Breast **A**ngiosarcoma **S**urveillance **S**tudy

BRASS

A National Audit of Management and Outcomes of Angiosarcoma of the Breast and Chest Wall

Audit Protocol Version 4

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BRASS: A National Audit of Management and Outcomes of Angiosarcoma of the Breast and Chest Wall

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Abbreviations:

AS: Angiosarcoma

ABS: Association of Breast Surgery

BAPRAS: British Association of Plastic Reconstructive and Aesthetic Surgery

CT: Computerised Tomography

MRI: Magnetic Resonance Imaging

MDT: Multidisciplinary Team

NCCN: National Comprehensive Cancer Network

RAAS: Radiation Associated Angiosarcoma

PI: Principle Investigator

Background

Angiosarcoma

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.

Primary angiosarcomas arise *de novo*, occurring most commonly in the head and neck area as cutaneous lesions, followed by the breasts and extremities [1]. Several authors have made comparisons between primary and secondary (often, but not exclusively radiation associated) angiosarcomas within the breast: Secondary breast angiosarcoma tends to affect older women, and are seen to be higher grade than their primary counterparts, though these conclusions are based on retrospective small series. [2,3]. Histologically, primary and secondary breast angiosarcomas are indistinct in morphology, but on immunohistochemistry overexpression of p53 was seen only in the primary angiosarcomas in one series [4]. Pathogenesis also seems to differ between the two subtypes; specifically, radiation associated angiosarcomas exhibit high level amplification of MYC and FLT4 which encodes for VEGFR3 [5]. 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. [6]

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 [7], 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% [8] 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[9]. There may also be a dose response relationship between the dose of radiotherapy given and the incidence of RAAS with a minimum of 10Gy 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[9].

Data on the optimal management and subsequent prognosis of RAAS is similarly lacking[9, 10]. 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 [9,10]. Chemotherapy with taxanes or other agents targeted against VEGF or components of the RET signalling pathway recently found to be up (MYC, KIT and RET) or downregulated (CDKN2C) specifically in secondary angiosarcoma may also be valuable[11] although so far results of such approaches have been disappointing[12]. Data on prognostic factors is similarly lacking although five year survival is poor ranging from 27-43% in two recent systematic reviews[9,10]. 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 [13]. 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 [14]. There is evidence to suggest that improved adherence to specific guidelines can improve outcomes for sarcomas, especially when applied in referral centres [15].

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 [16-21]. The on-going iBRA study[22], 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.

Aims and Objectives

This is a retrospective multicentre audit

BRASS aims to use the trainee collaborative model to

1. Define the incidence of primary and radiation induced angiosarcoma of the breast and anterior chest wall in the UK
2. Retrospectively describe the current practice in diagnosis, staging and management of primary breast AS and RAAS in relation to the National Clinical Practice Guidelines in Oncology Soft Tissue Sarcoma document, published by the National Comprehensive Cancer Network (NCCN). [23]
3. Evaluate the outcomes of patients treated for primary breast AS and RAAS in the UK and describe prognostic factors.
4. Generate data to help guide best practice guidelines in the future
5. To inform a potential prospective study of primary breast AS and RAAS.

Definitions

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

Audit Standards

As there are no guidelines specifically for the management of primary breast AS or RAAS, the following standards for the management of soft tissue sarcoma from the National Comprehensive Cancer Network (NCCN) will be used. [23]

1. All patients (100%) should be evaluated by a multidisciplinary team with experience of sarcoma.
2. All patients should have a biopsy (core or incisional) to establish grade and histological sub-type.
3. All patients should have cross-sectional imaging (MRI+/- CT) to provide details of tumour size, relationship to nearby visceral structures and neurovascular landmarks

From this patients will fall into one of two categories: Resectable, and non-resectable tumours.

In the case of resectable disease:

4. Surgical excision should be performed with adequate oncological margin (usually greater than 10mm)

In the case of non-resectable disease:

5. Patients should be considered for palliative chemotherapy or neoadjuvant chemotherapy in view of potentially improving surgical treatment options.

