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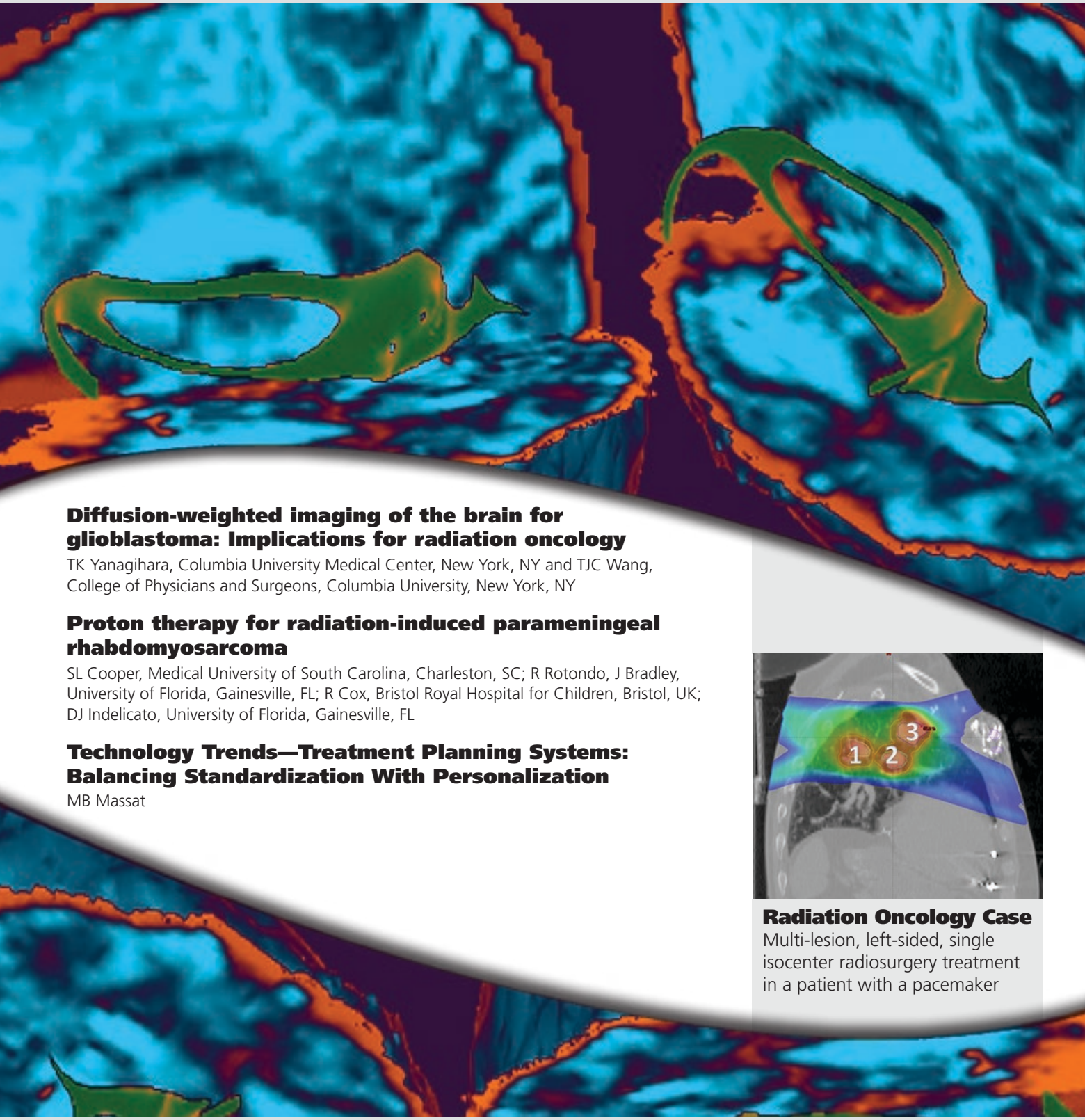

Diffusion-weighted imaging of the brain for glioblastoma: Implications for radiation oncology

TK Yanagihara, Columbia University Medical Center, New York, NY and TJC Wang, College of Physicians and Surgeons, Columbia University, New York, NY

Proton therapy for radiation-induced parameningeal rhabdomyosarcoma

SL Cooper, Medical University of South Carolina, Charleston, SC; R Rotondo, J Bradley, University of Florida, Gainesville, FL; R Cox, Bristol Royal Hospital for Children, Bristol, UK; DJ Indelicato, University of Florida, Gainesville, FL

Technology Trends—Treatment Planning Systems: Balancing Standardization With Personalization

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Multi-lesion, left-sided, single isocenter radiosurgery treatment in a patient with a pacemaker

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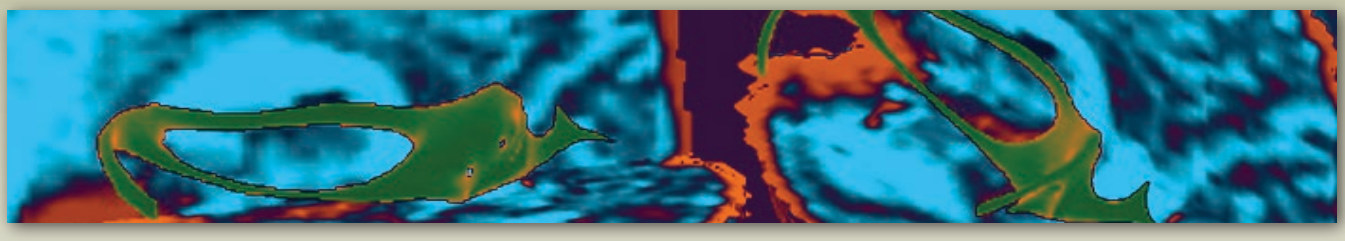

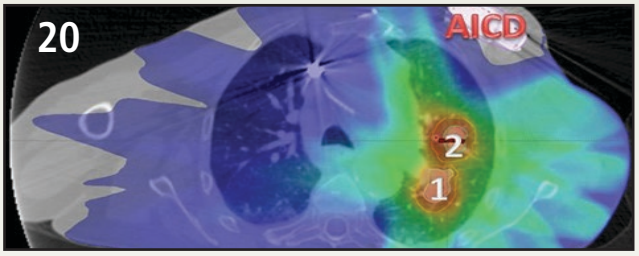

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Applied Radiation Oncology
2015 Article of the Year Contest

***Applied Radiation Oncology* is pleased to announce its new Article of the Year Contest for 2015!**

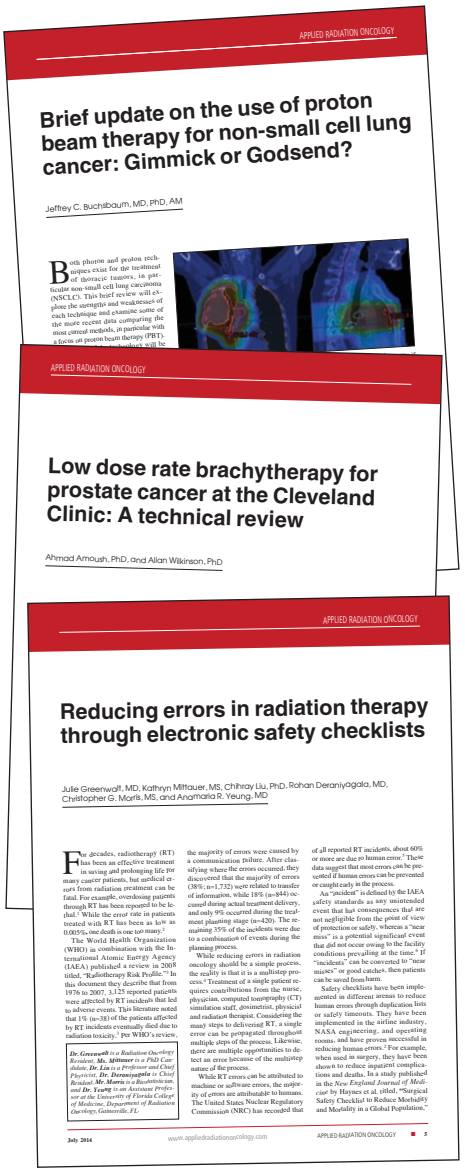
The first-place winner will receive a $500 American Express gift card for the best review article published in the ARO journal in February, June, September or December 2015.

The ARO Advisory Board will judge entries based foremost on practical application, but also on originality and presentation. A first-place winner and honorable mention will be announced in December 2015.

All review articles published in ARO in 2015 will be automatically entered into the Article of the Year contest.

Click here to review submission guidelines and submit your manuscript

Click here to see an example of a published review article



Thank you for supporting Applied Radiation Oncology!

We look forward to your participation in the contest!

EDITORIAL

A few of our favorite (new) things

John Suh, MD, Editor-in-Chief

Welcome to the December issue of ARO! This month we are pleased to share several exciting updates and launches as we round the corner to 2015. First, I am delighted to introduce four new members of ARO's esteemed advisory board:

- **Andrew Kennedy, MD, FACRO,** Sarah Cannon Research Institute, Nashville, TN, and North Carolina State University, Raleigh, NC
- **Keith Hsiu Chin Lim, MBBS, FRANZCR,** National University Cancer Institute, Singapore
- **Heath B. Mackley, MD,** Penn State College of Medicine, Hershey, PA
- **Suresh Senan, MRCP, FRCR, PhD,** VU University Medical Center, Amsterdam, The Netherlands

The advisory board plays a key part in critiquing review articles and case studies to ensure clinical interest, relevance and practical application. We are grateful for their time and expertise in tracking trends, securing contributors, and refining our efforts to produce high-quality, robust information. For titles and a complete list of the advisory board, please see p. 1.

We have several new initiatives in 2015. We will have a 2015 Article of the Year contest, which will give you the chance to win $500 (details on page 3). To provide timely updates in radiation oncology, vendor announcements, research developments, and related news and tips, ARO is also introducing a monthly e-newsletter in 2015. Finally, we are unveiling a new ARO website and rolling out a mobile app at the end of January. The website will incorporate a responsive design to facilitate use on various devices including tablets and smartphones. The app will be available for download on OS and Android devices.

Since facilitating information access continues to evolve in radiation oncology on a regular basis, this issue's Technology Trends explores advances in treatment planning systems and discusses the need to balance automation with personalization.

Also in the issue, Drs. Yanagihara and Wang from Columbia University in New York present *Diffusion-weighted imaging of the brain for glioblastoma: Implications for radiation oncology*. This in-depth review article examines diffusion imaging in neuro-oncology, experimental applications in glioblastoma, ways to overcome limitations, and future directions. In addition, *Proton therapy for radiation-induced parameningeal rhabdomyosarcoma* by Dr. Cooper and colleagues from Medical University of South Carolina, Charleston, outlines how patients with heritable retinoblastoma face a heightened risk of developing secondary malignant neoplasms—a risk that's significantly increased by radiotherapy. Read how proton therapy can reduce this risk and other effects of radiotherapy.

Lastly, enjoy the winning case report, *Multi-lesion, left-sided, single isocenter radiosurgery treatment in a patient with a pacemaker,* and runner-up, *Diffuse chest wall calcifications after post mastectomy radiotherapy for breast cancer*. Congratulations to our winners! We are thrilled to showcase these interesting cases, and encourage your submissions. Click here for contest details.

Thank you for your support in making 2014 another successful year of serving the radiation oncology community! We look forward to exciting changes ahead as we usher in 2015. Please enjoy the holiday season.

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

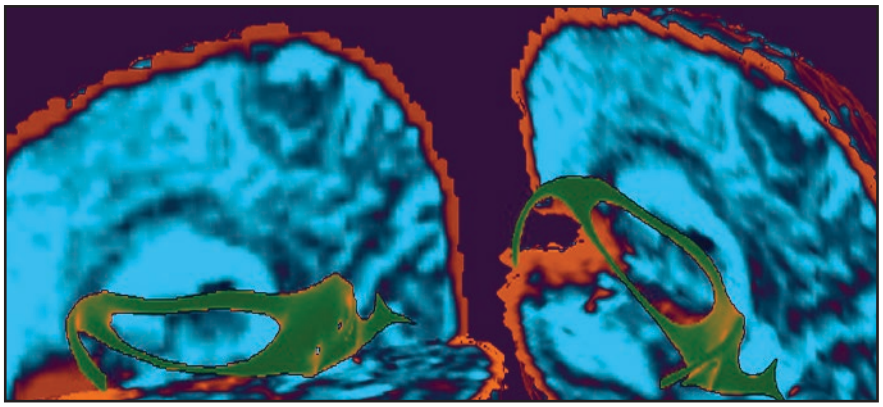
Diffusion-weighted imaging of the brain for glioblastoma: Implications for radiation oncology

Theodore K. Yanagihara, MD, PhD, and Tony J. C. Wang, MD

Magnetic resonance imaging (MRI) has become the foundation of diagnosis and monitoring in glioblastoma, and advanced techniques in data acquisition and analysis hold promise in improving clinical practice. Diffusion-weighted imaging (DWI) and diffusion-tensor imaging (DTI) represent 2 advanced image acquisition sequences that have been under development for over 2 decades and are now assuming a role in routine management of oncologic patients. These approaches are being investigated across body systems and have already established value in the diagnosis and management of prostate cancer.[1-3] In a similar fashion in glioblastoma, the use of DWI and DTI has begun to expand outside of research settings and into patient care.

