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Teaching Case

Preoperative Accelerated Hyperfractionated Whole-Breast Radiation as Treatment for Secondary Angiosarcoma of the Breast After Prior Accelerated Hypofractionated Whole-Breast Radiation Therapy: A Case Report and Review of the Literature

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Introduction

Sarcomas of the breast comprise <1% of all breast malignancies and are histologically heterogenous, nonepithelial tumors that arise from the connective tissue of the breast.[1,2] Development of breast sarcomas can be de novo or related to prior radiation therapy.[3] Radiation-induced malignancies are identified using the Cahan criteria, requiring that the secondary tumor is of a sarcomatous nature, different from the original tumor histology, that the development occurs in an irradiated area, and that there is a prolonged latency period between the 2 malignancies.[4] One large study demonstrated that 0.002% of women (35 of 16,705) developed secondary, radiation induced, sarcomas (RIS), after breast irradiation. Twenty-seven of the cases in this study fulfilled Cahan criteria, demonstrating an overall incidence of 1.6 cases per 1000. The study found a cumulative RIS risk of 0.07% (± 0.02) at 5 years, 0.27% (± 0.05) at 10 years, and 0.48% (±0.11) at 15 years.[5]

Histologically up to 50% of RIS are angiosarcomas. The remainder represent a spectrum that includes osteosarcomas, malignant fibrous histiocytomas, fibrosarcomas, leiomyosarcomas, and rhabdomyosarcoma, as well as undifferentiated sarcomas. Secondary angiosarcomas occur with a median onset of 10.5 years[6,7] and tend to occur in patents with a median age of 64 years, as opposed to primary breast angiosarcomas, which tend to present in younger patients.[8]

It is common for secondary angiosarcomas to present at an advanced clinical stage, as the initial development is often indolent, often characterized only by mild skin discoloration that resembles bruising.[4,9] This, and the limited treatment options, contribute to overall poor outcomes.

Radiation therapy is limited due to prior radiation exposure and to date there is no effective universally accepted chemotherapy. Surgical resection remains the most common treatment option for RIS patients. Complete surgical excision is critical to prevent recurrence[9] but even when negative surgical margins are achieved, the

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rate of recurrence and subsequent metastasis remains high. Up to two-thirds of patients recur with surgical excision alone after a median of 6 months.[10] Crude 5-year survival has been reported to be 32% to 36% and the median survival time is 25 to 34 months.[5,11]

Hyperfractionated accelerated reirradiation therapy (HART) has been shown to be safe in case series and phase 2 trials related to other malignancies, as well as effective in improving local control and survival in patients with breast RIS.[9,12,13] Patients treated with HART demonstrate increased survival rates compared with surgery alone, chemotherapy, or conventionally fractionated radiation therapy. One study demonstrated a 5- and 10-year overall survival rate of 79% and 63% in RIS patient treated with HART and minimal associated complications.[13]

To our knowledge, this is the first report of using preoperative HART RIS in a patient who previously received hypofractionated whole breast radiation therapy. Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Case Presentation

A 68-year-old woman was treated for a mucinous carcinoma of the left breast with local excision with adequate margins, sentinel lymph node biopsy and adjuvant hypofractionated whole breast radiation therapy to a total dose 4256 Gy in 16 daily fractions. The patient was subsequently maintained on anastrozole with a goal of 5 years of therapy.

Approximately 3 years later the patient was developed ecchymosis at the 4 o'clock position of the left breast with multiple inferior satellite bruises. A diagnostic mammogram 5 months prior was classified as BI-RADS 2. The patient denied any symptoms or findings (such as palpable nodules, nipple discharge, inversion, or pain). The patient underwent left breast ultrasonography, which revealed mild skin thickening in the area of concern but no discrete mass lesion. A breast biopsy revealed CD34 positive and ERG positive angiosarcoma.

Mammography and magnetic resonance imaging of both breasts revealed skin thickening along the lateral left breast from the 2 o'clock to 6 o'clock position (Fig 1). There were no sternal or costal lesions, no enlarged lymph nodes and no other lesions seen in either breast. Computed tomography of the chest with and without contrast was likewise negative.

In an effort to enhance local control and achieve negative surgical margins and given her prior hypofractionated radiation therapy, a course of preoperative HART was recommended. The patient completed a course of accelerated hyperfractionated whole breast radiation with a dose of 4500 Gy, delivered twice daily at 150 Gy per fraction, for 3 weeks, using tangential fields encompassing all clinical breast tissue, using 10 MV photons. Axial snapshot of the isodose lines with corresponding tangential fields shown in Figures 2 and 3. Cumulative dose volume histogram shown in Figure 4.

