

**Interview with Dr. Matthew Horton  
Basics of Lung Cancer Pathology, Part 2:  
The Spectrum of Neuroendocrine Lung Tumors,  
and Bronchioloalveolar Carcinoma (BAC)**

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**Dr. West:** I'm Jack West, medical oncologist and President and CEO of GRACE, the Global Resource for Advancing Cancer Education.

I'm here today with Dr. Matthew Horton, who is a pathologist at CellNetix Pathology here at Swedish Cancer Institute in Seattle, Washington. He also has a particular focus and expertise in thoracic oncology and we're going to avail ourselves of the opportunity to go over some of what's new in the field.

**Dr. West:** Small cell lung cancer is a part of a spectrum of neuroendocrine cancers. Can you just describe a little more of that whole spectrum from one end of carcinoid to large cell neuroendocrine and then small cell?

**Dr. Horton:** Sure. Small cell lung cancer, of course, is a different cell type. When we talked about squamous and adenocarcinomas, we talked about epithelium that has some type of structural function. In the case of non-small cell carcinoma, its epithelium related to the surface of the airways all the way down into the alveolar sacs. Small cell carcinoma involves neuroendocrine cells which are a separate class, they're epithelial cells, but they serve not so much as a structural function, but they function to produce bioactive substances. Some people have termed the neuroendocrine system as one big chemo receptor in the lungs, especially it will detect changes in pH oxygen density, carbon dioxide, all these types of things to produce paracrine or endocrine type substances.

Unfortunately every type of epithelium also has the capacity to undergo malignant transformation. When the non-small cell carcinomas undergo malignant transformation, we end up with squamous and adenocarcinomas. When the endocrine cells undergo a neoplastic transformation, we have a continuum of neoplasms that are actually quite distinct and very different from one another. At the most, if I could use the term, the most benign end of a malignant spectrum, is the carcinoid. And as the name signifies, it was a group of lung cancer patients that the oncologist was surprised that these patients were living so long; rather than call them carcinomas, decided to call them carcinoids. They are a neoplastic proliferation that has the capacity to metastasize, but the mitotic

rate is very low. Its biologic potential is not considered to be very aggressive, and they have excellent outcomes.

As we move on to a more malignant type of carcinoid we find atypical carcinoid which is a very gray area and can be difficult for some people to diagnose. It really, morphologically, looks similar to a carcinoid with the exception of increased mitotic activity.

But the real difference comes within atypical carcinoids and the two what are considered high grade neuroendocrine carcinomas; the small cell carcinoma and the large cell carcinomas. These are a high grade, high mitotic rate, very aggressive carcinomas. The large cell carcinoma was only recently identified, with the advent of immunohistochemistry. I think for a long time large cell neuroendocrine carcinomas were lumped into large cell carcinomas. They didn't show any evidence of squamous or glandular differentiation, so they tended to get categorized there.

Dr. West: And the distinction between large cell neuroendocrine and small cell is just based on how they look under the microscope?

Dr. Horton: Exactly. It's a morphologic distinction. Changes in nuclear size, changes in the presence or absence of what are called nucleoli which are foci within the chromatin of the nucleus. Their neuroendocrine differentiation is their only link.

Dr. West: Within the group of adenocarcinomas, there are different subtypes, and people have sometimes asked on the GRACE website about signet cells or acinar or papillary. Do you have any insight about different clinical behaviors or characteristics of one type versus another?

Dr. Horton: Well I think you talk about adenocarcinoma and subtypes, the first thing I would talk about would be bronchioloalveolar carcinoma.

And the subtyping of adenocarcinoma again has undergone quite a bit of transition in the last few years. In fact the term bronchioloalveolar carcinoma has been around since 1960. And it really was more of a morphologic descriptor than a separate lung cancer type. In 1999, the WHO decided to split off bronchioloalveolar carcinoma, or BAC as it's known, as a separate histologic entity very strictly defined. Now the problem is, this BAC terminology has been around for a long time and has been used in a lot of different circumstances. So to suddenly change its definition, now we've moved forward ten years and at least for my generation of pathologists, I think it has penetrated pretty well and we have good reproducibility, but the diagnosis of BAC made elsewhere sometimes doesn't have that same degree of reproducibility.

