Ann Surg Oncol (2017) 24:1064–1070
DOI 10.1245/s10434-016-5669-2

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – BREAST ONCOLOGY

Sentinel-Lymph-Node-Based Management or Routine Axillary Clearance? Five-Year Outcomes of the RACS Sentinel Node Biopsy Versus Axillary Clearance (SNAC) 1 Trial: Assessment and Incidence of True Lymphedema

Neil Wetzig, MB BS, FRCS, FRACS[1], Peter Grantley Gill, MB BS, MD, FRACS[2,3], David Espinoza, BArch, BSc[4], Rebecca Mister, Bsc, MSc[4], Martin R. Stockler, MB BS, MSc, FRACP[4,5], Val J. Gebski, BA, MStat[4], Owen A. Ung, MB BS, FRACP[6,7], Ian Campbell, MB ChB, FRACS[8], and John Simes, MD, BSc(Med), SM, FRACP[4]

[1]Wesley Medical Centre, Brisbane, QLD, Australia; [2]Breast, Endocrine & Surgical Oncology Unit, Royal Adelaide Hospital, Adelaide, SA, Australia; [3]Department of Surgery, University of Adelaide, Adelaide, SA, Australia; [4]National Health and Medical Research Council Clinical Trials Centre, University of Sydney, Sydney, NSW, Australia; [5]Sydney Cancer Centre, Royal Prince Alfred and Concord Hospitals, Sydney, NSW, Australia; [6]Department of Medicine, University of Queensland, Brisbane, QLD, Australia; [7]Centre for Breast Health, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia; [8]Waikato Hospital, Hamilton, New Zealand

ABSTRACT

Purpose. To determine whether the benefits of sentinel-node-based management (SNBM) over routine axillary clearance (RAC) persisted to 5 years.

Methods. A total of 1088 women with breast cancer less than 3 cm in diameter and clinically negative axillary nodes were randomized to SNBM with axillary clearance if the sentinel node was positive or RAC preceded by sentinel-node biopsy. The outcomes were: (1) objectively measured change in the volume of the operated and contralateral nonoperated arms; (2) the proportion with an increase in arm volume <15%; and (3) subjectively assessed arm morbidity for the domains swelling, symptoms, dysfunction, and disability. Assessments were performed at 1 and 6 months after surgery and then annually.

Results. Limb volume increased progressively in the operated and nonoperated arms for 2 years and persisted unchanged to year 5, accompanied by weight gain. Correction by change in the nonoperated arm showed a mean volume increase of 70 mL in the RAC group and 26 mL in the SNBM group ($P < 0.001$) at 5 years. Only 28 patients (3.3%) had a corrected increase >15% from baseline (RAC 5.0% vs. SNBM 1.7%). Significant predictors were surgery type (RAC vs. SNBM), obesity, diabetes, palpable tumor, and weight gain exceeding 10% of baseline value.

Conclusions. Subjective assessments revealed persisting patient concerns about swelling and symptoms but not overall disability at 5 years. Subjective scores were only moderately correlated with volume increase. SNAC1 has demonstrated that objective morbidity and subjective morbidity persist for 5 years after surgery and that SNBM significantly lowers the risk of both.

The Royal Australasian College of Surgeons Sentinel Node Biopsy versus Axillary Clearance (SNAC1) trial previously reported persistent arm swelling after 3 years of follow-up of 1,088 women with clinically node-negative early breast cancer up to 3 cm in diameter who were randomly assigned to either sentinel-lymph-node-based management (SNBM) or routine axillary clearance (RAC). The upper limb circumference was measured at 10-cm intervals, and the volume of the upper limb calculated for both the operated and the nonoperated upper limb at each episode of review. Subtracting the volume of the nonoperated upper limb from that of the operated upper limb can estimate the true risk of upper limb swelling due to fluid accumulation or lymphedema. This report describes these changes after 5 years of follow-up.

