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Title: Breast Angiosarcoma Surveillance Study – A UK National Audit of Management and Outcomes of Angiosarcoma of the Breast and Chest Wall

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Abstract

Background

Breast angiosarcomas (AS) are rare tumours of vascular origin. Secondary AS (SAS) occurs following radiotherapy (RT) for breast cancer (BC). AS have high recurrence rates and poor survival. This is concerning due to increasing use of adjuvant radiotherapy for the treatment of BC and in situ disease which may explain the rising incidence of AS. Outcome data is limited, providing poor evidence base for treatment. This paper presents a national, trainee-led, retrospective multicentre study describing the largest AS cohort published to date.

Methods:

Data from patients with a diagnosis of breast/chest wall AS between 2000-2015 were retrospectively collected from 15 centres.

Results:

The cohort included 183 patients: 34 primary AS (PAS) and 149 SAS. Median latency from BC to SAS: 6 years. Only 78.9% of patients were discussed at a sarcoma multidisciplinary team meeting. Rates of recurrence were high with 6/31 PAS (19.4%) and 60/134 SAS (44.8%) at 5 years, with many patients having multiple recurrences (total recurrences 90/165, 54.5%). Median survival was 4 (0-16) years for PAS, 3 (0-15) years for SAS. Development of SAS had a negative impact on breast cancer predicted survival (median 10-year PREDICT prognostic score for BC; 68.95%, versus observed predict cohort survival; 55.3%).

Conclusion:

This is the first study to estimate the detrimental impact of SAS on BC survival. Though non-statistically significant, almost all excess deaths are attributable to AS. The increased use of adjuvant RT to treat low risk breast cancer and DCIS is a cause for concern and warrants further study.

INTRODUCTION

Angiosarcomas (AS) are rare malignant endothelial cell tumours of vascular or lymphatic origin[1]. Breast AS account for less than 1% of all breast malignancies and differ in presentation, behaviour and outcome from other sarcomas such as malignant phyllodes[2]. They may develop spontaneously as a primary breast malignancy (primary AS; PAS), often in younger women between the ages of 20-40 years, or they may occur secondary to lymphoedema or radiotherapy (Radiation Associated AS;RAAS) in women previously treated for breast cancer[2,3].

RAAS is rare and is defined as the development of a sarcoma in a previous radiotherapy field with a latency period of at least three years and can be considered a secondary AS (SAS)[4]. The aetiology and precise relation to the radiotherapy given is poorly understood. The incidence of RAAS is estimated at between 0.04 and 0.18%[5] in women treated with radiotherapy . Within an American cohort of over 200,000 patients treated with radiotherapy for breast cancer, 80 developed RAAS, reflecting an incidence of 6.8 per 100,000 from 1973-2003 [6]. The rate does not appear to be influenced by the type of surgery performed (mastectomy or wide local excision), but there may be a link between the development of RAAS and the presence of lymphoedema in the radiotherapy field[7]. The association between radiotherapy and AS is increasingly important due to increased rates of wide local excision and radiotherapy[8] and expanded indications for chest wall radiotherapy after mastectomy[9]. Analysis of registry data has shown a significant increase in reported rates of RAAS from 0.9 per million in the period 1985 to 1987, to 1.5 per million in 2007 to 2009[16].

Due to the rarity of AS most centres will only encounter very few cases which has resulted in a dearth of reliable information on the clinical behaviour and recommendations on best management [7,10]. Frequently the diagnosis is not initially suspected, with a mixture of

malignant cutaneous, glandular, and benign/atypical vascular presentations. The histopathological appearances are challenging and reinforce the need for specialised pathological review. Surgery remains the mainstay of treatment but guidance on extent is limited to exhortation to achieve wide margins even though determination of tumour absence at a margin is not straightforward[11]. The paucity of evidence-based advice emphasises the need for the management of breast angiosarcomas within specialist sarcoma multidisciplinary teams and the rigorous collection of all associated clinical data[18].

