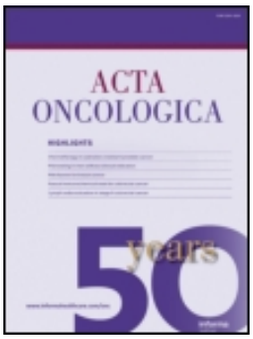

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ORIGINAL ARTICLE

Angiosarcoma after breast-conserving therapy: Long-term disease control and late effects with hyperfractionated accelerated re-irradiation (HART)

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Abstract

Background. Secondary angiosarcoma is a malignant cancer that develops in approximately 1% of patients treated with breast-conserving therapy (BCT) for primary breast cancer. Most treatments for secondary angiosarcoma have been unsuccessful and no consensus has been reached on what is the best therapeutic strategy. We report long-term outcomes of patients with secondary angiosarcoma treated with hyperfractionated and accelerated re-irradiation (HART). *Material and methods.* We retrospectively reviewed the medical records of, and established direct contact with, 14 consecutive patients with secondary angiosarcoma after BCT with axillary lymph node dissection who were treated at our institution with HART with or without surgery from November 1997 to March 2006. With HART, patients received three radiation therapy treatments each day, with a minimum interfraction interval of four hours, five days a week, at 1 Gy per fraction, to total doses of 45 Gy, 60 Gy, and 75 Gy for areas with a moderate risk for subclinical disease, a high risk for subclinical disease, and gross disease, respectively. The minimum follow-up for these patients was six years. *Results*. Median survival was 7.0 years (range 0.4–14.7 years), with five- and 10-year overall survival rates of 79% [95% confidence interval (CI), 51–93%] and 63% (95% CI 37–84%), respectively, and five- and 10-year cause-specific survival rates of 79% (95% CI 51–93%) and 71% (95% CI 44–89%), respectively. Toxicity was minimal. *Conclusion.* Our long-term study provides evidence that patients with secondary angiosarcoma after BCT can frequently be cured. Patients treated with HART have higher overall survival, progression-free survival, and cause-specific survival rates than patients who receive only surgery, conventional radiation therapy, or chemotherapy. HART is well tolerated.

Angiosarcoma is a rare secondary event occurring in 0.05–0.2% of breast cancer patients [1–3] at 3–12 years after breast-conserving therapy (BCT) alone or BCT with radiation therapy (RT) [1–5]. Typically, the natural history of angiosarcoma is extremely aggressive, occasionally preceded by an indolent period with a delay in diagnosis, but progressing rapidly locally before the patient experiences distant metastases and death. No efficacy for chemotherapy has been established and surgery alone has rarely been successful, with most patients developing progressive symptomatic local disease before succumbing to distant metastases. The following is an updated report of late effects and long-term disease control achieved with a novel and aggressive approach using hyperfractionated accelerated re-irradiation (HART) combined with surgery, when feasible.

Material and methods

Between November 1997 and March 2006, 14 consecutive patients with angiosarcoma following breast-conserving surgery and RT were treated with definitive re-irradiation with or without further surgery at the University of Florida. Under a University of Florida Institutional Review Board-approved outcome tracking protocol, patient outcome information was collected and analyzed. The minimum potential follow-up was six years; all living patients were contacted or evaluated within eight months of manuscript submission. The actual median follow-up was 7.0 years (range 0.4–14.7 years) with 11 patients followed for more than five years and two patients for more than 10 years.

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All 14 patients had in situ or early-stage breast cancer treated with breast-conserving surgery, axillary lymph node dissection, and postoperative RT to the breast. The median number of lymph nodes removed was 12.5 (range 7–33) in the 10 patients for whom detailed axillary dissection information is available. In each case, all lymph nodes were negative. Six patients received chemotherapy. The median RT dose to the tumor bed was 59.7 Gy (range 40.4–60.4 Gy). Only one of the 14 patients received initial breast cancer treatment at the University of Florida with the rest referred after diagnosis of angiosarcoma.

