APPLIED RADIATION ONCOLOGY™
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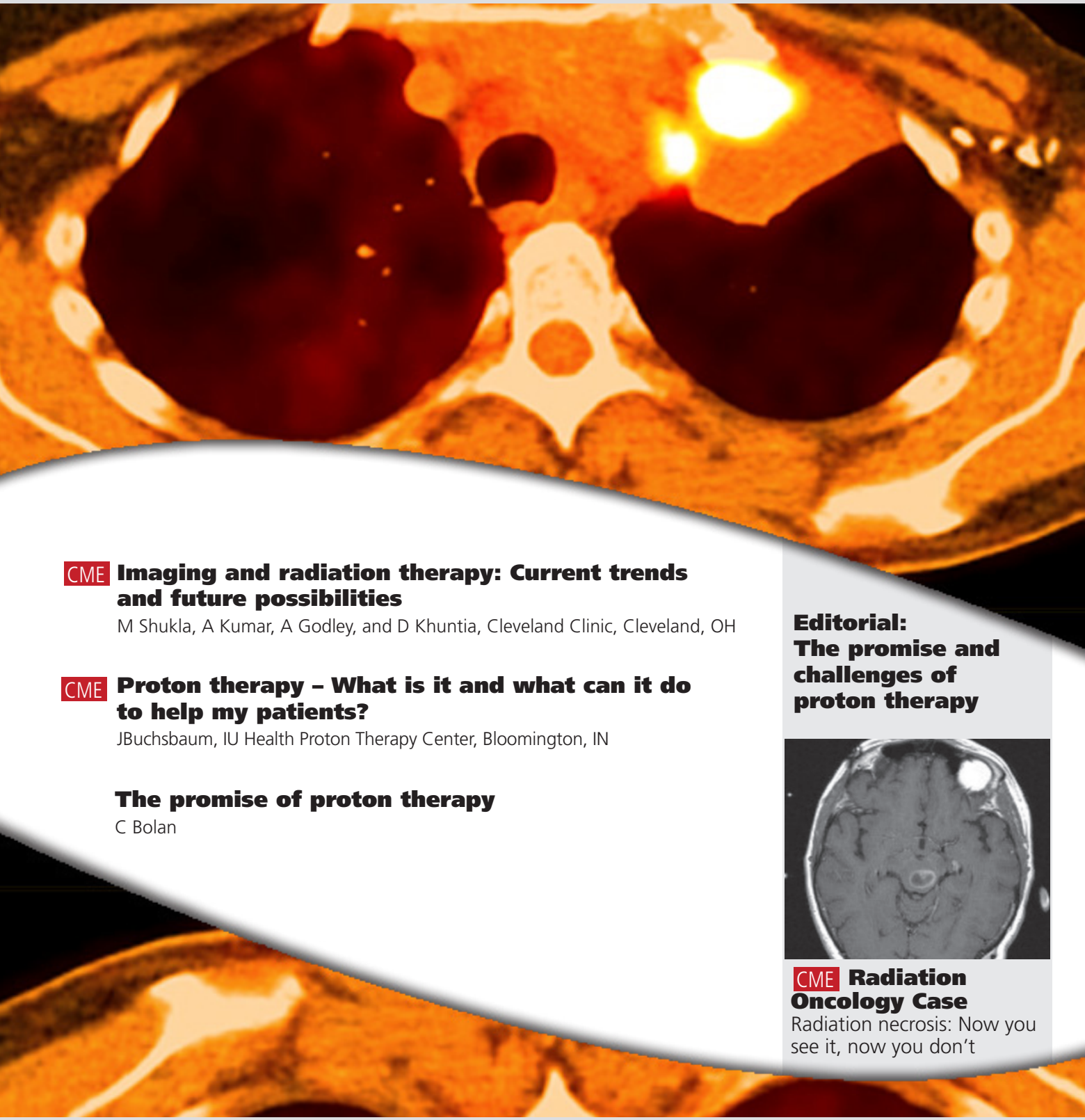

CME **Imaging and radiation therapy: Current trends and future possibilities**
M Shukla, A Kumar, A Godley, and D Khuntia, Cleveland Clinic, Cleveland, OH

CME **Proton therapy – What is it and what can it do to help my patients?**
JBuchsbaum, IU Health Proton Therapy Center, Bloomington, IN

The promise of proton therapy
C Bolan

Editorial: The promise and challenges of proton therapy

CME **Radiation Oncology Case**
Radiation necrosis: Now you see it, now you don't

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

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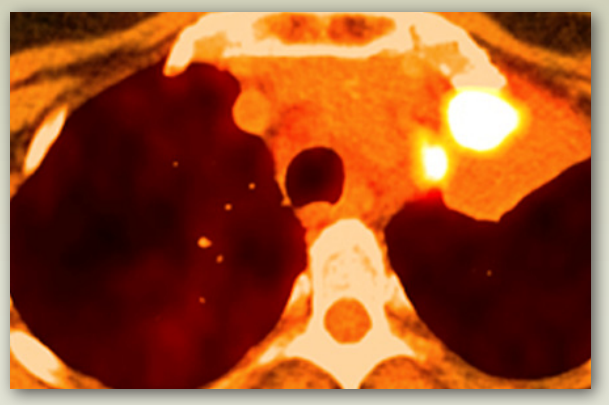

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CME Information

Activity description

In this issue of *Applied Radiation Oncology*, our faculty has assembled a number of articles and cases that we feel provide practical insight to radiation oncology professionals on topics, including proton beam radiation therapy, imaging in radiation treatment planning, management of radiation necrosis post-stereotactic radiosurgery, and acoustic neuroma.

Learning objectives

After reviewing this activity, participants will:

- Understand the basic differences between a photon beam and a proton beam, including cost considerations.
- Understand the accurate interpretation of radiation necrosis post-stereotactic radiosurgery treatment on T1 axial contrast-enhanced MRI.
- Understand the current and future methods of imaging in radiation treatment planning and delivery.
- Understand the management of radiation necrosis post-stereotactic radiosurgery.
- Understand the accurate interpretation of acoustic neuroma on T1W post-contrast MRI.
- Understand the epidemiology, pathophysiology, clinical presentation, and treatment of acoustic neuroma.

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Principal faculty and their credentials

Jeffrey C. Buchsbaum, MD, PhD, AM, Associate Professor, Indiana University School of Medicine, Departments of Radiation Oncology, Pediatrics, and Neurological Surgery, IU Health University Hospital, IU Health Proton Therapy Center, Bloomington, IN.

Monica Shukla, MD, is a PGY-4 Radiation Oncology Resident, Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH.

Sameera S. Kumar, BS, Medical Student, West Virginia University School of Medicine in Morgantown, WV.

Alan Lee, BS, Medical Student, State University of New York - Upstate Medical University, Syracuse, NY.

Target audience

Radiation oncologists, surgical oncologists, radiologists, and oncological imaging physicians.

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EDITORIAL

The promise and challenges of proton therapy

John Suh, MD, Editor in Chief

This so-called "medical arms race" by major medical centers and institutions to offer patients the latest in radiation oncology technology has greatly heightened the perception and expectations of this treatment.

Welcome to the first-quarter edition of Applied Radiation Oncology 2013! I hope everyone has fully recovered from various holiday festivities and is keeping up with their New Year's resolutions thus far.

In this edition, one of our articles deals with the promise of proton therapy, an emerging and expensive treatment option for cancer patients. Given its high acquisition and current treatment costs, and large space requirements, its potential promise has been under scrutiny, especially given the lack of prospective trials demonstrating clear benefit over other less expensive radiation treatment options that are available.

The keen interest in proton therapy is based on theoretical advantages, which include the precise delivery of radiation at a depth in the body using a spread out Bragg Peak (SOBP). This can reduce exposure to normal tissue and possibly minimize side effects. Unfortunately, little consensus exists on whether the dosimetric advantages translate to better outcomes, except for pediatric cancers, and skull base and sacral tumors. Currently, protons are used for a number of cancers, including brain, prostate, lung, esophagus, breast, and head and neck.

As we move toward comparative effectiveness research, value-based medicine, care paths, and emphasis on continuum of care, the value and benefit from protons will undergo additional scrutiny. Despite these concerns, acquisition of this technology has continued to increase. This so-called "medical arms race" by major medical centers and institutions to offer patients the latest in radiation oncology technology has greatly heightened the perception and expectations of this treatment. Since the initial costs are roughly twice that of conventional radiation treatment options, the costs associated throughout a patient's lifetime need to be factored in to help make the case for protons. Ultimately, prospective, randomized studies comparing proton therapy to intensity-modulated radiation therapy need to be completed to provide level I evidence that supports or refutes the wider adoption of protons.

In the future, the development of compact units, which are less expensive and have smaller footprints, may provide sufficient cost savings and increase its overall value, thus improving accessibility to more patients. The incorporation of intensity-modulated proton therapy (IMPT) should help optimize the therapeutic ratio, enhance efficiencies, and allow for hypofractionation, which should further drive down costs and augment the value proposition for protons.

In my opinion, it is important that current and future users of this technology participate in clinical trials, apply this treatment modality judiciously, and conduct treatment and follow-up that can assess the true value of this therapy to patients and society. This will allow proton therapy to more fully reach its potential as a valuable and effective treatment to help fight cancer. .

Sincerely,

John Suh, MD, FASTRO, FACR

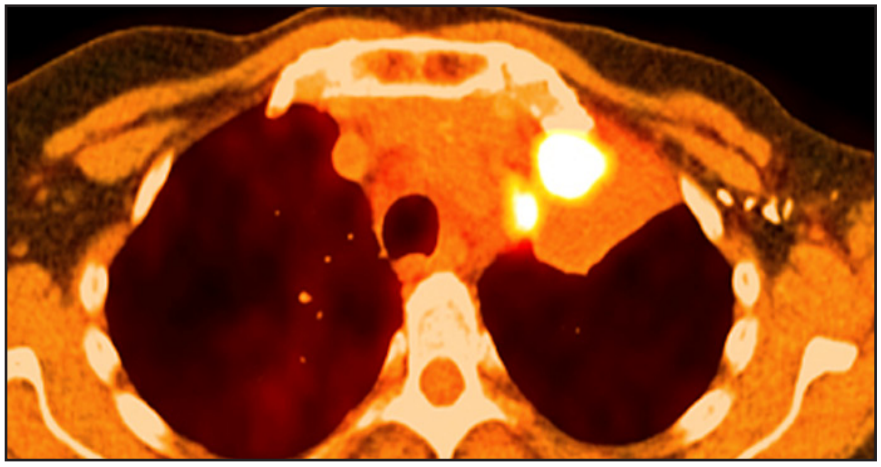
Dr. Suh is the Editor-in-Chief of Applied Radiation Oncology, *and Professor and Chairman, Dept. Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

CME SEE PAGE 3 FOR DETAILS

Imaging and radiation therapy: Current trends and future possibilities

Monica Shukla, MD, Aryavarta Kumar, MD, PhD, Andrew Godley, PhD, and Deepak Khuntia, MD

We have seen a tremendous boom in medical imaging use from the diagnostic side, but over the last decade, the technology has shown increased utilization in the therapeutic delivery of radiation. In this review, we summarize medical imaging's current role and future possibilities in both the planning and delivery of therapeutic radiation.



Imaging in treatment planning

Fluoroscopy and computed tomography

Early radiotherapy planning was based on body surface landmarks alone. Conventional or fluoroscopic simulation acquires 2-dimensional (2D) images for radiotherapy planning based on internal anatomic landmarks and limited tissue-density information. Computed axial tomography (CT) became available in the 1970s, but the developments in computer processing speed, memory, and applications specifically for use in radiotherapy did not allow CT simulation to become feasible until the late 1990s.[1] To compare traditional to modern techniques, a study was conducted of 30 patients whose cancer treatments were planned with surface markings, fluoroscopy, and CT simulation.[2] The authors showed that CT simulation increased the dose to the target and reduced the dose to surrounding normal structures more significantly than the older technologies using surface markers and fluoroscopy. The current standard in most countries is CT-simulator-based treatment planning for optimal coverage of target volumes and sparing of normal structures, although fluoroscopy simulation is still widely used in developing countries.

***Dr. Shukla** is a PGY-4 Radiation Oncology Resident, **Dr. Kumar** is a Radiation Oncology Resident, and **Dr. Godley** is a Physicist, Department of Radiation Oncology, Cleveland Clinic Foundation, Cleveland, OH; and **Dr. Khuntia** is a Radiation Oncologist and President at Spectrum Physics Corporation, Los Altos, CA.*

Magnetic resonance imaging

Magnetic resonance imaging (MRI) is a valuable cross-sectional imaging modality known for its superior soft-tissue delineation as compared to CT. Images are produced based on the interaction between hydrogen nuclei within tissues and a large external magnetic field, as well as radiofrequency bursts, which manipulate the spin of the hydrogen nuclei. Image acquisition parameters can be modified to enhance tumor characteristics (vascularity, extent of infiltration, peritumoral edema, etc). MRI is routinely used in treatment planning for primary and

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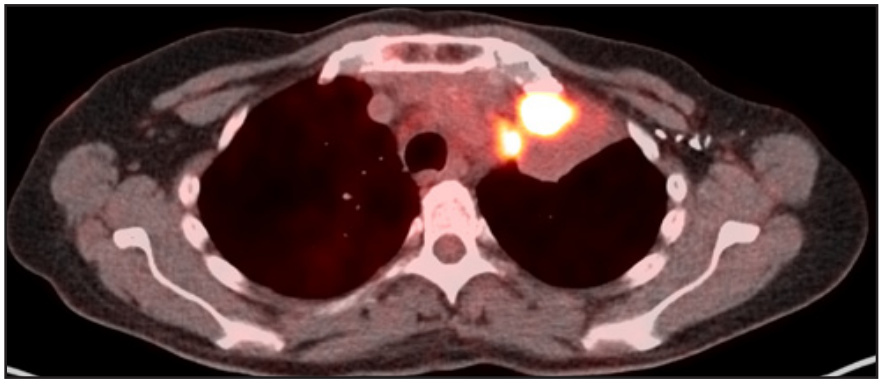

FIGURE 1. *FDG PET/CT image of a 55-year-old female with stage IIIA NSCLC. There is a hypermetabolic lesion in her left upper lobe, max SUV 18.3. The mass is compressing her left bronchus (not shown), resulting in an adjacent soft-tissue density consistent with left upper-lobe collapse. PET nicely differentiates tumor mass from atelectasis.*

secondary tumors of the brain and spine.[3] It allows better visualization of lesions near bone and is particularly helpful in diagnosing and treating lesions in the posterior fossa. For brain metastases, MRI is much more sensitive than CT, particularly at identifying small lesions (≤ 0.5 cm).[4] The ability to visualize these lesions prevents patients from aggressive definitive-intent local therapies and also allows these lesions to be targeted by techniques such as stereotactic radiosurgery, which can be delivered with submillimeter accuracy. Additionally, MRI is used for treatment planning in gastrointestinal,[5] genitourinary,[6] head and neck,[7] gynecologic,[8] and sarcomatous tumors[3] because its high soft-tissue contrast allows the assessment of extent and spread of disease, which ultimately influences radiation treatment volumes. One drawback of MRI for radiation planning is that it lacks the electron density information required for calculating photon attenuation so co-registration with a CT is usually required for planning purposes.

Positron emission tomography

Positron emission tomography (PET) is a type of molecular imaging that allows measurement of a metabolic process within tissues. In PET, the subject is injected with a radioactive isotope (eg, fluorodeoxyglucose, ^{18}F-FDG), which undergoes positron decay. The positron emitted travels for a short distance within tissues and interacts with an electron. Both particles are annihilated and produce a pair of 511-keV gamma photons, emitted 180 degrees apart. Photon pairs are collected and can be localized to point source within the tissue.[9] PET scans are co-registered to CT scans, which provide detailed anatomic information. Ideally, a PET scan is done at the time of CT simulation with the patient in the planned treatment position. If integrated PET/CT simulation is not available, a PET scan can be done at a later date with the patients positioned in their custom-created immobilization device. A common but less ideal scenario is when a diagnostic PET scan and a CT simulation are done in different positions. In this case, both sets of images are coregistered or "fused" as closely as possible.[10]

PET can add several key pieces of information for the radiation oncologist. PET often identifies targets not easily visualized on CT or MRI, such as satellite tumor lesions and lymph node metastases, which would alter radiation treatment volumes. It also allows exclusion of targets that appear ambiguous on CT, but are, with fair certainty, negative on PET. PET also allows alteration of radiation volumes and doses based on response to other antineoplastic therapies, such as in lymphoma treatment.[10]

^{18}F-FDG is the most commonly used radiotracer in combination with PET. ^{18}F-FDG is a glucose analogue taken up by cells via glucose transporters. After entering the cell, ^{18}F-FDG is phosphoryated by an enzyme called hexokinase, resulting in the molecule being trapped within cells. FDG accumulates in tissues with high cellular activity requiring increased glucose uptake and consumption. Particularly upregulated in tumor cells is the inefficient glycolytic pathway that is preferentially used for ATP generation.[11] ^{18}F-FDG uptake is not specific for tumor cells; it also localizes within inflamed and infected tissues that are also metabolically active and depend heavily on the glycolysis pathway.

