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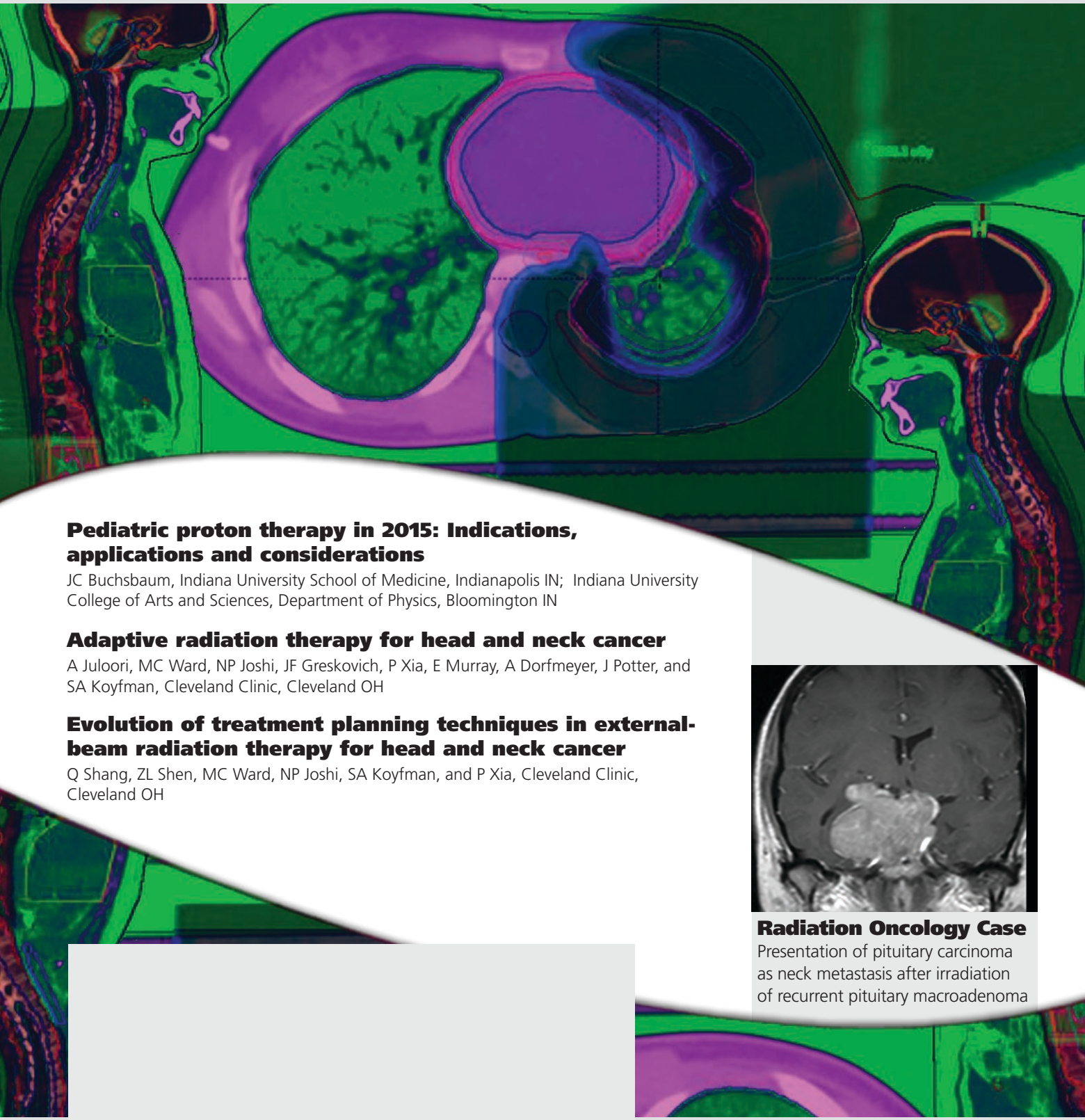

Pediatric proton therapy in 2015: Indications, applications and considerations

JC Buchsbaum, Indiana University School of Medicine, Indianapolis IN; Indiana University College of Arts and Sciences, Department of Physics, Bloomington IN

Adaptive radiation therapy for head and neck cancer

A Juloori, MC Ward, NP Joshi, JF Greskovich, P Xia, E Murray, A Dorfmeyer, J Potter, and SA Koyfman, Cleveland Clinic, Cleveland OH

Evolution of treatment planning techniques in external-beam radiation therapy for head and neck cancer

Q Shang, ZL Shen, MC Ward, NP Joshi, SA Koyfman, and P Xia, Cleveland Clinic, Cleveland OH

Radiation Oncology Case
Presentation of pituitary carcinoma as neck metastasis after irradiation of recurrent pituitary macroadenoma

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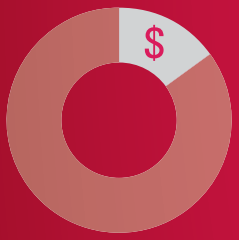

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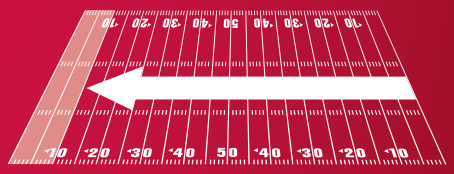

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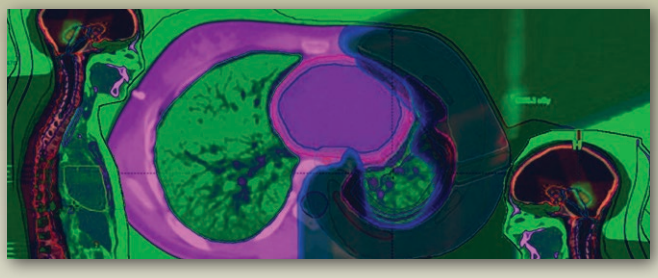

PROTON THERAPY REVIEW

HEAD AND NECK CANCER FOCUS

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EDITORIAL

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RADIATION ONCOLOGY CASE

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RADIATION ONCOLOGY CASE

TECHNOLOGY TRENDS

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EDITORIAL

State of (the) ART and additional updates in HNC treatment, proton therapy and more

John Suh, MD, Editor-in-Chief

Welcome to the September issue of *ARO*! This month we are pleased to offer a two-part focus on one of the most technically challenging treatment areas in radiation oncology: head and neck cancer.

Treatment of head and neck cancer with radiation therapy demands greater precision and efficiency than many cancer sites for several reasons — sizeable treatment regions, complex anatomy, proximal OARs and more. In *Evolution of treatment planning techniques in external-beam radiation therapy for head and neck cancer,* Qingyang Shang, PhD, and colleagues from the Cleveland Clinic, detail the emergence, efficacy, and acceptance of these technologies, from the traditional three-field technique, to IGRT, IMRT, VMAT, and the promise of ART.

In the companion article, *Adaptive radiation therapy for head and neck cancer,* Aditya Juloori, MD, and co-authors, further describe how ART can improve outcomes by allowing for modification in radiation planning, which is necessitated by anatomical changes of both tumor and normal tissue over the course of treatment. The article discusses the dosimetric benefits, clinical experience, indications and ideal timing, institutional practice from the Cleveland Clinic and other implications of this emerging, albeit controversial, practice.

The issue also features *Pediatric proton therapy in 2015: indications, applications and considerations*, by Jeffrey C. Buchsbaum, MD, PhD, of Indiana University School of Medicine. In this informative review article, Dr. Buchsbaum outlines concepts and epidemiological data that underscore practice patterns in proton therapy, as well as challenges and controversies that will likely spark continued healthy discussion and debate among radiation oncologists.

In addition, we are pleased to bring you two case reports this month: *Presentation of pituitary carcinoma as neck metastasis after irradiation of recurrent pituitary macroadenoma,* describes a patient with a pituitary adenoma that transformed into a pituitary carcinoma with metastasis to submandibular lymph nodes and the parotid gland. The second case report, *Radiographic changes of the lung after stereotactic body radiation therapy,* shows how the Ikezoe and Koenig systems can assess patterns of benign CT changes in the lung after SBRT, and how these changes can evolve even after 2 years. Additional advances in lung cancer treatment are highlighted in the Technology Trends article, *Breathing easier with SBRT, VMAT, 4D MRI and other advances in lung cancer treatment.*

As always, thank you for supporting ARO! I hope you enjoy the articles and case reports in the issue, and look forward to seeing you at the 57th Annual ASTRO meeting in San Antonio, Texas, Oct. 18-21, to learn more about the latest advances and studies in radiation oncology.

***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.*

Pediatric proton therapy in 2015: Indications, applications and considerations

Jeffrey C. Buchsbaum, MD, PhD

Proton therapy is a complex and important tool in treating cancer. It is not the only form of radiation therapy to use with children, nor is it always the best. However, in the right setting it offers significant advantages over other forms of radiation therapy, and should be considered the optimal choice for treating pediatric patients in those settings.

The first thought that comes to mind with proton therapy is pediatric cancer, especially for our youngest patients.[1] This is not a random thought; it is based on integral dose advantages protons have over standard photon radiation therapy when treating children.[2] This brief review of pediatric proton radiotherapy discusses the clear indications and contraindications of proton therapy in this population, how the latter may shift to the former, concepts and epidemiological data to support practice patterns, and problems and controversies when caring for pediatric cancer patients.[3,4]

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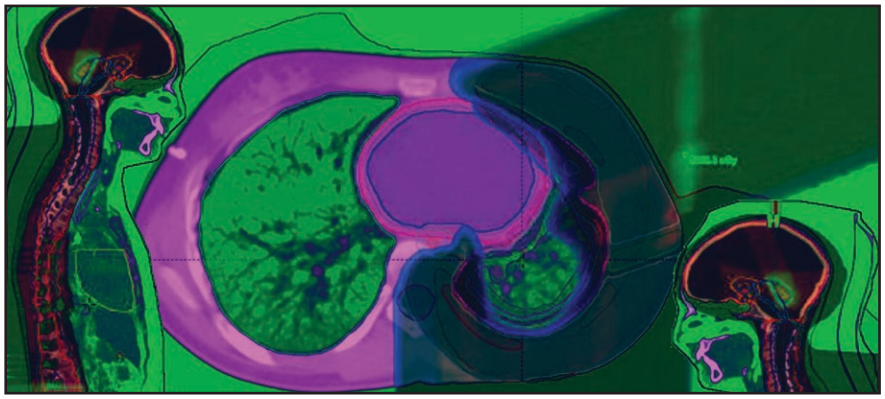


Next to curing the patient, the primary goal of pediatric radiation oncologists is avoiding late effects. In fact, both goals are nearly equal, as a cured child saddled with debilitating late effects that are preventable is an unacceptable outcome. To prevent late effects, radiation oncologists use the following: radiation avoidance, the lowest dose possible without causing loss of disease control, and dose modulation to avoid organs at risk (OARs). Use of protons is one method of modulating dose to avoid OARs when the dose is high and OARs are close. In adults, intensity-modulated radiation therapy (IMRT) may be ideal, but pediatric radiation oncologists must consider the whole body and OAR needs (beyond those typical for adults), with integral dose minimization a major goal. Models for second cancer development exist that strongly support proton therapy use to optimize normal tissue avoidance.[4-7] In one paper, the risk of developing a secondary cancer from craniospinal irradiation (CSI) in a young child is estimated at < 10% lifetime with passive scattered protons, and > 90% with photons.[4]

Strong indications for proton therapy

CSI

Patients with diseases requiring CSI are a clear-cut population benefitting from proton therapy. The benefit comes

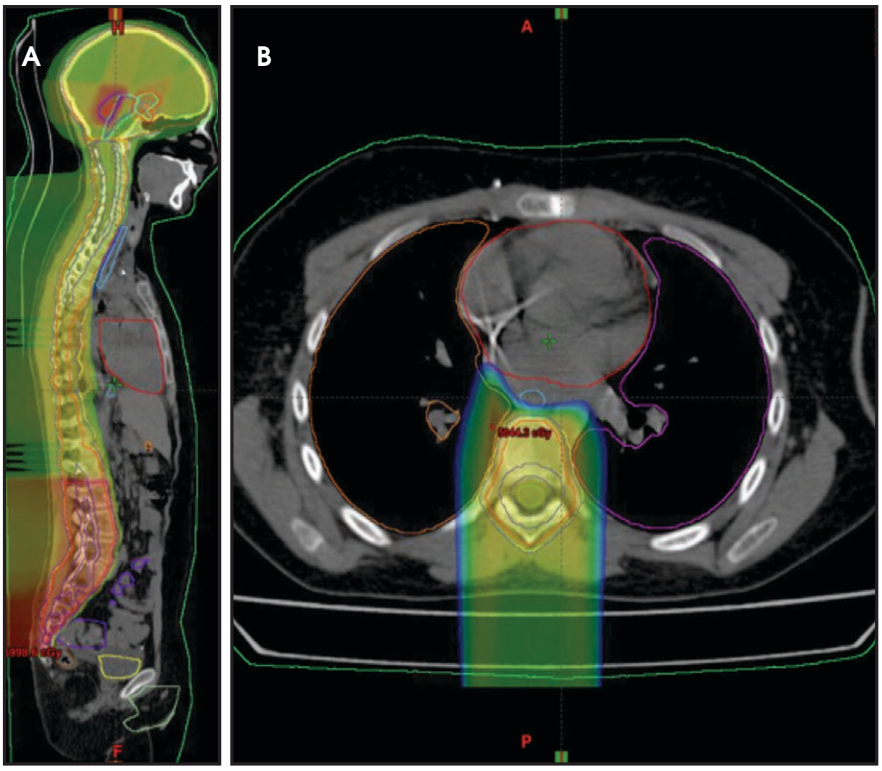


FIGURE 1. *A patient with metastatic glioma that progressed through chemotherapy was treated with proton CSI, with boosts to 54 Gy (A) and esophageal distal blocking (B).*

from 2 factors: 1) avoidance of anterior organs such as the heart, lungs, bowel, liver, esophagus, thyroid, and bladder; and 2) in addition to the primary fields, more conformal boosts allow better avoidance of critical brain structures such as the hippocampi and cochleae. In fully grown children, bone marrow dose can be minimized by sparing the anterior portion of the vertebral body. The latter advantage decreases with the total overall CSI dose, but is still important.[8,9] Figure 1 demonstrates supine CSI in an awake patient.

In atypical cases such as high-grade glioma and sarcoma (as in Figure 1), the doses one can achieve via proton beam typically treat less normal tissue and can avoid internal organs better than other forms of external-beam radiation therapy. For example, at the Indiana University Health Proton Therapy Center (IUHPTC), all forms of medulloblastoma were offered proton therapy, and other types of tumors adjacent to the spinal cord received high doses

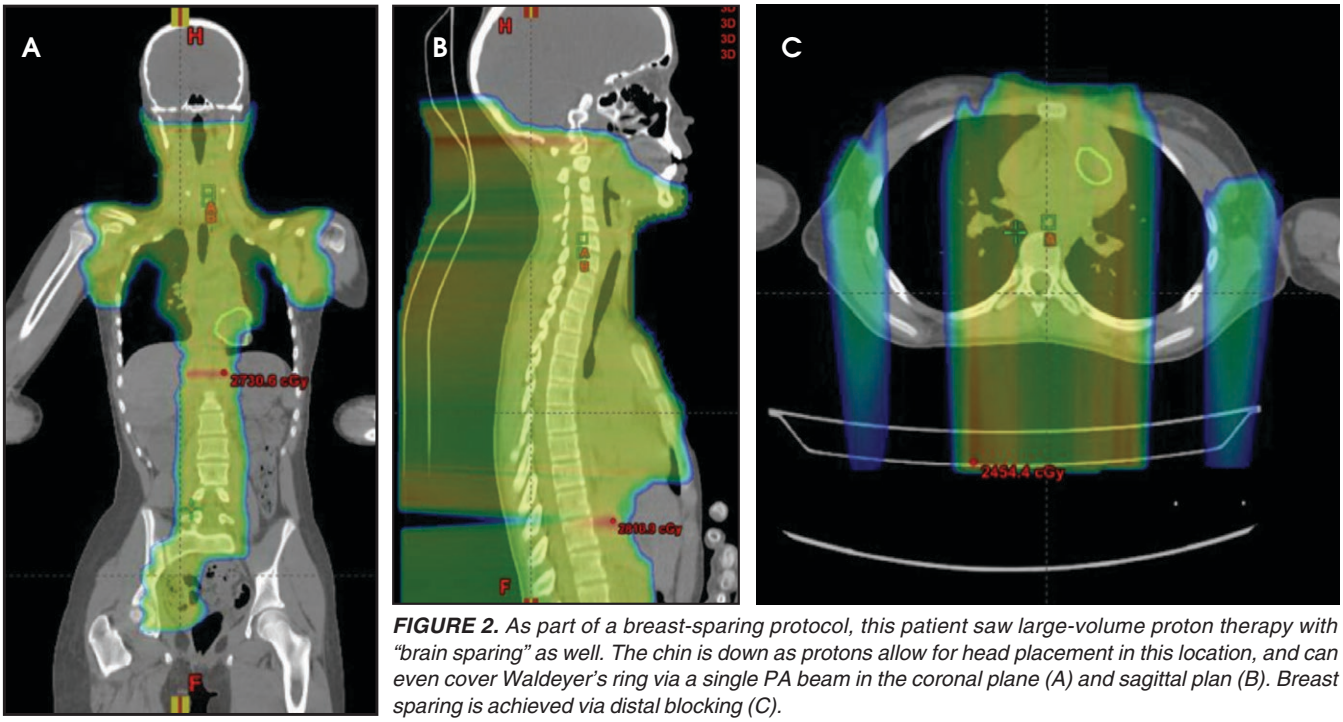


FIGURE 2. *As part of a breast-sparing protocol, this patient saw large-volume proton therapy with "brain sparing" as well. The chin is down as protons allow for head placement in this location, and can even cover Waldeyer's ring via a single PA beam in the coronal plane (A) and sagittal plan (B). Breast sparing is achieved via distal blocking (C).*

