Summit Meeting on Breast Cancer among African-American Women

Supplement to Cancer

Treatment Choices and Response Rates in African-American Women with Breast Carcinoma

Lisa A. Newman, M.D., M.P.H. 1
Richard Theriault, D.O. 2
Neil Clendinnin, M.D., Ph.D. 3
Dennie Jones, M.D. 4
Lori Pierce, M.D. 5

1 Department of Surgery, University of Michigan Comprehensive Cancer Center, Ann Arbor, Michigan.
2 Breast Medical Oncology, University of Texas M. D. Anderson Cancer Center, Houston, Texas.
3 Agouron Pharmaceuticals, San Diego, California.
4 Department of Internal Medicine, University of Texas at Galveston, Galveston, Texas.
5 Department of Radiation Oncology, University of Michigan, Ann Arbor, Michigan.

BACKGROUND. Breast cancer mortality rates are higher among African-American women compared with white American women, yet little is known regarding ethnicity-related variation in patterns of primary surgical treatment, locoregional recurrence rates, and response to induction chemotherapy.

METHODS. The available literature was reviewed to evaluate outcome from breast-conservation therapy in African-American women and response rates to systemic therapy.

RESULTS. Breast-conservation therapy appears to be underused among African-American women, a pattern that is noted also among white women with breast carcinoma. Higher rates of locoregional recurrence are seen among African-American women regardless of whether they receive breast-conserving treatment or undergo mastectomy, and this appears to be a function of primary tumor biology. Response rates to appropriately delivered systemic therapy are similar for African-American patients and white patients.

CONCLUSIONS. Despite the apparent increased aggressiveness of disease seen in African-American women with breast carcinoma, patterns of response to local and systemic therapy are similar to the patterns seen in white women with breast carcinoma.

DOI 10.1002/cncr.11015

KEYWORDS: breast cancer, African Americans, treatment, response.

There is an abundance of data documenting a worse long-term outcome and substantially higher mortality rates for African-American patients with breast carcinoma compared with white patients.1–6 However, there are limited reported data regarding ethnicity-related variations in locoregional treatment failures and in tumor responsiveness to induction systemic therapy. Improved understanding of these topics is warranted, because it is well known that each is predictive of outcome for the individual patient. In addition, closer scrutiny of these outcome patterns may reveal variations in care for breast carcinoma delivered to African-American patients.

Breast Conservation Therapy and Locoregional Recurrence

Breast conservation therapy (BCT), consisting of a margin negative lumpectomy (with or without a staging axillary procedure) and breast irradiation, is now well established as an oncologically safe and frequently preferred treatment for patients with early-stage breast carcinoma. Overall survival is equivalent for appropriately selected patients with breast carcinoma who are treated with BCT or who undergo mastectomy.7,8 In general, optimal candidates for BCT are defined as patients who have a solitary primary breast lesion that can...
undergo excision and achieve negative microscopic margins and who have no medical contraindications to chest wall radiation; these factors have been reviewed extensively elsewhere.9,10 Among patients who are treated with BCT, 9.3–22% will develop a locoregional recurrence at follow-up ranging from 40 months to 172 months despite careful patient selection.11 This form of disease recurrence can predict a greater risk of distant metastatic disease. Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-06 trial revealed that women who developed an in-breast tumor recurrence after they received BCT were 3.41 times more likely to develop a distant recurrence compared with patients who received BCT who did not develop a local recurrence.12 In addition, it has been reported that younger women with breast carcinoma have a greater risk of local recurrence for BCT;13 and it is known that African-American women have a younger age distribution for breast carcinoma.1,4

Therefore, it is logical to ask whether African-American patients with breast carcinoma have increased locoregional recurrence rates after BCT. The preponderance of available data suggests that, even if African-American women with breast carcinoma experience different patterns of locoregional recurrence, it is likely to be a manifestation of primary tumor biology that cannot be altered by categorically denying them BCT. This is a crucial message. Clinicians must remain cognizant of the fact that greater long-term risk for disease-related mortality does not indicate ineligibility for BCT.

