Clinics of Oncology

Research Article ISSN: 2640-1037 | Volume 7

Radiation-Induced Angiosarcoma of the Breast: Retrospective Analysis at a Regional Treatment Centre

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Received: 28 July 2023
Accepted: 04 Sep 2023
Published: 11 Sep 2023
J Short Name: COO

Citation:

Wong HH, Radiation-Induced Angiosarcoma of the Breast: Retrospective Analysis at a Regional Treatment Centre. Clin Onco. 2023; 7(1): 1-11

1. Abstract

Radiation-induced angiosarcoma (RIA) of the breast is an uncommon but morbid complication after radiotherapy for breast cancer. This retrospective study analysed the treatment and outcome of breast RIA patients at Cambridge University Hospital (CUH), a regional treatment centre in the East of England. Twenty-two patients were identified between 2010 and 2022. The median age of diagnosis was 65 years (range 41-78). The median time from completion of breast radiotherapy to RIA diagnosis was 6.5 years (range 2.4-16.0) – this interval appears to have decreased over the last 24 years (r2 = 0.6601). Tumours were often multifocal, with a median size of 65 mm (range 10-250). Two (9%) patients had metastasis at presentation while the rest had localised RIA. All patients underwent surgery (55% at CUH, 45% at local hospitals). Six (27%) patients received peri-operative pegylated liposomal doxorubicin in the first-line setting. Thirteen (62%) patients relapsed following their primary curative-intent treatments after a median of 28 months – ten with locoregional disease and three with distant metastases. Three patients with local recurrence received peri-operative weekly paclitaxel. The overall survival (OS) of all patients was 82 months (2-year and 5-year OS rates of 73% and 60%, respectively). Metastases occurred in eight (36%) of our patients, the commonest sites being lung (100%) and lymph nodes (50%), followed by bone and liver. Univariate analysis showed no correlation between progression-free survival and OS with tumour size, surgical margin, peri-operative chemotherapy, and whether surgery was performed at CUH. Patients aged >72 years have a median OS of 45 months, compared with 102 months in those ≤72 years (HR = 7.129 [95% CI 1.646-30.88]; P = 0.0086). RIA is an aggressive disease with high rates of recurrence and mortality and appears to be occurring sooner after breast radiotherapy. Further studies on its pathogenesis and effective treatment are warranted.

2. Introduction

Radiation-induced angiosarcoma (RIA) of the breast is an extremely rare and late complication following radiotherapy for breast cancer. The criteria used to qualify a sarcoma as radiation-induced were originally proposed by Cahan et al. and now include a prior history of radiation therapy, a latency period of several years between radiotherapy and diagnosis, a sarcoma arising within the radiation field, and histological confirmation [1, 2]. The pathogenesis of radiation-induced sarcoma remains poorly understood but is thought to be caused by irreversible sub-lethal DNA damage in the tissue that was irradiated [3].

First described in 1981, breast RIA typically occurs at a median interval of 5-8 years following irradiation, which is much shorter compared with RIA in other parts of the body [4–10]. The incidence of RIA after radiotherapy has been estimated to be around 0.05-0.16% [5, 11, 12]. Surgery, in the form of wide excision or mastectomy, is the primary treatment for localised disease. However, the outcome of patients with breast RIA is poor. Even in those with localised, resectable disease at diagnosis and an R0 resection, over half will develop recurrence or metastasis, with a median overall survival (OS) of only around 3 years [8, 9, 13]. A number

of prognostic factors have been found to be associated with poorer outcome, including excision margins, large tumour size, deep tumours and older age, while the use of peri-operative chemotherapy has been associated with reduced risk of local recurrence and improved survival [7, 8, 13–17]. There is as yet no general consensus on the best management approach given the rarity of this disease.

Our study aims to describe the management and outcome of patients with breast RIA at a regional treatment centre in the East of England and discuss treatment options.

3. Methods

Cambridge University Hospital (CUH) is a regional referral and treatment centre in the East of England for patients with suspected or confirmed soft-tissue sarcomas. We retrospectively identified all patients diagnosed with and treated for angiosarcoma of the breast between 2010 and 2022, at CUH as well as at four other regional district hospitals who were referred to us for treatment.

Patients' clinical records were obtained and examined. Diagnosis was confirmed by immunohistochemistry and reviewed by central specialist histopathologists (Figure 1). RIA was defined as histologically-proven angiosarcoma occurring within the field of previous irradiation for treatment of breast cancer.

Statistical analyses were performed using Microsoft Excel and GraphPad Prism. The Kaplan-Meier method and logrank test were used for survival analysis. Surviving patients were censored at last contact. Comparative analyses were shown as hazard ratios (HR) with 95% confidence intervals (CI). A P value of <0.05 was considered to be statistically significant. Progression-free survival (PFS) is the time interval from the start of treatment to clinical or radiological disease progression, as defined by the Response Evaluation Criteria in Solid Tumours.

