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Palpable Breast Cancers Are Inherently Different From Nonpalpable Breast Cancers

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Background: We examined the clinicopathologic profile of T1 cancers to determine whether palpable cancers are different from nonpalpable cancers.

Methods: A prospective database was reviewed. Palpable T1 cancers were compared with nonpalpable T1 cancers. Initial significance was determined by χ^2 analysis. Factors found to be significant were then reanalyzed, controlling for tumor size by logistic or linear regression, as appropriate.

Results: Of 1263 T1 cancers treated between 1981 and 2000, 857 (68%) were palpable and 401 (32%) were nonpalpable. Palpability correlated with pathologic tumor size, mitotic grade, nuclear grade, high S-phase, lymphovascular invasion, nodal positivity, and lack of extensive intraductal component, multifocality, and multicentricity. There was no significant difference in estrogen receptor, progesterone receptor or *Her-2/neu* status, ploidy, or DNA index. Breast cancer–specific survival was worse for patients with palpable cancers.

Conclusions: Palpable cancers are inherently different from nonpalpable cancers, with a less diffuse growth pattern, higher metastatic potential, higher proliferative activity, more nuclear abnormalities, and a worse prognosis.

Key Words: Palpable—Nonpalpable—Breast cancer—Clinicopathologic features.

The development of aggressive screening mammography programs over the past 2 decades has led to the diagnosis of more cancers before they become clinically apparent. However, in most studies, cancers that are nonpalpable and detected by screening mammography alone continue to make up only a minority of diagnosed breast cancers. Palpable cancers are generally thought to be more advanced cancers than mammographically detected cancers; that is, palpability is a function only of size. Although it is true that mammographically detected cancers tend to be smaller in size, there is significant overlap: some very small cancers are palpable, whereas some very large cancers are nonpalpable. It is possible that there is something inherently different about palpable breast cancers. There may be biological differences that cause both palpability and a more aggressive behavior. The purpose of this study was to determine whether the clinicopathologic characteristics of palpable breast cancers differ from those of nonpalpable breast cancers.

METHODS

A prospective breast cancer database was reviewed for breast cancers diagnosed in the period January 1, 1981, to December 31, 2000. Because of the known relationship between palpability and tumor size, the review was restricted to patients with cancers measuring 2 cm or less at pathologic evaluation. Cases of microinvasive ductal carcinoma in situ were excluded. Patients in this cohort (T1a,b,c) who presented with a palpable mass were compared with patients who had nonpalpable cancers. Information obtained from the database included age at diagnosis, palpability, tumor size and margin width (mm), nodal status, estrogen receptor (ER) status, progesterone

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receptor (PR) status, *Her-2/neu* status, cathepsin D status (CathD), Ki-67 staining, mitotic grade (MG), nuclear grade (NG), presence or absence of lymphovascular invasion (LVI), ploidy of the tumor cells, DNA index, percentage of cells in S-phase, presence or absence of extensive intraductal component (EIC), focality and centricity (multi- or uni-) of the tumor, type of treatment (mastectomy or breast conservation), and outcome.

Breast cancers were considered palpable if they could be appreciated on physical examination by at least one physician before treatment. Patients at our institution are routinely examined by multiple experienced clinicians before treatment. These include radiologists, surgeons, medical oncologists, and plastic surgeons. If the lesion was felt by any of these physicians, then it was scored as a palpable breast cancer. Nonpalpable tumors were identified through abnormal imaging studies. Patients were treated by either modified radical mastectomy or by lumpectomy and axillary dissection followed by radiotherapy to the breast (breast-conserving therapy). All pathologic data, including tumor size, nodal status, ER and PR status, *Her-2/neu* status, CathD and Ki-67 status, MG, NG, LVI, ploidy, DNA index, S-phase, EIC, and focality and centricity, were determined at the time of definitive treatment and recorded prospectively in the database. Patients were followed with physical examination at 6-month intervals and mammography at least annually to identify recurrence.

