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CASE REPORT

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Radiation associated angiosarcoma of the breast: a pictorial review of eleven cases highlighting a devastating complication of breast radiotherapy

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Abstract

Radiation Associated Angiosarcoma (RAAS) of the breast is a rare secondary malignancy following breast radiotherapy and associated with considerable diagnostic and therapeutic challenges. We report the experience of one UK breast unit with a case series diagnosed over the last 22 years. Data was prospectively collected on all patients who presented with RAAS from 2001 to 2023, including photographs obtained following formal patient consent. The characteristics of the original breast carcinoma, treatment received, presenting features of the RAAS, subsequent management and patient outcomes were recorded. Eleven patients were identified, all women, with a median age of 57 (range 39–82) at initial breast cancer diagnosis. The dose of breast radiation received varied from 40 to 70 Gy (median 50), including boosts. The commonest presentation of RAAS was with recent-onset skin discolouration at a median time of 70 months (range: 53–168 months) after radiotherapy. Mammograms and ultrasounds were often negative. Diagnosis was confirmed largely by punch biopsy, and 82% (n = 9) went on to have surgery. The median survival from the diagnosis of RAAS was 13 months (range 7–101). RAAS is a devastating complication of breast radiotherapy, with poor prognosis. As it often presents after the traditional 5-year follow-up period for breast cancer, can appear similar to post-radiotherapy changes and be associated with "normal" imaging, so the diagnosis hinges almost entirely on clinical suspicion. Thus, it is important to be aware of the possibility of RAAS in post radiotherapy breast cancer patients.

Keywords

Breast; Cancer; Radiation-associated; Angiosarcoma

1. Introduction

Angiosarcomas are aggressive endothelial cell tumours accounting for less than 1% of all soft tissue sarcomas [1]. Radiation Associated Angiosarcoma (RAAS) of the breast is a rare secondary malignancy which follows breast radiotherapy, with a reported incidence of 0.9 per 1000 patients 15 years after the radiation exposure [1, 2]. This incidence is increasing as a consequence of the improved long-term survival of breast cancer patients who have received radiotherapy [3]. The condition presents a diagnostic and therapeutic challenge [4]. Herein we report 11 cases of RAAS observed over a 22-year period in one UK breast unit which treats approximately 250 new breast cancers per year.

2. Materials and methods

Data was prospectively collected on all patients who presented with RAAS from 2001 to 2023. Photographs were obtained following formal, written, patient consent. The characteristics of the original breast carcinoma, treatment received, presenting features of the RAAS, treatment received for RAAS and patient outcome were collected and are documented in Table 1. Table 2 contains pathological data on diagnostic sampling type and pertinent immunohistochemistry findings.

3. Results

All patients were women, with a median age of 57 at initial presentation with breast cancer (range 39–82). One patient (Patient 1, Fig. 1) had inflammatory breast cancer at presentation and was treated with chemo-radiotherapy only with complete imaging response and had no surgery. Two patients had post mastectomy radiotherapy (Patients 5, Figs. 2,6); Patient 5 had a TRAM (transverse rectus abdominus muscle)-flap immediate reconstruction of the breast and the other patient had no reconstruction.

TABLE 1. Summary of original breast cancer characteristics, treatment, presentation and treatment of RAAS and survival.

Patient number and Fig(s)	Age at initial presentation with breast cancer (BC) in years	Original BC Stage	Treatment for initial BC	Radiotherapy Dose and Fractionation	Time between RT and RAAS (mon)	Presentation of RAAS	Treatment for RAAS and sequelae	Survival from pre-sentation with RAAS (mon)
1, Fig. 1	57	Inflammatory, (mixed IDC + ILC) T4N1M0	NAC, radiotherapy & endocrine therapy. Complete clinical and radiological response, no surgery	60 Gy in total. Delivered in 25 fractions to breast, axilla and SCF. 10 boost 5 fractions to breast	69	Swollen, firm ipsilateral breast. Metastatic disease on presentation	Supportive only	7
2, Fig. 3	39	Asynchronous Bilateral Breast Cancers13 months apart Grade II IDC, T2N0M0 Grade III IDC, T1N0M0	NAC (FEC). BCS and Axillary clearance. Radiotherapy. BCS and SLNB. Radiotherapy.	42 Gy 21 fractions to breast 40 Gy 15 fractions to breast + 10.5 Gy Boost in 3 fractions	60 (from first breast cancer)	Oedematous firm right breast with a small patch of skin discolouration medially. Lung metastases shortly after presentation.	Bilateral mastectomies on patient request. Palliative taxotere Chemotherapy Radiotherapy to brain metastases	13
3, Fig. 6A,B	52	Grade I IDC, T2N0M0	BCS and Axillary Clearance Radiotherapy Endocrine Therapy	45 Gy 20 fractions to breast	66	Breast skin discolouration—lower half	Wide Mastectomy with skin grafting to chest wall to close defect	8
4, Fig. 5.A–E	52	Grade III IDC, T1N0M0	BCS and Axillary Clearance Radiotherapy Endocrine Therapy	40 Gy in 15 fractions to breast	70	“Bruised” right breast with discolouration, oedema and thickening of the medial aspect of the breast	Mastectomy. Multiple operations for local and regional recurrence.	78

TABLE 1. Continued.

Patient number and Fig(s)	Age at initial presentation with breast cancer (BC) in years	Original BC Stage	Treatment for initial BC	Radiotherapy Dose and Fractionation	Time between RT and RAAS (mon)	Presentation of RAAS	Treatment for RAAS and sequelae	Survival from presentation with RAAS (mon)
5, Fig. 2	60	Screen detected T1 (multifocal) N1M0	Mastectomy, axillary clearance and immediate reconstruction of breast using TRAM flap. Radiotherapy Chemotherapy Endocrine Therapy	50 Gy 25 fractions to breast	84	"Cellulitis" of breast not responding to antibiotics. Discolouration of breast skin with multiple cutaneous nodules over both breasts.	Surgically irresectable at presentation with rapid progression. Palliative chemotherapy with doxorubicin (no response), taxol and oral thalidomide	7
6, Fig. 9	62	Asynchronous Contralateral Breast Cancers 6-years apart Left: Grade II IDC, T2N1M0, Right: 20 mm high grade Ductal Carcinoma *in Situ* (DCIS)	2000—left mastectomy, chemotherapy, radiotherapy and Endocrine Therapy (Tamoxifen followed by anastrozole) 2006—right mastectomy and SLNB	Unknown—received this in Mumbai.	168	Simultaneous lesions in the left mastectomy scar (chest wall) and left arm. Both confirmed histologically. Arm lesion most likely a cutaneous secondary deposit.	Excision of both lesions followed by weekly Paclitaxel chemotherapy. Cutaneous and liver metastases shortly afterwards treated with palliative care only.	12
7, Fig. 8	64	Grade II IDC, T1N1 (mic) M0	BCS & SLNB Chemotherapy Endocrine Therapy (Tamoxifen followed by Exemestane)	40.05 Gy to the breast in 15 fractions with 10.50 Gy boost in 3 fractions	84	Pigmented lesions left breast with underlying diffuse mass	Mastectomy. Excision of chest wall and scalp recurrences. Later lung Metastases treated with weekly Paclitaxel. Progressive disease with pleural effusion and liver metastases.	24

TABLE 1. Continued.

