Cost-effectiveness of routine mediastinoscopy in computed tomography– and positron emission tomography–screened patients with stage I lung cancer

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Objective: Accurate preoperative staging is essential for the optimal management of patients with lung cancer. An important goal of preoperative staging is to identify mediastinal lymph node metastasis. Computed tomography and positron emission tomography may identify mediastinal lymph node metastasis with sufficient sensitivity to allow omission of mediastinoscopy. This study utilizes our experience with patients with clinical stage I lung cancer to perform a decision analysis addressing whether mediastinoscopy should be performed in clinical stage I lung cancer patients staged by computed tomography and positron emission tomography.

Methods: We retrospectively reviewed our thoracic surgery database for cases between May 1999 and May 2004. Patients deemed clinical stage I by computed tomography and positron emission tomography were chosen for further study. Individual computed tomography, positron emission tomography, and operative and pathology reports were reviewed. The postresection pathologic staging and long-term survival were recorded. A decision model was created using TreeAgePro software and our observed data for the prevalence of mediastinal lymph node metastases and for the rate of benign nodules. Data reported in the literature were also utilized to complete the decision analysis model. A sensitivity analysis of key variables was performed.

Results: A total of 248 patients with clinical stage I lung tumors were identified. One hundred seventy-eight patients (72%) underwent mediastinoscopy before resection, and 5/178 (3%) showed N2 disease. An additional 9 patients were found to have N2 metastasis in the final resected specimen, resulting in a total of 14/248 patients (5.6%) with occult mediastinal lymph node metastases. Benign nodules were found in 19/248 (8%) of patients. Decision analysis determined that mediastinoscopy added 0.008 years of life expectancy at a cost of $250,989 per life-year gained. The outcome was sensitive to the prevalence of N2 disease in the population and the benefit of induction versus adjuvant therapy for N2 lung cancer. If the prevalence of N2 disease exceeds 10%, the sensitivity analysis predicts that mediastinoscopy would lengthen life at a cost of less than $100,000 per life-year gained.

Conclusion: Patients with clinical stage I lung cancer staged by computed tomography and positron emission tomography benefit little from mediastinoscopy. The survival advantage it confers is very small and is dependent on the prevalence of N2 metastasis and the unproven superiority of induction therapy over adjuvant therapy.

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Abbreviations and Acronyms

CT = computed tomography
FDG-PET = positron emission tomography with F-18 fluorodeoxyglucose
JCOG = Japan Clinical Oncology Group
NSCLC = non–small cell lung cancer
PET = positron emission tomography

Patients with non–small cell lung cancer (NSCLC) are typically offered surgical resection if they are felt to have stage I or stage II disease after clinical staging. The need to exclude N2 disease before thoracotomy is generally well accepted for clinical stage II NSCLC, but there is less widespread agreement that this is necessary for patients with clinical stage I disease. Many surgeons will accept the results of noninvasive methods for hilar and mediastinal nodal staging, particularly with the widespread incorporation of positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET) into the staging armamentarium. Given the reported high sensitivity of FDG-PET for nodal metastasis and the expected low prevalence of occult N2 disease in patients who have N0 disease based on computed tomography (CT) and FDG-PET, many surgeons are willing to skip the invasive staging and proceed directly to thoracotomy.

One estimate of the prevalence of N2 disease in resectable NSCLC comes from the data from van Tinteren and colleagues, who reported the presence of N2 disease in 4/92 patients and N3 disease in 2/92 patients after clinical staging to exclude nediastinal disease using CT and positron emission tomography (PET).[1] Choi and colleagues reported a series of 291 patients with clinical stage I lung cancer.[2] They observed 20 (6.9%) positive mediastinoscopies for N2 disease and another 25 cases of N2 disease at thoracotomy. The overall prevalence of N2 in that cohort was 15% without the use of PET screening. Kim and colleagues documented a 6.9% rate of occult N2 disease (negative mediastinoscopy and positive N2 at thoracotomy) in a cohort of patients with predominantly clinical stage I disease (80% described as stage I). FDG-PET scanning was not routinely used in this group, suggesting that routine use of PET to define clinical stage I might decrease the prevalence of N2 disease even further.[3]

Mediastinoscopy would theoretically benefit patients with N2 disease that was undetected by both PET and CT if there were an alternative to surgery alone that improved survival (induction therapy) or if there were an additional hazard caused by thoracotomy that could be avoided by knowing N2 status in advance of thoracotomy.[4,5] It is difficult to estimate the benefit or lack of benefit of preresection identification of the N2 disease for a patient with clinical stage I NSCLC and pathological stage IIIa NSCLC. Recent reports have demonstrated a benefit of adjuvant chemotherapy for selected patients with resected lung cancer.[6,7] It is arguable that for patients with minimal N2 disease, induction therapy and resection would hold similar benefit as resection followed by adjuvant therapy.

