The impact of lymph node station on survival in 348 patients with surgically resected malignant pleural mesothelioma: Implications for revision of the American Joint Committee on Cancer staging system

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Objectives: The propensity of malignant pleural mesothelioma to metastasize to N1 or N2 nodes and their corresponding prognostic value is unclear. The American Joint Committee on Cancer staging system groups N1 and N2 disease together as stage III. The goal of this study was to define the prognostic value of specific nodal stations.

Methods: Patients with malignant pleural mesothelioma who underwent resection were identified from an institutional database. Nodal stations were defined by the American Joint Committee on Cancer lung cancer node map classification. Survival was analyzed by the Kaplan–Meier method, log-rank test, and Cox proportional hazards analysis.

Results: From 1990 to 2006, 348 patients were identified: 279 men and 69 women with a median age of 67 years (range 26–85 years). Extrapleural pneumonectomy was performed in 223 cases, and pleurectomy/decortication was performed in 125 cases. Survival differences ($P < .01$) were observed between 2 groups: N0 or N1(+) (median survival = 19 months) and N2(+), N2/N1(+) and internal thoracic(+) (median survival = 10 months). Survival was influenced by the number of involved N2 stations (0, 1, 2, or more: $P < .001$). Multivariate analysis grouping all N2 and internal thoracic(+) versus N1(+) and N0 demonstrated a hazard ratio for survival of 1.7 ($P < .0001$) controlling for T3/T4 status (hazard ratio = 1.3, $P < .01$), non-epithelioid histology (hazard ratio = 1.7, $P < .0001$), extrapleural pneumonectomy (1.1, $P = .4$), and male gender (hazard ratio 1.4, $P < .01$).

Conclusion: This study confirms a preferential pattern of drainage of malignant pleural mesothelioma to N2 rather than N1 lymph nodes, but suggests that N1 only nodal involvement should be classified as lower stage disease. Multiple N2 nodal site involvement could potentially be classified as higher stage disease than single station N2. Our results emphasize the need for larger, confirmatory multicenter studies that could lead to revision of the current staging system.

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The current staging system for malignant pleural mesothelioma (MPM), proposed in 1995 by the International Mesothelioma Interest Group, is based on information about the relationships between T and N status and overall survival.[1-7] The staging system has been validated by several reports[8-12] and accepted by the Union Internationale Contre le Cancer and American Joint Commission on Cancer (AJCC) as the standard system for MPM. However, it was understood at its inception that revision would be necessary as more data became available.[13] Although previous staging systems have suggested separating N1 from N2 nodes, there have been little data to support this distinction. Data are also sparse regarding the influence of internal thoracic nodes on survival.[14]

The lymph node map for MPM is by default the same used by the AJCC for lung cancer staging.[15] However, the lymphatic drainage from the lung is thought to be

Abbreviations and Acronyms
AJCC = American Joint Commission on Cancer
EPP = extrapleural pneumonectomy
HR = hazard ratio
P/D = pleurectomy/decortication
MPM = malignant pleural mesothelioma

different from that of the pleura, and this may lead to different patterns of lymph node involvement.[9] It is conceivable that N1 nodes could even represent more advanced disease and portend a worse prognosis than N2 nodes in MPM if N2 nodes are actually the first site of drainage from the pleura. The current AJCC staging system groups N1 and N2 disease together as stage III because few data were available on the relative impact of these sites of lymph node involvement when the staging system was developed. The goal of this study was to provide more data regarding the prognostic impact of specific nodal groups, in particular N1 nodes.

Materials and Methods

Acquisition of Clinical Data

After approval from the institutional review board of Memorial Sloan-Kettering Cancer Center, all patients with biopsy-proven MPM who underwent surgical resection with complete mediastinal nodal dissection or sampling from 1990 to 2005 at Memorial Sloan-Kettering Cancer Center were identified from the thoracic surgery database. Patients who had incomplete nodal staging information were excluded from this study. Pathological diagnosis was based on histology, immunohistochemical analysis, and, when indicated, electron microscopy. Staging was performed using the sixth edition of the *AJCC Cancer Staging Handbook*.[1] Pathological stage was based on the pathologist's evaluation of the resected specimen and the surgeon's intraoperative findings. Dates of death were verified through the Social Security Death Index.