Patient number and Fig(s)	Age at initial presentation with breast cancer (BC) in years	Original BC Stage	Treatment for initial BC	Radiotherapy Dose and Fractionation	Time between RT and RAAS (mon)	Presentation of RAAS	Treatment for RAAS and sequelae	Survival from pre-sentation with RAAS (mon)
8	56	T2N0M0	NAC followed by BCS (2 mm residual carcinoma) Radiotherapy, Endocrine therapy	40.05 Gy to Left breast 15 fractions 10 Gy boost 5 fractions	73	Discolouration and thickening on inner aspect of left breast	Mastectomy	Alive February 2023 (101 mon)
9, Fig. 7	51	T1N0M0	BCS & SLNB Radiotherapy Endocrine Therapy	40.05 Gy in 15 fractions to breast with 10.5 Gy boost in 3 fractions	65	Discolouration left breast	Mastectomy Further excision for local recurrence	Alive February 2023 (79 mon)
10, Fig. 10	65	T1N1M0	BCS and axillary clearance Radiotherapy Endocrine Therapy	40 Gy in 15 fractions	53	Discolouration left breast	Mastectomy. Mastectomy scar recurrence 6 mon later (Fig. 9) with left pleural effusion. Treated with 12 cycles of Paclitaxel.	14
11, Fig. 4	82	T1N0M0	BCS & SLNB Radiotherapy Endocrine Therapy	40.05 Gy in 15 fractions with 6 MV photons.	116	Multiple bleeding skin lesions over the breast	Mastectomy	Alive February 2023 (27 mon)

BC: breast cancer; IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; NAC: neoadjuvant chemotherapy; SCF: supraclavicuar fossa; RT: radiotherapy; RAAS: radiation associated angiosarcoma; BCS: breast conserving surgery; SLNB: sentinel lymph node biopsy; TRAM: transverse rectus abdominus muscle; DCIS: Ductal carcinoma in situ.

TABLE 2. Histopathological data.

Patient Number	Diagnostic Sampling method	Immunohistochemistry
1	Core Needle Biopsy (CB)	CD34 and Factor VIII positive
2	Punch Biopsy (PB)	CD34 and Factor VIII positive
3	CB and PB	Information not available
4	PB	VWF and CD4 positive
5	PB	CD34 and Factor VIII positive
6	PB	CD34, CD31 and ERG positive c-MYC gene amplification positive
7	CB and PB	CD34, CD31 and ERG positivity c-MYC gene amplification positive
8	Excision Biopsy (PB inconclusive)	CD31 and ERG positive
9	PB	CD34, CD31 and ERG positive
10	PB	CD31 positive
11	PB	CD34 positive

CD: cluster of differentiation; VWF: von willebrand factor; ERG: ETS-related gene; c-MYC: cellular Myc.

The remaining 7 patients had breast conserving surgery (BCS) followed by radiotherapy; two of these patients (Patients 2, Figs. 3,8) had neoadjuvant chemotherapy prior to surgery.

Each patient's dose of radiation received for their original breast cancer varied from 40 to 60 Gy (median 40.05). Five patients (45.45%) received boosts in addition to this, at a median dose of 10.5 Gy (range 10–10.5 Gy). Overall, the total dose of radiation received therefore varied from 40 to 70 Gy (median 50). Two patients developed asynchronous contralateral breast cancer (Patients 2 and 6), the former 13 months and latter 6 years after the first breast cancer. One patient (Patient 6) also had a history of lung carcinoma which developed 11 years following the diagnosis of breast cancer, and was treated surgically.

The median time between radiotherapy and presentation with RAAS was 70 months (range: 53–168 months). The commonest presentation was with discolouration or "bruising" of recent onset of the skin overlying the treated breast with a vague underlying mass associated with negative imaging (normal or non-specific changes on mammogram and ultrasound). Patient 11 presented with multiple bleeding skin lesions (Fig. 4). Diagnosis was made mainly by punch biopsy of the affected skin, as per patient 4 (Fig. 5). Diagnosis was delayed in 2 patients (patients 3 and 8) by 2–3 months. Patient 3 presented with skin discolouration, and normal imaging, which was mistaken for post-radiotherapy changes initially and a punch biopsy was only performed on a follow-up visit 3 months later, confirming RAAS (Fig. 6A,B). For Patient 8, there was a clinical suspicion but initial punch biopsy of the discoloured skin, as well as a mammogram and ultrasound, were negative and excision biopsy of the lesion was performed due to clinical suspicion, which diagnosed RAAS. Initial punch biopsies were also negative in Patient 9 (Fig. 7), but a subsequent punch biopsy confirmed angiosarcoma. All 11 patients were referred to the regional sarcoma multidisciplinary team following the diagnosis, where treatment decisions were made.

Patient 2 had metastatic disease at presentation and two patients (6, and 7—Fig. 8) developed metastases shortly after presentation. Patient 5 (Fig. 2), who had TRAM-flap reconstruction, had surgically irresectable disease at presentation with disease affecting both breasts. Nine patients (81.82%) had surgery: mastectomy in 8 patients and excision of mastectomy-scar lesion and a co-existing left arm lesion in Patient 6 (Fig. 9). Four (36.36%) of these patients, patients 4, 7, 9 and 10 (Fig. 10) required further surgery for local recurrence(s). Three patients had adjuvant chemotherapy (27.27%) and 2 had palliative chemotherapy only (18.18%). The median survival from the diagnosis of RAAS was 13 months (range 7–101). Three of the 11 patients are alive as of February 2023. The 2-year survival rate was 36% (n = 4) and 5-year survival 27% (n = 3).

