Incidence and Outcome of Breast Sarcomas in England (2013-2018): An Analyses from the National Cancer Registration and Analysis Service

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Abstract

Background:

Breast sarcomas (BS) are rare cancers originating from mesenchymal breast tissue with a paucity of national population level data detailing their incidence and outcomes.

Methods: We performed an analysis of data collected by National Cancer Registration and Analysis Service (NCRAS) for patients diagnosed with BS between 2013-2018. Chi-square test was used to compare groups. Overall survival was calculated by Kaplan-Meier. Specialist sarcoma centres (SSC) were defined as centres with a sarcoma Multidisciplinary team (MDT).

Results:

There were 684 patients with BS (357 malignant Phyllodes Tumours [PT], 238 vascular tumours, 93 other morphology) with a median age of 64 (range 14-96); 187 (27%) had received breast radiotherapy for a prior malignancy; 633 (92%) had resection of the tumour within 12 months of diagnosis. Five-year overall survival was 82%, 54% and 48% in patients with PT, vascular tumours and other sarcomas, respectively and 55% for those with radiation-induced BS. Patients managed within SSC more frequently had a biopsy prior to surgery 83% vs 72%, $p < 0.05$) and were less likely to require multiple operations (26% vs 41%, $p < 0.05$).

Conclusion:

This is the first population series evaluating incidence and outcomes for BS. Patients treated at Non specialist sarcoma centres (NSSC) are less likely to have a biopsy prior to surgery and more likely to require multiple operations. Based on this observational data we would recommend all BS are discussed at a sarcoma MDT meeting early in their pathway and surgery to be considered at SSC where possible.

1. Introduction

Primary breast sarcomas account for less than 5% of all sarcomas and less than 1% of all breast malignancies, with an annual incidence reported as 4.6-4.8 cases per million women in the USA (1, 2). They are a heterogeneous group of non-epithelial tumours that arise from mesenchymal tissue of the breast. Due to their rarity, there are currently no randomised controlled trials to inform management. The key to diagnosis is a core biopsy of the lesion. However there are challenges with the diagnosis of malignant phyllodes tumour (PT) on core biopsies and some patients have to undergo excision biopsy (3).

For patients with localised disease, the most important component of treatment is surgery with adequate margins with the addition of radiotherapy and chemotherapy for selected high risk cases (1). Surgery can be with a mastectomy or wide local excision which have equivalent outcomes (4, 5). The definition of an adequate surgical margin in PT remains unclear (6-8).

The National Cancer Registration and Analysis Service (NCRAS) part of NHS digital, is the population-based cancer registry in England. NCRAS was established in 2013 and with the increased use of electronic records has enabled comprehensive analysis for service providers, clinicians, patients and charities on rare and less common cancers (9).

The aim of this population-based analysis was to determine incidence and outcome of patients diagnosed with breast sarcoma in England and describe factors that impact management and outcome, including centre of treatment.

2. Methods

2.1.Data Approvals and Collection

Patients with a histological diagnosis of breast sarcoma were identified in the National Cancer Registration Dataset between 1st January 2013 and 31st December 2018 were included, and linked to other datasets held by NCRAS. Data was selected from 2013 onwards as this was the first year specific data for sarcoma was collected using ICDO-3 and also follows the merger of 8 regional cancer registries to form a centralised database with unified standards of collection. Prior to 2013 (1995-2012) ICDO-2 and ICD10 were used for classification. All the diagnoses were made by specialist clinicians and coded by clinical coding specialists. The study population was identified initially by using ICDO-3 to select for PT and other breast sarcomas (**Error! Reference source not found.**). For PT, only malignant PTs were included in the analyses. The sarcoma cohort was then linked using patient identifiers to identify a history of previous breast cancer using ICD-10 codes C50 and DO5 (10, 11) . Patient demographics are collected through the cancer outcomes and services dataset (COSD). Surgical data was collected through NHS Hospital Episode Statistics (HES) and were divided into two groups, mastectomy and breast conserving surgery (Supplementary Table 1) (12) (13, 14). As per local guidelines, treatment was defined as occurring -31 days to +365 days from the date of pathological diagnosis. Radiotherapy data was obtained from the National Radiotherapy Data Set (RTDS) and pre-2009 from the cancer registry treatment tables (14-16).

A deprivation quintile was assigned to each patient based on their postcode of residence at diagnosis. The income domain score using the indices of multiple deprivation datasets was used to assign each Lower Super Output Area (LSOA) population in England to a deprivation quantile with approximately 20% in each quintile (quintile 1 represents the least deprived quintile, whilst the 5th represents the most deprived). Comorbidity status using the Charlson comorbidity index (CCI) was defined (17). Comorbidity data was obtained from HES and the cancer registry.

2.2.Definition of a Specialist Sarcoma Centre

The NHS Sarcoma Service Specification has designated 15 specialist soft tissue sarcoma centres in England that host specialist sarcoma Multi-disciplinary Team meetings (MDT) and offer multi-disciplinary care. As there are currently no sarcoma specialist centres specifically designated for breast sarcoma, for the purpose of this analysis we designated a breast specialist centre as a centre that holds a sarcoma MDT.

2.3. Statistical Analyses

Statistical analyses were performed using Stata version 15.1 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC). Overall survival (OS) was estimated using the Kaplan-Meier analyses and log-rank tests were used to compare survival distributions univariately. Chi square test for independence was used to compare characteristics between two samples. Univariate Cox's proportional hazard regression analysis was performed to obtain the hazard ratio for covariates. All tests were conducted at the 5% level of significance. Of the 688 BS tumours, 8 were ineligible for analysis. Of those, 4 tumours were excluded as they were a second primary BS (bilateral disease, 1st diagnosis retained). One tumour was excluded as the patient's age at diagnosis was outside 15-99 years age restriction. An additional 3

tumours were excluded due to data quality flags. Time at risk began at the date of diagnosis and continued until the point of embarkation, death, 5 years post diagnosis or the end of the follow-up period on the 31st December 2020.

3. Results

3.1. Patient Characteristics

Between 2013 and 2018, 684 patients were diagnosed with a breast sarcoma (**Table 1**, **Error! Reference source not found.**). There were 357 PTs, 238 vascular tumours and 92 tumours of other morphologies, which included 677 females and 7 males with a median age at diagnosis of 64 years (range 15-96). Three patients had bilateral tumours. Breakdown of age according to morphology is detailed in Table 1.

3.2. Previous Breast Cancer Diagnosis

There were 222 (32%) patients with a previous diagnosis of epithelial breast cancer (Supplementary Table 3**Error! Reference source not found.**). The median time from epithelial breast cancer to breast sarcoma was 7.5 years.

There were 187 (27%) patients who were documented as having previous radiotherapy to their breast/thorax. The median time to develop a breast sarcoma after radiotherapy was 7 years (range 0-23 years) (Figure 1A). The majority of radiation induced tumours were vascular sarcomas (174, 93%) (Supplementary Table 4).

