The BRASS (BRaest Angiosarcoma Surveillance Study): Protocol for a retrospective multicentre cohort study to evaluate the management and outcomes of angiosarcoma of the breast and chest wall

Jenny Banks, Charlotte Ives, Shelley Potter, Chris Holcombe, On behalf of the BRASS Steering Group

1. Introduction

Breast angiosarcomas (AS) are rare malignant endothelial cell tumours of vascular or lymphatic origin [1]. They account for less than 1% of all breast malignancies [2] and are poorly understood. Angiosarcomas may develop spontaneously as a primary malignancy, often in younger women between the ages of 20–40 or occur secondary to chronic lymphoedema (Stewart-Treves Syndrome) or radiotherapy in women who have undergone treatment for breast cancer [3,4].

Primary angiosarcomas arise de novo, occurring most commonly in the head and neck area as cutaneous lesions, followed by the breasts and extremities [1]. Primary breast angiosarcomas are found to tend towards the development of metastases, whereas secondary cases show a high local recurrence rate. Regardless of subtype, the overall outlook is similarly bleak [5].

Radiotherapy associated angiosarcoma (RAAS) is a rare, but established complication of treatment for early breast cancer. Defined as the development of a sarcoma in a previous radiotherapy field with a latency period of at least three years [6], its aetiology and precise relation to the radiotherapy given is poorly understood: The incidence of RAAS is estimated at between 0.04 and 0.18% [7] in women treated with radiotherapy and although this does not appear to be influenced by the type of surgery performed (mastectomy or wide local excision), there may be a potential interaction of radiotherapy and lymphoedema following treatment [8]. There may also be a dose response relationship between the dose of radiotherapy given and the incidence of RAAS with a minimum of 10 Gy associated with the development of the condition (but usually associated with higher doses) [9]. The impact of new techniques such as intensity modulated radiotherapy or hypofractionation are unclear and further study is needed [8].

Data on the optimal management and subsequent prognosis of RAAS is similarly lacking [8,9]. While surgery remains the mainstay of treatment, local recurrence rates range from 54 to 92% and the addition of further radiotherapy with or without hypothermia has been investigated in several small studies and may be beneficial [8,9]. Chemotherapy with taxanes or other agents targeted against vascular endothelial growth factor (VEGF) or components of the Ret proto-oncogene (RET) signalling pathway rarely found to be upregulated (V-myc myelocytomatosis viral oncogene homologue [MYC], V-Kit Hardy-Zuckerman 4 feline sarcoma viral oncogene homologue[KIT] and RET) or downregulated ((cyclin-dependent kinase inhibitor 2C (CDKN2C)) specifically in secondary angiosarcoma may also be valuable [10] although so far results of such approaches have been disappointing [11].

Data on prognostic factors is similarly lacking although five year survival is poor ranging from 27 to 43% in two recent systematic reviews [8,9]. These reviews, however, are based on small, single centre largely retrospective studies published between 1970 and 2013 with inconsistent definitions and outcomes which are unlikely to reflect current practice. This is particularly important given that wide local excision and radiotherapy has become the standard of care for early breast cancer and the incidence of RAAS may be increasing.

Knowing how to adequately manage these tumours is imperative; however there is currently no conclusive or valuable evidence looking specifically at breast sarcomas to guide surgical management. Much of the current proposals are derived from either small retrospective case reviews or extrapolated from non-breast sarcoma studies. Furthermore, a lot of the recent data consider breast sarcomas as a whole, despite the fact angiosarcomas can behave dependent kinase inhibitor 2C (CDKN2C)) specifically in secondary angiosarcoma and the incidence of RAAS may be increasing.

Attention has recently been focused on how we might make outcomes for patients with rare tumours better, and argument for breast sarcoma as a whole, despite the fact angiosarcomas can behave differently, with the survival rate of the latter being 40% lower [12]. There is evidence to suggest that improved adherence to specific guidelines can improve outcomes for sarcomas, especially when applied in referral centres [14].