Since the mid-1990's, several studies have shown that ^{18}F-FDG -PET increases the sensitivity and specificity of CT to properly stage cancers locally, regionally, and distantly. As such, PET often saves patients from unnecessary surgery or other aggressive treatments[12] and increases the accuracy of locoregional therapies. Several ^{18}F-FDG-PET studies were evaluated against standard imaging modalities, such as x-ray and CT for the definition of radiation treatment volumes. Use of FDG-PET in the target volume definition has been best studied in nonsmall cell lung cancer. On the whole, these studies suggest ^{18}F-FDG-PET can influence the definition of the gross target volume (GTV) in most cases[13-16] Particularly helpful in NSCLC lung cancer is PET's ability to discern atelectatic lung tissue from tumor mass and, with a higher sensitivity, to detect lymph-node metastases in the chest (Figure 1).[17-20] The main drawback of PET is its limited resolution for detecting tumors or lymph nodes with a diameter < 1 cm , unless the SUV is at least 4 times background levels.[10] Another area of controversy is the definition of the edge of the PET tumor volume, as the volume is greatly affected by windowing and thresholding.[21,22] For this reason, protocols must

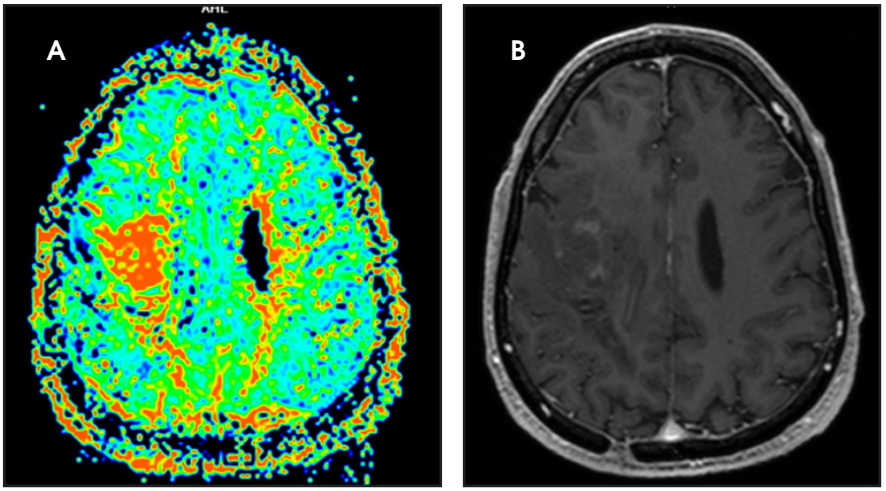

FIGURE 2. *This is a 54-year-old male (A) with a right frontal low-grade astrocytoma noted to have accelerated progression of the tumor 17 years after initial diagnosis. MRI (B) with contrast (bottom image) shows increased patchy enhancement in the right frontotemporal mass. There is increased CBV in the same area with a rough relative CBV ratio of 3.0:3.5, compared to the contralateral cerebral white matter indicating tumor progression (top image).*

use a clearly defined process for contouring tumors based on PET information. The most recent phase III NSCLC RTOG protocol 0617 recommended, but did not require, PET for planning purposes. If PET was used, tissues with a pretreatment SUV of > 3 were included in the GTV. Just as in NSCLC, PET is more sensitive than CT alone for detection of lymph node metastases in head and neck cancers, which is critical for dose and volume determination.[23] The specificity of PET, however, is reduced, as it will also detect inflammatory processes in lymph nodes and other lymphatic tissues. Also critical in treatment of head and neck cancers is the need for the planning PET to be done in the treatment position so that CT and PET targets match.[24] PET is also regularly used in diagnosis and treatment planning for SCLC,[25] esophageal cancer,[26,27] and lymphoma.[28,29]

Future trends

Dynamic contrast-enhanced CT/MRI

Dynamic contrast-enhanced (DCE) CT and MRI imaging allows visualization of vasculature within tumors and surrounding tissues. Vascular properties that can be examined include blood flow, blood volume, and permeability.[30] Blood vessels formed in angiogenesis are imperfect, displaying tortuosity and high permeability. In malignant gliomas, cerebral blood volume (CBV) and permeability assessed by DCE are consistently linked to worse outcomes. Several studies have related high-tumor CBV or a fraction of the tumor volume that has a high CBV with a shorter time to progression and worse overall survival (Figure 2).[31,32] CBV has been used during a course of RT to assess early treatment response.[33] With this information, additional radiation dose can be targeted to those to areas, which appear to have more neovascularization, indicating high tumor activity and aggressiveness. Despite neovascularization, areas of the tumor may still be inadequately perfused and hypoxic due to the poorly functioning nature of these vessels. Hypoxic tumors are more resistant to radiotherapy.[11] Several studies investigated DCE-MRI to identify poorly enhancing tumors, indicating areas of hypoxia that may be resistant to radiotherapy. A study in cervical cancer showed local control and overall survival were better in those with minimal areas of poor enhancement versus those patients with large areas of enhancement.[34] Similar studies have been done in SCC of the head and neck, relating poor tumor perfusion as assessed by DCE-CT/MRI with increased local recurrence.[35,36] The barrier to widespread use of DCE imaging is the lack of standardized imaging protocols that specify parameters for image acquisition, quantification of the results, and quality control for reproducibility and accuracy of the acquired images.[30] Several efforts are under way to address these technical issues and despite these hurdles, DCE imaging is currently being evaluated in over 40 clinical studies in the United States.

18F-fluorothymidine PET (FLT-PET)

The nonspecificity of FDG-PET for cancer cells has led to interest in other radiotracers such as 3′-deoxy-3′-[(18) F]fluorothymidine (FLT). FLT is selectively taken up by proliferating cells via various nucleoside transporters to be used in the pyrimidine salvage pathway, which is upregulated in the S-phase. After entering the cell, it is phosphylated by thymidine kinase 1 (TK1), trapping it within the cell.[37] Pathologically, FLT uptake has been correlated with rate of cellular proliferation, and markers thereof such as Ki-67.[38] An advantage that FLT has over FDG is the specificity for identifying actively replicating tissue. As mentioned above, FDG is not specific for proliferating tissues and is often taken up by normal tissue, leading to more false-positives. However, the converse of that is also true with FLT in some series, leading to more false-negative results. One particular example is if a tumor cell switches to synthesizing pyrimidines bases de novo, and not via the salvage pathway, FLT will not be taken up by actively dividing cells.[37] Despite these caveats, FLT is still a promising radiotracer being evaluated in several body sites for assessment to treatment response. Several studies have shown that FLT

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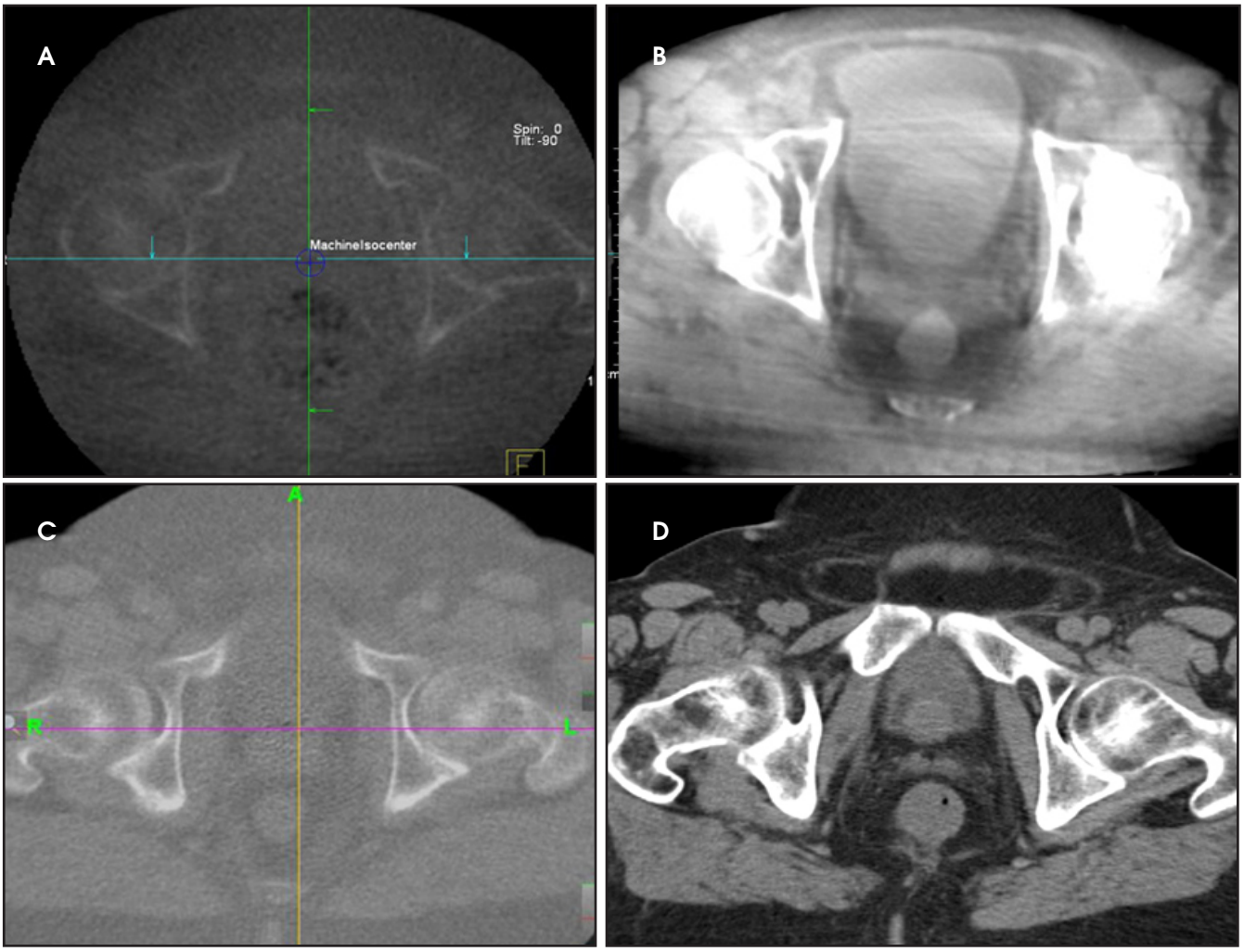

FIGURE 3. *IGRT image quality comparison. Clockwise from top left, MV CBCT (A), kV CBCT (B), kV FBCT (C), and MV FBCT (D) axial slice of separate prostate patients. MV images courtesy of N. Morrow, Medical College of Wisconsin, Milwaukee, WI.*

uptake declines earlier and more significantly than does FDG uptake. This has been shown following single-fraction radiotherapy in vitro, as well as in experimental models of esophageal carcinoma following docetaxel plus radiation.[39,40] Clinically, the level of FLT uptake reduction has been correlated to partial and complete response to chemotherapy in non-Hodgkin's lymphoma patients.[41] In oropharyngeal cancer patients, FLT showed a two-fold decrease in uptake in the first 2 weeks after initiation of RT and another two-fold decrease by week 4 into treatment. Due to the early response, the authors of this study proposed that the tumor subvolume with continued ^{18}F-FLT uptake could be selectively targeted with increased radiation dose.[42]

Copper(II)-diacetyl-bis(N4-methylthiosemicarbazone) PET (Cu-ATSM PET)

Tumors are heterogeneous populations known to contain hypoxic areas. Hypoxia stimulates angiogenesis and tumor progression and also confers resistance to tumor directed therapies.[43] With radiation therapy in particular, several studies have shown that dose-escalation may be one way to overcome this resistance to therapy.[11] Cu(II)-diacetyl-bis(N^4-methylthiosemicarbazone (Cu-ATSM) is a radiotracer that can identify hypoxic areas within tumor cells potentially allowing clinicians an opportunity to intensify local therapy to these areas.[44] Cu-ATSM was first reported in 1997 as a copper chelate that localized within ischemic cardiac myocytes while washing out of normoxic muscle.[45] Several early animal studies confirmed that ATSM accumulation was dependent on tumor oxygen tension.[46] Chao et al demonstrated the feasibility of using coregistered CT and CuATSM PET images to create an hGTV or a hypoxic tumor subvolume for selective dose escalation in a patient with node positive SCC of the right tonsil/BOT.[47] Since then, Cu-ATSM

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Table 1. Summary and comparison of IGRT techniques. Time includes the execution of both imaging and registration. Residual error, which reflects the relative accuracy of the modality, is calculated for breast in optical tracking, external markers for IR tracking, and prostate for all others.

Modality	Dose (cGy)	Time (min)	Residual error (mm)	Real-time	Notes	Examples
Ultrasound	NA	5-10	6	In development	User dependent, transducer can distort anatomy being imaged	Clarity, BAT, SonArray
MV Planar	1-5	2-4	5	In development	Potential exit dose measurement, treatment delivery verification	EPIDs
kV Planar	0.1-0.5	1-2	1.5	Yes	Imaging planes at 45° to orthogonal	Exactrac, Cyberknife
MV CBCT	5-20	4-6	4.5	No	Common isocenter, low soft-tissue resolution	Mvision
kV CBCT	1-3	4-6	3	No	No common isocenter, good soft-tissue resolution	XVI, OBI
MV CT	1-2	4-7	4	No	Reduced metal artifacts	TomoTherapy
kV CT	1-3	5-8	2.5	No	Needs markers to transfer treatment isocenter to CT	CTVision, ExaCT
IR tracking	NA	0.5-1	0.5	Yes	Registration of external surrogates not target	ExacTrac, DynaTrac, Cyberknife
Optical	NA	0.5-1	3	Yes	Skin needs to be visible, matches surface	AlignRT
RF tracking	NA	3-5	1.5	Yes	Requires implanted fiducials, special couchtop	Calypso, MicroPos
MRI	NA	1-10	—	In development	Special accelerator and treatment room	ViewRay, MRI-on-Rails

uptake has been studied as a predictor of response to chemoradiotherapy in several body sites, including the rectum,[48] cervix,[49,50] and head and neck.[51] One study in locally advanced head and neck cancer found that at 2 years post-chemoradiotherapy, pretreatment SUV max on Cu-ATSM PET/CT differed significantly between those patients that remained NED and those that had recurrent or residual disease, suggesting that the degree of pretreatment Cu-ATSM uptake is predictive of response to definitive chemoRT. No significant difference was seen between these two groups on FDG-PET.[52] Cu-ATSM is a promising radiotracer and is currently the subject of several pilot studies to assess its utility in NSCLC, brain metastases, head and neck cancer, prostate cancer, and esophageal cancer.

Imaging during treatment

The goal of image guidance during radiotherapy is to ensure proper targeting and delivery of radiation. Radiation planning, margins, and patient immobilization setups are very important and work alongside image-guided radiation therapy (IGRT) to assist with proper delivery.[53] Table 1 summarizes differences between IGRT techniques.

IGRT using ionizing radiation

Megavoltage (MV) and kilovoltage (kV) photon imaging are commonly used in today's radiation oncology practices.[54,55] Traditionally, port films were used to verify anatomic setup and were later replaced by electronic portal image devices (EPIDs) as quick snapshots of patient position and field shape that utilized low doses of MV radiation. These images represent a 2D projection of a patient with poor soft-tissue resolution. To improve on this, tomography technology was developed to help with 3D IGRT, and kV imaging was introduced to help with soft-tissue resolution.

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Peripheral kV imaging improves the contrast of anatomy over MV due to the larger range of attenuation of kV photons in tissue. However kV systems require accurate calibration to the treatment isocenter. For 3D imaging, cone-beam CT (CBCT) is reconstructed using a 'cone' of photons rotating around the patient, imaging an entire 10- to 30-cm section at once, while in conventional CT, the 3D image is formed by translating the patient and imaging only a few slices at a time with a 'fan' beam (FBCT). Due to the large width of the cone beam used to image the patient, considerable photon scatter degrades the CBCT image compared to the conventional CT image. The CBCT technologies can have energies in the kV or MV range with the caveat that kV technology is a peripheral imaging device. Tomotherapy (Accuray Inc, Sunnyvale, CA) uses a narrow fan beam for imaging, but with MV photons. For the best image quality, CT on rails places a diagnostic CT scanner in the treatment vault.[55-57] The difference between mega- and kilo-volt and cone- and fan-beam is illustrated in Figure 3. It should be noted that choice of IGRT depends on the target and surrounding structures. For example, the most efficient IGRT for a tumor adjacent to the vertebral column would be a plain film, however, an intra-abdominal tumor surrounded by soft tissue would benefit the most from CT-based imaging.