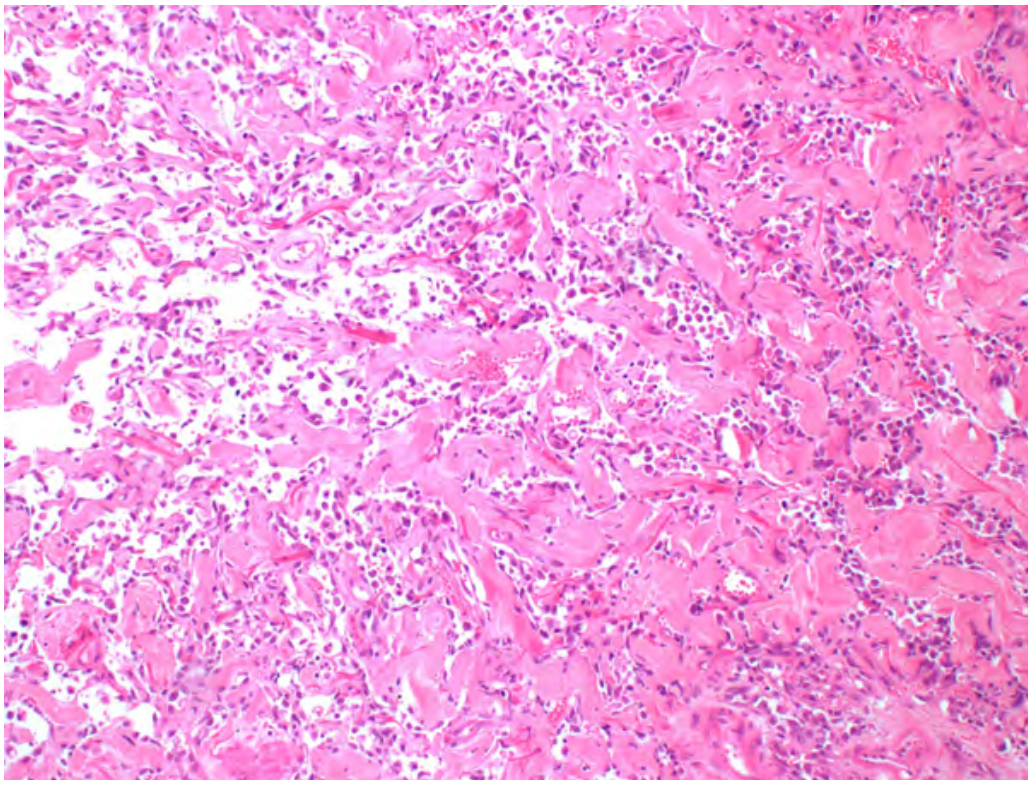

Figure 1: Radiation-induced angiosarcoma – haematoxylin and eosin staining of tissue (x100 magnification) showing ectatic vascular spaces dissecting through collagen and lined by cytologically atypical endothelium.

4. Results

4.1. Patient Characteristics

A total of 24 patients with breast angiosarcoma were identified from our database between 2010 and 2022, of which 22 of them had breast RIA, the remaining two patients being primary breast angiosarcoma. Patient characteristics of those with breast RIA are summarised in (Table 1). All patients were female. The median age of primary breast cancer diagnosis was 57 years (range 33-73), the most common histological subtype being invasive ductal carcinoma. These were diagnosed between 1994 and 2017. All patients had oestrogen receptor-positive tumours and had surgery and radiotherapy (40 Gy in 15 fractions). Four (18%) patients had a history of other neoplasms.

The median age of diagnosis of RIA was 65 years (range 41-78). Two (9%) patients had disease on the skin of their chest walls due to previous mastectomies. Twelve (55%) patients had more than one RIA lesions on their breasts/chests. The median tumour size was 65 mm (range 10-250). All but two patients presented with localised disease – one had evidence of axillary nodal involvement and one had lung metastases. Another patient had bone metastasis but this was felt to be related to her previous breast cancer.

The median time from completion of breast radiotherapy to RIA diagnosis was 6.5 years (range 2.4-16.0). This interval appears to have decreased over the last 24 years, with a coefficient of determination of 0.6601 (Figure 2). This relationship is independent of tumour sizes (data not shown).