The median time to diagnosis of angiosarcoma after BCT was 7.7 years (range 4.2–11 years). Three patients had low-grade angiosarcoma, one patient had intermediate/high-grade angiosarcoma, and 10 patients had high-grade angiosarcoma. In 10 patients, detailed histological information was available: the specimens were positive for CD31 in five patients, CD34 in seven patients, Vimentin in three patients, and Factor VIII in three patients; the specimens were negative for cytokeratin in six patients.

All patients had a mastectomy either before or after HART. Initial treatment for angiosarcoma was single-modality mastectomy in six patients: median time to recurrence of angiosarcoma after mastectomy in these six patients was 3.5 months (range 1 month–1.7 years). Very rapid recurrence after mastectomy in two early patients in the series led to a preference for starting HART as soon as feasible, preoperatively, rather than postoperatively, when possible. Patients who had undergone mastectomy before HART, but had macroscopic recurrent angiosarcoma present at the time of HART, received further surgery when feasible after HART to remove twice-irradiated tissue and confirm tumor response. For all patients who underwent post-HART resection, autogenous tissue transfer was performed if possible to facilitate healing. In several cases, extent of disease precluded any further surgery. Four patients were referred to our department shortly after mastectomy without overt recurrent angiosarcoma and treated electively with postoperative HART because of a high risk of recurrence. Patients are categorized in Table I as presenting for HART with recurrent angiosarcoma after one or more surgical procedures (six patients), presenting with first manifestation of angiosarcoma for preoperative HART with gross disease (four patients), or presenting postoperatively for presumed subclinical disease (four patients) for elective HART.

Table I also indicates the extent of disease present at the time of HART. At the time of HART, macroscopic disease was present in nine of 14 patients, varying from moderate macroscopic disease to extensive macroscopic disease. Local disease typically involved the skin with peau d'orange, brawny, or ecchymotic skin changes, and intact or bleeding nodular or vesicular satellite nodules. Extensive macroscopic disease extended around the chest wall posteriorly to involve skin of the back, inferiorly to the level of the umbilicus, superiorly to the clavicle, and occasionally medially across the midline, involved the sternum and transmural chest wall (patient 11), and/or biopsy-proven axillary lymph nodes (patients 3 and 14). Patient 14 had recurrent axillary nodal disease, with a painful, necrotic, infected mass that required incision and drainage prior to HART. Patients typically had a chest computed tomography (CT) scan and bone scan prior to HART. During the staging process, three patients (patients 9, 12, and 11) were found to have suspicious findings on thoracic CT, which were assumed to be benign and not further evaluated. Patients 9 and 12, who had extensive local disease, also had subcentimeter pulmonary lesions on staging chest CT scans, and patient 11 had several subcentimeter mediastinal nodes on CT. Biopsy was not feasible for any of these findings, nor was an effective treatment available or technically feasible had a positive biopsy been obtained. All three women went on to experience disease progression in the lung or mediastinum, but without local chest wall disease progression, and were not treated with chemotherapy.

Radiation treatment technique

The decision to use radiation for secondary angiosarcoma after initial BCT that included previous radiation was made because of institutional observations of universal rapid and extensive recurrence after surgery. Every patient was re-irradiated with curative intent with a highly customized and typically complex field arrangement. One patient was treated with 1.5 Gy per fraction twice a day with a six-hour interfraction interval; all other patients were treated three times a day with a dose of 1 Gy per fraction and a minimum four-hour interfraction interval. Three dose fractionation levels were used for tissues considered at risk for increasing burdens of disease: 45 Gy to clinically uninvolved tissue with a minimum 5-cm to 10-cm margin around clinically involved sites; 60 Gy to tissue within 2 cm of the primary tumor and thus considered at risk for a high burden of subclinical disease; and 75 Gy to areas with macroscopic disease that could not be surgically removed. The decision to use thrice-daily irradiation was based on institutional observations of rapid angiosarcoma progression during once-daily and twice-daily irradiation in angiosarcoma in the oral tongue and in the first case of post-BCT