Surgical and Multimodality Management

Operative intervention was recommended to patients with tumor localized to the hemithorax by computed tomography scan and adequate cardiopulmonary function determined by cardiac stress testing and pulmonary function testing. Routine mediastinoscopy was not performed. Extrapleural pneumonectomy (EPP) was defined as an en bloc resection of the pleura, lung, ipsilateral diaphragm, and pericardium. Pleurectomy/decortication (P/D), which removed all gross tumor without removing underlying lung, was performed in patients who had minimal visceral pleural tumor or poor pulmonary function. The decision to perform an EPP was primarily based on intraoperative findings of confluent visceral tumor not separable from the underlying lung and a partially or totally fused pleural space. Lymph node sampling or dissection was performed in the same manner as would be standard for a lung cancer resection, including lymph node stations 2R, 4R, 7, 8, and 9 on the right, and 5, 6, 7, 8, 9 for left-sided resections.[15] The decision to administer chemotherapy or radiation was based on the requirements of sequential clinical trials performed during this time period. When the patient could not participate in a clinical trial, treatment was usually administered according to protocol guidelines.

TABLE 1. Clinical and treatment characteristics of the 348 patients in the study

	n (%)
Male	279 (80%)
Histology	
Epithelioid	257 (74%)
Non-epithelioid	91 (26%)
Stage	
I	20 (6%)
II	83 (24%)
III	210 (60%)
IV	35 (10%)
Operation	
EPP	222 (64%)
P/D	126 (36%)
Adjuvant therapy	
Chemotherapy	38 (11%)
Radiotherapy	128 (37%)
Both	65 (19%)

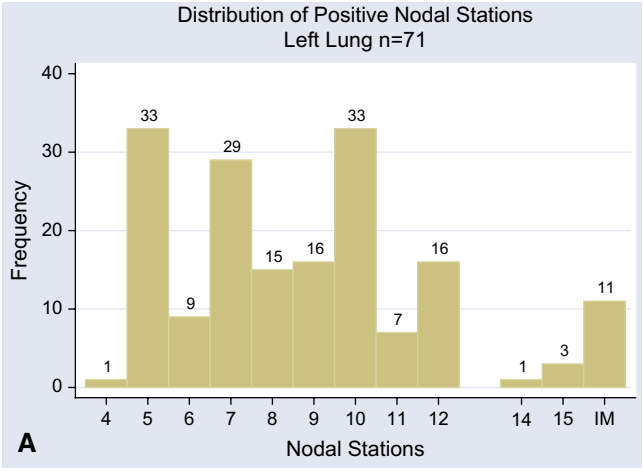
EPP, Extrapleural pneumonectomy; *P/D,* pleurectomy/decortication.

Statistical Methods

Operative mortality included all patients who died within 30 days of surgery or during the same hospitalization. Survival was calculated from the date of surgery until the date of death or date of last follow-up. Survival according to nodal station involvement (N1 vs N2) was analyzed by the Kaplan–Meier method. The log-rank test was used to assess the statistical significance of potential prognostic factors. A Cox proportional hazard analysis was used to assess the joint influences of known predictors on survival by nodal station. Insignificant variables were then dropped using a stepwise procedure, thus yielding the final model. The STATA 8 (StataCorp, College Station, Tex) statistical package was used.

Results

From 1990 to 2006, 348 patients were identified as appropriate for analysis. Patient characteristics are outlined in Table 1. As is typical for MPM, most patients were male and had epithelioid tumors and stage II or III disease at diagnosis. With a median follow-up of 20 months, the median overall survival for all 348 patients was 15 months, and the 5-year survival was 13%. Tumor histologic subtype and AJCC stage stratified patients by survival. EPP was performed in 223 patients, and P/D was performed in 125 patients, with a mortality of 2% (n = 5/223) for EPP and 2% (n = 3/125) for P/D. There were no significant differences in survival according to the surgical procedure performed ($P = .78$). The distribution of positive nodal stations for right and left-sided resections is shown in Figure 1, *A* and *B*. The most frequently involved lymph node stations were 4R, 7, and 10R for right-sided tumors and 5, 7, and 10L for left-sided tumors.



