Decision Tree Sensitivity Analysis for Cost-Effectiveness of FDG-PET in the Staging and Management of Non-Small-Cell Lung Carcinoma

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Preliminary studies have shown that PET is more accurate than CT for the staging of non-small-cell lung carcinoma (NSCLC). However, the potential effect of PET on the management of these patients and its cost-effectiveness has not been rigorously studied. Thus, we have used decision tree sensitivity analysis to assess the cost-effectiveness of a PET based strategy for staging of NSCLC. **Methods:** Two decision strategies for selection of potential surgical candidates were compared; thoracic CT alone or thoracic CT and thoracic PET. The first decision tree was conservatively constructed by requiring mediastinoscopy (biopsy) to confirm imaging results so that no patient with surgically curable disease would miss the opportunity for surgery in either strategy. A second less conservative tree in which only nonconcordant results are biopsied was also tested. The various paths of each strategy are dependent on numerous parameters which were determined from a review of the medical literature. Life expectancy was calculated using the declining exponential approximation of life expectancy and reduced based on procedural mortality. Costs were based on mean costs at our institution. For all possible outcomes of each strategy, the expected cost and projected life expectancy were determined. The effect of changing one or more parameters on the expected cost and life expectancy were studied using a sensitivity analysis. **Results:** The CT + PET strategy in the conservative decision tree showed a saving of $1154 per patient without a loss of life expectancy (increase of 2.96 days) as compared to the alternate strategy of CT alone. Both these effects were the result of improved staging of lung carcinoma prior to the decision for surgery. The CT + PET strategy in the less conservative decision tree showed a savings of $2267 per patient but misses 1.7% of potentially operable patients. **Conclusion:** These results show through rigorous decision tree analysis, the potential cost-effectiveness of using FDG PET in the management of NSCLC. These results form a basis for detailed study of the results obtained from multicenter trials on the accuracy of PET in NSCLC management. Furthermore, the techniques utilized for decision tree analysis have broad range of applicability to the entire field of nuclear medicine.

Key Words: PET; non-small-cell lung carcinoma; decision analysis; sensitivity analysis; cost-effectiveness

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Lung cancer continues to be a major health problem worldwide. The incidence and mortality rates of lung cancer in the United States are high and although declining modestly in men, they have been increasing in women (*1*). The estimated number of lung cancer cases in the United States for 1993 is 170,000 (100,000 men and 70,000 women), whereas the estimated mortality rate is 149,000 (93,000 men and 56,000 women) (*1*). Lung cancers are estimated to account for 15% of cancer incidence (17% in men and 12% in women) and 28% of cancer mortality (34% in men and 22% in women) in 1993 (*1*). Lung cancer has surpassed breast cancer in women and is now the leading cause of female cancer mortality (22% for lung cancer, 18% for breast cancer). Non-small-cell lung carcinoma (NSCLC) accounts for about 75% of all lung cancers. Small-cell lung carcinoma generally has distant involvement at the time of presentation and has less than a 1% 5-yr survival rate after "curative" surgical resection. The role of surgery in small-cell lung carcinoma is therefore less well defined. Alternatively, NSCLC has potential for surgical cure if detected prior to metastases.

Although therapy for primary lung carcinoma remains in evolution, the fundamental principle of management, once the diagnosis of lung carcinoma is confirmed pathologically, is patient evaluation for surgical treatment. The strongest prognostic factor for survival is whether the patient can be completely resected. Because there is significant morbidity, mortality and cost associated with the surgical treatment of lung cancer, it is important to identify and to exclude from primary surgical therapy those patients who will not benefit from attempts at resection. A frequent cause of treatment failure is local and distant nonresectable or residual disease. Studies that identify distant and local disease and a staging system that organizes such information into categories of prognostic and therapeutic importance are useful in planning and evaluating the efficacy of therapy. Improved staging techniques may decrease the number of surgically treated patients and result in improved survival figures for the more select group.

