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Overview

Cutaneous Angiosarcoma Secondary to Lymphoedema or Radiation Therapy — A Systematic Review

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Abstract

Aims: Secondary angiosarcoma is known to be associated with lymphoedema or radiation after cancer treatment. This systematic review aims to evaluate the clinical features and outcomes of secondary angiosarcoma commonly arising after breast cancer treatment.
Materials and methods: A systematic review was carried out according to the PRISMA protocol. Medline, EMBASE, CINAHL and Cochrane databases were searched for English articles to April 2018 with predefined strategy. Retrieved studies were independently screened and rated for relevance. Data were extracted by two researchers.
Results: There were 72 secondary angiosarcomas of the limbs. Most patients ($n = 68$, 94.4%) had a history of lymphoedema. The median latent period was 15 years (range 3–40 years). Thirty-eight (52.8%) patients received wide excision or amputation as a treatment for the angiosarcoma, two (2.8%) patients received isolated limb perfusion and one (1.4%) patient received systemic chemotherapy. The remaining patients received palliative care/undocumented treatment. The pooled median duration to mortality was 10.5 months (range 1–144 months). Of note, obesity was documented in seven (9.7%) patients. There were 83 breast angiosarcomas; all with known breast cancer history. Thirty-one (37.3%) patients received mastectomy as breast cancer treatment. Fifty-four (65.1%) patients had a history of adjuvant radiotherapy for the primary breast cancer. The median latent period was 6 years (range 2–50 years); the median size was 40 mm (range 8–200 mm). Forty-one (49.4%) patients received wide excision, 19 (22.9%) patients received completion mastectomy and 23 (27.7%) patients have undocumented treatment for angiosarcoma. The pooled median duration to mortality was 31 months (range 6–168 months).
Conclusion: Angiosarcoma in lympedematous upper limbs or after breast cancer irradiation remains uncommon. However, its long latency and high mortality warrant long-term vigilant surveillance.

Keywords: Angiosarcoma; lymphoedema; radiation

Introduction

Angiosarcoma is a rare but fatal tumour, comprising less than 1% of all sarcomas. It arises from the vascular endothelium, with aggressive behaviour and tends to infiltrate locally and metastasise. It is, however, difficult to diagnose on initial presentation and, hence, carries a poor prognosis. These tumours can occur anywhere in the body, but usually take preference on the skin or deep tissues.

In general, angiosarcomas of this region can be categorised into two groups – primary and secondary. Primary angiosarcomas occur spontaneously in younger patients without any known risk factors. Secondary angiosarcomas are known to develop in elder individuals who have previously received surgical treatment for primary breast cancer with adjuvant radiotherapy. About 1000 in 100,000 breast cancer survivors suffer from the development of angiosarcoma 10–15 years after primary breast cancer therapy including surgery and radiotherapy [1,2]. These tumours can occur at the primary site of the breast or develop on the ipsilateral upper limb (Stewart–Treves syndrome), which is often plagued by lymphoedema [3].

Lymphoedema is a recognised risk factor for the development of angiosarcoma. This condition, also known as Stewart–Treves syndrome, describes a cutaneous angiosarcoma arising from chronic lymphoedema after

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mastectomy and lymphadenectomy. Another known risk factor is breast irradiation. In fact, radiotherapy-induced fibrosis in itself can also cause chronic lymphatic obstruction. The latency period from radiotherapy to angiosarcomatous development is quoted to be on average 6–7 years in most studies.

Although uncommon, the incidence of secondary angiosarcomas is rising, due to the increased incidence of breast cancer and improved long-term breast cancer survival. As a result, long-term consequences of radiotherapy and lymphoedema were more commonly seen among breast cancer survivors.

This systematic review aims to evaluate the clinical features and outcomes of secondary angiosarcoma, commonly arising after breast cancer treatment.

Materials and Methods

The systematic review was conducted in accordance with the PRISMA statement and current methodological literature. As this was a systematic review/meta-analysis, institutional review board approval was not required (see Figure 1 for the PRISMA flowchart).

Data Sources and Eligibility

The Medline, Cochrane, EMBASE and CINAHL databases were searched for relevant English-language articles to April 2018. In addition, abstracts from bibliographies of selected studies and titles identified via an electronic search of leading journals in breast surgery and nursing care were also retrieved and screened for relevance. A search of relevant grey literature using the same combinations of key words was carried out.

