Use of Preoperative Breast Ultrasonography for Mapping of Breast Cancer Extent Improves Resection Margins During Breast Conservation Surgery

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Background: Positive margins after breast conservation surgery occur frequently and negatively influence local control rates.

Hypothesis: Preoperative breast ultrasonography reduces the incidence of positive margins during breast conservation surgery.

Design: Case-control analysis.

Patients and Intervention: One hundred twenty-two consecutive patients with invasive breast cancer were studied. Palpation or needle-wire–guided breast conservation surgery was used in the first 61 patients (group 1). Preoperative breast ultrasonography was added to the protocol in the last 61 patients (group 2).

Main Outcome Measures: Incidence of positive margins, distance to closest margin.

Results: There was a 3.7-fold reduction in positive margins \( (P = .04, 95\% \text{ confidence interval, 1.06-16.73}) \) and improved resection margins \( (P = .04, 95\% \text{ confidence interval, 0.14-3.88}) \) when breast ultrasonography was used. Reexcision of margins was done in 11% (7 of 61 patients) in group 1 and 3% (2 of 61 patients) in group 2 \( (P = .17) \).

Conclusion: Preoperative breast ultrasonography improves the margins of resection and decreases the incidence of positive margins during breast conservation surgery.

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WE HAVE WITNESSED significant changes in the treatment of breast cancer over the last 25 years.\(^1,2\) Among them, breast conservation therapy has evolved to be an effective approach for most patients with breast cancer.\(^3\) Large prospective randomized clinical trials have demonstrated breast conservation surgery (BCS) and breast radiotherapy provide survival rates equivalent to mastectomy.\(^1,2,4-7\) Successful BCS must achieve complete removal of the breast cancer while minimizing the volume of tissue removed. A surrogate measure for the success of BCS is assessment of the specimen margins. Surgical margins involved with tumor cells are associated with residual tumor in the adjacent breast tissue and negatively influence local control rates.\(^8-12\) Conversely, negative surgical margins are associated with success in local control. There is great variability (9%-50%) in the incidence of positive surgical margins during BCS.\(^13-16\)

Ultrasonography is increasingly being used in the diagnosis of breast lesions and the staging of breast cancer.\(^17\) Schwartz et al\(^18\) first described the use of ultrasonography to localize nonpalpable lesions prior to surgical biopsy. Since 2001, we have used breast ultrasonography (BUS) to define the extent of breast cancer and guide the volume of breast resection. The objective of this study is to determine if preoperative mapping of breast cancer with ultrasonography reduces the incidence of positive margins during BCS.

METHODS

This is a case-control analysis of a prospective database of patients diagnosed as having invasive breast cancer and treated with BCS between April 1, 1997, and June 30, 2003, at Harbor–UCLA Medical Center, Torrance, Calif. The following inclusionary criteria were used: (1) diagnosis of an invasive breast cancer, (2) visible lesion on BUS, and (3) subjects whose conditions were initially diagnosed by image-guided percutaneous biopsy. Patients with palpable or nonpalpable tumors were included in the study. Patients were excluded if (1) the diagnosis was established by excisional biopsy, (2) mastectomy was the primary surgical treatment, or (3) neoadjuvant chemotherapy was used.

From April 1, 1997, through December 31, 2000, patients (group 1) underwent BCS us-
operative physical examination by an experienced surgeon and palpation or needle-wire guidance. All patients underwent a pretreatment of BUS in addition to the traditional approach of palpation or needle-wire guidance. Their breasts were marked using the following formula:

\[ \frac{4}{3} \pi (r_1 \times r_2 \times r_3) \]

A specimen-tumor ratio was calculated by dividing the calculated specimen volume over the calculated tumor volume in each case. These data were also compared.

The chi-squared test or Fisher exact test was used to compare categorical differences between groups. The t test was used for analysis of continuous variables. P < .05 was statistically significant.

### RESULTS

A total of 659 patients were treated for breast cancer during the study period. One hundred twenty-two patients who underwent wide local excision for treatment of 125 primary invasive breast cancers met the criteria for inclusion in this study. The patients' demographic and tumor characteristics are listed in Table 1. There were no demonstrable differences between groups 1 and 2.

