

NCI 2007 PRE-OP THERAPY IN BREAST CANCER
5 SESSION 1_3_SINGH

DR. LAURA ESSERMAN: Our next speaker is Baljit Singh, who is the associate professor of the Department of Pathology in New York University Medical Center. And he's going to talk about the initial pathologic assessment and preoperative therapy.

DR. BALJIT SINGH: Good morning. I would like to start as well by thanking Drs. Winer, Gralow and Zujewski for inviting me. I will be talking about the initial pathology assessment to preoperative therapy, which essentially means how to get the pathological diagnosis correct. And in this setting, getting the pathology diagnosis correct is absolutely imperative.

The best way of going about this is to get a needle core biopsy, and this should not be done by fine needle aspiration. The reasons for this are enumerated on this slide – that, using a needle core biopsy, the diagnosis can invariably be made with accuracy. We can do biomarker assessment accurately as well. And, most importantly, we can procure tissue for doing all sorts of research projects.

Numerous people have studied the concordance of needle core biopsy with subsequent surgical specimens, and it works quite well in making an accurate diagnosis. But the other factors which we know impact treatment decision-making -- for example, lymph node status, tumor size, etc., cannot be accurately assessed by needle core biopsy.

However, in the multi-disciplinary setting, as mentioned by Dr. Hortobagyi, the size can be assessed quite accurately, with the combination of radiology and pathology. The grade of the tumor can be assessed fairly accurately in the low and intermediate categories. But there are higher-grade tumors which are benefited the most in the preoperative setting.

The grade may or may not be accurately assessed because mitotic count cannot be done with a fair degree of accuracy, primarily as a function of size of the tumor. Another

PRE-OP THERAPY IN BREAST CANCER
5 SESSION 1_3_SINGH

factor which impacts -- the lymph node status, for which the surrogate is lymphovascular invasion, [which] cannot be accessed accurately on a needle core biopsy; this is entirely a function of the sample [i.e., specimen] size.

To summarize, a needle core biopsy is adequate and ideal in the preoperative setting because it can make the diagnosis accurately. You can do a biomarker analysis and collect tissue for research. And it is important that you take multiple cores. I will continue to stress this [be]cause we need cores both to make diagnosis; we need cores for any future studies. So, that is absolutely imperative.

The Komen Foundation came out with a white paper on breast pathology last year, and these are the salient recommendations from that white paper: That most breast pathology programs should have a quality control program. Second opinions should be encouraged. This is not all that common amongst pathology practices as it is in all other areas of oncology. Most patients will go and see more than one medical or surgical oncologist, but they may or may not get a second pathology opinion. So, this cannot be overstressed. And pathologists should be integrated into patient care teams.

As Dr. Hortobagyi mentioned that the receptor status as determined in the needle core biopsy is a significant determinant in how these patients are going to do with preoperative therapy. So it is imperative that this status be assessed accurately.

And there are numerous studies which have looked into this comparison as to how does the biomarker status as assessed in the core biopsy compare with the final biomarker status on the surgical specimen. And, as is enumerated on this slide, the core biopsy is fairly accurate in assessing estrogen and progesterone receptor status of a tumor, especially with increasingly better reagents and quality control mechanisms for these markers.

PRE-OP THERAPY IN BREAST CANCER
5 SESSION 1_3_SINGH

In this trial, where the receptor status was assessed prior to randomizing patients to tamoxifen and an aromatase inhibitor, biopsies were done before and after the endocrine therapy. Central analysis of the receptor status revealed that there was a 12-percent discordance in the receptor status from the initial diagnosis in the various institutions in Europe.

I bring this up only to make the point that, as important as biomarker analysis is in our understanding of the biology of breast cancer and making treatment choices, it is not a standardized test. We can increasingly, with better reagents, we do a very good job with it. But, having said that, if you're used to running a laboratory, when there is a standardized test there are, you know, we have appropriate controls; there are standards of operation; there are accrediting mechanisms, and none of these exist for assessing biomarkers.

And thereby, there is a certain degree of false positive and false negative reporting for receptors, irrespective of whether they're done on a core biopsy or the final, surgical excision. So, one's needs to be cognizant of this issue.

With HER2, we have made a significant advance last year. That is, there are guidelines, both from ASCO and CAP, which lay out in a lot of detail as to how the HER2 testing should be done. What is relevant from this in the preoperative setting is that any needle core biopsy should be fixed at least for an hour in neutral, buffered formalin, and the laboratory which is performing this test should follow these guidelines, which will become mandatory in about a year or so. So, the HER2 testing should become fairly standardized and should meet the rigors of the standardized test soon.

Biomarker analysis in the clinical setting may be repeated -- or SHOULD be repeated -- especially when it is reported as negative or the percentage value reported is quite low. And if, doctors being doctors, if there is any sort of discordance between the receptor

PRE-OP THERAPY IN BREAST CANCER
5 SESSION 1_3_SINGH

status and morphology or your clinical suspicion, then the most prudent thing is to repeat the assay. This applies to receptors as much as it applies to any other biochemical assay.

And a very significant trial, the I-SPY trial, which took serial specimens to study varying pathological and molecular markers before and after systemic therapy, it has been shown in a presentation late last year that the method which is used to collect these needle core biopsies usually impacts the yield in these needle core biopsies. Namely, if the needle core biopsy is done with image guidance as opposed to palpation, there is almost a five times greater yield of cores with more than 50 percent tumor within them.

This is critical because a lot of the new assays -- the molecular assays -- which are advancing medicine at a very rapid pace, require a tumor-rich sample for them to be effective and accurate to answer the biological questions. So, this is an important advance and tells us that, irrespective of the morphology of the tumor, if the needle core biopsy is done with image guidance, the yield is significantly higher.

Last year, the NCI initiated a process in which multiple groups were formed to come up with standards of procedure to come up with guidelines -- standards of procedure -- for collecting tissue samples which included both formalin-fixed and frozen and also blood and serum samples. These guidelines have been posted on the Internet. The purpose of these [guidelines] is, as is pointed out in the slide, is that for an individual patient, the tumor is banked, this decreases all sorts of variables which will go into determining the molecular profile.

Anybody who does that kind of research knows that one of the significant variables in the profile that you get is how the tissue was preserved at the outset. And this cannot be over-emphasized. And if these guidelines are followed, this will minimize that degree of variability.

PRE-OP THERAPY IN BREAST CANCER
5 SESSION 1_3_SINGH

As far as fresh tissue in the preoperative setting is concerned, the tissue can be frozen... can be collected either at the time of the diagnostic biopsy or in the setting of a research biopsy, as was done in the I-SPY trial. And this can be achieved with a fair degree of success; we've heard from patient advocates, as it's also been shown in the I-SPY trial. And these procedures for professionals in the audience are, again, posted on the Internet and they have been used quite extensively in numerous trials in Europe.

To summarize initial pathology assessment prior to preoperative therapy: The best way to collect tissue is by image-guided core needle biopsies. And it is important to do multiple cores, both for getting an absolutely accurate diagnosis and for research purposes.

Accuracy of diagnosis is invariably achieved. But if there is any doubt, a second opinion should certainly be assessed. Bio marker assays are fairly accurate in a core biopsy; but, then, since receptor analysis is not a standardized test, doctors should be doctors and if you think it needs to be repeated, you should request that.

And the last point is perhaps the most important -- and this is particularly important in the setting of preoperative therapy because one of the major impetuses of doing preoperative therapy is that it allows us to study the biology of the tumor, and the best way to study the biology of the tumor is to collect samples before and after. And this can be done, or should be done, for all patients. Thank you.