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

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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 malignancies, 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 recently 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 ((cyclindependent 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 differently, with the survival rate of the latter being 40% lower [12]. Attention has recently been focused on how we might make outcomes for patients with rare tumours better, and argument has been made towards managing such cancers within a specialist centre, to allow greater access to specialist services in pathology and highly specialised Multi-Disciplinary Expert Panels [13]. 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 and 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).

2.5. Setting

All breast and plastic surgery units in the UK treating angiosarcoma of the breast or chest wall will be eligible to participate in the study. Trainees from across the UK will be invited to participate in the study through the Mammary Fold, the RSTN and, the National Research Collaborative network. Support will also be sought from the professional associations, the Association of Breast Surgery (ABS) and the British Association of Plastic, Reconstructive and Aesthetic Surgery (BAPRAS).

The study will be piloted in five centres; Liverpool, Exeter, Bath, Leeds and Birmingham (chosen as interested parties already engaged with the project residing in these centres) prior to national roll-out of the audit to evaluate the feasibility of trainees being able to identify appropriate patients and collect the necessary data ('successful pilot' defined as the identification and entry of a single whole patient data set). The pilot will also be used to test the acceptability and feasibility of on-line data collection using the REDCap database and modify the pro-formas as needed prior to national roll-out.

2.6. Participants

2.6.1. Inclusion criteria

All patients (male and female) over the age of 16 years with a histologically confirmed diagnosis of primary or secondary angiosarcoma of the breast, skin overlying the breast or anterior chest wall between 1st January 2000 and the 31st December 2015.

2.6.2. Exclusion criteria

Patients without a confirmed tissue diagnosis of primary breast AS or RAAS.

2.7. Outcome measures

The primary outcome measures include the percentage of patients undergoing diagnostic biopsy, cross sectional imaging and whom are discussed at an appropriate multidisciplinary team. These are based on the standards for the management of soft tissue sarcoma from the National Comprehensive Cancer Network (NCCN) [22].

Data regarding adequate oncological margin clearance for resectable disease and rates of recurrence (local and metastatic) will also be collected (Table 1).

Data fields for BRASS (Table 2).

Data will be recorded anonymously using a study identification number on a secure web based database. Though the data set for collection is extensive, the number of patients per centre is anticipated to be small. The data form will be trialled across the pilot centres prior to national roll-out and amended as necessary based on feedback received. This will ensure the data collection form is acceptable and complete prior to initiation of the main study.

2.8. Data validation and management

Following data collection, a random selection of approximately 5% of data sets will be selected. The principal investigator at the identified centres will be contacted and asked to independently validate a proportion of the data. If concordance is <80%, a further data sample will be selected. If concordance remains <80%, the centre will be excluded from the analysis.

Data collection will remain in accordance with Caldicott II principles. Data for each patient will be anonymised using a unique alphanumeric study identification number. Local collaborators will be asked to keep a spreadsheet linking hospital number to study number to prevent duplication of entries. This should be stored

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

securely on the local hospital server according to local IT policies. No patient identifiable data will be recorded for the purpose of this audit. No formal training is required for those collecting data.

Study data will be collected and managed using REDCap electronic data capture tools hosted at the University of Oxford. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources [23].

2.9. Anticipated recruitment

Based on experience from the iBRA study [24] approximately 40% of centres will participate in the study. There are 144 breast units within the UK. Scoping work in one pilot centre (Exeter) suggests that approximately 10 cases may be anticipated per centre over the 15 year period. We would therefore expect to collect data on approximately 570 cases which would be the largest series in the literature, with current retrospective series ranging from 1 to 160 cases [8]. This figure is flexible, and derived in order to give an estimate of anticipated recruitment. Regardless of total numbers the study will remain valid, as it will remain the first national collation of data of its kind.

2.10. Study timelines

November-January 2016/2017: Local pilot centre data collection, refinement of data collection forms and on-line database to optimise acceptability.

February–March 2017: Registrations of interest from plastic or breast surgery units. Completion of local audit approvals.

April 2017–June 2017: Main study data collection.

July–August 2017: data validation.

September 2017: Data analysis and dissemination.

2.11. Statistical analysis

All data analysis will occur centrally, with the support of statisticians and methodologists at the University of Liverpool Clinical Trials Research Centre.

Simple summary statistics will be calculated for each outcome and regression analysis used to control for confounding variables. Predictors for adverse outcomes will be explored.

3. Discussion

Angiosarcoma of the breast remains a significant management challenge as local recurrence rates are high and five year survival poor. Furthermore there are concerns that the incidence of secondary RA may be increasing as wide local excision and radiotherapy is now the standard of care for early breast cancer unless contraindicated [25].

There is a therefore need for high-quality outcome data to inform best practice and guide future research to benefit patients. The current evidence, however, is based on small single centre heterogeneous case series which cannot meaningfully be compared or combined. The BRASS study will collect standardised outcome data on a large cohort of patients with primary and secondary AS. This will be an incredibly powerful dataset which will allow prognostic factors to be meaningfully explored to provide better information for patients and multidisciplinary teams involved in their care. It is also hoped that the insights generated from the BRASS cohort will inform future research and ultimately allow outcomes for patients to be improved. The use of trainee collaborative methodology will ensure the study is completed in a time and cost-effective manner and further consolidate the infrastructure created by the iBRA studies and TeaM [21,26] It is anticipated that the BRASS study will grow this network by engaging oncology and pathology trainees to create capacity for future research.