IGRT using nonionizing energies

Sonography is a common IGRT modality requiring a probe in the appropriate position to aid setup before treatment commences. These images can be combined with CT-based imaging to help visualize the target. Real-time sonography with the transducer held in place by a robot during treatment is under development. In general, sonography provides the lowest resolution of IGRT and does have a learning curve, but is easy to set up, reduces the patient's exposure to ionizing radiation seen with other IGRT modalities, and clinically, it has been used in breast and prostate radiotherapy treatments.[58] Infrared (IR) tracking uses external reflective markers either directly on the patient, or on a stereotactic frame, as a proxy to track target motion. Similarly, optical tracking matches surface anatomy and so is limited to treatment regions close to the surface, such as in the breast. Radiofrequency targeting, such as Calypso (Varian Medical Systems, Palo Alto, CA), offers a method for real-time tracking and is FDA approved for use in prostate cancer patients[59] and was recently approved for use with skin-based fiducial markers.

MRI-based systems could offer the next step to increasing soft-tissue delineation. Technological challenges are being worked out, including the interference between the RF signals from the MRI coils and the RF pulses from the electron acceleration in the linac and the magnetic field's disruption of the treatment beam. ViewRay (View Ray, Inc., Cleveland, OH) has a product that uses 3 Co-60 teletherapy units and a split-magnet MRI system to offer real-time imaging during treatment. These systems are being constructed in a few centers in the United States. Other technology, such as PET-based IGRT, is currently under development.

Conclusion

We have summarized the current use of imaging in radiation oncology. As technology has evolved on the hardware side, there is a growing desire to increase the therapeutic ratio on the radiation delivery side of cancer care. We are now able to deliver radiation to submillimeter accuracy, further sparing normal tissues beyond what has ever been done before. Further, there has been a growing trend to hypofractionate (reducing the number of treatments while increasing the dose per treatment). This growing demand has resulted in a higher demand for imaging in daily radiation practices.

The future of imaging in radiotherapy also is exciting. As coined by Bentzen, the new field of "theragnostics" in radiotherapy that is in its infancy.[60] With the advent of theragnostics, advanced imaging techniques, such as FLT-PET, DCE CT/MRI, and Cu-ATSM imaging, may allow us to tailor our radiotherapy based on the response to initial chemotherapy and radiation treatment, further enhancing our ability to improve the therapeutic ratio.

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Proton therapy – What is it and what can it do to help my patients?

Jeffrey C. Buchsbaum, MD, PhD, AM

The birth of proton beam therapy could be designated as the publication, by Robert R. Wilson in his 1946 manuscript, of the concept of using the unique advantages relative to photons.[1] Twelve years later, a team from the Lawrence Berkeley National Laboratory in California published the first series of human treatments in 1958.[2] Many other forms of particle therapy, such as anti-proton, neon, carbon, oxygen, and neutron, have also been studied.[3-7] The most common type of particle therapy in use is electron therapy. It has far less mass than other particles and is not the subject of this essay because its lack of mass makes it unable to share in the dramatic physical advantage that heavier charged particles can demonstrate in the clinic; ie, very rapid stopping of the beam.

Dr. Buchsbaum *is an Associate Professor, Indiana University School of Medicine, Departments of Radiation Oncology, Pediatrics, and Neurological Surgery, IU Health University Hospital, IU Health Proton Therapy Center, Bloomington, IN.*

Rather, this review article focuses on proton therapy, currently the most common, clinically used heavy charged particle therapy worldwide. Indeed, it is now available to a large portion of patients being considered for advanced radiation treatment techniques.

The critical aspect of proton beam therapy—all heavy charged particles, really—that interests clinicians so greatly is its pronounced physical property known as the Bragg peak (Figure 1). The use of proton beams in the clinic is typically made up of a sum of multiple, single 2-mm- to 3-mm-thick pristine beams, or Bragg peaks. In Figure 1, 12 such peaks are shown to make one broader peak called a spread-out Bragg peak (SOBP). The shape of the SOBP is tailored to mimic the shape and location of a tumor as outlined by the treating physician. No clinician today would use a single x-ray beam to treat a tumor, so the demonstrated beam comparison in Figure 1 is an oversimplification of how things are actually done in the clinic for photons (conventional x-rays). Proton beam therapy is used because abruptly stopping the beam in a controllable fashion allows significant avoidance of normal structures while delivering high doses of therapy to tumors. Proton therapy is also used because its biology is similar, in dosimetric terms, to photons, with the relative biologic effect (RBE) felt to be about 1.1 relative to cobalt dose, making dosimetry use simpler than the higher RBE neutron, which lacks the Bragg peak.[8]

The simplest type of common tumor treated by both protons and photons is prostate cancer. In current prostate cancer therapy, lateral proton beams are typically used and multiple (usually 5 to 9) photon beams are used with intensity-modulated radiation therapy (IMRT) via a multi-leaf collimator (MLC). Thus, one typically

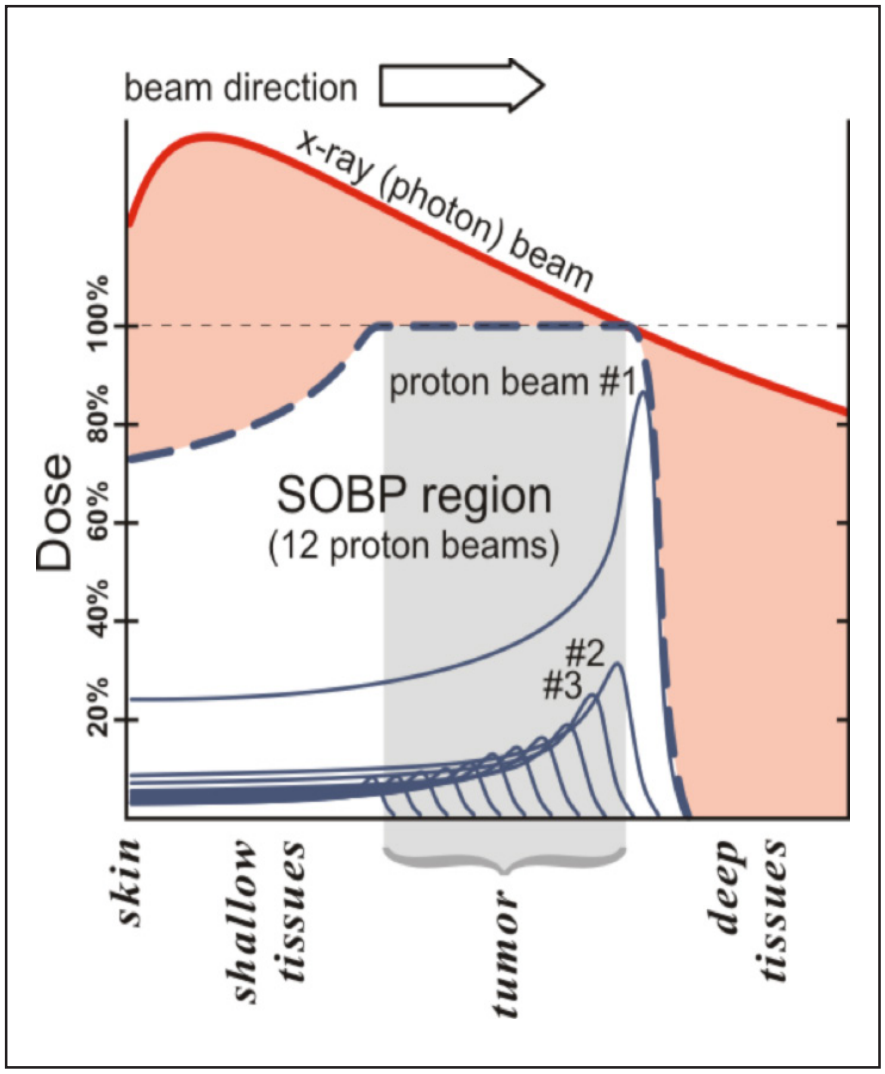

FIGURE 1. *The plot compares a single photon beam depth dose curve in matter to a single Bragg curve with its sharp peak and then to a sum of Bragg curves with different energies and proportions weighted to get the spread-out Bragg peak (SOBP) shown that covers a tumor's depth.*[32]

delivers half the dose via one beam in protons and 20% or less dose in photons. Because of this, the relatively high entry doses with photons, such as those shown in Figure 1, are mitigated because only 20% of a given dose is required at the depth of the tumor. However, the exit dose issue for photons remains; and integral dose, as a result of this necessary method to optimize photons, is almost always higher for photons than for protons. Multiple examples can be found in the literature comparing the dosimetry of protons and photons for multiple types of tumors in all age ranges of patients.[9-17] Proton beam therapy's ability to spare normal tissue is for the most part superior to IMRT, but it is not that simple because we are still learning when and how much normal tissue needs to be spared.

The use of proton beam therapy in the clinic is still relatively new; currently, it is being used primarily as a substitute for photon therapy at the same doses and fractionation schedules that photons would be used, but with improved normal tissue sparing. This is because we lack data suggesting that doing otherwise is superior.

Rationale for proton therapy in adults

In adults, proton beam therapy is governed by clinical situations where a tumor requiring a high dose lies adjacent to a normal structure that cannot tolerate the resultant dose from the best dose gradient IMRT without a very high risk for damage. Proton beam therapy is commonly used for tumors of the base of the skull,[18] spine,[19] pelvis, brain, and for recurrent disease in which all nearby tissue has already received maximal dose but more radiation must be delivered to the same tissues at a significant dose.

The classic example is clival chordoma (Figure 2). In these cases, the dose gradient has to fall from 78 Gy to 63 Gy or lower in several millimeters to protect the brainstem and the optic apparatus simultaneously. Nothing except charged-particle therapy allows this to happen in this specific anatomic and clinical context while also keeping safe the many cranial nerves in the region. The ability to keep the dose to the brainstem and optic nerves to a reasonable level is shown as well. This could not be achieved with photons.

A novel indication for proton therapy in adults perhaps may be breast cancer. When patients present with complex chest wall tumors with positive lymph node findings, photons often are unable to spare the heart and lungs. In a post-mastectomy case where the supraclavicular, axillary, internal mammary, and aortic window nodes were positive, a two-field proton chest wall plan was developed that spared the lung, heart, and esophagus (Figure 3).

No photon plan could be achieved to do the same without significant lung

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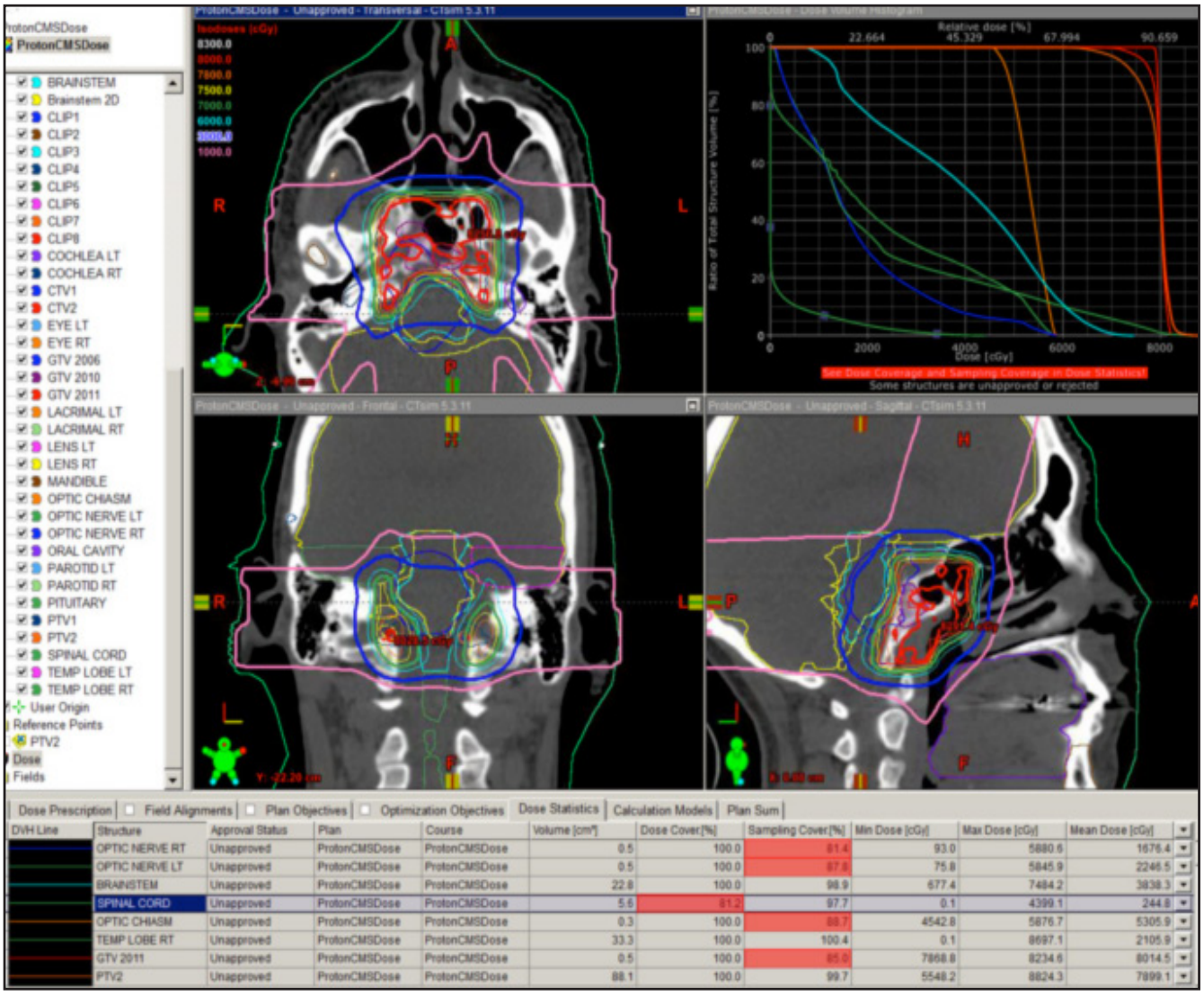

FIGURE 2. *A typical plan for a clival chordoma.[33] The prescription for the case is 79.2 Gy at 1.8 Gy per fraction. The patient was treated in a supine fashion while awake. Specifics of the case and anatomic issues regarding postoperative "space" between tumor and normal structures play a critical role in the capacity to do these cases. In this case, no space could be created between the lesion and the brainstem. Note the use of the vertex beam and the ability to spare the auditory regions from high dose.*

and cardiac doses. New data suggest cardiac radiation is associated with severe late toxicity in breast cancer patients, so the proton plan was far superior from this aspect. This kind of proton plan may allow the patient to receive higher doses of drugs toxic to the heart, to avoid otherwise unavoidable late effects of standard doses to the heart, or subsequently to receive more radiation near the heart without exceeding normal tissue tolerance.

Many clinicians believe the anatomic issues of prostate cancer justify the use of advanced technology, and these same issues make proton therapy a logical choice. Figure 4 depicts a typical prostate proton plan for reference. Most radiation oncologists will note that the posterior rectum and anterior bladder doses are very low as a result of the beams used (laterals). Some proton centers use one beam per day, alternating sides from day to day. Others deliver beam to both sides every day. Immobilization for proton therapy is different than for photon therapy because protons are more sensitive to small distance variations. At the Indiana University Health Proton Therapy Center (IUHPTC), patient immobilization includes a daily rectal balloon placement and a customized body mold device (similar to what is used in spinal surgery patients) to keep the patient's skin-to-prostate distance stable day to day.

