EDITORIAL

Can Less Be More for Individuals With Low-Risk Breast Cancer?

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Steady progress in reducing mortality from breast cancer is a testament to the benefits of randomized clinical trials, multidisciplinary collaborations, and data sharing. In the second half of the last century, surgical, medical, and radiation oncologists worked together to methodically and rigorously test de-escalating surgical interventions and include multimodality treatment approaches to reduce local and distant breast cancer recurrence (1,2). The stepwise approach led to abandoning the disfiguring radical mastectomy, giving women the choice of simple mastectomy or breast conservation, and providing guidance on the benefits and risks of adjuvant hormonal and systemic chemotherapy. Over the years, improvements in screening technology, uptake of screening, along with improved prognostic characterization of breast cancer, have identified subgroups of patients with low risk for recurrence. For those low-risk patients, the question becomes how much treatment is enough to reduce both risk of recurrence and adverse effects of treatment?

Women diagnosed with breast cancer face an increasingly complex array of treatment options. Despite the long history of randomized breast cancer treatment trials that guide therapy decisions, there are areas of remaining uncertainty. Trials have demonstrated the primary benefit of post-lumpectomy radiation therapy to reduce the risk of local recurrence but also the adverse effects (3,4). With improved ability to assess the prognosis of breast tumors, are there patients at sufficiently low risk of recurrence who could safely omit radiation therapy and thus avoid its acute and long-term adverse effects? What is the added benefit of post-lumpectomy breast irradiation? Could a clinical trial be feasibly conducted to determine if breast irradiation could safely be avoided for some patients? Two studies conducted by The Cancer Intervention and Surveillance Network-Breast Oncology Localized Disease (CISNET-BOLD) modeling group, address these questions. The article by Jayasekera et al. (5) is a pooled analysis that examined

individual-level data from clinical trials and evaluated radiotherapy after lumpectomy in patients at low risk for recurrence to better estimate risks of recurrence with and without use of radiotherapy. The information from the pooled analysis along with other published data were then used by Jayasekera and Li et al. (6) in the modeling study in which two models simulated outcomes of a proposed noninferiority trial omitting radiotherapy for women with low-risk invasive breast cancer.

In the pooled analysis, Jayasekera et al. (5) used individual-level patient data from seven trials that either evaluated or included radiotherapy after lumpectomy for women with low-risk breast cancer. "Low risk" was defined as node-negative invasive breast cancer 2 cm or less, hormone receptor-positive, HER2-negative and was adapted to include the OncotypeDX score, using a recurrence score of less than 18 (equivalent to a 10% risk of recurrence) to define low risk (7). Recurrence scores were imputed for six of the trials. Of note, this definition of low risk differs from the recently published TAILORx trial that used a recurrence score of 10 or less to define low risk (8). The analysis examined recurrence-free interval and, secondarily, by specific type of recurrence (locoregional and distant) and survival (overall and breast cancer-specific). The pooled analysis, based on data from 1778 women from the seven trials, observed statistically significant absolute differences in five- and 10-year adjusted recurrence-free interval rates of 4.4% (95% CI = 0.7% to 8.1%; 97.9% vs 93.5%) and 9.2% (95% CI = 1.8% to 16.6%; 95.3% vs 86.1%) in favor of radiotherapy. The benefit was due to a reduced risk of locoregional recurrence, not distant recurrence, and no differences were observed for overall or breast cancer-specific survival. This absolute benefit is smaller than that noted in a meta-analysis from the Early Breast Cancer Trialists' Collaborative Group that included 17 trials (3). The Jayasekera et al. (5) pooled analysis focused on a more favorable prognostic subset of patients than in the overview analysis (3), all with

hormone-sensitive breast cancer and further characterized by the OncotypeDX scores.

The pooled analysis (5) does have limitations to consider when applying these results in the clinical setting. The pooled dataset does not reflect random assignment to radiation, thus biases may be introduced. OncotypeDX scores were imputed for many of the participants and results may not extrapolate to more recent radiation regimens and/or use of adjuvant aromatase inhibitor therapy. Despite these limitations, the pooled analysis provides relevant clinical information that low-risk individuals, on average, reduce their risk of local recurrence with radiotherapy. Unfortunately, this study did not include estimates of the acute or long-term harms of radiation therapy. Estimating the risks as well as the benefits is critical, especially as progress is made in identifying even more favorable subgroups of patients where the absolute benefit may be offset by harms.

Although the Jayasekara et al. (5) pooled analysis demonstrated a statistically significant, but moderate, absolute benefit of post-lumpectomy radiation among a low-risk group of patients, uncertainty remains. For example: Would benefits and risks change with different hormone or radiation therapy regimens than were used in past trials? Are there some groups of patients with even better prognosis, a smaller absolute benefit to be gained, and thus more certainty that “less (treatment) is more?” Is it feasible to conduct a de-escalation trial among women with low-risk breast cancer to address the question of noninferiority of outcome when omitting radiotherapy?

