Doctor Homer, maybe we can start off by you telling us a little bit about yourself and what exactly you do.

So I've come to New Haven in 1979 to be part of the Yale MD PhD program. I did a PhD in Immunology, a residency in anatomic pathology, and then subsequently I sort of risen to the ranks eventually become a professor in 2009, so anatomic pathology is an area that I not sure a lot of people in the community are familiar with. It is a branch of medicine. So pathologists are those people.
who’ve gone to medical school.
We have medical training,
but we’ve then specialized really
in looking more on the diagnostic end rather than on, you know,
the immediate clinical care of patients.

11 way to say it is that we care so much about our patients.
We want to make sure everybody has the right diagnosis.

In my particular case,
the area of pathology that I’m in,
which is pathology, is a very broad field,
but the area which I specialize in predominantly involves looking at histologic sections of lung tissue.

In order to understand what’s going on with the patient,
we do review radiographs.
I look at X rays, CT scans and PET scans and other radiologic imaging routinely.
I look at other clinical information that’s available in patients,
but at the end of the day,
the particular skills that I bring is understanding the histopathology of a variety of diseases involving the lung,
in particular lung cancer,
but not only lung cancer.
So you know, we’ve talked on this show previously about lung cancer and the fact that almost universally, for most cancers, nearly everything starts with the pathologist everything starts with the biopsy so can you tell us a little bit about the different kinds of biopsy there are the The Advantages and disadvantages and how that impacts you as a pathologist. I think that’s a great question, so it is certainly true that for some tumors there are variety of ways of getting a diagnosis, but for lung cancer, particular, as you say, histopathology really is. Still is a central element of the diagnostic process. The kinds of biopsies when could obtain range from getting a what’s called a cytology or a smear of cells, and those cells can be obtained in a number of different ways. If a patient happens to have a what’s thought to be a possible metastasis in another site, you could put a needle in, maybe even through the skin, like into a lymph node around the
Just put a needle in, just obtain a smear and aspirate. With a syringe on it, a little suction on it, get a few cells into the Chamber and then smooth them onto a slide and stained and looked at it.

Historically, that was really the major way in which a lot of lung cancer diagnosis were made and there was a very simple classification that we used what’s called non small cell and small cell carcinoma and by and large that very simple technique of just putting smear cells on the slide was adequate for that.

And we still use things along those lines. It might involve, as I said, putting a needle into the skin into some very superficial part of the body.

Like I said, a lymph node or a lymph node under the armor around the neck.

But it might also involve a medical procedure where they put a bronchoscope down the patient into the lungs and just do a washing where you put in fluid, and then you aspirate the fluid and then again he is take that
fluid and you smear it on his slide. Or if you have fluid around the lungs that might take some of that fluid, and again smeared on a slide, those are all ways in which, again, you can use the vast majority of cases can make a diagnosis, as one might imagine, the sensitivity of that is going to depend on a lot of factors, the amount of tissue obtained, the kind of tumor it is, if it is in fact the tumor, what else is going on with the patient, and so those are all you know historically, that sort of the classic ways which we did it. More recently, I have to say that the we’re much more. We get more information out of what’s called the histopathology of tumors, whereas if you take that same smell, cell smear and then you can prepare it such that you could make a pallet of cells you make, take those cells, use pin them down, you make a collection of cells. You then actually can take a fix. Those cells in a fixative in process them as if they were regular. Tissue biopsy and then two sections of it.
And then you’ll have cells that you can actually look at in a slightly different way.
The advantage of that method is a couple of things. One is you can start looking at so-called immunostains. That is, we take antibodies against cellular components. We apply them to the tissue, and then we sort of see which elements of the cells are present and different cells will be able to stay in a different. The different patterns in a large part of my job has to do with understanding the exact patterns from different kinds of stains. They’re used again, they have different degrees of sensitivity. That is, you know, are they true positive if it stains, or if it’s negative, is that really a negative? And how you know?