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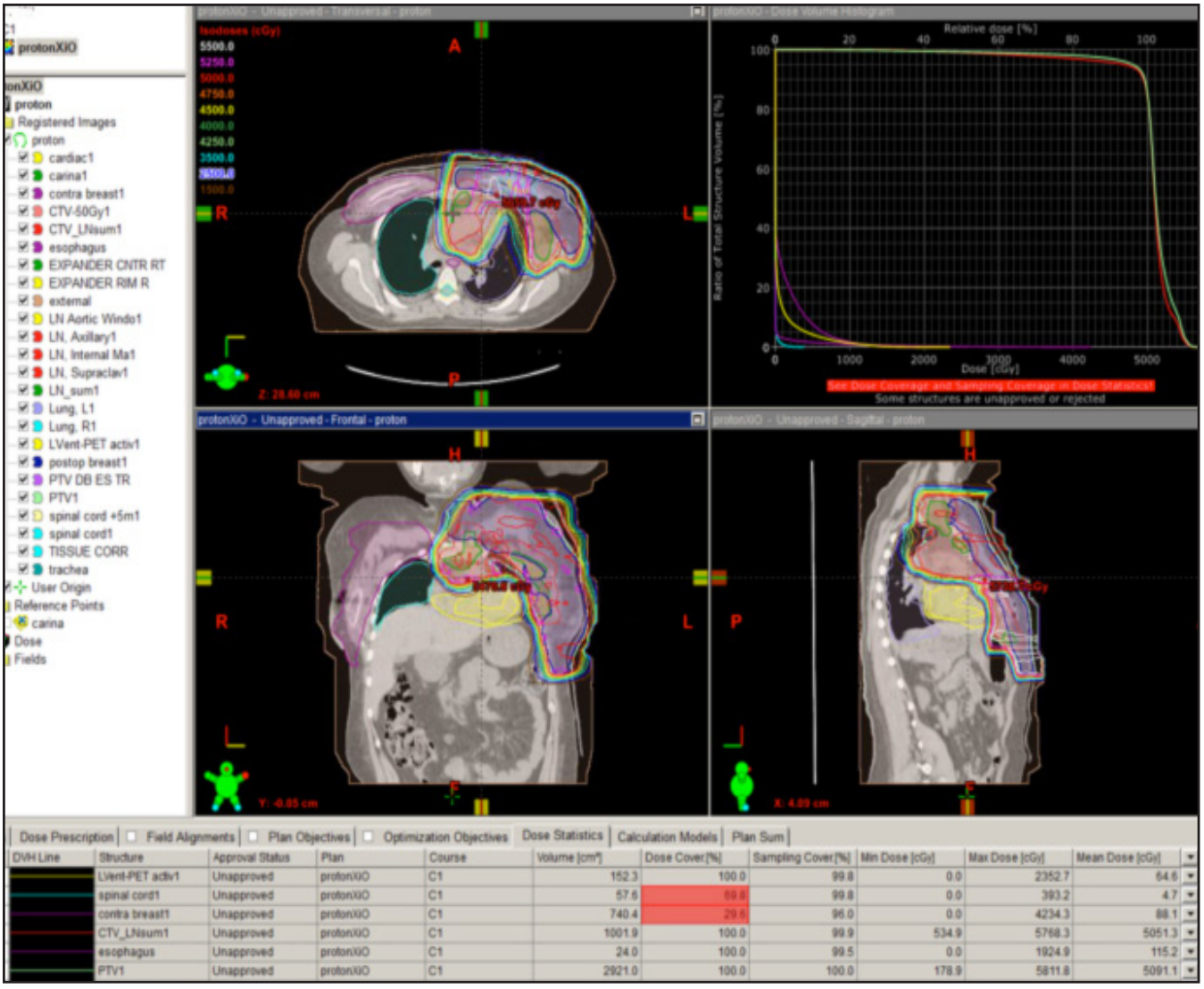

FIGURE 3. *The case of a postmastectomy breast cancer patient with biopsy-proven and/or PET/CT-positive lymphadenopathy in the left axilla, internal mammary region, subaortic arch, and supraclavicular region. The plan was able to spare the left ventricle, esophagus, and brachial plexus, while delivering 50 Gy to all involved nodal regions and the entire chest wall. Two 30-cm fields were employed.*[33]

Rationale for proton therapy in children

The same rationale used in adults holds for children, with the additional concern for total volume of dosimetric exposure and avoidance of secondary toxicities.[20,21] Data show that growing tissues are more likely to experience damage from radiation. To reflect this, pediatric dose tolerance is lower than what is used in adults. In addition, the total number of years before a child is likely to experience side effects is greater than that of an adult simply because the child may very well live long enough to have a side effect, while an adult may not. As a result, the general consensus in the specialty is that children are very well served by proton therapy; and that in general it is worth considering whether normal tissue can be spared to a significant degree. Early modeling and retrospective data reviews suggest decreased secondary malignancy rates and decreased toxicity.[22-26] Prospective studies are ongoing and most trials in the Children's Oncology Group (COG) currently allow proton therapy. Recently published data suggest that protons may lower in-field second malignancy rates by a factor of 2 to 10.[27]

The classic case that justifies proton therapy in a child is craniospinal irradiation (CSI) for medulloblastoma. Data presented within the last year

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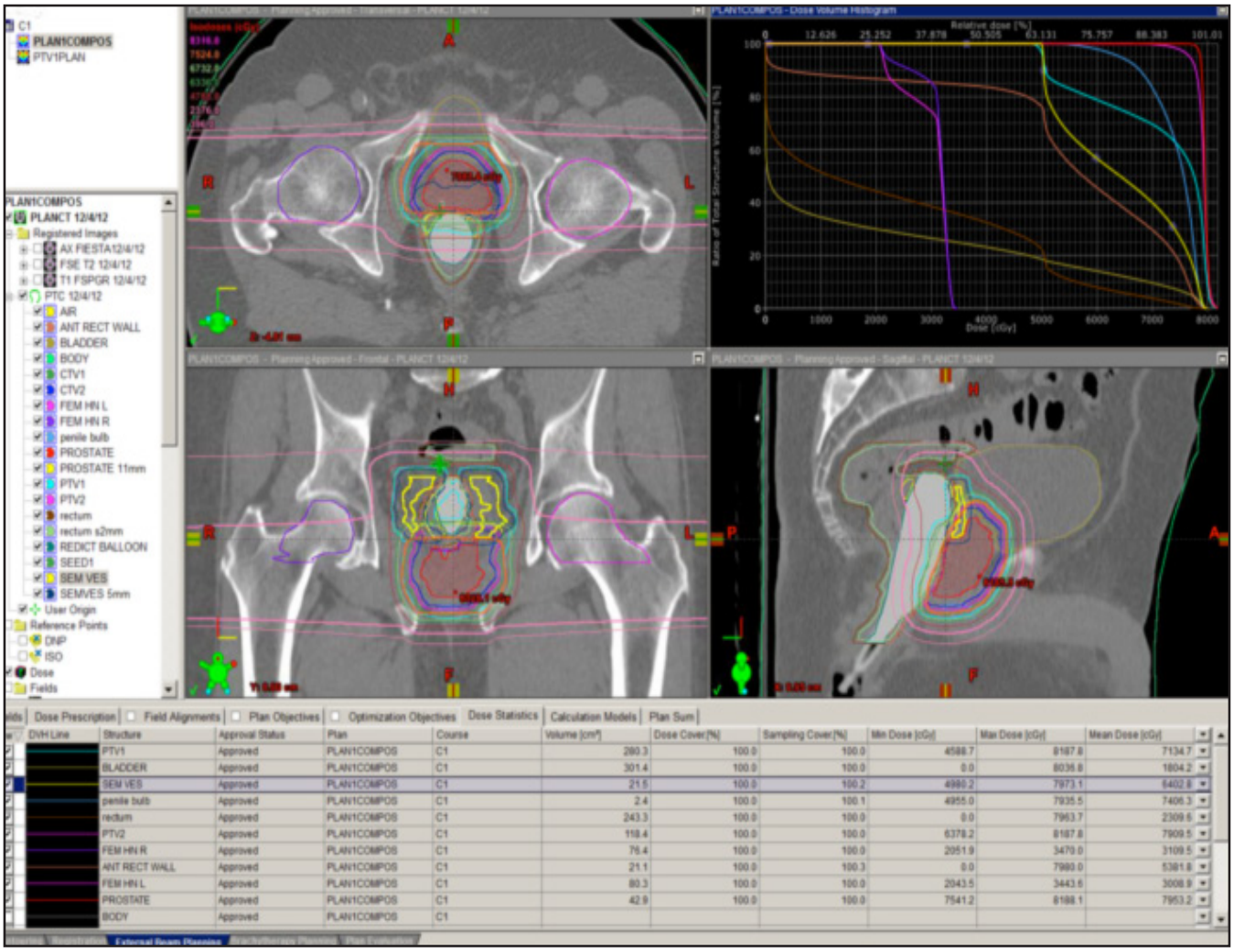

FIGURE 4. *A typical prostate treatment plan with lateral proton beams. Left and right laterals are employed every day at the IUHPTC. Larger field encompassing the prostate and seminal vesicles (PTV1) are treated to 50.4 Gy, and then the prostate with a margin is treated in a cone-down to 79.2 Gy (PTV2). Some centers only treat one side per day. Body molds, gold-seed fiducials, rectal balloons, and bladder filling protocols are employed to optimize treatment. The effect of the balloon in moving the posterior rectum away from dose is shown clearly.*[33]

suggest that the risk of secondary cancer is about 20% or lower with protons relative to photons. These data also suggest that protons have a lifetime secondary cancer risk of 7.7% in passive scattered form, while photons had a 93% lifetime risk for a young child with standard-risk medulloblastoma.[28] Supine proton CSI with dose stopping before the thyroid, breast, lungs, esophagus, heart, gut, and bladder is shown in Figure 5.[29]

Brain tumors in children also benefit from proton therapy. Figure 6 shows a typical fourth ventricular ependymoma case highlighting protons' ability to spare the cochleae, hippocampi, optic apparatus, and hypothalamus. Avoiding even low to moderate doses to these critical organs is impossible with IMRT or conventional radiation therapy.

Proton therapy also enables clinicians to treat tissues in the torso and yet spare patients from second malignancies not currently thought to be traditional proton cases. Figure 7 shows a case of Hodgkin's disease where breast tissue was spared on a local protocol. The next Children's Oncology Group (COG) study for Hodgkin's disease may allow proton therapy.

New technologies that are coming into focus

Proton beam therapy is expensive and cumbersome. The development of newer centers comes with evolutionary improvement and simplification of beam production and shaping. Cyclotrons requiring large staff in older centers are being replaced by simpli-

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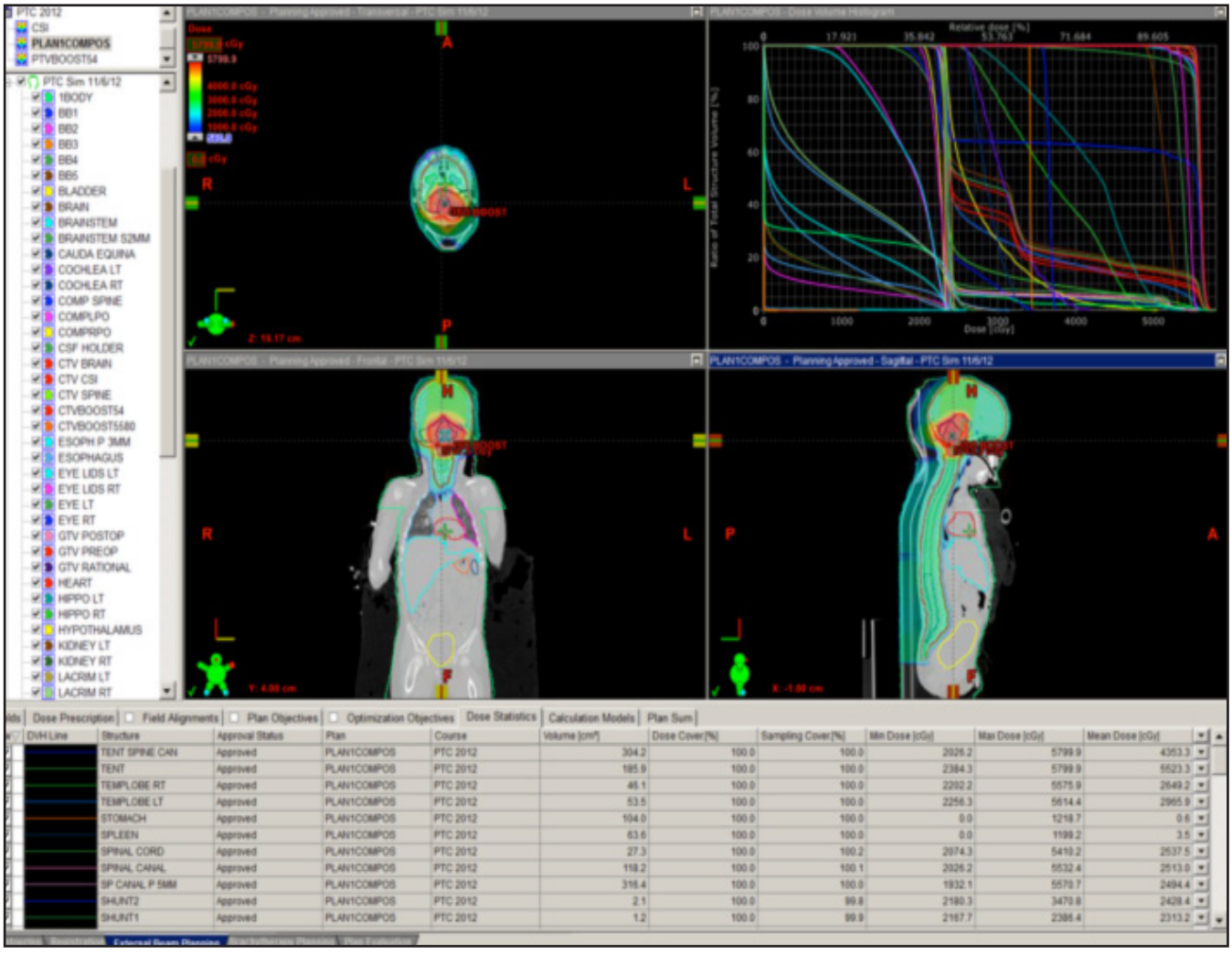

FIGURE 5. *A craniospinal case being treated for standard-risk medulloblastoma. The patient is being treated in a supine fashion using general anesthesia on a specific carbon fiber device designed to make supine craniospinal therapy with protons simple and effective.[29] Fields are abutted with hot matches and film dosimetry is employed for verification of all field junctions.[34] Patient set-up days take about 1 hour with 4 field patients (lateral posterior oblique brain fields and posterior spine fields) while delivery typically takes 30 minutes to 50 minutes each day.[35] Specifics based on age and tumor type drive specifics of each case. In this case, the patient's young age required full vertebral body dose coveragecoverage, and a laryngeal mask airway (LMA) is shown in place per our routine for general anesthesia.[33,34]*

fied devices that demand fewer staff. Beam stability and energy are being improved so that deeper tumor targets can be treated. Purchase price is falling via newer, simpler designs. Finally, patient-specific devices (PSDs) analogous to conventional edge and transmission blocks may be eliminated by so-called "pencil-beam" scanning systems.

This last item is perhaps the most clinically interesting and important development in proton therapy. While the physics and engineering of these devices is beyond the scope of this article, pencil beam proton therapy renders obsolete the use of metal apertures to shape the beam edge and Lucite compensators to shape the beam's distal range. The closest analogy in photon therapy is using the blocks in 3-dimensional (3D) conformal therapy with dynamic MLC-driven therapy. Pencil-beam proton therapy is truly a 3-dimensional dynamic form of intensity modulation. In addition, the proximal beam edge can be modulated to make proximal dose avoidance a reality. In theory, this technology requires fewer beams and far less hardware to deliver proton therapy than at present. These two features suggest that a cost savings, on top of superior clinical dosimetry, is achievable.

Pencil beam proton nozzle technology is in its infancy and the penumbra

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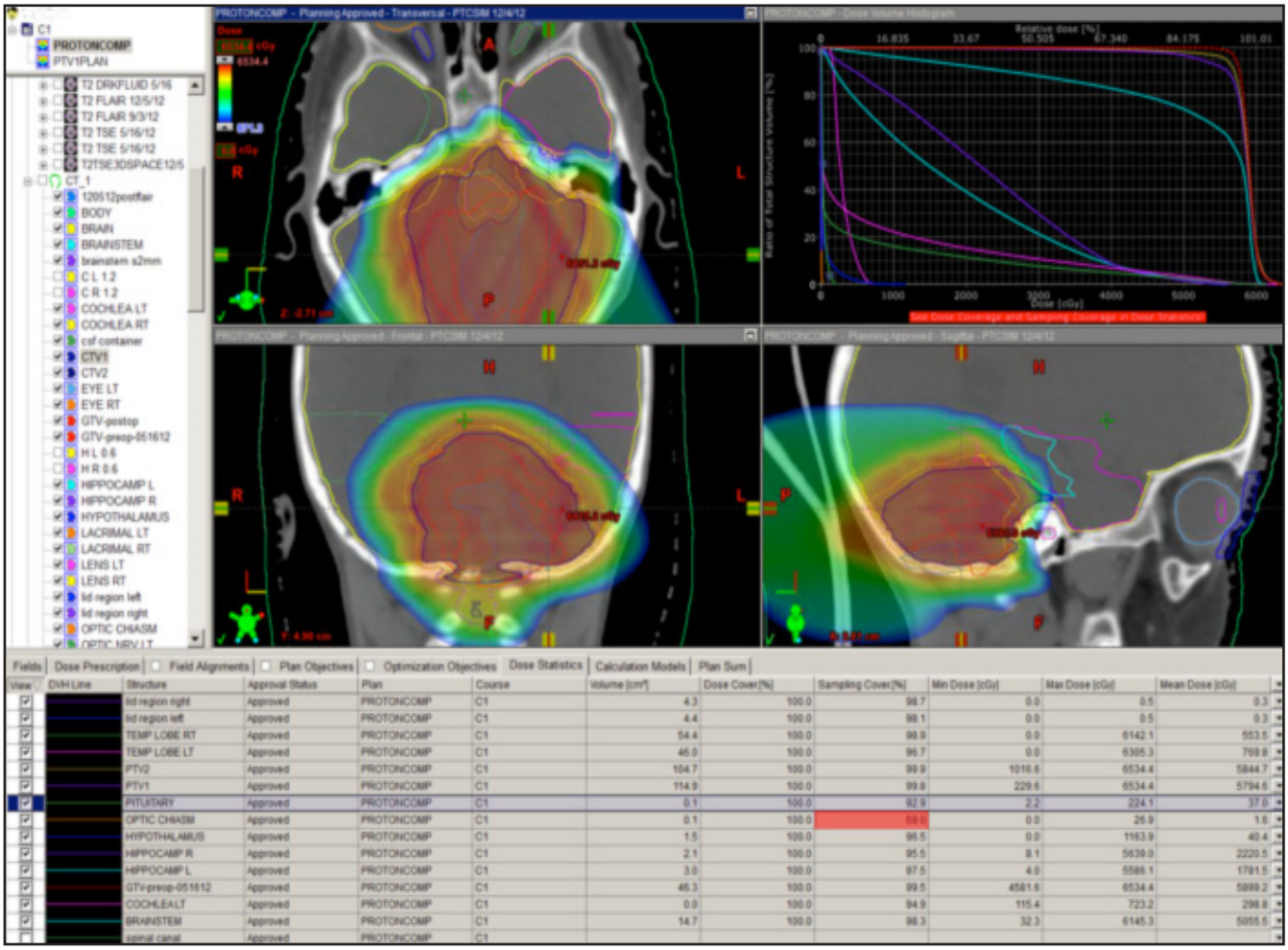

FIGURE 6. *The plan employed to treat a very young child with an anaplastic ependymoma. The patient was treated under general anesthesia each day in he supine position. The screen capture shows how dose stayed out of the cochlea via range-controlled or distal blocking. Very large tumors in the brain can be a challenge for any modality, but the ability to spare hearing, hormonal function, vision, and temporal lobe structures via proton beam therapy is a very powerful tool when treating brain tumors, especially in very young children.*[33]

achievable with the best devices is not yet as good as that achieved with apertures and compensators, but the lack of metal and material interaction, in theory, lowers the generation of neutrons, which is associated with the smaller but real risk of secondary cancers resulting from proton therapy. The next generation of these devices will likely radically improve proton therapy. It is an active area of research around the world.

