Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/project-oncology/epnec-diagnostic-challenges-emerging-strategies/48913/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Decoding epNECs: Diagnostic Challenges and Emerging Strategies

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

Dr. McDonough:
This is *Project Oncology* on ReachMD, and I'm Dr. Brian McDonough. Joining me to discuss the biology and clinical challenges of extrapulmonary neuroendocrine carcinomas, or epNECs for short, and their evolving biomarker landscape is Dr. Andrew Hendifar. He's a Professor of Medicine and the Medical Director of the Gastrointestinal Oncology Disease Research Group at Cedars-Sinai Cancer Institute in Los Angeles.

Dr. Hendifar, welcome to the program.

Dr. Hendifar:
Thank you for having me.

Dr. McDonough:
To start, Dr. Hendifar, when a community oncologist encounters a suspected high-grade neuroendocrine malignancy outside the lung, how should they think about epNECs within the broader spectrum of neuroendocrine neoplasms? And why is getting that classification right so critical for guiding the patient's care pathway?

Dr. Hendifar:
Excellent question. It's so important that we appropriately and correctly distinguish neuroendocrine tumors from neuroendocrine carcinomas. The reasons are multiple, but the main one is that the treatment paradigms are actually completely different, even though you might think of them being quite similar tumors.

The way I like to divide them is pathologically; carcinomas are poorly differentiated, and tumors are well differentiated. Poorly differentiated tumors often act more aggressively and are more likely to metastasize and unfortunately lead to the demise of the patient much sooner than tumors otherwise would. Radiographically, the differences are very important as well. Functional imaging for carcinoma includes an FDG PET/CT scan, the normal PET/CT scan you would order for most malignancies. On the other hand, for neuroendocrine tumors, the functional imaging is more in line with gallium-68. Gallium-68 tags the somatostatin receptor and is able to light up tumors that are well differentiated. And what this means for treatment is that well-differentiated tumors are able to be treated with somatostatin analogs, peptide receptor radiotherapy, or radioligand treatment, versus carcinomas, where the treatment is almost exclusively chemotherapy.

Also, one differentiating factor between a tumor and a carcinoma is that neuroendocrine carcinoma patients are frequently quite symptomatic. They might have weight loss or pain. They might have other symptoms that are debilitating, whereas tumors tend to be a little bit better tolerated in the body and might not manifest these other symptoms.

Dr. McDonough:
As a follow up to that, what clinical or pathologic features tend to signal that it's an epNEC, rather than a well-differentiated neuroendocrine tumor or another high-grade malignancy?

Dr. Hendifar:
The most important distinguishing factor is differentiation. So on the pathology report, you have to talk to your pathologist and say, "Is

© 2026 ReachMD

this tumor poorly differentiated or well-differentiated?" You don't want to get too caught up in the Ki-67, which is the proliferative index, because oftentimes a poorly differentiated carcinoma might have a proliferative index that's medium—closer to 50 percent—and you can have a well-differentiated tumor with quite a high proliferative index.

Therefore, the Ki-67 is probably not the best distinguishing factor; it's the differentiation. Now, it is true that most poorly differentiated tumors will have a very high Ki-67—frequently over 50 or 70, or almost 100 percent at times.

Dr. McDonough:
Now, given the aggressive nature of these tumors, how does the biology of epNEC translate into the urgency we see in clinical practice—from diagnosis through initial management decisions?

Dr. Hendifar:
This is crucial. Again, poorly differentiated neuroendocrine carcinomas biologically are very distinct from neuroendocrine tumors. And the easiest way to drive this home is not only whether they look different under the microscope, they look different on imaging, and the clinical symptoms are different. But if you interrogate the tumor with next-generation sequencing in these poorly differentiated carcinomas, they frequently have RB1 alterations and TP53 alterations. These are not typically found on well-differentiated tumors. And again, this translates into the clinic on how you treat these patients.

And again, for poorly differentiated epNEC, chemotherapy is the mainstay of treatment, whereas in neuroendocrine tumors, there is a multitude of therapeutic approaches that have been developed over the last 20 years, and most of them are actually not chemotherapy. There's often somatostatin and receptor targeting treatments, whether it's an analog or peptide receptor radiotherapy, and also VEGF tyrosine kinase inhibitors. These are all treatments appropriate for neuroendocrine tumors, but completely inappropriate for epNEC, or poorly differentiated neuroendocrine carcinomas.

