ORIGINAL ARTICLE

Current Issues in the Surgical Management of Breast Cancer: A Review of Abstracts from the 2002 San Antonio Breast Cancer Symposium, the 2003 Society of Surgical Oncology Annual Meeting, and the 2003 American Society of Clinical Oncology Meeting

Lisa A. Newman, MD, MPH, FACS

Associate Professor of Surgery and Director, Breast Care Center, University of Michigan, Ann Arbor, Michigan

■ **Abstract:** Three areas of development in the surgical management of breast cancer received significant attention in 2003—breast-conserving surgery, sentinel lymph node (SLN) biopsy, and ductal lavage. Provocative investigations focusing on these controversial aspects of surgical care were presented at major national oncology meetings throughout the year. The recently published 20-year updates by the National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Italian National Cancer Institute confirm the survival equivalence of breast-conserving surgery and mastectomy in early stage disease. Data reveal, however, that this strategy is underutilized in the United States when compared with other countries. A meta-analysis of close to 70 published trials on the use of SLN biopsy has revealed an overall SLN identification rate of greater than 90%, with a false-negative rate of 8.4%. Two major controversies remain to be resolved: Is there a subset of sentinel node-positive patients who may safely avoid complete axillary lymph node dissection? What is the best way integrate lymphatic mapping into neoadjuvant chemotherapy protocols? The strength of ductal lavage as a risk assessment adjunct is related to the ability to detect cellular atypia, a feature associated with a three- to fivefold increased risk for breast cancer. This technique continues to be rigorously evaluated in a number of ongoing studies. ■

BREAST-CONSERVING THERAPY

The National Surgical Adjuvant Breast and Bowel Project (NSABP) and the Italian National Cancer Institute recently published 2-year updates confirming the survival equivalence of breast-conserving therapy and mastectomy as management for early stage breast cancer (1,2). At the December 2002 San Antonio Breast Cancer Symposium (SABCS) the National Cancer Institute (NCI) in the United States presented additional long-term survival data regarding the breast-conserving approach (3). Poggi et al. (3) reported outcome data on 247 patients with primary breast tumors up to 5 cm in size who were randomized to lumpectomy with axillary lymph node dissection (ALND) versus modified radical mastectomy. With a median follow-up of 18 years, no difference in overall survival was noted. This confirms, on a decidedly long-term basis, the oncologic safety of breast-conserving surgery in patients with T1 and T2 breast cancers. These data also reaffirm a preexisting concept that distant relapse from breast cancer and breast cancer mortality are primarily consequences of underlying primary biology as opposed to what is surgically done to the breast.

Despite the numerous studies attesting to the safety of breast-conserving therapy, it is the aim of all breast surgeons to minimize the risk of local recurrence in lumpectomy patients. Strategies related to this effort as a function of margin control were the focus of two studies presented at the San Antonio meeting. An Australian study presented by Leong et al. (4) looked at risk factors for local recurrence in 542 node-negative patients who had been treated with lumpectomy and radiation; median follow-up was 5 years. This study revealed that a positive lumpectomy margin was one of the most significant predictors of local recurrence (12% compared to 3% for those patients with negative margins). Lumpectomy patients who were younger than age 35 years also had a relatively higher risk

Address correspondence and reprint requests to: Lisa A. Newman, MD, Breast Care Center, University of Michigan, 1500 East Medical Center Drive, 3308 CGC, Ann Arbor, MI, 48109, USA.

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of local recurrence. Smitt et al. (5), in a California study looking at the predictive value of positive margins in 535 patients with either stage I or II disease who underwent breast-conserving surgery and with a median follow-up of 6 years, had remarkably similar results; local recurrences occurred in 14% of margin-positive cases compared to 3% of the margin-negative cases, and women younger than 50 years were at increased risk for in-breast relapse (5). The value of margin control is therefore well established; however, there is no universal definition for what constitutes the optimal negative margin in a lumpectomy case. The previously noted phase III studies of breast-conserving therapy versus mastectomy are perfect examples of the variation that exists. The NSABP defines a negative margin as the absence of tumor cells at the inked surface (1); the Italians generally had relatively wide margin control, by routinely performing quadrantectomies for T1 tumors (2); and the American NCI study mandated grossly complete tumorectomies only, with no requirement for microscopically clear margins (3). Despite differences in margin status, these studies all found survival equivalence between the lumpectomy and mastectomy arms.