And that’s a large part of my job, has to understand just how good that processes and understanding it. In addition to staining again, these kind of small samples where you
take a smear and you can make a cell
so called cell block out of them.
You can also do biopsies of various types.
One biopsy technique is to again to take a
Bronchoscope,
which goes into the patient’s lungs,
and the bronchoscopies would then
maneuver it down into the lungs,
where he then takes a small piece of tissue.
Using a biopsy forceps and there’s
a variety of tissues they can get.
This way they can get some
lung tissue itself,
but they also they’re extremely good
at getting using that technique to
get lymph nodes within the chest,
which gives you a sense of whether
the tumor has spread or not
spread to adjacent lymph nodes.
And this is critical for understanding
a therapeutic approaches.
Alternatively,
sometimes the tumor or this deletion
of the suspicious lesion is in the very
periphery of the lung near the chest wall,
and sometimes you’ll then have a
go to CT scan and then you can have
someone who can put a needle through
the skin into the lung that way,
so and then of course,
people who have unfortunately more
advanced disease where they might have a lesion somewhere in the liver or in bones, those can be biopsied again by. Usually by CT scan or by under ultrasound guidance and obtain piece of tissue, which then again is submitted for routine Histology. Finally, not very commonly, but occasionally we’ll have cases where there might be a surgical intervention where you’re really not sure what the lesion is. And it might be small. It might be difficult to obtain and the one way you’re absolutely certain to obtain the tissue that’s diagnostic is to surgically resect it even without a specific diagnosis, because if you go through the appropriate work up from there, clinicians who really think, look, we really think this is probably a cancer, and the only way we can know for sure, it’s really take it out and really show the entire thing to a pathologist. Problem one of the problems in lung pathology is that. Lung cancers or lung tumors commonly
have areas where there’s lot of scarring and a lot of inflammation, and if you get a biopsy, which only shows that you’re never completely sure that you haven’t missed an actual cancer. And so again, with the appropriate work up and with really careful thinking and with discussion with the patient, you might go ahead and actually surgically remove a nodule entirely and then send it to a pathology. At that point, there’s really two choices. You can either send it to what’s called the frozen section area, where we have people who are stand by, you know all the time and we’ll take those and get make a rapid section out of that and you can do that by literally freezing the tissue and then cutting sections on specially equipped machines called cry items which can make sections which the pathologist can look at within a few minutes of the specimen arriving in pathology. Pathologist looks at that and very quickly makes a decision. Is this look like a cancer or does this look like something else?
And those are you know those though.

That kind of analysis is extremely accurate.

I just recently looked at our jails, institutions experience and,

you know, in almost all cases it’s not perfect.

There are certainly examples where

it’s not completely accurate,

but by and large it’s a very, very accurate technique and you can tell

immediately whether it is in fact a cancer.

Alternatively,

sometimes people will simply

take that tissue and submit it

whereas.

Where we process it as we would any other

specimen where we fix it in fixative,

we then section it.

We then submit it for routine astrology

and that usually takes overnight

if the tissue is small enough,

we might be able to do it the same day,

but usually we do it overnight.

And again we look at it the next day.

And in all these cases again,

we’re very commonly would be using.

As I said,

these stains that we can use to

highlight specific molecular

features of the tumor or to
understand exactly what it is and characterize it a little bit. 

So there are a whole variety, as you alluded to, of types of biopsies and types of techniques of looking at these tissues to come to a diagnosis. I think a few questions come to mind.

