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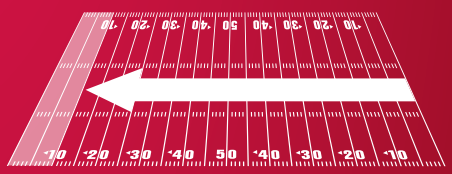

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BREAST CANCER FOCUS

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EDITORIAL

John Suh, MD, Editor-in-Chief

The Heart of Breast Care

As a prelude to Breast Cancer Awareness Month coming up in October, we are pleased to focus this issue on several evolving areas of breast radiation therapy.

The cover article, *Cardiac-sparing radiation therapy for breast cancer,* examines the wide variety of methods for adjuvant breast or chest wall RT that can help minimize radiation dose to the heart—a key contributor to coronary stenosis and other cardiac diseases. University of Pennsylvania authors provide an enlightened review of techniques to help individualize and, in turn, maximize cardiac-sparing radiation treatments, from a minimum standard of forward planning, to more advanced methods of prone positioning, deep-inspiration breath hold, intensity-modulated radiation therapy, and proton therapy.

Radiotherapy, including internal mammary nodal irradiation, and heart failure in patients receiving concurrent treatment with trastuzumab further explores the critical challenge of RT-induced cardiotoxicity. This University of Maryland study bolsters the small body of research that has failed to find a causal link between concurrent trastuzumab/RT and subsequent heart failure. It also identifies a strong trend toward a growing risk of heart failure in patients receiving anthracycline-based chemotherapy.

In *Accelerated partial-breast irradiation (APBI): An emerging standard of care,* Cleveland Clinic authors evaluate data supporting this underused, yet proven, technique for women with early stage breast cancer who have undergone breast-conserving surgery. This definitive review assesses applicator-based brachytherapy and its toxicity-related concerns, external-beam approaches, proton therapy, intraoperative radiation therapy, and the future outlook of APBI.

Finally in our breast cancer lineup, we present *Soft tissue sarcoma of the breast following breast-conserving therapy,* a helpful case report describing the challenge of re-irradiating the left chest while managing heart and lung dose.

We hope you enjoy our breast cancer coverage and additional offerings this month, including the Clinical Case Contest winner, *Subclinical recurrence of anaplastic astrocytoma: Demonstrating the difficulty in distinguishing progression from pseudoprogression*. Congratulations to Howard E. Morgan of LSU Health Science Center for an interesting look at how continued growth of a septated or cystic lesion without true nodular enhancement can suggest disease persistence or recurrence.

Speaking of contests, I am excited to introduce the Best Research Article contest for 2017, in addition to the Review Article of the Year, each with a $1,000 grand prize. The *ARO* Clinical Case Contest will become yearly in 2017 as well, featuring a $500 prize. These opportunities are a great way to contribute to the literature while reinforcing our ever-present, all-important goal: strengthening patient outcomes in radiation oncology. Please visit www.appliedradiationoncology.com for details.

Thank you for your support as we continue to grow and expand our efforts. I hope to see you in Boston this month at ASTRO 2016 for continued collaboration across the field!

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.*

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Cardiac-sparing radiation therapy for breast cancer

Gary M. Freedman, MD; Lilie Lin, MD

Radiation therapy has an essential role in the management of breast cancer that includes either postlumpectomy radiation for breast conservation in early stages, or postmastectomy radiation for the chest wall in multiple node-positive or locally advanced stages. Large meta-analyses of prospective randomized trials have confirmed that radiation reduces locoregional recurrences and reduces breast cancer mortality. However, the risk for late cardiac effects caused by the proximity of the heart and coronary vessels to the chest wall or regional nodes has historically mitigated some of these benefits of adjuvant radiation. The Early Breast Cancer Trialists' Collaborative Group reported a meta-analysis of prospective randomized trials of postmastectomy radiation that noted improved survival in node-positive women.[1] The 20-year improvement in breast cancer mortality comparing radiation to no radiation was 8.1% (p = 0.001), but the gain reducing death was only 5.0% (p = 0.01). For women with 1-3 positive

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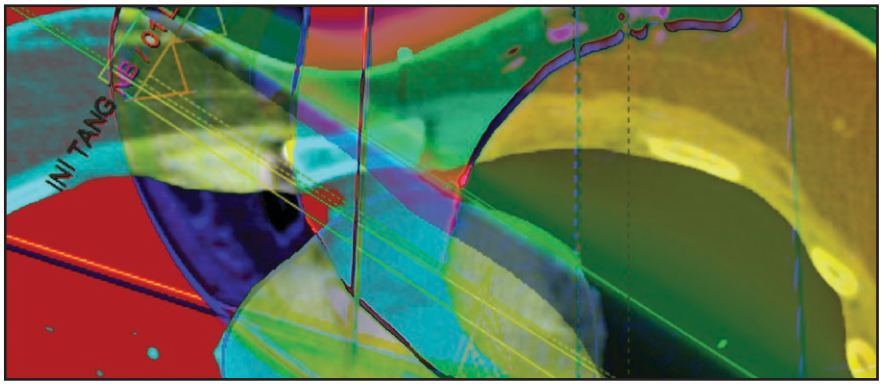

nodes, a group in whom the controversy about routine radiation has been particularly intractable, the difference between breast cancer mortality and survival was 7.9% (p = 0.01) and 3% (p = ns).

This 3% to 5% difference between breast cancer mortality and overall survival may, in large part, be due to an excess of cardiac disease caused by the radiation of that era of studies in the meta-analysis from 1964 to 1986.[1] In the Surveillance Epidemiology and End Results (SEER) database from 1973-1992, there was an excess rate of fatal myocardial infarction of 1% to 2% over the course of 8 to 18 years from treatment for patients receiving left-sided vs. right-sided adjuvant radiation.[2] A loss of 1% was also seen between the improvement in breast cancer mortality and overall survival in the postlumpectomy radiation setting from randomized prospective trials conducted between 1976-1999.[3] This greater difference of death from nonbreast cancer causes between the postmastectomy and postlumpectomy trials may be decreasing over decades due in part to technical improvements, but the difference may also be due to the greater use of regional node — specifically internal mammary node — radiation in the earlier postmastectomy trials. Radiation of the chest wall and internal mammary nodes (IMNs) has been specifically linked to coronary stenosis in distributions consistent with the radiation fields of conventional radiation.[4] For fear of late cardiac injury if IMNs were included for left-sided

breast cancer patients, a large prospective population-based cohort study of internal mammary node irradiation treated right-sided patients only.[5]

In a retrospective review of 2,168 women treated for breast cancer from 1958 to 2001, heart dose was estimated from idealized phantom measurements.[6] They found that the mean heart dose correlated with excess relative risk of coronary events by 7.4% per 100 cGy. In that period, the mean heart dose was estimated to be 6.6 Gy for women with tumors in the left breast. In a systematic review of 149 studies published during 2003 to 2013, the mean heart dose from left-sided breast radiation therapy was 5.4 Gy.[7] The lowest mean heart doses were from tangential radiation with breathing control (1.3 Gy) or proton radiation (0.5 Gy), and the highest inclusion of internal mammary lymph nodes (8 Gy). Aiming to reduce the mean dose is an important goal for modern radiation therapy in order to reduce ultimate late cardiac complications. In this way, the survival improvements associated with adjuvant radiation could be further improved if excess cardiac deaths could be eliminated altogether.

Forward Planning

Early whole-breast irradiation used photon beam 2D techniques consisting of opposed tangential beams of uniform radiation intensity across the field that could be modified with wedge compensators. The introduction of 3-dimensional computed tomography (3D CT) planning in the 1990s permitted the calculation of heart dose in a more precise manner than just observing the amount of the heart silhouette in a tangential portal film.[8] Early attempts to limit heart dose in a breast tangent would be adjusting the beam angle to avoid the heart or adding a block over the heart silhouette.[9] Forward planning then developed to optimize dose heterogeneity within the target by manually creating smaller fields using custom blocking or multileaf collimation within a larger tangent — what is known as a "field-in-field" technique.[10] In early experiences, such techniques of using beams of nonuniform fluence applied to a target structure were labeled as intensity-modulated radiation therapy (IMRT) but today are considered and reimbursed as 3D conformal radiation. Forward-planned tangential radiation has been shown to be superior to 2D tangential radiation using wedges in 3 prospective randomized trials for reducing desquamation, late skin telangeictasias and fibrosis.[11-13] The 3D conformal tangents with forward planning with custom blocking or predefined segments can decrease the heart dose[14,15] and normal tissue complication probability for late cardiac toxicity on average by 30%[16] compared to using simple wedged tangents.

Prone Positioning

Prone positioning may have advantages for some women with large or pendulous breasts, or left-sided breast cancers compared to traditional supine positioning. When supine, large- or pendulous-breasted women often have a large separation, or width, between the posterior entry and exit points of the tangential radiation field. This is a cause for large dose inhomogeneity that may only be partially overcome by advances in 3D conformal or IMRT. These women may also have large skin folds particularly in the inframammary region that increase acute dermatitis and risk for moist desquamation. For left-sided women, the lateral displacement of the breast in large women may require a deeper tangent for breast coverage that increases heart dose.

Prone positioning can reduce chest wall separation, deep skin folds, dose inhomogeneity, and heart dose for a large majority of breast cancer patients.[17,18] Prone is generally limited to treatment of the breast only, or breast and low axilla,[19] but full regional nodal coverage of the high axilla, supraclavicular and internal mammary nodes is generally not possible in the prone position. In addition, caution is needed during simulation for patient selection — judgment of the cardiac anatomy and possible breast tangent — because in a small minority of patients, prone positioning may increase heart dose. In a comparison study of 30 left-sided patients simulated both prone and supine, prone positioning reduced heart and left anterior descending (LAD) doses in 19 patients, increased it in 8 patients, and had no effect in 3 patients.[20] In a prospective study of 200 left-sided patients simulated both supine and prone, prone position was associated with an 85% reduction of in-field heart volumes compared to supine.[21] This did not reach significance in small-breasted women. A benefit was seen in 85% of patients to prone positioning for the heart volume in the radiation field, but supine position was better for 15%.

Intensity-modulated Radiation Therapy

IMRT describes an inverse planning technique in which beams of nonuniform fluence are created by optimizing coverage of a planning target volume (PTV). Much use of IMRT in adjuvant treatment of breast cancer has been using standard tangential beam arrangements. A benefit in dose homogeneity with inverse planned or hybrid IMRT techniques compared to forward-planned 3D conformal has been shown in some studies[22,23] but not all.[24] IMRT has been reported to reduce dose to heart compared to 3D in most studies[25-27] but not others.[28] There can be significant variation in patient anatomy so that there are overlapping ranges of heart dose for IMRT vs. 3D, and IMRT may be superior to 3D in heart dose for some patients but not all.[14] There may also be

Table 1. Summary of current studies comparing mean heart dose (cGy) with respiratory control (RC) vs. free breathing (FB)

Study	# of patients	FB	RC	p
Swanson, et al 2013[39]	87	423	254	< 0.001
Mast et al, 2013[27]	20	270/330	150/180*	< 0.01
Verhoeven, et al 2014[41]	17	350	160	< 0.0001
Comsa, et al 2014[44]	50	305/448	116/209†	< 0.001
Eldredge-Hindy, et al 2015[40]	86	270	90	< 0.001
Rochet, et al 2015[42]	35	250	90	< 0.0001
Tanguturi, et al 2015[43]	150	256	138	< 0.0001

*IMRT/3D; †2 fields / 3-4 fields

a tradeoff in reduced PTV coverage with IMRT that prioritizes cardiac sparing.[14,15] In some studies, an added benefit for IMRT is an overall reduced planning time and decreased dependence on dosimetrist experience compared to 3D conformal.[29,30]

ASTRO's Choosing Wisely campaign advocated against the routine use of IMRT to deliver whole-breast radiation therapy. The randomized Canadian multicenter study that showed reduced acute toxicity from tangential radiation with IMRT compared to 2D tangents did include patients treated with forward-planned or inverse-planned IMRT.11 However, the Cambridge Breast IMRT trial did not show a reduction in toxicity.31 The rates of IMRT for breast cancer increased dramatically from 2001 to 2011,32,33 and this increase in IMRT usage is associated with a markedly higher cost for adjuvant radiation.32 The Radiation Therapy Oncology Group trial 1005 was a phase III trial that created a database of CT plans for approximately 2,000 patients treated with whole-breast radiation from 2011 to 2014. The trial allowed field-in-field 3D conformal or IMRT as long as preset minimum constraints could be met. A subgroup analysis of differences in mean heart dose and late toxicity outcomes will be a useful prospective, although not randomized, comparison.

Certain patient subgroups may benefit from inverse planning IMRT compared to 3D conformal. This could be an option for some cases of challenging anatomy, such as large chest wall separation causing dose inhomogeneity; left-sided cases with a large amount of heart close to the chest wall or pectus excavatum; or where internal mammary node irradiation is needed. Inverse-planned IMRT has been shown to improve dosimetric coverage, homogeneity, and high doses received by the lung and heart for patients requiring internal mammary node irradiation compared to partly wide tangents or mixed-beam plans.[26] However, the tradeoff is that the addition of nontangential beams to IMRT increases the low-dose radiation to the heart and V5 dose.[34-38] IMRT should be considered and comparison plans created when 3D conformal forward planning is not able to achieve the initial desired dose goals.

Respiratory Control

There are several commercially available methods for respiratory control during radiation therapy for breast cancer. The purpose is to use an increase in lung volume and inferior displacement of the diaphragm to increase the distance between the heart and the breast/chest wall to reduce radiation dose. In one method, an active-breathing control (ABC) device is used for regulation of respiratory inspiratory volume. The other method relies on patient coaching for voluntary deep inspiration breath holding (DIBH) that is verified with either direct volume measurement or surface anatomy verification.

