

Canadian Association of General Surgeons and American College of Surgeons Evidence-Based Reviews in Surgery. 27.

Quality-of-life outcomes with sentinel node biopsy versus standard axillary treatment in patients with operable breast cancer

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CAGS and ACS Evidence-Based Reviews in Surgery

The term “evidence-based medicine” was first coined by Sackett and colleagues as “the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients.”¹ The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, as well as clinical knowledge.

The Canadian Association of General Surgeons (CAGS) and the American College of Surgeons (ACS) jointly sponsor a program entitled “Evidence-Based Reviews in Surgery (EBRS),” which is supported by an educational grant from ETHICON and ETHICON ENDO SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson, and ETHICON INC. and ETHICON ENDO-SURGERY, INC. divisions of Johnson & Johnson Inc. The primary objective of this initiative is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons, but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the early diagnosis of disease, and the effectiveness of treatment. A methodologic article is supplied that guides the reader in critical appraisal of the clinical article. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS website. As well, a listserv discussion is held where participants can discuss the monthly article. Members of CAGS and ACS can access EBRS through the CAGS website (www.cags-accg.ca) or the ACS website (www.facs.org). All journal articles and reviews are available electronically through the EBRS website. We also have a library of past articles and reviews that can be accessed at any time. Surgeons who participate in the monthly packages can obtain Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits and/or continuing medical education credits for the current article only by reading the monthly articles, participating in the listserv discussion, completing the monthly online evaluation and answering the online multiple choice questionnaire. For further information about EBRS, the reader is directed to the CAGS or ACS websites or should email the administrator, Marg McKenzie, at mmckenzie@mtsina.on.ca.

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In addition to making the reviews available through the CAGS and ACS websites, 4 of the reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 in the *Journal of the American College of Surgeons* each year. We hope readers will find EBRs useful in improving their critical appraisal skills and also in keeping abreast of new developments in general surgery. Comments regarding EBRs may also be directed to mmckenzie@mtsina.on.ca.

Reference

1. Evidence-Based Medicine Working Group. Evidence-based medicine. *JAMA* 1992;268:2420-5.

Selected Article

Mansel RE, 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.

Abstract

Objective: To compare quality of life and arm morbidity outcomes among patients with clinically node-negative invasive breast cancer who received either sentinel lymph node biopsy (SNB) or standard axillary treatment. **Methods:** A total of 1031 patients were randomly assigned to either SNB ($n = 515$) or standard axillary surgery ($n = 516$). Sentinel node biopsy was performed before the breast tumour was removed, according to a standardized protocol that used a radiopharmaceutical compound and a blue dye with routine preoperative lymphoscintigraphy. Standard axillary treatment was defined as either an axillary lymph node dissection or 4-node axillary sampling. Outcomes were evaluated by patients' self-assessments of arm morbidity and quality of life. The patients completed the assessments using the Functional Assessment of Cancer Therapy — Breast scale, version 4 (FACT-B) at follow-up visits 1, 3, 6, 12 and 18 months after the procedure. **Results:** The relative risks of any lymphedema and sensory loss for the SNB group compared with the standard axillary surgery group at 12 months were 0.37 (95% confidence interval [CI] 0.23–0.60,

absolute rates 5% v. 13%) and 0.37 (95% CI 0.27–0.50, absolute rates 11% v. 31%), respectively. Drain usage, length of stay in hospital and time to resumption of normal day-to-day activities after surgery were significantly lower in the SNB group ($p < 0.001$), and axillary operative time was reduced ($p = 0.06$). Overall patient-recorded scores for quality of life and arm functioning were significantly better in the SNB group throughout the follow-up period ($p \leq 0.003$). These benefits were observed with no increase in anxiety levels in the SNB group ($p \geq 0.05$). **Conclusion:** Sentinel node biopsy is associated with reduced arm morbidity and better quality of life than standard axillary treatment, and it should be the treatment of choice for patients who have early-stage breast cancer with clinically negative nodes.

Commentary

The ALMANAC Trial compared quality-of-life and arm-morbidity outcomes in patients with clinically node-negative invasive breast cancer who were randomly assigned to SNB or standard axillary treatment (axillary lymph node dissection or 4-node axillary sampling). The study provides clinically important information about SNB test characteristics and morbidity, and it provides insight into the challenges in measuring quality of life and interpreting the results.

