Positron emission tomography scanning with 2-fluoro-2-deoxy-D-glucose as a predictor of response of neoadjuvant treatment for non-small cell carcinoma

Robert James Cerfolio, MD, FACS, FCCP^a
 Buddhiwardhan Ojha, MD, MPH^b
 Sudipto Mukherjee, MD^b
 Amanda Harrison Pask, RN, BSN^a
 Cynthia Sale Bass, RN, MSN, CRNP^a
 Charles R. Katholi, PhD^c

Objectives: Surgical resection after preoperative chemotherapy in patients with non-small cell lung cancer might only be best for patients who are responders. We compared positron emission tomographic scanning with 2-fluoro-2-deoxy-D-glucose (FDP-PET scanning) with computed tomographic scanning to evaluate their ability to predict this response for the primary tumor, N1 and N2 lymph nodes.

Methods: All patients with non-small cell lung cancer who had an initial FDP-PET scan staging with tissue biopsy, neoadjuvant chemotherapy, repeat FDP-PET scanning, and repeat biopsies were prospectively studied.

Results: There were 34 patients (24 men; median age, 64 years). Eleven patients had N2 disease, and 7 had N1 disease. Twenty-seven patients received chemotherapy, and 7 patients received chemotherapy and radiation. All but 9 patients underwent resection. Statistical analysis showed FDP-PET scanning to be more specific ($P < .0001$), to have a higher positive predictive value ($P = .0018$), and to have a higher negative predictive value ($P < .0001$) than computed tomographic scanning for predicting residual tumor at the primary site. FDP-PET scanning was more sensitive ($P < .0001$) and more accurate ($P < .0001$), had a higher positive predictive value ($P < .0001$), and had a higher negative predictive value ($P = .0002$) than computed tomographic scanning for paratracheal nodes (number 2 and 4 lymph nodes). FDP-PET scanning had a higher positive predictive value ($P < .0001$) than computed tomographic scanning for the other N2 (numbers 5, 6, 7, 8, and 9) lymph nodes.

Conclusions: Repeat FDP-PET scanning is more specific and has a higher positive predictive value and negative predictive value than computed tomographic scanning for detecting residual tumor in the lung in patients with non-small cell lung cancer who have received preoperative chemotherapy. It is more sensitive and accurate for paratracheal N2 nodes as well. However, there is no significant difference in its detection of N1 lymph nodes.

From the Department of Cardio-Thoracic Surgery,^a the Department of Radiology, Division of Nuclear Medicine,^b and the Department of Biostatistics,^c University of Alabama at Birmingham, Ala.

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Address for reprints: Robert J. Cerfolio, MD, Associate Professor of Surgery, Division of Cardiothoracic Surgery, University of Alabama at Birmingham, 1900 University Blvd, THT 712, Birmingham, AL 35294 (E-mail: Robert.cerfolio@ccc.uab.edu).

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Over the last several years, positron emission tomographic (PET) scanning with 2-fluoro-2-deoxy-D-glucose (FDG-PET) has been used to help clinically staged patients with non-small cell carcinoma (NSCLC).¹⁻¹⁵ Despite these articles, the precise role of FDG-PET scanning for these patients is yet to be determined. Only a few studies have analyzed the use of FDG-PET scanning¹⁶ after neoadjuvant therapy in patients with non-small cell bronchogenic malignancy. This issue is becoming more and more important because more patients with lung

cancer are undergoing preoperative chemotherapy, radiotherapy, or both. Most general thoracic surgeons agree that if patients have recalcitrant N2 disease after neoadjuvant therapy, surgical resection offers little advantage. The 5-year survival after resection is 50% for those who respond and only 15% for those who still have cancer in the N2 nodes. Therefore repeat biopsy of previously involved nodal stations after neoadjuvant therapy is crucial for appropriate patient selection. These procedures, which include redo transesophageal ultrasound, redo mediastinoscopy, anterior mediastinotomy, video-assisted thoroscopy, and/or thoracotomy have morbidity and cost. A noninvasive test that could accurately predict who was downstaged or who was a responder would provide powerful information. Unfortunately, computed tomographic (CT) scans and chest roentgenograms are poor predictors of actual pathologic response. Therefore we wanted to evaluate the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value of FDG-PET. Our goal was to compare FDG-PET with CT scanning to determine whether it added important information or if it was merely a superfluous and expensive examination. We tried to evaluate each aspect of the staging system and compared the results of both CT and FDG-PET in predicting the patient's tumor response (T status) and N1 and N2 nodal status.

