

Current Concepts & Controversies in Locally Advanced NSCLC, Part 3: Managing Bulky Stage IIIB NSCLC, and the Outer Limits of Treating with Curable Intent, with Drs. George Blumenschein and Wally Curran

Dr. West: Case three is a patient with stage IIIB, unresectable disease. A 68 year-old prior smoker who had been undergoing a workup for some non-specific abdominal complaints, and in that workup she had a CT of the abdomen and pelvis that didn't show any pathology there, but did incidentally show a large lobular right lower lobe mass. That was followed by a dedicated chest CT that showed a 6 x 6.5 x 4.1 cm mass centrally in the right lower lobe and extending into the right hilum. She had mediastinal node enlargement up to 1.4 cm bilaterally, but most prominent superiorly, and also bulky supraclavicular nodes up to 2.6 centimeters on the left, which was contralateral and more than the right side.

I've shown some of the imaging which is quite impressive. You can see the various cuts that show the extent of her disease.

The PET scan showed a maximum SUV of 17 in the primary right lower lobe mass; extensive PET uptake throughout her bilateral mediastinum and in her bulky supraclavicular nodes. But there was no evidence of distant metastatic disease. She had a bronchoscopy and biopsies that were non-diagnostic. And an excision biopsy of the supraclavicular node on the left that showed moderately differentiated squamous cell carcinoma. Completing her staging, she had a head MRI that showed no intracranial metastatic disease.

She had some co morbidities, COPD with pretty modest lung function, anxiety, benign essential tremor; and potentially relevant, she lives alone. She does have a daughter living nearby -- she's widowed. Performance status is one: not bad, but she does have ongoing wheezing, which is really her baseline, and perhaps some escalating dyspnea on exertion.

And she is inclined toward pursuing aggressive therapy if feasible.

So just starting with the question: this is technically stage IIIB disease, with a contralateral N3 node, or several N3 nodes, but including the supraclavicular region on the opposite side from the primary tumor. Is this something that we can and should be treating with curative intent? Is this something that can be cured with chemo and radiation?

And then also practically, in terms of the radiation field is that something that can feasibly be done? Wally, let me start with you.

Dr. Curran: What I can tell you is years ago I looked at an institutional series at Penn and Fox Chase of irradiated patients with or without supraclavicular nodes,

and those patients actually had a similar survival to those without supraclavicular disease treated with the same intent. And there were selected long term survivors.

When you really are looking at this bulky disease, strictly speaking the patient does not meet the criteria of M1, and really still is stage IIIB disease. It's a challenge to treat such a patient anatomically, but even besides the anatomic considerations, you really have the biologic situation as to whether this patient really should be treated radically.

I've treated such patients aggressively with chemo/radiation, but I think that once you get to a certain bulk of disease, the expectation of long term disease control both in the primary and nodal area and outside it is probably unrealistic.

Dr. West: George, what are your thoughts here?

Dr. Blumenschein: My take is this patient has locally advanced disease which is pretty advanced, and I'd be inclined to start with systemic chemotherapy as an induction plan and then reassess after two cycles. Before embarking on radiation, on the off chance that the patient actually has micrometastatic disease, it might manifest in that time period.

I've treated patients like this with induction therapy, and they've responded and gone on to concurrent chemo/radiation with success. That would be my inclination because this patient has bilateral supraclavicular disease. So I would likely start them on some chemotherapy and then make treatment decisions based on the results.

Dr. Curran: I think that's reasonable approach, George, and the lack of development of distant mets is a good thing to look at in that setting. The only other thing I would say if that approach is taken, which I think is reasonable, is a lack of substantial response to the chemotherapy doesn't mean that the patient may not respond to chemo/radiation. Because there are patients who, again, don't have an imaging or in this case a response that you can detect by physical exam to the chemo. They don't develop mets, but it's still worth considering a combined modality approach by virtue of the fact that you may still get a better response with a combined modality.