Many patients with NSCLC may exhibit evidence of nonresectability during preliminary clinical investigation. The anatomic staging system for NSCLC is based on TNM staging developed by the AJC (*2*). The T, N, and M factors are combined to form stages 0–IV. Estimates of the percentage of patients whose disease is not resectable at presentation vary with criteria for resectability and patterns of referral and ranges from 65% to 80% (*3–6*). These include almost all patients with Stage IV (distant metastases), a majority of patients with Stage IIIb, and some patients with Stage IIIa disease. Therefore, patients with lung cancer who have metastases to the contralateral lung, involvement of the supraclavicular, cervical, and/or contralateral mediastinal lymph nodes or to other organs are not considered candidates for surgery. A possible exception to the policy of not resecting a lung cancer if a distant metastasis is present would be the patient with a resectable primary (non-small-cell) and a resectable solitary brain metastasis. Uncontrolled studies have suggested meaningful palliation and occasional long-term survival with resection of both the primary tumor and the brain metastasis (plus radiation to the brain) (*7,8*).

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It is reasonable to attempt to evaluate patients with potentially operable disease to ensure that no detectable metastases preclude surgical therapy. The history, physical examination, screening chemistries, and chest radiograph have limited accuracies of 49–51% (*9,10*) for detection of metastases. Therefore, other diagnostic studies [e.g., gallium scanning (*11,12*)] have been used for staging of patients with lung cancer.

Chest computed tomography (CT) as a staging tool has become the standard in the work-up of a patient with lung cancer. Over the past decade and a half, several studies have evaluated the diagnostic accuracy of CT in the assessment of the local extent of tumor, invasion of the chest wall and mediastinum, and in the staging of mediastinal lymph nodes. No single imaging method has provided all of the necessary information for the complete evaluation of the primary and distant metastatic disease (*13*); but an adjunct imaging method that could allow detection of tissue highly suspicious for malignancy and allow an overall search for malignant tissue throughout the body would be very desirable. PET utilizing [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) has the potential to be clinically useful in detecting tumors and metastases of various types (*14–21*), including NSCLC.

In determining the clinical utility of a test and developing a staging strategy in lung cancer, several variables should be taken into consideration. First, it is important to note the prevalence of different extents of lymph node metastases. Furthermore, other variables include the sensitivity, specificity and inherent risks of the various diagnostic tests, the natural history of the disease and the risks and benefits of the alternate therapies to be chosen on the basis of the test result (*22,23*). The cost-effectiveness of the diagnostic strategy must take into account not only the monetary costs of the diagnostic tests, but also the "downstream" effects the test has on both the cost of medical management and the patient's clinical outcome with or without the test (*22,23*).

The goals of this study were to quantitatively model under what conditions PET could play a cost-effective role in the staging of NSCLC by avoiding unnecessary surgery in a significant number of patients. We planned to develop a model which could account for the uncertainty involved in some of the relevant variables (e.g., prevalence, cost of PET). We initially restricted the use of PET to the thorax only in order to prove its applicability in a manner similar to which chest CT is currently used.

Although many decision analysis modeling categories can be potentially applied to model the role of PET in the staging of NSCLC (e.g., Markov processes), we chose decision tree sensitivity analysis (*22,23*). This was done to have methods available that could account for the uncertainty in the numerous variables of the model, while still being able to prove under what conditions PET may be cost-effective. To model the staging of NSCLC we used specific decision trees, sensitivity analysis, and data already available from the medical literature. Clinical utility or effectiveness was defined in terms of patient life expectancy, and cost was defined in terms of dollars of medical expenditure (*23*). Optimization of cost-effectiveness as defined by these terms was chosen to insure an algorithm in which the costs are minimized without any decrease in patient life expectancy. An additional goal was to demonstrate how decision analysis can be generally applied to quantitatively determine the role of any diagnostic imaging technique in the clinical management of a disease process.

TABLE 1
Baseline and Ranges of All Relevant Variables Used in the Various Decision Trees

Variable	Baseline	Range
Prevalence (%)	31	28–38
CT sensitivity (%)	67	61–73
CT specificity (%)	73	62–86
PET sensitivity (%)	90	82–100
PET specificity (%)	91	81–100
Mortality (%)		
PET	0	0–1
CT	0.0025	0–5
Surgery	3.0	0–20
Biopsy	0.3	0–5
Morbidity (yr)		
Surgery	0.083	0–1.0
Biopsy	0.007	0–0.1
Life Expectancy (yr)		
Surgical cure	7.0	1–15
Unresectable dis.	1.0	0.1–2
Cost ($)		
Thoracic CT	700	300–1,000
Thoracic PET	1200	700–1,500
Biopsy	3000	500–5,000
Surgery	30,000	10,000–50,000