secondary angiosarcoma. The decision to use 1.0-Gy fractions was based on the institutional impression that small fractional doses used in twice-daily irradiation for sarcoma and the head and neck resulted in fewer late effects. For practical purposes, the interfraction intervals during the day were a minimum of four hours, but a minimum of 12 hours between successive days and up to 60 hours over the weekend interval. The total dose and fraction size were initially empiric, but adopted as policy once tolerance and efficacy were established in the first three cases. BED and reparation calculations were not considered applicable because of the impossibility of accounting for potential incomplete repair between the four-hour interfraction intervals and variations in maximum interfraction interval. Due to concern for potential late effects in re-irradiated tissues (which had received up to 60 Gy initially and up to 75 Gy with HART), whenever feasible twice-irradiated tissue was resected. As the driving priority was disease control, no specific organs-at-risk constraints were employed, but, as discussed below, electron beam techniques were used to avoid or minimize dose to underlying organs at risk, such as lung and heart, which had frequently received substantial exposure during BCT.

For the four patients treated with preoperative HART as initial treatment for angiosarcoma, radiation was started a median of 2.5 weeks (range 2–3 weeks) after diagnosis. For the four patients treated with postoperative HART as initial treatment for angiosarcoma, the median time to the start of radiation after mastectomy was 2.75 months (range 1.5–4 months). For the six patients treated with HART for recurrent angiosarcoma, HART was started at a median 2.5 weeks after diagnosis of the recurrence (range 4 days–3 months). Variations in time to start of radiation reflect varying time to referral of patients or recovery time after mastectomy.

The technique for postmastectomy patients included multiple abutting en face electron fields with a 0.5–1.0-cm bolus to ensure the full prescription dose at the skin and an electron energy selected to place the 90% isodose line at the chest wall intercostal muscles and outer surface of the rib to minimize the risk of pulmonary or cardiac injury. A median of six abutting electron fields was required because of the extent of disease, variations in target depth, and curvature of the chest wall; however, some patients required more fields. For example, patient 3, whose disease wrapped around the chest wall posteriorly, required 11 fields and treatment in both the supine and prone positions. Fields were designed by the attending physician (NPM) using both clinical landmarks and CT planning to optimize beam angle entry and electron energy. The match lines between electron fields were treated with each field to minimize underdosage in the subcutaneous tissue, and the match lines between abutting electron fields were moved twice during treatment to reduce the recognized dose inhomogeneity at the field junctions. Electron energies typically ranged from 6 to 8 MeV in peripheral fields covering subclinical disease to 10–12 MeV in the central fields covering macroscopic disease. Patient 11 was treated with x-ray-based intensity-modulated radiation therapy (IMRT) to cover transmural chest wall disease.

When HART was given preoperatively to patients 5, 7, 9, and 13 who had intact breasts, tangential photon fields were used for the breast matched to adjacent electron fields to provide a minimum margin of 5–10 cm beyond any clinical evidence of disease. Both photon tangents and all electron fields were administered with a bolus to achieve the full prescription dose at the skin surface. Patients 3 and 14 had suspected or known lymph node involvement, respectively, and also received anterior and posterior photon fields to the axilla. Resection after HART involved removal of any areas suspicious for residual disease and as much twice-irradiated tissue as possible [6].

All statistics were obtained using SAS and JMP statistical software (SAS Institute, Inc, Cary, NC, USA). The Kaplan-Meier method was used to calculate the overall survival and cause-specific survival rates. The follow-up time was calculated from the date HART was rendered.

Results

Follow-up

The minimum potential follow-up was six years and actual median follow-up time was 7.0 years (range 0.4–14.7 years). No patient was lost to follow-up.