Search Terms

The search terms used were 'lymphedema' AND 'angiosarcoma' and 'Stewart-Treves syndrome'. A repeated search was also carried out using 'lymphoedema' instead of 'lymphedema' to avoid missing articles written in British English. Abstracts were screened by two reviewers independently for relevance and level of evidence. Articles from selected abstracts were retrieved.

Study Selection

Review articles, conference abstracts and non-research articles (such as comments) were excluded. However, references from review articles were checked for cross-reference. Identical articles and abstracts were identified to avoid duplication. Studies published by the same institution were reviewed and only the most recent study or the study with the most complete reporting of outcomes of interest were included to avoid data duplication. Data extraction was carried out independently by two investigators and the results were combined for analysis.

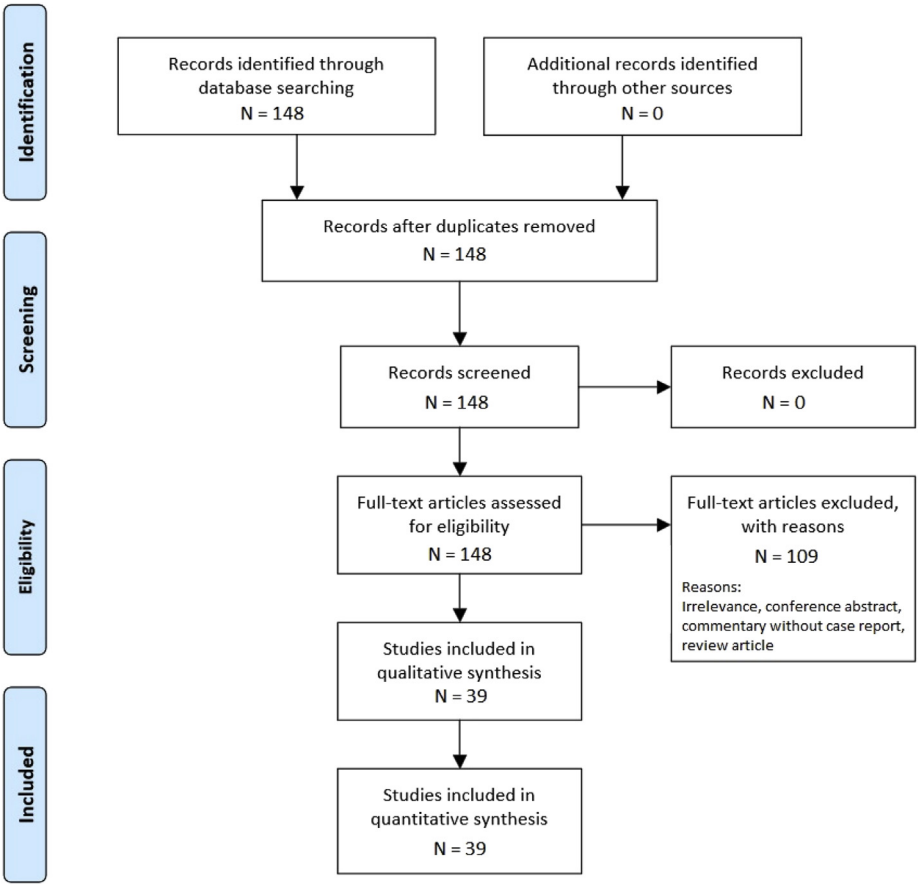

Fig 1. PRISMA diagram.

Results

In total, 148 studies or reports were identified using the preset key words defined in the study protocol. After excluding irrelevant papers (such as editorials or commentaries without case presentation, or conference abstracts), 39 studies or reports were included in the review [1–39]. There was no randomised controlled study on this topic in the literature; most were case reports or series.

All known patient data were entered into a database for pooled analysis. In total, 229 patients were included in the analysis from 39 studies, in which 166 (72.5%) patients were female. The median age of diagnosis was 65 years (range 17–90).

Documented sites of angiosarcoma included breast ($n = 83$), extremities ($n = 72$), scalp ($n = 26$), trunk ($n = 10$), internal organs ($n = 9$), bone ($n = 8$) and face ($n = 7$). Fourteen lesions had unspecified sites in the literature (Table 1).

In view of the heterogenous natural history of angiosarcoma of different anatomical sites, a subgroup analysis was carried out on individual sites. Angiosarcoma of the breast and extremities were analysed individually as these two sites are the major areas of concern in this review.