Controversies

The primary controversies in proton beam therapy are financially related: Who gets therapy and how to pay for expensive new centers. The cost of proton therapy limits patient access to proton therapy centers. The higher financial cost makes treatment for diseases treated well with conventional therapy controversial if treated with proton therapy, even with an established but small incremental clinical benefit. By far, the most controversy to date for proton therapy has resulted from a recent review of prostate cancer therapy. This has taken place in the context of a paradigm shift for prostate cancer as a whole, and with prostate cancer treatment comprising one of the largest sources of revenue for any radiation center, proton- or photon-based. The most recent and most robust research, published by a group at Yale, suggests that IMRT for prostate cancer may be nearly equally effective clinically as the more expensive proton therapy in men aged 66 and over. [30] If the two therapies cost exactly the same, the issue would be far less controversial. The study has not followed patients long enough to make any long-term conclusions as of yet with 12-months follow-up being reported, so it is unclear if this is a true statement long term. As costs come down, the use of proton and other particle therapies will become less controversial.

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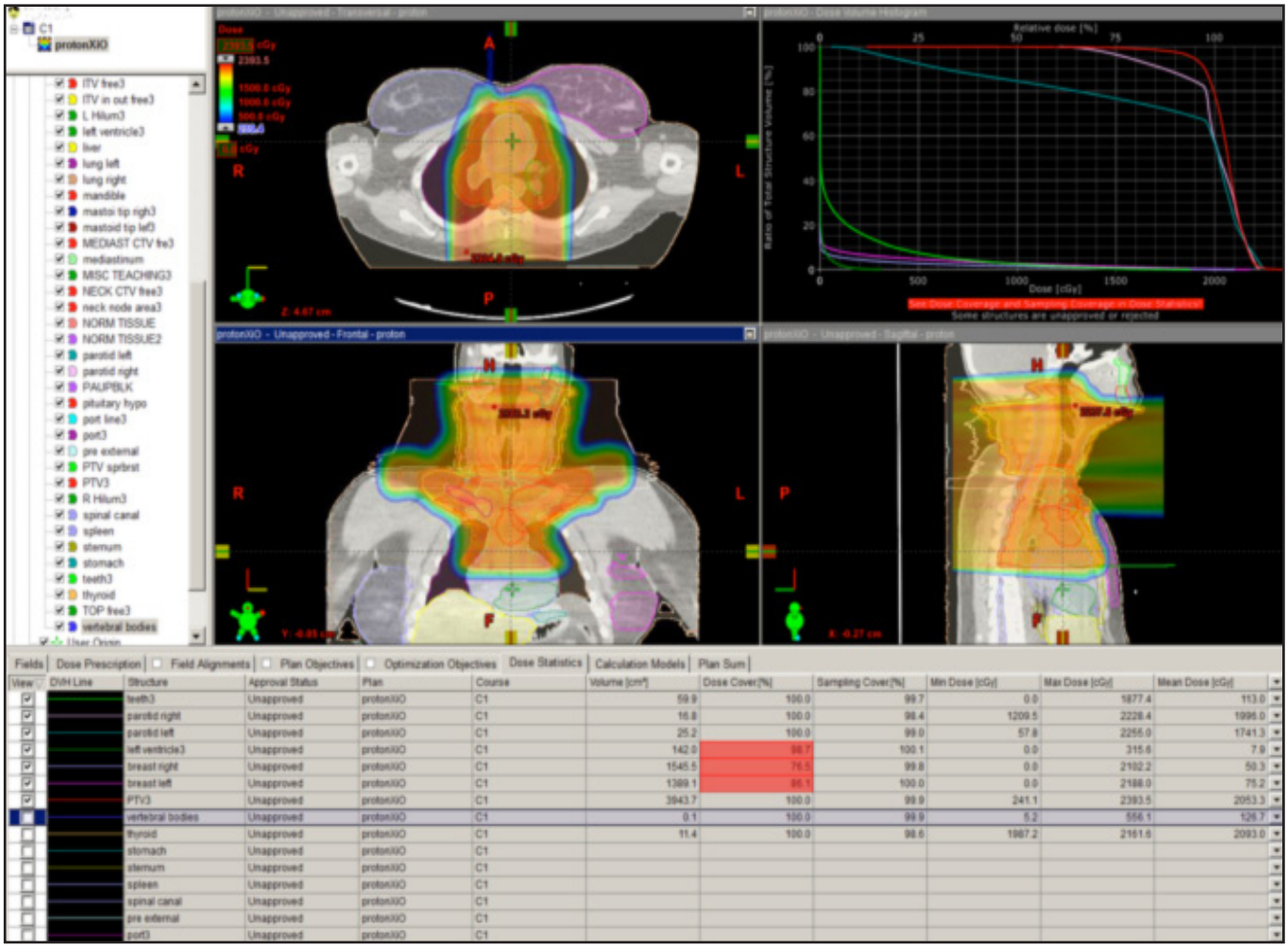

FIGURE 7. A young woman treated for very favorable Hodgkin's disease. She was enrolled on an institutional protocol addressing the capacity of proton therapy to deliver standard therapy to these patients while sparing breast tissue. These data were presented at an international meeting in Amsterdam in the July of 2011 by the author.[36] The author is the principle investigator of the study.[33]

Limitations of proton therapy

At present, protons have concrete limitations relative to photons that clinicians must understand to best take advantage of the treatment. First, proton therapy generally takes much longer than photon therapy to go from simulation to beam delivery. It is not currently best used for emergent radiation therapy because of this decreased nimbleness.

Second, proton therapy does not have widespread availability, so patients may not hear about it from referral physicians even when it would be superior to conventional therapy. Travel and housing costs can make the technology prohibitive even when patients and physicians want to employ protons.

Third, protons are inherently more complex than photons, and problems can be more difficult to fix on a daily basis. This means that staffing is more crucial for these centers than for photon-based centers. Physics staffing is likely 2 or 3 times that of image-guided photon therapy centers. The learning curve for protons is also steeper and the chance to learn how to do proton therapy is more limited, also making staffing more difficult for proton therapy.

Fourth, proton therapy requires the treatment team to have the appropriate expertise to treat the mix of tumors for which it is best employed: complex tumors next to the brain and spine in adults, children, and heavily pretreated patients. As the number of proton centers increases, the best ways to exploit it will be more widely understood and taught.

Fifth, the dosimetry of the proton beam, in terms of biology, is not linear, and methods exist for mitigation of the increased biologic dose at the end of the Bragg peak that are often not obvious to those who don't routinely

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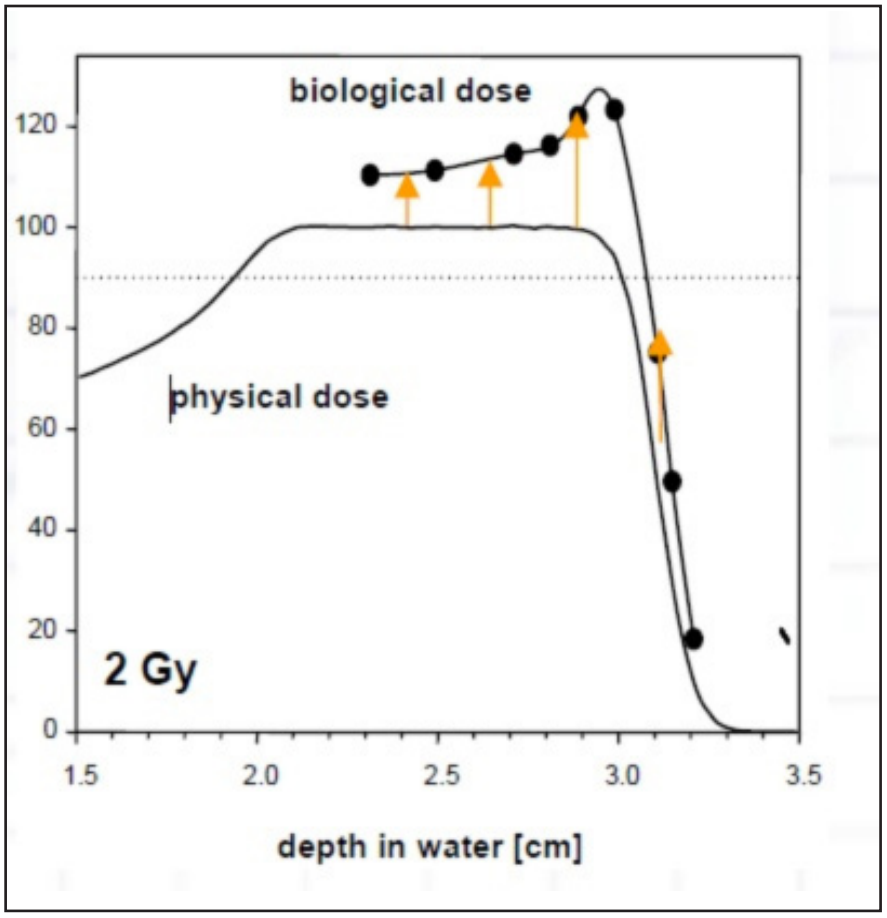

FIGURE 8. *This figure demonstrates the idea that relative biologic effect, RBE, increases nonlinearly at the very end of the SOBP. This is a complex idea that underlies the many decisions made daily by experts in proton therapy clinics. It is one of the main reasons that single-beam proton plans are not allowed on COG protocols. Note how the RBE curve is not the same as the "dose" curve shown here and in Figure 1. [Figure from PowerPoint slide used with permission from Professor Harald Paganetti, PhD, of the Massachusetts General Hospital, Boston, MA]*

practice proton therapy (Figure 8). Careful attention to beam selection, beam stopping location, and the number of beams is needed to prevent unexpected adverse biologic outcomes.

Finally, because proton therapy is so sensitive to distance from patient surface to the stopping point, it is far easier to have a geographic miss while using protons than it is while using photons. To correct for this, patients need to be assessed frequently and perhaps imaged with on-treatment, high-quality CT or MRI scans to assess changes. Departments using protons must be able to respond to range changes quickly for patients at risk for this issue. The development of photon-adaptive radiotherapy directly impacts this aspect of proton treatment because the identical issues must be addressed.[31]

Conclusions

Proton beam therapy is a clinically relevant, accepted form of radiation therapy that is likely to endure and is justified by current data. New technologies are emerging to improve treatment delivery. Proton beam therapy is benefiting indirectly from the progress made on all fronts of medicine to deliver better therapy to patients using better technology in planning and imaging. As cost decreases and availability increases, the technology will become more pervasive and data will be developed to further specify where and when it is best used.

Time will tell if we are able to lower the costs enough to make the technology more routine and less expensive for patients. Currently, protons are appropriate for first-line consideration in many pediatric, spinal, base-of-skull, head and neck, pelvic, and retreatment tumors. They may also prove superior for some subgroups of lung, breast, and prostate patients.

To be sure, proton therapy is no more effective, in many cases, than conventional therapy; due to geographic and other issues, it may even pose a greater hardship for some patients. Discussing cases with proton therapy centers will allow referral physicians to better establish options for their patients.

However, proton therapy is here to stay, and many clinical trials are under way to better understand how and when to use it. Keeping abreast of this technology will be exciting for all radiation oncologists, as the promise to treat cancer patients with fewer side effects is something for which we all strive.

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The promise of proton therapy

Cristen Bolan

An estimated 60% of all cancer patients undergo some sort of radiation therapy during their course of treatment,[1] and despite advances in radiation therapy technology, many suffer from side effects caused by conventional photon-based (x-ray) radiation therapy.

There is, however, a silver lining. As an alternative to conventional treatments, patients increasingly have access to proton radiation therapy. With proton therapy, the majority of radiation energy from a proton beam is actually deposited in the targeted cancer,[2] causing less damage to healthy tissue compared with other radiation alternatives, and resulting in fewer short- and long-term side effects.[3-9]

"What protons allow you to do is deliver the same type of treatment of x-ray therapy while sparing more normal tissue than with x-ray therapy," explained Dr. Carl Rossi, Medical Director of Scripps Proton Therapy Center, San Diego, CA.

While proton therapy has been used clinically for more than 2 decades, the high cost of the technology has limited access to the treatment. That is changing, however, as manufacturers develop more compact systems and cost-effective models, which lower the initial investment, enabling hospitals to offer a new life saving treatment, often resulting in a better quality of life.

The proton advantage

The unique dose distribution of protons and spread-out Bragg peak enable the delivery of highly conformal radiation to cancers located adjacent to critical normal structures without damaging healthy surrounding tissue.[2] This reduces the negative side effects of treatment and helps sustain patient quality of life.

"The advantage of proton therapy is that proton particles have mass, and you can control the depth of penetration better, as opposed to an x-ray that passes through the patient's body. Protons deliver the radiation to the tumor, and then the proton beam stops, so that there is not excess radiation delivered beyond the tumor," explained Henry Tsai, MD, a radiation oncologist at The ProCure Proton Therapy Center in Somerset, NJ.

This can result in sparing 60% to 80% of the healthy surrounding tissue, indicated Brian Chon, MD, Medical Director, The ProCure Proton Therapy Center of New Jersey. "Sparing healthy tissue and organs helps reduce the impact of side effects common in traditional photon therapy and allows for treatment in difficult locations of the body," said Dr. Chon.

The price of progress

Despite the clinical benefits of proton therapy, broad adoption of the technique has been greatly limited by the enormous cost, which can run into the $100 millions. In addition, there is the high cost of the large footprint and the technical complexity of traditional proton therapy systems.

A recent study by KLAS, an independent research firm, found that concerns about market saturation and an estimated initial investment of $150 to $200 million would likely deter investors from healthcare facilities in proton therapy over the next 5 years.[10,11] In addition to cost, survey participants also indicated they had reservations about return on investment due to the patient referral base, staffing requirements, and ongoing maintenance costs.

These factors contribute to the fact that over several decades just 2 large institutions in the United States—Loma Linda University Medical Center in Los Angeles, CA, and Boston's Massachusetts General Hospital (MGH)—have had the patient volume and funding to feasibly offer proton therapy. These traditional centers have 200-ton to 250-ton cyclotrons, requiring a very large infrastructure for treatment rooms.

However, with recent developments in proton therapy technology, cyclotrons have smaller footprints and run just a fraction of the cost of full-sized systems, thus changing the landscape from a $150 million investment to a $25 million solution.