The first is when you’re looking at these tiny cells. You know when you talked about putting a needle into something and aspirating a few cells. I’m sure that people wonder how easy is it for you to tell that. Is a cancer cell versus not a cancer cell or a non small cell cancer cell versus a small cell cancer cell? How sure are you when you make that diagnosis especially when it’s just a few cells. I think I agree that this is really part of the training, we’ve all you know, one of the things that pathology involves is really a lot of hands-on experience. That’s number one number two. We are very sensitive to the notion of
that we don’t want to, you know, call something a cancer that’s not cancer, and so again, as part of the training, we learn very carefully that there’s a minimum number of cells you really need in order to make a specific diagnosis. And there’s no, you know, magic number in terms of exactly how many cells that is. But I you know one cell is certainly not going to be enough. And you know, is 100 cells necessary? We certainly get down into, maybe, you know, 100 cells, or maybe in some cases fewer. But largely we’re very sensitive for the notion we really want to see a population of cells that are really clearly represent a malignancy. And the other thing we do is particularly on the smaller samples we commonly, you know, pathologists will commonly show things we, each other. We’re totally, you know, there’s no sense of you know, ego involved. We show each other things. What do you think? What do you think? Is this enough and we generally anything where there’s even a marginal call. We show things to each other and
we document that we’ve shown it to somebody else who agrees with us.
So that’s really sort of intrinsically baked into our process, and I think that the you know, if you actually were to go and look at the literature. You’d say that the based on you know if summaries people have done this in pathology extensively, whereas you ask and you go back and look at other peoples diagnosis. How often are you correct and you know, I can’t say everything is perfect. There’s nothing in life which is completely perfect. But by and large it’s extremely good. And so I think that you know if there is really any doubt you know patients can always ask for to send it to another institution. I don’t recall a case at Yale where you know we’ve had a change diagnosis along this line, certainly. People can have other opinions exactly how to classify a tumor, but by and large we are very careful to try to prevent anything where that’s really an issue. Terrific, well we’re going to learn a lot.
more about lung cancer pathology
right after we take a short break for a medical minute.
Please stay tuned to learn more about
lung cancer pathology with my guest
Doctor Robert Homer.
Funding for Yale Cancer Answers comes from Smilow Cancer Hospital,
where the breast Cancer Prevention Clinic provides comprehensive risk assessment,
education and screening for women at increased risk of breast cancer.
To learn more, visit yalecancercenter.org/genetics.
The American Cancer Society estimates that
over 200,000 cases of Melanoma will be diagnosed in the United States this year,
with over 1000 patients in Connecticut alone.
While Melanoma accounts for only about 1% of skin cancer cases,
it causes the most skin cancer deaths,
but when detected early,
it is easily treated and highly curable.
Clinical trials are currently underway at federally designated Comprehensive cancer centers such as Yale Cancer Center and at Smilow Cancer Hospital.
To test innovative new treatments for Melanoma,
the goal of the specialized programs of research excellence and Skin
Cancer Grant is to better understand the biology of skin cancer. With a focus on discovering targets that will lead to improved diagnosis and treatment. More information is available at yalecancercenter.org.

Welcome back to Yale Cancer Answers. This is Doctor Anees Chagpar and I’m joined tonight by my guest doctor Robert Homer. We’re learning more about lung cancer pathology and Doctor Homer, right before the break you were talking about the fact that there’s a lot of training that goes into being a pathologist, and that’s really important because. You know you really need to be able to recognize the difference between a cancer cell and a non cancer cell when making that diagnosis and when you have questions or concerns, do you have enough of a sample or it’s kind of a borderline call? There’s really no issue in terms of seeking another opinion and you as pathologists do that a lot. You’ll show that to other pathologists. So one question that people who
Are listening.

Ask is you know, should patients, when given a lung cancer diagnosis, seek a second opinion with regards to their pathology?

At another institution, if they’re not sure, and because, how can a patient really be sure, aside from the fact that most of us have a lot of confidence in the institutions that we frequent?

I think that anytime if there is a patient really unsure, you know I’m you know. I sort of think about this in medicine. I think this is sort of a general question about any medical advice.

So pathology report is is medical advice. I think that if you see an oncologist and aren’t sure about their advice you give, you should be free to seek another opinion. If you seek a surgeon and get different advice you want and you’re not happy with it or you’re concerned and you want to make sure that you’ve seen it, you can get a second opinion.

I don’t think that.

