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# New Therapeutic Possibilities in Primary Invasive Breast Cancer

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**Objective**

Current therapy for small invasive breast cancer, particularly when discovered mammographically, was re-examined. Axillary dissection may be avoided when lymph node metastases incidence is low (< 10%) or when primary cancer features determine adjuvant therapy. Radiation therapy may be avoided when risk of recurrence is very low.

**Summary Background Data**

Recent studies by the Surveillance, Epidemiology, and End Results program (SEER) have shown increases in small invasive breast cancers (< 1 cm) attributable to mammographic screening. The incidence of axillary metastases in mammographically discovered small cancers (< 1 cm) may be less than 10%. Follow-up data from the Breast Cancer Detection Demonstration Project (BCDDP) indicate a disease-free survival rate exceeding 95% at 8 years if the cancer was discovered mammographically.

**Methods**

Maximum diameter and lymph node metastases of invasive breast cancers diagnosed between 1969 and 1988 were analyzed and compared to cases diagnosed between 1929 and 1968. One hundred thirty patients have been treated without either axillary dissection or radiation therapy since 1980.

**Results**

The mean and median diameters of invasive breast cancers decreased to 2.31 and 2.0 cm, respectively, between 1984 and 1988; 13% were less than 1 cm in diameter. Only 13% of patients had axillary metastases if the primary cancer was 1 cm or less in diameter in the last 10 years; 71% had only 1 or 2 nodes involved. Isolated local recurrence, total local recurrence, and distant metastases were unchanged when radiated and nonirradiated patients were compared. Axillary nodal recurrence was decreased in irradiated patients because the lower half of the axilla was treated.

**Conclusion**

In selected patients with very small invasive breast cancers detected by mammography, breast conservation without axillary dissection or radiation therapy may be used. Entirely outpatient treatment markedly reduces morbidity and cost, and furthers the gains from screening programs.

A number of authors have recently addressed issues of altering current standard therapy in primary breast cancer by either eliminating axillary dissection for staging[1–4] or by restricting the use of radiation therapy[5–9] for the conserved breast in order to simplify therapy when the risk of regional lymph node metastases or ipsilateral in-breast occurrence may be low or node pathology is inconsequential for decisions regarding adjuvant therapy. The biological basis of the acceptability of such alterations in standard management has been established by the National Surgical Adjuvant Breast Program (NSABP) in the B-04[10] and the B-06[11] protocols, as well as other recent trials.[12] These prospective clinical trials establish the fact that lymph node metastases are "indicators, but not governors" of survival[13] and that survival is identical when comparing patients who have the axilla treated by either resection or radiation or who go untreated. Furthermore, the long-term survival of patients who do not have radiation therapy for the retained breast is identical to that of patients who do have radiation therapy, despite a marked increase in local ipsilateral in-breast recurrence.[11,14] Fisher et al.[14] have shown that the temporal rate or chronological appearance of in-breast recurrence is quite different for patients without breast radiation compared to those with breast radiation, and that the time of appearance of ipsilateral in-breast recurrence has a strong indicator function in predicting distant metastases, foretelling distant metastatic disease and survival while not being the cause of it.

Just as earlier trials of breast preservation were attempts to simplify surgical therapy and preserve the breast for cosmetic and functional gains, further attempts to reduce the magnitude of surgery, and therapy generally, should be investigated because of the markedly earlier disease now presenting at treatment facilities because of mammographic screening.[15,16] This earlier stage breast cancer results from the discovery of smaller cancers with fewer axillary nodal metastases.[1,2,17,18] Attempts to further simplify therapy, by avoiding general anesthesia for axillary dissection, may enable breast cancer treatment to be entirely an outpatient procedure, particularly when a variety of tumor prognostic factors are available besides axillary nodal metastases[19] that may be equivalent or satisfactory prognostic indicators in very small breast cancers.

The rigidities of formal cancer staging requirements by the tumor, node, metastases (TNM) system and the lack of agreement on the usefulness of the many varied prognostic tumor characteristics are all that stand in the way of avoidance of axillary dissection, the next step in less morbid breast cancer management in very early breast cancer. Markedly reduced cost of breast cancer therapy can be achieved by eliminating radiation therapy ($6,000 for 6000 cGy in Massachusetts) and/or avoiding hospitalization and general anesthesia for axillary dissection (estimated $10,000 total cost), if these two components of therapy can be avoided safely. "Safety" in cancer therapy may need redefining by reconsidering the cost-benefit and risk-benefit ratios in terms of accepting slight increases in nonlethal, relatively inconsequential, or extremely low-incidence recurrences in some patients for the sake of avoiding treatment morbidity and excessive cost for the overwhelming preponderance of patients when treatment effects are relatively small. For instance, if the 20-year mortality rate of patients with 1 cm or smaller invasive cancers is about 10%,[20] only a slight improvement can be achieved by adjuvant therapy as judged by the meta-analysis of the various breast cancer trials.[21] Thus, with a proportional 20% reduction in recurrence that occurs in only 10% of patients, the 2% recurrence reduction, while useful, means that 98% of patients underwent the treatment without benefit while acquiring all the risk of morbidity and the expense of treatment. For instance, the disease-free survival rate at 8 years in the Breast Cancer Detection Demonstration Project (BCDDP) of invasive cancers smaller than 1 cm in diameter was 98%,[22] indicating extremely low risk of recurrence in those nonpalpable cancers discovered during screening. Recent data from the Surveillance, Epidemiology, and End Results program (SEER) registry indicate that the 5-year survival rate for small, node-negative invasive breast cancers discovered mammographically is 98% or 99%.[23]

Simplification and reduction of morbidity of therapy are worthy goals of contemporary cancer management. Therefore, a randomized, prospective trial comparing ultraconservative therapy to the standard breast-preserving procedures of axillary dissection and radiation therapy is certainly justified in small, mammographically discovered breast cancers.