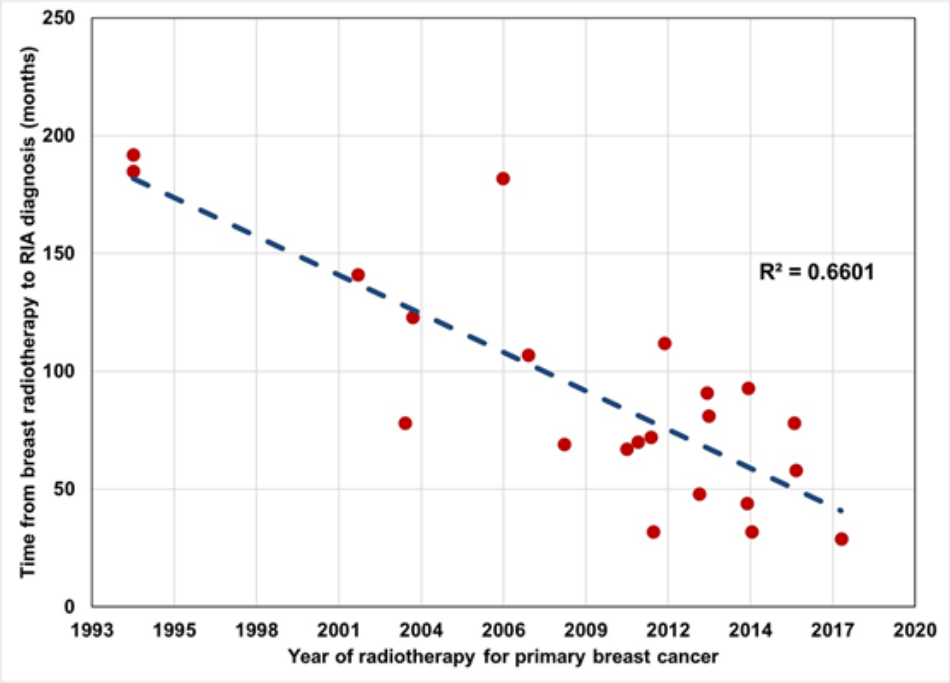

Figure 2: Time from breast radiotherapy to diagnosis of radiation-induced angiosarcoma from 1994 to 2018.

Table 1: Patient characteristics

Variables	N = 22
Median Age of Primary Breast Cancer Diagnosis (years)	57 (range 33-73)
Primary Breast Cancer Histology	
Invasive ductal carcinoma	12 (55%)
Invasive lobular carcinoma	2 (9%)
Mucinous carcinoma	1 (5%)
Tubular carcinoma	1 (5%)
Ductal carcinoma in situ	1 (5%)
Unspecified	5 (23%)
Surgery for Primary Breast Cancer	
Wide local excision +/- axillary lymph node dissection	20 (91%)
Mastectomy +/- axillary lymph node dissection	2 (9%)
Other Therapies for Primary Breast Cancer	
Chemotherapy	9 (41%)
5-fluorouracil, epirubicin, cyclophosphamide, docetaxel	4
5-fluorouracil, epirubicin, cyclophosphamide	
Docetaxel, cyclophosphamide	1
Doxorubicin, cyclophosphamide, docetaxel	1
Epirubicin, cyclophosphamide, docetaxel	1
Unknown	1
Endocrine therapy	22 (100%)
Radiotherapy (40 Gy in 15 fractions)	22 (100%)
Other Neoplasm	
Diffuse large B-cell lymphoma	1 (5%)

Endometrioid adenocarcinoma	1 (5%)
Pituitary adenoma	1 (5%)
Rectal neuroendocrine tumour	1 (5%)
Median age of RIA Diagnosis (years)	65 (range 41-78)
Median Time from Radiotherapy to RIA (years)	6.5 (range 2.4-16.0)
RIA Location	
Breast	20 (91%)
Chest wall (previous mastectomy for breast cancer)	2 (9%)
Single or Multiple RIA Lesions	
Single lesion	10 (45%)
Multiple lesions	12 (55%)
Median RIA Tumour Size (mm)	65 (range 10-250)
RIA Metastasis at Diagnosis	
No evidence of metastasis	20 (91%)
Axillary node	1 (5%)
Lung	1 (5%)

4.2. Treatment and Outcome

Other than the initial surgeries which could be performed at the local hospitals, all multidisciplinary team discussions, histology reviews, chemotherapies and follow-ups are done at CUH. The treatments and outcomes of patients with RIA are summarised in (Table 2). Twenty (91%) patients underwent mastectomy with or without axillary node clearance with curative intent. The remaining two patients had chest wall disease (previous mastectomy for breast cancer) – one underwent wide local excision, and the other patient with lung metastases had palliative excision for continuously haemorrhaging RIA. Twelve (55%) patients had their surgeries performed centrally at CUH, with the remaining at the local hospitals. Six (27%) patients received peri-operative chemotherapy in the form of pegylated liposomal doxorubicin (PLD) – three received this neo-adjuvantly because their RIA was too extensive or was actively bleeding, which resulted in one complete and two partial responses, enabling surgery to proceed (Figure 3). Four patients were given PLD as an adjuvant treatment after mastectomy (one of them had also received PLD neo-adjuvantly).

