Dr. Linda Yin:

Hello everyone and welcome to another episode of ENT in a nutshell, I will be your host. My name is Linda Yin. And I am joined today by Dr. Carol Bradford who is a head and neck surgeon. Dr. Bradford, thank you so much for coming on the show.

Dr. Carol Bradford:

Thank you. I'm really delighted to be here.

Dr. Linda Yin:

So today we're going to talk about Merkel cell carcinomas, which is a rare cutaneous malignancy. And although this can occur in sun exposed areas of the body and anywhere in the body really, for the purposes of this talk we're going to be focusing on the head and neck region. So, Dr. Bradford, when a patient comes to your clinic who might have a Merkel cell carcinoma, what is the typical presentation?

Dr. Carol Bradford:

So the typical presentation of a Merkel cell carcinoma is a firm purplish or reddish nodule on the skin. This lesion is usually non tender, and it's usually solitary. The epidermal changes can actually be quite subtle, and the lesion could even look like a subcutaneous mass with normal overlying skin. When we ask the patient about the history, they might note rapid growth. And usually the primary lesion is again, solitary and pretty small, less than two centimeters. And as a reminder, the head and neck region and the extremities are by far the most common sites of disease. The trunk is pretty unlikely, and we really think that that's related to sun exposure.

Dr. Linda Yin:

With this in mind, when a patient comes to see you, what sort of physical exam will you perform when you focus on assessing the Merkel cell?

Dr. Carol Bradford:

So you want to begin by assessing the primary lesion, its size. I always think it's good to palpate the lesion and assess its mobility, see if it's free from underlying tissues, things like the parotid gland or how close is it to any bone or cartilage of the nose or what have you. It's also really, really important because Merkel cell carcinoma can spread to the regional lymph nodes, do a very, very careful lymph node exam palpating the parotid basin and the cervical basins both in the front of the neck as well as posteriorly.

Dr. Linda Yin:

Now I understand that Merkel cell cancer is fairly rare. But can you tell us a little bit about the epidemiology. For example, what does that typical patient that comes to see you with Merkel cell look like?

Dr. Carol Bradford:

So it is a pretty rare tumor. It does occur in older patients. The most typical presentation, although not exclusively, is an elderly Caucasian male. And it turns out that Merkel cell cancers are much more common in people over the age of 65. In fact, a remarkable 24 times more common. And is more common in men than in women. And like many other forms of skin cancer, it's a rare malignancy but its incidence is definitely on the rise.

Dr. Linda Yin:

Now, we already talked about some risk factors for disease, outside of age and race, are there any other risk factors that can predispose someone to develop a Merkel cell cancer?

Dr. Carol Bradford:

So we already talked about sun exposure, and so sun exposure is really a risk for almost all forms of skin cancer. A unique risk for Merkel cell carcinoma, it's related to other skin cancers, but it's pretty prominent in Merkel cell cancer is a history of immunosuppression. For example, due to a previous transplant, organ, bone marrow, et cetera, other immunosuppressed conditions like HIV, and other hematologic malignancies. And these are really very significant risk factors for Merkel cell carcinoma. For those of you who like to remember mnemonics, AEIOU is sometimes used to remind learners of the risk factors and features of Merkel cell cancer. So asymptomatic for A, E is expanding rapidly, I is for immuno suppression, O is older than 50, and U is for UV exposed skin. And notably about 90% of patients with Merkel cell carcinoma have at least three of these five characteristics.

Dr. Linda Yin:

Now when a patient presents to you with these signs and symptoms, you're of course thinking and worrying about a Merkel cell cancer, but what else might be on your differential diagnosis?

Dr. Carol Bradford:

So that's a great question. It's really always important to think about all the things this could represent. So the three most common forms of cutaneous malignancy are basal cell carcinoma, squamous cell carcinoma, and melanoma. And so these are all in the differential diagnosis. But I again, especially, and each of these lesions has its own clinical presentation, but especially when it's a purplish, bluish or red nodule, that's pretty characteristic and none of the other tumors look exactly like a Merkel cell carcinoma. And you want to, when it's reddish or bluish, you definitely want to consider, especially in an older patient, Merkel cell carcinoma.