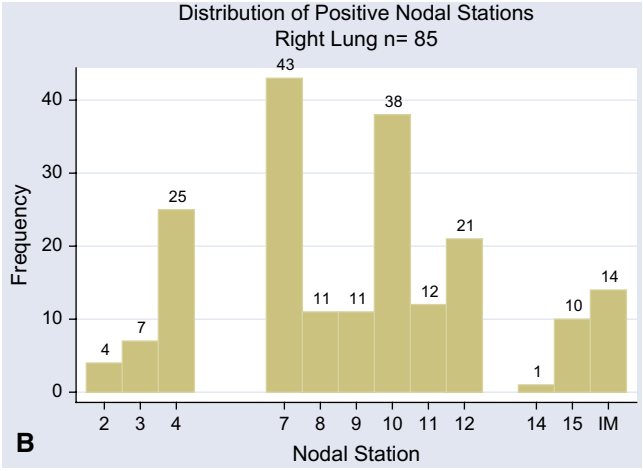


Figure 1. A, Distribution of positive node stations: left lung. Most patients who had lymph node metastases had more than 1 nodal station involved, so the number of metastatic sites exceeds the number of resections. B, Distribution of positive node stations: right lung. Most patients who had lymph node metastases had more than 1 nodal station involved, so the number of metastatic sites exceeds the number of resections.

Differences in overall survival were observed between patients who were N0 or N1 positive (median survival of 19 months) and those who were N2 positive, N2/N1 positive, and internal thoracic node positive (median survival of 10 months) (Table 2; Figure 2). Survivals by solitary N2 versus

TABLE 2. Table by positive and negative nodal groups (24 patients with positive internal thoracic nodes are not included)

	N2+	N2-	Total
N1+	65	22	87
N1-	45	192	237
Total	110	214	324

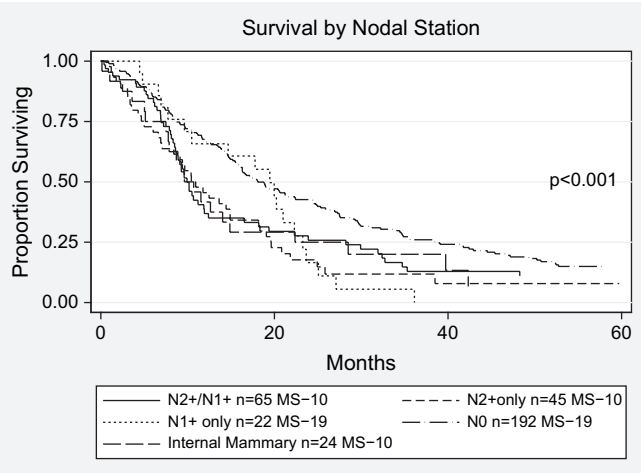


Figure 2. Overall survival of patients with N0, N1(+) versus N2(+), N2/N1(+) and internal thoracic(+) nodal disease.

solitary N1 disease, number of involved nodal stations, and N1/N2 positive versus N2 only positive are shown in Figures 3, 4, 5, and 6, respectively. When N2 disease was present, survival was not significantly different whether or not N1 disease was also present. Of note, there were differences in survival according to the number of involved N2 nodal stations with a significantly worse survival when 2 or more stations had metastatic disease. Survivals by grouping levels 4 and 7 versus 8 and 9 versus 5 and 6 were no different ($P = .36$).

Only 10 patients who underwent P/D had complete N1 nodal dissection, of whom only 1 patient had a positive N1 node only, 5 patients had positive N1 and N2 nodes, and 4 patients had documented negative N1 nodes. The N2 only and internal thoracic node positive patients (n = 31) were

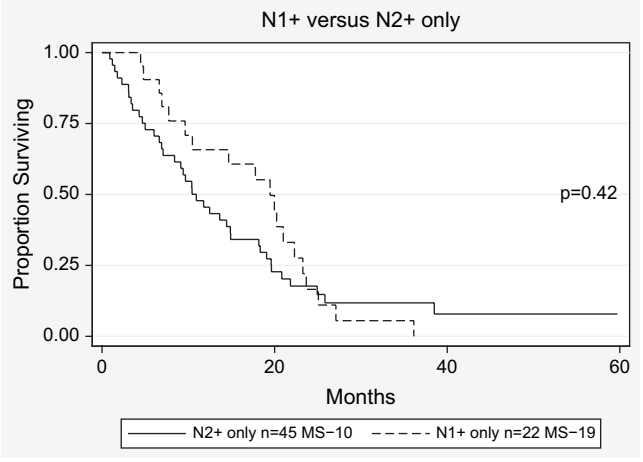


Figure 3. Overall survival of patients with N1 only versus N2 only nodal disease.