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it is our experience that these tumours are currently managed heterogeneously between the plastic, oncology and breast teams. We wish to review current practice and outcomes with a view to better understanding this disease and furthermore, improve care. Due to small numbers involved it is difficult to collate adequate data regarding this patient group within one centre, and a more cohesive, collaborative approach is required.

There is therefore a need to collect high-quality contemporaneous data regarding the current incidence and management of both primary breast AS and RAAS to describe variations in practice and inform the design of future prospective studies.

The challenges to the design and conduct of large-scale cohort studies are well-documented, but the trainee collaborative model has emerged as a time and cost-effective means of delivering high-quality prospective research and audit [15–20]. The iBRA study [21], a national audit of the practice and outcomes of implant-based breast surgery has demonstrated the model is transferable to breast and plastic surgery and has established a network of centres willing and able to participate in future projects. It is hypothesised that this network of highly-motivated enthusiastic breast and plastic surgical trainees and consultants can be utilised to deliver further high-quality audits in breast and reconstructive surgery.

2. Methods and analysis

2.1. Aims and objectives

BRASS aims to use the trainee collaborative model to describe the current practice in diagnosis, staging and management of primary breast and secondary AS in relation to the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology Soft Tissue Sarcoma [22]. Evaluate the outcomes of patients treated for primary breast and secondary AS in the UK and describe prognostic factors. Generate data to help guide best practice guidelines in the future.

To inform a potential prospective study of primary breast AS and RAAS.

2.2. Definition

Radiation associated angiosarcoma of the breast will be defined as

- an angiosarcoma occurring in the breast or chest wall (if previous mastectomy) following previous diagnosis and treatment with radiotherapy of breast cancer.

2.3. Hypothesis

Breast angiosarcoma is managed according to NCCN guidelines [22] for soft tissue sarcoma within the UK. Despite this, recurrence rates remain high (54–92%) and outcomes are poor with 5 year survival quoted as being as low as 27–43% [8,9].

2.4. Study design

This is a trainee-led retrospective multicentre audit coordinated by members of the BRASS steering group supported by members of the Mammary Fold Academic and Research Collaborative (MFAC) and the Reconstructive Surgery Trials Network (RSTN).
Table 1: Outcome measures.

| Outcome measure                  | Definition                                                                 |
|----------------------------------|---------------------------------------------------------------------------|
| Sarcoma MDT referral rate        | All patients (100%) should be evaluated by a multidisciplinary team with experience of sarcoma |
| Core or incisional biopsy rate   | All patients should have a biopsy (core or incisional) to establish grade and histological sub-type |
| Cross sectional imaging rate     | All patients should have cross-sectional imaging (MRI ± CT) to provide details of tumour size, relationship to nearby visceral structures and neurovascular landmarks |
| Resectable disease: Margin clearance | Surgical excision should be performed with adequate oncological radial margin (usually greater than 10 mm) |
| Non-resectable disease: Chemotherapy offered | Patients should be considered for palliative chemotherapy or neoadjuvant chemotherapy in view of potentially improving surgical treatment options |
| Recurrence rate                   | Rate of recurrence (local and metastatic) following initial treatment |

Patient care will in no way be affected by this study. Therefore research ethics approval is not required, as confirmed by the Health Research Authority (HRA) online decision tool. (www.Hra-decisiontools.org.uk/research). Local audit approvals will need to be obtained, with a supervising named consultant, if the unit lead is a trainee. This approval will be collected by the BRASS team.
### Table 2
Data fields for BRASS.