METHODS

The analysis for cost-effectiveness and patient life expectancy (clinical utility) was performed using quantitative methods of decision analysis (*23–25*). This method involves four major components:

1. Decision tree models were constructed with two competing strategies (CT + PET vs. CT alone). To each possible outcome of each strategy, dollar costs for medical care and patient life expectancy were assigned. The explicit probabilities of each outcome in the tree were obtained as a function of the variables listed in Table 1. These probabilities were computed using simple Bayesian analysis (*25*). Multiple decision trees were evaluated since there are several strategies whereby PET can play a role. These trees include strategies whereby almost no patients who are candidates for possible surgery will be missed (conservative strategy) as well as trees in which two positive imaging studies (CT and PET) will exclude the patients from further evaluation (this approach misses a small fraction of potentially operable patients and is henceforth referred to as the less conservative strategy).
2. The medical literature was surveyed to obtain a mean and range for all variables of interest. A comprehensive literature survey was used to arrive at the sensitivity and specificity of CT. A literature survey was also used to arrive at the sensitivity and specificity of PET based on the limited number of studies currently published. The literature was also surveyed to determine the prevalence of contralateral or distant metastases in patients undergoing staging for NSCLC, morbidity and mortality for all studies in each decision tree, as well as life-expectancy for an otherwise healthy 64-yr-old man. Cost variables were assessed in terms of mean costs at our institution. These costs refer to billed costs, and reimbursed amounts vary and are less than the billed costs.
3. Calculations of expected cost and clinical utility of competing strategies were calculated by summing the products of the probabilities and values (in terms of dollar cost and patient life expectancy) of the outcome of each strategy.

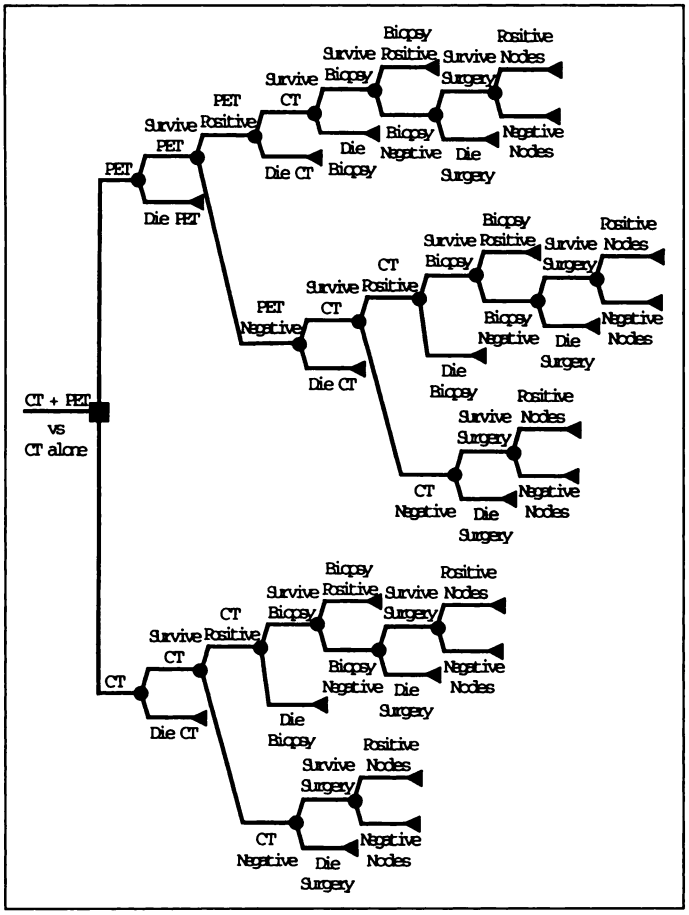

FIGURE 1. Conservative Decision Tree. The filled square is a decision node from which two competing strategies (CT versus CT + PET) originate. The filled circles are outcome nodes from which a study result leads to a particular management of the patient. The filled triangles are the end-points of each pathway and represent the final outcome (cost or life-expectancy) of a particular pathway. This decision tree compares the strategy of CT alone with that of CT + PET. The CT + PET strategy in this tree performs a biopsy on all patients who are PET-positive regardless of CT results.

