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The role of image-guided brachytherapy in the treatment of gynecologic malignancies

SR Amarnath, Cleveland Clinic Foundation, Cleveland, OH

Non-brachytherapy alternatives in cervical cancer radiotherapy: Why not?

S Kilic, B Cracchiolo, Rutgers New Jersey Medical School Newark, NJ; O Mahmoud, Rutgers New Jersey Medical School Newark, NJ and Robert Wood Johnson Medical School, Cancer Institute of New Jersey, New Brunswick, NJ

Technology Trends: Proton therapy treatment for breast cancer

MB Massat

Radiation Oncology Case
Palliative radiation therapy for metastatic squamous cell carcinoma to the parotid gland

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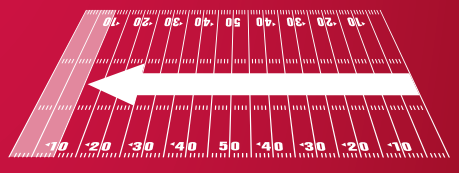

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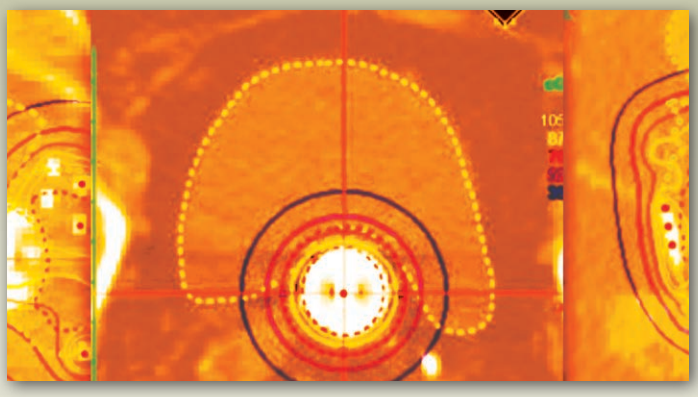

GYNECOLOGIC CANCER FOCUS

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DEPARTMENTS

EDITORIAL

Brachytherapy for Gynecologic Cancer: Applications and Alternatives

John Suh, MD, Editor-in-Chief

Welcome to the December issue of *ARO*! For this month's focus on gynecologic cancer, we are pleased to present two review articles that explore the evolving role of brachytherapy and non-brachytherapy alternatives in treating gynecologic malignancies.

Debuting in the early 2000s, image-guided brachytherapy (IGBT) has gained a stronghold in radiation oncology thanks primarily to its ability to bolster target delineation and optimize treatment planning. In *The role of image-guided brachytherapy in the treatment of gynecologic malignancies*, Sudha R. Amarnath, MD, of the Cleveland Clinic describes IGBT's clinical outcomes, advantages in planning, ongoing challenges, and guidelines for treating cervical cancer. While the benefits of IGBT in other gynecologic malignancies are less clear, Dr. Amarnath delineates how and why it can be a viable option for patients undergoing interstitial brachytherapy or intracavitary treatment with a tandem applicator.

In the accompanying article, *Nonbrachytherapy alternatives in cervical cancer radiotherapy: Why not?* Rutgers' Sarah Kilic, BA, MA, and co-authors review the well-established success of brachytherapy dose distribution before describing shortfalls and alternatives to the costly, complex technologies. The article discusses high-precision radiation therapy techniques, including SBRT and IMRT, which have been explored in selected patients. It also emphasizes requirements needed in order for boost techniques to challenge the long-standing and successful track record of brachytherapy dose distribution in cervical cancer treatment.

Together these articles help clarify when—and when not—to consider brachytherapy for gynecologic malignancies, and we welcome your comments and case reports to help enrich the discussion.

I am also pleased to announce this quarter's Clinical Case Contest winner: *Palliative radiation therapy for metastatic squamous cell carcinoma to the parotid gland*. Written by University of Florida's Shayna E. Rich, MD, PhD, and William M. Mendenhall, MD, the case offers an interesting look at how patients with advanced head and neck cancers can be treated with rapid courses of radiation therapy with little or no toxicity and good palliative effect. Congratulations to our winner!

Three additional case reports on CT changes of the lung following SBRT, recurrent GBM-PNET tumors, and palliative SBRT for head and neck cancer are also featured. The latter two reports involve expensive palliative treatments that may spark controversy and lively discussion surrounding the use of radiation therapy in these palliative settings. Given the focus on value, particularly in cancer care, the judicious use of radiation modalities will continue to be an area of focus for radiation oncologists.

Entries for the next Clinical Case Contest are due Jan. 15; please see guidelines at http://www.appliedradiationoncology.com/contests/case-contest.

Lastly, thank you for supporting *ARO* in 2015. We wish you a joyous holiday season, and look forward to serving the radiation oncology community in the New Year!

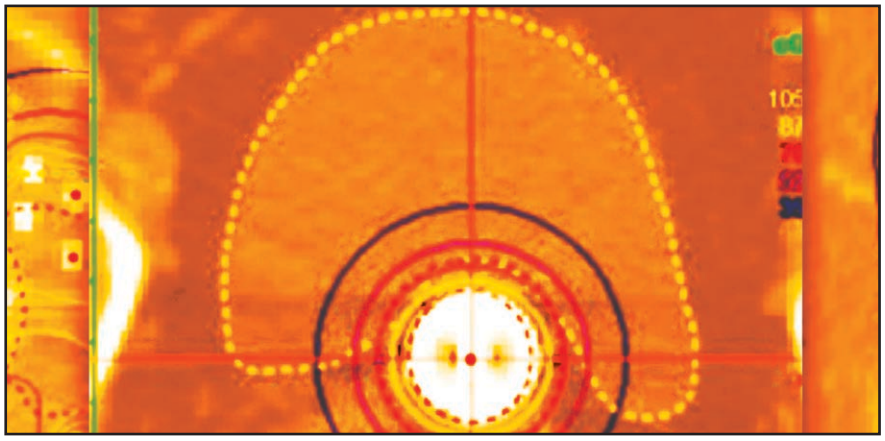
Dr. Suh is the Editor-in-Chief of *Applied Radiation Oncology,* and Professor and Chairman, Department of Radiation Oncology at the Taussig Cancer Institute, Rose Ella Burkhardt Brain Tumor and Neuro-oncology Center, Cleveland Clinic, Cleveland, OH.

The role of image-guided brachytherapy in the treatment of gynecologic malignancies

Sudha R. Amarnath, MD

Gynecologic malignancies, including uterine, cervical, ovarian, vulvar and vaginal cancers are diagnosed in approximately 71,500 U.S. women each year, 26,500 of whom will die from their disease.[1] The presentation and treatment paradigm for each of these cancers is somewhat distinct, and radiation therapy represents a mainstay of treatment for many patients diagnosed with a gynecologic malignancy — especially those with cancers of the cervix, uterus, vulva or vagina.

Although external-beam radiation therapy (EBRT) techniques are generally employed to treat microscopic disease within the pelvis, the dose required to definitively treat these tumors often exceeds the normal tissue tolerance of the small bowel and other organs in the pelvis, making treatment with EBRT alone a poor choice. Fortunately, the anatomy of the female genital tract is predisposed to the use of intracavitary or interstitial brachytherapy techniques, allowing for the delivery of higher doses of radiation therapy to primary tumors arising within the nonadnexal genital organs and sparing toxicity to surrounding normal tissues.



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Brachytherapy has been used for treating malignancies since 1901 — shortly after the discovery of radiation by Henri Becquerel. Intracavitary and interstitial techniques were widely used for a range of malignancies in the early and middle part of the 20th century, but fell out of favor for many cancer types due to improvements in teletherapy technology and its ease of delivery. External-beam planning and delivery techniques continued to improve over time, and since the 1990s, many patients in the United States (and largely worldwide) have been treated using computed tomography (CT)-based planning techniques. The ability to fuse diagnostic imaging (eg, MRI or positron emission tomography [PET]) to a planning scan to help delineate target volumes and organs at risk (OAR); and image guidance, which allows for more accurate patient setups and, thus, smaller target margins and better sparing of normal tissues; can potentially increase tumor control while decreasing normal tissue toxicity. Although brachytherapy stayed in the 2-dimensional "dark ages" longer than teletherapy, image-guided brachytherapy (IGBT) techniques using CT, MRI or ultrasound have been described since the early 2000s. These

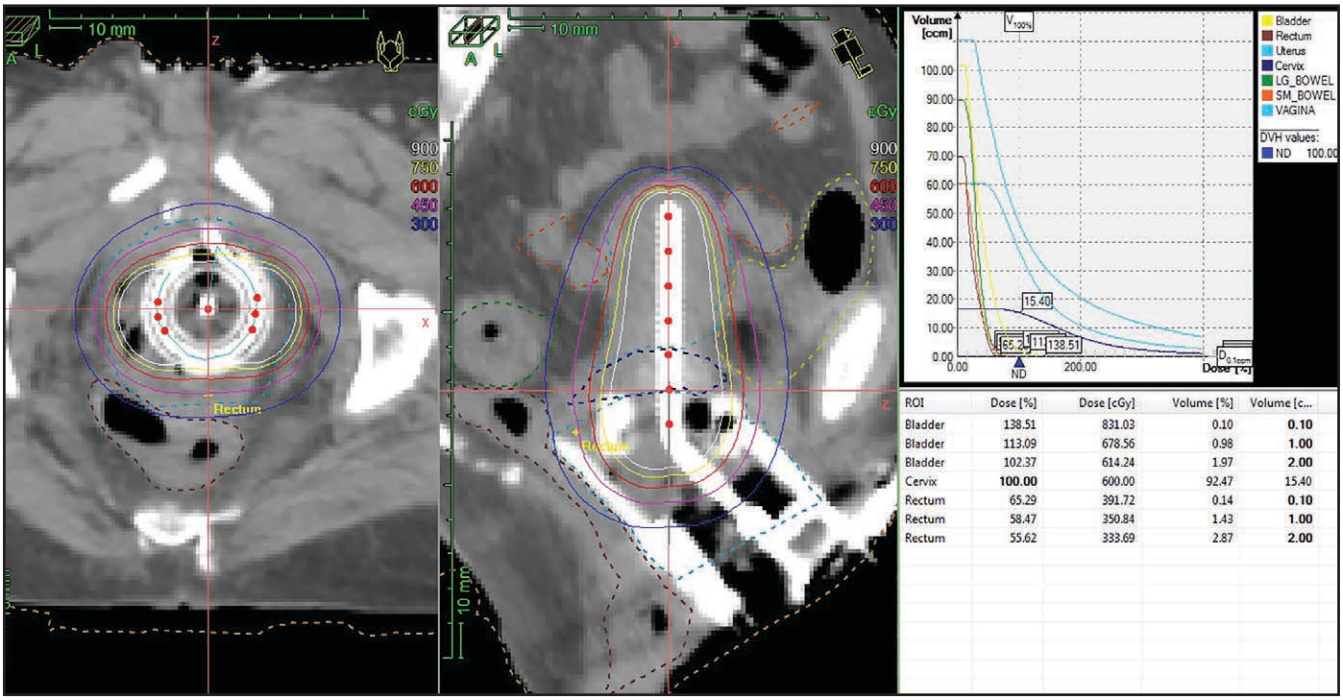

FIGURE 1. *Tandem and ring applicator with DVH using CT-based planning for a FIGO stage IIB cervical cancer.*

techniques are increasingly embraced by the radiation oncology community for the same reasons as image-guided teletherapy, namely improved target delineation and planning, potentially improving local control and normal tissue sparing. Here we describe the role of IGBT in the treatment of cervical, uterine and vaginal cancers.

Cancer of the cervix

Cervical cancer is the third most common cancer in women worldwide. In patients with locally advanced presentations, the standard treatment paradigm consists of chemoradiation therapy — external-beam radiation therapy to the pelvis +/- para-aortics (typically 45-50.4 Gy) with concurrent weekly cisplatin chemotherapy, followed by a boost dose of radiation delivered to the primary cervical tumor.[2,3] This boost has historically been delivered via brachytherapy, and the use of brachytherapy in these patients has been shown to confer a survival benefit over treatment with external-beam radiation treatment alone.[4,5] The boost is frequently delivered after completion of the initial pelvic RT to allow for tumor shrinkage and improved applicator geometry. High-dose-rate (HDR) brachytherapy has been shown to be noninferior to traditional low-dose-rate (LDR) techniques with respect to local control outcomes, with the added advantage of outpatient treatment (mitigating the need for inpatient stays and prolonged bedrest) and decreased exposure of ionizing radiation to healthcare personnel.[6] HDR brachytherapy is typically delivered in 5 fractions of 5-6 Gy per fraction given at least 72 hours apart.[7] Due to the need for multiple insertions of the applicator system with HDR brachytherapy and the potential changes in applicator geometry and/or pelvic anatomy (changes in bladder and rectal filling, and uterine position) between fractions that may affect dose distributions to target volumes (and therefore affect local control and toxicity outcomes), the use of 3-dimensional IGBT has been most extensively studied in this setting.

Advantages of 3-dimensional IGBT planning

Historically, treatment planning has been performed using 2-dimensional techniques with the dose prescribed to a modification of the classical Manchester system point A for target coverage and specified points for normal tissues on conventional radiographs. This technique follows a "one-size-fits-all" approach and does not allow for individualized dose distribution based on patient-specific factors. Three-dimensional IGBT allows a practitioner to modify dose distributions based on a patient's individual anatomy and tumor response, typically using CT and/or MRI. Ultrasound has also been used, but will not be discussed here. The Vienna group pioneered the use of IGBT (using MRI based on its superior soft

tissue contrast compared to CT imaging) for cervical cancer in the early 2000s with the goal of improving target coverage — especially in bulkier and more locally advanced presentations — and decreasing normal tissue toxicity by better understanding dose distributions to OARs since dose volume histogram (DVH) information from a brachytherapy insertion could now be obtained.[8-12]

Since then, several centers have compared 2-dimensional vs. 3-dimensional planning in dosimetric studies and have shown improved cervical tumor coverage and decreased dose to critical normal tissues with 3-dimensional planning. One study from the University of Alabama, Birmingham, revealed that prescription to point A allowed for excellent GTV coverage for earlier stage tumors, but overestimated tumor coverage in more locally advanced cases (IB1 98.5%, IB2 89.5%, IIB 79.5%, and IIIB 59.5%).[13] Other prospective studies from MD Anderson, Korea and Vienna have shown that standard specified normal tissue points (defined by ICRU 38) can underestimate the dose to the OAR.[14-16] These studies have also helped to obtain valuable correlative data on normal tissue dose and long-term toxicity to better define appropriate and clinically relevant normal tissue constraints with modern IGBT (see recommended guidelines).

Other potential advantages of 3-dimensional-based planning include (1) verification of tandem placement in the uterine cavity and decreasing the risk of treating a patient with a uterine perforation; (2) a better understanding of the doses delivered to other normal tissues at risk, especially the small bowel, and the potential to spare dose to these organs (Figure 1); (3) the ability to use more combined intracavitary/interstitial techniques (Vienna applicator) for locally advanced disease to achieve better coverage of gross disease while sparing normal tissue; and (4) optimized target coverage and normal tissue dose with adaptive replanning based on tumor response.[17]

Clinical outcomes with 3-dimensional IGBT

The emerging data for improved outcomes with 3-dimensional IGBT is promising. Georg et al from the University of Vienna published their initial experience of patients with IB-IVA cervical cancer treated with MRI-based IGBT as defined by the Groupe Europeen de Curietherapie/European Society for Therapeutic Radiology and Oncology (GEC-ESTRO) guidelines.[12,18] At a median follow-up of 51 months, local control was achieved in 95% (134 of 141 patients), an improvement over historic controls. Negative prognostic factors for local control included patients with a large tumor (> 5 cm) both at the time of diagnosis and implant (local recurrence 35%); however, significant tumor regression (< 5 cm tumor) after initial pelvic chemo-RT was a positive prognostic factor, with a local recurrence rate of 10.9%. A clear relationship between cumulative rectal dose and grade 2-4 late toxicity was also reported (D2cc: 67 Gy - 5%, 78 Gy -10%, 90 Gy - 20%) by the same group, indicating that image guidance to help lower rectal dose ultimately decreases late toxicity.[19] Interestingly, no correlation was found between total bladder dose and late toxicity.

Creutzberg et al reported improved survival outcomes in patients with IB-IVA disease treated with MR-based IGBT at Leiden University.[20] Comparing 83 patients treated with IGBT to 43 historical patients treated with 2-dimensional techniques, they reported a 3-year overall survival of 86% vs. 51% ($p = 0.001$) and complete remission in 98.8% vs. 83.7% ($p < 0.01$) favoring the IGBT group. Grade 3-4 toxicities reported at 3 years also showed a trend toward improvement with IGBT (8.4% vs. 15.4%, $p = 0.06$). This has also been corroborated in studies out of North America. The University of Pittsburgh published its experience earlier this year with 128 patients with IB1-IVA cervical cancer treated with a hybrid MR/CT-based IGBT technique (MR required for at least 1 fraction) after pelvic RT.[21] At 24.4 months follow-up, estimated 2-year outcomes were: local control 91.6%, disease-free survival 81.8%, and cancer-specific survival 87.6%. The 2-year actuarial rate of late grade 3+ toxicity was 0.9%. Predictors of local failure were adenocarcinoma histology and 3-month clinical response; importantly, a cumulative dose to the HR-CTV (dose to 90% of treatment volume, D90) of $\geq$ to 84 Gy in equivalent 2 Gy doses (EQD2) in adenocarcinoma was associated with improved local control (2-year LC 100% vs. 54.5%).

Despite excellent MR-based IGBT outcomes, unfortunately, many centers lack ready access to MRI scanners for MR-based IGBT, making widespread adoption of IGBT and GEC-ESTRO-based contouring challenging. A prospective international cooperative group trial compared CT-based IGBT to MR-based IGBT planning and revealed similar HR-CTV volume, height, and thickness contour measurements between the 2 imaging modalities, as well as similar DVH values for OARs.[22] HR-CTV width contours differed between the 2 modalities leading to significant differences in the volume treated to the prescription dose or greater (MRI 96% vs. CT 86%, $p = 0.01$) and D90 (MRI 8.7% vs. CT 6.7%, $p < 0.01$). However, clinical experience from Addenbrook with CT-based IGBT using GEC-ESTRO guidelines compared to 2-dimensional-based planning still showed a 20% improvement in local control ($p = 0.04$) favoring IGBT.[23] This study shows promise in improving outcomes for patients with IGBT planning in centers that only have CT imaging available.

