Sentinel-lymph-node-based management or routine axillary clearance? Three-year outcomes of the RACS Sentinel Node Biopsy versus Axillary Clearance (SNAC) 1 trial

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Synopsis

We compared sentinel-lymph-node based management (SNBM) versus routine axillary clearance (RAC) for women with early breast cancer in a large scale randomised trial. The benefits of SNBM over RAC persisted after 3 years of follow-up.

Abstract

Purpose

We sought to determine whether the benefits of sentinel-node-based management (SNBM) over routine axillary clearance (RAC) at 1 year persisted to 3 years of follow-up.

Methods

1088 women with clinically node negative breast cancer were randomly assigned to SNBM versus RAC. Upper limb volume, symptoms and function were assessed at 1, 6, 12, 24 and 36 months after surgery objectively with upper limb measurements by clinicians, and subjectively by patients' using validated self-rating scales.

Results

Upper limb volume increased in both groups over the first 2 years and differed between the two groups all time points beyond 1 month ($P<0.02$), but then plateaued. Upper limb swelling was no worse in women who had axillary clearance as two-stage procedure than in women assigned RAC as a one-stage procedure. Upper limb volume had increased 15% or more in 6.0% at 6 months and 17.6% at 3 years in those assigned RAC versus 4.2% and 11.9% in those assigned SNBM. Reductions in upper limb movement were also greater with RAC than SNBM over 6 months, but improved and were similar in the two groups from 1 to 3 years. Subjective ratings of upper limb swelling, symptoms, dysfunction, and disability over 3 years were worse in the RAC group. Upper limb swelling at 3 years was rated severe by few women (1.1%), but moderate by 9.4% in the RAC group and 2.5% in the SNBM group ($P<0.001$).

Conclusions

The benefits of SNBM over RAC persist 3 years after surgery.

Introduction

Axillary lymph node status is an important determinant of prognosis and adjuvant therapy in women with early breast cancer. The Sentinel Node Biopsy versus Axillary Clearance (SNAC1) trial of the Royal Australasian College of Surgeons compared upper limb morbidity in 1088 women with clinically node-negative early breast cancers of up to 3 cm in diameter who were randomly assigned to either sentinel-lymph-node based management (SNBM) or routine axillary clearance (RAC). Women in the SNBM group had axillary clearance if the sentinel node was not located or if positive nodes were found on sentinel node biopsy. One year after surgery, objectively measured upper limb swelling and subjectively measured upper limb symptoms were less in the SNBM group, particularly in women who did not require subsequent axillary clearance [1]. Upper limb swelling increased with time after surgery in both groups to one year, reinforcing the need for continued follow-up. This report describes changes in upper limb volume, movement, and symptoms out to three years after surgery.

Methods

Details of SNAC1 have been published previously [1]. In brief, 1088 women with clinically unifocal breast cancers up to 3 cm in diameter and clinically negative lymph nodes were randomly assigned to either sentinel-node-biopsy-based management (SNBM: sentinel-lymph node biopsy, with no further surgery if the sentinel node biopsy was negative and axillary clearance if the sentinel node biopsy was positive or the sentinel lymph node biopsy was unsuccessful), or routine axillary clearance (RAC: sentinel lymph-node biopsy followed by immediate axillary clearance).

As recruitment for the SNAC trial occurred before publication of results from the ASCOG Z011 trial, a positive sentinel node was regarded as a sentinel node with any

metastasis (isolated tumor cells, micrometastases or macrometastases). Exclusion criteria included prior breast surgery, age <18 years, pregnancy, allergy to blue dye or radioisotope, or evidence of metastatic disease. The baseline characteristics of the two treatment groups were well balanced, as previously reported [1]. Neither group underwent specific postoperative upper limb rehabilitation. Importantly, in each group wide local excision and subsequent radiotherapy was used to treat 70% of the cancers in each group [1]. Radiation fields applied after breast conservation were similar in both the RAC and SNBM groups.

All patients gave written informed consent. The study protocol was approved by the human research ethics committees of the participating institutions and was undertaken in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines (ARCTRN12605000357651).

Sentinel node biopsy

All women had an initial sentinel node biopsy, which used lymphoscintigraphy and peri-tumoral injection with antimony sulphide colloid combined with injection of patent blue V dye (89%) or with patent blue V dye alone (11%). All lymph nodes judged hot and/or blue were removed. Any other lymph nodes that were clinically suspicious at sentinel node biopsy were also removed as part of the sentinel node biopsy procedure. Women in the RAC group then had a standard axillary clearance of the level I and II lymph nodes. Women in the SNBM group had no further axillary surgery if their nodes were negative. If any node was positive for cancer or a sentinel node was not found, then an axillary clearance was performed. In most cases, when a positive axillary node was found, the axillary clearance was performed as part of a second procedure; if intraoperative histopathology was available, the finding of a positive node could be followed immediately by axillary clearance as part of the same

operation, although this occurred in only a few cases. Pathology procedures have been reported [1].

