Who Should Not Receive Chemotherapy? Data From American Databases and Trials

Monica Morrow, Helen Krontiras

The demonstration of the effectiveness of chemotherapy in both premenopausal and postmenopausal women, regardless of estrogen receptor (ER) status, raises the question of whether all breast cancer patients should receive chemotherapy. Several patient groups with such a favorable long-term prognosis that they will obtain an extremely small benefit from chemotherapy can be identified. They include patients with lymph node-negative tumors of 1 cm or less in size, those with grade 1 tumors between 1.1 and 2.0 cm in size, and those with tumors of favorable histologic type (tubular and mucinous) up to 3 cm in size. A patient subgroup in which it is not clear that the benefits of chemotherapy routinely exceed the risks is postmenopausal women with ER-positive, lymph node-negative cancers receiving tamoxifen. There is a wide variation in prognosis in this group, and chemotherapy should be reserved for those at high risk of recurrence. Finally, no benefit for chemotherapy in women aged 70 years and older has been identified. The high rate of death from causes other than breast cancer may negate small survival benefits, and after adjustment for quality of life, the duration of treatment exceeds the gain in life expectancy. [J Natl Cancer Inst Monogr 2001:30:109–13]

The Oxford Overview Analysis (1) has clearly demonstrated that adjuvant systemic chemotherapy reduces the risk of mortality for women with both lymph node-positive and lymph node-negative breast cancer and is effective in both premenopausal and postmenopausal women. In light of the proven benefit of chemotherapy, it is reasonable to ask whether there are any groups of breast cancer patients who should not receive this treatment. Potential patient groups who will not achieve a net benefit from chemotherapy include women with an extremely favorable prognosis, where the reduction in mortality from chemotherapy translates to an absolute survival difference of only a few percent; patients in whom the potential risks of chemotherapy outweigh the benefits; and patient subsets for which chemotherapy has not been proven to have a survival benefit. This article will discuss breast cancer patient groups who meet these criteria.

Favorable Prognosis Subgroups

Subsets of lymph node-negative breast cancer patients with a favorable prognosis have usually been defined on the basis of tumor size or histologic subtype. The use of screening mammography has resulted in the increasingly frequent identification of cancers of 1 cm or less in size. Several large datasets (2–6) confirm that tumors of this size have an extremely favorable prognosis. The Breast Cancer Detection Demonstration Project (BCDDP) was one of the earlier studies to report on the favorable outcome of patients with tumors less than 1 cm in size (2). In the BCDDP, the 880 patients with stage I cancer had an 8-year survival rate of 90%, and for those with tumors less than 1 cm in size, the survival rate was 96%. This favorable prognosis was observed for both the interval and screen-detected cancers, where the survival rates at 8 years were 94% and 96%, respectively (2). Eight-year survival rates above 90% were noted across all age groups for tumors of this size, with women aged 40–44 years having a 99% 8-year survival rate compared with 98% for those aged 50–54 years and 94% for those aged 60–64 years.

More recent studies (3–6) have confirmed these favorable survival rates in large, unselected groups of women. The National Cancer Data Base (NCDB) (3), a joint project of the American College of Surgeons Commission on Cancer and the American Cancer Society, has collected data from 1849 hospitals on 240031 patients who were diagnosed with breast cancer from 1985 to 1991. There were 94106 patients whose cancer was staged as T1N0, and these women had a 5-year relative survival rate of 95.3%. When this group was broken down further into patients with tumors less than 1 cm and those with tumors between 1 and 2 cm, the relative 5-year survival rates were 98.4% (n = 22288) and 94.4% (n = 71818), respectively.

Survival data from two different time periods reported by the Surveillance, Epidemiology, and End Results Program (SEER) are very similar to those of the NCDB. From 1977 through 1982, 57828 stage I breast cancers were reported (4). The 5-year relative survival rate was 96.3%, ranging from 99.2% for the 269 patients with tumors less than 5 mm in size to 98.3% for those with tumors 0.5–0.9 cm in size and to 85.8% for patients with tumors 1.0–1.9 cm in size. These results are confirmed in the most recent SEER report of patients diagnosed from 1988 through 1994 (5). In this time period, 7842 cancers less than 5 mm in size and 11543 cancers between 5 and 9 mm in size were reported. Both of these groups had 5-year relative survival rates of 100%. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-21 (6), a study of invasive cancers less than or equal to 1 cm in size with negative axillary lymph nodes, patient accrual took place from 1989 to 1998. The 5-year survival rate is 97% for the 1009 patients in the study, regardless of the treatment arm (radiotherapy, radiotherapy plus tamoxifen, or tamoxifen). These studies, using a large convenience sample, population-based data, and patients entered in a breast cancer clinical trial, confirm the favorable prognosis of patients with breast cancers less than 1 cm in size across patient groups.