Methods

From May 2000 to March 2002, we prospectively studied all consecutive patients who had biopsy-proven NSCLC, had a CT scan of the chest and upper abdomen, had a whole-body FDG-PET scan, underwent preoperative chemotherapy, and then were restaged with tissue biopsies or underwent thoracotomy, complete thoracic lymphadenectomy, and pulmonary resection.

All FDG-PET scans were performed on a dedicated ECAT EXACT PET scanner (CTI). The scans were performed after injection of 370 MBq of FDG intravenously, and the chest CT was available at the time for correlation. The patients were advised not to eat or drink fluids containing calories for 4 hours before arrival at the PET center. This was confirmed with the patient before injection of the radiotracer. Any suspicious lymph node, nodule, or mass on the CT scan or that was visualized by means of FDG-PET was further evaluated by means of conventional radiography or biopsy. Patients were then clinically staged, and they received neoadjuvant therapy with chemotherapy (with or without radiation). All patients then underwent repeat staging with a second CT scan of the chest and a repeat FDG-PET scan. Any suspicious lesion or lymph node determined by means of FDG-PET or CT scanning underwent biopsy. Patients whose test results were initially negative for N2 disease (including those whose results were initially positive and then rendered negative by neoadjuvant therapy) underwent thoracotomy. Complete thoracic lymphadenectomy was performed, and frozen-section analysis was made. If the N2 nodes were negative in frozen-section analysis, pulmonary resection was performed. If the N2 lymph nodes were still malignant, pulmonary resection was not performed because no survival benefit has been shown, and the increased morbidity of pulmonary

TABLE 1. Definitions

Sensitivity = $TP/TP + FN$
Specificity = $TN/TN + FP$
Accuracy = $TP + TN/\text{Total number of patients in series}$
Negative predictive value = $TN/TN + FN$
Positive predictive value = $TP/TP + FP$

TP, True positive; *FN*, false negative; *TN*, true negative; *FP*, false positive.

resection was avoided. Patients were excluded from this series if they did not have an initial FDG-PET scan before their neoadjuvant therapy or if the FDG-PET scan was not performed on a dedicated camera. All patients were staged by using the TNM classification system, as described by Mountain.¹⁷

Suspicious lymph nodes on FDG-PET scans were defined as any node with a mean standard uptake value (SUV) of greater than 3.0. This value was chosen on the basis of work previously performed and based on our center's mean mediastinal background SUV of 1.63 (SD = 0.31). Suspicious lymph nodes on CT scanning were defined as any N2 lymph node that was larger than 1.0 cm in any axis. This value was chosen to ensure that any lymph node that was even slightly enlarged on CT, whether in the short or long axis, underwent biopsy. Any indeterminate lesion outside the thorax underwent further investigation, biopsy, or both. The same criterion was used after the completion of the neoadjuvant protocol. However, if the initial FDG-PET scan questioned a lesion, a biopsy of the lesion showed it to be negative, and repeat FDG-PET showed the lesion to have the same SUV or less, repeat biopsy was not performed. However, if the lesion had a higher SUV or if the patient had a new suspicious lesion, it underwent biopsy.

Patients who underwent chemotherapy for biopsy-proven N2 disease underwent rebiopsy of the same N2 node after chemotherapy. If that node was still positive, the patient did not undergo thoracotomy but was included in this trial. Patients who were entered into the American College of Surgeons Oncology Group S9900 trial and who were randomized to chemotherapy were also included in this study. All patients who underwent thoracotomy and who had resection of their pulmonary lesion with intent to cure underwent complete thoracic lymphadenectomy. Pulmonary resection was performed by means of pneumonectomy, lobectomy, or segmentectomy only.

