Discussion of 2021-1762

OUTCOMES OF BREAST-CONSERVING SURGERY PLUS RADIATION VS MASTECTOMY FOR ALL SUBTYPES OF EARLY-STAGE BREAST CANCER: ANALYSIS OF OVER 200,000 WOMEN

**DR V SUZANNE KLIMBERG** (Galveston, TX): Breast conservation therapy (BCT) for early‑stage breast cancer has been a significant advancement in oncological practice. Several pivotal randomized clinical prospective trials conducted in the '70s and '80s demonstrated that breast radiotherapy after lumpectomy breast conservation, resulted in overall survival outcomes comparable to mastectomy (MST) for the treatment of early‑stage invasive breast cancer (Blichert‑Toft 2008, Fisher 2002, Litiere 2012, Veronesi 2002), leading to the National Institute of Health (NIH) Consensus Conference statement in 1991 supporting breast conservation treatment. As a result, lumpectomy with radiation became a viable option for mastectomy, and the rate of breast conservation among eligible breast cancer patients progressively increased to about 60% across the country and in your database.

 In your retrospective review of the SEER data, you hypothesized that breast conservation therapy yielded better outcomes in the mastectomy for Stage I and II breast cancers, regardless of subtype. Needless to say, any retrospective data has bias and may or may not be controlled by statistics.

 You used the AJCC Stage 7th edition manual for that, even though we know that the genetic makeup, ie the oncotype recurrence score of the tumor, is included in the 8th edition, and it is critical and certainly could affect your results as more aggressive tumors would be more likely to get chemotherapy upfront and in younger patients as in your study who chose mastectomy. I also did not see differentiation in lobular vs ductal histology. If you would please address that. Your classification of luminal A lumpectomy was also more common in breast conservation therapy. Again, another bias. We know from Exact Science data that 10% of those that seem to be luminal A actually have a more aggressive tumor type. Mastectomy was significantly more common in higher stages (T1N1, T2N0, T2N1, and T3N0 lesions), the younger and more aggressive subtypes. There were also significant differences in race among the groups in the rural versus urban patients. Can you comment on that and how you adjusted for that?

 Also, can you comment about mastectomy and who got radiation after mastectomy or neoadjuvant chemotherapy? Also, SEER databases do not release the receipt of hormone therapy due to the concern of data completeness, but this is a major factor in some cancers. When looking at subtype and hazard ratios for mastectomy vs breast conservation, did you account for the stage? I did not see that. How were the cases handled where this was not first cancer? Did you exclude those patients? If not, could this be impacting some of your treatments? Was there any sensitivity analysis completed for axillary surgery which could be a variable as well?

 Finally, just a word on shared decision‑making. We are always talking about "aggressive" surgeons performing too many mastectomies. I always give my patients the data, but if they want a mastectomy, they want a mastectomy. They come in knowing what they want. Just because they may not choose what I suggest doesn't make it a bad choice.

DR RONDA S HENRY‑TILLMAN (Little Rock, AR): The authors report being the first to support numerous retrospective reviews and their previous findings that in early‑stage breast cancer, overall survival in cancer‑specific survival was significantly better in receiving breast conservation therapy vs mastectomy. In a review of both prospective and recent retrospective reviews, as well as my professional experience and follow‑up care of early‑stage breast cancer, this is all quite hard to compare. The evolution and treatment of patients with early‑stage breast cancer is very complex. The complexity includes the advancement in surgical management and systemic treatment combined with factors and decisions based on types of treatment received, and shared decision‑making processes being highly geared toward the biological behavior of the breast cancer and patient‑specific factors leading to appropriate surgical/local and systemic therapy with shared decisions. It is clear that the evolution both technically, and the understanding of the biological behavior and subtypes and its relationship to local therapy, as well as our ability to perform technically breast conservation therapy on any patient with early‑stage breast cancer becomes a major factor in this decision.

 Chu and colleagues published a similar paper in 2021 demonstrating similar outcomes in a cohort in Louisiana. Previously discussed were the concerns of selection bias as a major flaw in the outcomes. In the second publication, the authors have addressed, and I appreciate that, and reduced some of those sampling errors by looking at a large number of cases in a diverse population through the use of the SEER database. They looked at many different sociodemographic factors and clinical variables to assess who is more likely to get breast conservation therapy vs a mastectomy. With patients who have sociodemographic factors that are associated with higher rates of mastectomy, those same factors are often associated with lower life expectancies and poor health outcomes in general. For example, those living in rural regions are also associated with multiple problems, determinants to overall health, including higher rates of smoking, obesity, poverty, being able to complete adjuvant therapy, lower rates of higher education, and more difficulty accessing healthcare.