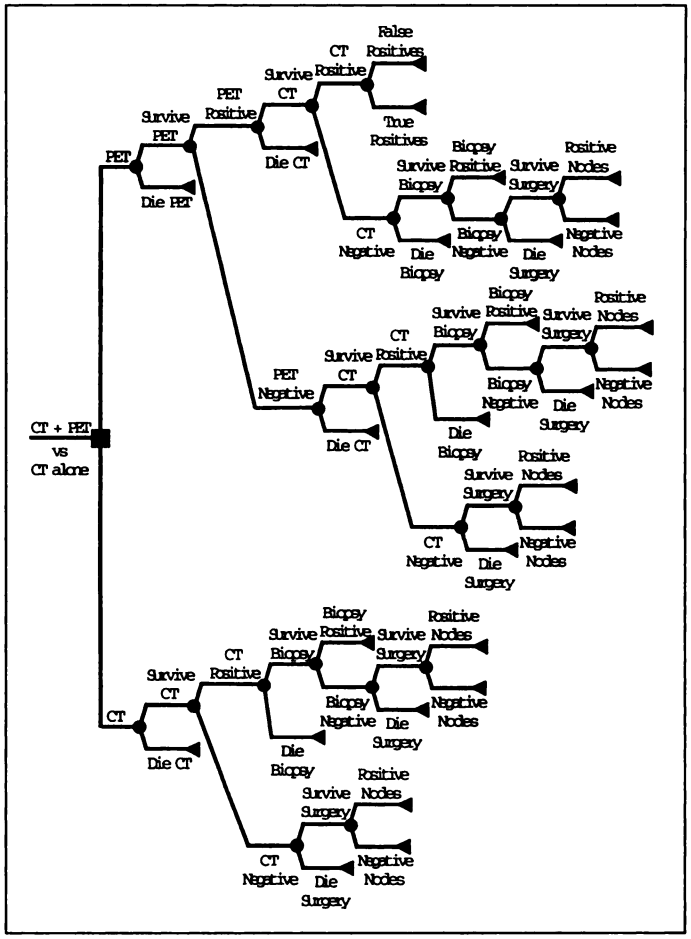

FIGURE 2. Less Conservative Decision Tree. Filled square is a decision node from which two competing strategies (CT versus CT + PET) originate. Filled circles are outcome nodes from which a study result leads to a particular management of the patient. The filled triangles are the end-points of each pathway and represent the final outcome (cost or life expectancy) of a particular pathway. This decision tree compares the strategy of CT alone with that of CT + PET. CT + PET strategy in this tree only indicates biopsy for those patients in whom CT and PET give discordant results.

4. Finally, since the precise value of the various variables are not known, a sensitivity analysis was performed on each decision tree. This involved evaluating each tree over a particular variable's range, and determining the break-even (threshold) point of each variable where the expected clinical utility or cost of competing strategies equal each other. Two-way sensitivity analysis was also performed to assess the effects of varying two variables simultaneously. New software developed in our labs (*26,27*) and the Data™ (Tree Age Inc.) software packages were used to construct and analyze each decision tree.

Structure of Decision Trees

Figure 1 depicts a conservative decision tree that directly compares strategies with and without thoracic PET (CT + PET vs. CT alone). In this and subsequent trees, PET-positive and CT-positive refer to positive for metastases. The Figure 1 tree has several important features. First, in the strategy with PET, all patients also have anatomical thoracic imaging (CT) to insure that proper anatomical information prior to biopsy and/or surgery is available to the surgeon. Furthermore, in the PET strategy, every patient who is PET-positive for contralateral mediastinal lymph node involvement (regardless of the CT results) goes on to have a biopsy to confirm that the patient is not a surgical candidate. This insures that almost no patients who have the chance for surgical cure are missed (assuming biopsy is 100% accurate).