All results are reported as ranges with medians. Comparisons were made by using a Kruskal-Wallis χ^2 test and comparison of population proportion with a Fisher exact test if needed. Table 1 depicts the definitions and calculations used to determine the sensitivity, specificity, accuracy, negative predictive value, and positive predictive value. The internal review board at the University of Alabama at Birmingham approved this study.

Results

The study included 34 patients (24 men) with a median age of 64 years (range, 43-76 years). All patients had biopsy-proven NSCLC, as determined with transthoracic or transbronchial needle biopsy. In addition, 25 patients had mediastinoscopy, 7 underwent transesophageal ultrasonography and fine-needle aspiration (FNA) of N2 lymph nodes, 3 had

TABLE 2. Initial stage of patients before neoadjuvant chemotherapy

Stage	No. of patients
T2 N0	7
T3 N0	8
T4 N0	1
N1	7
N2	11

Wang needle aspirate of N1 or N2 lymph nodes, 3 had an anterior mediastinotomy (Chamberlain procedure), and 2 had video-assisted thoroscopy with FNA of suspicious lymph nodes. The initial disease staging of the patients before neoadjuvant therapy is shown in Table 2.

Preoperative chemotherapy was administered to all patients. Thirty-two of the 34 patients received carboplatin and taxol (Bristol Meyers Squibb). Twenty-seven patients had preoperative chemotherapy only, and 7 had chemotherapy and radiotherapy. All 7 patients who received preoperative radiation received 45 Gy of chest irradiation. Fourteen patients were enrolled in the American College of Surgeons Oncology Group S9900 trial. All but 2 patients finished their planned neoadjuvant treatments. One patient with N2 disease had an allergic reaction to the chemotherapy and, despite being placed on other chemotherapeutic regimens and receiving radiation to the chest, had metastasis and did not have a resection. The second patient refused the final cycle of his chemotherapy and eventually underwent complete resection. The time interval between the end of the radiation and the second FDG-PET scan in the 7 patients who underwent chemotherapy and radiation was a median of 23 days (range, 10 days–2 years). The time interval between the last dose of chemotherapy and the second FDG-PET scan was a median of 23 days (range, 14 days–2 years).

Nine of the 34 patients did not undergo resection. Five patients with N2 disease had recalcitrant N2 disease. In 3 patients the disease was determined preoperatively through endoscopic ultrasonography with FNA, and in the other 2 patients the disease was proven at the time of thoracotomy. Three patients had progression or lack of regression of disease, had T4 disease at the time of exploratory thoracotomy, and did not undergo definitive resection. The final patient was found to have a metastatic nodule in another lobe of the same histologic type at the time of thoracotomy and did not undergo resection (Table 3). The remaining 25 patients underwent pulmonary resection and complete thoracic lymphadenectomy. The types of resections were lobectomy in 19 patients, pneumonectomy in 4 patients, and segmentectomy in 2 patients. All patients who had pulmonary resection also underwent complete thoracic lymphad-

TABLE 3. Final pathology after neoadjuvant chemotherapy and after restaging, pulmonary resection, or both

Stage	No. of patients
T0 N0	4
T1 N0	1
T2 N0	6
T3 N0	7
T4 Nx	3
N1	6
N2	6
Tx Nx M1	1

enectomy. The final pathology after chemotherapy, surgical resection (or both) or restaging is shown in Table 3. One patient underwent lobectomy, and although the N2 lymph nodes were all determined to be negative in frozen samples, he was found to have a microscopic deposit of cancer in one N2 lymph node on final pathologic examination.

