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COMMENTARY

Physician Perspectives on the Management of Patients with Resected High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck Who Are Ineligible to Receive Cisplatin: A Podcast

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Abstract

For the past two decades, cisplatin-based adjuvant chemoradiotherapy (CRT) has remained the standard of care for patients with resected, locally advanced squamous cell carcinoma of the head and neck (LA SCCHN) who are at high risk of disease recurrence. However, many patients are deemed ineligible for cisplatin-based CRT because of poor performance status, advanced age, poor renal function, or hearing loss. Outcomes with radiotherapy alone remain poor, so patients at high risk of disease recurrence who are ineligible to receive cisplatin represent a population with a significant unmet medical need. Although clinical guidelines and consensus documents have provided definitions for cisplatin ineligibility, there are still areas of debate, including thresholds for age and renal impairment as well as criteria for hearing loss. Treatment selection for patients with resected, high-risk LA SCCHN who are deemed ineligible to receive cisplatin is often based on clinical judgment, as treatment options are not clearly specified in international guidelines. Therefore, there is an urgent need to develop alternative systemic treatments to be used in combination with radiotherapy. In this podcast, we share our clinical experience and provide our perspectives related to cisplatin ineligibility in patients with LA SCCHN, discuss the limited clinical evidence for adjuvant treatment of patients with resected, high-risk disease, and highlight ongoing clinical trials that have the potential to provide new treatment options in this setting.

Key Points

There is a lack of treatment options for resected, cisplatin-ineligible, locally advanced squamous cell carcinoma of the head and neck, and guidelines to determine cisplatin eligibility are still debated.

Current treatment selection is generally based on the judgment of the treating physician; thus, alternative treatment options are urgently required.

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The podcast and transcript can be viewed below the abstract of the online version of the manuscript. Alternatively, the podcast can be downloaded here: https://doi.org/10.6084/m9.figshare.26968906.

1 Transcript

[00:05] Robert Haddad: My name is Robert Haddad from the Dana-Farber Cancer Institute in Boston. We are grateful you are joining us today in this podcast to be published in the journal of *Targeted Oncology*.

[00:15] Kevin Harrington: And hello, my name is Kevin Harrington. I'm at the Institute of Cancer Research in the Royal Marsden Hospital in London, UK.

[00:23] Robert Haddad: For today, the title of our discussion is "Physician Perspectives on the Management of Patients with Resected High-Risk Locally Advanced Squamous Cell Carcinoma of the Head and Neck Who Are Ineligible to Receive Cisplatin." We will be discussing about the

practical considerations and patients with advanced head and neck cancer receiving first-line cisplatin- or carboplatin-based chemotherapy. The key questions to introduce today are: What is the current standard of care for patients with locally advanced squamous cell carcinoma of the head and neck where chemoradiotherapy is the standard of care? We're going to be discussing eligibility for cisplatin and also patients who are ineligible for cisplatin therapy. We're going to be talking about, what are the universal criteria that are used to determine whether a patient is eligible or not to receive cisplatin in the locally advanced setting. We're going to talk about the treatment options available for those patients. We're going to be talking about the use and the efficacy of radiotherapy in patients who are not eligible to receive cisplatin and the ongoing randomized, phase III trials for non–cisplatin-based treatment regimens.

The key points we would like to highlight today: patients with comorbidities that make them not eligible for cisplatin-based chemotherapy have limited treatment options. We will be discussing about how we would manage those patients in our practice. We're talking about platinum 40 vs 100 mg, the two commonly used doses of cisplatin in head and neck cancer. Furthermore, we'd like to talk about standardization of criteria for eligibility for cisplatin to ensure that patients receive the most appropriate treatment in the resected locally advanced head and neck cancer patient.

[02:13] Kevin Harrington: So, let's get started, shall we? So, first of all, Robert, what I'd like to touch on, what I think we need to just set the scene with is, can you tell me a little bit about what's the incidence of locally advanced squamous cell carcinoma of the head and neck, and what would you see as the current standards of care in that space?

[02:36] Robert Haddad: Yes, so, head and neck cancer is a fairly common cancer. Globally, there's close to 500,000 new cases of head and neck cancer per year [1]. In the United States, for example, we see close to 40,000 cases per year [2]. Specifically, we are talking about cancers of the oral cavity, oropharynx, larynx, hypopharynx, also nasopharynx and sinus tumors. All of these are labeled under head and neck cancer [2]. There are three modalities that are used primarily in treating patients with head and neck cancer. Those are surgery, radiation therapy, and chemotherapy [1, 3]. In general, for patients with early-stage disease, they are usually managed with a single modality—surgery alone, for example, for stage I tongue cancer—or patients who have more advanced presentations that are managed with a multimodality approach that can combine surgery, chemotherapy, and radiation [1]. When we use chemotherapy in head and neck cancer patients, the agent that is commonly used is cisplatin. This is really the global standard for locally advanced head and neck cancer when combining it with radiation therapy [1, 3]. The dose of cisplatin is 100 mg/m^2 that's given every 3 weeks, and the other way to give cisplatin would be 40 mg/m^2 once a week [1, 4]. There's some distinction of how patients are treated as their initial approach of treatment. As a general rule, we tend to favor surgery for the oral cavity patient. So, once you do an operation, you have to decide, based on the pathology, whether to offer radiation, concurrent chemoradiation, or sometimes no further intervention, based on the final stage [1, 3, 5, 6]. For patients with more posterior-location tumors, for example, larynx and hypopharynx, we tend to favor nonsurgical approaches for those patients, such as radiation therapy alone or radiation therapy with cisplatin [1]. I would like to talk a little bit, Kevin, with you about the toxicities that we see when we give concurrent chemotherapy and radiation. In your experience, what are the key toxicities that are associated with cisplatin-based concurrent chemoradiotherapy?