Salty diagnosis or any different? I think you would put it in the same category as any other medical opinion, and you know if there’s really
any concern. I think that that’s a fine thing to do. And so you know, I think one of the big distinctions is cancer versus no cancer, and one of the things that you mentioned before the break was that you’re really very careful about calling cancer versus not cancer. And so tell us a little bit more about the nuances you mentioned that you know there’s classifications in terms of small cell and non small cell. How do you make that distinction and why is it important? Or is it important to patients treatment? So the historical distinction between so-called small cell and non small cell really goes back to the 1960s and 70s where it was understood that the vast majority of people with what’s so called small cell carcinoma were most likely had a systemic disease on presentation, and they responded to certain types of chemotherapy that patients with so-called non small cell carcinoma did not. And that’s really sort of become. Sort of a founding principle of the field of thoracic oncology for a long time. We certainly at the you know, back in the 60s to 70s we didn’t
have really any ancillary so called ancillary techniques like immunostains for molecular diagnostics and so that was really just based on the morphologic appearance of the cell. With a few relatively by our current standards, crude stains these days, it’s really pretty clear that you can improve the reproducibility of the diagnosis by getting some stains. There is a one particular paper that I use routinely. But that’s an international that show that international consensus of difficult cases that people agreed were not straightforward could be improved by using immunostains. And I also think that these days, with molecular diagnostics being as advanced as it is, there are very rare cases where that can be helped. It’s clear that, again, so called small cell carcinoma has a very distinct molecular signature, whereas tumors of so called non small cell have a range of other signatures which really would not be expected to be seen in that. So I think that there is,
you know,
the basic diagnosis is certainly suggested by just routine Histology,
and there’s clearly cell,
clearly tumors which are just not small cell.
If you just look at it and say there’s yeah,
that’s just not what it is,
you don’t really care about any of the other markers that are present and there’s other tumors where you say you know I’m just not sure those are relatively.
You know, maybe 5% of cases where people have that thing.
But of course you know at any larger Cancer Center.
So we do have a sort of a, you know,
like Yale or other large cancer centers,
we see enough cancers that they they show up.
You know, all the time.
So we do have a sort of a, you know,
a standard protocol for a for resolving that.
In terms of non small cell carcinomas,
we know that there is really two major subtypes within that admin,
so called adenocarcinoma and squamous cell carcinoma.
And there’s excellent markers that distinguish those two things from each other.
We know that there’s a large percentage of those cases which might be surgically resectable. We also know that all of the oncology protocols for patients who do not have resectable tumors. That’s like the first thing, pretty much in all the protocols is to understand which of those two pathways it is. It’s in pretty much all the molecular work up after that depends on that fundamental distinction, and a lot of the therapeutic. Decisions are based on that as well. Not entirely, but largely.

We have excellent markers that distinguish those two things these days, and all lung tumors that have enough tissue to evaluate would most likely get one of those, unless it’s, again, histologically. You know, quite straightforward.

And so that’s really important because it influences the type of treatment that that patients get. Is that right? It is it distinguished influences the treatment they get, but also to a certain extent the work up.

If you have somebody with which seems to be a like a localized, there rarely.
Again you have cases which are look like a localized small cell. The oncologist might try much harder to really convince himself or herself that that’s really a truly localized tumor. Because the likelihood that they’re probably missing something, so they might do a more extensive work up than they might otherwise. And it’s also true that a lot of our patients have more than one tumor, unfortunately, and so a lot of much of what I do, you know, is direct with fast conchology is a pathology or other is to really look at patients who have more than one tumor and really connect yourself that what you’re seeing is which of those you know. Is this really a primary lung tumor, or is this really coming from somewhere else? And so understanding that distinction is important in order to help with that decision making process as well. You know you mentioned molecular diagnostics a few times and I want to dive a little bit more into that.