In the absence of large established breast AS datasets it is important to collate data that is available on real practice which forms the main purpose of this study. Furthermore, BRASS intends to stimulate awareness of breast AS and promote a collegiate, collaborative approach to inform the design of prospective studies and best-practice guidelines by using what information is available while recognising, as with many rare tumours, the inability to be definitive at this time.

METHODS

This study was a national, trainee-led, retrospective, multicentre audit co-ordinated by members of the Breast Angiosarcoma Surveillance Study (BRASS) steering group, supported by members of the Mammary Fold Academic and Research Collaborative (MFAC) and the Reconstructive Surgery Trials Network (RSTN). The trainee-led approach was based on the prior successes of the iBRA study methodology[12]. The protocol is published online[13].

Trainees from all breast and plastic surgery units (inclusive of local cancer centres and regional referral units) in the UK treating AS of the breast or chest wall were invited to participate in the study through National Research Collaboratives, including the RSTN.

Support was sought from the relevant professional associations; the Association of Breast Surgery (ABS), the British Association of Plastic, Reconstructive and Aesthetic Surgery (BAPRAS) and the British Sarcoma Group (BSG).

Individual patient care was not affected by this retrospective study. Research ethics approval was not required, as confirmed by the Health Research Authority (HRA) online decision tool[14].

Local audit approvals were obtained. Collaborators were asked to upload data on all patients (male and female) over the age of 16 years who had a histologically confirmed diagnosis of primary or secondary AS of the breast or the skin overlying the breast or anterior chest wall, between the 1st January 2000 and the 31st December 2015. Dependent on local resources, cases were identified by the collaborators using local pathology databases or by coding means. Due to the retrospective nature of the study, pathology specimens could not be reviewed.

Study data were collected from case-notes and local databases and managed using REDCap electronic data capture tools hosted at Oxford University[15,16]. REDCap (Research Electronic Data Capture) is a secure, web-based software platform designed to support data capture for research studies, providing 1) an intuitive interface for validated data capture; 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 data integration and interoperability with external sources. A pilot ran within a small number of centres prior to national roll-out to assess for the feasibility of data collection using the REDCap database system, after which minor modifications were made to the data collection tool. This tool is included in appendix 1

Data collection complied with Caldicott II principles[17]. Data for each patient was anonymised using a unique alphanumeric study identification number and local collaborators were asked to keep a spreadsheet linking hospital number to study number to prevent duplication of entries. No patient identifiable data was recorded for this audit. The BRASS project was registered with ResearchRegistry.com, UIN: 2129.

Analysis

Endpoints of interest were to examine the effect of multidisciplinary optimisation, the variation in management of those treated for AS and outcomes including survival.

Statistical analysis was performed using the SPSS package 24 ed. (SPSS, Chicago, IL). Descriptive data are presented as medians plus ranges or mean and standard deviation (as appropriate). Chi-squared test was used to compare between categorical groups. Kaplan-Meier survival curves compared primary AS and RAAS overall survival rates using logrank (Mantel-Cox) testing.

Where a patient presented with AS within a year of their primary breast cancer, they were included within the secondary subgroup as the presumed aetiology could not be confidently excluded. Furthermore, due to the incomplete nature of retrospective data, those presenting with AS following treatment for breast cancer who did not receive radiotherapy were also analysed within the SAS group as they may still have had resulting lymphoedema.

Due to incomplete information about dates of surgery for the primary breast cancer and AS, dates of diagnosis of AS and breast cancer were used as a proxy measures, as surgery is usually performed within a few weeks of the cancer diagnosis.

The predicted survival of the initial breast cancer, had the AS not occurred, was calculated using the PREDICT on line algorithm (version 1.2) which is derived from modelling outcomes according to breast cancer stage, tumour biology and systemic treatment[18,19]. Median hypothetical 10-year survival outcomes without secondary AS were compared with observed survival to assess the impact of the secondary AS on breast cancer outcomes.

