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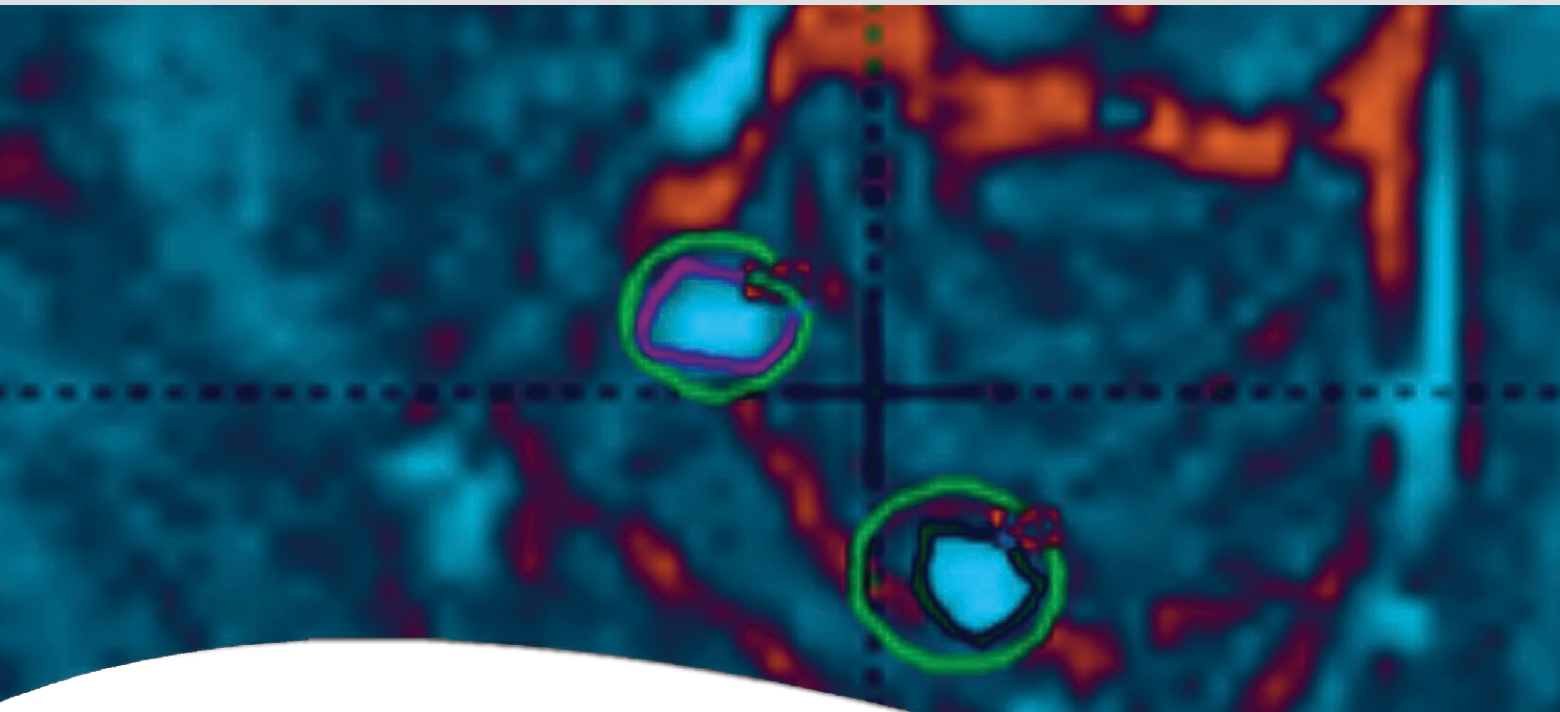


Target tumors, not yourself: A review of False Claims Act allegations against radiation oncologists

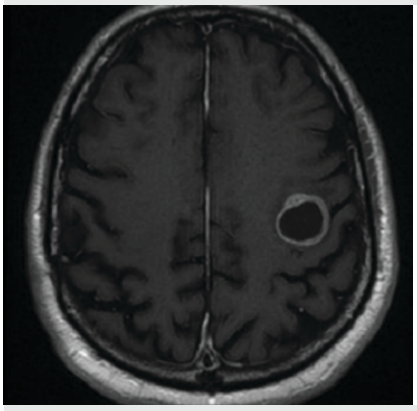
A Mastroianni, Cleveland Clinic, Cleveland, OH and JF McCaffrey, Tucker Ellis LLP, Cleveland, OH

Pediatric radiosurgery: A review

EW Jung, Therapeutic Radiology Associates, Hagerstown, MD; ES Murphy, Cleveland Clinic, Cleveland, OH; DL Jung, Case Western Reserve Medical School, Cleveland, OH; ST Chao, JH Suh, Cleveland Clinic, Cleveland, OH

Technology Trends—Updates in IMRT, VMAT of the head and neck

MB Massat



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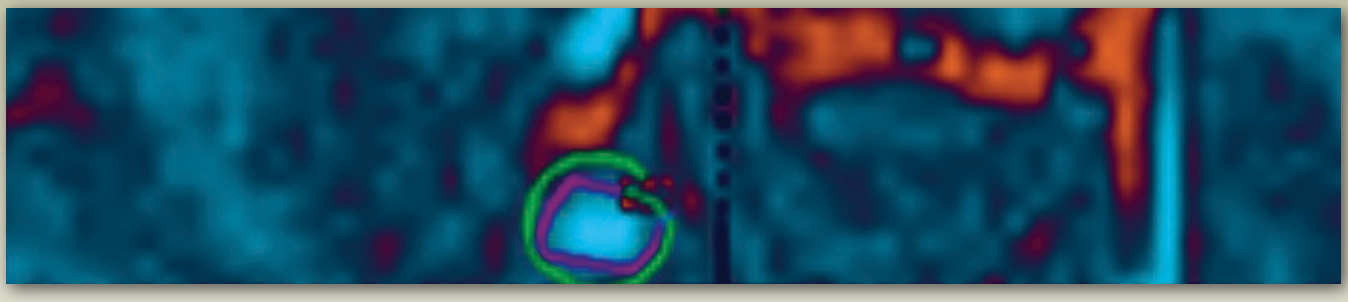

PEDIATRIC CANCER FOCUS

SPECIAL REPORT

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DEPARTMENTS

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Launched as an eJournal in 2012, Applied Radiation Oncology (ARO) is now available in print, online or on your mobile device. Published quarterly under the editorial guidance of John Suh, MD, Chairman of the Department of Radiation Oncology and Associate Director of the Gamma Knife Center at the Brain Tumor and Neuro-Oncology Center at Cleveland Clinic, each issue presents board--reviewed case presentations and clinical review articles that provide practical, actionable information that radiation oncologists can use to enhance the efficiency and quality of radiotherapy.

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EDITORIAL

Lawyers, stunts and money: Critical truths about false claims in radiation oncology

John Suh, MD, Editor-in-Chief

It's hard not to forget the headlines last year when radiation oncologists were listed in an OIG report for consistently receiving large Medicare payments for their services. Not surprisingly, the field has come under greater scrutiny for potential fraud and abuse,[1] prompting lawsuits against radiation oncology providers by the Department of Justice and plaintiff attorneys.

This month's article, *Target tumors, not yourself: A review of False Claims Act allegations against radiation oncologists,* addresses this issue, summarizing specific legal actions against providers, as well as the act's key points. Authored by radiation oncologist and former prosecuting attorney Anthony Mastroianni JD, MBA, MD, and John F. McCaffrey, JD, prosecutor and former FBI agent, the article helps radiation oncologists establish appropriate clinical practices, and examines actionable misconduct as well as common sense practices to avoid, especially when it comes to cost-containment strategies. We are pleased to present this in-depth review on what remains an important topic in our field.

This month's issue also features *Pediatric Radiosurgery: A Review,* in which Edward W. Jung, MD, and colleagues delve into the evolving treatment of pediatric CNS malignancies using stereotactic radiosurgery. The article explores benign CNS diseases, brain metastasis, malignant primary CNS diseases, and special considerations in pediatric radiosurgery (immobilization and localization, anesthesia, radiation necrosis and follow-up imaging).

In addition, *Technology Trends* provides insightful news on IMRT and VMAT for head and neck cancer, and a case study by Luis Moreno Sánchez, MD, describes linac-based SRS for a 70-year-old man with trigeminal neuralgia who suffered from facial pain for more than a decade.

Lastly, congratulations to our quarterly Clinical Case Contest winner, Camille Berriochoa, MD, and colleagues for their case on the use of adjuvant radiosurgery after resection of a brain metastasis. The authors discuss a patient with stage IV prostate adenocarcinoma with a solitary intracranial metastasis, who is doing well following resection and SRS.

Please visit *http://appliedradiationoncology.com/contests/case-contest* for information on how to submit your own interesting case report and have the opportunity to be our next quarterly Clinical Case Contest winner. While online, we invite you to sign up for our Facebook and Twitter feeds for regular news and updates regarding radiation oncology.

Enjoy the issue, and thank you for your continued support of *ARO!*

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

Reference

1. Weaver C, McGinty T, Radnofsky L. Small slice of doctors account for big chunk of Medicare costs. *The Wall Street Journal.* April 9, 2014.

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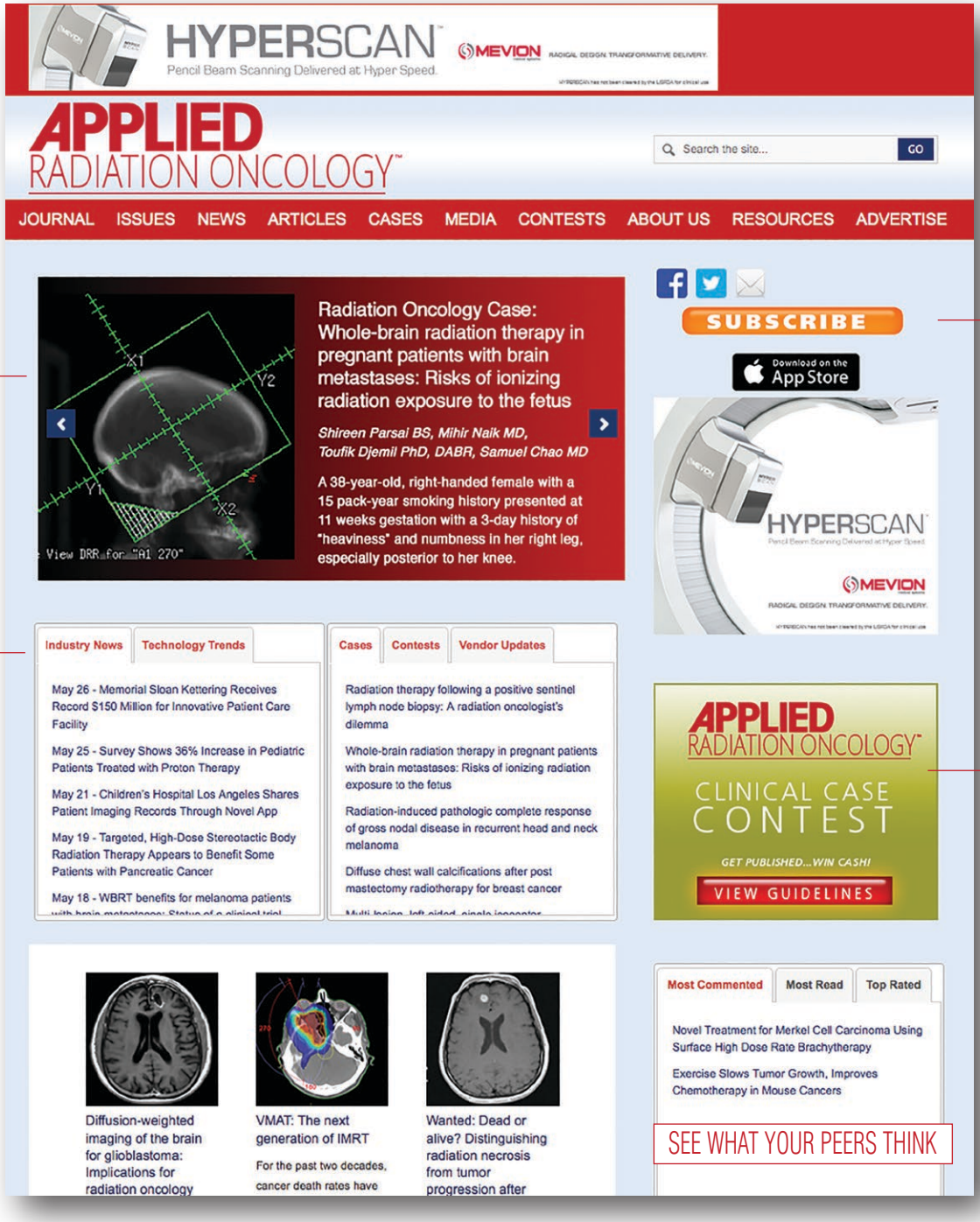

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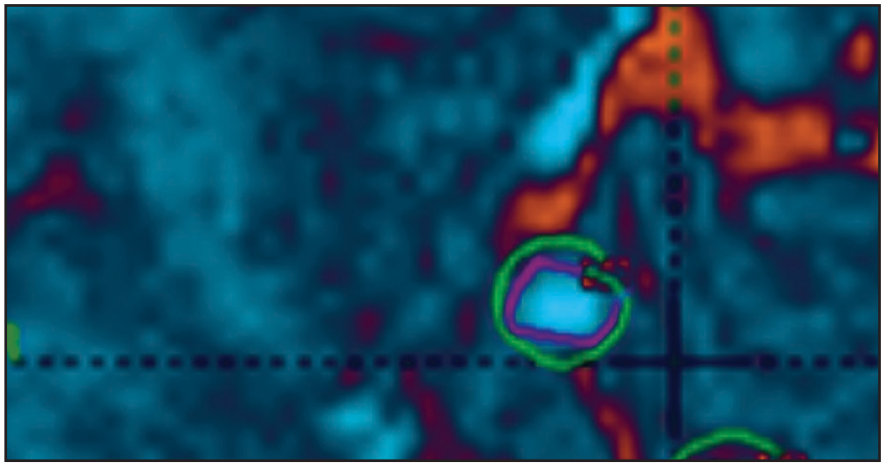
Pediatric radiosurgery: A review

Edward W. Jung, MD; Erin S. Murphy, MD; David L. Jung, MD; Samuel T. Chao, MD; John H. Suh, MD

Stereotactic radiosurgery (SRS) is a technique to precisely deliver high doses of hypofractionated radiation therapy with minimal or no treatment margins. There is a paucity of literature on the role of radiosurgery in the management of pediatric patients. Although radiosurgery has been established in the treatment of certain benign central nervous system (CNS) diseases in children, its role in the treatment of pediatric CNS malignancies is evolving. The purpose of this article is to review the literature and current applications of radiosurgery for the pediatric population.



Benign CNS diseases

Arteriovenous malformation (AVM)

Treatment for AVMs is by far the most well established use of radio-surgery in children. An illustrative case of a pediatric patient treated with SRS for a left frontal AVM is shown in Figure 1. The largest and most pertinent studies will be reviewed here.