Unfortunately international studies indicate that breast-conserving surgery is underutilized in the United States compared to other countries, despite confirmation of its safety in long-term reports. The Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, which compared the aromatase inhibitor anastrozole to tamoxifen in postmenopausal patients with early stage disease from 21 countries, revealed that American participants had a significantly higher rate of mastectomy (51%) compared to participants from the United Kingdom (42%). These findings were reported by Locker et al. at the SABCS. The disparity in utilization of the breast-sparing approach can be attributed to either patient or physician bias or both these factors.

Breast-conserving surgery has been studied in two other settings: ductal carcinoma in situ (DCIS) and in elderly patients. At the SABCS Cutuli et al. (7) reported a French study of more than 1600 patients with pure DCIS who were treated with either mastectomy, lumpectomy, or lumpectomy plus radiation therapy at a median follow-up of 83 months. As expected, because of the very favorable tumor biology associated with DCIS, the overall rate of distant metastasis was approximately 1%, although it was slightly lower in the mastectomy group. In the patients who were treated with breast-conserving surgery with or without radiation and who developed a local recurrence, approximately 50% of the recurrences were invasive cancer rather than DCIS.

Also at the SABCS, Truong et al. (8), from the British Columbia Cancer Agency, reported their experience with breast-conserving surgery in stage I and II breast cancer patients between the ages of 50 and 89 years, with stratification of results by age categories: 50–64, 65–74, and 74–89 years. They noted lower rates of utilization of radiation therapy in the oldest patients, and this was associated with a negative impact on both local rates of disease control and overall survival.

SENTINEL LYMPH NODE BIOPSY

A great deal of active research is under way in the area of lymphatic mapping and sentinel node biopsy, and this is reflected in the national meetings. Since the initial publications of studies on the use of sentinel lymph node (SLN) biopsy with concomitant ALND for breast cancer approximately a decade ago, nearly 70 published trials involving more than 8000 patients have appeared in the literature. A meta-analysis of these studies reported by Kim et al. (9) at the 2002 American Society of Clinical Oncology (ASCO) meeting revealed an overall SLN identification rate of more than 90%, and a false-negative rate of 8.4%. With the most recent studies revealing consistently lower false-negative rates as the learning curve is more widely overcome, SLN biopsy has emerged as a very promising means of minimizing the morbidity of axillary staging. Two major controversies remain unsettled in the SLN research arena: whether there is a subset of the sentinel node-positive patients who might safely avoid the complete ALND, and how to best integrate lymphatic mapping into neoadjuvant chemotherapy protocols.

Currently the standard of care is that patients with a positive SLN should have a complete level I/II ALND. However, the NSABP B-04 trial (10) showed that axillary relapse is a relatively rare event in patients who present with clinically negative axilla, despite the fact that a significant fraction will have occult nodal metastases. Furthermore, the SLN is the isolated site of metastatic disease in the axilla in 30–50% of patients, and there are also abundant data demonstrating that adjuvant chemotherapy and radiation can contribute to the eradication of residual micrometastatic disease in the axilla. The American College of Surgeons Oncology Group will address this question in an ongoing phase III clinical trial. This critical study will randomize patients with a positive SLN to either undergo complete ALND or axillary observation only, and it will therefore define the survival benefit of the standard ALND in patients with known node-positive disease.

Until the completion of phase III data, one avenue of research is to identify ways of predicting which patients are most likely to have residual metastatic disease in the non-SLNs left behind after a positive SLN biopsy. One such effort has been led by investigators at Memorial Sloan-Kettering Cancer Center, in a study reported at the 2003 Society of Surgical Oncology Meeting (11). This project involved 702 patients with positive SLNs who underwent complete lymph node dissection. The clinicopathologic findings in these patients were used to develop an algorithm for estimating the likelihood of finding positive nonsentinel nodes; contributing factors included primary tumor size and whether the sentinel node metastases were detected by immunohistochemistry or by routine hematoxylin-eosin staining, among several other factors.

