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Lack of Concordance Between Radiologic and Pathologic Responses in Neoadjuvant ICI Treatment of Melanoma: How Do I Assess Radiologic Progression?

Announcer:
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Dr. Gastman:
Hello, my name is Dr. Brian Gastman and I am the surgical and co-director of the Cleveland Clinic Melanoma and High-Risk Skin Cancer program. Today, I will be continuing our talk on lack of concordance between radiologic and pathologic responses in neoadjuvant treatment of melanoma, specifically focusing on immune checkpoint inhibitors.

Currently, metastasis, both distant and nodal, are best identified through imaging. This was shown in these three studies on your left to be far superior than either patient self-exam or physician examination with one study revealing metastasis identified 96% of the time using those type of modalities. This is in contrast to historical information in the way we followed melanoma. Further, in a paper in annal, "Surgical Oncology," in 2019, in a protocol where patients, after having definitive stage-three surgery, went on to have adjuvant therapy, they all had pre-systemic therapy imaging, which revealed that almost 20% of them had already started recurring at that point. These data indicate that the most powerful way to follow patient's tumor progression, relapse, and, likely, biology, is through imaging. But is that actually true in the setting of neoadjuvant therapy?

So, we know that neoadjuvant therapy is strongly related in the pathology of the tumor in terms of its response measure. On the right, you can see a paper that was published, showing various scenarios, including pathologic complete response, pathologic partial response, and pathologic non-response. And these have been associated with actual outcome in terms of relapse-free survival. Now, on your left is targeted therapy, where you can see that patients with various types of responses, other than complete response, did not actually do very well, and thus, only a pathologic complete response had any meaning. However, on your right, what you can see is patients with any partial pathologic response above 51% of the tumor being non-viable, all the way up to a pathologic complete response, all had excellent outcome. So, the pathology has a tremendous amount of meaning because the opposite is also true. Patients with, they would call, pathologic non-response did quite poorly and thus the pathology shows the actual prognostication and prediction of this therapy in terms of its efficacy in a very, very powerful way. And this is from pool data published in "Nature Medicine."

The paradox with neoadjuvant therapy is the following: First, different therapies cause different levels of pathologic response. So, on your left is the two types of immunotherapies in the various studies. In monotherapy, you can see about a third of patients had a pathologic complete response, near PCR, or a pathologic partial response. However, Ipi/Nivo, the combination group that number went significantly higher, although with many side effects. However, if you then go over to look at their radiology, you can see that patients who are, by recist criteria, had a complete response. Only 74% of them had a pathological complete response. Now, if you go down into the targeted therapy, it's pretty impressive the fact that 24% of patients that on radiology had a complete response, actually had a pathologic non-response. Luckily, in immunotherapy, at least, we don't see that and complete responses appear to be relatively

correlative with the pathology. However, other responses are not and that's a concern because this shows a disconnect between the radiologic evaluation and the pathology and we now know that the pathology is extremely powerful as I showed you previously, thus, reducing the power of imaging in this patient subset.

So, what does this mean? What if your radiology shows that the tumor is growing but then you resect the tumor and there's a strong pathologic response? What does that mean? Was it the tumor outgrowing its blood supply or does this still mean despite clearly clinical growth that there is a major response from the immunotherapy that's being given? Does this apply to larger tumors?

So, for example, you see the tumor on the right, much larger than 10, even 15 centimeters, but on your left, shows a culmination of all the major studies with an average of only 2.2 centimeters. So, perhaps this data that we're seeing only applies to small lesions, which can be effectively treated with these neoadjuvant regiments.

So, here's our patient that I had shown in a previous talk that was given two cycles of Rela/Nivo. His tumor grew in three times the size. We had to remove the axillary vein and strip it off the pleura. And despite clinical and radiology showing enlargement, there was 50% necrosis in the this large tumor specimen. Does that mean anything in terms of pathologic response? And again, is this just a result of the tumor outgrowing its blood supply causing necrosis? But interestingly, there were a significant amount of immune infiltrating cells in the specimen.

