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The Impact of Age on Outcome in Early-Stage Breast Cancer

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Abstract

Multiple studies have shown that breast-conserving therapy (BCT) and mastectomy have equivalent outcomes for large populations of women with early-stage breast cancer. For individual treatment decisions, however, it is important to appreciate the heterogeneity of disease. Recent molecular studies have suggested that “breast cancer” includes biologically distinct classes of disease; although these molecular distinctions are important, other patient-related factors also affect outcome and influence prognosis. One of the most important of these patient factors is the age of the patient at diagnosis. Numerous studies have shown very different breast cancer outcomes based on patient age; younger women typically have more aggressive tumors that are more likely to recur both locoregionally and distantly, and older women more commonly have less aggressive disease. The overall disease-specific outcomes, techniques, and doses for adjuvant radiation therapy and toxicity of treatments should be discussed within the context of age because breast cancer is a very different disease based on this factor. Arguments can be made that more aggressive locoregional therapy is warranted in populations of young women with breast cancer and perhaps less aggressive therapy in the elderly.

Patient age has been shown repeatedly to be a powerful prognostic indicator of the risks of both locoregional recurrence and distant metastases in patients with breast cancer. Multiple retrospective series and subset analyses of larger randomized trials have shown that women who develop breast cancer at a young age have more aggressive disease and an increased risk of recurrence. Significant research has been aimed at determining an underlying biological explanation for why young women have more aggressive disease, but these attempts have yet to fully elucidate the reasons. In contrast, elderly women with breast cancer appear to have a less aggressive course, which has led to investigations of whether less intensive treatment would be appropriate for these patients. Given the range of locoregional treatment options available for patients with breast cancer, most significantly breast-conserving therapy (BCT) versus mastectomy, the impact of age and its resultant effects on outcome may be important considerations in treatment. This review highlights the importance of age and its influence on outcome in the issue of locoregional treatment of breast cancer.

Breast-Conserving Therapy Versus Mastectomy: Data From Randomized Trials

A significant number of well-designed and well-executed randomized trials with extensive follow-up have shown that BCT, defined here as lumpectomy followed by whole-breast radiation therapy, is equivalent to mastectomy for women with early-stage breast cancer. As discussed by Drs Recht and Solin elsewhere in this issue, in a pooled analysis of randomized

prospective trials comparing BCT and mastectomy, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) found no statistically significant survival differences between the 2 treatments for patients with early breast cancer.¹ These data supported allowing women to have a choice in their treatment for early-stage disease. The trials in the meta-analysis included a large number of patients with breast cancer with relatively "common" patient characteristics; the median age for these trials ranged from 50 to 53 years. As expected, these trials did not include large numbers of patients at the extremes of age (very young or very old) because cancers are less common in young women, and older women were generally excluded from study.

One of the largest phase III randomized trials studying the role of locoregional therapy in breast cancer outcomes was the National Surgical Adjuvant Breast and Bowel Project B-06 study.² A total of 1,851 patients with stage I or stage II breast cancers and tumors ≤ 4 cm were studied from 1976 to 1984 and randomized to total mastectomy, lumpectomy alone, or lumpectomy followed by adjuvant radiation therapy (considered BCT for the purposes of this analysis). At a median follow-up of 20 years, there were no statistically significant differences in the 3 groups with regard to overall survival (OS) ($P = .57$), disease-free survival ($P = .26$), and distant-metastasis-free survival (DMFS) ($P = .34$). Comparing the 589 patients treated with mastectomy and 628 patients treated with BCT, there was also no difference in locoregional recurrence (LRR), which was defined as uncontrolled local disease on the chest wall. However, those patients treated with lumpectomy alone did have a statistically significant increase in ipsilateral breast recurrence compared with the risk of a chest wall recurrence in those patients treated with mastectomy (39.2% vs 14.3%, $P < .001$). In this trial, the authors indicated that "about 60%" of women were 50 years of age or older and that there were no statistically significant differences in age between the 3 treatment groups. However, they did not analyze the data based on age, so it is unknown whether the treatment modalities were equivalent for women of relative young or relatively old age.