"The technology has gone from something that had to be built in a national

FIGURE 1. *Varian Probeam treatment room. Scripps Proton Therapy Center is being developed by Advanced Particle Therapy, LLC of San Diego, CA, and will be operated by Scripps Health and Scripps Clinic Medical Group. The center is due to open for patient care in summer 2013.*

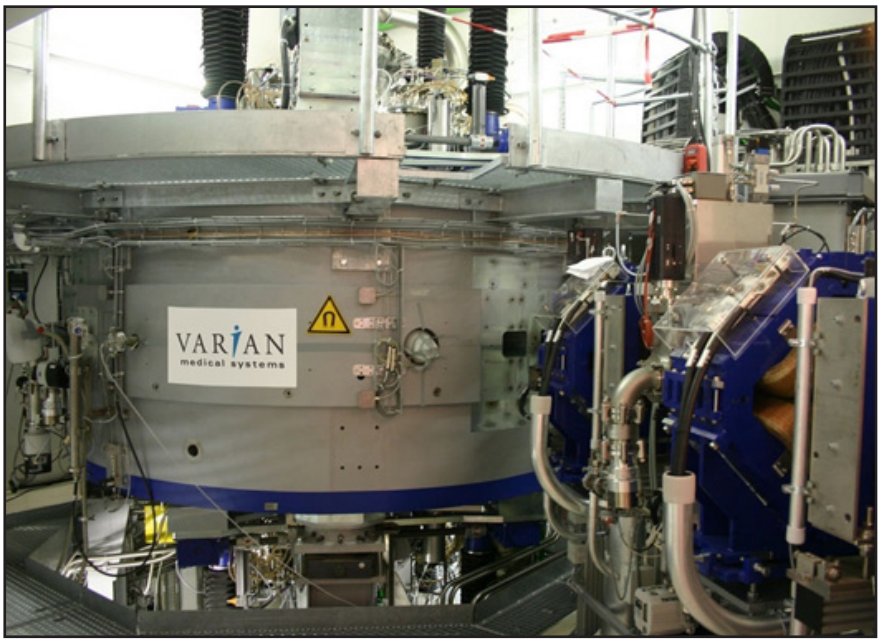

FIGURE 2. *Cyclotron Varian ProBeam. A 90-ton cyclotron (left) is the centerpiece of the fully integrated ProBeam proton therapy system at Scripps Proton Therapy Center. The technology is manufactured by Varian Medical Systems. (Photo courtesy of Varian Medical Systems).*

laboratory to something you can now buy. Today, there are a number of vendors you can chose from, and there is competition in the market, including Varian, Hitachi, IBA, and Mevion," said Dr. Rossi. "Facilities are now designed for a high-patient throughput. At our facility, with 5 treatment rooms, we expect to treat up to 200 patients a day—this allows us to spread the unit cost per treatment. We are now running a 16-hour treatment day. That's helping reduce the costs."

Currently, Scripps Proton Therapy Center is being developed by Advanced Particle Therapy, LLC of San Diego, CA, and will be operated by Scripps Health and Scripps Clinic Medical Group. The center is due to open for patient care in summer 2013. Scripps is installing Varian's ProBeam system and will offer active beam scanning, also called pencil-beam scanning or intensity-modulated proton therapy (IMPT). With IMPT the beam conforms more closely to the tumor, better sparing surrounding healthy tissue from harm.

In 2013, ProBeam is due for an additional upgrade with cone-beam computed tomography (CT) imaging. While 3-dimensional (3D) imaging is common in linear accelerators and used intensively for stereotactic radiosurgery, the standard for proton therapy is 2-dimensional (2D) stereotactic imaging. Cone-beam CT will allow for volumetric imaging, producing 3D image sets, and therefore enable radiosurgery with the cone-beam CT on the ProBeam system.

The Mayo Clinic is scheduled to treat its first patient with proton therapy at it's Rochester, MN-site in the summer of 2015 and at its Arizona location in 2016—all 8 treatment rooms will be operational by 2017. The Mayo Clinic Proton Beam Therapy Program will exclusively feature IMPT and is working with Hitachi Medical Systems America to implement a synchrotron.

TECHNOLOGY TRENDS

IBA-Philips Proton Therapy. IBA Group partnered with Philips Healthcare to install the Philips Ambient Experience at Willis-Knighton Cancer Center in Shreveport, LA. The room is designed to promote patient relaxation during proton treatments.

"[The Hitachi system] is a much smaller and less expensive version of what was used in the past. So the building does not need to be as large, and it is less costly to operate because there are fewer parts," explained Robert L. Foote, MD, Mayo Clinic's Chairman of Radiation Oncology. "We wanted to have the most state-of-art technology available when we started treating patients, and we thought that would be the intensity-modulated protons, not the scattered protons everyone is using now, and Hitachi had an FDA-approved intensity-modulated proton option available that was in use at MD Anderson Cancer Center. Our physicists worked with Hitachi to design a smaller, less expensive synchrotron, gantry, and robotic patient positioning system to reduce the cost of the equipment and the footprint of the building."

Designed to provide a turnkey solution, the model for ProCure Proton Therapy Centers (ProCure) is designed to cost-effectively open and manage proton therapy centers. Procure opened the first center in Oklahoma City, in July 2009, and in 2012 celebrated the inauguration of its tenth location in Somerset, NJ. The new site has 4 treatment rooms equipped with the IBA Proton Therapy System manufactured by IBA, SA (Belgium).

"While traditional centers have 200- to 250-ton cyclotrons, requiring a very large infrastructure for treatment rooms, the cyclotrons have a smaller footprint," explained Dr. Chon. The smaller footprint lowers the overall size and cost of the installation.

One of the leaders in proton therapy system technology is Ion Beam Applications SA (IBA) of Belgium, which has installments at MGH, University of Pittsburgh Medical Center (UPMC), in addition to the ProCure Proton Therapy Center of New Jersey. In 2009, IBA introduced a smaller and more economical 2-room treatment solution called Proteus Nano. Just one year later, the company rolled out an even more cost-effective solution, Proteus One, a single-room system one-third the size of the current gantry configuration and which offers a smaller cyclotron, a shorter proton-beam route from the cyclotron to the treatment room, and a more compact gantry. Proteus ONE's smaller treatment room is designed to reduce costs, minimize space, and shorten the installation time required to build a proton therapy center. In addition, the Proteus ONE supports pencil beam scanning proton delivery, or IMPT, and has integrated 3D cone-beam CT imaging that rotates around a patient, capturing detailed tumor images.

Another way IBA is pioneering innovation in proton therapy treatment is by creating a more comfortable environment for patients. IBA Group and Royal Philips Electronics have teamed up to build a state-of-the-art, patient-centered proton therapy treatment room. A new addition to the Willis-Knighton Cancer Center in Shreveport, LA, will house the first IBA installation to incorporate the Philips Ambient Experience. The Philips Ambient Experience promotes patient relaxation during proton treatments by permitting patients to selectively add comforting light, sound, and images to the treatment room environment before they begin therapy. The ambience is designed to transform the patient and staff experience into one that is comforting and reassuring. The $40 million project at Willis-Knighton marks the first center to utilize IBA's Proteus ONE, and is expected to begin treating cancer patients with protons in early 2014.

As manufacturers embrace the concept that less is more, another compact model is the MEVION S250 proton therapy system, a single-vault unit by Mevion Medical Systems that recently received FDA 510(k) clearance. The system's accelerator has a diameter of just 6 feet (1.8 m), which has a smaller footprint than most other systems. The first MEVION S250 installation will be completed at the Kling Center for Proton Therapy at Barnes Jewish Hospital at Washington University in St. Louis, MO, and Mevion will be delivering and installing more than a dozen MEVION S250 proton therapy systems worldwide within the next 2 years.

Another turnkey solution is available with the Conforma 3000 by Optivus, which provides an efficient modular design. The system evolved out of the technology used at the Loma Linda University Medical Center. With the Conforma 3000, facilities can be configured with 1 to 5 gantries using a variety of floor plans that can be developed to work with most existing facilities.

Quality-of-life

One of the biggest value propositions for proton therapy is that it minimizes side effects and morbidity, resulting in a better quality of life for patients compared to photon radiation therapy.

"The number one advantage of proton therapy is it is a safer treatment with fewer short-term and long-term complications, particularly in the pediatric and young adult population," indicated Robert Foote, MD, Mayo Clinic's Chairman of Radiation Oncology.

There is growing evidence that proton therapy results in a better quality-of-life for patients. In a recent study, investigators at MGH and UPMC evaluated patients fighting prostate cancer. They found those treated with proton beam therapy were likely to experience a better quality-of-life than those treated with traditional radiation therapy.

In a nonrandomized study,[12] researchers opened a comparison of proton beam therapy (PBT) and intensity-modulated radiation therapy (IMRT) for patients with localized prostate cancer. They evaluated the side effects of PBT, 3D conformal radiation therapy (3D CRT), and IMRT. They found patients undergoing PBT treatment had a higher quality-of-life in early follow-up and at 2 years, compared 3D CRT and IMRT.

Proton vs. Photon Therapy

Despite growing evidence that quality-of-life is better with proton therapy, there is an ongoing debate as to whether the difference between proton therapy and photon or x-ray based radiation therapy treatment is clinically significant.

"What people argue about is whether that difference in dose is clinically relevant. My counter to that is there is no unimportant radiation dose, if there's a way to not treat that normal tissue, you should pursue it," said Dr. Rossi.

The primary advantages of proton therapy, says Dr. Rossi, is it causes less damage to healthy surrounding tissue than photon therapy dose and it gives greater control over the radiation beam to better contour dose to the target.

"If you are talking about radiation dose to normal tissue, proton therapy is superior in virtually any situation you can think of. If you have a very small 2-cm or 3-cm field, there may not be that much of a difference. Beyond that, the larger the field you have to treat, the more irregularly shaped, the greater the disparity in normal tissue radiation dose between proton and IMRT," said Dr. Rossi.

Ultimately, said Dr. Rossi, "The main reason for offering proton therapy is that, irrespective of the type of x-ray therapy (XRT), you can do everything with proton that you can do with XRT, such as intensity-modulation and stereotactic, but you are using a radiation beam that stops. You can use the same type of set up with image-guidance like you use for high-precision x-ray therapy, but because you are using a beam that stops you treat far less normal tissue than you do with x-ray."

Nonetheless, the debate between proton therapy versus conventional radiation therapy continues. The authors of the study evaluating the side effects of PBT, 3D CRT, and IMRT[12] recognize the need for a randomized control trial. In fact, MGH and UPMC have partnered to launch a trial randomizing low- and intermediate-risk prostate cancer patients to IMRT vs. proton beam radiation to evaluate quality-of-life outcomes, cost-effectiveness, and physics and radiobiology endpoints.[12]

Increased control, less toxicity

From the patient's perspective, quality-of-life is second in importance to nonrecurrence in cancer. The increased control and lower toxicity of the proton beam may allow a larger amount of dose to be delivered per fraction, and therefore may prove more effective.

"In some instances, we can deliver more dose. In the brain or spine, where you want to deliver more radiation, there is a significant advantage with proton therapy, and it still delivers less radiation to surrounding tissues," Robert Foote, MD, Mayo Clinic's Chairman of Radiation Oncology.

Proton therapy is especially promising for treating organs affected by motion and near to other critical organs, including the prostate, which is adjacent to the rectum and bladder. A recent study on proton therapy demonstrated extremely low rates of grade > 3 GU and GI toxicities and extremely high disease control, presumably related to improved radiation dose distributions over what can be achieved with IMRT.[12] The low toxicity of proton therapy makes it particularly appropriate for pediatric patients, whose growing bodies are more sensitive to radiation.

Other clinical applications highly indicated for proton therapy include anatomical areas with highly sensitive surrounding structures, such as the brain and spine. Proton therapy, for example, effectively treats chondrosarcomas or chordomas involving the base of the skull or the spinal axis; as cranial nerves are located at the base of the skull, the optic nerves are close by, as well as the optic chiasm.

"In the brain or spine, where you want to deliver more radiation, there is a significant advantage with proton therapy, and it still delivers less radiation to surrounding tissues," indicated Dr. Chon. "Proton therapy can spare 60% to 80% of the healthy surrounding tissue. That is why we are treating pediatric

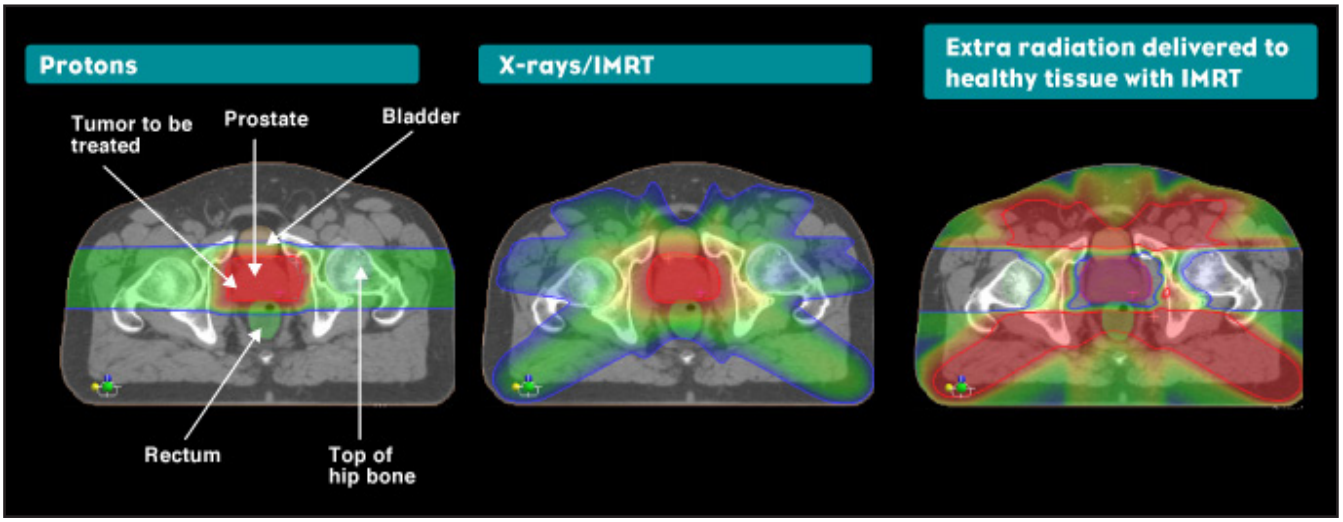

FIGURE 3. *Proton therapy achieves better conformation to the tumor and minimizes the dose to healthy tissue.*
Source: ProCure Training and Development Center

patients who clearly benefit from it. We are also treating patients with tumors of the skull, brain, and spinal chord, and are working on expanding proton therapy into the lung and abdomen."

Next-generation proton technique

While adoption of proton therapy is just beginning to blossom, the technology is already on to the next-generation proton therapy technique—IMPT.

Mayo Clinic, for example, has decided to use IMPT as opposed to scatter-beam therapy. Although Dr. Foote acknowledges there have not been phase III controlled clinical trials demonstrating the superiority of IMPT over scatter-beam technology in terms of safety or efficacy, Dr. Foote and his clinical team have observed the technique at MD Anderson in Texas and Paul Scherrer Institute in Switzerland where they have been using IMPT for many years. At those prestigious institutions, Dr. Foote explains, "they have found that IMPT compared to scatter-beam therapy seems to be as effective using typical doses to tumors, while reducing dose to normal organs and tissues."

"The scattered beam conforms very tightly to the distal edge of the tumor, but that creates some hot spots on the proximal end of the tumor and out into the normal tissue. With the intensity-modulated protons, we'll be using pencil-beam scanning, so a pencil-sized beam will put small "dots" of radiation energy within the tumor and magnets will scan the beam back and forth, painting dose within the tumor," he said. In summary, "The pencil-beam scanning is more targeted and precise, and you get rid of the expense of collimators and compensators. It is also more efficient for a higher throughput of patients," added Dr. Foote.

Dr. Rossi believes IMPT is the next generation of proton therapy treatment. "With an actively scanned beam, as compared to a scatter beam, I can spare far more normal tissue, and secondly, with an active-scan beam, I am now able to treat much larger treatment fields than I could in the past. Previously, our maximum beam size was 17 cm, that's fine for treating small structures like the prostate or brain tumors, but what if you have to treat someone's pelvis because they have lymph nodes involved, or what if you have to treat the pelvis or mediastinum in lungs. The probing system allows you to a treat a 40-cm x 30-cm field, the same size as you can treat on a linear accelerator," said Dr. Rossi.

Growing patient populations

While there are concerns surrounding sufficient volumes of patients seeking proton therapy, the leading centers do not foresee a shortage of patients in the coming years.

At Mayo Clinic, they expect to treat an estimated 1,240 patients per year in Rochester, and another 1,240 patients per year at their facility in Phoenix. The patient population will consist of pediatrics, adolescents, and young adults with cancers, such as brain tumors, rhabdomyosarcomas, and lymphomas. Mayo Clinic has an active and growing practice for ocular melanomas and a neurosurgery group doing skull-base and spine surgery for chordomas and chondrosarcomas. For certain types of cancer, they will treat lung, breast, and a variety of gastrointestinal cancers, such as esophageal, gastric, and hepato-biliary tumors. There will be some selected prostate cancers with high PSA, high Gleason score, and advanced T-stage treated with hypofractionation.