MG was defined by the criteria of the Bloom-Scarff-Richardson scale as modified by Elston and Ellis. MG was 1 if there were <10 mitotic figures per standardized high-power field (hpf), 2 if there were 10 to 20 mitoses per hpf, and 3 if there were >20 mitoses per hpf. S-phase was defined as high if $>10\%$ of cells were in S-phase as determined by flow cytometry. EIC was defined as an invasive breast cancer with at least 25% of the primary tumor mass being composed of ductal carcinoma in situ and a separate focus of ductal carcinoma in situ away from the primary tumor mass. Tumors were considered multifocal if there were two or more separate, distinct tumor masses identified within the same quadrant of the breast, and they were considered multicentric if there were two or more separate tumor masses identified in different quadrants of the breast. ER, PR, *Her-2/neu*, and CathD status were determined by immunohistochemistry and were considered positive if there was 2 or 3+ staining of tumor cells. Ki-67 status was determined by immunohistochemistry and was considered high if $>20\%$ of nuclei stained positive with the Ki-67 antibody. Ploidy and DNA index were determined by DNA histogram.

The objectives of the analysis were to compare tumor and patient characteristics at diagnosis between palpable and nonpalpable cancers and to compare outcome between these groups. Special attention was given to controlling for tumor size because palpability is highly associated with size. Comparisons of frequencies of tumor and patient characteristics between palpable and nonpalpable groups were based on the simple χ^2 test. When these were adjusted for tumor size or other variables, logistic regression or standard linear regression was used, as appropriate.[1] Differences in breast cancer–specific survival (BCSS) and local recurrence–free survival were analyzed by using product limit estimates with Greenwood standard errors and the log-rank test. A stratified log-rank test was used to adjust for tumor size in these analyses.[2] All quoted P values are two sided.

RESULTS

Patients

Review of the database revealed 1263 T1 breast cancers treated between 1981 and 2000. Pathologic data were not recorded for five patients (.2%), leaving 1258 assessable patients. Of these, 857 (68%) had palpable tumors and 401 (32%) had nonpalpable tumors. The mean age of women with palpable tumors was 52.7 years (range, 22–94 years), and that of women with nonpalpable tumors was 52.6 years (range, 32–93 years; $P =$ not significant). Women with nonpalpable tumors were more likely to elect breast-conserving therapy (53% vs. 62%, $P = .0014$) and were more likely to undergo breast reconstruction after mastectomy (53% vs. 33%, $P < .0001$) than women with palpable breast cancers.

Comparison of Palpable and Nonpalpable Tumors

Tumor size was recorded for all patients. The remaining pathologic factors were recorded in varying numbers of patients, ranging from 80 to 1189. Palpability was significantly associated with tumor size, nodal positivity, higher MG, higher NG, high S-phase, the presence of LVI, the absence of EIC, and the lack of multifocality or multicentricity (Table 1). There was no difference between palpable and nonpalpable tumors in terms of margin width, receptor positivity, *Her-2/neu* or CathD status, Ki-67 staining, ploidy, or DNA Index.

Figure 1 shows the relationship between tumor size and both palpability and nodal positivity. Both palpability and nodal positivity increase with tumor size. However, at every tumor size, palpable tumors are approximately twice as likely to be node positive as nonpalpable tumors, suggesting that the association between palpa-

TABLE 1. *Pathologic characteristics of palpable and nonpalpable T1 breast cancers*

Variable	n	Palpable	Nonpalpable	*P* value
Tumor size, mm (mean)	1258	13.86	9.80	.0001
% Margins ≤1 mm	1096	13.1	13.6	.804
% ER positive	826	74.3%	80.3%	.061
% PR positive	815	65.2%	69.8%	.193
% *Her-2/neu* positive	309	29.4%	28.8%	.895
% Cathepsin D positive	164	41.3%	44.4%	.687
% High Ki-67	80	41.6%	33.3%	.453
% Not diploid	468	47.9%	45.1%	.837
DNA index (mean)	456	1.32	1.29	.507
MG (mean)	668	1.40	1.20	<.0001
NG (mean)	1189	2.14	1.99	.0003
% High S-phase	384	55.8%	41.6%	.0433
% LVI	1165	15.5%	7.6%	.0002
% EIC	925	39.2%	49.0%	.0043
% Node +	1117	28.3%	10%	<.0001
% Multifocal	832	19.1%	34.0%	<.0001
% Multicentric	345	8.3%	16.5%	.031

ER, estrogen receptor; PR, progesterone receptor; MG, mitotic grade; NG, nuclear grade; LVI, lymphovascular invasion; EIC, extensive intraductal component.

bility and node positivity is, at least in part, unrelated to tumor size.