In the Milan I trial, performed from 1973 to 1980, 701 patients with tumors ≤ 2 cm were enrolled and randomized between radical mastectomy ($n = 349$) and BCT (quadrantectomy followed by adjuvant radiation therapy) ($n = 352$).³ With a median follow-up of 20 years, OS for patients treated with BCT was 58% and 59% for patients treated with mastectomy ($P = 1.0$). However, patients treated with BCT did have a statistically significant increase in local recurrence compared with those treated with mastectomy (crude rates at 20 years were 8.8% vs 2.3%, $P < .001$). Analyzing the population by age, the authors divided the group into patients ≤ 45 years, 45 to 60 years, and > 60 years of age. Although there was no difference in local recurrence based on age for patients treated with radical mastectomy, patients ≤ 45 years of age had a statistically significant increase in local recurrence when treated with BCT (rate of 1.05 per 100 woman years for women ≤ 45 years compared with 0.34 and 0.54 for women 45–60 and > 60 years of age, respectively). The authors suggest that this increased risk of IBTR in young women treated with BCT may reflect pathologic findings of multifocal and multicentric disease in these patients. They did not conclude, however, that young patients should be managed differently than older patients; the OS outcomes did not differ by age.

The National Cancer Institute performed a study investigating the relative outcomes of women with stage I and II breast cancers randomized between BCT and mastectomy.⁴ From 1979 to 1987, a total of 237 patients with tumors ≤ 5 cm were enrolled. With a median follow-up of 18.4 years, there was no difference in OS between the treatment arms (58% for mastectomy vs 54% for BCT, $P = .67$). As noted in the prior publication with 10 years of follow-up, there was no statistically significant difference in LRR between the groups (10% mastectomy vs 5% BCT, $P = .17$).⁵ Both the 10- and 18.4-year updates did not analyze the data by age group, however, the publication with 5 years of follow-up indicated no

statistically significant differences in local failure by age group (<39 years, 40–50 years, or >51 years); there was no reported analysis of the difference in treatment arms based on age.⁶

The European Organization for Research and Treatment of Cancer (EORTC) 10801 study compared the treatment of early-stage breast cancer with different locoregional approaches.⁷ From 1980 to 1986, a total of 868 women with breast tumors ≤ 2 cm in size were randomized to BCT or modified radical mastectomy. With a median follow-up of 13.4 years, there was no difference between the patients in 10-year OS (66% mastectomy vs 65% BCT, $P = .11$) or DMFS (66% mastectomy vs 61% BCT, $P = .24$). The rates of LRR, however, did differ, with patients treated with BCT having a 20% LRR rate and only 12% in the mastectomy group ($P = 0.01$). On multivariate analysis, the hazard ratio (HR) for BCT was 1.64 (95% confidence interval [CI], 1.12–2.38; $P = 0.01$). The authors analyzed the study with respect to age by comparing women ≤ 50 years and those >50 years of age. Comparing the 2 age cohorts, there were no statistically significant differences in DMFS and LRR. When taking into account both age and locoregional treatment, the data actually suggest that older women (defined here as >50 years) had a greater risk of LRR with BCT compared with mastectomy (HR = 1.73%, 95% CI 1.06–2.80); this was not observed for women ≤ 50 years of age (HR = 1.48%, 95% CI 0.84–2.62). The authors conclude that, consistent with other large trials, BCT and mastectomy are equivalent with regard to OS and the number of locoregional recurrences remains small compared with distant recurrence regardless of treatment technique.

The Danish Breast Cancer Cooperative Group (DBCG) has also contributed a randomized trial comparing the role of mastectomy and BCT.⁸ From 1983 to 1989, the DBCG enrolled women with early-stage breast cancer on trial DBCG-82 TM and randomized them to BCT or mastectomy. With 793 eligible patients and a median follow-up of 19.6 years, there was no statistically significant difference in OS (49% mastectomy vs 54% BCT, $P = .24$). There were no statistically significant differences in the reported rates of local failure (6.9% mastectomy vs 4.5% BCT, $P = .16$). The primary report did not analyze outcomes with regard to age; however, the data were pooled with that of the EORTC 10801 trial analyzed with regard to risk factors and published separately.⁹ With a total of 1,772 patients for study and a median follow-up of 9.8 years, there was no difference in local and distant recurrence comparing BCT and mastectomy for the entire study population. However, a multivariate analysis noted that patients ≤ 35 years of age treated with BCT had a statistically significant increased risk of local recurrence (7% mastectomy vs 35% BCT; HR = 9.24%; 95% CI, 3.74–22.81). In the patients treated with mastectomy, however, the patients ≤ 35 years of age had no statistically significant difference in local control compared with older patients (>60 years of age). The pathologic feature of extensive intraductal component was also found to correlate with a greater risk of local recurrence after BCT (HR = 2.52%; 95% CI, 1.26–5.00). The authors noted that young patients (≤ 35 years old) had a significantly higher risk of local recurrence that then dropped significantly with age. Young age also appeared to be a risk factor for distant disease, which was much more prominent after BCT. The authors conclude that BCT and mastectomy are equivalent for the majority of patients, as indicated by the randomized trials; however, they caution that mastectomy may be indicated for patients ≤ 35 years of age.