Long-term follow-up data are available for much smaller numbers of patients with cancers of 1 cm or less in size, since these tumors were infrequently diagnosed clinically. Rosen et al.
(7) reported a 10- and 20-year disease-free survival (DFS) for 171 patients with cancers of 1 cm or less in size and for 303 patients with cancers between 1.1 and 2.0 cm. In those patients whose tumors were less than or equal to 1 cm in size, the DFS at 10 and 20 years was 91% and 88% compared with 77% and 72%, respectively, for patients whose tumors were 1.1–2.0 cm in size. For women whose tumors were less than or equal to 1 cm in size, the probability of death from breast cancer did not exceed the probability of death from cardiovascular disease, other types of cancer, or other causes.

Single institution studies (8,9) have attempted to identify poor-prognosis subgroups of patients with lymph node-negative cancers on the basis of pathologic features, such as nuclear grade or lymphatic invasion. Leitner et al. (8) reported 218 patients with T1a and T1b disease with lymph node-negative breast cancer, with a median follow-up of 6.9 years. Poor nuclear grade and the presence of lymphatic invasion were found to be significant prognostic factors. Of the 196 patients with complete prognostic information, 20 (10%) had both poor nuclear grade and lymphatic invasion. Relapse-free survival for this group of patients was statistically significantly poorer than for patients with one or neither of these factors. Lee et al. (9) also found histologic grade, lymphatic invasion, hormone receptors, high Ki67, and bcl2 expression to be statistically significant prognostic indicators. However, only seven of the 87 patients in their series developed recurrence, precluding multivariate analysis. In contrast, Rosen et al. (10) were unable to identify a patient subset with a particularly high or low risk of recurrence on the basis of pathologic features. Of the 22,288 patients with cancers less than 1 cm in size reported to the NCDB (3), 10,312 (46.3%) had information on tumor grade. Five-year survival by grade is shown in Table 1. Even patients with high-grade tumors (3,4) had 5-year survival rates of 96% or greater. The NCDB results are similar to those found by SEER (5) and the Swedish Two-County Mammographic Screening Study (11), where survival rates for patients with tumors less than 1 cm in size approached 100%, regardless of grade.

The datasets cited above (2–7,11) clearly demonstrate a difference in prognosis between stage I cancers of 1 cm or less in size and those between 1 and 2 cm in size. The addition of histologic grade to tumor size for patients with T1c tumors allows the identification of additional patients with an extremely favorable prognosis. A major problem with the use of grade as a prognostic factor is that it is incompletely reported. In the SEER Program, the grade was reported for only 10.4% of the cases in the 1973 report compared with 34.4% of the cases in 1987 and 60.2% of the cases diagnosed from 1988 through 1994 (4,5,12). The SEER data indicate that survival is significantly better for grade 1 cancers, regardless of stage (12), with 5-year survival rates ranging from 93% for grade 1 cancers to 65% for grade 3 cancers. For patients with stage I, grade 1 cancers, 5- and 10-year survival rates were 99% and 95% compared with 94% and 85% for those with stage I, grade 3 cancers. The 10% survival difference at 10 years on the basis of grade is clinically significant and should be used to further stratify a patient’s risk of relapse. It is noteworthy that the incidence of grade 1 tumors increases as tumor size decreases. In the SEER dataset, 26% of tumors less than 5 mm in size were grade 1 compared with 12% of those 1.0–1.9 cm in size and only 4% of those between 3.0 and 3.9 cm in size (12). Since screening mammography results in the detection of a greater number of stage I breast cancers, failure to recognize the prognostic importance of grade may result in the overtreatment of increasing numbers of women.