Dr. McDonough:
For those just tuning in, you're listening to *Project Oncology* on ReachMD. I'm Dr. Brian McDonough, and I'm speaking with Dr. Andrew Hendifar about why timely treatment is critical in extrapulmonary neuroendocrine carcinoma and how biomarkers may shape diagnosis and care.

So, Dr. Hendifar, let's shift gears now and talk about biomarkers. What biomarkers are currently established in the evaluation of epNEC, where do we still see major evidence gaps, and how should we interpret results that are equivocal or discordant in practice?

Dr. Hendifar:
That's a fantastic question. So unfortunately, for epNEC, biomarkers are quite limited. The most clinically useful biomarker at this time is the identification of DLL3 expression for enrollment into clinical trials for T-cell engagers that bind DLL3 and the T-cell.

Outside of that, biomarkers can be interrogated in the tissue of poorly differentiated carcinomas, but that would mostly help with that for diagnostic purposes. P53 alterations and RB1 alterations are frequent. Microsatellite instability is actually quite rare in neuroendocrine carcinomas, unfortunately. Proliferative index can be used to help sort out whether this is a tumor or a carcinoma, but it doesn't really help identify a particular treatment.

And as time goes on and we develop our practice patterns and clinical trials, we'll see more and more understanding of DLL3: what is the threshold cutoff for DLL3 so the patient would qualify for a targeted treatment? And what would be the expression levels we would expect in neuroendocrine carcinomas, specifically from the different subtypes, whether it's GI, gynecologic, GU, or an unknown primary?

Dr. McDonough:
And if we zero in on DLL3 for a moment, what do we currently understand about the prevalence of its expression across epNEC tumor types—such as gastrointestinal, genitourinary, and gynecologic cancers—and how should we interpret novel findings while still balancing the current limitations in evidence?

Dr. Hendifar:
DLL3 is an inhibitory Notch pathway ligand that has been observed in many high-grade neuroendocrine carcinomas. And in small cell lung cancer, it's almost ubiquitously present, and you don't even need to test for DLL3 to prescribe and for patients to receive benefit from DLL3-targeted treatments.

I usually like to divide epNEC into four major categories. The most common site of disease outside of the lung is the GI tract; that includes the pancreas, the colon, the rectum, the anus, gallbladder, et cetera. Another category would be gynecologic neuroendocrine carcinomas, whether uterine or cervical. The third category is urologic malignancies, and predominantly it's prostate neuroendocrine carcinoma. That's the most prevalent, but we also see a bladder neuroendocrine carcinoma. And then the last bucket is those of unknown primary. In neuroendocrine carcinomas and tumors, there's a substantial group of patients where a primary is not identified.

© 2026 ReachMD

And why that is such a specific characteristic against tumor type is unclear, but it's important to recognize that oftentimes you won't find a primary.

Now, the DLL3 expression in these different subgroups is important to clarify, and this is something that's currently in development. But we know for a fact that in neuroendocrine carcinomas, DLL3 expression is inordinately elevated, whereas in tumors, it's also high. And then the second question after that is, how high of a DLL3 expression do we really need in order to derive benefit from DLL3 targeted therapies? So that's the second important question that we're currently answering in clinical trials.

Dr. McDonough:
As we come to the end of our program, Dr. Hendifar, do you have any final thoughts you'd like to share with our audience?

Dr. Hendifar:
Yeah. Neuroendocrine neoplasms, whether they're tumors or carcinomas, are oftentimes difficult to manage because of some of this overlap in the histologic diagnosis. So, although it's difficult for the practicing oncologist to do so, it's crucial that they get in touch with their pathologist, review the pathology material, and discuss whether this is poorly differentiated or well-differentiated. Obtain a proliferative index, such as Ki-67, to say, “Okay, this Ki-67 is quite high, or on the lower side. Does this help make a decision to classify this tumor better?”

And finally, I recommend next-generation sequencing. This will oftentimes help you identify the carcinomas and separate them from the tumors.

Dr. McDonough:
With those takeaways in mind, I want to thank my guest, Dr. Andrew Hendifar, for joining me to discuss how clinicians can better recognize and understand extrapulmonary neuroendocrine carcinomas.

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

Dr. Hendifar:
Thank you for having me. I enjoyed it.

Announcer:
This episode of *Project Oncology* was sponsored by Boehringer Ingelheim Pharmaceuticals, Inc. To access this and other episodes in our series, visit *Project Oncology* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!

© 2026 ReachMD