A study from University of California, San Francisco (UCSF) evaluated dose effects on obliteration rates of 80 pediatric patients treated with SRS for AVM. The study found a 3-year overall obliteration rate of 56% for dose prescription of 18-20 Gy, and 16% for dose < 18 Gy.[1] At 5 years following SRS, cumulative incidence of hemorrhage was 25%. Functional status improved or remained the same as before treatment in 66% of patients. The study concluded that low marginal dose minimizes SRS-related neuro-logical deficits but leads to low rates of obliteration and high rates of hemorrhage. To maximize AVM obliteration and minimize post-treatment hemorrhage, the authors recommended a prescription marginal dose of ≥ 18 Gy.

A study from the University of Virginia reviewed 51 unruptured pediatric AVM patients with actuarial AVM obliteration rates of 29%, 54% and 72% at 3, 5 and 10 years after radiosurgery, respectively.[2] The obliteration rate was significantly higher with dose ≥ 22 Gy ($p=0.003$) and for nidus with ≤ 2 draining veins ($p=0.001$). The annual post SRS hemorrhage rate was 1.3%, and the incidence of cyst formation was 2%. Incidence of radiographic, symptomatic and permanent SRS-induced changes were 55%, 16% and 2%, respectively.

The largest series published on SRS for pediatric AVMs is a study from the University of Pittsburgh, which

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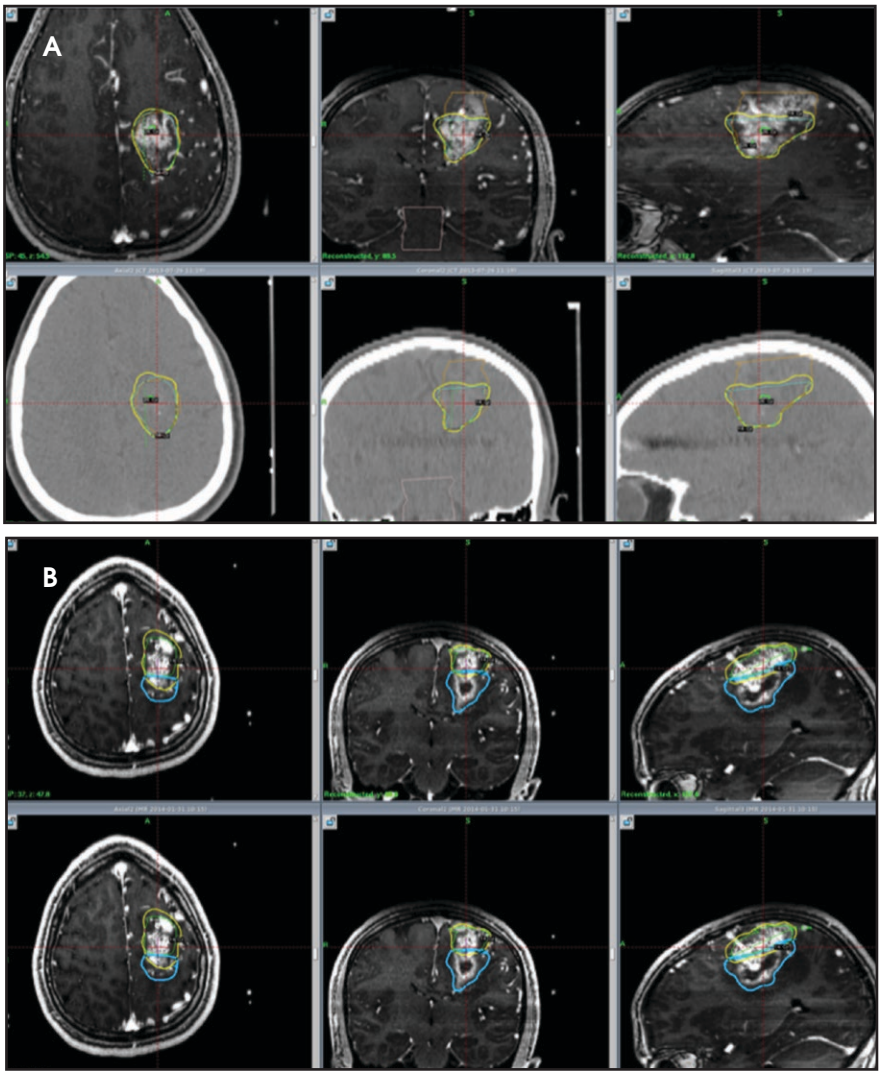

FIGURE 1. *(A) A 16-year-old boy with a 6 cm left frontal AVM treated with GKRS. A total of 14 Gy was prescribed to the 50% isodose line covering 100% of the target, which was initially the deeper portion of the AVM. The plan utilized 21 shots using composite sectors. Target volume = 18.41 cc. Maximum dose = 28 Gy. Maximum diameter = 5.5 cm. Maximum dose/prescription dose = 2. Planned isodose volume/target volume = 1.445. (B) Staged radiosurgery for AVM 6 months later. A total of 1400.0 cGy was prescribed to the 55% isodose line, which covered 100% of the target. The plan utilized 15 shots using 16 mm and 8 mm sectors. Target volume = 13.9 cc. Maximum dose = 2600.0 cGy. Maximum diameter = 5.1 cm. Maximum dose/prescription dose = 1.857. Planned isodose volume/target volume = 1.683.*

reviewed 135 children treated with Gamma Knife (Elekta, Stockholm, Sweden) radiosurgery (GKRS).[3] The median target volume was 2.5 cm^3 (range 0.1–17.5 cm^3), and median number of isocenters was 4 (range 1–17 Gy). Median GKRS prescription dose to the nidus margin was 20 Gy (range 15–25 Gy), which correlated with median maximum target dose of 40 Gy (range 30–50 Gy). A reduced dose was prescribed for large AVMs and nidus located in an eloquent area as per published risk/benefit prediction curves based on the 12 Gy volume.[4] Of note, the same dose selection criteria was used for both pediatric and adult patients treated at their institution. Pediatric AVM obliteration rates at 3, 4, 5 and 10 years were 45%, 64%, 67% and 72%, respectively. Median time to complete obliteration was 48.9 months. The overall annual AVM hemorrhage rate was 1.8%. Rates of hemorrhage at 1, 2, 3, 5 and 10 years were 0%, 1.6%, 2.4%, 5.5% and 10.0%, respectively. Permanent radiation-induced neurologic deficits developed in 2 children (1.5%) after SRS. Delayed cyst formation occurred in 1 patient (0.7%).

Despite promising results with SRS, advances in microsurgical resection have improved surgical outcomes for AVM. A large retrospective review from Boston Children's Hospital reviewed 94 pediatric patients treated with microsurgical resection for AVMs, of which 21% received adjunctive preoperative embolization. The obliteration rate was 94%, and the most recent 50 patients in the series underwent immediate perioperative angiography, which improved the obliteration rate from 86% to 100% ($p = 0.01$).[5] Perioperative neurological deficits occurred in 17% of the children treated. According to the modified Rankin Scale used for analysis, 94% of patients had good functional outcomes. A review of 1- and 5-year follow-up data indicated an overall annual hemorrhage rate of 0.3% and a recurrence rate of 0.9%.

In summary, surgical resection is still considered the standard management for AVM. The high rates of obliteration and low rates of post-treatment hemorrhage and neurologic complications reported in the Boston series suggest that radiosurgery should be reserved for nonsurgical cases or lesions in critical brain regions. The safety and efficacy of SRS in managing pediatric AVMs is well documented in the literature. The rates of obliteration and hemorrhage for SRS in children are congruous with expected results in the adult population.[6]

Vestibular schwannoma

SRS has been well established as a viable treatment option for vestibular

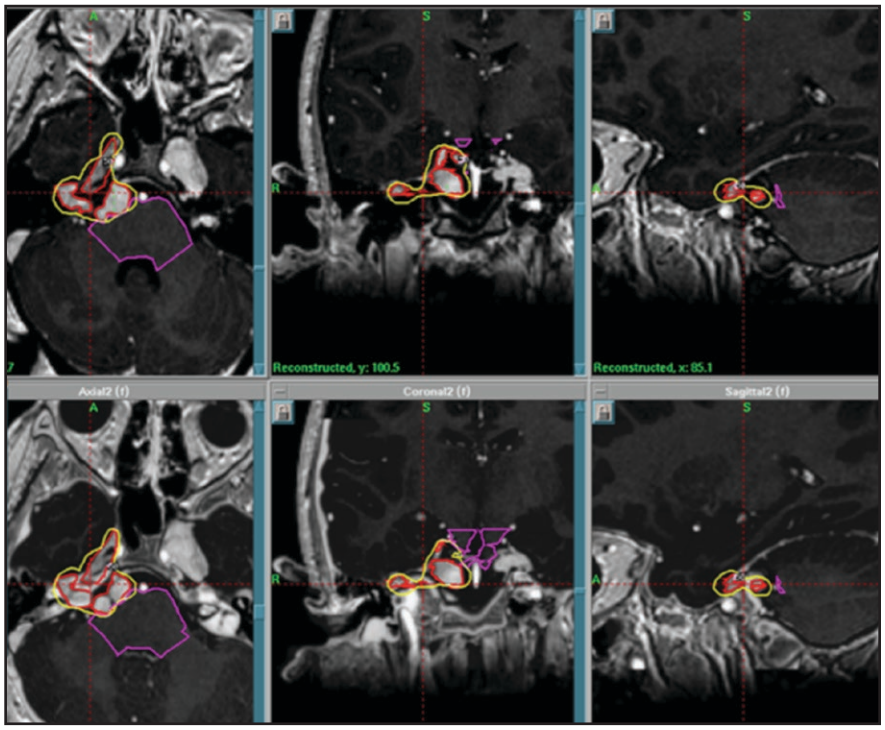

FIGURE 2. *A 12-year-old girl with NF2 status following prior microsurgical resection of a left vestibular schwannoma. She subsequently developed right ear tinnitus and decreased auditory acuity. She was treated for her right-sided vestibular schwannoma with GKRS. Her tumor was treated with 13 Gy prescribed to the 50% isodose line. The plan utilized 20 shots using an 8 mm helmet without plugs. Target volume = 3.9 cc. Maximum dose = 2620.0 cGy. Maximum diameter = 3.07 cm. Maximum dose/prescription dose = 2.015. Planned isodose volume/target volume = 2.103.*

schwannoma (VS) in adults.[7] In fact, one can argue that SRS is a superior treatment to microsurgical resection for vestibular schwanomma, considering equivalence in local control and superior functional outcomes and quality of life after treatment with SRS.[8,9] The excellent outcomes in adults have prompted investigation on the use of SRS in children.

A study from South Korea enrolled 24 children with neurofibromatosis type 2 (NF2) who underwent GKRS for VS.[10] The mean target volume treated was 4.8 ± 3.2 cm^3 and mean marginal dose was 12.4 ± 0.6 Gy prescribed to the 50% isodose line. With a mean follow-up time of 89.3 months, the tumor control rate was 35% at 3 years. The mean growth rate of VS was 0.33 cm^3 /year. The actuarial rate of useful hearing preservation was 67% at 1 year and 53% at 5 years. Disappointingly, these results are worse than previous reports in adults. It is important to note, however, that rates of tumor control and hearing preservation in general are worse for VS associated with NF2 than in sporadic cases.[11] Other treatment options are under investigation, including bevacizumab for tumors that express *vascular endothelial growth factor* (VEGF), but the limited results are not very promising as an alternative treatment.[12,13] Further investigation is needed to determine the efficacy of SRS for VS in children. Figure 2 describes a pediatric patient with NF2 treated with radiosurgery.

Craniopharyngioma

Craniopharyngioma is typically managed by surgical resection followed by adjuvant radiation therapy for residual disease. However, for residual or recurrent cases, radiosurgery has been implemented. A study in Japan of 107 patients with craniopharyngioma treated with SRS to a dose of 11.5 Gy included 38 children.[14] Progression-free survival (PFS) at 5 and 10 years was 60.8% and 53.8%, respectively, among the entire cohort. However, local control was worse when comparing children and adults, with 32% of children progressing after treatment, compared with 13% of adults. A study from South Korea included 14 pediatric patients who developed recurrence after gross total resection (GTR) for craniopharyngioma.[15] Five patients were treated with GTR, 1 with fractionated RT, 4 with GKRS, and 4 with subtotal resection followed by RT. GKRS tumor margin dose was 11.2 Gy (range 9-14 Gy) and mean target volume was 1719 mm^3 (range 424-6874 mm^3). Local control rate after GKRS or fractionated RT was 100% at mean follow-up time of 75 months after salvage treatment.

Brain metastasis

Advances in cancer therapy leading to prolonged survival may increase the incidence of brain metastases in children.[16] Despite this, the overall number of children with brain metastases is low, and the prognosis is poor. A retrospective review of pediatric oncology patients at MD Anderson found that only 1.4% of children either presented or developed a brain metastasis, with the majority (60%) presenting with a single brain metastasis.[17] Kaplan-Meier estimates for median survival in children treated with brain metastases is 8 months.

Although uncommon, secondary brain tumors are a feared side effect of fractionated radiotherapy to the brain. A single institution reported a median time frame of 114 months in development of secondary brain tumors after previous cranial irradiation in children treated at a median age of 8 years old.[18] SRS may potentially reduce the chance

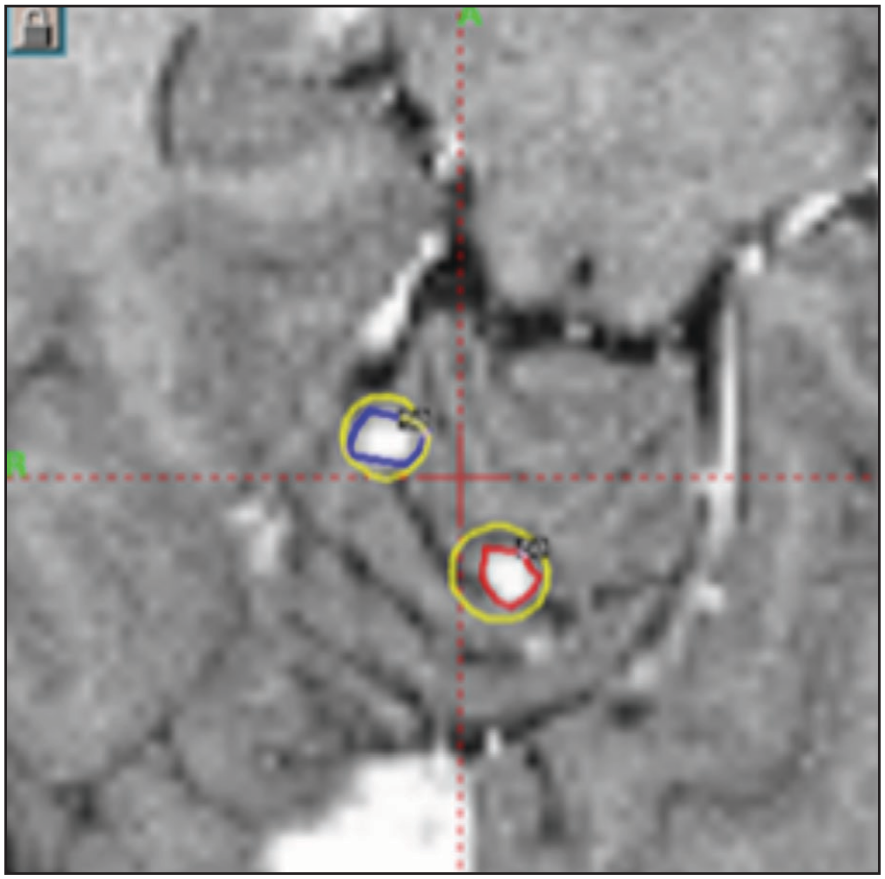

FIGURE 3. *A 16-year-old girl with high-grade sarcoma was treated with GKRS to 2 brain metastases involving the cerebellar vermis. A total of 2400 cGy was prescribed to the 50% isodose line, which covered 100% of both targets.*

of second malignancy by minimizing the volume of normal brain receiving radiation dose compared with whole-brain radiation therapy (WBRT).[19] As well, there is interest in minimizing cognitive compromise in children undergoing radiation therapy to the brain. SRS can reduce the likelihood of cognitive decline, which is a potential side effect of WBRT. Currently, there are no published papers in the literature on SRS for brain metastases in children. Instead, the impetus for SRS treatment of brain metastases in children relies on extrapolation from treatment results in adults. A recent meta-analysis of phase 3 trials evaluating SRS with or without WBRT demonstrated that SRS alone favored survival in adult patients ≤ 50 years of age.[20] In addition, omission of WBRT did not affect distant brain failures. Perhaps these results, which demonstrate that younger patients have improved outcomes with SRS alone, may persuade pediatric radiation oncologists to pursue studies of SRS alone in children. Figure 3 illustrates a case of pediatric brain metastases treated with SRS.