The Institut Gustave-Roussy Breast Cancer Group also performed a randomized trial comparing BCT and mastectomy.¹⁰ From 1972 to 1979, 179 patients with early-stage breast cancers and tumors ≤ 2 cm in size were enrolled and randomized. With a median follow-up of 22 years, there were no differences in rates of 10-year OS between the 2 arms (67% mastectomy and 65% BCT, $P = .16$). However, there was a difference in the rates of local recurrence, especially with time; within the first 5 years of follow-up, there were fewer local recurrences in the BCT arm compared with the mastectomy arm and then the reverse with a

longer follow-up. Overall, after 5 years after treatment, the relative risk of local recurrence was 12.4 for patients treated with BCT compared with mastectomy (95% CI, 1.6–97). The authors also noted that women who experienced a recurrence within the first 5 years after treatment were similar in age between the 2 groups (53 years for mastectomy and 57 years for BCT); however, those patients with recurrences between 5 to 10 and >10 years after treatment tended to be younger. The average age for patients with a local recurrence between 5 and 10 years after BCT was 46 and >10 years was 44 years; there was only 1 patient in the mastectomy group who experienced a local recurrence. Comparing the rates of local recurrence at 15 years by age, there were more local recurrences with BCT compared with mastectomy in younger age groups (36 events for BCT compared with 12 for mastectomy in patients ≤ 40 years of age), whereas these were equivalent in older women (12 events for BCT compared with 12 events for mastectomy in patients ≥ 61 years of age). The authors concluded that BCT had equivalent survival as mastectomy but higher rates of local recurrence. Furthermore, the authors indicated that younger patients should be informed of the higher risk of local recurrence with BCT.

The extensive randomized data comparing BCT with mastectomy was analyzed as part of the EBCTCG meta-analysis.¹ With data involving 4,125 women and 15 years of follow-up, there were no statistically significant differences based on the treatment type in OS (53.3% vs 53.8%, HR = 1.01, standard error [SE] = 0.08) or isolated 5-year local recurrence rates (4.7% BCT vs 7.9% mastectomy, HR = 1.08, SE = 0.22). The most notable finding in this analysis, however, was the relationship between the prevention of a local recurrence and mortality. For the first time, the EBCTCG meta-analysis suggested that the prevention of 4 local recurrences would result in the prevention of 1 death. This argues that data showing superiority of 1 treatment over another in terms of local control, even without an immediate survival benefit, may be important for long-term outcomes. The EBCTCG analysis did not delineate the differences in outcomes between patients treated with BCT and mastectomy based on age. As a result, it is not possible to draw conclusions about the superiority of 1 locoregional treatment over another for a given age group based on these data.

These compelling data from multiple randomized trials, which continue to withstand further follow-up, have provided women with breast cancer a choice regarding their best locoregional therapy, BCT or mastectomy. However, the general conclusion of these trials, namely that BCT and mastectomy are equivalent in terms of outcome, does not address whether subsets of women may do better with one or the other. Given the different characteristics and outcomes of breast cancer based on the age at which it develops, the impact of age on outcome in these patients is a relevant topic and may suggest that one is superior to the other if age is considered.

Definitions of Age: “Young” and “Elderly”

Establishing the definition of “young” patients with breast cancer has been the subject of some controversy. Breast cancer in women ≤ 40 years of age is relatively uncommon, reflecting only 5% of new breast cancers from 2002 to 2006.¹¹ Further data from the American Cancer Society indicate that women aged 20 to 24 had the lowest breast cancer incidence rate, with 1.4 cases per 100,000 women. Zhou and Recht¹² researched the definitions of “young age” by searching the MEDLINE and CancerLit databases and found that women “35 to 40 years of age or younger” defined a group of patients in which age was an independent risk factor for higher rates of recurrence. Other series have also suggested that the age of 35 might be most appropriate with which to define a “young” age group.^{9,13–16} Although controversy still exists, most series recognize patients ≤ 35 years old as a “young” population.