Characteristics	Number of Cases (patients)	Malignant Phyllodes Tumour	Vascular Tumours	Tumours of Other Morphologies*
Number (%)	684	357 (52%)	235 (34%)	92 (14%)
Female (%)	677 (99%)	NA	NA	NA
Male (%)	7 (1%)	NA	NA	NA
Median Age (Range)	64 (14-96)	54 (17-95)	71 (27-95)	69 (14-96)
CCI= 0	584 (85%)	325 (91%)	186 (79%)	73 (79%)
CCI ≥1	100 (15%)	32 (9%)	49 (21%)	19 (21%)
Previous Breast Cancer	222 (32%)	10 (3%)	197 (84%)	15 (16%)
Previous Radiotherapy	187 (27%)	<5 (1%)	174 (74%)	<10 (10%)
Median time from previous radiotherapy to breast sarcoma (years)**	7 (0-23)	NA	NA	NA

Table 1: Showing baseline characteristics of the cohort

*includes undifferentiated sarcoma, liposarcoma and leiomyosarcoma

** 92% of patients had radiotherapy >3 years previously

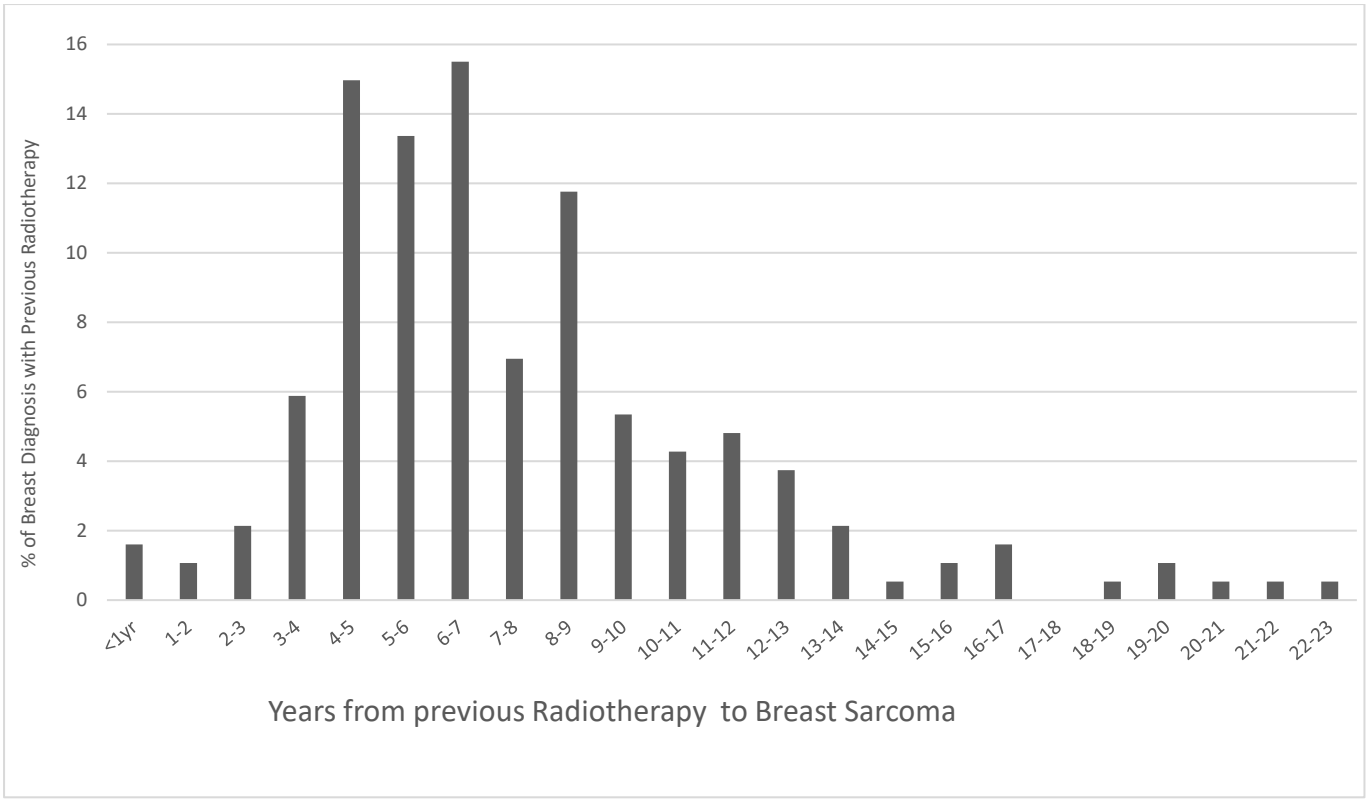
CCI = Charlson Comorbidity Index, NA – Not applicable

3.3.Treatment

The majority of patients had surgery within 12 months of diagnosis (n=633, 92%). In addition to surgery 114 patients (17%) received radiotherapy, 37 patients received chemotherapy (5%) and 20 (3%) patients received both chemotherapy and radiotherapy. For patients who did not have surgery within 12 months of diagnosis

(n=55), the majority were documented as receiving other care, which is most likely best supportive care (n=36, 5%); the others received chemotherapy and radiotherapy (3%). Of the patients aged over 75 years, 85% underwent radical surgery (**Figure 1**B). Patients with tumours of other morphology were less likely to undergo surgery 19% (Figure 2A).

A



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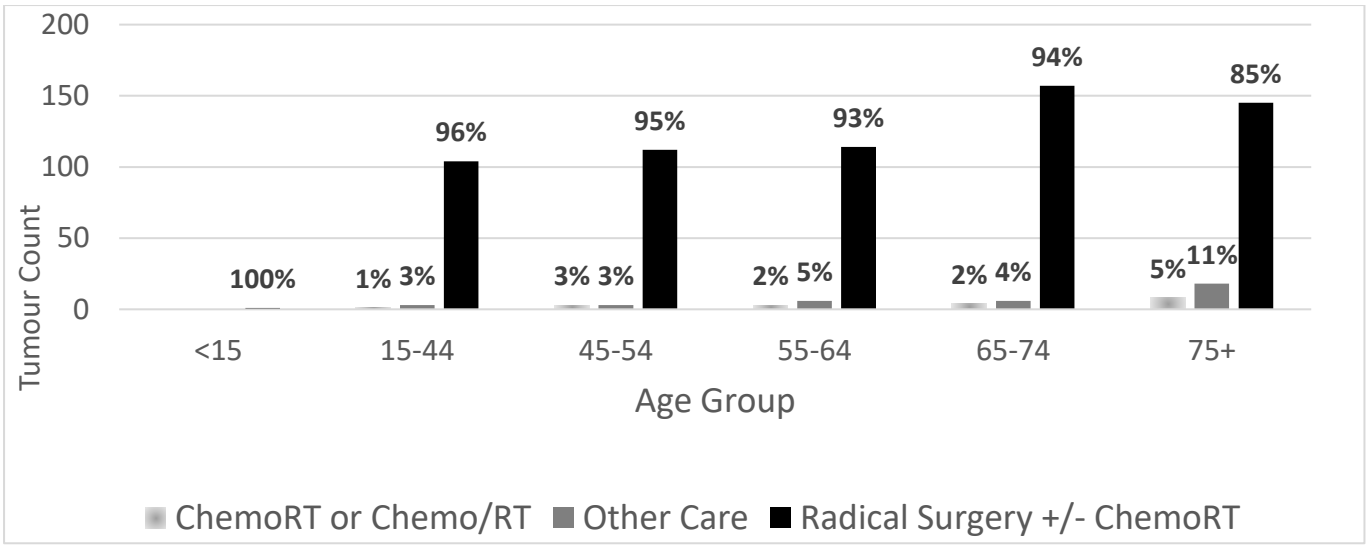


Figure 1: Bar Chart showing **A:** Number of years since the previous breast/thorax radiotherapy and development of breast sarcoma. Median =7 years (range 0-23)**; B:** age breakdown for the different treatments received (Chemo = Chemotherapy), RT=Radiotherapy)

3.4. Place of First Surgery and Biopsy Prior to Surgery

212 (33%) patients underwent their first operation at a specialist sarcoma centre; 49% patients with vascular tumours 26% of PT and 23% “other morphologies” respectively (Figure 2B). When a documented biopsy was performed prior to surgery 29% of patients underwent multiple operations compared to 58% of patients when a biopsy was not performed prior to surgery (<0.05, Chi Square) (Figure 3A). The rate of biopsy was higher in a specialist centre (83%) compared to a non-specialist centre (72%) (P<0.05, Chi Square) (Figure 3B).