Malignant primary CNS diseases

Ependymoma

The extent of surgical resection is the most important factor affecting prognosis for ependymoma. For children with incomplete resection, 5-year disease-free survival drops by approximately 50% compared with gross total resection, leading to lower overall survival.[21,22] SRS has been implemented as a boost for residual disease after fractionated radiotherapy and to treat recurrent ependymoma after initial management.[23] The largest published study in the pediatric population is a retrospective analysis of 21 children treated with SRS for recurrent ependymoma, which demonstrated 72% local control at 27.6 months.[24] The median prescription dose delivered to the tumor margin was 15 Gy (range 9-22 Gy). PFS was 78.4%, 55.5% and 41.6% at 1, 2 and 3 years, and distant tumor relapse rate was 33.6%, 41.0% and 80.3% at 1, 2 and 3 years, respectively. Overall, treatment was well tolerated with adverse radiation effects seen in 2 patients.

Low-grade gliomas

Low-grade gliomas are slow growing and usually managed with surgical resection alone, especially in the pediatric population. Adjuvant radiation therapy is generally not recommended. However, if the lesion is unable to be completely resected, radiation therapy may be warranted. Radiosurgery is being used for pediatric low-grade gliomas in cases of incomplete resection or recurrent disease.

A review of 24 pediatric patients treated at the University of Virginia with GKRS for unresectable, residual or recurrent gliomas demonstrates that good clinical control can be achieved.[25] The majority of the patients (80%) presented with low-grade gliomas. With a median tumor margin prescription dose of 15 Gy (range 4-20 Gy) and imaging follow-up of 74 months, decrease in tumor volume was 71% after GKRS. At last follow-up, ≥ 50% size reduction was seen in 75% of patients, and complete response was seen in 21%. PFS was achieved in 83% of patients treated. Of the 4 patients who progressed after treatment, 3 underwent repeat resection and 1 died.

A review of 50 patients treated with GKRS for newly diagnosed or recurrent juvenile pilocytic astrocytomas was

Table 1. PFS and local control (LC) following radiosurgery for pediatric brain tumors[33]

Tumor	# of patients	PFS (months)	3 yr LC
GBM/AA*	18	12	50%
Medulloblastoma	16	11	57%
Ependyoma	28	8.5	29%

* Glioblastoma multiforme/anaplastic astrocytoma

performed at the University of Pittsburgh.[26] The majority of patients had no prior radiation; only 5 patients underwent prior fractionated radiation therapy +/- chemotherapy. Median target volume was 2.1 cc and median marginal dose was 14.5 Gy (range 11-22.5 Gy). PFS after SRS (including tumor growth and cyst enlargement) was 91.7%, 82.8% and 70.8% at 1, 3 and 5 years, respectively. The authors suggest SRS for pilocytic astrocytomas when resection is not feasible or for recurrent disease.

Fractionated stereotactic radio-therapy (FSRT) is an alternative to SRS for radiation treatment of pediatric patients with minimal margins. FSRT utilizes SRS immobilization devices to minimize margins for treatment with daily fractionated radiotherapy. A large prospective trial of 81 pediatric patients with low-grade gliomas treated with FSRT for disease progression after initial chemotherapy or surgery was conducted at Dana-Farber Cancer Institute in Boston.[27] Of the patients evaluated, 50 had low-grade astrocytoma, 23 had craniopharyngioma, 4 had posterior fossa ependymoma, and 4 had other histologies. PTV included preoperative tumor + 2 mm margin. PFS was 82.5% at 5 years and 65% at 8 years. Local progression occurred in 6 patients, all within the primary tumor bed. Since no marginal failures occurred, the study results support the use of limited margins with FSRT to minimize late effects of radiation therapy. However, one of the biggest drawbacks of FSRT is that daily anesthesia may be required for younger children, which can be logistically challenging, lead to significant health care costs, and pose potential unnecessary health risks such as anesthesia-induced neurotoxic effects on the developing brain.[28] Because of this, radiosurgery appears to be more feasible and attractive over FSRT.

High-grade gliomas

The largest series of pediatric patients treated with SRS for high-grade gliomas is a review of 90 patients from the Joint Center for Radiation Therapy in Boston.[29] Breakdown by histology is: glioblastoma = 10, anaplastic astrocytoma = 8, medulloblastoma = 16, primitive neuroendocrine tumor = 5, ependymoma = 28, other histologies = 23. Intention to treat was for recurrent tumors in 62 patients and for initial management of residual tumors in 28 patients. Gross disease was present in 81 patients, and 9 patients underwent SRS to the resection cavity due to concern for high risk of local failure. Median prescription dose was 12.5 Gy (range 6–25 Gy), normalized to the 80% isodose volume (range 40% to 100%). Table 1 shows PFS and local control by histology. The 3-year risk of radionecrosis was 26%. Of the patients who underwent reoperation for radionecrosis, 9 of 19 patients on pathologic review had radionecrosis alone. Other findings included mixed tumor and necrosis in 8 patients, tumor alone in 1 patient, and benign findings in 1 patient.

Primitive neuroectodermal tumors (PNET)

At the University of Pittsburgh, 7 children with recurrent PNET were treated with GKRS. Median tumor volume was 4.6 cm3 (range 1.2-13.1 cm3), and median prescription dose was 16 Gy (range 13-20 Gy). Following salvage GKRS, 2 patients experienced early disease progression with median survival of 5 months, while 5 patients had late progressive disease with median survival of 30 months.[30] Of the 5 children with late progression, 4 were retreated with GKRS for disease relapse without any adverse radiation events. Median GKRS re-treatment tumor volume was 1.3 cm^3 (range 1.1-3 cm^3), and median re-treatment prescription dose was 13 Gy (range 9-16 Gy). One patient underwent a third GKRS procedure to a dose of 16 Gy without complications for re-treatment of a pineal PNET, which recurred after 2 prior GKRS treatments. This study highlights the safety of repeat GKRS for PNET recurrences.

Medulloblastoma

Radiosurgery was first proposed as an effective and safe treatment option for medulloblastoma by the Joint Center for Radiation Therapy.[31] With a modified linear accelerator, SRS was used to boost residual disease in 3 patients and was implemented for salvage treatment in 11 patients for recurrent tumors. Median tumor dose was 12 Gy, and median tumor volume was 6.9 cm.[3] All patients had prior craniospinal irradiation. With median followup of 27 months, none of the patients failed locally within the radiosurgery target volume. Median survival after SRS for recurrent medulloblastoma was 10 months, with distant recurrence within the CNS as the predominant site of failure. The authors conclude that although SRS is highly effective for local control in medulloblastoma, the high incidence of distant recurrence indicates that SRS alone is insufficient for long-term disease control. Systemic therapy should be used in conjunction with radiosurgery to improve survival in patients with recurrent medulloblastoma.

A study from Germany evaluated FSRT and SRS for recurrent medulloblastoma in 20 patients with 29 treatment sites.[32] All patients received prior craniospinal radiotherapy with boost to the posterior fossa for a total dose of 54 Gy. SRS was used to treat 8 areas of recurrence with a mean dose of 15 Gy (range 10-18 Gy), while FSRT was used to treat 21 lesions to a fractionated dose of 24 Gy. Overall local control was 89.7%. None of the patients developed late toxicities such as brain radionecrosis.

Taking into account prior experiences with radiosurgery for medulloblastoma, a small case series from the UK reported the utilization of dose escalated radiosurgery for metastatic relapse of medulloblastoma in 3 children.[33] GKRS treatments were taken to a much higher dose than previously published reports for medulloblastoma with a mode prescription dose of 25 Gy. A total of 6 treatments were well tolerated with no adverse events reported and prolonged PFS was achieved with complete remission seen in 2 patients with MRI follow-up of 30 months and 39 months. The other patient achieved stable disease at 4 years follow-up. This case study is a good example of how pediatric radiosurgery dose and treatment recommendations can evolve over time based on limited prior experiences in the literature.

Special considerations in pediatric radiosurgery

Immobilization and localization

Traditionally, SRS for brain lesions involves a fixed frame for immobilization to ensure accuracy and treatment precision. However, children < 2 years-old in particular have thin, deformable skulls, which may preclude fixation of a stereotactic localization frame. Some institutions use a special wrench to measure torque force applied to the child's skull during head frame placement to prevent head frame pins from penetrating the skull. To maintain accuracy, special posts of the Gamma Knife head frame are tailored to the curvature of a child's skull. A feasible alternative is frameless SRS, which may be more tolerable for children.[34] Image-guided radiation therapy (IGRT) is vital for accurate target localization for frameless radiosurgery. A common frameless SRS technique uses an Aquaplast (Qfix, Avondale, Pennsylvania) mask with optically monitored fiducial markers attached to a bite block or mask. To ensure precise immobilization, the optical markers can be tracked in real time during treatment with thresholds to beam off should the patient move outside the tolerated range.[35] Other modalities for IGRT include cone-beam CT and emerging technologies such as real-time MRI-guided tracking.[36]

Anesthesia

Local anesthesia alone is typically used when treating an adult patient with frame-based SRS. However, a young child may not be able to tolerate the treatment awake and may need general anesthesia. Anesthesia delivery systems with propofol for children is an area of ongoing research. A remote-controlled patient management system consisting of propofol-based general anesthesia with target-controlled infusion was designed in Japan specifically for pediatric GKRS.[37] However, patients who are < 30 kg and < 16 years-old cannot be managed with this system. Therefore, a manually controlled infusion method was developed to treat pediatric patients who are not candidates for the remote-controlled system.[38] Although the manual infusion is less accurate than the target-controlled infusion, propofol concentrations of 3.0-4.0 μg/ml, which are the recommended levels for pediatric GKRS, can be achieved.

Radiation necrosis

The pathophysiology of radiation necrosis is a coagulative process that predominantly affects white matter. It is caused by small artery injury and thrombotic occlusion. Initial management typically consists of high-dose steroids, but other options include vitamin E, pentoxifylline, and hyperbaric oxygen.[39] Bevacizumab has been shown to be effective in managing radiation necrosis in adults, but potential side effects include thrombosis, pulmonary embolism, GI perforation, wound dehiscence and severe hypertension.[40] Although not studied extensively in children, a case series from University of Colorado reviewed 4 children with diffuse pontine glioma who were treated with bevacizumab after developing radiation necrosis. On follow-up, 3 children had significant clinical improvement and were able to discontinue steroids. One child continued to decline, but on further imaging was found to have disease progression rather than radionecrosis. Bevacizumab was well tolerated in all 4 children.

A recent case series of 2 pediatric patients who developed medically refractory radiation necrosis after SRS for AVM were treated with bevacizumab.[41] In this study, a lower drug dose was delivered using a single intra-arterial infusion of 2.5 mg/kg bevacizumab after hyperosmotic blood brain barrier disruption (BBBD) as opposed to intravenous infusion. The goal was to decrease potential complications from high-dose bevaci-zumab administration in children while increasing target delivery. At 8.5 months follow-up, both patients experienced pain relief from previous headaches and resolution of cushingoid features after weaning off steroids. One of the children regained significant motor strength. There was > 70% reduction in cerebral edema on imaging follow-up. The study concludes that intra-arterial administration of a single low dose of bevacizumab after BBBD was safe and resulted in durable clinical and radiographic improvements at concentrations much less than required

Table 2. Recommended radiosurgery dose to target margin

Disease site	Institution/Country	Year	# of patients	SRS dose
AVM	Pittsburgh	2012	135	20 Gy (range 15-25 Gy)
AVM	UCSF	2014	80	>18 Gy
AVM	Virginia	2015	51	≥ 22 Gy
Vestibular schwannoma	South Korea	2014	24	12.4 Gy (range 11.8 - 13 Gy)
Craniopharyngioma	Japan	2005	38	11.5 Gy
Craniopharyngioma	South Korea	2012	4	11.2 Gy (range 9 - 14 Gy)
Ependyoma	Pittsburgh	2010	21	15 Gy (range 9 - 22 Gy)
Low grade glioma	Pittsburgh	2009	50	14.5 (range 11 - 22.5 Gy)
Low grade glioma	Virginia	2012	24	15 Gy (range 4 - 20 Gy)
High grade glioma	Joint Center (Harvard)	2001	90	12.5 (range 6 - 25 Gy)
PNET	Pittsburgh	2009	7	16 Gy (range 13 - 29 Gy)
Medulloblastoma	Joint Center (Harvard)	1995	11	12 Gy
Medulloblastoma	Germany	2002	8	15 Gy (range 10 - 18 Gy)
Medulloblastoma	United Kingdom	2014	3	25 Gy (range 15 - 25 Gy)

for systemic intravenous drug delivery. Advantages over the intravenous route may include decreased systemic toxicity, higher concentration of drug delivery to the affected brain, and lower cost.

Follow-up imaging

An important but often unaddressed aspect of patient management is follow-up indications and radiographic findings after treatment. A study from University of California, San Diego (UCSD) reviewed serial MRI brain scans following SRS for treatment of pediatric primary brain tumors. Among 21 lesions treated, 8 lesions met *Response Evaluation Criteria In Solid Tumors* (RECIST) v1.1 criteria for progressive disease at 6 months.[42] However, on further follow-up imaging, it was found that 3 of 8 initially assumed treatment failures on MRI represented transient tumor edema, with 2 of the lesions later developing a complete response at 15 months, and the other lesion qualifying as stable disease at 12 months. This study highlights that early lesion enlargement after pediatric SRS may not necessarily indicate treatment failure, and follow-up imaging may be warranted before pursuing further treatment or interventions.