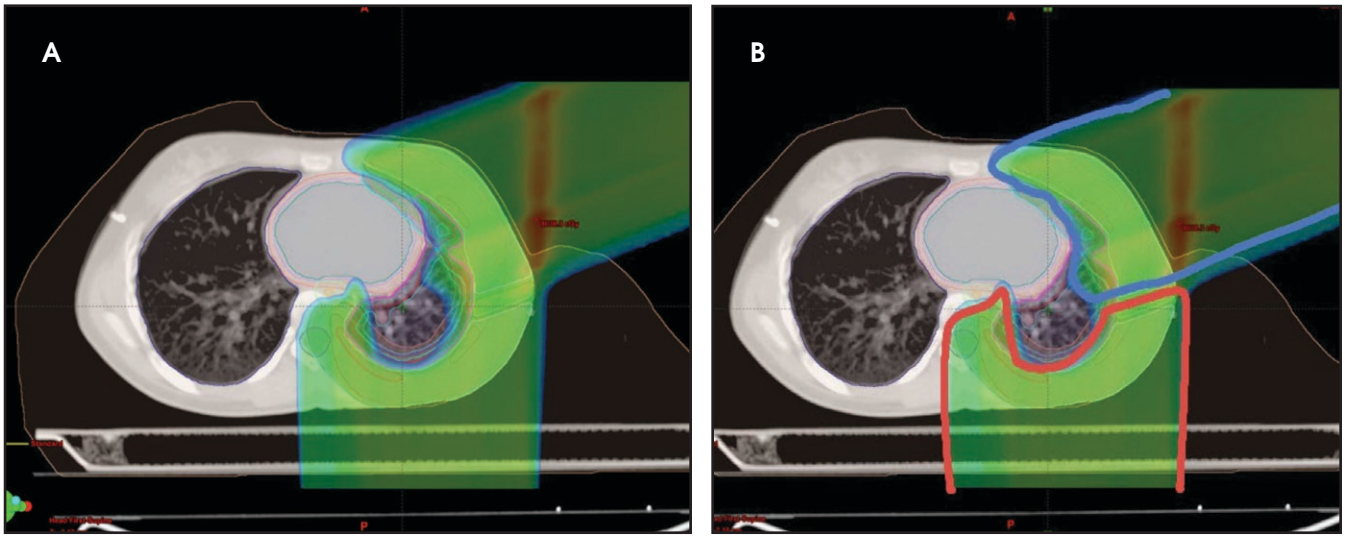


FIGURE 3. *This chest wall Ewing sarcoma tumor is treated with maximal lung and heart sparing (A). Example "patch" (outlined in red) and "through" (outlined in blue) fields (B).*

with protons, with no nausea induction or decreased blood counts in patients.[10] In rare cases, retreatment of spine lesions is possible to doses > 100 Gy with proton therapy with spinal-cord sparing; other forms of therapy would likely exceed OAR tolerance. Like photons, proton CSI is delivered with the patient supine or prone, using general anesthesia as needed.[11-12] And like photons, but to a much lesser extent, protons deliver small doses to adjacent tissue.[13-15]

Intracranial and base-of-skull tumors

Tumors of the brain, calvarium, and base of skull are often best treated with proton therapy, because the more we study the brain in terms of late effects, the more we find that every area of brain can cause late issues. Pediatric radiation oncologists try to avoid treating normal brain whenever possible, but especially the pituitary, hypothalamus, temporal lobes and/or the hippocampi, and optic apparatus. Work by Merchant has also shown that dosimetry impacts patient intelligence and quality of life in ways not otherwise predicted when examining low dose and intermediate dose region, in addition to standard high-dose regions.[16-18] Some skull base histologies such as chordoma and chondrosarcoma are of special interest to proton therapy as well because required doses are often 70 to 79.2 Gy, and cannot be delivered with the same degree of OAR sparing with standard radiation therapy due to the proximity of the optic apparatus anteriorly, the brainstem posteriorly, and the hippocampi and cochleae laterally.[19-22]

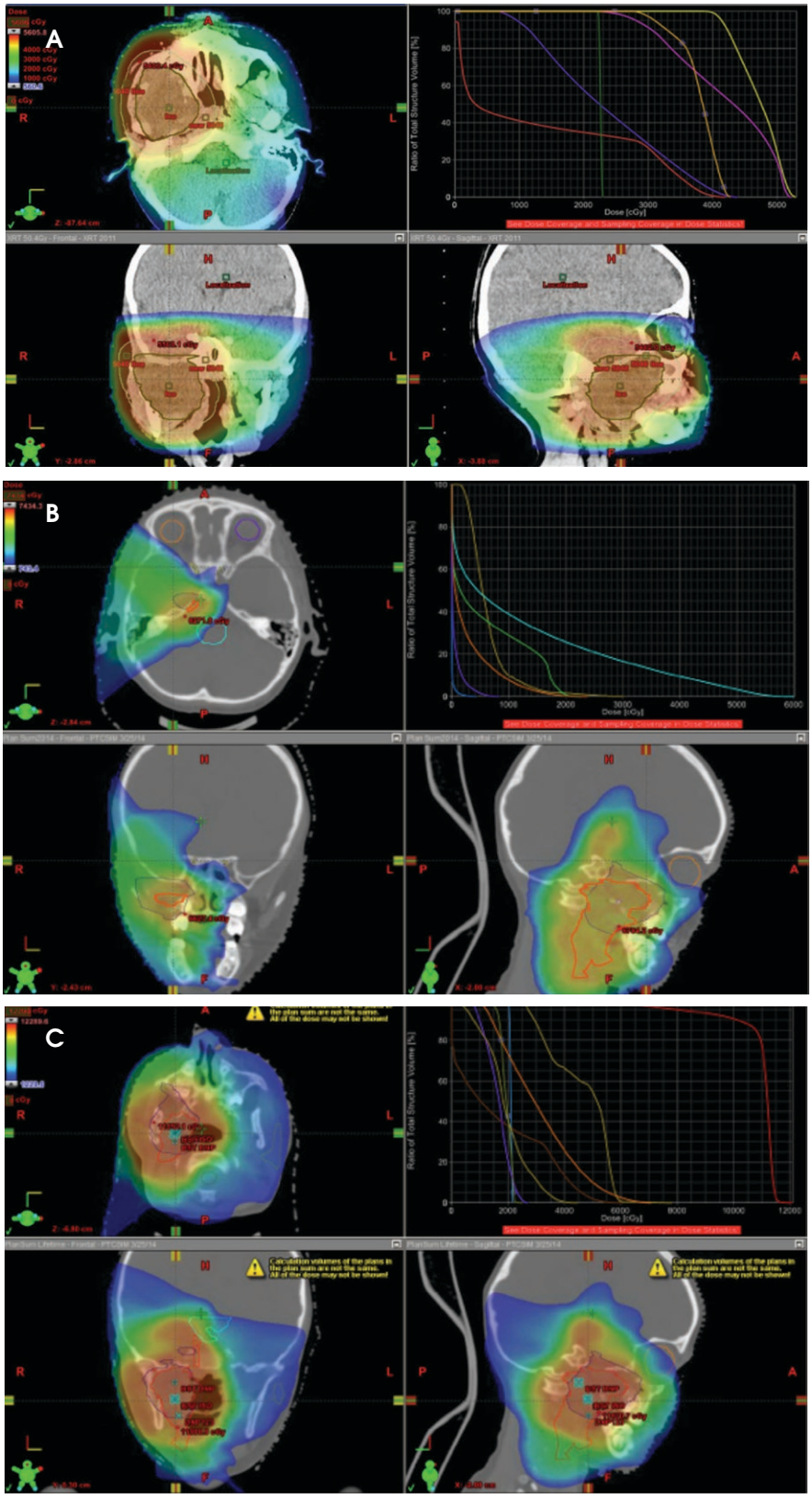
Spine tumors

Spine tumors are rare for patients of all ages. The anatomical juxtaposition of the spine and normal structures that poorly tolerate high doses of radiation make protons a superior choice for spine radiation therapy in children. A single beam can typically address these lesions, and is best demonstrated in cases involving both kidneys, as a single posterior beam can spare the renal parenchyma and bowel.[23,24]

More than just the end of the beam, the edge of a proton beam can be given a sharper penumbra than a photon beam —a less-appreciated technique of proton therapy called edge blocking. Using brass apertures, this penumbra varies with depth and can be 2 mm from full dose to no dose laterally for shallow tumors. As such, clever use of proton beams can sculpt dose around the spinal cord via only posterior oblique fields, sparing most, if not all, of the kidney, bowel and cord. This can be of immense value when high doses of radiation are needed for chordomas or retreatment.[25]

Hodgkin Lymphoma

When treating Hodgkin lymphoma, proton therapy is not typically the primary choice because doses in the pediatric setting are often < 30 Gy, and more typically 21 Gy, as directed in Children's Oncology Group (COG) studies. Because these children have high cure rates, many live long enough to experience second malignancy and other late toxicities.[26-28] In one series when radiation therapy was used definitively with much larger fields than today, upward of 40% of girls and women under 30 treated with radiation developed secondary breast cancer. The Childhood Cancer Study Group reported a high incidence of cardiac toxicity in this group as well. As a result, groups in Indiana and Florida have developed a method to avoid OARs in Hodgkins, including the female breast and heart. The newly opened COG protocol for Hodgkin disease allows for proton therapy based on these data.[26, 29-32] Figure 2 shows a stage IIIA case



with breast dose cut to about half photon dosing and intracranial sparing.

Tumors of the trunk (chest, abdomen, and pelvis)

Because proton beam therapy can avoid bowel, spleen, kidney, bladder, gonads, pancreas, and stomach exposure in ways otherwise difficult to address, pediatric tumors of the abdomen and pelvis can benefit from this treatment. When doses are relatively high, as with sarcomas and chordomas, proton use is relatively safe and well-tolerated even when doses exceed 60 Gy. When doses are both low and high, OAR sparing without very high integral dose remains a strength of protons. The use of protons in the pelvis and abdomen is not always superior to other modalities, however, and case-by-case comparison planning is often necessary. Tumors of the retroperitoneum can be addressed without significant dose to the bowel, which can be crucial in treating sarcomas.[33,34] Figure 3 shows an Askin's tumor with dose wrapped around the normal lung.

Retreatment

Retreatment is a new frontier in radiation oncology, and is rare in children. Despite this, several centers have retreated patients. At IUHPTC, we have treated a large number of patients a second time, many of whom were children. Data showing retreatment of gliomas and atypical teratoid/rhabdoid tumors (ATRTs) has recently been accepted for publication in two articles.[35]

We have also developed a novel method called "plugging" where beams are placed inside of other fields leaving dosimetric holes without dose, which is useful when retreating areas of the brain. This was used to deliver a second

FIGURE 4. *The patient came for proton therapy salvage after tumor regrowth following well-planned IMRT (A). Proton-only dose (B) and summation of both plans' dose (C) are shown.*

course of CSI without radiation-related toxicity for a patient treated with standard risk medulloblastoma, before the disease relapsed in a large spinal region lesion and outside of the CSI axis.[25] More established advanced methods in proton therapy, such as "patch and through," allow areas to receive no dose, while nearby areas see full dose.[36-38] In "patch and through," one beam stops (the patch) at the edge of another beam going all the way to the overall target volume's end (the through). One can wrap dose around objects in the manner shown in Figure 3 using this method. Figure 4 shows a patient treated with a photon plan who experienced recurrence < 2 years later, and required full-dose retreatment. The plan also employed the "patch and through" technique around the optic apparatus.

Miscellaneous indications for pediatric proton therapy

Sarcoma of the extremity can be treated with multiple approaches. Brachytherapy serves as the primary means of addressing dose conformality and minimizing integral dose in sarcoma. In many instances, however, brachytherapy is not an option and sarcoma treatment will cross joint spaces and/or involve a large amount of the subcutaneous tissue, making lymphedema likely. In these cases, proton therapy can allow for joint sparing and lymphedema avoidance. These indications are dosimetric in nature and are unlikely to undergo randomized testing. Tumors of the hands, feet, wrist, and near the gonads may be optimal for protons, but a special physics evaluation is crucial given shallow depths and small fields in these areas.[39]

Desmoid tumors of the trunk can often be treated to high dose using proton beam therapy without delivering dose to organs below the tumor given the nature of proton beam therapy. The lack of sharp margins makes field selection crucial, and the large fields of subcutaneous tissue are often impossible to treat with tangent fields due to field size and shape.[40]

Pediatric head and neck tumors are rare and commonly include nasopharyngioma and rhabdomyosarcoma. In this region, protons can treat the primary tumor to full dose while sparing OARs, and can treat the lymph nodes of the left and right necks without treating the esophagus, thus improving quality of life during, and potentially after, treatment.[19,41,42]

Contraindications for proton therapy

Wilm's tumor classic fields

Because there is no intent to "spare" any tissue, use of protons for whole abdomen and flank therapy is not indicated. Protons cannot "spare" normal structures to a degree that would make sense. Additionally, the fields are shaped in such a way that protons could prevent proper dosimetry. For example, for the whole abdomen, gas content changes and overall shape and size could, in theory, make dose inaccurate unless accounting for these variables, which would add complexity not found in a photon plan.[43-45]

Whole lung classic fields

The need to treat both lungs evenly with breathing motion and a beating heart makes photon anteroposterior and posteroanterior (AP-PA) fields the most logical approach. Dose is even with this method and motion is relatively well tolerated. Protons would not necessarily be able to handle the changes with the diaphragm well. Much like the Wilm's cases, this classic large volume is so straightforward that protons do not add to the process, and could cause dosimetric issues as the lungs develop atelectasis or another change, altering the net "range." Perhaps in the future we will see evidence that protons can spare the heart and whole lung. Until then, newer IMRT techniques may allow for timely treatment that proton therapy cannot address.[46]

Palliative care and rapid-start cases

While proton planning is inherently slower than photon planning, this difference will equalize as proton expertise increases. But for now, planning takes longer and cases requiring a quick start face delays due to processes intrinsic to protons. In addition, photons can be started in minutes; protons cannot. This reflects, in part, our comfort level with photons and electrons gained through vast opportunities for experience, which may change as experience with protons grows and processes are streamlined. In particular, the use of new methods that allow beams to be shaped without the standard requirement of customized field-shaping devices may decrease time from simulation to treatment. Because protons are slow to start, they are an unlikely contender for front-line emergency care. They can, however, be used with photons for rapid-onset situations such as a symptomatic leptomeningeal case, whereby one could start with photons and quickly shift to protons if indicated clinically.[47,48] As long as protons cost more than photons, however, their use in pediatric palliative care will remain rare.

Rapidly changing anatomical areas

Unless gating is used, protons are more sensitive to movement than photons, since range often alters with movement. If a large gas bubble in the gut moves, for instance, dose could rise or fall as a patient's shape changes. Or, as a patient breathes, a rib can shift its angle and become far thicker or far thinner. Without pre-emptive corrections, such changes can cause excessive dose irregularities, resulting in greater minimum dose. Patients who gain or lose weight rapidly throughout treatment are another example, as are patients with rapidly shrinking head and neck tumors, the latter of whom also require re-planning.[49] A worst-case scenario is a child with a nasopharyngeal tumor

Table 1. 2015 Matrix of Pediatric Proton Therapy

	Indicated	Varies	Not Indicated
CSI	X		
Brain	X	X	
Base of skull	X		
Spine	X		
Hodgkins (female)	X	X	
Hodgkins (male)		X	
Trunk tumors	X	X	
Retreatment	X	X	
Extremity		X	
Wilm's			X
Whole lung			X
Palliative			X
Kinetic target		X	X
Rapidly changing tissue volumes		X	X

that shrinks quickly, invalidating the proton plan and requiring rapid change and adaption. If not done, the protons could pass "through" the tumor area and could deliver unwanted dose to the temporal lobes — the very areas being avoided. If using protons in such cases where volumetric change could cause dose to be delivered to OARs, real-time imaging and adaptive planning are paramount. Without these tools, proton therapy is not likely the best option when anatomy is changing rapidly, even if the initial plan's dosimetry is superior to other treatments. This point is crucial and underscores a weakness of proton beam therapy relating to protons' unique capacity to stop quickly: increased sensitivity to change that can make a dosimetric miss far more likely.[50,51] New planning software and proton spot scanning will allow more rapid response, but the process is difficult even with these tools.

