# Melanoma and Skin Cancer Awareness

July 5, 2024

**Becca Battisfore:**

Welcome to the latest edition of the College of American Pathologist CAPcast. I'm Becca Battisfore, content specialist with the CAP. In this episode, our guest host, Dr. Gladell Paner, will be talking with experts about how the Cancer Protocols support pathologists in reporting skin cancer diagnoses.

Approximately 9,500 people in the US are diagnosed with skin cancer every day, according to the American Academy of Dermatology. Melanoma is the most serious type of skin cancer. In 2024 alone, the American Cancer Society estimates that more than 200,000 cases of melanoma will be diagnosed, as well as nearly 8,300 deaths from melanoma. Before we get into the questions, let's learn more about our guests. Dr. Paner, would you like to introduce yourself?

**Dr. Gladell Paner:**

Yes, I will. Thank you, Becca. Good afternoon everyone, and thank you for tuning in to CAPcast. I'm Gladell Paner, I'm a GU pathologist at the University of Chicago. And for the past seven years I had the opportunity to work with the cancer committee, and also with the CAP Pathology Electronic Reporting Committee, or the PERT committee.

As of now, besides doing the CAPcast, I'm also involved in creating two products for the CAP through the Council of Education. The first one is the CAP Gleason grading course. This is an educational online course. And the second is the CAP Prostate Cancer Slip Classroom Webinar. And we are scheduling these exciting products to be released at the end of this year and at the beginning of next year, so watch out for these products.

**Becca Battisfore:**

Great, and Dr. Shon?

**Dr. Won Shon:**

Hello, everyone. My name is Won Shon. I'm a pathologist at Cedars-Sinai Medical Center in LA, California, where I serve as the director for the Dermatopathology Service and Fellowship program. In the past six years, I also had the pleasure of working with the CAP Cancer Committee. And thank you for having me today.

**Becca Battisfore:**

Thank you for being here. And Dr. Kinonen?

**Dr. Chris Kinonen:**

Hello, my name is Chris Kinonen. I'm a dermatopathologist in private practice in Madison, Wisconsin. I've been practicing about 11 years. I'm actually one of four dermatopathologists in our practice. I'm fortunate to have some expert colleagues next to me. We work primarily for a large healthcare system that serves Madison, as well as a number of other hospitals and clinics in rural and urban Wisconsin. And we serve fairly robust dermatology practices, as well as a number of primary care physicians and surgeons who send skin biopsies.

**Becca Battisfore:**

Great. Thank you all for joining the podcast. Dr. Paner, I'll let you take it from here.

**Dr. Gladell Paner:**

Thank you, Becca. For this CAPcast, we're going to talk about the melanoma section and biopsy protocols. And I would like to start my question for you, Dr. Shon. CAP released these very new protocols, I think they were released on December of last year, so very fresh. My question for you is that, can you tell us why these protocols were created? And second is, can you also describe to us the process in creating these melanoma protocols?

**Dr. Won Shon:**

Similar to other CAP Cancer Protocols, we developed a melanoma protocol to help practicing pathologists provide clear and easily recognizable diagnosis and core data elements for clinical care. As you know, a synoptic format definitely enhances the consistency of reporting data elements. Although our melanoma biopsy protocol is currently optional, it is highly recommended for melanoma reporting, as the core elements are only present in the initial skin biopsy specimen, as you know.

I have to admit that creating a protocol is a pretty intense process. Like other CAP templates, we start by referencing the goal center, including key parameters for AJCC staging and WHO tumor classification terminology. The process actually starts with a Cancer Committee member who drafts the initial version, which is then reviewed by a team of expert authors, many are members of the AJCC panel or WHO authors. And then the initial draft is reviewed by the House of Delegates. We then meet to discuss the protocol, consider changes, and gather some feedback. And this feedback is incorporated, but really ensuring still alignment with the gold standards I just mentioned.

The final version undergoes another pretty rigorous QA process, I'll say. And I really want to emphasize that the Cancer Committee really ensures the protocol is applicable in various clinical settings, not just in academic environments, but also in community-based practices. Again, it is very important to note that these cancer protocols are not for research purposes. All included core required parameters are clinically relevant and actionable.