Rationale for diffusion imaging in neuro-oncology

This review focuses on diffusion imaging in glioma and, more specifically, on the ways DWI and DTI are becoming part of the management of patients with glioblastoma. These advances are based on the observation that tumor cell density is typically higher than normal tissue, and this increased cellularity leads to restricted extracellular water diffusion. DWI is sensitive to the degree of this water restriction and DTI offers a means of further quantifying the orientation of the restriction. The ability to use diffusion imaging as a noninvasive measure of cellularity has been demonstrated through extensive preclinical work. Recent studies have demonstrated that these methods might be used in patients to aid in the diagnosis and grading of tumors, estimate the extent of tumor infiltration, evaluate for residual or recurrent disease after an intervention, stratify a cohort based on the likelihood for an individual's response, modify radiation contours to avoid low-risk areas and target areas with subclinical disease, improve neurosurgical approaches, look for early responses or progression, and differentiate between true progression and pseudoprogression. How to sort through these lofty goals and identify what holds the most promise will be part of the challenge in glioblastoma management. This review is aimed at helping the reader gain an understanding of the concepts of diffusion imaging and several of the emerging applications of the technique for radiation therapy utilization.



Dr. Yanagihara *is a radiation oncology resident at Columbia University Medical Center, and* ***Dr. Wang*** *is assistant professor of radiation oncology, at the Department of Radiation Oncology, College of Physicians and Surgeons, Columbia University, New York, NY.*

Principles of diffusion imaging

The effect of molecular diffusion on the magnetic resonance signal was noted in the classic paper on spin echoes by E.L. Hahn in 1950, which forms the

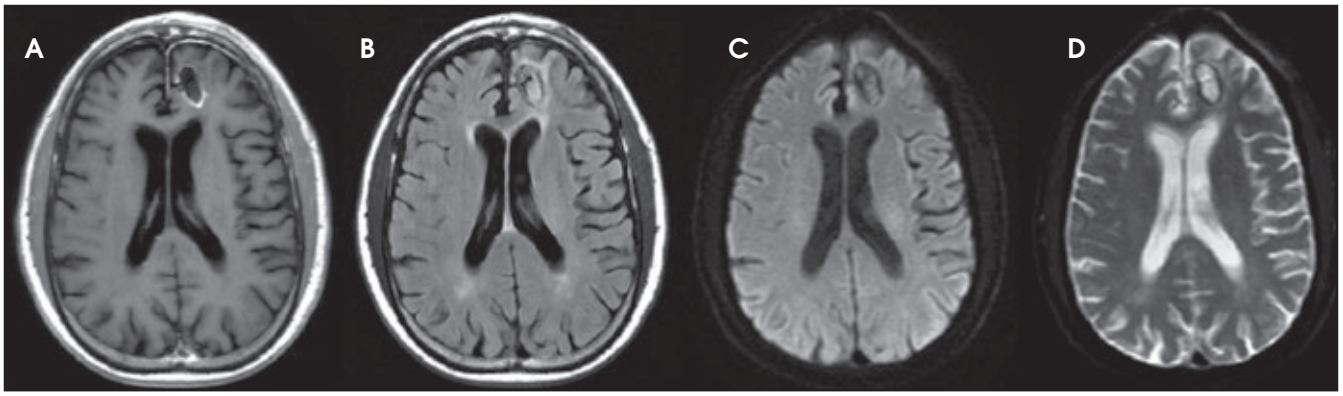


FIGURE 1. *Axial MRI taken for a patient with a left frontal glioblastoma with four sequences, A) T1 post contrast, B) T2 FLAIR, C) DWI and D) ADC map. ADC was calculated using b0 and b1000 diffusion-weighted images. These studies demonstrate the qualitative differences between imaging sequences that can highlight enhancing gross tumor involvement seen in image A, surrounding edema in B, and diffusion restriction at the rim of the tumor cavity along with unrestricted diffusion in the cystic/necrotic tumor core seen in images C and D.*

basis of DWI and DTI to this day.[4] Medical imaging is almost exclusively devoted to protons, which comprise about 2/3 of the atoms in the human body. Most of that is water, although the protons in the CH_2 groups in fat can also be imaged. Water molecules will diffuse according to the principle of Brownian motion (i.e., random walk) unless restricted by their environment. If water molecules diffuse in any volume where the external magnetic field is inhomogeneous (e.g., through application of transient external field gradients), this will affect resonant echoes of the protons being probed by MRI. Within the body, cell membranes provide a barrier to diffusion. Fluid in the extracellular space will diffuse less readily in a crowded environment, such as in cases of tumor infiltration or when cells swell from a shift of fluid intracellularly where restriction is high. Diffusion MRI pulse sequences allow detection of both the magnitude and direction of water diffusion.

Diffusion-weighted image acquisition

The concept of how diffusion of water molecules can affect their resonant signals is easy to grasp, but the physics and mathematics for this procedure are extremely technical in detail. Interested readers are referred to a very concise review by Le Bihan et al., or to Koh and Collins for an excellent overview of general clinical applications.[5,6]

For the purposes of this review, we must introduce some commonly used mathematical terms. In the idealized case of isotropic diffusion, and ignoring other flows such blood, the DWI signal would be expected to have a simple exponential relationship where b is an experimentally adjustable parameter that includes the timing and magnitude of the external magnetic field gradients used in the DWI pulse sequences, D is the diffusion coefficient, and A_0 is the signal in the absence of diffusion:

$$A = A_0 \exp(-bD)$$

For water in an isotropic medium, $D = 2 \times 10^{-3}$ mm^2/s at room temperature; note that the viscosity of water and, hence, self-diffusion is very temperature-dependent, with an increase of about 2% per degree C. Higher b values essentially mean that the image was acquired allowing longer times for diffusion to affect the signals detected. With b=0, one gets a standard T2-weighted image that depends on the other acquisition parameters.

By acquiring DWI images at even a few b-values, one can estimate the diffusion coefficient for the resonant protons. In fact, this is an empirical parameter since it likely includes other flow mechanisms besides simple Brownian motion. The result is called the ADC, the apparent diffusion coefficient. As the review by Koh and Collins notes, ADC's are often reported as indices of therapeutic response, but the actual numbers obtained for ADC can vary widely depending on the exact details under which the DWI images were taken, and standardization is lacking.[6]

Diffusion-tensor imaging

In the cerebrospinal fluid, diffusion is largely unrestricted and the motion of water molecules is isotropic. In white matter tracts, diffusion is restricted by axonal cell membranes and water diffuses anisotropically. By quantifying diffusion anisotropy along multiple directions within a tissue, the density and orientation of the cellular structure within a unit of measurement (i.e., a voxel) in an MRI image can be estimated.

A diffusion tensor is the mathematical description of the three-dimensional orientation of an ellipse, which in DTI represents the principal direction of water motion. While DWI acquires data in only 3 directional planes, DTI requires that at least 6 directions be imaged in order to calculate a diffusion tensor. The greater the number of diffusion directions acquired, the more accurately the calculated diffusion tensor represents the true direction of water movement.

Table 1. Differences in signal intensity vary based on a number of factors, and a general guide for relative signal intensities is provided. Bright (hyperintense) and dark (hypointense) notations are qualitative descriptors relative to other tissue components in the image.

	FLAIR	DWI	ADC
White matter	Iso/Hypo	Dark	Bright
Gray matter	Iso/Hyper	Bright	Dark
CSF	Dark	Dark	Bright
Dense tumor	Variable	Bright	Dark
Tumor necrosis	Variable	Variable	Variable
Cystic	Often dark for simple cysts and bright for proteinacious or tumor cysts	Variable	Bright
Abscess (centrally)	Bright	Bright	Dark
Edema	Bright	Bright	Bright
Acute infarct	Variable	Bright	Dark

Common parameters derived from DTI include the fractional anisotropy (FA) and mean diffusivity (MD). Occasionally, the components of fractional anisotropy are analyzed independently, such as axial and radial diffusivity or the isotropic and anisotropic components of FA. MD is used interchangeably with ADC, since the ADC is an average of the measured diffusion directions. While ADC and MD represent the magnitude of diffusion, FA describes the degree of anisotropy of diffusion. For example, in the body of the corpus callosum, diffusion is anisotropically oriented along the axis of fiber tracts as they cross from one hemisphere to another. The magnitude of FA will decrease as the anisotropy decreases, such as in areas of crossing fibers with different orientations or where there is more gray matter. FA, which varies between 0 and 1, will be near-0 in cerebrospinal fluid (CSF) and near-1 in white matter. An example demonstrating qualitative differences of MRI sequences in glioblastoma is shown in Figure 1.

Because DTI quantifies the degree of anisotropy across voxels in the brain based on the orientation of fiber tracts, a voxel-wise analysis may be performed to generate white matter fiber tracts. DTI tractography has developed into a large field of study with broad research and potential clinical applications.

Standard clinical applications

Clinicians are most familiar with diffusion imaging in the setting of neurovascular injury. DWI began being applied in the setting of stroke evaluation approximately 2 decades ago and is now routinely used in clinical practice to determine the presence and chronicity of stroke evolution.[7,8] In the setting of acute ischemia, it is hypothesized that extracellular fluid moves into the intracellular compartment where diffusion is relatively restricted. This displays a pattern of restriction, where areas of acute ischemia appear hyperintense (i.e., high value) on DWI and hypointense (i.e., low value) on ADC images. As ischemia resolves over the course of several weeks, ADC increases above normal and serves to highlight areas of more chronic injury. The sensitivity of DWI and ADC to distinguish between acute and chronic injury has led to their application as the standard imaging sequences in evaluating stroke. Other clinical uses of diffusion imaging include evaluating infection (e.g., abscesses), inflammation, demyelination (e.g., multiple sclerosis), edema, cysts and trauma. Signal intensities for benign and pathologic imaging findings vary across MRI sequences and a general overview of common descriptors is provided in Table 1.

Experimental applications in glioblastoma

Improved diagnosis and histologic subclassification

MRI provides a noninvasive means of identifying intracranial pathologies, and diffusion imaging has a natural role in separating certain benign (e.g., cystic or infectious) lesions from malignancies. There has been considerable interest in diagnostic radiology to apply diffusion imaging techniques in the setting of suspected neoplasia within the central nervous system. Innumerable studies in the literature aim to correlate diffusion parameters across disease sites with various pathologic findings and patient outcomes. These studies hypothesize that tumors with high cellular density will restrict extracellular diffusion and correlate with diffusion parameters.

An important topic in this area is the diagnosis and grading of primary glial tumors through imaging. A reliable noninvasive diagnostic method for suspected glioma may be useful in cases where a brain biopsy either cannot be safely obtained or if a biopsy is attempted and is nondiagnostic. Perhaps a more frequently encountered scenario is when a biopsy is positive for a low-grade glioma, but the presence of new clinical symptoms or the appearance of the disease by standard radiographic techniques suggests a more aggressive histology. In these cases, biopsy results indicating low-grade histology may be due to random sampling, such as in a lesion with mixed features. Furthermore, it may be possible to follow patients with a low-

grade glioma to noninvasively monitor for conversion to a higher grade.