Because of the strong effect of size on palpability, the factors identified as significantly associated with palpability were reanalyzed, controlling for tumor size. These results are shown in Table 2. MG, nodal positivity, and lack of multifocality were the only factors that were significantly associated with palpability independent of tumor size. High S-phase approached significance, and there was a trend toward higher NG, LVI, and lack of multicentricity.

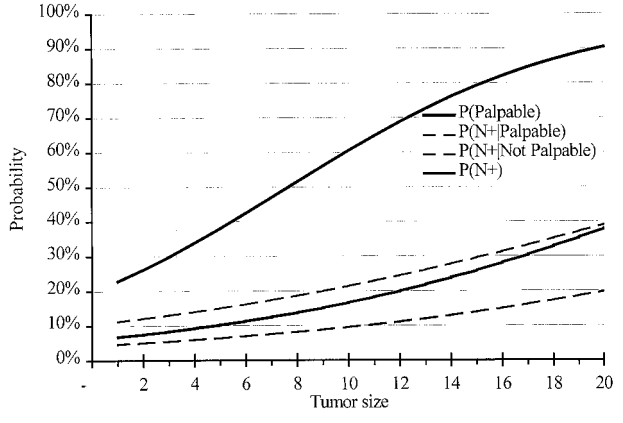

FIG. 1. Probability of nodal positivity and palpability by tumor size for T1 cancers (logistical model). P(Palpable), probability that a cancer of given size will be palpable; P(N+), probability that a cancer of given size will be node positive; P(N+ Palpable), probability that a palpable cancer of given size will be node positive; P(N+ Nonpalpable), probability that a nonpalpable cancer of given size will be node positive. Tumor size is expressed in millimeters.

Outcome

Figure 2 shows the recurrence-free survival and local recurrence–free survival for palpable and nonpalpable T1 tumors. There was no significant difference in recurrence rates between palpable and nonpalpable tumors. Figure 3 shows BCSS for T1 tumors. Women with nonpalpable tumors had significantly better 8-year survival than women with palpable tumors (95% vs. 87%, $P = .0065$). However, when controlling for tumor size, this difference does not quite achieve statistical significance ($P = .083$)

DISCUSSION

Despite aggressive public education and screening programs for women over the age of 40 years, nonpalpable cancers constitute only 17.5% to 58% of diagnosed cancers in published series.[3–12] There are several reasons

TABLE 2. *Comparison of palpable and nonpalpable T1 breast cancers, controlling for tumor size*

Variable	Palpable	Nonpalpable	*P* value (adjusted for tumor size)
MG (mean)	1.40	1.20	.0472
NG (mean)	2.14	1.99	.152
% High S-phase	55.8%	41.6%	.0746
% LVI	15.5%	7.6%	.112
% EIC	39.2%	49.0%	.313
% Node +	28.3%	10%	<.0001
% Multifocal	19.1%	34.0%	.0002
% Multicentric	8.3%	16.5%	.154

MG, mitotic grade; NG, nuclear grade; LVI, lymphovascular invasion; EIC, extensive intraductal component.