Leukemic cranial fields

Brain radiation therapy is well handled by conventional techniques. However, avoiding the lids and lenses of young children is sometimes difficult with three-dimensional conformal radiotherapy (3DCRT), the standard of care for whole-brain therapy. In theory, IMRT could help this issue, but the shape of childrens' brains, particularly in children under 5, can make even IMRT unable to spare the orbit while covering the frontal lobe and cribriform plate adequately. In these situations, protons are superior via oblique field use and distal blocking of the contralateral orbital region. While this is difficult to justify given cost issues, it will likely gain acceptance as proton therapy becomes more affordable. If costs were equal, the proton therapy approach would nearly always be at least equivalent, if not vastly superior, to the photon plan.[52]

Expanding indications for proton therapy

As noted, the primary reason proton therapy is not used for more pediatric indications such as whole brain is cost and time required for planning and treatment. Fortunately, proton therapy is more affordable than even a few years ago, and machinery prices will likely continue to drop. More centers are opening as well, making availability far greater than ever. Planning software is improving and spot scanning nozzles make construction of proton field-shaping devices a thing of the past. In time, these factors will likely result in the use of protons costing nearly the same as photons. While treatment ultimately may become financially bundled by disease, a disease will have a fixed payment regardless of treatment modality. As such, those who feel protons are superior will be allowed to use them as much as desired without penalty.[53,54]

Pediatric care and proton dosimetry

At the16th International Society of Pediatric Neuro-Oncology (ISPNO) meeting in Singapore last June, several speakers presented pre-publication data regarding unexpected toxicity seen with proton therapy.[55,56] These data, while not peer reviewed, were presented by leaders in the field from major institutions. One presentation examined 3 serious (NCI grade IV or higher) brainstem necrosis cases involving 3 proton centers.[55] In each case, a child either died or suffered a significant impact.[57,58]

At IUPTC we had no such issues. Perhaps it was luck, or it may have been due to a method we developed to avoid dose uncertainty at the end of the Bragg peak.[37] It is possible that beam modulation is needed to compensate for dose — an area not accounted for by planning systems. Our published method for avoiding toxicity is adaptable in a straightforward way to newer spot-scanning methods. The primary idea is the smearing of the distal beam end

to avoid high dose areas caused by the Bragg peak's higher biologic dose.[37]

Expanding research in proton therapy, like photon therapy, is underway across involved centers in plan robustness, image guidance, beam-selection algorithms, and biologic dose optimization. Each of these topics warrants a complete discussion that lies outside of the scope of this review.

Conclusions

Proton beam therapy for children and young adults is safe and can avoid large volumes of normal tissue due to unique characteristics of the beam's distal edge. Several areas of pediatric cancer such as the CNS and the head and neck have relatively clear indications for proton therapy; less clear areas may benefit as well when proton cost is no longer an issue. Table 1 shows the current rough matrix of where things stand in 2015 for pediatric proton therapy. Clearly, excellent care can and has been achieved for years without proton therapy and will continue to be done when protons are not available. Equally clear, there are cases where protons are not superior even in children. As costs decrease and the capacity to react to changing target shape and range improves, it is likely that proton therapy will become more strongly indicated for some types of pediatric tumors.

Proton therapy is a complex treatment that demands extreme expertise and care since it is easier to miss targets when dose falloff is so abrupt. Unexpected toxicity is possible, but at least 1 published report outlines an accessible method that avoids these pitfalls.

Protons are not always better, even for small tumors near critical structures.[59] But when contemplating which pediatric patients are best served by protons, physicians must consider several factors: the family's ability to travel, the capacity of the proton center to treat children and, finally, the center's expertise and support structures. Protons are an exciting aspect of pediatric radiation therapy that will ultimately become more available geographically as machine costs decrease. Proton therapy promises significant dosimetric improvements in many cases, but requires continued research and a sophisticated understanding of their limitations to use them well.

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Adaptive radiation therapy for head and neck cancer

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Radiation therapy has long played an integral role in the management of locally advanced head and neck cancer (HNC), both for organ preservation and to improve tumor control in the postoperative setting. In appropriate patient groups, definitive radiation can allow patients to avoid long-term morbidity associated with surgical resection.[1-3] Over the years, the delivery of radiation therapy has improved with innovations that have reduced toxicity without compromising locoregional control. Among these advances, the development of intensity-modulated radiation therapy (IMRT) has represented a major turning point in the treatment of HNC patients.[4] IMRT is characterized by its highly conformal dose distribution with improved ability to treat target volumes to therapeutic doses while avoiding normal structures such as the salivary glands, larynx, spinal cord, and oral cavity.[5-7]

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Because locoregional recurrence is the most common pattern of failure in HNC patients, improvement in outcomes focuses on local disease control.[8] Randomized trials have demonstrated that IMRT for HNC patients provides better outcomes regarding salivary toxicity when compared to conventional three-dimensional techniques.[9] Institutional experiences have also shown improvement in swallowing function and quality-of-life measures with IMRT.[10,11] More recently, image guidance has been used for adaptive radiotherapy (ART) — the adjustment of treatment planning during the course of radiation to account for anatomic changes and improve the therapeutic index. Here we review the current state of ART along with its utility and indications.

Why is ART necessary?

Head and neck radiation therapy provides a unique challenge in treatment delivery due to significant anatomic changes related to tumor response and weight loss that can occur during the course of treatment. With expected anatomical changes of both tumor and normal tissue during a 5- to 7-week course of radiation, relying solely on computed tomography (CT) images acquired before therapy could lead to (1) underdosing of the tumor and/or (2) unnecessary exposure of organs at risk (OARs) to higher radiation doses. Cone-beam CT (CBCT)[12] and CT-on-rails[13] have also been used during treatment of HNC patients to demonstrate set-up variability during the radiation course with use of rigid bony structures as landmarks. Traditional treatment planning may not be adequate to account for these set-up uncertainties. ART, is one proposed solution to these challenges, but significant effort is required to adapt a radiotherapy plan, and benefits are unclear.

Several studies have demonstrated compromised tumor coverage throughout the course of treatment. Barker et al tracked volumetric changes in gross tumor volume (GTV) as well as normal structures. They reported a reduction in GTV at a median rate of 1.8% per treatment day with a median cumulative reduction of 69.5% at the end of treatment. This study also noted changes in

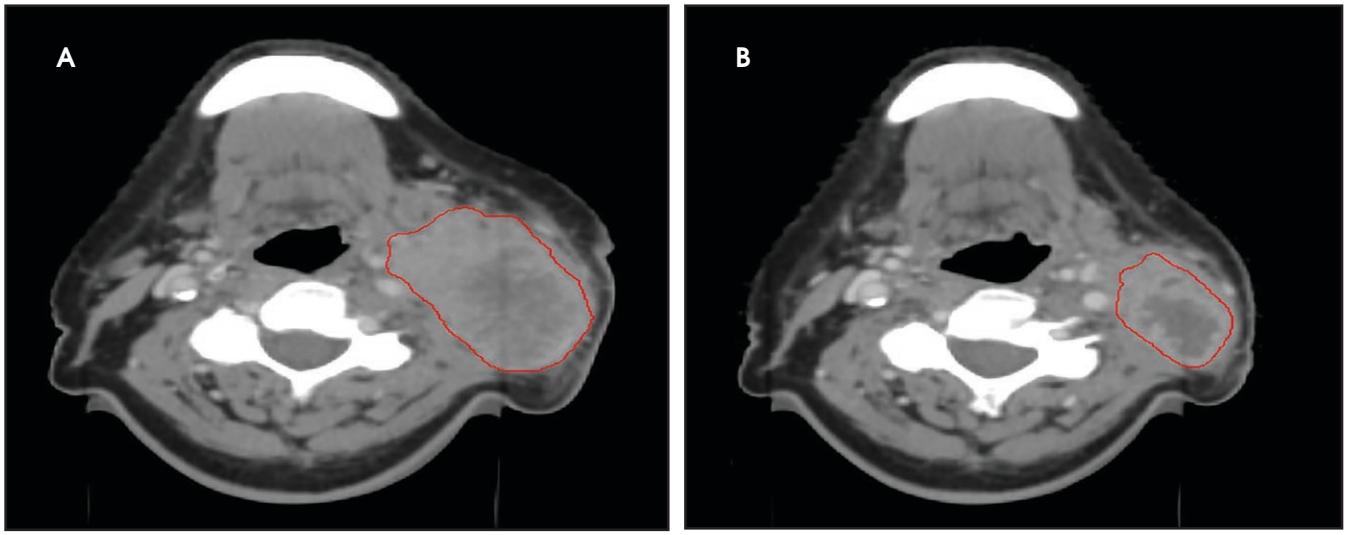

FIGURE 1. *Example of tumor volume change during treatment (A) before radiation and (B) after radiation. Volumetric reduction of GTV from 112.7 cc to 38.6 cc (65.8 % reduction rate). Reduction in largest diameter from 8.19 cm to 6.2 cm (24.3% reduction). GTV is shown in red contour.*

the geometric center of the GTV indicating that tumor reduction was asymmetric. Parotid glands decreased in volume as well, with observed medial displacement.[14] Figure 1 is an example of anatomic change during the course of treatment.

In another study, Hansen et al retrospectively reviewed plans for 13 patients with locally advanced HNC who had repeat CT imaging and replanning during the RT course in response to weight loss or tumor shrinkage. When compared with a replan, the original plans demonstrated decreased dose to target tumor volumes as well as an increase in D_{max} to the brainstem (24.9 vs. 22.3 Gy, p = 0.007) and spinal cord (23.3 vs. 19 Gy, p = 0.003).[15] D95% of the planning target volume (PTV) was reduced by a range of 0.8 to 6.3 Gy based on the original plan (22.7 vs. 25.7 Gy, p = 0.02). Also of note, O'Daniel et al demonstrated a significantly increased dose delivered to parotid glands (median 3.0 Gy ipsilateral, p = 0.026; median 1.0 Gy contralateral, p = 0.016) compared to what they had planned when CT scans done during treatment were used to recalculate initial dosimetry.[16]

As demonstrated, conventional IMRT planning can lead to underdosing of the tumor, as well as increased dose to normal critical structures when one does not account for anatomic changes over the treatment course. Recent advances have centered on using image guidance for ART to allow for changes in radiation planning over the radiation course. ART, or adaptive replanning, refers to any strategy that repeats the treatment planning process during the course of radiotherapy in response to anatomic changes in the target volume or nearby critical structures. These changes in the treatment plan can be made midcourse either manually or via automated algorithms to improve the therapeutic index and maximize local control while reducing toxicity. Below we review evidence demonstrating the benefits, challenges and future directions of ART.

Dosimetric benefits of ART

Initial prospective clinical trials have demonstrated a dosimetric benefit with use of ART in HNC patients. Schwartz et al reported on 22 patients with oropharyngeal squamous cell carcinoma who were prospectively enrolled at MD Anderson Cancer Center, Houston, Texas, to undergo adaptive replanning.[17] Daily in-room CT-on-rails or CB CT images were used to track anatomical changes, and deformable image registration was used to align baseline contours onto new images for replanning if needed, with all patients undergoing 1 or 2 replans. Adaptive replans were aggressively conformal with no PTV expansion. ART significantly reduced the mean dose to the ipsilateral parotid gland by 3.9% (p = 0.002) and contralateral parotid glands by 2.8% (p = 0.003). Dose reduction to the parotids was, in fact, more pronounced in patients who underwent a second replan during treatment (ipsilateral 9%, p = 0.001, contralateral 3.8%, p = 0.026). ART also reduced integral body dose (oral cavity, lower oropharynx, larynx) receiving 60 Gy by 31 cc (p = 0.019). Initial reports indicated excellent local control[18] although one outlier had significant disease progression between planning CT and the first treatment, which skewed target dosimetric data. Figures 2 and 3 demonstrate an adaptive replan with corresponding dosimetric implication.

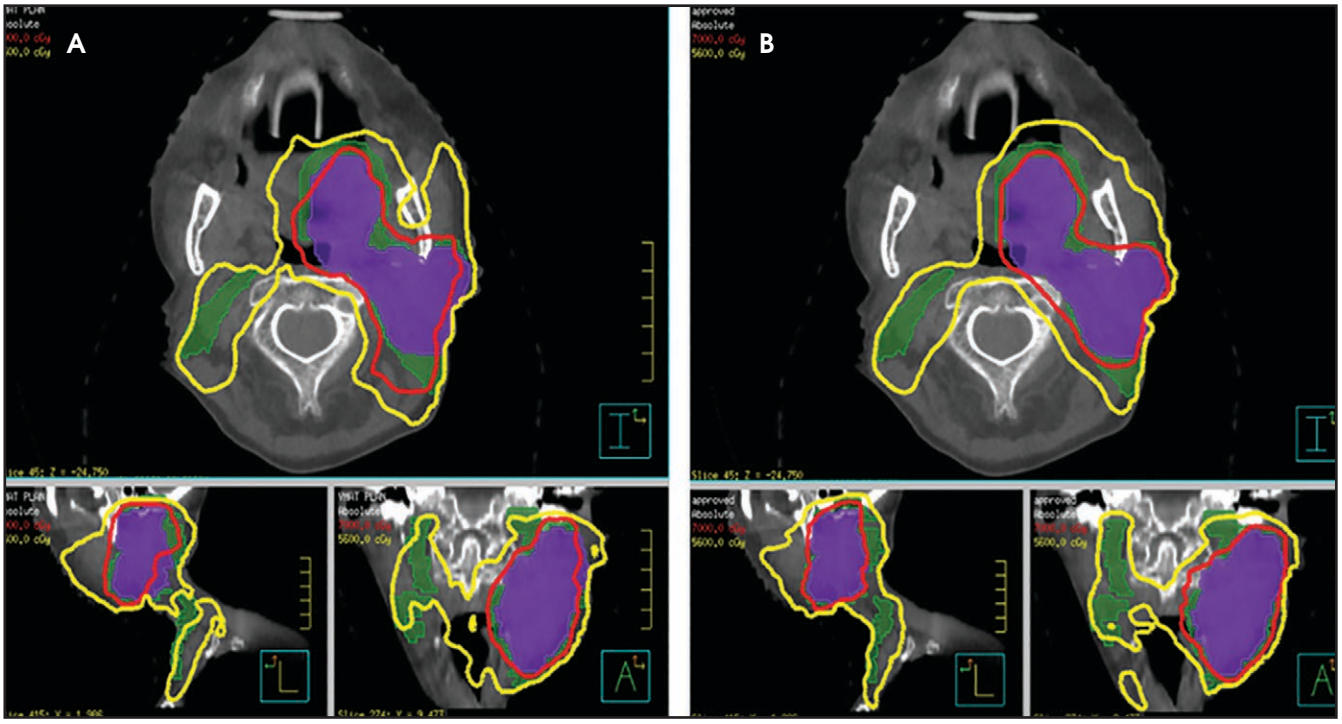

FIGURE 2. *Example of adaptive replan. The dose distributions after applying (A) the initial and (B) adaptive plans to the replanning CT. CTV70 and CTV56 are shown as purple- and green-shaded areas. The 70 Gy and 56 Gy isodose lines are shown in red and yellow.*

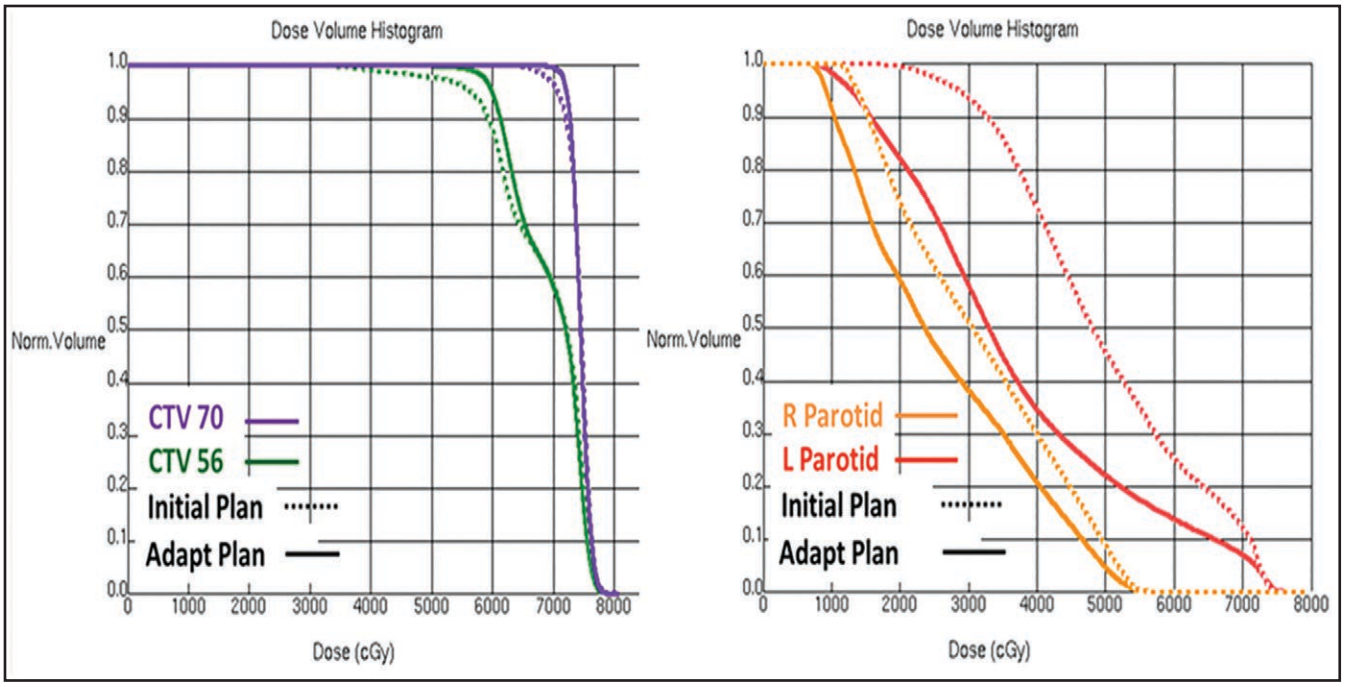

FIGURE 3. *Dosimetric evaluation of adaptive replan. DVH comparison between the initial and adaptive plans in Figure 2 for (A) the tumor volumes and (B) the parotids.*

Clinical experience

In reporting clinical outcomes, Schwartz et al demonstrated 100% local and 95% regional disease control at 2 years.[18] This was the first prospective look at clinical outcomes with ART, and acute toxicity at 1 year was equivalent to toxicity profiles observed with conventional IMRT. Tumor volume prior to treatment was significantly correlated with volumetric response to treatment. This further reduction in tumor size did not correlate with any increased toxicity, indicating that adaptive replanning could keep dose targeted to the tumor and away from normal structures even in patients with significant anatomical changes. However, the percentage of parotid volume reduction was correlated with increased duration of a percutaneous endoscopic gastrostomy (PEG) tube use.[18] The excellent disease control rates reported in this study also indicated that highly conformal ART did not lead to marginal target misses.

