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10-Year axillary recurrence in the RACS SNAC1 randomised trial of sentinel lymph node-based management versus routine axillary lymph node dissection

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A B S T R A C T

Background: Sentinel node-based management (SNBM) is the international standard of care for early breast cancer that is clinically node-negative based on randomised trials comparing it with axillary lymph node dissection (ALND) and reporting similar rates of axillary recurrence (AR) without distant disease. We report all ARs, overall survival, and breast cancer-specific survival at 10-years in SNAC1.

Methods: 1.088 women with clinically node-negative, unifocal breast cancers 3 cm or less in diameter were randomly assigned to either SNBM with ALND if the sentinel node (SN) was positive, or to SN biopsy followed by ALND regardless of SN involvement.

Results: First ARs were more frequent in those assigned SNBM rather than ALND (11 events, cumulative risk at 10-years 1·85%, 95% CI 0·95–3.27% versus 2 events, 0·37%, 95% CI 0·08–1·26%; HR 5·47, 95% CI 1·21–24·63; p = 0·013). Disease-free survival, breast cancer-specific survival, and overall survival were similar in those assigned SNBM versus ALND. Lymphovascular invasion was an independent predictor of AR (HR 6·6, 95% CI 2·25–19·36, p < 0·001).

Conclusion: First ARs were more frequent with SNBM than ALND in women with small, unifocal breast cancers when all first axillary events were considered. We recommend that studies of axillary treatment should report all ARs to give an accurate indication of treatment effects. The absolute frequency of AR was low in women meeting our eligibility criteria, and SNBM should remain the treatment of choice in this group. However, for those with higher-risk breast cancers, further study is needed because the estimated risk of AR might alter their choice of axillary surgery.

1. Introduction

Sentinel node-based management (SNBM) has become the international standard-of-care for managing the axilla in clinically node-negative breast cancer and was widely adopted before randomised evidence about cancer outcomes became available [1].

Most randomised controlled trials (RCTs) of SNBM, including SNAC1 [2–6], and apart from NSABP B32, [7] were primarily designed to detect differences in arm morbidity, with cancer outcomes as secondary endpoints. However, multiple series, and subsequently RCTs, have reported axillary recurrence (AR) rates lower than expected from the known false negative rates of SNBM (5·5–16% in the RCTs).

Most of these series had short follow-up times (median <5 years) [8], and frequently reported only ARs that were isolated or without distant disease. This is standard and reasonable in RCTs of drugs, in which a local or regional recurrence is regarded as less important than a distant recurrence. However, this is not appropriate when comparing local treatments for managing the axilla. In trials comparing management

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strategies for the axilla, all ARs are important for the affected patient, whether they occur first, in isolation, or with other sites of recurrence. We report here on pre-specified analyses of AR and other cancer-related outcomes in the SNAC1 trial after a minimum follow-up of 10 years.

2. Methods

1088 women with primary breast cancers that were unifocal, 3 cm or less in diameter, and clinically node negative were randomly assigned to either SNBM (sentinel node biopsy [SNB} followed by ALND only if the SN was positive), versus SNB followed by routine axillary lymph node dissection (ALND) regardless of SN involvement. We previously reported details of the SNB technique, pathology assessment, associated treatments, and effects on arm morbidity [2,9]. The study protocol specified follow-up for 10 years after randomisation of the last participant.

2.1. Statistical analysis

Change in arm volume was the primary outcome and basis of sample size calculations for SNAC1. ARs, breast cancer-specific survival, and overall survival were pre-specified as important secondary cancer-related outcomes. All analyses were performed by intention-to-treat and included all participants randomised. Comparisons of time-to-event endpoints, including overall survival and disease-free survival, were based on the log-rank test. We pre-specified that the main subgroup of interest was women with a negative SNB; the trial design allowed this subgroup to be identified in both randomly assigned treatment groups (women assigned ALND underwent sentinel biopsy before their ALND). We expected that any differences in outcomes caused by differences in the randomly assigned treatment would be observed in participants with a negative SNB, because those with a positive SN had an ALND in both treatment groups.

Associations between AR and other features were examined with multinomial logistic regression analyses, with and without adjustments for treatment group.