## METHODS

Between 1980 and 1992, we treated 130 patients in a nonstandard fashion by avoiding either axillary dissection or radiation therapy, or by avoiding both in a highly selective group of patients. All patients were informed of the variation from standard practice that these modifications involved and were given data involving the risks and benefits of these simplified treatments during prolonged discussion, which included family members whenever possible. The majority of patients had disease detected on screening mammography, including contralateral breast screening in seven patients after similar simplified treatment of the patient's first breast cancer. The reasons for the simplified and modified management ranged from a presumed very low risk of local recurrence or axillary metastases, to selection of adjuvant therapy regardless of nodal status, to physical infirmity

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or deformity, to patient refusal or selection. Wide local excisions (lumpectomy) were performed, with very few exceptions, under local anesthesia[24] with preliminary mammographic wire placement for localization of nonpalpable, mammographically discovered lesions, with skin incision placement and methods previously described by us.[25] The pathologic specimens have been linked, in recent years, using the Dickenson colored ink system[26] to orient and define margins, a system to be encouraged because of the increased ability to precisely localize histologically close or involved margins for possible re-excision and to quantify the excision margin. After complete histologic examination and evaluation of pathologic type, differentiation, size, presence or absence of extensive intraductal component (EIC),[27] and adequacy of margins, estimates of the risk of local ipsilateral in-breast recurrence and axillary metastases were made by the authors and discussed with the patient. Histologic features suggesting high risk of metastatic disease (*e.g.*, lymphatic vessel involvement, perineural invasion, poor nuclear grade, extremely poor histologic grade, or large size) that might lead to systemic adjuvant therapy, regardless of the axillary nodal status, led to suggestions of avoiding axillary dissection. This followed the diagnostic maximum that, if no change in therapy occurs as a result of obtaining a test, don't do the test.

Surgical judgments regarding possible high morbidity and risk from axillary dissection were made by the authors in patients with debility, physical deformity, advanced age, or high risk of arm edema. After counseling regarding the patient's decision, with assurances that inappropriate decisions would be strongly advised against, other aspects of therapy were addressed (*e.g.*, need for re-excision based on margin examination and the use of any appropriate adjuvant systemic or regional therapy if the risk-benefit ratios might encourage therapy).

After the initial local excision and appropriate treatments, follow-up consisted of detailed examinations of the breast, axilla, and regional area at three month intervals for the first 2 years and every 6 months thereafter. Mammograms were obtained every 6 months for the first 2 or 3 years and all areas suspicious for recurrence were documented by repeat biopsy. All patients have been observed for a minimum of 2 years or a median of 4 years for the patients seen between 1980 and 1990 inclusive. Two deaths due to intercurrent disease occurred in elderly patients while they were disease-free: one at 1 year after a local breast recurrence was treated with hormones and the other at 3 years after mastectomy without axillary dissection for extensive ductal carcinoma *in situ* around a small invasive cancer. Thus, no patients have been lost to follow-up.

All records of patients with primary breast cancer treated at the New England Deaconess Hospital were obtained by examining the tumor registry files, discharge diagnoses files, and pathology department logs for appropriate diagnoses. The cases discovered were characterized by the size of the primary cancer and the status of the lymph nodes for patients registered between 1969 and 1988. This analysis was similar to our previous report,[28] and results were compared to those previously analyzed patients with breast cancer from the same institution between 1929 and 1968.

A linear regression analysis was used to test for a time trend for the lymph node metastases and size. For node metastases, the percentages were computed over annual intervals and were regressed against time. For size, the means of the largest primary dimension were computed over annual intervals and were regressed against time. In both analyses, the time coefficients were used as estimates of the annual rate of change and for testing if the time trend was significant. Analyses were performed using SAS (Cary, NC). Definitions and analyses were identical to those of our previous report[28] and, therefore, trends and slopes and statistical significance values were determined for the entire time period (1929 to 1988) covered by both of our reports, when possible.

Fischer's exact test was used for chi square analysis when comparing recurrence rates.

The T or tumor classification used is that of the American Joint Committee's *Manual for Staging of Cancer.*[29] T1A cancers are equal to or less than 5 mm in diameter; T1B cancers are greater than 5 mm but equal to or less than 1 cm in diameter; T1C cancers are greater than 1 cm in diameter but equal to or less than 2 cm in diameter. T2 cases are those larger than 2 cm in diameter but smaller than or equal to 5 cm in diameter.

When patients experience failure locally in the ipsilateral breast and are free of nodal or distant metastases, a variety of treatment options are available, particularly if radiation therapy has not been used.[30] While most such patients underwent mastectomy, over one third of the patients were subjected to re-excision (3 of 7).

## RESULTS

Between 1969 and 1988, 1533 patients were discovered using case discovery as described. They had the mean maximum diameter and number of axillary lymph node metastases characterized. The mean maximum diameter decreased significantly, presumably under the impact of extensive mammographic screening. Therefore, between 1984 and 1988, the mean and median diameters of all invasive breast cancers at the New England Deaconess Hospital were 2.31 and 2.0 cm, respectively (Table 1).