Studies comparing mean heart dose with free breathing vs. respiratory control are shown in Table 1. In one study, moderate DIBH with ABC in 87 of 99 (88%) patients was associated with a mean heart dose of 254 cGy compared to 423 cGy with free breathing (FB) ($p < 0.001$).[39] In a prospective study of ABC for left-sided breast cancer, 72% of enrolled patients were ultimately treated with ABC with inability to tolerate the procedure being the predominant cause for ineligibility.[40] The mean heart dose was reduced by ABC compared to FB by > 20% in 88% of patients, and the median mean heart dose was 270 cGy for FB compared with 90 cGy for ABC. Mast et al compared free breathing (FB) to DIBH plans with tangential 3D conformal and IMRT techniques.[27] For the heart and LAD-region, a significant dose reduction was found with DIBH

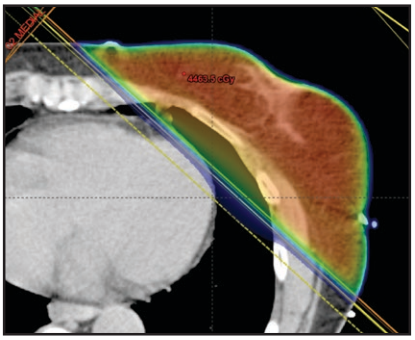

FIGURE 1. *Forward-planned field-in-field tangential radiation. The mean heart dose was 107 cGy, V5 1.6% and V20 0.1%.*

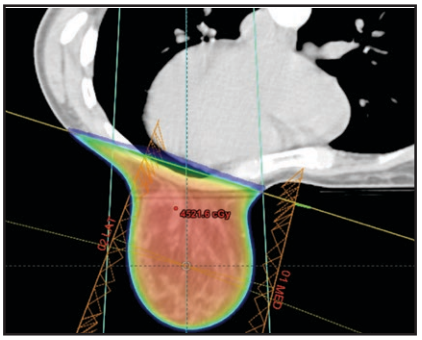

FIGURE 2. *Prone position with forward-planned field-in-field tangential radiation. The mean heart dose was 72 cGy, V5 0.1% and V20 0%.*

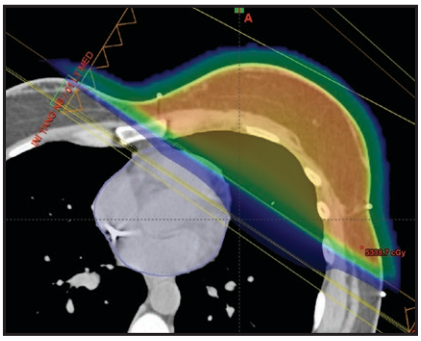

FIGURE 3. *Deep-inspiration breath holding with intensity-modulated radiation therapy for treatment of chest wall, flap reconstruction and internal mammary nodes. The mean heart dose was 302 cGy, V5 10% and V20 2.6%.*

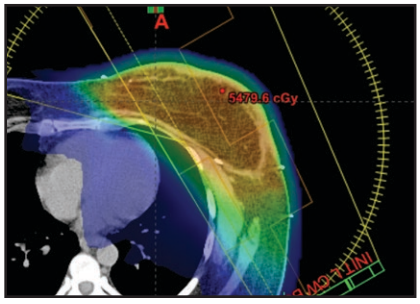

FIGURE 4. *Arc-based intensity-modulated radiation therapy for chest wall, flap reconstruction and internal mammary node treatment. Mean heart dose was 780 cGy, V5 70%, and V20 1.9%.*

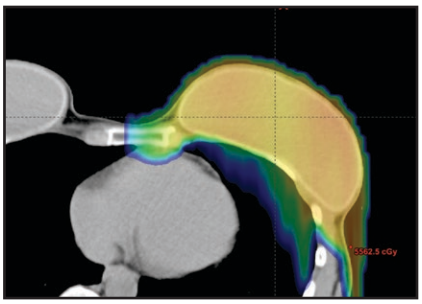

FIGURE 5. *Proton beam radiation for chest wall, implant reconstruction and internal mammary node treatment. The mean heart dose was 132 cGy, V5 5% and V20 2.7%.*

($p < 0.01$). The mean heart dose for 3D vs. IMRT in 20 patients was 180 cGy compared to 150 cGy in DIBH, and 330 cGy and 270 cGy in FB, respectively ($p = 0.01$). In a prospective study of 17 left-sided patients, supine position with DIBH significantly reduced the volume of the heart receiving 30 Gy, the mean heart dose, and mean LAD coronary artery dose compared to supine with FB and prone positioning.[41] In a study of 35 patients planned with FB or DIBH, mean dose for heart was 90 cGy vs. 250 cGy, ($p < 0.0001$)[42] and in 75% of patients there was felt to be a benefit to DIBH. In a prospective registry of 150 patients, in which patients were selected for FB (38) or DIBH (110) at physician discretion, DIBH plans were associated with a mean heart dose of 137.6 cGy compared to 255.7 cGy with FB ($p < 0.0001$).[43] On multivariate analysis, younger age, higher BMI, and larger change in lung volume between scans were associated with a greater change in mean heart dose between techniques.

The improvement of cardiac dose with respiratory control now seems well settled. These techniques have been shown to be clinically practical and have no significant impact on patient treatment time and throughput.[43,44] Whether this will lead to clinically evident reduction in cardiac events is unknown. In one prospective study of ABC vs. FB, there was decreased dose to the left ventricle but no change in myocardial perfusion changes 6 months after treatment.[45] Further research is also needed to determine how best to select patients. The IMN chain may be particularly sensitive to changes in position and dose coverage with respiratory motion,[46,47] and ABC has been shown to improve heart dose, particularly in the setting of IMN irradiation.[48] All patients with need for internal mammary node radiation would seem good candidates for respiratory control. However, treating all left-sided patients who may tolerate it may also lead to overutilization of resources in a significant minority of patients who may be appropriately treated with FB. Further research is needed to determine whether physicians can appropriately select patients at the time of simulation on a case-by-case basis,[43] or whether objective measures may predict accurately who will benefit most from respiratory control.[42]

Proton Beam Radiation

Proton radiation therapy may have dosimetric advantages compared to photons due to the property of the positively charged proton depositing the bulk of its energy in tissue in a finite range, or Bragg peak, with essentially no residual radiation beyond this depth. In clinical application to breast cancer, this could theoretically allow full breast or nodal target coverage within the Bragg peak with no dose to heart and lung posteriorly beyond the Bragg peak. Dosimetric studies have demonstrated the superiority of proton therapy in the postmastectomy radiation therapy setting with respect to low doses to organs-at-

risk while maintaining superior target coverage, particularly regional nodes.[49,50] In a report of 12 patients treated in a prospective clinical trial, 11 left-sided patients achieved an average mean heart dose of 44 cGy, and had 75% grade 2 acute skin toxicity (no grade 3) and only 1 grade 3 toxicity (fatigue).[51] In a report of 30 patients, most treated to internal mammary nodes, the mean heart dose achieved was 1 Gy for left-sided patients.[52] There was grade 2 dermatitis in 71%, moist desquamation in 29%, grade 2 esophagitis in 29%, and 1 grade 3 reconstructive complication. Proton therapy may reduce risk for cardiac toxicity of radiation compared to photon radiation by not only reducing mean heart dose, but dose to the critical coronary artery structures on the heart's surface.[53] In one study, a scanning proton technique for left-sided irradiation was associated with lower minimum, maximum, and dose to 0.2 cc of the LAD coronary artery than the best possible photon beam radiation technique (IMRT with DIBH).[54]

In practice, there are several limitations of protons. Coverage of the width of the breast and other targets in the patient requires creation of a wider spread-out Bragg peak (SOBP) that increases skin dose. Proton therapy distal range has intrinsic uncertainty that can lead to overshooting or undershooting the posterior target edge, and greater sensitivity to patient or organ motion. The potential advantage to protons is thought to be physical and not biological — protons are estimated to have a relative biologic effectiveness (RBE) of 1.1 compared to photons, which is taken into account for dose calculations by treatment planning systems. In actuality, there may be variation of proton linear energy transfer along the track length causing lower RBE in the SOBP and higher RBE at the end track that could potentially lower tumor control or increase complication probabilities compared to current planning system estimates.[55] Current methods of proton techniques such as double scattering have limitations in field size, matching, and dose shaping. More advanced techniques like pencil-beam scanning and intensity-modulated proton therapy could potentially treat some of the most challenging postmastectomy radiation therapy cases, due to breast reconstruction, internal mammary node coverage, or lower skin dose, but may not be clinically deliverable with current equipment.[53,56]

The RADCOMP breast proton vs. photon study [NCT02603341] is being conducted on the hypothesis that proton therapy for locally advanced breast cancer reduces major cardiovascular events, is noninferior in cancer control, and improves health-related quality of life compared to photon therapy. Participants in the trial will be randomized to either proton or photon therapy. The inclusion criteria is broad: mastectomy with or without reconstruction or lumpectomy, any type of axillary surgery, any adjuvant or neoadjuvant chemotherapy, and left- or right-sided breast cancer as long as internal mammary nodes are intended to be treated.

Conclusion

This report has reviewed the wide variety of techniques for adjuvant breast or chest wall radiation therapy for minimizing heart dose. Field-in-field 3D conformal (forward planning) may be seen as the current minimum standard for breast patients today (Figure 1). In many cases, greater cardiac sparing can be achieved with prone positioning (Figure 2), DIBH (Figure 3), IMRT with 2 or more fixed angles (Figure 3), IMRT with arcs (Figure 4), or protons (Figure 5). One challenge to the practicing clinician is acquiring the equipment and experience to have one or more of the options available for their patients, which is subject to constraints on department staff and resources. In a large radiation therapy department with all of these potential options, or a region where referral to specialty centers is possible, another challenge is developing the experience to select patients a priori or at the time of simulation for one or the other modality. Matching the best approach for each patient's unique target needs and anatomy is necessary instead of a one-size-fits-all approach to cardiac avoidance.

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Accelerated partial-breast irradiation: An emerging standard of care

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Breast-conserving therapy, consisting of breast-conserving surgery (BCS) followed by adjuvant radiation therapy, represents a mainstay in the treatment of early stage breast cancer.[1-3] Traditionally, radiation therapy following BCS has consisted of standard whole-breast irradiation (SWBI) followed by a tumor bed boost with a 5-7 week duration of treatment. However, the length of treatment is one factor associated with noncompliance with adjuvant radiation therapy following BCS.[4,5] To reduce treatment duration, decrease healthcare resource utilization, and potentially limit toxicity, alternatives to SWBI have been developed including accelerated whole-breast irradiation (AWBI) and accelerated partial-breast irradiation (APBI). AWBI represents a standard of care treatment option based on 4 randomized trials that have demonstrated comparable clinical outcomes and toxicity as compared to SWBI with long-term follow-up.[6-9] APBI can be delivered with anmultiple techniques including interstitial brachytherapy, applicator brachytherapy, and external-beam techniques. With the publication of 7 randomized trials, a large amount of data supports APBI as a standard-of-care treatment option following BCS in appropriately selected patients; however, data demonstrates that APBI remains underutilized despite the potential benefits for patients.[10] Therefore, the purpose of this review is to evaluate data supporting APBI and examine questions clinicians face regarding APBI.

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Randomized Trials

At this time, 7 randomized trials comparing APBI with SWBI and/or AWBI have been published in abstract or manuscript form with five (National Institute of Oncology-Hungary, GEC-ESTRO, University of Florence, IMPORT LOW, and Hospital de la Esperanza) publishing clinical outcomes while two (RAPID, NSABP B-39) presented only toxicity data (Table 1).

Interstitial brachytherapy represents the oldest modern APBI technique and, as such, the randomized trial with the longest follow-up utilized this technique. The National Institute of Oncology in Hungary performed a randomized trial of 258 women with early stage breast cancer (T1N0-1mi, Grade 1-2, nonlobular, negative margins), with patients receiving either SWBI (50 Gy/25 fractions) or PBI (interstitial 36.4 Gy/7 fractions or electrons 50 Gy/25 fractions). With 10-year follow-up, no difference in the rates of local recurrence were noted (5.1% SWBI vs. 5.9% PBI) with improved cosmesis for partial-breast patients (81% vs. 63% excellent/good cosmesis).[11] This trial was followed by the GEC-ESTRO trial, which was a multi-institutional randomized noninferiority trial comparing SWBI and APBI delivered with interstitial brachytherapy (high dose or pulsed dose rate). A total of 1,184 patients (pTis, pT1-2a ($\leq$ 3 cm), pN0/N1mi, margins $\geq$ 2 mm, age $\geq$ 40) were enrolled and, at 5 years, no difference in rates of local recurrence (0.9% SWBI vs. 1.4% APBI) were noted. Additionally, APBI was associated with a trend for improved late grade 2-3 skin toxicity and breast pain.[12]

With respect to external-beam APBI, several randomized trials have been published. The Randomized Trial of Accelerated Partial Breast Irradiation using Three-Dimensional Conformal External Beam Radiation Therapy (RAPID) trial randomized 2,135 patients (tumor < 3 cm, node negative, nonlobular, margins negative, age > 40) to SWBI/AWBI or APBI delivered with 3-dimensional conformal radiation therapy (3D-CRT) (38.5

Table 1. Randomized studies evaluating accelerated partial-breast irradiation

	Years of accrual	APBI technique	Number of patients	Follow-up (months)	Clinical outcomes	Toxicity
National Institute of Oncology	1998-2004	HDR multi-catheter interstitial BT (n=88) and limited electron field (n=40)	258	122	Local recurrence: 5.9% (PBI) vs. 5.1% (WBI) 10-y survival: 79.7% (PBI) vs. 82.1% (WBI)	Improved excellent/good cosmetic outcome with PBI (81% vs.63%), HDR patients had improved cosmetic compared to WBI with 6-9 MV photons (85% vs. 67%)
GEC-ESTRO	2004-2009	Multicatheter interstitial BT (HDR/PDR)	1,184	78	Local recurrence 1.4% (APBI) vs 0.9% (WBI) 5-y Survival: 97.3% (APBI) vs. 95.6% (WBI)	Trend for reduced late grade 2-3 skin toxicity with APBI (3.2% vs. 5.7%, p=0.08)
Barcelona	Not specified	3D-CRT	102	60	Local recurrence: 0% (PBI) vs. 0% (WBI)	APBI reduced acute skin toxicity, similar late toxicity and cosmetic outcomes
University of Florence	2005-2013	IMRT	520	60	Local recurrence: 1.5% (PBI) vs. 1.5% (WBI) 5-y survival: 99.4% (APBI) vs. 96.6% (WBI)	APBI fewer acute & late skin toxicity compared to WBI (p = 0.0001, p = 0.004, respectively); APBI improved physician-rated cosmesis (p = 0.05)
IMPORT LOW	2007-2010	IMRT	2,018	68	Local recurrence: 0.2% (SIB) vs. 0.5% (APBI) vs. 1.1% (WBI)	Reduced change in breast appearance with APBI compared to AWBI
Toxicity Only						
RAPID	2006-2011	3D-CRT	2,135	36	N/A	Grade 1 and 2 toxicities increased with APBI (p < 0.001), worse cosmetic outcomes with APBI, grade 3 toxicities rare for both arms
NSABP B-39	2005-2013	3D-CRT*	1,386	41	N/A	Fibrosis: grade 2 ≤ 12%, grade 3 ≤ 3%, grade 4-5 0%

APBI = accelerated partial breast irradiation, AWBI= accelerated whole-breast irradiation, HDR = high dose rate, PBI = partial-breast irradiation, WBI= whole-breast irradiation, GEC-ESTRO = Groupe Europeen de Curietherapie European Society for Radiotherapy and Oncology, PDR = pulsed dose rate, 3D-CRT = 3-dimensional conformal radiotherapy, IMRT = intensity-modulated radiation therapy, SIB = simultaneous integrated boost
*cohort presented

Gy/10 fractions, twice daily). Interim analysis demonstrated worse cosmetic outcomes with APBI as well as rates of grade 1/2 toxicity.[13] However, these findings are inconsistent with an analysis of the NSABP B39 3D-CRT cohort, which demonstrated 0% Grade 4/5 toxicity and < 3% Grade 3 toxicity, and a smaller randomized study from Barcelona that demonstrated reduced acute toxicity with 3D-CRT APBI.[14,15] More recently, a randomized trial of 520 patients (tumor < 2.5 cm, margins > 5 mm, age > 40) from the University of Florence compared SWBI with APBI, delivered with IMRT (30 Gy/5 fractions, every other day). At 5 years, no difference in the rates of local recurrence were noted (1.5% SWBI vs.