On the other hand, a patient with a suspicious lung mass that turns out to be benign would not benefit from mediastinoscopy. Patients without N2 disease (ie, the true negatives, the pathological stage I and II patients) do not benefit either, and thus might be harmed as there is no benefit to counterbalance the risks. Given all these considerations, it seems worthwhile to explore the value of mediastinoscopy in the typical patient with known or suspected early stage lung cancer to challenge whether routine mediastinoscopy is warranted in such patients. Using the techniques of decision analysis with specially designed software, a trial can be simulated to answer the question with existing data.

The primary objective of this article is to evaluate whether mediastinoscopy with lymph node biopsies identifies mediastinal lymph node metastasis in patients judged to have clinical stage I NSCLC after CT and FDG-PET with sufficient frequency to justify its routine use for these patients.

Methods

A decision analysis model was constructed using Tree Age Pro 2005 software (release 2, TreeAge Software, Inc, Williamstown, MA). The criteria were chosen to define a population of patients that would be representative of common clinical findings in patients facing a routine pulmonary resection for suspected lung cancer. This type of analysis is well described in the literature and the interested reader can find detailed explanations elsewhere.[8] There are specific examples of similar works that address topics of interest to the thoracic surgery community.[9-11] Such analyses are structured to include a base strategy and an alternative strategy. The results are reported as incremental cost-effectiveness: the ratio of additional costs imposed by the alternative strategy over the additional benefits gained. When one strategy is shown to be both more effective and less expensive than the other strategy, it is said to "dominate" the more expensive and less effective alternative.

Many of the results used to fuel the analysis came from our own clinical practice. A retrospective review was performed of the outcomes of surgery in patients with clinical stage I lung cancer at our center for the 5-year period from May 1999 to April 2004. This project utilized data from an ongoing thoracic surgery database that is approved by the institutional review board and covered by patient consent. Included patients were those with clinical stage I known or suspected NSCLC. Patients were excluded from the analysis if they underwent resection but did not have both FDG-PET and CT scans preoperatively. Patients who were managed nonoperatively (ie, with neither mediastinoscopy nor resection) were also excluded. The combined results of mediastinoscopy and mediastinal lymph node sampling were used to establish the prevalence of mediastinal metastasis in these patients. Both mediastinal sampling and mediastinal dissection were used during this time

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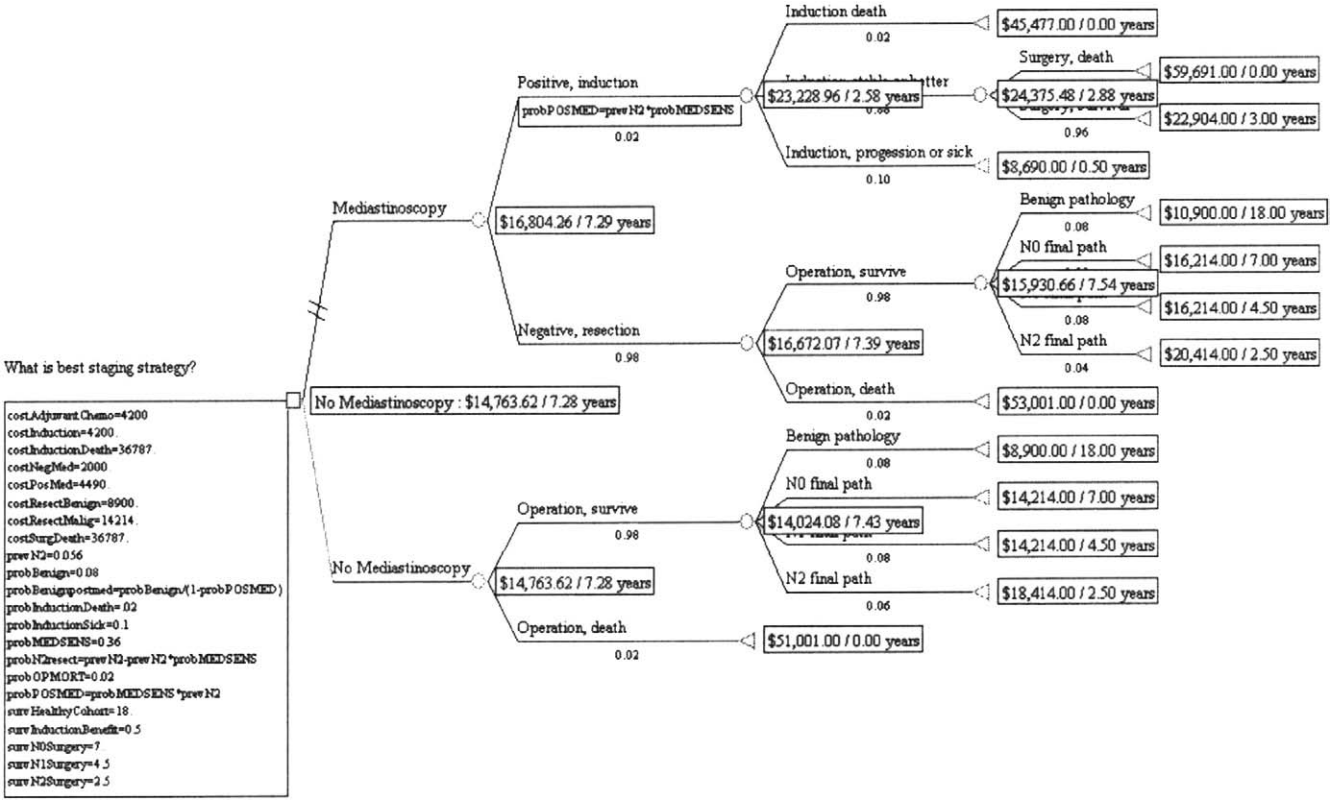

