Challenging Cases in Lung Cancer:
Managing Stage IIIA N2 Squamous NSCLC of Debatable Resectability

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 them 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

The next patient is a 62 year old man with a moderately differentiated squamous cell, non-small cell lung cancer, just under 5 cm in the right lower lobe. He has a modestly enlarged mediastinal node at 4R and also at station 7 that measure 1.2 and 1.7 cm on the CT. He also had a PET scan that shows uptake in the range of and SUV of 5. He ultimately sees a surgeon and has a mediastinoscopy that confirms involvement of disease in those two stations. But the rest of his work up shows no evidence of distance disease. At this point, it is multi-stationed, but it's not bulky. The question is, at your institutions or in your own recommendations, do you have a preferred approach for this situation of multi-station Stage IIIA N2 non-small cell lung cancer, in terms of surgery or non-surgical approach? And if it is a pre-operative approach, what do you tend to favor for a pre-operative strategy. I'll start with Bob, if you can.

Dr. Doebele:
Sure. So a Stage III lung cancer is one of the most interesting and gives us the most room to practice the art of medicine. Most of the institutions, I've worked at two institutions, and typically anything over single station disease, we favored chemo-radiation over surgery. Although, you bring up an interesting point that this is non-bulky disease. For single station N2 disease if this is PET avid disease, we might even treat with induction chemotherapy first and then do a mediastinoscopy after induction chemotherapy to see if there's been clearance. If there's not, then move on to more definitive chemo/radiation. I think with Stage III disease, the survival with either chemo-radiation or surgery and other modalities is often very similar. The five year survival rates typically hover around 20% and that, unfortunately, most of our patients fail more distantly because our staging techniques fail to pick up microscopic metastatic disease.

So, I think both are very reasonable. But typically for multi-station disease, I think we would favor chemo-radiation in this setting.

Dr. West:
If you do a surgical approach, do you favor chemotherapy alone or a smaller dose of, a shorter course of chemo and radiation then, leading into planned surgery?

Dr. Doebele:
I've done it at institutions where we've done it both ways. I think the outcomes are very similar. So typically when I've done chemo-radiation, we do a smaller dose, typically 45 Gray. Again, for multi-station, I've typically shied away from planning a surgical approach; in that case we go to a more definitive dose of radiation.

Dr. West:
Thanks. So, Jyoti, let me turn to you. How would you typically approach a patient with Stage III N2 that is more than one station but is not extremely bulky?

Dr. Patel:
So, generally I would agree with those comments in that we would treat this patient with chemotherapy and radiation. I reserve a chemotherapy alone strategy for patients who either have microscopic disease or have one station of confirmed disease by medistinoscopy. This is a subcarinal node and an R4 node. These are intervening nodes that you can't really get a good handle on with just mediastinoscopy often times. So, we have two confirmed areas. We would, at our institution, treat this patient with full dose cisplatin, etoposide, and our radiation would be generally go to 60 or 66 Gray. This is definitely a gentleman in which we would consider resection. And for the following reasons: this is a 62 year-old man presumably, like all of your most of your patients, these are very healthy people who are active and feeling well. So if he doesn't really have problems with COPD or other co-morbidities, so this is a well man, our approach would be to attempt tri-modality therapy. The patients in which we will not do surgery are patients who would require a pneumonectomy, for example, after chemotherapy and radiation, and we know there's increased mortality.

The inter-group study, Kathy Albain's study, looked at giving abbreviated radiation to 45 Gray and taking patients on to surgery or completing chemotherapy and radiation. My feeling is that break could be detrimental to patients. A re-evaluation at 45 Gray gives cancer cells a chance to repopulate and there's not really that much more information that you get at that point.

So we generally go full course. Our surgeons generally feel very comfortable doing it. If they are going to operate though, they want to do so within six weeks of chemo or radiation. These patients are followed very closely. We often do a CT scan to make sure we aren't running into toxicity issues in the fifth or sixth week of radiation to make sure we're all on the same page as to what's happening with the patient. But we definitely offer a lobectomy to patients with multi-station disease. Again, these 1.2 and 1.7 are small nodes. I think, traditionally they would call bulky adenopathy, things that are over 3 cm. So these are small nodes in a well gentleman, if he flies through full chemo/radiation, then we consider a resection. The intergroup study, again, most of the people that had problems were those that had to have bigger surgeries for clearance.

Dr. West:
So, the option of doing chemo/radiation at a full dose followed by surgery, tolerability has been ok, you've found? Let me ask also, do you use, do your surgeons do a mediastinoscopy after this as any kind of decision strategy of whether to proceed with the resection or not?

Dr. Patel:
They don't. If the patient has had a pre-operative mediastinoscopy, we would go by imaging alone. But they would probably sample the nodes, so their approach would be with that to look at the mediastinal nodes and consider the lobectomy if there was gross positive disease in those nodes and they would probably stop. Often, these patients, especially with R4 nodes and maybe subcarinal nodes, we would've sample endoscopically either with bronchoscopy or EGD. So we'll have the staging before, and then we'll give chemo/radiation and save the mediastinoscopy before we treat it. We won't do a repeat mediastinoscopy. Our feeling is generally that truly doing good stationing after chemo/radiation with EBUS is difficult.