The same difficulty in definition exists in establishing an “elderly” population of breast cancer patients for study. Multiple trials excluded women over 70 years of age by design, including the Milan I (3) and the EORTC 10801 trials.⁷ As a result, there are little data from large randomized trials that address the issue of the best locoregional treatment in this age group. This is particularly interesting in light of the fact that the highest incidence rate of breast cancer is in women aged 75 to 79 at 441.9 cases per 100,000 women.¹¹ Multiple series have established an “elderly” population as those women aged 70 and older; however, these have also subdivided this group, noting decreased risks of events in the older subgroups.^{17,18}

Studies of Locoregional Treatment Based on Age: “Young” Patients

Despite the wealth of data on the equivalence of BCT and mastectomy with regard to survival, the published data reflect a large and diverse cohort of patients; individual subsets, namely the “young” and the “elderly,” may have different outcomes that would suggest a preferred treatment option. In the 6 randomized trials comparing BCT and mastectomy, the median ages range from 50 to 53 (Table 1). Although each study includes a wider range of ages, the inclusion of patients at the extremes of age is limited, and the age groupings have varied considerably in the resultant analyses (Fig 1). As a result, individual retrospective analyses and subgroup analyses from the randomized trials have largely provided the data regarding appropriate age cutoffs that can be used to predict disparate risks in women with breast cancer.

As discussed previously, “young” patients with breast cancer have variably been defined in the randomized trials and retrospective reviews of breast cancer treatment. Regardless of the definition, however, most series suggest a worse prognosis in young women compared with older women. The reasons for these higher rates of recurrence are unclear. Multiple studies have evaluated potential biological differences that account for the disparate behavior of breast cancers in young women; young women tend to have more triple-negative and fewer luminal A and B breast cancers^{19–21} as well as tumors that are higher grade, have more extensive intraductal component, have more lymphovascular space invasion, and are more likely estrogen receptor (ER)-negative.^{22–25} Although young women do appear to have tumors with more aggressive biological characteristics, these factors alone seem insufficient to fully explain the differences in outcome that have been observed.^{13,20,26,27}

Looking at the options for treatment for young women with breast cancer, the higher rates of LRR that have been shown make the choice of BCT or mastectomy especially controversial. Using the most frequent definition of young age, patients ≤ 35 years old, there is evidence of higher rates of LRR when BCT is used as locoregional treatment.^{13,14,16,22,23,28–31} This raises the question of whether BCT should be considered appropriate management of young women with breast cancer.

There has been hesitation to use young age as an indication for mastectomy in part because of the nature of the data (largely retrospective), limitations on prior studies of treatment (historic datasets that may no longer be applicable in the time of modern surgery, radiation therapy, and chemotherapy), and the implications for individual patients (quality of life [QOL] and body image). One of the limitations to many of the retrospective and subset analyses examining the relationship between local control and young age is the lack of information regarding the use of postmastectomy radiation in the mastectomy cohort. We have previously reported LRR rates among 652 young women (≤ 35 years old) diagnosed with breast cancer and treated at the University of Texas MD Anderson Cancer Center from 1973 to 2006.³² Among young women with breast cancer, the 10-year actuarial LRR rate approached 20%. This was consistent with prior reports; Coulombe et al²⁹ noted an 18.0%