Figure 1. Decision tree depicting the decision analysis for the routine use of mediastinoscopy in clinical stage I lung cancer patients. The figure depicts the event probabilities, costs and outcomes associated with the use or non-use of routine mediastinoscopy in clinical stage I lung cancer patients. The symbols used in the diagram are described in the methods section of the text. The box in the lower left of the figure records the assumptions made for this analysis and these are reproduced in greater detail in electronic Table E1.

period as many of these patients were participants in a clinical trial comparing these staging strategies. We used our data in the decision tree for the point estimates for the prevalence of N2 disease, the prevalence of benign lesions, the sensitivity of mediastinoscopy, the mortality after operation, and the rate of positive mediastinoscopy results.

Data were also obtained by literature search to provide an estimate of costs of diagnostic and therapeutic intervention. The initial search strategy included use of Medline to search for works based on keywords "lung cancer" and "mediastinoscopy." These references were reviewed and were augmented with additional citations from the lists of references within the works chosen for closer scrutiny. The chosen references were then used to create reasonable estimates for the costs of the diagnostic and therapeutic interventions, the benefits accrued to the patients, and the probabilities of certain key events that would occur to the patients subsequent to the decision of mediastinoscopy versus resection. The specific point estimates were chosen from the range of reported values as subjective best estimates by the authors, but a liberal range of alternative values were included for the sensitivity analysis. The selected point estimates and the ranges of values discovered in the literature are reported in Table E1 along with the references that were used to make the estimates.

In keeping with the usual practice of decision analysis, a decision tree was constructed and loaded with the associated costs, benefits, and probabilities. The tree is shown in Figure 1. The tree reads from left to right and begins with a decision node (square) in which "no mediastinoscopy" is the base pathway and "mediastinoscopy" is the alternative pathway. From there, a series of probability nodes (circle) capture the likelihood of chance events in patients subjected to either of the two pathways. Finally, the terminal nodes (triangles) represent terminal states for the analysis and are labeled with the costs expended to reach that state as well as the life expectancy of patients reaching that location on the flow diagram. Once the model was run with the baseline assumptions and the initial estimates for probabilities, costs, and survivals, the model was then investigated with a sensitivity analysis. All variables were subjected to sensitivity testing and those demonstrating influence on the resulting incremental cost-effectiveness estimates were reported. The perspective of the analysis is that of the payor as we ignore other societal costs such as lost productivity by the patient or lost productivity by caregivers providing direct support to the patient. The time horizon for this study is 5 years from the onset of therapy. Incremental costs and incremental survival differences beyond 5 years are assumed to be negligible between the 2 strategies.

TABLE 1. Pathological stage in 248 clinical stage I lung tumors

Pathological stage	Number of patients (%)
T1N0	108 (43.5)
T2N0	71 (28.6)
T3N0	8 (3.2)
T4N0	3 (1.2)
T1N1	6 (2.4)
T2N1	11 (4.4)
T3N1	2 (0.8)
T1N2	4 (1.6)
T2N2	5 (2.0)
T4N2	1 (0.4)*
TXN2	4 (1.6)†
T1NX	4 (1.6)
T4NX	2 (0.8)
Benign nodule	19 (7.7)

*Includes 1 positive mediastinoscopy, resected anyway. †Includes 4 positive mediastinoscopy, no resection.