Response to HART

Post-HART surgery was performed in the seven of nine patients with macroscopic disease; all seven patients had a complete pathological response with no residual angiosarcoma; one patient had residual vascular hyperplasia.

Disease control and patterns of failure

Table II summarizes patient outcomes by grade. Five patients developed progressive disease, all in locations not covered by HART. One patient developed contralateral nodal disease at 2.3 years after HART (Patient 3), but was salvaged with a second course of HART to the contralateral axilla and breast

Table I. Patient characteristics and HART treatment sequence.

Patient #	Age at dx of breast cancer, yrs	Breast cancer stage	Breast cancer tx	Time after BCT to dx of AS, yrs	Node removed during BCT axillary dissection	Time from initial presentation of AS to definitive bx, mo	Prior TX for AS
1	59	DCIS	L+RT+CT	6.5	Unknown	24	S
2	62	T1N0	L+RT	5.7	12	7	S
3	67	T1N0	L+RT	4.7	21	1	S
4	50	DCIS	L+RT	9.2	Unknown	2	None
5	29	DCIS	L+RT+CT	9.0	Unknown	8	None
6	47	T1bN0	L+RT+CT	9.2	13	6	None
7	64	T2aN0	L+RT+CT	7.0	19	6	None
8	63	T2N0	L+RT	8.8	33	4	None
9	42	T2N0	L+RT	5.2	9	8	None
10	41	T1bN0	L+RT	9.4	7+	11	S
11	70	TxN0	L+RT	11.0	18	3	S
12	61	T1N0	L+RT	5.9	8	7	None
13	66	T1N0	L+RT	8.3	9	4	None
14	62	T1N0	L+RT+CT	4.3	Unknown	4	S, S

ANED, alive with no evidence of disease; AS, angiosarcoma; BCT, breast-conserving therapy; bx, biopsy; CT, chemotherapy; DID, died of intercurrent disease; DWD, died with disease; Dx, diagnosis; HART, hyperfractionated and accelerated re-irradiation; L, lumpectomy; mo, months; N/A, not applicable; RT, conventional radiotherapy; S, surgery; tx, treatment; yrs, years.

with post-HART axillary dissection; she survived another 8.3 years without further evidence of disease, ultimately dying of a cerebral vascular accident. One patient developed a local recurrence on the anterior chest wall 0.4 years after beginning HART, likely a marginal miss in an area with only a 2-cm margin on the clinical target volume (Patient 14); no salvage therapy was given and she succumbed to progressive local and metastatic disease at 3.5 years after initial HART. Three patients (patients 9, 12, and 11) with high-grade angiosarcoma, including two with pulmonary lesions of unknown significance at the time of HART and one with transmural involvement with subcentimeter mediastinal nodes of unknown significance, developed overt progressive pulmonary and mediastinal disease shortly after HART, dying of metastatic disease at 5.8, 0.8, and 0.4 years, respectively. Thus, HART with or without surgery was successful in achieving ultimate disease control in 10 of the 14 patients, including six of the 10 with high-grade angiosarcoma, as well as all four patients with low- and intermediate/high-grade angiosarcoma.

Survival

The five- and 10-year overall survival rates were 79% [95% confidence interval (CI), 51–93%] and 63% (95% CI 37–84%), respectively. The five- and 10-year progression-free survival rates were both 64% (95% CI 38–84%), and the five- and 10-year cause-specific survival rates were 79% (95% CI 51–93%) and 71% (95% CI 44–89%), respectively.

At the time of the last follow-up, eight of 14 patients were alive with no evidence of disease at a median of 8.1 years (range 6.0–14.7 years), two had

Table II. Summary of patient status.