Methods

This is a trainee-led retrospective multicentre audit co-ordinated by members of the BRASS steering group.

Trainees from across the UK will be invited to participate in the study through the Mammary Fold and the National Research Collaborative network. A local Trainee Lead will be identified at each centre. Trainee leads will be responsible for identifying a supervising consultant and obtaining local audit approvals at their centre. If there are no trainees within a unit, consultants, associate specialists, speciality doctors or research nurses will be encouraged to participate and enter data on behalf of their unit.

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).

It is anticipated that each Trainee Lead will contact the histopathology department within their centre with a view to identifying all patients who have been diagnosed with an angiosarcoma of the breast within the 15 year period spanning 2000 to 2015. Instructions and a toolkit for local audit registration and data collection will be provided to all Trainee Leads. It is envisaged that each local Trainee Lead will identify a small team of 2-3 people to help conduct the audit and liaise with the wider surgical team. The name and contact details of the unit's breast multi- disciplinary team (MDT) meeting co-ordinator will also be registered, to allow for continuity should contact be lost with the trainee lead due to rotational work or time out of training.

The study will be piloted in five centers; Liverpool, Exeter, Bath, Leeds and Birmingham 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. The pilot will also be used to test the acceptability of data collection pro-formas and the quality of data collection.

Inclusion criteria

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

Exclusion criteria

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

Data Collection

The following data-set will be collected

Section 1: Patient demographics

1.1 Sex
1.2 Age at diagnosis of breast cancer (if relevant)
1.3 Age at diagnosis of AS
1.4 Smoking status (non/current/ex-smoker)
1.5 Medical co-morbidities
1.5.1 At time of diagnosis of breast cancer (if RAAS) (free text)
1.5.1 At time of diagnosis of AS (if primary)(free text)

Section 2: Breast cancer treatment Data

2.1 Date of diagnosis (date of diagnostic biopsy)
2.2 Side (right/left/bilateral: if bilateral selected a second section 2 appears, and 'right' and 'left headings)

2.3 Date of final breast surgery (DD/MM/YY)
2.4 Final surgery performed to breast (wide local excision/mastectomy only/mastectomy and breast reconstruction/TM)
2.5 Final surgery to axilla (axillary sample/sentinel node biopsy/axillary dissection or clearance/none)

Histology

2.6 Type of lesion – Invasive ductal/ invasive lobular/ LCIS/DCIS/Mixed/Other: specify
2.7 Grade (1-3 or low-high)
2.8 Single or multifocal (– if multifocal enter worse diagnosis)
2.8 Size of invasive lesion (mm) (largest if multifocal)
2.9 Total size of whole lesion including DCIS, if any (mm)
2.10 Number of involved lymph nodes
2.11 Total number of lymph nodes in specimen
2.12 Receptor status (ER – positive/negative/not known; PR – positive/negative/not known; HER-2 – positive/negative/not known)
2.13 Lymphovascular invasion (yes/no)
2.14 Closest radial margin (mm)

Adjuvant therapy details

2.15 Intraoperative radiotherapy to breast or chest wall- yes/no
2.15.1 If yes, Dose (Gy) and energy
2.16 External beam radiotherapy to breast or chest wall – yes/no
If yes,
2.16.1 Dose (Gy) and energy
2.16.2 Number of fractions
2.16.3 Treated daily (yes/no)
2.16.4 Date treatment started (dd/mm/yy)
2.16.5 Date treatment completed (dd/mm/yy)
2.17 Radiotherapy: Axilla treated yes/no
2.18 Radiotherapy: Supraclavicular fossa treated yes/no
2.19 Boost given – yes/no
If boost given
2.19.1 Electrons (Energy – MeV)
2.19.2 Megavoltage (Energy – MV)
2.19.3 Orthovoltage (Energy kV)
2.19.4 Dose (Gy)
2.19.5 Number of fractions
2.20 Chemotherapy (yes/no/don't know)
2.20.1 Regimen given (need drop down box)
2.20.2 Start date (DD/MM/YY)
2.20.3 End date (DD/MM/YY)
2.21 Herceptin (yes/no;
2.21.1 Start date (DD/MM/YY)
2.21.2 End date (DD/MM/YY)
2.22 Endocrine therapy (yes/no)
2.22.1 Specify drug
2.22.2 Start date (DD/MM/YY)
2.22.3 End date (DD/MM/YY)