Results

In our center, from May 1999 to May 2004, there were 248 patients considered eligible for this analysis. Of these 248 patients, 178 (72%) underwent mediastinoscopy. Only 5/178 patients (3%) had involvement of the mediastinal lymph nodes detected by mediastinoscopy. One of these 5 patients underwent resection; the remaining 4 did not. Despite negative mediastinoscopy results, an additional 8 mediastinoscopy patients were found to have N2 mediastinal metastases at the time of thoracotomy, leaving a total of 13/178 (7.3%) patients classified as N2 disease after all 3 staging procedures. The sensitivity of mediastinoscopy in this population was therefore 5 of 13 (38%). Of the 70 patients for whom mediastinoscopy was omitted, 1 had N2 disease. Taken as a whole, the rate of N2 disease in the entire cohort is 14/248 (5.6%).

The mortality of thoracotomy in our patients was 1.6% (4/248). The final stage distribution of the entire cohort is recorded in Table 1. The 5-year survival of the entire cohort of 248 patients is estimated to be 70.9% after a median follow-up of 30 months. The median survival for the 14 patients found to have N2 disease is 36.1 months. If the 19 patients with benign disease are excluded, the 229 cancer patients experienced 21 recurrences (9.2%) in the first year of follow-up: 5 considered local, 8 regional, 7 distant, and 1 uncertain in location. The 5-year progression-free survival in the 229 patients with cancer is estimated to be 73%. There was no difference in the 5-year progression-free survival between the 169 cancer patients who had mediastinoscopy (72%) and the 60 who did not (77%; $P = .245$).

Additional data to bolster this analysis were kindly supplied by Dr. Rosalie Viney on behalf of her coinvestigators in the Centre for Health Economics Research and Evaluation, University of Technology, Sydney, Australia. These data were acquired in a prospective, randomized trial of PET in the management of clinical stage I and stage II lung cancer but the specific parameters were not able to be deduced from the article alone.[12] In that trial, 183 patients were enrolled and 42 of them were in stage I after both CT and PET. Of the 12/42 patients clinically staged T1N0, 1 was found to be benign, 10 were pathologically staged T1N0, and 1 was found to be T1N1 after resection. Of the 30/42 patients clinically staged T2N0, 25 were T2N0, 3 were T2N1, and 2 were T2N2. The overall prevalence of N2 disease in patients with clinical stage I disease after PET and CT screening was 2/42 (4.8%).

The results of the base case of the economic analysis are shown in Table 2. This shows that the strategy to employ mediastinoscopy routinely results in an estimated increase in survival of 0.008 years and, as a result, the cost per life-year gained is $250,989.

Sensitivity Analysis

The sensitivity analysis was conducted in several ways. All variables in the model were screened to identify influential variables that most heavily impact the estimated costs or survival durations of patients in either arm of the decision tree. Table E2 demonstrates the impact of the survival benefit of induction therapy versus postoperative adjuvant therapy on the incremental cost-effectiveness of mediastinoscopy. In a 1-way sensitivity analysis, shown in Figure E1, the impact of the prevalence of N2 disease on the incremental cost-effectiveness of the staging strategy is assessed. Finally, Table E3 contains a 2-way sensitivity analysis that analyzes the 2 important variables simultaneously: the prevalence of N2 disease in the population of interest and the benefit of induction therapy over adjuvant therapy for those specific patients.

TABLE 2. Result of decision analysis base case

Strategy	Cost ($)	Incremental cost (%)	Effectiveness (y)	Incremental effectiveness (y)	ICER
No mediastinoscopy	14,764		7.307		
Mediastinoscopy	16,804	2041	7.315	0.008	250,989

ICER, Incremental cost-effectiveness ratio in dollars per life-year.

Discussion

This analysis has determined that routine mediastinoscopy in patients judged to have clinical stage I NSCLC based on both CT and FDG-PET is an expensive diagnostic procedure that adds very little to the life expectancy of the typical patient. Depending on the willingness to pay of society or of a specific payer, this high cost per life-year gained may indicate that the routine use of mediastinoscopy could be omitted.