**Dr. Gladell Paner:**

Thank you, Dr. Shon. I like your explanation, and I agree with you that this is really a rigorous process. And of course, the goal is to have the optimal product and we can provide the pathologist. And to highlight one point that you made there, the review process done by the HOD, and this is very important. And also, the public review. And the reason for this is, of course, so we will have input to the creation of the protocols. Not only from expert, but also coming from the community practitioners. And we try to emphasize also the practicality of this protocols when we're using it. And just to raise a point there, you said that the excision protocol is the one that is required at this point?

**Dr. Won Shon:**

Yes.

**Dr. Gladell Paner:**

Okay. And the biopsy is only optional at this point. Thank you. Now I'd like to ask you, Dr. Kinonen, and I'm sure you're probably using this protocol, it's fairly new. Came out December, so I'm not sure if you have this already in practice. But asking you from the user's perspective as a pathologist at the other end, what benefit do you see in having melanoma reporting protocols in your practice?

**Dr. Chris Kinonen:**

Yeah, we definitely use the protocols. And I would agree with Dr. Shon, that most of the time all the material required to complete the protocols is usually in the biopsy. We use it for the biopsies, almost exclusively where most of the parameters are found. I think the protocols really help create standardized terminology so we're all using the same language, which I think has helped better align to clinical guidelines such as NCCN guidelines. I think it helps create more consistent reporting, so everyone, the pathologist, the oncologist, the surgeon, that we're all on the same page.

I think it also helps us to ensure we've dotted all our I's and crossed all our T's, and just remember to put all the required elements in a diagnosis. Cancer diagnoses have, in many ways, become more complex, and I think the protocols really help us ensure that we've included all the necessary components in the diagnosis. And overall, I think the intent of all this is that it will lead to consistently higher quality diagnoses with improved quality of care and increased patient safety.

**Dr. Gladell Paner:**

I like to emphasize what you said earlier about the use of these protocols. It's important for us to harmonize our protocols, the pathologist protocols with the clinical guidelines terminology. And I think the success of the clinical guidelines also rely on the pathology reporting protocols, because those parameters or those pathology factors are being asked in the clinical guidelines should be there, consistently being reported in this particular protocol. So you made a very good point there.

I want to go back to you, Dr. Shon. The WHO classification of skin tumors was also released last year, so fairly new. About the melanoma histologic subtypes, we know that it's further refined in this new WHO classification. Can you briefly describe the histologic subtyping of melanoma and how sun exposure matters? And why these tumors are categorized into pathways? I'm asking you also as a GU phatologist, I saw these Roman numbers one to nine, something like that. Can you please explain to us what this means?

**Dr. Won Shon:**

Yeah, sure. First of all, when I was a trainee, the cutaneous melanomas were primarily classified by their histopathologic growth pattern. However, based on the current epidemiological and molecular evidence, the new WHO classification proposes a multidimensional approach concerning the role of a UV radiation cell of origin and characteristic genomic alteration. This new classification really, as you mentioned, identifies nine distinct pathways for melanoma, with sun exposure being one of the key determinants of tumor subtype. For instance, first three pathways are linked to UV radiation as the primary mutagen, while six others have no clear relation to UV radiation.

This multidimensional pathway-based classification of melanoma clearly demonstrate that I'll say cutaneous melanoma is not a single disease, but a collection of distinct subtypes. Each differing in genetic features, clinical and histopathologic presentation, age of onset, preferred anatomic site and cell origin. However, just like other tumors, this classification is not perfect and still evolving relatively fast-paced. That's why we just keep updating our protocol.

**Dr. Gladell Paner:**

Thank you, Dr. Shon. There's a lot of differential diagnosis here, if you will. This is a question for you, Dr. Kinonen. In your practice with this histologic subtyping of melanoma, which among these subtypes or other types that are not listed here, which among these are difficult to diagnose, difficult or challenging for you to diagnose? And can you tell us, or share some of the pitfalls in making the diagnosis?

**Dr. Chris Kinonen:**

I think the main hurdle is first getting to the diagnosis of invasive melanoma regardless of the subtype, and sometimes that's very straightforward and sometimes it's very challenging. I think once you get to that, you're definitely in the invasive melanoma category. Then subtyping it, most of the time I think that fits into a small number of these subtypes. I think, at least in my practice, most of what we see is in the low cumulative sun damage category or high cumulative sun damage category. The lentigo maligna or superficial spreading melanomas. Nodular melanomas, to a certain degree desmoplastic melanomas. Similarly, I think most of the time it's usually pretty easy to put them into a category.