First Received: 6 September 2016;
Published Online: 15 November 2016

P. G. Gill, MB BS, MD, FRACS
e-mail: grantley.gill@adelaide.edu.au

METHODS

A total of 1088 women with unifocal breast cancers <3 cm diameter and clinically negative lymph nodes were randomized to sentinel-node biopsy followed by axillary clearance if the sentinel node was positive (SNBM) or sentinel-node biopsy followed by immediate axillary clearance (RAC). Details of patient and tumor characteristics, the biopsy technique, pathology assessment, and treatments have been reported.[1,2] All patients provided written, informed consent. The study protocol was approved by human research ethics committees of the participating institutions and was in accordance with the precepts of the Declaration of Helsinki.

Assessment of Outcomes

Assessments were done at 1, 6, and 12 months, and annually for 5 years. Arm volume was calculated from the six measurements of limb circumference at 10-cm intervals, as previously described and the formula for a truncated cone.[1–4] This calculated volume and that measured by volume displacement are highly correlated.[3] Both the operated and contralateral nonoperated arms were measured. Swelling was expressed as the percentage change in volume from baseline. Subjective changes were scored by using the SNAC study-specific scales (SSSS), which assessed seven symptoms, three dysfunctions, four disabilities, and difficulty sleeping. Performance of these scales in SNAC have been described in detail.[4,5]

Statistical Analysis

The primary measure of effect, selected before unblinding of the data, was a comparison of the percentage change in objectively measured upper limb volume between the group assigned SNBM and the group assigned RAC. A key endpoint was the proportion of women with an increase of 15% or more from baseline in upper limb volume. We chose >15% as a figure that could correlate with clinically significant lymphedema. The SNBM group included women who had only sentinel-node biopsy or who had biopsy and a subsequent axillary clearance because the sentinel node was not located or was positive. Secondary analyses compared the outcomes after SNBM and RAC in the subgroups of women who were sentinel-node-negative. The sample size of 1100 women was calculated to give 80% power to detect a 6% absolute difference in the rates of significant upper limb swelling, with a two-sided P value of 0.05 and greater than 90% power to detect one point difference on the SSSS with a two-sided P value of 0.01.

For each limb, the change in arm volume from baseline at 5 years was calculated. The percentage change was obtained by dividing this change by the baseline volume. Measurement of the nonoperated contralateral arm serves as a control, indicating changes in arm volume unrelated to surgery. Absolute limb volumes were calculated, and the difference between operated and nonoperated arms determined to derive the component of the increase due to increased fluid volume alone, excluding the effect of weight gain. Additionally, this difference in percentage change was dichotomized as being greater than or less than 15%.

These changes were summarized as means and standard deviations, and differences between treatment groups were compared by standard t test, with 95% confidence intervals. Categorical outcomes (difference in percentage change <15 or ≥15%) were compared by using chi-squared tests and logistic regression as appropriate. We calculated the percentages of women with differences in volume between their two arms of >5, >10, and >15% at 5 years from baseline.

Variable selection was performed using the backwards elimination process. All comparisons were two-sided, and 5% was selected as the nominal significance level.

RESULTS

Changes in Arm Volume, Operated and Contralateral Arms

Table 1 shows the mean percentage change in operated and contralateral arms according to surgical management in the two groups overall. The volume increased in all groups until 2 years after surgery, when it stabilized and then persisted to 5 years. The difference between the randomized groups was confirmed, but the proportionate increases in volume in the operated and nonoperated arms in the SNBM group were similar to that in the nonoperated arm of the RAC group. This was accompanied by a continuous gain in weight to 1.9% of baseline value at 5 years (confidence interval [CI] 1.27–2.55). For the RAC and SNBM groups, the absolute mean increases from baseline were 70 and 26 mL, respectively ($P < 0.001$; Table 2). Results for the node-negative subgroups were 45 mL ($P < 0.001$) and 11 mL ($P = 0.10$), respectively ($P < 0.002$; Table 2).

