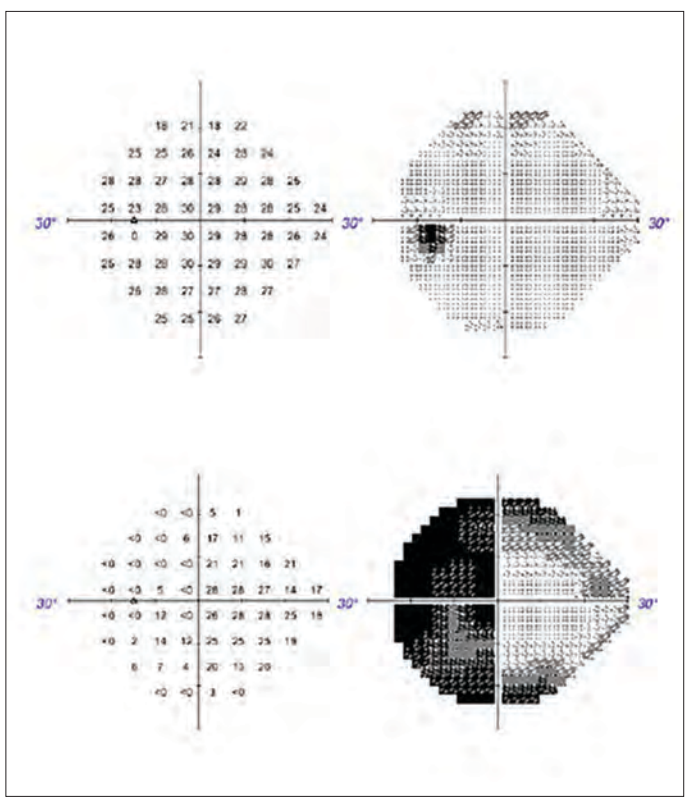


Figure 2. OS central 24-2 threshold test. Top: Pretreatment visual fields of the left eye. Bottom: Postradiation visual fields of the left eye at 14 months. The right eye quickly worsened and could not be tested reliably.



optic nerve max 51.86 CGE/mean 26.35 CGE, left optic nerve max 39.69 CGE/mean 6.09 CGE, and optic chiasm max 52.09 CGE/mean 50.85 CGE. Following radiation treatment the patient reported persistent right-sided facial numbness and tingling with intermittent headaches.

Approximately 1 year after treatment, the patient complained of a pressure sensation inside her head and further decrease in vision, worse in the right eye. Two months prior to presenting with these symptoms, visual acuity was OD 20/25 and OS 20/25-2 with full visual fields. The first examination after onset of radiation-induced optic neuropathy (RION) showed visual acuity OD hand motion and OS 20/40 with Ishihara color plates OD 0/11 and OS 5/11 with a right junctional scotoma with right eye generalized depression and left eye temporal depression on visual field examination. She also reported having hallucinations consisting of geometric shapes, lions with manes, and women's faces occurring primarily when her eyes were closed or before sleep at night,

Figure 3. Postoperative, preradiation treatment brain MRI with contrast.