The sensitivity of mediastinoscopy is lower in these particular patients than is reported in many other studies of mediastinoscopy. This is consistent with a phenomenon demonstrated by Gould and colleagues who evaluated the conditional performance of FDG-PET in the setting of various outcomes of an accompanying CT scan. Given a previous negative test, an additional screening test is likely to have lower sensitivity and higher specificity than that same test would have in an unscreened population.[14] Therefore, it is not surprising that after a negative CT and FDG-PET, mediastinoscopy demonstrates lower sensitivity and higher specificity than has been reported previously in less thoroughly screened populations.

It is notable that only 1 of the patients in our cohort who did not have a mediastinoscopy was subsequently shown to have mediastinal metastases. The low rate of N2 disease in our own patients for whom mediastinoscopy was skipped raises the concern that there was bias in the application of mediastinoscopy. If there was no bias in the application of mediastinoscopy, one would expect 5.6% prevalence of N2 in both groups: mediastinoscopy and no mediastinoscopy. In fact the rates were 13/178 (7.3%) in the mediastinoscopy group and 1/70 (1.4%) in the no mediastinoscopy group. The rates of benign lesions were 9/178 (5.1%) in the mediastinoscopy group and 10/70 (14.3%) in the no mediastinoscopy group. The differences in the rates of N2 disease and benign tumors suggest the existence of additional low-risk criteria that led to the selection of the no mediastinoscopy strategy. For the purposes of this article, however, the value of interest is the overall prevalence of 5.6%, as the question at hand is whether routine use of mediastinoscopy in all patients with clinical stage I NSCLC is justified.

The N2 patients in either arm of this decision analysis are patients with minimal N2 burden, as demonstrated by their negative CT and negative PET. As a result, the survival estimates from the literature for patients with N2 disease, which will be largely based on cohorts with CT-positive and/or PET-positive mediastinal disease, are likely to be worse than one might expect for the favorable group of patients considered in this study. A reasonable estimate of life expectancy after a pulmonary resection that demonstrates N2 disease can be obtained from the Japan Clinical Oncology Group (JCOG) study reported in 2004. These investigators randomized 119 patients with N2 disease after complete resection to receive or not to receive adjuvant chemotherapy. The median survival was 36 months for both groups. Given that the JCOG study included patients with more advanced disease than our patients with clinical stage I disease, it is likely that the N2 patients in the current study would do as well or better. Keller and colleagues reported a subgroup of 172 patients with single station N2 disease who had adjuvant therapy and experienced a median survival of 35 months.[15] There are no substantial published studies that allow for estimation of outcomes of patients with clinical stage I but pathological stage IIIa disease who are given induction therapy before resection.

One limitation of this analysis is the fact that no adjustment has been made for quality of life by using "utility" estimations for each of the terminal states of the analysis. In part this has been done by necessity: there are no good estimates for utility in patients with NSCLC after surgery, failed induction therapy, or postoperative adjuvant therapy. It is reasonable to assume that the average utility in either arm would be the same. There are no major differences in the anticipated morbidity or potential for disability between the mediastinoscopy and the no mediastinoscopy arms of this analysis. The mediastinoscopy procedure itself carries little risk of discomfort or debilitating consequences. The only impact of the omission of utilities would be the difference between the cost per life-year gained versus the cost per quality-adjusted life-year gained. If good estimates for utility were available, adjusting the survival of patients with NSCLC for utility would likely result in a reduction of the survival estimates by about 30% as one converts life-year to quality-adjusted life-year. In this manner, costs per quality-adjusted life-year would be higher than costs per life-year by a factor equal to the reciprocal of the utility of the average lung cancer survivor. If the utility of these survivors is 0.7, the cost per quality-adjusted life-year would be 1/0.7 or 1.4 times the cost per life-year gained. In the base case this would be $358,555 per quality-adjusted life-year, thus making routine mediastinoscopy appear even less attractive.

These findings may be of little surprise to many surgeons who have already omitted mediastinoscopy from the routine staging of their patients with clinical stage I disease. On the other hand, many surgeons who have been routinely employing mediastinoscopy on all patients prior to thoracotomy may have failed to adapt their inclusion criteria for mediastinoscopy to reflect the additional information that PET offers. For them, this analysis might provide an impetus to reevaluate their current staging strategy.

It should be noted that this study cannot address when to use a PET scan. Other studies have looked at the incremental effectiveness and the incremental cost-effectiveness of PET scan conditional on CT scan showing operable lung cancer, but such studies have not looked at the specific subset of clinical stage I lung cancer.[16,17] Future work may be needed to clarify

the order and relative importance of the many options available to the thoracic surgeon for staging patients with known or suspected lung cancer. Also, this study does not challenge the need to fully assess mediastinal lymph nodes in clinical stage I NSCLC. It is clear that mediastinal staging should be done in all patients, but it may be that the best time to do it for some is at the time of the resection.