4. Discussion

Locoregional treatment of breast cancer can, rarely, lead to development of secondary malignancies; chronic lymphedema following axillary dissection can lead to Stewart-Treves syndrome, and radiotherapy to the breast or chest wall after breast conserving surgery or mastectomy is associated with a small risk of contra-lateral breast carcinoma, lung carcinoma as well as radiation-induced angiosarcoma [1, 2, 5, 6]. While RAAS is rare, it is devastating in nature, often converting a breast cancer with a good prognosis at presentation to an incurable disease with very short survival [3].

Angiosarcoma is the most common secondary soft-tissue sarcoma, with an increasing incidence since there has been a move toward Breast Conserving Therapy. It differs pathologically and clinically from primary angiosarcoma by arising within the skin of previously irradiated tissue and invading adjacent parenchyma to variable degrees, versus primary which typically originates in the breast parenchyma [7].

The time interval between radiotherapy and presentation with RAAS is around 6–7 years, in keeping with the interval in this case series, but the latency period has been known to be shorter [1, 3, 5, 6]. Indeed, RAAS appears to have a shorter latency period than other radiation induced sarcomas [5, 8]. A dose effect dose has been described in the development of sarcoma, with as little as 10 Gy giving rise to the disease [5]. In breast radiotherapy, the maximal dose administered in usually 50 Gy with boosters sometimes given of an extra 10–20 Gy [2]; all our patients received a total radiotherapy dose within this range.

The impact of previous axillary surgery is also of interest and has been raised in the literature. In our series 45.45% of patients were known to have undergone previous axillary

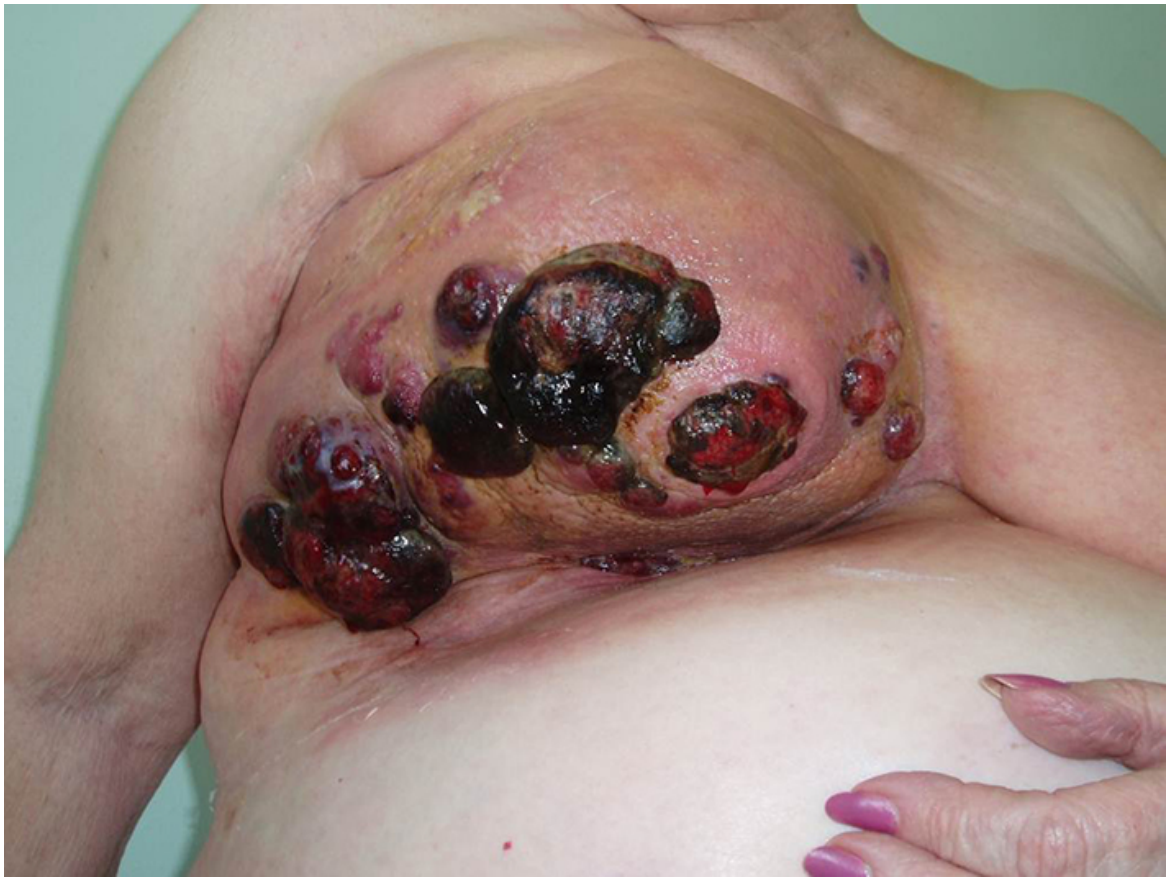

FIGURE 1. Patient 1, locally advanced angiosarcoma.