Only 28 (3.3%) women had a volume differential (or true increase due to fluid accumulation) of >15% (22% had >5% and 7.7 > 10% increase). At 5 years, this was 21 of 408 (5.0%) women in the RAC group and 7 of 405 (1.7%) in the SNBM group.

Significant univariate predictors of a volume increase attributable to lymphedema were surgical treatment, body mass index ($P < 0.05$), overweight at trial entry

TABLE 1 Progressive changes in upper limb volume expressed as percentage change from baseline in operated and nonoperated arms for RAC and SNBM groups

Visit	RAC		SNMB	
	Operated arm (%)	Contralateral arm (%)	Operated arm (%)	Contralateral arm (%)
1 month	1.1	0.3	0.3	0.3
6 months	4.8	2.1	2.8	2.2
1 year	8.4	3.6	4.0	4.0
2 years	14.3	7.3	7.9	7.3
3 years	15.5	9.9	8.3	8.6
4 years	15.4	11.1	10.0	9.3
5 years	15.9	12.5	11.7	12.8

RAC routine axillary clearance group, *SNMB* sentinel-lymph-node-based management group

TABLE 2 Mean changes in absolute arm volume from baseline

Variable	No.	Mean volume change (mL)	Mean volume difference (mL)	P^a
All women				
RAC group				
Operated arm	430	130		<0.001
Contralateral arm	429	61		<0.001
Difference			70	
SNBM group				
Operated arm	430	89		<0.001
Contralateral arm	429	61		<0.001
Difference			26[b]	
Node-negative subgroups				
RAC group				
Operated arm	296	102		<0.001
Contralateral arm	295	58		<0.001
Difference			45	
SNBM group				
Operated arm	274	74		<0.001
Contralateral arm	273	61		<0.001
Difference			11[b]	

RAC routine axillary clearance group, *SNMB* sentinel-lymph-node-based management group

[a] For increase from baseline

[b] $P < 0.001$ for the difference between the randomized groups

($P < 0.01$), and infection within 30 days of surgery ($P < 0.05$). Variables considered important in earlier studies, such as the extent of axillary clearance and numbers of nodes removed at surgery, were not significant predictors (results not shown). Significant predictors of a gain in volume exceeding 10% of the baseline value were adjuvant chemotherapy ($P < 0.001$), age ($P < 0.001$), the presence of palpable tumor ($P < 0.05$), and concurrent major comorbidities ($P < 0.05$).

A multivariate analysis of the predictors of lymphedema due to fluid accumulation where the volume exceeded baseline by 15% or more confirmed that the type of surgery was the most important factor (Table 3). Significant variables included obesity (body mass index [BMI] on entry to the trial), diabetes, palpable tumor, and weight gain >10% from baseline after surgery. The number of lymph nodes removed, postoperative infection, and treatment-related factors, such as chemotherapy, were not significant (results not shown).

TABLE 3 Multivariate analysis of factors predicting a 15% difference in arm volume from baseline 5 years after surgery

Factor	Categories	Odds ratio	95% CI	*P*
Treatment	SNBM vs. RAC	0.22	0.08–0.61	0.004
Tumor palpable	Yes vs. no	3.77	1.31–10.89	0.01
Diabetes	Yes vs. no	3.72	1.09–12.68	0.04
Body mass index[a]		1.15	1.06–1.23	<0.001
Weight gain	>10% gain vs. none or loss	3.34	1.17–9.48	0.02

RAC routine axillary clearance group, *SNMB* sentinel-lymph-node-based management group

[a] BMI is a continuous variable

Patient Self-Ratings of Arm Changes

Women assessed their arm changes at the times that clinicians performed objective volume measurements. The mean "patient self-ratings of arm changes" (SSSS) scores for four items at baseline and the changes from baseline scores after 5 years for both treatment groups is shown in Fig. 1. For swelling and symptoms, scores remained elevated at 5 years, and the difference between the two arms was significant ($P < 0.001$). Despite the differences in these two domains, mean scores for dysfunction and disability did not differ significantly between the two groups, and those for disability returned to baseline values. The overall mean SSSS score increased to 6 months and then declined but remained elevated at 5 years. Table 4 shows the relationships between the measured arm volume increase and SSSS scores in those women who had more than 15% increase in volume in the operated and nonoperated arms as well as between the two arms. There were moderate correlations among the five domains and between the objective increase in total volume in each limb and the adjusted volume of the operated one.