There are other benign lesions that can also be in the differential when you have a nodular lesion. Those could be an epidermoid cyst, a sebaceous cyst, even a fatty tumor, which usually does not have overlying skin changes, or benign cutaneous lesion like a pyogenic granuloma, which curiously actually is red and fleshy as well.

Dr. Linda Yin:

Okay. Let's move on to talk a little bit about pathophysiology now. So the question of the day is, what exactly is a Merkel cell?

Dr. Carol Bradford:

Well, that is a great question. So a little bit of history. It's named after a German anatomist by the name of Friedrich Merkel, who first described Merkel cells. Microscopically they appear as pale large cells in the basal layer of the epidermis. They form synapses with enlarged nerve terminals of sensory nerve fibers. Merkel cells function as McCanna receptors that are part of the neuroendocrine system. So embryologically they have a neural crest origin. And really a Merkel cell carcinoma is really a neuroendocrine carcinoma of the skin.

Dr. Linda Yin:

So how does a Merkel cell turn into a Merkel cell carcinoma? Or does it even derive from a Merkel cell?

Dr. Carol Bradford:

That is a fabulous question. So while Merkel cell carcinomas are neuroendocrine malignancies, it's not clear exactly which cell they arise from. They may arise from Merkel cells, but they could also arise from dermal fibroblasts that enter the Merkel cell differentiation pathway. So the bottom line is the pathogenesis of Merkel cell carcinoma is very complex and really not fully understood. And what's interesting is that in the last decade, we've really had an increased understanding of the causes of Merkel cell carcinoma. And a pretty dramatic discovery was made not very long ago, such that a virus called the Merkel cell polyomavirus is believed to cause the majority of Merkel cell carcinoma cases in the United States. Up to about 80%. And it's actually this viral etiology. And again, my understanding and is the link to perhaps the immunosuppressed post status.

Dr. Linda Yin:

That makes a lot of sense. So yeah, we can't talk about Merkel cell without talking about the polyomavirus. So can you tell me what this virus is and how does one get it?

Dr. Carol Bradford:

Well, that's again, a fabulous question. So this particular virus was only discovered in 2008. I would have actually guessed more recently, so it's just over 10 years ago. The Merkel cell polyomavirus is a double stranded DNA virus. The primary infection with this virus is not actually believed to cause any signs or symptoms. In general in fact, polyomaviruses do not cause illness in healthy patients, but may be associated with disease in immunocompromised patients. The primary infection likely occurs in childhood. The route of transmission is largely unknown, but fecal oral transmission has been considered as the virus can be found in the GI tract. In older patients or immunosuppressed patients, the polyomavirus genome is thought to integrate itself into the host genome, leading to changes in host gene expression that eventually leads to cancer. Integration is a rare event in polyomavirus infection. And it's really not known why integration occurs in some people, but not others. And curiously, some of this integration yes or no can also be said of another head and neck viral infection we all know pretty well, which is human papilloma virus.

Dr. Linda Yin:

Yes, there are a lot of interesting parallels here. But on pathology, this is a very different tumor than a squamous cell. Right? So you mentioned this as a neuroendocrine tumor. So what does a Merkel cell carcinoma look like on pathology?

Dr. Carol Bradford:

So it looks like a high grade aggressive neuroendocrine tumor. And what that means is that there is a high density of small blue round cells or small round blue cells. And we all know there's a bunch of small round blue cell neoplasms. And these cells have large nuclei scant cytoplasm and high rates of mitosis, apoptosis and necrosis. Really importantly, there is a immunohistochemical marker that's a highly sensitive marker, CK 20 or cytokeratin 20. And other neuroendocrine markers are positive, including neuron specific enolase, synaptophysin and chromogranin A. But that CK 20 is the most sensitive marker and is very specific for Merkel cell carcinoma.

Dr. Linda Yin:

Great. Let's talk a little bit about workup. So, after evaluating a patient clinically who has Merkel cell, we're going to need to stage the tumor. What imaging modalities are you using to help us stage that tumor?