	All Grades			High Grade			Intermediate-High Grade			Low Grade		
Patient Status	Number of patients	Median survival time (years)	Median survival Time range (years)	Number of patients	Median survival time (years)	Median survival time range (years)	Number of patients	Median survival time (years)	Median survival time range (years)	Number of patients	Median survival time (years)	Median survival time range (years)
ANED	8	8.1	6.0–14.7	6	8.1	6.0–14.7	N/A	N/A	N/A	2	7.4	6.7–8.2
DID	2	8.7	6.2–11.1	1	11.1	N/A	N/A	N/A	N/A	1	6.2	N/A
DWD	4	2.1	0.4–5.8	3	0.8	0.4–3.5	1	5.8	N/A	N/A	N/A	N/A
ANED + DID	10	8.1	6.0–14.7	7	8.3	6.0–14.7	N/A	N/A	N/A	3	6.7	6.2–8.2

ANED, alive with no evidence of disease; DID, died of intercurrent disease; DWD, died with disease; N/A, not available.

Table I. (*Continued*)

Time to disease recurrence after initial tx for AS, mo	Macroscopic disease present at time of HART	Grade of AS at time of dx	HART for recurrent or de novo AS	HART treatment sequence	Status at last follow-up, yrs
2	Yes	Low	Recurrent	HART -> S	DID at 6.3
2	Yes	High	Recurrent	HART -> S	ANED at 14.7
1	Yes	High	Recurrent	HART, HART -> S	DID at 11.1
N/A	No	High	De novo	S -> HART	ANED at 8.3
N/A	Yes	High	De novo	HART -> S	ANED at 8.5
N/A	No	Low	De novo	S -> HART	ANED at 8.2
N/A	Yes	High	De novo	HART -> S	ANED at 7.9
N/A	No	High	De novo	S -> HART	ANED at 7.3
N/A	Yes	Intermediate-High	De novo	HART -> S	DWD at 5.8
1	No	Low	Recurrent	S -> HART	ANED at 6.7
10	Yes	High	Recurrent	HART -> S	DWD at 0.8
N/A	No	High	De novo	S -> HART	DWD at 0.4
N/A	Yes	High	De novo	HART -> S	ANED at -5.9
5, 2	Yes	High	Recurrent	HART	DWD at 3.5

died from intercurrent disease at 6.2 and 11.1 years, and four had died of angiosarcoma at a median of 2.1 years (range 0.4–5.8 years) after HART.

Side effects and complications of treatment

During HART, most patients had only minimal skin reactions, but a few developed moist desquamation approximately one week after HART, which resolved within two to three weeks with prophylactic antifungal and topical antibacterial agents. Residual twice-irradiated areas frequently developed telangiectasia after several years and some areas that had developed moist desquamation during treatment showed small areas of hypopigmentation after healing. In two patients, hyperpigmentation and subcutaneous fibrosis developed in the matchline between electron fields which was intermittently pruritic, improved with selenium, and did not require further therapy. Three patients (patients 3, 7, and 14) developed mild-to-moderate lymphedema, which in two cases was treated with compression sleeves, lymphedema massage therapy, physical therapy, or a combination of these treatments. Massage therapy to the chest wall was used in patients 2 and 13 after they experienced persistent chest wall pain. Five years after completing HART, one patient (Patient 2) developed recurrent benign pleural effusions that were successfully treated with talc pleurodesis; at last follow-up, patient 2 was alive with no sign of disease or fluid accumulation 14.7 years after beginning HART and 8.7 years after pleurodesis. Four patients (patients 2, 3, 8, and 9) developed rib fractures in twice-irradiated areas a median time of 3.3 years (range 1.4–7.1 years) after HART; three asymptomatic fractures were noted incidentally on CT scans, and the one symptomatic rib fracture occurred after a traumatic fall. All resolved without intervention and none have recurred.