Outcomes of surgical resection are summarized in Table 2. Measurements of the distance to the closest margin were available in 62 of 63 tumor excisions in group 1 and in all 62 tumor excisions in group 2. Margins of resection were positive in 13 patients in group 1 and 4 patients in group 2. This was statistically significant (Table 2). Margins of resection were negative but reported as 2 mm or less in 18 patients in group 1 and 17 patients in group 2. Thirty-one patients in group 1 and 41 patients in group 2 had negative margins of resection and a distance greater than 2 mm from the inked margin. A graphic comparison of the measured margins of resection in groups 1 and 2 is shown in Figure 3.
Patients with positive margins of resection had a median (SD) age of 52 (9) years. Median (SD) tumor size was 2.1 (0.8) cm and the volume (SD) of tissue removed was 92 (77) mL. Patient age (P = .27), tumor size (P = .60), or volume of tissue removed (P = .21) was not significantly different in comparison to the patients with negative margins on analysis of variance. Two patients with positive margins had lobular histologic features compared with 4 among those with negative margins of resection (P = .18).

Seven patients underwent reexcision in group 1 and 2 in group 2. Negative margins were achieved on reexcision in all cases. No patient required mastectomy after attempted BCS.

### COMMENT

The 1990 statement of the National Institutes of Health Consensus Development Conference on Treatment of Early-Stage Breast Cancer acknowledged breast conserving surgery and radiotherapy is an appropriate method of primary therapy for most women with stage I or II breast cancer. This approach is preferable to mastectomy because it provides equivalent survival while preserving the breast. The incidence of ipsilateral breast recurrence ranges from 0.5% to 1% per year. Local failure of breast conservative therapy is a serious event in the life for a patient with breast cancer. Patients are often discouraged on the discovery of recurrent disease as it is perceived to be a life-threatening event. The patient’s anxiety is also increased by the almost certain recommendation for mastectomy.

The surgeon’s goal during BCS is to remove all evidence of cancer while simultaneously achieving a satisfactory cosmetic outcome. Thus, a balance is created between the zeal to remove the tumor with wide margins, providing better tumor clearance, and the need to remove the smallest volume of breast tissue to provide acceptable cosmesis. When this balance is disturbed, the consequence is an inadequate excision or a suboptimal cosmetic result. It is in this struggle that a positive margin can be encountered.

The success of breast conservation must ultimately be measured in terms of overall survival, disease-free survival, and local recurrence rates. However, the final outcome of surgery may be unknown until several years later. A surrogate measure for the technical success of BCS is the assessment of surgical margins of resection.

There is wide agreement that the presence of positive margins of resection negatively influences a patient’s likelihood of remaining disease free. Numerous reports document a 2- to 3-fold increase in the incidence of local recurrences after surgical resection with positive margins. This, however, has not been demonstrated universally.

Patient and tumor factors, such as young age, the presence of lymphovascular invasion, an extensive intraductal component, or ductal carcinoma in situ, and lobular histologic features have been associated with a higher prevalence of positive surgical margins. These factors may play a role in the decision-making process of patient selection for BCS or mastectomy. On the other hand, technical factors significantly contribute to the occurrence of positive margins. Veronesi et al have re-
ported a 4-fold reduction in the incidence of positive margins with wider resection (quadrantectomy) relative to local excision. The prevalence of positive margins is high, ranging from 9% to 50% when traditional surgical methods are used. Factors that may influence this wide range are the lobular histologic features, the presence of extensive intraductal carcinoma, the patient’s age, tumor size, method of biopsy, and the surgeon’s experience.13–16

Breast ultrasonography is used extensively as a diagnostic tool. It is also widely used as a guide for percutaneous biopsy of solid lesions and aspiration of cysts.17–20 The use of BUS for breast cancer surgery was first reported in 1999. Rahusen et al30 reported an 89% success rate in achieving negative surgical margins with the use of intraoperative ultrasonography in a pilot study of 19 patients. Simultaneously, Harlow et al31 reported a 97% success rate in achieving negative margins of resection. Moore et al32 have reported a 29% incidence of positive margins when traditional surgical methods of guidance (ie, palpation) are used in contrast with a 3.5% incidence of positive margins when intraoperative ultrasonographic guidance is used for excision of palpable breast cancers.

Different methods of ultrasonographic-assistance for breast cancer surgery have been reported. Smith et al33 report using ultrasonography to guide the surgical cut by following the “line of sight” intraoperatively. Israel et al34 use ultrasonography to place localization-retraction devices to facilitate surgery. Others use ultrasonography to mark the lesion with a wire and/or blue dye prior to surgical resection.35 During the study period, we did not have ultrasonographic equipment available for intraoperative use and, therefore, our technique differs from reports in the literature. We did use BUS in the preoperative examination to define the anatomical extent of breast cancer. The examination consisted of a detailed sonographic evaluation of the tumor and its margins. The presence of ductal extension, satellite lesions, and the location of the tumor in relation to the skin and pectoralis muscle were determined by ultrasonography. Then, markings were drawn on the skin of the breast by the operating surgeon to delineate the volume of breast tissue to be removed and to identify any skin or pectoralis muscle-fascia requiring excision. Using this technique of ultrasonographic mapping we documented a 3.7-fold reduction in the incidence of positive surgical margins.