Dr. Carol Bradford:

It's interesting and as we all know, how many imaging studies to order at the outset versus using sentinel lymph node biopsy to be the primary staging modality is really, really important. So because it is a rare tumor, there really is no consensus on the best imaging modality for diagnosis. My preference would be to begin with sentinel lymph node biopsy, which is both a regional staging modality, but also gives tremendous prognostic information. And then again, in my own practice I would typically reserve systemic imaging with PET scan MRIs or CT scans to patients who have more advanced stage of disease with node positivity.

Dr. Linda Yin:

Yeah. So let's talk about the patient that presents with an N zero neck. So what is the risk of having an occult node metastasis in a patient that comes in with a Merkel cell that seemingly has a negative neck?

Dr. Carol Bradford:

So, about 25% to 30% of patients presenting with clinically apparent nodal disease at presentation, so a third will have palpable nodes, and another 16% to 38% actually present with occult nodal disease. So in all, there's a pretty high risk of nodal disease in all and several lymph node biopsy to stage the N zero neck is really considered the standard of care in patients. And that's also consistent with the NCCN guidelines.

Dr. Linda Yin:

So can you educate us on what a sentinel lymph node biopsy is? I know you've done quite a bit of work with this for all cutaneous malignancies. How are you using it in Merkel cell?

Dr. Carol Bradford:

So, sentinel lymph node biopsy is really a very useful tool to stage the regional nodal basin in a number of cutaneous malignancies, specifically melanoma. Occasionally a growing role in squamous cell carcinoma of the skin, but it plays a key role in Merkel cell carcinoma. So preoperatively patients undergo a lymphoscintigram whereby a radioactive tracer is injected around the primary site, this is usually done in nuclear medicine, and pictures are taken, many times high resolution images are gathered, and what happens is those that radionuclide tracer die basically goes to the primary echelon or sentinel training node or nodes. And then the patient is brought to the operating room where a radioactive probe is used to identify the draining nodal, the specific nodes.

Many of us also add dye such as methylene blue, or Isosulfan blue dye, also injected around that primary site in the intradermal space to co-localize with the radioactive dye. And so what we're really looking for is those regional lymph nodes that are both hot, meaning radioactive and blue. And then those [inaudible 00:17:01] node or nodes, the sentinel nodes will be removed completely without rupture and sent to the pathologist for serial sectioning and immunostaining to look for signs of spread of Merkel cell to the lymph node.

Dr. Linda Yin:

We'll go into management a little bit later and talk about exactly what to do, but what is your typical understanding of the role that the sentinel lymph node biopsy plays in prognosis and in further steps of management?

Dr. Carol Bradford:

So, the status of the sentinel lymph node is clearly important staging tool because it indicates whether patients are N zero or N positive. But its ability to predict disease prognosis remains a bit less clear. And it's a little bit more controversial. And it's also unclear because, again, this is a rare tumor. There's not the robust body of evidence there are far more common types of cutaneous malignancies. So the real question is, if there is this positive sentinel lymph node, is the treatment paradigm? And again, we'll talk more about that. Is it completion neck dissection or radiation therapy? But I do think that accurate staging of all malignancies, including Merkel cell, and appropriate treatment of the sites of disease are the best ways we can to offer our patients the best chance to be cured, and I do think has some impact upon prognosis.

Dr. Linda Yin:

Let's talk about staging now. So NCCN guidelines and AJCC staging can get quite complicated, but can you give us a general framework to think about how Merkel cell is staged?

Dr. Carol Bradford:

Yes. We all love staging and for many complex staging systems, I think it's actually fair game to have a little laminated card in one's pocket. Because I think we want to make sure we're always staging patients accurately. And many cutaneous malignancy staging is pretty complicated. So stage one tumors are T1N0M0. This one's the easiest one, which means that the primary tumor is less than two centimeters in diameter, and there is no nodal or distance spread. Stage 2A tumors are T2, or T3N0M0. So more than two centimeters and less than five centimeters for a T2 and greater than five centimeters for a T3 but again, they're 2A because of that N0M0.

