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Navigating Classification of High-Grade Neuroendocrine Neoplasms

Announcer:
You're listening to *Project Oncology* on ReachMD, and this episode is sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. Here's your host, Dr. Charles Turck.

Dr. Turck:
Welcome to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and joining me to discuss practical applications of WHO criteria in high-grade neuroendocrine neoplasms is Dr. Rohit Thummalapalli. He's a gastrointestinal medical oncologist at Memorial Sloan Kettering Cancer Center in New York.

Dr. Thummalapalli, thanks for being here today.

Dr. Thummalapalli:
Of course. Thank you for having me.

Dr. Turck:
Well, I'd like to start with some background on the WHO criteria. This is a framework that classifies high-grade neuroendocrine neoplasms by differentiation and proliferation. It distinguishes well-differentiated Grade 3 neuroendocrine tumors, or NETs, from poorly differentiated neuroendocrine carcinomas, or NECs. But in practice, those factors—differentiation on the one hand, and proliferation on the other—don't always align.

With that being said, Dr. Thummalapalli, when you are approaching a new high-grade case and those factors are pointing in different directions, how do you decide which one takes precedence in your diagnostic thinking?

Dr. Thummalapalli:
Based on the updated WHO criteria, differentiation status is the first criteria you think about because, like you mentioned, the G3 NETs can also have a high Ki-67—sometimes above 20 to 30 percent. But we can also see them in rare cases being 40, 50, or 60 percent. And so, from a Ki-67 perspective, that can technically overlap with the poorly differentiated NEC population. But the key distinguishing feature is the grade of differentiation. And so, we have now appreciated that there is a subset of tumors that have well differentiated histology but can have high proliferative indices—more than 20 percent.

Dr. Turck:
Let's get into the specifics of morphology. Grade 3 NETs retain organoid patterns like nests and trabeculae with relatively uniform cytology; in contrast, poorly differentiated NECs tend to show sheet-like growth, marked atypia, nuclear molding, and extensive necrosis. So, when you're diagnosing patients, what's your approach to interpreting these differences, and how does the adequacy of the biopsy sample affect how much confidence you place in what you're seeing?

Dr. Thummalapalli:
Obviously, neuroendocrine neoplasms are rare overall. Within neuroendocrine neoplasms, high-grade NETs and poorly differentiated NECs are probably the rarest subsets of these diseases. And so, I think it is always important to have strong pathology collaborators who have a lot of experience with these rare tumor types.

Thinking about the adequacy of the sample, it depends on where the disease is. Oftentimes, with things like pancreatic primaries, we often are only able to get a limited cytology sample—for example, from FNA—which can make it challenging. Oftentimes, patients have liver metastases, which can allow us to biopsy tumors with a little bit more tissue involvement. So, the site of localized or metastatic

spread definitely influences the amount of tissue you're able to gather. The more tissue, always the better.

That being said, we're now five plus years into this distinction between G3 NETs and NECs, and the differentiation status really is a key dichotomy here. And we are often able to make this diagnosis even with limited pathology samples.

Dr. Turck:
Now, I want to talk a bit more about Ki-67 as a proliferation marker. Where did you see the most common misunderstandings when high Ki-67 values overlap between Grade 3 NETs and NECs, and how should Ki-67 be properly integrated into the overall diagnosis?

Dr. Thummalapalli:
As I mentioned, Grade 3 NETs are defined by well-differentiated histology with a Ki-67 above 20 percent. And the vast majority of these tumors have Ki-67 within the 20 to 40 percent range, which conventionally is thought to be significantly lower than the Ki-67 you would see with poorly differentiated NECs, which can be between 21 to 55 percent but is frequently above 55 percent.

But we are now understanding that there is a subset of well differentiated tumors that have different histologies, different genomics, and probably different cells of origin that can still have quite high Ki-67—upwards of 60 or even 70 percent—which we've seen in our practice. So, understanding that different tumor types with similar Ki-67s—say 50 to 60 percent—can either be well differentiated NETs or poorly differentiated NECs is a new understanding and an important distinction as we go forward.

Dr. Turck:
Speaking of which, how does this information factor into what the patient actually receives treatment wise?

Dr. Thummalapalli:
Generally, patients with poorly differentiated neuroendocrine carcinomas almost exclusively receive platinum-based chemotherapy. We often extrapolate from small cell lung cancer guidelines and think about regimens including etoposide and platinum-based chemotherapy. For our gastrointestinal neuroendocrine primaries with poorly differentiated tumors, we often think about 5-FU-based regimens. Those are, at the moment, standards of care for patients with poorly differentiated NEC.

Now, there has been some data that has come out over the last few years suggesting that patients with poorly differentiated histology and a lower Ki-67 between 21 and 55 percent may not respond as well to platinum-based chemotherapy. And so these are patients for whom we sometimes think about alternative—still chemo, but different chemo—options.