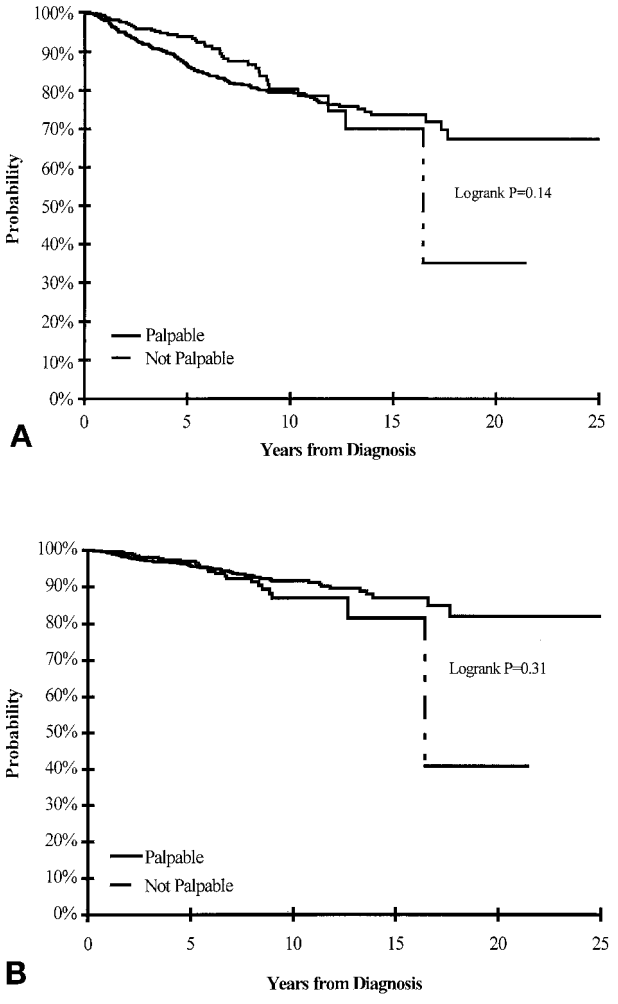

FIG. 2. (**A**) Recurrence-free survival by palpability: probability that a patient with palpable or nonpalpable cancers will remain free of disease versus time from diagnosis in years. (**B**) Local recurrence–free survival by palpability: probability that a patient with palpable or nonpalpable cancer will remain free of local recurrence versus time from diagnosis in years.

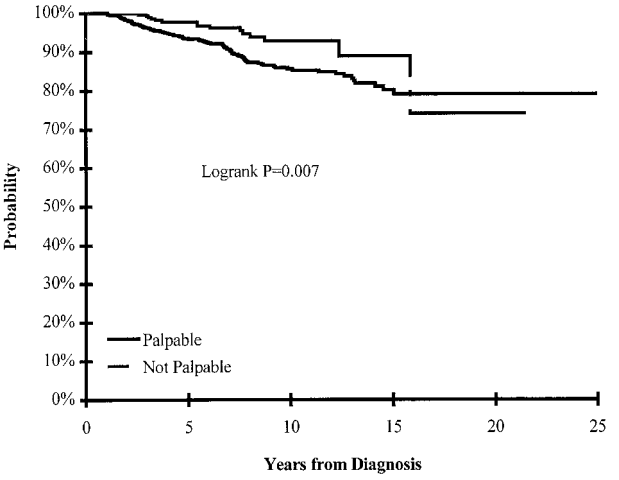

FIG. 3. Breast cancer–specific survival: percentage of women with palpable or nonpalpable cancers who have not died of breast cancer versus time from diagnosis.

for the persistence of palpable breast cancer. First, the only mechanism currently available for the detection of nonpalpable breast cancer is mammography, but <50% of women comply with the screening recommendations for regular mammograms.[13] Cancers diagnosed in women not undergoing annual mammography make up the largest portion of the palpable breast cancers. However, approximately 25% of breast cancers diagnosed in a screened population are cancers that become clinically apparent in the interval between mammograms. Fifty percent of these patients had missed at least one mammogram before diagnosis, so the true incidence of 12-month-interval cancers was 13%. These are cancers that were not detectable on prior mammograms.[14] These findings suggest that even if there were 100% compliance with annual mammographic screening and 100% accuracy of mammographic interpretation, 13% of breast cancers would still be detected only when they became palpable because they are mammographically occult. In 1988, Edeiken[15] reviewed the literature regarding the sensitivity of mammography in palpable breast cancers and found that 23% (range, 13%–39%) of palpable breast cancers were mammographically occult. There is something fundamentally different about the growth pattern of, or the stromal response to, these tumors that renders them mammographically undetectable.