Table 2a. Randomized studies evaluating 3-dimensional conformal radiotherapy accelerated partial-breast irradiation

	Years of accrual	APBI technique	Number of patients	Follow-up (months)	Clinical outcomes	Toxicity
RAPID	2006-2011	Randomized	2,135	36	N/A	Grade 1 and 2 toxicities increased with APBI ($p < 0.001$), worse cosmetic outcomes with APBI, grade 3 toxicity rare for both arms
NSABP B-39	2005-2013	Randomized	1,386	41	N/A	Fibrosis: grade 2 ≤ 12%, grade 3 ≤ 3%, grade 4-5 0%
Barcelona	Not specified	Randomized	102	60	Local recurrence: 0% (PBI) vs. 0% (WBI)	APBI reduced acute skin toxicity, similar late toxicity and cosmetic outcomes

APBI = accelerated partial-breast irradiation

Table 2b. Nonrandomized studies evaluating 3-dimensional conformal radiotherapy accelerated partial-breast irradiation

	Years of accrual	APBI technique	Number of patients	Follow-up (months)	Clinical outcomes	Toxicity
RTOG 0319	2003-2004	Phase II	52	63	6% ipsilateral breast failure	82% excellent/good cosmesis at 1 year, 64% at 3 years; adverse events: grade 1 = 36.5%, grade 2 = 50%, grade 3 = 5.8%
William Beaumont Hospital	2000-2011	Single institution-retrospective	192	56	Local recurrence: 0% Overall survival: 92%	81% excellent/good cosmesis, 7.5% grade 3 fibrosis
University of Michigan	2004-2007	Prospective	32	60	Local Recurrence: 3%	Fibrosis: grade 2 = 3.3%, grade 3 = 0%; excellent/good cosmesis 73%
Tufts University	2004-2007	Single institution-retrospective	60	15	—	Subcutaneous fibrosis: grade 2-4 = 25%, grade 3-4 = 8.3%; excellent/good cosmesis 82%

1.5% APBI) with improved cosmetic outcomes as well as reduced acute/chronic toxicity with APBI.[16] Similarly, the IMPORT LOW trial has been presented as an abstract; the trial compared AWBI (40 Gy/15 fractions) with APBI (40 Gy/15 fractions) and AWBI with a boost to the tumor bed (36 Gy/15 fractions whole breast, 40 Gy/15 fractions partial breast). The trial enrolled 2,018 patients (tumor < 3 cm, N0-1, margins > 2 mm, age ≥ 50) and found no difference in rates of local recurrence at 5 years (1.1% AWBI vs. 0.5% APBI vs. 0.2% simultaneous integrated boost). Additionally, APBI was associated with decreased breast appearance changes as compared to AWBI.[17] Taken together, several key conclusions can be drawn: 1) randomized data supports that there is no difference in local control with APBI as compared to SWBI, 2) randomized trials with multiple techniques have demonstrated consistent findings, and 3) toxicity data supports no difference in outcomes between interstitial APBI and SWBI, while data with external-beam

APBI favors IMRT or daily radiation compared to the 3D-CRT technique. At this time, there is limited ability to directly compare different APBI techniques, as the trials above used a single APBI technique (with the exception of the National Institute of Oncology trial). However, with the anticipated publication of mature outcomes from NSABP B-39, clinicians should have data to directly compare clinical outcomes and toxicity profiles between techniques.

Clinical Questions

What is the data supporting applicator-based brachytherapy?

The initial randomized trial evaluating APBI primarily used interstitial brachytherapy, a technically challenging modality used in a limited number of centers. However, with the advent of the single-entry balloon applicator, brachytherapy-based APBI became available and its use increased.[10,18] The MammoSite Registry included 1,449 cases treated with single-lumen applicators; with 5-year follow-up, the rate of ipsilateral breast tumor recurrence was 3.8% with 91% of patients having excellent/good cosmesis.[19,20] These findings are consistent with smaller applicator-based brachytherapy series and confirm excellent clinical outcomes with the technique.[21,22] Additionally, since the initial studies evaluating single-lumen applicators, multilumen and strut applicators have been developed, which have been shown to improve target coverage and reduce dose to organs at risk, potentially further improving outcomes.[23,24] It should be noted that interstitial and applicator-based brachytherapy use slightly different expansions, with applicator brachytherapy traditionally using a 1-cm expansion around the cavity, compared to 2 cm with interstitial brachytherapy.[11,12,25] More data is expected as applicator-based brachytherapy was included on NSABP B-39; in the interim, applicator-brachytherapy remains a standard APBI option for appropriate patients, with data supporting excellent clinical and toxicity outcomes.

Are there toxicity-related concerns regarding brachytherapy-based APBI?

Over the past few years, several observational studies demonstrated that while the incidence of brachytherapy increased, its use was associated with higher rates of subsequent mastectomy (reasons unclear), as well as infectious and noninfectious toxicity compared to WBI.[26, 27] However, despite the large number of patients in these studies, significant limitations exist including the retrospective nature, short follow-up, use of billing codes as surrogates for clinical outcomes, and concerns regarding reproducibility.[28,29] Additionally, the years evaluated occurred before the widespread use of multi-lumen applicators and included only patients 66 years or older. It is important to note that data from randomized and prospective studies have failed to validate these concerns and brachytherapy-based APBI remains a mainstay approach as noted by evidence-based guidelines from multiple societies.[30,31]

What external-beam approaches should be used?

Clinicians can consider several external-beam APBI approaches. The initial modern external technique was described by Baglan et al and delivered a dose of 38.5 Gy in 10 fractions twice daily using noncoplanar beams to a tumor volume that included a 1.5-cm clinical target volume expansion along with an additional 1 cm for internal target volume and planning target volume.[33] This technique was found to have excellent clinical outcomes and toxicity profiles in the William Beaumont Hospital experience.[32] Unfortunately, concerns regarding the toxicity profile with this technique have emerged, including outcomes from the RAPID trial, RTOG 0319 as well as data from Tufts University and the University of Michigan.[13,34-36] However, analysis of the 3D-CRT cohort from NSABP B39 and data from a Spanish randomized trial have failed to confirm these findings; as such, this remains an area of further study and is summarized in Tables 2a and b.[14,15] In the interim, alternatives to this technique have emerged. The first is the use of intensity-modulated radiation therapy (IMRT). This technique was evaluated by Lei et al and found to have low rates of local recurrence, 88%-90% excellent/good cosmesis, and low rates of toxicity using the same 38.5 Gy/10 fraction regimen.[37] An alternative IMRT approach used by Livi et al featured an every-other-day approach (30 Gy/5 fractions), with 1-cm CTV, and a 1-cm PTV expansion. Data from the randomized study demonstrated reduced toxicity with APBI IMRT compared to SWBI, and improved cosmesis.[16] Alternatively, instead of switching external beam techniques, one can switch the dose and fractionation from 38.5 Gy/10 fractions delivered twice daily to daily regimens such as the Florence regimen or a more protracted course of 40 Gy/15 fractions, which was utilized in the IMPORT LOW trial.[16,17] At this time, external APBI should still be considered for patients; while further data on the 3D-CRT technique will emerge from NSABP B-39/RTOG 0413, physicians should consider IMRT or daily fractionation to minimize toxicity risk and improve cosmetic outcomes.

What is the data surrounding proton therapy to deliver APBI?

Proton therapy represents an alternative external-beam technique, compared to 3D-CRT or IMRT, which use photons. Initial studies evaluating proton APBI demonstrated high rates of skin toxicity as well as subacute toxicity;[38] long-term follow-up confirmed these findings with increased rates of late toxicity and poor cosmetic outcomes.[39]

However, the technique has been refined, and phase II data from Korea (30 Gy/5 fractions) has demonstrated excellent clinical outcomes and low toxicity rates, although cosmetic outcomes appear to be lower than those seen with traditional APBI techniques and follow-up remains short.[40] Similarly, data from Loma Linda Medical Center included 100 patients and, with 5-year follow up, toxicity rates were low, with 90% of patients having excellent/good cosmetic outcomes.[41] Although recent data is promising and studies have shown proton APBI to be comparable in cost to some techniques and less expensive than others, the limited number of patients treated and lack of long-term outcomes suggest that proton APBI should continue to be used only on-protocol.[42]

How does intraoperative radiation therapy fit in the context of APBI?

Intraoperative radiation therapy (IORT) is a form of partial-breast irradiation in that it treats a target smaller than the whole breast, delivering treatment to the lumpectomy cavity. However, despite the promise of IORT as a way to complete local therapy in one visit, it should not be considered a form of APBI and the data available does not support IORT to be used off protocol at this time.[43] IORT differs from APBI with respect to 1) dose delivery to a margin beyond the lumpectomy cavity, 2) failure to have consistent image-guidance protocols, and 3) confirmation of dose with formal treatment planning.[44,45] Additionally, two randomized studies comparing SWBI and IORT have found increased rates of local recurrence with IORT with short follow-up, something not seen in the randomized APBI trials. The ELIOT trial used intraoperative electrons following BCS and randomized 1,305 patients (tumor $\leq$ 2.5 cm, age 48-75) to SWBI or IORT. With 5-year follow-up, the study found increased rates of local recurrence with IORT (4.4% vs. 0.4%, $p < 0.0001$); a unique feature of this trial was that patients did not receive remedial WBI.[46] In contrast, the TARGIT trial randomized 3,451 patients (invasive ductal, age $\geq$ 45) to SWBI or IORT with remedial WBI for some IORT patients (15% of all patients; 22% pre-pathology, 4% post-pathology). However, the study also demonstrated increased rates of local recurrence with IORT (3.3% vs. 1.3%, $p = 0.04$), although they were within the allowed noninferiority threshold except for the post-pathology cohort (5.4% vs. 1.7%, $p = 0.07$).[47] Significant controversy regarding the methodology of the TARGIT trial and the role of IORT exists; however, given the data, IORT should not be recommended off-protocol at this time, which is consistent with updated American Society for Radiation Oncology (ASTRO) guidelines put forth for review.[43,48-50]

What are the cost concerns?

With an increased focus on value-based healthcare, it is important to consider the costs associated with adjuvant radiation therapy. APBI 3D-CRT represents an APBI technique that is less costly than SWBI or AWBI and would be expected to have comparable cost to AWBI when using a daily regimen over 15 days similar to IMPORT LOW.[42,51] While brachytherapy-based APBI is more costly (based on reimbursement) than WBI or AWBI delivered with 3D-CRT, it has been found to be cost-effective when accounting for indirect costs and outcomes, and is less expensive than SWBI delivered with IMRT.[52] However, a recent study using time-driven, activity-based costing found increased costs associated with brachytherapy-based APBI.[53]

With respect to other APBI techniques, while proton APBI remains investigational, recent cost studies have demonstrated comparable cost for protons compared to 3D-CRT SWBI and alternative APBI techniques (brachytherapy), while finding protons more expensive than 3D-CRT AWBI and 3D-CRT APBI.[42] IORT has been heralded as a means to reduce the cost of adjuvant radiotherapy;[54] however, when factoring in the costs of supplemental WBI, increased OR time, and management of recurrences, SWBI, AWBI, and APBI are considered cost-effective.[55] Moving forward, to properly evaluate APBI cost-effectiveness, studies must move beyond absolute reimbursement and use techniques that incorporate patient costs associated with treatment duration, as well as the impact on quality of life and toxicity profiles.

What about patient selection?

One of the greatest challenges facing clinicians is determining which patients are appropriate for APBI. One way of assessing eligibility is to use the inclusion criteria from published randomized trials to guide selection. However, concerns exist, as data that evaluates outcomes for subsets within these trials is limited. Additionally, several societies have released consensus guidelines for treatment off-protocol, including ASTRO, the American Brachytherapy Society, Groupe Europeen de Curiethrapie-European Society of Therapeutic Radiology and Oncology, and the American Society of Breast Surgeons.[29,30,56,57] As data continues to emerge, these guidelines will evolve; however, the current ASTRO groupings have failed to correlate with risk of local recurrence. As such, further study is required.[58,59] At this time, ideal candidates for APBI include those 50 years or older with T1-2N0 tumors ($\leq$ 3 cm)/DCIS ($\leq$ 3 cm) and negative surgical margins without lymphovascular space invasion.

Where does APBI stand as a treatment option?

APBI is a standard-of-care treatment option for appropriately selected patients with early stage breast cancer. The basis of this recommendation is the publication of 5 randomized clinical tri-

als demonstrating no difference in rates of local recurrence compared to SWBI or AWBI with mature follow-up. Similarly, randomized data has demonstrated acceptable toxicity profiles for interstitial and IMRT APBI, while prospective data has demonstrated the safety and efficacy of applicator APBI. While the data has limitations, it justifies routine use of APBI in appropriate patients, with future data expected to refine treatment techniques and selection criteria rather than focus on APBI validation.

Future Directions

APBI continues to evolve as a technique with novel strategies to reduce treatment duration. Data from William Beaumont Hospital evaluated the feasibility of applicator-based APBI delivered in 2 days (28 Gy/4 fractions); with 4-year follow-up, no local recurrences were noted, with 98% of patients demonstrating excellent/good cosmesis, and 3 rib fractures noted in a cohort of 45 patients.[60] This study was performed using single-lumen applicators, and additional studies (eg, the TRIUMPH trial) are evaluating 2-day fractionation with multilumen and strut applicators.[61] Additionally, studies are investigating intraoperative-like, single-fraction APBI, providing the convenience of IORT with a technique that is image-guided, covers appropriate target depth, and allows for pathologic confirmation prior to treatment.[62]

Conclusions

With the publication of 7 randomized trials and availability of long-term outcomes, APBI represents a standard-of-care treatment approach following breast-conserving surgery. Patients eligible for SWBI and AWBI should be considered for APBI in light of significant overlap in eligibility criteria. Studies are underway to further shorten the treatment duration of APBI, thereby reducing the burden of adjuvant treatment for women with early stage breast cancer.

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Radiation therapy, including internal mammary nodal irradiation, and heart failure in patients receiving concurrent treatment with trastuzumab

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Abstract

The impact of radiation therapy (RT), including internal mammary nodal (IMN) RT on cardiac function in patients receiving concurrent treatment with trastuzumab, was studied.