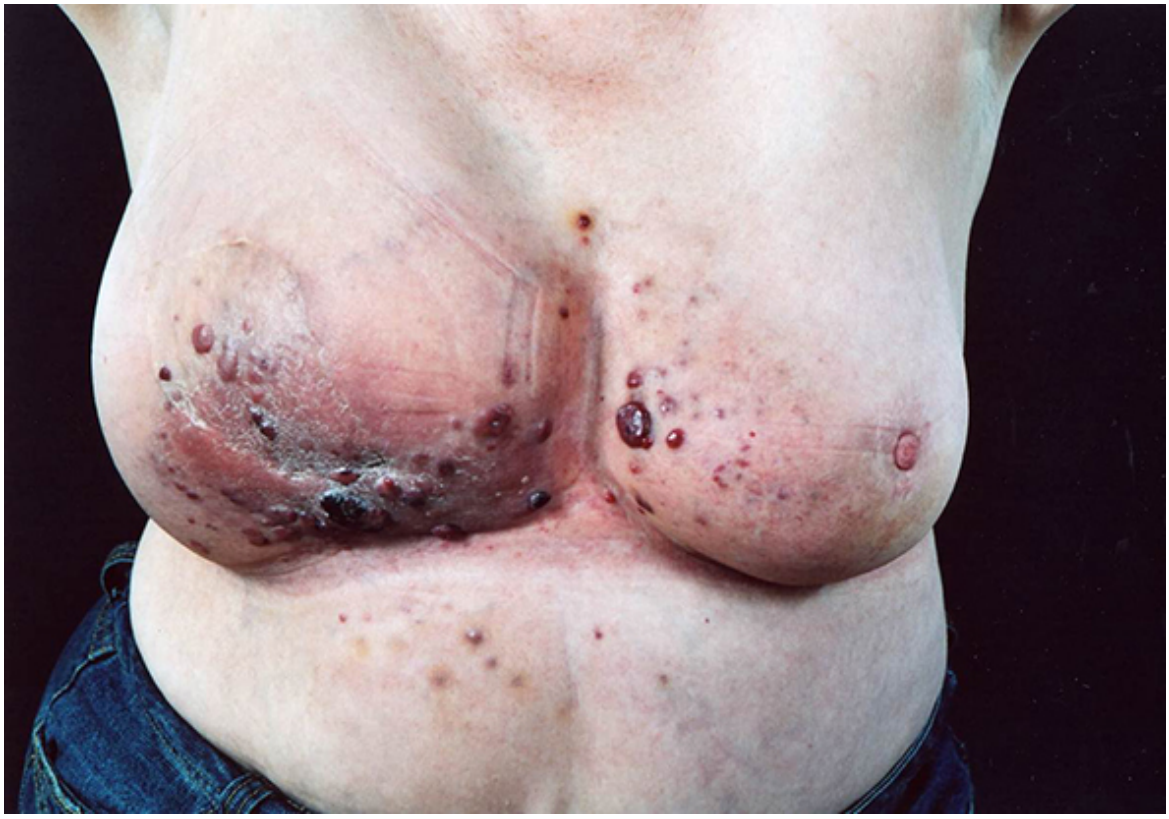

FIGURE 2. Patient 5 presentation with extensive RAAS following mastectomy and immediate TRAM flap reconstruction.

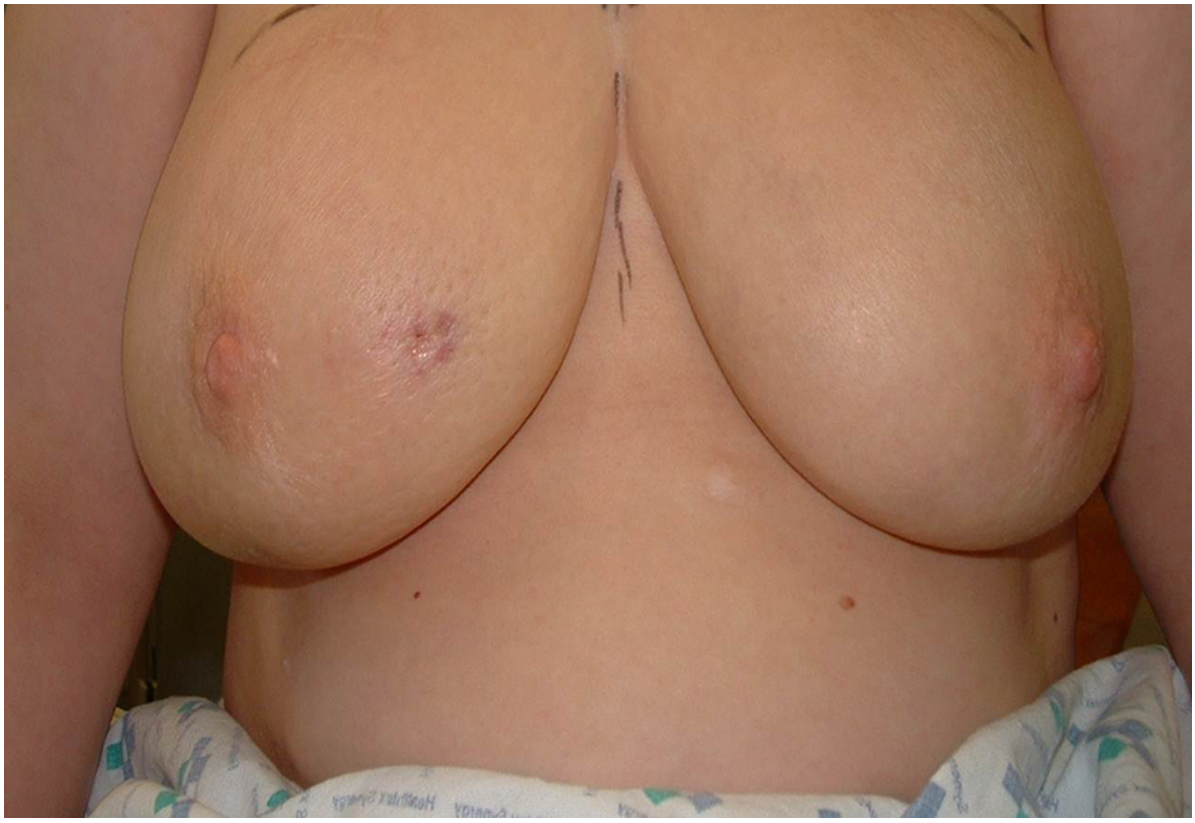

FIGURE 3. Patient 2, who had undergone BCS, presentation with subtle skin discoloration right breast.