For the well differentiated high-grade tumors, the treatment landscape is actually completely different. We don't have a lot of prospective data in this space that really highlights the G3 population, and that's because of the relatively recent pathologic distinction and appreciation for the G3 NET category. But in well-differentiated tumors in general, we think about somatostatin analogues, radioligand therapies targeting the somatostatin receptor, and other radioligand therapies. We think about targeted therapies and other drugs like that.

And so some of these treatments so far have had at least subgroups in clinical trials that have really looked at activity within the G3 population. Now, we have other more recent clinical trial data looking at radioligand therapies for the Grade 2 and Grade 3 NET population.. And so making that pathologic distinction between high-grade, well differentiated NETs and poorly differentiated NECs is really critical.

Dr. Turck:
Now, for poorly differentiated NECs, it can often be difficult to establish the site of origin. How does establishing the tumor as a pulmonary versus non-pulmonary tumor affect treatment decision making?

Dr. Thummalapalli:
There are times where we have a patient with clearly metastatic neuroendocrine carcinoma but no clear primary site, including no clear primary lung lesion or no clear primary pancreatic lesion, for example. And so oftentimes, these patients are treated as neuroendocrine carcinomas of an unknown primary. In this situation, it requires a dedicated search for the primary tumor site.

One thing that's underappreciated is that, although neuroendocrine carcinomas with liver involvement are often presumed to be metastatic tumors, there are primary biliary or primary hepatic neuroendocrine carcinomas. And so I do think for patients who do not have a clear lung primary, it is important to try to figure out what the primary neuroendocrine carcinoma site is.

The second is that for some of our gastrointestinal extrapulmonary neuroendocrine primaries, there are other clinical trials right now trying to investigate what the ideal chemotherapy backbone should be for these patients.

Dr. Turck:
Now, rare subsets of NECs can sometimes be classified as mixed differentiation tumors. How often is that seen, and how does that

affect treatment decisions?

Dr. Thummalapalli:
We often see this phenomenon of mixed adenocarcinoma and neuroendocrine carcinoma. The thought here is that these tumors likely were initially adenocarcinomas, and some component of the adenocarcinoma transformed into a neuroendocrine carcinoma subtype. When we see these tumors, it's important to, to confer with a pathologist to figure out what is the dominant histology that is seen.

Understanding the composition of a mixed tumor and what fraction is neuroendocrine versus adenocarcinoma are often important considerations.

Dr. Turck:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Charles Turck, and I'm speaking with Dr. Rohit Thummalapalli about distinguishing between Grade 3 neuroendocrine tumors and neuroendocrine carcinomas.

So, Dr. Thummalapalli, I'd like to talk now about confirming our diagnoses. When morphology alone doesn't give a clear answer, immunohistochemistry and molecular markers—things like DAXX or ATRX loss, aberrant p53, or RB1 loss—can add important supporting information. From your perspective, when do you reach for these tools in practice? Which do you find most actionable, and how do they shift your management strategies?

Dr. Thummalapalli:
If we are entertaining the diagnosis of G3 NET versus poorly differentiated NEC, I almost always get next-generation sequencing. And the reason is because of many of the topics we talked about already; we do, as a first pass, use differentiation status, and the second pass is Ki-67. But there are tumors, for example, with low tumor content and limited cellularity of a sample. There are tumors where just based on morphology in Ki-67 alone, we are unable to make that determination.

And so this is where I think molecular diagnostics can be very helpful. It's likely that Grade 3 neuroendocrine tumors likely originate from neuroendocrine cells from the organ of origin. But it is certainly possible that poorly differentiated neuroendocrine carcinomas could certainly be transformed adenocarcinomas and might have a different cell origin. And so this is where molecular diagnostics can be very helpful.

As you mentioned, for example, for pancreatic primaries, the G3 NETs can often have really characteristic mutations in ATRX and DAXX, MEN1, and TSC2. These are classic alterations that are seen in well differentiated pancreatic NETs, whereas for poorly differentiated neuroendocrine carcinomas, we can often see p53 mutations, RB1 mutations, or loss of function alterations. They're not universally seen, but they're commonly seen in neuroendocrine carcinomas, which can often help with this pathological distinction.

And then one more piece of molecular information that sometimes can be underappreciated is that neuroendocrine carcinomas can sometimes be, like I mentioned, transformed adenocarcinomas. And so we can sometimes see driver alterations that are commonly seen in the GI adenocarcinoma counterparts. So, for example, pancreatic NECs can often have KRAS mutations. Colorectal NECs can often have KRAS or BRAF mutations, ERBB2 amplification, and so on and so forth. And these are drivers that are quite rarely seen in G3 NETs.

Dr. Turck:
I want to thank my guest, Dr. Rohit Thummalapalli, for joining me to discuss how we can use WHO criteria to avoid misclassification in high-grade neuroendocrine neoplasms.

Dr. Thummalapalli, it was great having you on the program.

Dr. Thummalapalli:
Thank you. I really appreciate it.

Announcer:
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