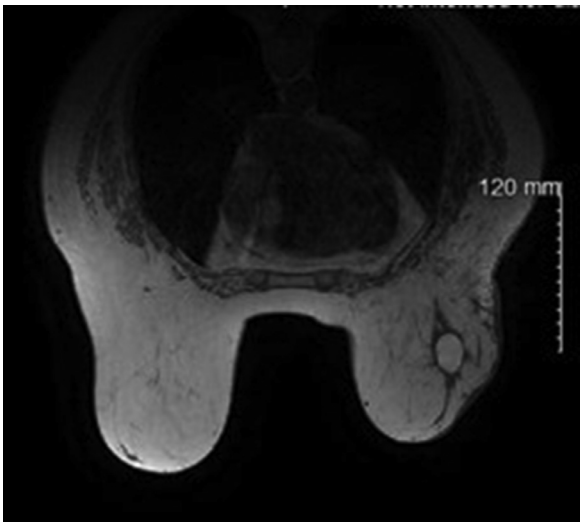


Fig. 1 T1 axial magnetic resonance image further demonstrating skin thickening with no enlarged lymph nodes and no enhancing lesions within the sternum.

Approximately 7 weeks after completion of radiation therapy, the patient underwent simple mastectomy of the left breast. Histologic evaluation revealed focal residual angiosarcoma and negative margins. The patient recovered with no significant complications, except for mild limitation in left shoulder range of motion, which was treated with physical therapy. Given the negative margins, adjuvant radiation therapy was not recommended, and the patient was advised to continue a maintenance therapy of anastrozole and close follow-up.

Discussion

Angiosarcomas of the breast are rare tumors accounting for less than <1% of all sarcomas. Angiosarcomas of the breast may arise sporadically or develop secondary to chronic lymphadenopathy or disruption of normal lymphatic drainage after radical mastectomy and axillary dissection, as well as breast conservation therapy involving radiation.[12,14,15] The incidence of secondary angiosarcoma of the breast is between 0.05% and 0.5% overall and the risk of development increases over time. Although the mutagenic effect of radiation therapy can directly contribute to malignant transformation, some authors propose that lymph node sclerosis or lymphatic blockage secondary to radiation therapy contribute to the development of these soft tissue sarcomas.[16]

Hypofractionated radiation therapy after breast conserving surgery has been used since the early 2000s.[17,18] In comparison with conventionally fractionated radiation

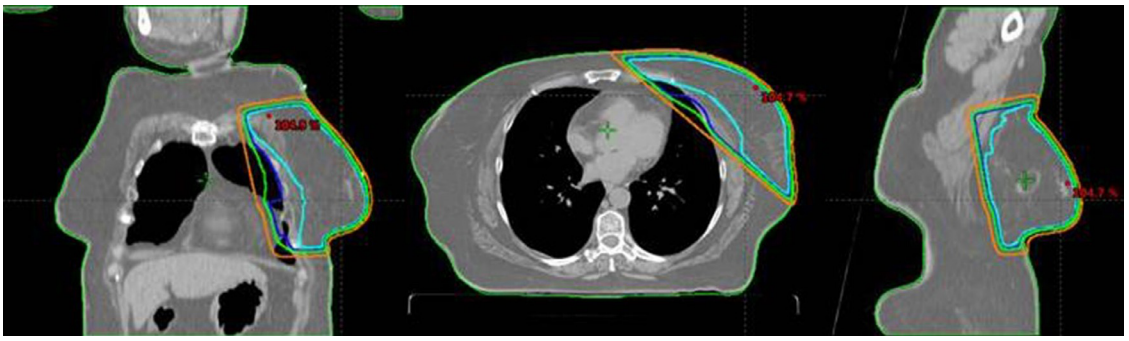


Fig. 2 Three views depicting the patient's radiation therapy plan.