[05:02] Kevin Harrington: Well, as you're well aware, Robert, platinum itself is a pretty potent and toxic cytotoxin. It's associated with relatively severe acute toxicities, including nausea and vomiting [7]. But when we think about combining it with radiation therapy in what is called chemoradiation, and that can be either in the definitive setting or, indeed, in the postoperative setting in patients who have undergone surgical excision of their primary tumor, the main toxicities that we worry about, and indeed, those which may impact upon our delivery of that treatment, I think we should think of those in terms of ototoxicity, so hearing- and balance-related toxicities; nephrotoxicity, the problems that we see related to renal function and EDTA clearance that we can measure; and then there is neurotoxicity [7, 8]. Now, we know that higher cumulative doses of cisplatin are associated with greater degrees of efficacy, and often we'll set the threshold for that dosing being a target dose approximately of 200 mg/m^2 over a course of treatment [4, 8–11]. We also know that those higher doses and those higher dose intensities, when given potentially at the 100-mg/m^2 dose, are associated with a greater degree of toxicity [12]. And the problem with giving platinum at these high doses as part of concomitant chemoradiation strategies is that a number of those toxicities can be irreversible. And this means that we are really rather wary of causing those toxicities, and it means that we will often need to back off on our dosing of patients. And many patients, indeed, will go through a course of chemoradiation without necessarily completing the full number or the planned doses of cisplatin, and that can have an impact, of course, on the efficacy of the treatment [4, 8, 9]. Now, having said that these toxicities are profound and obviously something that we worry about in the clinic, there have been a number of attempts to look at alternative platinum dosing schedules trying to maximize and maintain efficacy but minimize toxicity. And you yourself have

already touched upon the fact that we may use weekly dosing schedules, 40 mg/m^2 perhaps being the classical version of that. But, indeed, in some studies, that's gone as low as 35 mg/m^2 or even 30 mg/m^2 where the concern has been toxicity and tolerability of these approaches [4, 10, 13]. So, I think those are things that we need to consider.

It'd be really interesting to hear your perspectives around what you do when you have a patient, for instance, who develops quite significant toxicity on a high dose of platinum—maybe in cycle 1 you've given 100 mg/m^2. What do we see? What do you do then, if the patient isn't going to tolerate further cisplatin, for instance?

[08:15] Robert Haddad: Yeah, this is a great question, Kevin. And there's a lot of, really, heterogeneity in how these patients are managed. Carboplatin tends to be less offensive on the kidneys, for example [14]. So that would be an option for patients who are not eligible to receive cisplatin because they develop, for example, a rising creatinine, or they have severe tinnitus [9]. The other option is to combine carboplatin with a taxane, and the common combination is carboplatin-paclitaxel, for example. So that is another option. And the third option that I've seen used mostly in the Western world is to use an anti-EGFR inhibitor called cetuximab because we have data in the definitive setting that combining cetuximab with radiation is better than radiation alone [9, 15]. So, that is another option. And then, we've seen recent data also from India using an agent called docetaxel with radiation, and docetaxel tends to be a very potent radiosensitizer when combined with radiation [3, 9, 16]. So, mucositis could become an issue in those patients and has to be managed carefully [16]. And also, it's reasonable to consider for some patients, the appropriate intervention would be to not use further chemotherapy and to give radiation therapy alone [3]. And this is where, really, it becomes a conversation with the patient, assessing risk and benefit of using more chemotherapy.

[09:45] Kevin Harrington: Yeah, thank you. Fascinating insights. And I think I would agree with all of what you've said. I mean, I think it's fair to say that none of that represents a true standard of care [3], because, of course, essentially this is, this is adapting the treatment to an unwanted and unanticipated toxicity of the initial dose of cisplatin. And then it's about really making a clinical judgment about what the patient will tolerate and what you might be able to add to the radiation, to maximize the chance of getting that tumor control outcome that we're looking for. So, I think fascinating insights, and thank you for those.

[10:25] Robert Haddad: Thank you.

[10:28] Kevin Harrington: So, now, if we move on. We've touched upon this notion that, for some patients, the use of cisplatin, either at high dose or perhaps even at low dose, may not be ideal. And we've mentioned the concept of platinum eligibility and ineligibility. I'd like just to probe you on this now, Robert, if I may. What criteria would you use to decide whether or not a patient with high-risk, locally advanced head and neck cancer for whom you want to use platinum, what criteria do you use to decide, is that patient eligible, or indeed, are they ineligible for that treatment?