We expected deaths and recurrences outside the axilla (breast, chest wall, and distant) to be competing risks that would outnumber ARs. We therefore pre-specified time-to-event analyses for these outcomes would use cumulative incidence methods [10] and regression modelling in the presence of competing risks [11,12].

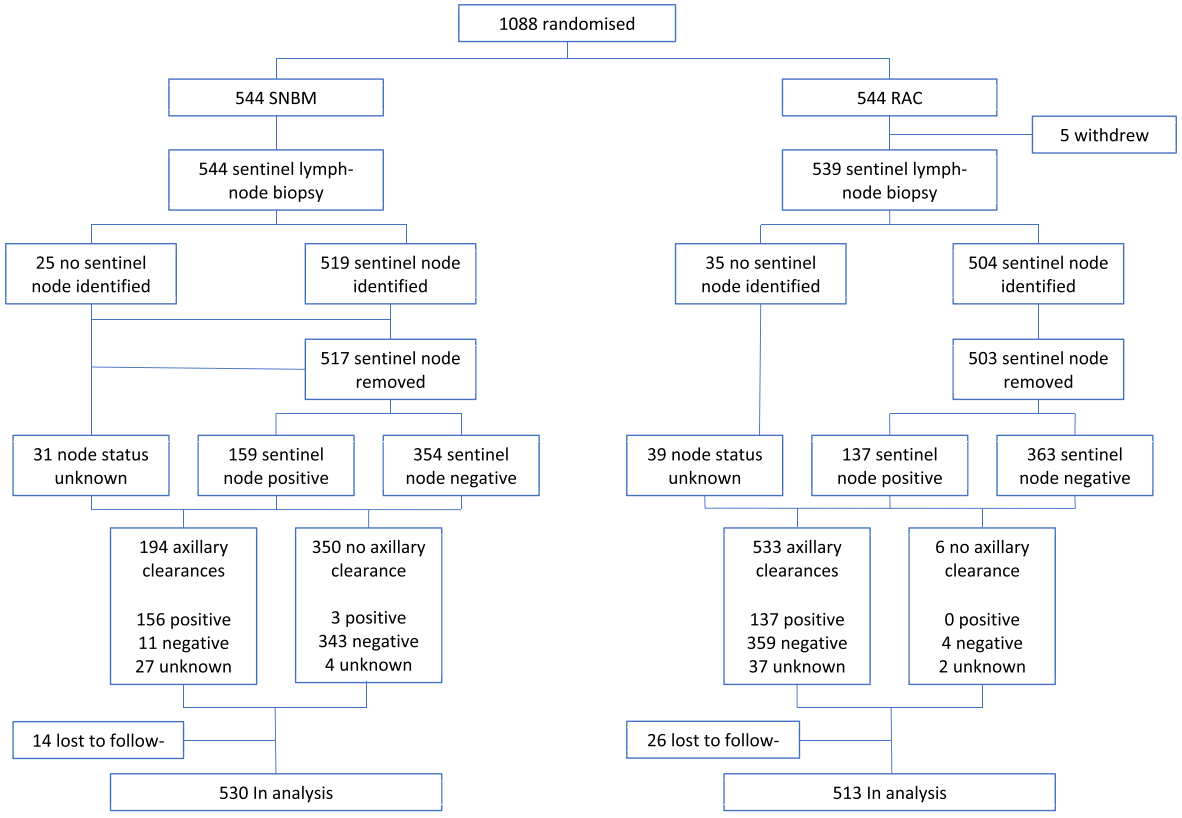
3. Results

1088 women, recruited by 51 surgeons at 31 sites in Australia and New Zealand, were randomly assigned (1:1) to SNBM or ALND (Fig. 1). The 2 groups were well balanced for age, type of presentation, tumour characteristics, and other treatments. Only 13% of participants were treated with mastectomy. Use of post-operative adjuvant systemic therapies was similar in the 2 groups (Table 1). Post-operative axillary radiation therapy was used in 14 assigned SNBM and 5 assigned ALND.

The median follow-up time for this analysis was 10 years (IQR 1·3–12). Follow-up was until death or >9·5 years in 1046 (96%) participants.

