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Preoperative Concerns Regarding Neoadjuvant Therapy and Delays in Surgery

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Dr. Gastman:
Hello, my name is Brian Gasman. I'm the surgical and co-director of the Cleveland Clinic Melanoma and High-Risk Skin Cancer Program at the Taussig Cancer Center in Cleveland, Ohio. I am continuing our talk in the series on preoperative concerns regarding neoadjuvant therapy and delays in surgery with specific emphasis on immunotherapy.

Overall neoadjuvant therapy, especially immunotherapy, can absolutely affect surgery. For one, the ideal patient would undergo some form of timing for the neoadjuvant therapy in terms of how often the therapy is given, how many cycles of those therapies are provided and some might feel it's necessary to still wait sometime between the end of that and then the actual surgery. Is that even necessary, as we will discuss. Adverse events can occur during new adjuvant therapy specifically immune related adverse events and this could delay or even cause patients to become to the point where they can never even have the therapy because they get hospitalized and other events occur as a result. There are other issues like the tumor can shrink to the point where it's not even seen on imaging or physical exam, or the opposite, the tumor can grow and become more difficult to operate on. require advanced reconstruction, patients can even become inoperable or even become stage four. These are all considerations that some surgeons would give pause to knowing that this might occur hopefully very rarely.

So, in terms of complications, do immunotherapy specifically, in the neoadjuvant setting, lead to worse surgical outcomes in terms of peri-surgical risk and the data to date has been no. A recent paper in head and neck cancer with neoadjuvant pembrolizumab showed no increase in morbidities. Papers in melanoma, looking at even the oligometastatic resectable disease has shown that immune checkpoint inhibition should not lead to interruption of surgery in one paper. And then the last paper on the bottom left hand corner I quote, "Patients undergoing treatment with immune checkpoint inhibitors or targeted therapies can safely undergo surgery." If you look on your right, this trial that was published in Lancet Oncology in 2019, the OpACIN-neo trial looked at various forms of IPI NIVO, given in the neoadjuvant setting and you could look at the type of overall presurgical complications, the most common being seroma. If you look at these numbers though, most surgeons would not consider these to be very significantly different than what they would normally experience for tends to be lymph node dissection. And if the only issue with seroma which appears to be two-thirds of the issues I think this will not give most surgeons pause as this is a common problem that has to be dealt with.

You then look at the adverse events that might occur from these various immunotherapies. Again, I'm focusing on them as opposed to targeted therapy, just for, to keep on track of the overall theme of this presentation, you can look at, Checkmate 067, which is the most famous trial probably in melanoma where they compared IPI NIVO or NIVO versus Ipilimumab, Checkmate 23, which is an adjuvant trial comparing Nivolumab to ipilimumab. Again, the OpACIN-neo trial, which I described in the previous slide, and then the single dose anti PD-1 trial in the neoadjuvant setting, all for melanoma. Now if you look carefully at the unresectable disease on your left IPI NIVO at a 59% grade three or four, adverse event rate where Nivolumab was around 21%. In the NIVO alone adjuvant setting in Checkmate 238,

you can see the rate was 25%, which is a little bit higher but in range, given the the size of these trials. Over in the OpACIN trial, which were all forms of IPI NIVO, grade three and fours were a little bit lower than we saw in Checkmate 067. And then if you look in the neoadjuvant single dose of anti PD-1, there were no grade threes or fours. In another earlier trial where they compared IPI NIVO versus NIVO in the neoadjuvant setting, you can see that the Nivolumab only arm, again, these are smaller numbers, had very few grade three and no grade four events but the number of grade three events was much much higher than the IPI NIVO group. So one can imagine that if you're going to use the combination therapy, specifically IPI NIVO, your risk of having significant adverse events goes way up and that could affect the patient getting to surgery in a timely fashion or at all. On the other hand, on the an anti PD-1 mono therapy like Nivolumab or Pembrolizumab, one would expect, more likely, that surgery would go as planned, but again you may not have the effect that you want from that therapy.