Preclinical work in rodent models has motivated the application of diffusion imaging to estimate tumor cellularity in humans. These studies have been discussed elsewhere and demonstrate a high sensitivity of diffusion parameters to changes in the cellular density of a tumor.[9-11] However, there are many added limitations when applying DWI in humans (e.g., patient heterogeneity, lower field magnets, head motion, restricted scan time and data acquisition, etc.). To test the ability of diffusion imaging to quantify the cellular density in humans, Sugahara and coworkers acquired DWI data from 20 patients with pathologically confirmed glial cell tumors.[12] The minimum ADC value was correlated with the density of cellular nuclei across a standard pathologic slide, and the authors found a strong relationship (r = -0.77) between the 2 variables. In a similar study of 10 patients, including WHO grade II and IV tumors, the authors also found a relationship between ADC and cell density of the same magnitude (r = -0.77).[13] In one of the largest series to examine this question, a Chinese group retrospectively evaluated over 100 glial tumors and correlated the minimum ADC value with glioma grade.[14] In their study, minimum ADC was significantly correlated with grades 2, 3 and 4 glioma (r = -0.524) and a weaker, but statistically significant, relationship was found between the minimum ADC and the Ki-67 mitotic labeling index (r = -0.312). These data along with other studies help to confirm preclinical findings that highly cellular tumors are associated with low ADC values, which supports this modality as a noninvasive measure of tumor grade.[15,16]

The tendency of glioblastoma to infiltrate along white matter tracts often leads to extensive disease and may underlie multifocal presentations or recurrences after treatment. Currently, edema (i.e., radiographically T2/FLAIR positive) is the best marker for the subclinical spread of tumor, but is a qualitative measure and is not specific to changes due to tumor infiltration. Diffusion imaging, particularly DTI, may offer an improved means of evaluating the presence of subclinical disease that is not only qualitative, but may also quantify spatial and temporal changes to assist in radiation treatment planning.

Because white matter is arranged in a highly organized pattern, diffusion is similarly restricted along the axis of fiber tracts, but as glioma cells infiltrate these tracts, they disrupt this order along with anisotropic diffusion (i.e., fractional anisotropy [FA]). Therefore, DTI measures should be sensitive to infiltrating the tumor and be particularly useful in identifying glioblastoma. This idea has been illustrated in a comparison between high-grade glioma and other brain tumors.[17] However, while some studies of FA have been promising, [18-20] others have questioned the utility of FA over other radiographic measures, including other diffusion parameters.[21-23] Many of these studies suffer from small sample sizes and a heterogeneous population of patients making negative studies difficult to interpret.

The most definitive test for FA in estimating the presence of a tumor is through pre-biopsy measurements. In one of the few studies to address this, 19 patients were scanned with DTI prior to stereotactic biopsy of brain tissue.[24] Here, FA was found to significantly correlate with cell density (r=0.73) and the Ki-67 labeling index (r = 0.8). Similarly, a Japanese group utilized DTI to calculate the FA and MD values within pathology-confirmed gliomas of grades I – IV.[20] In 41 patients, the authors found a clear separation in FA values between high grade (III – IV) and low grade (I – II) glioma. MD served less well as a marker for tumor grade, but results were still in-line with previous reports showing increased values for grade I relative to higher grade tumors. These studies represent a small sample of the promising work being done to apply DTI in clinical settings, but there are limitations in image quality, lengthened acquisition time and labor-intensive data analysis to overcome before the methods are more widely adopted.

Predicting and evaluating treatment response for glioblastoma

DWI has been proposed as a potential marker of early treatment response and may be used to predict who will benefit from a particular therapy before initiation of radiation treatment. The rationale is that necrotic tumors and/or those low in vascularity may be more resistant to either systemic agents (e.g., due to decreased delivery) or radiation (e.g., due to poor tumor oxygenation). Additionally, if a tumor is sensitive to treatment, its cellularity is expected to decrease either during or soon after a course of therapy. The role of diffusion imaging in respect to this topic has been investigated and reviewed largely by a group at the University of Michigan, who has performed a number of seminal studies on the topic.[25] They have reported results from a cohort of 60 patients with WHO grade III or IV glioma.[26] In this prospective study, DWI data were acquired at 3 time points during the course of treatment. Rather than taking an intra-lesion measure of ADC, a voxel-wise analysis was performed on each brain, and changes in this map across time were correlated with survival outcomes. Intriguingly, the authors found that increases in diffusion at 3 weeks into a course of radiotherapy were associated with improved rates of survival at 1 year. Other work has supported this use of diffusion imaging in guiding conventional radiotherapy and stereotactic radiosurgery with promising results.[27-32]

Bevacizumab is one systemic agent that has been used to treat glioblastoma,

although despite promising phase II data it was not shown to improve overall survival in a randomized controlled trial.[33] However, there is interest in identifying a subgroup of glioblastoma patients for whom bevacizumab may be appropriate, particularly because the drug improved progression-free survival when added to standard management. Ideally, a pretreatment marker would be used to predict response to the intervention, and this could be used to stratify patients in future trials. A group at the University of California, Los Angeles has proposed a method for filtering the ADC histogram taken from non-necrotic portions of tumor. These values likely correlate with more densely cellular regions of tumor, and the authors found that they were a reliable biomarker to predict a response to bevacizumab.[34] Moreover, the authors found that their quantification of the ADC distribution was a superior predictor of progression-free survival relative to the Macdonald criteria, a standardized post-treatment radiographic assessment.[35] Others have begun to validate the ability of ADC to serve as a biomarker of response and have published encouraging results.[36, 37]

ADC may also serve as a useful biomarker for early responsiveness to the current standard of care. The success of temozolomide (TMZ) and radiation therapy in a large randomized trial has established it as the first-line chemotherapeutic agent in this disease.[38,39] Furthermore, important work in understanding the biochemical mechanism of its effectiveness has led to a valuable epigenetic marker for predicting treatment response.[40] These advances have changed management of glioblastoma and revealed further subgroups of patients who may experience relatively dramatic improvements in survival. How to identify these patients early in their course of therapy has become an important question, particularly with the hope that novel interventions will provide options for alternative treatment courses for poor-responders. To test the ability of diffusion imaging to predict response to TMZ, Khayal and coworkers evaluated MRI data before, during and immediately after a course of concurrent RT-TMZ for glioblastoma.[41] The authors acquired DWI and DTI data between 3-5 weeks into a course of radiotherapy with daily TMZ. They quantified several diffusion parameters at this time point and compared these to a post-treatment scan. Here, an increase in ADC after chemoradiation relative to during treatment was correlated with a lower risk of 6-month progression. Many studies are underway to further characterize the ability of various diffusion measures to predict and evaluate treatment responses. Published literature has begun to establish this role, but should be interpreted with caution as these methods are experimental, often involve a small number of patients, and are subject to publication bias. Another significant problem raised on Koh and Collins review was the lack of standardization in the DWI acquisition parameters, which can affect results.[6] With the work of the Michigan group as a foundation, clinical trials may soon test the utility of DWI to assess a patient's disease during treatment. A convincing study will ensure standardized data acquisition and analysis techniques with quality assurance measures to remove poor-quality MRI scans. The implication is that DWI may provide an early marker of treatment response to guide modifications in radiation target delineation and dose prescription as well as chemotherapeutic modifications.

Monitoring for recurrence

In addition to predicting or tracking response to treatment, there is an interest in utilizing DWI to estimate the probability of recurrent disease after radiation therapy. Noninvasively assessing the existence of recurrent disease has long been a challenge due to post-surgical and radiation changes along with pseudoprogression or pseudoresponse.[42,43] This is a commonly encountered problem, with up to 50% of patients treated with standard management found to have pseudoprogression, with each case causing a clinical dilemma in determining further management.[44] Standard radiographic methods have been proposed, such as the Macdonald, RECIST and RANO criteria, but additional measures are clearly needed.[35,45-47] As described above, diffusion imaging is a sensitive measure of tissue cellularity, but its susceptibility to post-treatment artifacts has not been clearly defined.

To compare the ability of ADC values to distinguish progression versus treatment-induced changes, one study analyzed data from 18 patients in whom 7 had histologic confirmation of tumor recurrence.[48] ADC values were significantly lower on tissue identified as recurrent disease relative to areas of non-recurrence. These data are consistent with other work that has relied on long-term radiographic follow-up to distinguish progression versus pseudoprogression, but additional studies that utilize post-treatment biopsy or resection tissue are needed.[49-51]

Other work is underway to develop a multimodality approach, as opposed to a single measure, to describe post-treatment changes. In a recent example, Cha et al., analyzed patients who received standard therapy with surgery plus adjuvant chemoradiotherapy and were found to have possible radiographic progression.[52] Both ADC and regional cerebral blood flow (rCBV) histograms were generated from enhancing areas that were questionable for progression versus pseudoprogression. The authors found that the combined analysis was superior to either analysis alone, and that the multiparametric measure was predictive of progression-free and overall survival. They hypothesize that ADC and rCBV are particularly well-suited in evaluating tumor recurrence because they each supplement for some of the deficiencies of the other.

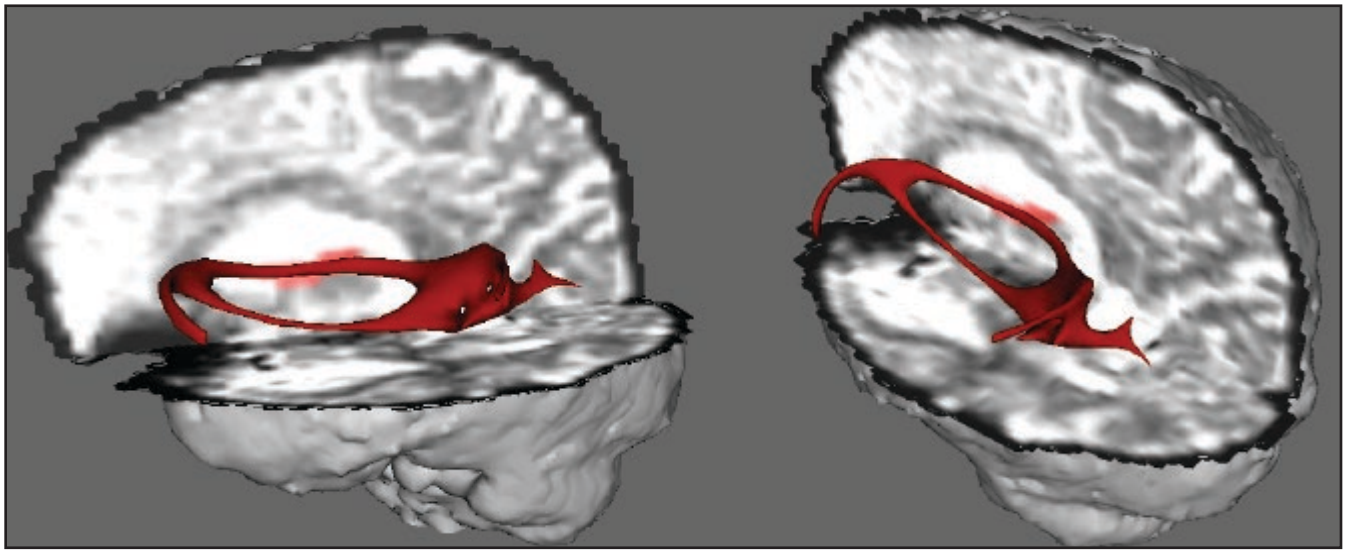


FIGURE 2. *DTI may be useful for neurosurgical planning, as in this example where an intracranial mass in the left hemisphere has produced mass effect. DTI fiber tractography was performed between language areas to map the arcuate fasciculus, which appears to be displaced and abnormally divergent into superior and inferior tracts.*

This principle has been applied in several other investigations aimed at developing multimodality measures (see below).

Overcoming limitations and future directions

Special challenges in data acquisition

A major limitation of single measures of ADC (e.g., minimum, maximum or mean) is the information lost in data reduction. This may greatly reduce the sensitivity of ADC measures of glioma, which are often heterogeneous lesions with areas of dense tumor, necrosis, cystic fluid, and hemorrhage all potentially within a single focus of disease. Many of the studies mentioned in this review are limited in this regard and others have described more sophisticated approaches to data analysis.

One method to address this obstacle is to perform voxel-wise ADC analyses as proposed by Moffat and colleagues,[30] or to perform ADC histogram analyses as described in several of the studies reviewed here.[34,52] This may be a particularly important consideration when analyzing tumor responses to therapy because there may be a nonuniform response to treatment that may not be captured by taking, for example, the mean ADC value across the full volume of a lesion, or even the non-necrotic portion of a tumor.