DISCUSSION

The results of the long-term follow-up of women in the SNAC1 trial confirm that the benefit of reduced arm swelling associated with SNBM persists 5 years after surgery. The difference between the treatment groups was maintained throughout the 5 years in both the overall trial cohort and in the sentinel-node-negative groups, thus reinforcing the validity of SNBM.

Both the operated and nonoperated arms were measured. A proportion of the increased volume in both arms was associated with progressive weight gain. We calculated the volume increase in both limbs, and therefore the difference can be attributed to swelling due to fluid accumulation after surgery. This increase, adjusted for changes in the nonoperated arm, accounts for true lymphedema due to axillary surgery. A particular aspect of SNAC1 is the observed progressive evolution of limb swelling over time. Previous studies have reported limb changes at much earlier time points after surgery. The axillary lymphatic mapping against nodal axillary clearance (ALMANAC) trial, for example, compared lymphedema at 1, 6, and 12 months, and Z0010 6 months, after surgery, whereas Hack et al. performed measurements at 6 or 12 months.[6–8] In another retrospective series, changes were assessed at a single variable time point.[9] Bilateral and contralateral arms as well as arm dominance were measured at intervals from baseline until 36 months in NSABP-32. This also allowed estimation of relative volume differences and established that residual edema persisted at 36 months. The sequential measurement of limb volumes in SNAC and B-32 provide contemporary prospective data on the temporal evolution of lymphedema.[10]

Mild lymphedema is generally defined as an increase of 10% but not more than 20% in arm volume. In this study, only 7.7% of women developed lymphedema to this degree. The frequency of any degree of upper limb swelling was greater in the RAC group (26%) than the SNBM group (17%). However, more marked upper limb swelling, which may reflect lymphedema, was limited to only 3.3% of trial participants, 5.0% of patients in the RAC group, and 1.7% in the SNBM group—less than early published lymphedema rates. They certainly are less than apparent community perceptions of the condition in Australia. More-recent studies also have described lower rates.[11–13] Earlier reports were frequently based on historical studies of women with extensive node removal and involvement and often nodal irradiation.[14–16] Other confounding factors include variation in the definition of lymphedema, different times when measured after surgery, and patient perceptions. The historical reports identified predictors of lymphedema following axillary clearance, and consistently established that obesity, the extent of surgery, the number of nodes dissected, nodal irradiation, BMI, and infection are important in this context.[17–21]

Our analyses differ in detail but are applicable in the current setting of early breast cancer and the practice of