Conclusion

When treating children with radiation therapy, radiation-induced toxicities such as cognitive decline are of particular concern. The combination of a steep dose gradient and high conformality makes radiosurgery a particularly appealing treatment option for the pediatric population by allowing physicians to deliver high dose to the target volume while minimizing dose to surrounding normal tissues. It is also a valuable treatment option for children who develop recurrent disease. However, one of the challenges in establishing guidelines for pediatric radiosurgery is the limited sample size of treated patients compared with the adult population. A summary of pediatric SRS prescription dose by disease site based on references from this review article is provided in Table 2. Moving forward, indications for the appropriate utilization of radiosurgery in children will need to be driven by the experience of centers of excellence in radiosurgery and pediatric radiation oncology, as well as clinical trials. A multidisciplinary research approach including neurosurgeons, radiation oncologists, pediatric oncologists, and anesthesiologists is paramount in optimizing the management of children treated with radiosurgery.

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Target tumors, not yourself: A review of False Claims Act allegations against radiation oncologists

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The Department of Justice is investigating radiation oncology service providers. Why? In the words of the infamous American bank robber Willie Sutton, "because that's where the money is." Last year, the Centers for Medicare & Medicaid Services (CMS) disclosed the amounts paid to physicians, and radiation oncologists were among the top recipients of federal monies.[1] Each year, CMS pays hundreds of millions in radiation oncology claims, which steadily rise with the growing use of complex and costly radiation treatments secondary to rapidly evolving technologies. As a result, the Department of Justice and plaintiff attorneys have pursued lawsuits against radiation oncology providers with claims of fraud, abuse and waste.

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Disclosure: *Both authors served together as assistant prosecuting attorneys for Cuyahoga County, Ohio, investigating and prosecuting economic crimes, and have no financial interest in the cases presented.*

This article provides an overview of the federal False Claims Act and discusses specific legal actions pursued against radiation oncology providers under the False Claims Act, either by the Department of Justice, a *qui tam* relator (one who brings an action on the government's behalf), or both. Most importantly, it examines the specific misconduct identified as actionable, and highlights common sense practices to avoid being named as a False Claims Act defendant, particularly when developing cost-containment strategies.

Overview of the False Claims Act

The False Claims Act, originally known as the "Informer's Act" or the "Lincoln Law," was enacted in 1863 at the height of the Civil War primarily to combat fraud allegations in the United States' procurement of Union Army supplies. The damages and penalties available under the False Claims Act are significant, and the misconduct actionable under the False Claims Act is broad and sweeping.

The False Claims Act is a federal statute that reaches not only the submission of a false claim, but also the making of a record or statement to obtain payment or approval of a false claim, the possession of property or money used to defraud the government, illegal purchases from a government officer or employee, and the making of a false record to "conceal, avoid or decrease" a financial obligation to the government.[2] The popularity of the False Claims Act as an anti-fraud weapon is due, in part, to the government's ability to obtain sizeable recoveries through treble damages and penalties of up to $11,000 per claim.

The most common act prohibited by the False Claims Act is where a person presents, or causes another to present, a false or fraudulent claim for payment, and the person involved knows the claim is false or fraudulent. Knowingly means 1) having knowledge 2) acting in deliberate ignorance of the truth or falsity of the information, or (3) acting in reckless disregard of the truth or falsity of the information. No proof of specific intent to defraud is required.[3] The government does not need to pay the claim for False Claims Act liability to arise. Also, penalties may be assessed even when there is no proof of damage to the United States.

In general, liability under the False Claims Act extends to deliberate ignorance and reckless disregard of the truth or falsity of information pertaining to claims for government funds. Deliberate ignorance requires proving that a provider would have had reason to believe its actions may have been unlawful and that the providers purposely failed to investigate any suspicions. In determining whether there was reckless disregard, courts have considered "clumsiness," "carelessness and foolishness in the extreme," "lack of slight diligence or care" and "omission in reckless disregard of a legal duty."[4]

The False Claims Act has been used in a variety of contexts against government contractors, Medicare providers, real estate developers, and other providers of goods and services procured by the federal government. Several states have enacted their own versions of the federal civil False Claims Act as well.

Qui Tam provision

Under the *qui tam* provision of the False Claims Act, a private person may bring a civil action on behalf of the United States. The plaintiff or "relator" must provide the Department of Justice with a copy of the complaint and a written disclosure of all material evidence and information known to the relator. The complaint remains under seal for at least 60 days, during which time the Department of Justice attorneys decide to either proceed with or decline to take over the action, leaving the relator with the right to conduct the action once the complaint is unsealed. The relator is entitled to a portion of the damages recovered in the action, regardless of whether the government proceeds with it. The relator's recovery can range from 10% to 25% of the proceeds, and may also include attorney fees.

The statute of limitations in the False Claims Act is the longer of either 6 years from the date of violation, or 3 years from the date "when facts material to the right of action are known or reasonably should have been known" by the government, but in "no event more than 10 years after the violation is committed."[5] This unique statute of limitations provision is applicable when the government fails to detect false claims at the time they are submitted because of the very deceptive nature of the fraudulent conduct.

Whistleblower protection

In the "whistleblower protection" provision, the False Claims Act creates a federal cause of action for any employee retaliated against by an employer for aiding in a False Claims Act prosecution.[6] Importantly, this cause of action is not limited to *qui tam* relators. As a result of an amendment to the original law, it covers any employee, contractor, agent or associated others. The amendment allows an action for retaliation to be based on relationships outside the traditional employer-employee relationship. Any protected individual who investigates, initiates, testifies, or assists in a False Claims Act action can bring a cause of action.[7]

A person who proves the necessary elements of a retaliation claim is entitled to "all legal relief necessary to make the employee whole," including "reinstatement with the same seniority status … 2 times the amount of back pay, interest on back pay, and compensation for any special damages."[7] The statute of limitations for a retaliation action is 3 years after the date the retaliation occurred. Several examples below involve claims following the termination of an employee who identified the alleged misconduct.

Department of Justice's role in a *qui tam* complaint

Once the government receives a *qui tam* complaint along with material evidence and information, it has several options. First, it can request an extension of the 60-day sealing period. Second, it can elect to intervene and take over the action. Third, it can notify the court that it declines to intervene, permitting the relator to conduct the action in place of the government. Fourth, it can move to dismiss or stay the *qui tam* relators proceeding with the matter on the grounds that action would interfere with an ongoing criminal investigation. Finally, the government can attempt to settle the action before declaring its formal intervention decision. Even if the government initially declines to intervene, it can do so later upon showing good cause.[8]

If the government elects to intervene in a False Claims Act *qui tam* proceeding, the government files its complaint in intervention, which generally includes the allegations identified in the original *qui tam* complaint. The government's complaint may add or delete certain allegations and parties, and plead specific common law claims, such as common law fraud, breach of contract, and unjust enrichment, which a relator cannot bring in a *qui tam* proceeding for lack of standing, an enforceable legal right to such claims.

When the government intervenes, the question may arise as to whether those newly pleaded claims relate back to the filing of the original *qui tam* complaint or may be barred by the statute of limitations. The False Claims Act provides that the government's complaint relates back to the date of the *qui tam* relator's complaint "to the extent that the claim of the Government arises out of the conduct, transactions, or occurrences set forth … in the prior complaint."[9]

Settlement of False Claims Act cases

What makes a False Claims Act proceeding most unique is that the subject of a False Claims Act investigation may have to simultaneously defend against a criminal investigation, a civil False Claims Act action, and the administrative threat of suspension or the outright exclusion from government

programs. Accordingly, the subject of a False Claims Act inquiry must view the implications of a False Claims Act investigation as a serious matter.

Because False Claims Act investigations may involve civil, administrative, criminal and a variety of state common law allegations (including claims raised under any applicable state false claims act laws), the resolution of parallel criminal and administrative claims is often sought in approaching a global settlement. The resolution of parallel criminal and administrative claims is also critical to avoiding potential suspension or debarment, or outright exclusion from federal programs. As a result, a False Claims Act defendant will often try to resolve all outstanding civil, criminal and administrative claims relating to the alleged false claims when settling a civil False Claims Act matter.

The Department of Justice, in contrast, typically offers only a narrow release out of concern that a broader release may capture claims not fully investigated. Further, the Department of Justice declines to release False Claims Act defendants from potential suspension and debarment proceedings when settling civil False Claims Act cases. In the healthcare arena, issues relating to exclusion from federal healthcare programs must be negotiated within the exclusive authority of the Department of Health and Human Services. This often requires separate, independent negotiations with the excluding or debarring authority who will need to evaluate the case and determine whether to settle permissive exclusion issues arising from the False Claims Act settlement once reached. Often, the excluding agency will require that the False Claims Act defendant demonstrate that it has internal compliance procedures sufficient to protect against future misconduct. If not, the False Claims Act defendant may be required to adopt a corporate integrity agreement, which may require an independent monitor to ensure that future misconduct will not occur. Such corporate integrity agreements can be onerous and expensive for a provider.

Recently settled *qui tam* actions involving radiation oncology providers

The claim for medically unnecessary services — those not properly supervised, or lacking proper documentation supporting the service — is typically the basis for recent False Claims Act actions against radiation oncology providers. Medicare reimburses, and participating providers agree to submit, claims only for services medically necessary to diagnose and treat an illness or injury, and for which the provider maintains adequate documentation justifying treatment.[10] Services performed without appropriate supervision are not considered reasonable and necessary and, therefore, are not covered under Medicare.[11] Failure to provide required supervisory care renders the service nonreimbursable because the services are deemed medically unnecessary.[12] The 3 levels of supervision (general, direct and personal) should be well known to all radiation oncology practitioners as they relate to services.[13]

A False Claims Act requires specific allegations concerning the allegedly fraudulent behavior of the defendants. Recently filed actions against radiation oncology providers all contain a common allegation: lack of, or improper supervision of procedures requiring either direct supervision (e.g., daily treatments, simulations and intensity-modulated radiation therapy [IMRT]) or personal supervision (e.g., stereotactic body radiation therapy [SBRT], radiosurgery, or brachytherapy). In addition to submitting claims for services provided when the physician was not present, some actions demonstrate the incredulous lengths to which providers have taken to circumvent supervision requirements. Other False Claim Actions allegations include overuse of CPT codes, illegal kickbacks, improper referrals, failure to provide appropriate services, improper treatment, and lack of operable equipment.

Some of the complaints below are relatively straightforward with simple fact patterns, while others are much more involved. We must stress that the cases and claims were allegations only, as contained in the complaints filed in district courts, and have been settled with no determination of liability.

United States ex rel. Refaei v. Vantage Oncology and Associates, Inc., *United States District Court S.D. of Ohio, Case No: 1:10-cv-833*

This case offers comprehensive allegations and alleged multiple schemes which, for simplicity, are summarized as follows:

Failure to render required supervisory care. Claims for treatment were submitted during periods when the physician was on vacation and or was at centers other than those where patients were treated and billed. In one instance, a patient undergoing treatment died with no physician available to aid in resuscitation efforts. To create the illusion of physician presence during treatment, "GoToMyPC" software was used despite a compliance officer's recognition that "virtual" review did not satisfy image-guided radiation therapy (IGRT) or IMRT supervision requirements. (Prior to 2009 — the time period for a majority of the claims in the *Refaei* complaint — IGRT required personal supervision, and subsequent to January 1, 2009, IGRT required direct physician supervision; IMRT required and continues to require direct supervision.)

Submitting false claims for services inappropriately administered and/or improperly documented treatment. Postimplant prostate brachytherapy

dosimetry revealed multiple patients receiving > 20% of the prescribed dose (1 patient received > 170% of prescribed dose) which, upon discovery, should have triggered medical event reporting. The relator reported the events to a vice president of medical physics and noted that the events were covered up by creating a second patient chart so the medical events were not reflected in records or reports. The relator claimed he was reprimanded after e-mailing the physician, requesting an independent peer review of the brachytherapy cases.

Overuse/overbilling. Allegations of routinely billing special treatment procedure (77470) charges for many patients without any documentation and policy of billing special medical radiation physics consult (77370) for most IMRT plans without a documented physician request or signature. The complaint alleged that a graduate physicist performed the physics consults but had the vice president of physics (who was not personally involved and out of state) sign plans; alleged pressure to bill special dosimetry charges (77331) for each plan, averaging 3 charges for each patient, without specifying devices to be used (thermoluminescent dosimeters, diodes); and stated that many measurements were taken unnecessarily, without justification or by unqualified personnel and signed off by a physicist weekly.

Failure to document and other sundry allegations. In addition to the documentation issues above, the complaint alleged that claims were submitted for complex simulations without documentation of immobilization devices or other items that would justify the charge. Documentation was also lacking to demonstrate the training of physicists, dosimetrists and therapists, or to support the use of IMRT. Other allegations included the overutilization of IMRT (despite Vantage's compliance department identifying inappropriate and overutilization of IMRT), lack of an operational simulator (yet charges for simulation), presence of a treating therapist who was only conditionally accredited to treat at one location, yet treated patients at another facility, and the hiring as manager someone with little or no training because he was the son-in-law of the CEO of a hospital in the planning stages of opening a radiation facility with Vantage.

Failure to perform services. Allegations that claims for other services were submitted but allegedly not performed: IMRT boost calculations, and phantom quality assurance for IMRT and computed tomography (CT) simulations (no films were obtained as the simulator was nonfunctional).

United States ex rel. Berger et al v Baylor University Medical Center at Dallas et al., *United States District Court N.D. Texas, Case No: 3:10-cv-1103*

This case involved a *qui tam* action brought by a radiation oncologist and radiation therapist alleging violation of physician supervision requirements at Baylor's radiosurgery center as well as violation of the Anti-kickback Statute and Stark Act.

Documentation supported Baylor and Texas Oncology's knowledge of supervision requirements for radiosurgery procedures, yet Baylor relaxed its existing supervision rules to allow Texas Oncology (TO) physicians to see patients at another location contemporaneous with ongoing radiosurgery procedures at the Baylor Radiosurgery Center. Physicians' patient schedules from both locations were available, documenting where physicians were (and were not) during radiosurgery cases.

The relators raised safety and supervisory concerns with top management of Baylor, Health Texas and TO, alleging that supervision concerns were overridden by financial incentives. In support of this claim, available meeting minutes of Baylor's radiosurgery council implicitly admitted knowledge of the supervision rules, granting permission for necessary physicians to be available by phone as a supervision rule workaround. At times, only a nurse and medical physicist were present during radiosurgery procedures, including a situation when a Gamma Knife (Elekta, Stockholm, Sweden) patient's condition changed, warranting transfer to the emergency room.

In another supervision workaround, Baylor misrepresented the training and education of the neurosurgeons and an otolaryngologist when including them on its radioactive material license to act as qualified users during Gamma Knife procedures, thereby accommodating TO radiation oncologists to see patients elsewhere.

Not only did the relator, concerned about patient safety, make management aware of the supervision and qualification rules, he also reported his discussions with the University of Pittsburgh Medical Center (UPMC), a center that remedied its supervision procedures after being cited by the Nuclear Regulatory Commission (NRC) for not meeting requirements. For his actions, the relator's contract was not renewed.