Histologic subtype of breast cancer is another prognostic factor, although it is one that affects a relatively small group of women. The favorable histologic subtypes of breast cancer include tubular carcinoma, mucinous carcinoma, papillary carcinoma, and adenoid cystic carcinoma. Together, these accounted for 4.5% of the 68,273 breast cancers reported to SEER in the 1988–1994 interval (5). Rosen et al. (7) observed that the 20-year DFS for patients with breast cancers of these favorable histologic types (plus medullary carcinoma) up to 3 cm in size was 87% compared with 70% for infiltrating ductal and lobular carcinomas (Fig. 1). The favorable prognosis of medullary cancer is not confirmed in all reports, and it will not be considered further (13,14). However, other data support the findings by Rosen et al. (7) for tubular and mucinous cancers (15–21). A literature review of 300 lymph node-negative tubular cancers of all sizes, the majority with long-term follow-up, identified only four relapses (15–20). These studies are summarized in Table 2. The criterion for inclusion in Table 2 was a tumor consisting of 90% tubular elements. In the 1101 tubular cancers reported to SEER (5), the 5-year survival was 100%, regardless of stage.

The SEER data also indicate that patients with mucinous carcinoma have a significantly better prognosis than those with infiltrating ductal carcinoma, independent of stage (21). From 1973 through 1990, 4082 mucinous adenocarcinomas and 139,154 infiltrating ductal carcinomas were recorded by SEER (21). Life-table analysis with Cox proportional hazards analyses to adjust for major covariates demonstrated that the relative risk (RR) of death because of breast cancer for women with mucinous carcinoma was 0.38 that of women diagnosed with infiltrating ductal carcinoma (95% confidence interval [CI] = 0.34 to 0.42). Similar to grade 1 lesions, special histologic tumor types are diagnosed more frequently in patients undergoing screening mammography (22,23), again raising the possibility of overtreatment of more women in the future unless the prognostic implications of tumor histology are clearly stated.

### Table 1. Impact of histologic grade on survival in lymph node-negative breast cancer less than 1 cm in size

<table>
<thead>
<tr>
<th>Grade</th>
<th>n</th>
<th>Percentage 5-y survival</th>
<th>SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2783</td>
<td>98.6</td>
<td>0.8</td>
</tr>
<tr>
<td>2</td>
<td>5008</td>
<td>98.2</td>
<td>0.6</td>
</tr>
<tr>
<td>3</td>
<td>2338</td>
<td>96.0</td>
<td>0.9</td>
</tr>
<tr>
<td>4</td>
<td>183</td>
<td>99.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

*SEM = standard error of the mean. Data from the National Cancer Data Base (3).*
weighed against the toxicity of treatment, particularly in the lymph node-negative patient with a relatively favorable prognosis.

The NSABP B-20 trial compared the use of tamoxifen alone with that of tamoxifen plus chemotherapy in women with lymph node-negative, ER-positive breast cancer (24). After 5 years, a 4%–5% improvement in DFS was seen with the addition of chemotherapy, and a subset analysis failed to identify a subset of patients who did not benefit from the addition of chemotherapy. However, only 27% of the study participants were aged 60 years or older, resulting in 201 patients in this age group in the methotrexate, 5-fluorouracil, and tamoxifen (MFT) arm of the study and 207 in the cyclophosphamide plus MFT (CMFT) arm of the study. A comparison of outcome on the basis of tumor size demonstrates that, for patients with tumors with a clinical size of 2 cm or less treated with tamoxifen alone, the event rate per 100 women per year was 2.75, which was reduced to 2.28 and 1.99, respectively, with MFT and CMFT. In comparison, for tumors clinically measured as 2.1 cm or larger in size, the event rates for tamoxifen, MFT, and CMFT were 4.96, 2.83, and 2.69, respectively, per 100 women. An analysis of the risk reduction seen with MFT or CMFT relative to tamoxifen alone on the basis of age is shown in Fig. 2. The magnitude of benefit is clearly greater for women aged 49 years or less. For those 50 years and older, MFT resulted in only a 10% reduction in the risk of events related to DFS, and a 26% reduction in these events was seen with treatment with CMFT. In both cases, the subset analyses do not demonstrate statistical significance (MFT: RR = 0.90 [95% CI = 0.64 to 1.25]; CMFT: RR = 0.74 [95% CI = 0.52 to 1.05]).