One third of patients have more than one operation within 12 months of their diagnosis (**Error! Reference source not found.**). If the first surgery is performed at a specialist centre 26% proceed to further surgery compared to 41% of patients having first surgery at a non-specialist sarcoma centre (P<0.05, Chi Square) (Figure 3D).

Patients undergoing mastectomy as their first operation were less likely to have subsequent surgery than those with local excision (8% versus 58%).

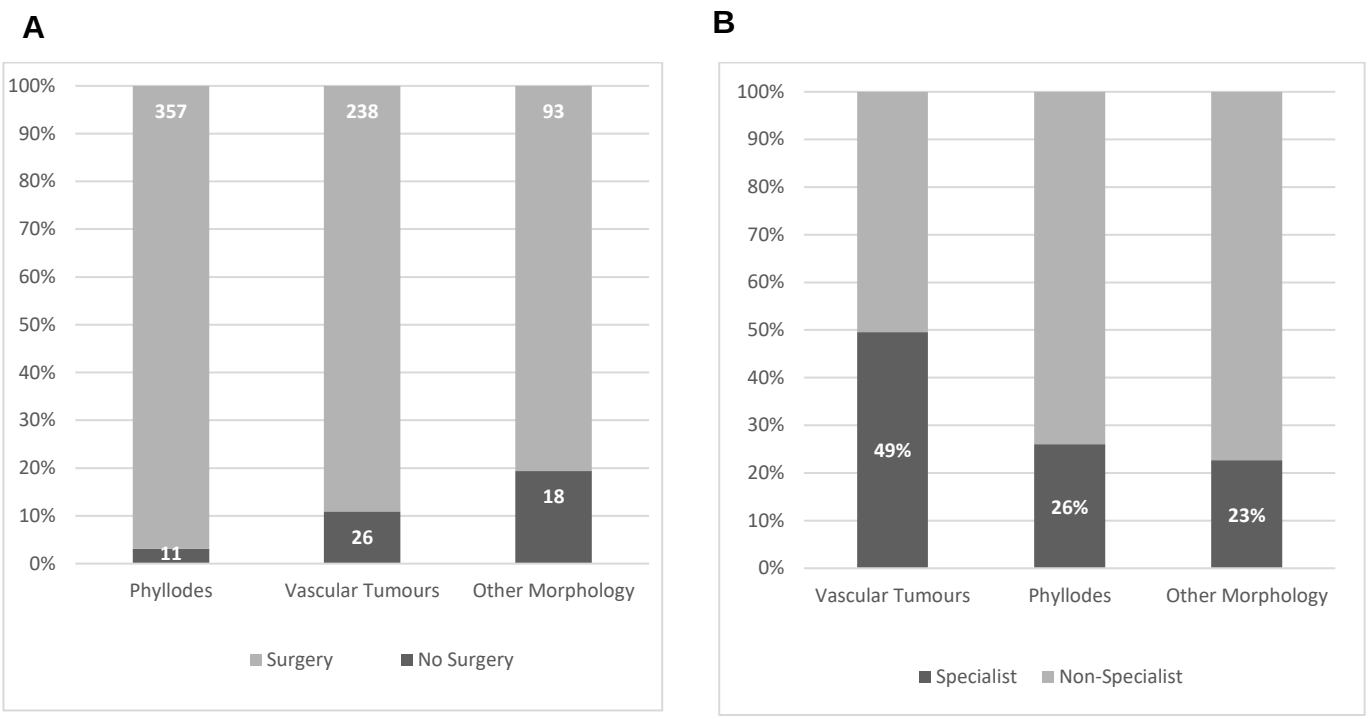


Figure 2**:** Bar charts showing: **A:** Morphological breakdown for those who had surgery and those who did not (numbers inside the bar represent actual counts) (P<0.05, Chi Square) **B:** A bar chart showing the proportion of patients undergoing their first operation in a specialist sarcoma centre compared to a non-specialist centre. (P<0.05, Chi Square