Angiosarcoma of the Breasts

There were 83 patients with angiosarcoma of the breasts, all with a known breast cancer history. Thirty-one (37.3%) patients received mastectomy as breast cancer treatment, 46 (55.4%) patients received breast-conserving surgery, while six (7.3%) had unknown breast surgery type for primary breast cancer. Axillary dissection was carried out in 31 (37.3%) patients. Fifty-four (65.1%) patients had a history of adjuvant radiotherapy for primary breast cancer, two (2.4%) had no history of adjuvant radiotherapy and 27 (32.5%) cases had an undocumented radiotherapy history.

The median latent period (from primary breast cancer treatment to the development of angiosarcoma) was 6 years (range 2–50 years) and the median angiosarcoma size was 40 mm (range 8–200 mm).

Concerning the treatment of angiosarcoma, 41 (49.4%) patients received wide excision, 19 (22.9%) patients received completion mastectomy and 23 (27.7%) patients had undocumented treatment for angiosarcoma.

The pooled median duration to mortality was 31 months (range 6–168 months).

Table 1
Baseline demographic of angiosarcoma

Age	Median 65 (range 17–90)
Gender	Male 63 (27.5%)
	Female 166 (72.5%)
Sites of angiosarcoma $n = 229$	Breast 83
	Extremities 72
	Scalp 26
	Trunk 10
	Internal organs 9
	Bone 8
	Face 7
	Unspecified 14
Cancer history (in patients with angiosarcoma of breast and extremities only) $n = 155$	Breast cancer 113 (72.9%)
	Pelvic malignancy 6 (3.9%)
	Lymphoma 1 (0.65%)
	Melanoma 1 (0.65%)
	No known history of malignancy 20 (12.9%)
	Undocumented 14 (9%)
Lymphoedema (in patients with angiosarcoma of the extremities only) $n = 72$	Yes 68 (94.4%)
	No 4 (5.6%)

Angiosarcoma of the Extremities

There were 72 patients who had secondary angiosarcoma of the limbs. Most patients ($n = 68$, 94.4%) had a history of lymphoedema. Concerning the past history of malignancy, 30 (41.7%) patients had a known history of breast cancer, six (8.3%) patients had a history of pelvic malignancy, one (1.4%) patient had a history of lymphoma and one (1.4%) patient had a history of melanoma; 20 (27.8%) patients had no known history of malignancy (i.e. primary lymphoedema or secondary due to parasitic infestations) and 14 (19.4%) patients were undocumented in the literature.

The median latent period to the development of angiosarcoma (from the onset of lymphoedema) was 15 years (range 3–40 years). Nineteen (26.4%) patients received wide excision as a treatment for angiosarcoma, another 19 (26.4%) patients received amputation, two (2.8%) patients received isolated limb perfusion and one (1.4%) patient received systemic chemotherapy. Five (6.9%) patients received palliative treatment only; treatment of the remaining 26 (36.1%) cases was undocumented in the literature.

The pooled median duration to mortality was 10.5 months (range 1–144 months). Of note, obesity was documented in seven (9.7%) patients.

Discussion

With increased breast cancer awareness globally, breast cancer patients are being diagnosed and successfully treated at early stages. These long-term breast cancer survivors are at risk of angiosarcoma secondary to the breast cancer treatment. Angiosarcoma is rare but is nearly always fatal unless diagnosed and treated early. Unfortunately, they are easily missed on presentation and difficult to diagnose, even with proper imaging. Thus, it is important to understand this disease and to have a low threshold to biopsy suspicious lesions given the clinical context.

Compared with spontaneous lesions, secondary angiosarcomas appear in a distinctly older age group, with a median age of diagnosis of 65 years on average. This is understandable as these tumours occur secondary to treatment of primary breast carcinomas, with a latency period ranging from 2 to 50 years. Breast angiosarcomas

showed a median latent period of 6 years, whereas limb angiosarcomas presented with a median latency of 15 years.

The two main risk factors for such angiosarcomatous development in a post-mastectomy patient are radiation and lymphoedema. In this systematic review, all patients with breast angiosarcoma had a history of primary breast cancer with surgical resection. More than 65% of these patients also had a history of adjuvant radiotherapy. It is well known that irradiated tissues are prone to developing secondary malignancies.