10-year LRR rate for patients 20 to 39 years old, and Elkhuisen et al³³ reported a 28.0% 10-year LRR rate for patients ≤ 35 years old. In contrast to preceding reports, however, the MD Anderson study explicitly segregated locoregional treatment into mastectomy with adjuvant radiation (MXRT), mastectomy alone, and BCT (rather than simply mastectomy vs BCT). We reported that patients treated with mastectomy alone consistently had the highest rates of locoregional failure compared with both MXRT and BCT. This effect was largely driven by high locoregional failure rates in women with stage II disease treated with BCT or mastectomy alone. In patients with stage II disease ($n = 296$), the locoregional treatment approach had a significant impact on LRR (17.7% BCT, 22.8% mastectomy, and 5.7% MXRT; $P = .02$). The improvement in outcome in patients treated with MXRT was observed despite the increased use of neoadjuvant chemotherapy ($P < .001$) and more advanced N stage ($P = .004$) in this group compared with mastectomy or BCT. On multivariate analysis, mastectomy alone ($HR = 4.45$, $P = .014$) and grade III disease ($HR = 2.24$, $P = .012$) were the variables that were predictive of LRR; the use of BCT was found to be of borderline significance ($HR = 3.40$, $P = .052$). These data suggested that patients ≤ 35 years old with stage II disease who choose mastectomy should be counseled that their LRR rate could be significantly improved with postmastectomy radiation. The use of adjuvant postmastectomy radiation must be carefully considered; it is not without risks and has a significant impact on surgical reconstructive options.^{34,35}

In this same analysis of women ≤ 35 years old, patients with stage I cancers were found to have significant LRR differences based on systemic but not locoregional therapy approaches.³² For the 101 patients with stage I disease, there were no differences in LRR between patients treated with BCT or mastectomy (18% BCT vs 19.8% mastectomy, $P = .56$). However, there was a statistically significant benefit in LRR for patients that received systemic chemotherapy (13.5% chemotherapy vs 27.9% no chemotherapy, $P = .04$). This suggests that even with relatively small tumors, young women may benefit from systemic therapy and that age should at least be considered in the discussion of comprehensive treatment.

The suggestion from multiple series that locoregional treatment approach does impact LRR in young patients is consistent with data from subset analyses from previous prospective trials. Evaluating the impact of age on LRR after mastectomy alone in patients treated as part of the International Breast Cancer Study Group Trials, Karlsson et al³⁶ found that young age was an independent risk factor for LRR after mastectomy that conferred similar rates of LRR as 4 or more positive lymph nodes.³⁶ In aggregate, most of these data suggest that young age is associated with higher rates of LRR and should be a consideration in selecting locoregional treatment approach. This is especially true in young patients with stage II disease. However, the data are not strong enough to recommend that young age alone be an indication for mastectomy itself; in fact, there are many unanswered questions as to how to incorporate these data for individual patient decision making.

It is certainly hoped that emerging technologies that assess the individual biology of each patient's tumor will lead to more individualized therapies and guide recommendations for the appropriate locoregional and systemic therapy. A recent study relating a 21 gene recurrence score (RS) to LRR makes significant progress in moving toward this goal of individualized medicine for young patients with breast cancer.³⁷ As discussed elsewhere in this issue, the 10-year Kaplan-Meier estimates of LRR for the Oncotype DX RS low, intermediate, and high groups were 6.8%, 10.8%, and 14.6%, respectively, after BCT ($P = .043$). Among the 505 patients who underwent mastectomy alone (without adjuvant radiation), the 10-year Kaplan-Meier estimates of LRR for the RS low, intermediate, and high groups were 2.3%, 4.7%, and 16.8%, respectively ($P < .001$). On multivariate analysis, both young age (defined here as < 50 years old) and RS independently predicted for higher

LRR (age: HR = 0.40%; 95% CI, 0.25–0.65; $P = .0002$ and RS: HR = 2.16%; 95% CI, 1.26–3.68; $P = .005$). Examining the risk of LRR by subgroups, young patients treated with BCT had higher rates of LRR than older women; a similar pattern was not observed in patients treated with mastectomy. Younger patients with high RS had 10-year LRR rates exceeding 20% after either tamoxifen alone or BCT, and younger patients with intermediate RS and who were treated with BCT also had LRR rates exceeding 20%. These are compelling data that necessitate further studies of this approach or a similarly defined molecular analysis to individualize treatment recommendations for young women.

Studies of Locoregional Treatment Based on Age: “Elderly” Patients

Most breast cancers develop in older women; from 2002 to 2006, the median age at the time of breast cancer diagnosis was 61 years.¹¹ However, defining an “elderly” population, at the extreme of older age, has had the same difficulties as defining a “young” population. Previous data suggest that approximately 50% of breast cancers occur in women ≥ 65 years of age and $>30\%$ of breast cancers occur in women >70 years of age.³⁸ Despite this pattern of incidence, women over 70 years of age have largely been excluded from randomized trials of breast cancer treatments. The purported reasons for these exclusions have included the presence of medical conditions that may affect the response to treatment, the possibility of poor compliance, and the potential difficulties with managing toxicities of treatment.³⁹ Establishing treatment recommendations for this population of “elderly” women with breast cancer is difficult because their experiences have not been fully evaluated in randomized studies.

