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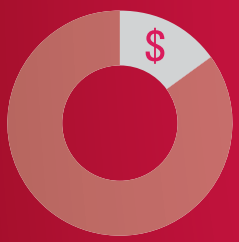

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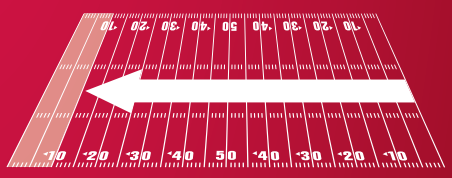

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Anderson Publishing, Ltd
180 Glenside Avenue, Scotch Plains, NJ 07076
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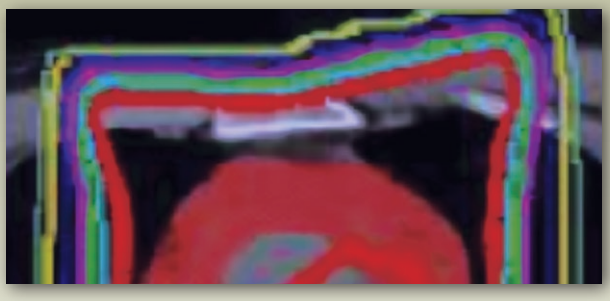
ESSN: 2334-5446 (Online)

APPLIED RADIATION ONCOLOGY™

June 2016
Vol. 5, No. 2



LEUKEMIA AND LYMPHOMA FOCUS

DEPARTMENTS

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CORRECTION

In the March 2016 issue (Vol 5, No 1, p. 5-16), Table 2 in *Interdisciplinary management of acoustic neuromas,* HJ Saadatmand, C-C Wu, T JC Wang, was incorrect. Here is the corrected version.

Table 2. Summary of quality of life measures in acoustic neuroma patients receiving microsurgical resection compared to stereotactic radiosurgery (SRS)

	Facial movement 3-month follow-up	Facial movement 1-year follow-up	Facial movement last follow-up	Serviceable hearing* at 3-month follow-up	Serviceable hearing at 1-year follow-up	Serviceable hearing at last follow-up
Surgery	61%	69%	75%	5%	5%	5%
SRS	100%	100%	96%	77%	63%	63%

*Defined as AAO-HNS Class A or B. Table based on data from Pollock et al.[44]

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EDITORIAL

John Suh, MD, Editor-in-Chief

Out for blood: Treatment updates in leukemia and lymphoma

Zombie blood drives and other creative campaigns targeting millennial culture are one strategy leukemia and lymphoma societies use to increase awareness and support the battle against hematopoietic cancers. In radiation oncology, efforts to assist the many Americans with leukemia, lymphoma or myeloma may be less imaginative, but the role of radiation therapy is very important in eradicating and curing these patients.

As part of this month's blood cancer focus, *Total body irradiation: A practical review* helps fill the gap in the modern literature by examining TBI's role in hematopoietic stem cell transplantation, which represents one of the most successful therapies for leukemia and lymphoma. Author Carson Wills, BS, Penn State Hershey College of Medicine, and colleagues discuss dosing, equipment, complications, and indications as they explore TBI's three-pronged purpose: eliminating residual cancer cells, creating space for stem cell engraftment through bone marrow depletion, and halting rejection of donor stem cells through immunosuppression.

We also bring you the enlightening article, *Substance or style? Evaluating advanced radiation therapy delivery techniques for Hodgkin lymphoma* by Johns Hopkins' Zachary D. Guss, MD, MSc; and Stephanie A. Terezakis, MD. This review assesses the roles of IMRT, respiratory management, and proton therapy as promising technologies that may lower toxicities beyond the traditional techniques of shrinking treatment fields.

Two case reports further underscore toxicity concerns. *Optimal treatment positioning to achieve better heart sparing in a left-sided, whole-breast irradiation case unfit for deep inspiration breath-hold treatment* by Vishruta A. Dumane, PhD, et al, Mount Sinai, NY, highlights the need for a careful comparison of both supine and prone positions when determining the optimal plan for a young patient with pre-existing cardiac risk factors. The winner of this quarter's Clinical Case Contest, this excellent case report offers a useful, real-world example of how to choose between techniques.

In *Chemoradiotherapy-induced toxicity with high-dose, three-dimensional conformal radiotherapy for lung cancer: Challenges with modern techniques*, University of Maryland's James W. Snider, III, MD, et al, detail a patient's significant toxicity following high-dose 3D-CRT chemoradiotherapy for Stage IIIA lung cancer. This report is a powerful reminder of potential complications related to radiation therapy and the heightened responsibilities that radiation oncologists face every day.

I hope you enjoy the articles in this issue, and our regular news updates and additional offerings at www.appliedradiationoncology.com. As always, thank you for your support of *ARO*. Best wishes for a restorative and fulfilling summer!

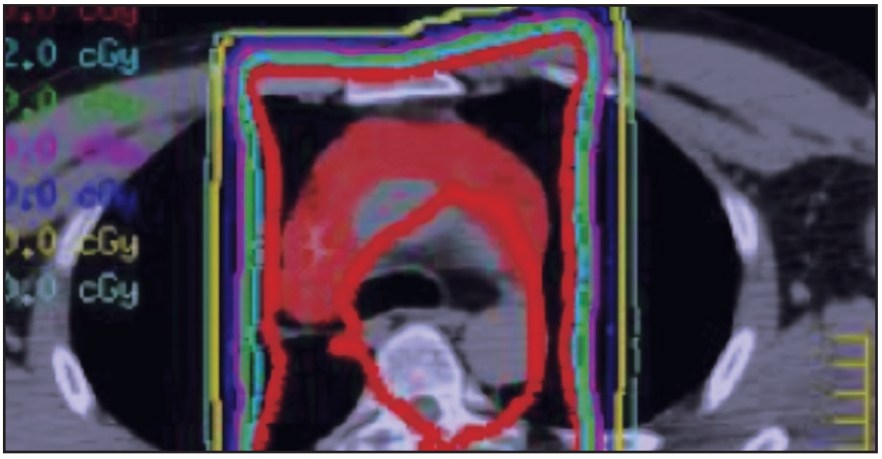
Dr. Suh *is the editor-in-chief of* Applied Radiation Oncology, *and professor and chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.*

Substance or style? Evaluating advanced radiation therapy delivery techniques for Hodgkin lymphoma

Zachary D. Guss, MD, MSc; Stephanie A. Terezakis, MD

Tools for treating Hodgkin Lymphoma (HL) with radiation therapy (RT) have proliferated rapidly over the past two decades. Innovations are principally divided into two categories: decreasing target size and improving treatment delivery. Progress in the former is reflected in the progression from extended-field RT (EFRT) to involved-field RT (IFRT), and more recently from IFRT to involved-node RT (INRT) and involved-site RT (ISRT). The therapeutic ratio is enhanced by using modern imaging modalities and knowledge of HL patterns of spread to minimize the volume of tissue irradiated while maintaining excellent disease control.[1-5] For treatment delivery, intensity-modulated radiation therapy (IMRT), respiratory management, and proton therapy (PT) are promising technologies that may further reduce toxicities beyond shrinking targets alone. This article will assess these three delivery techniques as they pertain to HL management.

Dr. Guss *is a resident in radiation oncology, Johns Hopkins University School of Medicine, Baltimore, MD.* ***Dr. Terezakis*** *is associate professor, Department of Radiation Oncology and Molecular Radiation Sciences, Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.*



IMRT

IMRT is commonly used in general radiation oncology practice in several varieties including static multileaf collimator (subsequently referred to as IMRT), helical tomography (HT), and volumetric-modulated arc therapy that can consist of a single arc (VMAT) or multiple arcs (B-VMAT).[6,7] Although each type of IMRT is unique, the principal dosimetric hallmarks of IMRT relative to 3D conformal RT (3DCRT) include higher conformality and better sparing of prioritized organs at risk (OARs) at the expense of greater low-dose bath. It is not guaranteed, therefore, that IMRT is always superior to 3DCRT for treating HL. Given the relatively low doses used in HL RT, it is unclear whether the absolute difference of dose to OAR using IMRT vs. 3DCRT is clinically meaningful. Furthermore, conscious sparing of one OAR might be achieved at the cost of increased dose to other OARs. A full review of the literature on this subject is outside the scope of this review article but is well summarized in a recent review by Maraldo

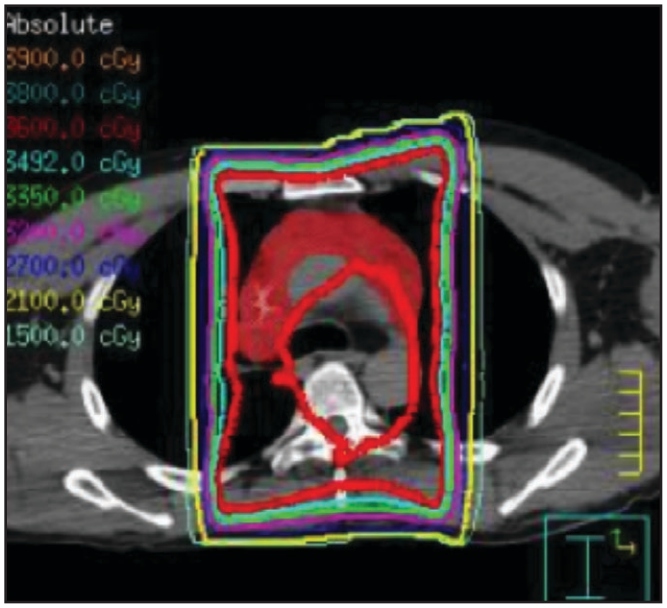


FIGURE 1. *3DCRT plan for a male patient with stage IIBX HL.*

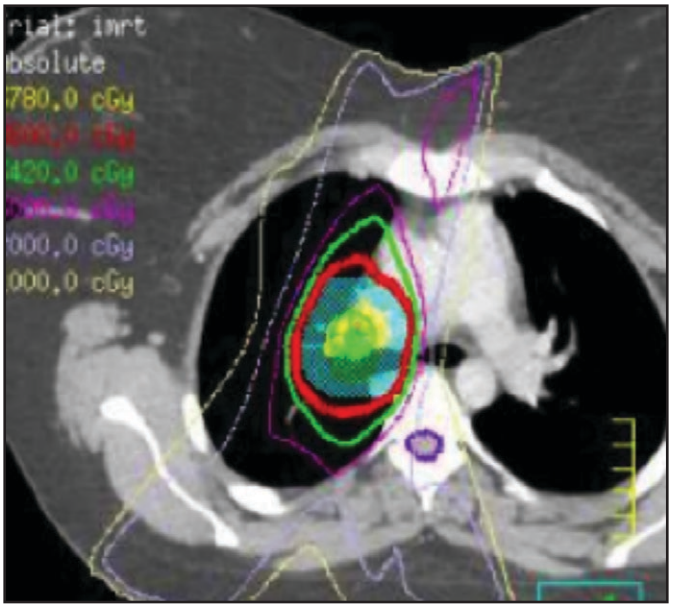


FIGURE 2. *IMRT plan for a female patient with stage IIA HL.*

and Specht.[8] Examples of 3DCRT and IMRT treatment plans are provided in Figure 1 and Figure 2, respectively.

Dosimetric and Clinical Outcomes of IMRT for HL

Due to favorable disease control rates and latency of toxicity, many studies have focused on dosimetric comparisons of IMRT vs. 3DCRT as a proxy for anticipated clinical outcomes. The Institute Curie in Paris has investigated the utility of IMRT for mediastinal HL. In 2014, this group published a dosimetric analysis of 3DCRT vs. HT for 10 female patients with early stage mediastinal HL.[9] HT resulted in significantly lower maximum dose to critical structures, including spinal cord and breast, as well as improved cardiac sparing, but increased low dose exposure to the breast. They also published the outcomes of 69 patients with stage I-III nodal mediastinal HL and NHL treated with RT.[10] Forty-nine patients were treated with 3DCRT and 20 were treated with IMRT, all under free breathing conditions. Local control was consistent with modern outcomes, with 1 local recurrence in the IMRT group and 5 in the 3DCRT group. Acute toxicities were mild. Three patients in the 3DCRT group experienced late toxicities compared to none in the IMRT group, and dosimetric comparison of the two radiation delivery techniques demonstrated similar findings as their previous study, accomplishing better conformity and high dose sparing with greater low dose bath in the HT group. The median follow-up for the IMRT group was only 10 months compared to 46 months for 3DCRT, precluding any meaningful insights into HT's impact on late effects. However, this institution's experience is valuable in demonstrating feasibility and mild acute toxicity with IMRT technique.

These results are concordant with the results of Filippi et al who reported the outcomes of ISRT IMRT vs. 3DCRT for 90 patients with early stage HL of the mediastinum.[11] Grade 2 acute toxicity was significantly lower in the IMRT group (9.8%) vs. the 3DCRT group (24.5%) ($p = 0.043$). Each group had one patient experience relapse, although median follow up was longer in the 3DCRT group (52.4 months) than the IMRT group (24.1 months). Koeck et al analyzed dosimetric features of 3DCRT and IMRT for IFRT and INRT.[12] They found that using INRT reduces OAR radiation exposure most significantly, and IMRT can be used to further spare select OARs such as heart and lung at the expense of increased dose to lung and breast. Goodman et al demonstrated that IMRT could reduce mean heart and lung dose relative to 3DCRT or conventional RT; however, lung V20 was greater in IMRT plans than in conventional plans.[13] These studies demonstrate promising early results, although longer follow up is required to determine whether late toxicities match dosimetric predictions.

