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Evaluating HER2 Testing Accuracy: A Brief Overview of the Updated ASCO & CAP Joint Guidelines

Announcer:
You're listening to ReachMD, and this episode of *Project Oncology* is sponsored by Lilly. On today's program, we're joined by Dr. Oudai Hassan, who's a Senior Staff Pathologist at Henry Ford Health System in Michigan. Dr. Hassan is here to share a brief overview of the updated ASCO and CAP joint guidelines and their recommendations in the ongoing mission for improving the accuracy of HER2 testing in breast cancer. Here's Dr. Hassan now.

Dr. Hassan:
So usually we test for HER2 for every first-time diagnosis of breast cancer. Most of the time it's on a biopsy specimen. Sometimes it's on a resection specimen, and sometimes also we retest for HER2 on resection specimens, even after we have done this test on a biopsy specimen.

So we have two ways to test for HER2. We have the immunohistochemistry method and we have the in situ hybridization method. Some labs will do both tests at the same time. Most of the labs will start with the immunohistochemistry, and later if they get an equivocal result, will resort to in situ hybridization. Though at my institution, we start with the immunohistochemistry, and with the immunohistochemistry we have four categories of results. We have the first category, which is when we call positive, when we have complete circumferential intense membranous staining in more than 10% of tumor cells. We call it +3 and positive, and these patients are candidates for HER2-targeted therapy. And then we have what we call HER2 negative with a score of zero – when we have no staining and we have very faint staining in less than 10% of tumor cells – and this is negative. The patient is not a candidate for HER2-targeted therapy. We have also another, subset of negative HER2 by immunohistochemistry, refer to +1, when we have faint staining, faint incomplete staining in more than 10% of tumor cells. Again, these patients are negative for HER2, and they are not candidates for, HER2-targeted therapy. And the last group is what we call equivocal, +2, when we have intermediate, complete membranous staining in more than 10% of tumor cells. These patients, we call them equivocal immunohistochemistry, and in these cases, we would resort to in situ hybridization. There are other, very rare situations. For example, when we have complete strong membranous staining in less than 10% of tumor cells. Also, in these cases, we will call equivocal +2, and we will resort to in situ hybridization.

So for in situ hybridization, we have two methods. We have the chromogenic in situ hybridization, or what's called CISH, and the fluorescent in situ hybridization, or what's called FISH. Some labs use the CISH, some labs use the FISH. At my institution, we have both. Most of the time, we are using the CISH, the chromogenic in situ hybridization. And in this method, we look at the HER2 gene itself, which is present as a long arm of chromosome 17, and we look also at the centromere of chromosome 17. We calculate our ratio for the numbers of HER2 copies and the number of centromere copies, and also we look at the absolute and the average absolute copy number of the HER2 gene. And when we do that inside the hybridizations of CISH, we end up with five groups. The two groups at the end of the spectrum are the easiest and definitive ones.

The first group is what we call Group One is when we have a ratio between the HER2 gene and the centromere, more than two, and an upper rash – HER2 copy number per cell. We look usually at 20 cells. If the average is more than four, and the ratio is more than two, this case is positive for HER2 amplification and the patient is a candidate for HER2-targeted therapy. The other end of the spectrum is what we call Group Five – is when we have a ratio between the HER2 gene and the centromere less than two, and an average copy number of the HER2 gene in 20 cells of less than four. These patients are negative for HER2 amplifications and are not candidate for HER2-targeted therapy.

Then we have three groups in the middle. The first group is the Group Two, is when we have a ratio of HER2 to centromere, which is

more than two, but that copy – the average copy number of HER2 is less than four. This is technically equivocal at this step, and we resort to some additional steps. The next step here would be the person who, or is reading, assessing the in situ hybridization, should go back to the immunohistochemistry slides from the same tissue he is looking at the in situ hybridization, and score the IHC again – the immunohistochemistry again. If he scores it again as equivocal, then another person should go back and read at least 20 other cells for in situ hybridization and this person should be blinded to the previous CISH results.

Group Three is kind of similar situation. Group Three is when we have a ratio of less than two between the HER2 gene and the centromere, uh, but an average copy number of HER2 bare tumor cell of more than six. In this case, again, the person who is reading the CISH should go back to the immunohistochemistry slides from the same tissue and score them. If he score it as equivocal, again a +2, then another person, blinded to his results, should rescore the in situ hybridization, counting at least 20 tumor cells.

The last group is Group Four. Group Four is when we have a ratio of less than two, but an average copy number of HER2, more or equal to four, but less than six. In this case, again, the person who scored the in situ hybridization should resort back to the IHC slide, read the IHC slide from the same tissue sample he read the in situ hybridization, and score them. If he scores the immunohistochemistry as 2+, then another person, blinded to his results, should rescore the in situ hybridization, counting at least 20 tumor cells.

So, technically, this is new ASCO and CAP guidelines, and the improvement it provided is with the previous guidelines, even after we resort to FISH or CISH, we still had a category where we would call it HER2 equivocal, and then we would leave the medical oncologist with the dilemma on what to do with the patients, because with these patients, they don't have a definitive answer if the patient is a candidate for HER2-targeted therapy or not, and they will have to make a decision based on their clinical judgment or other finding. With the new ASCO and CAP recommendations, we eliminated the equivocal category from the CISH, so whenever we report HER2, we have a definitive report. We have a definitive results, whether it's negative or positive, and from these results, the medical oncologist can move on, making a treatment decision.

Announcer:
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