Discussion

Angiosarcoma frequency and etiology

Angiosarcoma is a very rare complication of BCT whose etiology is still under investigation [5–10]. Recent studies indicate there may be a continuum between atypical vascular lesions and angiosarcoma [7] and there are genetic differences between primary angiosarcoma, secondary angiosarcoma, and atypical vascular lesions [8–10]. Recently, FISH has been used to distinguish angiosarcoma, which has MYC amplification, from AVL, which do not have MYC amplification [8,10,11]. Angiosarcoma after mastectomy alone or in conjunction with postmastectomy irradiation has been described as the Stewart Treves Syndrome, typically affecting an edematous upper extremity, rather than the chest wall, suggesting the possibility that chronic edema may be part of the etiology. None of the 14 patients in our study had overt arm edema after BCT, but all 14 had undergone an axillary lymph node dissection and may likely have had some minimal subclinical lymph stasis involving the breast. A review of the literature suggests that the vast majority, if not all, of the reported cases of angiosarcoma after breast cancer therapy either with mastectomy or breast conserving surgery have occurred after surgery, which included axillary dissection [4,12–15]. It is possible that with fewer axillary dissections, and less clinical and subclinical arm and breast edema, post-BCT angiosarcoma will become an even rarer complication in the future.

Literature review of surgery and chemotherapy treatment for secondary angiosarcoma

Other institutions have attempted to treat secondary angiosarcoma with chemotherapy, surgery, or both; however, results have been much less favorable than the results reported herein with HART. There have been four case studies [16–19] on the use of taxanes, thalidomide, or gemcitabine-taxane for treatment of secondary angiosarcoma. Only two of these studies, Gambini et al. and Perez-Ruiz et al., report patient survival time at the time of publication of five months and 48 months, respectively. Three studies employed continuous cycles (daily, weekly, or every three weeks) of chemotherapy for the remainder of the patient's life [16,17,19]. In the only phase II study of paclitaxel for angiosarcoma [20], nine of the 30 patients in the study had secondary angiosarcoma after BCT, and the median survival time of the 30 patients was 7.6 months with a four-month progression-free survival rate of 45%. The experience reported thus far with chemotherapy indicates only short-lived disease response.

Four recent surgical studies [3,12,21,22] report median follow-up times ranging from 15 months to 5.25 years. One study [21] of 33 patients treated with a mastectomy for secondary angiosarcoma reported a minimum follow-up of two years, a median survival of 48.5 months, and a five-year overall survival of 43.2%. Another study [22] of 31 patients treated with a mastectomy or local excision reported a median follow-up of 27 months, median disease-free survival of 16 months, and a median disease-specific survival of 37 months. A third study of 14 patients reported a follow-up time of 15 months and the five-year overall survival rate was 10% [3]. Finally Lindford et al. published a series of nine patients treated with a larger surgical margin of 3–5 cm who achieved a median survival of 4.1 years [12].

HART

We report herein our updated long-term results of a novel RT approach called HART used to treat angiosarcoma after BCT. While the number of patients reported in this study is small, the outcomes with respect to disease control appear substantially better than other reported approaches, with 79% achieving disease control with long-term follow-up significantly beyond typical intervals to recurrence. Three of the four patients in this series who succumbed to disease likely had metastatic disease present prior to HART and one patient failed HART likely because of inadequate field size, suggesting even higher efficacy with optimal patient selection and treatment design. We believe the critical elements responsible for the success of this approach are: 1) the rapid delivery of treatment; 2) the small radiation dose per fraction; and 3) the use of atypically generous radiation field margins.