Patients and Methods: Thirty-seven patients with stage I–III human epidermal growth factor-2 (HER2)–positive breast cancer treated with trastuzumab with or without concurrent RT met inclusion criteria. Changes in left ventricular ejection fraction (LVEF) were measured using multigated acquisition scans. The primary endpoint was heart failure (HF), defined as a ≥ 16% decrease in LVEF from baseline or a ≥ 10% decrease of baseline LVEF if this fell below 50%.

Results: HF incidence among the entire group of patients treated with trastuzumab was 24.3%. Of these HF cases, 55.6% were reversible within 1 year of trastuzumab initiation. Of those receiving RT, 28.1% had HF; of the group who did not receive RT, none had HF. Of patients treated with left-sided RT, 26.7% developed HF compared with 27.8% treated with right-sided RT. Of patients treated with IMN RT, 22.2% had HF compared to 30.4% who did not receive IMN RT. Eighty-nine percent of patients who developed HF received anthracycline-based chemotherapy compared to 54% who developed HF without anthracyclines.

Conclusion: Concurrent RT and trastuzumab administration was not found to significantly increase the risk of HF. No significant differences in incidence of HF by tumor laterality or IMN RT were noted. Age, race, and comorbidities did not correlate with increased HF risk; however, there was a strong trend toward an increasing risk of HF among patients receiving anthracycline-based chemotherapy.

Human epidermal growth factor receptor-2 (HER2) overexpression occurs in approximately 25% to 30% of all breast cancers and is associated with aggressive tumor growth and poor treatment outcomes. The development of trastuzumab, a recombinant monoclonal antibody that targets the extracellular domain of the HER2/neu receptor, has dramatically improved outcomes for this subset of breast cancer patients.[1] With the use of trastuzumab, outcomes are similar to those seen in patients with HER2-negative disease.[2-4]

The most prominent adverse effect of trastuzumab is cardiac toxicity, with up to 25% of patients developing trastuzumab-mediated cardiomyopathy, defined as a significant decline in left ventricular ejection fraction (LVEF). Accompanying signs and symptoms of congestive heart failure (CHF) in certain instances necessitate discontinuation of the drug.[5] Although the mechanisms by which trastuzumab induces cardiomyopathy are unknown, its effects on cardiac function tend to be reversible.[6]

In a similar fashion, radiation therapy (RT) has been shown to significantly reduce disease recurrence in early and locally advanced disease. This increase in local control has also improved overall survival.[7] Although the cardiotoxic effects of RT have been well-documented, the majority of these effects were

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Table 1. Characteristics of Patients Meeting Criteria for Heart Failure

Patient number	Time of HF[1] after initiation of trastuzumab (months)	Tumor laterality	IMN RT[2] (yes/ no)	HF[1] reversible within 12 months	Anthracyclines
Patient 1	3	Right	No	Yes	Yes
Patient 2	6	Left	Yes	Yes	Yes
Patient 3	6	Left	No	No*	Yes
Patient 4	6	Left	No	Yes	Yes
Patient 5	6	Right	No	No	Yes
Patient 6	6	Right	No	No	No
Patient 7	9	Right	No	Yes	Yes
Patient 8	9	Right	Yes	Yes	Yes
Patient 9	12	Left	No	No	Yes

[1]HF = heart failure. [2]IMN RT = internal mammary nodal radiation therapy. *Patient developed symptomatic HF requiring inpatient hospitalization.

documented decades ago in an era of older techniques now largely obsolete.[8]

The mechanisms by which cardiac damage occurs following radiation are not fully understood. Current theories propose that high doses of radiation received by small volumes of the heart and coronary vessels induce atherosclerosis, predisposing patients to coronary events. In contrast, low-dose exposure to the entire heart is believed to cause microvascular damage and fibrosis, precipitating CHF.[9] In a recent large national longitudinal study, Darby et al suggested that there may be no safe threshold below which damage is averted and that every 1 Gy increase in mean cardiac dose is associated with a 7.4% relative increase in the rate of major coronary events.[10]

Two recent major cooperative group studies suggest a substantial benefit to nodal irradiation that includes treatment of the internal mammary nodal (IMN) chain.[11,12] Such data will likely increase the use of IMN RT, with a resultant increase in mean heart RT dose from 2-4 Gy to 10 Gy.[13] This study was designed to examine in greater detail the techniques of RT used in a HER2-targeted subset of patients treated at a single institution, specifically examining the impact on cardiac function of concurrent treatment with RT and the known cardiotoxic systemic agent trastuzumab.

Patients and Methods

All breast cancer patients treated with trastuzumab with curative intent at the University of Maryland Marlene and Stewart Greenebaum Cancer Center between January 2000 and June 2011 were reviewed. This retrospective review was approved by the University of Maryland Institutional Review Board. During this time frame, patients were uniformly monitored for cardiotoxicity using multigated acquisition (MUGA) scans by a single medical oncologist. Each patient's LVEF, as reported by the MUGA scan, was measured prior to initiation of treatment with trastuzumab. Subsequent MUGA scans occurred at 3, 6, 9, and 12 months after initiation of trastuzumab.

To be included in this study, patients must have been: (1) diagnosed with HER2-positive (by immunohistochemistry or by fluorescence in situ hybridization) breast cancer; (2) diagnosed with stage I, II, or III disease; (3) treated with curative intent; (4) without treatment with thoracic RT previously; and (5) recommended for and received trastuzumab alone or in concurrence with RT at the University of Maryland Marlene and Stewart Greenebaum Cancer Center. Trastuzumab was administered at an 8 mg/kg loading dose followed by 6 mg/kg every 3 weeks for 16 or 17 doses or at a 4 mg/kg loading dose followed by 2 mg/kg weekly for 52 doses. The trastuzumab treatment regimen was selected according to the medical oncologist's preference. Patients with metastatic disease were purposely excluded.

The primary endpoint was heart failure (HF), defined as a ≥ 16% decrease in LVEF from baseline or a ≥ 10% decrease from baseline LVEF if falling below 50%. This definition is consistent with the criteria for discontinuation of trastuzumab from the prescriber manual.[14] To determine whether the dose of radiation to the heart contributed to HF, tumor laterality (ie, right- vs. left-sided RT) and employment of IMN RT were selected as statistical parameters. Cardiac RT dose is, of course, regularly higher for women with left-sided cancers, with the highest doses experienced when the IMN chain is targeted.[15] Data were also collected on each patient's age, race, tumor type, tumor grade, stage (TNM), chemotherapy regimen, and history of comorbidities (including diabetes melli-

Table 2. Patients with Additional Risk Factors in the Heart Failure and Nonheart Failure Groups

Characteristic	HF[1] (n = 9)	Non-HF[1] (n = 28)	P value	Total no. of patients
Age (y)	Mean = 54	Mean = 60	—	37 (Range: 39-75)
African-American	6 (67%)	23 (82%)	0.327	29
Diabetes mellitus	1 (11%)	4 (17%)	0.810	5
Hypertension	5 (56%)	17 (61%)	0.787	22
Hyperlipidemia	2 (22%)	7 (25%)	0.865	9
Smoker	4 (44%)	9 (32%)	0.502	13
Coronary artery disease	1 (11%)	1 (4%)	0.384	2
Anthracyline-based chemotherapy	8 (89%)	15 (54%)	0.057	23

[1]HF = heart failure

tus, hypertension, hyperlipidemia, coronary artery disease, and smoking).

Incidences of HF in the RT vs. no RT group, left- vs. right-sided RT, IMN vs. no IMN RT, and left- vs. right-sided IMN RT were assessed using the *Z*-test with statistical significance threshold of $P \leq 0.05$ in a 2-tailed analysis. Patients were also stratified by whether or not they were subsequently diagnosed with HF. Baseline characteristics were compared between the HF vs. no HF group using the *Z*-test. Patients meeting criteria for HF were considered to have reversible HF if their LVEF recovered following initial decrease below the predetermined thresholds.

Data were also collected on each patient to determine whether a major coronary event occurred during a median follow-up period of 5 years after treatment with RT. A major coronary event was defined per Darby et al as the occurrence of a myocardial infarction, coronary revascularization, or death from ischemic heart disease.[10]

Thirty-seven women with stage I–III breast cancer met the inclusion criteria (see Appendix Table A1 for patient characteristics). Of these patients, 32 were treated concurrently with RT, 15 patients were treated to the left, and 18 to the right. IMNs were targeted in 9 patients; 5 patients of whom received left-sided RT, and 4 of whom received right-sided RT. Five patients were treated with trastuzumab alone.

Results

A total of 130 radionuclide ventriculograms were performed during the study period. All patients underwent baseline imaging, 19 patients underwent imaging at 3 months following treatment, 28 at 6 months, 26 at 9 months, and 20 at 12 months. Four patients underwent MUGA scans at all five time points.

Based on LVEF as determined by MUGA scans, 9 patients met the criteria for HF (Table 1). All of these patients were treated concurrently with RT. Five of the 9 HF cases were reversible, ie, a MUGA scan acquired following the initial scan in which HF was detected but within 12 months after the start of trastuzumab, showed recovery of cardiac function above threshold. The remaining 4 patients who met criteria for HF did not achieve recovery of function above threshold within the 12-month period after initiation of treatment with trastuzumab. One of the 4 patients developed symptomatic HF requiring discontinuation of treatment with trastuzumab and inpatient hospitalization. Prior to ending treatment, the patient received a lumpectomy and 6 cycles of trastuzumab.

Twenty-eight percent of the patients (9/32) treated with RT developed HF; none of the 5 patients who did not undergo RT developed HF. Twenty-six percent of patients (4/15) who received left-sided RT developed HF compared to 28% of patients (5/18) who received right-sided RT. Twenty-two percent of patients (2/9) who had IMN RT developed HF compared to 30% of patients (7/23) who did not have IMN RT. Forty percent of patients (2/5) who received left-sided IMN RT developed HF; none of the 4 patients who received right-sided IMN RT developed HF.

Patients' comorbidities included diabetes mellitus, hypertension, hyperlipidemia, and coronary artery disease. No statistically significant difference was noted in the risk of HF based on these characteristics in this small series. Age, African-American race, and history of smoking also did not contribute to an increased risk of HF. However, 89% of patients (8/9) who developed HF had previously received anthracycline-based chemotherapy compared to 54% of non-HF patients (15/28) (Table 2).

Table 3. Characteristics of Patients with Major Coronary Events at Median Follow-up of 5 Years

Patient	Major coronary event/time after RT[1]	Tumor laterality	IMN[2] RT	Use of anthracyclines	HF[3] previously detected?	Stage	Previous comorbidities / race
1	Revasc[4]: 7 years	Left	No	No	No	II	HTN[5], smoker, African- American
2	MI[6]: 2 years	Left	No	Yes	Yes; irreversible	II	HTN[5], HLD[7], smoker, African- American
3	MI[6] + revasc[4]: 2 years	Left	No	Yes	Yes; irreversible	II	HTN[5], HLD[7],CAD[8], African- American

[1]RT = radiation therapy. [2]IMN = internal mammary nodes. [3]HF = heart failure. [4]Revasc. = revascularization. [5]HTN = hypertension. [6]MI = myocardial infarction. [7]HLD = hyperlipidemia. [8]CAD = coronary artery disease.

Each patient was further reviewed to determine whether a major coronary event occurred during a median follow-up of 5 years after completion of RT. Nine percent of patients (3/32) who received RT underwent a major coronary event (Table 3). None of the five patients (0/5) who did not receive RT had a major coronary event at a median follow-up of 5 years after treatment with trastuzumab alone.

Discussion

The cardiotoxic effects of treatment with trastuzumab have been well-established, whereas the additional impact of RT given concurrently with targeted HER2-based systemic therapy has been investigated in only a few series. The most comprehensive study performed to date involved assessment of 1,503 early stage, HER2-positive breast cancer patients. These patients were randomly assigned to different combinations of doxorubicin and cyclophosphamide, followed by weekly paclitaxel and later by trastuzumab. RT commenced within 5 weeks after paclitaxel, concurrently with trastuzumab. Results showed no significant increase in adverse or acute cardiac events associated with concurrent trastuzumab and RT after a median follow-up of 3.7 years. However, RT to the internal mammary lymph nodes was prohibited, so that the RT dose received by the heart was quite low.[16]

Additional smaller studies that assessed the combined effects of trastuzumab and RT have not found a significant increase in adverse events among patients receiving concurrent treatment. In one study in which skin and cardiac toxicities were evaluated in 57 patients receiving concurrent trastuzumab and RT, rates of abnormal LVEF and skin toxicity were deemed acceptable.[17] IMN radiation, however, was not assessed. In two additional studies in which acute cardiotoxicity was evaluated in 106 patients and in 59 patients who received concurrent trastuzumab and RT, no excess cardiotoxicity was observed with RT, regardless of the side irradiated or the addition of IMN RT.[18,19]

Our study further strengthens the small body of previous data that has failed to identify a causal link between concurrent trastuzumab/RT and subsequent HF. Unlike previous studies in which the incidence of cardiotoxicity was evaluated by quantifying LVEF using imprecise techniques, this study utilized a standardized, reproducible method at regular 3-month intervals in unselected patients. Moreover, previous studies may have underestimated the acute reversible effects on cardiac function from RT by using echocardiography, a less sensitive technique compared to the MUGA scans used in this study.[20]

Increasing Radiation Doses to the Heart as Measured by Tumor Laterality and IMN RT

The treatment of left-sided breast cancers with RT poses a risk of increasing cardiotoxicity.[15] Darby et al found a dose-dependent increased risk of late ischemic heart disease associated with RT of the left breast.[10] However, a recent large-scale clinical investigation showed that tumor laterality does not influence survival among breast cancer patients when treatment planning based on modern techniques, including computed tomography simulation, is utilized. In that study, 344,831 patients were followed for 10 years, and no difference in overall survival was noted by tumor laterality for patients treated for breast-only and breast-plus-regional-nodal RT. The authors, therefore, attributed Darby et al's findings to the use of outdated radiation techniques.[21]

The use of IMN RT in the treatment of breast cancer has remained controversial because of its potential to increase cardiac dose, with previous studies demonstrating no improvement in over-

all survival.[22] Recent data from a study published in the *New England Journal of Medicine* suggests that IMN RT in patients with early stage breast cancer may actually contribute to a benefit in overall survival, also improving disease-free survival, distant disease-free survival, and breast cancer mortality. This trial randomized 4,004 stage I–III breast cancer patients, who had undergone either mastectomy or breast-conserving surgery and axillary dissection, to regional nodal irradiation or to no regional nodal irradiation. The primary endpoint was overall survival, and the data were published after a median follow-up of 10.9 years. In addition to improvement in overall survival, the authors found a low rate of heart disease and death from heart disease.[11]