Another limitation is the variability in DWI sequences from one center to another, between scanners in the same center or in a single scanner across time. Also, the reliability of ADC depends on how the data are acquired. For example, diffusion neuroimaging in most practices is carried out by acquiring a b0 (i.e., T2-weighted) image and a b1000 image. ADC is calculated from these 2 points, which places the accuracy of the measure upon the quality of only 2 images. Furthermore, higher b-values are impaired by an inherently low signal-to-noise ratio. Added to the natural susceptibility of echo-planar imaging to artifacts and the particular sensitivity of diffusion-weighted imaging to head motion, these factors make high-quality data acquisition a challenge.[53,54] One way to improve data quality is through scan averaging, where multiple diffusion sequences are acquired and merged post-hoc. This can improve the accuracy of ADC while maintaining image resolution, particularly when data are acquired at higher field strengths. Another approach to improving accuracy is through acquiring additional b-values, which is more often performed in diffusion imaging of other body systems. The difficulties in obtaining high-quality diffusion data make it difficult to interpret negative studies, particularly when performed on a small cohort. Furthermore, in the clinical setting there are practical limitations to scan time, and these added MRI sequences must be well-justified both from the perspective of scan time for patients and health care costs.

Other challenges relate to data analysis, which can be time- and labor-intensive, and require proper equipment and expertise. While many commercial and public software packages are available, developing more standard protocols for data processing and quality assurance must precede adopting these techniques to general clinical practice.

Determining radiation treatment volumes

Over the past several decades, radiation treatment volumes for glioma have decreased from whole-brain irradiation with two-dimensional planning

to three-dimensional conformal partial brain radiotherapy often utilizing intensity-modulated radiation.[33,55,56] It has also been well-established that the majority of tumor recurrence occurs within the high-dose treatment volume, and that boosting presumed high-risk areas does not necessarily improve local control.[57-59] These findings bring into question the current standard in treatment volume delineation. While lower overall doses may negatively impact survival, it may be possible to continue the trend toward smaller treatment volumes by using diffusion imaging to tailor the high-dose region to areas at highest risk for subclinical spread.[60] Rather than using a somewhat arbitrary, but still standard 2 cm margin upon T2/FLAIR hyperintensity, a more sophisticated method of estimating subclinical spread of disease is needed. It may be that dose escalation studies have failed to improve outcomes because of overtreatment of low-risk areas of viable brain without sufficient dose intensification to the highest risk regions.

Many groups deviate from the traditional treatment volumes used in RTOG studies, but evidence-based alternatives to target delineation is lacking. Investigations by Price and colleagues have begun to address this.[17,19,61] In one study, the authors performed a prospective analysis of 20 patients who underwent standard and diffusion-tensor MRI followed by stereotactic or image-guided biopsies.[61] Histopathologic findings were correlated with the voxels corresponding to the sampled area and DTI data were analyzed. The authors found that the degree of isotropic and anisotropic diffusion was closely correlated with the presence of gross and infiltrative tumor. In fact, they describe their method as being 98% sensitive and 81% specific for disease.

Data-driven methods for defining radiation treatment volumes are unlikely to improve local control, but will likely reduce exposure of viable brain to high doses of radiation. With modest, but important improvements in survival with modern care, brain re-irradiation is becoming more common for treatment glioblastoma and is being tested in an RTOG trial (http://www.rtog.org/ClinicalTrials/ProtocolTable/StudyDetails.aspx?study=1205). By sparing as much normal tissue as possible in a patient's initial course of radiotherapy, additional radiation in the recurrent setting might fall within an acceptable therapeutic window.

Neurosurgical planning

Somewhat more experimental is the application of DTI tractography for neurosurgical planning purposes. Functional neuroimaging is used in some centers to better identify eloquent brain regions, such as language, motor or sensory cortices in an effort to preserve function after tumor resection.[62-65] DTI may improve delineation of important white matter fiber tracts that may be displaced or deformed due to tumor mass effects. Figure 2 illustrates a patient with a large tumor in the left temporal lobe that was planned for surgical resection. DTI and fiber tractography were performed between the left inferior frontal gyrus representing Broca's area and the left superior temporal gyrus representing Wernicke's area. Robust fibers were identified representing the arcuate fasciculus and mass effect from the tumor not only displaced the fibers medially, but also appeared to separate the arcuate into a superior and inferior tract with no coherent fiber orientation between the two. In conjunction with other presurgical and intraoperative assessments, these images can guide the resection approach and extent. Early work in this area has demonstrated the feasibility of the method with neurosurgical and even radiosurgical planning, but future studies are needed to determine its role in improving resection and treatment outcomes.[66,67]

Multifactorial modeling

The evidence presented in this review demonstrates a significant role for diffusion MRI techniques for the noninvasive clinical management of brain tumor patients. Along with improvements in diffusion MRI acquisition and analysis, there have been concurrent gains in other noninvasive strategies of tumor assessment. Namely, PET, MR spectroscopy and cerebral blood flow measures have become available in clinical practice and may be used in combination with diffusion imaging to help guide treatment decisions.

Numerous studies have begun to investigate the ability of multimodality imaging to better characterize tumors. As mentioned above, a recent study described a method for combined rCBV and ADC to distinguish between progression and pseudoprogression.[52] The same group has applied the method to evaluating brain metastases.[68] Others have employed combinations of imaging modalities to improve diagnostic capabilities,[69,70] perform noninvasive histologic assessment,[71,72] distinguish between disease and radiation injury,[73] and to correlate pre-treatment imaging with survival.[74]

A goal of research in this area is to formulate a standard multiparametric model to assess for the presence of subclinical disease. This would aid in nearly every stage of management for brain tumor patients, from diagnosis to tailoring treatment regimens. As these multiple noninvasive techniques continue to be refined, it will become more important for clinicians to understand their potential roles and limitations.

Summary

At present, diffusion imaging is not a primary modality in the diagnosis and characterization of glioblastoma, but practical applications are being developed. Results from prospective studies to validate findings from retrospective series have indicated how diffusion parameters may be correlated with tumor cellularity, invasiveness and prediction of treatment response. Early work has

demonstrated the feasibility of altering radiation target volumes based on findings from diffusion imaging, but there have been no trials to date implementing this in treatment planning.

MRI continues to develop fascinating imaging views due to the ability to manipulate the nuclear spin resonance via precisely determined rf pulse sequences, and also the addition of pulsed magnetic field gradients of sufficient size to dwarf any inhomogeneities in the static field created by the main superconducting coils. Taking advantage of differences in the nuclear spin relaxation times of protons in different tissues, rf pulse sequences can contrast out some tissues (or make them the main detected signal), at the discretion of the MRI experimentalist. DWI and DTI open new windows for the clinician due to its potential to directly observe small regions of high cellularity, which may indicate otherwise unobservable areas of malignancy both before and after standard treatment.

The most promising role of diffusion imaging may be in multiparametric analyses where advances in several modalities may be considered together. The next step in applying these techniques to clinical practice will be formalizing a standard means of data acquisition, analysis and interpretation. Functional diffusion maps and multimodal ADC histogram models appear to be the most promising approaches at this time and will require further validation. Finally, clinical trials involving larger numbers of patients with strictly defined imaging protocols are needed to move the promising experimental results into generalized clinical disease management for glioma.

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Proton therapy for radiation-induced parameningeal rhabdomyosarcoma

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Retinoblastoma is the most common childhood primary intraocular tumor, and occurs primarily in young children with 95% of cases arising before age 5. The *RB1* gene on chromosome 13q14 was the first tumor suppressor gene discovered, and inactivation of both alleles of the *RB1* gene is the initiating event in the formation of retinoblastoma.[1,2] Patients with heritable retinoblastoma have a constitutional *RB1* mutation and frequently develop bilateral retinoblastoma. One-fourth to one-third of patients with retinoblastoma present with bilateral disease and all of these cases are heritable. In addition, about 13% of cases of unilateral retinoblastoma are heritable.[2-4] However, the majority of heritable cases have a de novo germline mutation with no family history of retinoblastoma.[2]

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The incidence of retinoblastoma has remained constant worldwide at 1 case per 16,000 to 18,000 live births.[5,6] This corresponds to about 8,000 new cases annually, mostly concentrated in Asia and Africa where there are large populations with high birth rates. Great strides have been made in treating retinoblastoma in the developed world with 3% to 5% mortality in the United States, Canada, and Europe; however, mortality remains high at 40% to 70% in Asia and Africa.[2] Radiotherapy has a long-standing and well-established role in the adjuvant treatment of children with retinoblastoma at a high risk of local progression. However, the exquisite radiosensitivity of normal tissue in very young children and the increased incidence of radiation carcinogenesis in patients with *RB1* mutations have prompted new approaches of radiation avoidance or newer technology that might reduce the risk of collateral radiation injury in retinoblastoma patients. This case illustrates a unique example of a radiation-induced rhabdomyosarcoma in a child previously radiated for retinoblastoma in which proton therapy was recommended in hopes of mitigating additional radiation side effects.

Pediatric case

At 5 months, our patient, a white male, was diagnosed with bilateral retinoblastoma. His right eye was staged as Group D, according to the International Classification for Intraocular Retinoblastoma (large tumor with associated retinal detachment), and his left eye was staged as Group B (3 small peripheral tumors). The decision was made to treat with carboplatin, vincristine, and etoposide (CVE) chemotherapy in view of bilateral disease rather than proceeding with immediate enucleation. After an anaphylactic reaction to the first carboplatin infusion, he received ifosfamide, etoposide, and vincristine (IVE) for 6 cycles. His initial response to the chemotherapy was good with a response at all tumor sites. Unfortunately, at the end of the treatment examination he was noted to have an extensive relapse (local and vitreous base) in the right eye and a relapse near the macula in the left eye. In view of the early relapse, the prior use of ifosfamide (a major component of any chemotherapy relapse strategy) and

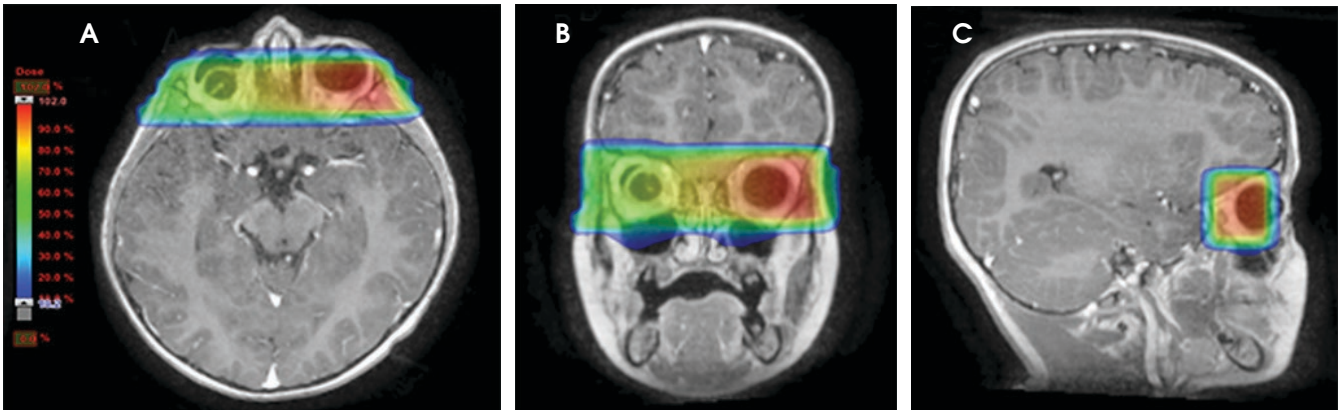

FIGURE 1. *Recreation of the original left lateral lens-sparing 6-MV technique prescribed to 2.5-cm depth.*

the prospect of no useful vision in the right eye, he underwent enucleation of the right eye and radiotherapy to 40 Gy to the left eye. A left lateral lens-sparing 6-MV technique exiting through the empty right socket was used, prescribed to 2.5-cm depth for 20 fractions for 4 weeks using a vacuum fixation of the eye (Figure 1). Following completion of this treatment, the patient has had no evidence of recurrence of his retinoblastoma. There was no family history of retinoblastoma, although on examination his father was noted to have a retinal scar (retinoma or regressed retinoblastoma). The family declined genetic testing.