What do you do if there's no radiologic disease like you see here? The tumor completely is eradicated, at least radiologically. Well, as I said earlier, at least in immunotherapy, that probably does present excellent pathologic responses as you can see here. Not true though with targeted therapy, which is also used in neoadjuvant paradigms.

A recent study, called the Prado study, published earlier this year, looked at patients who had two doses, or two cycles of low-dose ipilimumab and nivolumab. They had an index lymph node marked and that only was resected after the neoadjuvant therapy. Patients who had at least a major pathologic response or less than 10% viable tumor, did not have any further surgery but continued on with additional therapy. The other patients did have additional surgery and had the same type of follow-up in therapies. When looking at the outcomes of these patients, on your right, again, as we've seen in other neoadjuvant therapies, those patients with major pathologic response did the best. And this is despite the fact that the other groups had additional therapy. This not only emphasizes the fact that, perhaps, we can de-escalate the amount of surgery that we do, but then also having some level of surgery to assess the neoadjuvant effect on the tumor marked environment, is still the most powerful aspect of predicting overall outcome. Now on your left, you'll see the pathologic responses that were seen in this trial. The green is pathologic complete response, but if you go further to your left, these are the radiological responses, and you could see the complete response rate radiologically was only 14%. This disconcordance between radiology and pathology is persistent from all the other trials that have been reported out to date. And again, as a summation, reinforces the importance of pathologic assessment of the tumor.

So, from what I've told you, there are multiple ramifications to how you're actually going to enact neoadjuvant therapy. If you're talking about immunotherapy, the question then becomes, how many cycles to do? And that usually will also depend on the therapy you're choosing. And two cycles seems to be a very common theme in the field. But keep in mind, two cycles for an every two week, every three week, every four week, and even every six-week paradigm means big differences in terms of time prior to surgery. There's also issues. Should we even re-image these patients? Of course, we're always worried maybe these patients will become stage four. We hope that's unlikely and that may mean you wouldn't operate on them. Maybe the strongest reason to do imaging again right before surgery. But there are other reasons too. For example, we need more real-world data with different types of patients, different types of melanomas, different sizes of melanomas, different treatment histories. We're starting to see that complete response on radiology may actually equal pathologic or major pathologic response and may be the beginning of the paradigm to do less surgery. And of course, imaging is ever-changing. This is an example of CD8-PET scans, which reveals intratumoral T-cells. And this will have effect not just clinically but certainly from a discovery standpoint and I think this will continue to change as more modalities are developed. But there are other reasons not to do imaging potentially. For example, you're going to get pathology anyways. And what is imaging going to help you? Imaging could give you a false positive or false negative and you end up doing or not doing something you would've otherwise or should have otherwise. And some will say it won't change your management, only the pathology will really matter and not the imaging. So why bother? And then ultimately, which modality? CT scans, PET CT scans? Regardless, this will then add confusion when we speak these terms of whether or not to reimage.

Ultimately, this all reinforces why it's key to have a multidisciplinary team like we have at the Cleveland Clinic. You know, we see differences in timing, adverse events, pathologic responses, and overall responses between targeted therapy and immunotherapy, between nivolumab and ipi/nivo. But we're going to have emerging therapies like rela/nivo and many others and having groups of people there that coming from different directions, will ultimately allow for the best consensus opinion. In addition, each of us are hearing from our own societies, surgery, medical oncology. We're all learning from separate and distinct areas of information and

discovery. Radiology, will Recist or iRecist even manner in the neoadjuvant setting? Maybe a new iRecist 3.0 will have to be developed. Who knows? And in pathology, it's been a number of years since a consensus paper was published on how to evaluate new adjuvant specimens. Likely, this will change again. And who will let you know that these changes are occurring the fastest? Those of us in each of our own specialties, coming together, coming from our national means, reading our own literature and bringing the best and the most timely information toward the best patient outcome. And with that, I'd like to thank you for your time and attention.

Announcer:
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