There is some subjectivity. For example, the difference between low cumulative sun damage and high cumulative sun damage subclassification is somewhat subjective. There's some information about the size of the solar elastotic aggregates. It is being large amorphous aggregates versus fine single fibers that can help differentiate those two. But there's going to be a spectrum, and where you draw that cutoff may be somewhat subjective. The difficult ones. I would say desmoplastic melanomas are always a treacherous pitfall, especially if you're getting a superficial biopsy, and it can be a subtle, bland looking infiltrate. That's always one to be on the lookout for.

Similarly, nevoid melanomas are one of those treacherous diagnoses that at low power looks very much like a nevus, and you have to really study at high power to get it right. There's rare ones like Spitz melanomas where maybe once or twice in my career I made the diagnosis, that would be even as a dermatopathologist one that I would probably get expert melanocytic consultation on myself. I think that one can be very difficult.

And then there's these subtypes of melanoma arising within giant congenital nevus and melanoma arising in blue nevus. I guess I would say more broadly, melanoma arising within any nevus can sometimes be difficult. It can be the case where there's obvious biphasic proliferation where there's an obvious melanoma and an obvious bland looking nevus that it may have arisen in. But sometimes this differentiation can be quite hard, and it's hard to tell if it's MIS arising in the nevus or if it's invasive melanoma. So anytime there's an associated nevus, I feel like that can present challenges.

**Dr. Gladell Paner:**

Thank you, Dr. Kinonen. The way I understand is that the difficulty really is not only in the subtyping, but from the first glance of differential diagnosis within dysplasia to melanoma, melanoma invasive or non-invasive, and then subtyping. So there's different several layers there of challenges. Subtyping is only one of those. That's the way I understand it.

**Dr. Chris Kinonen:**

I think so, yeah.

**Dr. Gladell Paner:**

Dr. Shon, I like to look the same question for you. In your opinion, in your practice, which of these subtypes or which scenario would be the most challenging for you?

**Dr. Won Shon:**

I completely agree with Dr. Kinonen. There are some tumors that even experts cannot morphologically categorize definitively. And those cases sometimes require additional molecular workups, such as utilizing NGS platform. I think that things will improve as we learn more about these tumors using, as I've just mentioned, using more advanced but accessible tools. For example, the BRAF. Testing BRAF in our training was very difficult, we need PCR or additional molecular testing. But now we have a very nice immunohistochemistry, very nice surrogate marker to just quickly check the BRAF status that in their case we can. Vast majority cases is just Spitz, non-Spitz category. We can easily test it. Although, there's a small subset of Spitz or lesions can be positive for BRAF immunochemistry. Again, just like other tumors, it's very hard to just definitely categorize it.

Desmoplastic melanoma is the one subtype can be very difficult, and sometimes it's relevant in further clinical care. For example, desmoplastic melanoma is somewhat prognostically favorable among those thick melanomas. And definitely affects, at least in our practice, affects the recommendation of a central lymph node biopsy. Which is generally if you call pure desmoplastic melanoma, surgeons generally not recommended for additional sentinel lymph node procedure. Also, some of the unusual melanoma, classifying some unusual types of melanoma such as Spitzoid or Spitz melanoma of a childhood, or I also see nevus-associated melanomas. Those actually clinically important in some situation because the standard prognostic models sometimes just do not apply to those, some are rare subtypes.

**Dr. Gladell Paner:**

I agree with that. And that's really heightened the challenge if distinction between these two entities are clinically actionable, or it matters and we have to make the call. I'm just curious, being a geopathologist, for our carcinoma subtyping we use a lot of immunochemical stains. This is a question for both of you. Are you guys using immunostains for subtyping melanoma?

**Dr. Chris Kinonen:**

I say sometimes with the desmoplastic melanoma consideration, sometimes a MART and either SOX10 or S100 can be helpful. Desmoplastic melanoma should be standing with SOX10 and S100 and not always with MART-1. So sometimes that can be helpful. Otherwise, with the subtyping there's debate whether getting things like p16 can help in Spitzoid tumors. And PRAME is used a little bit more often now, but that's more to get to a diagnosis of melanoma potentially rather than a subtype of melanoma. Probably IHC doesn't play a big role in the subtyping for me.