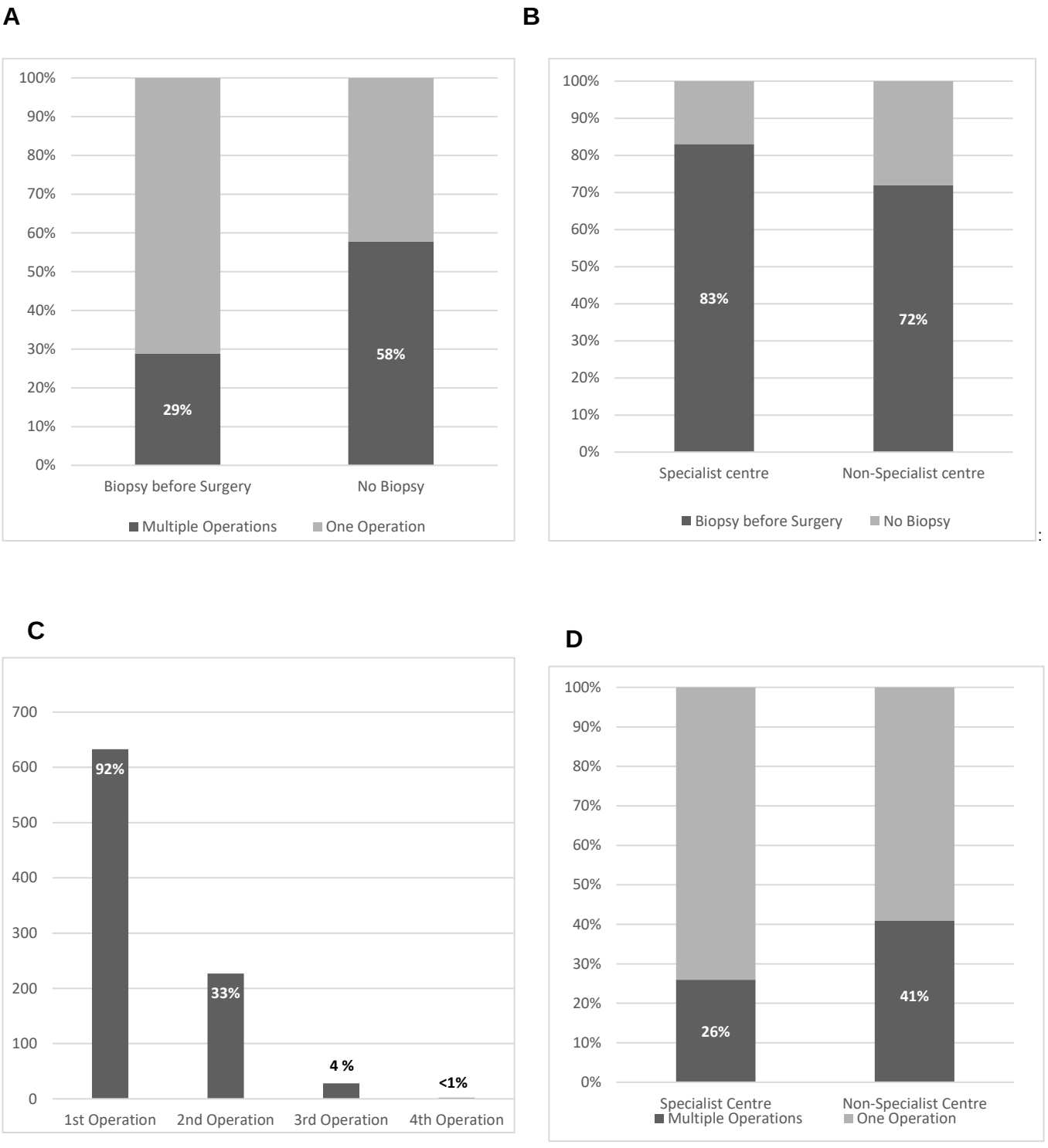


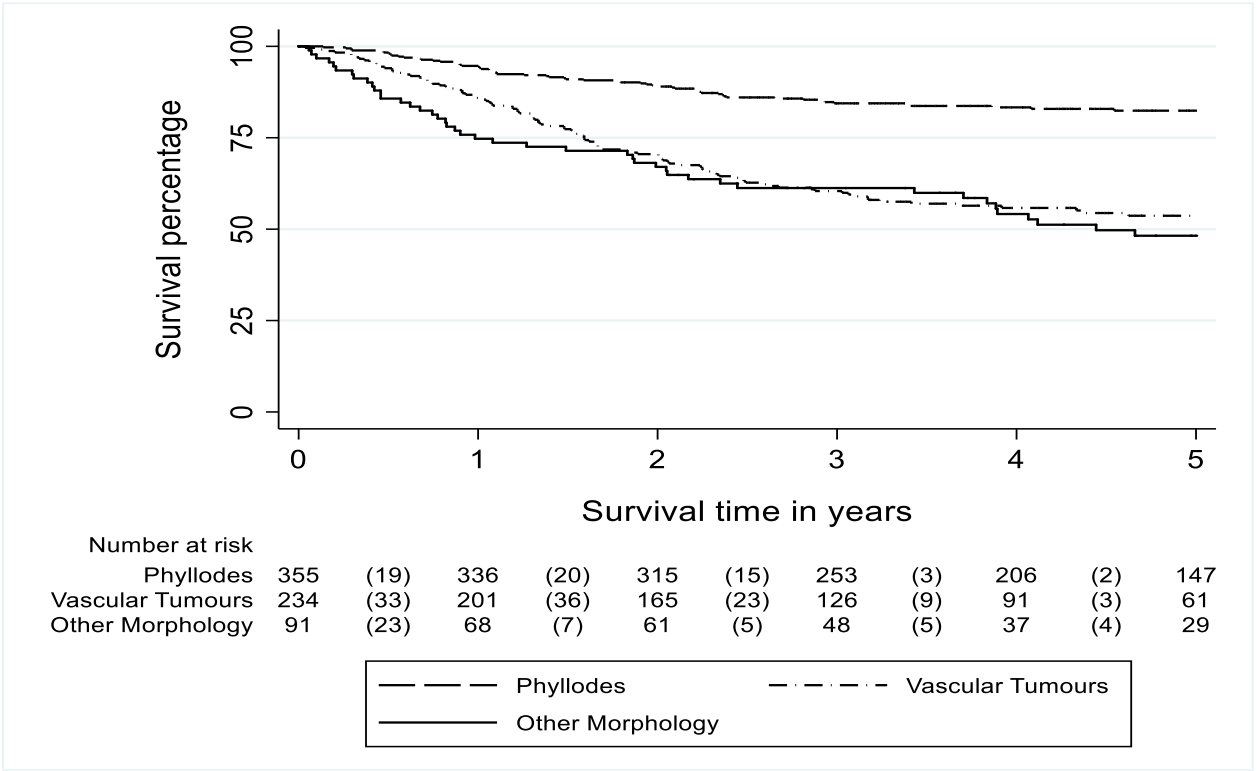
Figure 3: Bar charts showing **A:** how a biopsy prior to surgery influenced the number of operations (P<0.05, Chi Square). **B**: how the biopsy rate differs between specialist and not specialist centres (P<0.05, Chi Square). **C:** the proportion of patients who have more than one operation within 12 months of their diagnosis (x axis label is number of tumours). **D:** the rate of multiple operations depending if the first surgery is performed at a specialist centre or a non-specialist centre (P<0.05, Chi Square)

3.5.Survival

The 5 year overall survival for breast sarcoma was 68% (CI 64-71%). Outcome varied by morphology with 5 year survival for PT 82% (CI 78-86%), vascular tumours 54% (CI 47-60%), and tumours of other morphology 48% (CI 37-59%). (Figure 4A).

Survival reduced with increasing age; (Figure 4B). For patients with a previous diagnosis of epithelial breast cancer, the 5 year survival estimate was 54%, CI 47-61% and 55%, CI 48-62% in those who received previous radiotherapy (Supplementary Figure 1A & 1B). There was no difference in survival for the location of the first operation (Supplementary Figure 1C). There was no difference in survival for vascular tumours that occurred de-novo or secondary to radiotherapy (Figure 4C). Patients with a CCI score of greater than 1 had double the risk of mortality (Supplementary Figure 1D).

A



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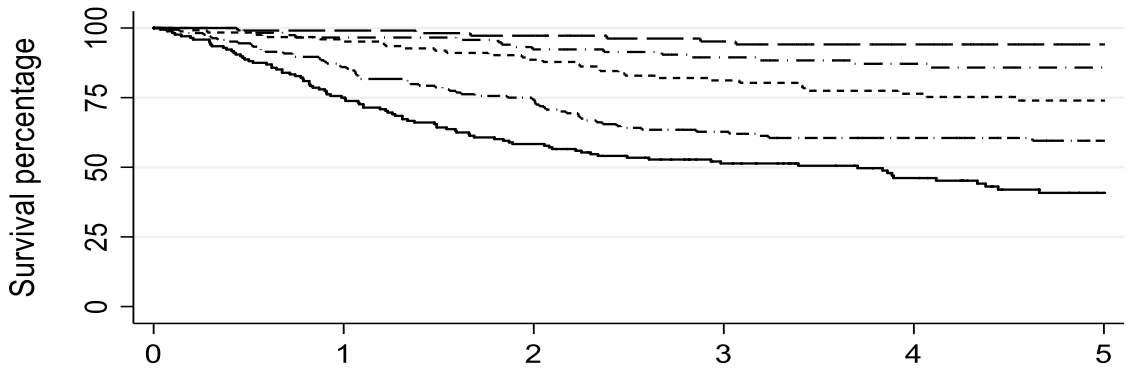

