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stage ER+ tumors when the treating team anticipates significant delays to surgery. An alternative conclusion from this research may be that the traditionally quoted 28-day delay from diagnosis to surgery could be overly conservative when considering the tumor biology of these early breast cancers. This would also benefit from being studied in a prospective multi-institutional study.

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**Conflict of interest/Disclosure**

None of the authors have any conflict of interest to declare.

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**Discussion**

**Dr. Zahraa Al-Hilli (Cleveland Clinic):** The COVID-19 pandemic has posed a unique set of challenges for breast cancer screening and patients diagnosed with the disease. And certainly, reorganization of breast services meant that a number of patients diagnosed with hormone receptor–positive breast cancer were offered treatment with neoadjuvant endocrine therapy during delays in surgery. The data presented by the authors adds to a growing body of literature on neoadjuvant endocrine therapy and may give reassurance for patients most impacted by treatment delays during the pandemic.

I have 3 questions for the authors. First, the duration of treatment with neoadjuvant endocrine therapy in the studies is perhaps too short to demonstrate a change in tumor size. Data, including those from clinical trials on neoadjuvant endocrine therapy, included patients treated for an average of 4 months or longer. So, the impact of shorter treatment duration remains unclear. Can you comment on the duration of treatment with neoadjuvant endocrine therapy and how this could have impacted the results? Second, your study compares patients treated with neoadjuvant endocrine therapy with patients who underwent primary surgery...
in <35 days and without a delay. Did you consider having patients with a delay in time to surgery but not treated with neoadjuvant endocrine therapy as the control group?

And, finally, what lessons from your study can we take with us to the post-COVID era? Do you recommend that neoadjuvant endocrine therapy be considered for patients experiencing delays for other reasons, such as further workup or medical optimization prior to surgery?

Dr. Dilena: Thank you, Dr. Al-Hilli for your thoughtful questions. For the first question regarding the duration of NET, I agree with you the duration of NET was a little bit short in our NET group. So just to explain this a little bit. Our delays to surgery were, in fact, two and a half times longer in our NET group compared with our historical control. But our duration of NET treatment was only 34 days. This can be explained by a couple of factors. First is what we used to standardize our date of diagnosis; we used the date of the first positive biopsy as the date of diagnosis for all patients across both cohorts. Obviously, this would lead to a delay between the date of diagnosis and the date that the patient first met with the surgeon. This is one element that explains this discrepancy. The second element is that, and this is more hypothetical, that perhaps the surgeons, when they first met with patients and consented them for surgery, did not actually know that there would be significant delays to surgery at that time. And this, I am speaking a little bit anecdotally, but in collecting the data, we observed that this is the case for several patients, so basically the surgeon would meet with them, consent them for surgery, and then only realize afterwards that there would be significant delays to surgery because they met with them in early March, for example, and then called the patients at home and explained NET to these patients. So that is the second element that may explain the discrepancy between the 73 days and the 34 days in our NET group.

Now, whether or not this was long enough for NET to actually have an impact is kind of unknown in this case. As you mentioned, specifically NET for a downsizing of tumors is given for 4 months or more in most patients. In our case, it was much shorter than that, as you mentioned. Whether or not these patients did not have upstaging because they received NET remains a little bit unknown in this scenario.

The second question that you had was the delays to surgery in the historical control. The objective of our study was really to determine whether or not patients during COVID saw their tumors be upstaged or had poor outcomes pathologically due to the delays to surgery during the COVID pandemic. We did not actually want to compare patients with historical controls who had significant delays. We wanted to compare them with the standard of care. That is why we picked the 35 days. I agree, though, that it is an interesting idea to look back and try to find patients who had significant delays in the past and compare those patients, by matching them for delays to surgery and compare whether or not those patients saw significant upstaging or not during that time period and determine whether NET had a protective effect in these patients. But we would have to go back and collect additional data to determine this.

Finally, to address your third question on the takeaway points from these data, I think there are 2 ways to interpret this, and I am not sure which is right. One possible explanation is that NET was indeed protective even if it were given for a short period of time. As you mentioned in your first question, this was really a short period of time and no one has really evaluated the use of NET for just a month to know whether or not this actually had an impact on tumor downsizing or at least on preventing progression of tumors. I think, like you mentioned, matching to patients who had significant delays to surgery and did not receive NET would be an interesting way to answer that question or to conduct a prospective RCT looking at those 2 kinds of patient populations. Another possible takeaway from this study, I think, is that perhaps we're overly conservative in our guidelines that recommend for operating on these patients within a month of diagnosis. If you think about the tumor biology of these small, luminal A type tumors, perhaps they never would have progressed in our 70 or so days. So maybe in 2 months and a half, they do not actually have that high likelihood of progressing and that explains our results, in which case perhaps we should change our guidelines and not be overly nervous about delaying care for these patients. And that is kind of the impression that was given in that survey, in the 2001 survey of physicians during the COVID—surgeons during the COVID-19 pandemic who were quite comfortable delaying their patients to OR by up to 2 months without treating them with NET. Maybe this is already a general impression among surgeons that is not really reflected in the data. But, again, these small, observational studies often raise more questions than they answer. I think that to adequately answer the questions, we would need proper prospective large RCTs.

Dr. Faizah Valencia (Loyola Medical Center): I have 2 brief questions. Did you guys utilize Oncotype at all in determining whether this was somebody that needed to be ushered to surgery sooner than later prior to putting them on the endocrine treatment? That is actually what panned out for us during the early onset of the pandemic in determining whether we needed to usher somebody to surgery, and in our case, we did not stop doing those surgeries, or whether to delay it, particularly if the patient had reservations about being operated on during the pandemic. My other question is, can you comment on what the pitfalls might be, if there are any, in putting somebody on endocrine treatment if there are delays, for whatever reason, anticipated?

Dilena: Regarding Oncotype, yes, so we did collect the data. In our whole cohort of 30 patients, there were, I do not want to say an exact number, but I think there were fewer than 10 patients who actually had an Oncotype DX that was performed. We perform them quite selectively at our institution. Typically, a multi-institutional tumor board has determined whether or not a patient needs Oncotype DX, and usually it is actually after the surgery, so not under biopsy. Not initially prior to their surgery. This was not routinely performed for patients and the surgeons would not have known the Oncotype DX routinely before deciding whether or not the patients would go to surgery. I do think that is an interesting idea, trying to profile these tumors and know whether or not they're more proliferative as kind of a guideline of whether or not to operate on patients.

Your second question was the potential pitfalls of putting patients on NET. I think that it requires careful monitoring, so we know that a certain subset of patients will progress on NET, and I think that carefully monitoring those patients is usually the standard of care, especially when you are using NET to downsize tumors. The issue, of course, was that patients were really scared to come to the hospital, and I do not think that it would have been feasible to routinely perform ultrasound during this period. Of course, going forward in a non-pandemic world, then I think that it becomes more feasible to monitor patients with imaging if we are going to do longer term NET. The other potential pitfall, I would think, would just be the side effect profile of the endocrine therapy, but this is the same as for adjuvant therapies. (Applause)