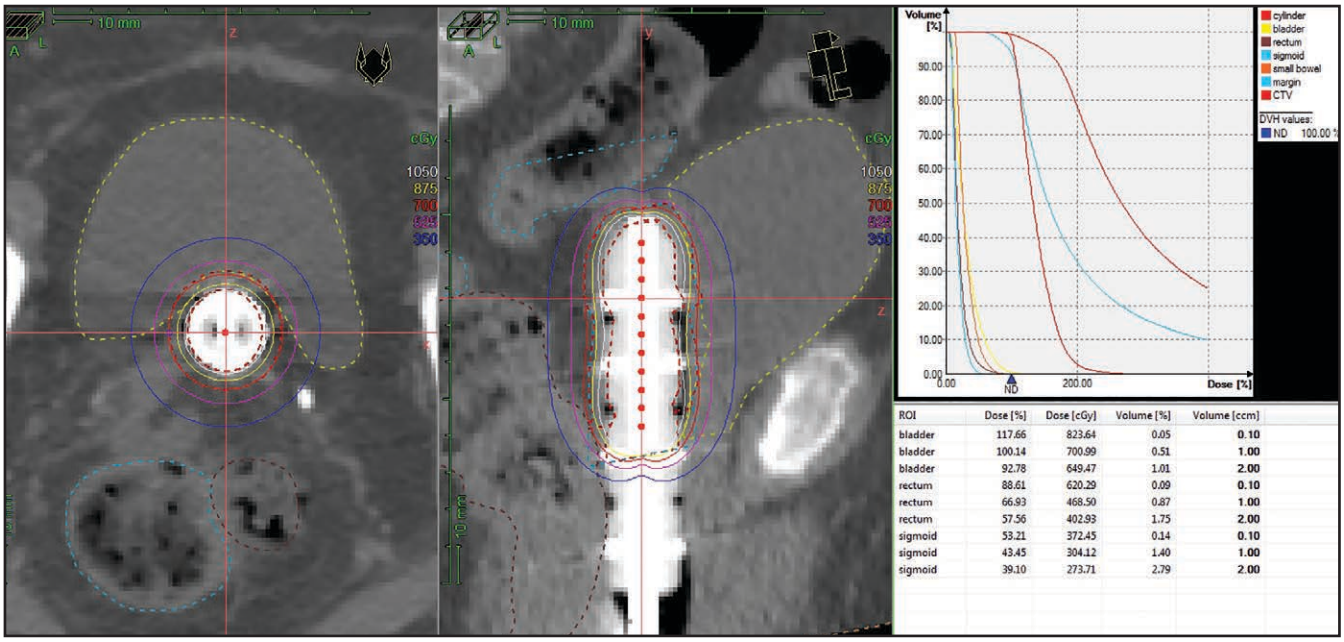

FIGURE 2. *Vaginal cylinder applicator with DVH using CT-based planning for adjuvant treatment of early stage endometrial cancer.*

Challenges with 3-dimensional IGBT

The biggest potential challenges of 3-dimensional IGBT planning include (1) the cost of software/hardware needed to perform treatment planning; (2) increased use of expensive imaging studies and resources for each patient; (3) dosimetric uncertainties both inter- and intrafractionally, given the anatomic variation of normal tissues in the pelvis (ie, bladder/rectal filling) and the potential movement of an applicator between image acquisition for treatment planning and radiation delivery; and (4) lack of experienced personnel for MR interpretation of tumor response and subsequent contouring of GTV and CTVs for treatment planning.[17] A recently published analysis, however, concluded that 3-dimensional IGBT for locally advanced cervical cancer is cost-effective compared to 2-dimensional treatment.[24]

Guidelines for planning with 3-dimensional techniques

Image guidance to verify applicator position and to rule out uterine perforation prior to treatment delivery is generally recommended. Also recommended is following the GEC-ESTRO and American Brachytherapy Society (ABS) published guidelines for IGBT for 3-dimensional IGBT treatment planning, including delineation of target volumes and OARs, and defining appropriate dosing and DVH constraints.[8,25-29] Both GEC-ESTRO and ABS guidelines center on MRI-based planning due to its superior soft-tissue contrast compared to CT-based imaging, but can be translated for use with CT, with improved outcomes over 2-dimensional planning.[30] If no MR planning is available, it is recommended that patients undergo repeat MR imaging after completing pelvic RT to aid in CT-based planning. Hybrid approaches have also been shown to be feasible with the first brachytherapy fraction MRI-planned and subsequent fractions CT-planned.[31-33] Image-based planning using point A is common; however, Beriwal et al have shown in dosimetric studies that prescription to point A generally leads to decreased D90 coverage of HR-CTV compared to volume-based planning.[34]

Cancer of the endometrium

Endometrial cancer is the most common gynecologic cancer in the United States. Brachytherapy is most often used in this disease in (1) the adjuvant setting to decrease risk of recurrence in the vaginal cuff for early stage disease (depending on risk factors after total extrafascial hysterectomy, bilateral salpingo-oophorectomy, and lymph node dissection of the pelvic and para-aortic nodes, if indicated), (2) the definitive setting for patients with medically inoperable disease, and (3) the salvage setting for patients with recurrent disease in the vaginal cuff. Less data exists for the use of 3-dimensional IGBT in the treatment of endometrial cancer compared to cervical cancer (and is summarized below), but many of the same principles apply — namely the potential for improved local control and decreased normal tissue toxicity when targets and OARS can be visualized and more clearly defined on 3-dimensional images, at the potential expense of increased costs and resources. No published guidelines exist for 3-dimensional IGBT for endometrial cancer.

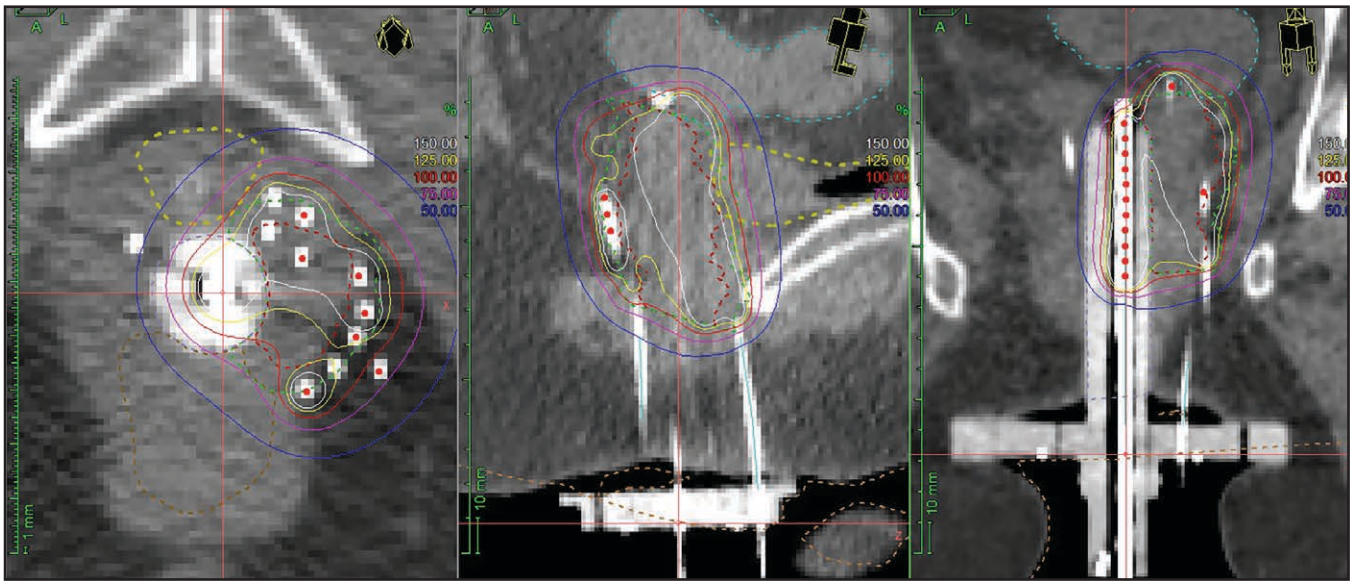

FIGURE 3. *Syed 3 interstitial applicator using CT-based planning for vaginal cuff recurrence from endometrial cancer.*

Adjuvant treatment to the vaginal cuff

Vaginal cylinder treatment as adjuvant therapy in early stage disease is the most common indication for the use of brachytherapy in endometrial cancer.[35,36] Two-dimensional imaging with anterior-posterior and lateral radiographs is used to verify cylinder placement and for treatment planning. At least 2 series have shown that 3-dimensional IGBT may allow for better target coverage by identifying air gaps after cylinder placement, which would otherwise reduce vaginal mucosal dose if not corrected.[37,38] Other potential advantages may include identification of vaginal cuff perforation by the cylinder, as well as DVH data for normal tissues (Figure 2) with the possibility to correlate to late toxicities and better define normal tissue constraints. Very limited data exists for this application though, and further studies are needed to better understand whether 3-dimensional IGBT can improve outcomes in the adjuvant setting.

Definitive treatment for medically inoperable patients

The University of Pittsburgh group recently published results using high-dose-rate 3-dimensional IGBT with MRI or CT-based planning in 38 medically inoperable stage I patients treated with IGBT alone (37.5 Gy in 5-6 fractions) or EBRT (45 Gy in 25 fractions) in combination with IGBT (25 Gy in 4-5 fractions).[39] Dose was prescribed to a CTV including the entire uterus, cervix and upper 1-2 cm of vagina; a GTV was also defined in patients undergoing MRI. Two year local control was 90.6% and overall survival was 94.4% with no grade 2-5 toxicities. GTV doses (D90 EQD2) ranged from 138-233 Gy, which was felt to account for the very high local control. Based on results, the authors conclude that 3-dimensional IGBT is feasible and potentially beneficial in this setting. The Vienna group achieved similar outcomes using a modified Heyman technique.[39]

Salvage treatment for vaginal cuff recurrences

Viswanathan et al evaluated the outcomes of patients treated with MR- or CT-guided salvage interstitial brachytherapy in 44 patients with vaginal cuff recurrences, 13 of whom had received prior RT.[41] At 2 years, local failure was 4% in patients with no prior RT and 39% in patients with prior RT, likely due to the lower doses achieved in patients undergoing re-irradiation (mean D90 EQD2 < 70 Gy vs. > 70 Gy if no prior RT). Grade 3 late toxicity was noted in 4 patients, only 1 of whom had not received prior RT. The authors conclude that 3-dimensional IGBT results in excellent local control and minimal toxicity. Similarly good outcomes were reported by Cormack et al in a prospective trial of 25 patients treated with MR-guided interstitial brachytherapy techniques. This study also reported low late toxicity rates with this method. They concluded that 3-dimensional IGBT with image guidance and planning can lead to excellent clinical outcomes and improved toxicity profiles.[42] Another series from the same group using HDR interstitial therapy in women with primary or recurrent gynecologic cancers concluded that 3-dimensional IGBT helps ensure adequate tumor coverage and minimized dose (D2cc) to the rectum that can result in late late rectal complications (Figure 3).[43,44] This has been corroborated by evidence from Aarhus University in Denmark.[45]

Cancer of the vagina

Vaginal cancer is the least common gynecologic malignancy worldwide. Treatment typically consists of an initial course of pelvic RT (with chemotherapy, if tolerated) followed by a boost to the primary tumor, often delivered via brachytherapy techniques, as extrapolated from other gynecologic malignancies.[46] Given the high doses needed to achieve local control, and the high risk for potential toxicity to normal tissues (bladder, urethra, rectum), 3-dimensional IGBT may have a large benefit for these patients. The Vienna group published their outcomes in 13 patients with locally advanced vaginal cancer using MR-based IGBT.[47] The mean D90 to the HR-CTV (defined based on a modification of the GEC-ESTRO guidelines) was 86 Gy. At a median follow-up of 43 months, 3-year actuarial local control was 92% and overall survival was 85%. Data with multi-channel cylinders using 3-dimensional IGBT is also promising.[48,49]

Conclusion

Three-dimensional IGBT is feasible and may improve clinical outcomes, including greater local control and decreased normal tissue toxicity in a wide range of gynecologic malignancies. The role of 3-dimensional IGBT is most well-defined for cervical cancer patients and is recommended for treatment planning. The benefit of 3-dimensional IGBT in other gynecologic malignancies is less clear given limited published data, and it may be harder for centers to adopt given the lack of published guidelines for contouring and planning. However, based on the available data, 3-dimensional IGBT should be considered for all patients undergoing interstitial brachytherapy or intracavitary treatment with a tandem applicator. More prospective data is needed to better define dosimetric constraints, but the use of the GEC-ESTRO guidelines for DVH evaluation is recommended.

References

1. Berman ML, Daling J, Haefner HK, et al. Get the Facts About Gynecologic Cancer. Inside Knowledge (Brochure) 2015. http://www.cdc.gov/cancer/knowledge/pdf/cdc_gyn_comprehensive_brochure.pdf. Accessed August 15, 2015.
2. Lanciano RM, Won M, Coia LR, Hanks GE. Pretreatment and treatment factors associated with improved outcome in squamous cell carcinoma of the uterine cervix: a final report of the 1973 and 1978 patterns of care studies. *Int J Radiat Oncol Biol Phys.* 1991;20(4):667-676.
3. Landoni F, Maneo A, Colombo A, et al. Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer. *Lancet.* 1997;350(9077):535-540.
4. Viswanathan AN, Moughan J, Small W, et al. The quality of cervical cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in radiation therapy oncology group prospective trials 0116 and 0128. *Int J Gynecol Cancer.* 2012;22(1):123-131.
5. Bandera L, La Face B, Antonioli C, et al. Survival and toxicity of radical radiotherapy (with or without brachytherapy) for FIGO stage I and II cervical cancer: a mono-institutional analysis. *Eur J Gynaecol Oncol.* 2014;35(2):121-127.
6. Narayan K, van Dyk S, Bernshaw D, et al. Comparative study of LDR (Manchester system) and HDR image-guided conformal brachytherapy of cervical cancer: patterns of failure, late complications, and survival. *Int J Radiat Oncol Biol Phys.* 2009;74(5):1529-1535.
7. Nag S, Erickson B, Thomadsen B, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2000;48(1): 201-211.
8. Haie-Meder C, Potter R, Van Limbergen E, et al. Recommendations from Gynaecological (GYN) GEC-ESTRO Working Group (I): concepts and terms in 3D image based 3D treatment planning in cervix cancer brachytherapy with emphasis on MRI assessment of GTV and CTV. *Radiother Oncol.* 2005;74(3):235-245.
9. Kirisits C, Potter R, Lang S, et al. Dose and volume parameters for MRI-based treatment planning in intracavitary brachytherapy for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2005;62(3):901-911.
10. Dimopoulos JC, Schard G, Berger D, et al. Systematic evaluation of MRI findings in different stages of treatment of cervical cancer: potential of MRI on delineation of target, pathoanatomic structures, and organs at risk. *Int J Radiat Oncol Biol Phys.* 2006;64(5):1380-1388.
11. Potter, R., et al., 3D conformal HDR-brachy- and external beam therapy plus simultaneous cisplatin for high-risk cervical cancer: clinical experience with 3 year follow-up. *Radiother Oncol.* 2006;79(1):80-86.
12. Potter R, Dimopoulos J, Bachtiary B, et al. Clinical impact of MRI assisted dose volume adaptation and dose escalation in brachytherapy of locally advanced cervix cancer. *Radiother Oncol.* 2007;83(2):148-155.
13. Kim RY, Pareek, P. Radiography-based treatment planning compared with computed tomography (CT)-based treatment planning for intracavitary brachytherapy in cancer of the cervix: analysis of dose-volume histograms. *Brachytherapy.* 2003;2(4):200-206.
14. Shin KH, Kim TH, Cho JK, et al. CT-guided intracavitary radiotherapy for cervical cancer: Comparison of conventional point A plan with clinical target volume-based three-dimensional plan using dose-volume parameters. *Int J Radiat Oncol Biol Phys.* 2006;64(1):197-204.
15. Yaparpalvi R Mutylal S, Gorla GR, et al. Point vs. volumetric bladder and rectal doses in combined intracavitary-interstitial high-dose-rate brachytherapy: correlation and comparison with published Vienna applicator data. *Brachytherapy.* 2008;7(4):336-342.
16. Onal C, Arslan G, Topkan E, et al. Comparison of conventional and CT-based planning for intracavitary brachytherapy for cervical cancer: target volume coverage and organs at risk doses. *J Exp Clin Cancer Res.* 2009;28:95.
17. Vargo JA, Beriwal S. Image-based brachytherapy for cervical cancer. *World J Clin Oncol.* 2014;5(5):921-930.
18. Potter R, Georg P, Dimopoulos JC, et al. Clinical outcome of protocol based image (MRI) guided adaptive brachytherapy combined with 3D conformal radiotherapy with or without chemotherapy in patients with locally advanced cervical cancer. *Radiother Oncol.* 2011;100(1):116-123.
19. Georg P, Lang S, Dimopoulos JC, et al. Dose-volume histogram parameters and late side effects in magnetic resonance image-guided adaptive cervical cancer brachytherapy. *Int J Radiat Oncol Biol Phys.* 2011;79(2):356-362.
20. Rijkmans EC, Nout RA, Rutten IH, et al. Improved survival of patients with cervical cancer treated with image-guided brachytherapy compared with conventional brachytherapy. *Gynecol Oncol.* 2014;135(2):231-238.
21. Gill BS, Kim H, Houser CJ, et al. MRI-guided high-dose-rate intracavitary brachytherapy for treatment of cervical cancer: the University of Pittsburgh experience. *Int J Radiat Oncol Biol Phys.* 2015;91(3):540-547.
22. Viswanathan AN, Dimopoulos J, Kirisits C, et al. Computed tomography versus magnetic resonance imaging-based contouring in cervical cancer brachytherapy: results of a prospective trial and preliminary guidelines for standardized contours. *Int J Radiat Oncol Biol Phys.* 2007;68(2):491-498.
23. Tan LT, Coles CE, Hart C, Tait, E.Clinical impact of computed tomography-based image-guided brachytherapy for cervix cancer using the tandem-ring applicator - the Addenbrooke's experience. *Clin Oncol (R Coll Radiol).* 2009;21(3):175-182.
24. Kim H, Rajagopalan MS, Beriwal S, et al. Cost-effectiveness analysis of 3D image-guided brachytherapy compared with 2D brachytherapy in the treatment of locally advanced cervical cancer. *Brachytherapy.* 2015;14(1):29-36.
25. Nag S, Cardenes H, Chang S, et al. Proposed guidelines for image-based intracavitary brachytherapy for cervical carcinoma: report from Image-Guided Brachytherapy Working Group. *Int J Radiat Oncol Biol Phys.* 2004;60(4):1160-1172.