In the most comprehensive study of possible ethnicity-related variation in BCT, Pierce et al.14 reported outcome for 75 African-American women and 615 white women with Stage I or II breast carcinoma who were treated at the Hospital of the University of Pennsylvania and the Fox Chase Cancer Center with excisional biopsy, axillary lymph node dissection, and breast irradiation. The African-American patients were significantly younger compared with the white patients (29% of African-American patients were age < 40 years compared with 18% of white patients; P = 0.02). At 5 years, local (in-breast only) recurrence rates were similar for African-American patients and white patients (5% vs. 6%). However, the African-American patients had significantly higher rates of regional recurrence as a component of first failure (16% vs. 4%; P = 0.001) and distant recurrence as the only site of first failure (20% vs. 11%; P = 0.01). Specifically, rates of regional failure in the supraclavicular lymph nodes differed only by race, whereas the frequency of axillary and internal mammary failure was comparable between the groups. The subset of young African-American patients had the worst outcome, with a 5-year overall survival rate for African-American patients age < 40 years of 78% compared with 92% for the subset of young white patients (P = 0.01). Overall survival rates for the older African-American patients and white patients were similar (84% vs. 91%).

The Fox Chase Cancer Center recently reported patterns of regional failure and the impact of regional radiotherapy in 346 women (12% African American) with early-stage, lymph node positive breast carcinoma who received BCT at their institution.15 Regional failure was defined as recurrence in the supraclavicular and/or axillary regions at any time; rates of recurrence in each of the lymph node regions and patterns of first failure were not defined specifically. Overall, the 5-year cumulative incidence of regional lymph node failure was 19% for African-American patients and 1% for white patients (P < 0.0001). For the subset of patients with one to three positive axillary lymph nodes who were treated with breast irradiation only (rather than breast and regional irradiation), the regional recurrence rate for African-American patients was 23% compared with a rate of 2% for white patients. The addition of regional irradiation decreased the regional recurrence rates to 12% and 0%, respectively (P < 0.0001). Although these results are provocative, information is not available regarding either the percent of women who failed only in the axilla or the median number of axillary lymph nodes dissected in each group. Because management options and prognoses differ for an isolated axillary recurrence, versus a supraclavicular recurrence, versus regional failures with concurrent systemic failures, no conclusions regarding regional irradiation based solely on ethnicity can be made until additional data specifically outlining patterns of failure are provided. Further investigation of these patterns is warranted, however, in light of the ongoing controversy regarding whether or not regional radiation should be offered to patients with metastases in one to three axillary lymph nodes.16

Newman et al.17 reported the University of Texas M. D. Anderson Cancer Center experience in a review of African-American patients with breast carcinoma who underwent surgery between 1975 and 1994. Of 211 African-American patients with T1 or T2 tumors, the BCT rate was only 19%. With a median follow-up of 67.8 months, no significant differences were found in local recurrence or survival rates between the African-American BCT and mastectomy groups. However, local recurrence was associated with decreased survival in both treatment groups.

Muss et al.18 found similarly low rates of BCT use among African-American women and white women who were evaluated in the National Cancer Institute
Black/White Cancer Survival Study. This project evaluated a subset of 160 African-American women with breast carcinoma and 145 age-matched white women with breast carcinoma who had Stage II, lymph node positive disease. The use of BCT for African-American patients was only 14%, compared with 28% for white patients ($P < 0.004$).

The NSABP B-06 study, which randomized women with early-stage breast carcinoma to receive BCT versus mastectomy, found a poorer prognosis among African-American participants (5-year survival rates, 74% vs. 89%), although specific data on local recurrence rates in different ethnic subsets were not reported.

The NSABP B-13 and B-14 studies, however, did report an unexplained low rate of BCT use among African-American patients compared with white patients. For the estrogen receptor negative participants in the NSABP B-13 study, 22.2% of African-American patients underwent lumpectomy compared with 35.8% of white patients ($P = 0.01$); whereas, among patients who were estrogen receptor positive in the NSABP B-14 study, 20.7% of African-American patients received BCT compared with 40.8% of white patients ($P < 0.001$). Outcome, which is discussed further below, focused on measures of survival rather than locoregional recurrence.