In the 5 years from 1984 to 1988, 31% of all breast cancers recorded at the New England Deaconess Hospi-

**Table 1. SIZE OF INVASIVE BREAST CANCER—NEW ENGLAND DEACONESS HOSPITAL**

| | No. of Cases | Mean Maximum Diameter (cm) | Medium Median Diameter (cm) | Smaller than 1 cm No. | % |
|---|---|---|---|---|---|
| Previous report[28] | | | | | |
| 1929–1938 | 665 | 3.40 | | | |
| 1939–1948 | 890 | 3.47 | | | |
| 1949–1958 | 910 | 3.20 | | | |
| 1959–1968 | 889 | 3.11 | | | |
| | 3354 | | | | |
| Current report | | | | | |
| 1969–1973 | 315 | 3.06 | 2.5 | 8 | 3 |
| 1974–1978 | 337 | 2.79 | 2.4 | 14 | 5 |
| 1979–1983 | 382 | 2.50 | 2.0 | 26 | 8 |
| 1984–1988 | 499 | 2.31 | 2.0 | 58 | 13 |

tal were either noninvasive or invasive cancers 1 cm or smaller in diameter. Thirteen per cent of all invasive cancers were smaller than 1 cm in diameter, and more than one third of these were cancers of only 1 or 2 mm in diameter; these were frequently initially listed by the pathologist as "too small to measure," in which case they were arbitrarily defined as being 2 mm in diameter. A few of these cancers were ductal carcinoma *in situ* with areas of definitive microinvasion.

The incidence of metastases in the axillary dissection progressively decreased also so that only 41% of breast cancers had a axillary dissection revealing metastatic disease in the most recent time period (Table 2). The proportion of the decreasing incidence of positive axillae that had only 1 lymph node metastasis increased to 34%, and the proportion with more than 3 positive axillary nodes decreased to 31% (Table 2). All of these trends (Tables 1 and 2) were highly statistically significant, with p values ranging from 0.004 to 0.0001. In the 20 years from 1969 to 1988, 31 patients had invasive cancers 1 cm or smaller in diameter with axillary nodal metastases. The proportion of these patients with smaller cancers who had positive nodes declined progressively and significantly ($p = 0.0453$) during the successive 10-year intervals of this analysis (Table 3). This undoubtedly reflects the increasing proportion of very small cancers as noted earlier. Of interest, during the same successive 10-year periods, the proportion of positive lymph nodes in patients with 2-cm invasive cancers ($p = 0.417$) or 3- or 4-cm invasive cancers did not change, since they represented a specific size and not a range of sizes subject to decreasing average size. Thus, the data showing decreasing proportions of positive nodes for the entire category of small cancers up to and including those 1 cm in diameter undoubtedly reflect the increasing proportions of extremely small cancers and the decreasing mean and median diameters. Of particular interest in those 31 patients was the fact that 42% had only 1 positive node, 29% had 2 positive nodes, and only 16% had more than 3 positive nodes (Table 4). Although not specifically recorded, many such patients with only one or two positive nodes have micrometastases rather than macrometastases. Patients with a single micrometastases have a prognosis similar to that for patients with negative nodes, at least in initial follow-up.[31,32]

Table 5 shows the modification of therapy during the years 1980 to 1990 (93 patients) and the years 1991 and 1992 (37 patients) in a highly selected group of patients. In the two most recent years, the lesions accepted for modified therapy were even smaller when discovered mammographically (median diameter 0.6 *vs.* 1.0 cm in

**Table 2. AXILLARY METASTASES IN INVASIVE BREAST CANCER—NEW ENGLAND DEACONESS HOSPITAL**

| | No. of Cases | Negative Nodes | Of Positive Nodes 1+ | > 3 |
|---|---|---|---|---|
| Previous report[28] | | | | |
| 1929–1938 | 665 | 38% | 23% | 45% |
| 1939–1948 | 890 | 39% | 24% | 51% |
| 1949–1958 | 910 | 47% | 23% | 48% |
| 1959–1968 | 889 | 53% | 31% | 42% |
| | 3354 | | | |
| Current report | | | | |
| 1969–1973 | 315 | 55% | 30% | 39% |
| 1974–1978 | 337 | 49% | 28% | 37% |
| 1979–1983 | 382 | 55% | 35% | 32% |
| 1984–1988 | 499 | 59% | 34% | 31% |
| | 1533 | | | |

**Table 3. AXILLARY METASTASES IN INVASIVE BREAST CANCER—NEW ENGLAND DEACONESS HOSPITAL**

| Size of Cancer (cm) | Axillary Nodal Metastases 1969–1978 No. | % | 1979–1988 No. | % |
|---|---|---|---|---|
| <1 | 13/48* | 27 | 18/137* | 13 |
| 2.0 | 18/68† | 27 | 32/95† | 34 |
| 3.0 & 4.0 | 56/128 | 44 | 42/94 | 45 |

* $p = 0.0453$.
† $p = 0.417$.

**Table 4. AXILLARY METASTASES IN INVASIVE BREAST CANCER—NEW ENGLAND DEACONESS HOSPITAL (INVASIVE CANCERS < 1 CM IN DIAMETER, 1969–1988)**

| All + Nodes | | 1+ | | 2+ | | 3+ | | > 3+ | |
|---|---|---|---|---|---|---|---|---|---|
| No. | % | No. | % | No. | % | No. | % | No. | % |
| 31/185 | 17 | 13/31 | 42 | 9/31 | 29 | 4/31 | 13 | 5/31 | 16 |

previous years) and a higher proportion had no radiation therapy (62% *vs.* 48%). Tumor size classification also indicated that in the last 2 years, more patients had only T1A or T1B cancers (73% *vs.* 51%) and fewer had T1C or T2 primary cancers (Table 6). The median diameter overall also decreased, when comparing these two time periods, from 1.1 to 0.8 cm. All of these changes indicate that the authors are becoming more selective in offering modified therapy to patients in the last 2 years.

Tables 7 and 8 demonstrate the criteria used to offer modification of therapy to patents in terms of avoidance of radiation therapy or axillary dissection during the years 1980 to 1990. The majority of both axillary failures[10] and local ipsilateral in-breast failure in the absence of radiation therapy[14] should appear within this follow-up period.

Table 9 indicates that of the 90 patients without axillary dissection, there were 8 axillary nodal failures (9%) and none of these was isolated nodal recurrence. All eight patients had simultaneous or rapidly appearing local recurrence or distant metastases or both.

