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EDITORIAL – BREAST ONCOLOGY

Less Remains Better: Morbidity After Axillary Surgery

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It took the best part of 50 years for radical mastectomy to be replaced by mastectomy and subsequently for breast-conserving techniques of segmental mastectomy with radiotherapy to be accepted for the majority of patients. Similarly, surgical staging of the axilla has evolved from radical clearance of the axilla with resection of the pectoralis minor muscle through axillary lymph node dissection (ALND) to our current standard of sentinel node biopsy (SNB). We now recognize that appropriately targeted node sampling, preferably with a dual (dye and isotope) technique, is the surgical approach of choice in clinically node-negative patients with breast cancer.[1–3] Minimizing axillary surgery should theoretically reduce postoperative complications and long-term morbidity, and trials that prospectively prove this hypothesis and quantify the changes have been increasingly reported in the literature.[4–8]

There are clear benefits in terms of morbidity for SNB over ALND, but neither approach is free of consequences for the patient. Although most studies have, understandably, focused on the short-term morbidities, the Australian and New Zealand community are to be commended in securing follow-up data in >80 % of their patients to 3 years with a consistent and meticulous examination of upper limb morbidity within the SNAC1 trial.[9] The patient population studied probably represents the real world for clinically node-negative breast cancers <3 cm (58 % were screen detected), and the application of validated (on the populations under study) objective and subjective measures up to the 3-year mark is laudable.

One strength of the SNAC1 trial is that they included both objective and subjective components to measure evidence of arm swelling, in contrast to the ALMANAC trial, which reported similar subjective results based on the FACT-B+4 instrument, and the NSABP B-32 trial and Italian GIVOM trial, which relied on objective measurements alone.[5–7] SNAC1 temporally extends the findings that patients who undergo ALND have higher arm volume changes, with more symptoms of arm swelling and disability reported by patients.

One concern is the definition of *lymphedema*—an issue that plagues all investigators attempting to quantify it. The investigators measured arm circumference at 10-cm intervals and report this as a percentage change in volume over preoperative baseline arm measurements. One possible source of measurement bias is that they do not factor contralateral arm circumference in their calculations, as other investigators have done.[4,6] Weight changes are common after breast cancer therapy and can certainly influence these measurements.[10] Use of contralateral arm volumes may help delineate how much of the change in the affected arm is secondary to therapeutic interventions. Although both ALND and SNB patient groups may be equally likely to gain weight, this might account for half of the patients with a >15 % change over baseline not reporting subjective symptoms of arm swelling. As ever, subjective measures may not concord with the (generally worse) objective measurement of upper limb swelling.

An interesting finding of the trial is that there was no particular disadvantage in terms of morbidity to the two-stage approach of a positive SNB being followed by a second trip to the operating room for axillary node dissection. The need for a second operation is now questionable in the light of several recent trials, such as ACOSOG Z0011, IBCSG 23-01, and AMAROS, which show no advantage to axillary clearance over SNB alone in clinically node-negative patients found to have small-volume nodal disease.[11–14] Morbidity has been reported from these trials with findings similar to the SNAC1 trial.[4] It is reasonable that the benefits to SNB alone shown in the

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SNAC1 trial may also apply to this new patient population who are spared ALND. In fact, the investigators show that 17.6 % of node-positive patients had a baseline change in arm circumference of >15 % at 3 years, compared with a similar proportion of node-negative patients randomized to axillary clearance (15.5 %). One might argue that not all SNB patients require that second operation of ALND.

And what of the techniques for ensuring the rehabilitation of the upper limb? The SNAC1 trial was permissive in that respect, with a third of the patients receiving some form of rehabilitation, although differences in approach are unlikely to have altered the comparative outcomes. It remains unclear how best to support mobilization and rehabilitation of the upper limb subjected to axillary surgery (and/or radiotherapy, for that matter); the Prevention Of Shoulder Problems Study (PROSPER), funded as a Health Technology Assessment in the United Kingdom, should provide answers to who needs what sort of rehabilitation and how it may be delivered. That said, it is notable that SNB is at least as good on all parameters, although the use of upper limb compression garments (in 10 % of women overall) was not confined to the axillary dissection group alone.

As is the case with all surgical procedures, SNB is not a procedure without complications or consequences, as the 2.5 % of women with upper limb swelling in SNAC1 demonstrate. Accepting a dual technique is more accurate than either isotope or blue dye alone (and the 2 % of women who have an allergic reaction to the latter): even through a small 2-cm incision, nerve damage, hematoma, and seroma may follow.[4–6] It is now clear that within the first 6 months to first year there is considerable recovery, and that by 2 years after surgery, it is likely that the longer-term consequences of SNB (as for axillary dissection) can be discerned.