Underuse of BCT by African-American women was found to be a function of relatively lower socioeconomic status in a study by Michalski and Nattinger of 41,937 Medicare patients with breast cancer. In that series of older patients (age 65–79 years), the use of BCT was uniformly low among 13.3% of 2339 African-American patients and 15.1% of white patients with similar socioeconomic status.

Higher rates of BCT were seen among African-American patients who were treated at the Henry Ford Hospital in Detroit. Velanovich et al. found similar rates (over one-third of patients) of BCT among 416 African-American patients and 834 white patients who were treated between 1990 and 1997. No data on recurrence patterns were reported in the NSABP, Medicare, or Detroit studies (Table 1).

It is interesting to note that Connor et al. recently reported on BCT outcome in African-American patients with Stage I or II breast carcinoma who were treated at the University of Kansas Medical Center between 1982 and 1998. With a mean follow-up of 53.4 months for 71 African-American patients who received BCT, there were 8 local recurrences (11%). By

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>African American</th>
<th>White</th>
<th>Study criteria</th>
<th>Median follow-up (months)</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conner et al., 2000</td>
<td>71</td>
<td>204</td>
<td>Stage I/II; all treated with BCT</td>
<td>53</td>
<td>Trend for higher local recurrence rate in African-American women (n.s.)</td>
<td></td>
</tr>
<tr>
<td>Nicolaou et al., 1999</td>
<td>41*</td>
<td>301*</td>
<td>Stage IIA/IEB; lymph node positive; all treated with BCT</td>
<td>73</td>
<td>Higher regional recurrence rate among African-American women (19% vs. 1%; $P &lt; 0.0001$)</td>
<td></td>
</tr>
<tr>
<td>Velanovich et al., 1999</td>
<td>416</td>
<td>834</td>
<td>Stages I-IV; treatment variable</td>
<td>NA</td>
<td>Similar rates of BCT among African-American women and white women (over one-third in both groups)</td>
<td></td>
</tr>
<tr>
<td>Newman et al., 1999</td>
<td>211</td>
<td>NA</td>
<td>T1-T2 tumors; treatment variable</td>
<td>68</td>
<td>BCT rate 19.9%; similar local recurrence rates and survival rates for BCT and mastectomy (9.8% vs. 8.9%)</td>
<td></td>
</tr>
<tr>
<td>Michalski and Nattinger, 1997</td>
<td>2339</td>
<td>37,462</td>
<td>Local or regional disease; all Medicare patients</td>
<td>NA</td>
<td>BCT rate lower for African-American women compared with white women (13.1% vs. 15.4%; $P &lt; 0.001$); low BCT rates related to socioeconomic factors</td>
<td></td>
</tr>
<tr>
<td>Muss et al., 1992</td>
<td>160</td>
<td>145</td>
<td>Stage II; lymph node positive; treatment variable</td>
<td>NA</td>
<td>Lower BCT rates among African-American women compared with white women (22% vs. 40%; $P = 0.004$)</td>
<td></td>
</tr>
<tr>
<td>Pierce et al., 1992</td>
<td>75</td>
<td>615</td>
<td>Stage I/II; all treated with BCT</td>
<td>56</td>
<td>Similar local recurrence rates for African-American women and white women (5% vs. 6%); higher regional recurrence rates for African-American women (16% vs. 4%; $P = 0.001$)</td>
<td></td>
</tr>
</tbody>
</table>

BCT: breast conservation therapy; n.s.: not significant; NA: not applicable.

* Sample size approximate, based on the percentage distribution reported in the study.
comparison, there were 11 local recurrences among 208 similarly treated white patients (5%) at a mean follow-up of 64.8 months. These differences were not significantly different; however, the trend led the authors to speculate that an ethnicity-related variation in tumor aggressiveness may be in effect. It should be noted, however, that there also was a trend for higher rates of margin positivity among the African-American patients (19% vs. 12%) as well as a relatively higher proportion of Stage II disease (58% vs. 47%). Although neither of these differences met statistical significance, they raise the concern that the combination of more advanced stage disease and suboptimal primary tumor resection may have an impact on the poorer rate of local disease control.