26. Potter R, Haie-Meder C, Van Limbergen E, et al. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol*. 2006;78(1):67-77.
27. Lee LJ, Das IJ, Higgins SA, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part III: low-dose-rate and pulsed-dose-rate brachytherapy. *Brachytherapy*. 2012;11(1):53-57.
28. Viswanathan AN, Beriwal S, De Los Santos JF, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. *Brachytherapy*. 2012;11(1):47-52.
29. Viswanathan AN, Thomadsen B. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. *Brachytherapy*. 2012;11(1):33-46.
30. Viswanathan AN, Erickson B, Gaffney DK, et al. Comparison and consensus guidelines for delineation of clinical target volume for CT- and MR-based brachytherapy in locally advanced cervical cancer. *Int J Radiat Oncol Biol Phys*. 2014;90(2):320-328.
31. Beriwal S, Kim H, Coon R. Single magnetic resonance imaging vs magnetic resonance imaging/computed tomography planning in cervical cancer brachytherapy. *Clin Oncol (R Coll Radiol)*. 2009;21(6):483-487.
32. Beriwal S, Kannan N, Kim H, et al. Three-dimensional high dose rate intracavitary image-guided brachytherapy for the treatment of cervical cancer using a hybrid magnetic resonance imaging/computed tomography approach: feasibility and early results. *Clin Oncol (R Coll Radiol)*. 2011;23(10):685-690.
33. Nesvacil N, Potter N, Sturdza A, et al. Adaptive image guided brachytherapy for cervical cancer: a combined MRI-/CT-planning technique with MRI only at first fraction. *Radiother Oncol*. 2013;107(1):75-81.
34. Kim H, Beriwal S, Houser C, Hug MS. Dosimetric analysis of 3D image-guided HDR brachytherapy planning for the treatment of cervical cancer: is point A-based dose prescription still valid in image-guided brachytherapy? *Med Dosim*. 2011;36(2):166-170.
35. Nag S, Erickson B, Parikh S, et al. The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the endometrium. *Int J Radiat Oncol Biol Phys*. 2000;48(3):779-790.
36. Small W, Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy*. 2012;11(1):58-67.
37. Humphrey P, Cornes P, Al-Booz H. Vaginal vault brachytherapy in endometrial cancer: verifying target coverage with image-guided applicator placement. *Br J Radiol*. 2013;86(1023):20120428.
38. Hassouna A, Bahadur YA, and Constantinescu C. Assessment of air pockets in high-dose-rate vaginal cuff brachytherapy using cylindrical applicators. *J Contemp Brachytherapy*. 2014;6(3):271-275.
39. Gill BS, Kim H, Houser C, et al. Image-based three-dimensional conformal brachytherapy for medically inoperable endometrial carcinoma. *Brachytherapy*. 2014;13(6):542-547.
40. Weitmann HD, Potter R, Waldhausl C, et al. Pilot study in the treatment of endometrial carcinoma with 3D image-based high-dose-rate brachytherapy using modified Heyman packing: clinical experience and dose-volume histogram analysis. *Int J Radiat Oncol Biol Phys*. 2005;62(2):468-478.
41. Lee LJ, Damato AL, Viswanathan AN. Clinical outcomes following 3D image-guided brachytherapy for vaginal recurrence of endometrial cancer. *Gynecol Oncol*. 2013;131(3):586-592.
42. Viswanathan AN, Cormack R, Holloway CL, et al. Magnetic resonance-guided interstitial therapy for vaginal recurrence of endometrial cancer. *Int J Radiat Oncol Biol Phys*. 2006;66(1):91-99.
43. Lee LJ, Viswanathan AN. Predictors of toxicity after image-guided high-dose-rate interstitial brachytherapy for gynecologic cancer. *Int J Radiat Oncol Biol Phys*. 2012;84(5):1192-1197.
44. Lee LJ, Damato AL, Viswanathan AN. Clinical outcomes of high-dose-rate interstitial gynecologic brachytherapy using real-time CT guidance. *Brachytherapy*. 2013;12(4): 303-310.
45. Fokdal L, Tanderup K, Nielsen SK. Image and laparoscopic guided interstitial brachytherapy for locally advanced primary or recurrent gynaecological cancer using the adaptive GEC ESTRO target concept. *Radiother Oncol*. 2011;100(3):473-479.
46. Beriwal S, Demanes DJ, Erickson B, et al. American Brachytherapy Society consensus guidelines for interstitial brachytherapy for vaginal cancer. *Brachytherapy*. 2012;11(1):68-75.
47. Dimopoulos JC, Schmid MP, Fidarova E. Treatment of locally advanced vaginal cancer with radiochemotherapy and magnetic resonance image-guided adaptive brachytherapy: dose-volume parameters and first clinical results. *Int J Radiat Oncol Biol Phys*. 2012. 82(5):1880-1888.
48. Kim H, Rajagopalan, MS, Houser C, Beriwal S. Dosimetric comparison of multichannel with one single-channel vaginal cylinder for vaginal cancer treatments with high-dose-rate brachytherapy. *Brachytherapy*. 2014;13(3):263-267.
49. Vargo JA, Kim H, Houser CJ, et al. Image-based multichannel vaginal cylinder brachytherapy for vaginal cancer. *Brachytherapy*. 2015;14(1):9-15.

Non-brachytherapy alternatives in cervical cancer radiotherapy: Why not?

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With more than 500,000 new cases diagnosed worldwide during 2014 alone,[1] cervical cancer poses a significant health problem. In patients presenting with locally advanced disease, brachytherapy (BT) is considered the gold standard technique to deliver boost radiation dose to cervical disease. Compared to external-beam radiation therapy (EBRT) alone, BT boost improves overall survival (OAS)[2,3] and reduces the local recurrence of disease (LR).[2,4] These findings affirm BT's role in the treatment of gynecologic cancers, which was first established in 1960.[5] Since then, BT boost supplementing concurrent chemotherapy and EBRT has been the treatment of choice for locally advanced cervical cancer.[6]

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The unique anatomical location of cervical tumors makes BT a superior delivery method compared to historic external-based techniques. Loading the radiation source within the cervical target volume accounts for the variations in target position (precipitated by bladder and rectal filling), a feature not shared with EBRT techniques, which would otherwise necessitate a large planning target volume (PTV) margin to account for these random variabilities in patient setup and organ motions. Furthermore, BT allows for delivery of a high dose to tumor tissue, while maintaining a steep dose gradient to surrounding normal tissue, thus allowing better sparing of the adjacent bowel and bladder. In addition to the unique dose distribution, the superiority of BT was boosted by the introduction of high-dose-rate (HDR) BT. This technique not only yields equivalent tumor control and a toxicity profile as low-dose-rate (LDR) BT,[7-10] it possesses several advantages such as enhanced dosimetric accuracy via dwell-time optimization, better consistency due to shorter delivery time, greater patient convenience with potentially fewer complications secondary to shortened bed rest, and lower costs associated with outpatient delivery.[11] These considerations have led to a surge in HDR BT adoption[12] overlooking the LDR's radiobiological advantages.[13]

Regardless of the BT technique, implementing and delivering an appropriate BT plan is plagued by several challenges. Assuming that applicators are placed accurately at each treatment, significant variations in inter- and intrafraction delivery remain common.[14] Further complications arise from inappropriate placement in a technique that is sensitive to physician skills: insufficient cavity packing reduces disease-free survival (DFS), and improper ovoid placement reduces both local control (LC) and DFS.[15] Clinician skills aside, the insertion of BT applicators is associated with heightened risk due to anesthesia complications and/or increased treatment costs due to operating and recovery room time.[16] Numerous patients are excluded from BT due to physical considerations that prevent applicator placement, such as decreased

Table 1. Studies Using Nonbrachytherapy Techniques to Deliver Boost Dose in Cervical Cancer Treatment

Study	Gyn (cervical)	MFU (month)	Med Pt Age (years)	Boost Technique	Setting	WPI Dose /dose per Fx	Boost Dose /dose per Fx	Tumor BED_{10}[c]	NT(rectal/ bladder) BED_3[c]	LC(%)[a]	>G2 Tox (%)[a]
Kagei et al (2003)[33]	(25)	139	62	Proton	Def	50.4/1.8	36/2.5-4	110	166	75	4
Molla et al (2005)[32]	16(7)	12.6	53	SBRT(Linac)	Adj	45-50.4/1.8	14/7-20/4	84-88	NR	86	0
Chan et al (2006)[22]	12(8)	23	NR	3DCRT	Def	45-50/1.8-2	25.2/1.8-2	85-90	NR	83	17
Matsuura et al (2007)[20]	(7)	17	81	3DCRT	Def	45/1.8	20-24/1.2-1.6[d]	80	NR	86	0
Barraclough et al (2008)[21]	44(38)	27	56	3DCRT	Def	40-45/2-2.5	15-25/1.8-2.5	66-87	91-128	79	2
Jorcano et al (2010)[31]	26(9)	47	62	SBRT(Linac)	Adj	45-50.4/1.8	14/7	84	NR	77	7
Park et al (2010)[23]	(10)	18	64	3DCRT	Def	50/2	30/5	105	NR	60	0
Marnitz et al (2013)[18]	(11)	6	53	SBRT(CK)	Def	50.4/1.8	30/6	108	103/137	100	0
Kubicek et al (2013)[26]	11(4)	4	62	SBRT(CK)	Def	45/1.8	25/5	77	110	75	25
Hsieh et al (2013)[24]	(9)	36	68	SBRT(HT)	Def	50-50.4/2-1.8	16-27/2-4.5	91.2	197/189[b]	78	0
Vandecasteele et al (2013)[30,g,i]	(30)	24	52	IMRT	Adj	45/1.8	62/2.48[f]	77	NR	96	14
Khosla et al (2013)[29h,g]	(25)	38	47	IMRT	Adj	46/2	30-35/2.3-3	96	NR	76	8
Wang et al (2015)[28,g]	(80)	34	45	IMRT	Adj	50.4/1.8	9/3-60.2/2.15[f]	72	NR	98	0

3DCRT = 3 dimensional conformal radiotherapy, Adj = adjuvant, BED = biologic effective dose, CK = Cyberknife, Def = definitive, Fx = fraction, HT = helical tomotherapy, IMRT = intensity-modulated radiation therapy, Gyn = gynecologic tumors, LC= local control, Med = median, MFU = median follow up, NR = not reported due to absent specific parameters for calculation, NT = normal tissue, Pt = patient, Tox = late toxicity, WPI = whole-pelvic irradiation

a = At median follow up
b = Maximum point dose
c = BED approximate estimates using linear quadratic formalism: $BED = nd\,(1+d/(\alpha/\beta))$
d = The boost dose was given twice a day with 6 hours interval in a hyperfractionated fashion
e = Sequential IMRT boost to uterus and cervix in 5 patients
f = Boost dose delivered as simultaneous integrated boost
g = Prospective
h = Residual cervical disease
i = IMRT was delivered neoadjuvantly followed by surgery
j = One patient had recurrence of disease and was not scored for stage

vaginal accommodation with age, uterine malformations, or excessive tumor volume.[17,18] Some patients simply refuse BT with concerns of invasiveness or discomfort.[18] Most concerning of all may be the low availability of BT: In 2012, only 25% of gynecologic cancer clinics used high-quality image-guided BT.[19]

Fortunately, the new generation of EBRT techniques, with highly precise dose distributions, present viable options that may offer an appropriate alternative to the costly, logistically complex and invasive BT. In light of the dogma that BT is irreplaceable, most studies using high-tech EBRT have been carried out in patients who could not receive BT for medical or personal reasons. Here we propose high-precision EBRT techniques, including stereotactic body radiation therapy (SBRT) and intensity-modulated radiation therapy (IMRT), as clinically effective alternatives to BT. In this review, all comparisons will be made to HDR BT due to its aforementioned prevalence in current practice.

Methods

A systematic literature search was performed using PubMed, and included studies published in English between January 1, 1990 and July 7, 2015. The search terms employed were "cervical cancer" or "gynecologic cancer" with "brachytherapy alternatives," "radiosurgery," "stereotactic body radiotherapy," "SBRT," "intensity-modulated radiation therapy boost," "simultaneous integrated boost," and "IMRT boost." The abstracts of all resultant articles were screened by 2 physicians to assess relevance to this review, and 78 publications were selected. Eligibility was limited to studies that reported outcomes on at least 5 patients whose primary cervical lesion received a boost via EBRT rather than BT, and who reported follow-up at a minimum of 4 months. Fourteen studies met these criteria, and the remainder were excluded due to the following reasons: (1) featured no reported clinical outcomes; (2) contained only a review or database queries; (3) targeted pelvic and/or para-aortic volumes without replacement of BT; or (4) managed recurrent rather than primary disease.

Results

There is scarce representation of next-generation EBRT techniques as alternatives to BT in the literature (Table 1). Most studies are retrospective analyses, with only 3 prospective studies to date. These studies are heterogeneous in treatment plan (delivery technique and dose fractionation) and follow-up time, include small patient populations, and often address other gynecologic malignancies in addition to cervical cancer. In most studies, the pelvic planning target volume (PTV) received photon beams to 45-50.4 Gy in 1.8 to 2 Gy per fraction. However, studies were inconsistent in their reporting of dosimetric information for normal tissue, precluding a dose-toxicity analysis. In most of these studies, the rationale for employing a BT alternative was either patient refusal of BT or anatomical constraints preventing proper BT delivery. In all but one study, a high-tech EBRT boost (SBRT or IMRT) of 16 to 36 Gy in 1.8 to 6 Gy per fraction was delivered after whole-pelvic irradiation.

In the exception, Matsuura et al used a hyperfractionated schedule: In the fourth week, a small conformal boost volume (1.2 to 1.6 Gy per fraction) was initiated concomitant with pelvic irradiation, and continued after the fifth week twice daily, with at least 6 hours between fractions. This study did not employ image-guided radiotherapy, and uniform 0.5 to 1 cm clinical target volume (CTV) to PTV expansion was used. Two-year local control was 85.7%, with the highest toxicity being grade 2 rectal bleeding, affecting only 2 out of 7 patients.[20]

Three studies employed similar conformal radiotherapy techniques. Two-year local control was reported as 79% by Barraclough et al,[21] 83% by Chan et al,[22] and 60% by Park et al.[23] Park et al used real-time tracking of gold fiducial markers implanted in the cervix, and observed no grade 3 or higher late toxicities. Therefore, although this study delivered a higher total dose and a higher dose per fraction than the 2 aforementioned studies, Park et al observed lower toxicity rates, likely due to the use of image guidance. In contrast, late grade 3 urinary and late grade 3 rectal toxicities were 2% in Barraclough et al and 17% in Chan et al, despite delivering lower total dose with lower biologic effective dose (BED), implying the importance of image guidance for accurate EBRT delivery.

Also of note, 4 recent studies employed SBRT for boost delivery, and each delivered 16 to 30 Gy to the cervix in 2 to 6 Gy per fraction. With the caveat that follow-up time was short (6 to 36 months), 3 of the 4 studies demonstrated encouraging results, with minimal late toxicity and local control rates of 78% (Hsieh et al), 100% (Marnitz et al), and 100% (Haas et al).[18,24,25] Marnitz et al and Haas et al used the CyberKnife (CK) system (Accuray Inc., Sunnyvale, California) to track gold fiducials implanted in the cervix for precise SBRT boost delivery. This may explain the studies' high rate of local control (both 100%) compared to Hsieh et al (78%). However, the findings of Hsieh et al may also be accounted for by a longer overall treatment time (79 days) and the inclusion of patients with advanced disease. From a toxicity perspective, the use of helical tomotherapy (HT) (TomoTherapy Inc., Madison, Wisconsin) for megavoltage CT imaging in advance of each fraction by Hsieh et al likely contributed to the lack of observed late severe toxicities by improving precision and delivery consistency.

Paradoxically, Kubicek et al observed high rectal toxicity despite using multiple measures to ensure accuracy:

CTV definition by MRI and a 0.5 cm PTV to CTV expansion, in addition to CK tracking of cervical fiducials.[26] However, cautious interpretation of these results is needed due to a small patient population (only 4 patients with cervical squamous cell carcinoma), short follow-up time (median 4 months), and heterogeneity of treatment plans: Two patients received 25 Gy in 5 fractions, 1 patient received 15 Gy in 3 fractions in addition to 12 Gy HDR BT, and 1 patient received 5 Gy in 1 fraction before having a stroke and transferring to hospice care. The latter patient was the only one who developed recurrence; the 3 patients who completed treatment remained free of recurrence.

Some cervical cancer patients treated with radical hysterectomy are at a higher risk of recurrence due to high risk factors such as small margins, involvement of the parametrium or vagina, or lymphovascular invasion. In these patients, a BT boost is often given after EBRT.[27] Five studies investigated the use of BT alternatives in this setting: 3 prospective studies using IMRT,[28-30] and 2 retrospective studies using SBRT.[31,32] Tumor control and toxicity profiles were promising: at median 13- to 38-month follow up, the local control rate was 76 to 96%, with only 0 to 14% occurrence of severe late toxicity.

In the studies employing SBRT, Molla et al and Jorcano et al used a linac-based system to deliver a 14 Gy boost in 2 fractions after 45 to 50.4 Gy of whole-pelvic irradiation.[31,32] Both studies used multiple methods to improve precision. The ExacTract infrared-guided system (Brainlab AG, Heimstetten, Germany) was used to link skin markers to the isocenter for the duration of delivery. Target organ motion was limited by insertion of an MR endorectal probe, enhancing reproducibility. Despite different follow-up times (Molla 13 months; Jorcano 47 months), both studies demonstrated comparable and acceptable local control (Molla 86%; Jorcano, 77%) and late toxicity rates (Molla 0%; Jorcano 7%), supporting the efficacy of image-guided SBRT techniques.