RESULTS

Fifteen centres (including 11 of the 13 English Sarcoma Referral Centres) across the UK contributed data. There was a median of 7 cases entered per site (range 2-57). Further centre details are summarised in appendix 2. In total 202 patients were initially entered, 13 of whom were removed as they were diagnosed outside the eligibility time frame and six for having less than 10% of data fields entered. 183 patients were included for analysis; 34 primary and 149 secondary AS (figure 1). The median length of follow up for PAS was 3.5 years (range: 0-14) and for SAS was 2 years (range: 0-14).

The median interval between the breast cancer diagnosis and secondary AS was 6 years (range 0-32). The majority of patients for both primary and secondary AS were staged with a CT scan; 29/32 (90.6%) and 112/126 (88.9%) respectively.

Most primary AS were moderately differentiated 11/27 (40.7%) at diagnosis whereas secondary AS were more likely to be poorly differentiated 70/95 (73.7%). The majority of

patients with either primary or secondary AS were treated with surgical excision (31/34 (91.2%) and 137/148 (92.6%) respectively) and mastectomy was the most common procedure 17/28 (60.7%) and 71/135 (52.6%) respectively. Clear margins, defined as no tumour at ink (due to there being no standardised reporting among those included), were achieved for primary and secondary AS in 21/30 (70%) and 93/113 (82.3%) respectively. A large number of patients with primary AS had adjuvant radiotherapy 17/29 (58.6%). In secondary AS radiotherapy had usually been delivered to treat the primary cancer, reflected by less frequent use of adjuvant radiotherapy for the sarcoma (5/122 (4.1%)) (table 1).

In patients presenting with secondary AS following treatment for breast cancer, most breast cancer primaries were invasive 114/127 (89.8%) and most commonly grade 2 (49/104, 47.1%). The majority of patients had undergone breast conserving surgery (BCS) 131/144 (91%). Radiotherapy was administered in 136/138 (98.6%) of patients. Only a third of patients received chemotherapy 43/123 (35%) but almost all had endocrine therapy 116/127 (91.3%) as part of their breast cancer treatment (table 2).

The estimated five-year survival for both primary and secondary AS was low (15/31 (48.4%) and 48/134 (35.8%) respectively) and recurrence occurred in both groups (primary AS 14/34 (41.2%) and secondary 80/149 (53.7%)). The majority of recurrences in both groups were local recurrence (primary AS 7/14 (50%) and secondary AS 59/80 (75.6%)). Where known, cause of death was almost entirely due to the AS for both primary and secondary AS; 7/7 (100%) and 39/42 (92.9%) respectively (table 3).

Of those presenting with SAS, 104 records had sufficient data to derive PREDICT overall median survival estimates at 5 and 10 years for the original breast cancer which were 85.4% (range 38.6-96.9%) and 68.95% (range 8.5-92.6%) respectively. 98 records in this PREDICT

cohort had sufficient data in actual observed survival; the observed overall survival from initial breast cancer at 10 years was 55.3% which gives some indication of the negative survival impact of SAS. For the whole secondary dataset observed survival was 59.1% (table 2).

Of the primary cases of AS, 66.7% (16/24) and 81.3% (100/123) of the secondary cases were discussed at a Specialist Sarcoma MDT meeting prior to treatment (as recommended in the NICE guidelines for sarcoma management [20]). Comparatively, post-surgery sarcoma MDT discussions occurred less frequently for both the primary and secondary AS groups; 57.1% (16/28) and 69.4% (84/121) respectively. The number of patients discussed in MDT meetings however, has increased since 2006 for both primary and secondary AS. There is a trend (though this cannot be feasibly statistically tested for significance) towards improved ten year survival in those with specialist sarcoma MDT input compared to those without; PAS 26.7% vs 25%; SAS 3.3% vs 0% (table 4).

DISCUSSION

To our knowledge, this is the largest UK multi-centre series of primary and secondary AS of the breast or chest wall. Limitations exist due to the multi-centre retrospective nature of the observational data. Although the data reflects a follow up of 14 years with a median of 3 years, in some cases, the follow up period is much shorter. This is most likely due to patients being treated in one centre and followed up in different centre with records not being accessible to the collaborator, or historical information becoming no longer available.