This was the first study to confidently report that the same proportion of women were found to be node-positive with SNB and axillary lymph node dissection, despite a false-negative rate of about 10% with

SNB. In terms of morbidity, only 5% of women who had SNB reported any swelling at the 12-month follow-up compared with 13% of women who had axillary lymph node dissection. It is important to note that the authors, in another publication,¹ noted that 4% of women in both groups reported swelling in the arm at baseline. Most women (> 80%) who reported swelling indicated that it was mild. Other morbidity outcomes included sensory loss of 11% after 12 months for women in the SNB group compared with a loss of more than 31% for those in the axillary lymph node dissection group. Shoulder movement was unaffected by either procedure in the long term. The study used several quality-of-life instruments or scales. The authors felt that the data on quality of life supported the performance of SNB and that SNB should be the treatment of choice for patients who have early-stage breast cancer with clinically negative nodes.

The methods of the study and data on quality of life warrant some scrutiny. Appropriately, the authors used a disease-specific assessment tool: the FACT-B, version 4, its arm functioning subscale and its trial outcomes index (TOI). The TOI instrument appears appropriate for assessing quality of life because it pertains to arm morbidity and is actually derived from FACT-B. These are validated quality-of-life scales that have been developed with and for breast cancer patients. In general, the scales performed appropriately: scores decreased for each group a month after surgery and then gradually improved toward baseline. Poorer scores were

observed in the axillary lymph node dissection group, and greater differences in scores were observed with the disease-specific instruments than with general instruments.

Although there were statistically significant differences between treatment groups in favour of SNB, the clinical importance of the differences is uncertain. For example, an 8% difference in reported swelling in the arm after 12 months is more meaningful than a score of 18.5 for SNB versus 17.1 for axillary lymph node dissection on the arm functioning subscale (maximum score 20). Details on what constituted a clinically important difference in the arm functioning subscale and FACT-B were not provided in the study. The authors reported that a difference of more than 5 in TOI scores would be clinically significant. This difference was only observed at the 1-month follow-up visit, whereas at all other visits, the differences in scores were less than 5. Analyzing the proportion of patients in each group who had scores that changed by more than 5 points from baseline does not seem appropriate as it appears to be an ad hoc analysis. Thus the quality-of-life measurements themselves do not provide compelling evidence in support of SNB as the treatment of choice.

Even if quality of life was shown to be convincingly superior, in the absence of equivalent recurrence and survival information between SNB and axillary lymph node dissection, it would be premature to recommend SNB as the treatment of choice. Survival is the chief concern of most cancer patients. It is unlikely that most patients, when given the choice between SNB and axillary lymph node dissection, would trade a gain in quality of life and/or decreased arm morbidity after SNB for even a small decrease in chance of survival. More than half of breast cancer patients would accept chemotherapy when the absolute survival benefit is

as little as 1%.² This study did not, and cannot in the future, address survival adequately. To exclude a small but clinically important difference in survival, such a study would require several thousand patients. The only trial that has been powered sufficiently to answer that question is the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial.³

Other methodologic issues with this study include multiple outcomes with multiple measures at multiple time points. Without stating the most important outcome of a study explicitly, the investigators can be suspected of something akin to “data dredging” or trying to increase their opportunity to report positive results. An indication of what an investigator believes to be important a priori should be reflected in the sample size calculation. The sample size of the study was based on swelling in the arm; however, it is unclear what measure of swelling the calculation is based on. If the investigators felt that quality of life was an important primary or even secondary outcome, they might have commented on the sample size as it related to the quality-of-life measures used.

There are also concerns with study generalizability to clinical practice. The study was multicentred and included women with clinically node-negative, early-stage breast cancer. Surgeons were required to be well versed in the SNB technique, with their training well documented. On the other hand, problems in generalizability include the use of 4-node sampling in 25% of participants in the axillary assessment arm; this method is not the standard of care in North America. This likely makes the results in this study less favourable toward SNB. Some subset analyses would have been useful. Another deviation from standard clinical practice is that 27% of women with positive sentinel nodes received axillary radiotherapy

rather than a complete axillary lymph node dissection. The effects on the results are uncertain.

The ALMANAC Trial provides important information on test characteristics of SNB in breast cancer and arm morbidity. The contribution of quality-of-life measures in this trial to the overall acceptance of SNB is uncertain because differences are small and their clinical importance is uncertain. The ALMANAC Trial does support the growing evidence and current practice of SNB, which is performed routinely by most surgeons caring for breast cancer patients, despite the absence of reliable data on long-term recurrence and survival. The question of whether SNB might result in a decreased chance of survival compared with axillary lymph node dissection is being addressed by NSABP B-32, the statistical power of which will permit the detection of survival differences as small as 2%. Until these data become available, it is premature to conclude that SNB is the treatment of choice for patients with early-stage clinically node-negative breast cancer.

Competing interests: None declared.

References

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