Overlooking supervision rules was alleged to be an inducement to refer radiosurgery and chemotherapy patients to Baylor, constituting illegal kickbacks under the Anti-Kickback Statute and violating the Stark Act. Also alleged as an inducement was the naming of a TO radiation oncologist as an associate director of Baylor's radiosurgery center even though he would not have any management or supervisory role — a position allegedly created as a means of inducing referrals for financial gain (Baylor owned the equipment so it received the technical fees).

Lastly, unbundling CyberKnife (Accuray, Sunnyvale, California) treatment codes was alleged, creating "fake" treatment plans (prior to 2006, billing planning codes separately

from global codes on the treatment's date was banned) and failure to perform daily quality assurance and/or backdating test results.

United States ex rel. Koch v. Gulf Region Radiation Oncology Centers Inc. (GRROC) et al., *United States District Court N.D. Fla. Case No. 3:12-cv-0050*

This case involved a $3.5 million settlement and supervision claims. For nearly 4 years, 2 radiation oncologists (GRROC) provided services for 3 locations; when on vacation, only 1 physician was available for the 3 locations. Of the 3 centers, one (Sacred Heart) contracted with GRROC to provide radiation services. When issues of coverage and billing were brought to the attention of Sacred Heart management, neither Sacred Heart nor GRROC were willing to pay for additional coverage or change billing practices. Not only were supervision claims brought for simulations, treatments and other procedures, but also, similar to other *qui tam* actions, the usual litany of claims related to lack of medical necessity documentation and/or routine claims on all patients for special physics consults, treatment procedures, devices and unbundling of IMRT-related charges were raised. Also similar to *Refaei,* allegations that no physician was present when a patient required transport to the emergency room strengthened the relator's allegations against GRROC.

United States ex rel. Montejo v. Adventist Health System et al., *United States District Court M.D. Fla. Case No. 8:13-cv-00206*

Inappropriate supervision as well as lack of supervision claims were among those alleged in this case, which settled for $5.4 million this year. The relator was a radiation oncologist who brought suit against his employer, Florida Oncology Network (FON), and the hospital system for which FON provided radiation oncology professional services. The complaint alleged that FON lacked sufficient radiation oncologists to be present at each of its multiple facilities, instead relying on nearby emergency room physicians, unaffiliated medical oncologists, nurse practitioners and physician assistants. Anywhere from 10 to 15 patients per day up to 80 to 100 patients per day were treated at sites covered by FON. None of the sites were scheduled to have full-time coverage by radiation oncologists except the location with the fewest patients on treatment; this was the only site where FON collected all technical and professional revenue. Two sites were scheduled to be covered by only 1 radiation oncologist simultaneously, and other physicians were scheduled to perform brachytherapy/IORT (intraoperative radiation therapy) simultaneously while external-beam patients were undergoing treatment.

As in the other actions, a patient sustained an injury at a site without a nurse or radiation oncologist present, at which time the presumed supervising, unaffiliated medical oncologist refused to offer medical attention. A more serious allegation concerned the simulation of a spine, where evidence of prior radiation could have been noted had a radiation oncologist been present, resulting in a patient's paraplegia secondary to radiation necrosis of the spinal cord due to re-irradiation. Similar to other actions presented here, the complaint reiterated investigations of radiation mishaps as reported in numerous newspaper articles.

The relator's concerns of appropriate coverage and patient safety made known to management were met with the response that patient volumes did not justify the cost of additional physician coverage. In addition, a biller's notice to management regarding supervision requirements were acknowledged, but ignored. When CMS inspectors were on site and for on-treatment visits (OTVs) days, Adventist published a radiation oncology coverage schedule, using initials only, to create the illusion that there was full coverage at all times. Some of the initials referred to physician assistants and nurse practitioners, not radiation oncologists.

Similar to other actions referenced, allegations regarding the routine use/billing for IGRT on palliative cases (such as whole brain) and IMRT for breast boosts were made. Unique to this action was the allegation that weekly management charges were billed when a nurse or physician assistant, and not the physician, saw the patient on OTV.

United States ex rel. Ana v. Winter Park Urology, et al., *United States District Court M.D. Fla. Case No. 6:10-cv-00806*

Not all actions resulted in settlements against all named defendants. The radiation oncologists who contracted with Winter Park Urology were successful in having the complaint against them dismissed on the eve of trial. This action alleged inappropriate physician supervision, unlike the preceding actions alleging inappropriate supervision by nonphysicians or absence of any physician during treatment.

Winter Park Urology contracted with a group of radiation oncologists (ROC) to perform radiation oncology services at its Orlando Cancer Institute (often referred to as a "urorad center"). The radiation therapists and administrators were employees of Winter Park Urology, which owned the radiation equipment. ROC operated its own radiation facility in Sanford, unrelated to the Orlando Cancer Institute. About 15% to 20% of the patients treated at the Orlando Cancer Institute had nonurologic primaries, many of which were breast cancer.

The relator was the director of medical physics who brought to management's attention that Orlando Cancer Institute was routinely billing

Table 1. ***United States ex rel. Ana v. Winter Park Urology, et al.***

Relator's Arguments

- Ability to take over performance of a procedure, change a procedure or the course of treatment to a particular patient;
- Must be a person who is clinically appropriate to supervise the service;
- Would be inappropriate if outside the scope of their knowledge, skills, licensure or hospital-granted privilege;
- The supervisory practitioner or nonphysician practitioner who is physically present should have the training and knowledge to clinically redirect the service or provide additional orders; and
- In order to furnish appropriate assistance and direction for any given service or procedure, the supervisory physician or nonphysician practitioner must have, within his or her state scope of practice and hospital-granted privileges, the ability to perform the service or procedure.

Defendant's Arguments

- Does not necessarily need to be of the same specialty as the procedure or service being performed;
- Medical staff that supervises the services need not be in the same department as the ordering physician; and
- Noted that the phrase: "physician or nonphysician practioner" was repeated multiple times in CMS discussions.

for special physics consults, without having a request from the physician, as was his practice at the nonaffiliated center owned by ROC. He was fired 4 days later despite "excellent" or "outstanding" evaluations, and later brought the *qui tam* action alleging inappropriate billing of special physics and special treatment procedure charges routinely on all cases. In addition, he also alleged claims for inappropriate supervision.

What differentiates this supervision claim from supervision claims in other cases was that the required physician supervision was allegedly inappropriate. While a urologist was present when patients were undergoing daily radiation treatment, the radiation oncologists were not routinely on site, estimating that 35% of all radiation procedures were performed when no radiation oncologist was present. The relator alleged that a radiation oncologist was never present for IGRT (IGRT required personal supervision prior to 2009, and direct supervision beginning in January, 2009); instead, the radiation oncologist would review the images weekly. In support of his allegations, the relator produced Orlando Cancer Institute's web page, informing patients that its radiation oncologists would perform physical and medical record examination and, if appropriate for radiation, would see patients regularly during their treatment.

Among several theories of defense pertinent to this review, counsel for ROC argued that there was ambiguity as to the physician supervision requirements. Counsel asserted there was no CMS requirement that a radiation oncologist, and only a radiation oncologist, was required to provide supervision of the daily radiation treatments. In addition to relying on CMS discussions, counsel also argued that the term "clinically appropriate" was ambiguous and not addressed by CMS. Citing case law, the relator argued that the absence of regulatory guidance was significant to showing that Winter Park Urology knowingly violated the law when interpreting that any physician (and not specifically a radiation oncologist) could supervise the services. Winter Park Urology stated that "perhaps it is better practice for a radiation oncologist to supervise IMRT or IGRT procedures; however, technical compliance with the law does not mandate this." Lastly, the defendants argued that reckless disregard could not be established because they made reasonable inquiry, obtaining legal advice, into the meaning of the law.[14]

Both the relator's complaint and defense counsel emphasized and reiterated CMS language throughout their respective pleadings, the highlights of which are summarized in Table 1. Readers are encouraged to read both 74 Fed. Reg. 60316, 60584 and 75 Fed Reg 72012. Multiple sources of legal analysis regarding these regulations exist.

Whether or not the urologists in this case had "the training and knowledge to clinically redirect the service or provide additional orders" to satisfy "direct supervision" was never adjudicated. The relator agreed to

dismiss the claims against the radiation oncologists. Readers will draw their own conclusions, but should not infer any sort of legal guidance. Unfortunately, those looking for resolution regarding controversies involving urorad centers,[13] including appropriate supervision, will remain in suspense.

Discussion

The most direct allegation against a radiation oncology provider is the allegation of lack of appropriate supervision where the claim for reimbursement requires a level of supervision not provided. Brachytherapy, radiosurgery and SBRT are the most frequently performed procedures requiring personal supervision. Most other radiation oncology procedures (e.g., daily treatment, IGRT and simulation) require direct supervision. No expert testimony is needed, nor is it a matter of opinion, to substantiate an allegation of lack of supervision, when the physician is on vacation or at another facility. Competing theories of expert testimony can be avoided altogether in such situations. Furthermore, when performing services requiring personal supervision, a physician is not considered "available" as required for direct supervision for any other contemporaneous treatments and/or procedures. Lack of supervision, as it relates to a physician's presence, can be easily established through a variety of electronic and documentary evidence such as: schedules, flight itineraries, credit card statements, interviews with other staff, and cell phone records.

While the definition of personal supervision is clear (attendance in the room during the procedure) Medicare has declined to define "immediate" for purposes of direct supervision in terms of time or distance. Defining "immediate" is beyond the scope of this article and the reader is directed to appropriate legal commentary.[15,16] Reports of radiation mishaps that occur secondary to a physician's lack of supervision are reported in the general media.[17] The tragic results reported in the referenced article were reiterated in the body of one of the *qui tam* actions discussed here,[18] emphasizing that the lack of a physician's presence during treatment is an effectively damaging and easily proven allegation.

Appropriate supervision is another matter, given the contentious discussion in the general media [19,20] and within professional medical societies involving "urorad centers," as this may not be well settled as in the *qui tam* action presented above.[21] It is clear that physicians lacking specified training may not be listed on a radioactive materials license (e.g., otolaryngologists, as in *Baylor*). While it may be a reach to suggest that ER physicians, nurses and assistants possess adequate therapeutic radiation training, the question of who may be appropriately qualified or privileged has not been conclusively answered in regulations or law.

CMS requires hospitals to carefully consider who are appropriate candidates (physicians and other healthcare practitioners) when appointing medical staff to practice at the hospital in accordance with state law. CMS requires that hospital committees examine credentials of all candidates, and make recommendations for medical staff membership and privileges to the hospital's governing body as a part of its Conditions of Participation and Conditions for Coverage that health care organizations must meet to begin and continue participating in the Medicare and Medicaid programs. The underlying premise is that health and safety standards are the foundation for improving quality and protecting the health and safety of beneficiaries.[15]

Another common False Claims Act allegation easily substantiated relates to claims for reimbursement that are not supported by appropriate documentation. Examples include billing for: 1) complex simulations lacking documentation of treatment/immobilization devices; 2) first-day simulations lacking documentation of physician review before treatment; and 3) special treatment procedures lacking substantiation (e.g., retreatment of a previously irradiated site, presence of medical devices in/near field, etc.). Although useful in facilitating the billing process, documentation does not always need to be written. For example, blocks, immobilization devices or the presence of devices in a treatment field can be easily identified in films or treatment plans and are, therefore, documented in the record to substantiate claims.

False Claims Act allegations that relate to kickback schemes, claims for inappropriate treatment and/or unnecessary charges present a greater evidentiary challenge to the government or *qui tam* relator than allegations relating to supervision or documentation. These allegations may likely require opinion testimony, which requires an expert witness. Similar to medical malpractice actions, proof required may resort to dueling experts. Such allegations may include the inappropriate use of IMRT, SBRT, Gamma Knife, physics consults and special treatment procedures. Substantiating the allegation may be easier if a particular modality was used for nearly every case, or where corporate "unwritten rules" dictate that a certain percentage of all cases must, for example, use IMRT. In addition to expert testimony, parties in an action may present National Comprehensive Cancer Network (NCCN) guidelines and care paths as another form of (pseudo) expert opinion that the trier of fact (i.e., the judge or jury) may consider in determining if services are unnecessary or inappropriate.

The easiest allegations to support, although not always financially rewarding, are those where outrageous misconduct occurs that shocks the conscience of the trier of fact. Examples presented above include: the death of a patient where no physician was present to administer aid; the failure to report untoward clinical outcomes or misadministrations; rationalizing that a virtual web or telephone presence constitutes personal supervision; the existence of alternate or "ghost" records; billing for films despite having a nonfunctional x-ray unit; record alteration; retaliation against personnel raising concerns of patient safety; hiring unqualified but connected personnel; and billing identical special charges for every patient. Allegations such as these add a certain "sex appeal" to the proceeding, which present unique challenges to the False Claims Act defendant.

Lastly, some of the allegations listed, while describing less than appropriate behavior, may not be sufficient on their own to bring an action. Examples include family connections to drive business, training levels of therapists or physicists, and frequency of any quality assurance. Some of the allegations, like overdosing or treating the wrong site (i.e., misadministration), may be covered under different civil statutes, while other allegations, like creating false charts for submission (i.e., tampering with records) may be covered by criminal statutes. Whether these allegations support a False Claims Act is not as important as how they serve to add additional color to the proceeding.

Conclusion

In improving the quality of radiation oncology practice, distilling the common mistakes alleged in False Claims Act actions reinforces what constitutes good practice, particularly with the increasing use of SBRT, which requires personal supervision by the physician along with concomitant physics and documentation requirements. A common thread woven throughout the False Claims Act cases is that each involved a *qui tam* relator whose quality concerns were rebuffed or outright ignored. Investigating concerns brought by relators often leads to the discovery of additional, actionable violations, which may be more easily substantiated and far more costly. This is not much different than the egregious acts allegedly committed by Al Capone that would have been much more difficult to prosecute than simple income tax evasion, which ultimately put him behind bars.

As supervision-related claims were the simplest claims to support in the above cases, supervision requirements must be adhered to, and are reasonably clear. The Office of the Inspector General and Department of Justice consider supervision important and critical to patient safety.[15] Less clear is who may supervise, which is an evolving issue that may be resolved by hospitals in complying with CMS rules for Conditions of Participation with respect to privileging.[22] While certain medical practices have expanded definitions of who can be privileged to perform certain procedures, cost-containment strategies that would allow anyone other than a physician trained in radiation oncology to supervise radiation treatments should be reviewed with legal counsel. CMS language, requiring "the training and knowledge to clinically redirect the service or provide additional orders," provides prudent guidance when establishing policies.

Finally, when making decisions on how to establish clinical practices, the best guidance to follow is simple: how would this decision be perceived if alleged in a lawsuit?