In the studies using IMRT, Wang et al and Vandecasteele et al both used simultaneous integrated boost (SIB) to perioperatively treat areas at risk.[28,30] Wang et al compared the efficacy of 60.2 Gy in 28 fractions SIB concurrent with 50.4 Gy pelvic IMRT to a sequential accelerated boost of 9 Gy in 3 fractions after the conclusion of 50 Gy in 2 fractions pelvic IMRT. Both groups had comparable local control (98% vs. 100%) and late severe toxicity (both 0%).[28] Vandecasteele et al took a different approach, administering SIB of 62 Gy in 4.28 Gy per fraction concurrent with pelvic IMRT of 45 Gy in 25 fractions prior to surgical resection. At the median 2-year follow-up, a promising 96% local control and 100% regional control were observed with only 4% late grade 4 intestinal and 14% late grade 3 urinary toxicity.[30] The final prospective IMRT study included patients with a particularly dismal prognosis exhibiting persistent gross residual disease in the vaginal vault after whole-pelvic radiotherapy of 46 Gy in 23 fractions. These patients were given either 30 Gy in 10 fractions concurrent with 20 Gy to the PTV, or with 35 Gy in 15 fractions concurrent with 30 Gy to the PTV.[29] This dose escalation proved beneficial with a local control of 76% at median 38-month follow-up, and only 8% of patients exhibited late grade 3 toxicity.

Proton beams have also been used as alternatives to BT boost delivering 86 Gy median tumor dose. The reported 5-year local control was 100% for stage IIB and 61% for stage IIIB/IVA lesions, and the grade 4 genitourinary and/or gastrointestinal side effects were only 4%, comparable to HDR BT outcomes.[33]

An established association between BED and treatment outcome can, in theory, be used to select the optimal SBRT or IMRT dose/fractionation schedule, analogous to those used in BT planning.[34] Even for BT, this correlation has been difficult to define: In one study, the BED at point A could not be related to either regional control or toxicity,[35] but other studies have demonstrated that above a rectal BED_3 threshold of 125 Gy_3 (rectal point)[36,37] or 140 Gy_3 (rectal maximum dose on CT)[38], excessive toxicity results. Such a correlation for BED and local control or toxicity in these IMRT and SBRT studies could not be defined. As shown in Table 1, the studies adopted different dose fractionation schedules leading to a highly variable tumor BED_{10} and normal tissue BED_3. This variability precluded correlating treatment outcome to either the resultant BED estimations or BED constraints established in the BT literature.

Discussion

1. Dosimetric perspective

Among all EBRT techniques, SBRT is, in theory, the most likely to replicate a BT dose distribution with sharp dose gradient. In SBRT, multiple noncoplanar beams intersect within the target volume. This allows high-dose delivery directly to the tumor, while maximally sparing the surrounding tissue. In fact, several dosimetric studies have favored SBRT for optimal target coverage and OAR sparing.[39-42] In one study, SBRT boost plans were created for 11 cervical cancer patients and compared in dose distribution to BT boost plans. Rectal dose to 1 cc (d_{1cc}), bladder d_{1cc}, and median target coverage by the 100% isodose line were all superior in the SBRT plans.[39] Another study generated volumetric-modulated arc therapy (VMAT) dosimetric plans for 51 gynecologic cancer patients, and similarly demonstrated that compared to BT, SBRT yielded favorable rectal d_{1cc}, d_{2cc}, and maximum dose, with comparable doses to bladder and bowel, although BT offered superior integral dose and PTV coverage.[43] The majority of these studies compared EBRT dose distribution

with brachytherapy dose distribution prescribed to point A. Currently, image-guided tailored brachytherapy dose distribution prescribed to target volumes rivals the classic prescription to reference points and may compare favorably against the EBRT technique. Whether extreme high dosage within the tumor is needed from a radiobiologic standpoint (to overcome hypoxic foci) is a matter of debate. However, the brachytherapy profile (characterized by very high dosage within the vicinity of the applicators) cannot challenge EBRT dose homogeneity within the target volume.

On the other hand, IMRT is based on the manipulation of many small subdivided beams, each with varying intensity. Because each beam can be manipulated individually, the dose distribution can be exquisitely controlled, and a highly conformal treatment field results.[44] These characteristics allow dose painting, a desirable quality of boost radiation delivery because it allows the pelvic field to receive a lower dose while delivering a high dose to the cervical PTV. Because this can reduce overall treatment time, such a method is especially favorable for rapidly proliferating tumors.[45] In fact, this strategy yielded favorable local control when delivered concomitantly with whole-pelvic irradiation.[46] IMRT is also superior to conformal radiotherapy as a boost alternative in patients unable to receive BT in respect to both target coverage and OAR sparing.[22]

2. Target motion and internal target volume dilemma

Variations in cervix position due to bladder and rectal filling are continuous, nonuniform, and significant: Cervical target volume motion can reach 18 mm.[47,48] Although tumor volume shrinkage during treatment is significant (reaching 79%),[49,50] target motion is so large that shrinkage cannot replace the need for large PTV margins.[51] To deliver an EBRT boost precisely, the target must be either immobilized or continuously tracked, such as with the above-mentioned gold fiducial markers or endorectal probes. A CT-compatible vaginal cylinder used in applicator-guided VMAT has been shown to decrease target volume motion such that a PTV margin of only 2 mm is necessary; the cylinder had the additional advantage of decreasing rectal dose compared to BT.[43] A study of gold fiducial markers as a readout for cervix position showed that PTV margins can drop to 6.7 to 8.3 mm when fiducials are used, and real-time tracking can further decrease these margins.[52]

3. Radiobiologic considerations

Any valid radiation treatment plan is constructed based on the balance between normal tissue complication probability (NTCP) and tumor control probability (TCP). Influencing this balance are the rate of repopulation, hypoxia and radiosensitivity, repair kinetics compared to the interfraction interval time, and the alpha/beta (α/β) ratio of normal and tumor tissues. A fractionation schedule that maximizes the therapeutic ratio must take all of these into account.[53]

Endorsed by the American Brachytherapy Society, 6 Gy for 5 fractions is the most popular HDR fractionation schedule.[54] Accordingly, radiobiologic disparities between this schedule and that adopted in most SBRT studies are expected to be negligible. When an interfraction interval sufficient to allow repair is present,[55] toxicity concern of high dose per fraction is negligible. Moreover, a hypofractionation scheme allows for reduction of the overall treatment time, a desirable feature in cervical cancer[53] with its rapid doubling time,[56] fast repopulation, and high (α/β) ratio.[57] Yet, the interfractionation gaps may lead to prolonged overall treatment time and interfraction repopulation which, consequently, leads to worse treatment outcome in cervical cancer.[58] Although, hypofractionated plans have been proven efficacious in several studies,[7,8,59] a shorter schedule avoiding interfraction gaps through dose-painting IMRT may provide a more efficacious fractionation schedule.[45]

Conclusions

Although relatively new and longer follow up is needed to ascertain favorable treatment outcomes, high-tech EBRT boost techniques, when properly executed, are highly promising for treating cervical cancer. Treatment outcomes are comparable to those reported in the BT literature: With local control, for example, values in HDR BT studies range from 62% to 84%.[8,36,60,61] Moreover, BT is associated with its own risks. The major complication rate of BT can reach 10%, including a 1.4% fatality rate,[60] largely due to the difficulty in executing appropriate BT implants in patient populations with different tumor volumes. Incorrect implementation of SBRT or IMRT can certainly lead to similar detriments. To challenge the impeccable BT dose distribution and long track record, boost techniques employing IMRT or SBRT must fulfill the following requirements:

1. Treatment volumes must be accurately defined (eg, with MRI).
2. Plans must be meticulously optimized to spare organs at risk.
3. Treatment delivery must be precise, with minimized target volume motion via applicator guidance, image guidance or target volume tracking.
4. Planning must be adaptive and modifiable based on repeat imaging.
5. Fractionation schedules must be optimized based on tumor kinetics, possibly guided by tumor kinetics biomarkers.

These measures should be considered mandatory, and boosting cervical disease with EBRT must not be delivered in their absence. Studies that use an

SBRT or IMRT boost but do not conform to these requirements may inaccurately portray these techniques as less effective.[62] Therefore, large prospective studies to definitively establish or invalidate non-BT alternatives for treating cervical cancer radiotherapy are urgently needed.

References

1. Cancer International Agency for Research on Cancer. Cervical cancer estimated incidence, mortality and prevalence worldwide in 2012. *World Health Organization* 2012.
2. Coia L, Won M, Lanciano R et al. The Patterns of Care Outcome Study for cancer of the uterine cervix. Results of the Second National Practice Survey. *Cancer.* 1990;66(12): 2451-2456.
3. Han K, Milosevic M, Fyles A, et al. Trends in the utilization of brachytherapy in cervical cancer in the United States. *Int J Radiat Oncol Biol Phys.* 2013;87(1):111-119.
4. Hanks GE, Herring DF, Kramer S. Patterns of care outcome studies. Results of the national practice in cancer of the cervix. *Cancer.* 1983;51(5): 959-967.
5. Henschke UK. "Afterloading" applicator for radiation therapy of carcinoma of the uterus. *Radiology* 1960;74:834.
6. Viswanathan AN, Thomadsen B. American Brachytherapy Society Cervical Cancer Recommendations Committee, American Brachytherapy Society. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part I: general principles. *Brachytherapy.* 2012;11(1):33-46.
7. Lertsanguansinchai P, Lertbutsayanukul C, Shotelersuk K, et al. Phase III randomized trial comparing LDR and HDR brachytherapy in treatment of cervical carcinoma. *Int J Radiat Oncol Biol Phys.* 2004;59(5):1424-1431.
8. Patel FD, Sharma SC, Negi PS, et al. Low dose rate vs. high dose rate brachytherapy in the treatment of carcinoma of the uterine cervix: a clinical trial. *Int J Radiat Oncol Biol Phys.*1994;28(2):335-341.
9. Okkan S, Atkovar G, Sahinler I, et al. Results and complications of high dose rate and low dose rate brachytherapy in carcinoma of the cervix: Cerrahpasa experience. *Radiother Oncol.* 2003;67(1):97-105.
10. Hareyama M, Sakata K, Oouchi A, et al. High-dose-rate versus low-dose-rate intracavitary therapy for carcinoma of the uterine cervix: a randomized trial. *Cancer.* 2002;94(1):117-124.
11. Gunderson LL, Tepper JE. *Clinical radiation oncology*. Third ed. Chapter 14: Elsevier Health Sciences; 2012.
12. Patankar SS, Tergas AI, Deutsch I, et al. High versus low-dose rate brachytherapy for cervical cancer. *Gynecol Oncol.* 2015;136(3):534-541.
13. Brenner DJ, Hall EJ. Fractionated high dose rate versus low dose rate regimens for intracavitary brachytherapy of the cervix. I. General considerations based on radiobiology. *Br J Radiol.* 1991;64(758):133-141.
14. Nesvacil N, Tanderup K, Hellebust TP, et al. A multicentre comparison of the dosimetric impact of inter- and intra-fractional anatomical variations in fractionated cervix cancer brachytherapy. *Radiother Oncol.* 2013;107(1):20-25.
15. Viswanathan AN, Moughan J, Small W Jr., et al. The quality of cervical cancer brachytherapy implantation and the impact on local recurrence and disease-free survival in radiation therapy oncology group prospective trials 0116 and 0128. *Int J Gynecol Cancer.* 2012;22(1):123-131.
16. Kirchheiner K, Nout RA, Czajka-Pepl A, et al. Health related quality of life and patient reported symptoms before and during definitive radio(chemo)therapy using image-guided adaptive brachytherapy for locally advanced cervical cancer and early recovery - a mono-institutional prospective study. *Gynecol Onco.l* 2015;136(3):415-423.
17. Odunsi K, Pejovic T. Gynecologic cancers: a multidisciplinary approach to diagnosis and management. New York: Demos Medical; 2014.
18. Marnitz S, Kohler C, Budach V, et al. Brachytherapy-emulating robotic radiosurgery in patients with cervical carcinoma. *Radiat Oncol.* 2013;8: 109.
19. Viswanathan AN, Creutzberg CL, Craighead P, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). *Int J Radiat Oncol Biol Phys.* 2012;82(1):250-255.
20. Matsuura K, Tanimoto H, Fujita K, et al. Early clinical outcomes of 3D-conformal radiotherapy using accelerated hyperfractionation without intracavitary brachytherapy for cervical cancer. *Gynecol Oncol.* 2007;104(1): 11-14.
21. Barraclough LH, Swindell R, Livsey JE, et al. External beam boost for cancer of the cervix uteri when intracavitary therapy cannot be performed. *Int J Radiat Oncol Biol Phys.* 2008;71(3):772-778.
22. Chan P, Yeo I, Perkins G, et al. Dosimetric comparison of intensity-modulated, conformal, and four-field pelvic radiotherapy boost plans for gynecologic cancer: a retrospective planning study. *Radiat Oncol.* 2006;1:13.
23. Park HC, Shimizu S, Yonesaka A, et al. High dose three-dimensional conformal boost using the real-time tumor tracking radiotherapy system in cervical cancer patients unable to receive intracavitary brachytherapy. *Yonsei Med J.* 2010;51(1):93-99.
24. Hsieh CH, Tien HJ, Hsiao SM, et al. Stereotactic body radiation therapy via helical tomotherapy to replace brachytherapy for brachytherapy-unsuitable cervical cancer patients - a preliminary result. *Onco Targets Ther.* 2013;6:59-66.
25. Haas JA, Witten MR, Clancey O, et al. CyberKnife Boost for Patients with Cervical Cancer Unable to Undergo Brachytherapy. *Front Oncol.* 2012;2:25.
26. Kubicek GJ, Xue J, Xu Q, et al. Stereotactic body radiotherapy as an alternative to brachytherapy in gynecologic cancer. *Biomed Res Int.* 2013; 2013: 898953.
27. Small W Jr., Beriwal S, Demanes DJ, et al. American Brachytherapy Society consensus guidelines for adjuvant vaginal cuff brachytherapy after hysterectomy. *Brachytherapy.* 2012;11(1):58-67.
28. Wang X, Zhao Y, Shen Y, et al. Long-term follow-up results of simultaneous integrated or late course accelerated boost with external beam radiotherapy to vaginal cuff for high risk cervical cancer patients after radical hysterectomy. *BMC Cancer.* 2015;15:257.
29. Khosla D, Patel FD, Rai B, et al. Dose escalation by intensity-modulated radiotherapy boost after whole pelvic radiotherapy in postoperative patients of carcinoma cervix with residual disease. *Clin Oncol (R Coll Radiol).* 2013;25(1):e1-6.
30. Vandecasteele K, Makar A, Van den Broecke R, et al. Intensity-modulated arc therapy with cisplatin as neo-adjuvant treatment for primary irresectable cervical cancer. Toxicity, tumour response and outcome. *Strahlenther Onkol.* 2012;188(7):576-581.
31. Jorcano S, Molla M, Escude L, et al. Hypofractionated extracranial stereotactic radiotherapy boost for gynecologic tumors: a promising alternative to high-dose rate brachytherapy. *Technol Cancer Res Treat.* 2010;9(5):509-514.
32. Molla M, Escude L, Nouet P, et al. Fractionated stereotactic radiotherapy boost for gynecologic tumors: an alternative to brachytherapy? *Int J Radiat Oncol Biol Phys.* 2005; 62(1):118-24.
33. Kagei K, Tokuuye K, Okumura T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 2003;55(5):1265-71.
34. Recommendations from gynaecological (GYN) GEC ESTRO working group (II): concepts and terms in 3D image-based treatment planning in cervix cancer brachytherapy-3D dose volume parameters and aspects of 3D image-based anatomy, radiation physics, radiobiology. *Radiother Oncol.* 2006;8(1): 67-77.
35. Petereit DG, Pearcey R. Literature analysis of high dose rate brachytherapy fractionation schedules in the treatment of cervical cancer: is there an optimal fractionation schedule? *Int J Radiat Oncol Biol Phys.* 1999; 43(2):359-366.
36. Hyun Kim T, Choi J, Park SY, et al. Dosimetric parameters that predict late rectal complications after curative radiotherapy in patients with uterine cervical carcinoma. *Cancer.* 2005;104(6):1304-1311.
37. Clark BG, Souhami L, Roman TN, et al. The prediction of late rectal complications in patients treated with high dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 1997;38(5):989-993.
38. Noda SE, Ohno T, Kato S, et al. Late rectal complications evaluated by computed tomography-based dose calculations in patients with cervical carcinoma undergoing high-dose-rate brachytherapy. *Int J Radiat Oncol Biol Phys.* 2007;69(1):118-124.
39. Cengiz M, Dogan A, Ozyigit G, et al. Comparison of intracavitary brachytherapy and stereotactic body radiotherapy dose distribution for cervical cancer. *Brachytherapy.* 2012;11(2):125-129.
40. Sethi RA, Jozsef G, Grew D, et al. Is there a role for an external beam boost in cervical cancer radiotherapy? *Front Oncol.* 2013;3:3.