The appropriate treatment for elderly women with breast cancer remains controversial. It is widely believed that older women have less aggressive biology than middle-aged women, who have less aggressive disease than young women, establishing a continuum of aggressiveness based on age; however, this remains an area of active investigation. A study of the Surveillance, Epidemiology, and End Results Registry noted that in patients ≥ 55 years old, there was an association between increasing age and more favorable biological characteristics; older patients had more ER-positive tumors, lower proliferative rates, and normal p53, among other molecular findings.⁴⁰ Nonetheless, other studies suggest that the outcomes for elderly women, when stage is taken into account, are similar to middle-aged women. Singh et al⁴¹ evaluated 2,136 patients treated at the University of Chicago and found that women >70 years of age were less likely to present with positive lymph nodes than younger women. However, after taking lymph node positivity into account, there was no difference in outcomes in women >70 years of age; the authors suggest that there is no evidence that breast cancer in elderly women is less aggressive than in younger patients. In a review of the literature in 1994, Morrow⁴² commented that the data suggest that “breast cancer in the elderly should not be considered an indolent disease.”

More recent studies have sought to address this issue by specifically evaluating the optimal treatment strategies and outcomes of elderly women with early breast cancer; in large part, these studies have investigated the possibility of treatment de-escalation in this population. The Cancer and Leukemia Group B performed a randomized trial of women with breast cancer ≥ 70 years of age in which 636 patients with clinical stage I, ER-positive tumors treated with lumpectomy were randomized between adjuvant radiation therapy and tamoxifen versus tamoxifen alone.¹⁸ The results of this study showed that the only statistically significant difference between the 2 arms was the 5-year rates of local or regional recurrence (1% tamoxifen/radiation vs 4% tamoxifen alone, $P < .001$). There were no differences in OS between the groups (87% tamoxifen/radiation vs 86% tamoxifen alone, $P = .94$). This study established low absolute rates of recurrence in elderly women with early-stage breast cancer regardless of treatment; however, it also indicated that more

treatment, namely adjuvant radiation, provides a statistically significant relative benefit, even in the setting of low rates of recurrence.

Another recent study looked at the population of patients ≥ 70 years of age with breast cancer within the Surveillance, Epidemiology, and End Results Database and compared those treated with lumpectomy and adjuvant radiation versus lumpectomy alone.¹⁷ The use of adjuvant radiation therapy after lumpectomy was associated with a 5-year absolute risk reduction of 4.0 events per 100 women and an 8-year absolute risk reduction of 5.7 events per 100 women. Further examining the subsets of patients that benefited most, women aged 70 to 79 years with no comorbidities had the largest benefit, with a number needed to treat to prevent 1 event of 21 to 22 patients. Adjuvant radiation was least likely to benefit patients who were ≥ 80 years of age with moderate to severe comorbid conditions (number needed to treat = 61–125 patients). Overall, for elderly women with early breast cancer, adjuvant radiation therapy was associated with a lower risk of a second ipsilateral breast cancer and subsequent mastectomy. Not surprisingly, patients aged 70 to 79 years with minimal comorbidity were the most likely to benefit, and older patients with substantial comorbidity were least likely to benefit.

In aggregate, the data on early breast cancer in elderly patients suggests that patients do gain a relative benefit from aggressive locoregional therapy. However, the baseline risks of recurrence are relatively low in this patient population so the magnitude of the benefit is limited. As such, there is a valid argument to discuss treatment de-escalation with some elderly patients, especially if they have significant comorbidities and competing health risks. Nevertheless, the data do indicate that breast cancer is not an indolent disease in this population and appropriate treatment is warranted; the scope of that treatment remains controversial.

The Impact of Boost Treatment in Outcomes Based on Age

One of the continuing controversies in the treatment of patients with BCT is the appropriate dose and fractionation of treatment. Given the differences in locoregional recurrence rates based on age, as discussed previously, the propriety of boost treatment in different age cohorts continues to be debated.