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Updates in IMRT, VMAT of the head and neck

Mary Beth Massat

Head and neck cancers refer to a group of cancers of the oral cavity (mouth), nose, pharynx, larynx, lip or sinuses. While rare, accounting for 3% of all cancers in the United States or nearly 46,000 new cases each year,[1] most head and neck cancers begin in the squamous cells that line mucosal surfaces in the mouth, nose and throat.[2] The 2 most important risk factors for these type cancers are tobacco use—including smokeless or chewing tobacco—and alcohol consumption. Infection by the human papillomavirus (HPV) is also believed to increase risk, specifically the HPV-16 genotype.[1,2]

Intensity-modulated radiation therapy (IMRT) is growing in use to treat cancer and tumors in more complicated areas of the body, such as the head and neck. It is well accepted and has been shown in the literature that a high-precision, more targeted delivery of external-beam radiation can improve treatment outcomes and tumor targeting, with less severe side effects.

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When Daniel J. Haraf, MD, professor of Radiation and Cellular Oncology and Medical Director, Radiation Oncology, at The University of Chicago Medicine, began using IMRT in 1998-1999, no textbooks existed to guide him in planning. Today, he notes, manuals and reference guides from the American Society for Radiation Oncology (ASTRO) help radiation oncologists avoid critical structures and understand dose tolerances for organs and tissues.

"IMRT is a tool and a means to an end," Dr. Haraf says. "The end [goal] is to get adequate radiation to where the cancer is lurking while limiting dose to normal structures. In a perfect world, we would only give radiation where it is needed and miss areas where it is not needed — it's all about tradeoffs."

Because of the many subtleties in developing an IMRT plan for head and neck cancer, it is important to know how the cancer is unique in each individual. IMRT, Dr. Haraf says, helps him do a better job of individualizing treatment. Individualized treatment plans also can benefit HPV-positive patients, who are at a higher risk for head and neck cancers, says Ping Xia, PhD, department head of medical physics at The Cleveland Clinic Foundation and an *Applied Radiation Oncology* advisory board member. Dr. Xia has been actively developing treatment planning techniques for head and neck cancer patients for over 15 years.

"HPV impacts the treatment because [these patients] are more sensitive to the radiation. We can de-intensify treatment for patients who are HPV positive, thus reducing treatment-related toxicity," says Dr. Xia, noting that HPV-positive head and neck cancer patients tend to be younger and appear to have better outcomes.

An early adopter of IMRT and volumetric-modulated arc therapy (VMAT) for treating head and neck cancer, Dr. Xia serves as a physics co-

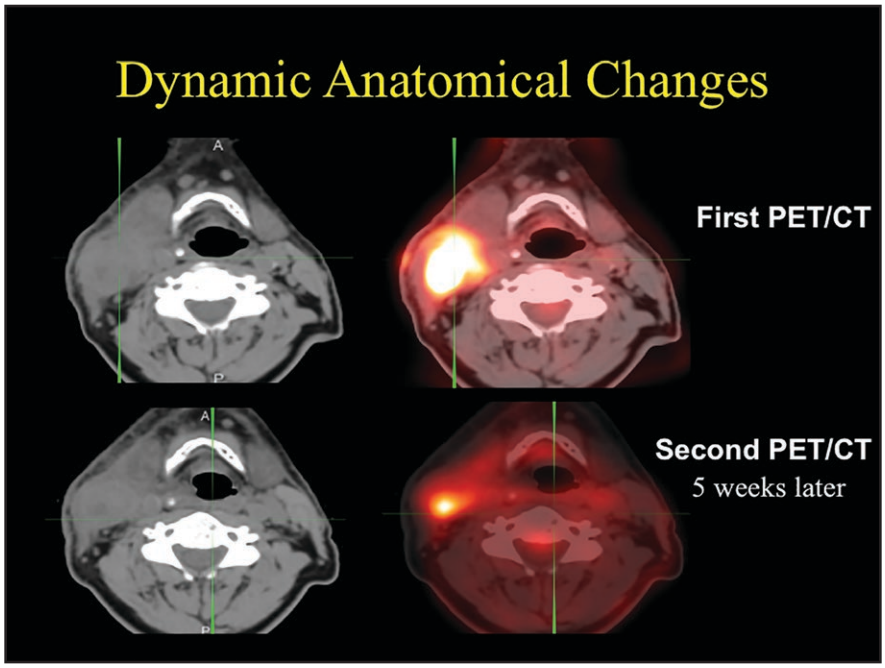

FIGURE 1. *The top panel is a cross-sectional PET/CT image, acquired 1 week prior to radiotherapy. The patient had enlarged neck lymph nodes on the left side, as shown in both CT and PET images. The bottom panel is a cross-sectional second PET/CT, acquired 4 weeks after IMRT, showing significant tumor shrinkage in response to IMRT treatment.*

primary investigator of NRG-HN002: A Randomized Phase II Trial for Patients with p16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer, NCT02254278. This trial is investigating a de-intensified treatment regimen for patients with HPV-positive oropharyngeal cancer.[3]

Reducing side effects is an important benefit of IMRT compared to conventional radiotherapy. A pivotal study conducted by researchers at the Royal Marsden Hospital and the Institute of Cancer Research in London, and published in the February 2011 issue of *Lancet Oncology*, was one of the first studies to compare IMRT to conventional radiotherapy.[1] The goal of the prospective, randomized study was to determine whether IMRT could spare salivary glands and reduce xerostomia, also known as dry mouth from reduced or absent saliva flow. The authors reported a "significant reduction of radiation-induced xerostomia" in patients treated with IMRT compared to those who received conventional radiotherapy. The IMRT treatments were designed to spare the parotid gland—the major salivary gland. The authors also reported improved salivary flow and better quality of life in patients who received IMRT.[4]

Difficulty swallowing is another potential side effect, notes Dr. Xia. Today, radiation oncologists and medical physicists aim to protect the larynx and other structures that affect swallowing during IMRT treatments. "Our knowledge is progressing. When we first started IMRT in 1997, we focused mostly on a few critical structures—the brain stem or spinal cord and parotid glands," she says. "In our current IMRT planning, the number of organs or structures we spare in our planning is 30, and this includes the larynx and oral cavity. Before, the patient had to live with these side effects; now we try to treat their disease and also improve their quality of life."

In addition to reducing toxicity to healthy organs and tissues, IMRT can improve survival rates. A 2014 study published in *Cancer* analyzed the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to determine cause-specific survival (CSS) for head and neck patients treated with IMRT compared to non-IMRT treatment delivery methods. The goal was to determine whether the widely accepted, yet more expensive, IMRT benefitted patients or exposed them to more risk regarding outcomes.

A total of 3,172 patients were identified with a median follow-up of 40 months. In the analysis, the authors reported that patients treated with IMRT had a statistically significant improvement in CSS (38.9%) compared to non-IMRT treated patients (18.9%). Even when accounting for variables such as account diagnosis, marriage, rural vs. urban setting, income and other factors, patients treated with IMRT still had a CSS benefit.[5] As a result of the analysis, the authors suggest that IMRT may improve patient outcomes in those with head and neck cancers. (See Figure 1 for an example of IMRT results in this patient population.)

Recently, a small sample-size study examined brain-sparing methods for IMRT in 10 patients with head and neck cancer. Both a hippocampus-sparing plan and a brain/hippocampus-sparing plan were generated, and dose volume histograms (DVHs) and dose difference maps were compared. In 8 of 10 cases in both types of treatment plans, the authors detected significant reductions in hippocampal doses relative to conventional plans. They suggest that IMRT has a high

probability of reducing neurocognitive function decline in head and neck cancer patients, and that results could be translated into a future clinical trial.[6]

Dr. Haraf has become a widely recognized leader in combining IMRT with chemotherapy for treating head and neck cancers. Efforts to decrease toxicity to critical organs, and thereby lower side effects of radiation treatment, are increasingly important. Combining chemotherapy with IMRT is an important step in this direction, he says.

Historically, head and neck cancers had a survival rate of 30% to 40%. With concomitant chemotherapy and radiation therapy, survival rates have increased to > 50 %, he says. In fact, Dr. Haraf is optimistic that about 70% of current head and neck cancer cases could be cured using radiation therapy and chemotherapy. IMRT has helped increase survival by better targeting cancer while limiting toxicity.

At the 2015 American Society of Clinical Oncology (ASCO) Meeting held May 29 to June 2 in Chicago, Dr. Haraf was co-author of a poster on a study that examined whether radiation therapy volumes could be reduced in patients who responded to induction chemotherapy.[7] The study examined the use of response-adapted volume de-escalation (RAVD) to guide a reduction in radiation therapy for chemotherapy responders, and found that outcomes were not compromised, and long-term toxicity could potentially improve.[7]

While IMRT has been shown in the literature to improve survival and quality of life while reducing side effects, Dr. Xia uses VMAT in the majority of head and neck cancer patients. She finds that VMAT provides more freedom in the beam angle and offers more variables in the treatment-planning process to better avoid critical structures while delivering more targeted, higher doses to the tumor site.

"VMAT is really an advanced form of IMRT and, clinically, the quality of the plan is better than a conventional step-and-shoot IMRT," Dr. Xia says. "Most important is the gain in delivery time. I remember in 1997 we had a 30 minute on-beam time. Now with VMAT, it is 5 minutes."

In addition to the higher efficiency and added patient convenience of the VMAT treatment plans, Dr. Xia and her team at The Cleveland Clinic Foundation also perform more daily image-guided radiotherapy using a cone-beam CT equipped on the linear accelerator.

"Two things happen to head and neck patients during treatment: With chemotherapy, they tend to lose weight. Also, the tumor responds to treatment and shrinks during radiation therapy," she explains. For most patients who receive radiotherapy, only one plan is designed for the entire treatment course. Yet, performing adaptive radiotherapy on all patients would require extensive resources—and the benefits are not yet clinically evident. Through research, Dr. Xia hopes to identify patients who would benefit the most from this advanced treatment.

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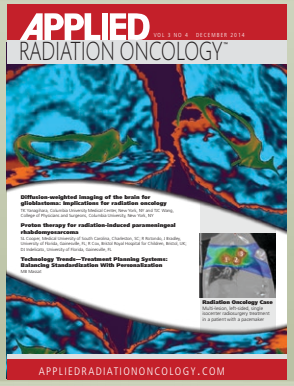

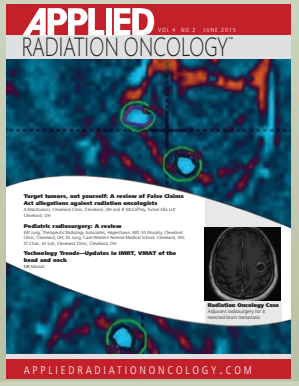

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Adjuvant radiosurgery for a resected brain metastasis: A case report and literature review

Camille Berriochoa, MD; Charles Marc Leyrer, MD; Michael Vogelbaum, MD, PhD; Samuel Chao, MD; Erin Murphy, MD

CASE SUMMARY

A 67-year-old Caucasian male with a remote history of prostate cancer treated with prostatectomy, salvage radiation, and anti-androgen therapy over 13 years ago presented with gradually worsening dysarthria and no other evidence of neurologic deficits. His PSA began to rise 2 years prior and was 3.6 ng/mL at the time of evaluation. MRI of the brain showed a 2.8-cm ring-enhancing lesion in the left frontal lobe (Figure 1); subsequent CT scans of the chest, abdomen, and pelvis were unremarkable. He underwent complete resection of the tumor with pathology revealing adenocarcinoma consistent with prostate origin. Adjuvant treatment with either whole-brain radiation (WBRT) vs. stereotactic radiosurgery (SRS) was discussed; the patient elected for SRS. Thirty-three days following gross total resection, he underwent Gamma Knife (Elekta, Stockholm, Sweden) radiosurgery, 18 Gy prescribed to the 51% isodose line to a target volume of 3.65 cc with a heterogeneity index of 1.961 and a conformality index of 1.504 (Figure 2).

*Prepared by **Drs. Berriochoa, Leyrer, Chao** and **Murphy,** Department of Radiation Oncology, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, Ohio; and **Dr. Vogelbaum,** Department of Neurosurgery, Rose Ella Burkhardt Brain Tumor and NeuroOncology Center, Taussig Cancer Institute, Cleveland Clinic Foundation, Cleveland, Ohio.*

IMAGING FINDINGS

Brain MRI showed a rounded peripherally enhancing juxtacortical mass centered along the anterior left precentral gyrus measuring 2.3 × 2.7 × 2.8 cm. Intraoperative postresection MRI demonstrated complete resection.

DIAGNOSIS

Stage IV prostate adenocarcinoma with a solitary intracranial metastasis.

DISCUSSION

Brain metastases are the most common form of brain tumor with up to 25% of patients with cancer diagnoses developing intracranial disease at some point over the course of their treatment. For several decades now, the standard of care for patients with brain metastases has been whole-brain radiation therapy (WBRT). In candidates for surgical resection, the addition of adjuvant radiation decreases local failure markedly from about 50% to 10%.[1] In recent years, however, controversy has increased among oncologists about the neurocognitive effects of WBRT, with studies suggesting increased rates of dementia associated with large fraction sizes, increased probability of neurocognitive decline, decreased quality of life, and even decreased overall survival with whole-brain treatment.[2-5] Other investigators have countered that neurocognitive decline is more representative of poor tumor control than radiotherapy-induced neuronal toxicity and that long-term survivors maintain neurocognitive function and equivalent overall survival.[6,7] Consequentially, some argue that WBRT should be deferred in favor of the improved neurocognitive profile of SRS directed to the resection bed (adjuvant SRS). Here, we describe a case of adjuvant SRS provided to the resection cavity and explore the literature supporting the rationale and techniques applied for its delivery.

In our patient, adjuvant radiosur-gery was favored given his excellent performance status, long interval between salvage prostate radiation and recurrence, and the solitary site of involvement. With this in mind, the timing and technique of his SRS needed further consideration based on existing data.

