

# Role of Primary Breast Cancer Characteristics in Predicting Positive Sentinel Lymph Node Biopsy Results

## A Multivariate Analysis

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**Hypothesis:** Certain primary breast tumor characteristics can be used to predict positive sentinel lymph node biopsy (SLNB) results and thus determine which patients should undergo SLNB.

**Design:** Retrospective review of patients undergoing SLNB for invasive breast cancer from March 1, 1998, through March 31, 2001.

**Setting:** University-affiliated tertiary care hospital.

**Patients:** Two hundred fifty-seven consecutive patients undergoing successful SLNB.

**Main Outcome Measures:** Correlation of patient age, tumor size, histological subtype, grade, lymphovascular invasion (LVI), host lymphoid reaction, border of neoplasm, characteristics of ductal carcinoma in situ, presence or absence of lobular carcinoma in situ, estrogen receptor, and *her-2-neu* oncogene status with positive SLNB results. Univariate and multivariate analyses were applied. Stepwise multiple logistic regression analysis identified variables predictive of positive SLNB results ( $P \leq .05$ ).

**Results:** Regression analysis identified tumor size and LVI as the only variables predictive of positive SLNB results. Results of SLNB were positive in 73 (28.4%) of 257 patients (T1a, 5/37 [13.5%]; T1b, 19/93 [20.4%]; T1c, 37/103 [35.9%]; and T2, 12/24 [50.0%]). Although LVI did not correlate with tumor size, it was highly predictive of positive SLNB results by means of the following equation:  $1/(1 + e^{-z})$ , where  $z = 0.3079 + 1.3814 (\text{LVI}) - 1.1869 (\text{T1a}) - 0.3235 (\text{T1b})$ , or  $+0.5724 (\text{T1c})$ .

**Conclusions:** Tumor size and LVI were the only variables independently predictive of positive SLNB results. Lymphovascular invasion was the strongest predictor. These data show a higher than expected incidence of positive SLNB for all tumor sizes, which may be explained by results of immunohistochemical analysis of sentinel lymph nodes, and which suggest that all patients with invasive breast cancer should be offered SLNB. Further studies with a larger cohort of patients are warranted.

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WITH THE increase in routine screening mammography, the number of T1a and T1b breast cancer diagnoses has increased proportionally.<sup>1</sup> The role of standard axillary lymph node (ALN) dissection (ALND), especially for T1a lesions, has been questioned. Before sentinel lymph node (SLN) biopsy (SLNB), several studies<sup>2-11</sup> were published on the predictive factors of ALN metastasis in small, invasive breast carcinomas to determine whether ALND could be avoided in this subset of patients. Many studies<sup>2-9</sup> found that younger age, increasing tumor size, and the presence of lymphovascular invasion (LVI) correlated with a higher incidence of ALN metastasis. Multiple studies have been unable to identify a consistent subset of patients in whom ALND could be avoided.

In the mid-1990s, SLNB was introduced as a minimally invasive alternative to ALND for patients with breast cancer.<sup>12-17</sup> The pathological analysis of the SLN differs from that of the standard ALND, and therefore it raises the question whether the same factors that predicted ALN metastasis could be used to predict SLN metastasis. The purpose of this study was to analyze characteristics of primary breast tumors in predicting positive SLNB results and to determine which patients should undergo SLNB.

## RESULTS

A total of 257 patients successfully underwent SLNB for invasive breast cancer. Results of SLNB were positive for metastatic disease in 73 (28.4%). Tumor size ranged from 0.1 to 4.5 cm, with a mean of 1.2 cm. Positive SLNB findings were detected in 5 (13.5%) of the 37 patients in