Overall, only 78.9% of patients were discussed by a sarcoma MDT meeting before surgery and only 67.1% postoperatively. National Institute for Health and Care Excellence (NICE) guidelines were produced in 2006, which recommended that all patients with a sarcoma

diagnosis in the UK are discussed in a sarcoma MDT[20]. There is an upward trend observed in the rate of discussion in a sarcoma MDT since 2006 and from 2010-2015 this increased to 78% which could be attributed to the influence of the publication of this NICE guidance, along with widening awareness of the importance of the role of the MDT in high-quality cancer care.

The trend, though non-significant in improved outcomes in those with specialist sarcoma MDT input is concordant with a recent case series of thirty-six patients showing that treatment in a regional sarcoma centre resulted in better survival outcomes and fewer recurrences[22]. A large proportion of patients within the BRASS cohort had at least one recurrence, 50% of primary and 75.6% of secondary AS, despite only 16% overall known to have involved margins at the time of resection, highlighting the inherent difficulties in histological assessment of angiosarcoma margins, treating angiosarcoma and perhaps indicating the need for more aggressive initial surgery.

This is the first published study to estimate the impact of developing a secondary angiosarcoma on predicted ten-year survival following breast cancer. The median PREDICT score for the breast cancer data at ten years was 68.5%[18]. The actual ten-year survival for our dataset of these patients at ten-years was 59.1% reflecting an overall decrease in survival of 9.6%: Developing an angiosarcoma has a significant impact on mortality, which is particularly unfortunate for those undergoing radiotherapy for pre-invasive disease. This estimate is likely to be conservative due to the long latent period of RAAS. This detrimental effect on overall mortality will tend to select women with good prognosis breast cancer or ductal carcinoma in situ (DCIS) who are eligible for breast conserving surgery and also who are more likely to live long enough to develop RAAS. The trend towards higher rates of radiotherapy use after primary breast cancer diagnosis in both the breast conservation and mastectomy setting is, therefore, a cause for concern, especially in those with an excellent predicted prognosis, some

of which may have been diagnosed by screening. Investigation into safely omitting adjuvant radiotherapy in lower risk breast cancers by means of the PRIMETIME study has the potential to prevent the development of some future secondary AS from occurring[23].

Within this cohort most patients with RAAS had previously received external beam radiotherapy with 50 Gray (Gy) in 25 daily fractions or 40 Gy in 15 daily fractions. These dose fractionation regimes are commonly used within the UK, the latter becoming standard practice following publication of the START trial just over a decade ago[21]. Where data was available the majority of patients didn't receive nodal radiotherapy or a tumour bed boost. It might be hypothesized that this is simply because patients receiving nodal radiotherapy, or a tumour bed boost would have a higher risk of breast cancer recurrence and therefore would be less likely to survive to develop a RAAS. In this study, all patients received whole breast radiotherapy, however with the development of new techniques, such as partial breast radiotherapy or intra-operative techniques, in the future the volume of breast tissue irradiated may reduce which potentially could reduce the risk of RAAS. Trials of these techniques are ongoing and further follow-up is needed to assess whether they reduce the incidence of radiation-induced malignancies.[24,25].

Due to the retrospective and historical nature of the dataset, there are limitations due to incomplete data. However, the observed impact on survival for those treated for breast cancer indicates that this is an area which needs to be further explored with a prospective study. Identification of women who may be at increased risk of RAAS should be a research priority. Efforts to better define the impact of RT dose patterns, genetic risk factors and AS biology are needed.

Currently, there are no specific guidelines for the management of AS of the breast or chest wall, yet this is a particularly aggressive subtype of sarcoma, in a complex group of patients,

having often had preceding surgery and prior radiotherapy. With a better understanding of the progression of this cancer, we may be able to shape more focused diagnostic and management guidelines and standardise treatment pathways, ultimately with the aim of improving outcomes.

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