[11:09] Robert Haddad: Yeah, so, head and neck cancer treatment is tough. Head and neck cancer treatment, as you had mentioned before, Kevin, comes with a lot of baggage and significant toxicities. So, there's definitely, really, a careful assessment that needs to occur prior to starting such an intense treatment. So, cisplatin as an agent has been around for a very long time. We know really quite well what cisplatin can do, what type of side effects we see [7]. You know the big three we think about are nephrotoxicity, which to me is really the number one issue that I have to be careful about when delivering cisplatin. So, a careful assessment of the renal function for the patient is essential, as we determine whether the patient is eligible for cisplatin therapy, and getting some sense of the patient's creatinine clearance is important as you embark on this treatment, especially if you really are in the camp that uses high-dose bolus cisplatin 100 mg/m^2 [17, 18]. So, having that careful assessment is important. Neurotoxicity, for example, in someone who's diabetic, who already might have some baseline neuropathy—important to ask the patient: What is their day-to-day function? Are they dropping things? Are they able to button their shirts? These subtle signs of neuropathy become really important as we try to determine whether we are going to really inflict more damage on this patient [4, 8, 9, 17, 18]. Remember, in those patients, we expect our treatment to be curative. We expect those patients to have a life expectancy that can go on for 10 or 15 or 20 years. So, we want these patients, while we are really delivering a curative-intent treatment, to also have a quality of life that is manageable and that is acceptable to the patient. So, neuropathy is another piece of the puzzle that we're trying to determine prior to starting treatment. And really avoiding cisplatin in those patients who have clear evidence of grade 2 or 3 neuropathy to start with [17, 18]. And again, these are conversations we need to have with the patients; for some patients, they might elect to still receive treatment with this agent, despite the risks of neuropathy. And the last one is really—that's, again, the textbook answer of cisplatin—you hear about hearing loss [4, 8, 9, 17, 18]. Personally, for me, that's not as much of a, call it 'deal-breaker,' than the other two, neuropathy and nephrotoxicity. But again, I think about the patients who tinnitus could become a big issue in their daily

activities or their daily living or their profession—musicians, for example, people who play music or people who perform—for them, this type of toxicity could be quite limiting, and they might not accept it. So, ototoxicity is another piece of information that we'd like to collect. And for some patients, we actually do obtain baseline audiograms [19]. Also, it's important to really determine what, you know, in oncology we call performance status—is the patient we are talking to in the clinic…is that patient fit to receive concurrent cisplatin-based chemoradiotherapy? What is, you know, their function, day-to-day activities? Are they spending more time in bed than outside? Are they ambulatory? What we call a performance status [17, 18]. That's really key because cisplatin-based chemoradiotherapy is not for everybody. So, the other pieces, obviously, we want to assess bone marrow—that, we assess with any chemotherapy—bone marrow function, nutritional status, cardiovascular risk [17]. Cisplatin requires a significant degree of hydration [17, 20], and that can overload someone, for example, who has a congestive heart failure. So, having that information is essential and is key as we determine whether cisplatin is the correct agent for patients.

And along the same lines, I would like actually to get your input, Kevin, as someone who's done this for quite a bit, about age and whether you use age as a determinant factor. We know that there's a meta-analysis that showed the decreased benefit of chemotherapy with aging—especially after ages 65, 70—and whether age for you also, for example, plays a role in determining cisplatin as an option for patients.

[15:39] Kevin Harrington: Yes, a fascinating point, Robert, and I think it's a key issue for us in the United Kingdom, where I think there is a broad application of those data, and you touched upon it. So, for the audience, this is the meta-analysis of chemotherapy from the MACH-NC Group based in the Institut Gustave Roussy in Paris, and that really has done a fabulous job in pulling together data in over 18,000 patients from over 100 clinical trials and meta-analyzing the individual patient data. And what was clearly demonstrated was, as you—and I'm envisaging as I speak; I'm envisioning the forest plot—and as you march up in terms of age banding, as you go through the 60 to 70 and then the 70-plus age groups, what you see is that the hazard ratio and the confidence intervals tend to cross the 1.0 hazard ratio line, and we see a loss of benefit when patients get more elderly [21]. And for us, we've applied, relatively across the board, the fact that if a patient has passed their 70th year, generally speaking, it would be very unusual in a UK center for that patient to receive concomitant chemoradiation. It's not an absolute contraindication, but it's been seen, I think, as a very strong relative contraindication. I think that's also true actually of other treatments as well. So, we've seen with hyperfractionated radiation therapy, for instance, the benefit is less strong when you, when you are more elderly [22]. And, so, this is probably a biological factor. And clearly, we don't have a test that we can use to determine whether or not someone will, or will not, benefit from platinum before you start treatment. So, generally speaking, we will avoid exposing those patients to high-dose or even weekly platinum in our practice.

[17:44] Robert Haddad: Yeah, thank you, Kevin. Kevin, I wanted to follow up with you on this notion of using cisplatin and eligibility. And in your in your experience, are the criteria used to determine cisplatin ineligibility standardized? And if not, why do you think that is? Why do you think there continues to be this debate about who gets cisplatin and who doesn't? What's been your take on this?