3.1. SN identification and performance

SN identification included peritumoral injections of both radiotracer and blue dye (Patent Blue V) in 953 participants (88%), and blue dye alone in 120 (11%). The mean number of lymph nodes removed across all participants was 1·8 for SNB and 16·0 for ALND. The false negative rate for SNB in the group assigned ALND was 5·5% (8/145 with positive nodes at ALND, including 3 with removal of a node that was palpable at SN biopsy, but not radioactive or blue).



Sentinel-lymph-node-base management: Lymph node biopsy followed by later axillary clearance if sentinel node was positive or not found.
Routine axillary clearance: Sentinel-node biopsy followed by immediate axillary clearance irrespective of sentinel node status.

Fig. 1. Study profile.

Table 1
Baseline characteristics.

		SNBM (N = 544)	ALND (N = 544)	ALL
SN biopsy status	Negative	381 (70%)	395 (73%)	776 (71%)
	Positive	157 (29%)	136 (25%)	293 (27%)
	Unknown	6 (1%)	13 (2%)	
Primary surgery	Wide local excision	472 (87%)	470 (86%)	942 (87%)
	Mastectomy	72 (13%)	69 (13%)	141 (13%)
	Unknown	0 (0%)	5 (1%)	
Histologic grade of tumour	1	175 (32%)	167 (31%)	342 (31%)
	2	232 (43%)	235 (43%)	467 (43%)
	3	131 (24%)	132 (24%)	263 (24%)
	Unknown	6 (1%)	10 (2%)	
Lymphatic invasion	Yes	111 (20%)	120 (22%)	231 (21%)
	No	431 (79%)	416 (76%)	847 (78%)
	Unknown	2 (0%)	8 (1%)	
Estrogen receptor status	Yes	450 (83%)	432 (79%)	882 (81%)
	No	90 (17%)	100 (18%)	190 (17%)
	Unknown	4 (1%)	12 (2%)	
Progesterone receptor status	Positive	366 (67%)	343 (63%)	709 (65%)
	Negative	137 (25%)	148 (27%)	285 (26%)
	Unknown	41 (8%)	53 (10%)	
Adjuvant radiation therapy	Yes	482 (89%)	466 (86%)	948 (87%)
	No	62 (11%)	73 (13%)	135 (12%)
	Unknown	0 (0%)	5 (1%)	
Axillary irradiation	No	472 (87%)	464 (85%)	936 (86%)
	Yes	14 (3%)	5 (1%)	19 (2%)
	Unknown	58 (11%)	75 (14%)	
Adjuvant endocrine therapy	Yes	372 (68%)	367 (67%)	739 (68%)
	No	172 (32%)	177 (33%)	349 (32%)
Adjuvant chemotherapy	Yes	169 (31%)	164 (30%)	333 (31%)
	No	375 (69%)	380 (70%)	755 (69%)

Note: N (%) shown unless indicated otherwise.

3.2. AR

First ARs were more frequent among those assigned SNBM rather than ALND (11 versus 2, cumulative risk at 10 years 1·85%, 95% CI 0·95–3.27% versus 0·37%, 95% CI 0·08–1·26%; hazard ratio 5·47, 95% CI 1·21–24·63; $p = 0·013$; see Fig. 2). Of these 13 ARs, 5 (38%) occurred as an isolated first event, 5 were diagnosed together with distant metastases, and 3 were diagnosed together with both local recurrence and distant metastases. AR occurred as a subsequent event after a previous diagnosis of distant metastasis in 1 participant (assigned SNBM).

In the subgroup with a negative SN biopsy, ARs occurred in 8 assigned SNBM (cumulative risk at 10 years 1·85%, 95% CI 0.83–3.62%) versus 0 assigned ALND ($p = 0·004$, Table 2). Tests for heterogeneity provided no evidence that the effect of SNBM versus ALND on first AR differed in subgroups defined according to baseline characteristics. (Supplementary Table 1).

Three of 11 SNBM participants with AR already had an ALND for lymph node involvement at SNB. There were no ARs among those assigned ALND who had a negative SNB, all of whom had ALND. All 5 participants with AR after ALND (including 2 in the ALND group) had over 15 lymph nodes removed at their initial surgery.