There is considerable debate regarding what is an acceptable surgical margin. A commonly accepted approach is to remove all evidence of visible-palpable tumor surrounded by a 1-cm rim of normal-appearing breast tissue.36 There is no consensus on the smallest acceptable microscopic margin to secure a low recurrence rate. Recommendations range from a minimum of 2 mm to the absence of tumor cells at the surgical cut of the specimen.3,36 Microscopically invasive margins in our series increased from a mean of 4.7 mm in group 1 to 6.7 mm in group 2, when ultrasonography was used. Two thirds of our patients who underwent ultrasonographic mapping had at least 2-mm microscopic margins. This was achieved in less than half the cases in the control group. Similarly improved outcomes have been reported by Moore et al32 and Kauffmann et al37 with the use of intraoperative ultrasonography.

Only 3% of the patients who underwent ultrasonographic mapping (group 2) underwent reexcision, compared with 11% in the control group (group 1). Overall, 9 (53%) of 17 patients with positive margins underwent reexcision. Many other factors influence the decision to do a second operation to obtain additional margins. DiBiase et al37 and others have documented that not all positive margins carry the same risk of recurrence.26,27 The extent of involvement of the margins must be considered. Patients who did not undergo reexcision in our series had only focally positive margins and often a high lymphatic tumor burden. Focally positive margins may have the same outcome as cases with negative margins with the use of radiotherapy plus a boost to the primary site.15,26,27 In addition, the extent of nodal metastases negatively influences the overall prognosis of breast cancer and decreases any potential benefit of reexcision.

Are there any other factors that may have influenced the outcomes seen in the group of patients who had a preoperative ultrasonogram? This study compared a population of consecutive patients with the same selection criteria. These patients were abstracted from a prospective database but the analysis of results is retrospective. Therefore, no random assignment of patients to each arm of the study was made. These 2 groups of patients, however, were clinically and statistically comparable based on patient and tumor characteristics noted in Table 1. We observed the mean tumor size to be slightly larger in group B, the ultrasonographic group, when compared with group 1. Similarly, a larger mean volume of tissue was removed in the ultrasonographic group. These differences were not statistically significant. Could these results be the effect of the surgeon’s conscious or unconscious excision of a larger volume of tissue when ultrasonography was used? We calculated a relationship between the volume of tissue excised and the volume of breast cancer. It was equivalent (P . 75). We believe the demonstrated improvement in obtaining negative margins is the consequence of ultrasonography exacting a more accurate definition of the tumor location and extent, thus promoting a more precise resection. Other investigators have reported that the use of intraoperative ultrasonography contributes to smaller volumes of resection.32,35 This may have a positive influence on the cosmetic outcome of breast cancer surgery and may be a potential benefit of intraoperative vs preoperative ultrasonography and warrants further study.

Based on this case-control study, we conclude that the use of breast ultrasonography for mapping the extent of invasive breast cancer prior to BCS improves the margins of resection and decreases incidence of positive margins.

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REFERENCES


DISCUSSION

Lawrence D. Wagman, MD, Duarte, Calif: The introduction of new technology or of an established technology into a classical management algorithm is a complex combination of appropriateness, value, effectiveness, cost, learning curve, and other factors. We have heard several papers over the last few days bringing us up to date on these opportunities. Dr Vargas and his colleagues have addressed an important element of successful BCs—the negative margin generated with a single operative procedure. Although not a holy grail, like a perfect sunset or a perfect wave, it is certainly a laudable goal worthy of pursuit and worthy of resources.

What we have to recognize from the outset is the cross-discipline skill that is exemplified by this paper. Dr Vargas and his colleagues have stretched their skill set and embraced a workhorse technology from breast radiology by accepting the responsibility to personally learn and match skills of the ultrasonographer. They have hurdled the often challenging obstacle of multidisciplinary approach, that of a timeliness and efficiency when an additional procedure is incorporated. To the average surgeon who has not had training in ultrasonography, how long would you anticipate it would take to become proficient? What would be the specific number of cases? What metric would measure capability? For example, if a 10% positive margin rate was identified in your first 30 cases, are you sent back to the learning resource center? Are there any standards? I noted in the finely prepared and timely delivered paper’s “Methods” section a reference to performing ultrasonography, not just immediately before in the preoperative area but days before the surgery. Now, in my limited experience with
all breast-imaging techniques and even with incision planning, I have noted that the spatial relationships of the tumor in the breast is highly dependent on position. Sometimes positioning in the anesthetized patient results in a different relationship than in the awake patient. Why not perform the ultrasonogram in the operating room after positioning the patient? Maybe at the same time you are massaging the breast to move the blue dye into the sentinel nodes?