At 6 years old, now with an additional diagnosis of autistic spectrum disorder, our patient re-presented to his general practitioner with a 1-week history of painless swelling of the right side of his face. With no prior history of trauma, an infectious cause was presumed and he received a course of amoxicillin clavulanate. When the swelling did not improve after 48 hours on the antibiotics, he was referred to his local ophthalmologist and then to the retinoblastoma specialist for further assessment. On examination, he was found to have a 4-×-4-cm diffuse swelling over the right zygomatic region with no palpable adenopathy. Ultrasound of the right face revealed an oval-shaped heterogeneously hypoechoic vascularized lesion that measured 4.5-×-1.1 cm overlying the right zygomatic bone with no disruption of the underlying bone seen. Magnetic resonance imaging (MRI) of the face and neck revealed a well-defined solid enhancing mass within the right infratemporal fossa with restricted diffusion in keeping with tumor. There was overlying soft tissue edema that extended anteriorly into the muscles of mastication and buccal fat on the right. There were some enlarged right parotid and right upper cervical chain lymph nodes (Figure 2). The lesion was noted to involve the right zygomatic arch, right skull base, and mandibular ramus.

Biopsy was performed of the mass overlying the right zygomatic bone as well as the right parotid lymph node and the right upper cervical lymph node. All 3 specimens showed rhabdomyosarcoma and favored alveolar type because of strong myogenin staining and cell morphology despite absence of PAX3-FOXO1 and PAX7-FOXO1 fusion transcripts by RT-PCR.

Approximately 6 weeks after presenting, the known right temporal mass had enlarged and now measured 5.7-×-2.8 cm. The additional right parotid lesion measured 2-×-1.3 cm. The lesion in the right submandibular region measured 3.6-×-2 cm. There were significantly enlarged right cervical nodes with smaller nodes present in the left side of the neck.

Metastatic workup was negative and the patient was staged as T2bN1M0, Intergroup Rhabdomyosarcoma Study (IRS) stage 3, group III. The decision was made to treat the patient according to the very high-risk group (H) of the European Pediatric Soft Tissue Sarcoma Study Group (EpSSG) RMS 2005 study (the patient was technically eligible for enrollment because this was a second tumor) with the application of proton therapy for local control. He commenced chemotherapy with ifosfamide, vincristine, actinomycin-D, and doxorubicin (IVADo) 2 months after presenting with right facial swelling. He tolerated chemotherapy poorly and lost 4 kg in the first 2 weeks of treatment. A percutaneous endoscopic gastrostomy (PEG) tube was placed to maintain his nutrition. He had significant nausea, vomiting, mucositis, and anorexia and was hospitalized through the majority of his first 4 cycles of chemotherapy. MRI after completion of 4 cycles of IVADo demonstrated an almost complete resolution of the right temporal mass and significant improvement in the right cervical adenopathy.

As per protocol, he continued on ifosfamide, vincristine, and actinomycin D (IVA) maintenance for 2 cycles prior to starting radiotherapy. MRI after the second cycle of IVA chemotherapy demonstrated no remaining disease. He commenced proton radiotherapy

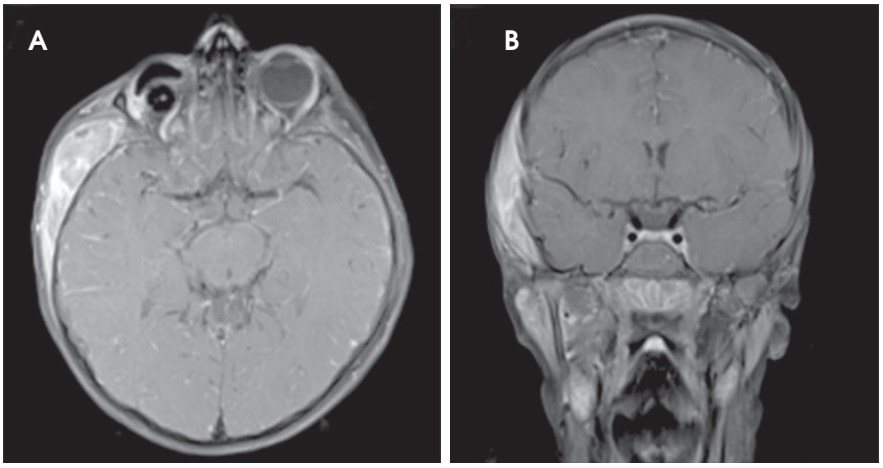

FIGURE 2. *MRI demonstrating a well-defined solid enhancing mass within the right infratemporal fossa involving the right zygomatic arch, right skull base, and mandibular ramus. Note the enlarged right parotid and right upper cervical chain lymph nodes.*

in conjunction with the third cycle of IVA chemotherapy. A total of 41.4 Gy (relative biological effectiveness [RBE]) was delivered at 1.8 Gy (RBE) per daily fraction (23 fractions) to a target volume based on the pre-chemotherapy extent of disease, including the right cervical nodal chain, and the right parotid region with a 2-field 3-dimensional conformal passive double-scattering proton plan. An additional 9 Gy (RBE) at 1.8 Gy (RBE) per daily fraction (5 fractions) was given to a target volume based on the post-chemotherapy volume for a total dose of 50.4 Gy (RBE) in 28 daily fractions (Figure 3).

The patient completed adjuvant chemotherapy with 6 cycles total of IVA, and then received maintenance therapy with vinorelbine and oral cyclophosphamide for 6 cycles. Currently he is alive and well 12 months after completing treatment. He has normal endocrine function, no abnormal audiology, no additional eye changes beyond his original diagnosis, and a reduced fractional shortening (28%) secondary to his anthracycline exposure. He continues experiencing nutritional difficulties and relies on his percutaneous endoscopic gastrostomy (PEG) tube for feeding, and his educational progress and difficulties pertaining to his autistic spectrum disorder have been compounded by the social complexities of his recent treatment away from his home.

Discussion

Even with successful treatment of retinoblastoma, patients with a constitutional *RB1* mutation are highly susceptible to developing secondary malignant neoplasms (SMNs). The risk of SMNs in patients with heritable retinoblastoma is estimated to be 36% to 48% at 50 years.[7,8] This translates to an increased mortality from SMNs at 50 years after diagnosis in patients with heritable retinoblastoma of 17% to 26%.[9,10] Recently, patients with an inherited germline mutation were found to have an increased risk for SMN compared to those with a de novo germline mutation, largely due to an increased risk for melanoma, and there was no increased risk for bone or soft tissue sarcoma.[11] The increased risk of SMN may have a genetic basis, as patients with recurrent nonsense mutations have been found to have an increased risk of SMNs and those with low-penetrance mutations have a lower risk.[12]

Radiotherapy results in a threefold increased risk of SMNs in patients with heritable retinoblastoma. An analysis of the Dutch retinoblastoma registry found that the risk of SMN was 13.3% at 40 years in patients with heritable retinoblastoma who did not receive radiotherapy, and this increased to 33.2% in those who received radiotherapy.[13] A cohort of heritable retinoblastoma patients from the United States demonstrated a cumulative risk of SMN of 21% at 50 years in those who did not receive radiotherapy, compared to 38% in those who received radiotherapy.[8] Soft tissue sarcomas account for a sizeable proportion of these SMNs in patients with heritable retinoblastoma who receive radiotherapy, with a 13% cumulative incidence at 50 years.[14] A further analysis demonstrated that irradiated survivors had an increased risk of death from SMNs with a standard mortality ratio (SMR) of 3 times that of nonirradiated survivors. Patients irradiated at 12 months or younger had a further increased risk of death from SMNs with an SMR of 2 compared to those irradiated older than 12 months.[10]

Of the heritable retinoblastoma patients who receive radiotherapy and develop an SMN, 40% to 70% of these will occur in the radiation field.[7,13,15] SMNs that occur in a radiation field develop at an earlier age than those that occur outside of a radiation field or those in patients who did not receive radiation therapy. One review of over 600 retinoblastoma patients with SMNs found a median age of diagnosis of 9 years for tumors in the radiation field. Approximately 70% of these tumors will be bone or soft tissue sarcomas. There also appears to be a radiation dose response for developing an in-field sarcoma, with a risk threshold as low as 5 Gy.[16] Patients with rhabdomyosarcoma had the youngest age of onset with a median age of 7 years,[13] very similar to our patient.

Radiation technique may also modify the risk of SMNs in patients with heritable retinoblastoma. One analysis found the cumulative risk of SMNs was 32.9% at 40 years in patients with

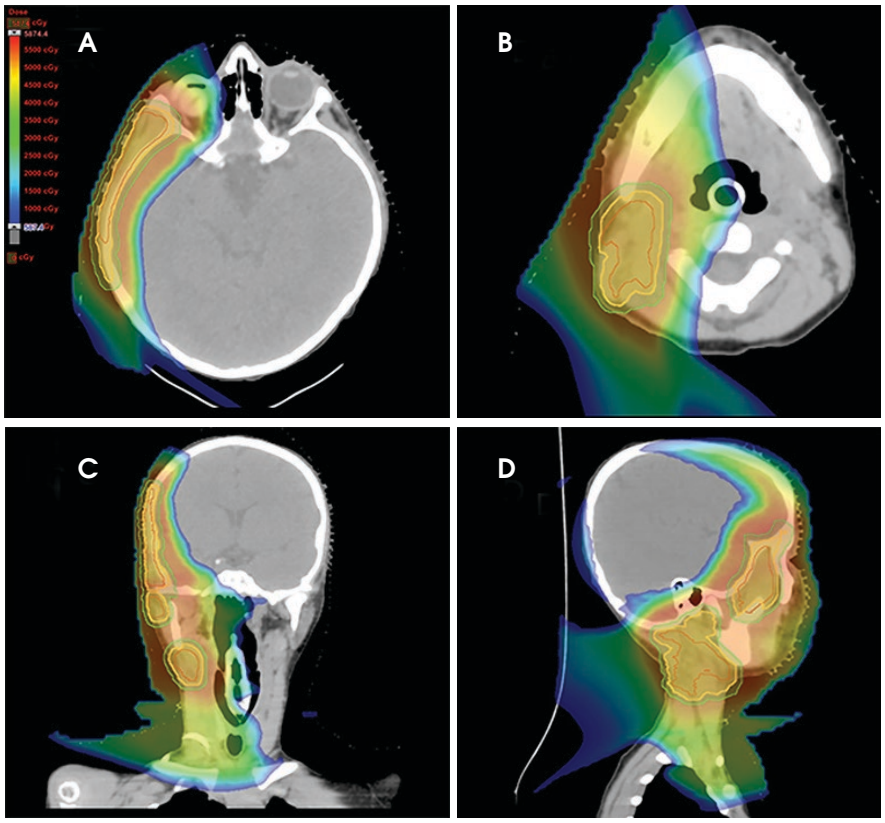

FIGURE 3. *Two-field proton plan encompassing the primary tumor, right upper cervical nodal chain, and the right parotid region.*

heritable retinoblastoma treated with orthovoltage (prior to 1960), and this decreased to 26.3% in those treated with techniques that generated less scatter.[7] Conformal photon techniques such as volumetric arc therapy may provide better conformality and may better spare the orbital bone and brain from higher doses compared to 2- or 3-dimensional conformal radiotherapy. However, these techniques also generate a higher integral dose of tissue receiving >5 Gy, which may increase the risk SMNs in patients with a germline mutation.[17-19] Dosimetric analyses have demonstrated that proton therapy results in optimal target coverage with the lowest dose to the surrounding orbital bone and reduced integral dose.[18,19] Proton therapy may reduce the risk of SMN in patients with germline mutations compared to electron or photon techniques. The first report on SMN of patients with retinoblastoma treated with proton therapy demonstrated a 10-year incidence of only 5%. Of the 52 patients from that single institution series, 85% had heritable retinoblastoma and the 1 patient with SMN suffered from a femoral osteosarcoma.[20] While promising, this small series with a median 6.9 years of follow-up will need continued follow-up to confirm these results.