Conclusion

The addition of mediastinoscopy to the routine evaluation of potential surgical candidates with known or suspected stage I lung cancer is of questionable value given the high cost per life-year gained by that strategy. Clearer estimates of the cost-effectiveness of such a strategy will be obtained by gathering stage-specific estimates of both the sensitivity of mediastinoscopy in detecting N2 disease and the specificity of FDG-PET and CT together to exclude it. Additional data to be sought in future efforts in this field should include survival estimates in the unique subset of N2 patients who have no evidence for nodal metastasis by CT or FDG-PET but are found to have N2 disease either at the time of thoracotomy or at the time of a screening mediastinoscopy. Finally, the use of actual cost data in patients who meet the criteria for inclusion into this study would also strengthen the arguments offered in our analysis.

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Discussion

Dr Cameron D. Wright *(Boston, Massachusetts).* Dr. Meyers and colleagues are to be congratulated on presenting this thoughtful study on the questionable benefits of mediastinoscopy in clinical stage I NSCLC. On the one hand, I think Dr Meyers is already preaching to the choir, as I believe the majority of US surgeons go straight to resection if the patient is clinical stage I based on CT or PET. I think this decision was based on old-fashioned clinical decision making, knowing the low prevalence of occult N2 disease, the difficulty and nuisance of performing mediastinoscopy, the questionable benefit of induction therapy, and the expected favorable survival of occult N2 disease patients. Now, Dr Meyers and colleagues have supported this practice pattern, if you will, with a decision analysis model that confirms the very low yield of occult N2 disease in patients with clinical stage I disease, which importantly highlights the surprisingly high cost of routine mediastinoscopy from a public health perspective. This is a timely report in this new era of evidence-based medicine where the best available clinical evidence is marshaled to support a particular process of care. It is strengthened by an economic analysis that emphasizes just how expensive a simple diagnostic surgical procedure can be and should give us pause as we spend our valuable and limited health care resources on our patients. I believe this well-done analysis indicates that routine mediastinoscopy in clinical T1 tumors is clinically unproductive and excessively costly. I do, however, have some concerns about generalizing this conclusion to all T2 tumors. We all know that prevalence of N2 disease increases with tumor size. Indeed, Dr Meyers has reconfirmed that fact with his data, with T1 tumors having a prevalence of about 3% of N2 disease and T2 tumors having a prevalence of close to 10%. In the 2 cited PET trials from his article, the incidence in a prospective fashion of N2 disease was 0% and 14% in T1 tumors and 7% and 20% in T2 tumors. Averaging this data together would suggest about 12% of clinical T2 tumors are N2. This prevalence then potentially comes close to being cost-effective in his model if the benefit of induction therapy is much greater than one half a year based on a 2-way sensitivity analysis. This is where the art of medicine comes in, I believe, as I do not think we have truly firm data about the value of induction therapy and its comparison with adjuvant therapy. Dr Meyers, how confident are you in the applicability of your conclusions to all T2 tumors within this clinical stage I group, and if presented next week with a patient with a 7-cm T2, right upper lobe, biopsy-proven adenocarcinoma with a negative CT PET, would you perform mediastinoscopy? I congratulate Dr Meyers and his coauthors on an excellent presentation and for clarifying difficult clinical decisions in a rigorous scientific way.

Dr Meyers. Thanks for the comments and the questions. Certainly there have been many articles that suggest that there is a difference between T1 and T2 patients, and I would agree. My confidence in the upper end of T2 is not strong, and I think that that would be a particular group of patients where additional recruitment or a prospective trial might be beneficial. If I were faced with the 7-cm tumor that you described, I would do a mediastinoscopy, but I have equipoise with smaller T2 tumors, and I certainly think that that issue would be a good subject for an eventual clinical trial to evaluate this strategy.

Dr Frank Detterbeck *(Chapel Hill, North Carolina).* There is a lot of data based on the CT literature that an adenocarcinoma or a central tumor has a very high false-negative rate, about a 20% chance of finding positive nodes. The PET literature really has not

looked at the differences between adeno versus squamous or central versus peripheral. Have you looked at that in this model or in your patient series, and if you haven't, I wonder if you should. I think that the differences between these categories is larger than the difference between T1 versus T2 in the CT literature.