| Field                                                                 | Options |
|----------------------------------------------------------------------|---------|
| **Section 1: Patient demographics**                                   |         |
| Sex                                                                   | Male/Female |
| Age at diagnosis of breast cancer (if relevant)                       | Age in years |
| Age at diagnosis of AS                                                 | Age in years |
| Tobacco smoking status                                                | Nonsmoker/smoker/ex-smoker |
| Medical co-morbidities:                                               | Free text |
| - At time of diagnosis of breast cancer (if RAAS)                     |         |
| - At time of diagnosis of AS (if primary AS)                          |         |
| **Section 2: Breast cancer treatment data**                           | DD/MM/YY |
| Date of diagnosis (date of diagnostic biopsy)                         |         |
| Side                                                                  | Right/left/bilateral |
| Date of final breast surgery                                          | DD/MM/YY |
| Final surgery performed to breast                                     | (WLE/Mastectomy only) |
| Final surgery performed to axilla                                     | Auxillary sample/sentinel node |
| Breast cancer histology data                                          | Invasive ductal/ invasive lobular/ LCIS/DCIS/Mixed/Other: Specify 1–3 Low-High Single/Multifocal |
| Type of lesion                                                        |         |
| Grade                                                                 |         |
| Single or Multifocal (if multifocal enter worst diagnosis for following fields) |         |
| Size of invasive lesion                                               | In millimetres |
| Total size of whole lesion including DCIS, if any                     | In millimetres |
| Number of involved lymph nodes                                        | Number |
| Total number of lymph nodes in specimen                               | Number |
| Receptor status                                                       | ER:Positive/negative/not known PR: Positive/negative/not known HER2: Positive/negative/not known Yes/No |
| Lymphovascular invasion                                               | In millimetres |
| Closest radial margin                                                 |         |
| **Breast cancer adjuvant therapy details**                            |         |
| Intraoperative radiotherapy to breast or chest wall?                  | Yes/No |
| If yes: Dose                                                          | Dose in Gy and Energy |
| External beam radiotherapy to breast or chest wall?                   | Yes/No |
| Dose                                                                  | In Gy and energy Number |
| Number of fractions                                                  | Yes/No |
| Number of fractions                                                  | DD/MM/YY |
| Treated daily                                                         |         |
| Date radiotherapy started                                             | DD/MM/YY |
| Date radiotherapy completed                                           | Yes/No |
| Axilla treated with radiotherapy?                                     | Yes/No |
| Supraclavicular fossa treated with radiotherapy?                     | Yes/No |
| Was a Boost given?                                                    | Yes/No |
| Boost Electrons                                                       | Energy – MeV Energy – MeV Energy kV |
| Boost Megavoltage                                                    | Gy Number |
| Boost Orthovoltage                                                   | Yes/No |
| Boost Number of fractions                                            | Yes/No/Don’t know |
| Did the patient receive chemotherapy?                                 | Free text |
| Chemotherapy: regimen given                                           | DD/MM/YY |
| Chemotherapy: Start date                                              | DD/MM/YY |
| Chemotherapy: End date                                                | Yes/No |
| Was the patient treated with Herceptin?                               | DD/MM/YY |
| Herceptin: start date                                                 | DD/MM/YY |
| Herceptin: end date                                                   | Yes/No |
| Was the patient treated with endocrine therapy?                       |         |
| **Section 3: Angiosarcoma (AS) Data**                                 |         |
| Date of diagnosis (diagnostic biopsy)                                 | DD/MM/YY |
| Location of tumour                                                    | Free Text |
| AS: Route of diagnosis                                                |         |
| Clinical presentation                                                 | Visible (cutaneous)/Palpable/ Radiological |
| Medical photography undertaken                                        | Yes/No/Don’t know |
| Histology: FNA                                                        | Yes: give details of report (free text)/ No |
| Histology: Punch biopsy                                               | Yes: give details of report (free text)/ No |
| Histology: Excision biopsy                                            | Yes: give details of report (free text)/ No |
| Imaging: Mammmogram                                                  | Yes: Give findings/ No |
| Imaging: USS Breast/Axilla                                            | Yes: Give findings/ No |
| Imaging: CT Thorax/Abdomen                                            | Yes: Give findings/ No |
| Imaging: MRI                                                          | Yes: anatomical region, findings/ No |
| Imaging: Other (e.g. PET)                                             | Yes: anatomical region, findings/ No |
| Was the patient discussed at a sarcoma MDT?                          | Yes/No |
| Was the patient discussed at a breast MDT?                            |         |
| Stage at diagnosis                                                    | Tumour: T1a/T1b/T2a/T2b Lymph nodes: N0/N1 Metastasis: M0/M1 |
| Was tumour considered resectable?                                     |         |
| Metastatic disease at presentation?                                   |         |
| AS: Management                                                        |         |
| Lead care provider                                                    |         |
| If regional sarcoma centre led care, which specialty led the patients follow up? |         |
| Lead surgeon specialty                                                | Breast/Plastic/Sarcoma |
| Lead oncologist sub-specialty interest                                | Breast/Sarcoma/Unknown |
| Type of operation performed                                           |         |
| Post-operative complications                                          |         |
| AS: Histology                                                         |         |
| Is tissue banked?                                                     | Yes/No/Don’t know |
| Size of tumour                                                        |         |
| Tumour markers: CD31                                                  |         |
| Tumour markers: CD34                                                  |         |
| Tumour markers: C-myc                                                |         |
| Tumour markers: Other IHC                                             |         |
| Distance to margins: Superior, Inferior, Medial, Lateral, Posterior   |         |
| Excision deemed adequate?                                            | Yes/No |