IMRT Technique

Relatively few studies have compared various IMRT approaches for HL, and they are limited to dosimetric analyses. Fiandra et al compared 5 delivery techniques (3DCRT, VMAT, B-VMAT, HT, and TomoDirect [Accuray, Sunnyvale,

California]) for 10 female patients with early stage mediastinal HL planned for INRT.[14] In general, IMRT modalities offered good target coverage and decreased high-dose OAR exposure at the expense of increased low-dose bath to OARs. Among the IMRT modalities, HT and VMAT offered the most conformal plans, whereas HT and B-VMAT seemed to balance these tradeoffs best. Although many dosimetric comparisons across modalities were statistically significant, most absolute differences were under 10% across various parameters. One can only speculate as to whether this degree of difference in OAR dose is clinically relevant, or whether the decrease in treatment time would be clinically beneficial due to reduced patient motion. Weber et al also demonstrated that arc-based delivery approaches may be valuable in select cases.[15] Over time, refinements in IMRT planning may mitigate the issue of low-dose bath. Voong et al recently published a "butterfly" technique for IMRT for young female patients with mediastinal HL, demonstrating that an anterior beam arrangement of 300-30 degrees and posterior beam arrangement of 160-210 degrees was able to reduce exposure to several OARs including heart, lung, and breast.[16]

Late Effects

Late effects for HL typically concern organ dysfunction and secondary malignancy. The cardiac toxicity associated with traditional HL radiation has been recognized for decades.[17] With significant late effects being relatively infrequent with long latent periods, many studies rely on risk estimates rather than clinical data. Pinnix et al performed a retrospective analysis of 150 patients treated at MD Anderson Cancer Center to identify predictors of radiation pneumonitis for HL and NHL patients receiving IMRT.[18] In this patient group, which received IMRT with 4D CT or breath-hold technique, 14% developed pneumonitis and 6.7% developed grade 3 radiation pneumonitis. There were no instances of grade 4-5 pneumonitis. The authors noted that multiple measures of lung dose were associated with increased risk of radiation pneumonitis, including V5 > 55%, V10 > 40%, V15 > 35%, V20 > 30%, and mean lung dose > 13.5 Gy, as well as clinical factors such as salvage chemotherapy or transplantation. These findings may help guide future dose constraints, and similar efforts are underway for cardiac dose constraints.[19]

There is still uncertainty regarding the potential for increased secondary malignancies with IMRT. Hall and Wuu cautioned that the transition from 3DCRT to IMRT could increase secondary malignancies due to larger volumes of normal tissue exposure as a result of an increased number of fields and greater radiation leakage from modulated fields.[20] They reasoned that the transition to IMRT could be responsible for second malignancies in 0.75% of surviving patients in general. These concerns have been recapitulated in the context of mediastinal HL. Schneider et al estimated second malignancy rates for free breathing (FB), deep inspiration breath hold (DIBH), 3DCRT, and VMAT for INRT using an Alderson phantom.[21] The lifetime attributable risk (LAR) was calculated for each combination of these techniques for breast, lung, esophagus and stomach. Whereas DIBH 3DCRT was associated with an 8% to 24% reduction in LAR for these sites compared to FB 3DCRT, DIBH VMAT was associated with a 7% reduction in stomach LAR and up to 104% increase in LAR for the other organs compared to FB 3DCRT. Similar findings were reported by Weber et al, who performed comparison IFRT and INRT plans for 3DCRT, IMRT, and VMAT to estimate the excess relative risk (ERR) of thyroid, lung, and breast cancer with nonlinear and linear models in female patients.[22] For INRT radiation therapy, the use of either IMRT technique increased the ERR with a linear model; however, the opposite was seen with a nonlinear model. Other studies have also shown that using IMRT for cardiac sparing is associated with increased dose to the breast.[23] While it is difficult to draw firm conclusions from these small studies, it is certainly possible that IMRT may be associated with a heightened risk of secondary malignancy. However, the absolute increase in secondary cancer risk is likely modest and this must be weighed against the ability to spare prioritized OARs. Ultimately, the decision regarding technique must be individualized.

Respiratory Management

For many anatomic sites, FB simulation may be sufficient for reproducible daily RT. For mediastinal fields, however, tumor position can vary significantly with the respiratory cycle. This motion was of lesser concern in previous decades when large extended fields delivering AP/PA were de rigueur. However, in the modern era of reduced volumes with ISRT and INRT, there is higher risk of a marginal miss. A variety of solutions have evolved to account for and manage respiratory motion for mediastinal lymphomas. One can obtain a 4D CT scan to generate an internal target volume (ITV), or use respiratory gating to treat at end inhalation or exhalation. One technique that exploits physiology to reduce lung and heart dose is DIBH, which can be active breathing coordinator (ABC) assisted.[24] These respiratory management solutions can also be used in conjunction with other advanced delivery techniques such as IMRT.

Several groups have reported dosimetric analyses of these respiratory techniques in the context of mediastinal lymphoma. Paumier et al reported a comparison of FB and DIBH INRT IMRT plans for 28 patients with early stage HL and mediastinal involvement.[25] They noted similar PTV coverage and 15% to 20% reduction of mean

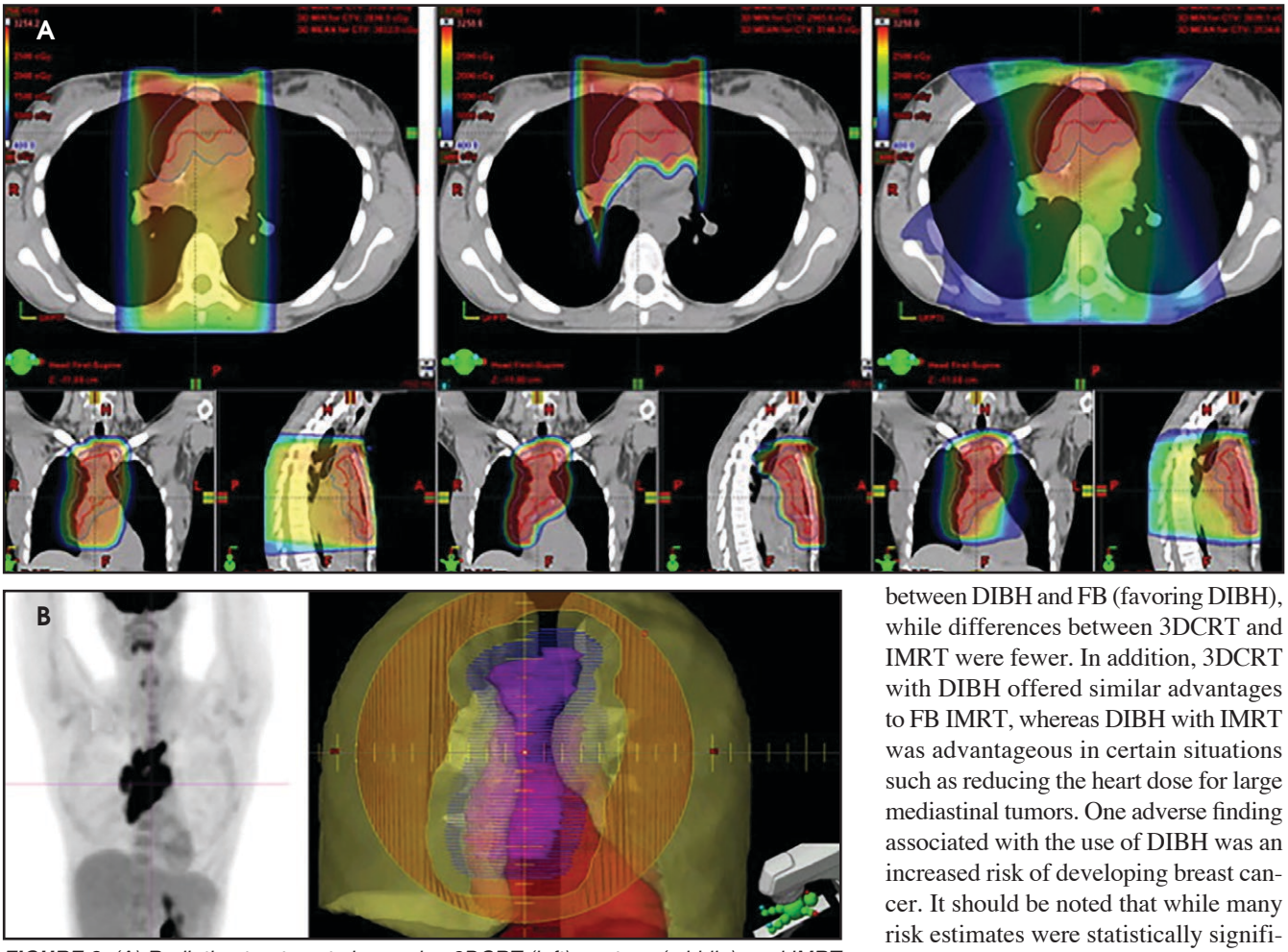


FIGURE 3. *(A) Radiation treatment plans using 3DCRT (left), protons (middle), and IMRT (right). The CTV is contoured in red and the PTV in blue with a color-wash dose distribution. (B) Pre chemotherapy positron emission tomography maximum intensity projection image for the same patient in A (left) and the single anterior field proton arrangement for the same patient (right). The PTV is shown in blue and the CTV in violet. The heart is shown in red and the lungs in yellow. 3DCRT = 3-dimensional conformal RT; CTV = clinical tumor volume; IMRT = intensity modulated RT; PTV = planning target volume. Reprinted with permission from Hoppe BS, et al[36]*

heart dose, mean lung dose, and lung V20 overall using DIBH compared to FB, and 26% to 50% reduction for upper mediastinal disease.

Prospectively, Petersen et al published the results of a phase II trial of DIBH vs. FB INRT for 22 patients with early stage HL.[26] Patients were simulated with FB and DIBH and were planned with 3D conformal RT (3DCRT) and IMRT techniques. Each patient was treated with the technique that afforded satisfactory tumor coverage while minimizing doses to OARs. Nineteen (86%) patients were treated with DIBH, and 12 (55%) were treated with IMRT. The group then conducted a dosimetric analysis of FB vs. DIBH and 3DCRT vs. IMRT to deliver INRT for 22 patients with early stage mediastinal HL to estimate the risk of late effects such as myocardial infarction or secondary malignancy using these techniques.[27] Each patient was planned on DIBH and FB simulations as well as 3DCRT vs. IMRT. Overall, the risk estimates showed a greater difference between DIBH and FB (favoring DIBH), while differences between 3DCRT and IMRT were fewer. In addition, 3DCRT with DIBH offered similar advantages to FB IMRT, whereas DIBH with IMRT was advantageous in certain situations such as reducing the heart dose for large mediastinal tumors. One adverse finding associated with the use of DIBH was an increased risk of developing breast cancer. It should be noted that while many risk estimates were statistically significant, the absolute estimated risks were small. For example, the percent risk estimate for myocardial infarction for the best performer, IMRT, was 2.1%, compared to 4.9% for 3DCRT FB ($p < 0.001$). Even smaller differences were observed for the more global assessment Life Years Lost (0.5 years for DIBH IMRT vs. 0.7 years for FB 3DCRT, $p < 0.001$).

These studies present several consistent messages regarding active respiratory management strategies such as DIBH. DIBH appears to confer significant dosimetric advantages for most patients with respect to many parameters, although it may be less beneficial for young women due to increased breast irradiation. Additionally, DIBH can be combined with other advanced delivery techniques such as IMRT.

Proton Therapy

Proton therapy (PT) benefits from the Bragg Peak, which provides modest entrance dose and sharp dose fall-off at the end of the ion's path.[28] The Bragg Peak is too narrow for clinical applications; therefore, the peak must be "spread out" to treat over ranges sufficient to deliver dose to tumor using techniques such as pencil-beam scanning or passive scattering. These attributes are highly desirable for many clinical applications of radiation therapy, such as when a tumor is close to an OAR, or in a patient with an excellent long-term prognosis in which reducing late effects is critical. This latter aim is particularly relevant for HL.

Compared to photon therapy, PT comes with several disadvantages. The Bragg peak is largely advantageous but could raise the risk of a marginal miss, particularly in anatomic regions with significant organ motion.[29-31] Additionally, the contribution of neutrons may increase the risk of secondary malignancies.[32] Although the relative biological effectiveness of PT is generally considered to be 1.1-1.2, these generalizations may not apply in all circumstances and could underestimate the morbidity of a PT plan.[33]

Owing to limited availability of PT centers, there are few published clinical outcomes. As with photon therapy, a rich diversity of imaging set-up and delivery techniques exists, resulting in significantly varied PT plans across facilities. Much of the published literature on proton therapy for lymphoma consists of dosimetric studies. Maraldo et al reported a dosimetric analysis of 37 patients with head and neck early stage HL.[8] All patients received chemotherapy and 3DCRT-INRT to 30.6 Gy, with comparison mantle field (MF), VMAT and PT plans generated for each patient. They demonstrated that INRT plans spared OARs more than MF. PT was able to spare some OARs such as the pharynx and larynx to a greater extent than 3DCRT, whereas VMAT plans suffered from an inferior low-dose bath without sufficient reduction of high-dose regions.

PT has also been applied to HL of the mediastinum, where tumors are juxtaposed to multiple OARs including the heart and lung. Hoppe et al demonstrated the potential to spare the heart using PT for mediastinal HL compared to 3DCRT or IMRT.[34] Li et al reported the outcomes of 10 lymphoma patients who received 3D-PT at the MD Anderson Cancer Center from 2007 to 2009.[35] Dosimetric comparison to conventional photon radiation demonstrated lower mean dose to several OARs including heart, esophagus, and lung with PT, although the breast received similar radiation dose across treatment modalities. Conclusions regarding therapy effectiveness are hard to draw from this heterogeneous group of HL and NHL patients who received doses ranging from 30-50 cobalt gray equivalents (CGE). Acute toxicities were mild and all but one patient with refractory disease exhibited disease control at last follow-up.

In the most robust series to date, Hoppe et al published the results of a phase II study of involved node PT (INPT) in combined modality therapy for HL.[36] Fifteen patients with HL were treated with INPT to 30.6-39.6 CGE after systemic therapy, after dosimetric comparison with 3DCRT and IMRT treatment plans showed superiority for PT. Representative treatment planning for these modalities is provided in Figure 3. Three-year relapse-free survival of 93% was similar to results with photons, and PT was well-tolerated. Small patient numbers combined with the heterogeneous chemotherapy regimens that patients receive may limit our ability to detect differences in late effects between this group and those who receive photon therapy.