[18:15] Kevin Harrington: Yes, so really, it's a tricky problem. So, I think if you put a group of experts in a room, you'd probably get broad consensus and agreement of what might be the absolute contraindications to the use of platinum. You've touched on them very eloquently earlier. We've discussed nephrotoxicity. I agree with you that, you know, if you've got a patient who's got an EDTA clearance that is less than 50 mL/minute, that patient should not be receiving platinum. I think everyone would probably agree with that, without much dissent [17, 18]. Similarly, patients who have preexisting grade 2 or above neurotoxicity, those patients who already have effects on their activities of daily living, those patients will not be given platinum by most people [17, 18]. Similarly, patients with high-order hearing loss or significant tinnitus that has an impact on quality of life—those patients will not receive platinum [17, 18]. And so, I think we can broadly agree there. But then there is a lot of discussion around, what would we do with the relative contraindications to the use of platinum, and those, I think, are more based around individual experience and individual practice. And of course, be also based on clinical judgment when discussing issues with the patients. And there is an absence of standardized criteria to guide us in this [4, 8, 9]. And so we need to think about how we should be approaching this, and, in particular, I think it's about assessing these relative contraindications and looking to see whether or not those are affecting the patient's activities of daily living and their quality of life and whether or not a further infliction of damage upon a patient is going to make a significant impact on their ability to carry on and live a good quality of life [17, 18, 23, 24]. Now, in response to some of these relative contraindications—so, for instance, you touched upon cardiovascular function, maybe recent or past history of myocardial infarction or cerebrovascular accident. We know that cisplatin is vasculotoxic [25], and therefore those may be weighed in the balance, and there may be a decision taken maybe not to use

the high doses of platinum but maybe to go with the weekly regimens, or maybe to use one of those alternate regimens that you touched upon—the carboplatin-taxane combinations or, in some jurisdictions, even cetuximab. So, I think there has been a real lack of a common ground amongst clinicians as to what would represent the standard selection criteria. And of course, this feeds through when we're doing clinical trials as to what might be seen as eligibility for platinum within those clinical trial protocols. Overall, I think, again coming back to the concept of consensus, when using cisplatin, most clinicians would take the view that they would use the drug if there is a reasonable expectation that the patient will receive a cumulative dose of 200 mg/m^2 or greater during the course of their treatment, and somebody who is judged to be less likely to achieve that rate of dosing may be considered for alternative approaches. And, of course, that also leads to the possibility that you touched on previously that maybe you omit systemic therapy altogether for some patients and go with radiation alone.

I'd be really interested to hear your perspective about what you see as how we factor these various relative contraindications.

[22:00] Robert Haddad: So, really, it's again, it's patient by patient. It's all what, you know, we have been talking about the past few minutes and trying to really put this puzzle together and making a decision. And there's going to be variability. I mean, it's not unclear—it's not uncommon to have patients, for example, who are recommended various treatments by various physicians for the same disease they have, and this, because again goes back to the notion of there is some art in how you decide these interventions, because, as you started by saying, there are the absolute contraindications. Somebody who walks into the clinic with the creatinine that's 3 or 4 where you know up front that this is not going to be a debate whether you give cisplatin [17, 18]. But there are the other, you know, pieces that we are talking about, that there could be some variability, like hearing loss, for example, or borderline performance status [4, 8, 9]. And this way, it becomes a conversation between the physician and the patient about risk and benefit and trying to make a final decision on the final treatment. And we do this every day. This is common practice. Really, there are many situations that could be labeled as gray zones. And as you said, sometimes you start with cisplatin and realize this is not going to work, and then you have to change your approach mid-treatment to either radiation alone or radiation plus one of the other agents we have discussed.

[23:21] Kevin Harrington: So, now we're going to switch the focus a little bit. And we're going to consider the landscape of the operated patient. So, when we've got a resected locally advanced head and neck cancer patient who has been judged by pathological factors to have high-risk disease. And I just want to get your perspective as to, where are we in in that space? What has been the change in practice that's occurred within the last decades? And then, of course, we can touch on where we may be going in the future. But, first of all, perhaps, Robert, if you could just set the scene for us. What would you consider a standard of care in this space?

[23:59] Robert Haddad: Yeah, and unfortunately, Kevin, the landscape has not changed a lot over the past many, many years. There were two large studies that looked at this question of patients that have surgery first and have high-risk features on their final pathology after surgery; those were defined as either a positive margin or extranodal extension, lymphovascular invasion, perinodal invasion, or multiple positive nodes. So, there were two studies that looked at these questions comparing radiation therapy alone versus radiation with high-dose cisplatin, and essentially bottom line from these studies is that when you look at cisplatin plus radiation, you actually do better with the combination than with radiation alone, especially with those patients who have a positive margin or extranodal extension [26–28], which really goes back to say that it is very important that you get, as a physician, this information from your pathologist. You get a description of the final margin status and also whether extranodal extension is present or not. And if you have these features, the standard of care currently calls for the use of cisplatin with radiation [1, 3]. Initially, everybody was giving high-dose bolus cisplatin. There was recent data from Japan that looked at weekly cisplatin in this setting that showed also benefit from the weekly regimen. So, many of us have moved from the bolus cisplatin to the weekly cisplatin [10], so I would say the landscape hasn't changed a lot for those patients after surgery. Cisplatin-radiation is the standard of care for those patients [1, 3].

[25:40] Kevin Harrington: And maybe now we can develop that theme a little bit further. So, I think I would agree with you entirely that disappointingly, we haven't seen significant changes in recent years. But let's talk now about that group of patients. And again, we come back to this question of platinum ineligibility, when we have an operated patient with resected high-risk disease, but the patient is ineligible to receive cisplatin as part of their postoperative chemoradiation. What do we do? Where are we with that?

