Caring for Older Women With Breast Cancer: Can Observational Research Fill the Clinical Trial Gap?

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Women aged 65 years or older (herein referred to as “older women”) constitute one-half of new breast cancer patients each year (1), and the absolute number of breast cancer cases will double by 2030, with the graying of America (2). Despite their growing numbers, guidelines for appropriate treatment of these older women are limited by the lack of clinical trial data that are specific to this age group, uncertainty about balancing treatment toxicity and benefits, the potential for therapy to amplify pre-existing medical conditions, and competing noncancer causes of mortality. There are also minimal data on older women’s preferences for treatment and its outcomes.

To address this conundrum, recent initiatives have focused on select clinical trials for older women. Randomized trials have long been considered the “gold standard” of clinical evidence. However, only 1%-2% of older women participate in clinical trials, and those that do are healthier than average because of narrow eligibility criteria. This selection bias raises concerns that a clinical trial result cannot be generalized to the community practice of older women.

The use of radiation therapy after breast-conserving surgery in women with small tumors with favorable prognostic provides an unprecedented opportunity to compare results from a clinical trial among women aged 70 years or older with observational results obtained from nationally representative data with virtually identical eligibility criteria. Many randomized trials over the last 20 years have shown that postoperative radiation therapy decreases the rate of ipsilateral recurrence but offers no survival benefit in women treated with breast-conserving surgery [e.g., (3,4)].

The risk of local recurrence is lower in older women and in those older women receiving adjuvant tamoxifen or chemotherapy. For these reasons, the Intergroup trial lead by the Cancer and Leukemia Group B (CALGB) assessed the benefit of tamoxifen alone or with radiation therapy in women aged 70 years or older who had small (T1) lymph node-negative, estrogen receptor-positive breast cancer. This first-of-its-kind trial, in which age was the primary entry criterion, found that, among 636 women, the rate of local recurrence at 5 years was reduced to 1% with combined radiation therapy and tamoxifen compared with 4% with tamoxifen alone. No differences in rates of subsequent mastectomy for treatment of recurrences were found (5).

In this issue of the Journal, Smith et al. (6) used the Surveillance, Epidemiology, and End Results (SEER)–Medicare database to assess the risk of local recurrence among 8724 women aged 70 years or older who also matched the CALGB trial inclusion criteria (defined as an ipsilateral cancer and/or mastectomy). They found that local recurrence were reduced by 4% at 5 years and increased to 5.7% by 8 years.

Most importantly, Smith et al. show that a well-designed observational study can not only reproduce estimates of the impact of treatment seen in the trial setting but, given its larger size, also provide new or complementary insights on subgroups. For example, they found that the maximum benefit of radiation therapy was in the groups that intuitively should benefit the most: younger women with no or minimal comorbidity.

This finding is critical because there is considerable heterogeneity in life expectancy among older women. For instance, a 70-year-old woman in the lowest quartile of health has a 9-year life expectancy, whereas a 79-year-old woman in the top quartile has a 14.6-year life expectancy. Because using radiation therapy to prevent local recurrences does not affect overall survival, patient preferences about the anticipated cosmetic results and worry about future recurrences may dominate a woman’s decision making. Conversely, some women will rightly choose not to have radiation therapy because approximately 95% of the time they will remain recurrence free and because of the time commitment. The CALGB trial noted that patient and physician ratings of cosmesis and pain were worse with radiation therapy for at least 2 years and were then predominantly resolved. Unfortunately, they did not measure less tangible outcomes, such as worry about recurrence, so we do not know the impact of omission of radiation therapy on this outcome. Secondary observational data cannot address this issue either and so this matter is left to personal preference.

Overall, this study highlights the power of observational data that meets the following rigid criteria (7): 1) there is a clinically relevant database with sufficient detail of known prognostic factors, 2) there is a easily defined starting point in the disease trajectory, 3) the technical quality of the intervention is not suspected to markedly differ between academic and community settings, and 4) the sample is thought to represent the real world. Under these conditions, observational data may not only approximate the clinical trial findings but could also provide the most relevant findings. Also, the use of secondary data can provide longer observations of follow-up at minimal cost. Overall, use of a dataset such as the SEER–Medicare database is cost efficient compared with the costs of conducting a multisite clinical trial. Unfortunately, there has been a paucity of studies in cancer that have used linked registry data other than the extensive use of SEER–Medicare (8,9).

Because it is unlikely that there will suddenly be a marked increase in enrollment of older women into clinical trials, more high-quality observational studies such as that by Smith et al. can be used to provide information for clinical and policy decision making for the rapidly growing older population of women at risk for breast cancer. These data could also be used to provide information for shared decision making between older women and their providers.

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