The present study did not find an increase in the incidence of HF based on tumor laterality or IMN RT in the setting of concurrent trastuzumab therapy. This may be the result of care taken to minimize the amount of radiation received by the heart using modern treatment planning and breath-hold techniques.[21,23] This also may be attributable to a bias toward treating patients with stronger baseline cardiac function with IMN RT. The small sample size of this study and the relatively short follow-up must also be considered; it is possible that a larger sample size followed over a longer period would have demonstrated a higher incidence of patients with HF. In general, early radiation-induced cardiac changes are believed to be detected as early as 6 months post-RT using single-photon emission computed tomography.[24] However, late effects of thoracic radiation generally become evident 3-29 years after treatment.[25]

Use of Anthracycline-Based Chemotherapy and Additional Risk Factors

The efficacy of anthracyclines in the treatment of early breast cancer, irrespective of receptor status, has been proven in multiple large cohort trials and meta-analyses.[26] Moreover, the use of trastuzumab combined with an anthracycline regimen has shown a significant benefit in both disease-free and overall survival in patients with HER2-positive disease.[2] However, the development of significant cardiotoxicity related to anthracyclines and the emergence of newer agents (such as taxanes), that appear to limit cardiotoxicity but with similar treatment efficacy, have called the use of anthracyclines into question.[26]

Our study demonstrates a trend toward an increase in HF among women treated with anthracycline-based treatment regimens. Future studies are needed to determine whether agents, such as taxanes, associated with less cardiotoxicity have equal anticancer efficacy in combination with trastuzumab. The newer agent pertuzumab, a humanized monoclonal antibody that targets a different domain of the HER2 receptor from that targeted by trastuzumab, should also be studied in combination with anthracyclines. Although limited, data suggest that when combined with trastuzumab, pertuzumab is well-tolerated, with LVEF remaining close to baseline.[27]

In addition to the use of anthracyclines, patient characteristics, such as age, race, and comorbidities, have been investigated as risk factors for developing HF in women treated with trastuzumab. One retrospective analysis conducted at the University of Maryland Medical Center, Baltimore, reported a higher risk of developing decreased LVEF in African-American women.[20] Several studies have also identified an association between older age or a history of heart disease and trastuzumab-induced cardiotoxicity.[28] The present study found no significant associations between age, race, history of previous heart disease, or history of smoking and treatment-induced cardiotoxicity.

Conclusions

In this single-institution experience, the concurrent use of RT did not appear to increase the risk of HF among patients receiving trastuzumab. Nor were increased radiation doses to the heart with left-sided radiation and/or targeting of the IMN chain found to be associated with an increased risk of HF. A strong trend toward an increasing risk of HF was identified in patients receiving anthracycline-based chemotherapy. Future studies are needed to confirm these findings in a larger sample size and with LVEF monitoring for periods ≥ 12 months. This could help determine whether there is a need to further lower radiation doses to the heart using more sophisticated radiation techniques such as proton therapy in women receiving systemic agents with known cardiotoxic effects.

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Appendix: Table A1. Patient Characteristics

Characteristic	n = 37 (% total patients)
Sex	
Female	37 (100%)
Median age (range)	57 (39–75) years
Race	
African-American	23 (62%)
Caucasian	11 (30%)
Other	3 (8%)
Tumor type	
Infiltrating ductal carcinoma	36 (97%)
Infiltrating lobular carcinoma	0 (0%)
Mixed	1 (3%)
Estrogen receptor+ (>1%)	20 (54%)
Progesterone receptor+ (>1%)	13 (35%)
Stage (TNM)	
I	4 (11%)
II	17 (46%)
III	16 (43%)
Radiation therapy (RT)	
RT	32 (86%)
No RT	5 (14%)
Left chest	15 (41%)
Right chest	18 (49%)
Internal mammary node (IMN)	9 (24%)
Left IMN	5 (14%)
Right IMN	4 (11%)
No IMN	28 (76%)
Additional chemotherapy	
Anthracyclines	23 (62%)
Herceptin dose	
8 mg/kg loading then 6 mg/kg q 3wk for 16 or 17 doses	29 (78%)
4 mg/kg loading then 2 mg/kg weekly for 52 doses	8 (22%)
Pre-existing conditions	
Diabetes mellitus	5 (14%)
Hypertension	22 (59%)
Hyperlipidemia	9 (24%)
Coronary artery disease	2 (5%)
Smoker	13 (35%)

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Lumbosacral plexus: An unattended organ at risk in irradiation of pelvic malignancies

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By virtue of inverse planning and improved target conformality, intensity-modulated radiation therapy (IMRT) reduces radiation dose to normal organs at risk (OARs) in the vicinity of the target, while allowing delivery of high doses to the tumor and regional lymph nodes. As a result, IMRT can reduce side effects by conforming the dose to avoid normal, uninvolved tissues, which may correlate with an improved toxicity profile.[1] Rates of rectal, urinary and hematological toxicities have decreased with the use of this technique.[2,3] However, dose to OARs that are not contoured remains an area of concern, and accurate delineation of all OARs is important for dose avoidance to these organs.

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Lumbosacral plexus (LSP) is such an organ that is not routinely contoured for patients undergoing IMRT for pelvic malignancies. This may lead to dose dumping, with higher than expected doses placed in the LSP because it is not specified as an OAR.[4] Radiation-induced injury to the LSP (RILSP) in pelvic malignancies is a rare but severely debilitating complication of pelvic irradiation, causing lower limb weakness, numbness and paresthesia. Presentation of RILSP injuries occurs as early as 3 months to several years after radiation completion. While the estimated frequency of RILSP is 0.3% to 1.3%,[5,6] the true incidence of this complication is under-reported. Neurologic deficits are irreversible and no effective therapy other than supportive care has been found. A standardized method for LSP delineation was devised by Yi et al for patients treated with IMRT for rectal and anal cancers.[7] In this study, we retrospectively evaluated the dose distribution to the LSP in patients with rectal carcinoma treated with IMRT where no specific dose constraint was used regarding the LSP.

Materials and Methods

Fifteen consecutive patients with rectal cancer who were treated with IMRT at our institute from January 2015 to August 2015 were included in the study. Eligibility criteria were: histologically proven rectal cancer, no evidence of distant metastases, no previous history of pelvic irradiation, and whole-pelvis radiation using IMRT. Patients with uncontrolled diabetes were excluded from the study. LSP was delineated in every patient from the L4-L5 interspace to the level of the sciatic nerve on the planning CT scan of 2 mm slice thickness by the radiation oncologist with the assistance of a radiologist, using the anatomic atlas developed by Yi et al. The LSP was contoured in relation to anatomic landmarks, which included the psoas

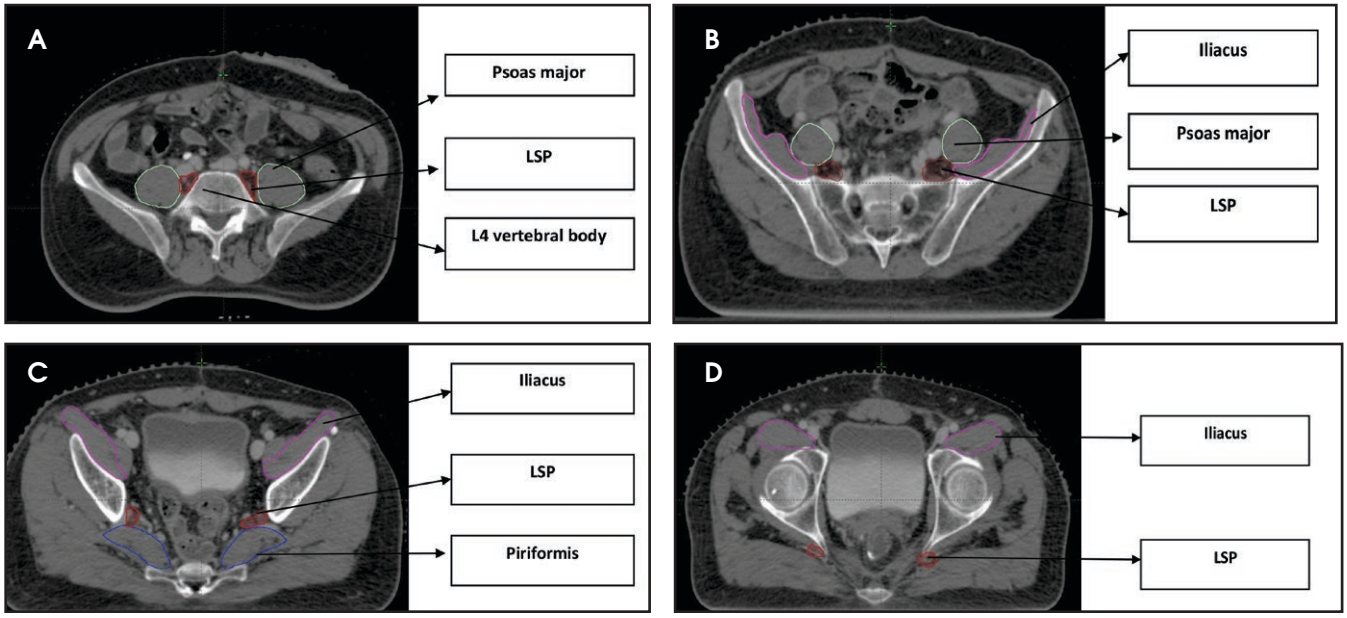

FIGURE 1. *(A-D) Axial sections of a planning CT scan from the level of the L4 vertebral body to the femoral head, representing the muscles and lumbosacral plexus in relation to the anatomic landmarks.*

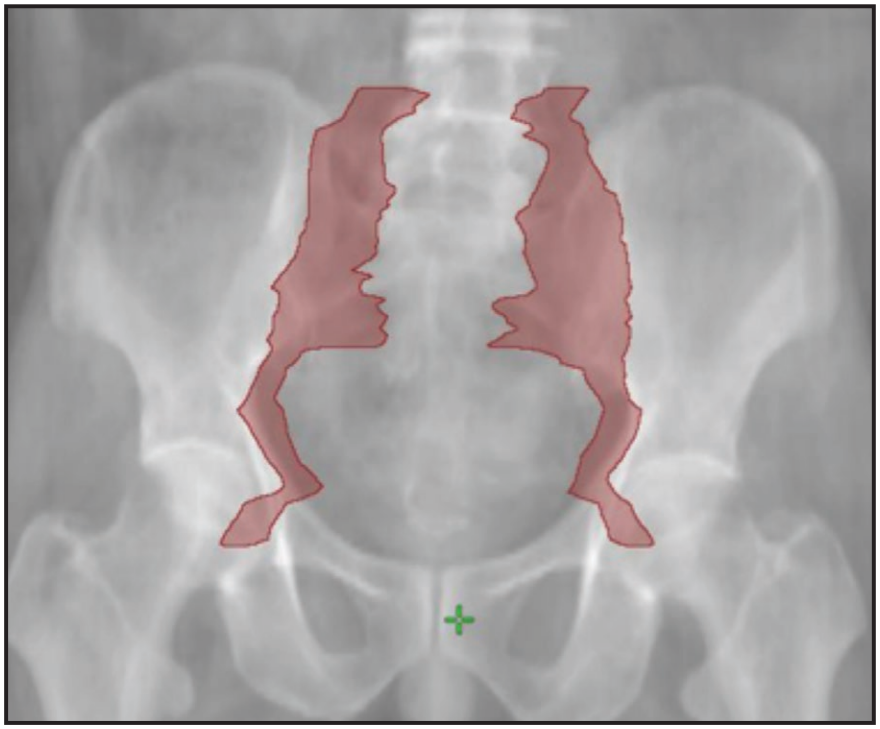

FIGURE 2. *Digitally reconstructed radiograph depicting the lumbosacral plexus.*

major, iliacus, piriformis, obturator internus, gluteus maximus muscles, and vertebral bodies and sacral bones.

The axial slices of the planning CT scan of a representative patient at various levels are shown in Figure 1, and the lumbosacral plexus is digitally reconstructed, as shown in Figure 2. Dose-volume histogram curves were created using a percentage of volume of the LSP receiving 30 Gy, 40 Gy, 50 Gy, 55 Gy and doses received by LSP, as shown in Figure 3. No dose limitation had been placed for this organ during initial treatment planning. After delineation, the dose-volume histogram of each patient was evaluated, and the total LSP volume; mean LSP dose; maximum LSP dose; and percentage of volume receiving 30 Gy, 40 Gy, 50 Gy, and 55 Gy were estimated.

Clinical and disease characteristics of all 15 patients are listed in Table 1. All patients were treated with IMRT on a dual-energy linear accelerator (6 MV and 15 MV) using 9-field dynamic IMRT with beams at 40-degree intervals. Prescribed dose covered 95% of the PTV, ranging from 50.4 to 66.6 Gy in 1.8 to 2 Gy per fraction. All but 2 patients received concurrent chemotherapy in the form of a 5-fluorouracil injection and leucovorin rescue, or oral capecitabine.