Number at risk

15-44	108	(1)	107	(2)	105	(2)	90	(1)	78	(0)	53
45-54	117	(4)	113	(5)	108	(3)	86	(2)	66	(1)	56
55-64	123	(5)	118	(9)	109	(9)	93	(5)	69	(2)	44
65-74	164	(23)	141	(19)	121	(18)	86	(3)	70	(1)	52
75+	168	(42)	126	(28)	98	(11)	72	(6)	51	(5)	32

C

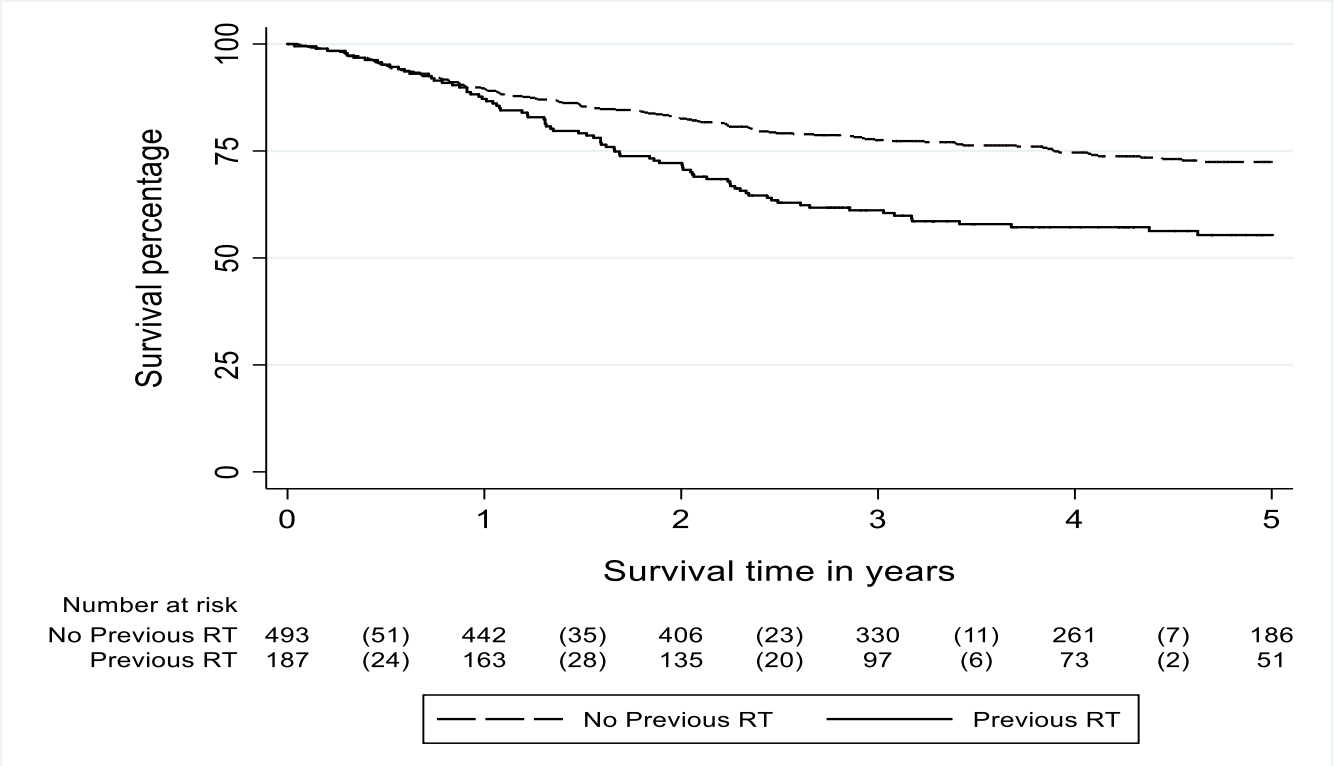

Figure 4: An unadjusted 5 year survival estimate stratified by; **A:** morphology (Log rank test, P<0.05), **B:** age at diagnosis (Log rank test, P<0.05) **C:** by radiotherapy history (Log rank test, P=0.74)

4. Discussion

This is the first population-based study to describe clinical and pathological characteristics of breast sarcomas in England and is the most comprehensive internationally. The incidence of breast sarcoma in this dataset was 4 cases per million women diagnosed per year in England, which is consistent with other historical datasets (1, 18). The median age of diagnosis in this cohort was comparable to other datasets. (1, 2, 19, 20). This analysis confirms surgery to be the mainstay of treatment

for breast sarcoma but additionally 28% of patients received either chemotherapy or radiotherapy or both. The benefit for adjuvant chemotherapy in non-phyllodes breast sarcoma remains unclear, but it is considered dependent on patient age, tumour size>5cm and risk of recurrence (1, 21). Adjuvant chemotherapy is not routinely used in PTs (3). The role of adjuvant radiotherapy is also unclear although is considered in high risk cases (tumour size > 5cm and close margins) (1, 19). A small proportion of patients (8%), did not have surgery, lower than published rates (19%) for localised epithelial breast cancer in the England but most often in older patients consistent with the epithelial breast cancer group (22, 23). Due to the lack of staging data we are unable to determine why surgery was not performed for this group, but there have been reported concerns that elderly people have reduced equitable access to cancer treatment compared to younger patients (24).

An overall 5 year survival estimate of 68% (CI 64-71%) was consistent with other published breast sarcoma series (25-28), although we believe this is the most comprehensive population-based analysis to date. The very wide variability of 5 year survival estimates in other series is likely due to the small numbers of cases and also the description of a heterogeneous group of cancers. Older age was associated with a significant risk of death as was co-morbidity.

The 5 year survival estimate of PTs 82% (CI 78-86%) and vascular tumours 54% (CI 47-60%) was similar to other large published cohorts. (29, 30). The other morphology group contains only 92 patients and a wide range of histotypes thus, it is not possible to compare with other analysis.

Our data support the importance of performing a diagnostic biopsy prior to surgery, as this was associated with a reduction in requirement for further surgery. The biopsy rate

was higher at specialist hospitals which suggests the experience of managing these rare tumours translates into improved radiological diagnosis of these tumours and a reduction in the number of operations.

The optimal operation for patients with vascular tumours is mastectomy and resection of all irradiated skin (for patients who have had radiotherapy) with negative margins. This procedure translates to superior local control and improved overall survival compared to a wide local excision (31). Our data shows that only 60% of vascular tumours have mastectomy as the first surgery and less than half of patients have their first operation at a specialist centre.

This analysis demonstrates a reduction in PTs receiving multiple operations when the first surgery is performed at a specialist centre. Optimal surgical management is crucial as malignant PTs have a local recurrence rate of approximately 20-30% and 20% develop distant metastatic disease (32). Currently it is not mandatory for patients with PTs to be referred to a specialist sarcoma centre for surgery, although patients may be transferred for subsequent surgeries. The National Cancer Registration Dataset does not have data on borderline or benign PTs, which have the same diagnostic challenges as PT, and a biopsy is not always able to classify them accurately. Borderline phyllodes have a reported local recurrence rate of 25% and can transform to a PT (33).