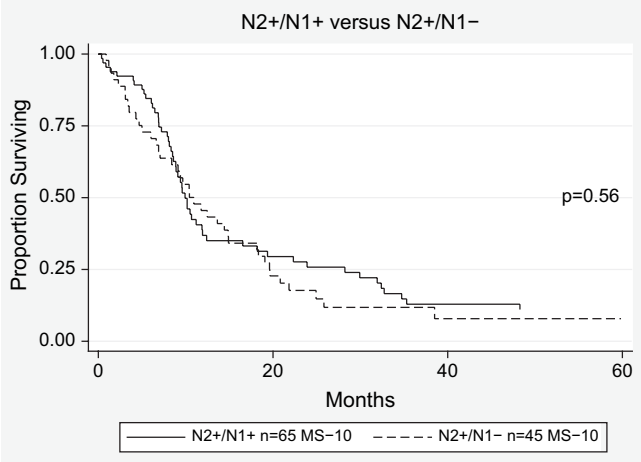


Figure 4. Overall survival of patients with N1/N2 versus N2 only nodal metastases.

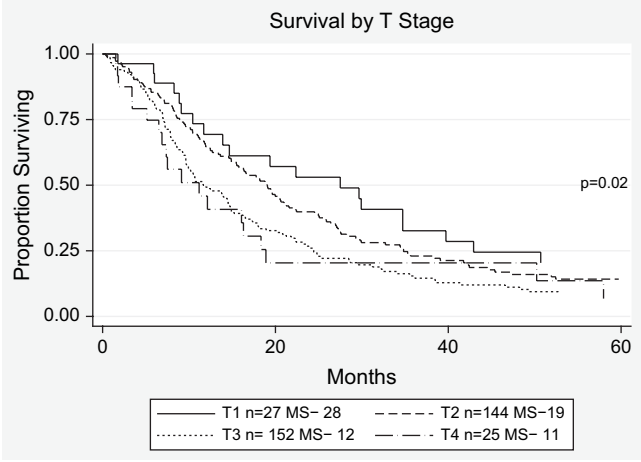


Figure 6. Overall survival of patients by T stage.

presumed to have negative N1 disease for the purpose of this analysis. Therefore, the same analysis in Figures 1, 2, and 4 was performed exclusively in patients undergoing EPP without demonstrating any change in the final results.

A Cox proportional hazards model grouping all N2 and thoracic positive nodes versus N1 positive and N0 nodal stations demonstrated a hazard ratio (HR) of 1.6 ($P < .0001$) controlling for T3/T4 status (HR = 1.3, $P < .01$), non-epithelioid histology (HR = 1.7, $P < .0001$), EPP (1.1, $P = .42$), and male gender (HR 1.4, $P = .01$) (Table 3). Surgical procedure was not significant in the multivariate analysis. The presence of metastasis to nodal areas by histology was not statistically significant by logistic regression, most likely because of the low number of patients with sarcomatoid carcinoma (n = 19).

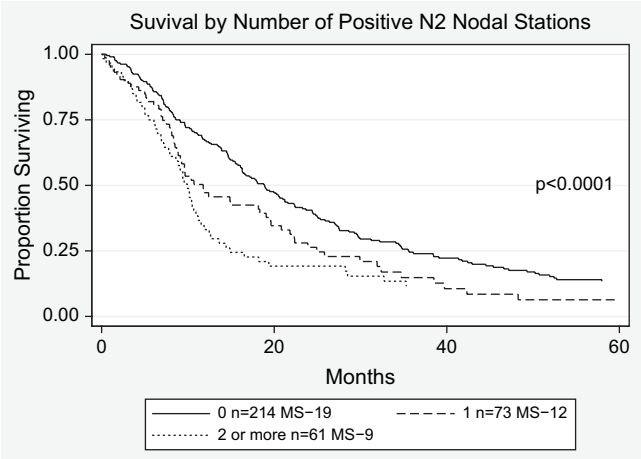


Figure 5. Overall survival of patients with 0, 1, and 2 or more nodal stations involved.