Collectively, these studies suggest that additional efforts are necessary to educate African-American women with breast carcinoma about the option of BCT. The data demonstrate comparable rates of success with breast conservation among African-American women and white women, as discussed above, despite the younger age distribution in the African-American cancer population. Any ethnicity-related variation in primary tumor biology that may exist appears to exert similar influences on outcome regardless of a breast-sparing approach compared with a mastectomy approach. Decisions to alter regional radiotherapy recommendations based on ethnicity await carefully designed trials that address patterns of failure, quality of life, and survival outcomes and that provide multivariate analyses correcting for confounding factors.

**Systemic Therapy**

The next issue to be addressed concerns the possible existence of ethnicity-related variation in response to systemic therapy. Adjuvant chemotherapy and/or hormonal therapy for both patients with lymph node negative breast carcinoma and patients with lymph node positive breast carcinoma is now accepted as a means of reducing the odds of developing recurrent breast carcinoma and death from disease by up to 30%. Are similar proportional gains in outcome achieved in African-American patients and white patients with breast carcinoma? If there is a greater prevalence of biologically resistant tumors in the African-American patient population, or if there is ethnicity-related variation in drug metabolism, then this may not be the case. The concept regarding differences in drug metabolism has been cited by some investigators and is supported by known interethnic differences in several enzyme systems. This question should be addressed at least in part by data from prospective, randomized trials of adjuvant systemic therapy that stratify the population of patients with breast carcinoma and that standardize management as well as follow-up. Subset analyses from some previously reported multinstitutional trials have been reviewed, because these are more likely to have sample sizes adequate for meaningful comparisons.

The NSABP trials have generated substantial information regarding systemic therapy for patients with breast carcinoma. Primary pathologic and disease response results for African-American participants have been reported and were reviewed recently by Dignam. The NSABP B-09 study evaluated melphalan and 5-fluorouracil (5FU) with or without tamoxifen for patients with Stage II breast carcinoma. A persistent survival disadvantage was noted for the African-American patients compared with the white patients (crude 5-year survival for the melphalan-5FU arm: 52% vs. 68%; \( P = 0.01 \); crude 5-year survival for the melphalan-5FU-tamoxifen arm: 57% vs. 65%). Controlling for the greater prevalence of adverse tumor features (e.g., lower estrogen receptor positivity; 37% vs. 52%, respectively) eradicated a portion of this survival disparity. The adjusted 5-year survival rate for African-American patients was lower but was not significantly different from the rate for white patients.

The NSABP B-13 and B-14 studies evaluated adjuvant therapy in patients with lymph node negative, estrogen receptor negative, and estrogen receptor positive (respectively) breast carcinoma. Subset analyses of these trials, with 311 African-American patients and 4625 white patients, revealed equivalent treatment benefits for adjuvant systemic therapy across ethnic categories. These data provided strong support for the concept of equally aggressive adjuvant treatment resulting in similar outcomes.

Roach et al. reported on ethnicity-related outcome among participants in the Cancer and Leukemia Group B (CALGB) 8541 trial, in which 1572 patients with lymph node positive breast carcinoma (12% African American) were randomized to one of three different dose schedules for a doxorubicin-based chemotherapy regimen. Although univariate analysis revealed worse overall survival and decreased time to recurrence for the African-American patients, multivariate analysis (adjusting for extent of axillary lymph node involvement, estrogen receptor status, age, and treatment arm) eliminated the ethnicity-related survival disparity.

Similarly, Briele et al. suggested that the survival disadvantage seen among African-American patients with breast carcinoma may be minimized with appropriately aggressive care. In a retrospective review of 526 African-American women with Stage I–III disease who were treated at Cook County Hospital in Chicago,
the authors found that 5-year and 10-year survival rates were similar to the rates in historic controls. The authors also found that adjuvant systemic therapy resulted in substantial survival gains among patients with lymph node positive disease. It is interesting to note that the greatest benefit was seen among patients with one to three positive lymph nodes.

Conflicting results were reported by Elledge et al. in a study that evaluated primary tumor features and survival among 4885 white patients, 1016 African-American patients, and 777 Hispanic patients with breast carcinoma. The African-American patients had the lowest rates of estrogen receptor positive tumors, and African-American patients with lymph node positive disease experienced significantly worse disease free and overall survival. These results could not be explained by differences in use of systemic adjuvant therapy.