We’ve talked about personalized medicine and targeted therapies. The idea that these days pathologists, can you know, look at these tumors in
a variety of ways to kind of unlock
the genomic signatures of them,
identify whether they express
certain receptors or certain
proteins that then are targetable.
With certain drugs, how common is that done?
It should, should patients be
going to their medical oncologists,
asking about you know whether they have
a BRAF mutation or a veg F mutation,
or that kind of thing?
Well, the good news is that there
are quite a number of consensus
statements on which tumors are
really the appropriate ones to do.
The mock their testing on their
variety of professional societies,
which include both pathology and oncology,
which is really very, you know,
very explicitly stated who should
get this kind of profiling.
So for example, as I mentioned,
the distinction adenocarcinoma
and squamous cell carcinoma is
really critical and it’s really
quite clear that the guidelines.
Or recommend that anyone with a
nano carcinoma should absolutely
have unlocked the profiling.
That’s really and at Yale.
Let’s say that 100% anyone with
adequate tissue will have that done. I should also point out the fact that even though we like to think of this as a tissue based process, there’s now also the options to get some of that molecular profiling done just by a blood test. It is not as sensitive as getting adequate piece of tissue, but if it’s, you know if it detects it, appropriate genetic abnormality, then it can be. I think we’re all pretty comfortable that we can rely on it.

On the other hand, as I said, having an adequate piece of tissue to do that is still considered the gold standard. Patients with squamous cell carcinoma, unless with relatively few exceptions, are not thought to benefit from sequencing.

Again, there are few. There are a few exceptions and because there are a few exceptions, some oncologists do would like to see their lung cancers from these patients sequence as well. But that’s a much, it’s more of a very specific decision. That needs to be done individually, I think now and I should also point
out the fact that from my perspective, even though we like to talk about Gnostics as being particularly important for specific therapeutic decisions, so do I have a mutation in a gene where there’s a specific drug that targets that specific mutation, which is great when we have it. It’s also true that from my perspective, sometimes that but profiling could be very useful to decide whether something is in fact a lung cancer or from somewhere else, or it’s actually fairly common to have patients who have had a lung cancer to then have a second lung cancer. And sometimes we use it to distinguish whether is this really the same tumor which is record? Or is this really a new tumor? And at the again there may be therapeutic implications from that, depending on the specific patient circumstance.

So it sounds like you know these decisions are are really critical and or can be. Now you mentioned that with Frozen section you can make a diagnosis in minutes, but in terms of getting all of the information you know small cell versus non small cell adeno versus squamous,
the molecular profiling. How long does that take?

So the add new versus squamous distinction so frequently that you know that depends on the specifics of the tumor.

It’s pretty common in a tumor which is so called well or moderately differentiated. That is still has histologic evidence that is producing these particular histologic features.

You can tell it just at the time of frozen section would be pretty comfortable with that. There are other tumors where it’s a very undifferentiated tumor.

It really does not the Histology of the just looking at it doesn’t really tell you very much.

They needed a stains. No, it depends on you know that could be a day or two. Might be your students aren’t terribly helpful.

You might do a second round, so that might be a few days and then the molecular work, which includes one marker which helps determine how available you are or how effective immunotherapy is likely to be. With civil PDL.

One stain that should be done
within another few days or a week, and then they’ll look up profiling. Again, should be done. There’s again national standards that should be done within two weeks. So it can take up to two weeks to get, you know, kind of a thorough pathologic work up of your cancer is that about accurate? I think that for lung cancer, I think that’s where we are the peripheral blood testing. If it shows something, might be a few days before that, but it’s not going to be. You know, it’s not going to be just a few days, it might be 10 days instead of two weeks, but that seems to be where we are at the moment. The reason I bring it up is because you know when patients and people hear that. You can make a diagnosis in minutes with frozen section. They often will then go to their clinician saying why is it taking so long to get the pathology back. On my lung cancer can we get started with treatment? So I think that you’ve kind of elucidated why it takes so long
and I personally have a maxim that says never rush the pathologist. Their opinion is too important. I appreciate that we all you know we want to get it right. We all. I think in pathology we're all really very aware that somebody is waiting for these diagnosis. You know we're not, you know, I, always personally have a feeling that you should be accurate, but you should also be fast and I think that they're both important. You know nobody is going to cut corners. On the other hand, nobody wants to, just, you know.

Slow walk this the diagnosis out the door yeah so in in our last minute or two maybe you can tell us what's on the horizon in thoracic pathology? What do we have to look forward to? That's a great question. I think one of the things going forward is really a better understanding of exactly how the immune system works.