**Dr. Gladell Paner:**

So it's just morphology. Okay.

**Dr. Won Shon:**

There are actually different pathways, and I'm not talking about just melanoma. But when we decide to, especially when I sign up with cases with my trainees, before we decide to which pathway we're going to go, sometimes I use a BRAF. Because some of the pathway, the very first initiative driver mutation is the BRAF V600E mutation. Sometimes I use a V1 to reach pathway we are dealing with. BRAF1 or the wind pathway markers such as the beta cutaneous like a D1, sometimes helpful to narrow down to deep penetrating nevus pathway. There are some so-called surrogate immunohistochemical marker for underlying genetic aberration. But again, but as Dr. Kinonen mentioned, that first thing first, is this benign or malignant? Because that's actually the most important, right? Yeah, exactly.

**Dr. Gladell Paner:**

Thank you. Now, let's dig deep into the contents of the melanoma protocols. There are several elements that are listed, and among them is the primary tumor thickness and anatomic levels. This is a question for you, Dr. Shon. Can you explain to us the importance of Breslow thickness and Clark levels, and how these elements are derived?

**Dr. Won Shon:**

I'd like to start with the Clark level, which are defined based on micro-anatomic compartments such as papillary dermis, reticular dermis, or subcutis. Although Clark level remains pretty good independent predictor of outcome, I have say the interobserver reproducibility for assigning Clark levels is relatively poor among pathologists/dermatopathologists. For this reason, it is not used in the current AJCC staging system for PT status, and it is included in our current melanoma protocol as an optional data item.

In contrast, Breslow thickness measured vertically from the top of the epidermal granule cell layer to the deepest invasive melanoma cell is the most important parameter for prognosis, and a key element for the current AJCC staging. It should be measured in millimeters and recorded to the precision of a single digit after the decimal, such as the nearest 0.1 millimeter. There's absolutely no need to record a numerical value beyond the single digit after the decimal.

**Dr. Gladell Paner:**

And I assume you must use a micrometer to measure?

**Dr. Won Shon:**

Yes.

**Dr. Gladell Paner:**

All right. And this is a question for you, Dr. Kinonen. From your experience, what are the challenges in deriving the Breslow thickness and Clark levels? And do you have any concern for the reproducibility? And how do you handle tumors that are transfected at the deep margin or those tumors with ulceration?

**Dr. Chris Kinonen:**

Well, first of all, I would mirror Dr. Shon's comments about the Clark level. It is not always as straightforward as Breslow thickness. And there's less reproducibility, as I understand, between pathologists and picking a category. I noticed that it was not a required element, and tried not including it one time. I got a call almost immediately from the clinician who wanted to put it in there, so I've since then just included it all the time even though it's not a required element. And that you just do your best to make the estimate. And that's all I can say is I just do my best to make the estimate.

The Breslow thickness is more straightforward. As Dr. Shon said, it's from the top of the granular, it's the deepest area of invasion or the base of the ulcer to the deepest area of invasion. This is similar to what the comment earlier that I think the first step is to make that diagnosis of invasive melanoma, and I think that's such a critical step. And I think this is the next most critical step is getting the Breslow Depth right. Because as Dr. Shon said, it's such a critical component to the next steps in patient management that getting this right is really important. If you didn't subtype it correctly, it may not have much clinical impact. But if you don't get the Breslow thickness correct, it could have a big clinical impact.

What are the challenges? Finding the deepest area. I would measure multiple areas. If I have deeper levels available to me, I would take a look at several different slides to make sure I'm actually getting the deepest level present, particularly if I'm near a staging cutoff. It can be difficult, as I talked about earlier, when there's nevus also present, it could be sometimes difficult to determine exactly where the melanoma starts and stops relative to the nevus, that can present a challenge. Excluding adnexal involvement can be a challenge. Melanoma could sometimes extensively involve adnexal structures, and if there are hair follicles or eccrine glands, or whatever that are involved by melanoma. On one level, it could look like there's a dermal component. If you cut deeper into it, you would see that that is actually part of adnexal structure, that melanoma. So making sure you're excluding involvement from adnexal structures can be one of the challenges.