Although comparative data is limited, 1 published study reported an institutional experience comparing ART outcomes with those of conventional IMRT in HNC.[19] Of 317 patients treated with IMRT at UC Davis Medical Center, Sacramento, California, who were retrospectively reviewed, 51 (16%) had undergone adaptive replanning during the course of treatment. Daily IGRT imaging was used, and there was no standardization for when or if ART was done. The decision to use ART was multifactorial and considered nutritional status, tumor reduction seen on daily images, and/or significant weight loss. The subset of patients who underwent ART had more advanced disease. Two-year overall survival was similar for patients undergoing ART in comparison to those without it; however; ART improved local control at 2 years, with 88% compared to 79% for those with conventional IMRT ($p = 0.01$). This finding was significant on matched-pair analysis as well. Also of note, the local failures with ART were within the high-dose PTV regions. The use of ART was not found to significantly reduce the incidence of grade 3 or higher toxicity, acute hospitalization, or the need for a feeding tube. Consequently, this retrospective study was the first to report a significant clinical advantage with the use of ART. While subject to selection bias, the findings are notable given that the patient subset who underwent ART had significantly improved local control despite more advanced T and N staging at baseline.

Although the studies discussed did not show a toxicity benefit, 1 study by Yang et al of 129 patients with nasopharyngeal carcinoma reported an improvement in global quality-of-life scales when IMRT with replanning was used, compared to those without ART.[20] The EORTC (European Organization for Research and Treatment of Cancer) Quality of Life Questionnaire C30 was given to patients before treatment and 1, 3, 6, and 12 months after treatment. Those who underwent replanning had improved quality-of-life measures starting at 1 month after treatment despite having worse measures before therapy. The improved quality of life was maintained at 12 months ($p = 0.012$). Toxicity benefits may have been precluded in other ART studies due to imbalance in tumor bulk between the standard and ART cohorts.

Indications and ideal timing

To this point, the theoretical advantage of ART for dosimetric and clinical parameters has been established in multiple studies; however, the challenge remains in developing a standardized mechanism that addresses when to initiate ART. ART is labor-intensive and should be reserved for those who are most likely to benefit. Ahn et al reported their experiences with 23 HNC patients who had prospectively planned rescans at 11, 22, and 33 fractions, but 35% of patients did not have a dosimetric benefit with ART, underscoring the need for careful selection.[21] In reporting their retrospective institutional experience comparing ART with conventional IMRT, Chen et al used markers such as significant weight loss, an ill-fitting immobilization mask, significant shrinking of palpable disease, or an extended treatment break to initiate replanning.[19] While not standardized, selection based on treatment factors that were expected to be associated with anatomical change demonstrated clinical benefit with ART.

In another study, Surucu et al retrospectively reviewed 48 patients with squamous cell cancer of the head and neck who had undergone replanning during treatment at a median dose of 37.8 Gy.[22] The authors examined patient and treatment factors including the reduced size of the GTV (%GTVΔ). Using decision-tree induction algorithms to build models that would predict which patient variable combinations were most associated with %GTVΔ, they found that chemotherapy type, age, tumor growth pattern, primary site, and Karnofsky Performance Status (KPS) were most predictive for significant tumor volume reduction. While this is a small patient group, decisions to use ART can be built off of such data. For example, in their review, the use of standard cisplatin rather than low-dose cisplatin or cetuximab was predictive for increased tumor volume reduction, which fits in line with data gathered from large meta-analyses.[23] While the published decision tree had an 88% predictive value for high %GTVΔ, it has not been prospectively validated.[22]

A study by You et al reported that easily measured anatomic changes in neck size and patient weight may be related to side effect profiles.[24] Patients undergoing IMRT for HNC were monitored for xerostomia. Those with increased (> 10%) reduction in neck diameter or increased (> 5%) weight loss

had a significantly greater rate of grade 2 or higher xerostomia. These patients also had a 23% increase in daily V0.75 Gy to the parotid glands by the end of treatment. While the patient group was small and there were confounding factors, the findings show a potential role for adaptive replanning in patients with visible anatomic changes.

Identifying patients who would benefit from ART remains challenging. Treatment schemes and prospective trials would benefit from standardized points for which to use CT rescans. Using weekly serial CT scans to monitor the volumetric changes of CTV during radiation in HNC patients, Bhide et al reported that the greatest percentage of volume reduction was observed on week 2 CT scans.[25] One weakness of the study, however, was that the baseline CT scan was performed prior to induction chemotherapy, so volumetric reduction was reflective of the initial radiation response as well as induction chemotherapy. Other studies have demonstrated that the most significant volumetric change in nonsmall cell lung cancer occurs *after* the second week of treatment.[26,27] Based on these findings, Yang et al argue that timing of ART for HNC patients should be in the fourth or fifth week of treatment to allow for adequate volumetric response to radiation while preserving adequate treatment time for the replan.[28]

Institutional practice

At our institution, the practice has been to use daily cone-beam imaging to monitor anatomic changes during treatment of HNC patients. Many have used parameters such as change in source-to-skin distance (SSD), percentage of weight loss, ill-fitting mask, and "significant" change in body/tumor contour on daily CBCT as possible triggers for ART. We do not know which approach is the best. Our institutional practice is to assess for adaptive replanning at weeks 3-4 of definitive radiation. Patients with significant weight loss or disease regression causing visible geometric changes to target volumes that excessively cover uninvolved organs or skin are targeted for ART.

In our institutional study, a cohort of 203 patients with locally advanced HNC who underwent IMRT from 2009 – 2014 was studied. Of them, 87 patients (43%) underwent adaptive replanning; patients were treated to a mean total dose of 70 Gy with adaptive replanning performed at a mean dose of 44 Gy.[29] Those undergoing ART had significantly higher rates of N2b-3 disease (83% vs. 62%; $p = 0.001$) and stage IVb disease (17.2% vs. 3.4%; $p = 0.0002$). Despite this increased burden of disease, patients undergoing ART had similar rates of locoregional failure (5.2% vs. 9.2%; $p = 0.24$) and 2-year overall survival (87.3% vs. 86.8%; $p = 0.79$) as those undergoing conventional IMRT. Acute toxicity rates were also similar between the 2 groups, suggesting a role for ART to offset expected increased toxicity in patients with more advanced disease.

The pattern of disease regression over the course of radiation is believed to be different for primary vs. nodal disease. While nodal disease (without extracapsular extension [ECE]) is expected to exhibit circumferential regression, the primary mucosal disease often regresses leaving discontiguous islands of disease. Our institutional practice has been to recontour the regressed GTV at the time of replan. However, our primary replanned CTV is then expanded to ensure that all initial mucosal extent of disease /adjacent involved structure is included in this volume, as suggested by the NRG-HN002 protocol. For nodal volumes, the adapted GTV represents the regressed nodal disease when there is no obvious evidence of ECE. When evidence exists for upfront ECE (e.g., loss of fat planes with adjacent muscle), the adaptive nodal CTV is again increased to include the initial areas at risk.

The initial simulation CT can be used to anticipate and prevent the need for an adaptive replan. For example, in the era of HPV-positive disease in the oropharynx, the presence of a cystic node can be expected to enlarge during the course of RT; thus, a larger PTV may initially be given to account for this growth. Some centers use deformable registration to adapt the latest CBCT to the initial CT scan and replan based off the CBCT. Our approach has been to repeat a CT simulation with a new aquaplast mask if necessary and recontour volumes, as described. With this approach, two datasets are now available for the same patient with differing anatomical contours. Creating a sum plan combining the initial plan and the new plan would be at best an arithmetic summation of dose for the various structures and not a true estimate of the dose. Our approach has been to generate a new plan and deliver the remaining fractions using the new plan. We believe this to be a safe, albeit labor-intensive, approach.

Other implications of ART

The value of ART may not only be limited to the adaptation of treatment volumes during therapy, but may also be used to determine which patients may benefit from dose escalation during treatment. Yang et al retrospectively reviewed the use of ART with 76 patients with oropharyngeal and hypopharyngeal cancers, and on multivariate analysis demonstrated that a primary GTV prior to treatment > 30 cc as well as tumor volume reduction rate < 50 % after treatment were prognostic for poor local control.[28] A similar finding was reported by Lee et al who noted that tumor volume reduction rate measured during ART in 59 patients with oropharyngeal cancer was a significant prognostic factor for local control on multivariate analysis.[30] These findings point to the importance of identifying patient groups with decreased volumetric response to therapy during

treatment. Prospective trials are needed to validate these theoretical considerations, and ART techniques will form the foundation for these protocols.

Conclusion

While there is no clear consensus as to which HNC patients should undergo adaptive replanning, the use of ART is becoming more commonplace in today's clinical practices. Multiple studies indicate the dosimetric benefits of ART when used in selective subsets of patients, although clinical implications of this remain unclear. A single institution retrospective study has demonstrated improved local control with use of ART, while toxicity benefits are yet to be clearly demonstrated. Much work remains to be done to clearly establish the benefits of routine use of ART. Initial retrospective studies have attempted to identify prognostic factors for tumor volumetric reduction to help decide at baseline whether a patient will need ART or not; however, further prospective trials are needed. ART still remains labor and resource intensive and future improvements in ART, including automated replanning processes and improved image guidance, will make ART a more economical option.

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Evolution of treatment planning techniques in external-beam radiation therapy for head and neck cancer

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Radiation therapy is a standard therapeutic option for many patients with head and neck cancer (HNC) but presents many technical challenges. Primary head and neck tumors are often situated in close proximity to numerous critical structures, and delivering an adequate radiation dose to the primary and regional lymph nodes requires special attention to protect these organs at risk (OARs). The treatment planning methods for HNC using external-beam radiotherapy have evolved from the traditional three-field technique in the early days to intensity-modulated radiotherapy (IMRT), and recently to the more efficient volumetric modulated arc therapy (VMAT). IMRT and VMAT require higher precision and accuracy in patient setup than conventional radiotherapy due to a highly conformal dose distribution and steep dose gradients. Thus, image guidance for head and neck radiotherapy has also evolved from weekly 2D portal imaging to daily 3D CT or cone-beam CT (CBCT) imaging. The rapid advancement in image-guided radiotherapy (IGRT) further allows the development of adaptive radiation therapy (ART). The purpose of this article is to review the technical evolution of treatment planning and delivery for HNC.

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Three-field technique

Head and neck tumors are most commonly treated with 6 MV photon beams. The three-field technique consists of 2 opposed lateral fields to irradiate the primary tumor and cervical lymph nodes in the upper and lower neck, and a third anterior field to irradiate the supraclavicular lymph nodes. The bilateral fields and the anterior field share the same isocenter and are matched at the isocenter plane to avoid field overlaps at the field junction line. It is also desirable to move the junction line during the treatment course to feather the junction dose distribution.

The three-field technique involves multiple sequential boosts, with several prescriptions associated with each plan. Figure 1 shows the beam's eye view (BEV) of a series of three-field plans with sequential cone-down boost fields. For this particular patient, the primary tumor and the upper neck nodal regions were treated to 72 Gy in 36 fractions (2 Gy/fx). The initial plan used the opposed lateral fields (Figure 1A) to irradiate the primary and upper neck nodal regions to 42 Gy. The lateral fields were then brought off the spinal cord through changing the blocks from 42 Gy to 54 Gy (Figure 1B). An additional cone-down of the lateral fields was performed from 54 Gy to 66 Gy to the primary tumor and the high-risk clinical target volume (CTV, Figure 1C), and again to the gross tumor volume (GTV) from 66

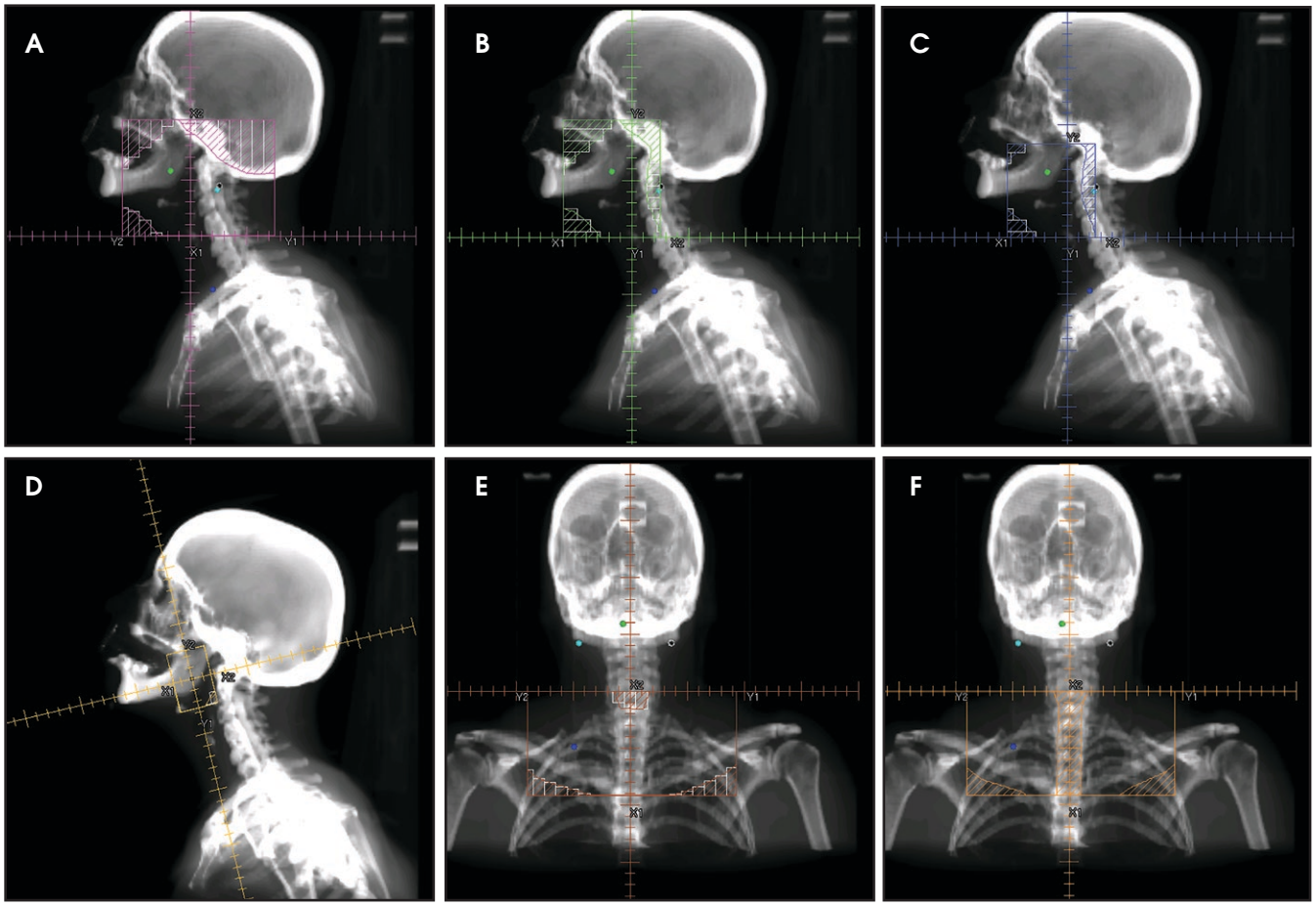

FIGURE 1. *A typical example of the conventional three-field technique. (A) The BEV of one of the bilateral fields for the initial 21 fractions. (B) The BEV of one of the off-cord lateral fields for the subsequent 6 fractions. (C) The BEV of the first cone-down to the primary tumor and the high-risk clinical tumor region for the next 6 fractions. (D) The BEV of the second cone-down for 3 more fractions. (E) The BEV of the anterior supraclavicular field for 22 fractions with a larynx block in the middle. (F) The BEV of the anterior field with the spinal cord block for additional 3 fractions.*

Gy to 72 Gy (Figure 1D). The supraclavicular region typically received 50 Gy in 25 fractions (2 Gy/fx) with an anterior field (Figure 1E). The middle block in Figure 1E was to protect the larynx. To further protect the spinal cord, the midline block was extended to the entire field as shown in Figure 1F from 44 Gy to 50 Gy. For patients with the enlarged posterior neck nodes, lateral electron beams were added to treat the neck nodes from 54 Gy to 66 Gy. Figure 2 shows a typical dose distribution of the composite sequential boost plans. As shown from Figure 2, a large volume of normal tissue was irradiated to a high radiation dose, thus increasing treatment toxicities such as xerostomia.