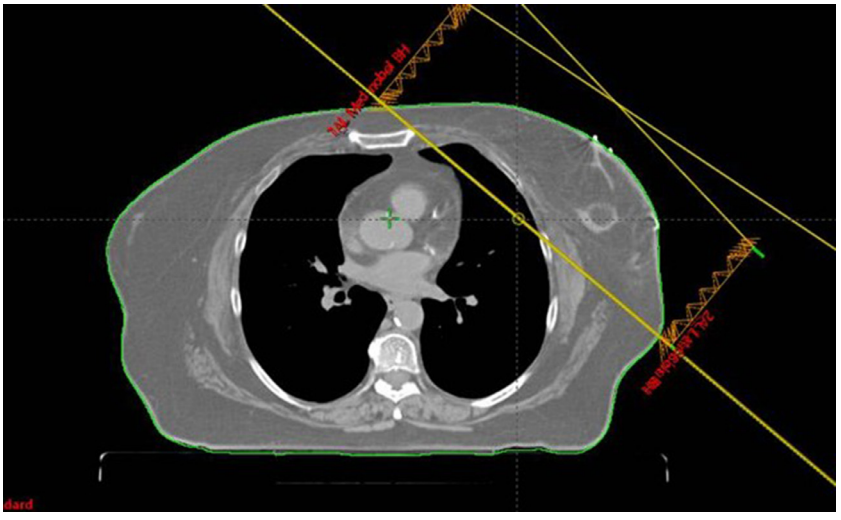
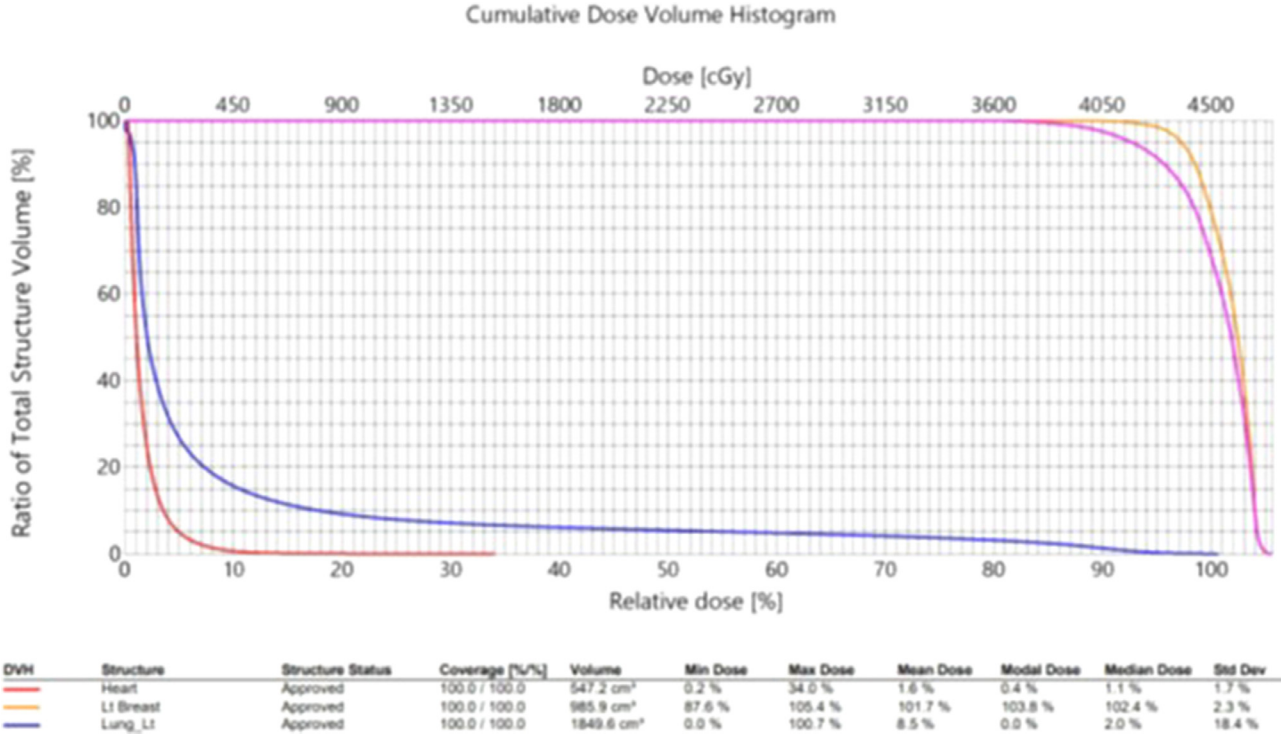


Fig. 3 Axial snapshot of the isodose lines with corresponding tangential fields.



DVH	Structure	Structure Status	Coverage [%/%]	Volume	Min Dose	Max Dose	Mean Dose	Modal Dose	Median Dose	Std Dev
	Heart	Approved	100.0 / 100.0	547.2 cm³	0.2 %	34.0 %	1.6 %	0.4 %	1.1 %	1.7 %
	Lt Breast	Approved	100.0 / 100.0	985.9 cm³	87.6 %	105.4 %	101.7 %	103.8 %	102.4 %	2.3 %
	Lung_Lt	Approved	100.0 / 100.0	1849.6 cm³	0.0 %	100.7 %	8.5 %	0.0 %	2.0 %	18.4 %

Fig. 4 Cumulative dose volume histogram.