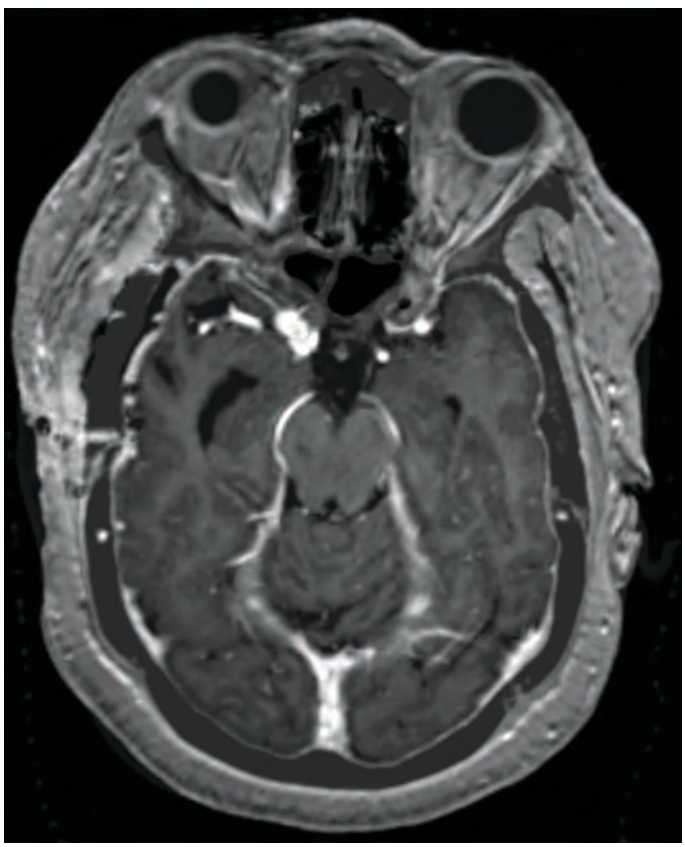
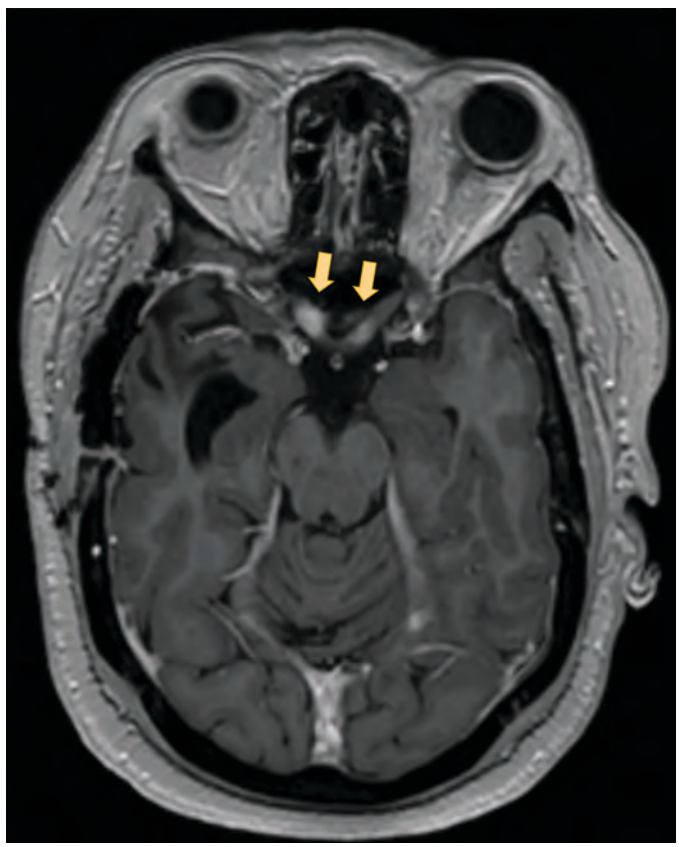


Figure 4. Brain MRI with contrast at 14 months following completion of radiation shows new enhancement at the right and left optic nerves (yellow arrows).



and upon awakening. MRI did not show obvious evidence of recurrent meningioma but showed areas of nonspecific enhancement in the bilateral intracranial optic nerves greater on the right, concerning for radiation optic neuropathy. She was started on dexamethasone, vitamin E, pentoxifylline, and bevacizumab. She was also started on nortriptyline, which helped with the pain on right side of her head. Bevacizumab was discontinued after 2 doses due to perforated diverticula. After a month of treatment, she reported mild improvement in the left eye but continued to have poor vision in the right eye. An ophthalmology examination showed improvement in acuity and foveal threshold with stable to mildly worse results on visual field testing (**Figure 2**). Vision loss progressed to acuity of OD with no light perception and OS 20/200 with inability to read Ishihara color plates and continued right junctional scotoma. The patient continued to have worsening visual hallucinations.

Diagnosis

In this patient's case, findings were consistent with RION. She was evaluated by a neuro-ophthalmologist and diagnosed with Charles Bonnet syndrome as a result of RION. Two years after radiation, her vision continued to deteriorate with almost no light perception in the right eye and greatly diminished vision in left eye although she was able to make out light and shapes, sometimes seeing red flashes from the right eye. Hallucinations increased over time as vision deteriorated. She declined medical treatment due to possible side effects and possible interactions with medications for her comorbidities.

Imaging Findings

A preoperative MRI of the brain revealed encroachment of the meningioma upon the region of the right cavernous sinus. The right carotid terminus and right M1 segment appeared to be anteriorly displaced by the mass. There was a moderate amount of hyperintense FLAIR (fluid attenuated inversion recovery) signal within the surrounding brain parenchyma suggestive of edema. There was mild encroachment upon the suprasellar cistern with mass effect on the right aspect of the optic chiasm and right mammillary body. A postoperative MRI demonstrated dural thickening deep to the craniotomy bed and over the anterior right hemisphere most prominently over the right temporal lobe (**Figure 3**). An MRI 14 months after radiation with high-resolution images through

the orbits demonstrated abnormal increased signal on the STIR (short tau inversion recovery) images with corresponding abnormal enhancement on the postgadolinium images involving the intracranial and intracanalicular segment of the right optic nerve and intracranial segment of the left optic nerve (**Figure 4).**