Patients with limb angiosarcomas seemed to have one thing in common – almost 95% of the patients in this review had lymphoedema. Literature has shown that lymphoedema on the ipsilateral arm of the operated breast affects 14% of those who undergo axillary dissection [3,40,41]. It is thought to induce an immunosuppressed environment that allows for abnormal angiomatosis and the development of malignancy. Normally, antigen-presenting dendritic cells, macrophages, and T lymphocytes travel from peripheral sites to regional lymph nodes to perform their immune functions [42]. Stasis in lymphatic drainage reduces effective removal of foreign antigen, affecting immunocyte production and causing local immunodeficiency. In such an environment, development of lymphatic collaterals serves as the 'precondition' for neoplastic change, as termed by Cui *et al.* [8], and ultimately leading to angiosarcoma formation. Studies also noted that the protein content of oedematous fluid differs from normal interstitial fluid, suggesting that the antigenic composition of tissue suffering from lymphatic congestion can be altered too [43,44].

The presentation of post-treatment breast angiosarcomas is not totally similar to usual carcinomas of the breasts. Although some may still present as a palpable breast mass or diffuse swelling, many others first appear as abnormal skin changes such as an erythematous rash, plaque or even bluish skin discoloration. Usually, they are non-tender and fast growing. They are believed to arise from the cutaneous tissue rather than the breast parenchyma, in contrast to primary angiosarcomas of the breast. For the upper limb, often there is underlying lymphoedema with variable appearance of swelling, bruising, nodular lesions and even ulceration. These skin lesions can merge and spread to adjacent tissue, e.g. from the arm to the chest wall, quite rapidly (Figures 2 and 3).

Imaging may be non-specific; although ultrasonography and mammography have a high accuracy in diagnosing breast carcinomas, findings are often non-specific with angiosarcomas. On ultrasonography, angiosarcomas of the breast appear as ill-defined lesions with variable echogenicity. On mammography, they are often not well-circumscribed and lack the typical calcifications seen on primary mammary carcinomas. Magnetic resonance imaging can sometimes be helpful in diagnosing high-grade lesions, showing a heterogeneous lesion of high T2 signal and rapid early enhancement on dynamic series.

For lesions of the upper limb, ultrasound (USG) and computed tomography are in general unable to define the lesion, with non-specific findings such as 'subcutaneous oedema' and 'fascial septal thickening' [45]. Magnetic resonance imaging is commonly ordered but with limited reliability in delineation. Tissue confirmation is still the most definite. Positron emission tomography–computed

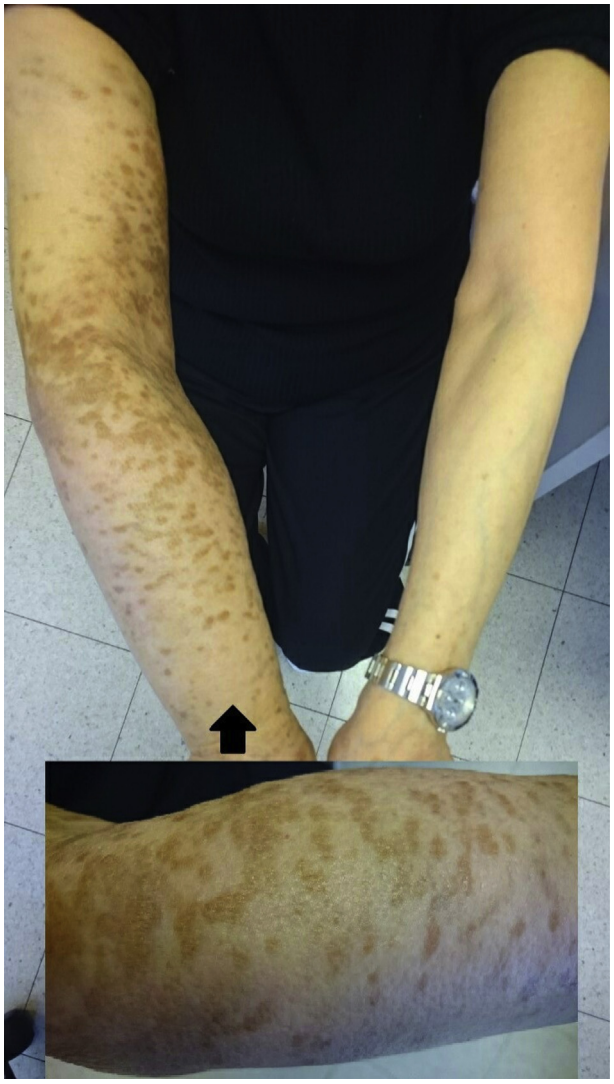

Fig 2. Angiosarcoma presenting as skin rash-like lesions on a lymphoedematous limb.