Dr. Suresh Ramalingam, Winship Cancer Center, Emory University, Atlanta, GA:
So this patient, having non bulky multi-station disease tell us clearly that he is at high risk for recurrent disease. This is Stage IIIA disease. This is something that we often discuss in the tumor board and there are many opinions. My own view is, the more the number of stations that are involved, the less likely that we are going to help them with surgery. Using the definitive chemo/radiation approach would be my choice, but I also know that another comfortable (I'll check transcript – this is wrong word, I'd bet, but keep it in recording) approach for managing this patient would be to give chemotherapy and then do surgery after they get an induction chemotherapy.

I'm not sure if I would use all three modalities in this patient. That is, giving chemo/radiation and then taking this patient to surgery. So, if one were to do an induction chemotherapy approach, I think it would be important to assess what kind of response this person has had after the induction therapy before making a decision about further surgery. So, I would approach this with definitive chemotherapy if we know that this patient clearly has multi-station N2 disease.

Dr. Jonathan Goldman, Premier Oncology, Santa Monica, CA:
This is a IIIA disease, but multi-station IIIA. I think you'd have to be very careful with a patient like this to not put him through excess toxicity without a real clear evidence of benefit.

I would probably lean against heading towards surgery. The options would be, in my mind, up front chemo/radiation, or occasionally I think there are times when one can think about induction chemotherapy. There's not harm, no worsening benefit by proceeding that way and seeing how things go. I do think that certainly there are some patients that appreciate that opportunity to show themselves to be better than expected. And to do better than expected, I mean. Occasionally, you'll see a nice response and that will open the door to possible surgery. As you

know, most of the trial comparing the addition of surgery have not shown a benefit in the overall population. So you have to be careful.

Dr. Julie Brahmer, Sydney Kimmel Cancer Center, Johns Hopkins University, Baltimore, MD:
So, we use actually lymph node size. If the mediastinal lymph nodes are extremely bulky – so, larger than 2 cm in size -- then we actually won't recommend surgery at any point and just stick with the chemotherapy and radiation as standard of care, which really is standard of care. For those patients with lymph nodes that are smaller than that, or even microscopic -- found at the time of mediastinoscopy -- I think we'll tend towards using chemotherapy and radiation in the neoadjuvant setting. But also an equal option would be chemotherapy by itself before considering surgery as well. A lot of times, we'll use whether or not a patient's tumor would require them to undergo a pneumonectomy. Then we would lean toward not doing radiation because of the high chance of post operative complications. And then if the patient would just need a lobectomy, we'll do chemotherapy and radiation.

Dr. West:
What chemotherapy, most typically?

Dr. Brahmer:
It depends. We usually try and use some Cisplatin based regimen because we want a really good response. Depending on the tumor subtype will depend on what we use in combination with that. If we combine it with radiation therapy, we'll use the standard regimen of cisplatin and etoposide that was used in the large trial looking at neoadjuvant chemotherapy and radiation and again, I think the cisplatin regimen will give you the best response with radiation.

Dr. Heather Wakelee, Stanford University Cancer Center, Palo Alto, CA:
So, with only two stations, not bulky, we would definitely consider a surgical approach. We would consider neo-adjuvant treatment and then we would have a big debate because we haven't reached a group consensus yet. In the old days, we would always give chemo-radiation and that's still what I would favor. Because I think, when adding in those modalities, you're much more likely to get your mediastinal nodes treated up front, which we know is the most important component of the neo-adjuvant treatment is clearing those mediastinal nodes.

Chemo alone can, but it's much less likely to do it than both. It's a shame that the inner-group trial that you were participating in didn't reach accrual in answering the question of chemo versus chemo-rads. I'd be on the chemo-rant camp. However, my newer surgeons are less-happy operating in a post-radiated lung. So, they will often argue against giving any neojuvant radiation.

Two of the surgeons are fine with it and two of them aren't. So it depends on who day it is on Tumor Board and how concerned we are with mediastinal involvement, as to whether they get chemo or chemo-rads.

Dr. Karen Reckamp, City of Hope Cancer Center, Duarte, CA
This is where we collaborate incredibly closely with our surgeons and our radiation therapists and have our multi disciplinary conference. Most of these cases should be presented at a multi-disciplinary conference, where there is input from all the fields, because you really need to see the location and have the surgeons weigh in on really how resectable this is. I have to rely on our surgeons to give me that information. There's no substitute for being in the room and having that conversation and looking at it together. Because all N2-positive disease is not the same.

So it sounds like, from this kind of case, I would anticipate our surgeons would say, this is potential resectable. And once they say, this is potentially resectable, we generally give neoadjuvant therapy, whether it's chemotherapy and radiation or chemotherapy alone. For squamous cell, probably, would be more likely chemotherapy and radiation, considering the size of the primary. Most of these cases where it's smaller N2 disease, our surgeons would give them the benefit of the doubt and we would move forward with neoadjuvant therapy.

Dr. West:
Are there situations in which you might foresee the surgeon says, "Well, we could do surgery", but you wonder whether it's the best approach?

Dr. Reckamp:
So that happens quite often, and it's usually when it's more bulky N2 disease, where I don't believe any amount of chemotherapy and radiation is really going to eradicate that disease. Then those are lengthier discussions. If the surgeon is fairly convinced that they have a chance, we generally go with the surgeon and give neoadjuvant, but we try to advocate for definitive concurrent chemo/radiation for those patients who have bulky N2 disease, truly bulky N2 disease.

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.