

Interview with Dr. Matthew Horton
Basics of Lung Cancer Pathology, Part 1:
Introduction to Histologic Subtypes of Non-Small Cell Lung Cancer (NSCLC)
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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. Thanks for joining us.

Dr. Horton: Thanks for having me, Jack.

Dr. West: The general field has been changing. The role of pathology in lung cancer has increased over the last few years with more and more focus on the pathology details and now molecular testing to determine our treatment plans. In fact, more and more, we're seeing oncologists co-authoring papers and running educational programs along with pathologists. So, many of the people who are learning about lung cancer just hearing or reading for the first time about the different subgroups of histology, say for non-small cell lung cancer, can you please just give a brief overview of the main ones?

Dr. Horton: Sure. First of all, you're right -- pathology is changing quite a bit, and in fact in the eight years since I did my pulmonary fellowship pathology has taken a much more leading role in not just the diagnosis, but also the treatment of lung cancer, which is something we weren't part of before.

Non-small cell lung cancer really is composed of two major groups: that's the squamous carcinomas and the adenocarcinomas. There are some less numerous groups namely large cell carcinoma which is a category that neither has squamous or adeno differentiation. And the least common group called the pleomorphic or sarcomatoid carcinomas.

Dr. West: Are large cell carcinomas the same as large cell neuroendocrine, or are there some large cells that are not with neuroendocrine features?

Dr. Horton: Well, you've hit on one thing about pathology, and that is the nomenclature can be very confusing. Large cell carcinoma is not the same as a large cell neuroendocrine carcinoma. In fact, large cell neuroendocrine carcinoma as far as pathologists are concerned didn't

really exist up until a few years ago, with the advent of immunohistochemistry. So large cell is a separate distinct group from large cell neuroendocrine.

Dr. West: Here we are talking about different subgroups, but eight or ten years ago, we often weren't hearing about the different subgroups because it didn't seem to matter that much. The main distinction we cared about was whether a lung cancer was small cell or non-small cell lung cancer. Nowadays, it seems to matter, and there are potentially relevant details like histology and special tests, but how equipped are pathologists to provide that kind of information in terms of their training and the amount of tissue that they have available? I mean, you've done a pathology fellowship, but there are probably not that many pathologists available how have that kind of training, and how necessary is that?

Dr. Horton: The questions of differentiation have always been a part of pathology training, always been a part of lung cancer pathology whether or not you did a fellowship. The thing that has changed is that, you mentioned ten years ago you were happy to get a diagnosis of non-small cell versus small cell, and pathologists were more than happy to oblige and not give you that added specificity mainly for two reasons. One is that we discovered the lung tumors like tumors in other organs but almost especially with lung tumors, they're very heterogenous. That means that an area that looks predominantly squamous a centimeter away could look predominantly adeno. And the other thing that goes along with that is we've been asked, of course, to do more with less. As the transbronchial and fiber optics has progressed, we get smaller biopsies and became the rule of the day that if you could get a non-small cell diagnosis made, even if you had findings that were squamous or adeno, you were better off not mentioning those because when the tumor then came out and was resected, you had the whole tumor to evaluate, oftentimes you'd find areas that would be different than your biopsy.

Dr. West: So, how do you differentiate between adenocarcinoma and squamous features or others? Is it largely based on visual inspection or are there particular tests like immunohistochemistry, and perhaps you can tell us more about that, that help you determine what you're going to call this?

Dr. Horton: That's a field that's been evolving as your needs have grown as oncologists. We've endeavored to change our methodologies and get more specific with our diagnoses.

Going back to the original definition of a squamous carcinoma—that indicates the presence of keratinization, which is a specific type of protein. That can be identified with the naked eye under a normal microscopic situation as an eosinophilic, or orange color to the cytoplasm, things called

intracellular bridging. All of these types of morphologic clues are visible to the naked eye.

Adenocarcinoma conversely is a more functional cell, meaning it usually produces mucin or some other type of intracellular protein that can be identified with light microscopic techniques -- nothing very fancy. These are the same techniques that have been around for a hundred years.

Now, there's always going to be tumors, either by volume biopsy or by their lack of differentiation, that aren't going to cooperate. They're not going to give us those visual clues that we've come to depend on, and that's where techniques like immunohistochemistry has really started to evolve. Immunohistochemistry uses monoclonal antibodies directed against very specific epitopes on the surface and sometimes in the nuclei of target cells that allow us to tease out a little bit more information beyond histology, but actually looking at the nuclear factors of growth and regulation. And one of these is called TTF-1 and that's a marker of Type II pneumocyte differentiation which, not always, but the majority of times will indicate an adenocarcinoma.

Conversely there is a nuclear protein called P63, another immunostain that does the same except for squamous differentiation. So we've evolved from using the light microscope to give us as much information as was possible through the naked eye; now going one step further and using immunohistochemistry to try to subclassify those less differentiated tumors.

Dr. West: Are there any particular features of a large cell carcinoma?

Dr. Horton: The definition, believe it or not, is one that doesn't show squamous or adeno features. So this has been accused of being a bit of a waste basket definition, and that those numbers of tumors classified as large cell are getting smaller because we're asked being put more of these more sophisticated techniques to them we're able to sub-classify them more accurate.

Dr. West: How confident should we be, then, that a report of a moderately differentiated squamous cell carcinoma is squamous cell carcinoma throughout? You'd mentioned that there can be a lot of heterogeneity. So, is this something that we should suspect could be variable throughout the tumor? Along the related lines, how often do you agree with the pathology report that comes from a different institution versus having a different interpretation of squamous versus adeno versus can't call it?

Dr. Horton: I think as pulmonary pathology has progressed, we've seen really a whole generation of pathologists who previously were not asked to make that

differential. Now, being sort of pressed and said we need to have more evidence one way or the other. So in those circumstances, when you get a diagnosis of a moderately differentiated squamous carcinoma, to use your example, I would feel that would be a pretty high likelihood of being reproducible. The ones that are, to me, less reproducible are when you have poorly differentiated tumors; but for the most part the pathologists who maybe don't see as much lung cancer as we do here at a cancer institute, they're the ones that are more likely to defer to non-small cell carcinoma and refer you to a center such as this or advocate getting more tissue of a resected tumor.

Dr. West: Poorly differentiated carcinomas aren't rare. So, how often are you calling a non-small cell just non-small cell lung cancer, not otherwise specified because of how it looks even with an adequate amount of tissue and you just can't tell, versus having a very, very limited amount of tissue and if you had more you could say more?

Dr. Horton: I would probably say the latter is more common.

Dr. West: That you just have limited tissue available.

Dr. Horton: We usually have limited tissue. The use of immunohistochemistry hasn't quite gotten out, I would say, to the entire community of pathologists, when I mentioned the TTF1 and P63. Those stains have been around for quite awhile. The utilization in this really has only come about recently from the advent of Avastin ® and some of the other chemotherapeutics that require that distinction.