Clinical observation of disease progression after surgery suggests few if any anatomic barriers for angiosarcoma to spread through the skin and subcutaneous vascular and lymphatic channels. Thus, we believe all areas suspected of harboring subclinical disease, should be covered in the radiation fields with minimum 5-cm and to 10-cm margins, if feasible, beyond any areas with even subtle signs of clinical involvement such as current or historical ecchymosis, erythema, nodules, and peau d'orange. The rapidity of progression after mastectomy suggests an unusually high proportion of actively dividing cells, likely to require rapid retreatment to avoid repopulation, hence the thrice-daily treatments. The use of small fractional radiation doses may provide some advantage for sublethal damage repair in normal tissues already exposed once to moderately high doses of radiation, hence the small dose per fraction of 1 Gy rather than the typical 1.8–2.0-Gy dose. The total dose of 60–75 Gy would be considered modest, if not inadequate, for a carcinoma or sarcoma of comparable size, but the relatively short overall time of delivery resulting from the thrice-daily fractions delivers a dose-intense treatment, likely biologically equivalent to a much higher dose of radiation. Unacceptable normal tissue damage would be anticipated with such doses delivered with the standard doses per fraction of 1.8–2.0 Gy, but has not occurred, possibly because of the smaller doses per fraction.

Other institutions have now published early experiences with HART. Biswas et al. reported on seven patients who received surgery as initial treatment of secondary angiosarcoma; all but one had at least one recurrence. HART was used after resection in one of only two survivors in this series [2]. Another investigator has documented success with this approach in a case report of a patient alive and well 3.8 years after HART [23]. In a third case series of four patients with secondary angiosarcoma, the only patient initially treated with HART postmastectomy was the only survivor at 2.4 years after treatment, whereas the other three patients succumbed to angiosarcoma at 0.5, 1.0, and 1.6 years [24] despite initial treatment with surgery alone or in conjunction with chemotherapy. These three papers demonstrate that HART treatment can be successfully replicated at other institutions.

Summary

This long-term outcomes study of 14 patients treated with HART at the University of Florida provides evidence of the potential curability of secondary angiosarcoma after primary breast cancer. Median

survival has not been reached but is at least 7.0 years. Disease progression has been documented only outside of the radiation fields, suggesting the potential for even higher efficacy with more extensive pretreatment staging and generous treatment of areas at risk for subclinical disease. Side effects and complications are minimal, with the judicious resection of as much twice-irradiated tissue as possible and autogenous reconstructive procedures. Finally, other institutions have replicated HART with similar successful results when HART is implemented early in treatment. Critical elements of the treatment are generous field margins, thrice-daily fractions, and moderate total doses delivered in small fractional doses over a short overall treatment period.

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References

[1] Abbott R, Palmieri C. Angiosarcoma of the breast following surgery and radiotherapy for breast cancer. Nat Clin Pract Oncol 2008;5:727–36.

[2] Biswas T, Tang P, Muhs A, Ling M. Angiosarcoma of the breast: A rare clinicopathological entity. Am J Clin Oncol 2009;32:582–6.

[3] Jallali N, James S, Searle A, Ghattaura A, Hayes A, Harris P. Surgical management of radiation-induced angiosarcoma after breast conservation therapy. Am J Surg 2012;203: 156–61.

[4] Marchal C, Weber B, de Lafontan B, Resbeut M, Mignotte H, du Chatelard PP, et al. Nine breast angiosarcomas after conservative treatment for breast carcinoma: A survey from French comprehensive Cancer Centers. Int J Radiat Oncol Biol Phys 1999;44:113–9.

[5] Wang XY, Jakowski J, Tawfik OW, Thomas PA, Fan F. Angiosarcoma of the breast: A clinicopathologic analysis of cases from the last 10 years. Ann Diagn Pathol 2009; 13:147–50.

[6] Palta M, Morris CG, Grobmyer SR, Copeland EM, 3rd, Mendenhall NP. Angiosarcoma after breast-conserving therapy: Long-term outcomes with hyperfractionated radiotherapy. Cancer 2010;116:1872–8.

[7] Santi R, Cetica V, Franchi A, Pepi M, Cesinaro AM, Miracco C, et al. Tumour suppressor gene TP53 mutations in atypical vascular lesions of breast skin following radiotherapy. Histopathology 2011;58:455–66.

[8] Fernandez AP, Sun Y, Tubbs RR, Goldblum JR, Billings SD. FISH for MYC amplification and anti-MYC immunohistochemistry: Useful diagnostic tools in the assessment of secondary angiosarcoma and atypical vascular proliferations. J Cutan Pathol 2012;39:234–42.