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## MATERIALS AND METHODS

We performed a retrospective review of patients who underwent SLNB for invasive breast cancer from March 1, 1998, through March 31, 2001, at Long Island Jewish Medical Center, New Hyde Park, NY, a university-affiliated tertiary care facility. Age of patients ranged from 31 to 84 years, with a mean  $\pm$  SD age of  $61.7 \pm 11.0$  years. Patients were selected for SLNB if they did not have palpable axillary nodes, previous lymph node surgery, or contraindications for technetium Tc 99m ( $^{99m}\text{Tc}$ ) or lymphazurin blue injection. The following 13 characteristics of primary tumors were evaluated: patient age, tumor size, histological type, presence or absence of ductal carcinoma in situ (DCIS), architectural pattern of DCIS, presence or absence of extensive DCIS, presence or absence of lobular carcinoma in situ (LCIS), border of neoplasm, LVI, host lymphoid reaction, grade of tumor, estrogen receptor status, and *her-2-neu* oncogene status. Both  $^{99m}\text{Tc}$  sulfur colloid and lymphazurin blue injections were used intraoperatively to identify the SLN(s). Nodes that were "hot" or radioactive, blue, or both were surgically excised as the putative SLN(s). Each sentinel node was examined by means of frozen section, standard hematoxylin-eosin (H&E), and immunohistochemical (IHC) analyses. A positive SLN was defined as metastatic breast cancer cells seen on results of frozen-section, standard H&E or IHC analysis. Data were subjected to univariate and then multivariate analysis. Stepwise multiple logistic regression analysis was used to identify variables that would predict a positive SLN ( $P \leq .05$ ).

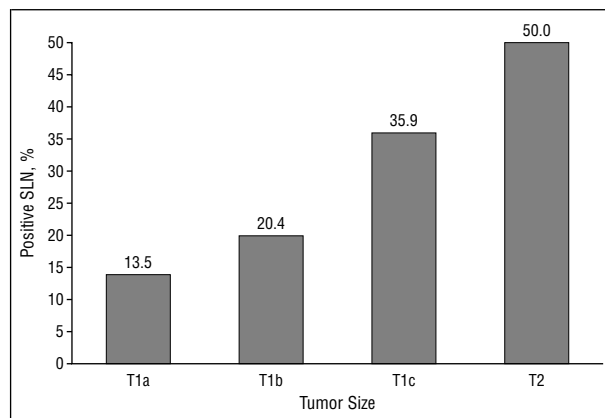
the T1a group, 19 (20.4%) of the 93 in the T1b group, 37 (35.9%) of the 103 in the T1c group, and 12 (50.0%) of the 24 in the T2 group (**Figure 1**).

Infiltrating ductal carcinoma was identified in 229 (89.1%) of the 257 patients. Twenty-eight patients (10.9%) had infiltrating lobular carcinomas. Positive SLNB findings were detected in 61 (26.6%) of the 229 patients with infiltrating ductal carcinomas and in 12 (42.8%) of the 28 patients with infiltrating lobular carcinoma.

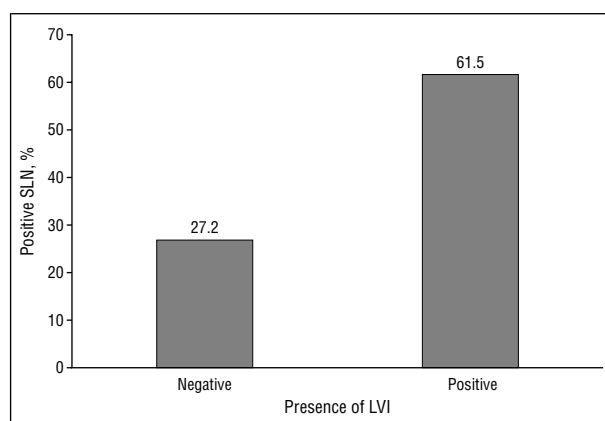
The presence or absence of LVI was available in 226 patients. Of these, 13 (5.7%) had LVI, whereas 213 (94.2%) did not. Of the 13 patients with LVI, 8 (61.5%) had positive SLNB findings. Of the 213 patients without LVI, 58 (27.2%) had positive SLNB findings (**Figure 2**).

The following tumor characteristics were not significant in predicting positive SLNB results and are summarized in the **Table**: histological type, presence or absence of DCIS, presence or absence of comedocarcinoma, presence or absence of extensive DCIS, presence or absence of LCIS, border of the neoplasm, presence or absence of host lymphoid reaction, tumor grade, estrogen receptor status, and *her-2-neu* oncogene status.

Seventeen (6.6%) of the 257 patients defined as having a positive SLNB result had positive findings of IHC stains only without detection of metastatic disease by means of frozen section analysis and standard H&E stains.



**Figure 1.** Stratification of sentinel lymph node (SLN) status by tumor size. The SLN biopsy findings were positive in 5 of 37 patients with T1a disease, 19 of 93 patients with T1b disease, 37 of 103 patients with T1c disease, and 12 of 24 patients with T2 disease.  $P = .46$  for T1a vs T1b;  $P = .01$  for T1a vs T1c;  $P = .003$  for T1a vs T2;  $P = .02$  for T1b vs T1c;  $P = .008$  for T1b vs T2; and  $P = .25$  for T1c vs T2.



