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# Resectable Head & Neck Cancer: A Team-Based Approach to Perioperative Immunotherapy

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**Dr. Haddad:**
The treatment landscape for locally advanced head and neck cancer is changing, and we want to share with you today insights on how we can integrate immunotherapy into the practice and how we can optimize multidisciplinary care.

I'm Dr. Robert Haddad from the Dana-Farber Cancer Institute. I am a medical oncologist.

**Dr. Uppaluri:**
And I'm Dr. Ravi Uppaluri. I'm a head and neck surgeon at the Brigham/Dana-Farber.

**Dr. Lee:**
And I'm Dr. Nancy Lee, head and neck radiation oncologist at the Memorial Sloan Kettering Cancer Center in New York.

**Dr. Haddad:**
Yeah. Thank you both. Dr. Lee, can you please start today's discussion by reviewing unmet needs in resectable squamous cell carcinoma of the head and neck?

**Dr. Lee:**
Yes. Today we still face a significant problem managing patients who have resectable, locally, regionally advanced head and neck cancer. Despite best effort after surgery followed by post-op radiation with or without chemotherapy, the relapse rate is still very high, and this has not changed for the past several decades.

Patients experience significant acute and late effects. These issues remain a significant challenge for this patient population. As a field, we try different approaches, but the relapse rate remains around 50%. We don't have a nonsurgical option for these patients, especially when it comes to a large oral cavity cancer, as we know that definitive chemoradiation is inferior to surgery followed by postoperative radiation therapy.

So we were, as a field, stuck for many, many decades. We could not advance our treatment. And this is why KEYNOTE-689 is very exciting to me, where we saw the benefits of enhancing tumor response rate, prolonged event-free survival, with the additional 2 cycles

of preoperative pembrolizumab as well as concurrent pembrolizumab followed by adjuvant pembrolizumab.

This trial leveraged the synergistic effect of RT-induced immunogenic cell death and immune checkpoint inhibition-mediated immune activation.

**Dr. Haddad:**
Yeah, so obviously we're talking about patients here who are undergoing surgical resection. So the starting point in this conversation is that, really, we're talking about patients who are determined to be a surgical candidate. And when you look at it globally, that's really the vast majority of patients, globally, are patients who are going to be treated with surgery.

So the importance of KEYNOTE-689, which is a randomized phase 3 trial that now sets a new standard of how we treat and how we manage these patients. In this trial, immunotherapy was given as the first intervention.

Once the patient is determined to be a surgical candidate they will proceed to receive neoadjuvant immunotherapy. The drug used in this trial is pembrolizumab for 2 cycles. Then the patient undergoes surgical resection, and this is followed by the standard of care for that patient—so it would be radiation and chemotherapy or radiation alone, based on the final pathology. And then immunotherapy/pembrolizumab, was added.

So to be eligible for this trial, you need to have a patient who had surgery as the primary treatment modality. The treatment met the primary endpoint of improvement in event-free survival for the ITT patient population, for the CPS 10 or more patient population, or for the CPS 1 or more patient population.

One of the major endpoints of this trial is the MPR, the major pathological response, which is less than 10% of viable squamous cell carcinoma in the surgical specimen—both lymph nodes and primary site. This is an important endpoint. That point was around 14% in the CPS 10 or more patient population.

So not only did this trial show an improvement in the primary endpoint of event-free survival, we were also able to show a significant degree of MPR in those patients. So we look at this intervention really from the perspective of a vaccination for the patient. You're really priming the immune system before you do the surgery, before the lymph nodes are touched, before the primary tumor is removed, before the radiation is delivered, and that's the importance of this intervention.

I will contrast that intervention with what was recently presented, what is known as the NIVOPOSTOP trial, a pure adjuvant trial. In that trial, patients had surgery first, and if they had high-risk features, they were randomized to chemoradiation with nivolumab or chemoradiation alone. The drug used was cisplatin, also like we did in KEYNOTE-689.

But the whole population of NIVOPOSTOP is a subset of KEYNOTE-689. Because remember, in KEYNOTE-689, we did include those patients with high-risk features; they received chemoradiation/pembrolizumab. But what was missed in the NIVOPOSTOP trial is all those intermediate patients who were receiving radiation after surgery, and those patients seem to derive a great benefit from the addition of pembrolizumab to the treatment. So that's really a big contrast between NIVOPOSTOP and between KEYNOTE-689.