Dr. Blumenschein: Oh I completely agree, and I would anticipate that if they didn't have evidence of distant metastasis after two cycles of induction, that if the field was manageable to go ahead and do give concurrent treatment; because ultimately that's your one opportunity to cure the patient. So I completely agree with you. It would just be on the chance that they develop a site of disease that makes them M1 that would put that approach on hold for me.

Dr. Curran: Now, talking about the technical aspects of radiation, the classic historic fields where the first five weeks of radiation or four weeks is done with what are called the anterior-posterior shape fields, and then there's off spinal cord fields using some sort of opposing oblique, that's anatomically

not possible with this patient. And there's really two solutions to consider: one is to actually divide the patients' disease into a superior component and an inferior component and treat them somewhat independently.

And the other approach is to use what's known as intensity modulated radiation, or IMRT. One of the problems with IMRT in the chest when you're dealing with large volume disease is you really can give a prohibitively high dose to the normal lung, which really makes it riskier than non-IMRT treatment. IMRT is great for small volumes, but when you get enlarged volumes the mean lung dose or the other parameters we measure, radiation dose to lung, can really be too risky and you're really not able to give a useful total dose of radiation in that setting.

Dr. West: If the patient was to undergo induction therapy with systemic therapy alone and has a very good response and a lot of tumor shrinkage, that's obviously a great thing. Would your radiation field be limited to the revised extent of disease, or would you feel compelled to cover all or most of what was there initially?

Dr. Blumenschein: Yeah, that's interesting. If you believe that the bulky nodes shrunk and you can encompass the nodal anatomy at risk with smaller fields, then the fields become smaller. If you had obstruction in the lung, and by shrinking the tumor you got rid of obstruction so you could see where the tumor began and ended and where the lung began and ended, then I think that the field would be smaller. The studies that have been done of radiating patients after chemo response in general show that the fields are a little smaller, but not a lot smaller.

Dr. West: Okay, so she actually did receive cisplatin/etoposide and concurrent radiation to 64 Gray, she tolerated it, not surprisingly, with difficulty -- toward the tail end she was hospitalized for IV fluids and failure to thrive, but she didn't end up needing treatment delays.

She had a PET/CT several weeks after the treatment ended that showed improvement, but residual masses in the right lower lobe and her supra-clavicular regions and a maximum SUV in the 4-5 range. So she has now had definitive RT and two cycles of cisplatin-based radiation.

She has imaging that's ambiguous, but concerning for residual disease. Are you comfortable with following the approach that was suggested by the HOG study and no consolidation and just watching her over time, or, George, would you consider anything further?

Dr. Blumenschein: I think this is a patient I have a talk with, because, you're right, the HOG data say one thing that we talked about, she has residual disease. It's been about a month since she finished therapy. Was her performance status good, or...

Dr. West: Well, it certainly dropped at the tail end, but it's back in the one range a month later. And so I would really say, what would your approach be for a patient who's 68 had some difficulty, but bounced back and then

somebody who has even had a good response, but they're asking about ,why would you give four cycles after surgery to someone with stage II disease but only two cycles to me?

Dr. Blumenschein: Right, I think I would walk her through the data that we have, the randomized data that we have, and she did receive concurrent chemo/radiation and her films showed some residual disease via PET correct?

Dr. West: They certainly did suggest that.

Dr. Blumenschein: I think it would be reasonable to watch her. It would depend on -- you know -- I think this is something where you I think giving her two cycles of chemo radiation, good therapy, and then the role for additional therapy can be debated and discussed with the patient; I would consider giving her additional therapy, just because of the amount of disease she had and I think here chemotherapy personally does offer some opportunities especially with more advanced disease. But it would be something I'd have to broach and take into account performance status, etc.

I would be comfortable leaving her after two cycles of systemic treatment with radiation. But it's something that I would at least discuss with her in length and see what her understanding was and what her comfort level was.