One of the largest studies to address the efficacy of boost treatment in patients with early breast cancer was the EORTC 22881/10882 study.⁴³ In this study, 5569 patients with early-stage breast cancer treated with BCT were randomized to either whole-breast radiation alone (50 Gy in 25 fractions) or whole-breast radiation with an additional 16-Gy boost to the tumor bed. With a median follow-up of 77.4 months, there was a statistically significant decrease in local failure by a factor of 2 using the 16-Gy boost ($P < .0001$). In addition, multivariate analysis showed that local control was correlated strongly with age ($P = .0003$), with older patients having decreased rates of relapse. Although there was a statistically significant benefit to the boost in all age groups, the absolute benefit was higher in young women because the LR rates were higher (Table 2). These data argues the relative benefit of a higher radiation dose in all groups although the absolute benefit in the older women may be limited. Further study, including the long-term recurrence rates and cosmesis, will help delineate the relative benefit of boost treatment in different age groups even further. Future studies investigating lower boost doses may be beneficial in tailoring treatment for individual patients.

QOL and Toxicity of Treatment Based on Age

The issues of QOL and the toxicity of various locoregional treatments are of paramount importance in the recommendation for therapy in patients with early breast cancers. A study

of the impact of the type of breast cancer surgery on the psychological well-being of the patients showed that patients who received BCT felt better in the first months after surgery and then began to feel worse.⁴⁴ In patients treated with the mastectomy, the trend was opposite. Overall, when comparing the effect of mastectomy and BCT on QOL, no statistically significant differences have been found in psychological adjustment, change of life patterns, or fears.⁴⁴ Despite these data, few studies have addressed the issues of QOL and toxicity with regard to age.

For patients with breast cancer, multiple studies have shown that adaptation and QOL are more difficult for younger patients.^{45,46} Standardized measures of depression and QOL suggest that younger women diagnosed with breast cancer have more significant changes in mood and poorer emotional functioning than do older women facing the same diagnosis.^{47,48} Nonetheless, most studies in younger women evaluate the impact of the long-term endocrine effects of comprehensive breast cancer treatment and fewer evaluate the role of locoregional treatment on QOL.⁴⁴ There is a dearth of information in this area, and future studies of breast cancer treatments would be well served to evaluate measures of QOL as well as toxicity for young women.

For elderly women, QOL is significantly impacted by open discussions with their medical team. In a study of 613 pairs of surgeons and older patients (defined as ≥ 67 years of age), patients who reported that their physicians mentioned multiple treatment options were more likely to have had a choice in treatment (HR = 2.21%; 95% CI, 1.62–3.01) and more likely to get BCT (HR = 1.33%; 95% CI, 1.02–1.73).⁴⁹ A high degree of physician-initiated communication was also linked to improved overall satisfaction. For patients treated on EORTC trial 10850, comparing women >70 years old treated with either mastectomy or wide local excision and adjuvant tamoxifen, a QOL analysis revealed no differences between the arms in terms of fatigue, emotional functioning, or fear of relapse.⁵⁰ However, this study did show that patients who underwent mastectomy had more arm problems and worsening of body image compared with those treated with local excision and tamoxifen. Figueiredo et al⁵¹ examined the relationship between body image, treatment choice, and treatment received in older women with breast cancer. In this study of 563 older women (defined as ≥ 67 years) with breast cancer, 31% stated that body image was an important factor in their treatment decision. Women who received BCT had better body image 2 years after treatment than those that received mastectomy ($P < .0001$). Overall, the issues of body image and QOL should be considered in the discussion of locoregional treatment approach for early breast cancer in elderly patients.

Given the relative paucity of data for women at the extremes of age treated with specific locoregional approaches for early breast cancer, it is understandable that there is even sparser data on the toxicities of treatment by age group. Although the EORTC 22881/10882 study reported that severe fibrosis was statistically significantly increased in women treated with boost radiation (10-year rates of 4.4% vs 1.6%, $P < .0001$), there is no subset analysis of differential toxicities based on age.⁴³ For young women, most studies investigating the role of locoregional treatment approach concentrate on the outcomes of treatment; there is a paucity of data regarding relative toxicities. For elderly women studied in the Cancer and Leukemia Group B trial that compared treatment with lumpectomy and adjuvant radiation therapy and tamoxifen versus lumpectomy and tamoxifen alone, there was evidence that adjuvant radiation therapy resulted in inferior overall cosmesis, breast pain, breast edema, and skin color changes during the first 2 years of follow-up; however, by the 4 years, these differences were no longer significant.¹⁸