Figure 2 illustrates an alternate less conservative decision tree. In this tree, the CT strategy is compared with an alternate type of PET-based strategy. In this tree, if both thoracic CT and thoracic PET are positive for metastases, then the patient is considered inoperable. Furthermore, if both CT and PET are negative then the patient goes to surgery. Only when there are discordant results between the two imaging modalities does the patient receive biopsy to determine the benefit of surgery. This type of decision tree is less conservative than the tree in Figure 1 because some patients who have both positive CT and PET results may still be surgical candidates (false-positive yield from both studies). These patients could potentially benefit from surgery, but are not operated on.

In both the trees of Figures 1 and 2, it is assumed that if patients have a positive biopsy, then they are not candidates for surgery. This assumes that there will be very few patients who will be falsely positive after biopsy because of the relatively high specificity of biopsy (*28–30*). Also, the trees do not account for pathways associated with bone scans, whole-body imaging and other miscellaneous tests as these will vary based on individual symptoms. Furthermore, those patients with nonresectable metastases will generally have conservative medical management. The cost of this medical management is assumed to be negligible in the current analysis.

Survey of Medical Literature

To determine the average reported literature sensitivity and specificity of thoracic CT for staging of NSCLC, we surveyed the

TABLE 2
Individual and Combined Sensitivities and Specificities of Chest CT for Staging of NSCLC Based on Patient Analysis

Lead author	No. of patients	Prevalence	(%)	Sensitivity	(%)	Specificity	(%)
1988 Gross	39	11/39	(28)	8/11	(73)	23/28	(82)
1992 McLoud	143	42/143	(30)	27/42	(64)	63/101	(62)
1994 Primack	159	60/159	(38)	38/60	(63)	85/99	(86)
1994 White	94	28/94	(30)	17/28	(61)	50/66	(76)
1994 Dillemans	569	174/569	(31)	120/174	(69)	280/395	(71)
Total	1004	315/1004	(31%)	210/315	(67%)	501/689	(73%)

Prevalence is based on patients.

English literature for the period of 1988–1995 (utilizing modern generation scanners) and selected a total of eight published studies that: (a) used total or near total sampling of mediastinal lymph nodes by mediastinoscopy/thoracotomy and (b) reported the results in enough detail to allow averaging of sensitivities and specificities between individual studies (*31–38*). Of these studies, five reported CT sensitivity and specificity on a patient-by-patient basis (*31,33,35–37*) (Table 2). A CT criterion of greater than or equal to 1 cm lymph node size in the short-axis diameter to represent lymph node metastasis was used in these studies. In three articles, the sensitivity and specificity of CT for detection of mediastinal lymph node involvement were reported on the basis of mediastinal lymph node stations (*32,34,38*) (Table 3). Prevalence of contralateral and/or mediastinal involvement in patients with NSCLC was estimated at 31% (315/1004 patients) (range 28%–38%) based on our review of the literature described above (*31,33,35–37*) (Table 2). It is important to note that this value is not the prevalence of NSCLC but the prevalence of inoperable patients in those patients that carry a pathological diagnosis of NSCLC and are being considered for surgery. It is of note that the data regarding individual nodal stations showed a wide range of sensitivity depending on location. The highest sensitivity was in the right paratracheal group (4R) (79%), and the lowest sensitivity was recorded for the mediastinal nodes of group 7 (the subcarinal group) (25%) and 11L, the left hilar group (17%). A well-recognized limitation of CT is that metastases to mediastinum lymph nodes are assessed only on the basis of nodal size. In the reported literature, false-negative CT scans are related to presence of metastases in normal sized lymph nodes. Moreover, false-positive CT findings are related to lymph node enlargement due to benign processes. Based on our review of the literature, detailed above, we adopted sensitivity and specificity of 67% (range 61%–73%) and 73% (range 62%–86%), respectively for thoracic CT (Table 2).

The sensitivity and specificity for thoracic PET are difficult to assess due to the preliminary number of patients studied and reported in the literature. Based on preliminary literature results in 121 patients (*39–41*) (Table 4), the sensitivity and specificity values used were 90% (range 82%–100%) and 91% (range 81%–100%), respectively.

The reported mortality associated with surgical resection of lung cancer ranges from 2.4% (*42*) to 20% (*43*). In the largest study, Ginsberg et al. (*44*) reported an overall mortality of 3.7% and a mortality of only 2.9% for lobectomy. We chose a baseline surgical mortality of 3% (range 0%–20%). In addition, we subtracted 1 mo (0.083 yr) (range 0–1 yr) for the morbidity associated with the recovery from thoracotomy, as others have done in decision analyses involving lung cancer surgery (*45–47*).