Results

As shown in Table 2, the mean LSP volume was 59.84 cc (range: 33-77.7 cc), mean dose to the LSP was 45.5 Gy (range: 39.7-55.5 Gy), and maximum

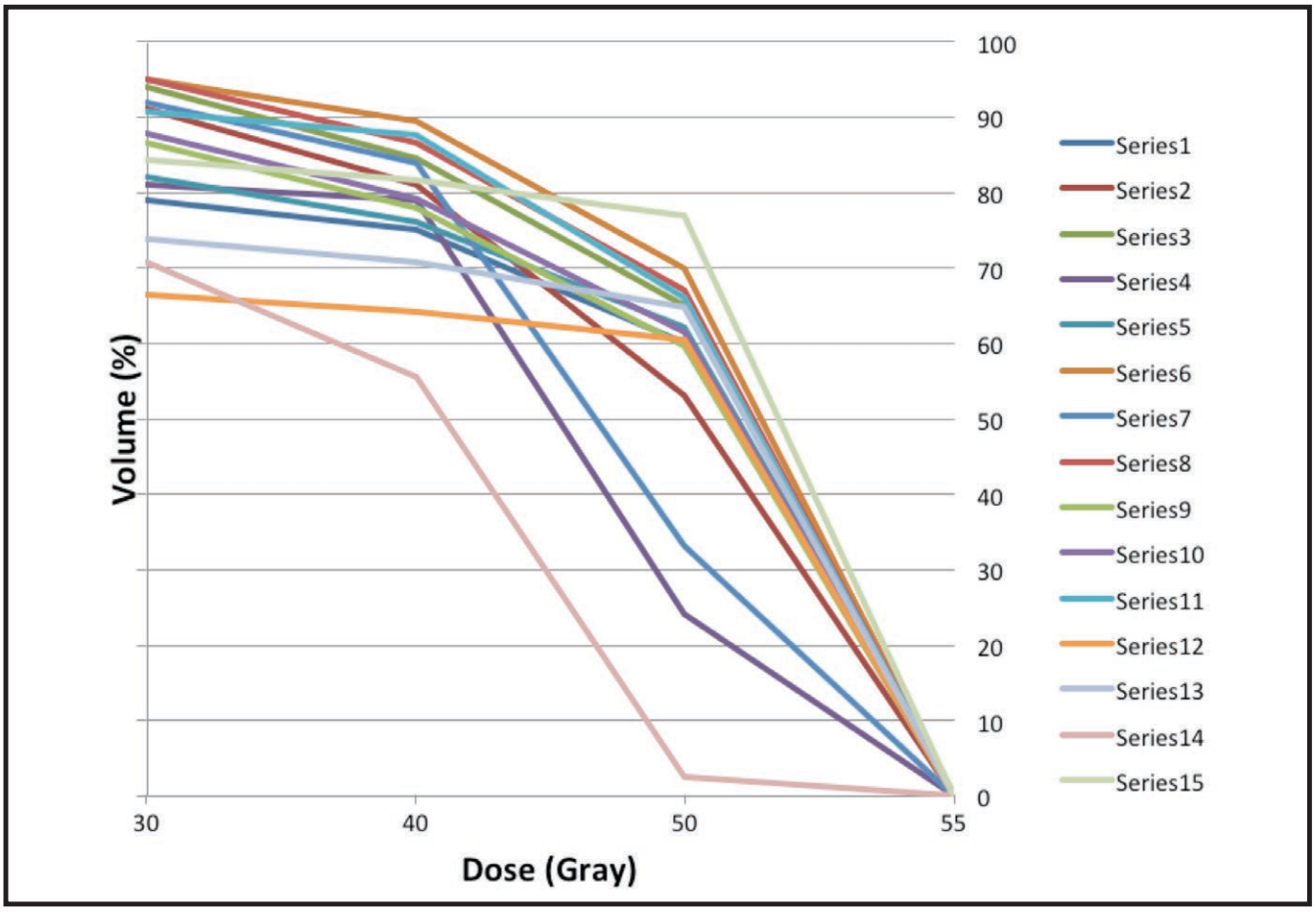

FIGURE 3. *LSP dose volume histogram of the percentage of volume receiving doses from 30-55 Gy for all 15 patients.*

dose to the LSP was 55.67 Gy (range: 36.6-63.8 Gy). Mean volume percentages of the LSP 30 Gy, 40 Gy, 50 Gy, 55 Gy were 84.6%, 78.16%, 55.04% and 0%, respectively. All patients received doses > 50 Gy, and no patient was found to receive > 55 Gy to the LSP.

Discussion

Radiation-induced plexopathies are relatively more common in the form of brachial plexopathies in patients receiving irradiation for breast carcinoma as compared to lumbosacral plexopathies. Increases in total doses and dose per fraction have been associated with heightened risks of radiation-induced brachial plexopathy, and have been seen in breast cancer survivors with a dose of 50 Gy/25 fractions.[8] Also, there are concerns about brachial plexopathy while treating unresectable superior sulcus tumors as well as head and neck cancers. Amini et al showed that in patients treated for superior sulcus tumors, a median plexus dose of > 69 Gy and a maximum dose of 75 Gy to > 2 cc are strong predictors of plexopathy.[9] Fraction size is the single most important predictor of this chronic toxicity and, therefore, SBRT for apical NSCLC also carries a significant risk of brachial plexopathy.[10] Compared to brachial plexopathy, few cases of LSP have been described in the literature. Tolerance to the spinal cord and cauda equina (TD5/5), from which LSP arises, has been estimated at 47 Gy and 60 Gy,[11] respectively, for full volume irradiation. Most cases have been described in patients receiving a combination of external-beam radiation therapy and intracavitary brachytherapy in cervical carcinoma. Higher incidence has been found in patients receiving 70 Gy to 80 Gy to the LSP.[12] Although RILSP is much more common in cervical carcinoma, a few cases have also been seen in patients with lower gastrointestinal malignancies, including rectal and anal cancers. It has also been noted that radiosensitivity of peripheral nerves is increased by concomitant chemotherapy, particularly with taxanes and platinum drugs.[13] Hence, we must be cautious when using doses of 50 Gy to 60 Gy with concurrent chemotherapy. Although, the exact mechanism is not clear, it is thought to be associated with localized ischemia and subsequent

Table 1. Clinicopathological and treatment characteristics

Serial No.	Age/sex	Stage		Dose	Concurrent chemotherapy
1	70y/M	pT3N0 cM0	Postoperative	50.4Gy/28fr	Cap Capecitabine
2	61y/M	pT3N2 cM0	Postoperative	50.4Gy/28fr	Cap Capecitabine
3	37y/M	cT4bN0M0	Preoperative	50.4Gy/28fr	Inj Leucovorin + 5FU
4	76y/F	cT4N0M0	Radical	66.6Gy/37fr	Inj Leucovorin + 5FU
5	49y/M	cT2N0M0	Preoperative	50.4Gy/28fr	Inj Leucovorin + 5FU
6	62y/M	pT3N2b cM0	Postoperative	50.4Gy/28fr	Cap Capecitabine
7	23y/F	cT3N2aM0	Preoperative	50Gy/25fr	Inj Leucovorin + 5FU
8	56y/M	pT3N1 cM0	Postoperative	50.4Gy/28fr	Cap Capecitabine
9	36y/M	cT3N0M0	Preoperative	50.4Gy/28fr	Inj Leucovorin + 5FU
10	57y/F	pT2N1c cM0	Postoperative	50.4Gy/28fr	No
11	48y/M	pT3N0 cM0	Postoperative	50.4Gy/28fr	Inj Leucovorin + 5FU
12	64y/M	pT2N1a cM0	Postoperative	60Gy/30fr	No
13	50y/M	pT3N1 cM0	Postoperative	50.4Gy/28fr	Inj Leucovorin + 5FU
14	57y/M	cT3N2M0	Preoperative	50.4Gy/28fr	Cap Capecitabine
15	78y/M	pT3N1M0	Postoperative	54Gy/30fr	No

Table 2. Dosimetric parameters of lumbosacral plexus

Serial No.	LSP volume	Mean dose	Max dose	V30Gy	V40Gy	V50Gy	V55Gy
1	77.7	41.66	53.7	79	75	60	0
2	54.3	45.25	53.68	91	81	53	0
3	87	47.7	53.7	94	84.6	65	0
4	60	42	69	81	79	24	0
5	75	43	55.5	82	76	62	0
6	59.3	48	54.2	95	89.4	70	0
7	33	44	54.2	92	84	33.2	0
8	54.4	48.4	55.1	95	86.6	67	0
9	50.3	44.8	54.55	86.5	77.8	59.6	0
10	67.6	44.8	54	87.9	79.2	61.5	0
11	55.8	46.5	54.4	90.6	87.6	65.9	0
12	69.2	39.7	64	66.4	64.2	60.4	0
13	53.9	43.2	63.8	73.8	70.8	64.8	0
14	55.5	55.5	36.6	70.7	55.5	2.5	0
15	44.6	48.18	58.7	84.3	81.7	77	0

soft-tissue fibrosis caused by microvascular insufficiency.[14] Clinical manifestations include painless weakness in the lower limbs, which is bilateral in 80% of the patients, and paresthesia. Sensory loss occurs in 50% to 75% of the patients. Deep-tendon reflexes are almost always abnormal at the knee and ankle. Distal lower extremities are more frequently affected compared to proximal counterparts. Differential diagnoses to consider are neoplastic lumbosacral plexopathy, diabetic lumbosacral plexopathy, degenerative joint disease, and chemotherapy-induced plexopathy. Because the management of these entities differs, it is important to distinguish the cause. Management of RILSP is difficult and there are no established guidelines. As mentioned, neurological changes are usually irreversible, which underscores the importance of prevention. Principal treatment remains symptomatic and options include pain management with oral opioids, steroids, and local peripheral nerve blocking agents. Other supportive management includes pharmacotherapy in the form of anticoagulants, antiepileptics, tricyclic antidepressants, etc. Hyperbaric oxygen is another management strategy to improve the symptoms of RILSP.[15]

As we have seen in our study, all patients received doses to the LSP approaching the target dose, because no constraint was placed at the time of planning. This article is an attempt to spread awareness of the need to contour the LSP and prevent dose dumping and formation of hotspots in this structure, thereby minimizing the risk of associated toxicity.

A major drawback of this study is lack of clinical correlation of dose distribution in LSP and late toxicity. Recruitment of more patients, evaluation of other pelvic malignancies where higher radiation doses are used—either dose escalation in prostate malignancies by external-beam radiation therapy only or a combined use of external-beam radiation therapy and brachytherapy as in gynecologic malignancies—and a further clinical correlation will be the next step to further strengthen this study.

Conclusion

The success of radiation oncology has lengthened patient survival but, in turn, has increased the chances of neurological toxicities. The lack of definitive treatment of these neurological complications is a call to do as much as possible to prevent them. One of the most important prevention strategies is limiting the radiation dose to the structures implicated in the causation of this pathology. A significant step toward this goal is to begin contouring and limiting the dose to the LSP in pelvic malignancies receiving IMRT, and limiting the mean dose to < 45 Gy.

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Subclinical recurrence of anaplastic astrocytoma: Demonstrating the difficulty in distinguishing progression from pseudoprogression

Howard E. Morgan, BS; Maxwell C. McDonald, MD; J. Ben Wilkinson, MD

CASE SUMMARY

A 47-year-old Caucasian man presented with progressive headaches over 6 months. A 4.3 cm x 3.4 cm mass was seen in the right cerebellum compressing the brainstem (Figure 1). Pathology after a near-total resection was consistent with a WHO grade III anaplastic astrocytoma with MGMT methylation, an IDH1 (isocitrate dehydrogenase) mutation, and KI-67 of 15%. Adjuvant intensity-modulated radiation therapy (IMRT) was delivered to the areas surrounding the tumor resection cavity (59.4 Gy/33 fractions) with concurrent temozolomide (TMZ) followed by adjuvant TMZ for 1 year.

Over the next 20 months, the patient reported no neurologic symptoms and had no notable physical examination findings. Follow-up MRIs showed a gradually enlarging septated lesion with limited areas of enhancement surrounding the cystic post-therapy changes.

*Prepared by **Mr. Morgan,** medical student at LSU Health Science Center, Shreveport, LA; **Dr. McDonald,** medical oncologist, Willis-Knighton Health System, Shreveport; and **Dr. Wilkinson,** radiation oncologist, Willis-Knighton Health System.*

IMAGING FINDINGS

MRIs showed slight peripheral enhancement that was gradually expanding: 1.6 x 1.4 cm at 3 months post-IMRT (Figure 2A) to 4.1 x 3.5 cm at 19 months post-IMRT (Figure 2C). However, no progressive nodular enhancement was noted at any interval. MRI spectroscopy and perfusion were considered but not obtained, as significant hemosiderin deposits in the area were felt to prohibit accurate test results. A positron emission tomography (PET) scan with brain protocol (Figure 3) showed overall decreased uptake in the right cerebellum with a faint line of increased fludeoxyglucose F 18 (FDG) avidity in the center; however, this area of uptake did not correspond to the area of thickened enhancement seen on the MRIs. Differential diagnosis for the area of progressive enhancement included tumor recurrence vs. pseudoprogression.

CLINICAL RESOLUTION

At 20 months post-IMRT, the patient began noticing nontender drainage from his prior suboccipital incision site. Due to concern for subclinical osteomyelitis and an enlarging cystic structure within the posterior fossa, a repeat craniotomy with subtotal resection was completed. Pathology revealed acute osteomyelitis and recurrent vs. persistent WHO grade III anaplastic astrocytoma with radiation changes. Ki-67 of the persistent disease was decreased to < 1%. Due to the presence of residual tumor cells in the re-excision specimen, the patient has restarted on temozolamide, and is being followed clinically with MRIs every 3 months.

DIAGNOSIS

Persistent vs. recurrent WHO grade III anaplastic astrocytoma with radiation changes.

DISCUSSION

Cerebellar gliomas are rare, comprising 1.8% of all gliomas, with the majority arising in the frontal (25.6%), temporal (19.6%), and parietal (13.8%) lobes.[1] As showed in this case, general presenting symptoms of anaplastic astrocytomas (AA) include headaches (53%) and visual symptoms (23%), in addition to seizures (56%), memory loss (26%), and weakness (25%).[2] However, this patient's recurrence was atypical, in that he showed no signs of clinical progression in the midst of a gradually expanding cystic lesion. In a retrospective cohort of grade III and IV gliomas,

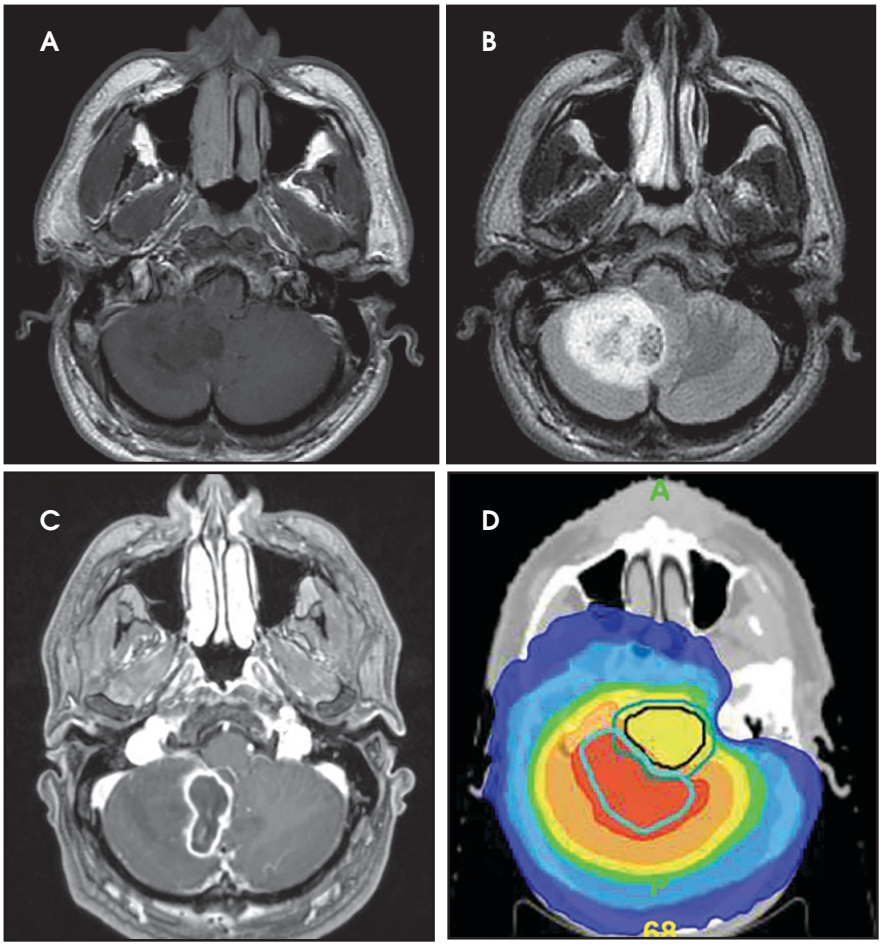

FIGURE 1. *Pre-resection, a 4.3 cm x 3.4 cm mass is visualized in the right cerebellar lobe with T1-weighted MRI plus contrast (A) and FLAIR (B). (C) At 2 weeks postresection, a 3.4 cm x 1.7 cm rim-enhancing lesion is noted in the right cerebellum. (D) IMRT plan to deliver 59.4 Gy over 33 fractions to resection cavity.*

67% with early progression showed neurological deterioration within 4 weeks of imaging findings (n = 18).[3] Although imaging in this case showed mild peripheral enhancement, strong nodular enhancement is more characteristic with recurrence.[4] This incongruent picture, in addition to the equivocal findings on PET, distinguished between progression and pseudoprogression that was unclear during surveillance, a growing problem that complicates the decision of when to intervene.