Intensity-modulated radiation therapy (IMRT)

Unlike the three-field treatment planning technique, IMRT delivers nonuniform beams across the tumor through a sequence of field segments with varying intensities that, in sum, deliver the desired dose distribution. IMRT can generate a conformal dose distribution and has steep dose fall-off at the boundary between the tumor and the normal structures. IMRT enables dose-escalation without increasing toxicity to the critical organs, potentially improving the therapeutic ratio.[1,2] HNC is the ideal disease site for IMRT due to the complex tumor shape, the large number of adjacent sensitive structures, and minimum organ motion in the region.[3-5] Furthermore, the ability of IMRT to produce inhomogeneous dose distribution allows the primary and secondary target volumes to be treated simultaneously.

Head and neck IMRT planning techniques include the split-field and the extended-field IMRT techniques.[6-9] For the split-field IMRT technique,

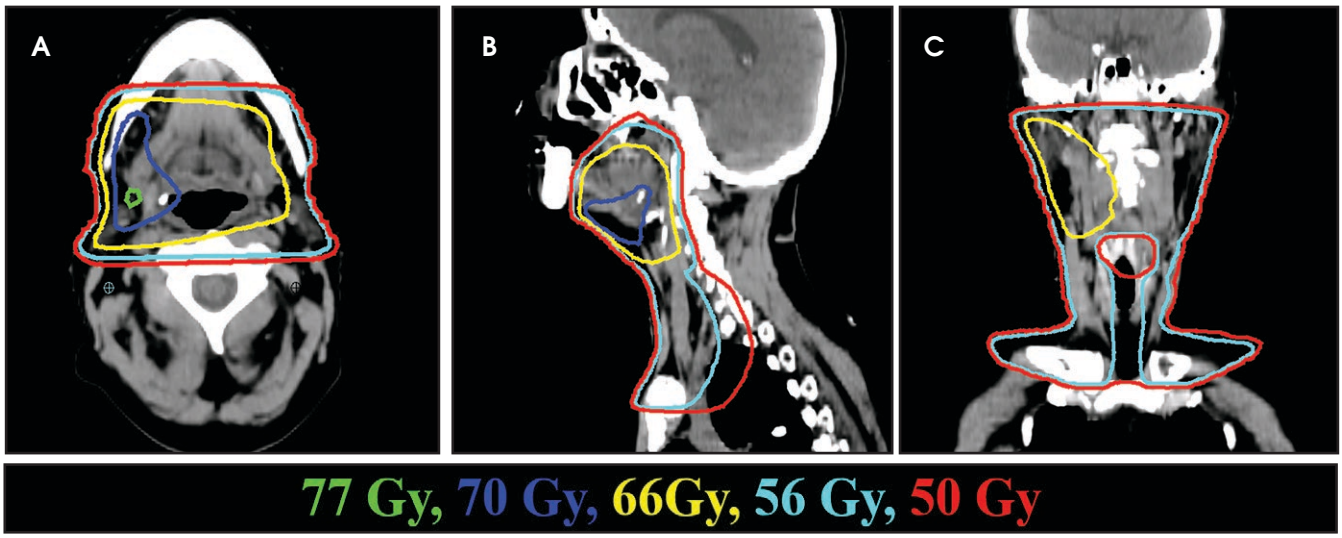

FIGURE 2. *The composite dose distribution in the axial, sagittal and coronal views from a series of three-field plans described in Figure 1. Isodose lines are color-coded as shown in the figure.*

Table 1. Typical dose constraints for head and neck IMRT planning

OARs	Dose constraints
Brainstem	Max < 54 Gy
Spinal cord	Max < 45 Gy
Chiasm	Max < 56 Gy
Optic nerves	Max < 55 Gy
Parotid	Mean < 26 Gy
Cochlea	Max < 55 Gy
Larynx	Mean < 35 - 45Gy
Eye	Max < 50 Gy
Lens	Max < 7 Gy
Mandible	D1cc < 75 Gy
Oral cavity	Mean < 40 Gy
Esophagus	Mean < 45 Gy
Supraglottic larynx	Mean < 50 Gy

the primary and the upper neck above the vocal cords are treated with IMRT, and the lower neck and the supraclavicular fossae are treated with the conventional anterior field. The IMRT fields are matched with the anterior field at the isocenter with a half-beam block technique. One concern of the split-field technique is the possible underdosage of the tumor at the field junction.[10] Alternatively, extended-field IMRT treats all tumor volumes simultaneously with different prescription doses to the primary tumor and the regional lymph nodes. This technique avoids field matching as in the split-field technique, but may increase the dose to the larynx if a special dose constraint is not applied to protect the larynx.[9,11] The extended-field technique can also deliver a high dose to any involved lymph nodes in the lower neck and supraclavicular region.

The GTV is defined as the gross extent of the primary tumor and any cervical lymph nodes felt to be involved on imaging or physical examination. The clinical target volume (CTV) is defined as the GTV plus a margin for potential microscopic spread of disease as well as the clinically negative but at-risk regional lymph nodes. As suggested by international guideline statements, intravenous contrast should be administered during the simulation scan to ensure accurate delineation of the GTV and cervical nodal levels.[12] The planning target volume (PTV) is defined as the CTV plus a margin, usually 3-5 mm, depending on the image-guidance techniques used and the frequency of image guidance applied, to account for setup uncertainties. At Cleveland Clinic, we use daily kilovoltage or megavoltage cone-beam CT to correct for daily patient setup.

When planning, fusion of an ^{18}F-fluorodeoxyglucose positron emission tomography (^{18}FDG-PET) with the treatment planning CT helps the delineation of the GTV. Studies have shown that PET-based delineation may lead to a significantly smaller GTV compared to CT-based delineation.[13-15] However, interobserver variation in target-volume delineation remains an important source of uncertainty during IMRT planning. Continuing efforts had been made to generate consensus guidelines for the delineation of the neck node levels in node negative, node positive, and the postoperative neck regions.[16]

The typical beam arrangement for the treatment of bilateral tumors consists of 9 coplanar 6 MV photon beams evenly distributed around the patient (0°, 40°, 80°, 120°, 160°, 200°, 240°, 280°, and 320°). The typical beam arrangement for the treatment of unilateral cases consists of 7 coplanar beams, angled from the tumor side. The gantry angle should avoid the lateral directions and can be adjusted slightly to avoid the shoulder or to minimize the beam path through the

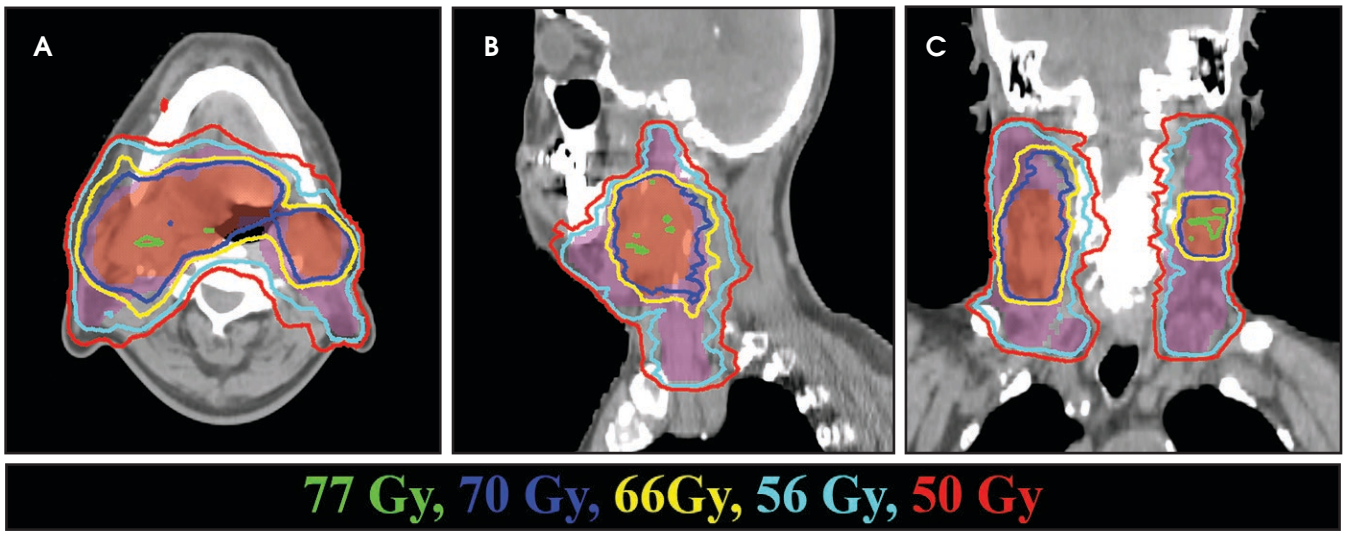

FIGURE 3. *Dose distributions in the axial, sagittal and coronal views for a 9-field IMRT plan. PTVs of primary and elective lymph nodes are shown as color-washed areas in red and magenta, respectively. Isodose lines are color-coded as shown in the figure.*

shoulder. Given that the field size is often relatively large for head and neck treatments, the isocenter is usually selected at the center of the irradiated region.

The general planning goal is that at least 95% of the PTV and 99% of the CTV receive the prescription dose. The plan uniformity, defined as the ratio of the maximum dose (to 0.03 cc) of the plan to the highest prescription dose, should be limited within 115%. Table 1 lists the typical dose constraints of OARs clinically acceptable in our institution. These constraints, however, are highly variable based on the individual case.

IMRT optimization has evolved from forward planning in the early days to inverse planning currently used by the majority of treatment planning systems. Forward planning uses the field-in-field technique to achieve a simple intensity-modulated dose distribution.[17,18] With forward planning, a planner manually adjusts the block shape and the beam intensity of each field through a trial-and-error process. Alternatively, inverse planning is a computer algorithm that adjusts the beam weighting and blocking to achieve an optimal plan based on dose objectives applied to the tumor targets and critical organs. Compared with forward planning, the inverse planning technique provides more conformal-dose distributions to the tumor volumes with significantly better sparing of critical structures.[19-24] However, care must be taken as marginal failure in the spared parotid gland has been reported due to potentially inadequate dose to possible microscopic disease.[25]

Even with computer optimization, IMRT planning for HNC is not a simple process. The most important task is the delineation of the tumor volumes and OARs. As listed in Table 1, some OARs are bilateral, resulting in more than 20 OARs to be outlined and evaluated for dose tolerance. Another key step is to define planning objectives for the targets and OARs during optimization, which can be specified as desired and displayed on a simplified dose volume histogram (DVH). For example, the dose coverage to the tumor target is often achieved by setting the maximum and minimum doses to the PTV, and the percentage of the PTV receiving the prescription dose. The maximum dose is usually the constraint of choice for serial OARs such as the spinal cord, while a mean dose or DVH-based planning objective is the constraint of choice for parallel OARs such as the salivary glands. Mean or DVH-based constraints allow a part of the parallel structures to receive a high dose in order to deliver a prescribed dose to the adjacent tumor volumes. By increasing the relative weight assigned to a particular planning objective, one can increase the probability of meeting a specific planning objective. Therefore, IMRT planning for HNC becomes an iterative process, involving multiple manual adjustments in the planning objectives according to the result of previous optimization. Frequently, planners also need to add artificial tuning structures to steer the optimizer to produce a plan that meets clinical requirements. Figure 3 shows a typical dose distribution for a nine-field IMRT plan, which is more conformal than that of the conventional three-field plan in Figure 2.

This process, which requires manual intervention, is partly due to the design of IMRT optimization. Most commercial IMRT treatment planning systems use a gradient-based optimization method. With this method, the solution obtained from the initial IMRT optimization is often not optimal because the optimizer may be trapped in a so-called "local minimum." Therefore, to escape

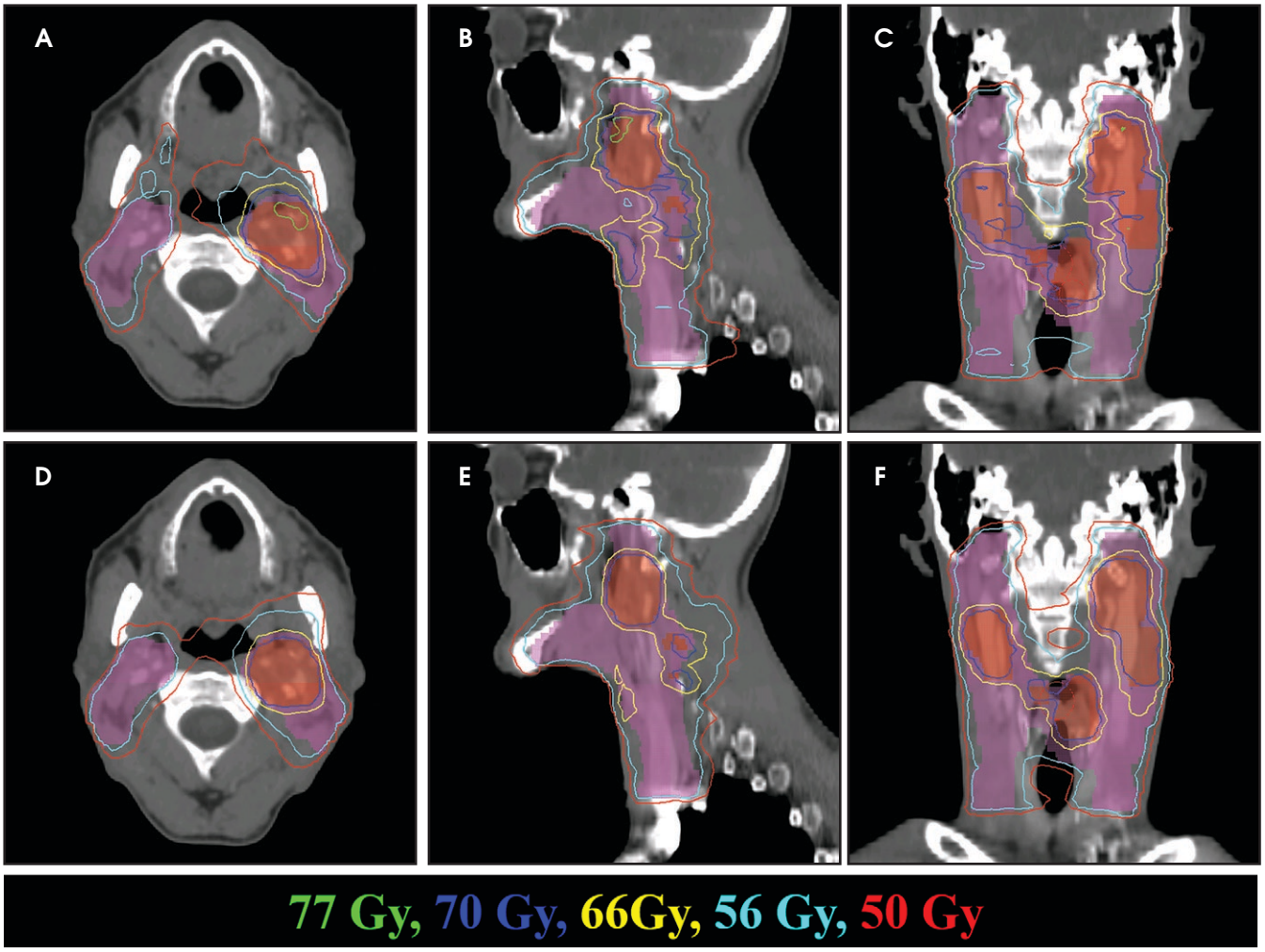

FIGURE 4. *Example of dose distributions in (A-C) IMRT and (D-F) VMAT plans for a larynx cancer case with bilateral cervical lymph nodes involved. The PTVs of primary tumor and elected lymph nodes are shown as color-washed areas in red and magenta, respectively. Isodose lines are color-coded as shown in the figure.*

the local minimum and find an optimal solution, manual adjustments of the planning objectives are necessary. The limitation of this optimization method is one of the compounding factors contributing to the large variations in IMRT plan quality.

