

**Expert Round Table with Drs. Anne Tsao and Alex Farivar
Part 1: Elderly Man with Indolent Bronchioloalveolar Carcinoma**

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Dr. West: I'd like to welcome everyone, thanks for coming out to our lunch with the experts.

I'd like to introduce Dr. Ann Tsao, who is an assistant professor at M.D. Anderson Cancer Center. She works in Thoracic, Head and Neck Cancer and has particular expertise in lung cancer as well as mesothelioma. She has grown up in Chicago and has trained and been living in Houston at M.D. Anderson for several years now.

Also joining us is Dr. Alex Farivar. He's a thoracic surgeon at Swedish Cancer Institute; had done training at the University of Washington and then went to the Harvard system working at Brigham & Women's Hospital for additional thoracic surgical training before coming back to Seattle to join the Thoracic Surgery group here.

The first case I wanted to bring up is a 75-year old Chinese man who has multiple medical issues that aren't particularly acute. He has coronary artery disease and atrial fibrillation. He has a remote prior smoking history. He actually quit smoking over four decades ago, quitting in 1962 and smoked a pack per day for 15 years.

He had what is called a ground-glass opacity, a small area on his chest CT that had been noted. This is not a solid mass, but more hazy. He underwent a left upper lobectomy so the top half of his left lung was removed in late 2002.

The pathology showed well differentiated lung cancer, a subtype called bronchioalveolar carcinoma in two different foci there. They were a few centimeters apart. They were both very small. One was a centimeter and one was 0.8 centimeters. There were several nodes removed that were negative. But the fact is that with two different areas of cancer in the same lobe, by our staging system up until a new revision that is just happening, this is considered T4, so a fairly higher stage than just a single focus of disease. If it was a single one centimeter area, that would be stage I. With two, this system would have it go all the way up to stage IIIB and that suggests a worse prognosis, but in fact that's not necessarily the case for this situation.

So a lot of this happened before I came on the scene. He transferred his follow-up care to Swedish Cancer Institute and he had CT scans over a

few years that raised the question of a couple of other ground glass opacities which would come and go. At least one spiculated right upper lobe lesion seemed to be enlarging over time, but still quite small; yes growing, but very slowly over time. I'll show the progress over time. Not surprisingly with a spot that is only growing from 5.5 mm to 7.5 mm, he didn't have symptoms associated with that. His lung function, that's listed here at the bottom with FEV1, is what's called a pulmonary function test showing that his lung function was good enough to be considered for additional surgery.

Here are his scans. Obviously, this is several years ago and you can see that, yes, there is a spot that becomes more prominent in the top portion of the right lung over time, but its changing on the order of a millimeter or less every year.

So I'd like to start with asking Alex, its not rare to have a situation where you have one larger or more easily visualized nodule and a background of a few questionable ground glass opacities. Oftentimes that one more dominant growing area is biopsied and shown to be an adenocarcinoma or specifically this bronchioalveolar carcinoma or BAC. When you see a patient who has one nodule but some background stuff that is questionable for multifocal disease, how concerning is that to you versus proceeding and ignoring the background stuff?

Dr. Farivar: I think in general, this is a classic case of bronchioloalveolar carcinoma with respect to some of the issues that arise. This patient's already had a lobectomy, is somebody who's starting to get a little bit older, 75 years old, has a smoking history, we're already starting to see that their pulmonary function tests are not quite as good as what we would expect had they not had surgery.

This scenario brings to light a lot of what we think about when we see patients with bronchioalveolar carcinoma. 20% of the lung has already been taken out. One of the five lobes is gone. We have some other lesions whose bronchioalveolar before and now you can see there is another nodule that's slowly increasing in size and it sits right in the middle of the upper lobe. So as a surgeon if we were to try to take that out, we have a 75-year old gentleman with not great pulmonary function test, resectable, could tolerate an operation, but would we be doing the patient a good service by taking out now another lobe to take out a very small lesion that's growing with time.

I personally would elect in this situation to continue to follow and I would not have a strong desire to remove that at the present time.