Palpable tumors are more likely to be found in younger women.[14,16,17] Women with palpable cancers are more likely to be premenopausal than those with nonpalpable cancers.[12] Whether this is caused by hormonal influences on the tumor, the decreased sensitivity of mammography in younger women with dense breast tissue, or the fact that younger women are less likely to undergo screening mammography is unknown.

There are significant differences in the pathologic features of palpable breast cancers when these are compared with nonpalpable cancers. It is well documented that palpable tumors tend to be larger.[12,17–20] However, if palpability is merely a function of size, why are some very large tumors nonpalpable? Clearly other factors play a role in palpability. Hislop et al.[14] found that cancers that became clinically apparent in the interval between screening mammograms were more likely to be poorly differentiated and to show lymphatic and venous invasion than screen-detected cancers. There was no difference in the distribution of histologic types or the

presence of neural invasion. Unfortunately, these results were obtained by comparing all interval cancers with all screen-detected cancers without controlling for size. Our data show that when confining the analysis to palpable and nonpalpable T1 tumors (≤2 cm in greatest diameter), LVI is significantly associated with palpability. However, when controlling for size, the difference is no longer statistically significant. These findings suggest that palpable cancers may have a higher metastatic potential than screen-detected cancers.

It has long been known that palpable cancers are more likely to be node positive.[12,17,19,20] The increase in nodal involvement has been believed to be caused by the increased size of palpable cancers. Our data suggest that the increased nodal involvement in palpable cancers is independent of tumor size. At any given tumor size, palpable cancers are approximately twice as likely to have spread to the regional lymph nodes as nonpalpable cancers, with a tendency for LVI. This increased metastatic potential translates to a worse prognosis with decreased BCSS.

It has been previously documented that palpable cancers tend to be of higher histological grade and have lower expression of ER and PR, higher S-phase, higher mitotic index, and higher expression of p53, Ki67, and *Her-2/neu*.[17,18,20,21] Again, these studies did not control for tumor size, so it was not clear whether these changes were independently associated with palpability or simply a function of palpable cancers being more advanced at the time of diagnosis. Our data show that T1 palpable cancers are more mitotically active, with a higher S-phase. These differences remain after controlling for size, although the difference in percentage of tumors with high S-phase does not achieve statistical significance ($P = .07$). This lack of significance is probably a result of the relatively low number of cases for which this information was available (only 384 of 1258 cases). These findings suggest that palpable cancers, independent of size, have higher proliferative activity than mammographically detected cancers. There was no significant difference in ER or PR positivity, a measure of cellular differentiation, in palpable compared with nonpalpable T1 tumors.

Palpable cancers also have more nuclear abnormalities than nonpalpable cancers. In this study, the NG of palpable tumors was significantly higher than that of nonpalpable lesions. However, this was not associated with chromosomal abnormalities; DNA index and ploidy were no different in the two groups.

No previous study has evaluated the growth patterns of mammographically detected cancers. Our data suggest that nonpalpable breast cancers have a more diffuse growth pattern than palpable tumors, with a propensity towards multifocality and multicentricity. In fact, this diffuse growth pattern probably contributes to the absence of physical findings, because a diffuse change is less likely to be palpable than a focal change. Nonpalpable breast cancers are also more likely to have extensive ductal carcinoma in situ associated with them than palpable tumors, and this contributes to a more diffuse growth pattern.

Palpable cancers are inherently different from nonpalpable cancers, with a less diffuse growth pattern, higher metastatic potential, higher proliferative activity, more nuclear abnormalities, and a worse prognosis. With the limitations of our current screening technology, a significant proportion of diagnosed cancers will continue to be palpable at the time of diagnosis. It is essential that annual mammography continue to be combined with clinical breast examination and breast self-examination to provide adequate screening for breast cancer, allowing diagnosis of mammographically occult tumors at the earliest possible stage. Further studies into the molecular biology of palpable cancers will contribute a great deal to our understanding of their unique biological characteristics and may allow more effective therapies.

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