Now, for those of you who stayed for a late presentation 4 years ago in San Francisco, Calif, probably at the exact same time as this one, you may remember a rather lackluster, but very provocative paper, challenging the worth of specimen mammography. I remain intrigued by the inability of the combined efforts of the surgeon and radiologist to identify tumor at the margins during the operative event. Do you think adding specimen ultrasonography will improve the accuracy of specimen mammography?

About the margins. In the traditionally resected group, there were 13 (21%) of 62 patients who had a positive margin with an impressive reduction in the ultrasonographic group with only 4 (6%) of 62 patients. But I would like to know something else that you showed us quickly in one of the bar graphs. When combining patients who had less than 2 mm but negative margins and positive margins, while 50% of the traditionally resected tumor margins met this criteria of close and positive, 66% of those done with the ultrasonographic guidance fell into this category. This result is less impressive than the gap between 21% traditional resection without ultrasonographic guidance and 6% with ultrasonographic guidance.

To conclude this line of questioning, we saw a 2-mm difference between the 2 groups (4.6-mm vs 6.6-mm margins). It was stated in the paper that the goal of the resection was 1-cm margins. I wondered how many patients in each of the groups actually achieved this preplanned objective. Now these patients all had invasive cancer, and I would say with confidence that usually all noninvasive images are reasonably similar within about a 5-mm difference. I wonder what the authors think would happen if we took this to DCIS (ductal carcinoma in situ), to invasive lobular of which there were only a few patients in this study, or lobular carcinoma in situ, given that these histologic features have a more insidious type of spread.

Finally, a small technical point. The specimen volume was reported based on a mathematical model of a regular geometric figure, an ellipsoid. Now this is really a crucial element because when you are looking at the difference in size between the resection and the tumor, you are trying to get to the right size of what is done as a lumpectomy. So I wondered if we report these elements we might be better measuring this volume with a liquid displacement technique, the Archimedes principle, and having that be more accurate. The question that comes at the end of all of these presentations, now that I know it can be done, is should I be doing it?

Theodore X. O’Connell, MD, Los Angeles, Calif: I have a question regarding method. This is not a randomized prospective study, and I think the conclusion is a post hoc proper hoc type of argument in that you did this ultrasonography and then you had better results, but could that be just because of increasing experience and knowing that you are trying to improve results? If you are testing a method, the Hawthorne effect, you do get better results. So could the results be a timeline experience-related and a Hawthorne effect? Why did you not do a randomized prospective study? Or are you planning to do one in the future?

Laura Esserman, MD, San Francisco, Calif: That was an excellent paper and I think really points out the importance of trying to use technology, and integrating it into our practice with the specific goal of achieving a better result such as clean margins. I wanted to echo the question that Dr O’Connell had and I wondered if the same surgeons performed the cases prior to the introduction of the ultrasonography. Thus, could the improved results be as likely because of a new team of surgeons working together to improve results over time?

Another way you might be able to get at that question is to look at whether there was a learning effect with ultrasonography between the first year, 2001-2002, and the second year, 2002-2003. Was there a further decrease in the margin excision rate? One other question was whether there was more EIC (extensive intraductal cancer) in one group than in the other. We know that DCIS is not palpable and often not visualizable by ultrasonography, even when calcifications are present.

My last question is whether in the operating room, if ultrasonographic guidance is used, do you still feel that you need to perform specimen mammography? Can you eliminate the specimen radiograph and is intraoperative ultrasonography considered to be an acceptable way to confirm that the lesion is in the specimen?

Stanley P. L. Leong, MD, San Francisco: I have 2 questions. For the margins, have you broken down [your analysis] to the lateral margins vs the superficial and deep margins because according to the videotape, I think that the lateral margins are well defined. But the deep margins seem to be somewhat difficult, especially when you are down about halfway in a large breast. I thought an intraoperative approach probably would define it better.

Dr Wagman has suggested the utility of intraoperative ultrasonography. Are you doing intraoperative ultrasonography and, for surgeons who are getting into this technique, would you recommend moving right into intraoperative ultrasonography or do you still prefer the preoperative approach?

John T. Vetto, MD, Portland, Ore: I would expect this technique to be most helpful for nonpalpable lesions, and yet 78% of the patients in your study had palpable lesions. So, my question is do you have any data to compare the preultrasonographic and postultrasonographic groups to perhaps show that most of the benefit was in nonpalpable lesions? I question whether we really need to be doing this for all easily palpable lesions.