At present, a growing body of literature is demonstrating the dosimetric advantages of protons, and early reports indicate that PT can be used for lymphoma with acceptable oncologic outcomes that appear similar to photon techniques. Although the theoretical secondary malignancy and late toxicity advantages of proton therapy have yet to be proven, additional evidence may also come from proton studies in other populations. Reflective of its growing acceptance as a potentially valuable tool in managing lymphoma, PT has been referenced as a potential therapeutic intervention in American College of Radiology appropriateness criteria for pediatric HL as well as non-Hodgkin lymphomas.[37-39]

Conclusion

The modern radiation oncologist has an abundance of delivery techniques to choose from when treating a patient with HL, but concrete evidence supporting the options remains limited. Concerning IMRT and its variants, respiratory management, and particle therapy, dosimetric advantages in one aspect of treatment planning may be counterbalanced by disadvantages. Therefore, the treating radiation oncologist must carefully consider each case, as no optimal solution applies to all patients. In certain clinical contexts, multiple techniques may be combined.

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Total body irradiation: A practical review

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Total body irradiation (TBI) with megavoltage photon beams is one component used in treating several diseases, including multiple myeloma, leukemias, lymphomas and some solid tumors.[1,2] In combination with chemotherapy, TBI is most commonly used as part of the conditioning regimen prior to hematopoietic stem cell transplantation.[1,3,4] TBI provides a uniform dose of radiation to the entire body, penetrating areas such as the central nervous system (CNS) and testes, where traditional chemotherapy is ineffective.[5,6] Additionally, it allows tailoring of therapy with the ability to shield or boost the dose to certain regions as necessary. The purpose of TBI is threefold: to eliminate residual cancer cells, to provide space for stem cell engraftment through bone marrow depletion, and to prevent rejection of donor stem cells through immunosuppression.[3,4]

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Dosing

The reported D_0 value—the amount of ionizing radiation necessary to eradicate a particular cell type—of hematopoietic stem cells is 0.5 to 1.4 Gy, while those of human leukemia cell lines are 0.8 to 1.5 Gy, indicating that both cells are radiosensitive.[4] The ideal dosing schedule depends on patient age, disease and the intended type of stem cell transplant.[6] Recommendations state that the most common dose schedule for myeloablative TBI is 12 to 15 Gy given in 8 to 12 fractions over 4 days, with 2 to 3 treatments daily.[6-8] Doses > 15 Gy have been shown to decrease relapse rate, but also increase the incidence of graft vs. host disease and decrease 2-year survival.[7-9] Dose rates are often 6 to 15 cGy/min, consistent with recommendations of the American Association of Physicists in Medicine (AAPM) TG-17 report, as it has been reported that dose rates < 20 cGy/min help reduce complications.[10] Low-dose TBI, with doses of 2 to 8 Gy given in 1 to 4 fractions in combination with chemotherapy, is an effective conditioning regimen for hematopoietic stem cell transplantation in patients who cannot tolerate myeloablation due to age or comorbidities.[6,11] Fractionated TBI has been shown to lead to a higher incidence of graft rejection than the same dose delivered in a single fraction, possibly due to DNA repair during interfraction intervals.[4,7,12] However, fractionation decreases the eradication of bone marrow stromal cells, which are necessary for successful hematopoietic stem cell engraftment, and is, therefore, considered the standard of treatment.[4,6] Whole-dose inhomogeneity should be maintained within ± 10% to minimize the risk of complications.[6] The AAPM TG-29 report provides instructions for dose prescription calculations.[13] To perform these calculations, patient

thickness should be measured at the prescription point, generally the level of the umbilicus.[6] One method to independently verify the accuracy of delivery is to perform in-vivo measurements. Penn State uses Landauer (Glenwood, Illinois) nanoDot OSLD dosimeters at the umbilicus position for the AP field, and an umbilicus-equivalent position facing the beam for the PA field, with ± 5% tolerance as advised.[14]

Equipment

Guidelines recommend the use of parallel opposed pairs of high-energy photon beams from 4 to 18 MV for TBI;[1,6] in our institutions we use 6 MV to avoid underdosing superficial bones such as the iliac crest and sternum. AAPM's TG-51 calibration protocol provides guidelines for dosimetry of high-energy photon beams.[15] Recent studies demonstrate the efficacy of helical tomotherapy and dynamic arc-based techniques for decreasing TBI treatment time and increasing homogeneity of delivered radiation; however, the use of this technique is not widespread.[16-19]

At Penn State, a Varian Clinac iX is used for TBI, and at Cleveland Clinic, a Siemens Artiste is used. In both institutions, another linear accelerator is identified as a backup in case the primary treatment machine goes down. At Cleveland Clinic, this is an identical Siemens Artiste, and at Penn State, it is a Varian Trilogy. At Penn State, both linear accelerators were commissioned using the same source-to-surface distance (SSD = 463 cm). The absolute dose for both machines was calibrated at 100 cm SAD (surface to axis distance) using a 10-x-10-cm field size according to the AAPM TG-51 protocol, but TBI treatments are delivered using a larger field (40-x-40-cm) and extended SSD. Thus, the dosimetry tasks for TBI commissioning included: a) measuring the output factor at the central point of treatment distance; b) generating the table of tissue maximum ratio (TMR) at the central point of treatment distance; and c) measuring the screen factor. At Penn State, this was performed using a PTW TN30013 ion chamber (PTW, Freiburg, Germany), a Fluke electrometer (Fluke Biomedical, Everett, Washington), and multiple 30-x-30-cm PVC phantoms. To independently verify dosimetrical accuracy, in-vivo measurements with nanoDot OSLD dosimeters[14] were performed with PVC phantoms after commissioning.

When opposing photon beams are used for TBI, patients are treated with 2 parallel-opposed fields, with each field treated in each fraction. If a single source of radiation is used, the patient is rotated 180 degrees along the longitudinal axis between doses.[4] For each field, the coronal midline of the patient is aligned with the treatment plane marked on the floor at the time of commissioning. Irradiation along the anterior-posterior/posterior-anterior (AP/PA) direction provides better dose uniformity.[4] TBI stands, treatment couches or tables are used to immobilize the patient lying supine/prone or standing upright if a vertical beam is used, or with the patient on his or her side if a horizontal beam is used. Pediatric patients under anesthesia may need to be irradiated using a lateral beam while lying supine due to airway concerns, but this technique should be avoided when possible for patients with large lateral separations.[4,6] Different setups and equipment used at the Penn State Cancer Institute are shown in Figures 1-3. Unlike conventional radiation therapy in which skin sparing is often desired, it is preferable for the skin to receive a full dose of radiation for certain types of diseases treated with TBI, such as leukemias that can circulate in the blood volume of the skin.[4] Beam spoilers scatter electrons as photons from the TBI beam pass through them, allowing energy to deposit near the surface of the skin.[4,20]

Lung shielding using lead or alloy attenuators, which reduce radiation dose to the majority of lung tissue, is recommended during normal—but not low—dose TBI to reduce the risk of pneumonitis, particularly in patients with concomitant lung dysfunction.[4,6,21] However, overcompensation through the use of lung shields can increase the risk of leukemia recurrence, so shields should generally correspond to a 10% to 50% reduction in radiation dose.[4] Lung thickness, size and density must all be considered when calculating radiation dose to the lungs.[1] Lung shields can be tailored to avoid shielding the thymus, hilum, thoracic vertebrae, and heart. An example of a radiograph showing lung shield placement and its corresponding digitally reconstructed radiograph produced during the planning process is shown in Figure 4.

Literature demonstrating the benefit of lung blocking is limited, with only small retrospective series available. One such study assessed 44 patients receiving 12 Gy TBI in 6 fractions over 3 days.[22] Twenty-three patients received this regimen without shielding and the remaining 21 received lead shielding to 50% dose reduction after the first 6 Gy, yielding a total lung dose of 9 Gy. Over the next 6 months, 6 out of the 23 patients (26%) who did not receive shielding developed interstitial pneumonitis, diagnosed either clinically with cough, dyspnea, or radiographically as bilateral interstitial infiltrates without an infectious etiology.[22] In half of these cases, the complication was fatal. No one who received shielding developed interstitial pneumonitis.[22] Although this level of evidence is not definitive, given the potential of lethality if interstitial pneumonitis develops, the Children's Oncology Group recommended, but did not require, the use of lung blocks in recent protocols, such as ASCT (autologous stem cell transplant) 0631.

Renal shielding is another common technique for reducing the level of radiation delivered to the kidneys. Bone marrow transplant nephropathy, consisting

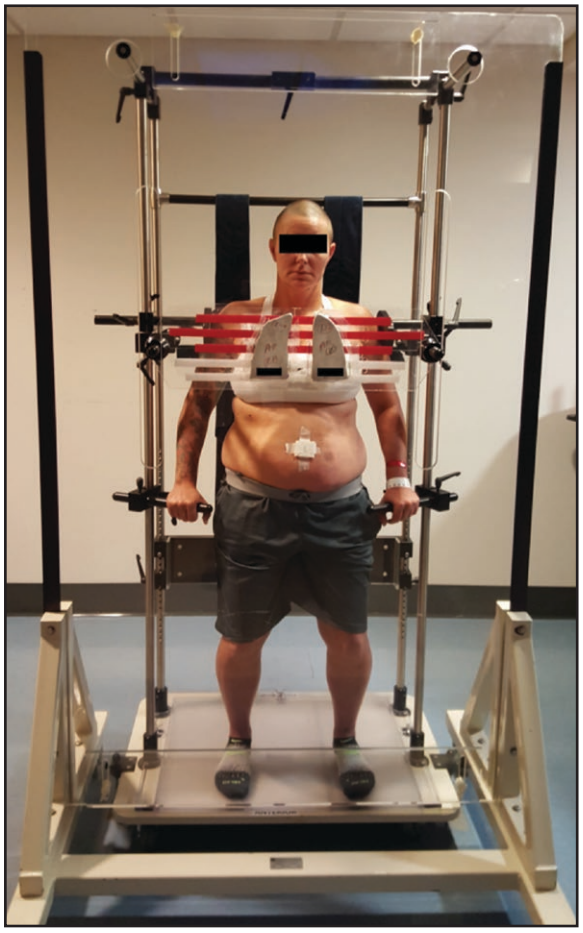

FIGURE 1. *This patient is in the upright position with a bicycle seat for support. Lung blocks are suspended in front of the patient, with positioning confirmed by plain films. A plexiglass beam spoiler is positioned in front of the patient.*

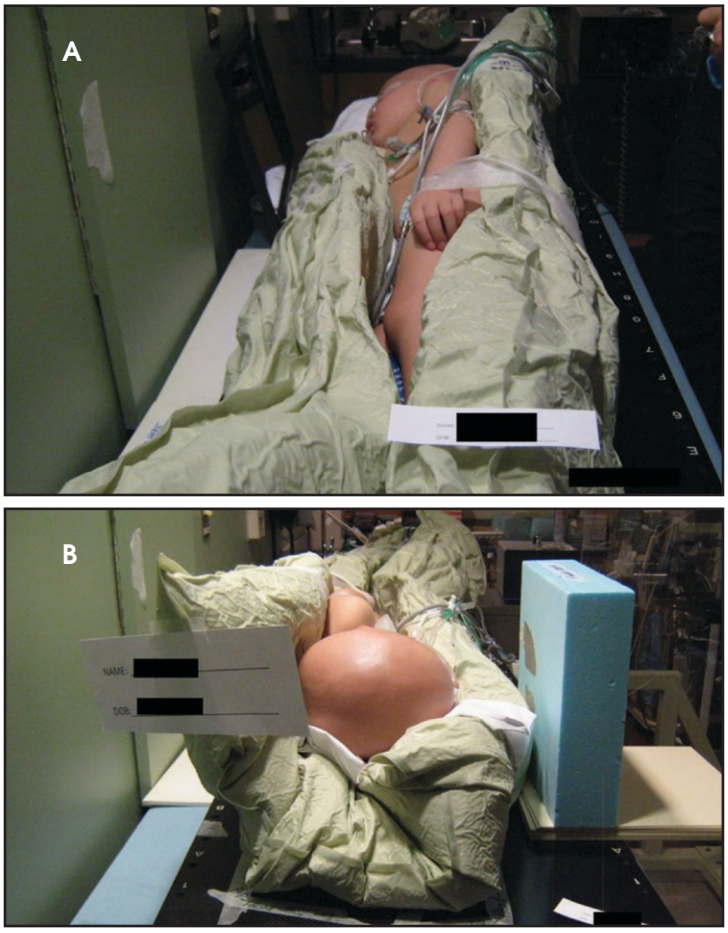

FIGURE 2. *(A) In this setup, used exclusively in small children, a patient under general anesthesia can still be treated with anterior-posterior and poster-anterior fields by placing the patient on his side within a vacuum bag. (B) The same patient with lung blocks within a blue Styrofoam block in place for the anterior-posterior beam.*