Dr. Foote noted, "We will be participating in clinical trials for prostate cancer

using just 5 treatments rather than the 40 or more treatments. We are currently reimbursed per treatment, so the best way to reduce the cost for proton beam therapy is to reduce the number of treatments. If we can safely reduce the number of treatments from 44 to 5, that will be in the best interest of the patient and the insurer."

He added, "The goal is to have everyone treated on a clinical trial so that we can document lowering of acute toxicity, and lowering of late complications as well as lowering overall costs associated with treating the cancer."

Cutting cost through better outcomes

As the technology evolves, the cost gap between x-rays and protons continues to narrow. In addition, reduced side-effects for patients impact their quality-of-life, likelihood of recurrence, and the overall cost to the healthcare system. While the initial cost of treatment with protons is higher than that of photon therapy, reduced side-effects results in an overall cost savings over a lifetime.

The cost of side-effects is well illustrated over the lifetime of a pediatric patient. Side effects of photon therapy include hypothyroidism and growth hormone deficiency, seizure disorders, and auditory and visual impairment after treatment have also been reported.[13,14] One study of children with medulloblastoma treated with X-rays estimated the risk of hearing loss at 13% because of radiation to the inner ear.[13] The risk of secondary cancers further adds to the cost of patient care. In one study where researchers assessed the potential influence of dose distribution on the incidence of secondary cancers in a pediatric patient with medulloblastoma, they estimated that the rate of secondary tumors would be 8 times lower with proton therapy than with IMRT (X-ray) treatment (0.05% vs 0.43%).[15]

"It is true that the initial cost with proton therapy is more than x-rays, but when you follow the young child throughout the course of their lifetime and find that their IQs are higher with protons, they don't need hearing aids as often, they don't need special education as often, they don't need growth hormone replacement as often, and they don't develop as many radiation-induced cancers; when you add up all the costs of these long-term side effects of x-ray therapy versus reducing those complications with proton therapy over that child's lifetime, then proton therapy becomes the far less expensive way of treating that child," said Dr. Foote.

Conclusion

According to some reports, proton therapy is expected to eventually replace the traditional methods of radiotherapy in the future.[1] But before that is even conceivable, more clinical studies need to show that the benefits of proton therapy outweigh the hefty cost of the treatment.

According to Dr. Rossi, cost not efficacy has slowed adoption of proton therapy. "The problem with protons has been the cost of building the facility," said Dr. Rossi. "Once the cost of proton facilities comes down, the cost of treatment will be similar to IMRT. At that point, there will be no doubt what treatment people would chose and that is treatment in the form of proton therapy."

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RADIATION ONCOLOGY CASE

CME SEE PAGE 3 FOR DETAILS

Radiation necrosis: Now you see it, now you don't

Sameera S. Kumar, BS, Abigail L. Stockham, MD, Samuel T. Chao, MD, Manmeet Ahluwalia, MD, and John H. Suh, MD

CASE SUMMARY

A 61-year-old woman with a large-cell neuroendocrine carcinoma of the lung, at her 10-month post-lobectomy and chemotherapy status had developed a 1.3 × 1.8 × 1.4-cm left thalamic/tectal lesion (Figure 1). Consideration was noted for metastasis, and it was treated with Gamma Knife stereotactic radiosurgery (SRS, Figure 2).

The lesion initially regressed (Figure 3). However, at 14 months post-SRS, the patient developed fatigue, right-sided hemianesthesia, thermoanesthesia and diplopia, and enhancement at the SRS site (Figure 4), which persisted despite dexamethasone treatment (Figures 5 and 6). After 4 doses of bevacizumab, the patient's symptoms stabilized, but she experienced a generalized tonic-clonic seizure, at which time magnetic resonance imaging (MRI) demonstrated near-resolution of enhancement (Figure 7). The lesion returned to its size at onset of radiation necrosis (RN) symptoms, and remained stable through 37 months post-SRS (Figure 8).

The patient was without evidence of active disease 45 months after SRS, with stable hemianesthesia, hemithermoanesthesia, exotropia, hypertropia, and diplopia.

*Prepared by **Dr. Kumar** while at West Virginia University School of Medicine in Morgantown, WV; **Dr. Stockham** at Taussig Cancer Center, Cleveland Clinic, Cleveland, OH; **Dr. Chao, Dr. Aluwahlia,** and **Dr. Suh** at The Rose Ella Burkhardt Brain Tumor NeuroOncology Center, Cleveland Clinic, Cleveland, OH.*

IMAGING FINDINGS

At diagnosis of presumed brain metastasis, axial T1 contrast-enhanced MRI demonstrated a 1.3 × 1.8 × 1.4-cm cystic, peripherally enhancing mass in the left thalamus/tectum causing obstructive hydrocephalus (Figure 1). At 11 months post-SRS, axial T1 contrast-enhanced MRI showed no discrete mass, mass-effect, midline shift or abnormal lesion (Figure 3). Three months later, axial T1 contrast-enhanced MRI demonstrated enhancement at the site of treatment (Figure 4). At 18 months post-SRS, axial T1 contrast-enhanced MRI showed radiographic stability (Figure 5). Advanced imaging techniques for differentiation of RN from tumor recurrence included relative cerebral blood volume (rCBV) MRI and diffusion weighted imaging (DWI) with associated apparent diffusion coefficient (ADC), demonstrated no restricted diffusion or increased perfusion (Figure 5). Fluorodeoxyglucose positron emission tomography (FDG-PET) revealed focal photopenia with decreased FDG uptake at the site of SRS, consistent with radiation changes (Figure 5). T1 contrast-enhanced MRI at 18 months post-SRS demonstrated a stable, persistently enhancing lesion at the site of SRS (Figure 6). After 4 cycles (2 months) of bevacizumab

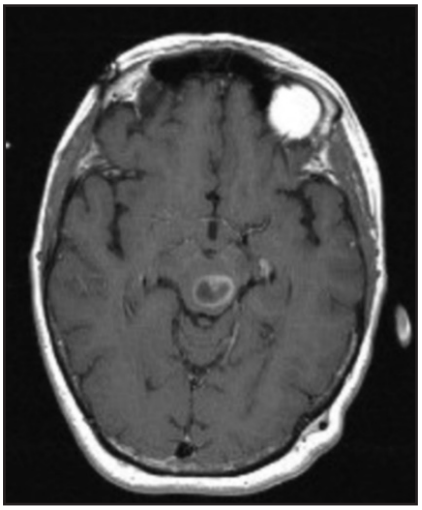

FIGURE 1. *Axial T1 contrast-enhanced MRI demonstrating a 1.8-cm ring-enhancing lesion at the left aspect of the tectum.*

(20 months post-SRS), T1 axial contrast-enhanced MRI demonstrated minimal enhancement, indicating substantial resolution of the lesion (Figure 7). At 37 months post-SRS, the left thalamic lesion was comparable in size to the MRI at 14 months post-SRS, at which point the patient had become symptomatic (Figure 8).

DIAGNOSIS

Differential diagnosis included RN, tumor progression, or mixed RN/tumor progression

DISCUSSION

As reviewed in a previous case study, diagnosing RN is complicated.[1] The only aspect of RN more controversial

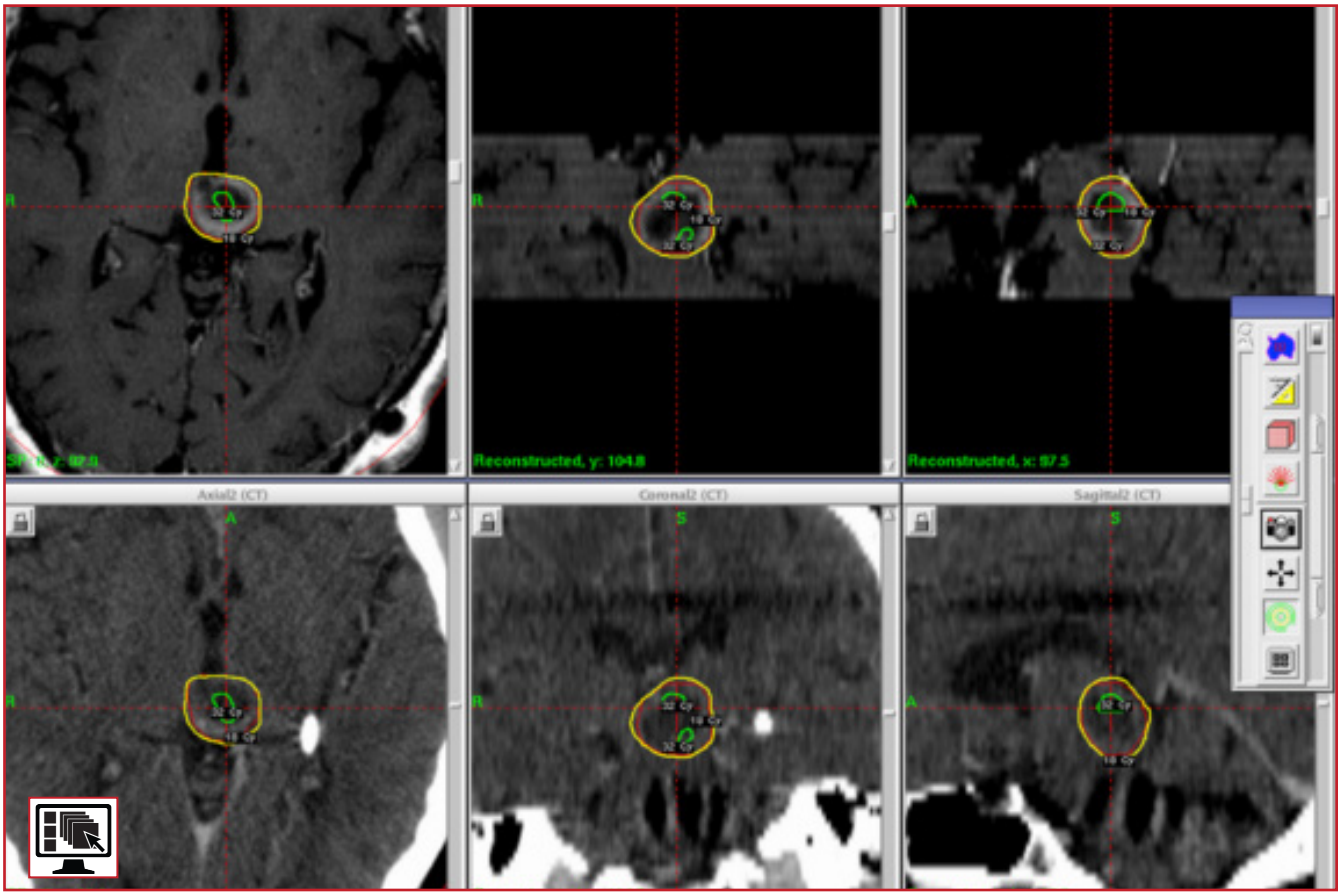

FIGURE 2. *SRS treatment plan for 18 Gy prescribed to the 50% isodose line, which covered 100% of the target. The plan utilized 18 shots using 16-mm, 8-mm, and 4-mm composite sectors. Target volume was 3.9 cm^3. The maximum dose was 36.0 Gy, maximum diameter was 2.1 cm, heterogeneity index (maximum dose/peripheral dose) was 2.000, and conformity index (prescription isodose volume/target volume) was 1.231.*

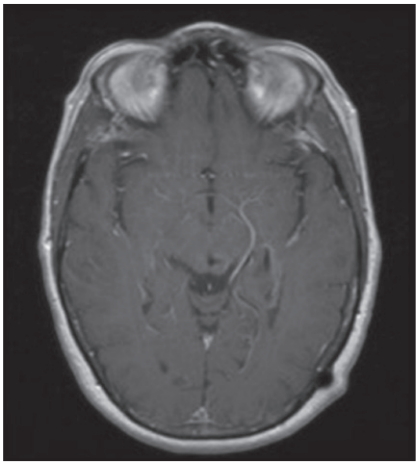

FIGURE 3. *MRI at 12 months post-SRS demonstrated no discrete mass, mass-effect, midline shift or abnormal lesion.*

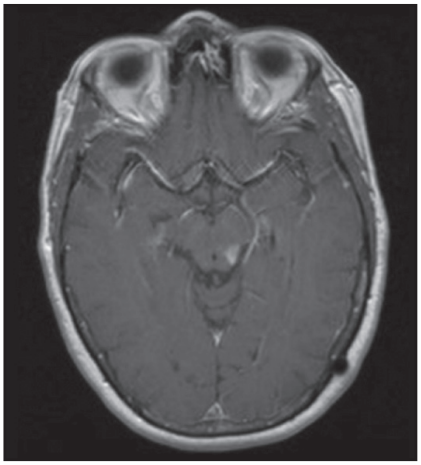

FIGURE 4. *The patient developed symptoms of fatigue and right-sided hemianesthesia, hemithermoanesthesia, and diplopia at 14 months post-SRS. Gadolinium-enhanced T1 axial MRI demonstrated a 0.9 cm x 0.4 cm focus at the site of SRS.*

than accurately diagnosing RN is its management.

Dr. Lars Leksell first published on post-SRS RN in 1987, more than 35 years after pioneering SRS and nearly 60 years after the first published case of intracranial RN. In the 26 years since Dr. Leksell's report, SRS use has increased, but treatment of RN remains nearly as perplexing now as it was then.

Current literature supports the findings of case reports from the 1930s and 1940s, which described clinical courses varying from indolent symptom development to rapidly progressive, fatal courses. Asymptomatic, or radiographic, RN may also occur.

Predictive models and parameters have been developed to reduce the risk of post-SRS RN, but once diagnosed,

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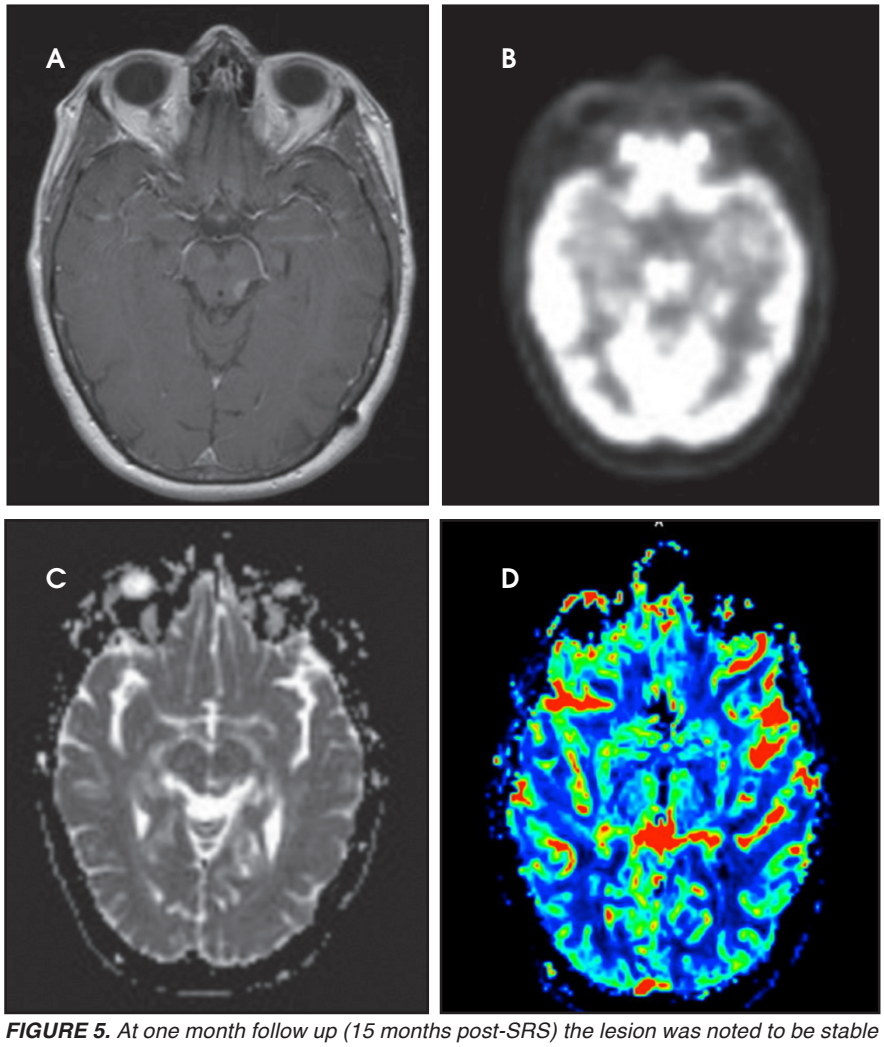

FIGURE 5. *At one month follow up (15 months post-SRS) the lesion was noted to be stable on standard series MRI (A). The treated area was photopenic on FDG-PET (B), demonstrated no decreased diffusion on ADC (C), and was without clear evidence for elevated blood volume in association with this lesion (D). The relative cerebral blood volume assessment was considered to be limited as the left PCA travels in very close proximity to the area of enhancement (within 2 mm) causing substantial increase signal symmetrically about the brainstem related to the arterial enhancement.*

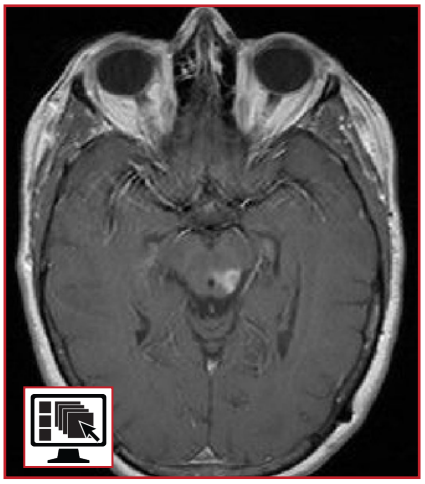

FIGURE 6. *T1W or T1-weighted, contrast-enhanced MRI at 18 months post-SRS demonstrates a stable, enhancing lesion at the site of SRS. Consideration of clinicoradiographic scenario by the multi-disciplinary tumor board yielded recommendation for administration of bevacizumab.*

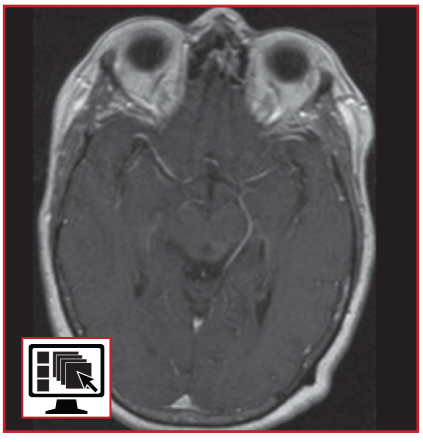

FIGURE 7. *After 4 cycles of bevacizumab (20 months post-SRS, 6 months after onset of new symptoms, and 2 months after commencement of bevacizumab) T1 axial contrast-enhanced MRI demonstrates minimal post-gadolinium enhancement at the site of SRS. No abnormal gadolinium enhancement was noted elsewhere in the brain.*

its treatment remains controversial, as a paucity of data exists regarding RN management.