Clinical follow up

If the patient was followed up in clinic were any of the following post-radiotherapy changes noted
2.23.1 Thickening of the skin – yes/no/not known
2.23.2 Lymphoedema of breast – yes/no/not known
2.23.3 Lymphoedema of the arm – yes/no/not known
2.23.4 Please give details (free text)
2.24. Date of last mammogram prior to diagnosis of angiosarcoma.

Section 3: Angiosarcoma Data

3.1 Date of diagnosis (diagnostic biopsy) (DD/MM/YY)
3.2 Location of tumour (free text)

Route of diagnosis:

3.3.1 Clinical presentation (Visible(cutaneous)/Palpable/Radiological)
3.3.2 Medical photography undertaken (yes/no/don't know)
3.3.3 Histology findings:
3.3.4 FNA (yes: give details of report/no/don't know)
3.3.5 Punch biopsy (yes: give details of report/no/don't know)
3.3.6 Excision biopsy (yes: give details of report/no/don't know)

Diagnostic imaging – where yes is indicated, finding field for free text provided due to differing nature of reporting

3.4.1 Mammogram (yes: findings/no/don't know)
3.4.2 USS of breast/axilla (yes: findings/no/don't know)
3.4.3 CT chest/abdo/pelvis (yes: findings/no/don't know)
3.4.4 MRI (yes: Anatomical part imaged, Findings/no/don't know)
3.4.5 Other (PET/etc: Yes: anatomical part, Findings)
3.4.6 Was the patient discussed at a sarcoma MDT? (Yes/No/not known)
3.4.7 Was the patient discussed at a breast MDT? (yes/no/not known)
3.4.8 Stage at diagnosis (drop down box)
3.5 Was tumour considered – resectable/non-resectable/not known
3.6 Metastatic Disease yes/no
3.6.1 If yes site(s)

Management

3.7 Lead care provider: Local cancer centre/ Regional sarcoma centre
3.8 Lead surgeon: Breast/ Plastic/ Sarcoma
3.9 Surgery – yes/no/not known
3.9.1 Date of surgery (DD/MM/YY)
3.9.2 Type of operation performed (drop down box to include options including reconstructive)
3.9.3 Post-operative complications yes: flap loss, poor healing, other: details /no/

Histology

3.10 Is tissue banked? (yes/no/don't know)
3.10.1 Size of angiosarcoma (maximum size in mm)
3.10.2 Grade (1 - low, 2, 3 - high)
3.10.3 Tumour markers
3.10.3.1 CD31 – postive/negative/don't know/not done
3.10.3.2 CD34 – positive/negative/don't know/not done
3.10.3.3 C-myc - positive/negative/don't know/not done
3.10.3.4 Other IHC, yes/no – please give details
3.10.4 Distance to margins (mm) superior, inferior, medial, lateral, posterior
3.10.5 Excision deemed adequate – yes/no/not known

Adjuvant therapy

3.11.1 Chemotherapy – yes/no/don't know
3.11.2 Regimen
3.11.2.1 Start date DD/MM/YY
3.11.2.2 End date DD/MM/YY
3.11.3 Biological therapy – yes/no/don't know
3.11.3.1 Agent
3.11.3.2 Start date DD/MM/YY
3.11.3.3 End date DD/MM/YY
3.11.4 Electrochemotherapy – yes/no/don't know
3.11.4.1 Date DD/MM/YY
3.11.4.2 Regimen
3.11.5.1 External beam Radiotherapy –yes/no/don't know
3.11.5.2 Dose (Gy) ?need energy as well
3.11.5.3 Number of fractions

