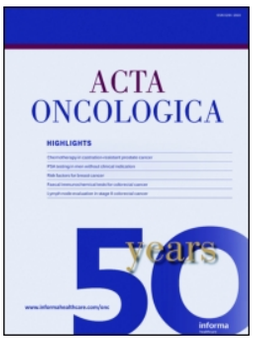

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LETTER TO THE EDITOR

First report of proton beam therapy for breast angiosarcoma from the prospective PCG registry

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Angiosarcoma is a rare neoplasm of the vascular endothelium. Breast angiosarcoma can present *de novo* or as a secondary malignancy after treatment for breast cancer. Postsurgical lymphedema [1] and prior radiotherapy (RT) [2] have both been associated with secondary angiosarcoma. Incidence of secondary angiosarcoma after breast cancer is 1 per 100,000 person-years without prior RT versus 7 per 100,000 person-years with prior RT [2]. Angiosarcoma is an aggressive malignancy, but secondary angiosarcoma after RT may be more indolent than primary angiosarcoma [3,4]. However, five-year survival has remained poor at 27–48% [5].

Due to its extreme rarity, the optimal treatment for secondary angiosarcoma is unknown. Surgery with wide margins is the mainstay of therapy [5,6]. However, surgery alone may be insufficient, with up to 90% local recurrence even after aggressive surgery [5–8]. Resection of all previously irradiated skin [9] and soft tissue [10] of the thoracic wall may improve local control. Chemotherapy has an unclear role [5,6] but may improve local control [11] and overall recurrence [12]. Paclitaxel has shown response in both metastatic or unresectable angiosarcoma [13] and secondary breast angiosarcoma [14]. Targeted therapies, such as bevacizumab [15] and sorafenib [16], have been the focus of recent studies. Radiation for angiosarcoma has faced a lack of enthusiasm given that many patients have prior RT and that the prior RT may have contributed to angiosarcoma development. However, multimodality therapy including RT has resulted in the best published outcomes, with reduced recurrence rates [6,17–21] and potential survival benefit [4,12]. To our knowledge, there are no reports in the literature on proton beam therapy (PBT) for breast angiosarcoma.

The proton collaborative group (PCG) REG001-09 trial is an IRB-approved, multi-institutional prospective registry of patients treated with PBT. We present four patients identified from the registry who received PBT for breast angiosarcoma. One patient had primary breast angiosarcoma. Three patients had secondary breast angiosarcoma in the context of prior breast conserving surgery and RT (60.8 Gy) for early stage breast cancer (Table 1). Median time from prior RT to secondary angiosarcoma was 88 months (82–154). After angiosarcoma diagnosis, all four patients had mastectomy including removal of skin and nipple with negative margins (minimum 19 mm). Immediate reconstruction with latissimus dorsi myocutaneous flap was performed in one patient. One patient received neoadjuvant paclitaxel and had negative axillary lymph node dissection. Another patient also had pectoralis muscle resected at time of mastectomy and received adjuvant doxorubicin–ifosfamide. Median angiosarcoma tumor size was 65.5 mm (47–110).

After mastectomy for angiosarcoma, all patients received postmastectomy PBT to the chest wall (Table S1; Image 1). One patient received regional nodal irradiation. Median total dose was 60.1 Gy (48.8–61.1). Mean lung dose ranged from 2.9 Gy to 10.3 Gy. Percentage of the total lung volume receiving greater than 5 Gy and greater than 20 Gy ranged from 16.7% to 35.9% and 4.3% to 21.3%, respectively. Mean heart dose was less than 2 Gy for all patients. Percentage of the heart receiving greater than 20 Gy was less than 2% for all patients. Skin max dose ranged from 60.5 Gy to 66.4 Gy.

Median follow-up after surgery and PBT is 11 months (2–24) (Table 2). PBT was well-tolerated. Each patient had grade 2 acute dermatitis. One patient had grade 2 acute breast pain. No patients had grade 3 or greater events. However, one patient elected to stop treatment after receiving adjuvant doxorubicin–ifosfamide and 48.8 Gy out of 60.8 Gy planned dose. This patient cited grade 2 dermatitis as the reason for stopping treatment. There have been no recurrences, local or distant. All patients are alive.

Multimodality therapy including RT appears to provide the best results for breast angiosarcoma. Despite aggressive surgery, local control and overall survival remain poor [5,6]. More aggressive surgery [9,10] and chemotherapy [5,6,11,12] may improve outcomes. Radiation has been added to surgery to improve control [6,17–21] and may even prolong survival [4,12]. Potential RT regimens have been associated with frequent grade 3 acute toxicity. Hyperthermia and RT [20] resulted in grade 3 or greater acute dermatitis in 31%. Hyperfractionated RT with or without surgery [18] has also been reported to cause frequent grade 3 acute dermatitis.

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Supplemental data for this article can be accessed here.

Table 1. Patient characteristics.

Patient Number	1	2	3	4
Age (years)	30	58	74	60
BMI (kg/m^2)	27.7	31.7	27.5	29.4
ECOG PS	0	0	0	0
Tobacco history	Current smoker	Prior smoker	Prior smoker	None
Prior breast cancer				
AJCC stage (seventh edition)	No prior breast cancer	Stage IA	Stage IA	Stage IA
Surgical management	No prior breast cancer	Lumpectomy	Lumpectomy	Lumpectomy
Adjuvant RT	No prior breast cancer	60.8 Gy	60.8 Gy	Dose unknown
Angiosarcoma				
Latency after prior RT (months)	No prior RT	82	88	154
Tumor size (mm)	69	62	47	110
Grade	3	1	3	3
Surgical management	Mastectomy	Mastectomy	Mastectomy	Mastectomy
Axillary management	ALND	None	None	None
Margins	Negative	Negative	Negative	Negative
Reconstruction	No	No	LDMF	No
Systemic therapy	Paclitaxel (NA)	None	None	Doxorubicin–Ifosfamide (A)

BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group Performance Status; AJCC: American Joint Committee on Cancer; RT: radiotherapy; ALND: axillary lymph node dissection; LDMF: latissimus dorsi myocutaneous flap; NA: neoadjuvant; A: adjuvant.

Table 2. Outcomes and toxicities after proton beam therapy for angiosarcoma.

Patient number	1	2	3	4
Follow-up (months)	6	24	15	2
Status	Alive	Alive	Alive	Alive
Local recurrence	No	No	No	No
Acute toxicity (all grade 2)	Dermatitis, pain	Dermatitis	Dermatitis	Dermatitis
Late toxicity	None	None	None	None
Any toxicity > grade 2	None	None	None	None

Proton beam therapy has emerged as a new approach to minimize excess dose and to decrease toxicity across many disease sites [22–24]. PBT decreases dose to the heart and lungs compared to conventional photon RT in breast cancer [25], as demonstrated by the minimal heart dose among our four patients. Furthermore, compared to conventional photon RT, PBT minimizes dose to surrounding tissue and decreases the rate of secondary malignancies following adjuvant RT for thymomas [26]. These potential benefits may be even more important in secondary breast angiosarcoma, as the surrounding tissues are at increased risk due to prior RT and have already demonstrated the capacity to develop secondary malignancy.

Breast angiosarcoma is likely to become more common as survival for breast cancer patients continues to improve. Multimodality therapy including RT appears to provide the best outcomes for these patients. PBT has potential benefits in this context. This is the first report of PBT for breast angiosarcoma. At this early follow-up, PBT was well-tolerated and effective. Further studies are needed to identify the optimal treatment and to define the role of PBT for breast angiosarcoma.

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