- Dr. West: Another issue specifically with BAC is that the pure form is a lot less common than an invasive adenocarcinoma with some degree of non-invasive BAC features, correct?
- Dr. Horton: Yes, yes, and that was part of somewhat the artificial nature of drawing a line and saying everything that was non-invasive was a BAC; everything that was invasive was not BAC. The truth is much more of a continuum, where you have a pure BAC non-invasive adenocarcinoma, which is actually quite rare. Once you strictly apply the 1999 rules, a pure BAC is quite rare. But it's not rare at all to have an adenocarcinoma that has some variable amount of bronchioloalveolar morphology.
- Dr. West: But when you only have a limited amount of that tissue available, it must be difficult to say anything with confidence about what the whole tumor should be like.
- Dr. Horton: Honestly, it's impossible, because you can have clues, you can have radiologic clues, the ground glass opacities, or conversely the more dense appearance on a CT that may imply invasion. But on a needle core biopsy or on a FNA cytology, really all you can give is a morphologic diagnosis of that biopsy. You can't confidently rule out that there's invasive acinar adenocarcinoma.
- Dr. West: There's a proposal that's being discussed and that may be adopted in 2010 to change the term non-invasive BAC, get rid of it entirely and call that adenocarcinoma *in situ*. This would presumably reflect that it has a much better prognosis and is not a malignancy. What do you think of that concept, as someone who's been watching and diagnosing a lot of BAC over the last decade? `00:18:03
- Dr. Horton: Well, I actually think that it's making clear what a lot of pathologists have thought all along, to be quite honest. I did my fellowship between 1999 and 2001, so I was right at the cusp of this new definition of BAC, and I can remember many people coming by and saying, "How are you going to draw a line between a non-invasive, partially invasive, completely invasive adenocarcinoma when it appears to follow the same model that we've seen in other organ systems?"

We have carcinoma *in situ*. We have squamous carcinoma *in situ* in the lung and we also have it in the cervix. It produces mild, moderate, severe dysplasia and then becomes invasive. Is it that hard to believe that the epithelium of the alveoli would do the same thing?; undergo a dysplastic or adenocarcinoma *in situ* type change, then progress to an adenocarcinoma? Now some never progress. Some progress quickly. Some progress without apparent *in situ* component. But it follows a model

that I think a lot more pathologists are more comfortable with than the old one.

Dr. West: When a new system comes out, there isn't universal, immediate adoption of this, and in fact, when you and I have discussed this at some points in the past, you expressed some concern or question about how well this would be taken up by the pathology community. Can you discuss some of those concerns and how you see the pathology community potentially accepting this or not?

Dr. Horton: Sure. I think with bronchioloalveolar carcinoma especially because it has been around for so long, it becomes so ingrained that I think at least when they first made the change in 1999, I kept seeing case after case coming in with bronchioloalveolar carcinoma as the lead diagnosis, but it yet having a minor component in the actual histology. So my confidence was a little shaken that how long is it going to take before the word gets out that BAC is only a non-invasive neoplasm.

With this latest change, though, I'm optimistic for two reasons. One, I've already stated — I think it intuitively and logically makes more sense. I think it appeals to a kind of a natural progression that pathologists have grown to understand in other organ systems. Secondly, I think the pathology community is not operating in a vacuum. I think they're becoming much more inclusive as far as getting oncologists, surgeons participating in a lot of these multidisciplinary panels where we understand what the clinician needs and we have the means to, through the College of American Pathologists, through our state and local societies, get this kind of information out, when the staging manuals come out, they have these changes in them. We can get the pathology community as a whole on the same page rather than sort of pockets deciding yes or no to believe in a certain diagnosis of BAC. Here it's a systematic change that's going to affect how the staging manuals are written and how the CAP puts out their educational materials. So I'm cautiously optimistic that this will actually get better traction.

Dr. West: That's interesting because you mention how multidisciplinary it's become, and it does seem that way that lung cancer now is a much more integrated approach and that we do need much more input from a pathologist about histology as well as molecular testing. But all of that is also predicated on having more tissue than you've been used to having for the last few years.

Dr. Horton: And I think for a while, you now, we tried to see just how much we could get out of how little cytology was very popular, the minimally invasive type of aspirates. Now with the need to not only be more specific with regard to histology, but to have additional material for molecular studies,

immunohistochemistry, those types of things, we might find ourselves going back to needing more tissue than we did before.

Dr. West: And we'd need to communicate well with our surgeons, pulmonologists, interventional radiology colleagues, things like that.

Dr. Horton: Exactly. They need to really all be on the same page to understand that what might have been sufficient even as little as five years ago really is not sufficient for a comprehensive workup today.

Dr. West: How often do you see the division of BAC in a report to mucinous or non-mucinous; first of all, how often are you doing that and secondly out in the community setting? And if you aren't seeing that much, is it because you really can't tell easily or has it been because that hasn't been felt to be an important distinction?

Dr. Horton: I think it deals with the experience of the person who's signing out the case, to be honest. Mucinous BAC is a very distinctive appearing lesion. When you see it you will not miss it. The truth of the matter is mucinous BAC is quite rare. We haven't seen that much of mucinous BAC. Your average pathologist has seen plenty of non-mucinous BAC. So when you get a report that just says bronchioloalveolar carcinoma period, my assumption, my assumption in that case is that it's always non-mucinous. If it's mucinous that will be noted. If it's non-mucinous it usually won't be although I try to get my colleagues to make that distinction whether it's mucinous or non-mucinous in writing.