Atalar et al addressed whether waiting to deliver adjuvant SRS would allow for shrinkage of the resection cavity and, thus, minimize the radiation dose to the surrounding normal brain. They found no significant volume change up to 33 days after surgery, and concluded that there is no benefit in waiting longer than 1-2 weeks to perform cavity SRS.[8]

Determining the optimal margin size for patients treated with SRS has also

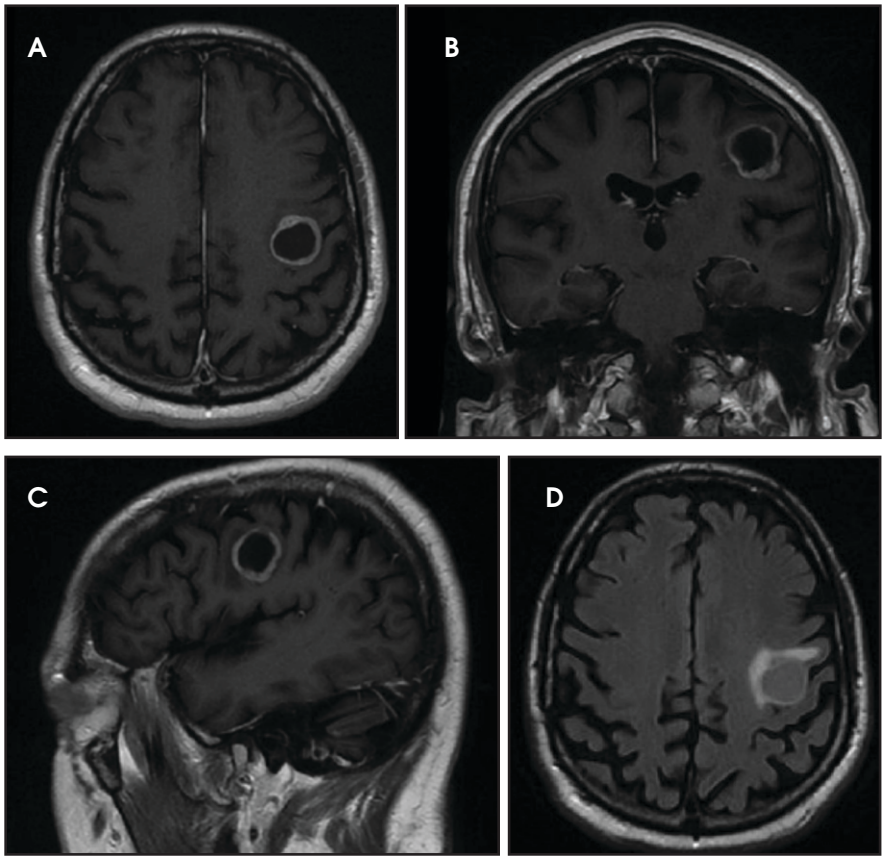

FIGURE 1. *Representative T1 MRI images with intraluminal contrast completed prior to resection in the (A) transverse, (B) coronal, and (C) sagittal views depicting a rounded peripherally enhancing juxtacortical mass centered within/along the anterior left precentral gyrus at the level of the centrum semiovale with areas of more discrete nodular enhancement along its anterior and inferolateral margins. (D) FLAIR MRI image with intraluminal contrast completed prior to resection, depicting mild surrounding vasogenic edema with no midline shift or significant mass effect.*

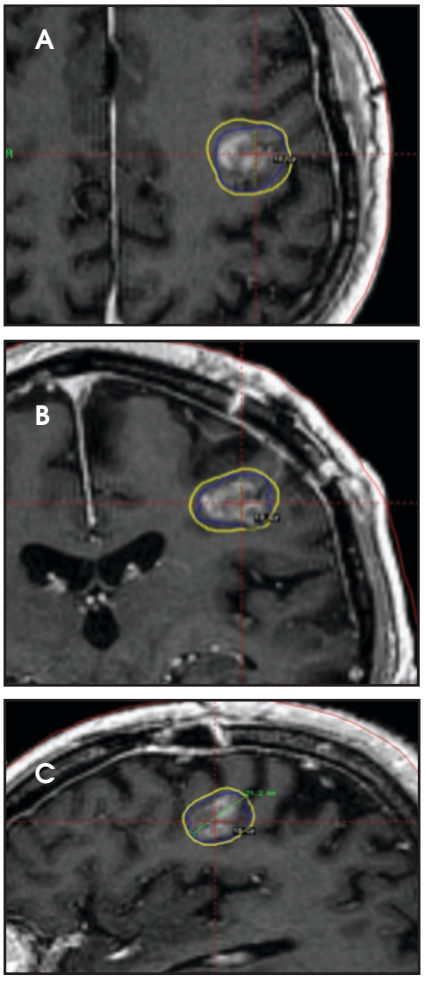

FIGURE 2. *T1 MRI images with contrast completed for Gamma Knife planning in the (A) axial, (B) coronal, and (C) sagittal views showing the gross tumor volume (GTV) (blue) and the dose coverage of the planning target volume (PTV) by the 18 Gy isodose line.*

been a subject of debate. In one of the largest series on postresection SRS, Soltys et al evaluated the local control rates associated with SRS delivered with a median marginal dose of 18.6 Gy.[9] At 12 months, 80% of tumors demonstrated local control, which compared favorably to Patchell's aforementioned study. Interestingly, among treatment factors evaluated on univariate analysis, increasing conformality and decreasing margin sizes were associated with worse local control, with authors concluding that a 2-mm margin is optimal. Another trial attempted to answer this specific question by randomizing patients to receive SRS using either 1-mm or 3-mm margins.[10] Excellent 12-month local rates were detected (> 90% in both arms) with no statistically significant difference between the 2 arms; however, biopsy-proven radiation necrosis was observed more frequently in the group for which a 3-mm margin was used ($p = 0.10$), raising the concern that a larger margin increases the risk of radiation necrosis. Authors concluded that a 1-mm margin was preferable since the risk of radiation necrosis may be lower with no compromise in local control.

The risk of intraoperative spill of tumor at the time of resection and subsequent risk for leptomeningeal disease (LMD) when isolating radiation to a small, highly focused volume has been evaluated in previous studies and warrants extra consideration when treating with SRS. A retrospective review found that SRS was associated with an 11% risk of LMD at 12 months, with breast histology accounting for the majority of this risk (univariate HR = 2.96).[11] A subsequent study compared outcomes between WBRT vs. localized radiotherapy and again found an increased risk of LMD (HR 2.45) in those treated with highly focal radiation.[12]

Conflicting results and physician biases complicate the interpretation of

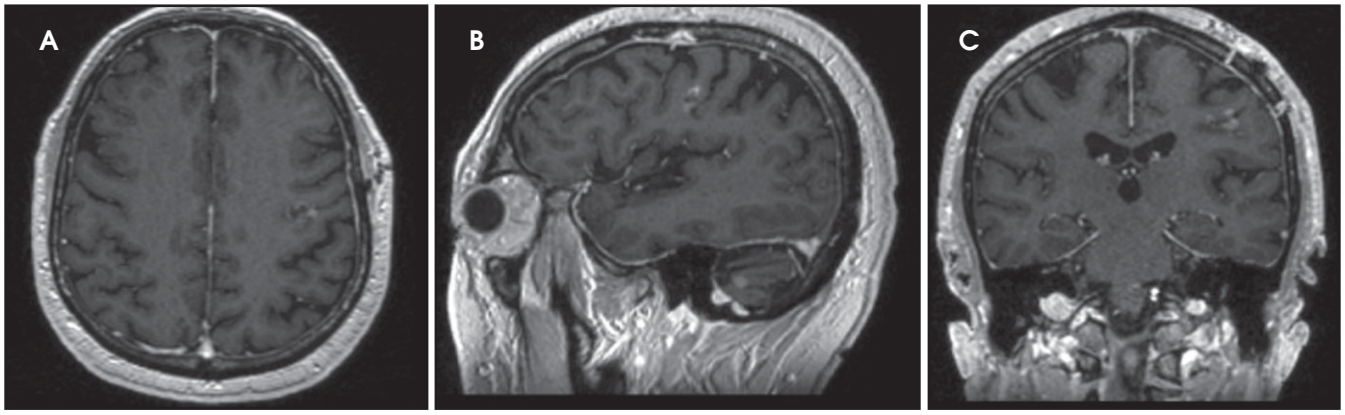

FIGURE 3. *T1 MRI images with contrast completed ~1 month after Gamma Knife in the (A) axial, (B) coronal, and (C) sagittal views showing a small ring-like area of susceptibility artifact in the subcortical white matter of the left paralytic white matter, but no areas of definite enhancement identified.*

Table 1

Lesion volume	Dose
< 4.2 cc	20 Gy
≥ 4.2 to < 8.0 cc	18 Gy
≥ 8.0 to < 14.4 cc	17 Gy
≥ 14.4 to < 20 cc	15 Gy
≥ 20 to < 30 cc	14 Gy
≥ 30 cc to < 5cm	12 Gy

some of this data and the subsequent decision-making process about when to employ SRS vs. WBRT as adjuvant therapy. The ongoing ALLIANCE N107C trial will help determine which modality may lead to better outcomes. This question is particularly relevant in an era of heightened reluctance to contribute to neurocognitive risks, contrasted with the need to decrease medical costs, as WBRT is significantly less expensive than SRS. In this trial, patients who have undergone resection of 1 metastasis are randomized to adjuvant WBRT vs. SRS. Primary endpoints are overall survival and neurocognitive progression. SRS dose in this trial is defined by surgical cavity volume rather than size with doses ranging from 12 to 20 Gy (Table 1) delivered with 2-mm margins.

Following resection, our patient's dysarthria initially worsened but then improved (Figure 3). He remained on androgen-deprivation therapy. Seven months after treatment, he was found to have a new single 0.7 cm intracranial metastasis in his cerebellum for which he received definitive treatment with SRS to 24 Gy. Approximately 1 year later, he developed a 3.8-cm left temporal metastasis and enrolled in an institutional protocol that permitted delivery of neoadjuvant SRS, 15 Gy in 1 session, followed by complete resection 2 days later. He continues to be monitored regularly and is doing well overall 20 months after his initial postresection radiosurgery.

CONCLUSION

This report illustrates that while there is no clear consensus on the use of SRS vs. WBRT following resection of a single brain metastasis, there is growing retrospective and phase II evidence indicating that SRS is safe and can provide effective local control in appropriately selected patients. The currently accruing N107C trial will help answer the question of whether overall survival and neurocognitive function are more affected by adjuvant WBRT vs. adjuvant SRS.

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APPLIED RADIATION ONCOLOGY

RADIATION ONCOLOGY CASE

Linac-based stereotactic radiosurgery for trigeminal neuralgia

Luis Moreno Sánchez, MD; Nathalie González Cazaño; Enrique Mendoza; Frankie Viñals; Antonio Ivo Rodríguez; Víctor Moreno Geraldo; and Mario Ruiz

CASE SUMMARY

A 70-year-old male patient was referred to the CDD Unit of Radio-therapy and Radiosurgery Abreu Clinics in Santo Domingo, Dominican Republic, with a history of lower left jaw pain that evolved over 10 years into severe left hemifacial pain and dysphagia. He was treated unsuccessfully for many years with pregabalin and carbamazepine, until maximum doses eventually caused liver toxicity.

A cerebral MRI with contrast revealed a vascular image: a superior cerebellar artery (SUCA) contacting the upper surface of the left V cranial nerve, near its apparent origin.

After confirming a diagnosis of trigeminal neuralgia (TN), we treated the patient with intracranial stereotactic radiosurgery (SRS). Twenty-four hours after treatment, the patient was completely asymptomatic. At the 25-month follow-up, our patient remained pain-free, had no swallowing disorders, and did not require pain medication.

*Prepared by **Dr. Moreno Sánchez,** a radiation oncologist and nuclear medicine physician; **Dr. González Cazaño**, a radiation oncologist; **Drs. Mendoza and Viñals,** neurosurgeons; **Dr. Rodríguez**, a radiation oncologist and nuclear medicine physician; **Dr. Moreno Geraldo,** a radiation oncologist and medical oncologist; and **Dr. Ruiz,** a medical physicist, Unit of Radiotherapy and Radiosurgery Abreu Clinics, "CDD Radioterapia," Santo Domingo, Dominican Republic.*

IMAGING FINDINGS

We performed a brain MRI with contrast and cranial computed tomography (CT), with subsequent image fusion and stereotactic frame placement. We used the Brainlab system (iPlan; Munich, Germany) for treatment planning, and performed SRS using the Clinac 21iX linear accelerator (Varian Medical Systems, Palo Alto, California), conforming the cisternal target with 1 isocenter, 31 semi-arches and 7 arcs, all noncoplanar conformed with a 4-mm conical collimator. The prescription dose was 73 Gy to 90% isodose line, in 1 session (Figures 1 and 2).

DIAGNOSIS

Trigeminal neuralgia (TN)

DISCUSSION

In 1756, Nicolas André described TN as a "painful tic of the face;" it was also known as Trousseau's neuralgia, and later epileptiform neuralgia. TN is a facial pain disorder occurring in 4 out of 100,000 people. It typically affects patients older than 50, and is more common in women than men (1.5:1 to 2:1, respectively). TN is associated with a decreased quality of life and impaired daily function, affects employment in 34% of patients with depressive symptoms, and can be severely disabling with high morbidity.[1-3]

Initial treatment is typically oral carbamazepine, producing complete or acceptable relief in 69% of cases.[2] With prolonged use, the therapeutic response drops to 50%, despite a progressive increase in dose. Traditionally, treatment has involved additional invasive neurosurgical procedures, including microvascular decompression of the affected nerve, and various procedures to interrupt pain transmission using heat, osmotic intervention or mechanical compression.[2-4] TN was first treated with SRS by Lars Leksell in 1951. More recently, SRS has been established as a less invasive alternative to surgical procedures for patients who are refractory to medical treatment, cannot tolerate medical or surgical treatment, or who have recurrent pain.

TN is one of the fastest growing indications for SRS. From its initial use by Leksell to treat idiopathic TN, SRS has evolved as an accepted tool