Regarding the SLN and neoadjuvant chemotherapy issue, it remains unknown whether chemotherapy will have a uniform effect on all axillary nodal metastasis or if it might actually alter lymphatic drainage patterns; either scenario could have an adverse effect on the accuracy of a SLN biopsy performed after delivery of neoadjuvant chemotherapy. A substantial body of evidence does exist showing that chemotherapy can eliminate some axillary nodal metastasis. In the NSABP B-18 study (12), the effect of chemotherapy on axillary metastases can be inferred from the substantially higher rate of axillary node negativity in patients treated with preoperative chemotherapy (59%) compared to those treated postoperatively (43%). As direct evidence of chemotherapy-induced sterilization of axillary metastases, we also have data on patients who were staged at presentation by axillary ultrasound accompanied by sonographically guided fine-needle aspiration (FNA) of abnormal-appearing lymph nodes. Studies from the M. D. Anderson Cancer Center (13,14) and from the Institut Curie (15) demonstrated that in patients with a positive axillary FNA who then received neoadjuvant chemotherapy followed by complete ALND, 25–33% were rendered completely node negative.

The question then turns to whether a SLN biopsy performed after neoadjuvant chemotherapy will reliably identify the completely node-negative patients, or whether the effect of incomplete chemotherapy on axillary metastases might increase the false-negative rate for the mapping procedure. Mamounas et al. (16) presented the largest analysis of this question to date at the 2003 ASCO meeting, where they reported accuracy data for SLN biopsies performed with concomitant ALND following neoadjuvant chemotherapy in participants of the NSABP B-27 trial. Surgical findings for 428 cases were studied, with an 85% SLN identification rate and an 11% false-negative rate.

An alternative strategy would be to stage neoadjuvant patients with a SLN biopsy performed prior to the delivery of neoadjuvant chemotherapy. A German study reported at the SABCS (17) evaluated 11 neoadjuvant chemotherapy patients, 10 of whom had the SLN identified prior to therapy; 6 of these patients had a positive sentinel node and all 6 were completely node negative on subsequent ALND. Sabel et al. (18), from the University of Michigan, reported on 24 patients who were staged with SLN biopsy prior to delivery of neoadjuvant chemotherapy; of the 10 patients who were node positive before chemotherapy and who then underwent postchemotherapy ALND, 30% were rendered node negative. Clearly the disadvantage to the prechemotherapy SLN biopsy sequence is that some of the prechemotherapy node-positive patients will be committed to an "unnecessary" complete ALND following chemotherapy, chemotherapy will eradicate some axillary metastases, and in others metastases were limited to the previously resected sentinel node(s).

DUCTAL LAVAGE

The efficacy of surgical (prophylactic mastectomy, prophylactic oophorectomy) and medical (chemoprevention with tamoxifen) strategies to reduce breast cancer risk have been well documented, resulting in the increased significance of maneuvers designed to identify and stratify high-risk women. Ductal lavage is a minimally invasive procedure involving cannulation and lavage of fluid-yielding nipple orifices, thereby yielding cytologically evaluable specimens. The strength of ductal lavage as a risk assessment adjunct is related to the ability to detect cellular atypia, a feature associated with a three- to fivefold increased risk for breast cancer. A multicenter study by Dooley et al. (19) confirmed the value of ductal lavage (compared to direct nipple aspirates) in detecting cellular atypia. Ductal lavage continues to be rigorously evaluated in a number of ongoing studies.

Investigators from George Washington University (20), Rush–Presbyterian St. Luke's Medical Center (21), and the University of Florida Health Science Center (22) all reported their institutional experience with ductal lavage, revealing cytologically evaluable fluid in 70–80% of cases and atypia in 5–24% of lavaged patients. Khan et al. (23) studied the topographic relationship between a lavaged ductal system and the location of a breast tumor in mastectomy cases from Northwestern University; a quadrant-matched correlation was found in approximately two-thirds of cases.

In another study evaluating ductal lavage in breast cancer patients and reported at the 2003 Society of Surgical

Oncology meeting (24), investigators at the University of Oklahoma found an inverse relationship between the likelihood of atypia on ductal lavage of the contralateral breast and increasing size of the primary tumor. These data are consistent with past findings from Page et al. (23) demonstrating that most of the increase in breast cancer risk associated with atypia is expressed in the first 5 years after diagnosis, after which the risk appears to return to baseline if tumorigenesis has not occurred. These patterns suggest that in a subset of breasts there may be a gradually evolving field effect of abnormal proliferative activity that follows an exposure, and after reaching a maximum level, there is a subsequent decline. If a cancer develops during this interval, decreasing rates of atypia will be seen elsewhere in mammary tissue as the index tumor continues to progress and enlarge over time.

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