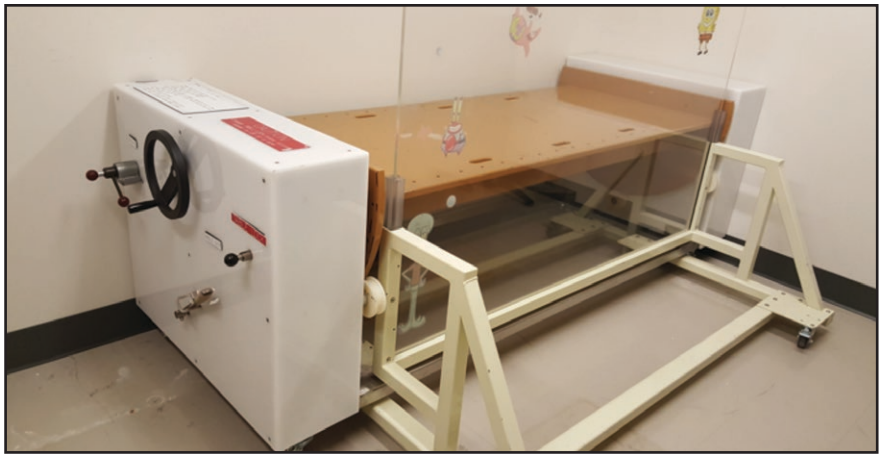

FIGURE 3. *This image illustrates a table that rotates along a horizontal axis, used for pediatric patients who do not require general anesthesia. The patient lies flat on the table with custom vacuum bags built up around her to enable reproducibility in both the anterior-posterior and posterior-anterior positions.*

of renal dysfunction with hypertension, proteinuria, edema, anemia, and decreased glomerular filtration rate, is a serious possible complication of TBI.[23] Because kidneys are not a sanctuary site, kidney blocks have been used standardly at the Cleveland Clinic. The kidneys shift inferiorly significantly when patients move from a supine to upright position, so kidney blocks should be designed based on scans performed in the desired TBI position.[24,25] At the Cleveland Clinic, an intravenous urogram in the standing position is performed at 5, 10, and 15 minutes, and the image with the best kidney outline is used for block design. Additionally, the radiologist reports exactly at what distance the top and

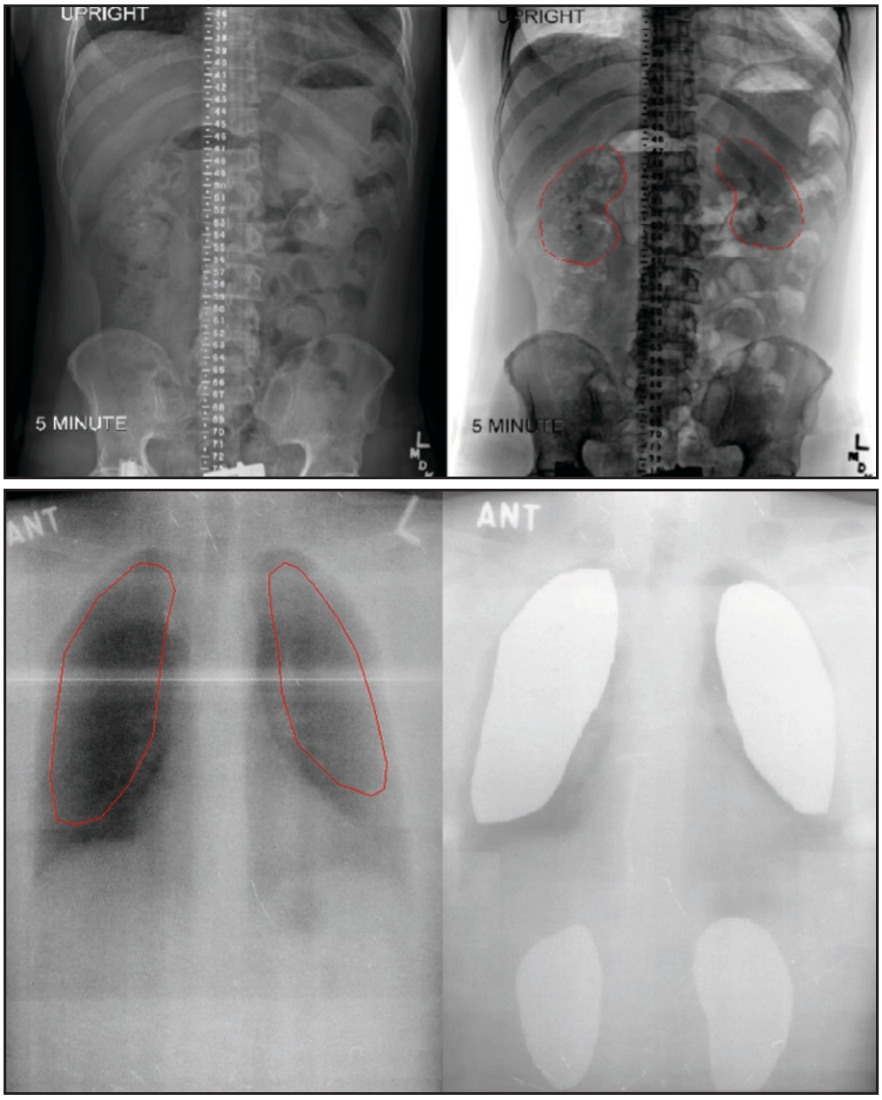

FIGURE 4. *Radiographic images showing the positioning of kidney (top) shields and the combination of kidney and lung (bottom) shields on TBI patients at the Cleveland Clinic.*

bottom of the kidneys are with reference to the central distance marker. Examples of radiographs showing the placement of kidney and the combination of lung and kidney shields from the Cleveland Clinic are shown in Figure 4.

As with lung blocks, the level of evidence in support of kidney blocks is limited to retrospective studies. One such example assessed 157 patients receiving 14 Gy TBI and surviving at least 100 days for the development of nephropathy over 2.5 years from treatment. The authors report a nephropathy rate in the 72 patients who did not receive kidney shielding of 29 +/- 7% and 14+/- 5% in the 68 patients who received 15% renal shielding. No incidents were reported in the 17 patients who received 30% kidney shielding. The authors concluded that shielding should be used in those who require doses > 12 Gy.[23] Although this is standard practice at the Cleveland Clinic, it is not the practice at the Penn State Cancer Institute, which follows Children's Oncology Group protocols whereby only lung shields, and not kidney shields, are allowed. Finally, both gonad and thymus shielding have been used by some clinicians,[21] but are not used in either of our institutions.

Complications

Without careful medical monitoring and hematopoietic stem cell transplantation, TBI is a potentially fatal therapy.[6] Immediately following TBI, the most common acute symptoms include nausea, emesis, loss of appetite, diarrhea, mild erythema, pruritus, headache, xerostomia, parotitis and fatigue syndrome.[26] Therapies to control these side effects include intravenous hydration, antimucositis and antiemetic agents.[6,27] Long-term complications of TBI include secondary malignancies, infertility, cardiovascular disease, pneumonitis, nephritis, cataracts, and learning deficits and growth failure in children.[6,28] Attention to calculations and careful technique is critical to minimize the risk of late-term sequelae.

Indications

TBI is used as part of the conditioning regimen for both autologous and allogeneic hematopoietic stem cell transplantations. A study of German stem cell transplant patients by Heinzelmann et al found that approximately 10% of autologous transplant patients receive TBI, with chronic lymphocytic leukemia (80%) and non-Hodgkin's lymphoma (35%) being the most common disorders for which TBI was used.[29] The same study found that 50% of allogeneic transplant patients received TBI, with acute lymphocytic leukemia (85%), acute myeloid leukemia (45%) and chronic myeloid leukemia (49%) being the most common disorders.[29]

Acute Lymphoblastic Leukemia

Acute lymphoblastic leukemia (ALL) is a disorder of malignant lymphoid progenitor cells. Although ALL affects children and adults, the majority of patients are diagnosed between ages

2 to 5 years.[30] Approximately 6,000 cases of ALL are diagnosed annually in the United States, many of which are idiopathic. The majority of initial treatment regimens for ALL, which include a remission-induction phase, an intensification phase and continuation therapy, achieve overall disease-free survival rates of 80% to 90%.[30] Both allogeneic and autologous stem cell transplantation have been successfully used in treating ALL, but allogeneic transplants are more common.[31] Transplantation is the most intensive type of therapy for ALL and is typically considered in patients with high-risk ALL (such as those with Philadelphia chromosome-positive disease), those with early relapse (within 3 years of primary remission), or those who have a poor response to induction therapy.[3,30] Long-term survival rates > 65% have been demonstrated for ALL patients transplanted during the first relapse.[32,33] In a retrospective study using data from the International Bone Marrow Transplant Registry by Davies et al that compared cyclophosphamide plus TBI (CY/TBI) vs. busulfan plus cyclophosphamide (Bu/CY) conditioning regimens for childhood ALL, CY/TBI was found to have a higher 3-year leukemia-free survival rate (55% vs. 40%), lower treatment-related mortality, and a lower rate of treatment failure compared to Bu/CY.[34] The addition of etoposide to the CY/TBI regimen may also improve survival.[35]

Acute Myeloid Leukemia

Acute myeloid leukemia (AML) is a disorder of the myeloid cell lineage, characterized by rapid growth and arrested maturation of cells.[36] AML is the most common acute adult leukemia, with an incidence of approximately 2.4/100,000 in the United States. Despite improvements in treatment, the survival rate of patients under age 65 is < 50%.[3,36] Treatment for AML is typically divided into induction and postinduction phases. Options for postinduction therapy consist of allogeneic bone marrow transplantation, autologous transplantation, or chemotherapy. Allogeneic transplants can cure 50% to 60% of recipients and have relapse rates of < 20%,[36-38] while autologous transplants have survival rates of 45% to 55%.[41] Greater leukemia control can be obtained through the use of conditioning regimens with TBI (such as CY/TBI), but the survival rate is comparable to chemotherapy combinations.[40]

Chronic Lymphocytic Leukemia

Chronic lymphocytic leukemia (CLL) is a malignancy of disordered apoptosis and proliferation of the lymphoid cell lineage. It is the most common type of leukemia in North America and Europe, and predominantly affects adults.[41] Unlike ALL and AML, CLL is incurable and, although treatment exists, most patients relapse. There are generally 3 subsets of CLL patients: one-third experience slow disease progression with treatment consisting of watchful waiting, one-third exhibit an indolent phase followed by progression, and one-third need direct treatment for aggressive disease.[41] Chemotherapy or autologous stem cell transplants are used to aid remission efforts. However, Ritgen et al found that an unmutated variable heavy-chain gene plays a role in whether the transplant is successful.[42] Relapse was inevitable in the group with unmutated genes, whereas patients with mutated heavy-chain genes went into remission following autologous transplant.[42] In elderly patients, the myeloablative conditioning regimen for transplant has a treatment-related mortality of 40% to 50%, so lower doses of radiation are typically used.[43]

Chronic Myeloid Leukemia

Chronic myeloid leukemia (CML) is a disorder of malignant myeloid cells. It was the first leukemia for which a distinct chromosomal aberration, the 9;22 translocation that results in a BCR-ABL fusion gene, or Philadelphia chromosome, was discovered.[44] CML is relatively rare, with an incidence of 1 to 2 per 100,000 people, and is more common in the elderly population.[44] Imatinib, a drug that competitively binds to and inhibits the BCR-ABL tyrosine kinase, is the treatment standard and results in up to an 87% remission.[44,46] Allogeneic stem cell transplants are recommended as second-line therapy if imatinib fails, or in cases of high-risk disease.[46] Five-year survival rates after allogeneic transplants are around 50%, with relapse rates around 20%.[46] Reduced-dose TBI has been effective in lowering morbidity associated with myeloablation, but is not standard.[43]

Multiple Myeloma

Multiple myeloma is a malignant monoclonal proliferation of plasma cells, and accounts for 13% of hematologic cancers.[47] Interactions between malignant plasma cells and bone marrow cells increase tumor growth and progression.[47] Treatment for multiple myeloma depends on disease severity and patient age. Active or symptomatic disease requires immediate treatment, whereas asymptomatic disease only necessitates clinical observation.[47] Symptomatic patients under age 65 who present without significant co-morbidities should be started on chemotherapy plus stem cell transplantation. Patients over age 65 or those with co-morbidities should be evaluated for autologous stem cell transplantation with low-intensity conditioning, or remain on traditional chemotherapy regimens.[47]

Lymphoma

There are many types of lymphoma, which can be divided into the categories of Hodgkin lymphoma, which is characterized by the presence of Reed-Sternberg cells, and non-Hodgkin lymphoma, which encompasses all other types of lymphoma. Treatment of Hodgkin lymphoma typically includes chemotherapy followed by involved-field radiotherapy or involved-site radiotherapy, which target specific lymph nodes rather than

the entire body.[48] Stem cell transplants are used as second line therapy for Hodgkin lymphoma that is difficult to treat or unresponsive to traditional therapy. Chemotherapy is the standard treatment for non-Hodgkin lymphoma, and stem cell transplants are only considered for patients unresponsive to chemotherapy, although new protocols are under investigation.[49,50]

Melanoma

Melanoma is a type of skin cancer with a lifetime risk of 1 in 59 in the United States.[51] The most common risk factor for melanoma is sun exposure, and surgical removal is the treatment standard for cutaneous melanoma with negative lymph nodes.[52] Metastatic melanoma is treated with chemotherapy or immunotherapy, including interleukin-2 or interferon alpha.[52] Adoptive cell transfer therapy is a relatively new treatment option that has shown antitumor responses in > 50% of patients with advanced-stage melanoma. In this treatment, chemotherapy is used to reduce host lymphocytes, and T cells harvested from tumors or peripheral blood that are specific for cancer antigens are infused into a patient.[52,53] TBI can be used as part of the conditioning regimen before adoptive cell transfer, and is associated with higher tumor response.[53,54]

Conclusion

TBI is an effective component of conditioning for hematopoietic stem cell transplant procedures. Although several adverse side effects are associated with TBI, treating various forms of leukemia and lymphoma with transplantation remains one of the most successful forms of therapy. More research is needed on the effects of low dose or nonmyeloablative irradiation, particularly for elderly patients, to reduce treatment-related morbidity and mortality. In addition, research on faster, more uniform methods of radiation delivery, such as helical tomotherapy, may make TBI more accessible to a wider spectrum of patients. For centers interested in starting a TBI program, we recommend following appropriate AAPM reports referenced above; having an identified, commissioned backup treatment machine in case of primary machine downtime; and following cooperative group or IRB-approved research protocols for treatment delivery.

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Implementing adaptive radiation therapy for pancreatic and pancreatobiliary cancers

Mary Beth Massat

Image guidance using computed tomography (CT) and MRI has helped revolutionize the delivery of external-beam radiation therapy (EBRT). While imaging has been embraced for planning with most EBRT—intensity-modulated radiation therapy (IMRT), stereotactic body radiation therapy (SBRT), and 3D conformal—it is primarily used for initial treatment plans rather than for changes during the course of treatment. That, however, is changing thanks to the emergence of adaptive radiation therapy (ART).