As you all know, KEYNOTE-689 led to FDA approval of pembrolizumab in resectable head and neck cancer for patients with a CPS of 1 or more. That FDA approval came in June of 2025.

This is really important work now, because this builds on essentially 2 decades of trials where we have been trying to incorporate immunotherapy into the curative treatment of head and neck cancer. So the first trial I was part of with Dr. Lee, was the avelumab phase 3 trial known as the JAVELIN trial, where we added avelumab to chemoradiation, compared that to chemoradiation alone. And then building on the JAVELIN trial, we saw the presentation of KEYNOTE-412, which was a similar trial where also pembrolizumab was added to chemoradiation. And the INVOKE phase 3 trial, which was a large, randomized phase 3 trial where we gave atezolizumab after the curative therapy in a randomized fashion.

So really a massive investment in the past 10 to 15 years in adding immunotherapy to the curative treatment of head and neck cancer, but no benefit up until KEYNOTE-689, which fortunately is a positive trial and allowed patients to receive a neoadjuvant intervention for patients being treated with surgical resection.

But also biologically, it makes sense to think about a neoadjuvant intervention, where you are intervening before surgery. And because of the model that we use in 689, it becomes extremely important that the multidisciplinary clinic is involved early on—that the surgery is not happening before the patient has the opportunity to meet with this medical oncologist and radiation oncologist to discuss a treatment package that will include all these modalities.

And taking up on that, I'm going to actually ask, Dr. Uppaluri, how can we envision we can optimize perioperative immune checkpoint inhibitors for patients with head and neck cancer going to surgical resection?

**Dr. Uppaluri:**
Yeah, I think the fundamental piece that we'll talk through is the multidisciplinary collaboration. First, before I get into that, I really want to say that I also want to express my excitement about this first sort of change to the potential surgical paradigm for head and neck cancer patients in a couple of decades.

So with that point, though, that comes up to consideration of how do we make this effective for patients? As many of us know here, that the vast majority of these patients present to surgeons up front—whether it's head and neck surgeons or oral maxillofacial surgeons. So it's really critical, to have this succeed, to have that initial touchpoint to be also checking the box to move this forward to integrate the multidisciplinary piece.

So in this spectrum, ultimately with the KEYNOTE-689 regimen, the involvement of medical oncology is going to be critical up front. So I think with any locally advanced head and neck cancer patient, stage III or IV, that is planned for surgery, or they will be a surgical candidate, I think integrating the medical oncologist in particular up front, and obviously the radiation oncologist also, is going to be a key aspect of this. So our surgeons need to really embrace this to take advantage of the potential impact of this.

With respect to the concerns around delaying surgery—I've heard this for many years, this is a question from surgeons—is this approach going to impact my surgery or what I can offer as a curative approach to patients?

What's really reassuring about this is at a couple different levels: first of all, what KEYNOTE-689 showed us is that the immune-related adverse events are really minimal in this setting. Now, there certainly are patients who may have some issues, and that's where collaborating with our medical oncologists up front is also a key piece, because they can help us manage these.

Many of the adverse events that we're seeing in 689 were related to hypothyroidism, which did not necessarily affect completing surgical ablation. In particular, only 1 out of 322 patients in the pembrolizumab plus standard of care arm was found to be unresectable from a surgical standpoint. So I think that's a big piece to consider.

I think additional consideration is, when the biopsy is done, that the surgeon should think about requesting a CPS score, which helps facilitate moving this forward also.

Ultimately, I would say that our own experiences have been very positive with this. The key approach that I mentioned earlier is that, for the first time here, we've developed an approach to consider—in a subset of patients—to de-intensify treatment.

The other big question I get asked is, from a surgeon's perspective, is do we modify our surgery? On our original design, we maintained them; we would resect to the original margins. As all surgeons know, we make intraoperative decisions based on what we see.

The key effect we're aiming for here is the vaccination piece that Dr. Haddad mentioned. Are there going to be odd situations where we potentially need to modify surgery? And again, it will be dependent on the surgeon as they see the tumor intraoperatively and make a decision based on that.