Stage 2B tumors are T4, which are locally advanced but are still N0M0, meaning no nodal or distant disease. Stage 3A tumors are the ones with occult nodal metastasis detected by sentinel lymph node and this is where that sentinel lymph node biopsy is really important in detecting micro metastatic disease, which is clinically occult. Stage 3B tumors have clinically apparent nodal disease, so N positive palpable nodal disease or in transit metastasis. And then finally, stage four tumors are patients who have distant metastatic disease.

Dr. Linda Yin:

And before we go on to talk about management, now with the Merkel cell polyomavirus, there are a lot of serology tests coming out, sometimes patients come with them. What does this mean? And how should we be using this in our workup?

Dr. Carol Bradford:

You know, great question. And this is actually a very new area and it's a very active area of research. So the current NCCN guidelines do state that polyomavirus oncoprotein antibodies can be considered part of the initial workup. There are actually two different types of antibodies commonly detected in Merkel cell cancer patients. VP1 is a major capsid protein detected in a high proportion of healthy adults, but more frequently in Merkel cell cancer patients. And it turns out again, this is newer work that patients

with high VP1 antibodies may actually have a better prognosis. And zero negative patients may have a higher risk of recurrence.

A second antibody is against the T antigen, and T antigens are regulatory proteins from the polyomavirus with oncogenic potential. Antibodies against the T antigens may be a sign of tumor burden and more advanced disease progression.

Dr. Linda Yin:

Still very early and sort of difficult to interpret. Let's talk about some things that we have a better grasp on. So we alluded to the fact that this is a highly aggressive tumor. What is the general prognosis like for this disease without treatment?

Dr. Carol Bradford:

So without treatment like most aggressive malignancies, without treatment this cancer has a very poor prognosis, especially compared to other cutaneous malignancies. And further, Merkel cell carcinoma of the head and neck region appears to have a worse prognosis than Merkel cell carcinomas from other body sites. Meta analyses have shown that at least half of Merkel cell cancer patients develop lymph node metastasis at some point over the course of their illness, and up to a third will actually develop distant metastases. And the most common sites of distant metastases include the bones, lungs, and liver.

Unfortunately, recurrence rates are also quite high in this disease and can be up to 50% of all cases. On the more positive note, local disease control rates at five years are about 80%. Regional disease does actually decrease the five year survival of patients to about 50%. So that really reflects on the importance of the sentinel lymph node biopsy for patients with occult nodal disease because it has a big impact upon survival rates. And patients with distant metastatic disease really have quite a poor five year survival rate at about 10% to 20%.

Dr. Linda Yin:

So at your institution, or at most institutions, I should say, how is the best way to manage Merkel cell carcinoma?

Dr. Carol Bradford:

Well, that's a really great question. I'm proud to say that I was part of one of the first Merkel cell tumor boards, multidisciplinary tumor boards launched in the country, and the group at my institution was, I think, pivotal in really providing very early guidance about treatment algorithms for this disease. So like in many cancer teams, it's important to have surgeons for purple cell of the head and neck that's oftentimes an otolaryngologist head and neck surgeon. Medical and radiation oncologists are key members of our multidisciplinary team, plus pathologists, and radiologists, and many times nurses, social workers and other members of our interdisciplinary teams.

Dr. Linda Yin:

Let's get into some details. So for Merkel cell cancer that is localized and without regional spread, what is the standard of care treatment?

Dr. Carol Bradford:

So the primary treatment of the vast majority of Merkel cell cancers who, unless there's very extensive distant disease burden, but the primary modality is surgery. So typically that would be surgical resection, wide local excision with generous margins approximately two centimeters to even three centimeters, but three centimeters as we all know is hard to achieve in the head and neck. Mohs microsurgery may be an alternative but I'll state for this audience that I personally prefer wide local excision in this case. We would definitely recommend that sentinel lymph node biopsy for regional staging be offered and performed and all cases of localized Merkel cell cancer without obvious nodal disease. And this is really important given what we've discussed already, which is high rates of occult nodal metastasis.