In addition to the relatively small benefits in DFS and overall survival, the addition of chemotherapy to tamoxifen resulted in significant toxicity. Grade 3 or 4 overall toxicity was experienced by 4% of the patients in the tamoxifen group, by 17% in the MFT group, and by 25% in the CMFT group (24). In particular, the addition of chemotherapy to tamoxifen resulted in an increase in the number of thromboembolic events, from 1.8% in the tamoxifen group to 6.5% in the MFT group and to 7.0% in the CMFT group.

These findings suggest that identification of higher risk subsets of ER-positive, lymph node-negative postmenopausal women would be useful. In an analysis of 4000 breast cancer patients with negative lymph nodes and positive hormone receptors who participated in the NSABP B-14 trial (25), substantial variation in survival in this patient group was identified. Clinical tumor size, age, progesterone receptor status, and ploidy were found to be statistically significant predictors of outcome. Women over the age of 50 years at the time of surgery were found to have an increased risk of death compared with those aged 50 years at the time of surgery, suggesting that this group would experience benefit from the addition of chemotherapy to tamoxifen. However, after censoring other causes of death such as second primary cancers and deaths before recurrence of breast cancer, the rate of treatment failure for women over the age of 50 years was relatively constant (25). This emphasizes the importance of considering an individual woman’s competing risks for mortality when considering adding chemotherapy to tamoxifen. Overall, the addition of chemotherapy to tamoxifen is associated with a relatively small survival benefit and results in a moderate increase in toxicity. On the basis of this information, it does not seem reasonable to recommend chemotherapy for all lymph node-negative, ER-positive postmenopausal women. This treatment should be reserved for those at higher risk of breast cancer recurrence, identified by larger tumor size, high S-phase frac-

**Table 2.** Prognosis in lymph node-negative tubular carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>No. of patients</th>
<th>Size, cm</th>
<th>No. of recurrences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose et al. (7)</td>
<td>24</td>
<td>≤2*</td>
<td>0</td>
</tr>
<tr>
<td>Cooper et al. (15)</td>
<td>12</td>
<td>1.5†</td>
<td>0</td>
</tr>
<tr>
<td>Winchester et al. (16)</td>
<td>40</td>
<td>1.0†</td>
<td>1</td>
</tr>
<tr>
<td>Deos et al. (17)</td>
<td>90</td>
<td>0.8†</td>
<td>0</td>
</tr>
<tr>
<td>Parl and Richardson (18)</td>
<td>17</td>
<td>1.6‡</td>
<td>1§</td>
</tr>
<tr>
<td>Peters et al. (19)</td>
<td>16</td>
<td>1.8‡</td>
<td>0</td>
</tr>
<tr>
<td>McDivett et al. (20)</td>
<td>123</td>
<td>0.9‡</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>393</td>
<td></td>
<td>4 (1.3%)</td>
</tr>
</tbody>
</table>

*One T2 case, size not specified.
†Median.
‡Mean.
§Clinically lymph node negative, axilla not dissected.
tion, and negative progesterone receptors, who are at a low risk of death from other causes.

**Subgroups With Lack of Proven Benefit From Chemotherapy**

The Oxford Overview Analysis demonstrates no improvement in relapse-free or overall survival in patients aged 70 years and older with ER-negative breast cancers treated with chemotherapy (1). However, only 600 women in this age group were available for analysis. The lack of benefit for chemotherapy has been interpreted by some as a problem of insufficient sample size (26). However, it is equally likely that, if chemotherapy has the same effect in women aged 70 years and older as it does in those aged 50–59 years (11% reduction in the risk of overall mortality), the 2% gain in 10-year survival that would result in lymph node-negative women would be negated by the high rate of death from other causes. This would result in the failure to observe a substantial survival benefit, even in a large group of women.

The 1998 consensus panel at the St. Gallen Breast Cancer Conference recommended that women older than 70 years receive chemotherapy for ER-negative tumors greater than 2 cm in size with negative lymph nodes (27). However, this recommendation is not well supported by the available data. Diab et al. (28) examined the outcome of 4011 breast cancer patients aged 75 years and older who did not receive any adjuvant therapy and were followed a median of 5.3 years. Fifty-three percent of the patients were aged 80 years or older, and 89% had ER-positive tumors. Only 13% of the group had tumors less than 1 cm in size. The 5-year overall survival rate for lymph node-negative patients was 70% compared with 69% for an age- and sex-matched group from the general population. For lymph node-positive patients, the 5-year survival rate was 52% compared with 67% for the general population.