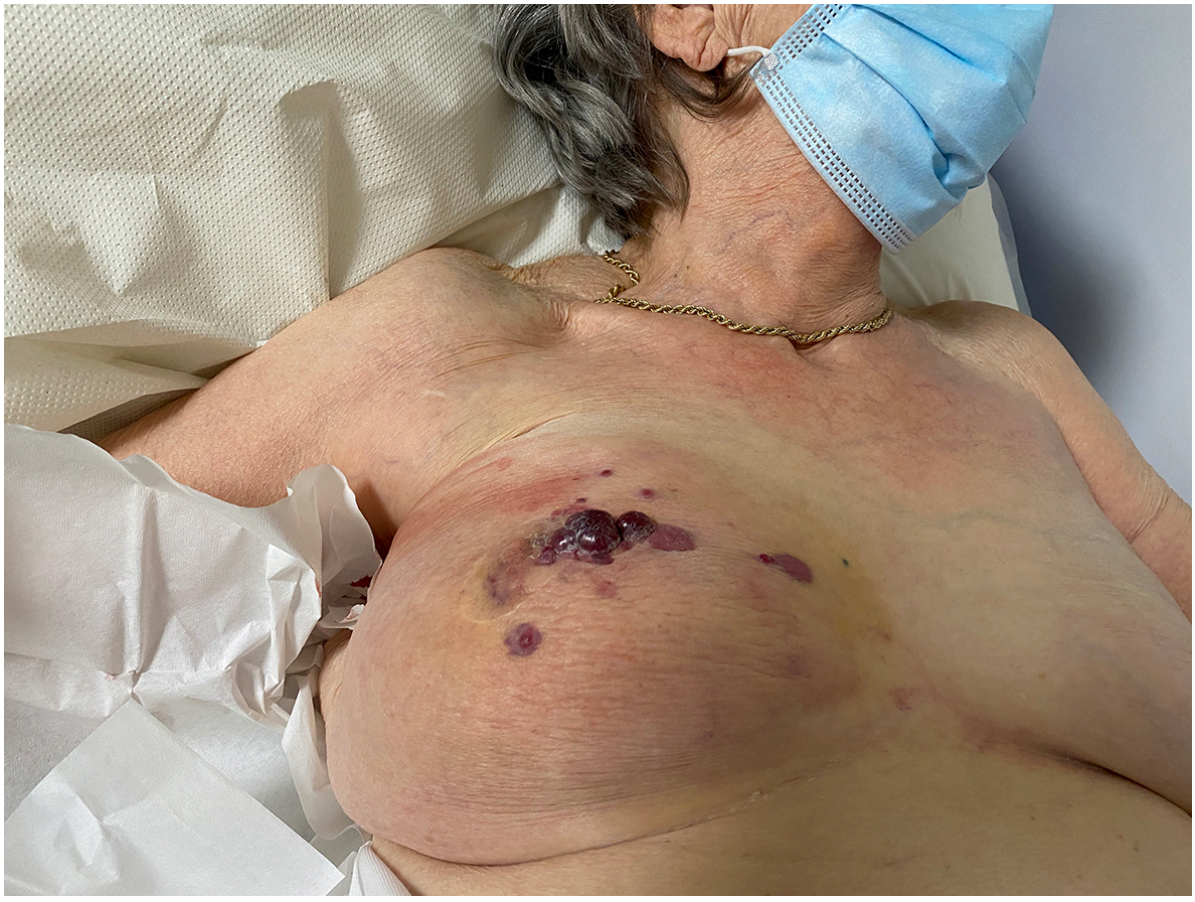

FIGURE 4. Patient 11 presentation with multiple bleeding skin lesions.

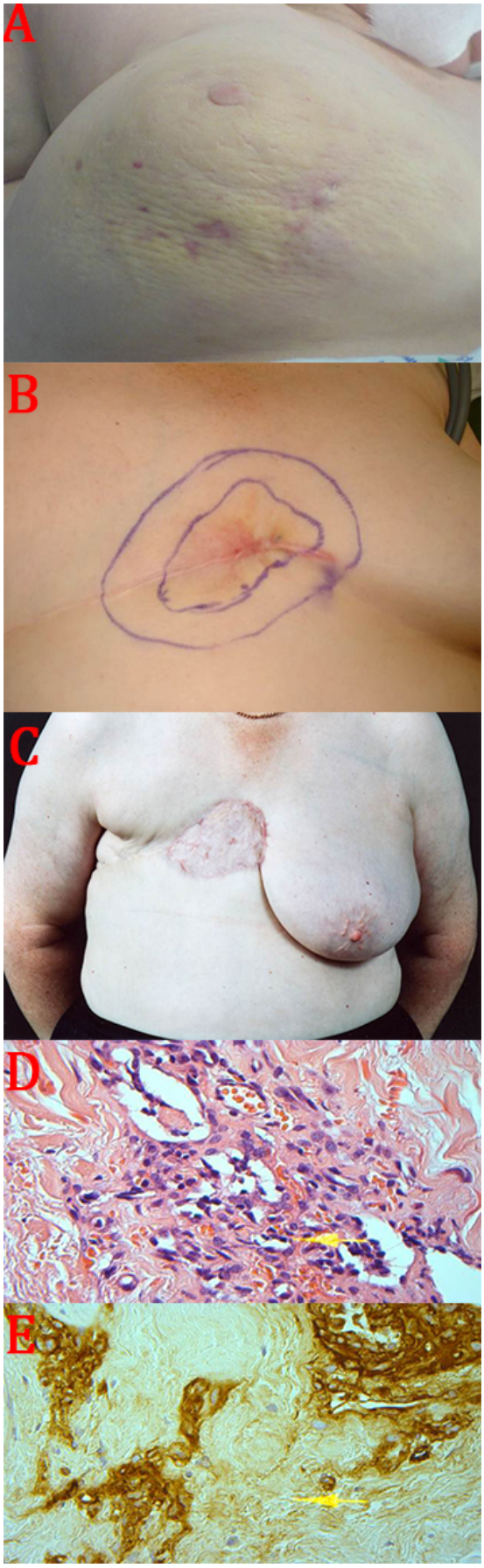

FIGURE 5. Patient 4. (A) presentation—multiple small patches of discoloured skin (B) mastectomy scar recurrence (C) following wide excision, omental graft and skin grafting of mastectomy scar recurrence, (D) histology, H & E stain (E) Histology, factor VIII related antigen immunostain.

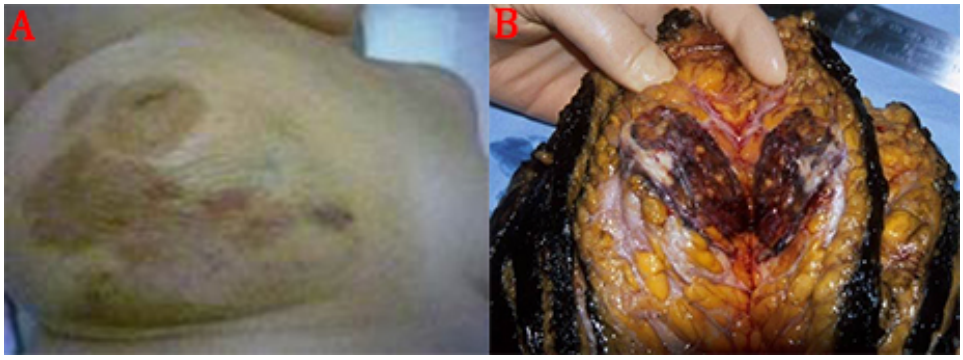

FIGURE 6. Patient 3. (A) presentation with extensive skin discoloration. (B) macroscopic tumour invading the breast parenchyma in mastectomy specimen.