[9] Manner J, Radlwimmer B, Hohenberger P, Mossinger K, Kuffer S, Sauer C, et al. MYC high level gene amplification is a distinctive feature of angiosarcomas after irradiation or chronic lymphedema. Am J Pathol 2010;176:34–9.

[10] Guo T, Zhang L, Chang NE, Singer S, Maki RG, Antonescu CR. Consistent MYC and FLT4 gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions. Gene Chromosome Cancer 2011;50:25–33.

[11] Mentzel T, Schildhaus HU, Palmedo G, Buttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: Clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol 2012;25:75–85.

[12] Lindford A, Bohling T, Vaalavirta L, Tenhunen M, Jahkola T, Tukiainen E. Surgical management of radiation-associated cutaneous breast angiosarcoma. J Plast Reconstr Aesthet Surg 2011;64:1036–42.

[13] Billings SD, McKenney JK, Folpe AL, Hardacre MC, Weiss SW. Cutaneous angiosarcoma following breast-conserving surgery and radiation: An analysis of 27 cases. Am J Surg Pathol 2004;28:781–8.

[14] Mery CM, George S, Bertagnolli MM, Raut CP. Secondary sarcomas after radiotherapy for breast cancer: Sustained risk and poor survival. Cancer 2009;115:4055–63.

[15] Stewart FW, Treves N. Lymphangiosarcoma in postmastectomy lymphedema; a report of six cases in elephantiasis chirurgica. Cancer 1948;1:64–81.

[16] Gambini D, Visintin R, Locatelli E, Galassi B, Bareggi C, Runza L, et al. Paclitaxel-dependent prolonged and persistent complete remission four years from first recurrence of secondary breast angiosarcoma. Tumori 2009; 95:828–31.

[17] Perez-Ruiz E, Ribelles N, Sanchez-Munoz A, Roman A, Marquez A. Response to paclitaxel in a radiotherapy-induced breast angiosarcoma. Acta Oncol 2009;48:1078–9.

[18] Arnaout A, Wedman DM, El-Sayed S, Acharya V, Lad S. Neoadjuvant gemcitabine-taxane chemotherapy for radiation-induced angiosarcoma of the breast: A case report. Breast J 2012;18:276–8.

[19] Raina V, Sengar M, Shukla NK, Deo SS, Mohanty BK, Sharma D, et al. Complete response from thalidomide in angiosarcoma after treatment of breast cancer. J Clin Oncol 2007;25:900–1.

[20] Penel N, Bui BN, Bay JO, Cupissol D, Ray-Coquard I, Piperno-Neumann S, et al. Phase II trial of weekly paclitaxel for unresectable angiosarcoma: The ANGIOTAX Study. J Clin Oncol 2008;26:5269–74.

[21] Morgan EA, Kozono DE, Wang Q, Mery CM, Butrynski JE, Baldini EH, et al. Cutaneous radiation-associated angiosarcoma of the breast: Poor prognosis in a rare secondary malignancy. Ann Surg Oncol 2012;19:3801–8.

[22] Seinen JM, Styring E, Verstappen V, Vult von Steyern F, Rydholm A, Suurmeijer AJ, et al. Radiation-associated angiosarcoma after breast cancer: High recurrence rate and poor survival despite surgical treatment with R0 resection. Ann Surg Oncol 2012;19:2700–6.

[23] West JG, Weitzel JN, Tao ML, Carpenter M, West JE, Fanning C. BRCA mutations and the risk of angiosarcoma after breast cancer treatment. Clin Breast Cancer 2008; 8:533–7.

[24] West JG, Qureshi A, West JE, Chacon M, Sutherland ML, Haghighi B, et al. Risk of angiosarcoma following breast conservation: A clinical alert. Breast J 2005;11:115–23.