Pseudoprogression is an obstacle in the surveillance of brain neoplasms, since it mimics MRI findings of recurrence within the field of radiation without representing true disease. It is reported to occur in approximately 20% of malignant gliomas following chemoradiotherapy, with 50% of those showing early MRI findings of recurrence within 4 weeks to actually be pseudoprogression.[3] Pseudoprogression should not be confused with radiation necrosis or pseudoresponse. Pseudoprogression is distinguished by being an early and transient treatment-related effect, with T1-weighted, MRI postcontrast findings of increased enhancement, usually appearing within 3 months post-treatment and subsiding in 6 months.[5] In contrast, radiation necrosis is a late and irreversible treatment-related effect, with MRI findings appearing > 3 months post-treatment but never completely

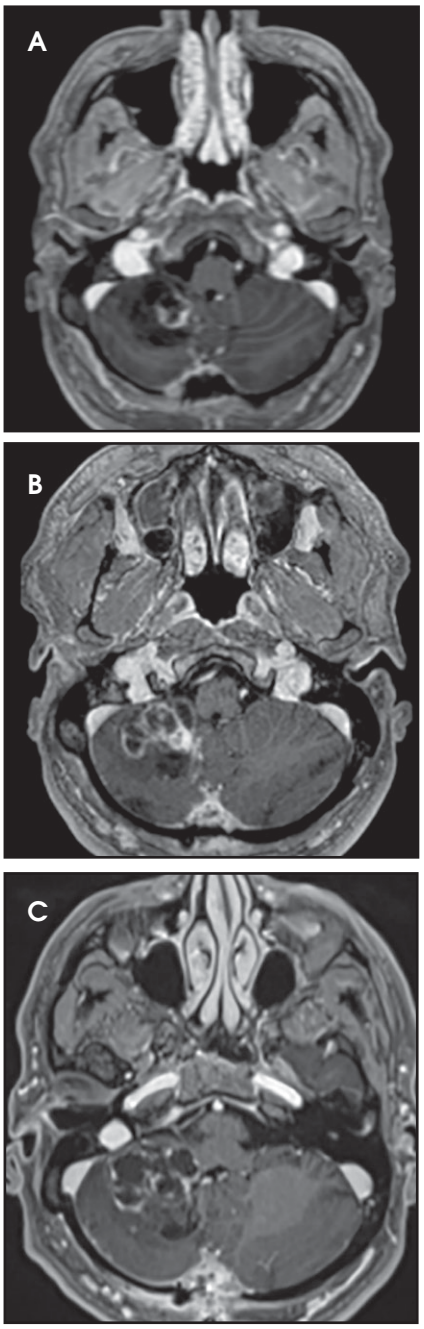

FIGURE 2. *T1-weighted MRI images showing an evolving cystic lesion in the right cerebellum. (A) At 3 months postradiation, the postsurgical cavity has decreased to 1.6 cm x 1.4 cm, and shows mild rim enhancement when compared to Figure 1C. (B) At 10 months postradiation, the cavity increased to 3.3 cm x 3.5 cm with increased rim enhancement. (C) At 19 months postradiation, the cavity increased to 4.1 cm x 3.5 cm, with extension to middle cerebellar peduncle.*

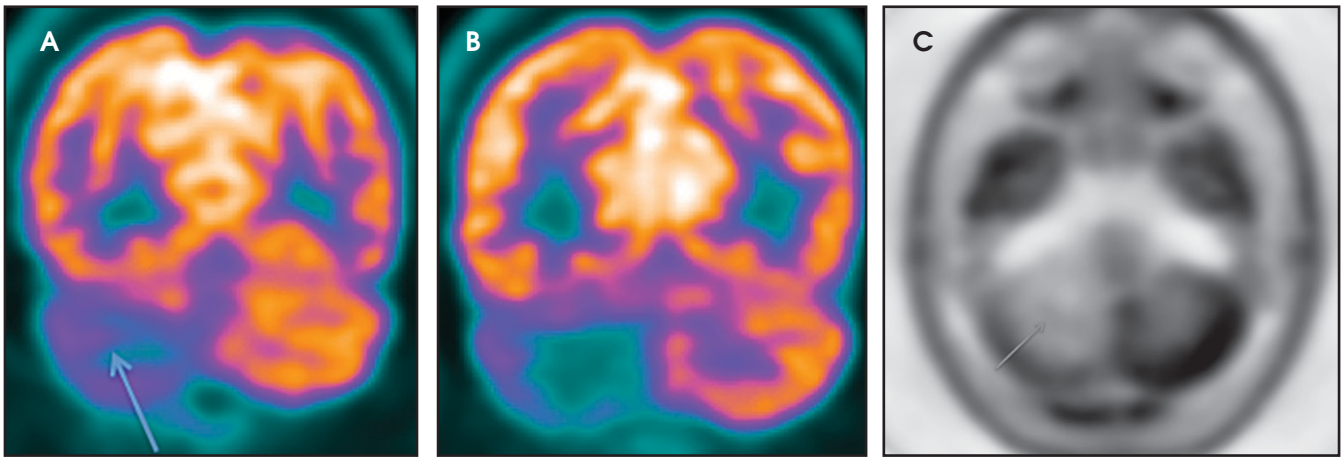

***FIGURE 3**. At 14 months postradiation, an FDG-PET scan showed decreased uptake of FDG in the right cerebellum (coronals A and B, and axial C). A faint linear area of increased FDG uptake was found in the middle of the lesion (blue arrow), but did not correspond with septations when superimposed on the MRI.*

subsiding.[5,6] The MRI findings of radiation necrosis can be broad, with peripheral enhancement resembling a "spreading waveform" (98%) vs. nodular (2%), internal enhancement with a "soap bubble" appearance (90%), cystic components (75%), and central necrosis (89%).[7] On the other hand, pseudoresponse is characterized by decreasing enhancement on MRI during treatment with anti-angiogenic medications such as bevacizumab, which may be confused with a positive response to treatment.[5]

Despite increasing awareness of these treatment-related effects, no reliable method distinguishes them from real progression on MRI,[8] aside from a pathological diagnosis as shown in this case. Pseudoprogression may not be recognized until gradual dampening of enhancement by 6 months and radiation necrosis may be further confused by the persistent presence of enhancing lesions > 6 months post-treatment.[5,6] In addition, the lack of a significant difference between neurological complaints of real progression (67%) and pseudoprogression (33%)[3] further complicates their distinction, as clinical correlation may not be reliable. National Comprehensive Cancer Network (NCCN) guidelines for surveillance of malignant gliomas after chemoradiotherapy include obtaining the first MRI 2-6 weeks after therapy completion, then at 2-4 month intervals for 2-3 years before lengthening.[9] To reflect the growing awareness of treatment-related effects, the Macdonald Criteria–imaging criteria for assessing treatment response–have recently been revised to avoid diagnosing progression at < 3 months after therapy within the 80% isodose lines of radiation, a time with high incidence of pseudoprogression.[10]

Although MRI has not been reliable in distinguishing pseudoprogression, other modalities have shown promise, including FDG-PET, C-Met-PET, MR spectroscopy, and MR perfusion.[8] In our case, FDG-PET showed a faint area of FDG uptake in the center of the resection cavity and not overlapping with the area of enhancement. Although FDG PET has higher accuracy than MRI, its sensitivity (77%) and specificity (78%)[11] still limit its utility in equivocal cases. A recent study examining the parameters of PET and CT perfusion in predicting progression has suggested that it is not the magnitude of uptake but the ratio of uptake to blood flow that correlates best with progression. They proposed that poorly perfused lesions may show reduced FDG uptake overall, while still being more metabolically active due to an increased extraction of FDG per volume of blood encountered.[12]

In addition to imaging, the molecular profile has also shown promise in stratifying those at increased probability of pseudoprogression. MGMT promoter methylation, a marker for increased response to TMZ treatment, has been associated with an increased incidence of pseudoprogression,[13] and when combined with MRI findings, increases the accuracy of identifying pseudoprogression in glioblastomas.[14] A positive prognostic marker 1p19q codeletion has been linked to a decreased incidence of pseudoprogression (3% with codeletion vs. 31%) in grades II and III oligoastrocytomas and oligodendrogliomas.[15] IDH1 mutation, a positive prognostic marker, was suggested to be associated with a higher incidence of pseudoprogression in a smaller study (n = 28, with 3 cases of pseudoprogression), but likely needs confirmation with larger sample sizes.[16] In this case, the histology was MGMT-methylated, which may have contributed to the increased risk of pseudoprogression mixed with recurrent vs. persistent glioma.

CONCLUSION

Determining when a malignant glioma progresses on MRI after chemoradiotherapy has become increasingly difficult with the growing awareness of treatment-related effects. While the

most definitive way of differentiating these entities is biopsy or surgical resection, noninvasive means are needed to lower time to intervention for those progressing. Many such noninvasive measures have shown promise, including FDG-PET as discussed in this report, and molecular markers for risk stratification, with MGMT being the most studied. Close clinical observation with short-interval MRIs, even in the presence of negative advanced imaging studies, is a reasonable clinical strategy. In our experience, continued growth of a septated or cystic lesion without true nodular enhancement can be a sign of disease persistence or recurrence, and warrants repeat craniotomy or a change in therapeutic management depending on the patient's condition.

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Oncology EMRs: More than a patient record

Mary Beth Massat

In healthcare, an electronic medical record (EMR) is often viewed as a digital version of a paper-based patient record. It tracks data over time; identifies patients due for screenings or other preventive examinations; and can help clinicians compare patients against certain measures or groups, such as vaccinations or medical tests.

Yet in oncology, the EMR is more than a repository of patient information or data source for analytics. It documents activities, optimizes treatments, simplifies management of complex therapies, and helps ensure safe patient care.

"The oncology EMR is the window to the soul of the department," says Marc D. Posner, MD, medical director, Center for Advanced Radiation Medicine, Northwestern Lake Forest Hospital, Lake Forest, Illinois. "It is a solution that we interact with every day."

In fact, Dr. Posner says he and his staff interact with the EMR more than the treatment delivery machine or linear accelerator. A key reason: The oncology EMR helps perform three distinct functions in his practice—record and verify, maintain patient records and films, and treatment planning.

***Ms. Massat** is a freelance healthcare writer based in Crystal Lake, IL.*

Because of this, the most important feature of an oncology EMR is the integration to other systems, Dr. Posner says. Dr. Posner's practice has been using MOSAIQ (Elekta, Stockholm, Sweden) for more than 10 years, and he has experienced the ongoing integration of modules, such as treatment planning, into MOSAIQ.

"Having the treatment plans available in the oncology EMR for the physician to review and approve is huge," he says. "Since I don't have treatment planning software on my computer, previously I would go into the physics department and interrupt what they were doing in order for me to review and approve. Now, our physicist electronically pushes the plan to me and I can review it right in my office on my desktop computer."

This workflow efficiency in reviewing and approving plans saves time for Dr. Posner and his physicist, further benefitting patient care. "Right now, we are operating at a very efficient pace with an incredibly fast turn-around-time on plans and quality assurance—from simulation to treatment," he adds.

"There's a second advantage to having the plan in the EMR," says Dr. Posner. "If that patient needs further treatments then we need to know [details regarding] what they had the first time." Or, for example, if a dentist needs dose information on a patient treated for oral cancer, he can pull up the information, export it to a PDF and email it. "I can answer these questions immediately—even in 15 seconds—and that's so important for patient care."

Transitioning to Value-based Care

The shift in the U.S. healthcare system to a value-based care environment will also require changes in IT systems and software, explains Sukhveer Singh, vice president of Oncology Continuum Solutions, Varian Medical Systems, Palo Alto, California.