The median time (range) to any AR was 3·5 years (1.0–10), to an isolated AR was 2·8 years (1·1–9·2), and to AR with distant metastases was 5·8 years (1–10·2). Five of the 11 first ARs in the SNBM group occurred beyond 5 years, as did the single AR that occurred as a second or subsequent event (Fig. 2).

Associations between the risk of AR and other features, including baseline characteristics; methods for identifying SNs, breast surgery, and ALND; histopathological features; and, use of adjuvant therapies are

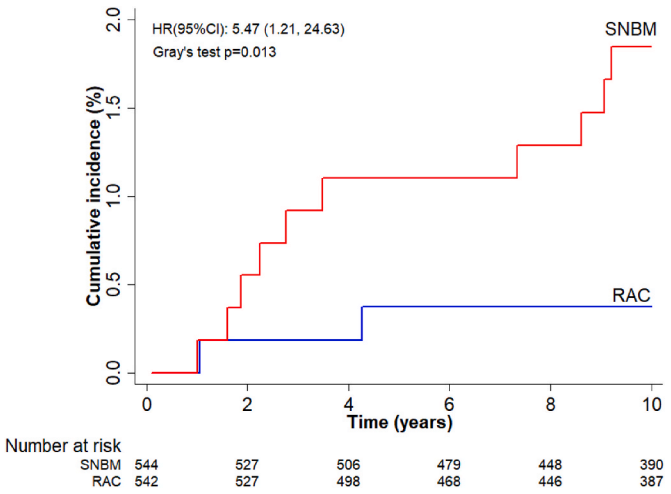


Fig. 2. Cumulative incidence curve of time to first axillary recurrence, by treatment arm.

Table 2
Cumulative incidence of first ARs.

Treatment	N	First ARs[a]	Competing risk events[b]	Censored	Cumulative incidence (%) (95% CI)	P-value[c]
5-year analysis						
SNBM	544	6	45	493	1·10 (0·46–2·29)	0·16
ALND	542	2	52	488	0·37 (0·08–1·26)	
10-year analysis						
SNBM	544	11	116	417	1·85 (0·95–3·27)	0·013
ALND	542	2	110	430	0·37 (0·08–1·26)	
10-year analysis by SNB status[d]						
SNB-negative						
SNBM	381	8	71	302	1·85 (0·83–3·62)	0·0041
ALND	394	0	68	326	0·00 (0·00–NA)	
SNB-positive						
SNBM	157	2	44	111	1·27 (0·25–4·16)	0·89
ALND	136	2	40	94	1·48 (0·29–4·80)	

[a] First AR defined as the first documented recurrence in the axilla, regardless of concurrent recurrence at another site.
[b] Competing risk event defined as death prior to any recurrence, or first recurrence at sites other than the axilla.
[c] Gray's test for equality of cumulative incidence functions.
[d] Treatment by SNB status interaction p-value <0·0001.

shown in Supplementary Table 1. There was no compelling statistical evidence that any of these characteristics modified the effect of SNBM versus ALND on the risk of AR.

Baseline characteristics associated with the risk of AR included palpable tumour ($p < 0{\cdot}001$) and diabetes ($p = 0{\cdot}015$).

SNB and surgical techniques were not associated with the risk of AR, including the method of SN mapping, whether ALND was immediate or delayed, the number of axillary lymph nodes removed, and the type of breast surgery.

Pathological features that were associated with the risk of AR included oestrogen receptor status ($p = 0{\cdot}002$), histologic grade ($p < 0{\cdot}001$) and lymphovascular invasion ($p < 0{\cdot}001$).

There was modest evidence that use of subsequent adjuvant therapies was associated with the risk of AR: adjuvant endocrine therapy ($p = 0{\cdot}004$), adjuvant axillary radiation ($p = 0{\cdot}05$) and adjuvant chemotherapy ($p = 0{\cdot}08$).

3.3. Disease-free and overall survival

Disease-free survival and overall survival were similar among those assigned SNBM versus ALND. Disease-free survival rates at 10 years were SNBM 79% versus ALND 82%, HR 1·12, 95% CI: 0·87–1·45; $p = 0.36$, see Fig. 3). Overall survival rates at 10 years were SNBM 84% versus ALND 87%, HR 1·20, 95% CI: 0·89–1·61; $p = 0{\cdot}22$, see Fig. 4).