In terms of duration Neoadjuvant therapy and what happens between then and surgery, Is that a delay in surgery? Obviously this is planned, so in one way you could say it's not. When you could see on the left hand side that in the various trials, which included TT, which are targeted therapies and IT, immunotherapy, there was different types of therapies and different cycles given. So the number of weeks varied from three all the way up to 12 weeks. There was some time in between them and then surgery. And then you could see in blue many of those trials included postoperative adjuvant therapy. Six weeks, eight weeks seems to be a pretty common thread especially when you're dealing with two cycles of drugs like Nivolumab, Pembrolizumab, or IPI NIVO. And on the right, you can see if you look at time to surgery the average time was seven weeks regardless of the type of therapy given with an average for immunotherapy of six weeks. So, if you give, for example, six weeks of neoadjuvant therapy and an additional six weeks of surgery, that is a total of 12 weeks from the time you met the patient and, in this case, register them for a clinical trial. So that's a fair amount of time compared to typical where these patients in the previous, the neoadjuvant era, would likely be scheduled two to four weeks after being seen in the office.

So, what does this all mean? What if radiologically the tumor is growing but there is still a pathologic response? We know that pathologic response pretends to potentially excellent outcome, especially if it's a major pathologic response despite the clinical lack of efficacy. And what about larger tumors? And I bring this up because the average tumor size in most modern neoadjuvant trials was around 2.2 centimeters. This is in stark contrast to the patient you see on your right, which might be a patient that we see in the real world. Is this really appropriate to compare? Can we translate this data to patients like the one that you're seeing here?

So, this patient I brought up before had two doses of revo grew through it, and we had to take the axillary vein and strip off the pleura, on the right you can actually see the pleura in view. Luckily there was no pneumothorax. We were just on the outside of it, but that probably wouldn't have occurred had we not done the neoadjuvant therapy. So, was it worth it? And honestly, this was technically resectable. It was a huge resection, but resectable, all surgeons know, is very subjective.

So, here's a case of a patient that the tumor eroded through the skin. A large amount of skin had to be resected along with the axilla, and if you look in the upper middle you could see the abdominal markings, that entire abdominal skin was transposed to the axilla, also called a rectus abdominis myocutaneous flap, which is a big reconstruction, may not have needed to be done had the tumor been operated on earlier. And these are kind of things you may need to consider. For many surgical oncologists who don't do these kinds of reconstructions, they then need to enlist other surgeons specifically plastic and reconstructive surgeons.

So, what about if there's no radiological disease left after the neoadjuvant therapy? Does the radiology, that's A, equal B, the pathologic response, which we already know leads to excellent outcome predictability especially if there is more than 51% non-viable tumor in the resection specimen. And so here's a case where the patient had no residual tumor in the bottom as opposed to the top where this significant disease in the axilla. And if we go back to the major papers, you can see that overall if you have a complete response, CR by radiology in the targeted therapy which again is not our main focus here there was a significant number of patients who really had no response pathologically. Luckily in immunotherapy, at the very bottom, you could see that all patients with a radiological complete response had either a near pathologic complete response or a pathologic complete response. Both are very strong predictors of outcome. So I would say there we say that the radiology might be as good as the pathology. However, if you look at other responses based on radiology, partial responses, stable disease their ability to equate to something pathologically is much weaker even in immunotherapy. But if you think about it does A equals B, equal C? Well maybe it does for significant or reduction in tumor and specifically where there's no evidence of disease where could that matter?

Well, if we turn over to the recently published PRADO study, we know that patients who had an index tumor, only resected after neoadjuvant therapy, who then had a major pathologic response, who had no further therapy, meaning they did not have any full lymph ectomy they did as well as the rest of the patients who had poor pathologic responses who did have additional surgery. Meaning if we knew that index tumor had a major pathologic response, we now know they may not need further lymph adenectomy surgery. Well, if we could have predicted that major pathologic response without even doing that biopsy vis a vis what I just showed you with radiology,

maybe the radiology A, would equal the major pathologic response B, and then C, the excellent outcome which is shown at the bottom there, thus maybe radiology could have relieved us from even doing any surgery and I'm sure there are clinical trials either underway or being devised to answer that very important question. And with that I'd like to thank you for your time, attention.

Announcer:
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