Discussion

The current AJCC staging system was built on previous staging systems but incorporated specific TNM descriptors based on emerging information about their influence on survival.[13] The purpose of the staging system was to describe the anatomic extent of disease and group staged subsets by survival, but as with other solid tumor staging systems, it does not take into account tumor biology. It was understood at its inception that revision of the staging system might be appropriate as additional data about the influence of nodal involvement on survival became available.

Little is known about the lymph node drainage pattern of the parietal pleura. Studies from rat and pig experiments suggest preferential drainage to the superior mediastinum.[16,17] However, to our knowledge the patterns of lymphatic drainage from the pleura have not been determined in live humans. Cadaveric studies have shown diaphragmatic pleural drainage to the peritracheobronchial lymph nodes via the pulmonary ligament and periesophageal tissue.[18] MPM provides a unique clinical scenario from which to gain insight into the pleural nodal drainage patterns in humans.

TABLE 3. Multivariate analysis of prognostic factors and overall survival

	HR	CI	*P* value
EPP	1.1	(0.87–1.4)	.42
Non-epithelioid histology	1.7	(1.3–2.2)	<.0001
T stage III/IV	1.3	(1.1–1.7)	<.01
Male gender	1.4	(1.1–1.9)	<.01
All N2 and ITA(+) nodes	1.6	(1.3–2.0)	<.0001

HR, Hazard ratio; *CI,* confidence interval; *EPP,* extrapleural pneumonectomy; *ITA,* internal thoracic artery.

This study demonstrates the expected characteristics of any MPM cohort: a predominance of male patients, epithelioid histology, and later stage, confirming the adverse impact of N2 disease on overall survival.[11,14] This study also confirms our previous data in a smaller number of patients showing that MPM has a greater propensity to metastasize to N2 nodes than N1 nodes, and that nodal involvement is common, occurring in approximately half of patients at surgery.[11] Similar percentages of nodal involvement have been reported in other studies by Edwards and colleagues,[19] Pass and colleagues,[9] de Perrot and colleagues,[20] and Aziz and colleagues,[21] exceeding the 25% reported by Sugarbaker and colleagues.[14] Our data emphasize the importance of performing both N1 and N2 nodal dissections in patients undergoing P/D to ensure complete staging.

Solitary metastasis to N1 nodes demonstrated a trend toward improved survival when compared with solitary metastasis to N2 nodes, thus implying earlier stage disease. In addition, further evidence for separating N1 disease from N2 disease in the staging system is provided by our data showing no further decline in survival in N2/N1 positive patients when compared with patients with solitary N2 disease. Because we demonstrated significantly worse survival for patients with 2 or more positive N2 nodal stations, one would expect survival for the N2/N1 positive (or 2 station nodal disease) patients to be worse than that of the patients with solitary N2. However, the survival was no different, thus supporting a recommendation that N1 be staged differently from N2 disease.

The internal thoracic lymph nodes have been included as N2 disease in the current staging system based on hypothetical reasoning rather than data. Our data confirm that internal thoracic lymph nodes can be appropriately considered N2, stage III disease. There were also no survival differences observed according to involvement of nodal stations 4, 5, 6, 7, 8, and 9. Therefore, it is appropriate to classify all these nodal stations as N2 disease and stage III.

A salient result from our study is the adverse impact of multiple versus single N2 lymph node stations on survival. This finding corroborates our previous data suggesting that the number of involved lymph nodes influences survival.[11] Because the counting of lymph nodes is potentially unreliable because of the difficulty for pathologists in identifying nodal fragments from entire nodes in surgical specimens, the number of involved lymph node stations is a more reproducible data point for universally acceptable staging.

Trials investigating induction chemotherapy have sparked increased interest in pre-resectional nodal staging.[22,23] Although the routine use of invasive preoperative nodal staging is controversial, newer preoperative staging modalities, such as endobronchial ultrasound to identify N1 disease and esophageal ultrasound to identify N2 disease at levels 8 and 9, may prove useful in clinical trials as more effective chemotherapy becomes available.[20,24-27]

Conclusions

This study confirms a preferential pattern of drainage of MPM to N2 rather than N1 lymph nodes, but suggests that N1 only nodal involvement should be classified as lower stage disease. Multiple N2 nodal site involvement could potentially be classified as higher stage disease than single station N2. Our results emphasize the need for larger, confirmatory multicenter studies that could lead to revision of the Union Internationale Contre le Cancer and AJCC staging systems.