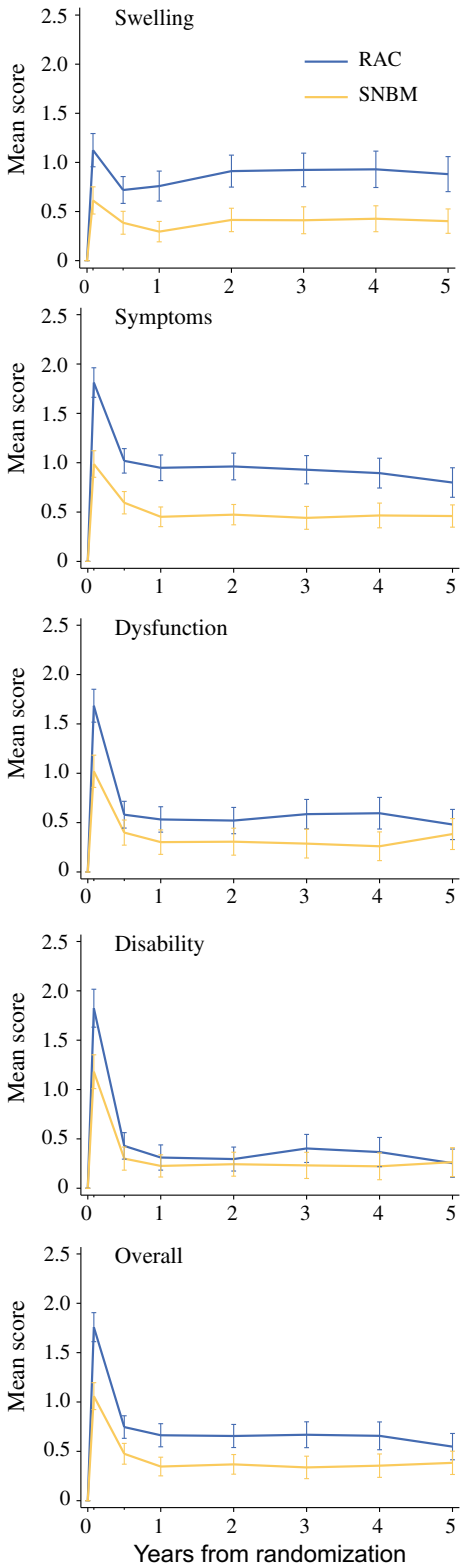

FIG. 1 Changes in SNAC study-specific scales for the domains of self-reported arm morbidity over time following surgery. Scores did not return to preoperative baseline levels, except for disability. The scores for swelling and symptoms remained significantly elevated at 5 years ($P < 0.001$). Scores for other domains did not differ significantly between randomized groups at 5 years

SNBM. Multivariate analysis of data for the SNAC1 group who had >15% increase in corrected arm volume confirmed that the surgery type (RAC compared with SNBM) is a major determinant of such. The key role of SNBM was thus confirmed. Other significant factors were obesity (BMI at randomization), palpable tumor, diabetes, and weight gain exceeding 10% of baseline. Obesity has been consistently established as a predictor of lymphedema. Our results additionally identify comorbidities, such as diabetes, weight gain after surgery, and a palpable primary cancer, and that infection within 30 days of surgery is significant. The results of NSABP-32, in contrast, showed that volume differences were related to age (older), concordance of the dominant and affected arm, and receipt of radiation to the axilla.[10] Radiation to the axilla was a specific protocol exclusion in SNAC. In current surgical practice, however, it is likely that many women who undergo SNBM also will receive radiation to the lower axilla, and it thus is an important contemporary contributor to volume increase. Weight gain after surgery has been attributed to chemotherapy and hormone therapy, but neither of these significantly predicted increased volume in the present study.[22] Although adjuvant chemotherapy was not a predictor of swelling, it was significantly so for weight gain, as were the presence of major comorbidities and young age. These identify women at risk. Hormone therapy was not related, which is consistent with published results.[23] These findings define specific patient characteristics that could enable targeted counselling at the time of primary treatment regarding risk, weight control, diabetes, prevention of early infection, and injury to the arm.

The impact of surgery on the subjective SSSS scores at 12 months and 3 years has been previously reported.[5] The current findings that scores for arm swelling and for symptoms remained significantly elevated from baseline at 5 years are consistent with the increases in volume, as are the differences in SSSS scores between the two allocated surgical groups. The early rise in SSSS scores at 6 months coincided with restriction of shoulder movements, which had recovered by 12 months. Volume changes probably had a minimal contribution to subjective change at that time. Despite the persistent scores for swelling and symptoms, women did not report significant disability at 5 years. The correlation between measured volume change and subjective scores varied for each domain and was only moderate overall. This is consistent with the view that arm swelling and symptoms and the perception of such are not always reflective of lymphedema.[12,13] Sensory changes and pain are likely to contribute. This also is consistent with the results from NSABP-32, which showed that residual edema was not a predictor of overall quality of life but that morbidity and sensory changes were.[24] McLaughlin et al. reported discordance between patient perception and

TABLE 4 Pearson correlations for change in volume and change in SSSS score for women who had >15% difference in volume between the operated and contralateral arm