The in-field alveolar rhabdomyosarcoma with lymph node metastases that developed in our patient occurred in a typical time frame from his initial radiation for his retinoblastoma. Patients with clinical group III (unresectable at diagnosis) rhabdomyosarcoma who were treated on IRS IV had a 5-year freedom from treatment failure rate of 77%; however, this was lower at 63% for those with parameningeal primaries.[21] Patients on IRS IV with lymph node metastases had a significantly worse 5-year freedom from treatment failure rate at 46% compared to 73% for patients with N0 disease. This difference was more pronounced in those with alveolar histology,[22] although the adverse prognosis seen with alveolar histology is likely driven by the 70% to 80% of these patients who have a PAX-FOXO1 fusion gene. A recent analysis attempted to combine stage, age and molecular data to develop a better risk stratification for patients with rhabdomyosarcoma and defined 4 clinicomolecular risk groups. Patients such as ours who were stage 3 and did not have a PAX7-FOXO1 or PAX3-FOXO1 fusion were placed in clinicomolecular risk group 2 with a 5-year overall survival rate of 65%.[23]

Our patient received standard European chemotherapy and the decision was made to use proton radiotherapy for local control because it has been shown to reduce the dose to the optic structures, brain, hypothalamus, pituitary, and all contralateral structures in a parameningeal rhabdomyosarcoma.[24] The reduced integral dose was also thought to be particularly important in this patient with a history of heritable retinoblastoma and already 1 radiation-induced SMN. The first clinical series of patients with parameningeal rhabdomyosarcoma treated with proton radiotherapy demonstrated comparable tumor control, with survival and toxicity comparing favorably to contemporary series.[25] In our patient, the proton plan delivered no dose to his optic nerve, pituitary, hypothalamus, or contralateral facial structures. Less than 50% of his ipsilateral temporal lobe received >20 Gy. His bilateral hippocampi and contralateral (left) temporal lobe were entirely spared, which was critical given his pre-existing developmental delay and autistic spectrum disorder.

Patients with heritable retinoblastoma who survive an SMN remain at risk for further neoplasms. Examination of the Dutch registry demonstrated a 7-fold hazard ratio for the risk of a

third malignancy compared to the risk of a second malignancy. All of the third malignancies developed within 20 years of the SMN and only one of 11 were in the radiation field. Developing a third malignancy was also associated with a fivefold worse survival than developing a second malignancy.[26] Of 211 patients with SMN after retinoblastoma followed at a clinic in New York, the risk of developing a third primary was 22% at 10 years, and the 10-year survival rate for patients with a third malignancy was 30%. The median time to developing a third malignancy was 6 years.[27]

Patients with heritable retinoblastoma are at an increased risk of SMN, and this risk is significantly increased by radiotherapy. Using proton therapy over photon therapy may reduce this risk as well as other late effects of radiotherapy. In this unique setting where radiotherapy is determined to be necessary for an optimal chance of disease control, then proton therapy specifically should be considered to minimize long-term toxicity and the risk of subsequent malignancies.

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RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for December 2014!

Multi-lesion, left-sided, single isocenter radiosurgery treatment in a patient with a pacemaker

Joshua Binks, BS; Zachary D. Horne, MD; Kimmen Quan, MD; and David A. Clump, MD, PhD

CASE SUMMARY

An 85-year-old male with a history of ventricular arrhythmia requiring an automatic implantable cardioverter/defibrillator (AICD), and a T2N0M0 basaloid squamous cell carcinoma of the base of tongue treated with definitive cetuximab and external-beam radiotherapy to 70.2 Gy 2-and-a-half years prior, was referred to our department after his AICD fired and triggered a workup by his primary care physician (PCP). An initial chest x-ray revealed new pulmonary opacities, prompting a CT of the chest, which showed 4 left-sided pulmonary lesions as well as 1 right-sided pulmonary lesion. Pathology from a CT-guided biopsy was consistent with his primary basaloid squamous cell carcinoma from the base of tongue. Due to his multiple comorbidities, chemotherapy was an ill-advised option. The physical exam was unrevealing.

IMAGING FINDINGS

Preoperative magnetic resonance imaA PET/CT scan revealed 4 hypermetabolic lesions within the left lung, measuring from 2.2-×-2.8 cm in diameter with SUVmax values of 11.6 to 15.4. There was also a right-sided para-esophageal mass measuring 1.4-×-2.4 cm with an SUVmax of 10.4 and no further evidence of metastatic disease.

DIAGNOSIS

The patient was diagnosed with oligometastatic basaloid squamous cell carcinoma from his base of tongue primary.

DISCUSSION

As a result of this entity's rarity, stereotactic radiosurgery (SRS) has become the standard of care in treating small pulmonary lesions, both primary and metastatic, in the medically inoperable population.[1] More recently, it has been used in patients with so-called oligometastatic disease. Oligometastases are isolated tumor deposits that appear to have a different natural history from widespread metastatic disease.[2] When treated adequately, patients with oligometastatic disease can have significant local control of their tumor deposits with an apparent increase in expected overall and progression-free survival.[3,4]

Typically, oligometastatic lesions would be treated sequentially if spatially disparate, or at the very least, each with their own unique isocentric plans. In this particular patient, however, his 4 left-sided lesions were arranged in a configuration such that we were able to use 1 isocenter and treat all 4 simultaneously (Figures 1 and 2).

Furthermore, his AICD provided a unique challenge in the planning phase (Figure 3). As most devices have a recommended dose tolerance of 2Gy[5] and our plan was to deliver a total dose of 48Gy in 4 fractions to his lesions, his plan required deft beam arrangements to avoid overdosing his AICD. The motion of each lesion within a common gating window was assessed individually and taken into account when creating the PTVs, and a pre-treatment cone-beam CT was used to ensure alignment. Twelve beams were used for treatment delivery. Upon a physics evaluation, it was estimated that his pacemaker would receive approximately 20 cGy per fraction, totaling 80 cGy throughout the course of treatment, a dose well below the tolerance of his device.

Each treatment required approximately 45 minutes. He completed treatment without incident and went on to have his right para-esophageal lesion treated with SRS as well. At his 6-month follow up, a PET/CT scan indicated that he had no residual activity

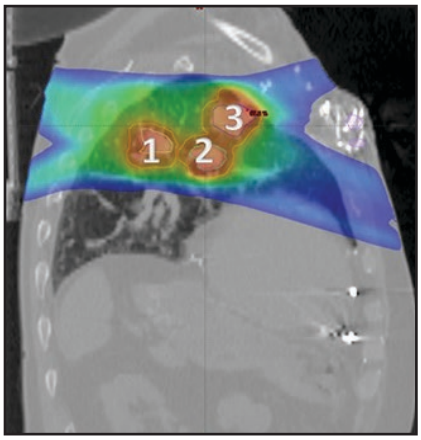

FIGURE 1. *Dosimetric planning showing left-sided lesions 1-3.*

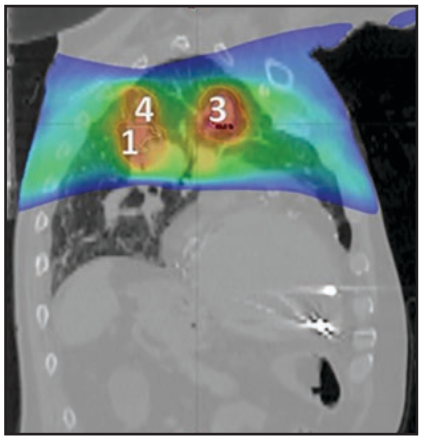

FIGURE 2. *Dosimetric planning showing left-sided lesions 1, 3 and 4.*

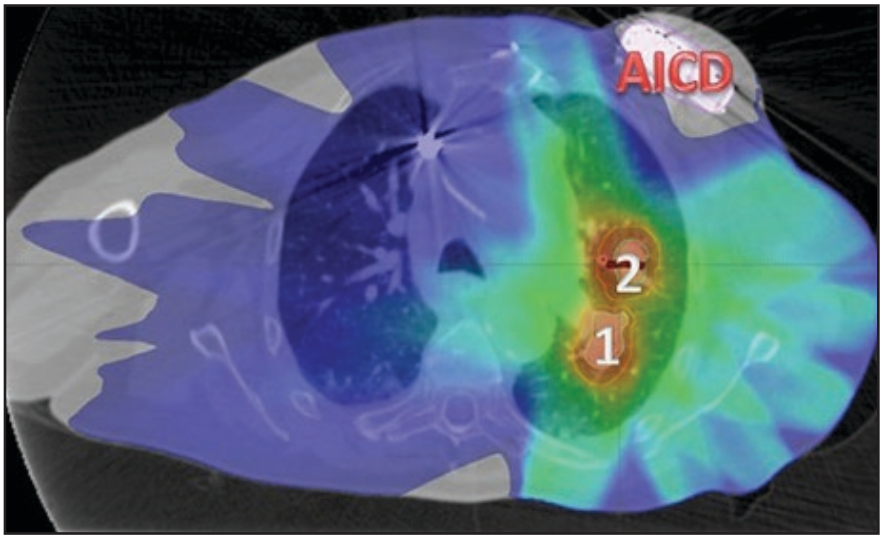

FIGURE 3. *Dosimetric planning showing left-sided lesions 1 and 2 as well as the patient's AICD, demonstrating beam arrangement to avoid dosing the pacemaker.*

in any of the 5 lesions. Interestingly, he had no further AICD firing events.

CONCLUSION

To date, there have been no reports of multi-lesion, single isocenter SRS treatments for extra-cranial disease. The technique has been used, however, for multiple intracranial lesions with excellent results.[6,7] Extrapolating from the central nervous system (CNS) model, we were able to achieve a treatment plan for our patient's 4 left-sided oligometastases that used a single isocenter. This is a critical achievement for a number of reasons. By using a single (as opposed to multiple) isocenter, we were able to treat this patient in a 45-minute time slot. A multi-centric treatment plan would require treatment times proportional to the number of lesions being irradiated: Each lesion may require table shifts and verification in addition to beam-on time. Reducing time-on-table is important not only for patient comfort and satisfaction, but it may also be related to clinical outcomes and is under investigation at our institution. Additionally, in an environment where growing healthcare costs are always of concern, unicentric plans are less expensive than multicentric plans as a result of fewer dosimetric and physics charges.

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RADIATION ONCOLOGY CASE

Diffuse chest wall calcifications after post mastectomy radiotherapy for breast cancer

Prashant Gabani, BS, Beant Gill, MD, Carolyn De La Cruz, MD, and Sushil Beriwal, MD

CASE SUMMARY

A 56-year-old female with stage IIIA ER+/PR+/Her2- infiltrating ductal carcinoma of the right breast underwent total mastectomy and axillary lymph node dissection, adjuvant AC-T, radiotherapy (50 Gy in 25 fractions to the chest wall and supraclavicular nodes with a 10 Gy in 5 fraction electron scar boost), and hormonal therapy. Thirteen years later, she presented with a 4-month history of an enlarging right chest wall ulcer with multiple firm subcutaneous nodules around the scar. She denied recent trauma, although was found to have a subclavian arterial thrombosis, managed by thrombectomy and stent placement and resulting in partial regression of the ulcer. A chest computed tomography (CT) scan was completed following her clinic visit. A conservative excisional biopsy was negative for malignancy. She thus underwent a wide resection including the lesion, skin and underlying rib followed by reconstruction, confirming the diagnosis.

IMAGING FINDINGS

Physical examination revealed right chest wall skin atrophy with scattered telangectasias and multiple small subcutaneous nodules near a scabbed lesion along the right chest wall scar (Figure 1). Chest CT revealed multiple hyperdense, discrete subcentimeter nodules in the chest wall subcutaneous tissue (Figure 2). No lymphadenopathy or metastatic disease was seen.

DISCUSSION

Pathologic evaluation of resected tissue revealed dense fibrosis and foci of necrosis, granulation tissue and calcifications without any malignancy. Thus, the final diagnosis was chest wall ulceration and diffuse subcutaneous calcifications as a result of late-radiation related changes. In all, increasing awareness has been brought forth regarding delayed radiation effects. Although such occurrences are now less common after breast and chest wall radiotherapy due to higher energy photons and greater dose homogeneity, late radiation changes still occur in this population where expected cancer-related survival is prolonged. Identifying radiation-related changes can be challenging but, as seen in this case, the clinical presentation may prove most helpful. Late skin complications of radiotherapy include pigmentation changes, skin atrophy, fibrosis, telangiectasia, necrosis and ulceration. Such changes often progress slowly and manifest over the span of months to years, with more rapid development in cases of an associated vascular or traumatic event.

Interestingly, the patient presented here developed a subclavian artery thrombosis with no prior coronary or peripheral artery disease. Studies have implicated breast or chest wall radiotherapy to such thrombotic events, including within the arteries of the heart.[1] Partial improvement of her ulceration after re-vascularization of the subclavian artery may implicate her thrombosis as the inciting event for such late radiation changes.