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Discussion

Dr. W.R. Smythe (Temple, Texas): Drs. Wright and Jones, members, and guests:

Thanks for the opportunity to discuss this paper.

Pierre Denoix was a French pathologist who did the initial work on the TNM staging system in the early 1940s. He was at the National Institute of Hygiene there. What you may not know, actually, is that not only do we have New York to thank for this group and all of their contributions to thoracic surgery, but we also have New York to thank for the TNM staging system in general, as the National Institute of Hygiene was funded by the Rockefeller Foundation of New York, allowing

Dr. Denoix to do his work.

It seems amazing to me that we have resisted for such a long time the notion that mesothelioma is any different from any other tumor. There are idiosyncrasies of this disease, but certainly tumor extent, histologic type, and nodal status are just as important as they are for breast cancer and for lung cancer, and that really shouldn't come as a surprise to us.

This work is really a continuation of the work been that has been done by Dr. Rusch and her colleagues since the mid-1990s, and I think now we have unequivocal proof that the TNM staging system for this disease is useful and should be adhered to. And, as Dr. Ginsberg said in 1995 when I was a fellow listening to Dr. Rusch make one of the first presentations about this concept at this meeting that we had 7 or 8 staging systems, we really should have one. I think that the proof is in the pudding now. The pudding is done. It's time for us just to have one staging system, and we appreciate your efforts.

I just have three questions. First, in considering the importance of the sarcomatous histologic subtype in this disease, did you see any difference in the metastatic patterns for sarcomatous versus epithelial to the nodal stations, and if you did, are there any implications for the staging system in regards to histologic type, knowing how badly those patients do?

The second question is, if you're suggesting that we should stage patients at the N1 level, how do we do that? These lungs are often encased in tumor. How do we convince our pathology colleagues actually to dissect these nodes out of these lungs that are so heavily encased with disease in the fissure, disease that often travels up the bronchus into the hilum?

Lastly, now that we know the importance of N2 disease, and, again, it has been shown by many groups, including yours and ours in Texas and so forth, how do we clinically stage these patients for N2 disease, especially in locations that are extratracheal locations, like levels 8, 9, and the internal mammary chain? I think there were 79 patients in your study that had disease in these areas. If you only have disease in these areas, how do you clinically stage the patients before surgery? The tumor oftentimes is adjacent to the nodes. It's difficult to discern the node from the tumor in regards to PET scanning. And in our experience in Texas, we found that regardless of nodal size, even a 3 mm lymph node at levels 8, 9, and the internal mammary chain can harbor tumor. How do we clinically stage these patients and make good decisions about who to operate on and who not to operate on in regards to their stage?

Again, thanks for the opportunity. It was a great paper. Thanks for giving me the paper ahead of time. It was very well written, succinct, and clear. I appreciate it.

Dr. Flores: With regard to the first question about the differences in nodal spread based on histology, we have found a decent amount of nodal disease in patients who have had sarcomatoid and mixed tumors. However, the numbers of sarcomatoid patients are very, very small. The mixed tumors tend to spread to the nodal stations in a similar way as the epithelioid patients. The sarcomatoid patients, while there were some metastases, the numbers are too small to make any dramatic conclusions from.

As far as the N1 dissection is concerned, when we have extrapleural patients, our pathologists do get in there and follow the bronchus down and get the multiple nodal stations from the N1 levels. Our main point with this paper was we took it for granted that, you know, you do a mediastinal nodal dissection when you do a pleurectomy, and until we did this paper, we realized we weren't staging the N1 nodes at the time of pleurectomy. So now it will be our routine to go ahead if we're doing a pleurectomy to try and get the level 10 nodes out, et cetera.

As far as clinically staging these patients, it's quite difficult, as you pointed out, where you have the pleural rind and right near that pleural rind is a level 7 node or a level 8 or 9 node, and it's very difficult to tell whether you're hitting the node or whether you're hitting tumor regardless of whether you're doing it by endoscopic ultrasound or endobronchial ultrasound. Although I think those roles will come into play later on down the line, it's a difficult problem and I don't think we'll be able to understand that. Right now the best tools that we have for preoperative staging are CAT scan and PET scan together, and that's about it.