Comparisons were made between the FDG-PET scan results, the CT scan of the chest and upper part of the abdomen, and the final pathology results. These results are summarized in Tables 4 and 5. As seen in these tables, true-positive, true-negative, false-positive, and false-negative results were calculated for the residual viable lung tumor (T status), for N1 lymph nodes stations (ipsilateral lymph nodes 10, 11, 12, 13, and 14), for paratracheal N2 lymph nodes (ipsilateral nodes 2 and 4), and for the rest of the N2 lymph nodes (ipsilateral nodes 5, 6, 7, 8, and 9). From these results, the sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for FDG-PET and CT scanning were calculated for each parameter. These results are shown in Tables 6 and 7.

Statistical analysis shows that FDG-PET scanning when compared with CT scanning for predicting the presence or absence of residual cancer in the primary tumor was more specific ($P < .0001$), had a higher positive predictive value ($P = .0018$), and had a higher negative predictive value ($P < .0001$). For the paratracheal lymph nodes, FDG-PET scanning was more sensitive ($P < .0001$) and more accurate ($P < .0001$), had a higher positive predictive value ($P < .0001$), and had a higher negative predictive value ($P = .0002$) than CT scanning. For the other N2 lymph nodes, FDG-PET scanning had a higher positive predictive value than CT scanning ($P < .0001$).

Discussion

FDG-PET scanning has been studied in thousands of patients with NSCLC and has been found to be an important preoperative examination that can detect unsuspected metastatic disease and improve patient selection for pulmonary resection. However, in our experience¹⁸ FDG-PET scanning has a significant number of false-positive results. This

seems to be especially true in areas like the Southeast, where histoplasmosis is endemic. As seen in this trial, when a baseline FDG-PET scan has been performed and definitive biopsy specimens of suspicious nodes are performed before chemotherapy, it is an extremely accurate and noninvasive test. Although expensive (an FDG-PET scan costs around \$2000 in Birmingham, Ala), it accurately predicts the presence or absence of recalcitrant malignant disease in the primary tumor and in the N2 lymph nodes. Perhaps most important in this series is the fact that the test results were correct every time for the paratracheal lymph nodes. If future multicenter trials can corroborate our finding of a 100% negative predictive value for the paratracheal lymph node, then perhaps FDG-PET scanning can obviate the need for redo mediastinoscopy, which is a difficult and often risky procedure. Perhaps patients with a negative FDG-PET scan result in N2 stations that were previously positive and involved with cancer might be best served by means of thoracotomy and frozen-section analysis of the nodes before resection.

Akhurst and colleagues¹⁶ found that FDG-PET scanning after induction therapy accurately detected viable primary tumor but not the involvement of mediastinal lymph nodes. Unlike that study, we compiled data for each lymph node station and also subdivided the N2 lymph nodes into the mediastinoscopy-accessible paratracheal nodes versus the rest of the N2 nodes. Also, in the report by Akhurst and colleagues, there were 56 patients, although only 14 had an initial FDG-PET scan before neoadjuvant chemotherapy that was available for comparison. In our series, similar to the study of Akhurst and colleagues, most patients had chemotherapy only, but unlike their series, all of our patients had an initial FDG-PET scan before the chemotherapy for comparison.

Careful analysis of Tables 6 and 7 shows that FDG-PET scanning is at least as good and usually superior to CT scanning in all categories. It is more specific, has a higher positive predictive value, and has a higher negative predictive value than CT scanning for detecting residual tumor in the primary mass. Only FDG-PET scanning correctly predicted complete resolution of disease in the 4 patients who had T0 N0 disease (complete responders). When the FDG-PET scan was incorrect for the T status, it was because it could not accurately differentiate a T3 lesion from a T2 lesion or it failed to detect a T4 lesion (a small satellite nodule in the same lobe). FDG-PET scanning could not differentiate a small satellite T4 lesion in the lung (ie, ≥ 5 mm) from a metastatic N1 lymph node. FDG-PET scanning could not differentiate a T3 tumor with chest wall extension from a T2 lesion unless the CT scan was viewed concomitantly, as it was in this series.