Discussion

CBS is caused by damage to the optic pathway resulting in visual hallucinations. It has not been well described in the setting of damage from radiation therapy. CBS was first described in 1760 by Swiss scientist Charles Bonnet when his 90-year-old grandfather experienced hallucinations after his vision deteriorated following cataract surgery.[1] There have been a number of definitions of CBS since the original description; however, the most widely accepted definition is the Gold and Rabins' definition, which describes hallucinations as stereotyped, formed, varied in complexity, persistent, or repetitive in nature.[2,3] The deafferentation theory, or sensory deprivation theory, is the most widely accepted theory elucidating the phenomenon associated with CBS whereby loss of sensory visual input is accompanied by increased excitability within the visual association cortex resulting in visual hallucinations.[1,4-6] Visual hallucinations may be a consequence of ocular or optic pathway pathology and subsequent deterioration in vision. The incidence of CBS is variable and ranges from 0.4% to 30% with statistically higher incidence noted with worsening visual acuity.[1] In a study of 100 consecutive patients with macular choroidal neovascularization, Brown et al noted increased incidence of formed hallucinations in patients with macular degeneration associated with bilateral choroidal neovascularization.[4] Moreover, patients with a more sudden onset of vision loss are more likely to experience hallucinations than those experiencing a more gradual loss of vision.[4,7]

Visual hallucinations of CBS may include people, animals, buildings, landscapes, and geometric designs.[1,7] Hallucinations may last for a few seconds to hours and may be simple or more complex in nature. Patients are typically aware that they are fictitious in nature and do not pose a threat. Patients may also report feeling stressed with hallucinations; however, this may stem more from worry regarding possible causes of the hallucinations vs the actual hallucination. Of note, patients with CBS experience some level of impaired vision and often report that hallucinations have better clarity than any residual vision.[1,4] There is no age limit in CBS, although it most often affects older people due to an increase in eye diseases. Hallucinations in children are similar to adults and have been reported as images such as flashing lights, people's faces, houses, animals, ballerinas, snowballs and colored balls.[8] Visual hallucinations associated with CBS may eventually disappear spontaneously and also with complete blindness; however, they may persist for years in some cases.[1,7] In a large prospective study conducted in the Netherlands, Teunisse et al found that hallucinations disappeared as blindness progressed in patients with macular and corneal degeneration.[9] Frequency and duration of episodes may decrease over time and some studies have suggested people may get used to hallucinations over time.

Radiation-induced optic neuropathy is a rare late effect following radiation, caused by damage to the optic nerves or chiasm and is thought to result from radiation-induced microangiopathy associated with endothelial cell loss resulting in demyelination.[10,11] Symptoms may be seen several months to several years after treatment and may lead to unilateral or bilateral blindness.[10] RION typically presents in the clinical setting with onset of visual symptoms in the majority of patients within 3 years of therapy completion.[12] Peak incidence of RION is 1 to 1.5 years after completion of radiation and is associated with characteristic findings on MRI with gadolinium contrast, which demonstrates marked enhancement of the optic nerve and chiasm on T1-weighted images.[10,12] Both eyes are often involved serially. Consequently, vision in both eyes should be evaluated at the earliest onset of vision loss.[12] There is no established effective treatment for RION.[12,14] A few small studies have suggested the use of hyperbaric oxygen treatment if initiated within 72 hours of visual loss, but results have been limited.[12,14] Treatment with steroids, pentoxifylline with vitamin E, and bevacizumab have also had limited benefit.[10,12,14]

Radiation tolerance to optic structures is a critical component and cumulative doses that exceed a fractionated schedule of 55 Gy up to 60 Gy, with fractions of 1.9 Gy or less, or a single dose of 10-12 Gy, are associated with increased risk factors for developing RION.[10,13,14] Proton doses are defined in terms of Gy, or cobalt Gray-equivalent (CGE), with relative biologic effectiveness equaling proton Gy x 1.1.[13] The risk of developing RION above these thresholds is approximately 5%.[13,15] Some patients have reported developing vision loss at lower doses.[10,19] RION occurs with different radiation modalities; however, proton therapy has been of particular interest in the treatment of tumors involving these structures due to the ability to deliver higher doses while sparing organs at risk (OARs) near the treatment field. Other contributing risk factors in the development of RION include older age, female sex, optic nerve compression, chemotherapy, previous radiation, hypertension, diabetes mellitus, hyperlipidemia, and smoking history.[11-13,16] Additionally, pre-existing compression of the optic nerves and chiasm may predispose these structures to

RION.[12] The diagnosis of CBS is one of exclusion and other etiologies should be investigated to determine possible treatment modalities. Patients who have received radiation and have signs and symptoms of RION should be referred to ophthalmology emergently as well as to a neuro-oncology team for initial assessment and management if diagnosis is confirmed. Antipsychotics, anticonvulsants, anti-anxiety medication, and selective serotonin reuptake inhibitors have been reported as treatments for CBS. However, none of these have been shown to be particularly effective for CBS.[1,17,18] Behavioral techniques such as blinking during hallucination or rapid eye movement from one object to another, away from the hallucination field of vision, may be helpful in suppressing hallucinations.[7]

Even though the incidence of RION is rare, patients should be counseled by providers for potential late effects of radiation treatment with surveillance routinely following treatment. Older patients with ocular diseases and other comorbid risk factors should be closely monitored. Ophthalmologists and other optical providers should be aware of the potential for visual hallucinations in patients with visual impairment and optical pathology. Early recognition of CBS symptoms can lessen distress and anxiety experienced by patients with CBS.