"The next transformation is what we do with the data to make better care decisions, promote rapid learning, and advance patient outcomes," Singh says. "Big data has meaning in oncology—

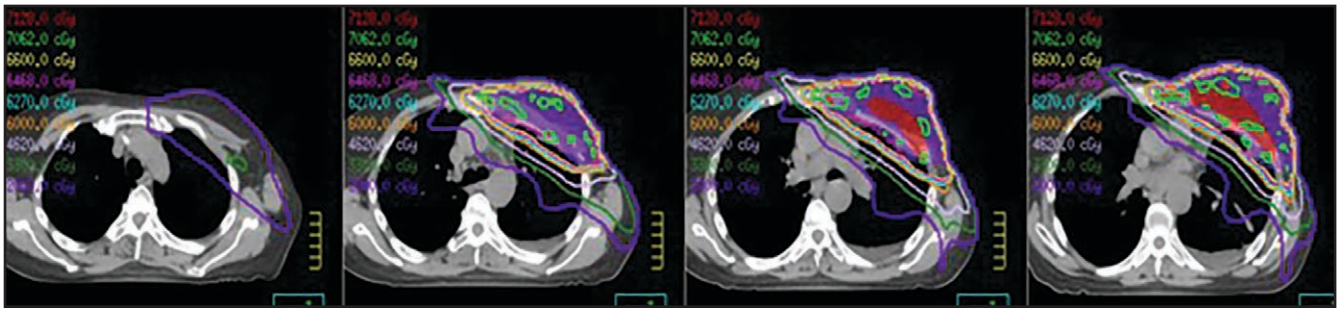

FIGURE 2. *Axial images of treatment plan.*

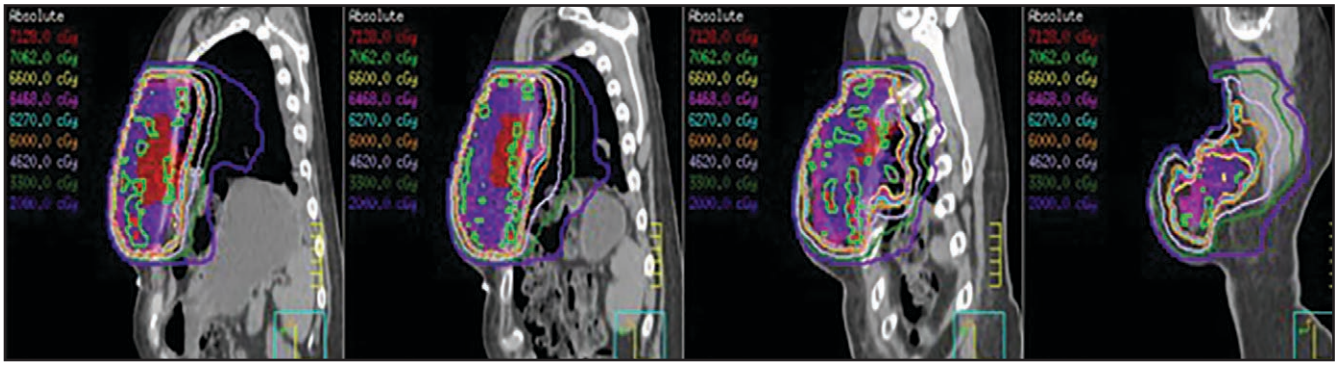

FIGURE 3. *Sagittal images of treatment plan.*

to combine acceleration and hyperfractionation with a fractional dose of 1.5 Gy delivered twice daily to a total dose of 66 Gy. The goal was to reduce the risk of chronic toxicities while maintaining tumor control, understanding the potential for increased acute and subacute toxicities.[5] Similarly, to reduce dose to the heart and lungs, the clinical target volume (CTV) was reduced,[6] the initial imaging was fused to the treatment planning scan to allow for creation of a pre-surgical gross tumor volume (GTV). Subsequently, a CTV was created expanding 2 cm beyond the GTV with a 1 cm radial expansion while limiting the CTV expansion into the lungs and heart. A planning target volume expansion of 0.5 cm was utilized. Despite being adjacent to the heart, the intensity-modulated radiation (IMRT) plan allowed for a mean heart dose of 18.1 Gy and a mean left lung dose of 23 Gy, with much of the lung dose confined to an area already irradiated by the initial breast tangents. Image guidance was performed daily with cone-beam CT, with alignment to the reconstructed chest wall (Figures 2 and 3). During the course of radiation therapy, the patient experienced fatigue with Grade 1 radiation dermatitis and no other acute toxicities. Subsequent follow-up at 3 months demonstrated no subacute or chronic toxicities to date.

CONCLUSION

Re-irradiation can be considered for secondary sarcomas following breast cancer radiation therapy. Clinicians should take advantage of fractionation, IMRT, reduced target volumes, and image guidance to maximize local control while minimizing the risk of late toxicities.

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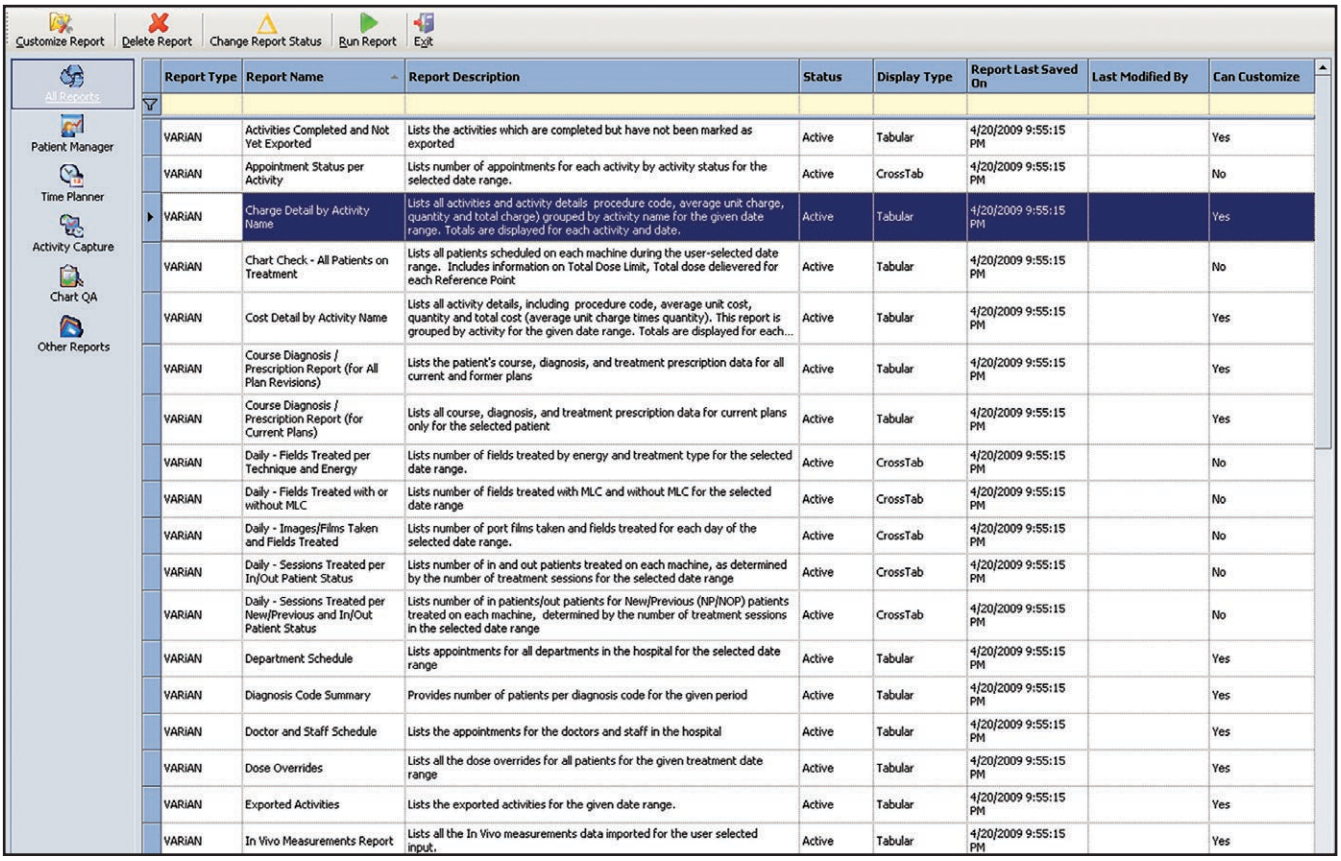

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Screenshot of Varian Medical Systems' Aria oncology information system.

the information in our systems is a collective digital experience. How we use that experience to coordinate care is extremely important in oncology."

To achieve big data analytics, system integration needs to move beyond historical healthcare information to include new data sources, including genomics and social media, to aid in research and innovation, says Anna Theriault, director, Business Line Management, Data Solutions, Elekta.

"Oncology EMRs need to move from transaction to workflow-driven systems with integrated decision support," says Theriault. "They will need to incorporate genetic data with diagnostic information, as an example, to support personalized care."

Healthcare interoperability and big data have the potential to improve treatment and, ultimately, patient outcomes, she adds. "To do this, oncology EMRs must be able to integrate with other healthcare information technology to ensure all of the information is captured, aggregated, and stored in a meaningful way. However, the vast amount of data generated by patients that needs to be incorporated to aid in care delivery and also research and development of new treatment protocols is complex and sometimes incomplete. Current information is captured in disparate systems, which may not have standard communication protocols."

Compared to traditional EMRs that capture inpatient or outpatient visits, an oncology EMR must also connect multiple points of care across care providers, clinics and departments—laboratory, radiology, genomics, oncologists, therapists, dosimetrists, social workers, etc.

"Oncology EMRs need to be integrated with other systems that have diagnostic, treatment, and follow-up data across the care continuum to ensure the patient treatment is optimized," Theriault says.

Singh adds, "We need to create a single source of truth about the patient. It's really about creating a system where everyone has access to the same information from different data sources, with the idea of making data and workflow accessible and collaborative across the team," he adds. "The term, Internet of Things, is particularly relevant to oncology—how do we bring it all together for a complete picture that connects multiple points of care."

To achieve this type of integration, standards and open access should apply to data sharing, Singh adds. Similar to the financial industry whereby funds are transferred worldwide across different systems safely and securely, interoperability across oncology systems needs

Elekta's MOSAIQ Radiation Oncology integrated information system.

to be a fundamental component of IT and EMRs.

To achieve greater interoperability, Varian is moving beyond the traditional interface engine to web-based application programming interface (API) interoperability with bidirectional and secure exchange of data. The company is also focusing on ways to shorten the benchside-to-bedside cycle. "A big motivator is to continually raise the bar to find new standards of care—we call it a rapid learning cycle," Singh says.

Varian's RapidPlan is a knowledge-based planning solution shown to reduce treatment planning time. One study presented at ASTRO 2015 found that IMRT treatment planning time for cervical cancer using a Rapid Plan model based on 86 previously treated cases took an average of 6.85 minutes compared to manual planning that would typically require 2-6 hours of optimization. Singh adds that this study is a key example of combining prior digital knowledge with machine learning to improve outcomes.[1]

Elekta is also keenly focused on integration. Theriault explains that MOSAIQ is a comprehensive oncology EMR that incorporates medical and radiation oncology allowing for improved provider collaboration and seamless workflow across the cancer care continuum. MOSAIQ Oncology Analytics integrated with the EMR provides a comprehensive quality outcomes and operational performance management analytics solution.

Key Considerations

While integration and data analytics are key considerations when looking at oncology EMRs, other important considerations require looking inward.

"We are at the mercy of our IT departments," Dr. Posner says, "so part of that consideration is the IT infrastructure: It's necessary, and without it you may go nowhere." This includes an evaluation of existing and planned future systems, networks, and staff. Regarding solutions already in place, there is a difference between compatible and optimized, he adds.

"Both Varian and Elekta have very good quality systems and machines," he says. For his practice, the big question was the historical data and keeping it on one system vs. going through the often timely and costly endeavor of data migration.

Singh advises that facilities take the time to fully understand their workflows and how it all connects together. "How does data flow from one system to another? Know what you have today and how it will change with a new solution," he urges.

Don't underestimate the impact or volume of change management efforts, he adds. "There is a tendency to replicate paper-based workflows in an electronic workflow," Singh says. "Look at the enterprise to realize the full potential of the technology. That overnight switch of the technology goes well beyond training."

Theriault also encourages providers and facilities to evaluate how the system can help minimize waste and improve patient-provider collaboration for optimal care.

As Singh reminds, "It takes a village to treat a cancer patient."

Reference

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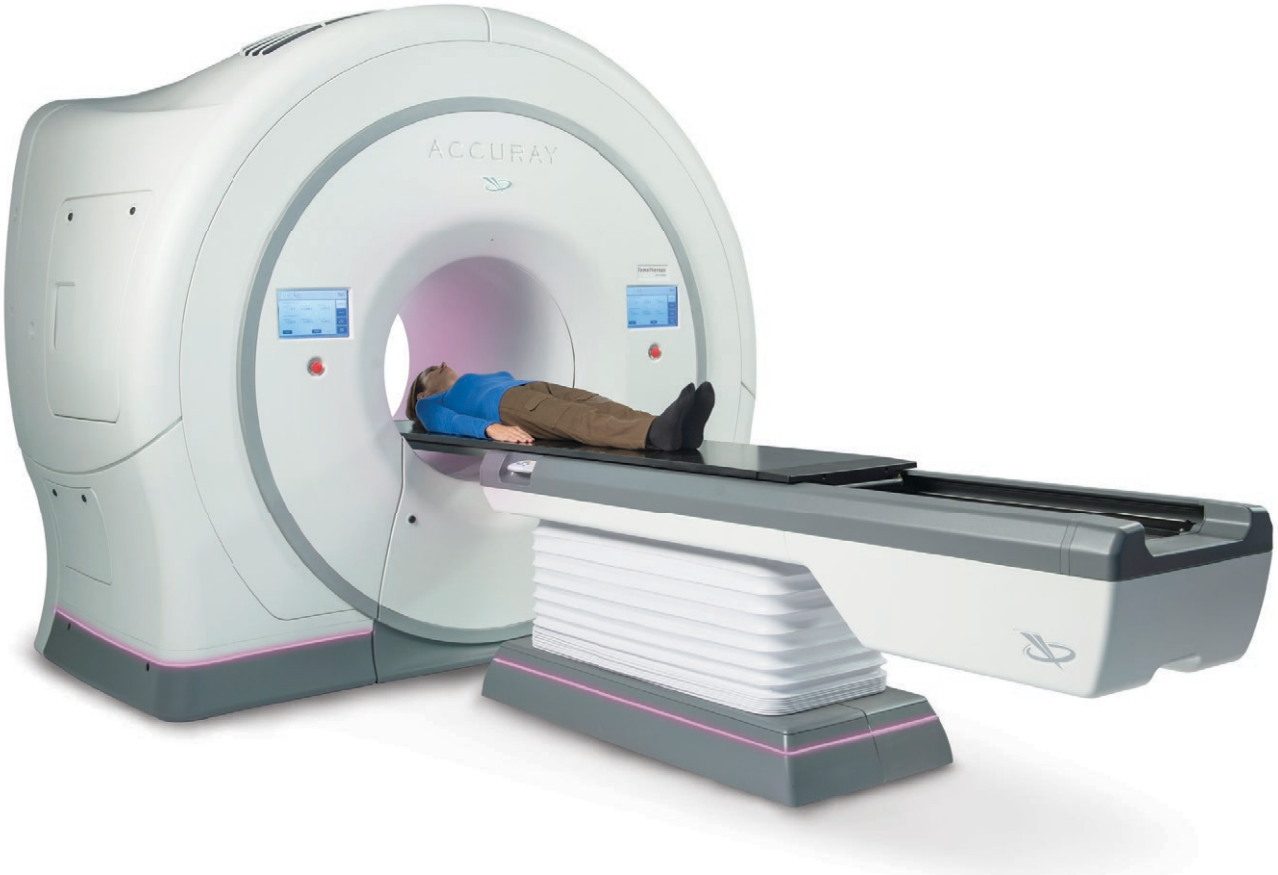

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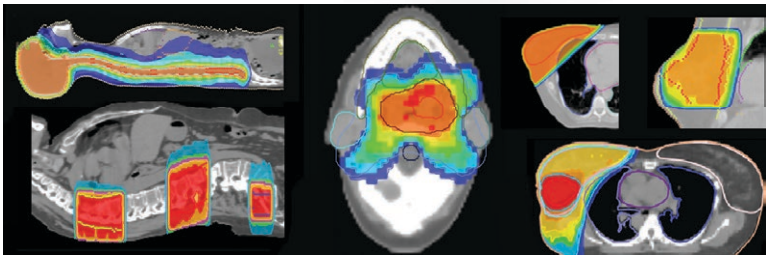

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