(continued)
prior to the commencement of data collection. Patient consent is not required as no patient identifiable data is being recorded.

Dissemination of the protocol will be via national trainee collaborative groups: The Reconstructive Surgery Trials Network (RSTN) and the Mammary Fold Breast Trainee Group Academic and Research Collaborative (MFAC). Individual centres will have access to their own data, and data will be fed back to participating centres at the end of the study.

Results of the study will be presented at scientific meetings and published in peer-reviewed journals.

The study report will be prepared according to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) reporting guidelines for observational studies [27].

The BRASS project is registered with ResearchRegistry.com, UIN: 2129.

Authors contributions

All authors conceived the study. Author 1 and 3 drafted the protocol. Author 1 wrote the first draft of the paper. All authors critically revised the manuscript and approved the final version prior to submission.

Ethical approval

None required.

Competing interests

The authors have no competing interests to declare.

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Table 2 (continued)

| Field                                      | Options                      |
|--------------------------------------------|------------------------------|
| AS: Adjunct therapy                        |                              |
| Patient received chemotherapy              | Yes/No/Don't know             |
| Chemotherapy regimen                       |                              |
| Chemotherapy start date                    | MM/YY                        |
| Chemotherapy end date                      | MM/YY                        |
| Patient received biological therapy?       | Yes/No/Don't know             |
| Biological agent used                      |                              |
| Biological therapy start date              | MM/YY                        |
| Biological therapy end date                | MM/YY                        |
| Patient received Electrochemotherapy       |                              |
| Electrochemotherapy regimen                |                              |
| Date of Electrochemotherapy                | MM/YY                        |
| Patient received external beam radiotherapy?|                              |
| Radiotherapy dose                          | Gy/Energy                    |
| Number of fractions                        |                              |
| Section 4: Follow up surveillance          |                              |
| Recurrence                                 | Yes/No                       |
| Date of recurrence                         | MM/YY                        |
| Type of recurrence                         | Local/Metastatic; give location |
| Management of recurrence                   |                              |
| Closest margin of re-excision              | mm                           |
| Chemotherapy used for recurrence?          | Yes/No                       |
| Chemotherapy: Regimen                      |                              |
| Chemotherapy: Start date                   | MM/YY                        |
| Chemotherapy: End date                     | MM/YY                        |
| Other salvage treatments used?             | Yes/No/Don't know             |
| Further recurrence?                        | Yes (Repeat section 4 thus far)/No |
| Outcome                                    |                              |
| Patient deceased?                          | Yes/No                       |
| Cause of death                             |                              |
| Last patient contact                       | MM/YY                        |
| Last imaging date                          | MM/YY                        |
| Imaging modality                           | CT/MI/Plain film             |
| Imaging site                               |                              |
| Imaging result                             |                              |

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