Median survival after an isolated AR was 2.5 years (range 0·8–8·1). Median survival after an AR diagnosed together with distant metastases was 1.4 years (range 0.0–2·8). Five of 13 participants with AR were alive at the end of the study, and only 1 had survived more than 5 years after AR.

4. Discussion

ARs were more frequent after SNBM than ALND for small, unifocal breast cancers in SNAC1; this differs from previously published randomised trials. This was despite the fact that SNAC1 had the lowest false negative SNB rate (5·5%) of any randomised trial reporting this endpoint in the ALND arm [2,4–6,13]. Evidence that AR rates were increased by SNBM is strengthened by this difference being most apparent among those with a negative SNB, in whom treatment of the axilla actually differed according to the study design.

AR is uncommon after a well-performed axillary dissection, reported in 1% or fewer with stage 1 or 2 disease [14,15]. However, AR is also an adverse prognostic sign, with a reported 5-year survival rate of 24% compared with 60% for ipsilateral breast recurrence [16]. SNAC1 had a

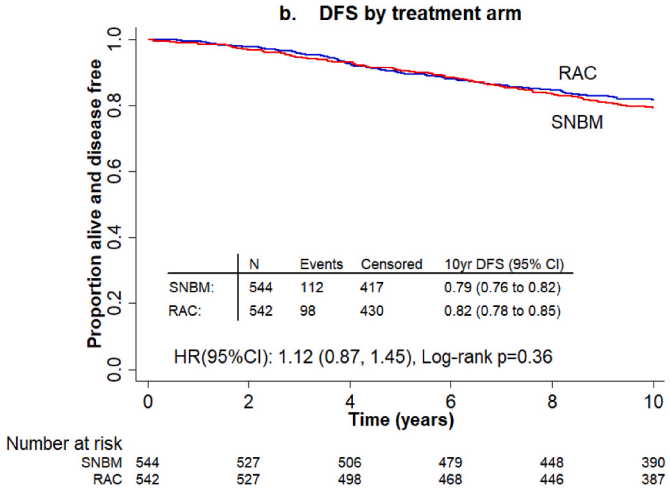


Fig. 3. Kaplan-Meier estimate of disease-free survival at 10 years, by treatment arm.

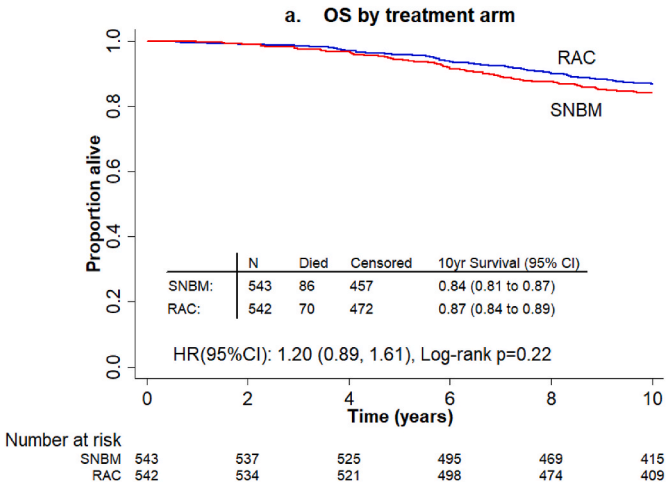


Fig. 4. Kaplan-Meier estimate of overall survival at 10 years, by treatment arm.

low frequency of AR in the ALND group (0·38%), and a high mean number of nodes was removed, supporting the thoroughness of axillary dissection. The poor survival after AR in SNAC1 raises the controversial hypothesis that AR might be a source of metastatic disease, and perhaps therefore a cause of a bad outcome, rather than just an indicator of 'bad biology'. The latter view has held sway since NSABP B04 was reported [17]. However, recent large trials of regional nodal radiation that showed improved local control, also showed improved distant disease-free survival, and in some cases overall survival, raising this question once again [18–20].