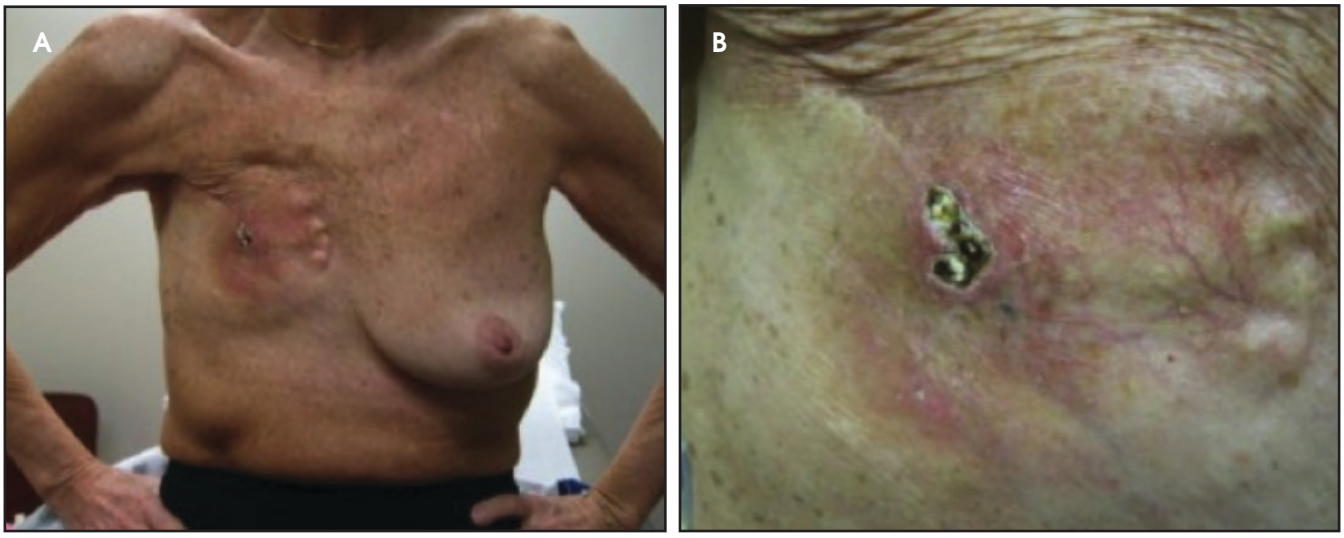

FIGURE 1. *(A) Photograph of the patient's right chest wall 13 years following radiotherapy, demonstrating benign skin changes measuring 1.0-x-2.0-cm with surrounding erythema, telangiectasias and diffuse subcutaneous calcifications. (B) Benign chest wall changes, late radiation-related changes (ulceration, calcifications), and non-infectious granulomatous disease of the skin.*

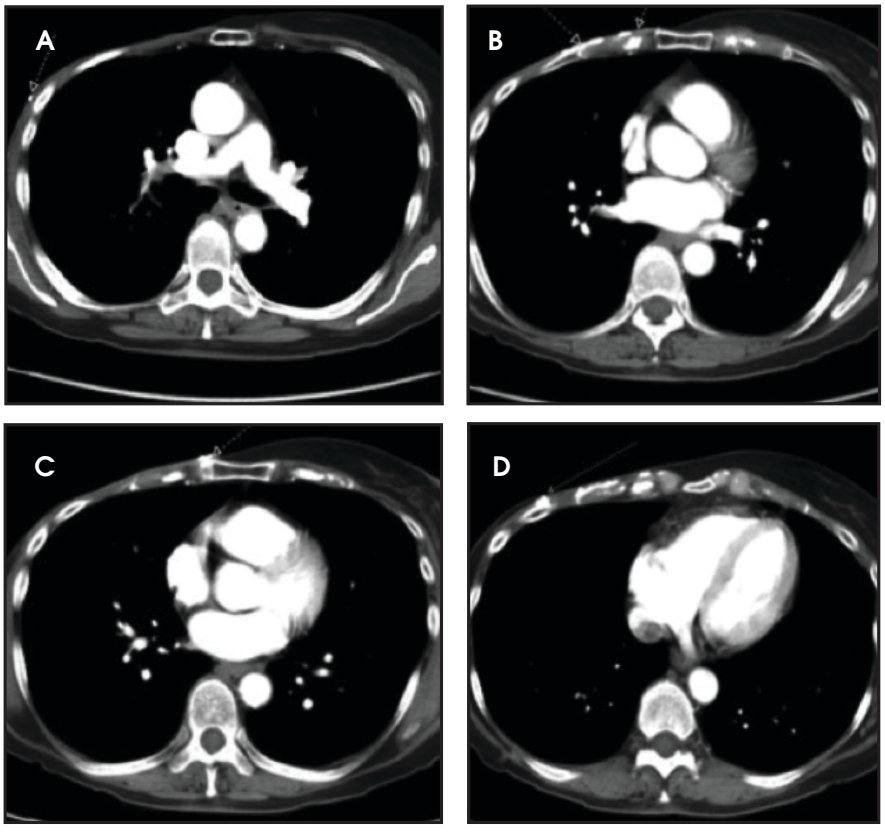

FIGURE 2. *(A-D) Axial CT illustrating diffuse, well-defined, hyperdense subcutaneous calcifications (arrow) along the right chest wall.*

In general, calcification is often regarded as a component of the healing process, generated as a physiologic defense designed to contain, wall off and stabilize injured or damaged tissue. This process of inflammation causing coronary artery calcification has been well-documented.[2] The pathogenesis of radiation-induced dystrophic calcification is obscure, but it may be caused by persistent inflammation, leading to phosphate binding to denatured proteins, or from a dysregulation of intracellular Ca2+ concentration of mitochondria in dying cells.[3] In addition, mineralizing micro-angiopathy is also considered to play a role in the development of calcifications. This calcification often develops in irradiated tissue secondary to the leakage of plasma fluid from damaged vessels, and regional ischemia resulting from impairment in the microcirculation secondary to the mineralizing micro-angiopathy.[4]

The presence of subcutaneous calcifications has been shown previously in case reports to be a sign of delayed

Table 1. Published reports of subcutaneous calcifications secondary to radiotherapy

	n	Fractionation scheme (Gy/fractions)	Other skin findings	Time to calcifications (years)
Present report	1	60/30	Atrophy, fibrosis, erythema, telangectasias	13
Plzak J et al. (2011)[7]	1	60/30	Ulceration, necrosis, erythema	13
Arévalo N et al. (2009)[8]	1	58.8	Fibrosis	26
Zaka Z et al. (2008)[9]	1	40/20	Atrophy, fibrosis, hyperpigmentation	25
Lewis VJ et al. (2004)[10]	1	50/25	Fibrosis, ulceration	8
Carl UM et al. (2002)[11]	15	40-90/-	Fibrosis, ulceration, telangectasias	19 (median)
Amin R et al. (2002)[6]	6	40-45/10-20	Fibrosis	11 (mean)
Steinert M et al. (2001)[12]	1	NR/NR	Fibrosis	32
Cowie F et al. (1999)[5]	1	40/10	Fibrosis, telangectasias	NR

Abbreviations: Gy=Gray, NR=not reported

radiation changes. Based on a literature review, a total of 28 cases of subcutaneous calcifications has been reported following radiotherapy for oncologic conditions, all exceeding doses of 40 Gy (Table 1).[5-12] The first reported case by Cowie et al. demonstrated calcifications along the match line between the chest wall and supraclavicular fields, implying a relationship to dose hot spots.[5] These findings were also seen in a case series by Amin et al., again implying formation along the match line.[6] Nonetheless, in all the reported series, additional skin sequelae were seen and, thus, emphasize the importance of long-term follow-up and documentation of clinical findings.

CONCLUSION

This case, along with a small body of literature, demonstrates the finding of subcutaneous calcifications as a delayed toxicity from radiotherapy. Determining whether chest wall or breast skin changes are a result of radiotherapy or cancer recurrence remains challenging. Presence of multiple skin findings presenting years following radiotherapy, particularly in light of an inciting traumatic or vascular event, may help guide management. Aggressive biopsy or surgical intervention should be pursued cautiously if post-radiotherapy toxicity is suspected, as wound-healing can be problematic.

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Treatment planning systems: Balancing standardization with personalization

Mary Beth Massat

Advanced technology continues to reshape the field of radiation therapy (RT), most notably with improvements in the precision of therapy delivery. Image-guidance during treatment is now possible, including the real-time tracking of moving tumors such as those in the lungs or abdomen. Beam modulation has helped open the door to new techniques like volumetric modulated arc therapy (VMAT), which optimizes the plan in many angles, and then sequences it into stacks of apertures at every angle followed by delivery of the beam with multiple connected arcs. Stereotactic body radiation therapy (SBRT) is another emerging treatment plan that localizes the lesion and delivers limited, yet precise, high-dose radiation—often in a single high dose or in a few fractionated treatments.

An integral component for achieving these advanced RT delivery schemes remains the treatment planning system (TPS), the "brains" of modern day RT. The continued evolution of computerized solutions and image-guidance has helped reduce the morbidity and toxicity of cancer treatments. Enhancements to automated planning, consistency in planning across patients and institutions, robust algorithms, and quantitative knowledge-based planning will further advance physicists' ability to generate high-quality, efficient treatment plans.

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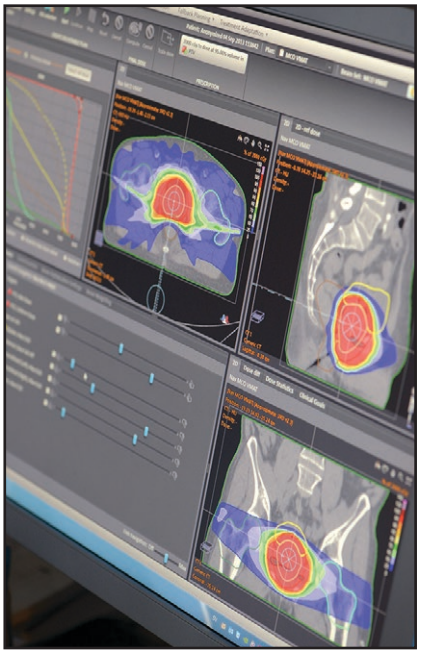
Balancing best practices with personalized medicine

Reducing variability to provide consistency in care is an important consideration in any TPS. "We follow protocols where we can, but in some cases there is an issue that prevents us from achieving a certain goal," says Jeremy Donaghue, MS, DABR, chief medical physicist at Akron General Medical Center in Ohio. "That's where personalization comes in."

Using a multi-criteria optimization (MCO) technique available in the RayStation TPS (RaySearch Labs, Stockholm, Sweden, and Garden City, New York), Donaghue can evaluate different scenarios based on various requirements. He starts with certain anchor points that define the plan. Then, by adjusting additional elements, he can see what the impact will be. For example, in a prostate plan Donoghue can balance out the type of coverage delivered near critical structures such as the rectum and the bladder. Using MCOs helps him reduce variability, which



Multi-criteria optimization in RayStation.

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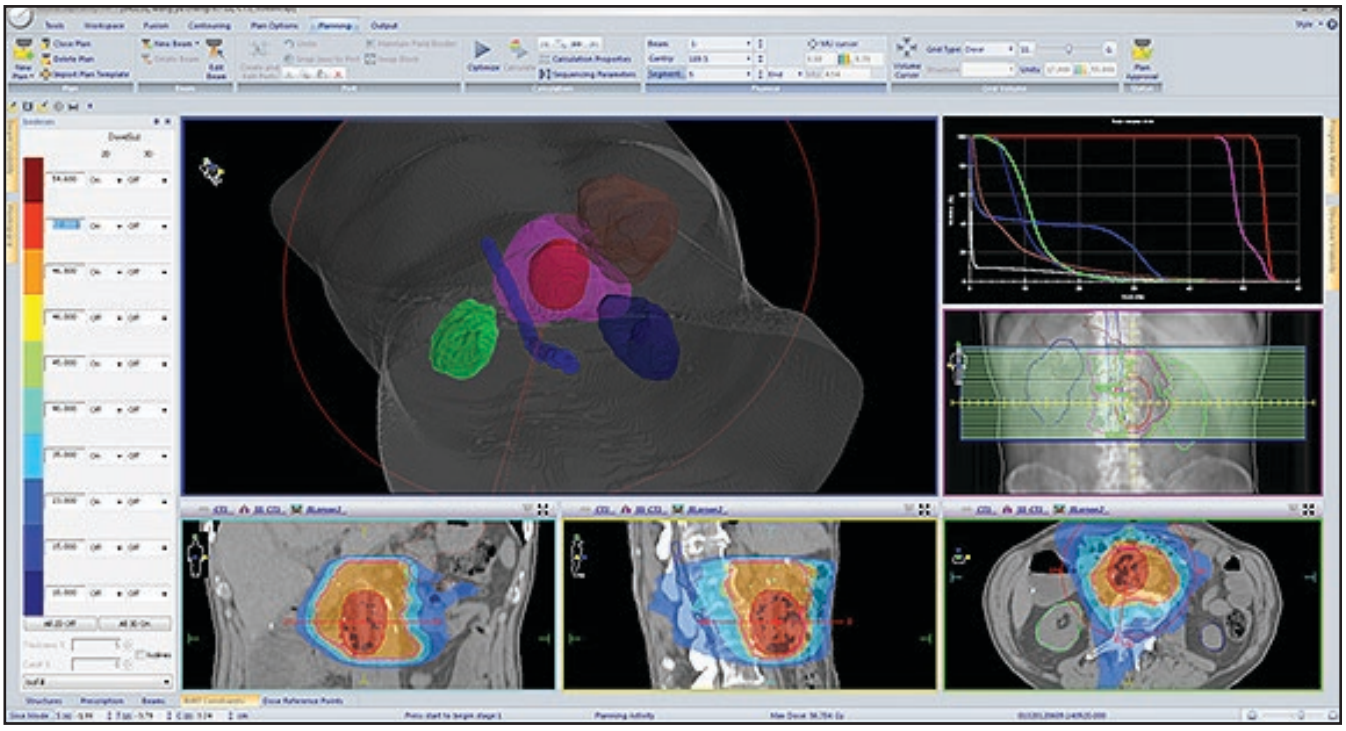


Elekta's Monaco VMAT TPS features a new workflow and system architecture to improve processing speed and enhance planning productivity. Monaco features the accuracy of Monte Carlo plus the speed of the Collapsed Cone algorithm to aid planning.

leads to greater consistency in care across patients with similar disease.