FDG-PET scanning did not offer any significant advantage over CT scanning in the diagnosis of N1 lymph node

TABLE 4. Data for true-positive, true-negative, false-positive, and false-negative results for FDG-PET

	Path +	Path -	Total
PET lung tumor			
PET +	31	0	31
PET -	1	2	3
Total	32	2	34
PET N1 only			
PET +	2	3	5
PET -	9	60	69
Total	11	63	74
PET paratracheal nodes			
PET +	7	0	7
PET -	0	48	48
Total	7	48	55
PET other N2			
PET +	4	0	4
PET -	4	98	102
Total	8	98	106

TABLE 5. Data for true-positive, true-negative, false-positive, and false-negative results for CT scanning of the chest and upper abdomen

	Path +	Path -	Total
CT lung tumor			
CT +	31	2	33
CT -	1	0	1
Total	32	2	34
CT N1 only			
CT +	3	4	7
CT -	8	59	67
Total	11	63	74
CT paratracheal nodes			
CT +	4	1	5
CT -	3	47	50
Total	7	48	55
CT other N2			
CT +	2	1	3
CT -	6	97	103
Total	8	98	106

metastasis. This is especially true in this series because patients with T1 small tumors were not included. Most patients had large bulky T2 or T3 lesions, and these large tumors obscure the intrapulmonary regional lymph nodes. It is therefore imperative that FDG-PET scans be reviewed, along with the current CT scan. In some cases fusion of functional FDG-PET and anatomic CT images with software programs might offer some advantage over visual correlation. PET-CT systems, which feature a PET and CT scanner in one machine, are acquired in one sitting for the patient. They are registered and fused to form a single 3-dimensional image that shows the anatomic location from the CT scan, along with the metabolic activity of PET. This type of system might provide the best way to image N1

TABLE 6. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for FDG-PET scanning after neoadjuvant therapy

Test	Residual tumor	N1 lymph nodes	Paratracheal N2 nodes	Rest of the N2 nodes	All lymph node
Sensitivity (%)	97	18	100	50	50
Specificity (%)	67	95	100	100	99
Accuracy (%)	94	84	100	96	93
PPV (%)	97	40	100	100	81
NPV (%)	67	87	100	96	94

PPV, Positive predictive value; NPV, negative predictive value.

TABLE 7. The sensitivity, specificity, accuracy, positive predictive value, and negative predictive value for CT scanning of the chest and upper abdomen after neoadjuvant therapy

Test	Residual tumor	N1 lymph nodes	Paratracheal N2 nodes	Rest of the N2 nodes	All lymph node
Sensitivity (%)	94	18	57	22	30
Specificity (%)	0	92	98	98	96
Accuracy (%)	88	81	92	92	88
PPV (%)	91	29	80	50	50
NPV (%)	0	86	94	93	91

PPV, Positive predictive value; NPV, negative predictive value.

nodes in the future. Randomized trials of CT-PET scans are needed.

As described above, perhaps the most important finding in this series is in patients with N2 disease. Although only 11 patients in this report had N2 disease, repeat FDG-PET scans correctly predicted the absence or presence of cancer in all the N2 paratracheal lymph nodes in all patients. However, as we found in our previous report,¹⁸ FDG-PET scanning is not as accurate in the other N2 stations. It seems less accurate in the number 5, 6, and 7 lymph node areas. This is valuable information for the surgeon.

The real question is whether 2 FDG-PET scans are cost-effective and whether it adds enough information not given by the repeat CT scan that makes this additional cost worth it. This article seems to suggest that it is worth it, although a cost analysis was not performed.

All patients received chemotherapy, and 27 of the 34 patients received chemotherapy only. Because FDG-PET scanning seems to be sensitive without false-positive results at any time during chemotherapy, perhaps its true importance might be to help us tell who is responding to chemotherapy after 1 or 2 cycles. Perhaps, in the future, if a patient is not responding to the preoperative regimen (as determined by means of repeat FDG-PET scans), then a different chemotherapeutic regimen, radiation, or both could be added early in the neoadjuvant therapy. Although we only had 7 patients who received radiation in this trial and the numbers were too small to make any solid conclusions, radiation, in our experience, can lead to a false-positive FDG-PET result for up to 6 months.