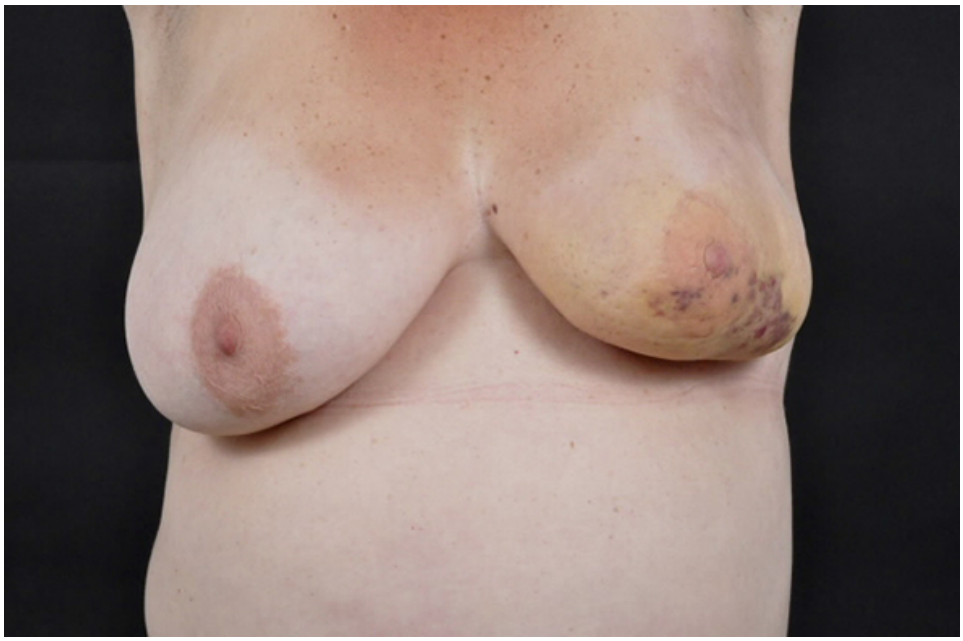

FIGURE 7. Patient 9, presentation with extensive discolouration of lower half of left breast.

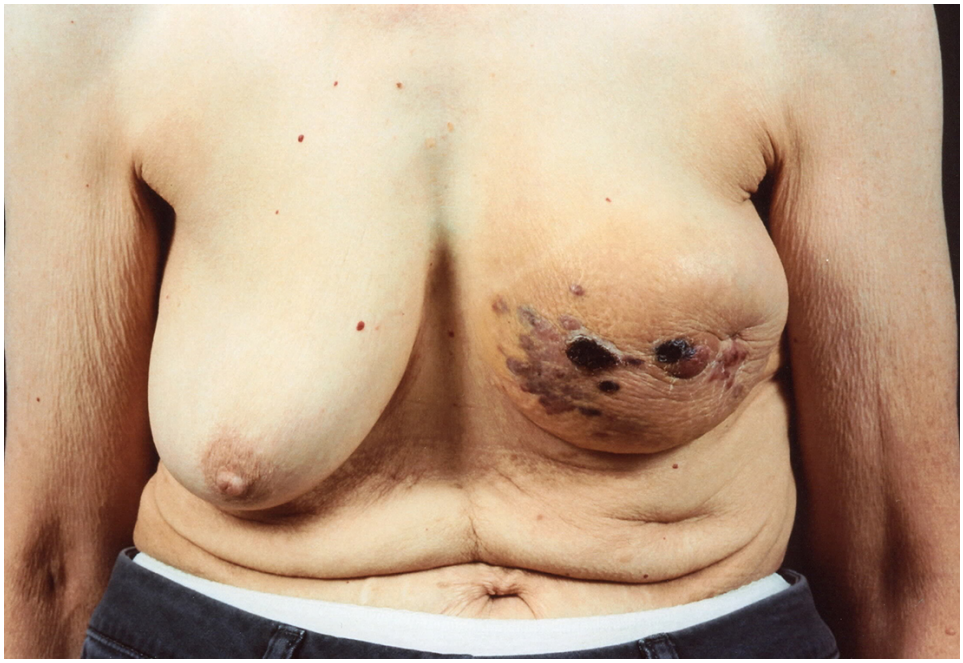

FIGURE 8. Patient 7 on presentation.

