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How and When Should I Assess Response to Neoadjuvant and Adjuvant ICI Therapy?

Announcer:
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Dr. Spicer:
Hello, my name is Jonathan Spicer and I am a thoracic surgeon from McGill University in Montreal, Canada. In this session, I will be talking to you about how and when should we assess RECIST response to neoadjuvant and adjuvant immune checkpoint inhibitor therapy. I think it is important to start with a disclaimer that there is very little definitive data to guide our decisions in this space. Most of us will apply the approved regimens of immunotherapy before or after surgery, and unfortunately, we do not have much to guide our decisions other than our usual clinical practices that we have been using in the space of pre or postoperative therapy, which are limited to imaging responses. Nonetheless, I think there are some important things to learn from current practice as well as emerging data from some of the new technologies we can potentially apply to this patient population.

So, in my practice, some of the key measures of response after neoadjuvant therapy are both CT chest, and I prefer contrast infused scan, particularly for more complex anatomy, as well as PET scans. These are the primary imaging metrics that were utilized in CheckMate 816, as well as many of the ongoing phase 3 peri-adjuvant studies. So, as I said, CT chest with contrast infusion was required by all the neoadjuvant immunotherapy protocols to date, provides very helpful information on clinical down staging. And although the correlation with pathological response between RECIST findings, objective response rates and what we see under the microscope once the tumor is resected is ill-defined at this point, the scans are quite helpful for surgical planning.

PET scans were not required by all the neoadjuvant protocols in the post induction space. They were as part of the staging requirements for inclusion. And I do think that they can provide some very helpful information particularly looking at the change in SUV before and after treatment. And indeed, they can be more sensitive than CT with regards to assessing distant or contralateral metastatic progression which remains an extremely unusual scenario. But I think for that purpose it has value. That said, PET scan can generate some spurious data with which we are sometimes faced to not really know what to do. And this was well demonstrated by Tina Cascone and the team at MD Anderson where they described this notion of nodal immune flare that occurs after preoperative immunotherapy.

I think it is worth going into some detail about this because patients after induction or neoadjuvant immunotherapy may have new nodal disease that lights up on PET scan, which was not present preoperatively. So, the top set of panels is a nice example of that where the patient had a fairly focal 4L lymph node prior to treatment and then afterwards, the patient looked like they had increased uptake in those lymph nodes as well as new uptake in the contralateral.

For our position at resection, this turned out to be a benign and was indeed a case of nodal immune flare. But there are also scenarios where such lymph nodes will emerge, such as the one that came up here in the pre-vascular space on the J panel which was indeed metastatic lung cancer. So, PET scanning is not something that I routinely do in my current clinical practice unless indicated by size significant increase, or of contralateral, or unresectable nodal or distant metastatic disease. And the reason I do not do PETs on a

regular basis is that we know from NeoSTAR that anywhere from 10 to 20% of patients will have this nodal immune flare which will trigger invasive mediastinal staging that will turn out to be benign. And so, for efficiency's sake, at least in my practice, I limit the investigation to contrast infused CT and will resect provided the disease remains resectable which the vast majority of time it is.

So, this, again, brings us to this point which I have touched on briefly on the notion of invasive mediastinal re-staging. Most of the data we do have on this approach arise from neoadjuvant chemoradiation trials where some centers would not progress to surgery if there was persistent N2 disease, but other centers would progress to surgery even if there was persistent N2. And so, there is some disagreement or controversy about that. I think in the current setting with immunotherapy and with the latest data that has been presented relating event-free survival based on degree of pathological response the nodes versus the primary tumor, it seems to be a compelling argument to proceed to surgery regardless of whether there is persistent N2 as long as the disease remains resectable. And for that reason, in my own practice I do not perform routine invasive mediastinal re-staging. ctDNA is another adjunct that has been explored in the trial space, although we do not really have any compelling evidence to use it routinely in clinical practice. It does seem that patients who develop a complete molecular response who had detectable ctDNA at baseline and develop a complete molecular response after induction treatment have a higher likelihood of having a pathological complete response. But we have not figured out how to use that information to tailor the care of the patient at this point. And the sensitivity of the technology does remain low, particularly for non-squamous histologies.

When we compare the CheckMate 816 and the NADIM II trials for the correlation between complete pathological response and survival. On the left CheckMate 816 is with regards to event-free survival. And on the right, it is with regards to overall survival. But regardless, the occurrence of a pCR does translate to excellent survival outcomes and is a very important prognostic signal to share with patients. So, in summary, for neoadjuvant therapy, there are few data to support our decisions prior to surgery. Like I said, contrast infused CT, I think, is the minimal requirement and really should be applied before and after for a safe surgical plan to be executed and to rule out any gross progression of disease.

PET scan in my practice and perspective rarely changes the management and it can lead to some confusing findings, but it is a potentially useful modality to use in routine practice. Certainly, its greatest asset is in terms of excluding distant metastatic spread. With all of these imaging modalities, there are none that consistently predict the degree of pathological responses. Invasive mediastinal re-staging should be done when there is convincing evidence of contralateral nodal progression or if, for whatever reason, the disease seems to no longer be resectable, ctDNA assessments remain, I think, in the realm of research at this point and have no proven utility for modifying our approach to patients in the current setting. And I think pathological complete response is clearly our most meaningful measure of response at this point in the context of neoadjuvant chemo-immunotherapy.

So, what are the key measures of response in the adjuvant setting? Well, adjuvant therapy has always been a little bit challenging for the medical oncology community because you are essentially treating blind with no measurable disease on scan to know whether the treatment being given has any efficacy. And I think it is important to note that a recent trial conducted in Spain comparing surveillance CT chest versus chest x-ray after complete resection for early-stage lung cancer demonstrated no survival benefit. So, when we are trying to see if measuring molecular residual disease or ctDNA might improve outcomes, we already have evidence that more sensitive tests, such as CT chest, has no survival advantage over a less sensitive test like chest x-ray. So, it is hard to imagine that molecular detection of disease would really be the difference maker. But because of the unmet needs in these early-stage patients who do frequently recur, I think it is valuable to continue to explore how to better adjudicate postoperative treatments for these patients. So, in this regard, tumor informed ctDNA to measure molecular residual disease is currently the only potential surrogate measure of response to adjuvant ICI, and some trials have attempted to be designed to address this question, but there are ongoing significant technical challenges with the execution of such a diagnostic and treatment plan. What we do know without any doubt is that molecular residual disease positivity post-resection is highly prognostic for survival where we see patients that do have ctDNA in the blood have much worse outcomes than those who do not. Adjuvant immunotherapy seems to provide benefit regardless of ctDNA positivity, and I will go through the data supporting that moment from the IMpower010. And really putting it all together, I think MRD remains research-based with no clear evidence of clinical utility other than its prognostic significance at this point in time.

So, this is the ctDNA data from IMpower010. We clearly see that having positive ctDNA brings much worse survival, but there seem to be survival benefits at least at the DFS endpoint, both in the ctDNA-negative and positive cohorts suggesting that while it may be a bad sign to have positive ctDNA, it is not a decisional finding with regards to whether or not to administer postoperative immunotherapy.

So, in conclusion, I think we need a more granular data about re-staging practices and the utility of invasive staging after neoadjuvant chemo-immunotherapy to guide our management in real world practice. We need to better understand how to utilize pathological complete response data beyond simple prognostication. I think ctDNA technology is promising but remains purely prognostic at this point. And I think more trials acting on ctDNA data are needed to see if it helps us identify that cohort of early-stage patients who really do benefit from perioperative systemic therapy to optimize their survival outcomes. Thank you very much. Have a great day.

Announcer:
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