There are two ways to adapt a treatment plan—"offline" and "online," explains Parag J. Parikh, MD, associate professor of radiation oncology, at Siteman Cancer Center, affiliated with Washington University School of Medicine and Barnes Jewish Hospital in St. Louis, Missouri. "Most radiation therapy is administered day-by-day, fraction-by-fraction. After delivering some fractions, the oncologist may make a change in the plan and have it ready for future treatment delivery. Most sites do this type of offline adaption, reacting to a change in the patient or the tumor."

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While such changes do not require specialized technology, they do call for restarting the planning process, says Dr. Parikh.

"ART is a new way of thinking about the delivery of radiation therapy that requires new tools, software, processes, time and people to implement it," he says. "What we are looking at is the ability to do online ART, meaning while the patient is on the table we are making a change in the plan based on what we see today." That makes radiation therapy less like the classic description of EBRT and more like a series of operations.

Image Quality

At Froedtert Hospital and the Medical College of Wisconsin in Milwaukee, Beth Erickson, MD, FACR, FASTRO, and X. Allen Li, PhD, FAAPM, have been investigating the use of online ART for pancreatic and pancreatobiliary cancers for several years.

"Implementing online ART is technically challenging," says Dr. Li, who uses ART for prostate cancer treatment. "Most sites use cone-beam CT for daily imaging; however, with CT there isn't sufficient tissue contrast to delineate the pancreas from critical structures." Image quality is the first challenge for ART of the pancreas. Another significant challenge is the QA process—verifying the plan to ensure safe delivery.

Protecting organs at risk is paramount as well. One subset of pancreatic cancer patients are those with locally advanced disease for whom surgery is not an option, explains Dr. Erickson. These patients receive a higher dose of radiation, which increases concerns regarding toxicity to the stomach and duodenum.

"We have a very fine line between what we need to deliver to the tumor and what the stomach and duodenum can handle. It is in this setting where ART can provide the biggest benefit," she says. "With higher radiation, we have more local control for advanced disease. However, injury of the closely positioned GI tract can lead to the need for interventions, including surgery, so it's a real concern."

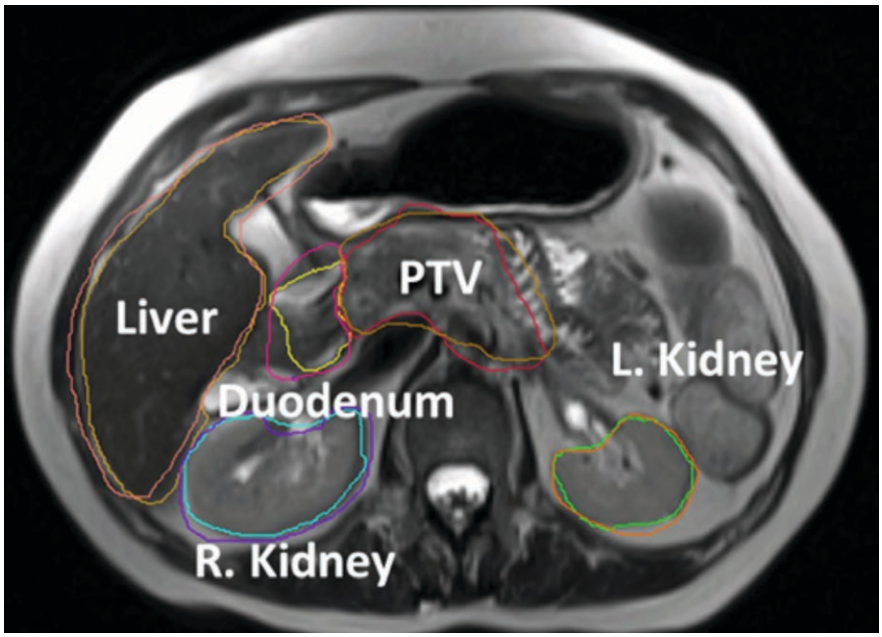

FIGURE 1. *Contours of a planning target volume (PTV) and 4 organs at risk obtained at 2 consecutive treatment fractions are overlaid on MRI. Online ART would correct for the anatomic changes, improving PTV coverage and duodenum sparing. Image courtesy of Froedtert & Medical College of Wisconsin.*

This is where MRI can provide higher quality images needed to delineate the tumor from the normal pancreas, she adds. While Froedtert has been using MR simulation for several years, Dr. Erickson plans to implement Elekta's (Stockholm, Sweden) forthcoming integrated high-field 1.5T MR-guided linear accelerator to help better delineate the tumor and critical structures to enable plans with dose escalation.

For most pancreatic cancer patients, the traditional pre- or postoperative dose is approximately 50 Gy, Dr. Erickson explains. However, for locally advanced pancreatic cancer, the dose needs to be closer to or > 60-70 Gy to control the disease, she says. "That is a big gap between historical doses and where we would like to be," she says. "We need to fill the gap with better imaging that enables us to pull the dose away from those critical structures while giving the tumor the dose that it needs."

Drs. Li and Erickson are studying the ability to push the radiation dose close to 70 Gy with MR-based treatment planning, and have published several studies on ART for pancreatic patients. One study found that using ART with respiratory gating can reduce the dose to the duodenum from 69% to 18%.[1] "If we can spare the duodenum, then we can escalate the dose," Dr. Li says.

Image Registration

One roadblock to implementing online ART in the clinic is the need for a seamless, automated framework. Indrin J. Chetty, PhD, director of the Radiation Physics Division in the Department of Radiation Oncology at Henry Ford Hospital, Detroit, Michigan, has been working with his team in the area of deformable image registration and automation of the adaptive RT planning process for over a decade.

The automated process for estimating the dose-of-the-day involves: (A) deformable registration of the CBCT and planning CT datasets; (B) automatic deformable contour propagation of the target and normal organ contours from the CBCT to the planning CT, and email notification to the oncologist for review of these contours; and (C) computation of the dose on the deformed planning CT and accumulation of the dose for estimating the dose-of-the-day using tools such as DVH review.

There are technical challenges to the deformable image registration and dose mapping process, says Dr. Chetty. These include validation of the deformable image-registration algorithms; dealing with scatter and artifacts on cone-beam CT, which degrades image quality; and other issues such as registration of the planning CT with truncated cone-beam CT datasets for some treatment sites.

"The primary goal of deformable dose accumulation is to determine whether the intended dose at the planning stage is actually being accurately delivered to the patient," Dr. Chetty explains. "By comparing the deviations between dose-of-the-day and the planned dose on a daily basis, we can see if we are indeed delivering what we intended; if we are missing the target or exceeding normal organ tolerance doses, then the oncologist will decide on how to adjust the plan, if considered necessary."

Daily volumetric imaging and online correction enables us to reduce treatment planning margins. Deformable dose accumulation allows us to determine whether the target is being properly covered, which is especially important when planning margins are reduced. With regard to normal tissues, deformable dose accumulation captures interfraction variation in normal organ volumes, which provides better estimates of the doses to these organs over the course of fractionated treatment. Using the dose-to-date information from deformable dose accumulation, and based on the clinical judgment of the team, the treatment plan can be reoptimized midtreatment to meet the goals of the initially planned dose distribution.

For routine use of ART in the clinic, Dr. Chetty says that automation of the workflow process is a key element. "If,

with the click of a few buttons, daily cone-beam CT images can be automatically submitted to the treatment planning system, deformably registered with the planning CT along with propagated contours, and be ready for the physician review, then such an automated process will facilitate broader utilization of deformable dose accumulation technology."

Other challenges that have been resolved to some degree involve the accuracy of the deformable registration algorithms for contour propagation, he adds. However, the issue of estimating accurate deformed dose on a voxel-by-voxel basis is complex and requires much more investigation. Among the various algorithms used at Henry Ford Hospital, Dr. Chetty notes that Velocity (Varian Medical Systems, Palo Alto, California) for multimodality image registration, has performed well against benchmarks.

Dr. Chetty points out that ART takes a clinical champion (often a physician) interested in pursuing prospective studies involving computation of the dose-of-the-day. However, even with a clinical champion, the ART-based process is resource-intensive, and may not be feasible in many clinics without appropriate staff resources to implement it properly. In this regard, automation of the various steps will certainly provide impetus for increased clinical utilization of these tools, he says.

ART as a QA Tool

Compared to other types of EBRT, SBRT delivers higher doses of targeted radiation to treat tumors. At the Cancer Treatment Centers of America at Western Regional Medical Center, Phoenix, Arizona, Benjamin Slane, MD, and Matt West, PhD, have been treating pancreatic patients with SBRT using offline ART to minimize risk of toxicity when delivering high doses near critical structures such as the bowel. "We run ART to ensure that we are delivering the dose that we signed off on," says Dr. Slane. "If not, we can make those changes on the first fraction."

The center began using ART to help determine the precise dose delivered when anatomy changes. It's a second QA step that takes about 5 minutes, says Dr. Slane.

"Early on we realized we could evaluate patient set-up and the robustness of the plan, including the direction of the beams," adds Dr. West, who over the last 7 years has used the TomoTherapy System (Accuray, Sunnyvale, California) with some form of adaptive planning, and is an advocate for both online and offline ART.

ART is also ideal if the patient needs to be re-planned, says Dr. Slane, noting that ART has reduced the need for re-planning and re-contouring because it allows him to see that critical structures are safe from toxicity. "ART is a great decision tree tool," he says. "It brings us all together—the therapist and oncologist—to identify patients at risk and decide whether we involve the physicist or proceed with treatment."

The Value of ART in GI Cancers

Dr. Parikh uses online ART for pancreatic and pancreatobiliary cancers with real-time MR guidance on the MRIdian system (ViewRay, Cleveland, Ohio). ART is an important tool for pancreatic—or other gastrointestinal—cancers not because the tumor changes, Dr. Parikh says, but because of the need to track daily changes that can occur in the gastrointestinal system.

"These changes in the stomach and intestine are not repeatable," he explains. "It is hard to get EBRT into the pancreas; but if we can adjust every day we deliver radiation, then maybe we can use higher doses."

Another concern is intrafraction motion, in which anatomy moves during treatment. In the abdomen, this is often caused by respiratory motion. "This is an area where it seems online ART may help us deliver better treatments," Dr. Parikh says. The real impact, he adds, is the ability to treat certain areas in the abdomen with higher doses knowing that he can evaluate dose safety while the patient is on the treatment table.

"I can adjust that dose around the organ at risk, and although we are giving the patient a more aggressive dose, we aren't seeing higher toxicity," he says. "It's a change from tumor-specific to toxicity-specific dose delivery."

ART is also a patient-centered approach, much like in the surgical suite. "You have to schedule the patients around the physicians—the work cannot happen without the physician being there, so this requires a change in how we work." He likens it to brachytherapy or radiosurgery, where the oncologist is not only present during therapy, but is delivering it.

Perhaps most important, Dr. Parikh adds, is what radiation oncologists do with the information from online ART: "ART is more than just having images available; the key is to act on them."

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RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for June 2016!

Optimizing treatment positioning to achieve better heart sparing in a left-sided, whole-breast irradiation case unfit for deep-inspiration breath-hold treatment

Vishruta A. Dumane, PhD; Stanislav Lazarev, MD; Ren-Dih Sheu, PhD; Yeh-Chi Lo, PhD; and Sheryl Green, MD

CASE SUMMARY

A 33-year-old, premenopausal, BRCA-negative woman with Adriamycin-induced cardiomyopathy and left ventricular dysfunction presented to our department in 2015 for adjuvant treatment of ductal carcinoma in situ (DCIS) of the left breast. Her medical history was significant for Wilm's tumor diagnosed at age 10, treated with surgery followed by Adriamycin-based chemotherapy, which resulted in dilated cardiomyopathy. She remained on several medications for cardiomyopathy over many years, and has been followed closely by cardiologists. Her left ventricular ejection fraction, prior to initiating radiation, was estimated to be 37%.

Three months prior to presentation, the patient sustained an episode of congestive heart failure exacerbation, and was found to be 13 weeks pregnant. Cardiology assessed that the patient was at high risk for decompensating with pregnancy, and was advised to undergo an elective termination, which was subsequently performed without complication. She nevertheless continued to exhibit moderate heart failure symptoms, and was started on high-dose diuretics with ultimate symptom resolution.

With regard to the DCIS diagnosis, she initially presented with bloody left nipple discharge. Breast imaging studies were obtained, demonstrating suspicious microcalcifications in the retroareaolar region of the left breast. Core biopsy of the microcalcifications revealed intraductal papilloma. Lumpectomy was performed, with pathology consistent with a diagnosis of DCIS. Adjuvant radiation with 3D-conformal radiation therapy was recommended, following extensive discussion with her breast surgeon and cardiologist. Additionally, given the positivity of ER and PR hormone receptors, she was recommended a 5-year course of Tamoxifen upon completion of left breast irradiation.

*Prepared by **Dr. Dumane**, assistant professor of radiation oncology; **Dr. Lazarev**, resident in radiation oncology, PGY2; **Dr. Sheu**, assistant professor of radiation oncology; **Dr. Lo**, chief physicist; and **Dr. Green**, associate professor of radiation oncology, Department of Radiation Oncology, Icahn School of Medicine at Mount Sinai, New York, NY.*

IMAGING AND PATHOLOGY FINDINGS

Initial left breast diagnostic mammogram showed grouped microcalcifications in the retroareolar region. Diagnostic ultrasound of the left breast showed a 1-cm cyst cluster that was 4 cm from the nipple, and dilated retroareolar ducts with minimal intraluminal debris. Subsequent bilateral breast MRI demonstrated a suspicious 8-mm mass medial to the nipple of the left breast, and suspicious nonmass enhancement in the retroareolar region of the right breast, as well as an 8-mm enhancing mass in the superior mid portion of the right breast. Ultrasound-guided core biopsies of the subareolar axis of the left breast and of retroareolar axis of the right breast revealed intraductal papillomas. The patient underwent an additional core biopsy of the left breast inferior outer quadrant, which also revealed intraductal papilloma. She then underwent bilateral lumpectomies. Whereas the right breast surgical specimen contained intraductal papilloma, her left breast lumpectomy pathology revealed an 8-mm focus DCIS, EORTC intermediate grade, with negative margins, ER+, PR+.