41. Low DA, Grigsby PW, Dempsey JF, et al. Applicator-guided intensity-modulated radiation therapy. *Int J Radiat Oncol Biol Phys.* 2002;52(5):1400-1406.
42. Neumann O, Kluge A, Lyubina O, et al. Robotic radiosurgery as an alternative to brachytherapy for cervical cancer patients. *Strahlenther Onkol.* 2014;190(6):538-545.
43. Pedicini P, Strigari L, Caivano R, et al. Local tumor control probability to evaluate an applicator-guided volumetric-modulated arc therapy solution as alternative of 3D brachytherapy for the treatment of the vaginal vault in patients affected by gynecological cancer. *J Appl Clin Med Phys.* 2013;14(2): 4075.
44. Halperin EC, Perez CA, Brady LW. *Perez and Brady's principles and practice of radiation oncology.* 5th ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
45. Guerrero M, Li XA, Ma L, et al. Simultaneous integrated intensity-modulated radiotherapy boost for locally advanced gynecological cancer: radiobiological and dosimetric considerations. *Int J Radiat Oncol Biol Phys.* 2005;62(3):933-939.
46. Kavanagh BD, Gieschen HL, Schmidt-Ullrich RK, et al. A pilot study of concomitant boost accelerated superfractionated radiotherapy for stage III cancer of the uterine cervix. *Int J Radiat Oncol Biol Phys.* 1997;38(3):561-568.
47. Haripotepornkul NH, Nath SK, Scanderbeg D, et al. Evaluation of intra- and inter-fraction movement of the cervix during intensity modulated radiation therapy. *Radiother Oncol.* 2011;98(3):347-351.
48. Taylor A, Powell ME. An assessment of interfractional uterine and cervical motion: implications for radiotherapy target volume definition in gynaecological cancer. *Radiother Oncol.* 2008;88(2):250-257.
49. Lee CM, Shrieve DC, Gaffney DK. Rapid involution and mobility of carcinoma of the cervix. *Int J Radiat Oncol Biol Phys.* 2004;58(2):625-630.
50. van de Bunt L, van der Heide UA, Ketelaars M, de Kort GA, Jurgenliemk-Schulz IM. Conventional, conformal, and intensity-modulated radiation therapy treatment planning of external beam radiotherapy for cervical cancer: The impact of tumor regression. *Int J Radiat Oncol Biol Phys.* 2006;64(1):189-196.
51. Beadle BM, Jhingran A, Salehpour M, et al. Cervix regression and motion during the course of external beam chemoradiation for cervical cancer. *Int J Radiat Oncol Biol Phys.* 2009; 73(1): 235-241.
52. Yamamoto R, Yonesaka A, Nishioka S, et al. High dose three-dimensional conformal boost (3DCB) using an orthogonal diagnostic X-ray set-up for patients with gynecological malignancy: a new application of real-time tumor-tracking system. *Radiother Oncol.* 2004;73(2):219-222.
53. Fowler JF. Biological factors influencing optimum fractionation in radiation therapy. *Acta Oncol.* 2001;40(6):712-717.
54. Viswanathan AN, Beriwal S, De Los Santos JF, et al. American Brachytherapy Society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. *Brachytherapy.* 2012;11(1):47-52.
55. Orton CG. High-dose-rate brachytherapy may be radiobiologically superior to low-dose rate due to slow repair of late-responding normal tissue cells. *Int J Radiat Oncol Biol Phys.* 2001;49(1):183-189.
56. Tsang RW, Fyles AW, Kirkbride P, et al. Proliferation measurements with flow cytometry Tpot in cancer of the uterine cervix: correlation between two laboratories and preliminary clinical results. *Int J Radiat Oncol Biol Phys.* 1995;32(5): 1319-1329.
57. Thames HD, Bentzen SM, Turesson I, et al. Time-dose factors in radiotherapy: a review of the human data. *Radiother Oncol.* 1990;19(3): 219-235.
58. Chen SW, Liang JA, Yang SN. The adverse effect of treatment prolongation in cervical cancer by high-dose-rate intracavitary brachytherapy. *Radiother Oncol.* 2003;67(1):69-76.
59. Teshima T, Inoue T, Ikeda H, et al. High-dose rate and low-dose rate intracavitary therapy for carcinoma of the uterine cervix. Final results of Osaka University Hospital. *Cancer.* 1993;72(8):2409-2414.
60. Ferrigno R, dos Santos Novaes PE, Pellizzon AC, et al. High-dose-rate brachytherapy in the treatment of uterine cervix cancer. Analysis of dose effectiveness and late complications. *Int J Radiat Oncol Biol Phys.* 2001;50(5): 1123-35.
61. Wong FC, Tung SY, Leung TW, et al. Treatment results of high-dose-rate remote afterloading brachytherapy for cervical cancer and retrospective comparison of two regimens. *Int J Radiat Oncol Biol Phys.* 2003;55(5):1254-1264.
62. Gill BS, Lin JF, Krivak TC, et al. National Cancer Data Base analysis of radiation therapy consolidation modality for cervical cancer: the impact of new technological advancements. *Int J Radiat Oncol Biol Phys.* 2014;90(5):1083-1090.

RADIATION ONCOLOGY CASE

Congratulations to our Clinical Case Contest winner for December 2015!

Palliative radiation therapy for metastatic squamous cell carcinoma to the parotid gland

Shayna E. Rich, MD, PhD; and William M. Mendenhall, MD

CASE SUMMARY

A 90-year-old woman underwent surgical resection of skin lesions of the face and fine-needle aspiration of a left parotid mass, with pathology of squamous cell carcinoma. Approximately 2 weeks after surgery, the patient presented to the emergency department with increasing pain and odynophagia due to the increasing left parotid mass (Figure 1A). CT showed an 8-cm left parotid nodal conglomerate encasing the internal carotid artery. An ear, nose and throat (ENT) evaluation found her tumor burden to be unresectable. Radiation was given to 20 Gy in 2 fractions delivered 7 days apart. Prior to the second dose of radiation, she had a 50% tumor response and no toxicity. At 1 month, she had complete clinical tumor response with no complications, including no acute toxicity (Figure 1B). She was eating a normal diet, and her Dobhoff tube was removed. Approximately 1 month later, she developed right neck recurrence treated with radiation to 25 Gy at 5 Gy/fraction. She then enrolled in hospice and died at home 2 months later.She had no acute toxicity from the second course of radiation.

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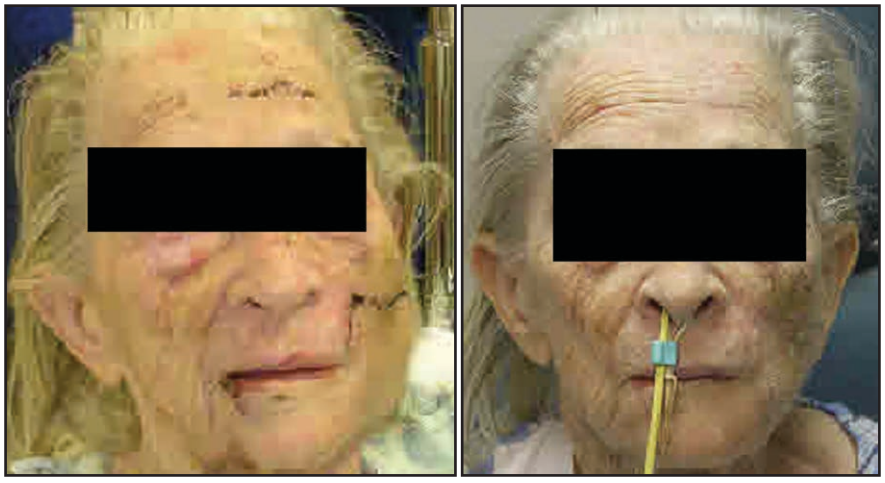

FIGURE 1. *Patient facial appearance. (A) Prior to radiation therapy, showing left parotid mass and facial incisions, and (B) one month after radiation therapy showing resolution of parotid mass.*

IMAGING FINDINGS, DIFFERENTIAL DIAGNOSIS

Postoperative CT of the head and neck demonstrated a large conglomerate necrotic lymph node mass in the left upper neck with obvious extracapsular extension, invading the sternocleidomastoid muscle, left parotid and submandibular glands, and focal areas of skin (Figure 2). There was also bony erosion of the posterior margin of the left mandible. Other necrotic metastatic lymph nodes were seen in the neck bilaterally. A possible left tonsil primary cancer was also seen. CT of the chest showed no evidence of metastatic disease. The differential diagnosis included a skin cancer metastatic to parotid and a second primary head and neck neoplasm including a mucosal primary lesion.

CT of the head and neck at 1 month post-RT showed soft tissue swelling and fat stranding surrounding the left parotid gland, reflecting post-radiation

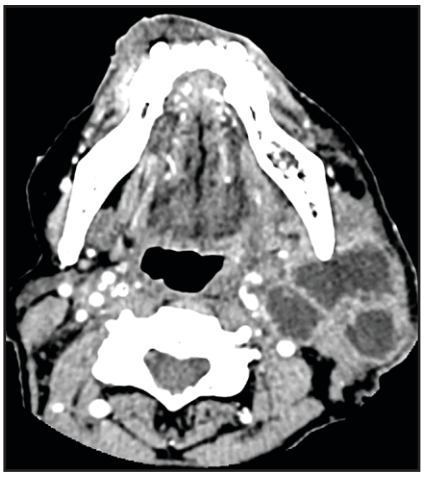

FIGURE 2. *CT of the neck prior to radiation therapy, showing left cervical nodal conglomerate involving parotid gland and encasing the internal carotid artery.*

change. There was also extensive bilateral necrotic lymphadenopathy involving levels 2 and 3. Enlargement was seen in the right necrotic lymph node posterior to the mandible.

DIAGNOSIS

Metastatic squamous cell carcinoma to the left parotid gland and cervical lymph nodes

DISCUSSION

Advanced cancer of the head and neck may cause symptoms including fungating wounds, bleeding and infection. For advanced cancers of the head and neck, curative treatment often requires surgical resection of the gross tumor followed by radiation. Radiation therapy is the main treatment for patients who are inoperable due to unresectable disease or medical comorbidities. It can result in excellent palliative control and even cure. Chemotherapy may be used concurrently with radiation therapy if the toxicity is not too overwhelming.

Hypofractionated radiation treatment courses have been shown to treat advanced cancers of the head and neck effectively with little toxicity. Options have included treatment to a total dose of 30 Gy in 10 fractions daily, 20 Gy in 2 fractions 1 week apart, 30 Gy in 5 fractions 2 days/week, and the so-called "Quad shot" of 14 Gy in 4 fractions twice daily at least 6 hours apart on 2 consecutive days. The Quad shot was designed for up to 3 4-week cycles if the patient tolerates it and the tumor does not progress.

Patients treated with these dose schedules had excellent symptom improvement. In a study of 40 patients with advanced squamous cell carcinoma from mucosal sites, 12 of 22 patients treated to 30 Gy had a symptomatic response at 1 year post-treatment, whereas 7 of 18 patients treated to 20 Gy had a symptomatic response at 1 year.[1] The 20 Gy schedule was typically used for patients with poor life expectancy or poor performance status.

Studies of the Quad shot regimen have found that 60%-85% of patients had improved symptoms.[2-5] In the initial study of the Quad shot regimen, of 30 patients with incurable head and neck cancer, 85% had stable or improved dysphagia, 56% had stable or improved pain, and 67% had stable or improved performance status after treatment.[2] Sixteen patients had an objective response including 2 with a complete response. Median overall survival was 5.7 months, with a median progression-free survival of 3.1 months. Other studies have had similarly good findings for the Quad shot[3-5] or another regimen.[6]

Despite the rapid dose schedules used for advanced cancers of the head and neck, treatment toxicity is usually minor,[2] and the low total doses used generally ensure that long-term complications are very rarely seen. Patients may develop a skin reaction including erythema or skin desquamation in the treatment area, especially if orthovoltage or electron therapy is used. They may experience fatigue for 1-2 weeks following radiation therapy. For tumors involving or near the parotid gland or mucosal sites, patients may develop mild xerostomia or mucositis that usually resolves shortly after treatment.[2] Patients with scalp tumors may develop minor alopecia. Long-term complications may include nonhealing wounds, osteoradionecrosis of any radiated bones, brain necrosis if the treatment area is directly over the brain, blindness or cataract formation if the optic structures were radiated, or chronic xerostomia.

CONCLUSION

Patients with advanced cancers of the head and neck can be treated with rapid courses of radiation therapy with minimal or no toxicity and with good palliative effect. Although these courses should not be used with curative intent, a fraction of patients will have a complete response with surprising durability. Response to radiation may be rapid, so radiation therapy should be considered a viable option for patients with advanced cancers of the head and neck with significant symptoms, even if they have a short life expectancy.

REFERENCES

1. Erkal HS, Mendenhall WM, Amdur RA, et al. Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head and neck mucosal site treated with radiation therapy with palliative intent. *Radiother Oncol.* 2001;59:319-321.
2. Corry J, Peters LJ, Costa ID, et al. The 'QUAD SHOT'—a phase II study of palliative radiotherapy for incurable head and neck cancer. *Radiother Oncol.* 2005;77:137-142.
3. Lok BH, Jiang G, Gutiontov S, et al. Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. *Oral Oncol.* 2015;51:957-962.
4. Ghoshal S, Chakraborty S, Moudgil N, et al. Quad shot: a short but effective schedule for palliative radiation for head and neck carcinoma. *Indian J Palliat Care.* 2009;15:137-140.
5. Carrascosa LA, Yashar CM, Paris KJ, et al. Palliation of pelvic and head and neck cancer with paclitaxel and a novel radiotherapy regimen. *J Palliat Med.* 2007;10:877-881.
6. Porceddu SV, Rosser B, Burmeister BH, et al. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment—"Hypo Trial." *Radiother Oncol.* 2007;85:456-462.

RADIATION ONCOLOGY CASE

Stereotactic body radiotherapy for palliation of rapidly progressive locoregionally confined sarcomatoid squamous cell carcinoma of the head and neck

Sara J. Zakem, BS; Matthew C. Ward, MD; Nikhil Joshi, MD; Ping Xia, PhD; Shlomo A. Koyfman, MD

CASE SUMMMARY

A 65-year-old male's extensive oncologic history began in September 2009 when he presented with a T4N1M0 squamous cell carcinoma (SCC) of the right floor of mouth and hemimandible. The patient underwent a right segmental hemimandibulectomy, floor of mouth resection, right selective lymph node dissection, left fibular free-flap and postoperative radiotherapy to 60 Gy in 30 fractions to the primary site and superior ipsilateral neck. He tolerated this treatment well, but in September 2012 underwent segmental mandibulectomy with fibular free-flap reconstruction for osteoradionecrosis of the mandible.

He was without evidence of disease until March 2013 when he developed firmness in the floor of mouth and was found to have a local recurrence of his disease on fine-needle aspiration. He subsequently underwent definitive surgical composite resection of his recurrent disease with segmental mandibulectomy, excision of the lip and floor of mouth, left selective lymph node dissection, right fibular free-flap reconstruction and tracheostomy. Unfortunately, approximately 7 months later, his disease recurred involving the entire hard palate. In January 2014, he underwent a right total maxillectomy with total palatectomy with wide local excision of the oral cavity recurrent tumor involving the right lower lip, buccal cavity, right lateral tongue and a right selective lymph node dissection. The pathology at this point was consistent with spindle cell carcinoma with bone invasion. In February 2015, the patient noticed increasing oral secretions and dysphagia. A positron emission tomography (PET) scan was performed demonstrating a hypermetabolic mass originating from the floor of mouth (Figure 1). The patient underwent direct laryngoscopy with biopsies, which revealed recurrent squamous cell carcinoma with sarcomatoid features of the supraglottis and floor of mouth. Given his extensive surgical history and size of the recurrence, he was felt not to be a candidate for additional surgical resection. Due to the patient's preference to avoid a protracted conventional treatment course, he and his wife opted to pursue a short-course of stereotactic body radiotherapy (SBRT).

He was treated with SBRT to 45 Gy in 5 fractions to the gross disease (SBRT plan, Figure 2) delivered every other day. He tolerated this well and was found to have a complete response within the SBRT field at his 1-month follow-up visit. Unfortunately, however, a second asymptomatic, discontiguous exophytic, vascular parastomal recurrence was discovered within 1 month of completing SBRT in the paratracheal region inferior to the previous field (Figure 3). Given his previous excellent response, he again was treated with SBRT to 45 Gy in 5 fractions to the gross disease with an elective neck volume to 30 Gy in 5 fractions (SBRT plan 2, Figure 4). The second SBRT plan was assessed along with the first in a composite fashion to ensure there was no overlap (Figure 5). Again he tolerated this well

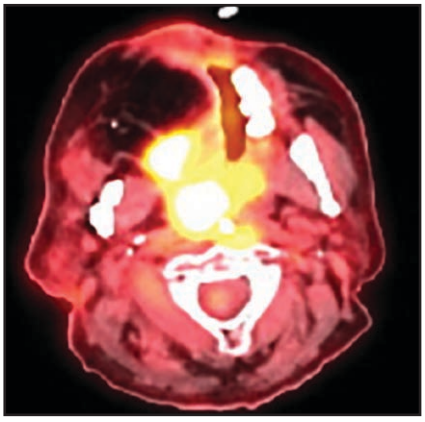

FIGURE 1*. PET scan demonstrating floor-of-mouth enhancement, consistent with recurrent squamous cell carcinoma of the supraglottis and floor of mouth.*

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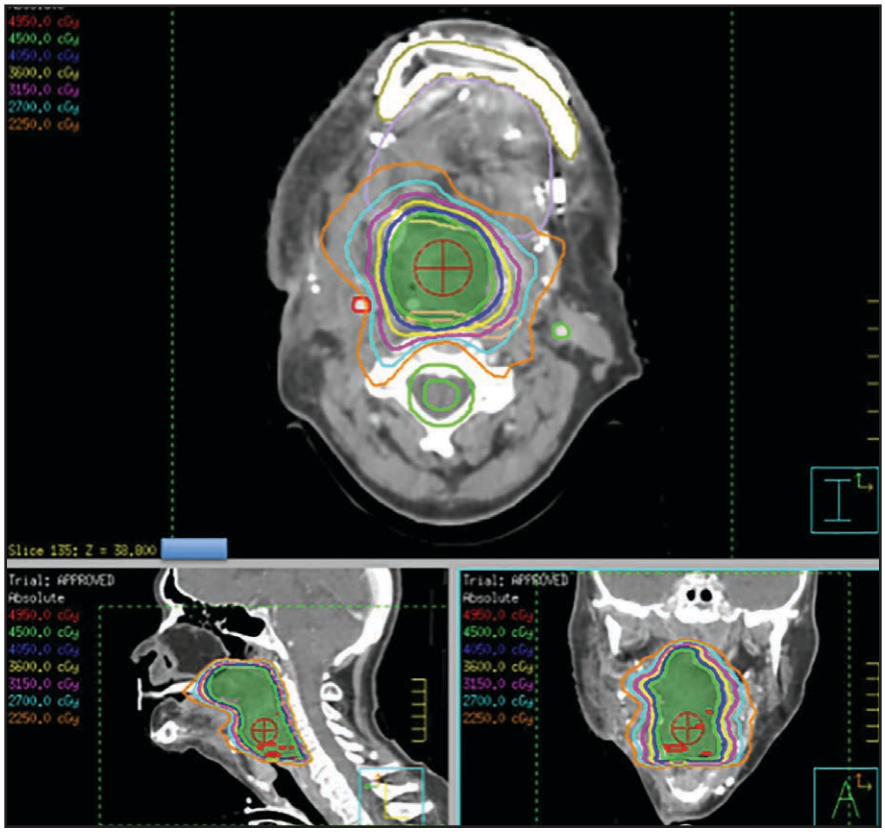

FIGURE 2. *Initial SBRT plan to 45 Gy/5 fractions every other day to GTV only, with no elective volume.*

with the exception of a brisk but focal moist desquamation of the parastomal skin (CTCAE v4.0 grade 3 radiation dermatitis). At his 1-month visit he was found to have a complete response without evidence of active disease (Figure 6). Unfortunately, at his 3-month follow-up, a recurrence within and superior to the original SBRT field was noted. He was felt not to be a candidate for further treatment and enrolled in hospice care. Approximately 3 months later he died at home.