[26:13] Robert Haddad: And again, it's an area of unmet need, I would call it. I would call this really an area where we need to develop new interventions and new drugs because we have not seen advances in this setting, and we will talk later of some of the opportunities we and others are looking at in this space. Currently, what we do outside of a clinical trial is, we offer patients a combination of platinum with

taxane. So, my go-to regimen for those patients would be something like carboplatin with paclitaxel. We give carboplatin at the low dose of AUC of 1.5–2. We give paclitaxel at a dose 35 mg/m^2. That's one option. The other option would be to use single-agent taxane. And we have data from India about single-agent docetaxel in that space [16]. That also was promising. And then another option is cetuximab, which is an anti-EGFR agent, in combination with radiation [29]. So, those are the options that are available when we decide that we do want to give systemic treatment with radiation because there's positive margin, there's extranodal extension. If the patient is not eligible even for those interventions, then radiation alone is a standard of care for those patients [3] and is a reasonable option because we have to remember that in these patients, the bulk of the benefit is coming from radiation [30]. And we do want to make sure that the patient is able to receive their radiation therapy and complete their radiation treatment. And if chemotherapy, carboplatin, paclitaxel, or docetaxel is going to compromise delivery of radiation, I personally favor radiation alone for those patients. So again, going back to, there's some art in how this is done, and there's really…this shouldn't have to be made on a week-to-week basis about whether chemotherapy is the right intervention or not, based on everything we've been talking about—performance status, comorbidities, and toxicities.

[28:18] Kevin Harrington: Now, I'd echo all of those comments, and I think it's important to emphasize, as you made such a central point, that it is the radiation that is the central focus of the adjuvant treatment that delivers the greater benefit in terms of improving cure rates, and the drugs that are added as systemic therapies layered on top of that deliver an extra benefit that may be to the tune of between 6% and 10%, but we should not compromise on radiation delivery [30].

[28:50] Robert Haddad: Yeah. And yeah, Kevin, and maybe we can actually take you up from here and talk a little bit about radiation in this setting and whether you have seen any changes or advances in how radiation therapy is delivered for those patients. You know, when you make a decision that, okay, for this patient, I'm doing radiation therapy alone after surgery—what's your take on where the field is today with radiation therapy for those patients?

[29:15] Kevin Harrington: And again, I think, from that perspective, I think we have to look back at history first of all and see where we've come from. So, I think it's important to recognize that there have been attempts to look at altered radiation fractionation schedules, particularly twice-daily radiation schedules, which we know, actually, when you can deliver them, can deliver a benefit that is equivalent to the benefit that you might receive from adding platinum [30]. The meta-analysis suggests a 6–8% benefit, for instance [30]. But very few centers are able routinely, for most of their patients, to be able to apply twice-daily fractionation. The constraints on resource mean that that's not so easy. I think the greatest benefit that we have seen in the last two decades has been the introduction of novel radiation and treatment techniques. So, the doses generally are the same. So, typically in a postoperative setting, we would deliver between 60 and 66 Gy, the higher dose perhaps when there's an involved margin or there's extracapsular extension from a resected lymph node; 60–66 Gy, given in daily doses of between 1.8 and 2.0 Gy per fraction. So that's so-called conventional dose fractionation [3, 31]. But now the change has been away from the old type of radiotherapy, which would be considered to be 2-dimensional radiation, going through 3-dimensional radiotherapy. So, computerized planning and insertion of blocks that would conformally shape the radiation beam or, later, multileaf collimators to shape the beam to try to spare normal tissues, that we've now got to a much more refined form of treatment, where intensity-modulated radiotherapy or volumetric modulated arc radiotherapy, so IMRT or VMAT, as they are called, are now seen as the gold standards of treatment in the vast majority of centers across the world. And these have been demonstrated to improve toxicity burden of treatment, making treatment more tolerable both in the acute phase, less obvious in that regard, but particularly in terms of late toxicities. A number of key publications, sparing of salivary toxicity, sparing of swallowing function, for instance. We know that these high-quality radiation techniques and better conformality of dose is associated also with improved overall survival when compared with old-fashioned radiation techniques, so there's been a real move towards novel radiation techniques which now would be regarded as gold standard [3, 31–35]. I want to just mention very briefly, of course, we've got the awareness now and increased availability of proton beam therapy, and the role of that in the postoperative adjuvant setting, I think, remains to be defined clearly. But there will be a number of scenarios where that may well be seen as being a good option, especially for patients where there will be no concomitant delivery of drug therapy, and so you're relying upon the radiation therapy to do the heavy lifting and to control the disease. So, I think in closing, I guess I would say that adjuvant radiation alone can be a really important—and is a really important—treatment and can improve cure rates. But there is no question that where possible and where tolerable, the addition of concomitant and systemic therapies—gold standard being cisplatin—those improve to a greater extent the overall survival [1], and we should certainly not miss opportunities to apply those treatments for our patients.

Robert, we're now just going to move on, if we may, and just think about the use of non–cisplatin-based treatment

regimens being used in the patients who are cisplatin ineligible but who still have high-risk disease in the adjuvant space. Could you perhaps give us an idea of what are the ongoing trials that are being done or have even perhaps completed recruitment in this area, and what can we look for in the future?

[33:48] Robert Haddad: Yeah. And as I mentioned before, Kevin, this is an area of unmet need, and this is why there are a number of clinical trials that are trying to address this question of adjuvant treatment for both platinum-eligible and platinum-ineligible patients. And there are many trials in this adjuvant setting, and these trials are really looking at high-risk populations who've had surgery first and then have a positive margin or extranodal extension, and a number of interventions are being looked at [36, 37]. Those include, of course, immunotherapy—the checkpoint inhibitors, PD-1 or PD-L1 inhibitors—and looking at the combination of those with radiation and chemoradiation [38]. We know that in the definitive setting, those interventions were not successful, but there are ongoing efforts to look at these agents in the adjuvant setting. There are also efforts to look at cetuximab with docetaxel with IMRT, one of the RTOG trials [39]. And along the same lines, Kevin, I'm going to take this up further into maybe broader questions, and maybe you can just give us a quick sense of what is going on in the treatment of locally advanced squamous cell carcinoma of the head and neck. Where is the field today, and in terms of clinical trials and investigation for those patients—adjuvant but also definitive?

