Notice of Correction

Cerfolio RJ, Bryant AS, Ojha B. Restaging patients with N2 (stage IIIa) non-small cell lung cancer after neoadjuvant chemoradiotherapy: A prospective study. *J Thorac Cardiovasc Surg.* 2006;131:1229-35.

Due to an administrative error, the Discussion for the above article was not published in the June 2006 issue. It is printed herewith.

Discussion

Dr R. Korst (*New York, New York*): I have the privilege of beginning this discussion, and I congratulate Dr. Cerfolio and his colleagues at Birmingham on really another significant contribution regarding PET scanning and thoracic malignancies.

Using a prospective series of nearly 100 patients with N2 disease who underwent neoadjuvant chemoradiotherapy prior to surgical resection, these investigators acquired and are reporting upon an impressive dataset regarding the accuracy of CT/PET in restaging the mediastinum after completion of induction therapy. Of additional significance, and we discussed this a little bit earlier, is that all PET scans were performed using the same scanner and the same scanning regimen, essentially eliminating the potentially confounding effect of interscanner variation. This focus on post-induction restaging implies that therapeutic decisions will be made on the restaging results. As an example of this, Dr. Cerfolio's algorithm calls for patients with residual mediastinal disease after neoadjuvant chemoradiotherapy to be referred back to the oncologist without an attempt at surgical resection. The issue of persistent N2 disease after induction therapy, however, is extremely controversial. Some retrospective series have suggested that patients with residual N2 disease after induction therapy have a negligible cure rate after surgical resection; however, other reports, including a single report from our own institution, have shown 5-year survival rates approximating 20% for this cohort of patients who undergo surgery. In addition, data from the surgical arm of the North American Intergroup 0139 randomized trial have demonstrated that patients with residual mediastinal disease after neoadjuvant chemoradiation have a 5-year survival rate of 24% when resection is performed. In summary, although a complete pathologic response in the mediastinum is ideal, it seems clear that some patients with residual N2 disease benefit from surgery.

Given this information, I have essentially only two questions. First, what treatment do you offer patients with residual

N2 disease after induction therapy if you do not offer surgical resection, and what is the survival rate in this cohort? Are the results of alternative treatments as good as the nearly 25% cure rate seen in the intergroup trial, especially given the interruption in radiation therapy that must occur during the restaging process. Second, even if decisions will be made on post-induction restaging results, given the significant false-positive and false-negative rates of CT/PET that you mentioned after neoadjuvant chemoradiation, do you continue to advocate the performance of this examination in the post-induction setting?

I want to thank Dr. Cerfolio for forwarding me the manuscript ahead of time and the Association for the privilege of discussing it.

Dr Cerfolio. Dr. Korst, those are great questions, thank you. The reason that we use a neoadjuvant chemoradiotherapy dose of 63 Gy or 66 Gy is so that there is no interruption between our neoadjuvant therapy and definitive therapy. About 5 or 6 years ago we made the cognitive leap to use higher doses of chemoradiotherapy so that we would not affect the efficacy of the patient's radiotherapy. He has already received "curative doses of chemoradiotherapy," so if he does not go on to resection you have at least maximized his medical therapy. Once he completes his radiation, you wait 4 weeks and rePET and re-CT him. Then you do a mediastinoscopy or a repeat EUS, and if he has residual N2 I usually do not resect the patient, but rather send him back for more or different chemotherapy and then reassess his N2 disease again. Once N2 negative, I will consider resection. Some selected patients—those who are young, have excellent PFTs, have minimal operative risk, and who can have all disease resected without the need for a pneumonectomy—I may resect with known residual or recalcitrant N2, but that is not my usual practice.

The second part of the first question is what is the survival of these patients. We all know that N2 patients are a heterogeneous group. So I can look at patients who have microscopic N2 disease and tell you their survival is quite good, maybe 40 or even 50%, but I can also evaluate patients with bulky recalcitrant N2 disease and tell you that even with resection their survival is poor, probably 10%. You and I know that that's not really a surgical disease, and they don't do well with surgical resection. So it comes down to really patient selection to answer that question.

J Thorac Cardiovasc Surg 2006;132:565-7

0022-5223/\$32.00

Copyright © 2006 by The American Association for Thoracic Surgery

doi:10.1016/j.jtcvs.2006.06.006

Finally, your third point, do I recommend PET for these patients? In short, I absolutely do. So much information can be gleaned off the PET if we as surgeons just carefully look at it and if the nuclear radiologists provide us with reports that help us. At UAB our integrated FDG-PET/CT reports have the maxSUV of each lymph node that's greater than the background, each lymph node is labeled with a number, ie, 2R or 4R, etc., the repeat and initial scan are both done here ideally, and the percent change of the primary tumor's maxSUV and of each node is calculated. This provides outstanding biological information as to the efficacy of the neoadjuvant therapy, and that is what I want to know as a surgeon who is contemplating resection for patients with N2 stage IIIa lung cancer. Do they have favorable or unfavorable disease? Thank you.

Dr Mark J. Krasna (*Baltimore, Maryland*). I want to compliment Dr. Cerfolio on another excellent presentation. Rob, like Dr. Sonett's group, Dr. Daly's group, and our own, you have been embracing high-dose chemoradiation as well as careful surgical staging, and I really laud you for that. On the other hand, I must make two comments. Number one, I'm surprised at your low complete pathologic response rate given that you use very high-dose chemorads, and I really wonder if you could comment. Just grabbing it off your slide, it looked like it was about a 17% path CR rate, which is way lower than, as we had discussed among several of our groups in the past, we have seen in larger groups. So if you can comment on that.