Volumetric-modulated arc therapy (VMAT)

VMAT is an advanced form of IMRT. With a number of fixed gantry angles, the conventional IMRT plan delivers a number of small fields (segments) formed by the multileaf collimator (MLC) either by sequentially moving the MLC leaves to various positions and then delivering the radiation dose (step-and-shoot method), or by continuously moving the leaves during the beam-on time (sliding window method). VMAT delivery allows motion of the MLC and gantry while simultaneously adjusting MLC leaf speed, gantry speed, and dose rate while the radiation beam is on.[26,27] VMAT has emerged as a mainstream treatment option for HNC.[28] Given the complexity of the anatomy in the head and neck region, a VMAT plan usually consists of 2-3 full or partial arcs, depending on whether the treatment targets are bilateral or unilateral. VMAT plans increase the number of beam angles, and are therefore capable of creating a more conformal dose distribution to the target volume when compared to traditional IMRT. VMAT plans provide similar PTV coverage as the fixed gantry IMRT plans with improved homogeneity.[29-31] Most importantly, the delivery time for a VMAT plan is much shorter (about 5 minutes) than that of a fixed gantry IMRT plan (10-15 minutes).[31,32] Figure 4 compares the dose distributions from a two-arc VMAT plan and a nine-beam IMRT plan for a larynx cancer case with bilateral cervical lymph node in-

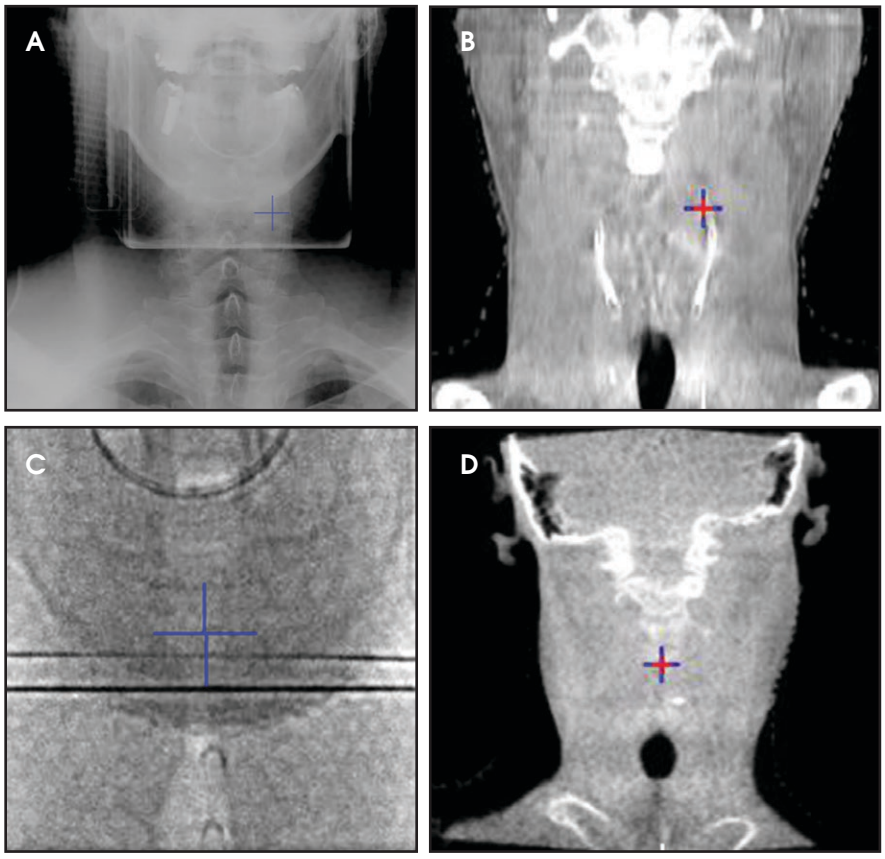

FIGURE 5. *Comparison of different image guidance modalities. (A) kV portal image and (B) kV coronal CBCT image. (C) MV portal image and (D) MV coronal CBCT image. The crosshairs indicate the tumor isocenters.*

volvement. The doses prescribed to the PTV of the primary tumor and elective LN are 70 Gy and 56 Gy in 35 fractions, respectively. Both VMAT and IMRT achieved adequate PTV dose coverage. The degree of OAR sparing is comparable for VMAT and IMRT,[29,30] although occasionally the contralateral OAR sparing may be improved with VMAT.[33]

Image-guided radiation therapy (IGRT) for HNC

To improve the precision and accuracy of treatment delivery, IGRT uses various imaging techniques immediately before treatment to verify correct patient positioning. A conventional method to verify patient positioning is to match 2D kilovoltage (kV) or megavoltage (MV) radiographs with the digital reconstructed radiographs (DRRs) from the planning CT. As shown in Figure 5A and 5C, bony anatomy can be visualized in 2D kV and MV radiographs, detecting large positioning errors. However, 2D radiographs have poor image quality and limited soft tissue visualization and are incapable of detecting rotational errors in patient positions.

Three-dimensional in-room imaging techniques, such as CT-on-rails, kV-CBCT, and MV-CBCT have improved the detection of treatment positioning errors. The CT-on-rails system connects a conventional CT scanner with a linear accelerator (linac) by sharing the same treatment table, which can be rotated 180 degrees to acquire a diagnostic quality CT before each treatment. Similarly, if a dedicated CT-on-rails system is not available, CBCT images can be acquired by the treatment portal (MV) or by an orthogonal kV source. Figure 5B and 5D show an example of kV-CBCT and MV-CBCT images for HNC patients. On the kV-CBCT image, both bony anatomy and some soft tissues are visible while only bony anatomy can be visualized on the MV-CBCT image. CBCT imaging has been routinely used for interfraction correction where image registration software is used to align the CBCT image taken prior to the treatment with the planning CT and applies table shifts accordingly. However, frequent CBCT imaging can add significant doses to the patient. Imaging doses ranging from 0.1 to 3.5 cGy for kV-CBCT and 3 to 10 cGy for MV-CBCT per acquisition have been reported in the literature.[34]

One additional advantage of adding image-guidance to conformal techniques such as IMRT or VMAT is the ability to reduce the planning margins, potentially decreasing treatment-related toxicities, such as xerostomia and mucositis. Chen et al showed that the CTV-to-PTV margin can be safely reduced from 5 mm to 3 mm because there were no differences in overall survival, locoregional control, and distant metastasis-free survival among HNC patients treated with either a 5-mm or 3-mm margin.[35] Den et al demonstrated that daily IGRT allows a 50% reduction in CTV-to-PTV margin for HNC patients, which may potentially reduce unnecessary toxicity.[36] Schwarz et al compared a margin-based non-IGRT approach with a margin-reduced IGRT approach for postoperative HNC patients.[37] They found that although both approaches achieved sufficient CTV coverage, IGRT is dosimetrically beneficial for spinal cord sparing due to the reduced PTV margin.

Although IGRT for HNC appears beneficial, challenges remain. First, one size of the CTV-to-PTV margin may not be fit for the entire treatment

course.[36] Second, IGRT is unable to correct for nonrigid positional changes, such as neck flexion and shoulder rotation. Therefore, proper patient immobilization via a thermoplastic mask is critical. Five-point masks are used to stabilize the shoulders when the treatment area extends to lower neck and are necessary for nearly all head and neck cases. Third, aligning to different bony landmarks may result in different patient position corrections. Typically, cervical vertebrae 1 and 2 (C1-C2) have been suggested as a reference landmark for standardizing IGRT for head and neck IMRT.[38] In our practice, the alignment focal landmark for HNC patients is patient-specific and is part of the written prescription.

Adaptive radiation therapy (ART)

For a typical treatment course of 6-7 weeks, IMRT plans with reduced planning margins that are designed based on the original planning CT may become inadequate, particularly for patients with bulky gross tumors that shrink during treatment, and for patients who have experienced significant weight loss.[39-42] A companion article from our institution is focused on the topic of ART.[43] Briefly, at our institution, ART is performed on a case-by-case basis for HNC patients with significant tumor volume reduction, or for patients who experience dramatic weight loss.

The process for replanning midtreatment is as follows: First, a second simulation CT (replanning CT) is acquired at the midcourse of treatment. To facilitate tumor volume and OAR delineation, the replanning CT is registered with the initial planning CT by aligning the bony anatomy near the gross tumor. Deformation of the original simulation CT is acceptable in this situation and may facilitate the recontouring process. After the initial contours are transferred from the initial planning CT to the replanning CT, they are manually edited by the radiation oncologists. The adaptive plan is computed and evaluated using the total prescription dose but then delivered with a reduced number of fractions to match the total dose originally intended. Both initial and adaptive plans are evaluated on the dosimetric criteria discussed above. A composite plan that includes the number of fractions from both plans can be created through either rigid or deformable image registration, although challenges exist with both. Because of anatomic changes, a composite plan generated through rigid image registration cannot take into account soft-tissue changes occurring between the two planning CTs. Although deformable image registration improves the evaluation of changes due to soft-tissue deformation, composite plans created this way also bear dose uncertainties related to the accuracy of the computer algorithm. Therefore, the dose distribution from the composite plans is most useful for evaluating OARs that do not change volume during the course of treatment.

Conclusion

Head and neck radiation therapy is considered one of the most technically challenging treatments in radiation oncology because of the number of targets with different dose prescriptions, the large treatment regions, complex patient anatomy and the surrounding OARs. Nowadays, IMRT and VMAT are the mainstream treatment planning and delivery options for HNC. The technologic advances in IGRT and ART make patient-specific radiotherapy plans possible and have led to the next stage of individualized radiation therapy.

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RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for September 2015!

Presentation of pituitary carcinoma as neck metastasis after irradiation of recurrent pituitary macroadenoma

Jacob A. Miller, BS; Ehsan H. Balagamwala, MD; Steven Oh, MD; Shlomo A. Koyfman, MD; John H. Suh, MD

CASE SUMMARY

A 56-year-old female presented with acute-onset third cranial nerve palsy. Her history is significant for a pituitary macroadenoma (Figure 1A) treated with subtotal resection (STR) 6 years prior (Figure 1B). One year after STR, she developed progressive disease and underwent intensity-modulated radiotherapy (IMRT) (45 Gy/25 fractions).

Three years after completing IMRT, MRI again demonstrated disease progression (Figure 2A) requiring repeat STR. Pathology demonstrated pituitary adenoma with Ki-67 of 75%. Six weeks postoperatively, the patient required admission for rapidly progressive lethargy. MRI demonstrated further progression; given the aggressive nature of this lesion and her prior radiotherapy, she underwent concurrent pulsed low-dose rate IMRT (54 Gy/27 fractions) with temozolomide (TMZ) (Figure 2B).[1,2]

One month after completing chemoradiotherapy, repeat MRI demonstrated stable sellar disease with blood products in the right middle cranial fossa (Figure 3A). However, at this time she detected a right submandibular mass (Figure 3B). Biopsy was consistent with metastatic pituitary carcinoma and she underwent a resection of the right submandibular gland and lymph node. Three months later, she developed a right parotid mass (Figure 4A) requiring parotidectomy and supraomohyoid neck dissection, again consistent with metastasis. Postoperatively, she underwent unilateral neck IMRT (55 Gy/20 fractions) (Figure 4B) utilizing an accumulated dose plan (Figure 4C).

*Prepared by **Mr. Miller**, a medical student at Cleveland Clinic Lerner College of Medicine, Case Western Reserve University, Cleveland, OH; **Drs. Balagamwala** and **Oh,** Resident Physicians; **Dr. Koyfman**, Assistant Professor; and **Dr. Suh**, Chairman, Department of Radiation Oncology, Cleveland Clinic, Cleveland, OH.*

IMAGING FINDINGS

Imaging of the submandibular mass demonstrated a heterogeneous, mildly enhancing 3.4 cm lymph node adjacent to the right submandibular gland (Figure 3B). At the time of her parotid metastasis, CT of the neck demonstrated a 3.1 cm right parotid mass (Figure 4A) extending into the deep lobe of the parotid gland.

DIAGNOSIS

Pituitary macroadenoma with malignant transformation to a pituitary carcinoma accompanied by right parotid and submandibular lymph node metastases.

DISCUSSION

While pituitary adenomas are common benign tumors, they nevertheless may result in significant morbidity secondary to mass effect or secretory phenomena. Invasive adenomas, which account for 25-55% of adenomas, exhibit more aggressive and locally invasive behavior.[3] Although the 2004 WHO classification of pituitary tumors is grounded in secretory products, a subset of "atypical" or "aggressive" invasive adenomas was also delineated.[3,4] These adenomas are typically characterized by a high mitotic index, Ki-67 ≥ 3%, and extensive positive staining for p53. The significance of this delineation is apparent in the 2 proposed tumorigenesis models of pituitary carcinomas: the sequential and de novo models.[4] While the first model reflects an adenoma-to-

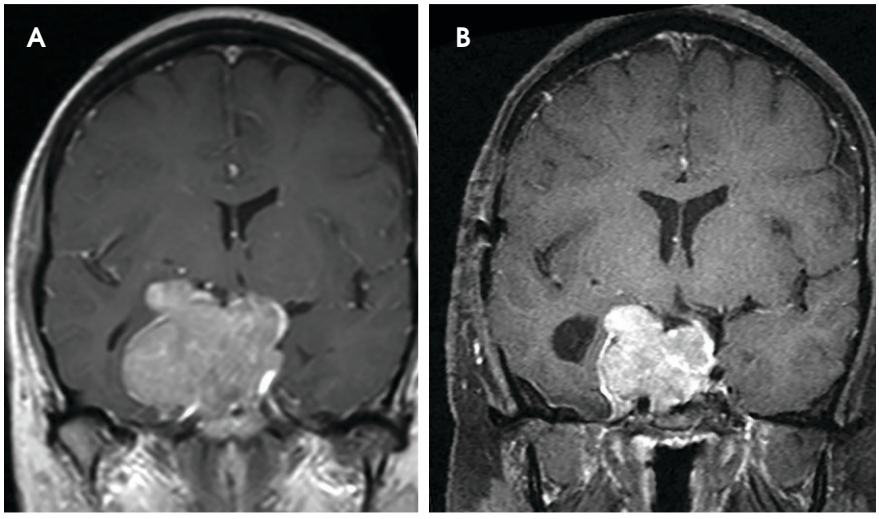

FIGURE 1. *(A) Coronal view of macroadenoma (3.3 × 4.5 × 4.9 cm) upon initial presentation demonstrates a sellar mass invading through the right cavernous sinus into the middle cranial fossa. The infundibulum and optic chiasm have been displaced to the left. (B) Coronal view of stable lesion (3.2 × 3.3 × 4.3cm) following first STR.*

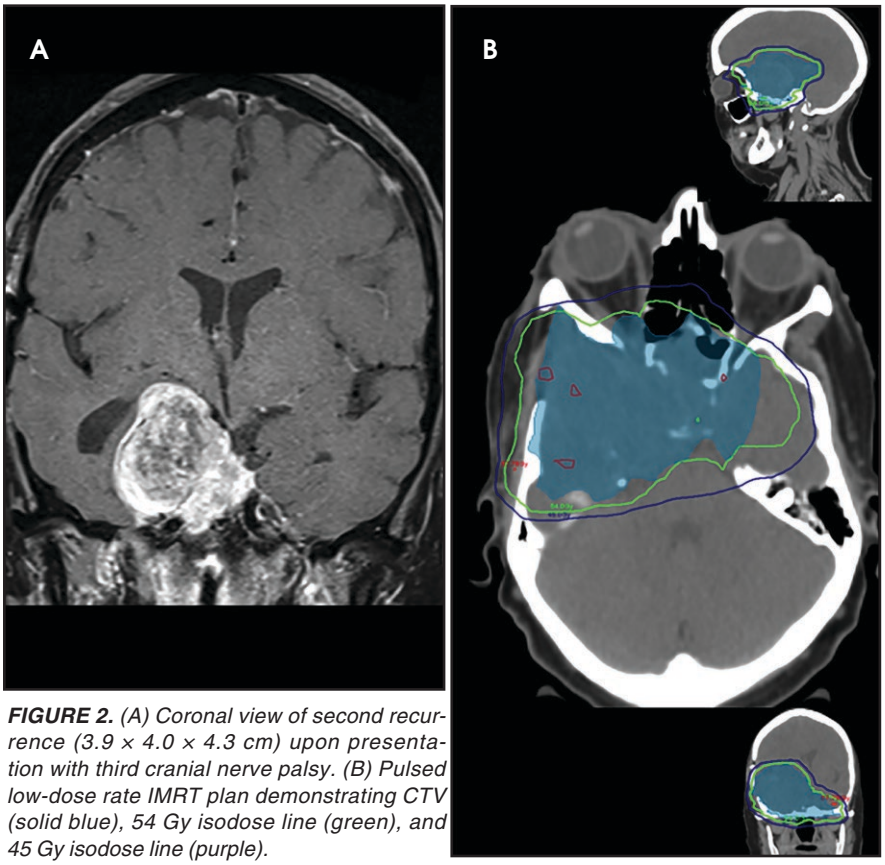

FIGURE 2. *(A) Coronal view of second recurrence (3.9 × 4.0 × 4.3 cm) upon presentation with third cranial nerve palsy. (B) Pulsed low-dose rate IMRT plan demonstrating CTV (solid blue), 54 Gy isodose line (green), and 45 Gy isodose line (purple).*

carcinoma sequence, the second suggests that aggressive adenomas form de novo with the potential for subsequent malignant transformation. In both models, the significance of the aggressive adenoma is paramount, as it represents the precursor lesion to pituitary carcinoma in the vast majority of cases.