**Figure 2.** Stratification of sentinel lymph node (SLN) status by the absence or presence of lymphovascular invasion (LVI) ( $P = .02$ ).

If these patients had undergone standard ALND, the metastatic disease would not have been detected. Of these 17 patients, 5 had T1a lesions; 4, T1b lesions; and 8, T1c lesions. Axillary node dissection was completed in 4 of the 17 patients with positive IHC results only.

Univariate analysis showed that LVI and tumor size were the only statistically significant variables. Multivariate regression analysis confirmed that tumor size and LVI were the only variables predictive of positive SLNB results. Using the multivariate logistic regression analysis, the following equation was developed to predict the likelihood of positive SLNB results based on LVI and tumor size:  $1/(1 + e^{-z})$ , where  $z = 0.3079 + 1.3814$  (0 for no LVI; 1, LVI),  $-1.1869$  (T1a),  $-0.3235$  (T1b), or  $+0.5724$  (T1c).

## COMMENT

The status of the axilla is an important prognostic indicator and directs subsequent adjuvant therapy for patients with invasive breast cancer. Levels 1 and 2 ALND is the standard method for surgical evaluation of the axilla. More recently, SLNB has emerged as a minimally invasive alternative to ALND. The pathological analysis of the SLN differs from that of the standard ALND. In the

### Summary of Positive SLN Findings by Primary Tumor Characteristics\*

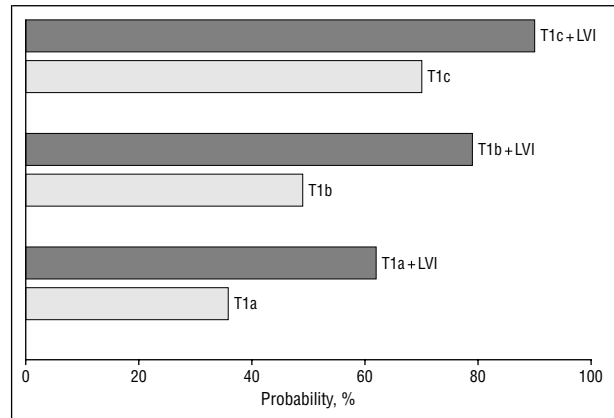
Variable	No./Total No. (%) of Patients		P Value
	Positive SLN	Negative SLN	
Lobular carcinoma	12/28 (42.9)	16/28 (57.1)	.08
Ductal carcinoma	61/229 (26.6)	168/229 (73.4)	
DCIS in specimen	53/192 (27.6)	139/192 (72.4)	
No DCIS in specimen	16/55 (29.1)	39/55 (70.9)	NS
Comedo DCIS	21/67 (31.3)	46/67 (68.7)	
Noncomedo DCIS	28/110 (25.5)	82/110 (74.5)	
Circumscribed border	2/17 (11.8)	15/17 (88.2)	NS
Infiltrating border	65/210 (31.0)	145/210 (69.0)	
No host reaction	52/189 (27.5)	137/189 (72.5)	
Host reaction	15/39 (38.5)	24/39 (61.5)	NS
No extensive DCIS	21/65 (32.3)	44/65 (67.7)	
Extensive DCIS	6/19 (31.6)	13/19 (68.4)	
ER negative	9/34 (26.5)	25/34 (73.5)	NS
ER positive	60/210 (28.6)	150/210 (71.4)	
Her-2-neu oncogene negative	57/195 (29.2)	138/195 (70.8)	
Her-2-neu oncogene positive	9/34 (26.5)	25/34 (73.5)	NS
Grade 1	35/129 (27.1)	94/129 (72.9)	
Grade 2	20/73 (27.4)	53/73 (72.6)	
Grade 3	14/46 (30.4)	32/46 (69.6)	NS
No LCIS	28/95 (29.5)	67/95 (70.5)	
Yes LCIS	17/44 (38.6)	27/44 (61.4)	

\*SLN indicates sentinel lymph node; DCIS, ductal carcinoma in situ; ER, estrogen receptor; LCIS, lobular cancer in situ; and NS, not significant.

standard ALND, each node is bisected and evaluated by means of H&E stain. In SLN analysis, multiple thin-cut sections of each node are examined by means of H&E and IHC stains. This enhanced pathological analysis results in a more detailed analysis of each sentinel node and, therefore, a higher probability of detecting micrometastatic disease. From a technical standpoint, any lymph node can be analyzed by means of IHC stain. However, the lymph nodes from an ALND traditionally are not subjected to IHC stain. With SLNB, IHC staining was introduced as part of the lymph node analysis, in part because of the concern of a higher false-negative rate. To compensate for removing only a few lymph nodes, each node was examined more thoroughly by means of multiple thin sections and IHC stain.

