

## Challenging Cases in Lung Cancer: Adjuvant Therapy for a Patient with a Smaller Node-Negative NSCLC Tumor?

### Dr. West:

Hello and welcome. My name is Dr. Jack West, and I'm a medical oncologist and the Founder and CEO of GRACE, the Global Resource for Advancing Cancer Education. Our program today is made possible through generous support from the LUNgevity Foundation.

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The same series of cases was discussed with multiple experts in the field of lung cancer from several different institutions to provide a better sense of where there is consensus and where there is still a wide range of treatment styles that might all be considered appropriate.

Each podcast starts with a brief thumbnail of a case presentation and then discussion from a live program done with Dr. Robert Doebele, Assistant Professor of Medical Oncology at the University of Colorado Medical Center in Denver, and Dr. Jyoti Patel, Associate Professor of Medical Oncology at the Feinberg School of Medicine at Northwestern University in Chicago.

The discussions will then continue with commentary by the several other clinical experts, including:

- Dr. Suresh Ramalingam, from Winship Cancer Center, Emory University in Atlanta, GA,
- Dr. Jonathan Goldman, from Premier Oncology in Santa Monica, CA.
- Dr. Julie Brahmer, from Sydney Kimmel Cancer Center at Johns Hopkins University, in Baltimore, MD
- Dr. Heather Wakelee, from Stanford University Cancer Center in Palo Alto, CA
- Dr. Karen Reckamp, from City of Hope Cancer Center in Duarte, CA

A 71-year-old woman with a good performance status is referred to you about four weeks out from a right upper lobectomy for what the pathology showed was a 3.5-cm poorly differentiated adenocarcinoma with some lymphovascular invasion. She's worried about that and is certainly willing to do chemotherapy but she's also not absolutely steadfast about it. This is a cancer that's not as large as we would definitely recommend chemotherapy. So Jyoti, if I could start with you, what would you be thinking about a tumor that is smaller than what we might consider our typical cut-off but is higher-grade and has some worrisome features in terms of getting adjuvant chemotherapy.

**Dr. Patel:**

The first thing that I would address is how confident I felt about the surgery. Tumor this size at my institution, we would probably plan to do a preoperative mediastinoscopy and then in the pathology I would look carefully to make sure that I felt there had been enough sampling.

If it was certainly the case, if the patient had been what I believe was truly a pathological stage, then the conundrum is tough. Certainly she is at high risk of recurrence by oncologic standards, but again she's in a good scenario by lung cancer.

One in five of these people will have recurrent disease and so we have looked to give patients adjuvant chemotherapy for a couple decades. The available evidence suggests that chemotherapy for her stage of disease – meaning no lymph nodes positive – would suggest that chemotherapy would be detrimental and may actually reduce her survival in a population

However, she has features that are high-risk and she does have a difficult tumor that could be susceptible. I don't think in 2011, though, we can pick out those patients and the chemotherapy comes with toxicity so I would likely suggest to just follow her expectantly and to hold off on adjuvant chemotherapy.

**Dr. West:**

Bob, how would you approach this kind of case of little smaller node-negative but some higher risk features?

**Dr. Doebele:**

First of all, I definitely agree with making sure that an adequate staging was done with mediastinoscopy – I think that's an excellent point. I also agree that currently there's no good data to suggest a benefit in this patient population. It is our standard that patients with IB disease, no matter the size or features, do get referred to a medical oncologist for a discussion of the potential risks and benefits of adjuvant chemotherapy in this group.

Even in a case where the tumor is greater than 4 cm -- and there was some post-hoc analysis suggesting that there may be a benefit in this group in the CALGB 9633 trial -- it's still a very difficult conversation, because if you look at the data from Stage IIA non-small cell lung cancer, the absolute improvement is about 5%. Out of a hundred patients that you treat with chemotherapy, only five are going to benefit, it's an incredibly difficult conversation under the best of circumstances.

I've considered chemotherapy in this group before, but I typically won't recommend. I'll have a very long and careful discussion with the patient about the potential risks and I agree with Jyoti's point that there actually can be harm and there was a suggestion of decreased survival in patients with tumors less than 4 cm in that group.

**Dr. Suresh Ramalingam, Winship Cancer Center, Emory University, Atlanta, GA:**

For node negative cancers that are less than 4 cm, the current data are not supportive of use of chemotherapy. In the CALGB trial, there was some disease free survival advantage, but there was no clear survival benefit that was statistically significant. And that has change our practice – that and the results from the NCI-Canada trial in which the subset analysis also showed that 4 cm to be a determinant of robust benefit vs. lack of benefit.

So when I have patients with less than 4 cm, my overall recommendation for them is a wait-and-watch approach -- or a regular routine follow-up approach. I struggle with these issues when there are these features in the tumor that would suggest maybe this person is at a higher risk, but I think the stage does capture their overall prognosis with variations from one to the other.

My thought is to observe them and not offer chemotherapy.

**Dr. West:**

Do you think that in some of these patients with smaller patients we may be causing more harm than benefit from giving chemotherapy?

**Dr. Ramalingam:**

In Stage IA, at least the meta-analysis showed that the hazard ratio was 1.4 with adjuvant chemotherapy where it clearly is indicative of harm. In Stage IB patients in that meta-analysis the hazard ratio was 0.92, which is as close to 1 as you can possibly get; and that tells us that at that level there may be some patient where it may be helping and a few others within Stage IB that we are not helping and potentially be harming with chemotherapy.

Those are all considerations when we make these decisions and that's why I tend to use this 4 cm as the cut-off based on the best available evidence as of now.