The other final piece I would say, Dr. Haddad, here is that, from a surgeon's perspective, there's not been any signal of surgical morbidity or mortality related to the neoadjuvant immune checkpoint inhibitor. Again, reassuring for surgeons to adopt the regimen.

**Dr. Haddad:**
Yeah. Thank you, Ravi. This is great.

Dr. Lee, from a radiation oncologist—obviously these patients are going to all receive radiation whether this is stage III or stage IV—can you give us your perspective as a radiation oncologist who's now going to treat patients with radiation and immunotherapy at the same time?

**Dr. Lee:**
Yes, thank you. And just like Dr. Haddad and Dr. Uppaluri stated, the importance of multidisciplinary team approach. Even though radiation oncology comes after surgery, but it's always good to involve them early on. Because you can imagine, radiation oncology is all about our field design. How big is our field? What do we need to target? It's a critical piece, when we design the field, to have very close connection and collaboration with our surgeon.

And given that the radiation field design is quite large for these locally, regionally advanced, resectable head and neck cancer, not only do we have to cover the postoperative bed, but also bilateral necks. It's not ideal to give above a 2 Gy dose per day so we don't run into toxicity issues.

And now, standardly, for high-risk patients—those with positive margin, ECE—we have been giving chemotherapy, high-dose cisplatin, or weekly. And then you can imagine, patients have substantial grade 2/3 mucositis, dysgeusias, xerostomias, quite substantial.

And what's exciting about this trial—and Dr. Uppaluri stated earlier and Dr. Haddad as well—is that there is an experimental arm, there is a portion of patients that significantly did not need to have post-op chemoradiation, but rather, they're downstaged to receive radiation only. And with additional pembrolizumab concurrently, it's very easy to give. It's much easier than high-dose cisplatin, so the toxicity that patients experience is tremendously less.

You can look at the median dose of RT between the experimental arm and the standard arm is about 6 Gy. And you may say 6 Gy is not a big deal, but it is, actually, when we are giving high doses of radiation. The fact that we can downstage, meaning less need of having chemotherapy, which means less dose of radiation as well, because we don't have to deal with the positive margin or extracapsular extension—then that is really a tremendous benefit that our patients can receive.

So in summary, from a radiation oncologist, I cannot overly emphasize the importance of working together as a team—both with the surgeon and the med onc surgeon—because we need to know our target, our field design, and then keeping the standard 2 Gy dose per fraction. Which is important, because as we increase the dose per fraction, we may have some unwarranted late effect, and that's not what we want to see for this group of patients, especially if we're going to prolong their survival.

**Dr. Haddad:**
Thank you, Nancy. This is great. This has certainly been a fascinating conversation with 2 really world-renowned experts in head and neck cancer treatment. And essentially the take-home message is, if you have a patient with a stage III or stage IV head and neck cancer, where surgery is going to be the primary treatment modality, think of that patient as an ideal patient for a neoadjuvant intervention. Get your multidisciplinary clinic on board early on. Talk to your medical oncologist and to your radiation oncologist so that an opportunity is not missed for that patient to receive a neoadjuvant intervention before their operation.

**Dr. Uppaluri:**
I think the final take-home message really is that, first of all, this is a really exciting time for head and neck cancer patients with the results of KEYNOTE-689. But the key thing to make this successful is a multidisciplinary approach to optimize patient selection, the toxicity potential management, and the treatment sequencing.

**Dr. Lee:**
And I echo what Dr. Uppaluri said. It's very exciting, because for the first time we see a synergistic effect of radiation with immune checkpoint inhibition in the postoperative setting, enhancing tumor control and preserving function.

And then I cannot emphasize enough, as our 2 prior speakers did, that we need to work together as a multidisciplinary team. Then we can really, together, benefit our patients.

**Dr. Haddad:**

This is great. That's all the time we have today, unfortunately. I want to thank our audience for listening in and thank you, Dr. Uppaluri and Dr. Lee, for sharing all your valuable insight and expertise today. Thank you and goodbye.

**Dr. Uppaluri:**
Thank you very much.

**Dr. Lee:**
Thank you.

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