So what's interesting about Merkel cell carcinoma that's really different from melanoma is that this is actually a very radio sensitive tumor, whereas melanoma is very radio resistant. And so, when we should use adjuvant radiation therapy and localized early stage Merkel cell cancer is pretty unclear, but it's pretty effective. And so it can be used if there's sort of a more significant primary tumor, or in cases where sentinel lymph node biopsy might not be able to be performed or is not successful. But you can also use radiation therapy obviously as adjuvant therapy when there are positive regional nodes.

Dr. Linda Yin:

So in the case of localized disease, where your sentinel lymph node is negative, how do you manage these patients?

Dr. Carol Bradford:

In cases with a negative sentinel lymph node biopsy and widely clear margins at the primary site, one option could definitely just be close observation and surveillance. If there are any indications that the margins are close or it has some other aggressive features, lymphovascular invasion or et cetera, or you're worried about close margins, in those cases one can consider adding adjuvant radiation therapy, which can certainly be a useful adjunct to attaining local control.

Dr. Linda Yin:

Shifting gears now in the patient with regional disease. So either patients... Well, let's talk about both situations. So patients with obvious nodal disease and then patients with the positive sentinel lymph node biopsy, what are the next steps in management?

Dr. Carol Bradford:

Great. So with palpable nodal disease, the definitive management of the neck is neck to section and or radiation therapy. Patients who have a positive sentinel lymph node should also undergo definitive management of the neck. And like in melanoma, this is an evolving area. Especially with the radio sensitivity of this tumor type. But completion neck dissection can and should definitely be offered to patients. And patients can also again, be discussed at your multidisciplinary tumor board to discuss the role of adjuvant radiation therapy that can depend upon the extent of lymph node involvement, and presence of extra capsular extension. But it's also possible you can probably actually get pretty decent regional control. If you have a positive sentinel lymph node and you choose not to do a completion neck to section, you can add radiation therapy, and that also will likely provide very reasonable regional control. Importantly, there's really no role for adjuvant chemotherapy in the patients who are N positive. Platinum agents really have no response in this disease entity.

Dr. Linda Yin:

That brings us to the question of metastatic disease. Usually for squamous cells, we think of platinum agents and other systemic chemotherapies. How is this managed in Merkel cell?

Dr. Carol Bradford:

As in many malignancies, distant metastatic disease that is associated with a very poor prognosis, this is an active area of investigation and there are ongoing clinical trials. Because of the impact of immunosuppression, it's always a really good strategy to contact the physicians managing the immunosuppressant medications and ask if those can be minimized. Because your immune system is your greatest adjunct to helping fight the cancer.

But what's important is the now immune checkpoint inhibitors are now becoming the gold standard for metastatic Merkel cell carcinoma. And there are a number of them. Avelumab is a PD-L1 inhibitor. It's a newer one, it's a newer agent and this is actually first line therapy. And other perhaps better known immunotherapy drugs including pembrolizumab, nivolamab and ipilimumab are also effective. Again, you would want to consult with a medical oncology who would assess the risks and benefits of these treatments in the patient.

There are also some future directions on the horizon. Cellular adoptive immunotherapy with tumor infiltrating lymphocytes specific to Merkel cell polyomavirus are a very, very active and interesting area of investigation. Because there's really unknown target, it's that Merkel cell polyomavirus. So, it'll be interesting to learn how those trials pan out.

Dr. Linda Yin:

All right. And finally, after we've managed the patient with surgery or a combination of surgery and radiation on systemic therapy, how do you typically follow up with these patients after treatment?

Dr. Carol Bradford:

Surveillance is really, really important. And we as the head and neck surgeons can do that but we can also ask our dermatology colleagues and our primary care colleagues to be partners in the routine follow up of these patients. So every one of these patients needs a follow up plan and needs to be seen every three to six months for the first three years, and then typically every six to 12 months.

So a question that often arises is, when should we order routine imaging? And I would say that in the lower risk, early stage, stage one and two patients, probably those patients may not actually need routine serial imaging. But it's still important to do a careful physical exam and a robust review of symptoms and systems, and if symptoms do arise that are concerning, use those symptoms to guide staging modalities. Now patients who are N positive and have more advanced nodal disease, I think really in partnership with your medical oncology and radiation oncology teams, many of those patients may actually benefit from consideration of periodic imaging which can be CAT scanning, and or PET scanning.