The other article from CISNET-BOLD, by Jayasekera and Li et al. (6), is a modeling study that used simulation models to address the question of the feasibility of a NRG Oncology proposed clinical trial omitting post-lumpectomy radiotherapy for women with low-risk breast cancer (node-negative invasive breast cancer, < 2 cm, hormone receptor-positive, HER2-negative OncotypeDX score <18). Two models, model M and model GE, simulated trial outcomes. The primary endpoint was recurrence-free interval, based on relative hazard ratios rather than absolute risk differences. As proposed in the trial, noninferiority would be demonstrated if the two-sided 90% confidence interval of the recurrence-free interval hazard ratio of omitting radiotherapy vs radiotherapy was below 1.7. With a 5% type 1 error rate and 80% power, 88 events were required. One thousand simulations were performed with each model. The information from the Jayasekara et al. (5) pooled analysis was used in model GE, which examined outcomes by type of recurrence (eg, locoregional vs distant). Model M used published data from the seven randomized trials in the Oxford collaborative study that evaluated post-lumpectomy radiation (3) and was not able to assess differences by type of recurrence.

The Jayasekera and Li et al. (6) modeling study is an excellent example of how statistical modeling can inform research design as well as decisions regarding resource allocation. For both models, the majority of simulated trials did not meet the criteria for noninferiority (82% for model GE and 96.3% for model M). Across the 1000 trial simulations, the five-year recurrence-free interval absolute benefit in favor of post-lumpectomy radiation was 2.8% (SD 0.02) for model GE and 6.1% (SD 0.03) for model M. The simulated mean five-year recurrence free interval rate with radiotherapy was 95.5% (SD 0.02) for model GE and 94.5% (SD 0.02) for model M. The main benefit for the addition of radiation therapy was to decrease locoregional recurrence (model GE). An advantage of modeling is the ability to simulate with different inputs, and the modelers examined varied case definitions of low risk, including different recurrence score cutpoints, age of

participants, and grade of tumor. The results of the models also demonstrate the importance of using absolute risk rather than relative risks to measure efficacy. Noninferiority could not be demonstrated even with very low relative risks for recurrence. However, for some subgroups, the risk of recurrence may be so low that the absolute benefit may be outweighed by the risks of radiation therapy. The trial simulations, however, did not include adverse outcomes. Including both benefits and risks in simulations would increase the relevance of modeling approaches to clinical care as well as research designs.

As emphasized by the Jayasekara and Li et al. in their modeling study, simulated data cannot substitute for real data obtained by well-conducted randomized clinical trials. Indeed, the data for model inputs were based on results from prior randomized clinical trials. Models that predict trial results, however, can inform the decision of whether it is feasible to proceed with a proposed trial, or can inform the design of the trial by identifying key factors (parameters) that influence outcome or deciding the most appropriate trial outcome. But the weight given to the results of modeling should take into consideration the degree of uncertainty of the input parameters and predictions.

In 1968, Fisher et al. published on the results of “a decade of cooperative investigation” (1). Over the ensuing decades, remarkable progress in the treatment of breast cancer has been made because of the continued collaboration of multidisciplinary teams of researchers and the women who took part in these trials, resulting in decreased breast cancer mortality. Researchers doing system modeling approaches, exemplified by CISNET-BOLD, are another addition to this multidisciplinary collaborative research effort. These two studies by this collaborative modeling group provide more refined estimates of the absolute benefit of post-lumpectomy radiotherapy among women with low-risk invasive breast cancer to assist in clinical decision making as well as future research efforts. Future work should incorporate estimates of harms as well as benefits of radiotherapy to further enhance clinical decision making. These studies demonstrate the value of long-term follow-up of trial participants, data sharing, and use of modeling approaches to improve clinical care and decision-making, inform research design, and the wise use of resources.

Notes

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References

1. Fisher B, Ravdin RG, Ausman RK, et al. Surgical adjuvant chemotherapy in cancer of the breast: results of a decade of cooperative investigation. *Ann Surg*. 1968;168(3):337–356.
2. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med*. 2002;347(16):1233–1241.
3. Early Breast Cancer Trialists' Collaborative Group, Darby S, McGale P, et al. Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet*. 2011;378(9804):1707–1716.
4. Taylor C, Correa C, Duane FK, et al. Estimating the risks of breast cancer radiotherapy: evidence from modern radiation doses to the lungs and heart and from previous randomized trials. *J Clin Oncol*. 2017;35(15):1641–1649.

5. Jayasekara J, Schechter C, Sparano JA, et al.; for the CISNET-BOLD Collaborative Group. Effects of radiotherapy in early-stage, low-recurrence risk, hormone-sensitive breast cancer. *J Natl Cancer Inst.* 2018;110(12):1370–1379.
6. Jayasekara J, Li Y, Schechter C, et al.; for the CISNET-BOLD Collaborative Group. Simulation modeling of cancer clinical trials: application in omitting radiotherapy in low-risk breast cancer. *J Natl Cancer Inst.* 2018;110(12):1360–1369.
7. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med.* 2004;351(27):2817–2826.
8. Sparano JA, Gray RJ, Makower DF, et al. Adjuvant chemotherapy guided by a 21-gene expression assay in breast cancer. *N Engl J Med.* 2018; doi: 10.1056/NEJMoa1804710.