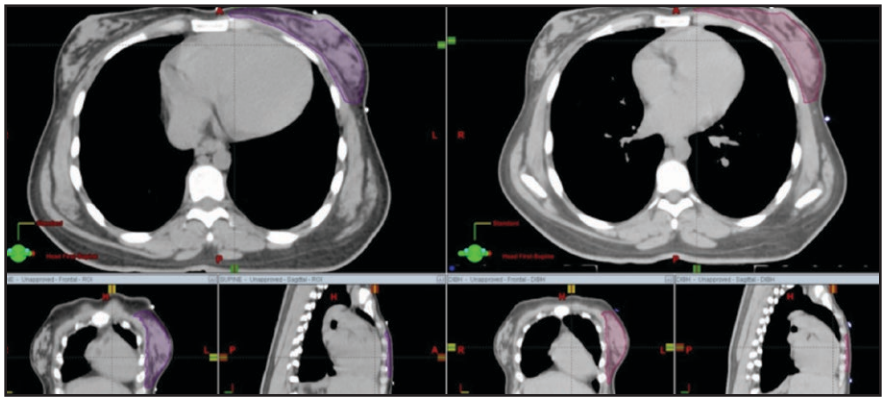

FIGURE 1. *Heart position relative to the chest wall in the supine position with FB on the left and DIBH on the right.*

DIAGNOSIS

The final diagnosis was AJCC stage 0 (Tis N0 M0) ductal carcinoma in situ, intermediate grade, ER+/PR+.

DISCUSSION

This report describes the case of a left-sided breast DCIS in a young woman with dilated cardiomyopathy. Considering the patient's left-sided breast carcinoma, previous exposure to Adriamycin-based chemotherapy, dilated cardiomyopathy, left ventricular ejection fraction of 37%, and young age, choosing a radiotherapy treatment plan that maximized cardiac sparing was essential. In a recent population-based case-control study, Darby et al[1] have demonstrated that exposure of the heart to ionizing radiation during radiotherapy for left-sided breast cancer significantly increases the risk of having a major coronary event, such as myocardial infarction, coronary revascularization, or death from ischemic heart disease.[1] This risk is found to increase linearly with the mean heart dose (MHD). For every 1 Gy increase in the MHD, the rate of major coronary events increased by 7.4%. Moreover, because the study by Darby et al included few women who were younger than 40 years and received radiation for left breast cancer, it was cautioned that the risk of women younger than 40 is likely to be even higher than what they reported. Therefore, the aim of designing a treatment plan for this patient was to minimize the heart dose without compromising coverage to the breast tissue. The use of deep inspiration breath hold (DIBH) has been demonstrated as a highly effective technique for reducing cardiac dose.[2,3,8] In this technique the patient takes a deep breath, trying to increase the distance between the chest wall and heart, allowing adequate treatment of the breast while minimizing irradiated cardiac volume. In a large series of breast cancer patients receiving whole-breast radiation, it was shown that the MHD was reduced from 5.2 Gy with free breathing to 2.7 Gy with DIBH.[3] However, DIBH requires the patient to hold her breath for ≥ 20 seconds, and its dosimetric benefit depends on the adequate expansion of the chest wall and the distance of the heart from it. As the chest wall expands anteriorly with deep inspiration, it pulls more lung into the treatment field.[2] DIBH is known to treat more absolute volume of the lung than with free breathing (FB) while sparing the heart.[3] Prone breast irradiation, on the other hand, has consistently provided lower lung doses but has shown varied results concerning cardiac dose.[4-7] Since this position displaces the heart anteriorly toward the chest wall, it increases the likelihood of heart exposure to radiation.[6] In a prospective trial comparing the prone vs. the supine position, while 87% of the patients had lower cardiac exposure in the prone position, 13% of the patients were noted to have a higher heart dose.[4] Another comparative study of both these positions reported that patients with a whole-breast clinical target volume (WB CTV) ≥ 1000 cc benefited from the prone position when it came to heart sparing, whereas patients with WB CTV volume < 1000 cc had higher heart doses.[5] Larger breast volume enabled the breast to be pulled under gravity anteriorly in relation to the chest wall, allowing the placement of shallower tangents to better spare the heart, proving prone to be better than supine positioning in these patients.

A comparison of the prone position using FB with supine using DIBH was recently performed in a prospective study.[7] Noncontrast CT scans for 17 patients were acquired in the supine position with FB, supine position with DIBH and prone position with FB. For insignificant differences in planning target volume (PTV) coverage and homogeneity, the MHD was consistently highest in the prone position at 5.4 Gy (3.5 Gy to 6.2 Gy) and lowest with DIBH in the supine position at 1.6 Gy (1.2 Gy to 2.2 Gy). The ipsilateral lung V20 Gy was consistently lowest in the prone position at 2.3% (1.4% to 3.4%) and highest in the supine position with FB at 7.3% (5.7% to 9.7%). The study concluded that both treatment positions had advantages and disadvantages; prone being the best position to reduce dose to the lungs, and DIBH with supine being the best to reduce dose to the heart. It also recommended that a patient unfit to handle DIBH be treated supine using FB rather than in the prone position.

Since sparing the heart from radiation was of the highest priority in this case and since the major advantage of DIBH is to reduce dose to the heart, it first was decided that the patient should be simulated in the supine position for DIBH. The patient was positioned supine with both arms up using the C-Qual Breastboard (CIVCO, Orange City, Iowa). The

Table 1. Dosimetric comparison of parameters for CTV and OARs

Structure	Parameter	Supine	DIBH	Prone
CTV	Volume (cc)	206.4	207.7	205.9
	D95 (%)	100.1	100.3	100.0
	V95 (%)	99.2	99.3	99.6
	D05 (%)	110.5	110.2	110.8
	D_{max} (Gy)	111.6	111.6	111.8
	HI	0.1	0.1	0.1
	CI	2.6	2.5	1.8
Left Lung	Volume (cc)	783.8	1460.5	816.2
	Mean (Gy)	5.0	6.4	0.7
	V20 Gy (%)	8.1	11.2	0.0
	V5 Gy (%)	14.5	18.4	1.4
Heart	Volume (cc)	475.8	478.0	475.9
	Mean (Gy)	8.8	6.0	1.6
	V40 Gy (%)	12.2	7.4	0.0
	V30 Gy (%)	14.0	8.8	0.4
	V20 Gy (%)	15.6	10.2	1.0
	V5 Gy (%)	22.2	15.9	5.1
Left Ventricle	Volume (cc)	236.9	238.2	238.8
	Mean (Gy)	13.3	10.1	2.5
	V40 Gy (%)	19.1	13.3	0.0
	V30 Gy (%)	21.7	15.8	0.7
	V20 Gy (%)	24.2	18.1	1.8
	V5 Gy (%)	33.9	27.4	8.5

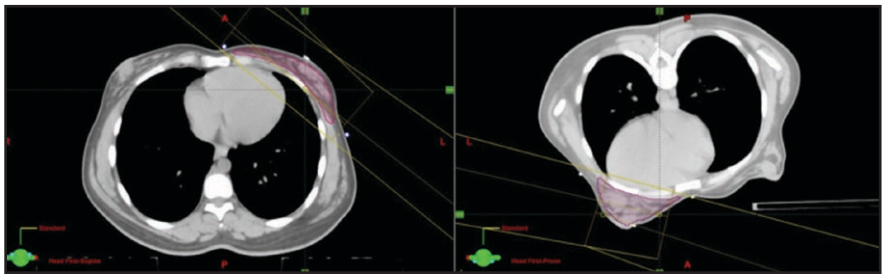

FIGURE 2. *Tangential field arrangement to cover the CTV in the supine position with DIBH on the left vs. the prone position on the right.*

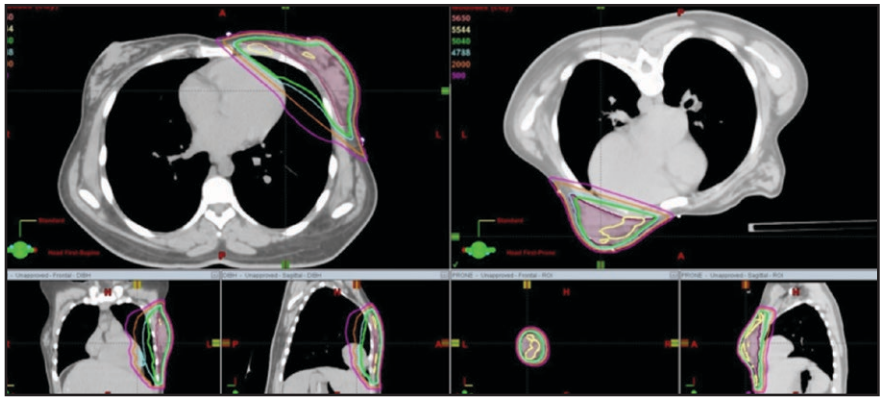

FIGURE 3. *Dose distributions in the axial, coronal and sagittal planes for the supine position with DIBH on the left and prone position on the right.*

breast tissue was palpated and outlined with a radio-opaque wire. Two scans were acquired, namely supine using FB and supine with DIBH. Upon comparing the FB and DIBH scans for this patient (Figure 1), the position of the heart with respect to the chest wall did not appear to differ remarkably. At this juncture, the patient's efforts to breathe deeper—to allow for increased separation of the heart from the chest wall and to take a new scan with DIBH—were also diminishing. Due to these impediments, we decided to scan the patient in the prone position, the advantage being that the patient did not need to hold her breath for prolonged periods, which improved comfort and compliance in receiving radiation therapy. Studies have shown that setup errors are larger in the prone than in the supine position and that elderly and obese patients especially have difficulty positioning themselves on the prone board, leading to challenges in reproducing setup during treatment.[9,10] In this case, the patient had a normal BMI (body mass index) of 24.4 at the time of therapy, raising less concern pertaining to reproducibility of setup. For this position, the Prone Breast System (Bionix, Toledo, Ohio) was used. The patient lay prone on the board with both arms raised above the head, which was turned to the contralateral side. The board has an adjustable aperture that allows the breast tissue to be treated to fall freely within the opening. The contralateral breast was held up and away using support cushions and wedges as needed to keep it out of the path of the treatment fields.[10] The palpable breast tissue was again outlined with a radio-opaque wire and the patient was scanned with 3-mm slice thickness.

CT data from scans in all 3 positions (supine using FB, supine using DIBH, and prone with FB) were transferred to the Eclipse V2 (Varian Medical Systems, Palo Alto, California) treatment planning system for planning and dose calculations. The CTV and organs at risk

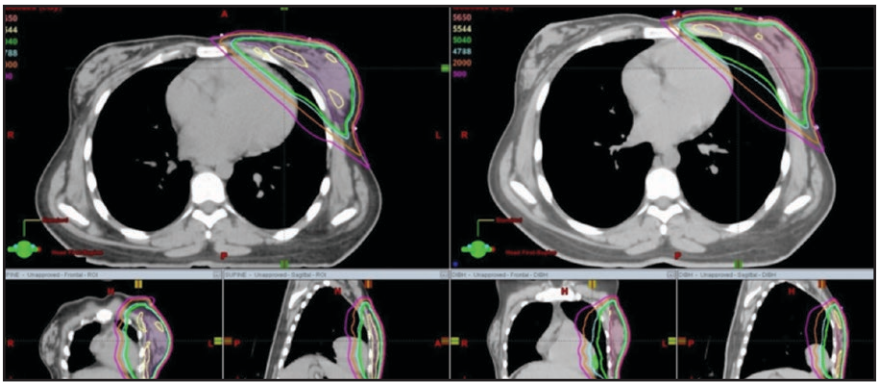

FIGURE 4. *Dose distributions in the axial, coronal and sagittal planes for the supine position with FB on the left and supine position with DIBH on the right.*

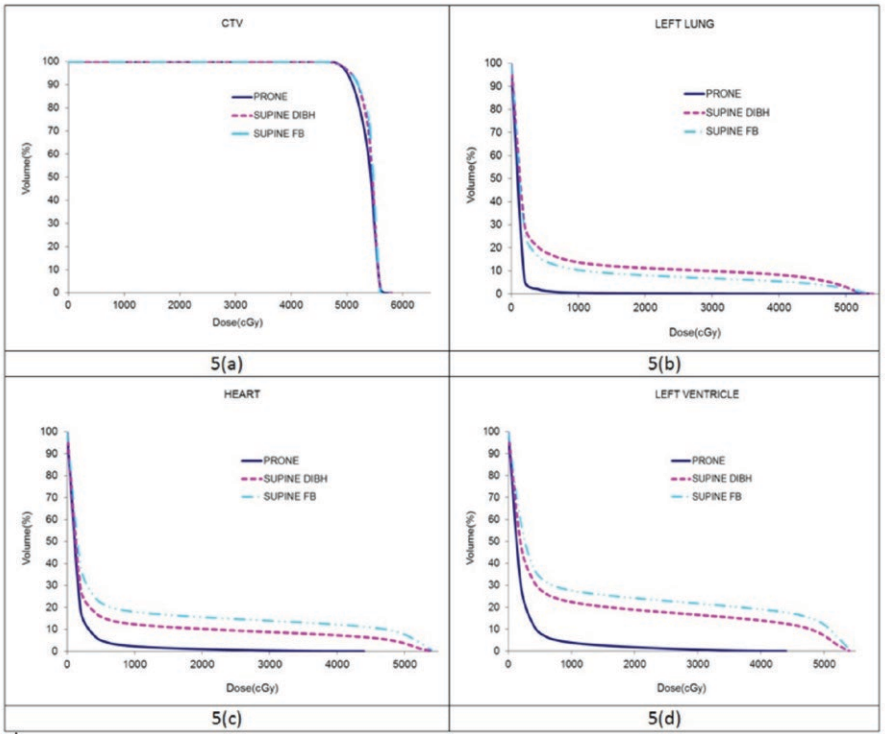

FIGURE 5. *Comparison of DVHs for the CTV, left lung, heart and left ventricle in the 3 simulated positions.*