[35:15] Kevin Harrington: Yeah, I mean, it's a very interesting and active area, at the moment, Robert. There's another very interesting approach, which is an intratumoral or intranodal injection of a hafnium dioxide nanoparticle. This is in the form of the NANORAY-312 study, and in that study, patients who are platinum ineligible are receiving either radiation or radiation plus cetuximab with or without the injection of the hafnium dioxide particle. And again, that study is currently recruiting [40]. In terms of the adjuvant situation, we've seen a press release at least, and we await the full data from the IMvoke010 study, which sought to use adjuvant atezolizumab, an anti–PD-L1 monoclonal antibody, in patients who had completed definitive treatment, be that chemoradiation or surgery followed by adjuvant therapy [38]. And those data have already been press released and, regrettably, that study did not show a benefit in patients [41]. There are a number of studies that are ongoing in the neoadjuvant space, and in particular, I would reference studies such as the REDUCTION-I study, which involves tislelizumab [42]. So, in the neoadjuvant setting, there are three studies at least that are ongoing. So, the REDUCTION-I, the Illuminate-2, and the KEYNOTE-689 studies, for instance, and the KEYNOTE-689 study, as many of the listeners may be aware, involves both neoadjuvant and then adjuvant pembrolizumab in patients treated with surgical intent [42–44].

And maybe now we can, just as we come to a close, look towards future directions. And maybe I could ask you, Robert, what do you think the future will hold for patients with resected high-risk locally advanced squamous cell carcinoma who are ineligible to receive cisplatin? So, again, returning to this ineligible population.

[37:31] Robert Haddad: Yeah, Kevin, so really, a number of trials are addressing this question, as stated before. The Intergroups are also interested in this area. There's a look at addition of cetuximab-docetaxel to radiation. That's one of the RTOG trials that's addressing this question [39]. I had mentioned this before. So, immunotherapy is an area of interest [38]. Cetuximab is an area of interest [29]. Unfortunately, I expect it's going to be some time before we see a change in the standard of care, as many of these trials are going to take a few years to complete. So, on the short term, I expect that cisplatin continues to be the standard of care for the patients that are platinum eligible, and for those patients who are not platinum eligible, we really strongly encourage enrolling patients on clinical trials, as we need to advance this field and address this question of what is the best treatment for those patients. But short of a clinical trial, we hope that we have given the listeners the menu of options of drugs that can be used for those patients who are not cisplatin eligible.

[38:46] Kevin Harrington: So, as we bring this to a close, I'd just like to try and distill—both of us, maybe, just to distill—some take-homes from this. So, I think maybe the first thing is a recognition that since the mid-2000s, over the last 20 years, adjuvant cisplatin-based chemoradiation has been the standard of care for patients with resected high-risk disease [1, 3]. But for those in whom there is high-risk disease, but they are ineligible to receive platinum, we really still have quite limited options, and there is a big unmet need that we need to address. And coming to that point of cisplatin ineligibility, we've, I hope, summarized that there are some absolute criteria, and then there are more relative contraindications that are related to preexisting comorbidities and the likelihood of developing long-term platinum-related toxicities [4, 8, 9, 17, 18, 21]. But these criteria are really rather more difficult to define, and actually, they are not necessarily applied in the same standardized way across the world.

[40:05] Robert Haddad: Yeah, great points, Kevin, and I will conclude by saying, you know, thank you for joining me on this podcast—and for the listeners, I really want to thank you for listening to this podcast—and really, Kevin and I try to just stimulate this conversation. We wanted investigators,

physicians, to be mindful of this group of patients that are cisplatin ineligible as a group of unmet need. And I hope that we gave you a flavor in this podcast of how Kevin and I think about these patients and also present to you what's currently being done in terms of clinical trials for these patients. And we always encourage that for this group of patients, participation in trials is essential and is key as we seek to advance the field. So, think about this group of patients as a group of patients that are really in need for new interventions and new drugs, and try as much as you can to refer these patients for clinical trials that might be available to you in the area that you are practicing. Thank you for joining us in this podcast and looking forward to chatting further down the road. Thank you.

[41:18] Kevin Harrington: Thanks, indeed, Robert.