Thirteen (62%) patients developed disease recurrence after their primary curative-intent surgeries – ten with locoregional disease and three with distant metastases, after a median interval of 28 months (Figure 4). Out of these, five (38%) had surgery only and four (31%) had chemotherapy only. Three (23%) patients were treated with peri-operative weekly paclitaxel chemotherapy (two adjuvantly and one prior to planned surgery) – the latter patient achieved complete radiological and pathological response (on repeat biopsy) so that surgery was not performed (Figure 5); however, she developed local recurrence and lung metastasis 15 months later. One 53-year-old patient with local recurrence decided not to have conventional surgery but went to Mexico for alternative therapies including T-cell therapy, dendritic cell vaccine, cyclophosphamide, capecitabine, metformin, celecoxib and various supplements. She developed extensive cutaneous and metastatic disease 4 months later and died shortly afterwards. Two other patients, who developed locoregional relapse following initial excision for local recurrence, received pre-operative PLD which resulted in partial response, allowing further excisions to proceed.

In total, metastases occurred in eight (36%) of our patients, the commonest sites being lung (100%) and lymph nodes (50%), followed by bone (25%), liver (25%), brain (13%) and spleen (13%) (Figure 6).

Table 2: Treatments and outcomes of radiation-induced angiosarcoma

	N = 22
Primary Treatment for RIA	
Mastectomy +/- axillary node clearance (curative intent)	14 (64%)
Peri-operative chemotherapy with PLD + mastectomy (curative intent)	6 (27%)
Wide local skin excision (curative intent)	1 (5%)
Palliative skin excision	1 (5%)
Primary Surgery Performed at	
Cambridge University Hospital	12 (55%)
Other hospitals	10 (45%)

First Relapse after Primary Surgery with Curative Intent (n = 21)	
Locoregional	10 (48%)
Metastasis	3 (14%)
Treatment of First Relapse (n = 13)	
Surgery for locoregional recurrence	5 (38%)
Peri-operative chemotherapy + surgery for locoregional recurrence	3 (23%)
Palliative chemotherapy	4 (31%)
Patient opted for non-standard alternative therapy	1 (8%)
Best Response to Chemotherapy	
Neoadjuvant PLD (n = 3)	1 CR, 2 PR
Neoadjuvant PLD for local recurrence (n = 2)	2 PR
Neoadjuvant paclitaxel for local recurrence (n = 1)	CR
Palliative PLD (n = 3)	2 PR, 1 PD
Palliative paclitaxel (n = 2)	2 PR
Palliative gemcitabine and propranolol (n =1)	PD
Sites of Distant Metastasis (n = 8)	
Lung	8 (100%)
Lymph node	4 (50%)
Bone	2 (25%)
Liver	2 (25%)
Brain	1 (13%)
Spleen	1 (13%)

PLD: pegylated liposomal doxorubicin; CR: complete response; PD: progressive disease; PR: partial response