Outcome assessment

Women were assessed at baseline before surgery, and then at 1 month, 6 months, 1 year, 2 years and 3 years after surgery. Upper limb volume was estimated by the formula for truncated cones based on six measurements of upper limb circumference at 10 cm intervals. A previous publication by one of the authors has demonstrated a highly significant correlation between circumferential and volumetric upper limb measurements ($P<0.0001$ in the Australian setting, particularly when a narrow measuring tape is used, as in this trial [2]. While volumetric methods may be more precise, upper limb measurement was readily applicable in trial centres and use of this technique unlikely to lead to any differential bias between the groups, as the same measures were used in all cases. Upper limb swelling was expressed as the percentage change in volume from baseline; the percentage of women who developed a 15% or greater increase in upper limb volume from baseline was also analysed. Shoulder movement was assessed by the degrees of lateral abduction and forward flexion between the humerus and the lateral chest wall, with elbow extended and thumb pointing forward, measured with a goniometer (Rolyan; Smith and Nephew Inc.). Subjective upper limb symptoms were measured with the SNAC Study Specific Scales (SSSS) [3], including 15 items assessing seven symptoms, three dysfunctions, four disabilities, and difficulty sleeping, each rated from 0 (no trouble at all) to 10 (worst I can imagine), and averaged to obtain an overall score (from 0 to 10).

Statistical analysis

The primary measure of effect pre-specified before unblinding of the trial was a comparison of the percentage change in objectively measured upper limb volume

between the group assigned SNBM and the group assigned RAC done by intention to treat. Secondary endpoints included the proportion of women with an increase in upper limb volume from baseline of 15% or more. The SNBM group includes women who had sentinel lymph node biopsy only, and women who had a subsequent axillary clearance because the sentinel node was positive. Secondary analyses compared the subgroups of women assigned SNBM and RAC who were node-negative: the former had sentinel node biopsy only, the latter sentinel node biopsy and immediate axillary clearance. Patient self-ratings were assessed as the differences between treatment groups in mean changes in scores on each scale between baseline and 3 years. The sample size of 1100 women was calculated to give over 80% power to detect a 6% absolute difference in the rates of significant upper limb swelling with two-sided *P* value of 0.05 and over 90% power to detect one point difference on the SSSS with a two-sided *P* value of 0.01.

Results

Results of the surgery have been reported [1]. Upper limb measurements were completed for 99% of women in both groups. Mean percentage changes in upper limb volume from baseline are shown in Figure 1. Upper limb volume increased in both groups over the first 2 years of follow-up, and differences between the randomly allocated groups were statistically significant at all time points beyond 1 month ($P<0.02$, Figure 1a). Comparison of the lymph-node-negative subgroups showed greater differences in upper limb volume (Figure 1b). Upper limb swelling was no worse in women who were assigned SNBM but required a subsequent axillary clearance ($n=125$) than in women assigned RAC ($P=0.56$, Figure 1c).

The proportions of women with an increase in upper limb volume of 15% or more from baseline almost tripled from 6 months to 3 years in those assigned RAC and

those assigned SNBM, and differences between the randomly allocated groups were statistically significant at 1, 2, and 3 years (P<0.02, Table 1). In the subgroup of lymph-node-negative women, the proportions were somewhat lower, but almost twice as many women had a 15% or greater increase in upper limb volume at 3 years in the RAC group than in the SNBM group (15.5% vs 8.3%, P=0.006).

Reductions in upper limb movement were greater with RAC than SNBM over the first 6 months of follow-up, but improved and were similar in the two groups from 12 months to 3 years (Figure 2). Comparisons of the node-negative subgroups gave similar results and conclusions.

Average subjective ratings of swelling, symptoms, dysfunction, and disability over the 3 years of follow-up were low, but consistently worse in the RAC group than the SNBM group, particularly for upper limb swelling, symptoms and the overall average, but less so for dysfunction and disability (Figure 3). Differences between RAC and SNBM were greatest before 6 months, but persisted to 3 years for swelling, symptoms and the overall average. Upper limb swelling was rated severe at 3 years by few women in either group: 6 (1.3%) in the RAC group versus 5 (1.0%) in the SNBM; but was rated moderate by 45 (9.4%) in the RAC group versus 12 (2.5%) in the SNBM group (P<0.001).