Dr. West: My sense in discussing this with various folks around the country is that we're all aware of the data from the Hoosier Oncology Group (HOG) that did not show any benefit to additional therapy, and yet we're all pretty uneasy with stopping and resting on our laurels and saying that the cure rates we achieve with this approach are good enough. And so even in the absence of evidence, we either bite our lips and are just uneasy about it, or we still give therapy and say, "Well, I don't know -- but I'm not happy with what we've done so far."

Dr. Blumenschein: I would agree with that.

Dr. West: Then just the question of it seems like in my experience you are almost always dealing with ambiguity after the chemo and radiation. You don't see very many complete responses, and for months after the chemo and radiation we are following scans that we're not sure if its changes in the disease or post-chemo/radiation effects in the treated field. Is there anything else that you all do to assess for disease versus just post treatment effects? How often are you doing scans? And do you do PET/CTs or just CT scans to look for the evolving changes in the chest after chemo radiation? Wally ,what are your thoughts?

Dr. Curran: I don't do the PET right away. I like to wait three months, because it's too confusing before that. It gives you a chance to look, and even at that point it can be misleading as to what is inflammation and what is residual disease. But I think the PET and the CT give the best information. I

mean, the CT is good, but PET gives a whole different dimension. So when possible, getting a PET now and then is helpful for a patient.

Dr. West: George?

Dr. Blumenschein: We utilize PET scan periodically, and if there's a question of some recurrence on a subsequent cat scan then I might obtain a PET scan to better evaluate that area. But typically I get scans about every three to four months after completion of treatment.

Dr. West: Wally, what is the typical timeline when you'd expect to see radiation pneumonitis?

Dr. Curran: The peak period, and it is a bell shaped curve, happens anywhere from three to ten weeks after completion of radiation. There are some people who believe some of the more intensified chemo/radiation regimens change the length of period of risk and move the median time a little closer to the treatment. I'm not sure we know that, but that's a possibility.

What we do know now is that we have analytic tools and radiation treatment planning where we can estimate the risk of significant treatment-related pneumonitis in a way we couldn't before. And clearly at this point, in a patient who is not on a clinical trial with a defined radiation dose, I base my tumor dose on what the normal lung parameters are of the dose given to the mean lung dose or what's known as the V20, that volume of normal receiving 20 Gray or more.

So some patients, because I want to keep the V20 below 35%, their total tumor dose may only be 58 Gray. Other patients because of a more favorable plan or anatomy in an off-study situation we could go to 70 Gray and still have a relatively low risk of treatment-related pneumonitis.

Dr. West: One thing that we scratch our heads about is if there is an interval scan done just in the course of the radiation treatment, just for refining planning, and it shows a very significant tumor shrinkage four weeks in to a seven week course; do you reduce the radiation field for that or do you hold the course for the original degree of disease. I guess that's probably pretty similar to the question of what you would do after induction chemotherapy, but is there any standard teaching on this in the radiation literature? Or is there a lot of variability in practice if you were to do an interval scan and see a very significant tumor shrinkage that would reduce the field.

Dr. Curran: Historically, radiation oncologists were taught in lymphoma to shrink fields in that setting, and they always planned accordingly. The same applies to head and neck cancer. We haven't had that luxury, unfortunately, in lung cancer in general. So there's no teaching about it. What we do now have, though, is modern imaging tools right in the radiation oncology suite, so you can get a reasonable quality CT scan from the latest linear accelerators. So you do have that information. My sense in general is that most patients, even who do well, don't have significant reduction in tumor of non-small cell lung cancer enough to change the fields.

Dr. West:

Yeah, I guess it would be a nice problem to have more commonly. Well, Wally and George, thank you so much for taking the time and sharing your expertise with us. These are tough cases that oftentimes we really have to adapt our best judgment because there still a paucity of data, and the patients don't always fit neatly into any category that the data speak to.

So thank you for taking the time and have a good night.