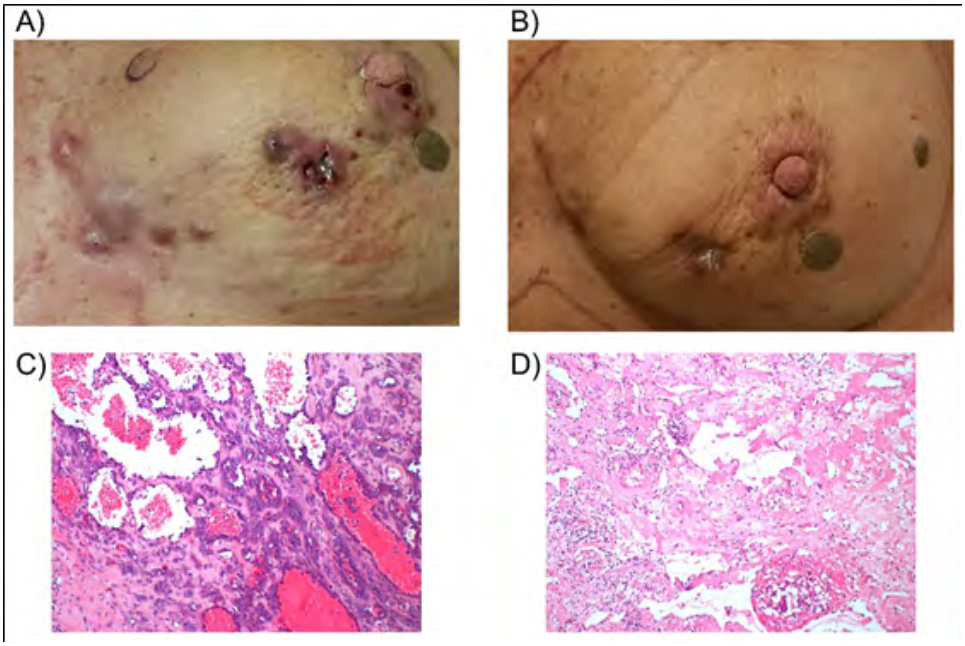

Figure 3: Radiation-induced angiosarcoma before (A) and after (B) treatment with pegylated liposomal doxorubicin, prior to mastectomy. (C) Haematoxylin and eosin staining of tissue (x100 magnification) showing irregularly shaped, tightly packed vascular spaces lined by cytologically and architecturally atypical endothelium typical of angiosarcoma. (D) Region of post-chemotherapy regressed disease from the same specimen showing hyaline fibrosis, inflammation and vascular spaces lined by non-atypical endothelium.

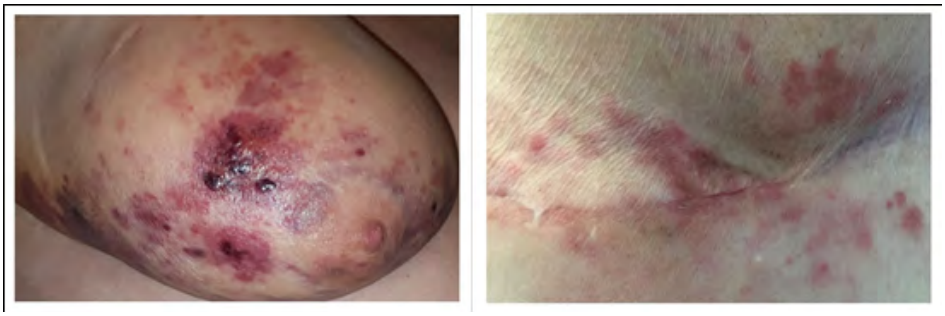

Figure 4: Radiation-induced angiosarcoma of the breast and local recurrence 6 months after primary mastectomy.

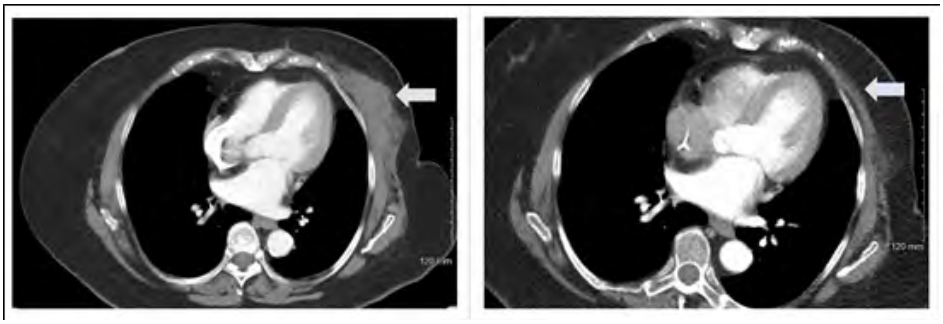

Figure 5: Radiological response of local recurrence of radiation-induced angiosarcoma to treatment with paclitaxel chemotherapy.

Figure 6: Radiation-induced angiosarcoma with metastases to the base of skull, brain, and lung.

4.3. Survival

After a median follow-up period of 66.5 months, the median PFS following primary curative-intent surgery was 28 months (2-year and 5-year PFS rates of 55% and 33%, respectively), while the median overall survival (OS) was 82 months (2-year and 5-year OS rates of 73% and 60%, respectively) (Figure 7). Analysis of potential prognostic variables were performed, namely on age (≤72 vs >72 years), tumour size (<5 vs ≥5 cm), surgical margin (≤1 mm vs >1 mm), hospital where the primary surgery was performed (CUH vs other hospitals), the use of peri-operative chemotherapy (vs surgery only), and peri-operative chemotherapy regimen (PLD vs paclitaxel) (Table 3). No factors other than age were found to be statistically significant in affecting PFS and OS. Patients of age >72 years have statistically shorter median PFS following primary surgery (6 vs 29 months; HR = 4.586 (95% CI 1.184-17.76); logrank P = 0.0275) as well as OS (45 vs 102 months; HR = 7.129 (95% CI 1.646-30.88); logrank P = 0.0086) than those who were ≤72 years (Figure 8).