Data on primary breast tumor response after induction chemotherapy in African-American women would be meaningful; however, this area of research has been particularly limited. African-American women are more likely to be diagnosed with locally advanced breast carcinoma (LABC), and standard-of-care management for patients with LABC includes neoadjuvant chemotherapy. This approach permits tumor shrinkage that facilitates subsequent surgical resection, and in vivo assessment of response to treatment is predictive of outcome. Although survival from LABC generally ranges from 30% to 70%, survival for patients who achieve a complete clinical and pathologic response is substantially better. There will be a greater likelihood of increasing the pool of these complete responders as novel systemic therapy agents become available as crossover regimens. The University of Texas M. D. Anderson Cancer Center reviewed outcome among 373 patients with LABC who participated in prospective trials of induction chemotherapy; the 5-year survival rate for the complete responders was 88%. Subset analysis of this data set based on ethnicity revealed similar disease free and overall survival rates for African-American patients and white patients; a trend was noted for the African-American patients age < 50 years to be more likely to have a clinical partial or complete response, but this did not translate into a survival advantage.

Ethnicity-related variation in response to treatment for metastatic carcinoma was evaluated by the Piedmont Oncology Association. Their study of 74 African-American patients and 74 white patients with advanced disease who were treated on the same systemic therapy protocols demonstrated poorer survival for the African-American patients despite apparent equality of clinical management and treatment. The studies regarding adjuvant, induction, and palliative systemic therapy results in African-American patients underscore the importance of pursuing innovative and aggressive systemic therapy options in this patient population that is known for its high risk of disease recurrence and mortality.

Delivery of Care and Other Issues

Appropriately aggressive local and systemic therapy for African-American patients with breast carcinoma appears to result in favorable outcome for the majority of women. However, several studies have documented a survival disadvantage for African-American patients with breast carcinoma, even after controlling for stage at diagnosis and equivalent access to medical care. This constellation of findings prompts the question: Are ethnicity-related disparities in breast carcinoma outcome explained by disparities in treatment offered and/or delivered to African-American patients?

Looking at the BCT data, it appears that the low rate of BCT may be related at least in part to poorly informed patients. However, it also is possible that there are socioeconomic and cultural barriers to completing the 6-week course of radiation therapy that is a necessary component of this treatment alternative.

Breen et al. reevaluated data from the National Cancer Institute Black/White Cancer Survival Study by stratifying patients based on whether they received minimum expected therapy, as defined by stage-related standard-of-care practices and National Institute of Health Consensus Conferences. Overall, 21% of African-American women, compared with 15% of white women, did not receive this minimum expected care.

CONCLUSIONS

This review has focused on discrete ethnicity-related variations in outcome after standard treatment for patients with breast carcinoma. Several important related issues have not been reviewed but certainly deserve mention. Future areas of research should evaluate results from lymphatic mapping and sentinel lymph node biopsy for African-American women with breast carcinoma. This is worthy of particular attention, because African-American women are at greater risk for presenting with lymph node positive disease and because it will generate data regarding the incidence of micrometastatic disease in this patient population. In addition, some studies have demonstrated that African-American women are at greater risk for complications and disability related to standard axillary lymph node dissection. The interaction of ethnicity-related variations in body mass index and
the incidence of comorbidities also deserves closer attention in future studies.

From the available data, it can be concluded that African-American women with breast carcinoma potentially may respond as well to appropriate local and systemic therapy as white women with breast carcinoma. Health care providers should take special care to ensure that these women are fully informed of BCT options. There are data indicating that African-American women are at high risk for disease-related mortality, and early evidence suggests that they are at greater risk for particular patterns of locoregional recurrence. Explanations for these findings will be obtained only by appropriate representation and possibly by oversampling of African-American patients in prospective, randomized treatment trials.

REFERENCES

16. Kuske RR. Adjuvant irradiation after mastectomy in women with one to three positive axillary nodes; then no; now yes. Semin Radiat Oncol. 1999;9:254–258.