"MCO helps me determine the best plan that I can get," explains Donaghue. "Even if I can't achieve all that I want in a plan, it helps me know the limitations. Using this tool streamlines the plan for the physicians and the dosimetrist. Even though we want to try and treat each patient similarly, it helps me personalize it to their specific anatomy so I can turn around the plan more efficiently."

Donaghue also uses a scripts feature to compare and standardize data across different patients. This allows him to take data from similar patients and create an average and standard deviation. He can then compare a plan to the standard deviation and identify segments that fall outside that norm.

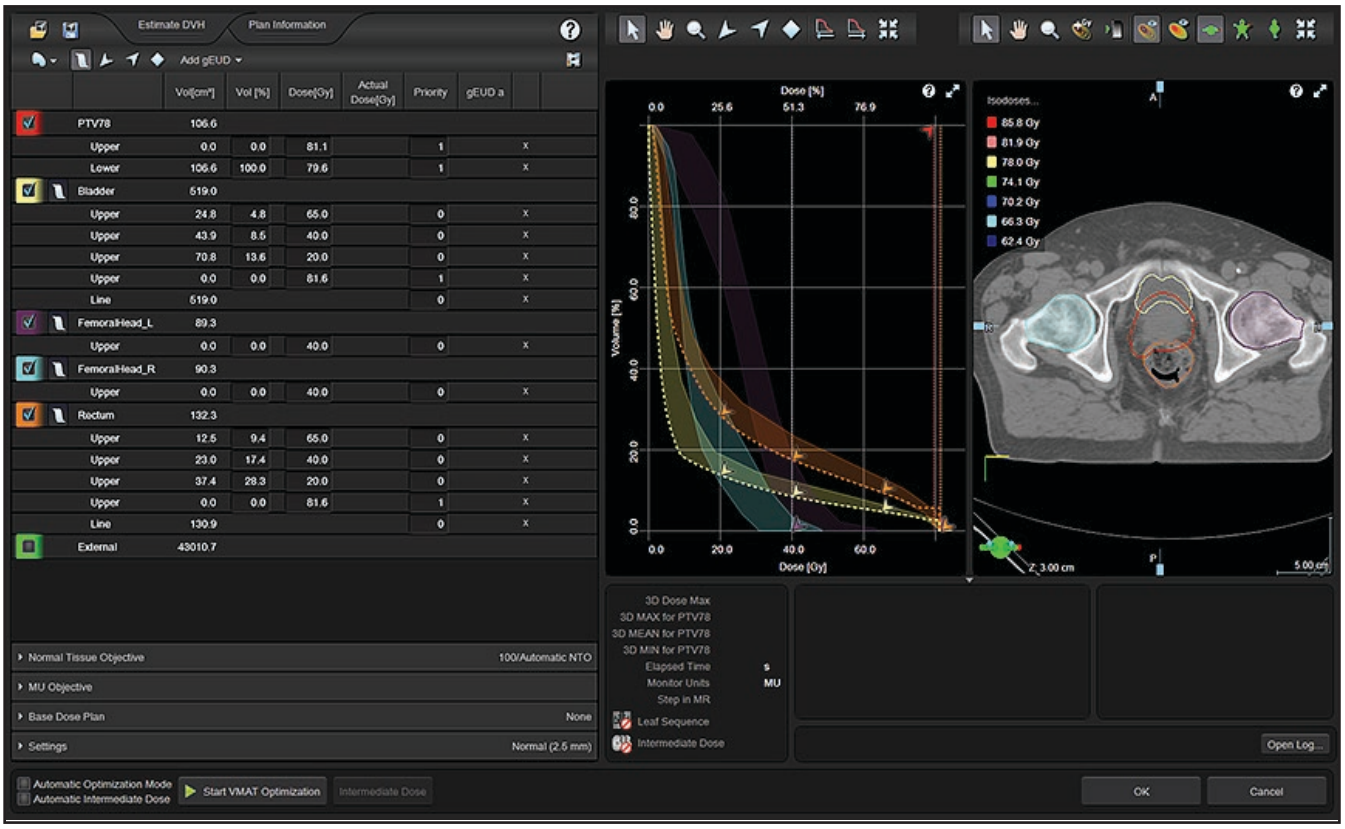
At Kettering Medical Center, Kettering, Ohio, Christopher M. Wennerstrom, MS, DABR, medical physicist, agrees that achieving the right balance between standardization and personalization is important. At his facility, he uses Monaco (Elekta, Atlanta, Georgia) to help build a solid starting point in treatment planning.

"Efficiency and a good class solution lead to better care, not only for that particular patient, but it also further affects the plans for others," he says. By efficiently enhancing that specific starting point for a certain type of treatment plan, he can spend additional time on more complicated plans.

"Class solutions help me to develop best practices, so there isn't mass variability. Yet it provides the flexibility for individualized medicine," he adds. For example with Monaco, when he brings in a template for a VMAT SBRT lung plan, the template is expecting a set of contour names. However, if he has changed one descriptor, for instance a specific planning target volume (PTV), he can select that one contour name in the prescription from a drop-down menu without invalidating the entire class solution.

The calculation algorithm's robustness is most important, adds Wennerstrom. "As planning systems have evolved and use more robust algorithms, the difference between what we are seeing on the screen and reality is becoming smaller. However, the tradeoff for that is often calculation speed. Moving forward, what we need from our vendors is the most robust, best planning algorithms with as much speed and computational power as possible. What we definitely don't need is speed without accuracy."

For the last several years, Kevin Moore, PhD, DABR, assistant professor, Department of Radiation Medicine and Applied Sciences at the University of California, San Diego, has researched ways to predict and quantify when a treatment plan can be improved.



Display of DVH estimation for a prostate cancer treatment plan, created using Varian's RapidPlan knowledge-based TPS.

"This is a hugely underappreciated problem," he says. While patient privacy regulations and competition between cancer centers impact TPS data sharing, patients should not be getting vastly different treatment plans from different treatment centers, Dr. Moore adds.

Using quantitative, patient-dependent benchmarks is the core of best practices, but is not inherent in today's TPS, he states. "They are still designed to prepare a plan for a single patient," says Dr. Moore, "not to help you learn a larger sense about cohorts of patients."

Dr. Moore has licensed some of his research and work to Varian Medical Systems (Palo Alto, California) on synthesizing prior patient treatment plans into predictive models that help automate and optimize future treatment plans for use in RapidPlan, a knowledge-based planning system that allows clinicians to develop and apply best practice models for automated planning. While he says RapidPlan is a step in right direction and provides a quality control baseline, there is room for improvement across all vendors' TPS products, "as evidenced by published studies that show wide variability and suboptimal planning," Dr. Moore says.

Trends and unmet clinical needs

Variability across patients should be eliminated in the treatment planning process, says Dr. Moore. The motivation for much of his work in developing knowledge-based treatment planning based on statistical learning of past experiences is to help further reduce complications in current and future plans. These quantitative predictions will help physicists develop quality, standardized plans that also allow for personalization.

He would like to see this type of work extended across institutions. That knowledge will help account for clinical tradeoffs in a way that doesn't digress too far from an optimal plan. The goal is to ensure the plan adapts to tradeoffs in a manner that is consistent across plans.

"The ability to perform aggregate studies and give the user the ability to perform queries across multiple patient treatment plans with novel questions is not something today's TPS [is] designed to do," Dr. Moore adds. "With statistical learning, week by week and year by year, we can expand that

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> "We'll need to get to a point where we can add dose together from different dose fractionation schemes and have it be an accurate reflection of the remaining dose that a critical structure can safely absorb."
>
> Christopher M. Wennerstrom, MS, DABR

knowledge base to understand the average of what we are doing and planning on a larger scale." Today, this is a manual process, but Dr. Moore believes that including these types of tools in a TPS that enables cross-institutional collaborative planning could be an element of the modern radiation oncology department.

Donaghue sees a movement by the industry to provide a one-stop shop for all treatment planning needs. For example, he can now perform deformable registration within his TPS solution, and he anticipates that his vendor will provide capabilities for brachytherapy in the near future. More adaptive planning and integrated record-and-verify tools are also on the rise, says Dr. Moore.

One limitation Donaghue would like addressed is for a TPS to provide a check for minor/obscure parts of AAPM TG 53 (American Association of Physicists in Medicine Task Group 53). TG 53 provides a framework for physicists to develop and implement a comprehensive quality assurance program that encompasses image-based definitions of patient anatomy, 3D beam descriptions for complex beams including 3D MLC apertures, 3D dose calculation algorithms, and complex plan evaluation tools, including dose-volume histograms.[1]

Wennerstrom also says the ability to develop multiple types of plans in one TPS—from 3D conformal to VMAT—will continue. Specifically, the ability to generate SBRT plans that take into consideration the dose levels of prior treatments is important, he says. Many departments that start offering SBRT will find that the number of patients being re-treated with this type of therapy will be higher than expected, he notes.

"With SBRT, what we used to know by heart about dose to critical structures goes out the window," Wennerstrom says. "It is difficult to deal with dose subtraction, how much dose we have to play with in a structure using the current dose scheme, or the dose fractionation that we are trying to deliver, and justify how much dose is left for that critical structure."

As TPS technology evolves, the industry will develop novel ways to deal with these issues, whether it's via the biologic effective dose or another method. "We'll need to get to a point where we can add dose together from different dose fractionation schemes and have it be an accurate reflection of the remaining dose that a critical structure can safely absorb," says Wennerstrom. "A centigray is not the same when it is delivered in a higher fractionation."

With a high efficacy and good outcomes, it's no wonder that SBRT is gaining momentum. "SBRT is making targets treatable that weren't previously treatable with high doses that are very targeted," he adds.

"We can't simply multiply the dose across the entire treatment region by one number. Different critical structures and tumors respond differently to the same dose. Assuming that we could correctly recalculate those doses, while respecting the radiobiology and physiology of each structure, would be a better solution within the TPS to use all of that dose voxel information."

It is seems clear that automated planning coupled with a knowledge-based approach are key components enabling more efficient plans that reduce variability between patients. While barriers remain, namely across different treatment plans and institutions, that divide appears to be slowly closing.

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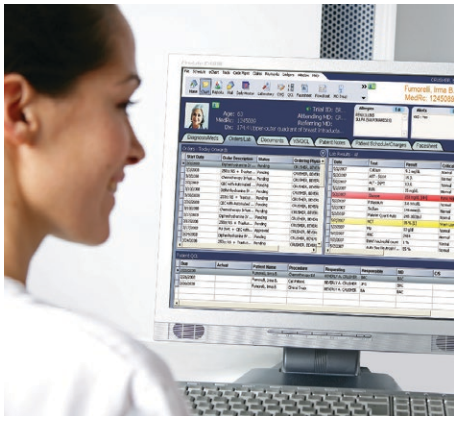

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