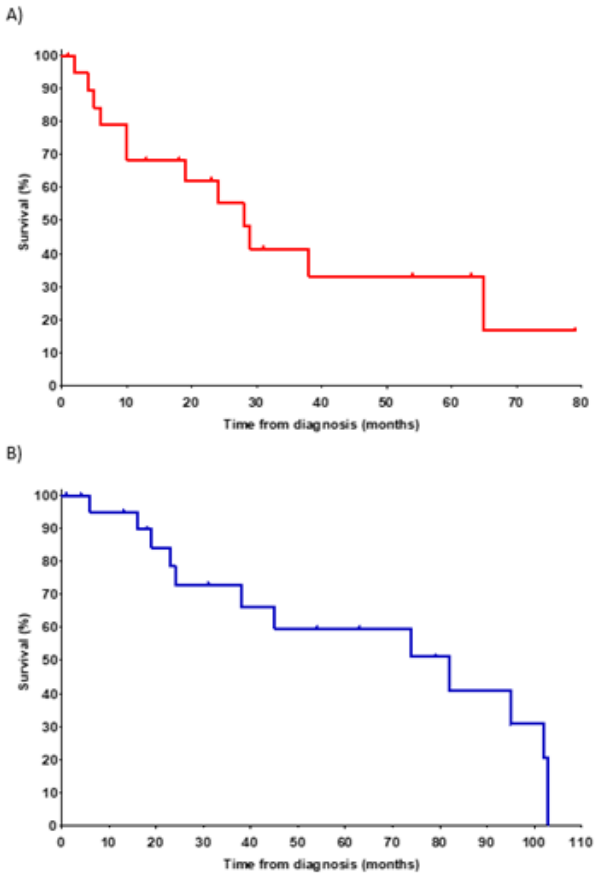

Figure 7: Kaplan-Meier plots of (A) progression-free survival and (B) overall survival following primary surgery for radiation-induced angiosarcoma.

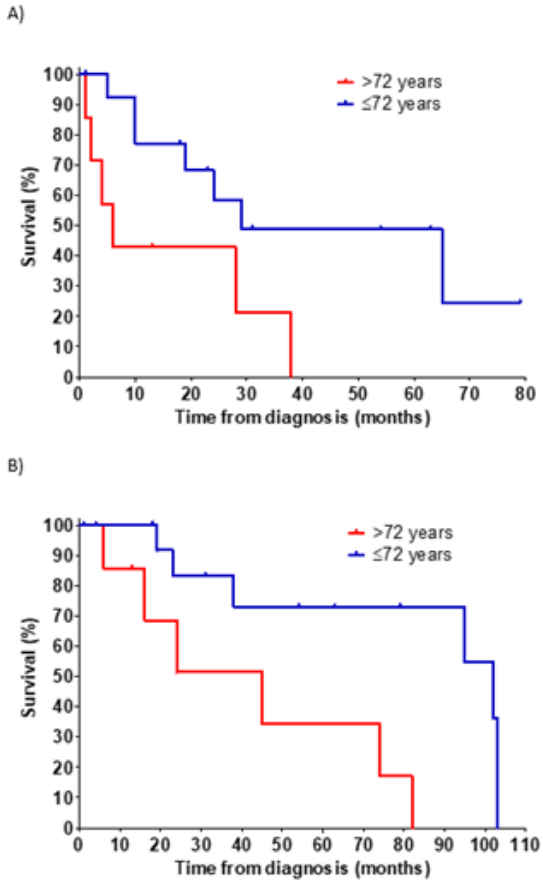

Figure 8: Kaplan-Meier plots of (A) progression-free survival and (B) overall survival stratified by patient's age.

Table 3: Analysis of potential prognostic variables of radiation-induced angiosarcoma

Variables	Median PFS from primary Treatment to First Recurrence	Median OS
Age		
≤72 years	Reference	Reference
>72 years	HR = 4.586 (95% CI 1.184-17.76) P = 0.0275*	HR = 7.129 (95% CI 1.646-30.88) P = 0.0086*
Tumour size		
<5 cm	Reference	Reference
≥5 cm	HR = 1.268 (95% CI 0.3632-4.425) P = 0.7099	HR = 0.3698 (95% CI 0.07993-1.711) P = 0.2031
Surgical Margin		
≤1 mm	Reference	Reference
>1 mm	HR = 0.4417 (95% CI 0.08511-2.293) P = 0.3308	HR = 1.646 (95% CI 0.3817-7.098) P = 0.5038
Primary Surgery Performed at		
Cambridge University Hospital	Reference	Reference
Other hospitals	HR = 1.281 (95% CI 0.3997-4.107) P = 0.6767	HR = 1.353 (95% CI 0.4096-4.471) P = 0.6198
Primary Treatment		
Peri-operative chemotherapy + surgery	Reference	Reference

Surgery only	HR = 0.7931 (95% CI 0.2240-2.808) P = 0.7194	HR = 1.680 (95% CI 0.4860-5.806) P = 0.4125
Peri-operative Chemotherapy Regimen		
Pegylated liposomal doxorubicin (n = 8)		
Paclitaxel for local recurrence (n = 3)	HR = 0.5679 (95% CI 0.1422-2.268) P = 0.4233	

* Logrank $P < 0.05$

4.4. Primary Breast Angiosarcoma

Two patients in our series were diagnosed with breast angiosarcoma without prior radiotherapy.