Dr Meyers. Actually we have not looked at adenocarcinoma versus other subtypes or central tumors versus peripheral tumors. What we were trying to challenge was the notion of routine mediastinoscopy for all patients. Therefore, we looked at all of the T1-T2 patients or stage I patients as a whole. Certainly with more patients you would have more ability to parse out subgroups. Such a focus would take more patients than one center can provide.

Dr Robert J. Korst *(New York, New York).* I also enjoyed that talk. My question again revolves around the assumptions made in any decision analysis model, and obviously the model is really only as good as the assumptions that are made. What I liked about this article was that it was based on a lot of hard data and not that many assumptions were made. However, 1 assumption that is at the crux of this model is that the detection of CT occult and PET occult disease, or essentially micrometastatic mediastinal disease picked up by mediastinoscopy, improves survival by means of induction therapy. Although historical data suggest that mediastinoscopy-positive N2 disease carries a poor prognosis compared with mediastinoscopy-negative N2 disease, these data may not apply when both CT as well as PET are negative in the mediastinum. I guess that boils down to the role of induction therapy for occult micrometastatic disease in the mediastinum. Many patients are long-term survivors after surgical resection alone for such occult mediastinal disease, compared with those with radiographically obvious disease. I wanted to know where you got the numbers to put into your model to answer that question, specifically, where the data came from for patients with occult disease who just go to surgery.

Dr Meyers. Well, in order to challenge the conventional wisdom of performing mediastinoscopy in all patients, I had to make the same assumptions that are needed to support the conventional wisdom. You would have to assume superiority of induction over adjuvant to even make an argument about this topic or simply to have this discussion. There are no good data from which to make a true assessment of the state of the art regarding benefit of induction therapy. In my baseline scenario I estimated the induction strategy would offer a 6-month survival advantage over the adjuvant therapy strategy, but as you remember from my oral presentation, I allowed that there might be no benefit, in which case there is no support for mediastinoscopy in those patients whatsoever.

Dr Korst. Exactly, because there will absolutely be no benefit if induction therapy does not improve survival in patients with such minimal disease in the mediastinum.

Dr Meyers. Right. We agree.

Dr Benedict Daly *(Boston, Massachusetts).* Bryan, I just have a quick comment. Most of us recognize the clear difference between stage Ia and stage Ib lung cancers, but I think that there is also a significant difference between peripheral and central clinical stage I lung cancers. Even if you just look at stage Ia lung cancers, for example, the incidence of unsuspected mediastinal lymph node metastases in that small subset of patients with central tumors is almost 16 times greater than it is for patients with peripheral tumors. Do you really think that your conclusions apply to patients with central tumors?

Dr Meyers. Well, I base my conclusions on our global assessment of stage I lung cancer patients in our experience, and I do not think that we have statistical power with the small number of occult N2 cases that we detected to really parse it into T1a and T1b. I share the suspicion of an increased risk of occult N2 disease in the T2 patients. But still, you would have to go back to what Dr Korst said in his discussion: unless you know that there is a benefit to induction over adjuvant, then the knowledge that you would gain by doing a routine mediastinoscopy in a 7-cm T1b patient is not enough to merit mediastinoscopy.

Dr Daly. No, I am really talking about a patient with a 2.5-cm central tumor and a negative CT scan.

Dr Meyers. Right. If you have a positive mediastinoscopy, what is your action? If you skip the mediastinoscopy and find a single N2 at thoracotomy, what is your reaction? What is the difference in the outcomes between those 2 scenarios? You have to consider the whole downstream decision making together. One cannot just pick 1 bit of the data and criticize it; you have to look at the whole strategy, and when we do that, I think that it is still difficult to justify routine mediastinoscopy in the T2 patients.

GTS

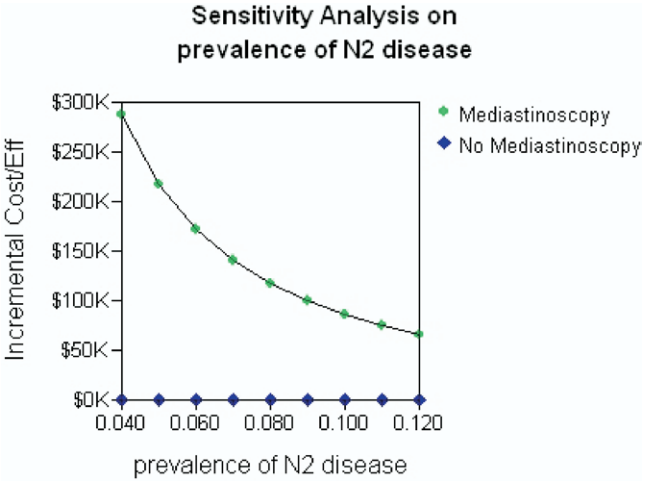

Figure E1. One-way sensitivity analysis based on the sensitivity of mediastinoscopy.