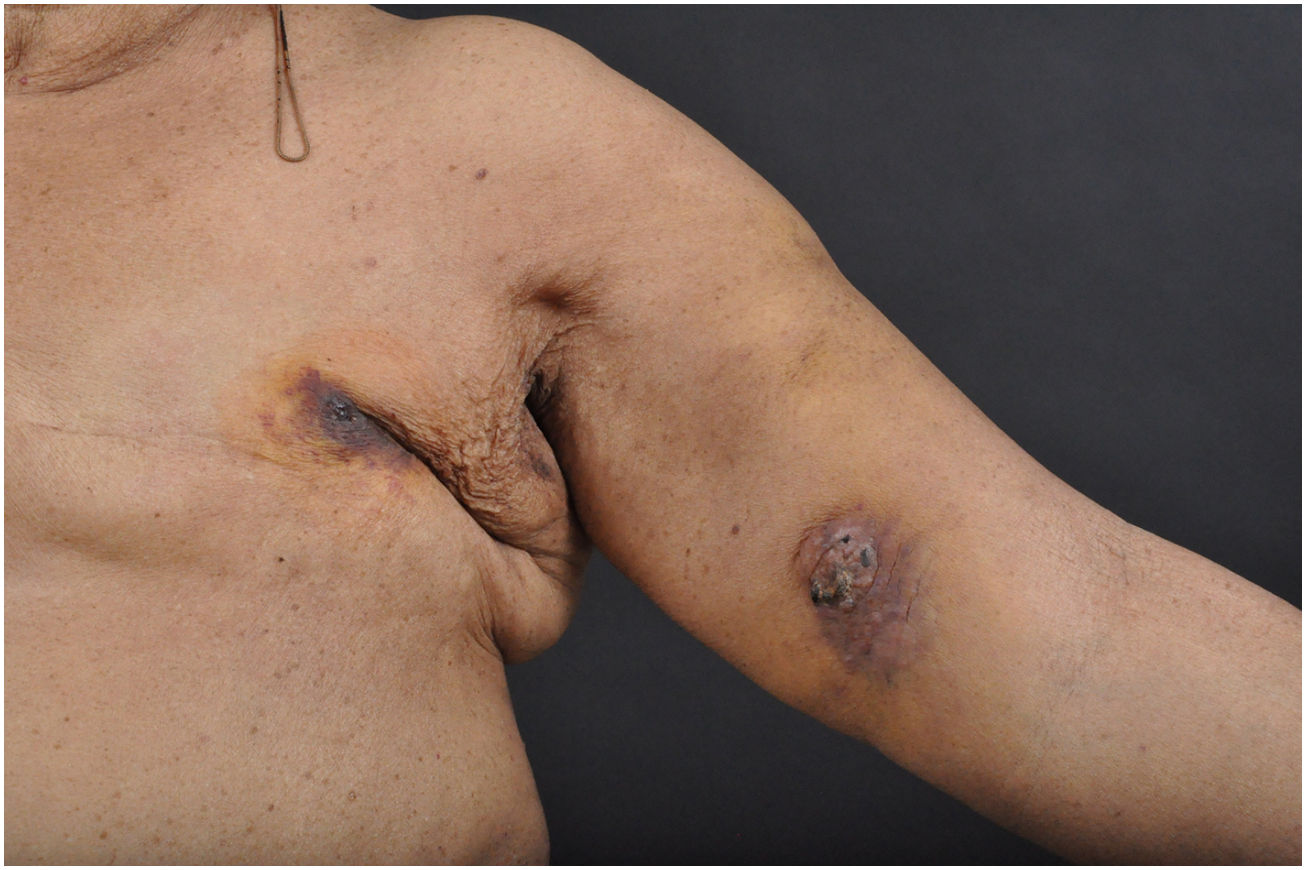

FIGURE 9. Patient 6, simultaneous RAAS lesions left mastectomy scar and left upper limb.

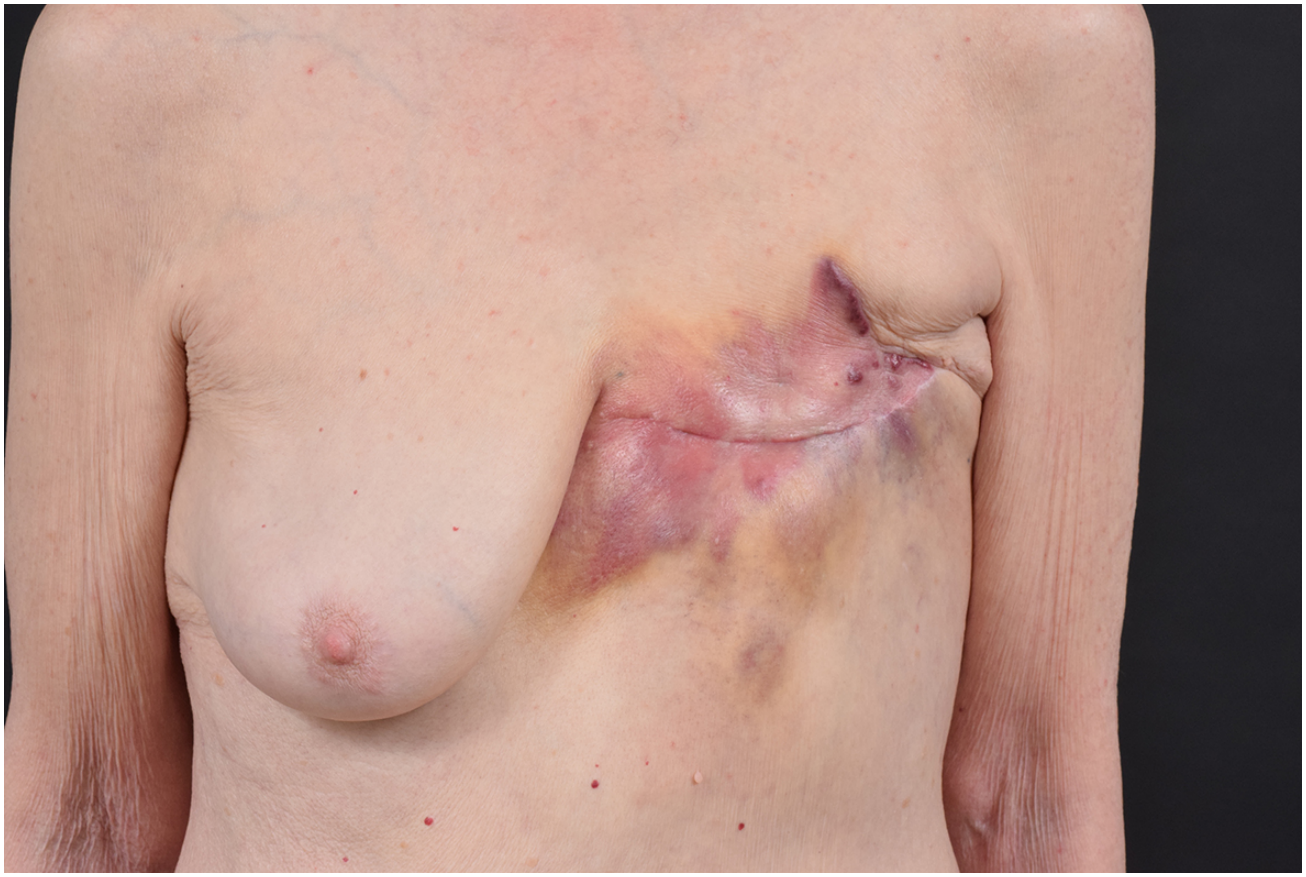

FIGURE 10. Patient 10, presentation with extensive mastectomy scar recurrence (and malignant left pleural effusion) 6 months after mastectomy for RAAS.

clearance, implying a possible synergistic effect of impaired lymphatic drainage as a result of this axillary surgery, with radiotherapy. Indeed, it has been hypothesized that this may compound and accelerate the development of RAAS, in a process comparable to Stewart-Treves syndrome [9].