Table 10 shows the failures noted in all patients between 1980 and 1990 with modified therapy and, separately, that proportion of patients with T1 cancers. Failures in the patients without radiation therapy occurred in smaller cancers compared to those who did receive radiation therapy (all cases with a median diameter of 1.0 *vs.* 1.5 cm; T1 cases with a median diameter of 1.0 *vs.* 1.2 cm). There clearly is a higher failure rate in all categories of failure analysis for the nonirradiated *versus* the irradiated patients and these failures occurred in patients with smaller cancers; however, because of small numbers, none of these differences achieves statistical significance or is clinically important, except regarding nodal failure. The decrease in axillary nodal recurrence with radiation is statistically significant and reflects the technique of opposed tangent fields that gives about 4500 cGy to the lower half of the axilla.

There were four cases of unexpected and disturbing recurrences in patients with small primary cancers whose local recurrence behaved in a very aggressive fashion, despite the primary cancers being totally excised and without histologic evidence of high risk of recurrence. These patients had tumors with maximum diame-

**Table 5. MODIFIED THERAPY FOR PRIMARY BREAST CANCER FOR SELECTED PATIENTS**

| | 1980–1990 | | 1991 and 1992 | |
|---|---|---|---|---|
| Patients treated | 88 | | 35 | |
| Breasts treated | 93 | | 37 | |
| No axillary dissection | 90 | 97% | 37 | 100% |
| No radiation | 45 | 48% | 23 | 62% |
| No radiation or axillary dissection | 42 | 45% | 23 | 62% |
| Mammographic detection | 72* | 77% | 24 | 65% |
| Median diameter in cm (range) | 1.0 (0.1–3.0) | | 0.6 (0.1–1.7) | |

* Number.

**Table 6. MODIFIED THERAPY FOR PRIMARY BREAST CANCER FOR SELECTED PATIENTS—SIZE AND TUMOR CATEGORY (TNM)**

| | 1980–1990 | | 1991 and 1992 | |
|---|---|---|---|---|
| Primary Cancer | No. | % | No. | % |
| $T1_A$ | 14 | 15 | 8 | 22 |
| $T1_B$ | 31 | 34 | 19 | 51 |
| $T1_C$ | 35 | 39 | 8 | 22 |
| Total T1 | 80 | 88 | 35 | 95 |
| T2 | 11 | 12 | 2 | 5 |
| Not measured | 2 | | | |
| | 93 | 100 | 37 | 100 |
| Median diameter | 1.1 cm (0.1–3.0 cm) | | 0.8 cm (0.1–2.5 cm) | |
| <1.0 cm | 28 | 31 | 20 | 54 |

**Table 7. MODIFIED THERAPY FOR PRIMARY BREAST CANCER FOR SELECTED PATIENTS (1980–1990)**

| | Reasons for Avoiding Radiation Therapy (45 Patients) | |
|---|---|---|
| Reason | No. | % |
| Small size | 18 | 40 |
| Low grade | 6 | 13 |
| Aged—poor medical state | 14 | 31 |
| Patient refused | 4 | 9 |
| Mastectomy | 2 | 4 |

**Table 8. MODIFIED THERAPY FOR PRIMARY BREAST CANCER FOR SELECTED PATIENTS (1980–1990)**

| Reason | Reasons for Avoiding Axillary Dissection (90 Patients) No. | % |
|---|---|---|
| Small size | 38 | 42 |
| Low grade | 7 | 8 |
| Aged—poor medical state | 16 | 18 |
| Adjuvant therapy regardless | 13 | 14 |
| Severe shoulder disability | 3 | 3 |
| Extreme medial location | 3 | 2 |
| Patient refused | 3 | 3 |
| Unclear from record | 8 | 9 |

ters of 5, 7, 8, and 10 mm. All were EIC negative and two of the four were estrogen receptor and progesterone receptor positive. Two of the patients had in-breast recurrence that resembled inflammatory breast cancer and three of the four had nodal recurrences as well as local recurrences. Three of the patients have metastatic disease. These four cases emphasize the need for accurate tumor features for prognostication and selection of adjuvant therapy, as well as the fact that poor prognosis and metastatic breast cancers may have such features inherently even at very small size and may not develop more aggressive biological behavior over time or with increasing size.

## DISCUSSION

The impact of population screening with mammography is being encountered and reported frequently in the United States.[17,33,34] There has been a well documented and marked downward trend in mean and median diameter, and the proportion of all invasive breast cancers seen that are smaller than 1 cm in diameter has shown a striking upward trend from about 9 cases per 100,000 per year in 1982 to about 36 cases per 100,000 per year in 1989.[16] The striking increase in small cancers has also been accompanied by a sharp increase in *in situ* cancers, which have quadrupled in incidence (from about 12 cases per 100,000 per year to about 45 cases per 100,000 per year), and in cancers between 1 and 1.9 cm in diameter (from approximately 40 cases per 100,000 per year to 84 cases per 100,000 per year in the 7-year interval from 1982 to 1989).[16] At the same time, there has been a downward trend in breast cancers 3 cm or larger in diameter and in those cancers presenting with regional disease and distant metastases.[16] Thirteen per cent of all invasive cancers seen at the New England Deaconess Hospital between 1984 and 1988 were smaller than 1 cm in diameter, corresponding to national trends.[16] With the demonstrable increase in survival in patients older than 50 years of age undergoing screening mammography[33] and decreasing size, there is every expectation that further modification of therapy may well be possible in this increasing proportion of small, excellent prognosis cancers. While controversy exists about the extent of lymph node metastases in very early breast cancer discovered mammographically, a number of recent reports suggest that lesions 5 mm or smaller in diameter may have an extremely low incidence of lymph node metastases.[1,2,17,18] In our own cases, only 13% of the invasive breast cancers 1 cm or smaller in diameter in the years 1984 to 1988 had positive axillary nodes. Silverstein et al. recently reported only a 3% incidence of positive axillary dissection