In our study, this more detailed analysis identified 17 patients with positive SLNB findings who otherwise would have received a negative diagnosis based on results of ALND only. When SLNB was introduced at our institution, the protocol stipulated that a positive SLNB finding required ALND, and thus 4 of the 17 patients underwent completion ALND. However, as more data accumulated on SLNB and the questionable significance of positive IHC findings only, patients selectively underwent ALND after a positive SLNB result. On the basis of the February 2001 Consensus Conference, most surgeons are no longer completing ALND.

In many of these patients, the positive lymph node status altered adjuvant therapy by “upgrading” treatment of (“up treating”) the patients. For example, the patient



**Figure 3.** Probability of a positive finding of sentinel lymph node biopsy based on predictive model stratified by tumor size and lymphatic vascular invasion (LVI).

with a 0.3-cm invasive ductal tumor and positive IHC finding only received radiation therapy and tamoxifen citrate. If the lymph node findings were negative, she would have undergone radiation therapy only. Patients who normally would have received chemotherapy consisting of cyclophosphamide (Cytoxan), methotrexate, and fluorouracil received an upgrade to a regimen based on doxorubicin hydrochloride (Adriamycin). In some other cases, the positive IHC finding did not alter adjuvant therapy. Each patient's treatment was individualized. The clinical significance of micrometastatic disease is unclear.<sup>18-21</sup> In a retrospective review, Dowlatshahi et al<sup>18</sup> reported a survival disadvantage in patients with micrometastatic disease. Long-term follow-up and case-controlled studies are needed to determine the clinical significance of SLNs with positive IHC findings only.

Some authors<sup>2</sup> have suggested that ALND may be avoided in patients with T1a tumors on the basis of the low incidence of positive lymph node findings in this subgroup. However, we found a 16% incidence of positive SLN findings in the T1a group. Therefore, we propose that patients with T1a lesions should not be excluded from some form of ALN analysis.

Previous studies have shown that age,<sup>3,4,7,11</sup> grade,<sup>2,3,5,11</sup> LVI,<sup>2-6,9,10,11</sup> and tumor size<sup>2-9,11</sup> predicted positive ALND findings. This study confirms that LVI and tumor size were the only 2 variables predictive of positive lymph node findings. Unlike previous studies, grade and age did not correlate with positive SLN findings. Lymphovascular invasion was the strongest predictor of positive SLN findings. On the basis of our data and multivariate analysis, we developed our equation to allow clinicians to predict the likelihood of positive SLNB results on the basis of LVI and tumor size and thus select patients for SLNB, ALND, or no axillary sampling. For example, using this predictive model, we can determine that a T1a lesion with no LVI has a 36% probability of having a positive SLN finding compared with a T1c lesion with LVI, which has a 90% probability (**Figure 3**). A prospective study with a larger cohort of patients is in progress to evaluate this predictive model. Given the higher than expected incidence of positive SLN findings in T1a lesions, tumor size alone should not preclude an SLNB.

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## DISCUSSION

Blake Cady, MD, Providence, RI: That was a beautiful presentation by Dr Chen; I particularly point out the quality of those slides. Those kinds of slides should be the standard for our slide presentations at our meetings. Her paper addresses a major issue with sentinel node biopsy today: how to analyze the nodes and use the information. Sentinel node biopsy in breast cancer is now widely practiced and widely accepted. Fortu-

nately, it gives us the opportunity to decrease the last major surgical morbidity in the treatment of breast cancer by getting rid of axillary dissection for negative nodes. This situation has arisen because screening for breast cancer has resulted in smaller cancers with fewer node metastases. The median maximum diameter now in Rhode Island, New England, and across the country is only 1.5 cm, and 35% are now T1a and T1b. The positive node rate in traditional node analysis is only about 30%. By 2008, if the American Cancer Society challenge goals can be met with 90% screening of the appropriate population from 40 to 75, the median maximum diameter of all invasive breast cancer will be only 1 cm; 50% will be T1a and T1b, and the traditional node analysis of that entire population by that time would show only 20% positive nodes.