The challenges associated with RAAS are diagnosis and treatment. The disease often happens after the traditional 5-year follow-up period for breast cancer treatment. The most common manifestation is a bruise like red—purple cutaneous discolouration (Fig. 8), however, cutaneous features can range from skin thickening to nodules and ulceration (Figs. 4A,B, 5,9,10) [5–8]. The diagnosis hinges almost entirely on clinical suspicion. Breast cancer follow up is often relegated to the less experienced clinicians or nurses and it is, therefore, important for them to be aware of this problem. The skin changes can be easily mistaken for the usual post radiotherapy skin changes or non-specific skin conditions. The imaging (mammogram and ultrasound) is often unhelpful. Indeed, in our series, routine breast imaging was not often performed and, when performed, this was usually negative. A Finnish study of 58 patients with RAAS of the breast found mammograms to have a sensitivity of only 43% and ultrasound 50%, versus Computed Tomography (CT) (84%) and Magnetic Resonance Imaging (MRI) (92%) [4]. None of our patients had an MRI for us to comment, but certain features have been reported in the literature. These include diffuse T2 high signal skin thickening and rapidly enhancing intraparenchymal lesions on post contrast T1 weighted imaging. The study which these findings were taken from reported that suspicious features on MRI were present on all cases which had indeterminate mammogram and ultrasound findings, indicating that MRI may provide an important tool in the diagnosis and assessment of RAAS [7].

Histologically, RAAS originates in the dermis and subcutis of the irradiated breast [6]. Despite this superficial origin, a punch biopsy can be negative as was the case for two of our patients (Patients 8 and 9) and thus does not rule out RAAS. Core biopsy of the breast may be of use in cases of parenchymal involvement, but an excision biopsy of the lesion may be necessary. This is consistent with findings reported elsewhere, identifying punch biopsy sensitivity of 84% for RAAS of the breast, incisional biopsy 93% and core needle biopsy 18% [4]. A recent, international multicentre analysis indicated that even surgical biopsy can fail to allow adequate histological evaluation, further highlighting the challenges posed by RAAS [9].

The best diagnostic strategy is, therefore, to be aware of the existence of RAAS, not accept the initial negative imaging and biopsy results at face value if there is a strong clinical suspicion, and consider close follow up and an excision biopsy as the last resort if imaging and standard biopsies—core and punch are negative. Further diagnostic challenge arises in differentiating RAAS from an atypical vascular lesion of the breast [10]. Amplification of c-MYC oncogene appears to be a feature of RAAS and may help in differentiation [8]. The *BRCA-1* gene mutation may represent a more aggressive course due to increased radiosensitivity [5].

There are no evidence-based guidelines on the management for RAAS and instead the literature points to local management strategies, adapted to the individual patient [9]. Currently the mainstay of treatment in RAAS is surgical, being a mastectomy in all patients who previously had BCS [5]. Indeed, mastectomy was performed on all suitable patients in this case series. A wide margin with excision of as much tissue as possible within the previous radiation field has been recommended to reduce the common problem of local recurrence [11, 12]. As a guide, a wide excision or mastectomy with margins of 2–4 cm has been recommended in the literature for large lesions infiltrating skin, while 1 cm has been reported as adequate for small lesions [9]. Despite adequate resection, the risk of local recurrence and distant metastasis is high [1, 2]. This is thought to be related to occult microsatellite lesions beyond resection margins indicating that surgery alone in the treatment may not be sufficient [8].

Some studies have shown chemotherapy may be of benefit following surgery [5, 12]. However, in our case series, the recommendation of the regional sarcoma Multidisciplinary Team (MDT) with regards to adjuvant chemotherapy had been inconsistent and was used mainly in the advanced cases. On literature review, opinions on neoadjuvant and adjuvant chemotherapy vary widely. A recent study of 53 patients with RAAS of the breast found no statistical difference in local recurrence or overall survival, although chemotherapy regimes were heterogenous, with implication on the validity of this assertion [9]. Some have indicated that gemcitabine-taxane or paclitaxel are of benefit in primary or recurrent RAAS [13, 14]. Neoadjuvant Paclitaxel has also shown some benefit in primarily unresectable RAAS [15]. In our series, however, the longest surviving patients received no chemotherapy for RAAS at all.

The role of radiotherapy in the treatment of RAAS is controversial due to concerns about tolerance and cumulative risk of toxicity [5, 8]. One study, however, indicated improved local control with radiotherapy after surgical excision of RAAS [1]. Hyperfractionated and accelerated radiotherapy (HART) has been combined with surgery in some studies, which have shown lower incidences of recurrences [16]. More recently, contact-free, thermography-controlled water-filtered infrared-A superficial hyperthermia (wIRA-HT) has been developed as a radiosensitizer to reduce the toxicity associated with radiotherapy [17], but overall the role of adjuvant radiotherapy in RAAS remains unclear [1, 7, 15].

The overall 5-year survival of RAAS of the breast is poor, and reported to be around 43% [1]. In our series, this was lower, at 27% (n = 3). Multiple skin lesions appear to indicate a poorer prognosis with a 2-year survival of 0%, versus 50% survival at 2 years for single lesions [5]. Other studies have indicated that the size of the lesion is the only independent prognostic factor [15]. In our series of 11 patients, 8 have died, 7 (64%) within 2 years of RAAS diagnosis.

5. Conclusions

While radiotherapy to the breast reduces local recurrence and facilitates breast conservation, it can be associated with this rare but devastating complication. Due to the low incidence of RAAS, the benefit of radiotherapy for breast cancer still outweighs the risk, but being aware of the possibility is vital

as RAAS tends to present after the standard UK breast cancer follow up period. The value of adjuvant therapy is uncertain in this condition and only early diagnosis and radical surgery appear to offer any chance of survival.

ABBREVIATIONS

BC, breast cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; NAC, neoadjuvant chemotherapy; SCF, supraclavicular fossa; RT, radiotherapy; RAAS, radiation associated angiosarcoma; BCS, breast conserving surgery; SLNB, sentinel lymph node biopsy; TRAM, transverse rectus abdominus muscle.

AVAILABILITY OF DATA AND MATERIALS

The data are contained within this article.

AUTHOR CONTRIBUTIONS

ESP and DR—designed the research study, wrote the manuscript. KK, LDS and DR—contributed data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Formal ethics approval was not required as this study was a case series, rather than research, and was conducted retrospectively. However, all patients signed formal, written, consent prior to the photographs being taken by the medical photography department of the Luton and Dunstable Hospital and consented to their use for future education/ publication purposes.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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