**Table 9. MODIFIED THERAPY FOR PRIMARY BREAST CANCER FOR SELECTED PATIENTS (1980–1990)**

90 Patients without axillary dissection
8 Nodal failures (9%)
No isolated nodal failures
3 Nodal plus local failure
4 Nodal, local, and distal failure
1 Nodal and distal failure

**Table 10. MODIFIED THERAPY FOR PRIMARY BREAST CANCER OF SELECTED PATIENTS (1980–1990)**

| | No Radiation | | Radiation | |
|---|---|---|---|---|
| | No. | % | No. | % |
| Failure—all 93 patients | (n = 45) | | (n = 48) | |
| Local failure only | 4 | 9 | 3 | 6 |
| Local failure total | 10 | 22 | 4 | 8 |
| Nodal failure | 7* | 16 | 1* | 2 |
| Distal metastases | 5 | 11 | 3 | 6 |
| Total patients failing | 11 | 24 | 6 | 13 |
| Median diameter in cm (range) | 1.0 (0.1–2.5) | | 1.5 (0.1–3.0) | |
| Failure—all T1 patients (n = 80) | (n = 39) | | (n = 41) | |
| Local failure only | 3 | 8 | 2 | 5 |
| Local failure total | 7 | 18 | 3 | 7 |
| Nodal failure | 6† | 15 | 1† | 2 |
| Distant metastases | 4 | 10 | 3 | 7 |
| Total patients failure | 8 | 21 | 5 | 12 |
| Median diameter in cm (range) | 1.0 (0.1–2.0) | | 1.2 (0.1–2.0) | |

* p = 0.03.
† p = 0.054.

in nonpalpable, mammographically discovered, invasive $T_{1A}$ cancers.[34] Clearly, more data need to be accumulated to resolve this controversy about the incidence of lymph node metastases in very early breast cancers.

The well-established contemporary biological understanding of breast cancer behavior indicates that the details of local excision, while relating to the incidence of local recurrence, do not govern survival.[11,14] Therefore, taking precautions to prevent an ipsilateral in-breast recurrence by the use of quadrant resection of the breast, mastectomy, or adjuvant radiation therapy after lumpectomy may possibly be avoided when the risk of such local recurrence is very low. The NSABP B-06 trial[11] analyzed palpable breast cancers up to and including those 4 cm in diameter. Data regarding the differential recurrence rate comparing conserved irradiated or nonirradiated breasts in NSABP trial B-06 for cancers 1 cm or smaller in diameter have not been published. Thus, the B06 trial data indicating an extremely high risk of local in-breast recurrence without radiation may have little pertinence for lesions 1 cm or smaller in diameter detected mammographically. In our own study, the differential total risk of local recurrence in the breast comparing a group of patients having $T_1$ cancers with and without radiation therapy to the breast was only 11%, the difference between 18% in the nonirradiated patients and 7% in the irradiated patients. In those patients displaying local failure *only*, the rate of ipsilateral in-breast recurrence in the nonirradiated patients was 9% and in the irradiated patients it was 6%, only a 3% decrease by adding adjuvant radiation therapy. While some of these recurrences in the nonirradiated breast occurred in tumors that were quite small, the implication is that the risk of in-breast recurrences in very small invasive breast cancers may be quite low and the small reduction in risk using radical radiation therapy may not be justified considering the expense, time, skin changes, and the edema or fibrosis that occurs frequently in the irradiated breast. Careful follow-up examination by palpation and mammography may also be less satisfactory after radiation therapy.

Similarly, NSABP trial B-04[10] has firmly established the concept that lymph node metastases are "indicators but not governors" of survival[13] and do not actually need to be treated in order to achieve whatever survival is possible. Lymph node metastases are prognostic indicators and selectors of adjuvant therapy because they do convey a worse prognosis and have traditionally been used as the principal indicator for adjuvant systemic therapy. When risk of lymph node metastases ranges between 20% and 40%, there may be little argument for using axillary dissection to find those patients who might benefit from adjuvant therapy, if there are no other prognostic indicators of equivalent power. However, with the increasing emphasis on the treatment of node-negative patients with poor prognostic features, such as large size or other tumor indicators such as poor differentiation or aneuploidy by flow cytometry, there is decreasing need to know the actual presence of lymph node metastases to select adjuvant therapy. In patients with primary cancers 1 cm or smaller in diameter with negative nodes, the prognosis is better than 95%[22,23]; the proportional reduction in recurrence achieved by adjuvant therapy as reported by meta-analysis of all randomized trials[21] can hardly justify the treatment because the chance of improving the outcome of these patients is so small and the overwhelming predominance of patients do not benefit, may experience toxicity, and incur the expense.

The other issue with lymph node dissection is the justification of doing 10 or 20 axillary dissections for the sake of finding one patient with a positive node (10% or 5% positive node rate), considering the considerable morbidity associated with axillary lymph node dissection and the significant costs of hospitalization (*e.g.*, general anesthesia with surgery, anesthesia, operating room, and recovery room fees). We would estimate the total cost of an admission for an axillary dissection to be close to $10,000. Thus, the 100 axillary dissections required to discover the 10 patients with metastases, if there is a 10% risk of positive nodes, would cost approximately $1,000,000. In patients with a 10% risk of an axillary lymph node metastases, of whom more than 40% have only a single lymph node metastases, the overall prognosis is still very good. The better survival resulting from 100 axillary dissections and selection of adjuvant systemic therapy in 10 patients might be manifest by showing a decreased recurrence and improved survival in only 1 of 100 patients undergoing adjuvant therapy selection in that fashion (Table 11). Thus, in early breast cancers detected by mammography, we may well be reaching a point of extremely diminished returns in attempts to improve prognosis unrealistically by use of axillary dissection to determine the very few who need adjuvant therapy. For every situation where there is only a 1%, 2%, or 3% increase in disease-free, long-term survival by the use of adjuvant treatment based on axillary dissection, 99%, 98%, or 97% of patients operated on do not benefit and are subjected to the morbidity of the treatment. It may be that local anesthesia biopsy of a "sentinel node" selected by lymphatic mapping, as described by Morton et al.,[35] may resolve issues of axillary lymph node dissection if the reliability of this technique in breast cancer can be proven.