Dr. West: Anne, what are your thoughts because we often do see patients where we're struggling not so much with "can we do this?", but "should we do this?" You have something that has maybe proven as cancer, in this case hasn't been yet, but even if you knew that, you've raised the question of whether its going to be clinically relevant to the next five or more years.

Dr. Tsao: I absolutely agree with Alex. I think in this situation we need to monitor the patient very closely. He's already proven over two year's time that this is very indolent disease. I think in this situation we would advocate not going forward with surgery even though it could be done, but monitoring him closely because of the biology of the disease. Our first credo is to do no harm.

Dr. Farivar: I could have easily said this operation can be done without a doubt. It's the question of should it be done? I don't think given the information that we have and given the location of that lesion and the pathology we have and the progression of this cancer that we should move forward.

Dr. West: Backing up a bit to somebody who has two or maybe three different spots of disease in the lobe that's resected, say it's the first time, that is suggestive that this is more likely to be an issue down the road and it may be metastatic. Does that make you, Anne, more likely or less likely to recommend systemic therapy after surgery?

Dr. Tsao: Well it's certainly a consideration. This would be what we call multifocal bronchioloalveolar carcinoma. All that means is that this patient has a different biology of this disease. So, while we bear in mind that this patient might have future episodes where the disease comes back in particular areas, we know already that this gentleman has a very slow growing disease. It doesn't like to spread. It doesn't like to do very much. So he's very lucky in the sense that we are able to not have to treat him. I usually err on the side of being very conservative with these patients. I don't see any great need to treat him provided he has a) no symptoms, and b) provided that his disease remains very well controlled, which I would say by itself is very well controlled.

Dr. West: Let's say a couple of years go by and he has multiple new foci that are growing. What would you be inclined to recommend for systemic therapy? Would you say chemotherapy in a gentleman who is an Asian *remote* prior smoker, would you use the tissue that's already from a prior surgery to test for an EGFR mutation or would you want to get another biopsy at the time that you're considering treatment?

Dr. Tsao: Sure. In this particular patient, at the time that he shows that there is more disease growth that would be the time we would come in and repeat a biopsy so we could look at the particular genetic profile.

If they are carrying a mutation in the epidermal growth factor receptor gene, or EGFR, this definitely would be someone I would treat with a pill called erlotinib, or Tarceva.

This pill has been shown in patients who carry this mutation to actually have incredible benefit for the patients. This patient may be fortunate enough to be on a pill for a couple of years.

Dr. West: Would you be inclined to suggest or recommend that pill therapy if you did not have mutation testing available?

Dr. Tsao: I think that that is a difficult issue because practicality versus what we should technically do are very different here. Technically we should get an EGFR mutation test if this isn't a patient who has not had prior chemotherapy. However, the practical nature is its very hard to repeat core biopsies on our patients, especially in the lung, and there are certain complications that could potentially occur.

Dr. Tsao: I would prefer to see an EGFR mutation status on the tissue for any patient period. However, there are some patients that are more likely to carry this mutation. Those would be patients who have adenocarcinoma histology, those who are Asian, women and these are all patients who usually have never-smoking history or less than 15-pack year smoking history. That's not to say though that a man who has a 20-pack year smoking history couldn't carry the mutation -- they could, provided they have an adenocarcinoma histology. If a patient had all the clinical hallmarks that make them more likely to carry the mutation and I absolutely could not get any tumor tissue on them, sometimes on a practical side you might want to go ahead and treat them with the Tarceva, but you have to follow them very closely. You have to see them at four weeks and make sure that the drug is working. If the drug is not working, you need to immediately put that patient on to chemotherapy.

Now there could also be an argument said that in those patients where you can't get the EGFR mutation, you should automatically go to chemotherapy and then sequence them and give them an EGFR inhibitor later. I don't think that we know the answer to that. Right now either which way I think would be clinically acceptable for the treatment of the patient.

Dr. West: This is an old look at what PET scans would show several years ago. Not surprisingly the PET uptake was not even perceptible, very low. He actually had undergone a VATs wedge resection, so a video-assisted thoracic surgery, and a wedge resection which is less than a full lobectomy.