Similarly, you're not supposed to measure to microsatellites, you're not supposed to measure to perineural invasion. You're not supposed to measure the lymphovascular invasion. It's really just supposed to be making sure you identify those areas of true dermal invasion. Another challenge is inflammation. Dense inflammation can sometimes mask dermal melanocytes. So sometimes IHC can be helpful there to see if there's melanocytes lurking within a densely inflamed area. And then the last thing I would just say is just the mechanics itself of measuring with a micrometer. This is where it's so worthwhile to just check and double check and triple check, and make sure you're using the right objective, that you have the measurement right. This is one of those double checks just to make sure it's right. And it's an area where if I'm close to a staging cutoff, I'll get a consultation from one of my colleagues just to make sure it's correct. It's really worth spending time to do this.

And for the other question about what I do with melanomas that are transected, I just report that it is transected. I report to the depth go to at least whatever level, and so it's staged at least whatever that corresponds to. And just note that it's transected at the base. And most of the time in our practice that results in an additional excision to be more definitive about staging before they do a subsequent therapy decisions. But it depends on the clinical situation.

**Dr. Gladell Paner:**

And just to clarify this, to say measurement will be used for the staging itself, right? For the two categories.

**Dr. Chris Kinonen:**

Correct. Yes.

**Dr. Gladell Paner:**

For A and B. Okay. I'd like to move to another element here, which is the mitotic count. And I read that there's really a long discussion about mitosis for the melanoma protocol. This is a question for you, Dr. Shon. The mitotic count, we know it's important in the prognosis of melanoma. What is the recommended approach in enumerating mitosis?

**Dr. Won Shon:**

Tumor mitotic rate is measured. First of all, it should be reported as the number of mitosis per square millimeter of tissue, specifically including only the invasive dermal component of the tumor. So you don't count the inside too. The count should start in an area known as the hotspot, where mitosis occur more frequently. Personally, measuring mitotic rate remains a very valuable data item for refining melanoma prognostic models. But I have to admit that at this point I'm not entirely sure whether it should be absolutely required in the cancer protocol. Especially, since as of today it is no longer necessary for AJCC staging purposes. It used to be, but not our current edition. I guess this is actually one item I like to actually discuss with our current author panel. As you know, currently it is still a core require parameters to report in both the CAP and ICCR melanoma templates.

**Dr. Gladell Paner:**

It's very interesting. This is not no longer included in the AJCC categories. Before it was included. Okay, that's interesting. Because in my field too, the criteria is evolving, parameters are evolving, especially for staging. And just to recap what you said, so the counting should be in the invasive component. You should find a hotspot, and then in that hotspot that where you're going to focus, and then you have to count it. I think the new WHO is using the millimeter squared. I think this is common for all tumors instead of the high power field. And I like to look this question to you, Dr. Kinonen, and since this is something that is a borderline right now, this mitotic count. It is important, not important, should we take it off the protocols? What do you think about mitosis? What's the weight of this in terms of pathologic factors, in terms of your practice and experience?

**Dr. Chris Kinonen:**

Well, Dr. Shon's point is, I think, very appropriate in that if it's not really part of the staging anymore, necessarily part of clinical decision-making, that maybe there is some question about whether we should include this. This is one of the things we can spend a lot of time looking for is mitotic figures. And if it's not clinically impactful, maybe there isn't a role for it. I have, in conversations with clinicians, gotten the impression that it's at least a curiosity for them, even if it may not impact their decision-making. They're like, "Oh, how many mitosis are there? Oh wow, there's seven." That sounds like a lot to them, versus there's zero, one or so. I suspect that it probably is a curiosity and an interest to a lot of clinicians who have been seeing it for a lot of years, even though it may not, strictly speaking, be directly relevant to management.

**Dr. Gladell Paner:**

That's a very good point. And I think this is one of those elements. I think Dr. Shon, we have an experience of some elements like this in the GU protocols. And actually, we brought that question to the HOD, something like a survey. If the pathologists want to keep it or not. I'm sure many probably would like to keep it off the protocols as a required element.

**Dr. Chris Kinonen:**

It does help me sometimes when the diagnosis of melanoma is hard. If I am finding dermal mitosis, that is one thing that can influence the initial diagnosis of invasive melanoma. So there's no absolute quantitative cutoff. But if I see one, it's going to be different from if I find 10. It does have a diagnostic role in identifying dermal mitotic figures, even if it doesn't, strictly speaking, impact staging.