In cardiology, most patients who get calcium channel blockers for a particular effect benefit somewhat (about 60%); some benefit greatly (about 15%), a few (about 10%) do not get any therapeutic benefit, and even fewer (about 5%) experience serious toxicity. Most patients

**Table 11. PRIMARY BREAST CANCER—AXILLARY DISSECTION COST AND BENEFIT ANALYSIS***

| Of 100 Patients | 10-Year Survival Rate | No. of People Alive at 10 Yrs |
|---|---|---|
| No axillary dissection/ no adjuvant therapy | | |
| 87 − nodes | 95% | 83 |
| 13 + nodes | 70% | 9 |
| | | 92 |
| Adjuvant therapy of + nodes after axillary dissection | | |
| 87 − nodes | 95% | 83 |
| 13 + nodes | 80% (33% reduction) | 10 |
| | | 93 |

* 0.6-cm invasive cancer; 13% + node rate.

who experience significant toxicity are also those who get the most benefit. In cancer management, we have accepted treating a large number of patients with inherent toxicity for the sake of small gains in a few. Mammographic screening and detection of very small primary breast cancers may enable us to re-examine this whole motif in an increasing proportion of patients with breast cancer. Due to the heightened anxiety among patients about the diagnosis of cancer and the lack of realistic or factual explanation of the concept of proportional gains, we find an increasing number of patients being encouraged to accept prolonged toxic or expensive therapy for relatively minor reductions in recurrence. Also, the possibility of *not* using such adjuvant therapy, even in the smallest cancers with negative nodes and an extremely low risk of recurrence, is virtually ignored or disparaged by treating physicians. With significant cost controls facing the medical profession, such explicit cost-benefit and risk-benefit analysis should be strongly considered and acted upon by both physicians and patients.

The goals of further modification and simplification of breast cancer treatment have to do with decreasing the morbidity, expense, and time of therapy in suitable patients. In a fashion similar to malignant melanoma, where early detection and better understanding of the risks of local recurrence and lymph node metastases have enabled a reduction in excision margins and primary closure without skin graft and without nodal dissections, and where all surgery can now be performed as an outpatient procedure, breast cancer is now the beneficiary of the increasing impact of an effective widespread screening program.

However, to answer further the questions about suitability of simplified management for early breast cancer, a prospective, randomized clinical trial is clearly needed. This should initially be used in cancers 1 cm or smaller in diameter that have been detected mammographically, apportioning the patients between axillary dissection and observation. Patients with axillary dissection who have positive nodes obviously would receive adjuvant systemic therapy. In addition, guidelines would be developed to treat patients with a constellation of tumor prognostic factors with adjuvant therapy in a randomized fashion. Correlations with poor outcome should be documented in these very small cancers by having an untreated control group. Furthermore, each arm of the trial assignment could be further randomized between receiving and not receiving radiation therapy to the breast. Such a trial would accumulate the very important information related to the true incidence of positive lymph nodes and ipsilateral in-breast recurrence in very small, mammographically discovered carcinomas; such a trial is now being considered by the Society of Surgical Oncology. The trial with an untreated control group would also help answer some essential biological questions that have been raised by Mueller[36] relating to the nature of node-positive and node-negative breast cancers. He disputes the notion that node-positive breast cancer is merely an advanced form of node-negative breast cancer. He substantiates his argument by depicting the fact that survival curves for the two stages are not parallel, which would be consistent with a time delay, but continue to diverge for at least 40 years of follow-up in long-term studies, suggesting a biologically different disease process. If node-positive breast cancer were merely an advanced form of node-negative breast cancer, then after an initial lead time delay, the survival curves should be parallel. The fact that there is a practically linear relationship between the incidence of node metastases and the size of the tumor raises questions about this argument. Obviously, observations of a large number of patients with extremely small size cancer with a very low incidence of lymph node metastases would finally help determine the validity of Mueller's[36] thesis.

Another biological question that could be answered by observing a large number of very small breast cancers would quantify the presence of that small proportion of breast cancers that behave in a unique and aggressive fashion. Fox[37] pointed out that a proportion of patients with breast cancer die at the rate of 25% per year, and all have died by 7 years (before adjuvant systemic therapy). That fraction of patients is also found in the Connecticut Tumor Registry Study as cited by Mueller.[36] Do such biologically inherently poor prognosis breast cancers exist at extremely small sizes and are they are detected by mammographic screening? Would it be possible for these aggressive cancers, if detectable, to be excised at a small size and to actually interrupt their otherwise rapid clinical course? "Interval" cancers, those that appear between two consecutive mammographic screenings, are generally reported to be poor prognosis lesions because these patients are not recognized by mammographic screening and the cancers tend to grow rapidly in a short interval[33] and may be consistent with this poor biological type described by Fox.[37] The presence of such an aggressive breast cancer variant, even at very small size, can certainly be suggested by the four patients with very small cancers in our series, who had a rapid recurrence manifested by an extremely aggressive presentation akin to inflammatory breast cancer with early metastases.