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References

1. Machiels JP, René Leemans C, Golusinski W, Grau C, Licitra L, Gregoire V. Squamous cell carcinoma of the oral cavity, larynx, oropharynx and hypopharynx: EHNS-ESMO-ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2020;31(11):1462–75. https://doi.org/10.1016/j.annonc.2020.07.011.
2. Psyrri A, Rampias T, Vermorken JB. The current and future impact of human papillomavirus on treatment of squamous cell carcinoma of the head and neck. Ann Oncol. 2014;25(11):2101–15. https://doi.org/10.1093/annonc/mdu265.
3. National Cancer Comprehensive Network. NCCN Clinical Practice Guidelines in Oncology. Head and Neck Cancers. V1.2024.
4. Espeli V, Zucca E, Ghielmini M, et al. Weekly and 3-weekly cisplatin concurrent with intensity-modulated radiotherapy in locally advanced head and neck squamous cell cancer. Oral Oncol. 2012;48(3):266–71. https://doi.org/10.1016/j.oraloncology.2011.10.005.
5. Lee YG, Kang EJ, Keam B, et al. Treatment strategy and outcomes in locally advanced head and neck squamous cell carcinoma: a nationwide retrospective cohort study (KCSG HN13-01). BMC Cancer. 2020;20(1):813. https://doi.org/10.1186/s12885-020-07297-z.
6. Kong A, Chiu G, Shah SR, et al. Patient characteristics and treatment patterns of newly diagnosed locally advanced head and neck squamous cell carcinoma (LA HNSCC): a retrospective cohort analysis of real-world data in England. Ann Oncol. 2022;33(Suppl. 7):Abstract 682P.
7. US Food and Drug Administration. Cisplatin prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/018057s092lbl.pdf. Accessed 01 Dec 2023.
8. Porceddu SV, Scotté F, Aapro M, et al. Treating patients with locally advanced squamous cell carcinoma of the head and neck unsuitable to receive cisplatin-based therapy. Front Oncol. 2019;9:1522. https://doi.org/10.3389/fonc.2019.01522.
9. Szturz P, Cristina V, Herrera Gómez RG, Bourhis J, Simon C, Vermorken JB. Cisplatin eligibility issues and alternative regimens in locoregionally advanced head and neck cancer: recommendations for clinical practice. Front Oncol. 2019;9:464. https://doi.org/10.3389/fonc.2019.00464.
10. Kiyota N, Tahara M, Mizusawa J, et al. Weekly cisplatin plus radiation for postoperative head and neck cancer (JCOG1008):

a multicenter, noninferiority, phase II/III randomized controlled trial. J Clin Oncol. 2022;40(18):1980–90. https://doi.org/10.1200/jco.21.01293.
11. Ang KK. Concurrent radiation chemotherapy for locally advanced head and neck carcinoma: are we addressing burning subjects? J Clin Oncol. 2004;22(23):4657–9. https://doi.org/10.1200/jco.2004.07.962.
12. Astolfi L, Ghiselli S, Guaran V, et al. Correlation of adverse effects of cisplatin administration in patients affected by solid tumours: a retrospective evaluation. Oncol Rep. 2013;29(4):1285–92. https://doi.org/10.3892/or.2013.2279.
13. Noronha V, Joshi A, Patil VM, et al. Once-a-week versus once-every-3-weeks cisplatin chemoradiation for locally advanced head and neck cancer: a phase III randomized noninferiority trial. J Clin Oncol. 2018;36(11):1064–72. https://doi.org/10.1200/jco.2017.74.9457.
14. Lokich J, Anderson N. Carboplatin versus cisplatin in solid tumors: an analysis of the literature. Ann Oncol. 1998;9(1):13–21. https://doi.org/10.1023/a:1008215213739.
15. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567–78. https://doi.org/10.1056/NEJMoa053422.
16. Patil VM, Noronha V, Menon N, et al. Results of phase III randomized trial for use of docetaxel as a radiosensitizer in patients with head and neck cancer, unsuitable for cisplatin-based chemoradiation. J Clin Oncol. 2023;41(13):2350–61. https://doi.org/10.1200/jco.22.00980.
17. Ahn MJ, D'Cruz A, Vermorken JB, et al. Clinical recommendations for defining platinum unsuitable head and neck cancer patient populations on chemoradiotherapy: a literature review. Oral Oncol. 2016;53:10–6. https://doi.org/10.1016/j.oraloncology.2015.11.019.
18. Kim SS, Liu HC, Mell LK. Treatment considerations for patients with locoregionally advanced head and neck cancer with a contraindication to cisplatin. Curr Treat Options Oncol. 2023;24(3):147–61. https://doi.org/10.1007/s11864-023-01051-w.
19. Colevas AD, Lira RR, Colevas EA, et al. Hearing evaluation of patients with head and neck cancer: Comparison of Common Terminology Criteria for Adverse Events, Brock and Chang adverse event criteria in patients receiving cisplatin. Head Neck. 2015;37(8):1102–7. https://doi.org/10.1002/hed.23714.
20. Crona DJ, Faso A, Nishijima TF, McGraw KA, Galsky MD, Milowsky MI. A systematic review of strategies to prevent cisplatin-induced nephrotoxicity. Oncologist. 2017;22(5):609–19. https://doi.org/10.1634/theoncologist.2016-0319.
21. Lacas B, Carmel A, Landais C, et al. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 107 randomized trials and 19,805 patients, on behalf of MACH-NC Group. Radiother Oncol. 2021;156:281–93. https://doi.org/10.1016/j.radonc.2021.01.013.
22. Haehl E, Rühle A, David H, et al. Radiotherapy for geriatric head-and-neck cancer patients: what is the value of standard treatment in the elderly? Radiat Oncol. 2020;15(1):31. https://doi.org/10.1186/s13014-020-1481-z.
23. Verdonck-de Leeuw IM, Buffart LM, Heymans MW, et al. The course of health-related quality of life in head and neck cancer patients treated with chemoradiation: a prospective cohort study. Radiother Oncol. 2014;110(3):422–8. https://doi.org/10.1016/j.radonc.2014.01.002.
24. Rettig EM, D'Souza G, Thompson CB, Koch WM, Eisele DW, Fakhry C. Health-related quality of life before and after head and neck squamous cell carcinoma: analysis of the Surveillance, Epidemiology, and End Results-Medicare health outcomes survey linkage. Cancer. 2016;122(12):1861–70. https://doi.org/10.1002/cncr.30005.
25. Herrmann J, Yang EH, Iliescu CA, et al. Vascular toxicities of cancer therapies: the old and the new—an evolving avenue. Circulation. 2016;133(13):1272–89. https://doi.org/10.1161/CIRCULATIONAHA.115.018347.
26. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. N Engl J Med. 2004;350(19):1945–52. https://doi.org/10.1056/NEJMoa032641.
27. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N Engl J Med. 2004;350(19):1937–44. https://doi.org/10.1056/NEJMoa032646.
28. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501). Head Neck. 2005;27(10):843–50. https://doi.org/10.1002/hed.20279.
29. Machtay M, Torres-Saavedra P, Thorstad WL, Nguyen-Tan PF, Siu LL, Holsinger FC, et al. Randomized phase III trial of postoperative radiotherapy with or without cetuximab for intermediate-risk squamous cell carcinoma of the head and neck (SCCHN): NRG/RTOG 0920. Int J Radiat Oncol Biol Phys. 2023;117(4): Abstract LBA 01.
30. Pignon JP, Bourhis J, Domenge C, Designé L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet. 2000;355(9208):949–55.
31. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol. 2011;12(2):127–36. https://doi.org/10.1016/s1470-2045(10)70290-4.
32. Kearney M, Coffey M, Leong A. A review of image guided radiation therapy in head and neck cancer from 2009–201—best practice recommendations for RTTs in the clinic. Tech Innov Patient Support Radiat Oncol. 2020;14:43–50. https://doi.org/10.1016/j.tipsro.2020.02.002.
33. Buciuman N, Marcu LG. Adaptive radiotherapy in head and neck cancer using volumetric modulated arc therapy. J Pers Med. 2022;12(5):668. https://doi.org/10.3390/jpm12050668.
34. Kam MK, Leung SF, Zee B, et al. Prospective randomized study of intensity-modulated radiotherapy on salivary gland function in early-stage nasopharyngeal carcinoma patients. J Clin Oncol. 2007;25(31):4873–9. https://doi.org/10.1200/jco.2007.11.5501.
35. Pow EH, Kwong DL, McMillan AS, et al. Xerostomia and quality of life after intensity-modulated radiotherapy vs. conventional radiotherapy for early-stage nasopharyngeal carcinoma: initial report on a randomized controlled clinical trial. Int J Radiat Oncol Biol Phys. 2006;66(4):981–91. https://doi.org/10.1016/j.ijrobp.2006.06.013.
36. Matzinger O, Viertl D, Tsoutsou P, et al. The radiosensitizing activity of the SMAC-mimetic, Debio 1143, is TNFα-mediated in head and neck squamous cell carcinoma. Radiother Oncol. 2015;116(3):495–503. https://doi.org/10.1016/j.radonc.2015.05.017.
37. Thibault B, Genre L, Le Naour A, et al. DEBIO 1143, an IAP inhibitor, reverses carboplatin resistance in ovarian cancer cells and triggers apoptotic or necroptotic cell death. Sci Rep. 2018;8(1):17862. https://doi.org/10.1038/s41598-018-35860-z.
38. ClinicalTrials.gov. A study of atezolizumab (anti-Pd-L1 antibody) as adjuvant therapy after definitive local therapy in patients with high-risk locally advanced squamous cell carcinoma of the head and neck. https://clinicaltrials.gov/ct2/show/NCT03452137. Accessed 01 Dec 2023.

