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Surrogate Endpoints for ICIs in Early-Stage Melanoma: Does an MPR Reliably Predict Patient Outcomes?

Announcer:
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Dr. Tetzlaff:
Hello, my name is Michael Tetzlaff. I'm a professor of pathology and dermatology at the University of California San Francisco. And I'm happy to talk today about our efforts in assessing pathologic response in patients with resectable melanoma following neoadjuvant therapy with the specific question, does a major pathologic response reliably predict outcomes? And more globally, how do we assess pathologic specimens following neoadjuvant therapy? It's important to emphasize that the material expressed in this presentation is the property of myself and the University of California San Francisco. Reproduction is not permitted without written permission from myself and UCSF.

So neoadjuvant trial strategies in melanoma, I think, have been well outlined in the context of this course. I think the important point is that the central premise of neoadjuvant therapy in melanoma and its advantage is that the extent to which melanoma tumor cells respond to a given agent provides us with an interval assessment of response that ideally would correlate with measures of clinical outcome, things like progression-free survival, disease-specific survival, overall survival. Would also guide, perhaps, subsequent treatments in the adjuvant setting. So, patients who don't respond might have their regimen adjusted to accommodate that resistance. And then obviously provides important tissue for biomarker studies to understand mechanisms of response and resistance. But the central really advantage and premise of a neoadjuvant regimen is the ability to have this interval evaluation of tumor response.

One of the challenges that we've seen in neoadjuvant trial strategies in melanoma, certainly true for many other organ systems, is that in the early days of this, there are important challenges to overcome. Multiple small, independent trials at different institutions, each enrolling a small number of patients for each study, slightly different designs, slightly different populations and durations of therapy.

And so, this creates a critical need for us to come together as a community to harmonize our efforts. And that was really something that was recognized by melanoma researchers across the globe and prompted coming together as the International Neoadjuvant Melanoma Consortium of which I'm proudly a part. And this group was established with members from Australia, from the Netherlands, from multiple centers in the United States, including leadership from the MD Anderson Cancer Center in Houston, Texas, to bring medical surgical oncologists together with pathologists and radiologists, and translational scientists to facilitate an organized approach into the investigation of neoadjuvant treatment of melanoma. And the singular goal of our group is to advance treatment strategies for patients with melanoma, specifically in the neoadjuvant setting.

And so this group has published a number of recommendations regarding neoadjuvant systemic therapy in melanoma from this manuscript in "The Lancet Oncology," which really provided a soup to nuts, a set of recommendations for trial design, surgical and pathologic assessment.

And what was recognized by our group very early on was that because pathologic response is a fundamental endpoint in most all of the neoadjuvant trials, it would be critical for us as pathologists across these different centers to establish consistent definitions of what a complete pathologic response is and to be consistent about other response categories early in the design and development of these different trials. And that also brought into question how we process the tissue to determine the pathologic response. How much tissue in a treated tumor bed do we need to examine to reliably determine the extent of that pathologic response? And standardizing the gross assessment is a really critical effort to undergo in order to, again, facilitate comparison across trials, presuming that trials utilize a similar approach to tissue processing and similar pathologic response categories that will facilitate coming together with a pooled analyses to determine even more information than we learned in each individual trial.

And so, this prompted our efforts from the pathology team within the INMC to publish our recommendations on the pathologic assessment of resection specimens following neoadjuvant therapy for metastatic melanoma. And in this manuscript, we worked together to first define the pathologic response categories, to provide a template for pathologic reporting, and, most importantly, to provide our recommendations for gross handling of specimens so that specimens across the board would be processed and managed in a similar fashion.

So the central question that we sort of faced as pathologists in the setting of neoadjuvant therapy is, if this is a gross image of a treated lymph node following neoadjuvant therapy, the central question becomes whether the tumor bed looks like this image on the left with just sheets of melanophages and a little fibrosis, but no evidence of viable tumor, versus this image on the right which is a similar appearance in the background of melanophages, but viable tumor nests percolating throughout that. And so how much of the treated tumor bed consists of viable tumor? And how much of that tissue do we need to submit in order to distinguish between these two possibilities? So, what we came up with was that we recommended, in accordance with other organ systems, any grossly evident node that was less than five centimeters in greatest dimension, you would submit all of that tissue. Lymph nodes that measured greater than five centimeters in largest dimension, what we recommended is to submit a complete cross section of tumor per one centimeter of that node. Not one representative section, but one complete cross section of tumor per centimeter. And that gives us the ability to have a sort of systematic topographic map of that tumor across the length of the treated tumor bed and gives us a really systematic approach to not missing viable tumor in that treated tumor bed.

We also then made our definitions of pathologic response categories, and this is really a function of surface area of the treated tumor bed. So we defined pathologic complete response as the complete absence of viable tumor in the treated tumor bed. Basically 0% of that surface area occupied by viable tumor. A near pathologic or so-called major pathologic response is when the treated tumor bed is occupied by less than or equal to 10% of its surface area as viable tumor. A partial pathologic response, the tumor bed is occupied overall by less than or equal to 50% of its surface area of viable tumor, whereas a pathologic non-response or non-responder, the treated tumor bed is occupied by greater than 50% of its surface area by viable tumor. Important to recognize that all of these are empirical cutoffs. They're not data-driven, they're not validated, certainly open to resolving this by different mechanisms, but something that's very reproducible from a pathology perspective across different institutions.

So, this like-minded pathology processing approach enabled us to come together and pool the analysis from multiple different trials that were carried out across the world and culminated in this very important study from the INMC, from multiple institutions in which we pooled 192 patients from six trials, including patients treated with immunotherapy and targeted therapy to understand the significance of the pathologic response.

What we showed first and foremost is that for all comers, it's clear that a pathologic complete response is a critical endpoint, and those patients do better than patients with a non-pathologic complete response. When you break it down according to the response categories, again, you see that complete responders and near complete responders do better than partial responders, and those do better than non-responders.

When you break this down according to targeted therapy versus immunotherapy, again, you could see that the pathologic response categories very nicely delineate patients who have an improved recurrence-free survival from those patients who have a less successful recurrence-free survival. This underscores the importance of reliably establishing the pathologic response and the respective pathologic response categories.

And I think that I've shown you that accurately determining the extent of pathologic response is a critical variable to optimizing patient management and outcomes following neoadjuvant therapy. And the extent of that pathologic response correlates with recurrence-free survival following neoadjuvant therapy. Thank you very much for the chance to talk to you today. I've really enjoyed being a part of this course.

Announcer:
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