Another biological question to be answered is that raised by Holland et al.[38] regarding the extent of histologic multifocality of early ductal carcinomas of the breast. They found rather extensive surrounding areas of noninvasive and invasive carcinoma accompanying $T_1$ cancers such that significant quantities of residual disease would be left behind by programs of limited excision even, by implication, in very small cancers. It needs to be learned whether in extremely small cancers detected mammographically these areas of surrounding noninvasive and invasive carcinoma would be quantitatively and qualitatively less in extent and therefore lend themselves to local excision without radiation therapy. In duct carcinoma *in situ,* Lagios et al.[39] have presented data that would suggest a very small unifocal origin and later spread intraductally from this epicenter so that the ability to excise locally, without recurrence, occurs in all but about 15% of cases. Clearly, as the proportion of cancers that are discovered by mammography at extremely early stages continues to increase, much greater understanding about the origins and development and progression of breast cancer will occur. It is hoped that more selective treatment patterns can be developed as a result, as suggested in this article.

This report attempted to explore the possible value of further modifications in the treatment of breast cancer to simplify treatment, reduce morbidity for patients, and decrease cost to the medical system. It is hoped that a prospective trial might focus on the biology and curability of extremely early primary breast cancers, as well as the technical aspects of successful therapy. The advent of widespread screening mammography allows this exploration of biology and treatment alteration, and promises a virtual revolution in the outcome of breast cancer treatment.

## References


1. Unzeitig GW, Frankl G, Ackerman M, O'Connell TX. Analysis of the prognosis of minimal and occult breast cancers. Arch Surg 1983; 118:1403–1404.
2. Wong JH, Kopald KH, Morton DL. The impact of microinvasion on axillary node metastases and survival in patients with intraductal breast cancer. Arch Surg 1990; 125:1298–1302.
3. Deckers PJ. Axillary dissection in breast cancer: when, why, how much, and for how long? Another operation soon to be extinct? J Surg 1991; 48:217–219.
4. Haffty BG, McKhann C, Beinfield M, et al. Breast conservation therapy without axillary dissection. Arch Surg (in press).
5. Crile G Jr, Cooperman A, Esselstyn CB Jr. Results of partial mastectomy in 173 patients followed for from five to ten years. Surg Gynecol Obstet 1980; 150:563–566.
6. Ghossein NA, Vilcoq J, Stacey P, Asselain B. Is it necessary to irradiate the breast after conservation surgery for localized cancer? Arch Surg 1987; 122:913–917.
7. Greening WP, Montgomery ACV, Gordon AB, Gowing NFC. Quadrantic excision and axillary node dissection without radiation therapy: the long-term results of a selective policy in the treatment of stage I breast cancer. Eur J Surg Oncol 1988; 14:221–225.
8. Moffat FL, Ketcham AS, Robinson DS, et al. Segmental mastectomy without radiotherapy for T1 and small T2 breast carcinomas. Arch Surg 1990; 125:364–369.
9. Reed MW, Morrison JM. Wide local excision as the sole primary treatment in elderly patients with carcinoma of the breast. Br J Surg 1989; 76:898–900.
10. Fisher B, Redmond C, Fisher ER, et al. Ten-year results of a randomized clinical trial comparing radical mastectomy and total mastectomy with or without radiation. N Engl J Med 1985; 312:674–681.
11. Fisher B, Redmond C, Poisson R, et al. Eight-year results of a randomized clinical trial comparing total mastectomy and lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med 1989; 320:822–828.
12. Lichter AS, Lippman ME, Danforth DN, et al. Mastectomy versus breast-conserving therapy in the treatment of stage I and II carcinoma of the breast: a randomized trial at the National Cancer Institute. J Clin Oncol 1992; 10:976–983.
13. Cady B. Lymph node metastases: indicators, but not governors, of survival. Arch Surg 1984; 119:1067–1072.
14. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet 1991; 338:327–331.
15. Simon MS, Lemanne D, Schwartz AG, et al. Recent trends in the incidence of in situ and invasive breast cancer in the Detroit metropolitan area 1975–1988). Cancer 1993; 71:769–774.
16. Miller BA, Feuer EJ, Hankey BF. Recent incidence trends for breast cancer in women and the relevance of early detection: an update. Ca 1993; 43:27–41.
17. Reger V, Beito G, Jolly PC. Factors affecting the incidence of lymph node metastases in small cancers of the breast. Am J Surg 1989; 157:501–502.
18. Silverstein MJ, Gamagami P, Rosser RJ, et al. Hooked-wire-directed breast biopsy and over penetrated mammography. Cancer 1987; 59:715–722.
19. Osborne CK. Prognostic factor for breast cancer: have they met their promise (editorial)? J Clin Oncol 1992; 10:679–682.
20. Rosen PP, Groshen S, Saigo PE, et al. A long-term follow-up study of survival in stage I ($T_1N_0M_0$) and stage II ($T_1N_1M_0$) breast carcinoma. J Clin Oncol 1989; 7:355–366.
21. Early Breast Cancer Trialists' Collaborative Group. Systemic treatment of early breast cancer by hormonal, cytotoxic, or immune therapy. Lancet 1992; 339:71–85.
22. Seidman H, Gelb SK, Silverbert E, et al. Survival experience in the breast cancer detection demonstration project. Ca 1987; 37:258–290.
23. Carter CL, Allen C, Henson D. Relation of tumor size, lymph