For the overall group one third of patients with breast sarcoma undergo multiple operations within 12 months of their diagnosis, higher in non-specialist centres (41%) compared to specialist centres (26%). This important finding may be due to the lower biopsy rates at non-specialist centres, but nonetheless demonstrates an unacceptable

disparity. For epithelial breast cancer the acceptable re-excision rates for close margins in the UK is 15% (34).

Our analysis does not demonstrate a significant survival benefit for the location of the first surgery for non-PT tumours. We have hypothesised that patients referred to specialist centres have larger more aggressive tumours as suggested by other cohorts, which has a negative impact on survival but unfortunately due to lack of availability of stage, tumour size and grade we are unable to confirm this (35).

There is extensive data to support centralisation of breast sarcoma diagnosis and management to specialist sarcoma centres due to superior treatment and survival outcomes (25-28). The Scottish Sarcoma Group and a single centre analysis from the Royal Marsden have recommended centralisation of breast sarcoma surgery in the UK due high rate of positive margins in non-specialist hospitals (35, 36). Our data support this recommendation. A national guideline is required to ensure consistency of management.

There were 222 (32%) patients with a previous diagnosis of an epithelial breast cancer and 187 (27%) patients who had previous thorax/breast radiotherapy. Not all the patients with a previous history of epithelial breast cancer were documented as having had radiotherapy. It is likely that patients diagnosed with breast cancer and a subsequent BS may have had a cancer pre-disposition syndrome increasing the risk of multiple cancers. The 5 year survival estimates for our cohort who have had previous epithelial breast cancer and also breast cancer radiotherapy (54-55%) is higher than the only other series published which reported survival which also contained patients with high grade bone sarcoma (27-35%) (37). There was no

survival difference for patients who developed radiation induced vascular tumour and those who developed de-novo vascular tumours.

Radiation induced breast sarcomas are most commonly caused by the use of adjuvant radiotherapy in epithelial breast cancer and also thoracic radiotherapy after lymphoma (38). For our cohort of patients who have received previous thorax/breast radiotherapy the median time from radiotherapy to breast sarcoma development was 7 years (range 0-23 years), which was consistent with the literature (6 months to 20 years) (2, 39). The majority of radiation induced sarcoma in our cohort were vascular tumours (93%). Current UK screening guidelines recommend breast screening after radiotherapy to the thorax 8 years after radiotherapy or to start at age 25 or 30 (40). Based on our data, we would not suggest changing the UK screening guidelines as screening is unlikely to pick up angiosarcoma which are cutaneous lesions, and therefore education is key for patients who are under self-managed follow up. The 5 year survival estimate for all histotypes in our cohort of patients appears superior (55%, CI 48-62%) than the published data (27-48%), but due to lack of staging and tumour specific data a direct comparison cannot be made. Recent changes in the way radiotherapy is delivered for epithelial breast cancer such as partial breast radiotherapy, and hypofractionation, may have an impact on the future frequency and distribution of radiation induced breast sarcoma.

5. Conclusion

This is the first population-based analysis of incidence and outcome of breast sarcoma in England demonstrating incidence comparable to previous population-based

analyses and survival outcomes to be equivalent or better. Older patients and those with co-morbidities have a worse survival outcome. Only one third of patients have their first operation at a centre with a sarcoma MDT. Patients who are treated in non-specialist hospitals are less likely to have a biopsy performed and are more likely to require multiple operations. We recommend patients with a suspected breast sarcoma be discussed at a specialist sarcoma MDT as early on in the pathway as possible and surgery be performed at designated sarcoma centres whenever possible.

6. Declaration of Interest Statement

Nothing to declare

7. References

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8. Supplementary Material

OPCS4 CODE	DESCRIPTION	SURGERY TYPE
B271	Total Mastectomy And Excision Of Both Pectoral Muscles And Part Of Chest Wall	Mastectomy
B272	Total Mastectomy And Excision Of Both Pectoral Muscles Nec	Mastectomy
B273	Total Mastectomy And Excision Of Pectoralis Minor Muscle	Mastectomy
B274	Total Mastectomy Nec	Mastectomy
B275	Subcutaneous Mastectomy	Mastectomy
B276	Skin Sparing Mastectomy	Mastectomy
B278	Other Specified Total Excision Of Breast	Excision of Lesion
B279	Unspecified Total Excision Of Breast	Excision of Lesion
B281	Quadrantectomy Of Breast	Excision of Lesion
B282	Partial Excision Of Breast Nec	Excision of Lesion
B283	Excision Of Lesion Of Breast Nec	Excision of Lesion
B284	Re-Excision Of Breast Margins	Excision of Lesion

B285	Wire Guided Partial Excision Of Breast	Excision of Lesion
B286	Excision Of Accessory Breast Tissue	Excision of Lesion
B287	Wire Guided Excision Of Lesion Of Breast	Excision of Lesion
B288	Other Specified Other Excision Of Breast	Excision of Lesion
B289	Unspecified Other Excision Of Breast	Excision of Lesion
B341	Subareolar Excision Of Mammary Duct	Excision of Lesion
B342	Excision Of Mammary Duct Nec	Excision of Lesion
B343	Excision Of Lesion Of Mammary Duct	Excision of Lesion
B352	Excision Of Nipple	Excision of Lesion
B353	Extirpation Of Lesion Of Nipple	Excision of Lesion
B374	Capsulectomy Of Breast	Excision of Lesion
B401	Interstitial Laser Destruction Of Lesion Of Breast	Excision of Lesion

B408	Other Specified Destruction Of Lesion Of Breast	Excision of Lesion
B409	Unspecified Destruction Of Lesion Of Breast	Excision of Lesion

Supplementary Table 1: OPCS V4 Breast Surgical Codes

Morphological Subgroup	Morphological Description	Morphological Code	Counts
Phyllodes	Phyllodes Tumour, malignant. Cystosarcoma phyllodes, malignant	9020	357
Vascular Tumours	Haemangiosarcoma, Angiosarcoma of soft tissue	9120	232
	Angiomyosarcoma	8894	6
Undifferentiated Sarcoma	Spindle Cell Sarcoma	8801	27
	Undifferentiated pleomorphic sarcoma	8802	8
	Undifferentiated sarcoma	8805	8
Other malignant soft tissue tumours	Sarcoma, NOS	8800	18
	Osteosarcoma, NOS	9180	<5
	Stromal sarcoma	8935	<5
Tumours of uncertain differentiation	Myoepithelial carcinoma	8982	<10
	Epithelioid sarcoma	8804	<5
Myxoid fibroblastic sarcomas	Myxofibrosarcoma	8811	6
Liposarcoma	Liposarcoma, NOS; fibroliposarcoma	8850	<5
	Myxoid Liposarcoma; myxoliposarcoma	8852	<5
Leiomyosarcoma	Leiomyosarcoma, NOS	8890	5
Myofibrosarcomas and other fibroblastic sarcomas	Fibrosarcoma, NOS	8810	<5
	Solitary fibrous tumour, NOS	8815	<5
Rhabdomyosarcoma	Embryonal rhabdomyosarcoma;	8910	<5