IMAGING FINDINGS

PET/CT was performed prior to the first course of SBRT and showed a new collection of increased metabolic activity (SUV 11.9) present in the right floor of the mouth extending posteriorly and inferiorly along the right oropharynx, measuring 11 × 4.5 cm concerning for recurrent neoplasm (Figure 1).

DIAGNOSIS

Poorly differentiated recurrent squamous cell carcinoma with sarcomatoid features of the supraglottis and base of tongue.

DISCUSSION

Locoregional recurrence is the most frequent pattern of failure in patients with head and neck cancer, with approximately 30% of patients developing locoregional failure within 5 years following cessation of multimodality treatment.[1,2] While 50%-60% of patients will ultimately die as a consequence of locally recurrent disease,[3] many locoregional recurrences are not immediately life-threatening, and patients who experience a confined recurrence can survive for months, suffering significant morbidity from progressive uncontrolled disease. Historical palliative radiotherapy regimens can temporarily improve quality of life and reduce the burden of symptoms in the majority of patients,[4-7] but are not sufficiently aggressive to induce durable locoregional control. Here a case of multiple-recurrent head and neck cancer is presented. In this case, despite a radioresistant and aggressive sarcomatoid histology, durable local control was obtained with a short course of SBRT for nearly 6 months with minimal acute or late toxicity.

For this reason, SBRT has emerged as an alternative treatment strategy for aggressive palliation of primary or recurrent head and neck tumors in patients who are not candidates for curative definitive therapy. The IMRT-based planning approach delivers highly

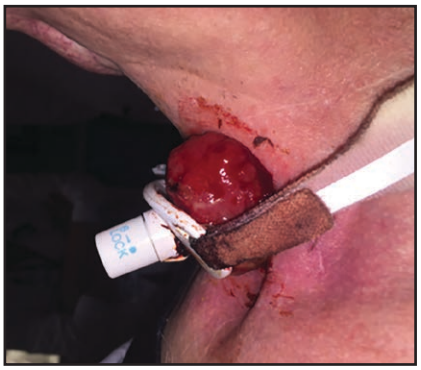

FIGURE 3. *Exophytic, vascular parastomal recurrence discovered 1 month following completion of original SBRT course in the paratracheal region, inferior to the previous SBRT field.*

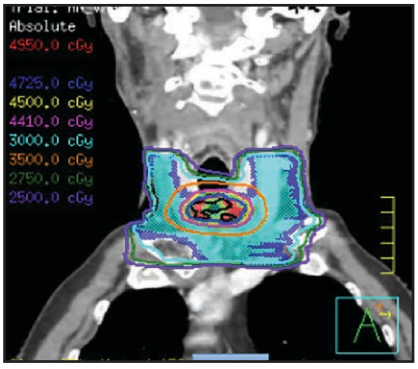

FIGURE 4. *Subsequent SBRT plan to the out-of-field failure to a dose of 45 Gy/5 fractions every other day with an elective 30 Gy/5 fraction nodal volume treated with a simultaneous technique.*

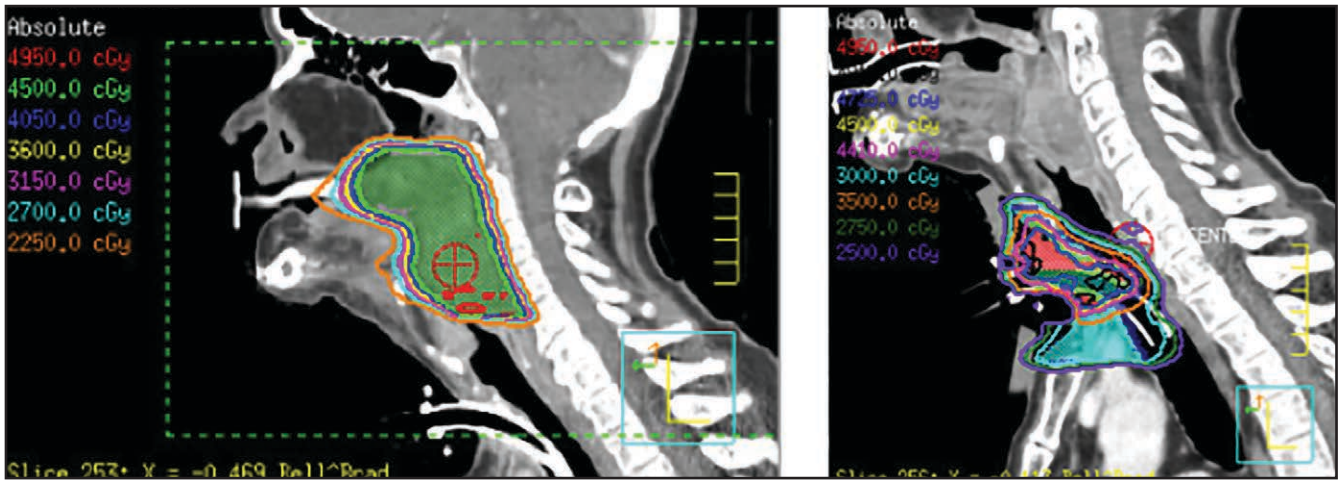

FIGURE 5. *Side-by-side comparison of original SBRT plan (left) and SBRT plan for recurrence (right). Both plans were assessed in a composite fashion to ensure there was no overlap between treatment volumes.*

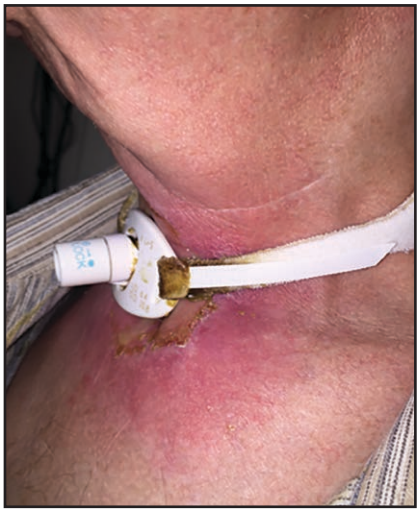

FIGURE 6. *Patient 1 month following second course of SBRT with a brisk parastomal skin reaction and without evidence of active disease.*

conformal radiation in high doses per fraction, making this regimen both effective for patients requiring durable local control and convenient for patients with otherwise limited survival expectations when the goal of treatment is palliation.[8] Several studies have demonstrated encouraging efficacy outcomes with modest toxicity profiles[9-18] (Table 1).

The University of Pittsburgh conducted a phase I dose escalation study to evaluate the safety and efficacy of SBRT for recurrent SCC of the head and neck. In a study of 25 patients, doses were escalated from 20 Gy in 5 fractions up to 44 Gy in 5 fractions, administered over 2 weeks. Only 4 patients experienced grade 1 or 2 acute toxicities, and no grade 3 or 4 dose-limiting toxicities occurred. Four objective responses were observed on PET/CT for an objective response rate of 17%. Median overall survival in the cohort was 6 months. The results led the authors to conclude that re-irradiation up to 44 Gy using SBRT is well-tolerated in the acute setting.[16] Additionally, in a separate study, the authors found a relationship between higher doses, tumor volume and local control. Patients were stratified in to 4 dose groups: 15-28 Gy, 30-36 Gy, 40 Gy, and 44-50 Gy. SBRT dose and tumor volume were significant predictors of LRC, wherein doses ≥ 40 Gy, and tumors with GTV ≤ 25 cm^3 were associated with increased LRC ($p = 0.02$ and $0 = 0.0001$, respectively).[19] The Pittsburgh experience using SBRT in this setting has expanded to include over 150 patients treated with doses of ≥ 40 Gy, with or without the use of concurrent targeted therapies such as cetuximab, with statistically significant improvement in various quality of life measures.[20] Thus, SBRT to doses ≥ 44 Gy appears to be a feasible and efficacious treatment strategy, with a clear dose-response and tumor volume-response relationship. Additionally, treatment toxicity appears relatively mild.

Other studies have further evaluated the role of concurrent targeted therapies with SBRT. In a recent prospective phase II trial examining SBRT plus cetuximab in patients with recurrent SCC of the head and neck, cetuximab improved tumor response rate compared to prior studies of SBRT alone.[14] In this study, 50 patients received 40-45 Gy in 5 fractions on alternating days over 1-2 weeks. Locoregional progression-free survival as reported by the authors was 37%, with a 1-year overall survival of 40%, similar to conventional three-dimensional conformal and intensity-modulated radiotherapy (IMRT) controls. Acute and late grade 3 toxicity was minimal, each observed in 6% of patients, respectively. Thus, targeted therapies carry the potential to improve tumor response rates vs. SBRT alone with a tolerable toxicity profile, further making SBRT an attractive treatment option.

The palliative benefit of SBRT was recently reported by Khan et al in an institutional experience investigating the efficacy of head and neck SBRT for symptom control in medically unfit or frail patients, including quality-of-life parameters pre- and post-SBRT. In this

Table 1. Summary of Head and Neck SBRT Series

Study	Patients	SBRT dose, fractionation	Median follow-up, months	Median survival, months, 1 year OS	Response rate (CR+PR)	Tumor control or locoregional progression	Toxicity
Siddiqui, et al[9]	44 total tumors; 10 primary, 21 recurrent,	13-18 Gy single fraction or 36-48 Gy in 13 metastatic	Primary: 32.3 Recurrent: 6.7 5-8 fractions	Primary: 28.7, 70% Recurrent: 6.7, 38.1%	77% (entire cohort)	83.3% primary group 60.6% recurrent group	Primary: 2 pts grade ≥ 3 (facial pain, cataract) Recurrent: 5 pts grade ≥ 3 (dysphagia ×2, fistula ×3)
Roh, et al[10]	36 pts (35 of 44 sites evaluable), all recurrent tumors	18-40 Gy in 3-5 fractions	17.3	16, 52%	80%	11.4% LRF	Grade 3 acute toxicity observed in 13 pts; grade ≥ 4 late toxicity observed in 3 patients (soft tissue/bone necrosis/ death)
Unger, et al[11]	65 total (56 evaluable); 38 treated definitively 27 treated palliatively	21-35 Gy in 2-5 fractions	16	20, 40%	80% (entire cohort)	32% LRF in definitive group, 2 yr locoregional control 30% in definitive group	No grade > 3 acute toxicity, 9% late grade 4 late toxicity (arterial hemorrhage, soft tissue necrosis, fistula, dysphagia) and 1 death
Kodani, et al[12]	34 total; 13 primary, 21 recurrent	19.5-42 Gy in 3-8 fractions	16	16, 71%	71% (entire cohort)	8% LRF for patients with no prior RT 14% LRF for previously radiated patients	28% late grade ≥ 3 (hemorrhage and death ×2, mucositis, skin necrosis, chronic ulcer)
Cengiz et al[17]	46 pts recurrent, unresectable, previously radiated tumors	18-35 Gy in 1-5 fractions	7	12, 46%	57%	13.5% LRF	4% grade 3 acute toxicity, 7 treatment-related deaths (carotid blowout in patients with tumor encasing carotid > 180° receiving prescribed dose)
Comet et al[13]	40 pts, recurrent or new primary tumors in previously radiated field	36 Gy in 6 fractions	26	14, 58%	79%	23% LRF	10% grade 3 toxicity; no grade 4 toxicities
Vargo et al[15]	132 pts, recurrent, 27 treated palliatively	35-50 Gy in 5 fractions	6	17, 49%	Not reported	44% LRF	7% grade 3 toxicity, no grade 4 or 5 toxicities
Khan et al[18]	21 patients with 24 tumor sites, 17 primary, 7 recurrent, all treated palliatively	35-48 Gy in 5-6 fractions	8	60%	92%	33% control at 9 months for entire cohort, 87% control at 1 year for de novo pts	No grade ≥ 3 toxicity

Key: OS = overall survival, CR = complete response, PR = partial response, Gy = Gray, pts= patients, LRF = locoregional failure, RT = radiation therapy

retrospective review, 21 elderly patients with de novo or recurrent tumors of the head and neck were treated with SBRT to a median dose of 40 Gy in 5 fractions with a complete response rate of 25% and a partial response rate of 67%. Quality of life was assessed using the European Organization of Research and Treatment of Cancer Quality of Life-Head and Neck module (EORTC QLQ-H&N35) questionnaire on the first day of treatment, and following the fifth treatment fraction, evaluating symptom-related items such as pain, swallowing, and taste. With lower scores correlating with better quality of life, pretreatment scores for the entire cohort were 53/130, with follow-up scores of 38/130, indicating a decrease in symptom burden following treatment with a trend toward statistical significance.[18] Vargo et al similarly found that improved tumor control associated with SBRT treatment led to an increase in quality-of-life measures following SBRT re-irradiation in the recurrent setting.[20] Taken together, these studies indicate that SBRT is an effective treatment strategy for symptom palliation leading to improved quality of life in both the de novo and recurrent tumor settings. It should be mentioned, however, that long-term late toxicity data is lacking.

Our patient was treated for his recurrence using SBRT to a dose of 45 Gy in 5 fractions based on the prior studies mentioned demonstrating that doses > 44 Gy are safe and associated with increased LRC. Due to the regional parastomal failure inferior to the first SBRT volume, during the second course of SBRT a limited elective neck volume was added to a dose of 30 Gy in 5 fractions treated simultaneously. Although previous SBRT studies have not included an elective volume, this may serve to reduce the risk of marginal or regional recurrence. The dose of 30 Gy in 5 fractions is extrapolated from previous well-established regimens in the primary setting with conventional techniques.[21] It should be noted that this regimen has not been established in the recurrent setting and further study is warranted. While this patient unfortunately failed within the first SBRT volume and has since died, SBRT treatment seemed to provide durable symptom palliation and minimal treatment toxicity, which likely would not have been accomplished with standard palliative techniques.

CONCLUSION

The optimal role for SBRT in head and neck cancer is evolving and remains unclear. Considering that long-term "cure" is an unreasonable expectation for many patients with locoregionally recurrent disease, SBRT appears to be an excellent option for safe, durable and convenient aggressive palliation in patients at risk of long-term morbidity from locoregionally confined disease. Further investigation into the ideal dose, fractionation, target volume and concurrent therapies is needed.

REFERENCES

1. Bayman E, Prestwich RJ, Speight R, et al. Patterns of failure after intensity-modulated radiotherapy in head and neck squamous cell carcinoma using compartmental clinical target volume delineation. *Clinical Oncol.* 2014;26(10):636-642.
2. Due AK, Vogelius IR, Aznar MC, et al. Recurrences after intensity modulated radiotherapy for head and neck squamous cell carcinoma more likely to originate from regions with high baseline [18F]-FDG uptake. *Radiother Oncol.* 2014;111(3):360-365.
3. Hong WK, Bromer RH, Amato DA, et al. Patterns of relapse in locally advanced head and neck cancer patients who achieved complete remission after combined modality therapy. *Cancer.* 1985;56(6):1242-1245.
4. Corry J, Peters LJ, Costa ID, et al. The 'QUAD SHOT'--a phase II study of palliative radiotherapy for incurable head and neck cancer. Radiother Oncol. 2005;77(2):137-142.
5. Paris KJ, Spanos WJ Jr., Lindberg RD, et al. Phase I-II study of multiple daily fractions for palliation of advanced head and neck malignancies. *Int J Radiat Oncol Biol Phys.* 1993;25(4):657-660.
6. Chen AM, Vaughan A, Narayan S, Vijayakumar S. Palliative radiation therapy for head and neck cancer: toward an optimal fractionation scheme. Head & neck. 2008;30(12):1586-1591.
7. Porceddu SV, Rosser B, Burmeister BH, et al. Hypofractionated radiotherapy for the palliation of advanced head and neck cancer in patients unsuitable for curative treatment--"Hypo Trial". *Radiother Oncol.* 2007;85(3):456-462.
8. Brown JM, Carlson DJ, Brenner DJ. The tumor radiobiology of SRS and SBRT: are more than the 5 Rs involved? *Int J Radiat Oncol Biol Phys.* 2014;88(2):254-262.
9. Siddiqui F, Patel M, Khan M, et al. Stereotactic body radiation therapy for primary, recurrent, and metastatic tumors in the head-and-neck region. *Int J Radiat Oncol Biol Phys.* 2009;74(4):1047-1053.
10. Roh KW, Jang JS, Kim MS, et al. Fractionated stereotactic radiotherapy as reirradiation for locally recurrent head and neck cancer. *Int J Radiat Oncol Biol Phys.* 2009;74(5):1348-1355.
11. Unger KR, Lominska CE, Deeken JF, et al. Fractionated stereotactic radiosurgery for reirradiation of head-and-neck cancer. *Int J Radiat Oncol Biol Phys.* 2010;77(5):1411-1419.
12. Kodani N, Yamazaki H, Tsubokura T, et al. Stereotactic body radiation therapy for head and neck tumor: disease control and morbidity outcomes. *J Radiat Res.* 2011;52(1):24-31.
13. Comet B, Kramar A, Faivre-Pierret M, et al. Salvage stereotactic reirradiation with or without cetuximab for locally recurrent head-and-neck cancer: a feasibility study. *Int J Radiat Oncol Biol Phys.* 2012;84(1):203-209.
14. Vargo JA, Ferris RL, Ohr J, et al. A prospective phase 2 trial of reirradiation with stereotactic body radiation therapy plus cetuximab in patients with previously irradiated recurrent squamous cell carcinoma of the head and neck. *Int J Radiat Oncol Biol Phys.* 2015;91(3):480-488.
15. Vargo JA, Heron DE, Ferris RL, et al. Examining tumor control and toxicity after stereotactic body radiotherapy in locally recurrent previously irradiated head and neck cancers: implications of treatment duration and tumor volume. *Head Neck.* 2014;36(9):1349-1355.
16. Heron DE, Ferris RL, Karamouzis M, et al. Stereotactic body radiotherapy for recurrent squamous cell carcinoma of the head and neck: results of a phase I dose-escalation trial. *Int J Radiat Oncol Biol Phys.* 2009;75(5):1493-1500.
17. Cengiz M, Ozyigit G, Yazici G, et al. Salvage reirradiaton with stereotactic body radiotherapy for locally recurrent head-and-neck tumors. *Int J Radiat Oncol Biol Phys.* 2011;81(1):104-109.
18. Khan L, Tjong M, Raziee H, et al. Role of stereotactic body radiotherapy for symptom control in head and neck cancer patients. *Support Care Cancer.* 2015;23(4):1099-1103.
19. Rwigema JC, Heron DE, Ferris RL, et al. The impact of tumor volume and radiotherapy dose on outcome in previously irradiated recurrent squamous cell carcinoma of the head and neck treated with stereotactic body radiation therapy. *Am J Clin Oncol.* 2011;34(4):372-379.
20. Vargo JA, Heron DE, Ferris RL, et al. Prospective evaluation of patient-reported quality-of-life outcomes following SBRT +/- cetuximab for locally-recurrent, previously-irradiated head and neck cancer. *Radiother Oncol.* 2012;104(1):91-95.
21. Ang KK, Peters LJ, Weber RS, et al. Postoperative radiotherapy for cutaneous melanoma of the head and neck region. *Int J Radiat Oncol Biol Phys.* 1994;30(4):795-798.