In conclusion, repeat FDG-PET scanning is a highly accurate noninvasive test that helps predict the T and N2 status in patients with NSCLC who have undergone neoadjuvant chemotherapy. It is superior to CT scanning in predicting the absence or presence of residual cancer in the primary tumor and in N2 nodes, especially paratracheal lymph nodes. Its role in this setting, especially in patients with N2 disease, requires further prospective multi-institutional trials.

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Discussion

Dr Douglas E. Wood (*Seattle, Wash*). Dr Cerfolio, your center has certainly become one of the leading PET centers for thoracic malignancies, and I know this is largely due to your own leadership in this area. We all struggle with how to manage patients who have undergone induction therapy for locally advanced lung cancer, particularly those with N2 disease. You are absolutely correct that the current imaging is very unreliable for determining the degree of pathologic response. In fact, the error cuts both ways, with complete radiologic responders having residual microscopic disease and those with a negligible response sometimes having complete sterilization of the tumor. Although redo mediastinoscopy is possible, the risks of the procedure are higher, and the accuracy is certainly less than expected from the initial mediastinoscopy. If we had a test with a very high positive and negative predictive value, it could potentially obviate the need for invasive staging or a nontherapeutic thoracotomy. In fact, at one extreme, it might even allow the avoidance of surgical resection altogether if we had reliable assurance of a complete pathologic response.

Your own expectations of PET providing this information are more optimistic than my own. Your series is certainly intriguing and provides a preliminary indication of efficacy. However, the knowledge of how PET works makes me skeptical that this will provide a major clinical benefit. The sensitivity of PET is dependent on tumor cell volume, tumor density, and cellular avidity for fluorodeoxyglucose. Microscopic disease could easily be missed with our current technology, resulting in poor sensitivity. On the other hand, the effects of treatment, particularly radiation, might produce fluorodeoxyglucose uptake in the absence of tumor, resulting in poor specificity and the tragedy of clinical overstaging.

I note that the majority of your patients had chemotherapy alone without radiation, and this is partially due to enrollment in the S9900 clinical trial. However, most centers treat patients with N2 disease with combination chemoradiotherapy. Do you think that inclusion of radiation will likely confound the positive predictive value of PET that you found in this series?

The only other question I have concerns the rationale of separating out paratracheal lymph nodes from other mediastinal lymph nodes in your analysis. I know of no evidence from centers other than yours of a difference in PET accuracy for different N2 nodal stations. I also do not know of evidence that one group of nodal stations confers a difference in prognosis or treatment recommendations. Is there a good reason for complicating this analysis by separating out 2 different sites of N2 nodal disease, and does this have clinical significance?

Dr Cerfolio. Thank you very much, Dr Wood, for the kind comments. I appreciate them.

As you mentioned, as a pioneer in some of this PET scan work, I would like to have some confirmation from other centers to show that we are either right or way off base, but it would be nice to get some confirmation. That leads me to your second question first. We have shown, in the article that we presented at the meeting of The Society of Thoracic Surgeons this past year on PET scanning, that PET scanning does seem to have a different accuracy, sensitivity, and specificity in different N2 lymph node stations. Whether that is important, I do not know, but we do know clinically that patients with left upper lobe disease that have number 5 and number 6 N2 involvement have higher survival of especially adenocarcinomas than those who have N2 disease in a right upper lobe with number 2 and number 4 involvement. Therefore there might be clinically important prognostic indicators from that. We have found that in the number 7, number 5, and number 6 lymph node stations, PET scanning is a little less accurate than it is in the number 2 and number 4 stations. I think that answers your second question first.

Your first question is about the radiation. There is no question that we have seen that radiation leads to false-positive PET results up to 6 months and even up to 6.2 months in one patient, so at least 6 months. For that reason, we prefer chemotherapy. We also think oncologically that chemotherapy is better for patients with N2 disease because it better tests the biology of a patient's tumor. If they do not respond to chemotherapy, because most patients with N2 disease fail systemically, we do not think they should be treated with resection. Radiation does not test that biology as well as chemotherapy, and therefore we prefer just chemotherapy for N2 disease, as opposed to chemotherapy and radiation.