 The paper looks at multiple factors which influence choice of surgery. Few would argue that the surgery was a major determining factor and the difference in overall cause‑specific 5‑year survival between the two surgeries within the four main cancer subtypes. There are numerous factors that come into play with this shared decision. Unfortunately, it fails to take those two large groups and integrate them to see if it is truly the local regional treatment making this difference, or if it is factors that lead the patient to need a mastectomy in the first place, that are the causes in the difference in survival. Correlation does not equal cause.

 How do we propose we address ongoing access that leads to these barriers in women who are poor, with health inequities in our rural populations, and those who cannot complete treatment? The SEER data cannot give us that information. Can you address correlation and cause as it relates to your findings and some of the limitations of the SEER data, such as receiving biological behavior tumors?

**DR MARISSA M HOWARD‑McNATT** (Winston Salem, NC): Do you think lumpectomy patients did better in your data set in comparison to mastectomy patients because breast‑conserving patients receive radiation therapy treatments? Did all patients in your cohort receive radiation? Some groups have shown in randomized controlled trials that breast‑conserving surgery plus radiation is at least equivalent, or even superior, to mastectomy alone (Lichter AS, 1992). In contrast, in the current treatment of breast cancer, there is a movement toward de‑escalation of care. One example of this is the Hughes CALGB 9343 trial. This study randomized women >70 years of age with clinical Stage I estrogen‑receptor positive breast cancer who underwent a lumpectomy to radiation with Tamoxifen vs Tamoxifen alone. Currently, we have NRG‑BR007. BR007 is examining patients with a Stage I estrogen‑receptor positive breast cancer with an Oncotype Recurrence Score less than or equal to 18 and eliminating radiation on this group. How do you feel de‑escalation of care will affect surgical choices and outcomes? Finally, as Dr Henry‑Tillman alluded to, every patient does not have easy access to a radiation center or may not choose to have a lumpectomy. Please address the issue of shared decision‑making and a breast cancer patient's surgical choice.

DR QUYEN D CHU (Shreveport, LA): I agree with Dr Klimberg that this study is certainly retrospective in nature. It is not meant to be the definitive study. It is an exploratory study to really ask the question that we all believe is dogma, which is basically saying a mastectomy is equivalent to BCT. And with the new era of better management, better imaging, better delivery of radiation and better systemic therapy, we need to ask whether that dogma of equivalency still stands. In our data, it appears that perhaps it should be questioned that we need a new set of
Phase III trials answering the question, does the mastectomy provide the same outcome as a BCT for early‑stage breast cancer? So, again, we do acknowledge that this is a retrospective study. It does have biases and is subjected to certain biases. We did not have data on Oncotype DX, and certainly that could influence the outcome, but we suspect even when we control for Oncotype DX, that we will see a similar outcome. And then we did not have the data to separate out the neoadjuvant or the adjuvant group because SEER does not provide the date of the start of the chemotherapy.

 We did not differentiate between lobular and invasive, and as you all know, we tend to treat these two histologies similarly, and newer data demonstrated that lobular actually has a different biologic behavior than the invasive subtypes or the ductal subtypes. So certainly, this is something worthwhile to pursue in the future.

 In terms of adjusting for younger age, other socioeconomics, demographic status as well as stage, we did control for all of those. And despite controlling for all of those in the adjusted variable, BCT still yielded better outcomes for overall survival as well as cancer‑specific survival. We did not perform a sensitivity analysis for axillary surgery, and I suspect that if we do, we will probably still see the same outcome that a mastectomy portends a poor outcome.

 And for Dr Henry‑Tillman, what your message resonates with me, as well as others, is that lack of access certainly is a major barrier. As COVID‑19 reveals to us, such a lack of access, as well as health disparities, has become worse over the years. What it really comes down to is the social determinants of health. What are the social determinants of health that basically led us to have more patients to receive a mastectomy than patients that would otherwise require for BCT? In fact, in our database, we found that younger women ages 29 to 39 years, over 70% of them had a mastectomy. Now, whether that is because women were scared, or whether it is because of poor counseling by physicians, we believe this is just too many patients undergoing mastectomy unnecessarily, and our retrospective study demonstrates that it does not yield a better outcome, that it actually had a worse outcome. Now, again, there are other variables that can lead to that, but at least even after controlling for the known variables, we still see that a BCT yielded better outcome than a mastectomy.

 And then finall, all of our BCT had radiation therapy. We want to make sure that it was a peer cohort that we are comparing. And I entirely agree that the study based on the CALGB by Hughes and others, as well as the British PRIME II, demonstrated that radiation is not necessary for patients ages 70 years or older or in the PRIME II 65 years or older, and we certainly see that there is a select group of patients, elderly patients that need de‑escalation of therapy. But, interesting, in our data, the extreme age group had a significantly higher rate of mastectomy. So even though we are de‑escalating radiation, it appears that we are escalating surgery. I think data suggests we should look back and question whether, for the elderly group, we should curtail on the mastectomy.