AR is also uncommon after SNBM for smaller breast cancers, with reported rates of 2% or less [21]. A meta-analysis of 50 studies involving over 26,000 participants reported the risk of AR at 5 years was 1%, and at 8 years was 1·4% [22]. However, the median follow-up in this meta-analysis was only 3 years, not all ARs were reported in some studies, and over 75% of participants had T1 tumours. As for axillary dissection, AR after SNBM was an adverse prognostic sign, even as an isolated event, with median survival of 3·8 years [23]. The 10-year AR rate in the SNBM group of SNAC was 2%, slightly higher than reported above, and reflecting 10 years median follow-up, and inclusion of all axillary first events, not just those that were isolated.

There are 5 major biases in observational studies of SNBM versus ALND. These are: (i) treatment selection bias, (baseline characteristics of those selected for SNBM versus ALND are usually biased in favour of better cancer outcomes for SNBM, and multivariable analyses are unable to fully account for these biases); (ii) variable quality of follow-up; (iii) short duration of follow-up (50% of locoregional recurrences occur beyond five years [21,24]); (iv) variable definitions of 'SNB alone' (e.g., a recent series in which the group classified as having 'SNB alone' had removal of 5 or more 'SNs' in 29%, and 10 or more in 3% [23]); and (v) the baseline characteristics of those included (predominantly small, unifocal breast cancers). These factors mean that observational studies underestimate recurrence rates after SNBM.

Variable definitions of AR are also problematic: some studies reporting only first ARs, or only first ARs without coincident distant metastasis. For example, in the initial report of the Swedish SNBM cohort, isolated AR accounted for less than half of all ARs, despite short follow-up [25]. A subsequent report with longer follow-up reported only on first ARs in the absence of distant metastasis, and despite this the AR rate at 10 years was 2·2% [24].

This focus on first recurrences in the axilla without distant metastasis comes from randomised trials of adjuvant therapies that typically use a hierarchical approach to first events with more than one site of recurrence. These assign greater importance to distant metastasis than to a local or regional recurrence, so that if both regional and distant events

are diagnosed, then they are counted and reported as a distant first event. This underestimates the total number of ARs. This is appropriate for trials of adjuvant systemic therapy, but not for trials of axillary treatment (surgery or radiotherapy). All ARs are important to those affected, whether they are isolated or occur together with recurrence elsewhere. All ARs can cause local symptoms, sometimes severe, for example lymphoedema or brachial plexopathy, and requiring further axillary therapy. Studies of axillary treatments should report all ARs.

Our study reports all ARs, but our analysis focuses on first ARs, because treatments after recurrence are not randomised and may influence subsequent events. In SNAC1, only 5 of all 13 (38%) first ARs were isolated (diagnosed in the absence of metastatic disease). The frequencies of AR at 10 years by treatment group in SNAC1 (SNBM 1·85% vs 0·37% ALND) are consistent with those reported in NSABP B32 (SNBM 0·5% vs 0·2% ALND) [26], the largest randomised trial of SNBM versus ALND. NSABP B32 is the only randomised trial of SNBM versus ALND that was designed and powered to determine non-inferiority in terms of overall survival [26].

A meta-analysis of published results from 8 RCTs including 8560 participants (assigned SNBM 4301 vs ALND 4259) reported that there was 'no statistical difference' in AR rates [15]. However, the frequency of AR was higher with SNBM than ALND (OR = 1·65, 95% CI: 0·77–3·56), even though not all ARs were reported in these trials. As in SNAC1, there were no apparent effects on disease-free survival (HR = 1·00, 95% CI: 0·88–1·14) or overall survival (HR = 1·07, 95% CI: 0·90–1·27). This meta-analysis did not include SNAC1, but the pooled results of trials that reported on the subgroup with a negative SNB, as did SNAC1, showed a HR for overall survival of 1·19 (95% CI: 0·97–1·46), almost identical to the 1.20 reported here for SNAC1. The upcoming Early Breast Cancer Trialists Collaborative Group meta-analysis of individual patient data with updated follow-up from all available randomised trials is eagerly awaited.