Mediastinoscopy has been reported to have no deaths in over 1000 consecutive mediastinoscopies, although serious complications occurred in 0.2% of patients (*48*). Anterior mediastinotomy, which is used primarily for sampling the anterior mediastinal and aortopulmonary nodes, is a more invasive procedure with a higher complication rate. Data from the two largest series (*49–50*) report that two deaths occurred among 162 patients (1.23% mortality), although both patients who died had significant concurrent disease. In addition to the normal morbidity of recovery from a small thoracotomy, serious complications occurred in 9% and 16% of cases. However, newer techniques for performing mediastinoscopy and mediastinotomy may greatly reduce the complication rate without sacrificing accuracy (*51*). In two small studies of patients undergoing percutaneous transthoracic needle biopsy of the mediastinum, there were no deaths and minimal morbidity (*52,53*). The mortality rate for percutaneous needle biopsy of the lung is approximately 0.1% (*54*). Experience with transbronchoscopic needle biopsy is limited but shows promise (*55*). Because mediastinoscopy is performed about three times as often as anterior mediastinotomy for the purpose of staging lung cancer, we used a baseline mortality of 0.3% (range 0%–5%) for the biopsy procedure, as has been done by other investigators (*45*). We estimated the average morbidity for anterior mediastinotomy to be about 0.028 yr (10 days), one-third of that for curative surgical resection. Because the morbidity associated with the other biopsy procedures is insignificant, we used a baseline morbidity of 0.007 yr (2.5 days) for the biopsy procedure and a range of 0–0.1 yr. The accuracy of biopsy was assumed to be 100%.

The risk associated with CT is primarily attributable to intravenous administration of contrast material. The most widely reported figure for the mortality of intravenous contrast material is one in 40,000, or 0.0025% (*56*). Most patients with lung cancer probably

TABLE 3
Individual and Combined Sensitivities and Specificities of Chest CT for Staging of NSCLC Based on Nodal Station (LN) Analysis

Lead author	No. of Patients	No. of LN	Prevalence	(%)	Sensitivity	(%)	Specificity	(%)
1991 Webb	155	642	33/155	(21)	48/92	(52)	379/550	(69)
1993 Seely	104	362	22/104	(21)	12/29	(41)	311/333	(93)
1994 Yokoi	113	114	37/113	(33)	23/37	(62)	61/77	(79)
Total	372	1118	92/372	(25%)	83/158	(53%)	751/960	(78%)

Prevalence is based on patients.

TABLE 4
Individual and Combined Sensitivities and Specificities of PET for Staging of NSCLC Based on Nodal Station (LN) Analysis

Lead author	No. of LN	Sensitivity (%)	Specificity (%)
1994 Wahl	27	9/11 (82)	13/16 (81)
1995 Valk	53	15/18 (83)	32/35 (91)
1995 Madar	41	22/22 (100)	19/19 (100)
Total	121	46/51 (90%)	64/70 (91%)

have some other morbidity associated with smoking (e.g., coronary artery disease and chronic obstructive pulmonary disease) and a higher risk of a fatal reaction than the general patient population (*56*). On the other hand, the newer low-osmolality contrast agents are believed to be safer, and the mortality is perhaps as low as one in 250,000, or 0.0004% (*57*). We chose a baseline mortality of 0.0025% (range 0%–5%). The risk associated with PET is assumed to be negligible, as there have been no reports to date of reactions or complications from the injection of FDG.

Baseline life expectancy was calculated using the declining exponential approximation of life expectancy (DEALE) method developed by Beck et al. (*58–59*): average life expectancy (yr) = 1/(ASR + DSR). ASR is the annual mortality rate of the general population specified for age, sex, and race of the patient and DSR is the additional average mortality rate attributable to the patient's disease. The ASR for a healthy 64-yr-old white man is 0.067 (1/15 yr). The DSR for a 2.3-cm (average diameter of T1N0M0 tumors (*6*) lung cancer has been estimated to be 0.075 (*47*). The combined annual mortality rate for our typical patient is equal to 0.142 and his life expectancy would be the reciprocal of this sum, 7.0 yr. We used a baseline of 7.0 yr (range 1–15 yr).