node status, and survival in 24,740 breast cancer cases. Cancer 1989; 63:181–187.
24. Grannan KJ, Lamping K. Impact of method of anesthesia on the accuracy of needle-localized breast biopsies. Am J Surg 1993; 165:218–220.
25. Cady B. Choice of operations for breast cancer: conservative surgery versus radical procedures. *In* Bland KI, Copeland EM III, eds. The Breast—Comprehensive Management of Benign and Malignant Disease. Philadelphia: WB Saunders, 1991, pp 753–769.
26. Cady B. Duct carcinoma in situ (DSIS). Surg Oncol Clin North Am 1993; 2:75–91.
27. Osteen RT, Connolly JL, Recht A, et al. Identification of patients at high risk for local recurrence after conservative surgery and radiation therapy for stage I and II breast cancer. Arch Surg 1987; 122:1248–1252.
28. Cady B. Changing patterns of breast cancer. Arch Surg 1972; 104:266–269.
29. American Joint Committee on Cancer. Manual for Staging of Cancer. 3rd ed. Philadelphia: JB Lippincott, 1988, p 146.
30. Cajucom CC, Tsangaris TN, Nemoto T, et al. Results of salvage mastectomy for local recurrence after breast-conserving surgery without radiation therapy. Cancer 1993; 71:1774–1778.
31. Attiyeh FF, Jensen M, Huvos AG, Fracchia A. Axillary micrometastasis and macrometastasis in carcinoma of the breast. Surg Gynecol Obstet 1977: 144:839–842.
32. Rosen PP, Saigo PE, Braun DW, et al. Axillary micro-and macrometastases in breast cancer. Ann Surg 1981; 194:585–591.
33. Andersson I, Aspergren K, Janzon L. Mammographic screening and mortality from breast cancer: the Malmo Mammographic Screening Trial. Br Med J 1988; 297:943–972.
34. Silverstein MJ, Gamagami P, Senofsky GM, et al. Mammographically detected nonpalpable breast carcinoma: superior survival when compared with palpable breast cancer. Presented at the Annual Meeting of the Society of Surgical Oncology, Los Angeles, California, March 20, 1993.
35. Morton DL, Wen D-R, Wong JH, et al. Technical details of intraoperative lymphatic mapping for early stage melanoma. Arch Surg 1992; 127:392–399.
36. Mueller CB. Stage II breast cancer is not simply a late stage I. Surgery 1988; 104:631–638.
37. Fox MS. On the diagnosis and treatment of breast cancer. JAMA 1979; 241:489–494.
38. Holland R, Veling SHJ, Mravunac M, Hendriks JHCL. Histologic multifocality of Tis, T1–2 breast carcinomas. Cancer 1985; 56:979–990.
39. Lagios MD, Margolin FR, Westdahl PR, et al. Mammographically detected duct carcinoma in situ: frequency of local recurrence following tylectomy and prognostic effect of nuclear grade on local recurrence. Cancer 1989; 63:618–624.

## Discussion

DR. ROBERT E. HERMANN (Cleveland, Ohio): Dr. Reemtsma, Members and Guests of the Association, I enjoyed this paper by Dr. Cady very much and I congratulate him on his continuing studies on variations in the treatment of small or early breast cancer.

Our group at the Cleveland Clinic has continued to explore conservative methods for treating early stage breast cancer, the studies started by Dr. George Crile, Jr., in 1955. We have questioned the necessity to treat all patients who have had a partial mastectomy with postoperative adjuvant radiation.

Routine postoperative radiation therapy for all patients after partial mastectomy has not improved survival in any reported study. It increases the time of treatment, triples its cost, causes some early and late morbidity, and makes small recurrences in the breast more difficult to identify both mammographically and by clinical exam. Its only benefit, in past studies, has been to decrease local recurrence.

We have tried to identify or select a group of patients, as has Dr. Cady (patients with Stage 0 or Stage I breast cancer who have no evidence of multifocal disease by mammography or by biopsy), and treat these patients with partial mastectomy without postoperative radiation therapy. We attempt to have a 1- to 2-cm negative margin and do an axillary dissection in all of these patients.

From 1975 through 1988, we have treated 620 patients of a total group of 2020 patients by partial mastectomy without adjutant radiation therapy. Overall survival and disease-free survival were the same as in those patients treated by total mastectomy with an axillary dissection or by partial mastectomy with axillary dissection and postoperative radiation. Local recurrence in these selected patients at 5 and 10 years was not in the range suggested by the NSABP studies (i.e., 30% to 40%), but was only 11% at 5 years and 14% at 10 years.

Dr. Cady has stated that their local recurrence rate in patients after partial mastectomy without radiation therapy, I believe, was 18%. I wonder if he would clarify that? It was 16% in the abstract, but I think he showed it to be 18% on one of his slides.

Finally, I'd like to congratulate him and his colleagues on these studies.

DR. C. BARBER MUELLER (Hamilton, Ontario): Dr. Cady, while you've addressed the fact that mammography now brings a new group of patients into the Cancer Registries, they have smaller tumors, but as yet there is no direct evidence that they are earlier tumors.

It seems obvious to me and I think to most of us to conclude that these are early versions of garden variety breast cancer, but it is possible, maybe even probable, that they are a variant that is less lethal.

Could I have my slide, please? This is the survival curve of NSABP B-O4. You saw it earlier in Dr. Cady's presentation. It shows the 10-year survival of Stage I *versus* Stage II. I have calculated that the half death time is different in these two. And, if there had been one disease with a delay in diagnosis, the slopes should have been parallel. But they are not. This slide represents two distinct variants, as distinct as two radioisotopes that decay with different half lives. These are two diseases, not early and late.

Now, the DCIS survival curve, a small curve that is published in several places, is somewhere up here. At 10 years we're looking at 85% or 90% survival. Tom Nealon had an article on this. Well, Dr. Cady, how do you make sure that the tumors you are finding are early versions of a true breast cancer, not just a pathologist's whim, which gives us a different entity?

I would remind you that in 1940 Shields Warren at your institution did this to us with papillary cancer of the thyroid. He identified a cancer that had measurable but minimal lethality. It took us 25 years to recognize that fact and to treat thyroids appropriately. Are we now going to have a repetition of