	Increase operated arm	Increase contralateral arm	Difference between arms	SSSS swelling
Increase operated arm	1.00			
Increase contralateral arm	0.81	1.00		
Difference between arms	0.83	0.34	1.00	
SSSS swelling	0.40	0.25	0.39	1.00
SSSS symptom	0.48	0.32	0.44	0.93
SSSS dysfunction	0.56	0.33	0.56	0.71
SSSS disability	0.52	0.43	0.41	0.46
SSSS overall	0.56	0.39	0.51	0.80

SSSS SNAC study-specific scales measuring subjective morbidity

measured lymphedema in 41% of 936 women.[13] Swelling, however, correlated well with symptoms, dysfunction, and SSSS scores.

SNAC1 has clearly demonstrated that altered objective and subjective measures of morbidity persist for at least 5 years after surgery and that SNBM significantly lowers the risk of both. SNAC-1 is the first large prospective, randomized trial to assess accurately these parameters 5 years after surgery. With modern technique, and in this large and carefully assessed group of women, it is interesting that the incidence of objective lymphedema after axillary clearance is much lower than in many previous reported studies. The prospective conduct of SNAC1 using validated objective and subjective assessment methods has enabled confirmation of existing and the addition of new information about arm morbidity in the contemporary surgical context.

ACKNOWLEDGEMENT Funded by Grants from the Australian National Health and Medical Research Council (NHMRC, 1046018, 512378, 1037786), the National Breast Cancer Foundation, the Australian Department of Health and Ageing, MBF Australia, and the Scottwood Trust, New Zealand. Rhana Pike, from the NHMRC Clinical Trials Centre, assisted with the manuscript. Funded by the Australian National Health and Medical Research Council, the National Breast Cancer Foundation, the Australian Department of Health and Ageing, MBF Australia, and the Scottwood Trust.

DISCLOSURE The authors report no conflicts of interest.

REFERENCES

1. Gill PG, Wetzig N, Gebski V, et al, and the SNAC Trial Group. Sentinel-lymph-node-based management or routine axillary clearance? One-year outcomes of sentinel node biopsy versus axillary clearance (SNAC): a randomized controlled surgical trial. *Ann Surg Oncol*. 2009;16:266–75.
2. Elmadahm AA, Gill PG, Bochner M, Gebski V, Zannino D, Wetzig N, Campbell I, Stockler M, Ung O, Simes J, Uren R.. Identification of the Sentinel Lymph Node in the SNAC-1 Trial. *ANZ J Surg*. 2015;85(1–2):58–63.
3. Tewari N, Gill P G, Bochner M, Kollias J. Comparison of volume displacement versus circumferential upper limb measurements for lymphoedema: implications for the SNAC trial. *ANZ J Surg*. 2008;78:889–93.
4. Smith MJ, Gill PG, Wetzig N, et al. Comparing patients' and clinicians' assessment of outcomes in a randomised trial of sentinel node biopsy for breast cancer (the RACS SNAC trial). *Breast Cancer Res Treat*. 2008;117:99–109.
5. Wetzig N, Gill PG, Zanno D, Stockler MR, Gebski V, Ung O, Campbell I, Simes J. Sentinel-lymph-node-based management or routine axillary clearance? Three-year outcomes of the RACS sentinel node biopsy versus axillary clearance (SNAC) 1 trial. *Ann Surg Oncol.* 2014;16:266–75.
6. Mansel RE, Fallowfield LJ, Kissin M. Randomised multicentre trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst*. 2006;98(9):599–609.
7. Wilke LG, McCall LM, Posther KE, Whitworth PW, Reintgen DS, Leitch AM, et al. Surgical complications associated with sentinel lymph node biopsy: results from a prospective international cooperative group trial. *Ann Surg Oncol*. 2006;13(4):491–500.
8. Hack TF, Kwan WB, Thomas-MacLean JL, Towers A, Miedema B, Tilley A, et al. Predictors of arm morbidity following breast cancer surgery. *Psycho-Oncology.* 2010;19(11):1205–12.
9. Erickson VS, Pearson ML, Ganz PA, Adams J, Kahn KL. Arm edema in breast cancer patients. *J Natl Cancer Inst*. 2001;93(2):96–111.
10. Ashikaga T, Krag DN, Land SR, Julian TB, Anderson SJ, Brown AM, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. *J Surg Oncol*. 2010;102(2):111–8.
11. Coen JJ, Taghian AG, Kachnic LA, Coen JJ, Assaad SI. Risk of lymphoedema after regional nodal irradiation with breast conservation therapy. *Int J Radiat Oncol Biol Phys.* 2003;55(5):1209–15.
12. Dayes IS, Levine MN, Julian JA, Pritchard KI, D'Souza DP, Kligman L, et al. Lymphoedema in women with breast cancer: characteristics of patients screened for a randomized trial. *Breast Cancer Res Treat*. 2008;110(2):337–42.
13. McLaughlin SA, Wright MJ, Morris KT. Prevalence of lymphoedema in women with breast cancer 5 years after sentinel lymph node biopsy or axillary dissection: patient perceptions and precautionary behaviours. *J Clin Oncol*. 2008;26(32):5220–6.
14. Kissin M, Querci-Della-Rovere G, Easton D, Westbury G. Risk of lymphoedema following the treatment for breast cancer. BJS. 1986;73:580–4.