The use and choice of interventions for upper limb swelling or symptoms were not specified by the protocol and were left to the discretion of individual surgeons and women. Physiotherapy was used for upper limb symptoms in 215 women in the RAC upper limb and 171 in the SNBM upper limb (odds ratio 1.64, CI 1.28 – 2.11, P<0.001). Compression garments were used by 65 women assigned RACS and by 40 assigned SNBM (OR 1.75, CI 1.16 – 2.65, P=0.008).

The association between objective increases in upper limb volume and subjective ratings of upper limb swelling at 3 years was modest and is shown in Table 2. Only 20 of the 132 women with an increase in upper limb volume of 15% or more rated their upper limb swelling as moderate or severe; the other 40 women who rated their upper limb swelling as moderate or severe had increases in upper limb volume of less than 15%. The missing data consisted of 18 withdrawals, 22 deaths, 20 non-English speakers, 1 patient with dementia, 39 unreturned forms, and the remainder incomplete.

Discussion

Continued follow-up of this large scale randomised trial shows that the previously reported benefits of reduced upper limb swelling and symptoms with SNBM versus RAC persisted to 3 years after surgery. The unique feature of this dataset is that while rates and differences in upper limb volume between the randomly allocated groups increased to 2 years, they then plateaued, both in all women, with data analysed by intention to treat, and in the subgroup of node-negative women. The protocol did not necessitate active intervention for women experiencing upper limb swelling therefore this data suggests that the majority of patients experiencing increasing upper limb volume after axillary surgery will do so within two years of the surgery. Differences in women's subjective ratings of swelling and symptoms followed a similar pattern.

As reported previously [1], the mean number of nodes removed in the SNBM group was 2, compared with 14.6 nodes in the RAC group. This study therefore provides a genuine comparison of a minimalistic approach to axillary assessment (SNBM) versus an adequate axillary clearance including level I and II lymph nodes.

The lymphedema literature is complicated by poor definitions of the condition, varied means of upper limb volume measurements, retrospective analyses of the condition,

and often the information is based on historical cases prior to screening programmes when women presented with more advanced tumours. The SNAC trial is a prospective assessment of both objective measurements and subjective ratings in a cohort where 58% of the cases were screen detected [1].

Previously reported reductions in lateral abduction that were greater in the RAC group than the SNBM group over the first year of follow-up [1] diminished over the subsequent 2 years and were no longer significantly different. Again, no specific intervention was required by the trial protocol if upper limb mobilisation was hampered; therefore, the improvement in upper limb mobility after the first postoperative year, particularly within the RAC group, may occur spontaneously with natural reductions in restriction due to scar tissue settling in the treated axilla. The improved range of movement associated with SNBM seems to be confined to the first 6 postoperative months. Differences in subjective ratings of upper limb dysfunction and disability were even more modest, and also diminished over time.

Of the 1088 women in the study, 878 completed the SSSS (Table 2), a high completion rate that provided a robust basis for the overall comparison of objective measures of upper limb volume and subjective measures of upper limb swelling. About 1 in 6 women had a 15% or greater increase in upper limb volume, but only about 1 in 6 of those women (<3% of the total) were troubled by the increase. However, most women who rated their upper limb swelling as severe had an increase in upper limb volume of 15% or more. This supports the validity of the women's subjective ratings as a true reflection of the difficulties experienced after axillary surgery.

Our results are consistent with those of other trials and a meta-analysis [4–8]. Our previous results showing a difference between the treatment groups at 6 and 12

months after surgery have been confirmed and strengthened by a meta-analysis showing an odds ratio of 0.3 (95% CI, 0.14–0.66) in favour of sentinel node biopsy in relation to upper limb swelling [4]. The current results apply to the two groups of patients analysed by intention to treat. The SNBM group included those patients who had a sentinel node biopsy followed by an axillary clearance because the sentinel node was positive or not located. Therefore, the study provides a real-life estimate of the average benefit for women who undergo SNBM, regardless of whether they subsequently require an axillary clearance. Secondary analyses confirmed that differences between the two groups were greater in the subgroup of node-negative patients, confirming the comparability of our results with those for similar patients in the NSABP-B32 trial [7,8]. This provides a direct comparison of axillary clearance and sentinel-node biopsy alone and further validates SNBM.

Before the trial commenced we chose the 15% increase in upper limb volume from baseline as a prespecified secondary endpoint. This enables a specific comparison of objective upper limb volume changes across the various groups. Various definitions are quoted in the literature [7,8]. Generally, lymphoedema of 10% or more is considered significant, and moderate lymphoedema has been defined as a 20% increase in upper limb volume. We chose an intermediate figure. The percentage of patients with an increase in upper limb volume of this extent rose from 9.6% in the RAC group at 1 year to 17.6% at 3 years. These rates are similar to published rates of lymphedema [11].