The frequency of AR after SNBM is low. However, the morbidity of ALND has diminished over time, perhaps due to the development of more careful operative techniques resulting in less damage to lymphatics around and above the axillary vein, improved theatre protocols, use of prophylactic antibiotics, and fewer infective and other complications of ALND. Whatever the reasons, the frequency of significant arm swelling at 5 years in SNAC1 was only 5% in the ALND group, and 1·7% in the SNBM group (defined as an increase in arm volume of 15% or greater compared with the contralateral arm) [9]. Using a lower threshold of a 10% increase in arm volume, the frequencies were 11% and 4%, respectively. SNAC1 was primarily designed to determine the effects of SNBM versus ALND on arm swelling, discomfort, and disabilities with careful measurement of arm volumes based on multiple arm diameters and detailed assessments of patient-rated outcomes for 5 years after surgery. Perhaps of greater importance, only 1·1% of women rated their arm swelling as severe [27]. These well-established findings of reduced arm swelling and improved patient-rated outcomes compared with ALND need to be considered in the light of our new finding that ARs were increased by SNBM.

Randomised trials of SNBM have primarily included women with small, 'good biology' breast cancers. However, SNBM is now routinely used for almost all women with clinically negative nodes, and ALND is now often omitted for those with only micrometastases on SNB [28,29]. However, many series have reported AR rates that are 3–7 times higher for breast cancers that are high-grade, hormone receptor negative [21,22,24], or have micrometastases in SNs [21,22]. Even if the false negative rates (defined as the percentage with a positive axillary node not detected by SNB) were similar for those with larger tumours, or following neoadjuvant therapy, which in many series they are not [30], the absolute proportions with involved nodes left in the axilla after negative SNB would be higher, because those with tumours that are larger, or have other adverse prognostic features, are more likely to have positive axillary lymph nodes. The implications of our findings in SNAC1 are that higher-risk tumours (expected to have higher rates of axillary lymph node involvement) are also likely to have higher rates of both false-negative SN biopsies, and ARs.

Reported AR rates increase with longer follow-up, especially if ARs diagnosed together with distant metastases are included (median time to recurrence 5.8 years with distant metastases vs 2·8 years for isolated AR in SNAC1). In the Swedish series, the median time to recurrence was 4 years for the whole cohort; 7.5 years for luminal A tumours, and 1.8 years for hormone receptor-negative tumours [24]. In a large French retrospective series, the median time to AR was 43 months, despite median follow-up of only 55 months [21].

Lower rates of AR and/or false-negative SNB have also been reported when more than two or three nodes were removed, or using additional preoperative axillary imaging with ultrasound. [13].

Our findings from SNAC1 have important implications. When clinicians estimate the frequency of an AR after SNBM, they should consider doubling the rates reported in most other studies, which include only first ARs. After accounting for this, and considering other factors, such as large tumour size, multifocality, high tumour grade, negative hormone receptor status, and lymphovascular invasion, there may be many clinical scenarios where the risk of AR with SNBM is similar to the risk of lymphoedema with ALND. Women with these higher-risk features were the target population for SNAC2, our following randomised trial planned for reporting in 2025 after minimum follow-up of 10 years. In the meantime, women with early breast cancer, particularly those at elevated risk of lymph node involvement and AR with SNBM, should be informed of the long-term outcomes of SNAC1. We believe that some might prefer and choose ALND over SNBM in this setting.

5. Conclusion

When all first axillary events were considered, and in contrast to other previously reported randomised trials in early breast cancer with clinically small, unifocal tumours, ARs were more frequent among women assigned SNBM than ALND. Given the importance of AR for those affected, whether in isolation or together with distant metastases, we recommend that studies of axillary treatments should report all ARs to give a more accurate indication of outcomes. Using this approach, the absolute frequency of AR in SNAC1 over 10 years was low, and not expected to change decision-making in women meeting the eligibility criteria for SNAC1. However, for those with higher-risk breast cancers, further study is needed because the frequency of AR might alter their choice of axillary surgery.

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Ethical approval

The Protocol was approved by the Human Research Ethics Committees (HREC) of each participating institution, with Lead HREC approval from The University of Sydney HREC. Written informed consent was obtained from all participants.

Declaration of competing interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2023.06.009.

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