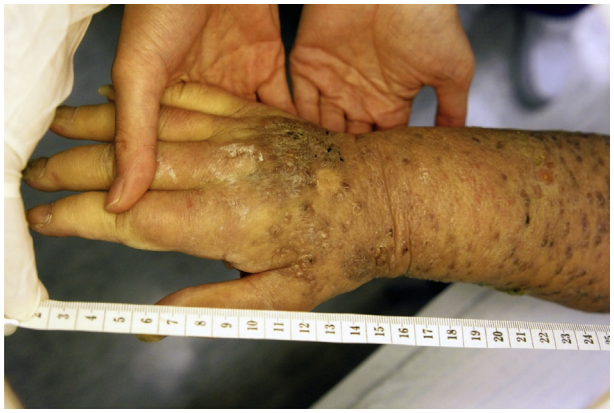

Fig 3. Angiosarcoma presenting as rapidly enlarging scaly skin patches on a lymphoedematous limb.

Table 2
Summary of angiosarcoma of the extremities and breasts

	Angiosarcoma of extremities	Angiosarcoma of breasts
Precipitating factors	History of breast cancer 41.7% History of lymphoedema 94.4%	History of breast cancer 100% History of radiotherapy 65.1%
Median latent period	15 years (range 3–40 years)	6 years (range 2–50 years)
Treatment	Wide excision 26.4% Amputation 26.4% Isolated limb perfusion 2.8% Unknown/others 44.4%	Wide excision 49.4% Mastectomy 22.9% Unknown/others 27.7%
Survival since diagnosis	10.5 months (1–144 months)	31 months (6–168 months)

tomography (PET-CT) has been described in the literature for detecting angiosarcoma in lymphoedematous limbs, but its role as a diagnostic tool has been limited by its low specificity in diagnosis. In fact, PET-CT should better be used as an imaging tool for metastatic work-up [18].

Core biopsy is preferred to fine needle aspiration in order to avoid false negatives and to accurately examine the abnormal angiogenesis and histological abnormalities. Histology typically reveals anaplastic cells with irregular vascular channels, nuclear atypia, hyperchromia and increased mitotic figures. Endothelial markers such as factor VIII-related antigen and CD31/CD34 have also been identified in association with post-mastectomy angiosarcomas [46].

Due to the rarity of post-mastectomy angiosarcomas there is still no consensus on management guidelines. Surgical excision with a wide margin of the tumour is the mainstay of treatment, either by breast-conserving surgery or mastectomy for breast lesions. In the case of upper limb lesions, wide local excision or even forequarter amputation can be carried out, although the latter is falling out of favour as the main goal of surgery is to obtain negative resection margins.

The choice of adjuvant therapy is even more debatable. Options include systemic chemotherapy and radiotherapy. The most commonly utilised chemotherapeutic agents are of the cytotoxic group. Taxanes and doxorubicin in particular have been found to be more effective with angiosarcomas [46], although the dosage and duration of chemotherapy vary to some extent in the literature. Re-irradiation of the breast is occasionally carried out, but obviously limited by the surrounding breast tissue that has been previously irradiated during initial breast cancer treatment. Immunotherapy has been recommended as palliative treatment of malignant metastatic effusion [47]. In general, adjuvant therapy is usually only considered when there is multifocal or disseminated disease – and even so, there is no proven survival benefit compared with surgery alone. So far, most studies seem to agree that achieving complete excision, rather than the type of surgery, plays a crucial role in gaining local control [48] and improved survival [49,50].

Even with successful surgery, the prognosis of breast angiosarcomas remains poor. Many of these tumours recur even after negative margin resection, often within months [45]. Our results showed that the median duration to mortality could be as low as 10.5 months.

Although the prevention of lymphoedema remains the best management, a high index of suspicion is the only hope to detect the disease early, hoping for a cure. So far, there is no evidence to belittle the role of adjuvant radiotherapy in reducing the recurrence of breast cancers of indicated situations. Lymphoedema, however, can be prevented, controlled and managed by various means, without affecting breast cancer survivors' quality of life [51]. With the recent de-escalation of treatment to the axilla, including sentinel node biopsy, and the early detection and treatment of lymphoedema, the incidence of angiosarcoma will hopefully decrease [52].

Conclusion

Angiosarcoma secondary to lymphoedema/radiotherapy remains a deadly disease with a long latent period (see Table 2 for a summary).

Conflict of interest

The authors declare no conflict of interest.

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