He had some modest complications with some atrial fibrillation -- he was in the ICU for a little while -- but he recovered from that.

He did not have a big surgery where they took out lymph nodes, but did have an 8 mm well differentiated BAC.

Alex, in general whether it's the first surgery or a subsequent surgery, how do you feel about a lobectomy versus a sub-lobectomy, a wedge resection or a segment in this situation, for say a 1 cm well differentiated BAC?

Dr. Farivar: If I knew the pathology and the pathology clearly told me that it was a BAC, I would have absolutely zero reservation doing a sub-lobectomy operation. I do not think BACs need to have an anatomic resection. In fact, I think it's preferable to preserve as much lung as you can for this exact reason. If additional lesions come up over the course of several years, you don't want to have already taken out more lung than the patient's going to be able to tolerate in the future and require oxygen and have difficulty with their breathing.

So that assumes that we know its BAC. If we do, then I'm comfortable doing less than a lobectomy.

Dr. Tsao: If I could add, one of the new technologies that's under development is stereotactic radiosurgery which, not to detract from our surgeons that is a possibility to try to spare lung tissue in patients that may not be the best surgical candidates also.

Dr. West: That's really something that we haven't looked at very much. Its come on to the scene so recently and in truth a lot of patients would really prefer to have it out if they can. But I agree that that idea of trying to control what is likely to be a very controllable cancer while causing as little collateral damage and losing lung tissue is an attractive idea.

The idea behind the sub-lobectomy, can you talk about what evidence there is in Japan or the United States to support the concept?

Dr. Farivar: we've found that BACs tend to recur with time. There have been certain classification systems developed; in particular the Noguchi classification system. If you have a BAC and they're not very large, we've found that with Noguchi A and B which tend to be smaller, that literature supports doing a sub-lobar resection in this scenario.

Dr. West: Anne, a little different situation, but let's say you have somebody who has a 4.5 cm BAC with some solid component. It's not majority invasive, but there's some invasive adenocarcinoma and a lot of non-invasive BAC

which is a common situation that's its not pure but a mixture of some invasive and some non-invasive. Does that make you less inclined to suggest adjuvant chemotherapy postoperatively to reduce the risk of the cancer, either because you think it's less likely to recur than other cancers or because it's not as likely to respond to chemo as a BAC?

Dr. Tsao: BAC is tough because it's usually less than 3% of all lung cancer, so it tends to be a little bit more rare. We understand now that there's a wide spectrum of BAC -- that's why there are so many classification systems that have been created for it. If one had a primarily invasive adenocarcinoma component that is a little bit more of an aggressive phenotype than just a pure BAC. In those patients I would be more inclined to treat them as if they were a pure adenocarcinoma patient.

So, if they had no other evidence of disease elsewhere, they had a resection for a 4 cm tumor that was predominantly adenocarcinoma, I would pretty much go to the adjuvant treatment guidelines which do suggest that for stage IB patients who have a 4 cm or greater tumor that they do get some benefit from adjuvant chemotherapy. In that patient I would consider that.

But I would also test them to see if they have the EGFR mutation and if they did, then I would consider giving them adjuvant Tarceva.

Dr. West: That's interesting, because it is something we scratch our heads about now because we don't have data showing a benefit with Tarceva in the adjuvant setting and yet if we knew someone had a mutation, that's exactly the person you'd think would benefit the most from it.

Dr. Tsao: There is a Phase III clinical trial ongoing right now called the RADIANT Study that is looking at adjuvant Tarceva which hopefully we'll get some data from that and we'll know more.

Dr. Farivar: I think from a surgical standpoint as those lesions become larger, 4-5 cm and have components that are solid in them, it makes a surgeon more worried that we're dealing with more than just BAC.

In that scenario, I would more likely want to do a lobectomy and a lymph node dissection. In the case that you've presented, after the first, once you have as much pathology as you have and we know what we're dealing with, then I'd feel more comfortable going on with a sub-lobar resection. But in the scenario you just presented I would not feel comfortable with a wedge.