The first patient was a 41-year-old female who presented to her local hospital with a breast lump which was felt to be a haemangioma on biopsy. Four months later this started to bleed and was treated with arterial embolisation. CT scan at the time showed two small lung nodules and multiple liver lesions which were thought to be haemangiomas. Unfortunately, she presented 5 months later with severe back pain from peritoneal bleed from the worsening liver lesions and she died shortly after. Central review of her scan images and pathology confirmed that she did have primary breast angiosarcoma with lung and liver metastases.

The second patient is a 35-year-old female who presented with a left breast lump. MRI scan showed a 76 mm left breast mass as well as a smaller 17 mm right breast lesion. Biopsies confirmed bilateral primary breast angiosarcoma. Whole-genome sequencing of the tumour revealed mutation of PLCG1 without MYC amplification, consistent with a primary, rather than radiation-induced, angiosarcoma [18, 19]. No pertinent germline mutation was identified. She underwent bilateral mastectomy followed by adjuvant doxorubicin chemotherapy. She remains disease-free 11 months after her surgery.

5. Discussion

We performed a retrospective analysis of 22 patients diagnosed and treated for breast RIA. While the interval between breast radiotherapy and RIA diagnosis in our study was consistent with those reported in the literature [4–10], our data appears to suggest that this is getting shorter over the years. The reason for this is unknown, but possible explanations include the small sample size, improved survival of breast cancer patients and more being offered radiotherapy, changes in radiotherapy techniques, the more widespread use of chemotherapy (particularly taxanes) in the later years for breast cancer, unknown factors predisposing irradiated cells to develop into RIA, and earlier recognition and diagnosis of RIA. With regards to the latter, we have not observed a trend of smaller tumour sizes in recent years. Most cases of RIA arise following a total irradiation dose of 40-50 Gy, although the relationship between radiation dose and the risk of RIA remains uncertain [20–22]. Karlsson et al. reported a radiation dose-risk effect with the occurrence of sarcomas but not angiosarcoma following breast cancer treatment [22]. It remains unknown as to whether newer radiotherapy techniques, such as the intensity-modulated radiation therapy (IMRT), could affect the risk of RIA development. IMRT results in a larger volume of normal tissue being exposed to lower doses of radiation, with the theoretically increased risk of sarcomagenesis, but conversely IMRT could also decrease the volume of tissue exposed to high radiation doses [23]. Taxanes were introduced in the early part of this century for the neoadjuvant/adjuvant treatment of breast cancer [24], and in our series the first patient treated with taxane was in 2010. Lymphoedema is a known risk factors for the development of angiosarcoma and there is data, albeit controversial, to suggest that taxanes increase the risk of lymphoedema in breast cancer patients [25–28]. Taxanes have not been shown to increase the risk of secondary malignancies [29], but it is not inconceivable that RIA could potentially be attributed to the combination of chemotherapy, radiotherapy, subclinical lymphoedema, environmental factors and genetic susceptibility. Patients with other neoplasms (n = 4) in our series, which might suggest an underlying genetic predisposition to malignancy, did not appear to develop RIA more quickly than other patients. This type of risk may become more apparent with wider uptake of whole-genome sequencing of all sarcomas.

Although a number of factors have been found to be associated with worse outcome, it is large tumour size that appears to be more consistently described [7, 8, 13–17]. Our data did not show this but there are various reasons clouding this issue. Unlike a soft-tissue lump of a ‘typical’ sarcoma, accurate and objective clinical measurements of the often-multifocal cutaneous lesions were difficult to achieve. Subsequently, obtaining measurements from pathological specimens was also challenging, and the analysis would not be valid if patients have had neoadjuvant chemotherapy prior to surgery. Surgical margins have been reported to affect local recurrence risk and survival in some but not all studies [7–9, 15, 30]. We did not observe a difference in PFS and OS between patients with R0 and R1 excision, but again, this could be explained by the multifocal nature of the disease characterised by occult microsatellite lesions beyond the apparent R0 margins and some patients having pre-operative chemotherapy.