Although radiographic and surgical staging have been, to date, separate approaches, we will no doubt see procedures in the future that merge techniques to allow for minimally invasive assessment of the axilla. Could the current SNB procedure, usually performed under general anesthesia, be converted to a less invasive procedure done under local anesthesia alone? Preliminary studies are evaluating ultrasound and gamma probe–guided vacuum-assisted needle core biopsy, which is feasible in skilled hands. Indeed, where licensed, the ultrasound-detected micro bubble technique may well take the place of blue dye, providing a dual isotope/microbubble technique to identify and then excise (using a vacuum core needle) the sentinel lymph node(s) under ultrasound guidance.[15,16] Alternatively, do we need to consider abandoning surgical intervention in the axilla in selected patients? This is the hypothesis under test in the sentinel node versus observation after axillary ultrasound (SOUND) trial.[17]

While the use of SNB is now accepted in clinically node-negative women, there is still great controversy over the use of sentinel lymph node dissection in clinically node-positive patients, especially those who receive neo-adjuvant chemotherapy. A large proportion of these women will convert to node-negative with systemic treatment, yet we still have no way to accurately identify which women so that we can offer less extensive axillary surgery. The ACOSOG Z1071 trial was designed with the hypothesis that sentinel lymph node dissection would accurately assess nodal response to chemotherapy with a false-negative rate of <10 %.[18] The reported false-negative rate of 12.6 % has led to considerable national discussion and efforts to improve the accuracy of the technique. One approach currently under investigation at M.D. Anderson is of targeted axillary dissection (TAD) using ultrasound-guided needle biopsy with clip placement for axillary metastasis. I^{125} seeds are subsequently placed in the clipped node preoperatively and selectively removed in combination with SNB. Currently, patients undergo completion ALND, but a registry trial is accruing to compare the results of TAD to ALND. The ultimate goal is to offer patients less extensive, targeted axillary surgery when systemic therapy eradicates nodal metastases.

Although this 3-year follow-up of the consequences of the SNAC1 trial may not be practice-changing, given the global shift to SNB, it is certainly practice-affirming and provides reassurance to patients and clinicians that the late Don Morton might well have appreciated, regarding the objective symptomatic consequences and advantages to SNB over axillary dissection. On the basis of the SNAC1 data, taken together with other large trials of SNB, it is not likely that we will see unexpected long-term adverse consequences of SNB at 5, 10, or 20 years. The challenges of managing the morbidity, appropriately broadening the indications, and refining the techniques remain.

REFERENCES

1. Veronesi U, Paganelli G, Galimberti V, et al. Sentinel-node biopsy to avoid axillary dissection in breast cancer with clinically negative lymph-nodes. *Lancet*. 1997;348:1864–7.
2. Giuliano A, Dale P, Turner R, Morton D, Evans S, Krasne D. Improved axillary staging of breast cancer with sentinel lymphadenectomy. *Ann Surg*. 1995;222:394–9.
3. Krag D, Anderson S, Julian T, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol*. 2010;11:927–33.
4. Lucci A, McCall A, Beitsch P, et al. Surgical complications associated with sentinel lymph node dissection (SLND) plus axillary lymph node dissection compared with SLND alone in the American College of Surgeons Oncology Group Trial Z0011. *J Clin Oncol*. 2007;25:3657–63.

5. Ashikaga T, Krag D, Land S, et al. Morbidity results from the NSABP B-32 trial comparing sentinel lymph node dissection versus axillary dissection. *J Surg Oncol*. 2010;102:111–8.
6. Del Bianco P, Zavango G, Burelli P, et al. Morbidity comparison of sentinel lymph node biopsy versus conventional axillary lymph node dissection for breast cancer patients: results of the sentinella-GIVOM Italian randomised clinical trial. *Eur J Surg Oncol*. 2008;34:508–13.
7. Fleissig A, Fallowfield L, Langridge C, et al. Post-operative arm morbidity and quality of life. Results of the ALMANAC randomised trial comparing sentinel node biopsy with standard axillary treatment in the management of patients with early breast cancer. *Breast Cancer Res Treat*. 2006;95:279–93.
8. Mansel R, Fallowfield L, Kissin M, et al. Randomized multicenter trial of sentinel node biopsy versus standard axillary treatment in operable breast cancer: the ALMANAC Trial. *J Natl Cancer Inst*. 2006;98:599–609.
9. Wetzig N, Gill P, Zannino D, et al. 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.*
10. Saquib N, Flatt S, Natarjan L, et al. Weight gain and recovery of pre-cancer weight after breast cancer treatments: evidence from the women's healthy eating and living (WHEL) study. *Breast Cancer Res Treat*. 2007;105:177–86.
11. Giuliano A, McCall L, Beitsch P, et al. Locoregional recurrence after sentinel lymph node dissection with or without axillary dissection in patients with sentinel lymph node metastases: the American College of Surgeons Oncology Group Z0011 randomized trial. *Ann Surg*. 2010;252:426–32.
12. Giuliano A, Hunt K, Ballman K, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA*. 2011;305:569–75.
13. Galimberti V, Cole B, Zurrida S, et al. Axillary dissection versus no axillary dissection in patients with sentinel-node micrometastases (IBCSG 23-01): a phase 3 randomised controlled trial. *Lancet Oncol*. 2013;14:297–305.
14. Rutgers E, Dinker M, Straver M, et al. Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial (10981/22023). *J Clin Oncol.* 2013;31(Suppl.):abstr LBA1001.
15. Sever A, Mills P, Weeks J, et al. Preoperative needle biopsy of sentinel lymph nodes using intradermal microbubbles and contrast-enhanced ultrasound in patients with breast cancer. *AJR Am J Roentgenol*. 2012;199:465–70.
16. Sever A, Mills P, Hyvelin J, et al. Percutaneous removal of sentinel lymph nodes in a swine model using a breast lesion excision system and contrast-enhanced ultrasound. *Eur Radiol*. 2012;22:545–50.
17. Gentilini O, Veronesi U. Abandoning sentinel lymph node biopsy in early breast cancer? A new trial in progress at the European Institute of Oncology of Milan (SOUND: Sentinel node vs Observation after axillary UltraSouND). *Breast*. 2012;21:678–81.
18. Boughey J, Suman V, Mittendorf E, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. *JAMA*. 2013;310:1455–61.