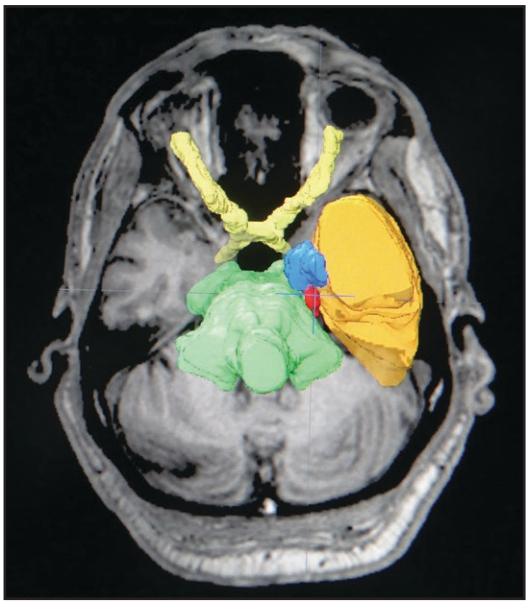

FIGURE 1. *Target and OARs delimitation.*

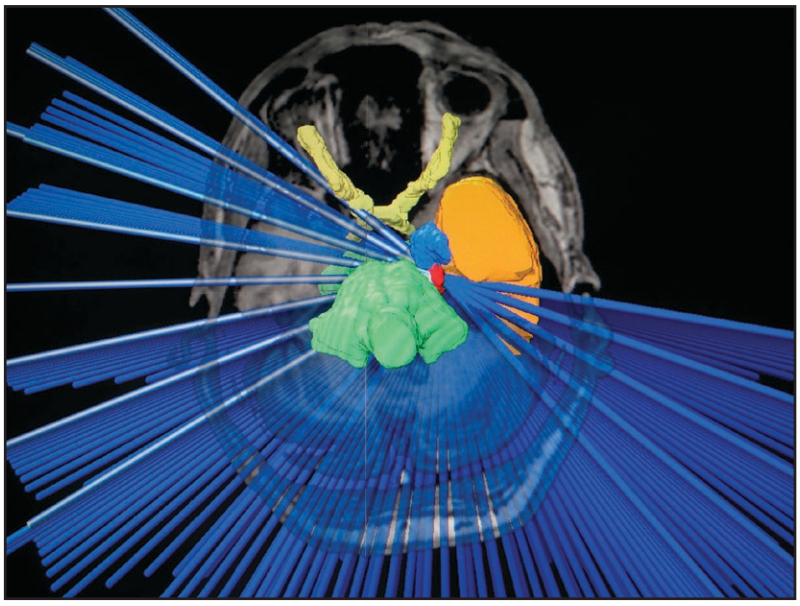

FIGURE 2. *SRS planning, caudal view, 3-dimensional reconstruction.*

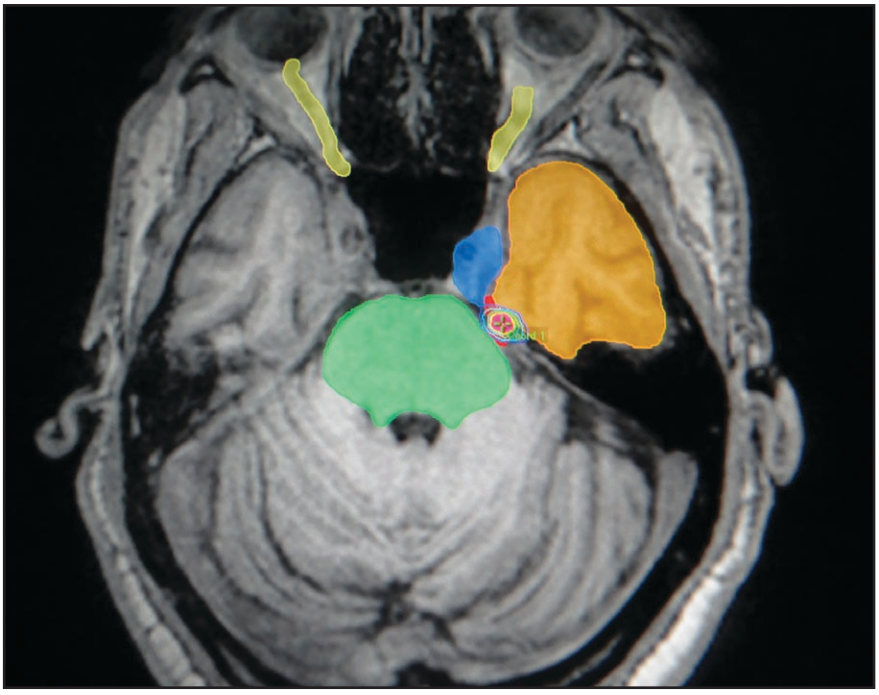

FIGURE 3. *SRS planning dosimetry.*

for functional neurosurgery. For TN, SRS is a safe, highly effective noninvasive treatment that provides initial pain relief in 75% to 89% of patients. Of note, radiosurgical studies excluding patients who previously underwent surgery demonstrated complete pain relief in 74% to 90% of patients — similar to results achieved with conventional surgery.[5]

At present, there is no data suggesting any benefit from giving a dose > 70 Gy with linear accelerator-based SRS, or to increase the length of the nerve irradiated (increase irradiated volume).[6-8] In fact, the only data available comparing patients treated with higher doses (90 Gy) vs. typical doses (70-80 Gy) showed a significant increase in patient morbidity, and no benefit in treatment response (Figures 2 and 3). Increasing treatment volume to include a longer nerve length does not significantly improve pain relief, and may increase complications such as numbness and paresthesia.

Another controversy surrounding radiosurgery for TN involves position of the target (posterior or anterior).[9] Massager et al reported excellent pain relief in 68% of patients, and satisfactory pain improvement in 83%.[10] These authors demonstrated that using an anterior target (retrogasserian - cisternal) results in fewer complications compared with a posterior target (dorsal nerve input) with the same radiation dose. As such, the target should be 5 mm to 8 mm from the brainstem to achieve an optimal balance between pain control and complications of nerve dysfunction. Whether to deliver anterior or posterior irradiation to the nerve remains unclear and is the subject of phase III studies.[9,10] The reason for comparing the anterior (distal) and proximal (more posterior) targets

Table 1. Main series of the literature, comparing published studies between Gamma Knife and linear accelerator

Study	Year	# Patients	Device%	Max Doses (Gy)			Median F/U (months)	% Patients			
				<70	70-80	>80		without pain	>90%	side effects	recurrrence
Loescher et al	2012	72	GK	0	100	0		39	71	31	-
Dos Santos et al	2011	52	LINAC	46.2	53.8	0	26.6	17.3	53.8	36	28.8
Kondziolka et al	2010	503	GK	1.6	94.9	3.4		89	89	10.5	42.9
Pusztaszeri et al	2007	17	LINAC	17	0	0	12 (2-60)	35	90	5.8	29.4
Régis et al	2006	110	GK	0	85 (70-90)		>12	83	97	10	17
Richards et al	2005	28	LINAC	0	100	0	49 (12-70)	46	61	52	23
Massager et al	2004	47	GK	0	0	100	12 (1-40)	57	75	14.2	46
Chen et a	2004	32	LINAC	37	0	67	14.1 (3-31)	40	70	17.5	17
Cheuk et al	2004	112	GK	75	0	0	8	78	87	0-9.3	-
Frighetto et al	2004	22	LINAC	70-85	17		-	80.2	89.6	5.2-10.4	-
Gross et al	2003	25	LINAC	0	0	25	18 (8-52)	76	100	32	0-44
Kannan et al	1999	6	GK	0	100	0	10 (5-16)	66	100	0	0

is to achieve better pain control and lower complication rates. Kondziolka et al considered the proximal trigeminal nerve and root entry zone an appropiate anatomical target, identified as the dorsal root entry zone (DREZ).[14,15] Marshall et al considered the concept that better pain relief occurs when the isocenter is placed closer to the brainstem. This placement results in greater denervation in the zone where peripheral myelin formed by Schwann cells transforms to central myelin formed by oligodendroglia. Meanwhile, Régis et al considered the retrogasserian zone (RGZ) an adequate target, reporting 87% pain relief in 57 patients, with maximum doses of 75 to 90 Gy.[16,17]

In a recent study of 169 essential TN patients treated with linear accelerator-based SRS, > 88% achieved significant relief, similar to reports of SRS using the Gamma Knife (Elekta, Stockholm, Sweden).[8,11,12] Of patients who received SRS as initial treatment, > 90% experienced complete pain relief. Previous treatment has been a negative prognostic indicator in other studies; our patient only received drug treatment, and had no previous surgery.

Patients usually achieve maximum pain relief 1 month after treatment. The disappearance of activation areas or frank pain relief occurs within 24 hours of treatment in up to one-third of patients, as reported in our case. Complete pain relief within 1 week of treatment has been reported in > 40% of patients. In addition, > 75% of patients with partial and complete response have responded within 3 months of treatment, and > 90% of complete responses are seen after 6 months.[5,13] No deaths, systemic complications, or induced malignancy have been reported after treating TN with SRS (Table 1).

After a 25-month follow-up, our patient remains asymptomatic. Some

reviewed studies with follow-up times of 8 to 49 months show that side effects could vary between 0% and 52%, with facial numbness as one of the most common. Improvement in pain relief, side effects and recurrence rates should not be attributed to equipment used for radiosurgery (Gamma Knife, linear accelerator, CyberKnife [Accuray, Sunnyvale, California]). Rather, a very short-term follow-up in final analysis, a diagnosis of multiple sclerosis, and previous surgical treatment of TN on the same side have been linked to a lower rate of pain control, shorter nerve, younger age, hypertension, etc. Regarding the procedure, physicians should consider the dose rate, maximum dose, location of the shot, and integrated dose to the nerve. High doses have allowed for pain relief of 90% to 95%, a relapse rate of 10% to 35%, and long-term pain relief of 70%. However, depending on shot location, loss of sensation could be 58.3%; major hypoesthesia, 19.4%; and subjective sensation of dry eye and decreased corneal reflex, 30.5%.[18,19]

CONCLUSION

SRS is currently the less invasive treatment for TN. Initial results re- garding recurrence rates and pain control seem to be in line with other surgical ablation techniques. For TN, SRS holds a unique place as a safe, noninvasive and effective treatment, providing initial relief in 75% to 89% of patients. At present, no published data suggest any benefit of >70 Gy dose, or to increase the length of the irradiated nerve. Patients without previous surgical procedures and typical symptoms are associated with better outcomes.

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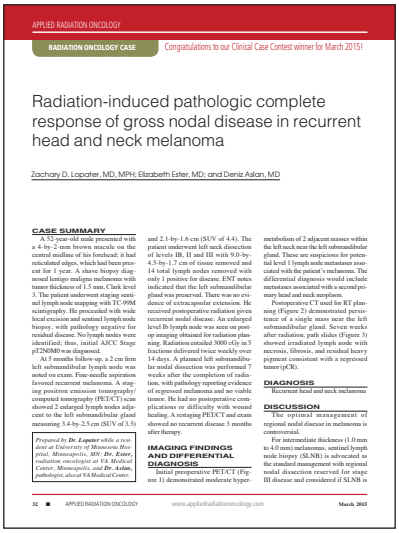
CONTEST OPPORTUNITIES



APPLIED RADIATION ONCOLOGY

RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for March 2015!

Radiation-induced pathologic complete response of gross nodal disease in recurrent head and neck melanoma

Zachary D. Lopater, MD, MPH; Elizabeth Ester, MD; and Deniz Aslan, MD

CASE SUMMARY

A 52-year-old male presented with a 4-by-2-mm brown macule on the central midline of his forehead; it had reticulated edges, which had been present for 1 year. A shave biopsy diagnosed lentigo maligna melanoma with tumor thickness of 1.5 mm, Clark level 3. The patient underwent staging sentinel lymph node mapping with TC-99M scintigraphy. He proceeded with wide local excision and sentinel lymph node biopsy, with pathology negative for residual disease. No lymph nodes were identified; thus, initial AJCC Stage pT2N0M0 was diagnosed.

At 5 months follow-up, a 2 cm firm left submandibular lymph node was noted on exam. Fine-needle aspiration favored recurrent melanoma. A staging positron emission tomography/computed tomography (PET/CT) scan showed 2 enlarged lymph nodes adjacent to the left submandibular gland measuring 3.4-by-2.5 cm (SUV of 3.5) and 2.1-by-1.6 cm (SUV of 4.4). The patient underwent left neck dissection of levels IB, II and III with 9.0-by-4.5-by-1.7 cm of tissue removed and 14 total lymph nodes removed with only 1 positive for disease. ENT notes indicated that the left submandibular gland was preserved. There was no evidence of extracapsular extension. He received postoperative radiation given recurrent nodal disease. An enlarged level Ib lymph node was seen on post-op imaging obtained for radiation planning. Radiation entailed 3000 cGy in 5 fractions delivered twice weekly over 14 days. A planned left submandibular nodal dissection was performed 7 weeks after the completion of radiation, with pathology reporting evidence of regressed melanoma and no viable tumor. He had no postoperative complications or difficulty with wound healing. A restaging PET/CT and exam showed no recurrent disease 3 months after therapy.

Prepared by ***Dr. Lopater*** *while a resident at University of Minnesota Hospital, Minneapolis, MN;* ***Dr. Ester****, radiation oncologist at VA Medical Center, Minneapolis, and* ***Dr. Aslan****, pathologist, also at VA Medical Center.*

IMAGING FINDINGS AND DIFFERENTIAL DIAGNOSIS

Initial preoperative PET/CT (Figure 1) demonstrated moderate hypermetabolism of 2 adjacent masses within the left neck near the left submandibular gland. These are suspicious for potential level I lymph node metastases associated with the patient's melanoma. The differential diagnosis would include metastases associated with a second primary head and neck neoplasm.

Postoperative CT used for RT planning (Figure 2) demonstrated persistence of a single mass near the left submandibular gland. Seven weeks after radiation, path slides (Figure 3) showed irradiated lymph node with necrosis, fibrosis, and residual heavy pigment consistent with a regressed tumor (pCR).

DIAGNOSIS

Recurrent head and neck melanoma

DISCUSSION

The optimal management of regional nodal disease in melanoma is controversial.

For intermediate thickness (1.0 mm to 4.0 mm) melanomas, sentinel lymph node biopsy (SLNB) is advocated as the standard management with regional nodal dissection reserved for stage III disease and considered if SLNB is

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CLINICAL CASE CONTEST

ARO's quarterly Clinical Case Contest is an excellent opportunity to share your thoughts on management of a controversial or uncommon situation. Enter your clinical case for review by an international audience of your peers and the ARO advisory board, and a chance to win a $250 American Express Gift Card. The winning case will be published in the next issue of *Applied Radiation Oncology.*

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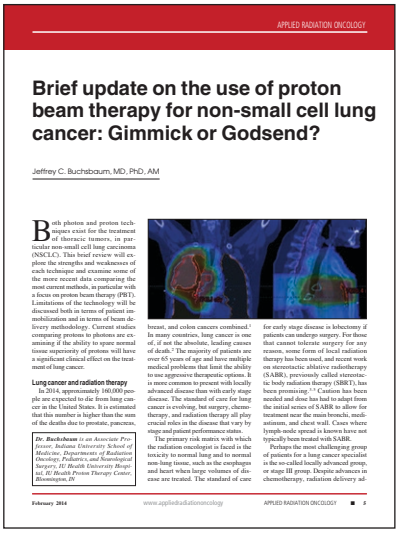

APPLIED RADIATION ONCOLOGY

Brief update on the use of proton beam therapy for non-small cell lung cancer: Gimmick or Godsend?

Jeffrey C. Buchsbaum, MD, PhD, AM

Both photon and proton techniques exist for the treatment of thoracic tumors, in particular non-small cell lung carcinoma (NSCLC). This brief review will explore the strengths and weaknesses of each technique and examine some of the more recent data comparing the most current methods, in particular with a focus on proton beam therapy (PBT). Limitations of the technology will be discussed both in terms of patient immobilization and in terms of beam delivery methodology. Current studies comparing protons to photons are examining if the ability to spare normal tissue superiority of protons will have a significant clinical effect on the treatment of lung cancer.

Lung cancer and radiation therapy

In 2014, approximately 160,000 people are expected to die from lung cancer in the United States. It is estimated that this number is higher than the sum of the deaths due to prostate, pancreas,

breast, and colon cancers combined.[1] In many countries, lung cancer is one of, if not the absolute, leading causes of death.[2] The majority of patients are over 65 years of age and have multiple medical problems that limit the ability to use aggressive therapeutic options. It is more common to present with locally advanced disease than with early stage disease. The standard of care for lung cancer is evolving, but surgery, chemotherapy, and radiation therapy all play crucial roles in the disease that vary by stage and patient performance status.

The primary risk matrix with which the radiation oncologist is faced is the toxicity to normal lung and to normal non-lung tissue, such as the esophagus and heart when large volumes of disease are treated. The standard of care for early stage disease is lobectomy if patients can undergo surgery. For those that cannot tolerate surgery for any reason, some form of local radiation therapy has been used, and recent work on stereotactic ablative radiotherapy (SABR), previously called stereotactic body radiation therapy (SBRT), has been promising.[3,4] Caution has been needed and dose has had to adapt from the initial series of SABR to allow for treatment near the main bronchi, mediastinum, and chest wall. Cases where lymph-node spread is known have not typically been treated with SABR.

Perhaps the most challenging group of patients for a lung cancer specialist is the so-called locally advanced group, or stage III group. Despite advances in chemotherapy, radiation delivery ad-

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