The results from clinical trials such as this enable improved information to be provided to patients when they are considering various treatment options. As outlined above, the plateau in upper limb volume 2 years after surgery suggests that estimates of lymphedema rates at 2 years may be an accurate estimate of the long-term rates of

lymphedema after RAC. This is consistent with the results of a long-term cohort study in which 77% of patients with lymphedema developed it within 3 years after RAC [12]. Patients can also be advised that the risk of a significant increase in upper limb volume developing after axillary clearance is about 1 in 6.

Although intra-operative imprint cytology of sentinel nodes was allowed in our protocol, most women with a positive sentinel node had a delayed axillary clearance as a second procedure. There is a perception that a delayed axillary clearance can be more difficult to perform because of axillary scarring following a previous sentinel node biopsy. Whether measured by objective measures or subjective ratings, a prior sentinel node biopsy with subsequent axillary dissection resulted in similar rates of upper limb swelling, symptoms and dysfunction to that with axillary clearance performed as a one-stage procedure, confirming the results of Goyal et al.[13]. Women can be reassured that a second operation does not appear to result in a higher risk of upper limb problems.

This is the first, large, prospective assessment of upper limb morbidity following breast cancer surgery in Australia and New Zealand and therefore provides invaluable information for local women undergoing breast cancer surgery. The results also have global significance. The data provide clinicians with important information to advise women who require an axillary dissection as part of their breast cancer surgery. Women undergoing either an axillary clearance or a sentinel node biopsy can be advised that limitations in upper limb movement are likely to be moderate over the first 6 months, and then recover to near normal levels and stabilise. The benefits of SNBM over RAC reported at one year after surgery [1] are maintained to 3 years. These include less upper limb swelling, symptoms and disability rated by patients and measured by clinicians. No additional long-term adverse effects regarding quality of

life and upper limb restrictions have emerged in either the RAC or SNBM groups. Longer follow-up is needed to determine rates of locoregional and distant recurrence, and long-term outcomes.

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Figure Legends

Figure 1. Mean percentage changes in upper limb volume from baseline, (a) in all participants, (b) in node negative participants, and (c) according to whether axillary clearance was done during the initial axillary operation, or as a second procedure.

Figure 2. Changes in degrees of upper limb movement.

Figure 3. Changes in women's self-ratings of upper limb (a) swelling, (b) symptoms, (c) dysfunction, (d) disability, and (e) overall average.

Table 1: Numbers and proportions of women with a 15% or greater increase from baseline in upper limb volume

	All women randomised			Node-negative subgroup		
	RAC	**SNBM**		**RAC**	**SNBM**	
Visit	***n*=544**	***n*=544**	***P***	***n*=363**	***n*=356**	***P***
1 month, *n* (%)	5 (1.0)	3 (0.6)	-	4 (1.1)	1 (0.3)	-
6 months, *n* (%)	29 (6.0)	21 (4.2)	-	16 (4.8)	9 (2.8)	-
1 year, *n* (%)	47 (9.6)	29 (5.8)	0.02	28 (8.4)	13 (4.0)	0.02
2 years, *n* (%)	81 (16.7)	47 (9.7)	0.001	47 (14.3)	25 (7.9)	0.01
3 years, *n* (%)	82 (17.6)	55 (11.9)	0.01	49 (15.5)	25 (8.3)	0.006

RAC, routine axillary clearance, SNBM sentinel node based management.

Table 2: Numbers (percentages) of women with changes in upper limb volume and scores for upper limb swelling at 3 years (*n*=878). Percentages are of their respective column, except those starred, which are of all 878 women with complete data.

	Change from baseline in upper limb volume				
SSSS for upper limb swelling at 3 years	**≤ 5%**	**> 5– 10%**	**> 10–15%**	**> 15%**	**Total**
0 (none), *n* (%)	344 (75.3)	125 (74.9)	73 (59.8)	67 (50.8)	609
1-3 (mild), *n* (%)	93 (20.4)	37 (22.2)	34 (27.9)	45 (34.1)	209
4-6 (moderate), *n* (%)	19 (4.2)	5 (3.0)	14 (11.5)	14 (10.6)	52
7-10 (severe), *n* (%)	1 (0.2)	0 (0.0)	1 (0.8)	6 (4.5)	8 (1.1)*
Total	457	167	122	132 (15.0)*	878

SSSS, SNAC Study Specific Scale.

* Percentage of all 878 women.