**Dr. Gladell Paner:**

That's a very good point. Another element here which is required is microsatellite lesions. This is a question for you, Dr. Kinonen. What is the importance of microsatellite lesions and their importance in the management? I think this is important for treatment of melanoma. And what are the criteria or challenges in their identification?

**Dr. Chris Kinonen:**

It does impact management quite significantly if you find microsatellite lesions, it will change the end stage. Even in the absence of metastatic disease within a lymph node, it will change the end category to at least N1C or N2C or N3C. And that changes the clinical stage to stage three, which does make the patient, I believe, eligible for potential systemic therapy. And consideration for further staging as well as molecular analysis of their tumor. It can be very clinically significant to find or not find microsatellites.

They're defined as the presence of a microscopic discontinuous focus of melanoma that's adjacent or deep to a primary melanoma on pathologic exam at the primary tumor site. The tumor cells have to be discontinuous from the primary tumor and separated from the primary tumor by normal stroma. If the tissue in between is fibrotic or inflamed, it's not supposed to indicate a microsatellite, because those changes may represent aggression in the intervening tumor. And there's no size threshold or distance threshold that the focus needs to be from the primary tumor, which is I think is different from previous versions of the tumor synoptic.

So that's a lot. I think, generally it's recommended before diagnosing the presence of a microsatellite to get some deeper levels, because you do want to make sure that it's not a focus that got deeper levels would become apparent that it's linked up to the primary tumor. I think that's one of the more important things. And as I mentioned earlier with this adnexal involvement, you also want to make sure that whatever you might be seeing in the dermis isn't actually linked up to it in adnexal structure. Again, deeper sections can help there. And I guess those are the two primary pitfalls that I recognize, other than is there subjectivity in defining what might be fibrotic or inflamed. Are there some subtle changes there that may be hard to interpret?

**Dr. Gladell Paner:**

That's true. The histology should be pristine in between this trauma, in between should be something like clear, pristine, and there's nothing, no changes there. Nothing that tells us that there's a process of regression there that's happened before. Or something that caused this two-phosphate to be disconnected. Yeah, it can be tough.

**Dr. Chris Kinonen:**

One of the challenges I've had here in this area is if it's a deep melanoma and the lesion was previously biopsied, partially sampled, there's a lot of inflammatory changes. And in that setting it can be difficult if you've got tumor cells deep to this previously biopsied inflamed area that are separate from the rest of the tumor. How to sort that out into whether they're microsatellites or just part of the original tumor can be challenging.

**Dr. Gladell Paner:**

And it's interesting, this will require re-excision. If the microsatellite lesion was already... The margin was negative, the microsatellite lesion was not reaching the margin at the initial excision, it still would require re-excision because the mere presence of microsatellite lesion. Is that correct?

**Dr. Chris Kinonen:**

Dr. Shon can correct me if I'm wrong, but I think it would depend on how big the excision was that you got. If they, in the margin status of the main melanoma lesion, if the main melanoma is a centimeter clear and there's a microsatellite a few millimeters from the margin, I don't know if they would re-excise that or not, or if they would just go on to systemic therapy. I'm not sure.

**Dr. Gladell Paner:**

Dr. Shon?

**Dr. Won Shon:**

Yeah, I agree. Yeah, it really depends on case. And then, again, that's why also it depends on the tumor subtype and then the location of the body, and then also the exact margin status. In our practice melanoma is, regardless of microsatellite or not, if it's less than three millimeter from the closest margin, clinicians actually at least consider re-excision. And also, it depend on subtype. Some melanomas tends to be skipped. So really depends on case by case. But that's why the WHO proposed this new pathway based classification.

**Dr. Gladell Paner:**

Thank you, Dr. Shon. Before I proceed with my next question, I would like to congratulate you and your excellent team for putting out this melanoma protocols, and being part of the cancer committee before. I know that, as you described earlier, it's a tedious process. This takes a while to have this developed. I like to congratulate you and your team. I would like to mention their names. In addition to Dr. Shon, we have Dr. Nagarajan, Dr. Frishberg, Dr. Gershenwald, Dr. North, Dr. Prieto, Dr. Scolyer, Dr. Flotte, Dr. McCalmont, and Dr. Smoller. Again, congratulations guys for having the melanoma protocols. And starting with last year and this year we finally have this melanoma protocols for excision and for biopsy.