Last November, there was a consensus conference in Washington about prognostic factors in breast cancer. Maybe to your surprise, only 4 features were agreed on as being reliable prognostic factors: size, nodes, grade, and hormone status. There is too much variability and unreliability in doing the other prognostic tests, another great example of the new technology of testing exceeding the knowledge of how to use it.

You all know my biases by this time. Node metastases are indicators, not governors, of survival and outcome. Nobody has ever died of node metastases. They are the speedometer in the oncologic vehicle, not the engine, and you can tape over the speedometer, or throw it away, and it will not change how the cancer or the engine behaves.

A major issue now in breast cancer is the technology of immunohistochemical staining. This test supersedes the knowledge of what to do with the resultant information. The wisdom of how to apply this sophisticated information is simply unknown at the present time.

Just to indicate this, in a single slide, these are patients with negative cytokeratin staining of both bone marrow and lymph node. These are patients with both bone marrow and lymph node immunocytochemical positivity, and this group has a very serious prognosis: around 50% recurrence by 4 years. But patients who have IHC staining of either the node or the bone marrow have identical survival curves. So, the fact that single cells or cell clusters are seen has some survival implication, but notice at 4 years that this curve is flat and is above 80% disease free. The vast majority of people with IHC staining of cells, either in the bone marrow or the sentinel nodes, are going to survive perfectly well. You can know that by the fact that IHC staining in T1a cases may show 25% or 30% with positive bone marrow cells in patients that we know have a 95% 15-year survival. We simply do not know what to do with the information of finding metastatic cells.

In a consensus meeting on sentinel node biopsy held this spring, the conclusion was to not do IHC staining of sentinel nodes routinely. Eighty percent of American breast cancer units are doing that, but it should not be done. We do not. We have chosen not to do such analysis in our unit since we simply do not know what these things mean. If you do use IHC staining, you should not use any collection of cells that are less than 0.2 mm for any therapeutic decision; that includes all these IHC-stained micrometastases. It is another great example of how our technology has outrun our knowledge and our wisdom in how to use it.

One major problem in breast cancer today is the massive overtreatment of patients with excellent prognoses, and IHC staining of these nodes is severely exacerbating this problem. Patients with a 4-mm tubular carcinoma with an IHC cell in the node are getting doxorubicin-cyclophosphamide chemotherapy. This simply cannot be justified. This is a magnificent example of the "Will Rogers" phenomenon: we are "upstaging" patients on new technology that we simply do not know the meaning of in the long term.



What were the node-positive rates if only the H&E with multiple sections were done for T1a and T1b? Keep in mind that T1a and T1b cases have the greatest proportion of micromets [micrometastases], so it may be that half of those metastases that you showed may be just IHC micromets. Twenty-five percent of all your node metastases were IHC-only micromets.

How do you use the IHC-positive sentinel nodes to determine use of axillary dissection, selection of systemic chemotherapy or hormonal use, or use of radiotherapy to the axilla, and estimation of prognosis when you talk to the patient?

You said you change the therapy with the IHC-positive sentinel nodes, but did not tell us how that therapy was changed. Should we really upstage our patients based on IHC staining when we do not know what it means?

If the cancer is LVI (lymph vessel invasion) positive and grade III, you already know that the patients ought to be treated with systemic therapy. How will even sampling the sentinel node help with that judgment about systemic therapy? I was brought up in medical school that, "if the results of a test do not change what you do, don't do the test." If you have a patient who is LVI positive and grade III and you are going to use chemo anyway, you should not even be doing the sentinel node.

Why do you do a frozen section of the SLN? Tell us how you use that information.

That extremely complicated formula that you developed is much too sophisticated for us simple surgeons. It probably will not be used, and how does it really help?

It was an excellent paper, and it certainly highlights one of the principal issues in contemporary breast cancer now.

**Kenneth Kern, MD, Hartford, Conn:** I want to congratulate Dr Chen on looking at a very important topic of prediction of sentinel node positivity, because each of us facing a patient who is presenting with the option of sentinel node dissection needs predictive information. In particular, we need it in the small tumors. These are the ones that we want to give an optimistic approach to, that we might say it is likely you will not have a positive sentinel but we are going to go ahead and try, and yet then we go ahead and we get fooled by the fact that there is unpredictability in which of these small tumors will have positive nodes.