Given the rarity of metastasis in patients with primary pituitary lesions, it has historically been difficult to distinguish pituitary carcinoma from aggressive adenoma.[5] Moreover, most patients with pituitary carcinoma exhibit histories such as that described here, with sequential progression from benign adenomas with low proliferative indices to aggressive adenomas with the ultimate development of metastasis.[3] Despite this challenge, pituitary carcinomas are exceedingly rare. While pituitary tumors account for 10-15% of central nervous system neoplasms, pituitary carcinomas represent 0.1-0.2% of pituitary tumors and require evidence of craniospinal or systemic metastasis for diagnosis.[3,6,7]

The natural history of pituitary carcinomas differs with respect to the degree of local invasion and sites of metastasis. The clinical features of invasion and mass effect include pain and cranial nerve palsies. In general, patients with macroadenomas may classically experience bitemporal hemianopsia, decreased visual acuity, ptosis, diplopia and facial numbness.[3] While this report is of a nonsecretory carcinoma, the majority of pituitary carcinomas are secretory; as such, patients may present with signs and symptoms of Cushing's disease, hyperprolactinemia, or acromegaly.[7] Although the 5-year overall survival for invasive adenomas is approximately 80%, pituitary carcinoma confers a 30% 5-year survival, with systemic metastasis more common than craniospinal metastasis.[8]

Radiologic differentiation of pituitary carcinomas from aggressive adenomas is generally not possible in the absence of observed metastasis.[8,9] Both lesions may reveal invasion of the clivus, sellar floor, and cavernous sinus with intracranial extension.[3,4] Following definitive or adjuvant therapy, recurrence is not only more common but also more rapid among carcinomas, with a median time to

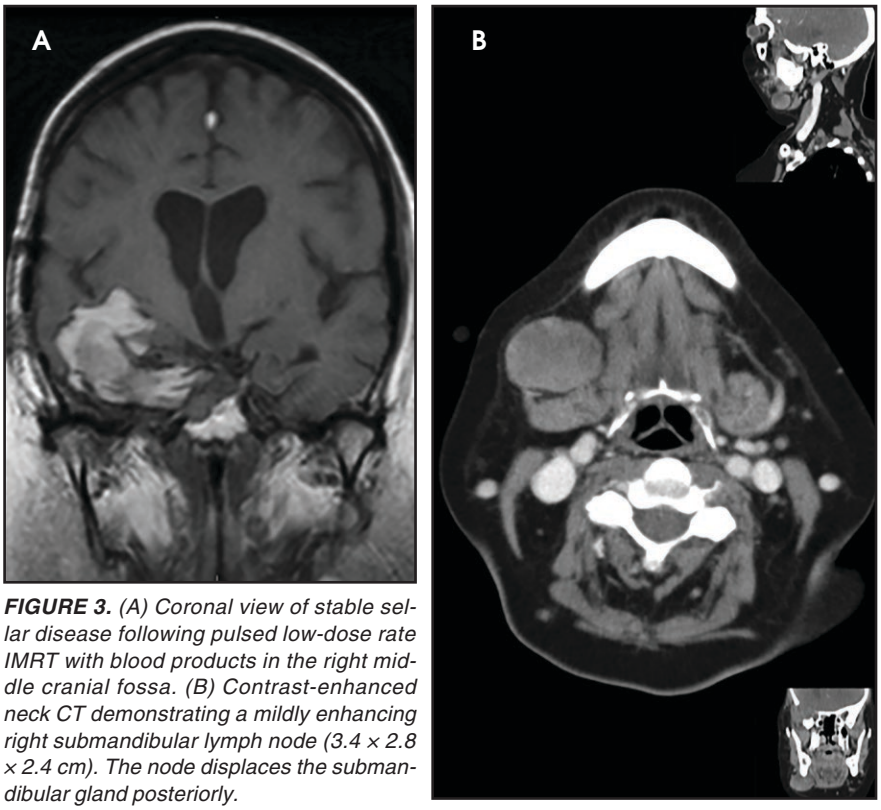

FIGURE 3. *(A) Coronal view of stable sellar disease following pulsed low-dose rate IMRT with blood products in the right middle cranial fossa. (B) Contrast-enhanced neck CT demonstrating a mildly enhancing right submandibular lymph node (3.4 × 2.8 × 2.4 cm). The node displaces the submandibular gland posteriorly.*

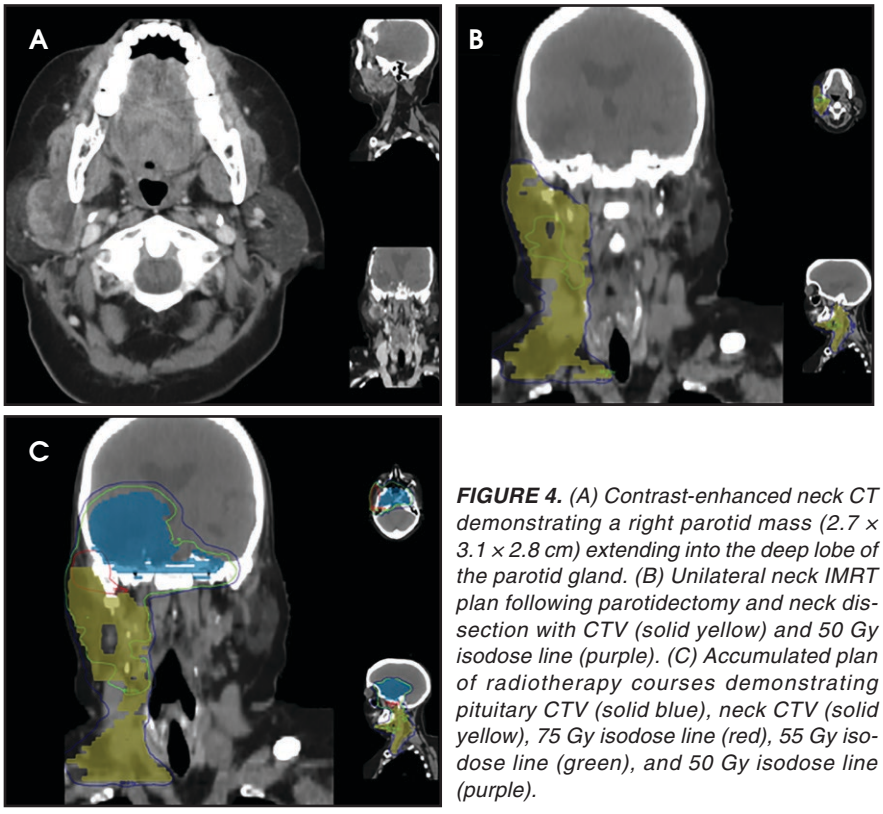

FIGURE 4. *(A) Contrast-enhanced neck CT demonstrating a right parotid mass (2.7 × 3.1 × 2.8 cm) extending into the deep lobe of the parotid gland. (B) Unilateral neck IMRT plan following parotidectomy and neck dissection with CTV (solid yellow) and 50 Gy isodose line (purple). (C) Accumulated plan of radiotherapy courses demonstrating pituitary CTV (solid blue), neck CTV (solid yellow), 75 Gy isodose line (red), 55 Gy isodose line (green), and 50 Gy isodose line (purple).*

recurrence of 6-12 months and a median time to metastasis of 5 years.[3,7] Metabolic imaging with positron emission tomography/computed tomography (PET/CT) offers higher sensitivity than MRI for detection of metastasis; moreover, octreotate-bound nuclides such as 68Ga may be superior to 18F-FDG for detection of metastasis and local recurrence.[10]

Pathologic differentiation between aggressive adenomas and carcinomas is similarly challenging. Normal pituitary tissue exhibits a low rate of cellular division and, thus, adenomas generally exhibit Ki-67 ≤ 2%.[4] Staining above 3% has been suggested to offer reasonable sensitivity (73%) and specificity (97%) for distinguishing invasive from noninvasive behavior.[9,11] Nuclei for high-grade lesions are hyperchromatic and accompanied by prominent nucleoli. Immunohistochemical staining to p53 offers excellent sensitivity for malignant lesions: While 15% of invasive adenomas are p53 positive, 100% of carcinomas are positive.[3,12] Benign and malignant histologies may both stain with antibodies to pituitary hormones; as such, this is less helpful for identifying carcinoma, but is crucial for medically directed therapies.[7] Although no single test may diagnose pituitary carcinoma before observed metastasis, certain clinicopathologic prognostic criteria have been proposed, including a combination of Ki-67 > 3%, > 2 mitoses per high-powered field, and p53 positivity.[9]

Unfortunately, many patients with aggressive pituitary lesions will suffer multiple recurrences, which may require repeat radiotherapy. This presents a challenging situation due to nearby critical structures including the optic nerves, optic chiasm, brainstem and the carotid arteries. A repeat course of fractionated radiation therapy is a possibility for some patients after careful consideration of treatment options, interval since first course of radiation therapy, and details of prior radiation treatment.[13]

In this case, we extrapolated from the glioblastoma literature and utilized a pulsed low-dose rate technique in hopes of minimizing late toxicity.[2,14] This technique relies on the radiobiological advantage of normal tissue repairing sublethal damage when exposed to dose-rates between 0.01 and 1.00 Gy/min. Furthermore, recent literature has indicated that cytotoxic chemotherapy with temozolomide (TMZ) can provide clinical and radiographic response rates of 60-70%.[1] While MGMT (O-6-methylguanine-DNA methyltransferase) methylation is prognostic for glioblastoma, there appears to be no correlation between response to TMZ and MGMT methylation status in patients with aggressive pituitary tumors.[15,16]

In the present report, pathologic data highlighted this challenge in distinguishing aggressive adenoma from carcinoma. Tissue from the first stage of repeat STR demonstrated a Ki-67 index focally in excess of 75%, with 15-20% staining with p53. In the second stage, Ki-67 index was 3-4% focally and p53 staining was < 5%. One month later, correlation with MRI demonstrated a heterogeneously enhancing mass suggestive of marked recurrence, followed shortly thereafter by clinically evident metastasis.

CONCLUSION

In this report, a 56-year-old female exhibited an adenoma-to-carcinoma tumorigenesis sequence with metastasis to submandibular lymph nodes and the parotid gland. While differentiating aggressive adenomas from carcinomas is challenging, certain clinicopathologic criteria may offer insight into the risk for malignant transformation. This differentiation is clinically significant, as a diagnosis of pituitary carcinoma confers a 5-year survival of 30%.

Despite prognostic differences, both aggressive adenomas and pituitary carcinomas require multidisciplinary care. Emerging diagnostic and therapeutic technologies in the form of metabolic imaging and targeted therapies may provide additional benefit in the monitoring and treatment of these lesions.

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Breathing easier with SBRT, VMAT, 4D MRI and other advances in lung cancer treatment

Mary Beth Massat

Lung cancer remains the top cancer killer in the world, accounting for nearly 1.6 million cancer deaths in 2012.[1] In the United States, lung cancer resulted in more deaths than colorectal, breast and prostate cancers combined, and will cause approximately 27% of all U.S. cancer deaths this year.[2,3] While survival rates are on the rise for many cancers, lung cancer's 5-year survival rate of 17.8% is decidedly lower than many leading cancer sites: Colon is 65.4%, breast is 90.5% and prostate is 99.6%. Moreover, only 15% percent of lung cancer cases are diagnosed at an early stage; and once the cancer spreads to other organs, that 5-year survival rate drops to a meager 4%.[4]

Yet there is hope. If lung cancer is detected when the disease is still localized, the 5-year survival rate is as high as 54%. With recent Medicare reimbursement approval of lung cancer screening using low-dose computed tomography (CT) in people ages 55-77 with a history of smoking in the last 15 years, chances are greater for detecting lung cancer at an earlier stage when it is localized and, therefore, more treatable and potentially curable.

"The data suggests that lung cancer screening can reduce mortality by 20%," says Russell Hales, MD, director of the Thoracic Oncology Multidisciplinary Program at Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, and associate professor of radiation oncology and molecular radiation sciences at Johns Hopkins University School of Medicine, Baltimore, Maryland. While screening allows for tumor detection at an earlier stage, Dr. Hales warns of the potential to overuse other tools, such as biopsy, and incur potential side effects.

Technologies such as intensity-modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT) have helped make lung cancer treatments safer and more accurate, but have not affected outcomes for stage III patients.

"Technology allows us to give higher-quality treatments, but there is also a learning curve to using them correctly," Dr. Hales says. Take volumetric-modulated arc therapy (VMAT), for instance. While it may provide more flexibility in planning around critical structures such as the heart or spine, it can add a significant low-dose bath to normal structures, such as the lung. As a result, treatment can unintentionally cause more toxicity than other approaches.

SBRT: The future of lung cancer treatments?

According to Benjamin Movsas, MD, chair of the Department of Radiation Oncology at Henry Ford Hospital in Detroit, Michigan, the biggest advance in radiation oncology that directly benefits lung cancer patients is stereotactic body radiation therapy (SBRT), also referred to as stereotactic ablative radiation therapy (SABR). "This technique has revolutionized what we can offer our patients with early stage, non-small cell lung cancer," says Dr. Movsas. "It's a new standard of care for patients who are not surgical candidates."

Dr. Movsas explains that in these cases, conventional radiation therapy administered daily (Monday-Friday) over 6-7 weeks has a local control rate of about 50%, while the higher biological dose of SBRT (over 3-5 treatment sessions) has been shown to achieve local control rates above 90%.

"This is where the field is starting to ask fundamental questions," he says, citing recent work by Chang et al that examined outcomes of surgery (e.g., lobectomy) vs. SABR based on data pooled from 2 small randomized, phase 3 trials of SABR in patients with operable stage 1 non-small cell lung cancer (NSCLC). While both trials closed early due to slow accrual, preliminary findings show SABR as a viable option for treating operable stage I NSCLC with results that appear to compare favorably with surgery. However, because of the small patient sample size, further studies are needed.[5]

"It's important for patients to know that surgery remains the gold standard

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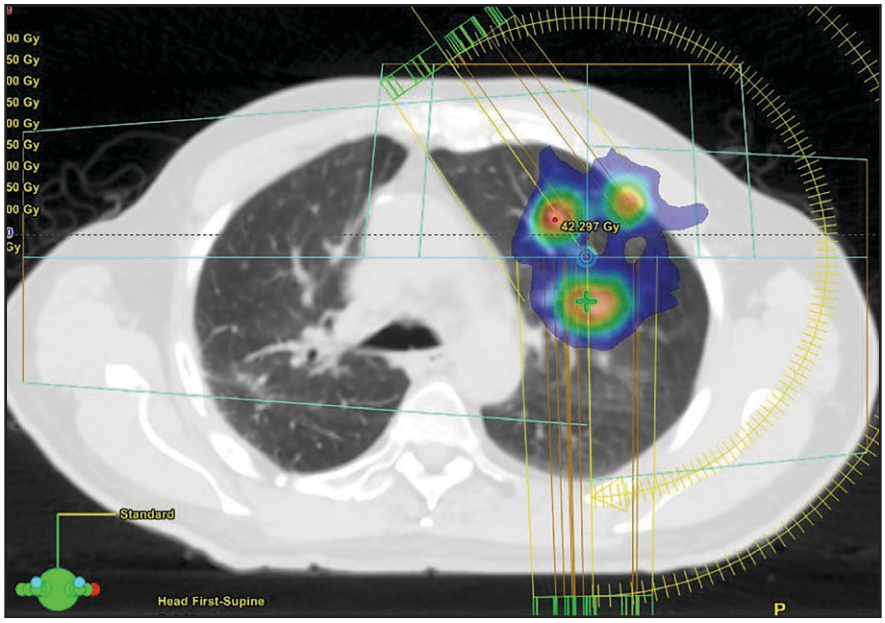

Example of 3 lung lesions treated with 1 isocenter using VMAT. Total time was 35 minutes compared to the usual 90 minutes to treat 3 lesions.

in this setting; however, surgery is not always a viable option, especially for high-risk patients," says Dr. Movsas, "and having an alternative option can be key in select cases."

In 2014, Dr. Movsas and colleagues completed a study of the Edge Radiosurgery system (Varian Medical Systems, Palo Alto, California) and found that localization accuracy was within 1 mm. "Moreover, with a very high dose rate, this unit can deliver treatments more rapidly, which can enhance patient comfort and convenience."

Larry Kestin, MD, medical director, Michigan region, and national director of thoracic and lung services at 21st Century Oncology, Farmington Hills, Michigan, agrees that SBRT is one of the most significant advances for treating stage I NSCLC lung cancer. He also notes that additional advantages of SBRT are possible when it is combined with VMAT.