15. Larson D, Weinstein M, Goldburg L, Silver B, Recht A, Cady Y. Oedema of the arm as a function of the extent of axillary surgery in patients with stage 1-2 carcinoma of the breast treated primary radiotherapy. *Int J Radiat Oncol Biol Phys*. 1986:12;1575–82.
16. Liljegren G, Holmburg L. Arm morbidity after sector resection and axillary dissection with or without postoperative radiotherapy in breast cancer stage 1: results from a randomised trial. *Eur J Cancer*. 1997;33;193–9.
17. Helyer LK, Varnic M, Le LW, Leong W, McCready D. Obesity is a risk factor for developing postoperative lymphoedema in breast cancer patients. *Breast J*. 2010;16(1):48–54.
18. Herd-Smith A, Russo A, Muraca MG, Del Turco MR, Cardona G. Prognostic factors for lymphoedema after primary treatment of breast carcinoma. *Cancer*. 2001;92(7):1783–7.
19. Soran A, D'Angelo G, Begovic M, Ardic F, Harlak A, Samuel Wieand H, et al. Breast cancer-related lymphoedema—what are the significant predictors and how they affect the severity of lymphoedema? *Breast J*. 2006;12(6):536–43.
20. Aitken R, Gayes M, Rodger A, Chattey U, Forrest A. Arm morbidity within a trial of mastectomy and either node sample with selective radiotherapy or axillary clearance. *BJS*. 1989;76:568–71.
21. Tsai RJ, Dennis LK, Lynch CF, Snetselaar LG, Zamba GK, Scott-Conner C. The risk of developing arm lymphoedema among breast cancer survivors: a meta-analysis of treatment factors. *Ann Surg Oncol*. 2009;16(7):1959–72.
22. Villarini A, Pasanisi P, Raimondi M, Gargano G, Bruno E, Morelli D, et al. Preventing weight gain during adjuvant chemotherapy for breast cancer: a dietary intervention study. *Breast Cancer Res Treat*. 2012;135:581–9.
23. Sestak I, Harvie M, Howell A, Forbes JF, Dowsett M, Cuzick J. Weight change associated with Anastrozole and tamoxifen treatment in postmenopausal women with or at high risk of developing breast cancer. *Breast Cancer Res Treat*. 2012;134:727–37.
24. Kopec JA, Colangelo LH, Land SR, Julian TB, Brown AM, Anderson SJ, et al. Relationship between arm morbidity and patient-reported outcomes following surgery in women with node-negative breast cancer: NSABP protocol B-32. *J Support Oncol*. 2013;11(1):22–30.