	sarcoma botryoides; botryoid sarcoma		

Supplementary Table 2: Detailed morphological breakdown using ICD0-3rd Edition

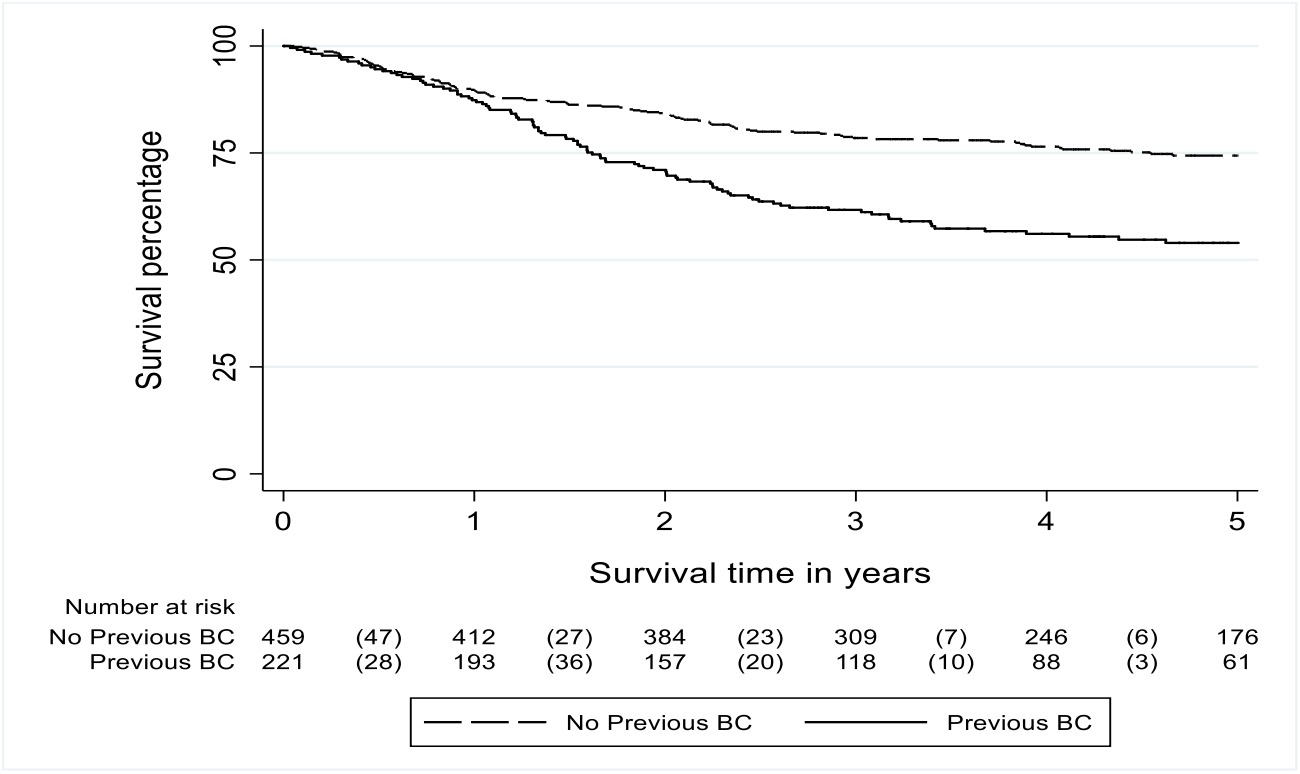
Previous Breast Cancer Histology	Number of Cases
Infiltrating duct carcinoma, NOS	169
Lobular carcinoma, NOS	30
Tubular adenocarcinoma	8
Intraductal carcinoma, noninfiltrating, NOS	8
Infiltrating duct and lobular carcinoma	7
Mucinous adenocarcinoma	<5
Lobular carcinoma in situ, NOS	<5
Infiltrating duct mixed with other types of carcinoma	<5
Adenocarcinoma NOS	<5
Comedocarcinoma NOS	<5
Intraductal papillary adenocarcinoma with invasion	<5
Invasive micropapillary carcinoma of the breast	<5
Paget disease and intraductal carcinoma of breast	<5
Metaplastic carcinoma, NOS	<5
Heamangiosarcoma	<5
Neoplasm, malignant	<5
Carcinoma NOS	<5
Unknown	<5

Supplementary Table 3: Previous breast cancer diagnosis prior to be diagnosed with a breast sarcoma

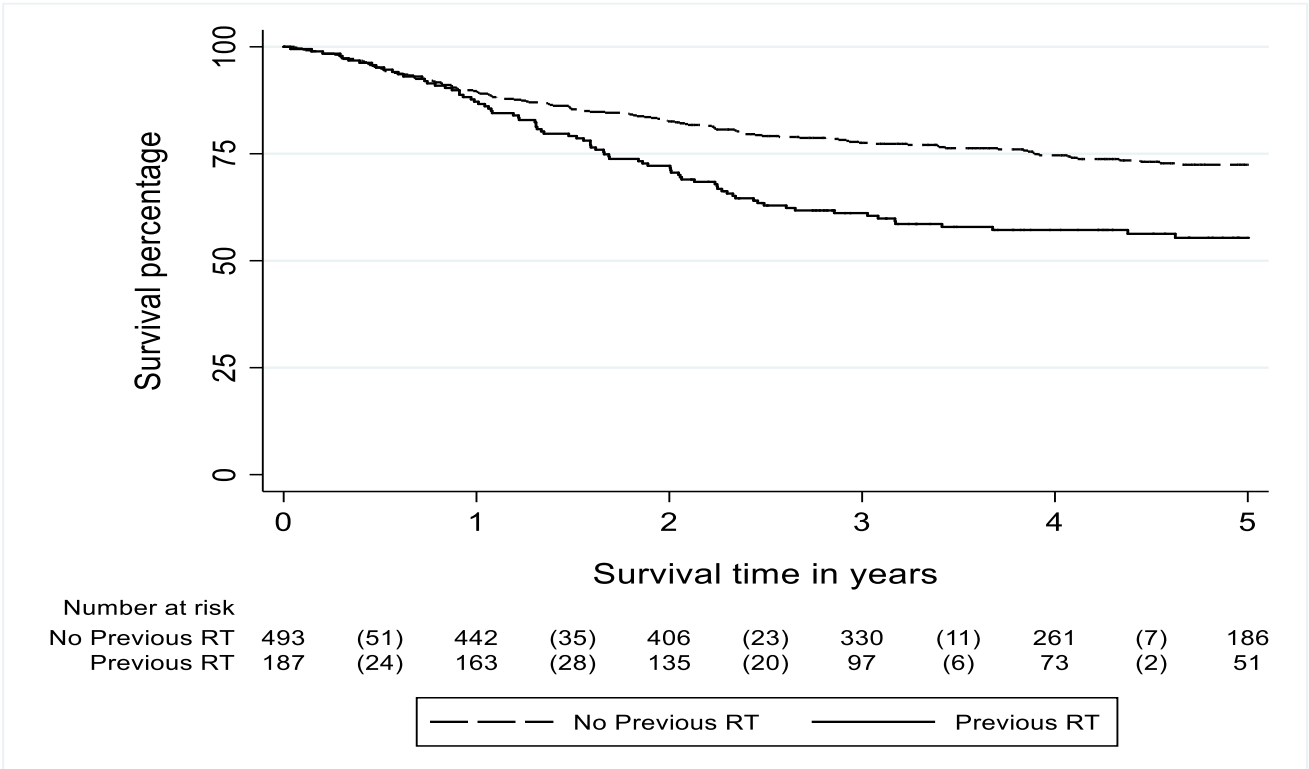
Morphology	Previous Radiotherapy	Number
Vascular Tumour	Yes	177
Vascular Tumour	No	61
Phyllodes	Yes	<5
Phyllodes	No	~350
Other Morphology	Yes	9
Other Morphology	No	84