RADIATION ONCOLOGY CASE

Radiographic changes of the lung after stereotactic body radiation therapy

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

CASE SUMMARY

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

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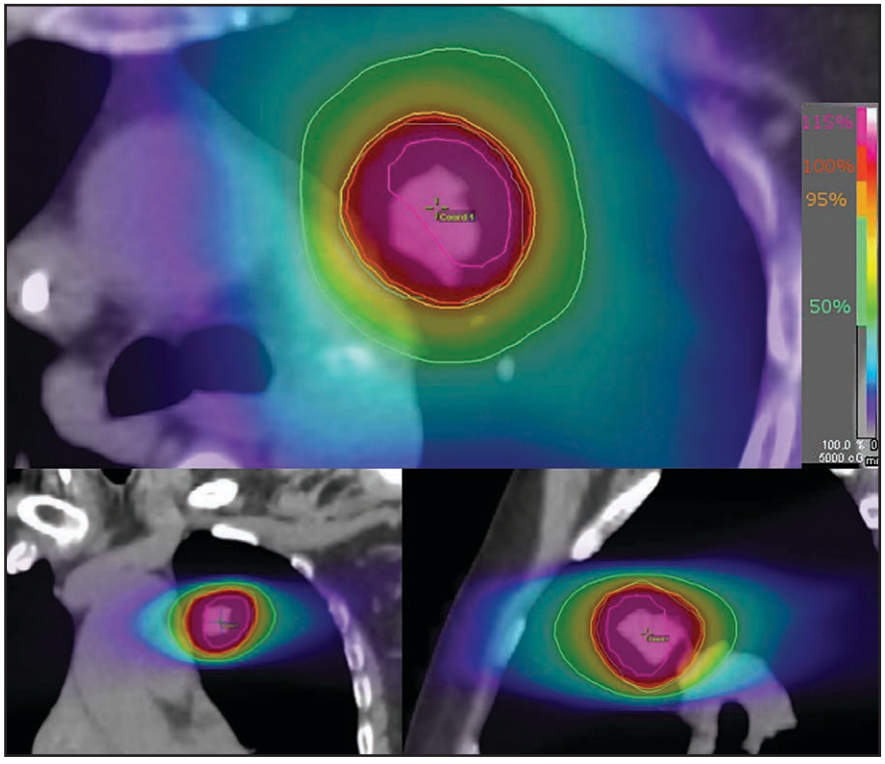

FIGURE 1. *Isodose lines of the SBRT plan.*

IMAGING FINDINGS

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

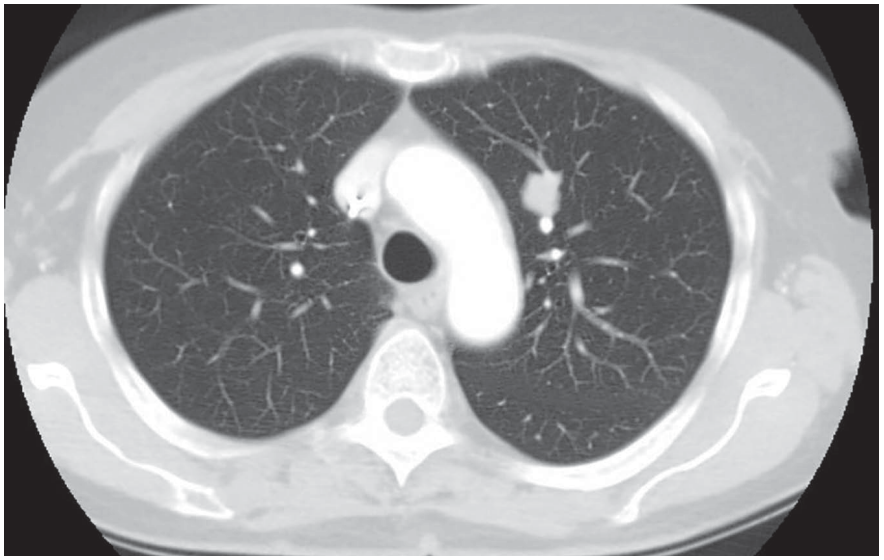

FIGURE 2. *Initial lung lesion prior to treatment.*

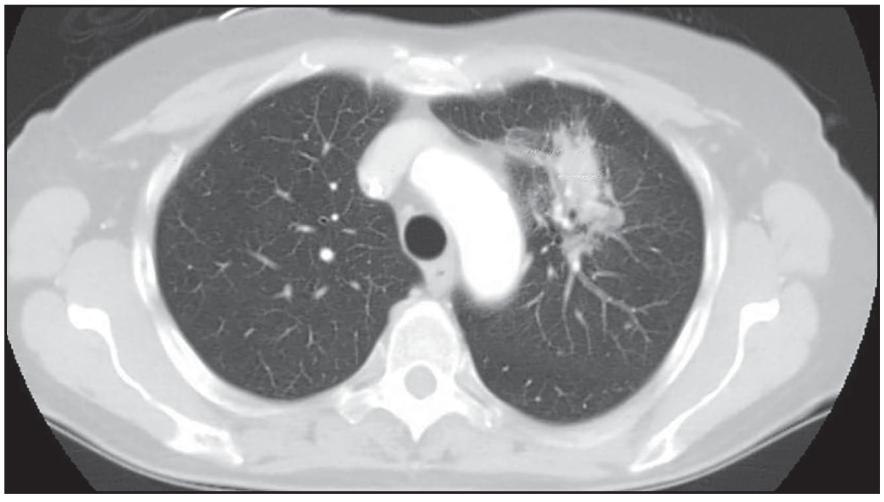

FIGURE 3. *Mass-like confluence at 8 months post-SBRT.*

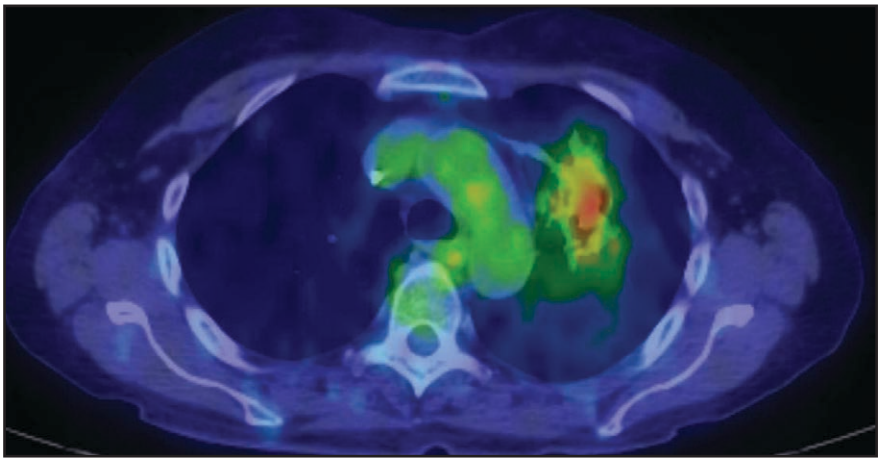

FIGURE 4. *PET scan at 8 months post-SBRT.*

Table 1. High-risk Radiographic Findings

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

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

DIAGNOSIS

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

DISCUSSION

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

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

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

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

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

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

The Koenig system consists of 4 categories:

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

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

CONCLUSION

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

REFERENCES

1. Libshitz HI, Shuman LS. Radiation-induced pulmonary change: CT findings. *J Comput Assist Tomogr.* 1984;8(1):15-19.
2. Ikezoe J, Takashima S, Morimoto S, et al. CT appearance of acute radiation-induced injury in the lung. *Am J Roentgenol.* 1988;150(4):765-770.
3. Koenig TR, Munden RF, Erasmus JJ, et al. Radiation injury of the lung after three-dimensional conformal radiation therapy. *Am J Roentgenol.* 2002;178(6):1383-1388.
4. Aoki T, Nagata Y, Negoro Y, et al. Evaluation of lung injury after three-dimensional conformal stereotactic radiation therapy for solitary lung tumors: CT appearance. *Radiol.* 2004;230(1):101-108.
5. Trovo M, Linda A, El Naqa I, et al. Early and late lung radiographic injury following stereotactic body radiation therapy (SBRT). *Lung Cancer.* 2010;69(1):77-85.
6. Kimura T, Matsuura K, Murakami Y, et al. CT appearance of radiation injury of the lung and clinical symptoms after stereotactic body radiation therapy (SBRT) for lung cancers: are patients with pulmonary emphysema also candidates for SBRT for lung cancers? *Int J Radiat Oncol Biol Phys.* 2006;66(2):483-491.
7. Dahele M, Palma D, Lagerwaard F, et al. Radiological changes after stereotactic radiotherapy for stage I lung cancer. *J Thorac Oncol.* 2011;6(7):1221-1228.
8. Huang K, Dahele M, Senan S, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR)--can we distinguish recurrence from fibrosis? A systematic review of the literature. *Radiother Oncol.* 2012;102(3):335-342.
9. Mattonen SA, Palma DA, Haasbeek CJ, et al. Early prediction of tumor recurrence based on CT texture changes after stereotactic ablative radiotherapy (SABR) for lung cancer. *Med Phys.* 2014;41(3):033502.

RADIATION ONCOLOGY CASE

A responsive yet persistently recurrent GBM with PNET features

Allen Chu, PhD; Daniel J. Bourgeois, III, MD, MPH; Dheerendra Prasad, MD, MCh, FACRO

CASE SUMMARY

A 49-year-old male presented to his primary provider with a 6-month history of unilateral resting tremor and tingling facial sensations. Cranial MRI revealed a 6 × 3.1-cm hemorrhagic lesion in the right temporal lobe (Figure 1). The patient underwent gross total resection (GTR) revealing tissue consistent with glioblastoma multiforme (GBM). While the large lesion was in close proximity to multiple meningeal structures, neither imaging nor intraoperative assessments strongly indicated leptomeningeal disease. However, neuroblastic foci positive for synaptophysin with a Ki-67 proliferation index approaching 100% were also identified. As a result, the diagnosis of GBM with primitive neuroendocrine tumor (PNET) features was made. The patient underwent adjuvant volumetric-modulated arc radiation therapy (VMAT) at 59.4 Gy in 1.8 Gy fractions followed by a stereotactic radiosurgery (SRS) boost at 17 Gy to the 50% isodose line to an area of residual enhancement. Adjuvant temozolamide was also provided.

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Imaging performed 1 month after completion of the patient's initial course of treatment showed dural-based lesions in bilateral frontal lobes that were also hypermetabolic on positron emission tomography (PET) (Figure 2). Hence, approximately 8 months from initial surgical resection, the patient underwent a left-sided craniotomy and GTR of the largest lesion, which confirmed an out-of-field, contralateral recurrence of his GBM with PNET features. Another round of adjuvant radiation via VMAT at 55.8 Gy with concurrent temozolamide was initiated, targeting the resection cavity and the right-sided lesion.

The patient retained stable functional capacity with no new neurological symptoms or complaints. However, follow-up imaging showed a local recurrence in the right temporal lobe where the initial resection had been performed 12 months earlier (Figure 3A). The patient started a regimen of etoposide and vincristine, but after 1 cycle, he developed seropurulent drainage from his craniotomy site with projectile vomiting, neck stiffness and low back pain. He was diagnosed with acute meningitis requiring craniectomy with bone washing and intravenous antibiotic therapy. After recovering, he began a regimen of procarbazine, lomustine, and vincristine (PCV) with bevacizumab. Subsequently, resolution of the previously noted contrast enhancement had resolved, and all therapies were discontinued.

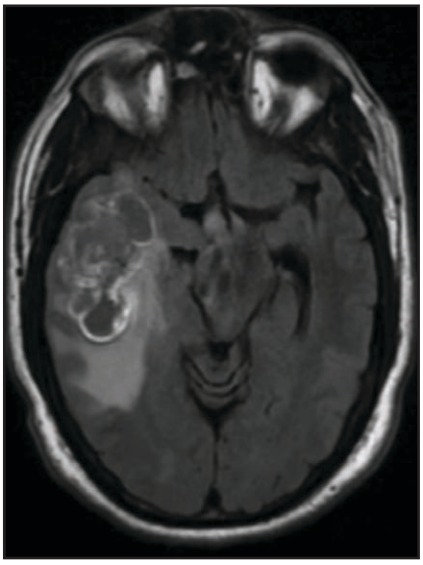

FIGURE 1. *Preoperative T1-weighted cranial MRI. The lesion was accompanied by a midline shift, a leftward subfalcine herniation and an uncal herniation. Functional MRI revealed language localization of the left, and the mass to be separated from the motor strip.*

Nevertheless, in the follow-up 24 months after his initial craniotomy, imaging revealed another local recurrence with contrast enhancement in the temporal lobe (Figure 3B). With minimal morbidity and stable performance status, the patient wished to pursue aggressive treatment, so the recurrent

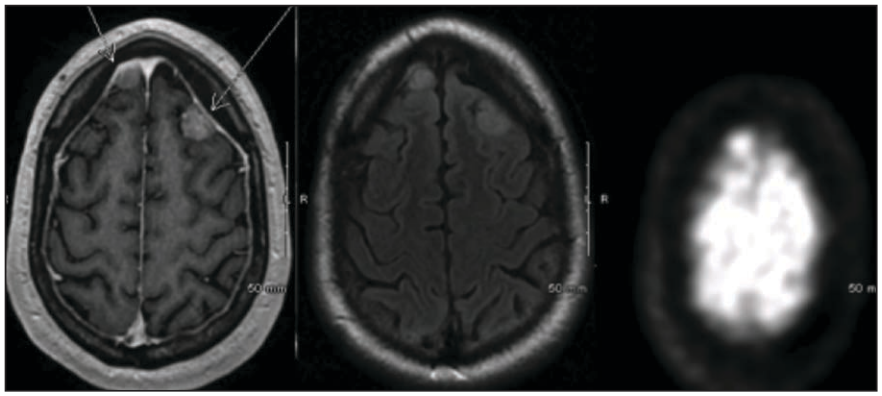

FIGURE 2. *MRI of brain with and without contrast (left and center). Two new enhancing extra-axial right frontal and left frontal mass lesions are identified by arrows, likely representing dural-based metastatic deposits. A PET scan (right) of the same region demonstrates increased uptake in the left frontal lobe.*

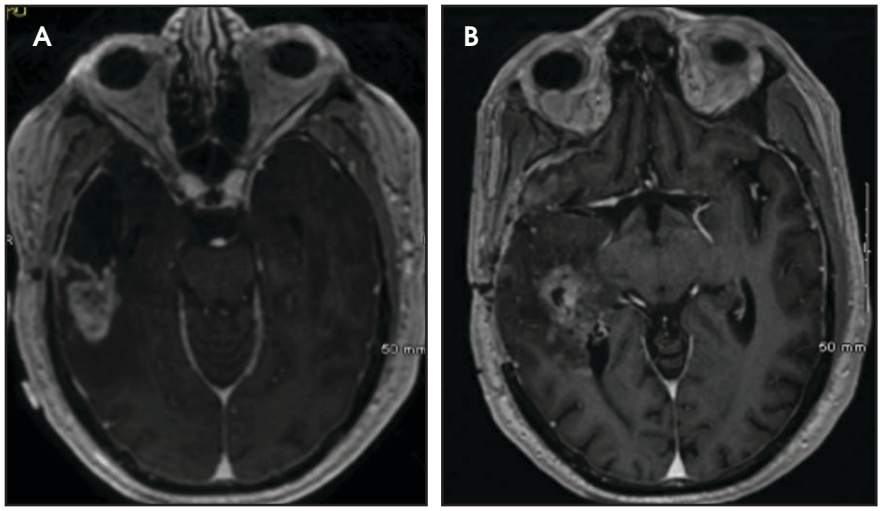

FIGURE 3. *Follow-up T1-weighted cranial MRIs showing local recurrence at the initial site following a second round of radiation and temozolamide therapy (A) and then after an additional 12 months of chemotherapy and hospitalization for meningitis (B).*

area was given a third round of VMAT to 39.6 Gy with concurrent temozolamide and bevacizumab, followed by adjuvant etoposide, carboplatin and bevacizumab.

Two months following therapy, the patient complained of weakness, somnolence, weight loss and low back pain. Brain imaging remained stable, but spinal imaging demonstrated extensive leptomeningeal disease. Although a palliative course of radiation was initiated, the patient succumbed to his disease shortly thereafter, approximately 28 months following initial diagnosis and resection.

IMAGING FINDINGS

Initial diagnostic MRIs showed a heterogeneously enhancing mass in the right temporal lobe with peritumoral edema, midline shift, and uncal herniation. The T1 phase of this exam is provided in Figure 1. Functional MRI also revealed language localization of the left, and the mass to be separated from the motor strip. The patient's initial recurrences in bilateral frontal lobes were also enhancing, yet more homogenously, and were closely approximated to the cerebral meninges. This exam, as well as a PET/CT of the brain showing the increased metabolic activity at these sites, is shown in Figure 2. After treatment for these lesions, follow-up imaging showed a local recurrence at the initial site following a second round of radiation and temozolamide therapy (Figure 3, left), followed by persistent disease after an additional 12 months of chemotherapy and a lengthy hospitalization for meningitis (Figure 3, right). And finally, the patient's disease eventually spread to his sacral spine via leptomeningeal dissemination, which was seen on lumbosacral MRI exams as "sugar-coating" confluent lesions of the cauda equina and thickening of the surrounding meninges and dura.

DIAGNOSIS

Multipally recurrent glioblastoma multiforme (GBM) of the right temporal lobe with primitive neuroendocrine tumor (PNET) features and leptomeningeal dissemination.

DISCUSSION

Currently, standard treatment for GBM includes local radiation therapy and temozolamide. Although GBM has classically been considered a purely astrocytic tumor, lesions with mesenchymal and epithelial constituents are increasingly being described. GBM with PNET components are thought to represent approximately 0.5% of GBM cases, and arise from the development of PNET-like foci within pre-existing gliomas. In contrast to conventional GBM, PNETs typically have a histology similar to medulloblastoma and are often managed with combined craniospinal radiation and platinum-based chemotherapy.

