

Canadian Association of General Surgeons and American College of Surgeons Evidence Based Reviews in Surgery. 23.

ASCO recommended guidelines for sentinel lymph node biopsy for early-stage breast cancer

Leigh Neumayer, MD; Sarkis Meterissian, MD; Kelly McMasters, MD; for the Members of the Evidence Based Reviews in Surgery Group*

CAGS 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 and the American College of Surgeons 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 methodological article is supplied that guides the reader in critical appraisal of the clinical article. Both methodological 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 the Canadian Association of General Surgeons and the American College of Surgeons can access Evidence-Based Reviews in Surgery through the Canadian Association of General Surgeons website (www.cags-accg.ca) or the American College of Surgeons 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 website or should email the administrator, Marg McKenzie, at mmckenzie@mtsina.on.ca.

*The CAGS Evidence-Based Reviews in Surgery Group comprises Drs. J.S.T. Barkun, K. Brasel, T.H. Cogbill, C. Suzanne Cutter, G.W.N. Fitzgerald, H.J.A. Henteleff, A.W. Kirkpatrick, S. Latosinsky, A. Maclean, T.M. Mastracci, R.S. McLeod, L.A. Neumayer, S. Smith, M.C. Taylor and L.R. Temple and Ms. M.E. McKenzie.

Correspondence to: Ms. Marg McKenzie, RN, Administrative Coordinator, EBRS, Mount Sinai Hospital, L3-010, 60 Murray St., PO Box 23, Toronto ON M5T 3L9; fax 416 586-5932; mmckenzie@mtsina.on.ca

In addition to making the reviews available through the CAGS and ACS Web sites, 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

Lyman GH, Giuliano AE, Somerfield MR, et al. American Society of Clinical Oncology guideline recommendations for sentinel lymph node biopsy in early stage breast cancer. *J Clin Oncol* 2005;23(30):7703-20.

Abstract

Objective: To develop a guideline for the use of sentinel lymph node biopsy (SLNB) in early-stage breast cancer **Data sources:** Electronic search of MEDLINE, Cochrane Library, Best Evidence, DARE, Dissertation Abstracts, as well as hand-searching techniques **Study selection:** Only studies that included full lymph node dissection, regardless of the results of SLNB were included. Sixty-nine trials met the eligibility criteria between 1994 and 2004. **Data extraction:** Studies were extracted and evaluated by 2 blinded observers. Recommendations were based on review of the literature and expert opinion as well as consideration of the Guidelines for Performance of Sentinel Lymph Node Biopsy for Breast Cancer developed by the American Society of Breast Surgeons in 2003. **Main results:** A review of the available literature, including 1 published randomized controlled trial comparing SNLB with axillary lymph node dissection (ALND), 4 meta-analyses and 69 published single-centre and multi-centre trials showed that, when performed by experienced clinicians, SNLB appears to be a safe and acceptably accurate method for identifying

early-stage breast cancer without the involvement of the axillary lymph nodes. There are no data on the effect of SLNB on long-term survival. **Conclusion:** SLNB is an appropriate initial alternative to routine staging with ALND for patients with early-stage breast cancer with clinically negative axillary nodes. Completion ALND remains standard treatment for patients with axillary metastases identified on SNLB. However, appropriately identified patients with negative results of SLNB, when done under the directions of an experienced surgeon, need not have completion ALND. Data suggest that SLNB is associated with less morbidity than ALND.

Commentary

A guideline was developed for the use of SLNB in early-stage breast cancer. The specific questions the guideline addressed were:

1. Can full axillary lymph node dissection be avoided in patients who have negative findings on SNLB?
2. Is full axillary lymph node dissection necessary for all patients with positive findings on SNLB?
3. What is the role of SNLB in special circumstances?
4. What factors affect the success of SNLB?
5. What are the potential benefits and harms associated with SNLB?

An expert panel of the American Society of Clinical Oncology conducted a systematic review of the literature available through February 2004 and then developed guidelines based on the available evidence as well as

their expert opinions. The guideline was also reviewed by selected experts in the field and on the ASCO Health Services Committee. Overall, the panel identified 4 limited meta-analyses and 69 published single-institution and multicentre trials with sufficient information to compare the performance of SLNB with that of ALND.