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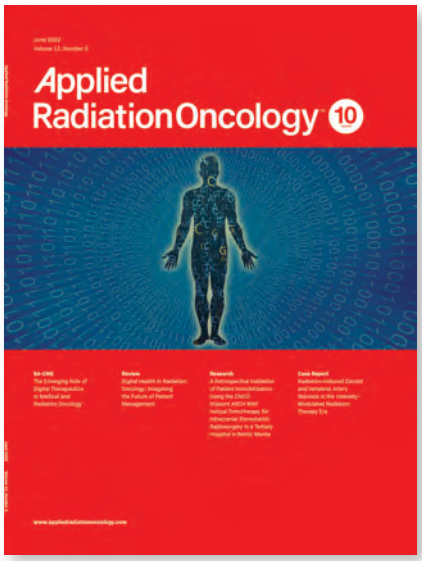

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Opportunities Are Knocking, Are You Listening?

Kyra N. McComas, MD*

Dr. McComas is a PGY3 resident physician, Department of Radiation Oncology, Vanderbilt University Medical Center

We are trained to use evidence-based medicine from the beginning of medical school; residency hones these skills. Radiation oncology is a particularly data-driven field. When we start residency, we know we are going to be doing a fair amount of research, likely via lab projects or evaluating treatment outcomes in one disease site or another. But numerous other possibilities outside of clinic have powerful benefits, particularly regarding advocacy.

Radiation oncology is a cost-effective, innovative field that is fundamental to cancer treatment and is well-suited to modern technological advancements. Unfortunately, it has been hampered by decreased funding, political constraints (including partisan deadlock, insurance mandates, and lack of information), and diminished interest from medical students (largely due to unsubstantiated claims and fears surrounding the job market). We continue to see the effects of this every year in the National Resident Matching Program. As such, advocacy plays a vital role, but our training grants us little exposure.

Understanding the political nature of our field can teach us how to challenge policy, educate and inspire prospective students, and fight for our patients. This is especially important for trainees, as this is the field we will inherit. One of the best ways to do this is to become involved in volunteer organizations. There are countless opportunities to engage in advocacy and leadership; sometimes all it takes is a cold email. Before you know it, you might find yourself on a teleconference with leaders of major global cancer organizations, lobbying heads of state, flying to a climate conference in the Middle East, or exploring any other charted or uncharted territory. These possibilities not only foster your professional development (and have obvious resume benefits), but also influence your personal life and growth. While I still think patients are the most rewarding part of our work, being involved in volunteer organizations and leadership can create a very well-rounded resident.

Going beyond the traditional residency research routes and exploring new avenues of engagement with our field can challenge your perspectives, broaden your network, introduce you to mentors, strengthen your skills as a physician, and ultimately change you as a person. It can open new doors that not only were closed, but which you didn't even know existed. I have been fortunate enough to discover some of these doors, from participating on the emergency taskforce of the Global Coalition for Radiotherapy and working with global oncology leaders, to learning about our carbon footprint with the Climate Health, Equity, and Sustainability Taskforce. And I hope to one day climb the Dolomites with the Radiating Hope society.

I encourage all residents to seek opportunity, reach out to big names and little names, connect with other residents, and simply ask around; the worst someone can say is "no." There is great satisfaction and joy in being involved in things that are bigger than you, especially doing so in fun and engaging ways that play off your passions and curiosities. When you can do this while contributing to the greater needs of the field, it is even more fulfilling. It reminds you that being a radiation oncologist isn't one size fits all; we get to choose our own adventure.

Disclosure: The author has no conflicts of interest to disclose and has not received outside funding for the production of this original manuscript. No part of this article has been previously published elsewhere.
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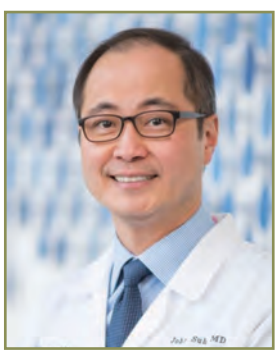

John Suh, MD, FASTRO, FACR

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