"We can deliver SBRT with three-dimensional conformal, with more classic IMRT, or with VMAT," Dr. Kestin says. "Any of these technologies can deliver SBRT, which is a certain way to plan the treatment [to deliver] large doses per fraction (e.g., 12 Gy x 4 or 5 fractions, or 18 Gy x 3 fractions. SBRT reduces the total number of treatment fractions, and the best way to deliver SBRT today is with VMAT since it shortens treatment delivery time but maintains the dosimetric advantages of IMRT."

In an effort to determine the optimal dose to prevent local recurrence, Dr. Kestin and colleagues from 5 institutions pooled data on SBRT and determined that a biologically equivalent dose (BED) of 105 Gy is sufficient to control the tumor.[6] "Some commonly used regimens use higher doses," he says. "This study calls into question whether you need to deliver that high of a dose. We found that 105 Gy seemed optimal."

Dr. Kestin adds that much of the earlier U.S. data on SBRT indicates that higher doses (e.g., 20 Gy x 3 fractions) are optimal; however, his study also incorporated image-guided radiation therapy (IGRT). "Using IGRT allows us to reduce the margin of normal tissue around the tumor," he explains. "All patients in the study had CT-based IGRT and were treated in the same fashion, so we know that the dose planned more closely matches the dose that was actually delivered, than for patients treated in the past without IGRT."

Looking ahead, Dr. Kestin hopes that the advantages of SBRT or hypofractionation can be studied with stage III lung cancer, the most commonly diagnosed stage. "Some studies indicate there are advantages to applying hypofractionated radiation therapy in stage III patients—down to 15 or even 10 fractions. SBRT has been shown in stage I to provide higher cure rates, so it is possible also for stage III to have higher cure rates without increasing toxicity to the patient. It's an exciting area to investigate."

Workflow efficiency in planning

Knowledge-based planning may also play an important role in treatment planning. Lung cancer cases can be very complex and often take significant time in the planning stages. Dr. Movsas and colleagues have been studying the use of knowledge-based models (Rapid Plan, Varian Medical Systems, Palo Alto, California), which create treatment plans based on existing plans from a library of one or more institutions. "We have been very pleased with the plans generated by this computer algorithm and found they are comparable to carefully generated clinical plans. We expect that this option will help us improve efficiency in planning over time," he says, adding, "The more we can learn from our prior collective experiences to help the next patient, as well as our colleagues, the better."

Respiration and 4D imaging in planning

Another challenge of treating lung cancer is that it is a mobile target, says

ASTRO's New NSCLC Guidelines

In May, ASTRO issued the guideline, "Definitive and adjuvant radiotherapy in locally advanced non-small cell lung cancer: An American Society for Radiation Oncology (ASTRO) evidence-based clinical practice guideline." The guideline's executive summary was published in the May-June issue of Practical Radiation Oncology (PRO), and can be found at http://www.practicalradonc.org/article/S1879-8500(15)00082-X/fulltext.

Dr. Hales. Most clinics use respiratory gating or fiducial markers (both skin and implantable) to track tumor movement during the respiration cycle. Tumor movement will vary, he adds, based on its location and size, as well as the patient. While some tumors are static—moving less than 1 mm—others, particularly those in the lower lung close to the diaphragm, can shift more than 20 mm per breathing cycle, he says.

As part of an NIH grant, Dr. Hales is investigating dynamic, or 4D, MRI to track tumor movement. While 4D CT is often used to determine how a tumor moves during therapy, it only captures 10 to 12 seconds and delivers ionizing radiation to the patient, he says.

"With dynamic MRI, we can track the tumor for 20 to 30 minutes with a safe, nonionizing method that can allow us to better understand how a patient breathes and how the tumor moves," Dr. Hales explains. He can then use this information to see how accurately the tools used in treatment track the tumor. Dr. Hales anticipates the study will enroll its last patient in the fall.

Dr. Kestin estimates that 60% to 70% of U.S. sites use 4D imaging to some degree in treatment planning. While it is important to consider motion in planning, he says that if 4D imaging can be efficiently used on the treatment machine, it would be more widely applied in the treatment room as well. He also hopes that 4D dose calculations on the treatment planning system, where clinicians can use the data to include tumor movement in their planning, become more widely available.

Another approach is to use an internal target volume (ITV) based plan using 4D CT simulation to track the respiratory cycle over time. This technique allows users to incorporate those changes when targeting the tumor in the treatment plan.

Personalized treatment planning

While technology is making treatments better and safer, improving survival and curative rates is what's most important. With systemic burden a key issue in treating lung cancer, it's imperative that radiation oncology and medical oncology explore the combined use of immunotherapy with radiation therapy, says Dr. Hales.

Dr. Movsas agrees that personalized medicine is making an important impact in the overall management of lung cancer patients, and genetic testing will play an even more significant role in the future. Beyond the future of molecular genetics, Dr. Movsas is passionate about patients' quality of life (QOL). He and his team are about to embark on a phase I/II clinical trial evaluating the safety of the proprietary compound BIO 300 (Humanetics Corp., Minneapolis, Minnesota) and whether it can lessen damage to normal lung tissue and enhance QOL during concurrent chemotherapy and thoracic radiation therapy in stage III lung cancer patients.

The introduction of novel PET agents may also help further personalize oncology treatments. Dr. Kestin says that while 18-FDG works well in helping clinicians diagnose and stage cancer, it may also show uptake due to inflammation. It's important to identify response of the tumor before and after treatment for patient follow-up, and having a PET marker that is less susceptible to inflammation would be helpful. One such marker being studied is 18-FLT, which has been shown to be an effective measure of cell proliferation. Increased cellular proliferation has been shown to correlate with poorer outcomes for many types of cancer; therefore, FLT or other markers may be a useful prognostic predictor of a patient's outcome.[7]

"Lung cancer is not a one-size-fits-all," reminds Dr. Hales. "It has a unique molecular structure in patients, and we need to personalize each patient's care moving forward by understanding the specific profile of a tumor." Dr. Hales says.

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Radiographic changes of the lung after stereotactic body radiation therapy

John Park, MD; Chris McClinton, MD; David Deer, MD; and Fen Wang, MD, PhD

CASE SUMMARY

A 67-year-old female with a FIGO (an International Federation of Gynecology and Obstetrics) stage IIIC endometrial cancer developed a left upper lobe lung nodule 1.5 years after initial treatment. The lesion was closely followed with imaging, and continued to increase. A fine-needle aspiration of the mass guided by computed tomography (CT) was ordered and found a poorly differentiated adenocarcinoma consistent with endometrial origin. The patient underwent stereotactic body radiotherapy (SBRT) to the lung lesion to a total dose of 50 Gy in 5 fractions (Figure 1). One- and 4-month follow-up scans showed a continued decrease in the size of the lesion, however, 8 months later, a confluent infiltrating mass, which was also hypermetabolic on PET, was seen in the same area. After multidisciplinary discussion, a left upper lobe lobectomy with mediastinal lymphadenectomy was performed, which found no evidence of malignancy in the lung or dissected lymph nodes.

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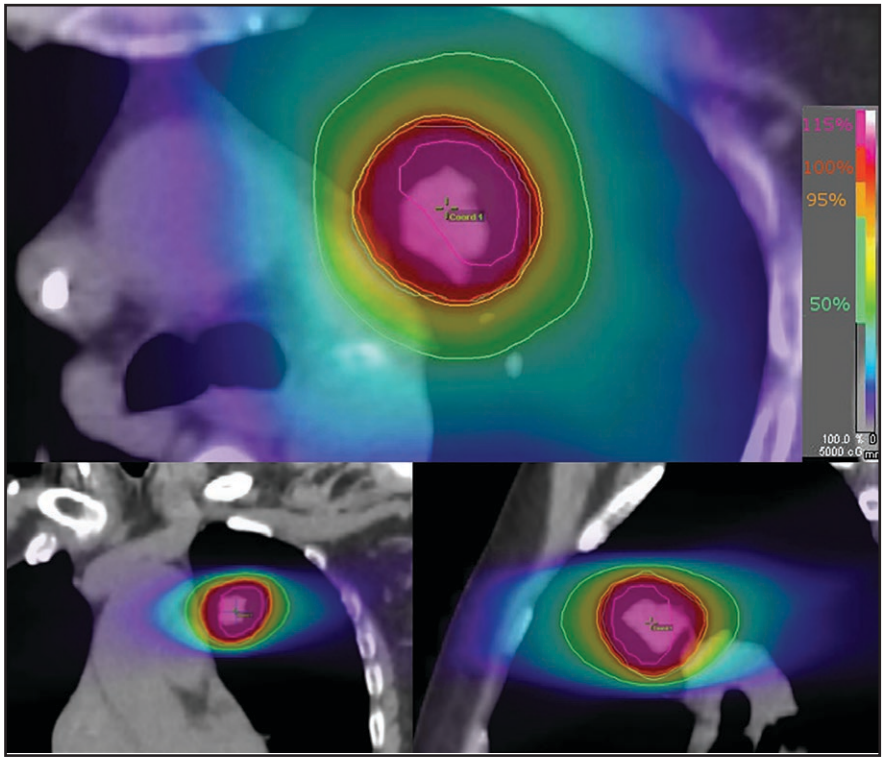

FIGURE 1. *Isodose lines of the SBRT plan.*

IMAGING FINDINGS

The patient initially was found to have a 1.5 × 1.7-cm left upper lobe pulmonary nodule with an associated positron emission tomography (PET) standardized uptake value (SUV)

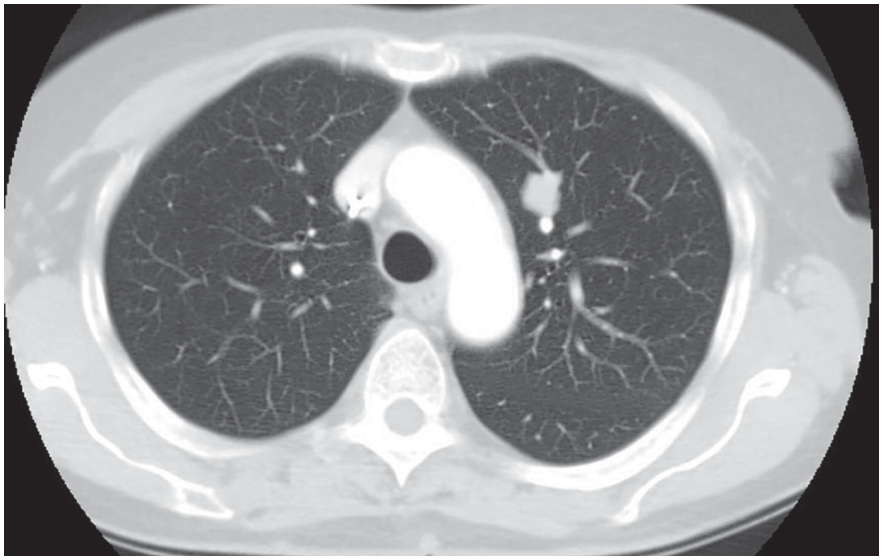

FIGURE 2. *Initial lung lesion prior to treatment.*

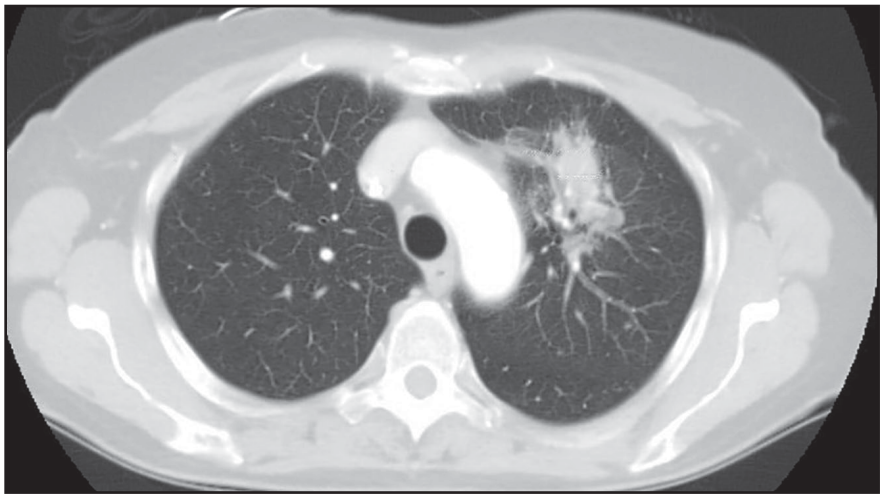

FIGURE 3. *Mass-like confluence at 8 months post-SBRT.*

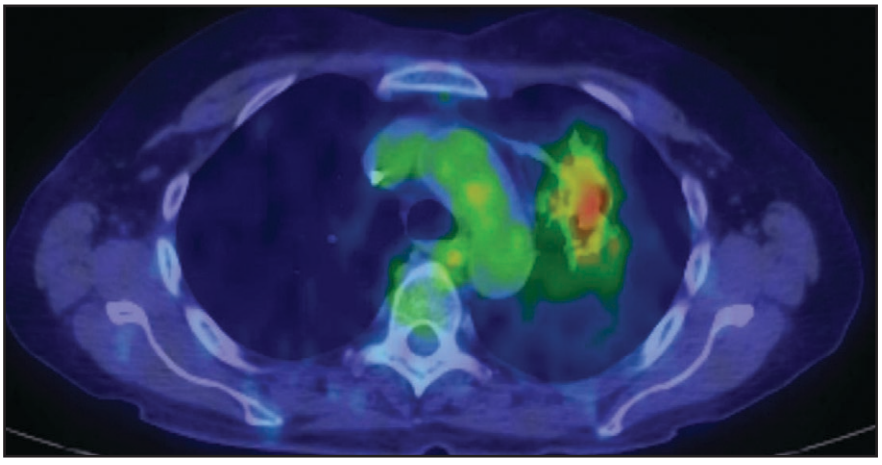

FIGURE 4. *PET scan at 8 months post-SBRT.*

Table 1. High-risk Radiographic Findings

Enlarging opacity
Sequential enlargement
Enlargement after 12 months
Bulging margin
Linear margin disappearance
Loss of air bronchogram
Craniocaudal growth of ≥ 5 mm and 20%

of 5.69. A CT scan of the chest 1 and 4 months post-SBRT found further decrease in the size of the nodule. At 9 months, a confluent infiltrating mass measuring 4.7 × 2.0-cm was seen with an associated PET SUV of 3.55.

DIAGNOSIS

Final pathologic diagnosis from the patient's lobectomy was consistent with benign inflammatory changes of the lung. Differential diagnosis of this patient includes residual disease, recurrent tumor, infection, lobar collapse, and lymphangitic carcinomatosis.

DISCUSSION

Stereotactic body radiation therapy (SBRT) is now frequently used for the treatment of early stage non-small cell lung cancers and oligometastatic disease of the lung. Understanding the radiographic changes after SBRT is important to correctly identify recurrence and administer salvage therapy. This case highlights some of the more salient features of radiographic changes to the lung after SBRT.

Lung changes associated with conventional radiation therapy have been characterized using different methods, including the Libshitz-Shuman, Ikezoe, and Koenig systems.[1-3] The Libshitz-Shuman system consists of 4 patterns:

(1) Homogeneous increase
(2) Patchy consolidation
(3) Discrete consolidation
(4) Solid consolidation

Using this method, Aoki et al found that all patients had changes, with patchy consolidation most commonly seen within 6 months, and solid consolidation after 6 months.[4]

The Ikezoe and Koenig systems examine the period from 2-6 months and 7 months or greater, respectively.[2,3,5] The Ikezoe system consists of 5 categories:

(1) No evidence of increasing density
(2) Patchy ground-glass opacities (GGO)
(3) Diffuse GGO
(4) Patchy consolidation and GGO
(5) Diffuse consolidation

The Koenig system consists of 4 categories:

(1) No evidence of fibrosis
(2) Scar-like pattern
(3) Mass-like pattern
(4) Modified conventional pattern

Many centers in Asia, Europe and the United States have adopted the Ikezoe and Koenig systems to judge CT changes after SBRT.[5-7] In this case report, although the mass progressively decreased within 6 months, there was a considerable size increase at 8 months (Figures 2 and 3). These changes are consistent with radiation fibrosis occurring after 6 months. In fact, radiographic changes can continue to evolve even after 2 years.[7] PET scans may also aid in the differentiation between benign lung changes and local recurrences. A review of multiple studies looking at post-SBRT PET scans found that maximum SUV values < 5 were correlated with benign lung changes.[8] This group also produced an algorithm to predict recurrences. The first branch point is enlargement of CT density around the primary site and consideration of high-risk radiographic findings (Table 1), of which our patient had 4.[9] The second branch point is whether the post-treatment PET is > 5 or > than the pretreatment SUV. The final branch point, for those with a high suspicion of recurrence, are for further treatment evaluation based on operability status with either a biopsy, resection, or nonsurgical salvage. For our patient, the maximum SUV was < 5 (Figure 4) and, as predicted, she had no evidence of disease following lobectomy.

CONCLUSION

Patterns of benign CT changes in the lung after SBRT can be assessed using the Ikezoe and Koenig systems. Evolution of these changes can continue to occur even after 2 years. PET SUV of > 5 after 6 months may predict local recurrences. Patients with the typical pattern of radiation fibrosis and SUV of < 5 should be considered for observation.

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