Given the scarcity of RIA, there are no prospective randomised controlled trials to guide treatment. Management is often based on a multidisciplinary team approach. Surgical excision with adequate clear margins remains the primary curative treatment modality. Due to the wide area of radiotherapy-induced tissue changes and infiltrative nature of RIA, mastectomy is often the preferred

option over breast conserving surgery to achieve negative margins, but studies have not demonstrated a survival benefit with the more radical approach [9, 14, 16]. Involved margins were reported to be fewer when surgery for breast sarcomas was performed at a high-volume specialist sarcoma unit [31]. In our series, patient outcome does not appear to be significantly different whether the surgery was performed centrally at CUH or at other peripheral hospitals, or whether patients received peri-operative chemotherapy, although patients with more advanced disease were given chemotherapy and were operated on at CUH which may have caused a bias in the results. While there is no evidence to support the use of neoadjuvant or adjuvant chemotherapy, it is often considered, as with many other soft-tissue sarcomas, for large tumour or close margins. In our series, excellent clinical responses were observed with PLD and weekly paclitaxel – these drugs have previously been shown to have activity in angiosarcoma in general, with reported objective response rates (ORR) of approximately 50% for PLD and 18-62% for paclitaxel [32–36]. All of our patients who received peri-operative chemotherapy and mastectomy at initial presentation was given PLD instead of weekly paclitaxel, primarily due to the less frequent administration of PLD given the large geographical region of our patients and the avoidance of alopecia that is associated with paclitaxel (patient preference). Paclitaxel was highly effective in our relapsed patients. Italiano et al. have previously compared doxorubicin and weekly paclitaxel in metastatic angiosarcoma – both demonstrated similar efficacy but were particularly effective in radiation-related disease, while paclitaxel also resulted in higher response rate in cutaneous angiosarcoma [36]. Comparison of PLD and paclitaxel would be of interest in future studies of breast RIA treatment. Gemcitabine-based chemotherapy is also an active agent in angiosarcoma, with reported ORRs of 38-68% when used as a single agent [37–39]. Preclinical data suggests that β-blockade could induce apoptosis in malignant vascular tumour cells – however, the role of β-blockers such as propranolol in angiosarcoma is still largely unproven as benefits have only been shown in small case series/reports, and mostly in combination with chemotherapy [40].

Our RIA patient who received gemcitabine in the third-line setting with propranolol derived no benefit from the treatment.

Molecular studies have delineated the genomic landscape of angiosarcoma, and found that different clinicopathologic subgroups have differing genetic profiles [41]. RIA is typically characterised by amplification of MYC which is seen in >90% of cases, while being rare in other subtypes (e.g. cutaneous or deep visceral angiosarcoma) [19, 41]. FLT4 (encodes for the vascular endothelial growth factor receptor (VEGFR)-3) is co-amplified in approximately 25% of RIA, with recurrent co-mutations of PTPRB, PLCG1 and KDR (VEGFR-2), which again are more common in RIA relative to other subtypes [18, 42, 43]. To this end, anti-angiogenic receptor tyrosine kinase inhibitors (e.g. pazopanib, regorafenib, sorafenib) and the anti-VEGF antibody bevacizumab have demonstrated activity in angiosarcoma, although the reported ORRs of 3-20% were somewhat disappointing given their mechanisms of action, and the activity of pazopanib appeared to be similar between radiation- and non-radiation-induced angiosarcomas [44–48]. Identification of potential markers of response, such as amplification or specific mutations of FLT4, might help to individualise treatment [49, 50].

Immune checkpoint inhibitors (ICI) such as antibodies against the programmed cell death protein-1 (nivolumab, pembrolizumab) and cytotoxic T-lymphocyte-associated protein-4 (ipilimumab) have demonstrated activities in angiosarcoma, with reported ORRs of 18-71% and they are particularly effective in cutaneous tumours arising from the head and neck areas [51–55]. This subtype of angiosarcoma has a dominant ultraviolet-damage mutational signature and high tumour mutation burden and tumour inflammation signature, which could explain its sensitivity to ICIs [53, 56]. Nonetheless, other subtypes such as visceral and radiation-associated angiosarcomas could also respond to ICIs [51–54]. Increased expressions of DNMT1, BRD3/4 and PDGFRB have been reported in secondary (from radiotherapy or chronic lymphoedema) angiosarcoma, which suggests possible roles for epigenetic drugs such as the DNA methyltransferase inhibitors or BET inhibitors, as well as agents targeting the platelet-derived growth factor receptor-β such as imatinib (the latter was reported to demonstrate excellent efficacy in an advanced angiosarcoma case report) [56, 57].

6. Conclusion

RIA is an aggressive disease with high rates of recurrence, morbidity and mortality. It is clear that more effective and personalised systemic therapies, selected or developed through in-depth understanding of the molecular and genetic basis of RIA, are desperately needed to improve the outcome of this group of patients. The current availability and provision of whole-genome sequencing for sarcoma patients in the UK could help to achieve this.

7. Data Availability

This study uses information from confidential patient records and these are not available for public release, although some data are available from the corresponding author upon reasonable request.

8. Conflict of Interest

The authors declare that they have no conflicts of interest.

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