Supplementary Table 4: Table showing the breakdown of the number of radiation induced sarcoma

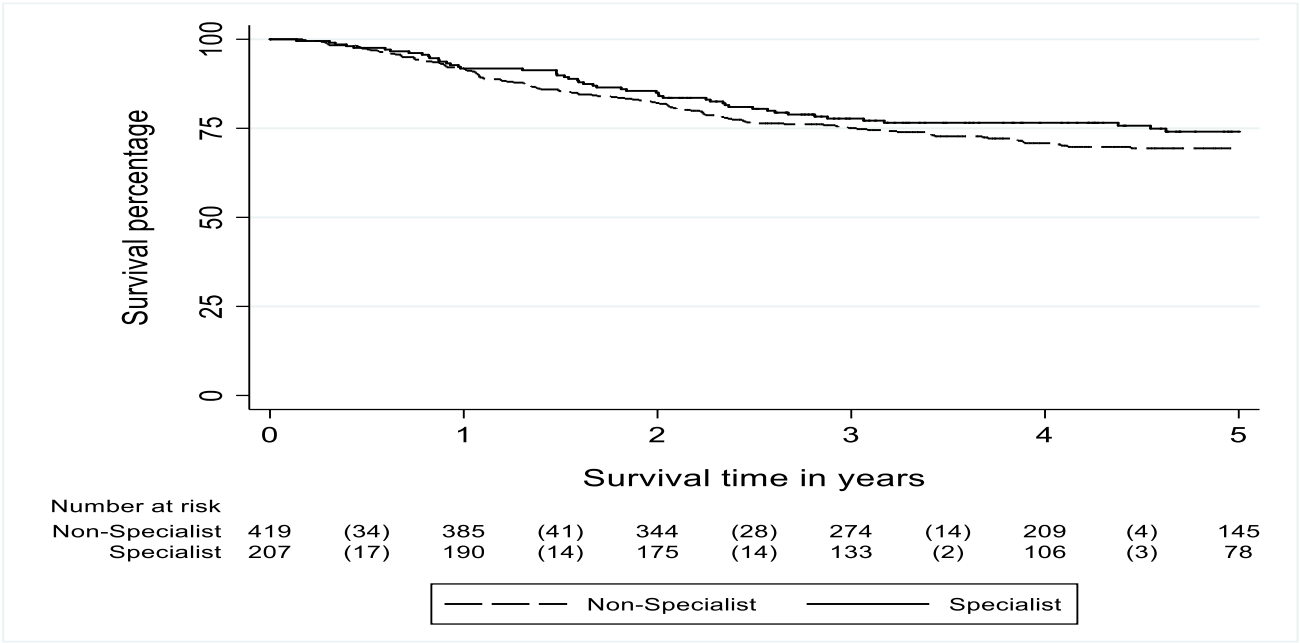
A


Survival percentage
0
25
50
75
100
0
1
2
3
4
5
Survival time in years
Number at risk
No Previous BC 459 (47) 412 (27) 384 (23) 309 (7) 246 (6) 176
Previous BC 221 (28) 193 (36) 157 (20) 118 (10) 88 (3) 61
No Previous BC
Previous BC

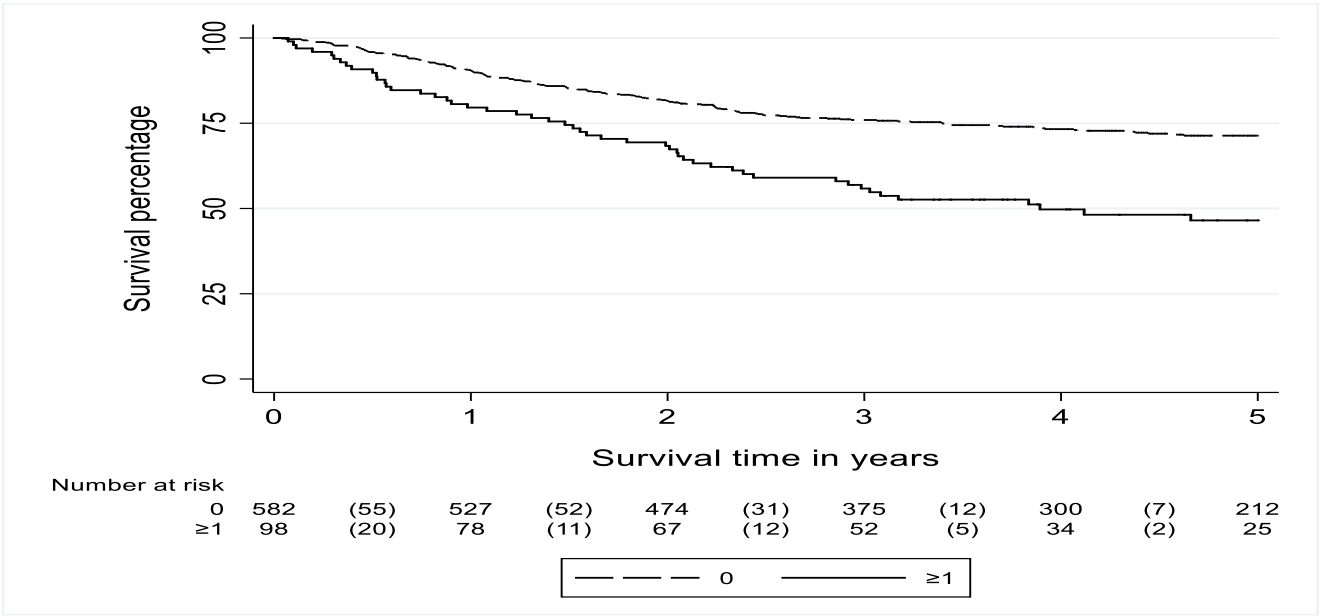
B


Survival percentage
0
25
50
75
100
0
1
2
3
4
5
Survival time in years
Number at risk
No Previous RT 493 (51) 442 (35) 406 (23) 330 (11) 261 (7) 186
Previous RT 187 (24) 163 (28) 135 (20) 97 (6) 73 (2) 51
No Previous RT
Previous RT

C



D



Supplementary Figure 1. Unadjusted 5 year survival estimate stratified by; **A:** history of previous breast cancer (BC) (Log rank test, P<0.05) **B:** history of previous radiotherapy (Log rank test, P<0.05) **C:** location of the first operation for all morphologies. There is trend in favour of surgery in the specialist hospital (log-rank test 0.24) **D:** Charlson Comorbidity Index (CCI). Patients with a CCI score ≥ 1 had double the risk of mortality (log-rank test P<0.05).