The majority of GBM tumors are resistant to therapy, and mean survival is approximately 15-17 months. Although the prognosis for PNET patients is also fairly poor, the response rate to therapy is more marked, with an estimated 4-year survival rate of 38%. An established clinical feature of PNETs is a high risk for metastatic

spread into the cerebrospinal fluid (CSF). Although the clinical data is sparse, recent studies have suggested that patients with GBM-PNETs are also at increased risk for CSF dissemination. In a recent multi-institutional series of 53 patients with GBM-PNETs, Perry et al reported leptomeningeal metastasis in up to 40% of patients. This frequency is in sharp contrast to the approximate 1% CSF spread rate seen in adult patients with conventional GBM. Three of the patients in the study with leptomeningeal spread were eventually switched from temozolamide to cisplatin, with moderate responses in each.[3]

Our case of GBM-PNET was treated with 3 successive rounds of combined radiation and temozolamide therapy, including an SRS boost, with salvage PVC and bevacizumab therapy. This approach resulted in modest local responses and control. This patient, whose age, performance status, and therapy would suggest a median overall survival of 16-21 months, survived 28 months from initial resection.[9] The patient did experience a prolonged hospitalization for treatment of acute meningitis, but his neurocognitive and functional deficits remained mild and transient until late in his progression. Other than fatigue noted around the late and subsequent weeks of his radiation treatments, which was milder than expected, this patient experienced very minimal neurocognitive decline until his last few weeks of life, and, outside of his infection-related hospitalization, only rarely reported episodes of headache, nausea, or other forms of acute toxicity. Nevertheless, all therapies ultimately failed to control leptomeningeal spread. Although this is insufficient data to provide conclusive therapeutic recommendations, given the differences in metastatic potential between GBM and PNET tumors, it can be speculated that patients with histologically confirmed GBM with PNET features may benefit from craniospinal irradiation, a commonly used therapy for treating PNETs and medulloblastoma, or the early introduction of platinum-based chemotherapy.[3,10]

Our experience is consistent with the scant literature and clinical guidelines concerning management of GBM-PNETs. Conventional GBM tumors rarely undergo metastatic spread, and standard management is directed toward the control of local disease. As identifying PNET components in GBMs may have prognostic and treatment ramifications, the method of tumor sampling during biopsy may influence management considerations. Tumors are spatially heterogeneous; therefore, determining both the distribution and functionality of PNET foci within primary lesions is likely help predict clinical behavior. One study suggests that the diffusion coefficient on MR imaging may help distinguish astrocytic and ectodermal tumor components, potentially guiding biopsies.

CONCLUSION

GBM-PNET tumors are aggressive neoplasms of mixed embryologic origin that demonstrate high rates of local recurrence and dissemination into the CSF. Our patient with GBM-PNET was treated with multiple courses of surgery, radiation and chemotherapy. Therapy provided favorable local responses with an overall survival of 28 months after extensive therapy without debilitating morbidity. The patient tolerated his multiple courses of radiation therapy with minimal complaints of acute toxicity, and, unlike many high-grade glioma patients who do not survive long enough to experience late toxicities, he experienced late toxicity only in the last weeks of his survival. The patient did, despite all aggressive therapy, eventually manifest leptomeningeal spread, which led to a rapid symptomatic decline and death from his disease. This case suggests that aggressive therapies may be utilized in attempts to prolong survival with acceptable toxicity during this period in select patients with favorable performance status. And furthermore, patients with diagnoses of GBM-PNET may benefit from advanced techniques of diagnostic imaging and pathologic analysis, as well as craniospinal irradiation and early platinum-based chemotherapy due to the propensity for CSF dissemination.

REFERENCES

1. Hegi ME, Diserens AC, Gorlia T, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med.* 2005;352:997-1003.
2. Sarkar C, Deb P, Sharma MC. Recent advances in embryonal tumours of the central nervous system. *Childs Nerv Syst.* 2005;21(4):272-293.
3. Perry A, Miller CR, Gujrati M, et al. Malignant gliomas with primitive neuroectodermal tumor-like components: a clinicopathologic and genetic study of 53 cases. *Brain Pathol.* 2009;19(1):81-90.
4. Stupp R, Mason WP, van den Bent MJ, et al. Radiotherapty plus concomitant and adjunat temozolomide for glioblastoma. *N Engl J Med.* 2005;352:987-996.
5. Johnston DL, Keene DL, Lafay-Cousin L, et al. Supratentorial primitive neuroectodermal tumors: a Canadian pediatric brain tumor consortium report. *J Neurooncol.* 2008;86(1):101-108.
6. Hong TS, Mehta MP, Boyett JM, et al. Patterns of treatment failure in infants with primitive neuroectodermal tumors who were treated on CCG-921: a phase III combined modality study. *Pediatr Blood Cancer.* 2005;45: 676-682.
7. Song X, Andrew Allen R, Terence Dunn S, et al. Glioblastoma with PNET-like components has a higher frequency of isocitrate dehydrogenase 1 (IDH1) mutation and likely a better prognosis that primary glioblastoma. *Int J Clin Exp Pathol.* 2011;4:651-660.
8. Ali S, Joseph NM, Perry A, et al. Apparent diffusion coefficient in glioblastoma with PNET-like components, a GBM variant. *J Neurooncol.* 2014;119:353-360.
9. Mirimanoff RO, Gorlia T, Mason W, et al. Radiotherapy and temozolomide for newly diagnosed glioblastoma: recursive partitioning analysis of the EORTC 26981/22981-NCIC CE3 phase III randomized trial. *J Clin Oncol.* 2006;24(16):2563-2569.
10. Packer RJ, Gajjar A, Vezina G, et al. Phase III study of craniospinal radiation therapy followed by adjuvant chemotherapy for newly diagnosed average-risk medulloblastoma. *J Clin Oncol.* 2006;24(25):4202-4208.

Proton Therapy Treatment for Breast Cancer

Mary Beth Massat

When treating breast cancer with radiation therapy, several rare, yet serious, long-term side effects may occur. These include heart disease, radiation pneumonitis (inflammation of the lung), rib fractures, and the very rare side effect, brachial plexopathy, which is caused by radiation damage to the nerves in the upper chest (the brachial plexus).

With proton therapy, the energy distribution of protons into tissue can be more precisely directed and controlled than with conventional photon therapy, allowing it to potentially reduce long-term side effects in breast cancer patients. Protons are energized to specific velocities, and as they move through the body, they slow down and increase interaction with the electrons orbiting the atom of molecules, a fundamental component of all body tissue. Because proton beam therapy targets only the cancerous cells, there is less damage to surrounding healthy tissue.

In September 2014, initial results of a clinical trial using proton therapy for treating breast cancer reported excellent survival rates and cosmetic outcomes. The trial was conducted at the James M. Slater, MD, Proton Treatment & Research Center at Loma Linda University Medical Center (LLUMC) in Loma Linda, California, the first U.S. hospital-based proton therapy center. After opening in October 1990, LLUMC has treated more than 18,000 patients and over 20 types of cancer. According to principal investigator David Bush, MD, vice chairman of the Department of Radiation at LLUMC, the study included 100 women with early stage disease who had small, localized tumors that had not spread. The patients were monitored for an average of 5 years following treatment. Results showed that in-breast, recurrence-free survival rate was 97% with minimal side effects, and a good-to-excellent cosmetic rate in 90% of the cases.[1]

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"We were able to show that by treating a smaller area of the breast, we could essentially eliminate exposure to the heart, chest wall, and lung," Dr. Bush says. "There was no toxicity in those structures, tissues or organs, and the cosmetic rate was very good."

Dr. Bush is embarking on another proton therapy breast cancer trial with 150 enrolled participants. The new study will also examine rate of recurrence; disease-free survival; and complication rates in the breast, chest wall and skin. While the new trial is similar to the first, it includes women with more adverse factors and slightly more advanced tumors. In general, Dr. Bush explains that ideal candidates for breast proton therapy are women with breast cancer who have small localized tumors < 3 cm, and whose disease has not spread, including to the lymph nodes.

An Evolution in Technology

Since its inception, proton therapy has used image guidance, notes Dr. Bush. Imaging, along with the use of implanted fiducial markers, are key ways LLUMC and many other sites manage uncertainty. Patient immobilization is also critical since proton therapy delivers a higher radiation dose than conventional photon therapy, and the breast is prone to movement from the patient's respiratory cycle.

There is also the challenge of managing dose to the skin, Dr. Bush adds. "The targets we are treating are not deep in the body—they are often close to the skin line. So we need to reduce the dose to the skin to avoid burns by immobilizing the breast in an accurate, reproducible way."

To do this, LLUMC developed a patented customized foam. The patient lies prone during treatment and the skin is in contact with this immobilization device, which eliminates motion due to breathing in an accurate and reproducible way, thus helping to spare the skin.

Scanning beam is another advance in proton therapy delivery under development at LLUMC. A scanning-beam technique electronically or magnetically steers a narrow beam (sometimes referred to as a pencil beam) as it "paints" the treatment volume in layers, voxel by voxel. "We believe that scanning-beam technology will likely be well-suited to treat patients who have large, more complicated volumes that need to be treated,"

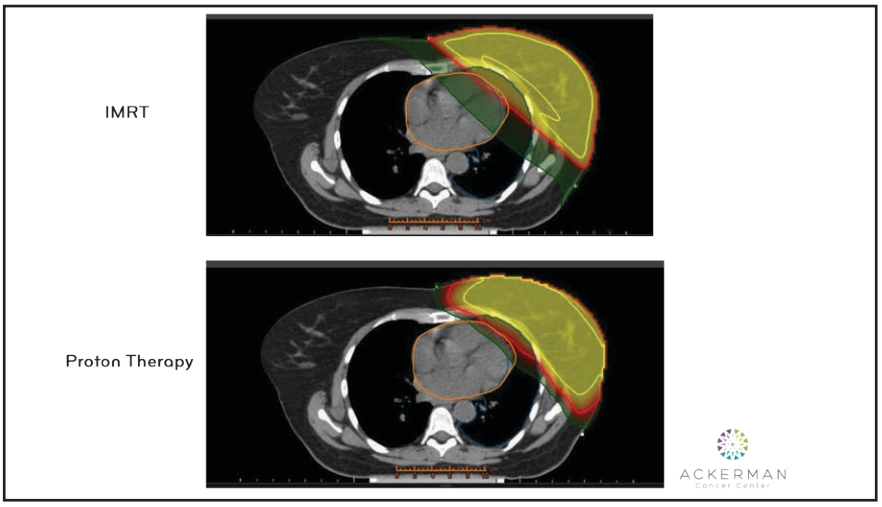

FIGURE 1. *Plans comparing the use of proton therapy vs. IMRT in a breast cancer patient. The plans demonstrate considerably reduced levels of radiation exposure in healthy tissue when treated with proton therapy (compare green, red, and yellow shading).*

says Dr. Bush. This includes patients requiring whole-breast radiation or lymph node treatment.

Proton Therapy at Ackerman Center

As a physician-owned private proton therapy center, Ackerman Cancer Center in Jacksonville, Florida, began treating patients with the Mevion S250 Proton Therapy System in April 2015. "I believe proton therapy is an important part of the future of radiation oncology," says Scot Ackerman, MD, medical director of the center. Approximately 10% to 15% of his patients have breast cancer, half of whom are receiving proton therapy treatment.

With every breast cancer patient, Dr. Ackerman and colleagues create a proton therapy and a conventional photon therapy plan to compare which course of treatment will be most efficient and effective (Figure 1).

"We generate comparative dosimetry plans with IMRT, proton beam and conformal radiation therapy to look at the dose delivered to the brachial plexus, lungs and heart," Dr. Ackerman explains. "We also look at homogeneity in the patients we want to treat. Frequently, proton therapy is the superior plan, with lower radiation dose to the heart and significantly lower dose to the lungs."

Women seek out Ackerman Cancer Center because they believe that proton therapy may offer them better care than traditional radiation for treating breast cancer, he adds. "Every 100 centigray of dose to healthy organs such as the heart can increase the risk for long-term complications, including coronary artery disease and congestive heart failure," Dr. Ackerman says. With increased life expectancy, even if these complications manifest over 20 years, a marginal reduction in mean dose to healthy organs and tissues can be important considerations for women seeking treatment.

Proton therapy is generally considered for breast cancer patients receiving radiation therapy in the adjuvant setting. That said, every patient has a unique anatomy, and some physiological compositions make proton therapy more advantageous, such as in a woman whose heart is close to the chest wall, says Dr. Ackerman. This is because the protons "stop" before reaching the critical organ.

Dr. Ackerman uses daily image guidance as well as surgical clips placed at the time of lumpectomy to help manage uncertainty. "We use robust planning with each beam covering the entire treatment volume," he explains. "We perform simulation 2 times, with the patient on the table, off, and then on again with a qualitative and a quantitative check to be sure the position is reproducible."

The women are also directed to do shallow breathing, and the second simulation is performed to visualize movement of the chest wall and lungs.

Currently, the proton therapy system at Ackerman Cancer Center performs passive scanning, and the center has contracted for a second Mevion system featuring pencil-beam technology delivered at hyperspeed for spot scanning. "This system will allow us to treat more challenging cases, such as ones with lymph node involvement," Dr. Ackerman says. It may also reduce treatment times.

Dr. Ackerman's advice for clinicians interested in providing proton therapy is to invest sufficient time, energy and effort to train technical staff on the nuances of proton therapy. In addition to training off-site, Dr. Ackerman's radiation therapists, dosimetrists, and medical physicists generated, reviewed and practiced comparative plans for 6 months before treating their first proton patient.

"It is also important to have well-trained support services, from oncology-certified nurses to social workers and nutritionists," Dr. Ackerman adds. "As oncologists, we should be committed to treating the whole patient. This includes a focus on the patient's wishes for effective treatment and positive long-term outcomes. The strength of [our] technology unlocks that opportunity for us in treating breast cancer with proton therapy."

Reference

1. Bush DA, Do S, Lum S, et al. Partial breast radiation therapy with proton beam: 5-year results with cosmetic outcomes. *Int J Radiat Oncol Biol Phys.* 2014;90(3):501-505.

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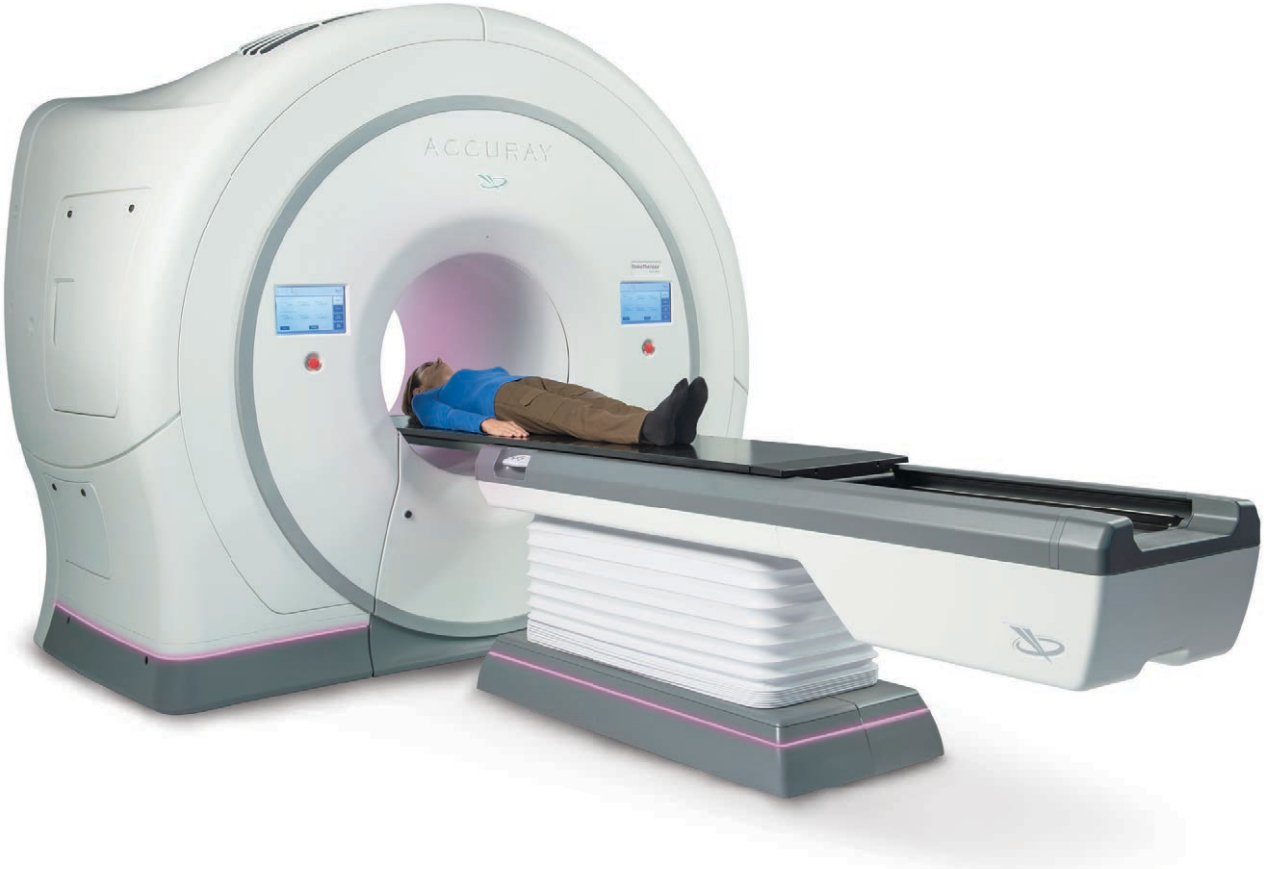

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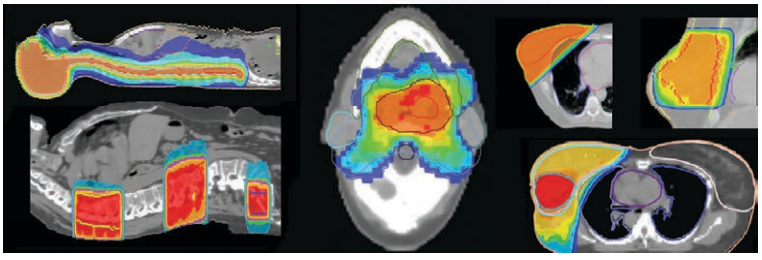

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