**Dr. Jonathan Goldman, Premier Oncology, Santa Monica, CA:**

I think adjuvant chemotherapy is a very special circumstance that you face as a medical oncologist because you hope to have the opportunity to cure a patient. You have to weigh against that the toxicity and also the uncertainty. You never know which patient you've benefitted and which you didn't. As you said, when the tumor is greater than 4 cm, most medical oncologists are advising to undergo chemotherapy and certainly when there is lymph node involvement, those are more clear cases.

A slightly smaller tumor then really your doing your best to weigh risk and benefits without clear evidence behind you. It comes down a lot to the patient. In this case, this woman it sounds like otherwise she's healthy and the values that she has. In this circumstance, many people lean towards wanting to do whatever is possible. You have to advise a patient to not go too far in that direction. Since you don't know how much you're benefitting a patient, you have to temper all of the decisions and not try to rationally try to make a decision just out of fear. At the same time, someone in this circumstance with a 3.5 cm tumor, that's quite close to 4 cm. if someone is wanting to undergo more therapy, I think it's reasonable. I have other patients with 1 and 1.5 cm tumor and there I feel quite strongly to advise a patient not to. Some of the data even shows a detriment for those smaller tumor patients.

**Dr. Julie Brahmer, Sydney Kimmel Cancer Center, Johns Hopkins University, Baltimore, MD:**

I think size isn't all of the answer unfortunately. Certainly discussing adjuvant chemotherapy with this woman. She's not an elderly woman, but certainly on the cusp. Ideally cisplatin based chemotherapy would be what you'd want to use in this case. But not all patients can tolerate cisplatin, so certainly that has to be taken into consideration. The poorly differentiate adenocarcinoma makes you a little bit uncomfortable suggesting not doing chemotherapy just in the fact that this may be more of an aggressive tumor. So some of the history behind that would be good to know.

Like, how quickly did this come up? If there was any sort of history of a nodule there previously. And also sometimes we'll look at actually EGFR mutation as well as KRAS mutation, and in

someone who would be KRAS mutation positive adenocarcinoma, that may be a little bit more aggressive type of tumor: I may want to try some chemotherapy in hopes to prevent the tumor from coming back. But even as a stage I tumor, she actually has a high chance of this not coming back. But unfortunately, not all patients are that lucky and do have the tumor come back in about 30% of the patients.

**Dr. West:**

Do you even use molecular factors like ERCC1, which in the IALT bio retrospect of analysis suggested it might of some use in discriminating who is more of less likely to benefit or does its lack of prospective validation keep you from using it?

**Dr. Brahmer:**

I think the lack of prospective validation does keep from using it. However, some of my patients do come with that data already, and I try to incorporate it with the caveats that we talk about. If the person looks like that they would benefit from platinum, their tumor would benefit from platinum, then potentially we would push a little bit harder than someone who we know whose tumor probably wouldn't. But we don't know that in a prospective fashion. I don't routinely order it on my patients.

**Dr. West:**

I believe the data from the JBR10 adjuvant trial suggested that the people who have a RAS mutation don't benefit from adjuvant chemotherapy even if they have a worse outcome overall. So it's tough when the data might suggest that, if anything, you might provide no more benefit for those particular people.

**Dr. Heather Wakelee, Stanford University Cancer Center, Palo Alto, CA:**

Part of it is going to depend obviously on how fit she is. If she is very fit then it makes it a little harder question. If she's not so fit that makes it easier because there is certainly potential harm from the chemo.

Part of it is her anxiety level about getting treatment and feeling like she's done everything possible. And then I would talk about the data with her and explain that for a tumor that small we don't really have any firm data of benefit, but that being said I don't think there's anything magical about 4 cm. I think there's a continuum of benefit and probably in the smaller tumors, there isn't any benefit and in the bigger tumors there definitely is – obviously in the absence of lymph nodes.

Where is that magic number? I don't think we know. Four cm is what's they looked at in a couple of trials and that's certainly what we use in clinical trials that are ongoing right now, like (ECOG) 1505, so she won't qualify for that. But 3 cm, she's going to be anxious and feeling like she's not done everything. She's otherwise healthy I don't think that giving her four cycles of cisplatin would be wrong and I would certainly give that to her as a possibility.

The lymphovascular invasion is an interesting component. We don't really know what to make of it. There was an abstract percentage at the Chicago Lung Meeting in December where they looked at micro- basically vascular invasion and showed that that was as significant in their analysis as having some nodal involvement or having a bigger tumor and so I don't think that's validated enough yet to really use it but it certainly adds to the discussion with her.

So I wouldn't strongly endorse it, but if she came across after that discussion and said, 'You know, I really would want to do it', I wouldn't feel that it was a wrong thing to do.

**Dr. Karen Reckamp, City of Hope Cancer Center, Duarte, CA**

So I think the first thing I think about is the size, and based on the subgroup analysis looking at chemotherapy for Stage IB, I use the 4 cm rule. Other high risk features -- I know the NCCN guidelines talks about other high risk features, but those haven't been clearly identified in any clinical trial. So in a patient like this, I take the performance status and other co-morbidities into account and would have a detailed discussion about the risk and benefits because even with chemotherapy, they're in the range of 20%, grade 3, grade 4 toxicity is related with it. So, I think I would recommend in this case for close monitoring and probably not recommend chemotherapy but would give a balanced discussion of the risks and benefits of chemotherapy.

**Dr. West:**

I hope that the program was helpful, and we'd also like to again thank the folks from LUNGeVity Foundation for their partnership on this program.