The BRASS study has limitations which require consideration. This is a retrospective study with risks of missing and incomplete data. Angiosarcoma, however is rare and a retrospective review provides the opportunity collect standardised data on a large cohort of patients. This will allow exploratory analyses to be undertaken and therefore represents an excellent starting point for future research. The dataset is complex which may further increase the risk of missing data and reduce the value of the study. The data collection pro-formas however will be rigorously piloted in several centres to ensure they are complete and user friendly prior to roll out of the main study. Data logic will also be used to ensure that only relevant fields are displayed during data entry, minimising the workload for collaborators. Finally, the management of the condition may have changed over the 15 year study period. While this is an important consideration, the data generated from the BRASS study will be valuable in helping to provide a better understanding of the patterns of disease. This may inform management and lead to novel research strategies which will ultimately benefit patients.

Ethics and dissemination

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
Smoking status	Nonsmoker/smoker/ex-smoker
Medical co-morbidities: At time of diagnosis of breast cancer (if RAAS) At time of diagnosis of AS (if primary AS)	Free text
Section 2: Breast cancer treatment data	
Date of diagnosis (date of diagnostic biopsy)	DD/MM/YY
Side	Right/left/bilateral
Date of final breast surgery	DD/MM/YY
Final surgery performed to breast	(WLE/Mastectomy only/ Mastectomy and breast reconstruction/ Therapeutic mammoplasty)
Final surgery performed to axilla	Axillary sample/sentinel node biopsy/axillary dissection or clearance/ none
Breast cancer histology data	
Type of lesion	Invasive ductal/ invasive lobular/ LCIS/DCIS/Mixed/Other: Specify
Grade	1–3 Low-High
Single or Multifocal (if multifocal enter worst diagnosis for following fields)	Single/Multifocal
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
Lymphovascular invasion	Yes/No
Closest radial margin	In millimetres
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 of fractions	Number
Treated daily	Yes/No
Date radiotherapy started	DD/MM/YY
Date radiotherapy completed	DD/MM/YY
Axilla treated with radiotherapy?	Yes/No
Supraclavicular fossa treated with radiotherapy?	Yes/No
Was a Boost given?	Yes/No
Boost Electrons	Energy – MeV
Boost Megavoltage	Energy – MeV
Boost Orthovoltage	Energy kV
Boost Dose	Gy
Boost Number of fractions	Number
Did the patient receive chemotherapy?	Yes/No/Don't know
Chemotherapy: regimen given	Free text
Chemotherapy: Start date	DD/MM/YY
Chemotherapy: End date	DD/MM/YY
Was the patient treated with Herceptin?	Yes/No
Herceptin: start date	DD/MM/YY
Herceptin: end date	DD/MM/YY
Was the patient treated with endocrine therapy?	Yes/No
Which endocrine agent was used	Tamoxifen Aromatase inhibitor (specify) Other: specify
Endocrine therapy start date	DD/MM/YY
Endocrine therapy end date	DD/MM/YY
Breast cancer clinical follow up	
If the patient was followed up in clinic, were any of the following post- radiotherapy changes noted?	
Thickening of skin	Yes/No
Lymphoedema of the breast	Yes/No
Lymphoedema of the arm	Yes/No
Date of last mammogram prior to the diagnosis of angiosarcoma	DD/MM/YY
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: Mammogram	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?	Yes/No
Stage at diagnosis	Tumour: T1a/T1b/T2a/T2b Lymph nodes: N0/N1 Metastasis: M0/M1
Was tumour considered resectable?	Resectable/Non-resectable/Not known
Metastatic disease at presentation?	Yes; specify site/No
AS: Management	
Lead care provider	Local cancer centre/ Regional sarcoma centre
If regional sarcoma centre led care, which specialty led the patients follow up?	Surgery/Oncology/Joint
Lead surgeon specialty	Breast/Plastic/Sarcoma
Lead oncologist sub-specialty interest	Breast/Sarcoma/Unknown
Management involved surgery	Yes/No
Type of operation performed	Wide local excision/Mastectomy/ Wide local excision plus autologous reconstruction/ Mastectomy plus autologous reconstruction/ Mastectomy plus implant reconstruction
Post-operative complications?	Yes: Flap loss/ Yes: Poor healing/ Yes: Other; specify/ No
AS: Histology	
Is tissue banked?	Yes/No/Don't know
Size of tumour	Size in mm
Grade	1 - low/ 2/ 3 -high
Tumour markers: CD31	Positive/Negative/Don't know/Not performed
Tumour markers: CD34	Positive/Negative/Don't know/Not performed
Tumour markers: C-myc	Positive/Negative/Don't know/Not performed
Tumour markers: Other IHC	Yes: give details/ No
Distance to margins: Superior, Inferior, Medial, Lateral, Posterior	Distance in Mm
Excision deemed adequate?	Yes/No/Don't know

Table 2 (*continued*)

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

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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