Section 4: Follow up surveillance

4.1 Recurrences (please give details of all recurrences)yes/no
4.2 Date of recurrence (DD/MM/YY)
4.3 Type of recurrence (local/metastatic – please give details)
4.4 Management of recurrence:
    4.4.1 Details of surgical management (free text)
    4.4.2 Closest margin of re-excision (mm)
    4.4.3 Chemotherapy yes/no
        4.4.3.1 Regimen
        4.4.3.2 Start date (DD/MM/YY)
        4.4.3.3 End date (DD/MM/YY)
    4.4.4 Other salvage treatments (free text)
4.5 Further recurrence? yes/no (yes repeats items 4.3 – 4.5)

4.6 If dead, please give date of death (MM/YY)
4.7 Cause of death where known (free text)
4.8 If alive, please give
    4.6.1 Date of last clinical contact (MM/YY)
    4.6.2 Date of last imaging (MM/YY)
    4.6.2.1 Modality
    4.6.2.2 Site imaged
    4.6.2.3 Imaging result

Data validation and quality assurance

It is anticipated that participating centres will enter all patients identified as having primary AS of the breast or RAAS of the breast or anterior chest wall diagnosed within the study period (Jan 2000-Dec 2015) into the audit.

Following data collection, a random selection of approximately 5% of data sets will be selected. The PI 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 management and storage

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 securely on the local hospital server according to local IT policies. No patient identifiable data will be recorded for the purpose of this audit.

Study data will be collected and managed using REDCap[17] electronic data capture tools hosted at the University of Bristol. 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 [24].

Data 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.

Publication and authorship policy

All presentations and publications will be made on behalf of the BRASS Study Group and the Mammary Fold Academic and Research Collaborative.

The International Committee of Medical Journal Editors (ICMJE) criteria (www.icmje.org) for authorship is based on the following four criteria:

1. Substantial contribution to the conception or design of the work; or the acquisition, analysis or interpretation of the data for the work and

2. Drafting the work or revising it critically for important intellectual content and

3. Final approval of the version to be published and

4. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

The ICMJE states 'when submitting a manuscript authored by a group, the corresponding author should specify the group name if one exists and clearly identify the group members who can take credit and responsibility for the work as authors. The byline of the article identifies who is directly responsible for the manuscript and MEDLINE lists authors whichever names appear on the byline. If the byline includes a group name, MEDLINE will list the names of individual group members who are authors or who are collaborators, sometimes called non-author contributors, if there is a note associated with the byline clearly stating that the individual names are elsewhere in the paper and whether those names are authors or collaborators.'

All citable collaborators will therefore be listed at the end of the paper and their roles identified.

Criteria for citable collaborators status

Citable collaborators will have been required to make considerable contribution to the study. These will include Unit leads and ANY other team members (including consultant surgeons or pathologists, clinical nurse specialists, trainees, oncologists, research nurses or students) who have recruited at least ten patients to the study. Recruitment in this context includes the submission of at least ONE completed data sets. Judgement may be used to determine participation according to local centre practice. Unit leads will be asked to provide details of their local team and whether individuals fulfil the criteria for citable or acknowledged collaborator status.

Acknowledged collaborators

Acknowledged collaborators will include consultant surgeons and oncologists who contributed patients to the audit, but did not personally collect data and individuals who have made a lesser contribution to patient recruitment and data collection than that required for citable collaborator status. Individuals who are acknowledged contributors will also receive a certificate of participation for inclusion in their portfolios.

Local collaboratives and hospital Trusts will have ownership of their own data and will be able to present it locally if they wish. The final reports will be prepared in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [25].

Study Management

Oversight of this audit will be by the Audit Steering Group which will have wide representation from surgeons, trainees, the professional societies, patient representatives and those with experience of study management and statistics. This group is expected to meet twice a year, but may also meet more frequently if necessary.

There will in addition be a smaller, executive group for day to day running of the audit. It is expected that this will mainly work in a virtual/email forum.

A writing and data analysis group will be convened

Proposed Study timelines

August - September 2016:	Registrations of interest
October 2016 - January 2017:	Local pilot
February - April 2017:	Main study commences
April - May 2017:	Data analysis and abstract submission
June – August 2017	Write up
December 2017:	Presentation at San Antonio Breast Cancer Symposium

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