Published rates of clinical, or symptomatic, RN vary, but may range from 10% to14%. Asymptomatic, or radiographic RN, may occur in 14% to 50% of patients.[1,2] Patients with RN are often treated with corticosteroids, which disrupt the blood-brain barrier, impact VEGF, demonstrate anti-inflammatory effects, and modulate vasodilation, all of which have been linked to the pathophysiology of RN. Patients with RN often demonstrate vasogenic edema, which may result in increased intracranial pressure, focal neurologic symptoms, and seizures. Corticosteroids may bridge these patients through a self-limiting process or they may have therapeutic benefit.[3-5]

Surgery provides histopathologic confirmation and, in many cases, offers sufficient therapeutic intervention. However, not all lesions are amenable to surgical intervention. Non-invasive treatments explored in the treatment of RN include anticoagulation, non-steroidal anti-inflammatory agents (NSAIDs), pentoxifylline with or without vitamin E, bevacizumab, and hyperbaric oxygen therapy (HBOT).

Pentoxifylline with vitamin E was reported in a post-SRS RN case series in which 10 of 11 patients demonstrated

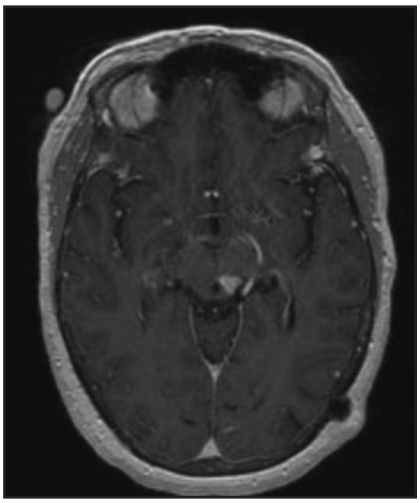

FIGURE 8. *At 37 months post-SRS, the left thalamic lesion has gradually increased in size. At most recent imaging, the lesion was comparable in size to the MRI at 14 months post-SRS, at which point the patient had become symptomatic. Perfusion imaging demonstrates no increase in rCBV.*

volumetric reduction in RN-related edema.[6] The patient without response was subsequently diagnosed with tumor recurrence. No clinical correlation was provided.

One study of 101 brain metastases in 78 patients randomized to post-SRS HBOT demonstrated radiation injury in 11% of HBOT patients and 20% of observation patients.[7] HBOT decreased rates of white matter injury, but not RN incidence.

Bevacizumab (Avastin®) was studied prospectively in a randomized, controlled trial in patients previously treated with fractionated radiotherapy.[8] All patients randomized to bevacizumab, and all cross-over patients, demonstrated clinicoradiographic response to bevacizumab. At 10 months of follow up, 2 of 12 patients analyzed demonstrated radiographic changes consistent with RN recurrence.

Our patient experienced progressive symptoms and radiographic findings despite corticosteroids. Bevacizumab was administered, with dose escalation after 2 cycles for minimal clinicoradiographic response. After 4 cycles, the patient experienced a generalized tonic-clonic seizure and bevacizumab was discontinued. MRI at that time demonstrated resolution of enhancement. Follow-up imaging demonstrated recurrence of enhancement at the site of SRS. The patient currently has persistent, stable radiographic enhancement with right hemianesthesia, right hemithermoanesthesia, and diplopia.

It is unclear whether our patient would have had clinicoradiographic progression without pharmacologic intervention. The lesion may have stabilized after onset of symptoms at 18 months post-SRS. Anecdotal experiences at our institution support case reports denoting varied clinicoradiographic courses of RN.[9,10] Escalation of therapeutic interventions through corticosteroids (without standard "trial" duration), additional pharmacotherapies, HBOT, and surgical intervention is not well established.

The pathogenesis of RN of the brain is not well-understood. No prospective, randomized controlled trials exist regarding post-SRS RN. Interventions remain based on agents effective at mitigating radiation effects in other areas of the body as understanding of post-SRS and its treatment continues to develop.

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CME SEE PAGE 3 FOR DETAILS

Acoustic neuroma

Alan Lee, MS, Samuel Chao, MD, and Erin Murphy, MD

CASE SUMMARY

A 59-year-old ambidextrous male presented with progressive right-sided hearing loss over several years. Pertinent physical exam findings included decreased hearing acuity on the right side and intact facial and trigeminal nerves.

IMAGING FINDINGS

Magnetic resonance imaging (MRI) of the brain showed a 1.5- to 1.8-cm solid and cystic mass that enhances on T1 with contrast at the right cerebellopontine angle and extends into the internal auditory canal, abutting the cerebellum medially (Figure 1).

On the day of treatment a stereolocalization MRI showed a mass in the right cerebellopontine angle extending into the right internal auditory canal with heterogeneous enhancement and cystic peripheral areas. Mass measured approximately 2.5 × 2.1 × 1.2 cm in craniocaudal (CC), transverse, and anteroposterior (AP) dimensions, respectively. There was mild mass effect on adjacent brainstem. Remainder of the cranial nerves were normal in course and caliber. (Figure 2)

Mr. Lee *is a medical student at State University of New York-Upstate Medical University, Syracuse, NY;* ***Dr. Chao*** *and* ***Dr. Murphy*** *are Radiation Oncologists at Rose Ella Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic Foundation, Cleveland, OH.*

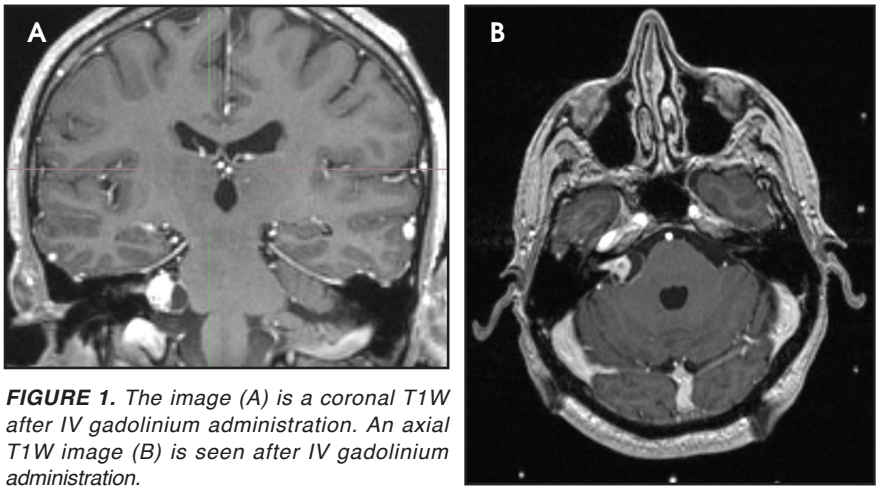

FIGURE 1. *The image (A) is a coronal T1W after IV gadolinium administration. An axial T1W image (B) is seen after IV gadolinium administration.*

DIAGNOSIS

Acoustic neuroma (vestibular schwannoma)

DISCUSSION

Acoustic neuromas, or vestibular schwannomas, are benign Schwann cell neoplasms arising from the myelin sheath of the vestibular portion of the eighth cranial nerve, and rarely the cochlear portion. These tumors comprise 80% to 90% of the tumors of the cerebellopontine angle, and 8% of intracranial tumors overall. The incidence is about 1/100,000 per year[1] and has been rising due to the increase in MRI usage and subsequent incidental discovery. The median age of diagnosis is 50,[1] and the tumors are seen unilaterally in 90% of cases with no predisposition for either side. Patients with neurofibromatosis type 2 are frequently seen with bilateral acoustic neuromas. Risk factors and associations for the development of this tumor include exposure to loud noise, childhood exposure of the cerebellopontine angle to low-dose radiation, and parathyroid adenoma.

The classical presentation of this lesion is unilateral hearing loss in about 95% of patients.[2] Higher frequencies and speech discrimination are disproportionately decreased compared to overall hearing loss. Tinnitus

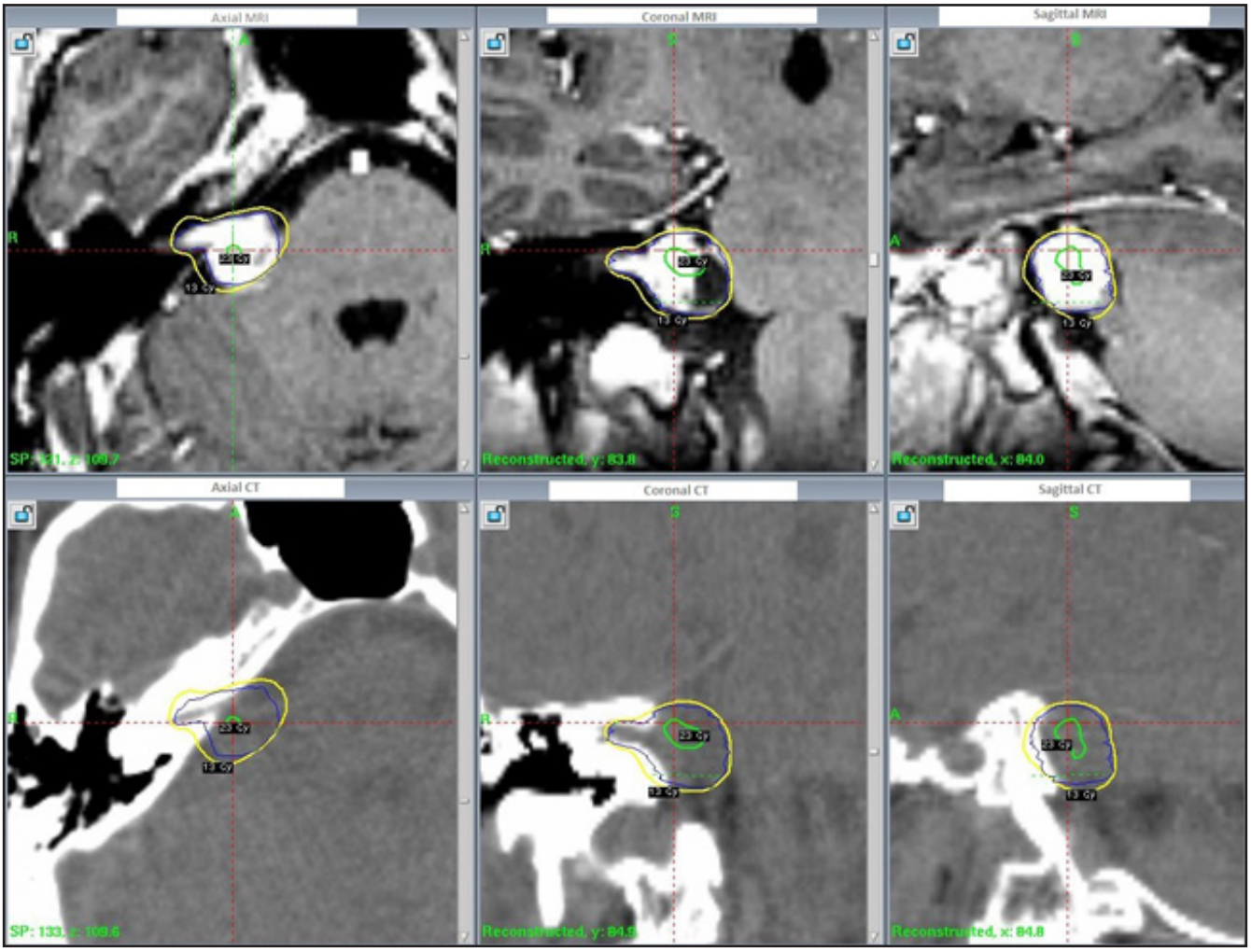

FIGURE 2. *The figure shows Gamma Knife MRI/CT treatment planning contours.*

is also a common symptom, seen in about 63% of patients. Other symptoms can also arise if the tumor compresses nearby structures, such as the facial nerve, trigeminal nerve, brain stem, and cerebellum. Tumor progression can result in herniation of the cerebellum as well as hydrocephalus and involvement of lower cranial nerves. Interestingly, Romberg and other conventional office balance tests are typically normal even in patients presenting with dizziness.

The differential diagnosis for such a lesion is extensive and includes meningioma, facial nerve schwannoma, glioma, cholesterol cyst, cholestetoma, hemangioma, aneurysm, arachnoid cyst, lipoma, and metastatic lesion. MRI can detect lesions as small as 1 to 2 mm in diameter and should be performed with gadolinium contrast. Alternatively, computed tomography (CT) can be done with and without contrast; however, the resolution is much more poor. An enhancing lesion on MRI/CT in the region of the internal auditory canal with possible extension into the cerebellopontine angle is the typical radiological finding.

Treatment options include observation, surgery, radiosurgery, fractionated radiotherapy, and proton therapy. Observation alone can be considered when the patient is older than 60, has significant comorbities, has a small tumor size, lacks symptoms, or due to patient preference. About 43% of patients will progress, 51% will remain stable, and 6% will regress with conservative management.[3] Surgery has about a 15% to 20% 10-year recurrence rate for partially or incompletely resected tumors.[4,5] Preservation of remaining hearing is between 37.5% and 57% and can vary greatly depending on the technique.[6,7] The chance of mortality from surgery for acoustic neuromas is about 1% and depends heavily on the size of the tumor and surrounding structures.[8] Surgical intervention would be indicated if the lesion is causing any mass effect symptoms. Radiosurgery is typically used for tumors ≤ 3 cm and has an

excellent local control rate of > 95% in most institutions.[9] Radiosurgery is typically defined as radiotherapy treatment utilizing a single fraction. Fractionated radiotherapy typically involves 5 or 6 weeks of therapy. There are similar outcomes between fractionated radiotherapy and radiosurgery, but fractionated radiotherapy requires a more intense time commitment for the patient.[9] Hearing preservation is achieved in about 55% to 71% of cases with very low facial and trigeminal nerve toxicities.[9] Proton therapy is the newest treatment technique used for acoustic neuromas, but the outcomes have not yet been on par with that of other more conventional therapies.[9,10] In addition, the cost of proton therapy is also much greater than more established therapies.

This particular patient opted for radiosurgery. The radiotheraputic technique used was GammaKnife stereotactic radiosurgery and the patient was treated with 13Gy to the 51% isodose line in a single fraction. The treatment planning was performed using a high-resolution, thin-slice MR after the fitting of a head frame (Figure 2). Subsequent follow-up at 6 months displayed cessation of tumor progression and the patient's hearing loss was stabilized. He will continue to be followed with yearly MRIs.

CONCLUSION

Acoustic neuromas are relatively common benign intracranial lesions, which present typically with hearing loss and, less commonly, tinnitus. MRI findings will show an enhancing lesion arising from the internal auditory canal and possibly extending into the cerebellopontine angle. The incidence is rising due to increasing utilization of MRI. The current standard of care at most institutions is radiosurgery due to the very high local control rate, and relatively low rates of morbidity when compared to other treatments.

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