My next question is regarding the rest of the elements. There are other elements there that are required, and some elements that are not mandated or required. Dr. Shon, can you tell us briefly some of these other elements in the melanoma reporting protocols, and their significance?

**Dr. Won Shon:**

I guess I'd like to revisit and comment on observation. Which is, as you know, is a key dominant independent prognostic factor in invasive cutaneous melanoma. And again, it's a core component of the current AJCC staging system. I really like to emphasize that only non-traumatic tumorigenic ulceration should be recorded as ulceration. So if ulceration is present due to a prior biopsy or any prior procedure, the tumor should not be considered ulcerated for staging purposes. And this is actually very important.

I'll say, regarding regression, I'd say it's still controversial, and it's conflicting data out there. Currently, regression is not part of any staging system, so it is optional in our current protocol. However, we have made a minor modification in the most recent release, adding the option to report margin involvement by tumor regression. To me, I think that this is important, because the presence of regression at the margin may prompt consideration for re-excision as it may suggest the possibility of residual melanoma beyond the actual visual margins.

**Dr. Gladell Paner:**

Thank you, Dr. Shon. Going back to that ulceration, you used the word non-traumatic, right? Versus a traumatic-

**Dr. Won Shon:**

Yeah. So non-traumatic tumorigenic.

**Dr. Gladell Paner:**

Okay. For the audience, can you tell us the difference between the two and how do you make a distinction? Some practical tips, basically.

**Dr. Won Shon:**

Yeah. Again, the history is very, very important. Whether it was a prior procedure or prior biopsy is very important. Sometimes it's very, very hard. And some of the features that the fibrinous exudate presence of the fibrinous exudate, and then the underlying tissue response such as granulation tissue is the clue for true tumorigenic ulceration.

But sometimes really hard. Another point actually I want to make is sometimes you have a tumor with a very large and deep ulcer. And as Dr. Kinonen mentioned, when you measure breast thickness with the ulcerated tumor, you measure from the base of the ulcer. So if you have a very thick, large deep ulcer, this may actually lead to underestimating actual tumor thickness, because you are basically excluding the thickness actually overlying the tumor. Which is very rare. But I tell my trainees when we are dealing with those cases, yeah, probably we are underestimating actual tumor thickness.

But I think that this relatively small error usually doesn't really affect the prognosis. Because most of the tumor with a big large ulcer, they already have very thick and they have other high-risk features anyway. Typically, because of consistency, I usually just tell them to just follow the protocol and just measure from the base of the ulcer to down. But back to your question, sometimes it's very subjective. And without the appropriate clinical history then it's very hard. That's why when you look at our protocol, there's actually option to indeterminate. We have to be very honest, and then-

**Dr. Gladell Paner:**

Yeah, exactly.

**Dr. Won Shon:**

Sometimes we have to just put the indeterminate without the appropriate clinical history.

**Dr. Gladell Paner:**

Yeah, this indeterminate option in the protocol, it's been discussed a lot. But in many situations it can be helpful, I would say. And we use it often. I would say that these two melanoma protocols are really, truly helpful, beneficial to our practice. To the practice of general surgical pathologist, for the clinicians use, the correlating with the requirements or the pathological factors needed in the guidelines. With this ongoing advances in the field in melanoma, this question is for both of you. What do you think are in the horizon for pathologists in melanoma reporting? I would like to start with you, Dr. Kinonen.

**Dr. Chris Kinonen:**

Well, I find predicting the future hard. I guess I would say, as with a lot of other areas of cancer, it seems like molecular classification is evolving, and it seems like that's a good candidate for some area where we would see... There's a lot of molecular diagnostics used in melanoma, especially in academic centers. I would guess I would expect that's probably a leading candidate for changes that we may see in the future. I don't have specifics to suggest there, but I guess that's an area that we probably should expect.

In general, I guess I would say in cancer in general and melanoma, I actually think there's a lot more that we don't know than we do know. I think there could be any number of breakthroughs that just give us some really important insight into why certain lesions metastasize, why another lesion doesn't. I think we know so little about the process really, which isn't to say we don't know a lot, but I just suspect there's a lot more that we don't know. And so, I would just say that it could be the unpredictable, it could come around the corner in five or 10 years.

**Dr. Gladell Paner:**

Exactly. It could be enormous change there in the future. We don't know at this point in time. And for you, Dr. Shon?