Dr Wood. I just want to follow-up on your first answer because I think that we are talking about 2 different things. With regard to the aspect of separating lymph node stations out, I agree that for very specific circumstances, there might be different prognostic implications of, for example, a station 5 lymph node for a left upper lobe tumor, but that is not what your article is about. Your article is about detecting response to therapy, and in your algorithm you have decided to not treat patients surgically that have persistent N2 disease or any N2 disease. Therefore essentially, it is an all or none phenomenon, and it does not matter whether it is a 4R lymph node, a 5, a 7, an 8, or a 9. I would ask you again, why is it necessary to separate those out?

Dr Cerfolio. The reason we separate out the different lymph node stations is because we believe the strength of PET is that it helps inform the surgeon where and how to target biopsies for N2 disease. If it is more accurate in one N2 station compared with another, then one may choose a mediastinoscopy or an esophageal ultrasound with FNA over video-assisted thoracic surgery or a Chamberlain procedure, etc. Also, in the future, we may find a difference in survival or prognosis; as good scientists, our job is to present the data. For instance, we may later find that there is a difference in survival or recurrence patterns for different stations: for instance, we now know that a positive No. 9 station is a bad actor. For these reasons we think it is important to report the difference accuracy for the N2. Another reason is that, unfortunately, not all the patients are seeing surgeons, and a lot of oncologists are using PET scans to deny people operations. What we are trying to tell them is to be careful, that all patients need biopsy for all stations, but that in certain stations the PET scan is even less accurate than it is in others. The bottom line is biopsies are still needed.

Dr John Benfield (*Los Angeles, Calif*). If I understood correctly, you did not proceed with resection when, after induction therapy, the mediastinal lymph nodes remained positive. That certainly is a reasonable approach with which I agree. I was not clear what you do when the intralobar lymph nodes, the N1 lymph nodes, are positive after induction therapy.

Dr Cerfolio. We perform resection in those patients.

Dr Benfield. Why do you do that?

Dr Cerfolio. Our belief is that it not only improves local control but potentially improves survival. The jury might be out on that, but our belief is that it is probably going to lead to improved survival.

Dr Benfield. I will look forward to additional data on that point because it is my belief, my hypothesis at least, that after induction therapy, an N1 lymph node that remains positive is evidence of

systemic disease. I would predict that long-term results will show that such patients also do not benefit from resection.

Dr Cerfolio. What if the patient started off with an N2 lymph node? You just asked what do we do with N1, and therefore if they have been downstaged from N2 to N1, we would resect. If they have N1 disease and continue to have N1 disease, that is a different situation. We treat them by resection, but I think that their survival benefit might be less. I concur.

Dr Benfield. I am just giving you food for thought and a basis for next year's article.

Dr Cerfolio. Thank you.

Dr Thomas Rice (*Cleveland, Ohio*). I want to ask about microscopic residual disease. How often did you find it, and how often was PET not able to see it? You have very good sensitivities and positive predictive values, which means the tumor is still there. Do you think this is more effective in ineffective chemotherapy than good PET scanning, and how do you use the information when your PET scan says that the patient has persistent N2 disease after induction chemotherapy? Would you perform a biopsy of those nodes or not perform an operation on that patient?

Dr Cerfolio. I will take the last question first. We do a biopsy of every node, no matter what the PET scan shows, to determine whether it is correct or incorrect. If the patient has residual N2 disease, we resect only if the patient is young with low risks and if we can resect without doing a pneumonectomy.

As to the question about microscopic disease, it depends on how you define it. If the pathologist very carefully cuts the specimen, one might find microscopic disease and one might not. The ones where results indicated the patients were complete responders, we asked them to go back and very carefully cut, and they found no microscopic disease. Certainly PET scanning is going to miss microscopic disease of less than 6 mm, and we found that in this series as well.