My second question is related to the question about whether the same surgeons were doing this [procedure]. I am wondering if margin excision, which a lot of us do, was routinely used in both the preultrasonographic and the postultrasonographic phases.

Ronald G. Latimer, MD, Santa Barbara, Calif: The example shown was very nice. I noticed that there was no bruising, no distortion from the core biopsy. Unfortunately, that is not always the case. I would ask if there is an interval between the core biopsy to let the hematoma resolve before you use your technique and what would you recommend? Also, I would like to follow up the question about specimen mammography. When do you have the pathologist not come to the operating room to examine the specimen to look at margins?

Nathalie M. Johnson, MD, Portland: One of my questions was the relevance of pathologic evaluation of the tumor and margins within the operating room as most of these were palpable or easily visible by ultrasonography, and usually our pathology colleagues can help us intraoperatively with margins on these particular cancers as opposed to tumors not visualized by ultrasonography. It occurs to me that this technique might be helpful as we move into the age of mammosite intracavitary brachytherapy. As you know, the cavities need to be a certain size and shape to adequately accommodate the mammosite balloon or intracavitary brachytherapy catheters. I think this technique may be valid as we move into the new age of breast cancer partial breast irradiation.

Bruce E. Stabile, MD, Torrance, Calif: I would like to congratulate my colleague, Dr Vargas, on a superb presentation and...
In response to Dr Leong's question, ultrasonography is helpful in defining all margins of resection. It helps define the segment of skin to be removed and, if the tumor is close to the deeper margins, we certainly resect the fascia.

Do our results relate to a learning curve? Surgery was done by the same surgical team. This is a retrospective study. I do not know, Dr O'Connell, if this is a result of the same surgeon having more experience. We have been pretty careful and are always cognizant of the goal of getting negative margins. I do not think the desire to achieve negative margins has changed. This is a retrospective review of a prospective database; therefore, it is unlikely that we were biased and removed a larger volume of tissue because we were using ultrasonography. It is apparent that ultrasonography has helped us and potentially can help other surgeons because we all struggle with the issue of obtaining positive margins.

In terms of pathologic consultation in the operating room, we have a protocol where we ink our own specimens and we do serial resectioning of the specimens for gross assessment. The gross pathologic assessment is done by the surgeons. If we have grossly close margins, we excise more tissue. If the tumor is within a comfortable distance of the margin, then we do not.

In terms of specimen mammography, we do use it when surgery is done for calcifications. Specimen ultrasonography and serial resectioning of the specimen provide the best surrogate estimation of margins for mass lesions. But with microcalcifications, we certainly use specimen mammography.

**ARCHIVES OF INTERNAL MEDICINE**

The Tattooing Paradox: Are Studies of Acute Hepatitis Adequate to Identify Routes of Transmission of Subclinical Hepatitis C Infection?

Robert W. Haley, MD; R. Paul Fischer, MD

**Background:** The Hepatitis Branch of the Centers for Disease Control and Prevention does not recommend routine regulation and inspection of tattoo parlors because surveillance of hepatitis C virus (HCV)-positive acute hepatitis cases rarely identifies tattooing in the incubation period. However, the majority of seroepidemiological studies agree that tattooing is a strong, independent risk factor for subclinical HCV seropositivity. We postulated that this paradox might be explained if transmission of HCV by tattooing generally caused subclinical HCV seropositivity without the acute hepatitis syndrome.

**Methods:** We reanalyzed data from a prior seroepidemiological study of 626 consecutive patients who were unaware of their HCV serologic status and whose risk factors were ascertained by interview of an internist. Separate multiple logistic regression models were developed to predict a history of the acute hepatitis syndrome and HCV seropositivity.

**Results:** A history of injection-drug use was strongly associated with both HCV seropositivity (adjusted odds ratio [AOR], 7.2; 95% confidence interval [CI], 3.1-16.5) and a history of acute hepatitis (AOR, 5.9; 95% CI, 2.5-13.8), whereas having a commercially applied tattoo was strongly associated with HCV seropositivity (AOR, 6.5; 95% CI, 2.9-14.4) but not with a history of acute hepatitis (AOR, 1.2; 95% CI, 0.5-3.3).

**Conclusions:** Intravenous injection of relatively large quantities of inocula of HCV may be more likely to result in the relatively rare acute HCV hepatitis syndrome, whereas intradermal exposure to small quantities of inocula may cause only subclinical HCV infections. If so, public policy on regulation and inspection of tattoo parlors should be determined by seroepidemiological studies rather than by the Sentinel Counties Study of acute hepatitis cases. (2003;163:1095-1098)

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