Desch et al. (29) used a Markov model to determine the benefit of adjuvant chemotherapy in hypothetic cohorts of women aged 60–80 years with ER-negative, lymph node-negative breast cancer. The model used a risk of recurrence of 5% per year, or 23% at 5 years, and estimated a 20% reduction in the risk of recurrence with chemotherapy. In a 60-year-old woman, a survival gain of 5.5 months was seen with chemotherapy, falling to 2.8 months after adjustment for quality of life.

For a 75-year-old woman, the survival gain was 2.9 months, or 1.8 months after adjustment for quality of life. The gain in active life expectancy, defined as being fully independent in bathing, dressing, transfer, and eating, for a 75-year-old woman was 0.7 months. Regardless of the calculation used, the gain in life expectancy never exceeded the 6-month duration of chemotherapy. These results are consistent with the findings of Gelber et al. (30), who performed a meta-analysis of quality-adjusted survival on 3920 patients aged 50 years or older with lymph node-positive breast cancer who were treated in randomized trials with chemotherapy plus tamoxifen or with tamoxifen only. Even in this group with a poorer prognosis, a survival gain of only 2 months was observed, which was not statistically significant after adjusting for quality of life. Actual data on the outcome of chemotherapy in elderly women and the impact of comorbidity on outcome are urgently needed to clarify this issue. On the basis of the available data, it is not possible to conclude that all ER-negative, lymph node-negative breast cancer patients over age 70 years will benefit from treatment. Therapy should be reserved for the woman with large T2 tumors in good overall health, where breast cancer is clearly the major risk factor for mortality.

**Conclusions**

At present, chemotherapy is administered routinely to women with lymph node-negative breast cancers greater than 1 cm in size. Use of the 1-cm cutoff appears to be appropriate, since a group of women with tumors less than 1 cm with a poor prognosis has not been identified in large datasets. Increased recognition of the extremely favorable outcome and the corresponding lack of a major benefit from chemotherapy are needed for women with lymph node-negative breast cancers 1–2 cm in size that are grade 1 and for those with tubular and mucinous cancers up to 3 cm in size. With the increased use of screening mammography, these cancers will make up a greater percentage of the breast cancer burden, increasing the need for consideration of their prognostic implications.

In women with ER-positive, lymph node-negative breast cancer, the benefit of adding chemotherapy to endocrine therapy is small and is often outweighed by added toxicity. Improved definition of prognostic subsets and stratification of outcomes on the basis of comorbidity are needed to better define therapeutic
recommendations in this diverse subset of women. In women aged 70 years and older with lymph node-negative breast cancer, death from causes other than breast cancer is a major issue. A survival advantage for chemotherapy has not been clearly demonstrated and, if present, is likely to be quite small. Treatment in this group should be reserved for those women at high risk of relapse from breast cancer in whom major comorbidities are absent. Philosophically, this is a substantially different recommendation than advocating therapy in older women unless major comorbidity is present. Ultimately, the decision to have chemotherapy is made by an individual patient after a discussion of the risks and benefits of treatment in her individual case. For some patients, an improvement in survival of 1%–2% is meaningful, and they will opt for chemotherapy, even if they fall into the favorable prognostic groups discussed above. However, the available data do not justifiably mandate chemotherapy for all patients in the categories discussed in this article.

REFERENCES


(8) Leitner SP, Swern AS, Weinerberger D, Duncan LJ, Hutter RV. Predictions of recurrence for patients with small (one centimeter or less) localized breast cancer (T1a,b N0 M0). Cancer 1995;76:2266–74.


NOTES

1 Editor’s note: SEER is a set of geographically defined, population-based, central cancer registries in the United States, operated by local nonprofit organizations under contract to the National Cancer Institute (NCI). Registry data are submitted electronically without personal identifiers to the NCI on a biannual basis, and the NCI makes the data available to the public for scientific research.

Supported by the Avon Products Foundation and by Public Health Service grant P50CA89018 from the NCI, National Institutes of Health, Department of Health and Human Services.