I wanted to ask the question that, in this regression analysis, did you subcategorize IHC-positive-only patients? Because what we are finding is we get a negative frozen section, we do the later cuts, we get IHC-positive cells, the patient is upset, and everyone is surprised. That is where we need predictability, and yet in this regression analysis, it is all combined into 1 group. You might have some thoughts about the predictability of IHC-only positive cells. In other words, what I would really like to know is, when you get to the T1a patients, is there any factor that can help you predict whether the nodes will be positive, because we already know the size and we know the rate of positivity, and they do not have LVI, and yet some were positive. What else do we have? Do you have any thoughts on what other factors you might look at in the future?

**Barbara Ward, MD, Greenwich, Conn:** I am just a little surprised that age did not come up more, and at least we think that younger patients have worse disease. I just wondered even if it was not statistically significant, could you tell us a little bit more about how age impacted on survival trends.

**Dr Chen:** To answer the questions, the first question was the positive node rate on the T1a, T1b, excluding IHC only. When we first started our analysis, we noticed these IHC positives only and the higher rate of the T1a lesions. We initially had the impression that this was in the T1a lesions, but when we actually looked at it, the IHC positives only were evenly dis-

tributed through all sizes. I do not have the actual number for the SLN positivity of IHC only. I think in the T1a there was only one which was upgraded, which showed just the IHC.

As far as what are we doing with this information on IHC positive only, it has been very variable as time has gone on, and we have gotten more data. In our initial experience when we first started doing the procedure, any node that was positive, even in retrospect by IHC only, these patients went back to the OR for a full axillary node dissection. However, as time has gone on—and this was especially true if the lesion was greater than 1 cm—as time has gone on, we now do not go back. We do not routinely go back, I should say (because there are multiple surgeons in this group), for IHC positive if it is less than 2 mm and the lesion is less than 1 cm. We had a tumor board conference this Thursday, and the latest consensus is that nobody should be going back if it is IHC positive only.

One thing that I did not elaborate on is upstaging. We have had reports where they do not see it on frozen section or on H&E. They see it on IHC and then they retrospectively go back and look at the H&E and say, yes, uh-huh, we identify it on the H&E, we just missed it. Those patients were not considered IHC only because when you read the report it says positive by H&E and IHC. It's only by talking with the pathologist that we would know that it was retrospectively discovered on the H&E, once they knew that there were some positive cells on the IHC.

We are not doing radiotherapy for these patients for positive IHC to the axilla.

What happened in our group of patients, at least some of them, when they were diagnosed by IHC only, their treatment, if you will, I call it being upgraded to the next step. For example, one of the patients had a 0.3-cm lesion postmenopausal who had an IHC positive only. Now normally she would have just gotten radiotherapy and not tamoxifen. In her particular case, tamoxifen was added to her regimen, so she did not go on for chemotherapy. We have a multitude of oncologists involved in these patients' care, so it is not standardized as to what happens when these patients are diagnosed by IHC only.

As far as the patient who was a T1c lesion and LVI, why do we do an SLN? For us, it dictates the type of chemotherapy. As a general rule, T1c with no nodes positive would probably receive a regimen like cyclophosphamide-methotrexate-fluorouracil. If the nodes were positive, then an Adriamycin-based chemotherapeutic agent would be added. So, no, it does not alter the decision for chemo or not, but it alters the type of chemotherapy that is given.

As far as why we do the frozen section, it will not help in just the micrometastatic disease, but since we had been doing full axillary node dissection for patients who had positive nodes, it was to avoid a second operation if we could. We would know it at the time of the frozen section, what was positive, we would go on with axillary node dissection.

As far as IHC in looking at T1a lesions, it is a good question. Most of the T1a lesions in fact that were SLN positive did not have LVI. We need to be looking at other factors and also expanding our patient population. There were only 39 patients in the T1a lesions.

As far as age is concerned, past studies have indicated that age is important; the younger the patient, the more aggressive the tumor. We did not find this to be a statistically significant number. I do not know the exact *P* number, but it was not significant at all. It may be perhaps that we are seeing—as patients are becoming more and more educated, even in young patients who are not going for screening mammography but with self-breast exams—we are also finding smaller tumors in these younger patients.