My question relates to what Dr. Korst was alluding to, also. If you are going to use the PET/CT, one alternative that has actually been recommended by the Germans at actually this meeting a year or so ago is to use the repeat PET/CT early in the therapy as a way of determining if the patient is responding or not and perhaps adjusting either your schedule or your dose based on that information. So the question, then, is if you can't use the PET/CT where you're using it with better accuracy, and, like Dr. Korst, I'm concerned about those false-negatives and -positives, and you yourself have such an excellent tradition of TBNA and EUS-FNA, why not EUS-FNA and TBNA everybody up front and then do a mediastinoscopy on everybody after the chemorads?

I enjoyed your paper.

Dr Cerfolio. Well, your third question has gotten into another study that we have completed, so I'll answer that quickly. At the 2006 Western in Idaho this year we'll be presenting exactly that---a prospective study of patients with integrated PET/CT and CT scan N2 negative. We did an upfront EUS-FNA and mediastinoscopy on all of them, and it was rarely positive unless they had suspicion of N1 disease, a maxSUV of the primary of 10 or greater, or upper lobe adenocarcinoma. So I cannot recommend those two tests up front unless N2 disease is implicated. If N2 is suggested, it makes sense to reserve the med for after the

radiotherapy if you can prove the N2 by EUS-FNA. This has been a strategy we and others have done for many years in our patients with Pancoast, but this has the disadvantage of missing occult N3 disease (EUS-FNA does not really find N3). This is uncommon for Pancoast but not for bulky N2, and knowing that before the adjuvant therapy makes a difference in your treatment algorithm.

Your first question was about why the low complete response rate. I think it has to do with your pathologist and how diligently he or she examines the final specimen. We used a very strict definition of no viable tumor before we labeled it CR. You and I have talked about this before. If we had accepted a few viable cells and called it a CR, our percentage rate would have been much higher. We had a lot of T1's that you may have called complete responders.

Finally, your second question, what about using a repeat PET during the therapy, I caution you not to use that if you're using neoadjuvant radiotherapy with the chemo as we did in this manuscript. If the patient only has induction chemotherapy, we do exactly as you suggest, we use interval integrated PET to look at efficacy or effectiveness of chemotherapy. However, here we are using induction chemoradiotherapy, and that is quite different. It is difficult to reinterpret a PET in the middle of radiotherapy, so I caution you on that. We are currently studying our data, via ROC curves, to find the most accurate time to re-PET a patient after neoadjuvant chemoradiotherapy, and we believe it is about 5 to 8 weeks after the last dose of radiation.

Dr Claude Deschamps (*Rochester, Minn*). Cerf, that was a great paper. Thank you very much. I have one comment and one question. I wonder if you had a typo in your first slide, the introduction, when you said standard of care is chemoradiation and maybe surgery. Are you aware that some of us don't give chemo to some of those patients or don't give radiation, especially radiation? Maybe you can comment on that comment.

My question is, when you restage those patients, do you use redo mediastinoscopy, endobronchial ultrasound of the bronchus? Do you use transesophageal ultrasound? Do you use Wang biopsy?

Dr Cerfolio. Thank you very much, Dr. Deschamps, I appreciate your question, especially as one of my teachers when I was at Mayo. No one travels more than you, sir, so certainly it's not from my travels. I agree that it is controversial and I actually put that up there intentionally, it is not a typo. I thought we left it up there to be intriguing. It is my standard of care in my practice for N2 disease, and I think most surgeons have moved or are moving to it instead of resection alone or chemotherapy alone. But it is not unreasonable to use induction chemotherapy. Some might argue that for microscopic N2 disease it's reasonable just to resect. So I think, again, it depends on your point of view and the

type of N2 we are talking about. But, no, it's not a typo. It was in there intentionally.

Your second question, how do we restage these patients, I do not do repeat mediastinoscopy. First of all, I think it is potentially dangerous. We haven't had any bleeding yet or mortalities, but it's harder to do, and you're a little more nervous doing a repeat mediastinoscopy after 65 Gy of radiation than you are doing a sleeve lobectomy, in my opinion. But more importantly is that I don't think it's accurate, that is the big point. So we use repeat EUS, and more recently we're about to launch a prospective study looking at repeat EBUS, which I think will be very good, although I'm not sure about the N2. It's really more for N1. We don't use repeat Wang because I think repeat Wang has been replaced by repeat EUS—one actually sees where the needle is going.

Dr Timothy Anderson (*Boston, Mass*). Cerf, I enjoyed your paper. I didn't hear a word about the Chamberlain

procedure in level 5, level 6. That may be a somewhat privileged area with a better prognosis, maybe somebody you might go on to resection with. How do you tackle that area?

Dr Cerfolio. Actually, I just worked on an abstract for a meeting in hopefully a few months on that. I don't do Chamberlain anymore, I do repeat VATS for number 5 and number 6. So we're looking at the accuracy of getting to 5 and 6 and finding that EUS-FNA doesn't get there very accurately. I don't do extended mediastinoscopy, as some of you may do. So I'm left with repeat VATS, and we're finding in these data that we just looked at that a VATS is the best way in my hands to get to the 5 or the 6. There's usually a large tumor, so it's hard to get there with Chamberlain. So VATS has supplanted Chamberlain for that number 5 and that number 6 area that we're finding out in our data is really EUS-FNA blind; the EUS gets to the 4L, not the 5.