In addition to QOL, the relative risks of contralateral breast cancer (CBC) and cardiovascular toxicity in different age groups should be considered when weighing

treatment options. Age has been shown to impact the development of both of these long-term complications; however, there are little compelling data that there is a differential effect favoring BCT or mastectomy. In Fowble et al,⁵² a series of 1,253 women with stage I to II breast cancers treated with BCT were assessed for the development of secondary malignancies; with a median follow-up of 8.9 years, 176 patients developed a second malignancy (87 CBC and 89 non-breast cancer malignancies).⁵² Young age was associated with an increased risk of CBC ($P = .03$), and older age was associated with an increased risk of non-breast cancer malignancies ($P < .0001$). This is similar to outcomes of prior studies showing a greater risk of CBC for young patients treated with BCT^{53,54}; however, data directly comparing the rates of second malignancies after BCT versus mastectomy have shown no increased risk with BCT.⁵⁵ Although it is clear that young women are at an increased risk of CBC, there is no compelling evidence that BCT puts patients at increased relative risk over mastectomy.

The data on cardiovascular toxicity after BCT with regard to age are complicated by the significant changes in radiation therapy technique over the last several decades. Although historic data suggested increased cardiac toxicity with radiation to left-sided breast tumors, either with BCT or as part of postmastectomy radiation, modern series have shown more mixed results.^{56,57} For patients treated with BCT, younger women have a longer time to exhibit potential cardiac consequences of radiation therapy; however, older women are more likely to have preexisting cardiovascular risk factors that may act synergistically with radiation itself to cause cardiac injury. Overall, the potential cardiac toxicity of BCT has not been well characterized by age, and further study is needed to understand if the concern for future cardiac morbidity and mortality should impact treatment recommendations for patients of a young or old age.

Conclusions

Although the specific relationship between age at diagnosis, tumor biology, and locoregional recurrence remains unknown, the preponderance of data suggests that the risk of LRR after early-stage breast cancer decreases with age. For young women, who have relatively high rates of LRR, maximizing locoregional therapy should be prioritized; this may involve the recommendation for adjuvant radiation therapy after mastectomy for those with stage II disease and chemotherapy for those with stage I disease. In this population, novel treatment approaches that involve treatment de-escalation, including altered fractionation⁵⁸ and partial-breast irradiation,⁵⁹ should be considered with caution. Conversely, for elderly women, the low baseline risks of recurrence suggest that maximal locoregional therapy may not be warranted for all patients despite the relative benefits. Among women ≥ 70 years of age with very favorable disease, the competing risks of comorbid conditions may outweigh the local control benefit of traditional postlumpectomy radiation. Overall, age has a significant impact on the outcomes of patients with early-stage breast cancer, even accounting for biological characteristics and stage; it should be considered with regard to locoregional treatment decisions and warrants further study.

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Figure 1.

Definitions of age in the 6 randomized trials of BCT and mastectomy. Each shaded bar represents the delineation of age groups in the respective trials; each divided patients into age groups in a unique way. *All included age in the discussions of locoregional treatment with the exception of the Danish 82-TM trial; this trial did not have a separate analysis based on age but was used in the pooled analysis with the EORTC trial and age definitions were as indicated here.⁹

Table 1

Randomized Trials of Mastectomy Versus breast-conserving therapy*

Study	Number of Patients	BCT	Median Age, (y)	Mastectomy	Median Follow-up (y)	Overall Survival (%)	
						BCT	Mastectomy
NSABP B-06 (2)	1217			NP	20	46	47 (20 yr)
EORTC (7)	868			53	13.4	65	66 (10 yr)
Milan I (3)	701			51	20	58	59 (20 yr)
Danish (8)	793			51	19.6	54	49 (20 yr)
French (60)	179			51	22	65	67 (10 yr)
NCI (4)	237			50	18.4	58	54 (18 yr)

NP, data not provided in the original reference.

* Breast-conserving therapy is defined here as lumpectomy and adjuvant whole breast radiation therapy.

Table 2

Absolute Local Failure Benefit in EORTC 22881/10882 Boost Trial by Age Group (43)

Age group (years)	Local Failure, No Boost	Local Failure, Boost
<40	23.9%	13.5%
41–50	12.5%	8.7%
51–60	7.8%	4.9%
>60	7.3%	3.8%