(OARs) were delineated as the entire palpable breast tissue that was outlined by the radio-opaque wires plus any additional breast tissue that felt needed to be included as a part of the CTV. The radio-opaque markers were used to help define the superior, inferior, medial and lateral field borders. The posterior border of the CTV was defined by the pectoralis major muscle, and the anterior border was limited to 5 mm from the skin surface. Contouring of the heart and the left ventricle was according to published guidelines.[11] Table 1 summarizes volumes of the CTVs and OARs. The volumes of the heart and the left ventricle are equivalent in the prone and the supine position (with FB or with DIBH) as were the volumes of the CTVs. However the ipsilateral lung volume in the supine position with FB in this study was found to be lower by 4% compared to the prone position. Similar results for the CTV and these OARs have been reported previously by Chen et al.[12] For treatment planning, standard opposed tangential fields were used to cover the CTV as shown in Figure 2. The planning technique used was field-in-field. Each plan was optimized to cover the breast CTV such that the D95 and V95 were both ≥ 99% while maximizing heart and ipsilateral lung sparing and keeping the plan as homogeneous as possible. The dose prescribed was 50.4 Gy in 1.8 Gy fractions over 5 weeks using 6 MV photons. The normalization point was placed at 1 cm anterior from the lung chest wall interface and in a plane 1.5 cm inferior from the superior border of the tangential field. The dose calculation algorithm was AAA (analytical anisotropic algorithm) with a calculation grid size of 2.5 mm. Definitions for the homogeneity index (HI) and the conformity index (CI) were taken as described and utilized in the literature for these cases.[12]

Dosimetric results comparing CTV coverage as well as the heart, left ventricle and the left (ipsilateral) lung have been tabulated in Table 1. Dose distributions comparing the supine DIBH plan vs. prone is shown in Figure 3, while that between supine FB vs. supine DIBH is shown in Figure 4. A comparison of the dose volume histograms (DVHs) in all 3 cases is shown in Figure 5. D95 and V95 of the CTV were comparable between the 3 cases as were the D05 and the maximum doses. All 3 plans were just as homogeneous as indicated by HI; however, the plan in the prone position was the most conformal as previously reported.[12] The MHD was 9 Gy in the supine position with FB, and the use of DIBH was able to reduce the MHD to 6 Gy. Planning this patient in the prone position helped reduce the mean heart dose to < 2 Gy and the mean left ventricle dose to < 3 Gy. As found in the Darby study, a 40-year-old woman receiving radiation for breast cancer with an MHD of < 2 Gy and at least one

cardiac risk factor has an absolute risk of death of 0.5% from radiation-related ischemic heart disease (IHD) by age 80 years. For an MHD of 6 Gy and 9 Gy, this risk is 1.4% and 2.1%, respectively. The absolute risk of at least 1 radiation-related acute coronary event (ACE) by age 80 years is < 1.1% for an MHD of < 2 Gy, while the risk is 3.3% and 4.9% for MHD of 6 Gy and 9 Gy, respectively. Using the prone position for this patient has helped lower these risks compared to the supine position with or without the use of DIBH. Also, contrary to reports of a dosimetric study by Kirby et al,[5] although the patient's whole-breast volume in this case study was ~200 cc, this patient benefited from the prone position compared to supine with regard to cardiac sparing. The prone position also best spared the ipsilateral lung with a V20 Gy of 0% and a mean dose of < 1 Gy.

Recently, a decision-making flow chart has been proposed for WBI, which recommends treating a left-sided breast cancer patient that is unfit for DIBH with FB in the supine position.[7] In the case study presented here, the patient was not a good candidate for DIBH. Moreover with DIBH in the supine position, the MHD was at 9 Gy, making the plan nonviable for treatment. The prone position best spared both the heart as well as the lung. The choice of the treatment technique and optimal beam arrangement to cover the target depends on how the patient is set up at the time of simulation as well as on the patient anatomy for that particular simulated position. This case study is an example of a situation in which other treatment positions may need to be explored in addition to recommendations made by studies.[7]

The patient successfully completed radiation therapy as planned without any cardiac episodes. The increase in the rate of major coronary events per 1 Gy depends on the length of time after completing radiotherapy.[1] Within 0 to 4 years, the rate is 16.3%, and between 5 to 9 years it is 15.5%. The current follow-up time for the patient in our case report is too short for manifestation of cardiac injury; however, by reducing the MHD from 9 Gy to 1.6 Gy, we were able to minimize the risk of a major coronary event in this patient. She is currently maintained on anti-estrogen therapy with Tamoxifen and follows up with her cardiologist regularly. At her 1-month follow-up appointment she reported feeling well overall and denied chest pain, pressure, palpitations, dyspnea on exertion or orthopnea. She also did not experience any shortness of breath, wheezing, coughing or hemoptysis. She denied any breast pain, swelling or palpable masses. She had normal range of motion in the bilateral upper extremities without any edema and denied any weight changes, fatigue or appetite disturbances post treatment, and was able to resume working fulltime. She will continue to receive regular mammograms and follow-up with her multidisciplinary team of physicians.

CONCLUSION

In conclusion, we highlight a case of a 33-year-old woman treated with Adriamycin-based chemotherapy for Wilm's tumor at age 10 years, and recently diagnosed with DCIS of the left breast, requiring whole-breast radiation. Due to Adriamycin exposure, she suffers from dilated cardiomyopathy. Considering her young age and pre-existing cardiac risk factors at the time of radiation therapy, sparing her heart as much as possible from exposure to radiation was the highest priority while planning this case. While DIBH is known to reduce dose to the heart, this patient was not a good candidate. The prone position has shown inconsistent results with respect to sparing of the heart. While other studies recommend not treating in prone position if the patient is unfit for DIBH or has a smaller breast volume, our case required a comparison of both positions before deciding on the optimal plan.

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RADIATION ONCOLOGY CASE

Chemoradiotherapy-induced toxicity with high-dose three-dimensional conformal radiotherapy for lung cancer: Challenges with modern techniques

James W. Snider, III, MD; Tejan Diwanji, MD; Pradip Amin, MD; Steven J. Feigenberg, MD

CASE SUMMARY

A 58-year-old African-American woman presented with a slowly enlarging, inferior right upper lobe ground-glass opacity (2.8 cm) for which biopsy proved well-differentiated adenocarcinoma of lung origin. Seven years earlier, the patient had undergone concurrent chemoradiotherapy at an outside institution for a stage IIIA adenocarcinoma of the right middle lobe. She had received weekly carboplatin/paclitaxel with concurrent radiation prescribed to 74 Gy using a 3-dimensional conformal radiotherapy technique (3D-CRT). The arrangement employed 2 parallel-opposed, oblique fields (only a few degrees off laterals) for the entire course (Figure 1).

*Prepared by **Dr. Snider,** chief resident, **Dr. Diwanji,** resident, **Dr. Amin,** associate professor, and **Dr. Feigenberg,** professor, Department of Radiation Oncology, University of Maryland Medical Center; Baltimore, MD.*

Upon re-presentation, she suffered from treatment-induced pulmonary fibrosis, chronic pericardial effusion, fractured ribs, chest wall fibrosis, and gastrostomy-tube dependent dysphagia (Figure 2). Because of the new lesion's estimated abutment of the prior radiation's superior field edge (Figure 2D) and her previous toxicity, the patient elected to undergo sublobar resection. Pulmonary function tests indicated only a mild restrictive pattern (FEV1-1.97L/73%;FVC-2.65L/82%;TLC-3.98L/79%). Surgery was relatively uncomplicated, but the patient suffered severe postoperative acute respiratory distress syndrome. This precipitated a complicated hospital course that ultimately led to death.

IMAGING FINDINGS

CT examination of the thorax at re-presentation demonstrated dramatic soft tissue changes corresponding to the previous radiation lateral field arrangement (Figures 1 and 2). Extraordinary bilateral rib fractures and chest wall fibrosis bracketed linear band-like pulmonary fibrosis traversing the patient's chest as well as a moderate pericardial effusion.

DIAGNOSIS

Severe, late chemoradiotherapy-induced, lung, esophageal, heart, and chest wall toxicity, compounded by post-treatment surgical complications.

DISCUSSION

Radiation oncologists have a substantially increased workload in treatment planning and delivery when compared with the 2D and early 3D eras. Numerous treatment details and patient factors must be considered, and failure to do so can yield dramatic and unexpected toxicities. In particular, tumor and normal tissue delineation has

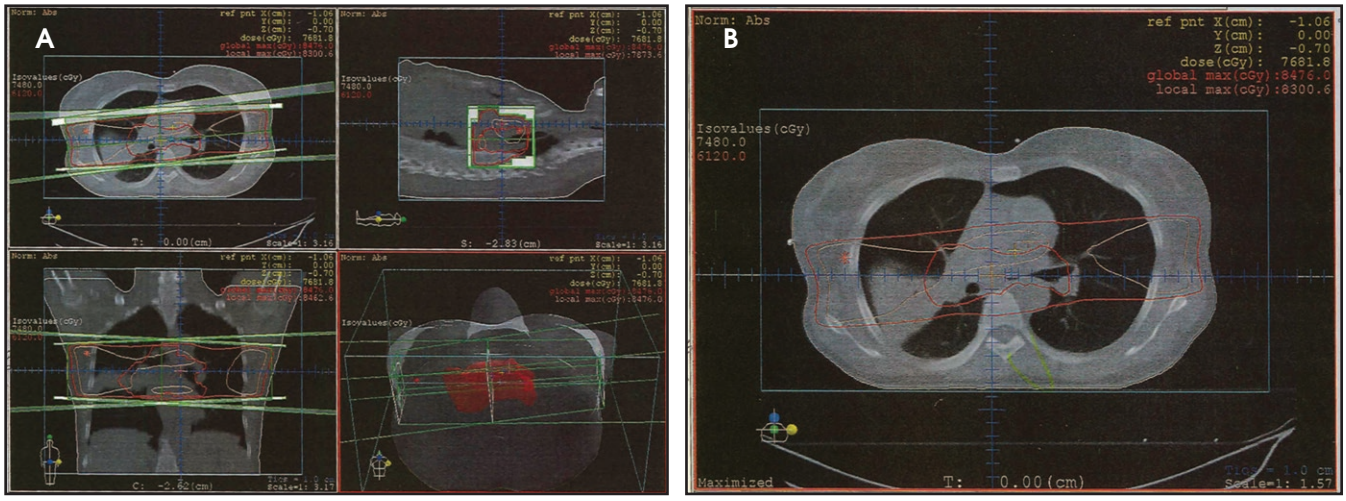

FIGURE 1. *(A) 3D-CRT plan with lateral oblique field arrangement. Top, axial and sagittal; bottom, coronal and 3D orientations. Red = 61.2 Gy; orange = 74.8 Gy. (B) Enlarged axial orientation.*

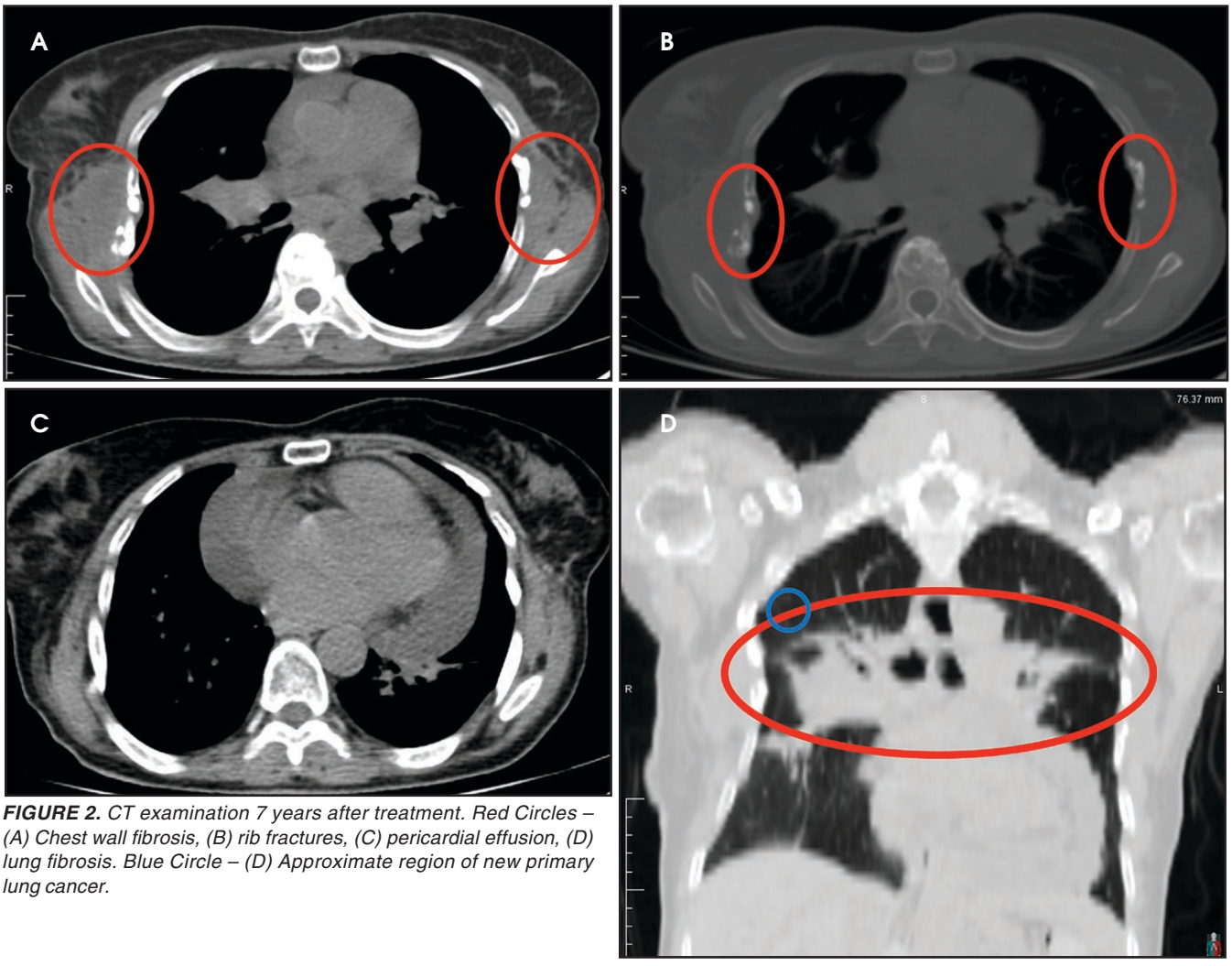

FIGURE 2. *CT examination 7 years after treatment. Red Circles – (A) Chest wall fibrosis, (B) rib fractures, (C) pericardial effusion, (D) lung fibrosis. Blue Circle – (D) Approximate region of new primary lung cancer.*