39. ClinicalTrials.gov. Testing docetaxel-cetuximab or the addition of an immunotherapy drug, atezolizumab, to the usual chemotherapy and radiation therapy in high-risk head and neck cancer. https://clinicaltrials.gov/ct2/show/NCT01810913. Accessed 18 Aug 2024.
40. Yom SS, Takacsi-Nagy Z, Liem X, et al. NANORAY-312: a phase III pivotal study of NBTXR3 activated by investigator's choice of radiotherapy alone or radiotherapy in combination with cetuximab for platinum-based chemotherapy-ineligible elderly patients with locally advanced HNSCC. Int J Radiat Oncol Biol Phys. 2022;114(3 Suppl):e313.
41. Wong DJ, Fayette J, Teixeira M, et al. IMvoke010: a phase III, double-blind randomized trial of atezolizumab after definitive local therapy vs placebo in patients with high-risk locally advanced squamous cell carcinoma of the head and neck. Cancer Res. 2024;84(7_Supplement):CT009.
42. ClinicalTrials.gov. Tislelizumab combined with chemotherapy followed by surgery versus up-front surgery in resectable head and neck squamous cell carcinoma (REDUCTION-I). https://clinicaltrials.gov/ct2/show/NCT05582265. Accessed 16 Aug 2024.
43. ClinicalTrials.gov. Neoadjuvant anti-PD-1 and TP versus TPF on pathological response in OSCC. https://clinicaltrials.gov/ct2/show/NCT05125055. Accessed 16 Aug 2024.
44. ClinicalTrials.gov. Study of pembrolizumab given prior to surgery and in combination with radiotherapy given post-surgery for advanced head and neck squamous cell carcinoma (MK-3475-689). https://clinicaltrials.gov/ct2/show/NCT03765918. Accessed 16 Aug 2024.