The sensitivity of SLNB for node involvement ranged from 71% to 100%. The false-negative rate averaged 8.4% but ranged from 0% to 29%. The false-negative rate was significantly lower if more than 100 patients were included in the series, if the successful mapping rate was greater than 90%, and if patient characteristics and measures of test performance and variability were given. The use of both dye and radiolabelled colloid resulted in lower false-negative rates but did not reach statistical significance ($p = 0.07$). The proportion of successful mappings was significantly higher when radiolabelled colloid was used. The authors concluded that, when performed by experienced clinicians,

SNLB appears to be a safe and acceptably accurate method for identifying early-stage breast cancer without involvement of the axillary lymph nodes.

However, they cautioned that, although the diagnostic accuracy of SLNB has been demonstrated, further randomized controlled trials are needed to evaluate long-term outcomes.

The high rate of additional nodal disease if the SNLB is positive (48.3%, 95% confidence interval [CI] 35–62, according to a recent meta-analysis)¹

led the panel to recommend routine ALND for patients with a positive SNLB by routine histopathologic examination, as well as for patients with micrometastases measuring 0.2–2.0 mm. They also determined that there were insufficient data to determine which patients with a positive SLNB might be appropriately treated with breast or axillary radiation in place of ALND.

With regard to SLNB in special circumstances, the panel concluded that

SLNB is not recommended for large or locally advanced invasive breast cancer (T3 and T4); inflammatory breast cancer; DCIS when breast-conserving surgery is to be done; pregnancy, in the setting of prior non-oncologic breast surgery or axillary surgery; and in the presence of suspicious axillary nodes.

Unfortunately, there was again insufficient evidence on which to base these recommendations, and it appears that most are based on the expert opinion of the group.

With regard to factors that affected the success of SLNB, the panel concluded that the strongest predictor of a low false-negative rate is the proportion of patients for whom mapping is successful and that, in most instances, the lowest false-negative rate was achieved by using 2 dyes (radiolabelled and blue dye). They also strongly support the Guidelines for Performance of Sentinel Lymphadenectomy for Breast Cancer developed by the American Society of Breast Surgeons. This guideline rec-

ommends that a false-negative rate of 5% or less should be achieved to abandon axillary dissection.

The last question the panel set out to answer concerned the potential benefits and harms of SLNB. They recommend that patients be fully informed, which includes an explanation of the implications of a false-negative result as well as the complications of SLNB, which are in general thought to be less than with ALND. There is a good review of the relevant literature, with objective data regarding the incidence of the most common complications.

The most obvious limitation of this guideline is that in 2005 there were insufficient data to make this guideline “evidence-based.” The randomized controlled trials designed to answer the questions of whether ALND can be avoided when SNLB is negative and whether ALND is necessary for all patients with positive findings on SNLB have yet to be reported. The guideline, therefore, is based more on expert opinion and current practice in the United States. Further, the recommendations for the use of SLNB in “special circumstances” are based on very few data. Even in the last 2 years, practice has changed, and many patients in the “not recommended” categories are now being offered SLNB. For instance, many clinicians will proceed with SLNB in patients with “clinically suspicious” nodes or T3–T4 tumours unless the patient has histologic proof of lymph node involvement.

The other fairly substantial limitation of the guideline is the definition,

or lack thereof, of what constitutes an “experienced team.” The panel strongly supports the guidelines developed and updated by the American Society of Breast Surgeons; these recommend an SLNB identification rate of 85% and a false-negative rate of 5% or less. This is an interesting recommendation in light of the data reviewed by the panel, where false-negative rates, even in the most favourable subgroups of trials, ranged from 6.2% to 7.8%.

A final limitation is that the panel did not address the question of what are the preferred techniques for performing SLNB. Recently, with shortages of isosulfan blue dye and reports of skin necrosis with methylene blue, some surgeons have switched to using only radiolabelled dye. This is acceptable when the surgeon is experienced, but relatively few surgeons can easily learn the technique without also using blue dye. In addition, there are sufficient data to support subareolar injection over peritumoral injection. Subareolar injection results in a higher rate of node identification and is easier for most surgeons to learn (and more easily tolerated by the patient as the volume of injection is 1 mL instead of 8 mL).

Competing interests: Dr. Neumayer was a paid consultant for Myriad Genetics.

Reference

1. Kim T, Giuliano AE, Lyman GH. Lymphatic mapping and sentinel lymph node biopsy in early-stage breast carcinoma: a meta-analysis. *Cancer* 2006;106:4-16.