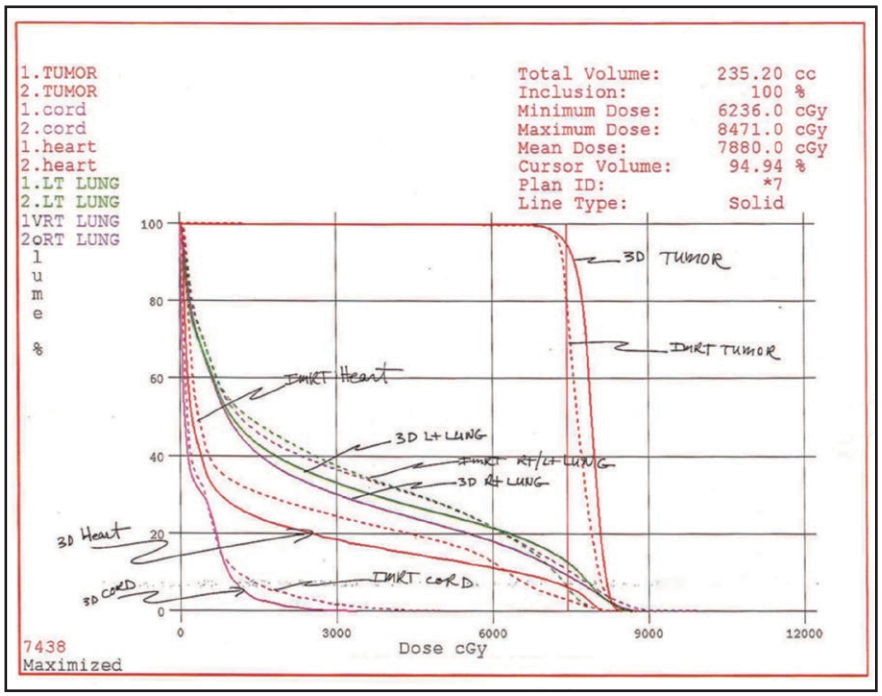

FIGURE 3. *Comparative dose–volume histogram with original notation*

become a labor of love, with contouring more akin to wielding the surgeon's knife than the wax pencils of old. Physicians are then called upon to critically examine a variety of treatment criteria before selecting the "optimal" plan.

Rising concern focuses on chemoradiation-induced toxicities in treatment of locally advanced, nonsmall cell lung cancer (NSCLC). Publication of results from RTOG 0617 (randomized phase III comparison of standard-dose [60 Gy] vs high-dose [74 Gy] conformal radiotherapy with concurrent and consolidation carboplatin/paclitaxel ± cetuximab in patients with stage IIIA/IIIB NSCLC) has intensified uneasiness. Increased utilization of higher radiation doses, expansion of low-dose wash with intensity-modulated radiation therapy (IMRT), and potent radiosensitization with carboplatin/paclitaxel have each been implicated as contributors to treatment-induced morbidity/mortality.[1-3]

Recurrences and local failures in lung cancer remain common. Attempts to further intensify therapy have been met with mixed results. RTOG 0617 was initiated as a randomized, 2-by-2 factorial, phase III effort to investigate both the addition of cetuximab and dose escalation from 60 Gy to 74 Gy.[1] Unfortunately, neither cetuximab nor dose escalation proved beneficial in this trial. Most disconcerting to radiation oncologists was the survival detriment in the 74 Gy arm, often attributed to treatment-related toxicity because no differences were noted in disease recurrence. On multivariate analysis, the prescription dose, maximal grade of esophagitis, planning target volume, heart V5, and heart V30 were each independent predictors of shorter overall survival.

When delivering such high doses of radiation therapy, IMRT is commonly employed to reduce dose to critical structures, such as the lung, heart, and esophagus. By using multiple computer-optimized and modulated fields, IMRT can achieve highly conformal dose distributions, with rapid fall-off toward nearby critical structures, that compare favorably with results from 3D-CRT.[4] Quality of life (QoL) data from RTOG 0617 confirmed worse toxicity in the high-dose arm, but IMRT lessened clinically meaningful declines in QoL.[5] It has been argued, however, that IMRT represents a double-edged sword, because it increases exposure of nearby normal tissue to a bath of lower doses (< 10 Gy). Healthy lung tissue may be particularly at risk.

The lung V20 first emerged as the most predictive marker for pneumonitis in early 3D-CRT approaches (APPA followed by parallel opposed obliques off-cord).[6] With modern 3D-CRT/IMRT techniques, the entire dose–volume curve has increased in significance. Retrospective data from MD Anderson Cancer Center have posited that the V5, V25, V35, V45, and absolute volumes may each predict for radiation pneumonitis.[7,8] Ultimately, balancing low- and high-dose conformality seems to produce optimal plans.[9] Additional recently presented findings from RTOG 0617 suggest that IMRT reduces rates of clinically significant pneumonitis despite increased integral dose.[10] Multiple published IMRT clinical experiences, reporting reasonable rates of toxicity, are reassuring,[7,8] In the patient presented, a comparative IMRT plan was generated but rejected in favor of 3D-CRT.

In this case, 3D-CRT was nominally utilized, although the resultant plan is relatively non-"conformal." The dose-volume histogram (DVH) in Figure 3 accompanied the treatment fields. The delivered plan possessed a lower V5 and V20 than the comparison IMRT plan (unavailable). However, the lateral fields resulted in large hotspots in normal lung, chest wall, heart, and esophagus, with a maximum point dose of 84.76 Gy (~115%) (Figure 1). The IMRT plan had a similar V5 and V20, raising concern that the number of fields employed may have been similarly few and not thoughtfully oriented. Despite the superficial appearance of 3D-CRT dosimetric superiority in this case, selection of this plan was misguided.

In addition, the heart, esophagus, and bilateral chest walls in this relatively young patient demonstrated life-altering toxicity: feeding-tube dependence for 7 years; multiple rib fractures/chest wall fibrosis; and chronic pericardial effusions. Only one of these structures (heart) was contoured. With either forward or inverse planning techniques, the ideal radiation therapy plan can be achieved only with thorough and thoughtful contour delineation. Optimal technique selection in modern planning is built on a foundation of accurate, reproducible volumes.

CONCLUSION

This case serves as a potent reminder that radiation oncologists must be diligent in contouring and plan evaluation. Beam arrangement, radiotherapy dose, conformality, modulation complexity, homogeneity, patient-specific features, and chemotherapeutic regimen (among others) must be examined. IMRT remains a viable and useful approach in the appropriate clinical setting. It should be noted that, despite initial stage IIIA disease, the patient had a durable response to initial chemoradiotherapy—but this came at a terrible cost.

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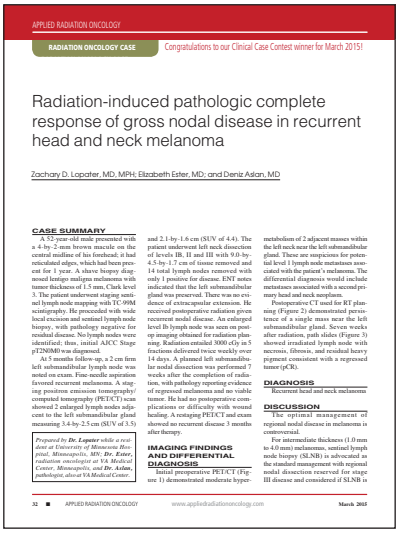

APPLIED RADIATION ONCOLOGY

RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for March 2015!

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

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

CASE SUMMARY

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

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

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

IMAGING FINDINGS AND DIFFERENTIAL DIAGNOSIS

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

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

DIAGNOSIS

Recurrent head and neck melanoma

DISCUSSION

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

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

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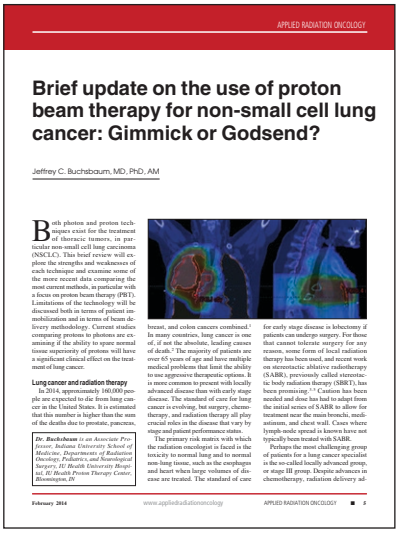

APPLIED RADIATION ONCOLOGY

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

Jeffrey C. Buchsbaum, MD, PhD, AM

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

Lung cancer and radiation therapy

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

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

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

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

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

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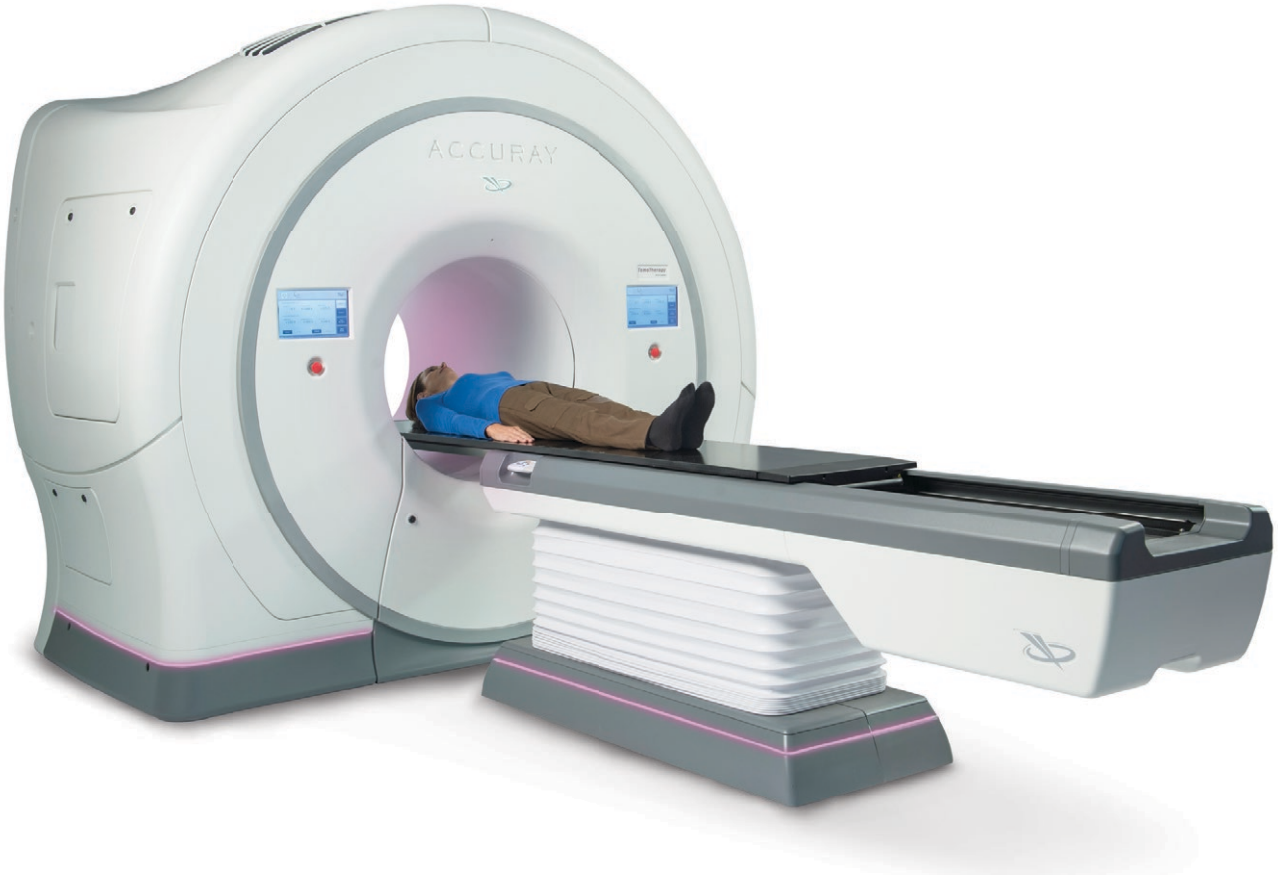

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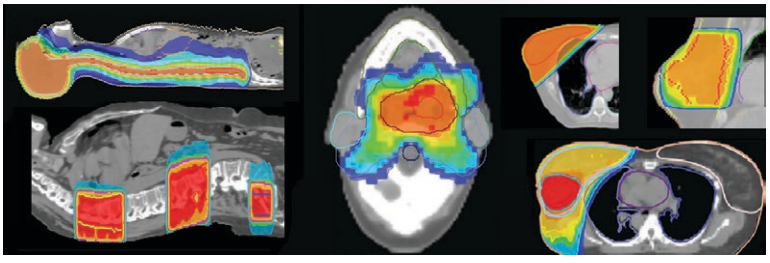

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