Table 1 Radiation induced sarcomas treated with hyperfractionated accelerated reirradiation therapy

Study	No. of patients in study	Average time to diagnosis (mo)	Treatment modality	Timing of radiation	Follow-up (mo)	Rate of recurrence	Time to recurrence (mo)	Radiation-related complications	Overall survival
Donovan et al[23]	9	109.7	Surgical excision and HART	Adjuvant	19.0	11.1%	9.0	78% with mild acute toxic effects: erythema, edema, hyperpigmentation and desquamation of the skin; 3 patients with chronic toxic effects	77.8%
Smith et al[13]	4	99.0	Surgical excision and HART	Adjuvant	72.6	25.0%	5.0	Most patients with minimal toxic effects in the skin: desquamation, hypo- or hyperpigmentation and telangiectasia; 1 patient with pleural effusion after 5 y	75.0%
Smith et al[13]	4	88.5	Surgical excision and HART	Neoadjuvant	84.3	25.0%	47.0	Most patients with minimal toxic effects in the skin: desquamation, hypo- or hyperpigmentation and telangiectasia; 1 patient with pleural effusion after 5 y	75.0%
West et al[24]	1	37.0	Platinum-based chemotherapy and HART		N/A	45.0%	0.0%		No complications reported
West et al[25]	1	131.0	Surgical excision and HART	Adjuvant	26.0	0.0%		No complications reported	100.0%
Current study	1	36.0	Surgical excision and HART	Neoadjuvant	12.0	0.0%		Mild limitation in left shoulder range of motion	100.0%
	Total number of patients								
	20	83.5			43.1	10.2%	20.3		87.9%
		Range, 37-131			Range, 12-84				

Abbreviations: HART = hyperfractionated accelerated reirradiation therapy; N/A = not applicable.

therapy (CFTR, up to 50 Gy in up to 2 Gy daily fractions over 5 weeks), hypofractionated radiation therapy consists of fractions >2 Gy in shorter intervals,[17,18] and over a shorter treatment time.[19] Hypofractionated radiation therapy has become the preferred treatment for breast cancer due to increased patient convenience, the ability to safely deliver a higher radiation dose, and potentially reduced treatment cost. Despite some concerns about late tissue toxicity, there is robust level I evidence to support equivalence between hypofractionation and CFTR with respect to cancer outcomes as well as cosmesis.[18,20,21] There is currently no sufficient data to differentiate hypo- and conventionally fractionated radiation therapy with regard to the development of RIS.

The patient received 3 weeks of preoperative hyperfractionated radiation therapy as treatment for her angiosarcoma before mastectomy. Despite concerns of increased toxicity with reirradiation, the use of hyperfractionated radiation therapy (HART, at <2.0 Gy per fraction), in case reports and phase 2 trials, has been reported as a safe treatment for secondary angiosarcomas and other malignancies (ie, medulloblastoma, non-small cell lung cancer, Burkitt's lymphoma, bladder cancer, soft tissue sarcomas, esophageal cancer, and squamous cell carcinoma of the head and neck).[9,12,13] The smaller doses per treatment may mitigate the potential toxicity to the surrounding tissues and are usually well tolerated. In addition, angiosarcomas have a very high growth fraction, making them potentially more likely to regrow between once-daily fractions in CFRT. Previous case studies reported that 3 daily fractions may allow for the least likelihood of tumor cell repair between treatments.[12]

Retrospective cohort studies on patients who received a diagnosis of RIS not treated with HART have shown recurrence rates from 54% to 61% after a median of 6 to 10 months.[10,22] Overall survival is reported to be 32% to 36% with a median follow-up of 25 to 34 months.[5,11] In our review of the literature, we found a total of 20 patients who received a diagnosis of with RIS and were treated with HART in the adjuvant or neoadjuvant setting. These patients had an improved recurrence rate of 10.2% after a median follow-up time of 43.1 months (Table 1).

At 12-months follow-up, our patient is without evidence of recurrence or significant radiation-related toxicity, except for mild skin erythema and hypersensitivity over the irradiated area. This case illustrates that preoperative use of HART may contribute to tumor regression and the ability to achieve a negative margin resection. Close follow-up will be needed to confirm durable tumor control as well as assess the patient for late effects of HART.

Conclusion

Angiosarcoma of the breast should be considered in all patients presenting with unexplained ecchymosis of the breast, especially in the context of previous radiation exposure. Prior hypofractionated radiation therapy may increase the risk for development of angiosarcoma. Given the overall more advanced stage at time of diagnosis surgical therapy alone is likely insufficient to achieve local control and acceptable disease-free and overall survival rates. The addition of hyperfractionated reirradiation may improve local disease control and overall patient survival. When used in the neoadjuvant setting, HART may help to improve the probability of margin-negative surgical resection. HART appears to be well-tolerated even after prior hypofractionated whole breast radiation therapy.

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