And again, a new and evolving area is patients who are actually Cyril positive for Merkel cell polyomavirus oncoprotein antibodies, rising titers of the T antigen antibody may actually be an early sign of recurrence. So in this case, that actually could be a very specific serologic or blood test that would be consistent with recurrence, and that would also then guide a search for recurrent disease. So fascinating area of investigation with lots of progress being made in this unusual tumor, but one that is growing a bit and its prevalence.

Dr. Linda Yin:

Interesting indeed. Yes. So those were all of the questions that I had about Merkel cell cancer. Is there anything else that you want to emphasize for the listener, anything that we haven't appropriately covered?

Dr. Carol Bradford:

So I think it might be helpful to just sort of complete our session together with, what are the take home points for Merkel cell? So Merkel cell is a fairly unusual tumor. It's really a red fleshy tumor that occurs most typically in older men, but also can occur in immunosuppressed patients. We believe it is caused by the Merkel cell polyomavirus in the vast majority of cases. Merkel cell has a very high rate of nodal involvement with roughly a quarter or a third of the cases being palpable, and another quarter or third being occult. So for patients with no palpable regional nodal disease, sentinel lymph node biopsy really plays a key role in staging the disease and defining the treatment paradigm.

So, surgery is the main state of treatment, wide local excision of the primary to attain widely clear surgical margins, and management of the regional base in either via the staging modality of sentinel lymph node biopsy or for node positive disease, therapeutic lymph node dissection, which may include parotid for those lesions that drain through the parotid basin and neck dissection. But also, radiation therapy in this radio responsive tumor plays a very important role in more advanced primary tumors and advanced nodal disease.

And finally, distant metastatic disease has a poor prognosis, but there's actually been meaningful progress in this regard with immunotherapy or immune checkpoint inhibitors. So there's a lot of growing promise in the treatment of this disease. Thank you.

Dr. Linda Yin:

Yes. Thank you so much for being here, Dr. Bradford, I appreciate your time and I definitely learned a lot and I hope the listener does as well.

Dr. Carol Bradford:

Well, thank you so much. It's really been a true honor and privilege to participate in this educational podcast on Merkel cell carcinoma. Thank you so much.

Dr. Linda Yin:

All right. And usually we would do a summary section here, but because Dr. Bradford gave such a great summary of the key points in the talk, I think we'll go ahead and go straight into your question and answer session. So, now I'll provide some questions that highlight some key points and I'll give a brief pause and then I will provide the answers. So, what are the hallmark risk factors and signs of Merkel cell carcinoma?

The major hallmarks and signs of Merkel cell carcinoma can be remembered by the mnemonic AEIOU. A stands for asymptomatic, E stands for expanding rapidly, I stands for immunosuppression, O stands for older than 50 and U stands for a UV or sun exposed skin. More than 90% of patients with Merkel cell will have at least three of these five characteristics.

What type of cell is a Merkel cell?

A Merkel cell is a mechanoreceptor. That means that they live in the basal layer of the epidermis and they form synapses with the nerve terminals of sensory nerve fibers. When touch occurs on the skin, the Merkel cells are able to sense this and then transmit the signal down the axon of the sensory nerve back to the central nervous system.

What is the typical appearance of Merkel cell carcinoma on pathology?

Merkel cell carcinoma appears as a high grade aggressive neuroendocrine tumor on pathology. This means that it has small round blue cells and this can form a trabecular or a sheet like pattern. There are high rates of mitosis and apoptosis and necrosis and the hallmark marker on immunohistochemistry positive for Merkel cell is CK 20.

How should we manage the N zero neck in Merkel cell carcinoma?

Merkel cell cancer has a very high rate of occult metastasis and therefore according to NCCN guidelines all patients with an N zero neck should undergo sentinel lymph node biopsy for staging. If a sentinel lymph node biopsy is positive, typically it's recommended to complete treatments for that neck either in the way of a completion neck dissection or in radiation.

Those are all my questions and that's the show, thanks for listening in and we'll see you next time.