**Dr. Won Shon:**

I guess I'd like to mention about the TIL, which is the one of the component in our protocol, the tumor infiltrating lymphocyte reporting. Historically, there are three categories: the absent, non-brisk, and brisk TIL. And at least my understanding, the inter-observer reproducibility is actually relatively good, at least in academic center. With a recent development of a AI-based algorithm, especially utilizing digital pathology platform, I believe there will be more comprehensive reporting to evaluate the tumor microenvironment. Not just simply, oh, there's absent, non-brisk, and brisk.

And especially with the advanced immunotherapy, we are living in the immunotherapy era. Speaking of immunotherapy, I think that more and more patient will receive new adjuvant therapy for advanced melanoma. And as a pathologist, I think we will definitely encounter those specimens after new adjuvant therapy, whether it's the targeted or immunotherapy, or combination of fashion. I believe the International Neoadjuvant Melanoma Consortium has already developed a reporting template for melanoma. And I think that it could be another actually potential protocol for the skin cancer committee to create, or possibly similar to other cancer type incorporate into our current melanoma protocol.

**Dr. Gladell Paner:**

This tumor-infiltrating lymphocytes is also used as a predictive marker for immunotherapy, is that what you're saying?

**Dr. Won Shon:**

We don't know yet. But in the clinical trial setting, that's actually something that not only just simply... Currently it's optional, and then we just use absent non-brisk and brisk. At least, my experience in doing part of the clinical trial, TIL is sometimes very important component. And I think that if you ask me what's in the horizon, I think this is the one thing we do advance of digital pathology. I think this is the one area that maybe will do somewhat differently than our current practice.

**Dr. Gladell Paner:**

I'm curious, in terms of doing molecular testing right now for any purpose treatment or diagnostic, roughly what percent of your diagnosis of melanoma you order those molecular testing, Dr. Shon?

**Dr. Won Shon:**

In our practice, because of our clinician who's probably three more melanoma than anybody else in Southern California, and then many of them are advanced, the melanoma patient with the phase one clinical trial. Pretty much all of our actually patients are... I've already done extensive workup and then they do additional more, acquiring additional molecular workup. But they're all stage four melanoma patient. Stage one or... It's not that often they're asking the molecular testing. I see more and more requests. I'm not sure, Dr. Kinonen your experience. But at least in Southern California, more and more actually dermatologists asking Castle test for GP or gene expression profile classification. I don't think we have enough time to talk about it, but it's somewhat controversial area. But that's another thing. It's not required, but I'm getting more and more requests from, not oncologists, but the dermatologists.

**Dr. Gladell Paner:**

That's interesting. And for you, Dr. Kinonen, how often do you order molecular testing? Or how often does your clinician order molecular testing for that?

**Dr. Chris Kinonen:**

Well, for the Castle comment, we do get some dermatologists that ask about that periodically. We're not getting pressed too hard about it, but it does come up sometimes. In our practice, we don't have molecular... The community hospital I'm at, we don't have molecular diagnostics in-house. And we've talked about maybe partnering with someone that can do it for us. We've elected to just not do it ourselves. And when we do have cases that we think would benefit from molecular classification, we'll send it to an academic center for consultation. And that's how we handle it. And then usually it depends on where we send it. Certain academic centers do molecular analysis more than others.

Sometimes all of the cases we send for consultation will get molecular. And in other places, some small percentage will get molecular testing. Overall, I don't know what percentage of melanocytic cases... We have four dermatopathologists, we can usually handle most stuff in-house without molecular analysis. It's probably pretty low, one, 2% of our cases that we'll send out for assistance, something like that. Maybe it's a little bit higher. But I would say, for better or worse, we handle most things without molecular diagnostics.

**Dr. Gladell Paner:**

Thank you, Dr. Kinonen. And unfortunately that's all the time we have for today. This is a great conversation. I learned a lot. And thank you both for sharing your expertise and insights regarding the content and use of the melanoma reporting protocols. I'd like to turn this over to you, Becca.

**Becca Battisfore:**

Yes. Thank you to Dr. Paner for leading the conversation, and to our guests for sharing your insights on melanoma reporting protocols. And I want to thank you all for listening to this CAPcast. You can find links to the CAP's protocols in the show notes, including those mentioned during this episode. If you have questions or comments about any of the protocols, please email CancerProtocols@CAP.org. And for more information about the CAP, visit CAP.org.