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TABLE E1. Values for variables used in decision model

	Est	Range	Refs
Cost of item ($)			
Induction chemotherapy	4200	3600-5000	18,19
Induction death	36,787	25,000-48,574	20,21
Negative med	2000	1500-3000	22-25
Positive med	4490	3500-5500	22-25
Resection benign mass	8900	7100-10,700	22
Resection malignant mass	14,214	13,178-14,800	22
Surgical postoperative death	36,787	25,000-48,574	22
Survival (y)			
Healthy people age 66	18	15-22	26,27
Induction and surgery	2.5	1.5-3	10,20,21,28,29
Resection with pN0	7	5.0-10	30-32
Resection with pN1	4.5	3.0-5.5	33,34
Resection pN2, adjuvant	3	1.6-3	10,15,20,21,34-37,*
Survival benefit of induction	0.5	0.1-2.0	20,21
Probabilities			
Prevalence of N2	0.056	0.04-0.12	1,12,13,17,38-40,*
Benign lesion in lung	0.08	0.01-0.3	23,38,*
Death during induction	0.02	0-0.05	28,41,42
Progression during induction	0.1	0.05-0.2	28,41,42
Sensitivity of med	0.37	0.03-0.06	4,23,43-45,*
N2 resection after mediastinoscopy	0.04	Dependent on sens and prevalence	
Death after operation	0.02	0.01-0.05	30,36,42,46-48,*
Death after induction + surgery	0.04	0.01-0.06	20,21,29,42,49,50
Positive mediastinoscopy	0.02	Dependent on sensitivity and prevalence	

med, Mediastinoscopy; sens, *Values for which the current report serves as reference source.

TABLE E2. One-way sensitivity analysis based on benefit of induction therapy versus adjuvant therapy in the described cohort

Induction benefit (y)	Strategy	Cost (%)	Incremental cost	Effectiveness (y)	Incremental effectiveness (y)	ICER
0.10	No	14,764		7.31		
	Med					
	Med	16,804	2041	7.31	0.00	1,548,382
0.42	No	14,764		7.31		
	Med					
	Med	16,804	2041	7.31	0.01	304,068
0.73	No	14,764		7.31		
	Med					
	Med	16,804	2041	7.32	0.01	168,587
1.05	No	14,764		7.31		
	Med					
	Med	16,804	2041	7.32	0.02	116,624
1.37	No	14,764		7.31		
	Med					
	Med	16,804	2041	7.33	0.02	89,147
1.68	No	14,764		7.31		
	Med					
	Med	16,804	2041	7.34	0.03	72,148
2.00	No	14,764		7.31		
	Med					
	Med	16,804	2041	7.34	0.03	60,594

ICER, Incremental cost effectiveness ratio in dollars per life-year gained; *med,* mediastinoscopy.

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TABLE E3. Two-way sensitivity analysis of incremental cost-effectiveness (cost per life-year gained) of routine mediastinoscopy: impact of the prevalence of N2 disease and the benefit of induction therapy over adjuvant therapy

incr surv induction =>	0.1	0.417	0.733	1.05	1.367	1.683	2
prev of N2							
0.12	213,094	97,565	63,266	46,810	37,147	30,791	26,293
0.107	280,379	117,316	74,177	54,235	42,743	35,270	30,021
0.093	386,307	144,033	88,522	63,894	49,987	41,053	34,827
0.08	568,491	181,630	108,075	76,923	59,713	48,795	41,253
0.067	926,143	237,250	136,042	95,366	73,413	59,677	50,270
0.053	1,809,083	325,537	178,845	123,297	94,073	76,050	63,823
0.04	5,591,276	481,412	251,566	170,271	128,686	103,421	86,452

Columns indicate assumed benefit, measured in years of survival, after induction therapy versus adjuvant therapy for N2 disease. Rows indicate assumed prevalence of N2 disease in the population studied. Shaded cells in the upper right indicate combinations of survival estimates that yield incremental cost-effectiveness ratios of less than $50,000 per life-year gained. Unshaded cells are combinations in which the mediastinoscopy strategy yields an incremental cost effectiveness ratio in dollars per life-year gained; med, mediastinoscopy (ICER) between $50,000 and $100,000 per life-year. Shaded cells in the lower left indicate combinations that result in ICER greater than $100,000 per life-year gained.