The life expectancy for unresectable lung cancer for patients with highly advanced disease (evident on chest radiograph) has been shown to be 0.47 yr based on surgical data and the DEALE method (*46*). While there are few data concerning the life expectancy of patients with mediastinal metastasis not evident on chest radiographs, these patients are expected to live longer than those with metastasis evident on the radiograph. Therefore, we chose a slightly greater baseline value of 1.0 yr (range 0.1–2 yr). For patients with false-positive CT and PET scans (Figure 2), and are not operated on, we chose a mean life expectancy of 2 yr. We assigned a value of 0 for all death outcomes, as is usually done (*46–47*).

We used the mean and range dollar costs (combined technical and professional charges) of thoracic CT, thoracic PET, biopsy, and curative surgery as $700 ($300–1,000), $1200 ($700–1500), $3000 ($500–5,000), and $30,000 ($10,000–50,000), respectively. The mean estimates are based on approximate billed costs at our institution. The range of values are based on approximate costs across various types of medical practices in the U.S. The biopsy costs can vary considerably depending on the exact type of biopsy used, and therefore the range is greater. These numbers refer to billed cost, and collected amounts are generally less and vary. The DRG reimbursement costs for thoracotomy are considerably less (approximately $17,000) (*60*).

RESULTS

Decision Tree of Figure 1

Analysis of the tree in Figure 1 reveals that the mean cost of the CT + PET strategy to be $24,480, and a mean cost of the CT alone strategy to be $25,634. This translates to a savings of $1154 per patient for the CT + PET strategy. This savings for choosing the CT + PET strategy is without a loss of life expectancy (increase of 2.96 days) as compared to the alternate CT alone strategy. These figures translate to approximately

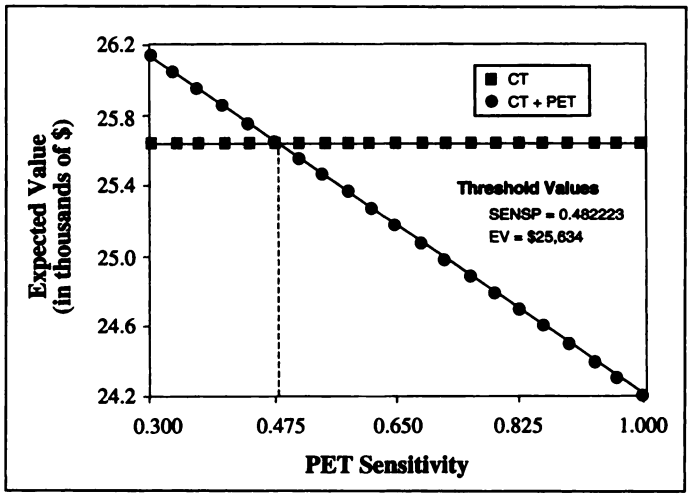

FIGURE 3. Results of the sensitivity analysis for PET sensitivity on the mean cost (expected value (EV)) for the CT strategy versus the CT + PET strategy of the decision tree in Figure 1. The threshold or break-even value requires a PET sensitivity of 48% for the CT + PET strategy to have the same cost as the CT strategy. For a PET sensitivity greater than 48%, the CT + PET strategy saves increasing amounts of health care dollars. These calculations assume that the baseline values of all variables are as listed in Table 1.

$98,000,000 in health care cost savings per year, assuming approximately 85,000 patients (based on national cancer statistics) undergo the diagnostic algorithm per year. Both the cost savings and life expectancy gain are the results of improved staging of lung carcinoma prior to the decision for surgery. More patients are detoured away from surgery due to a higher probability of detecting metastases with the use of CT and PET than with the use of CT alone.

To be more cost-effective than the CT alone strategy, the thresholds for PET sensitivity and specificity were determined to be 48% (Fig. 3) and 12% (Fig. 4), respectively. These relatively low values are because of the added power of two tests (CT and PET) in the CT + PET strategy reducing the mean costs significantly. The threshold values for all other variables for the tree in Figure 1 are listed in Table 5. These values represent the cut-off (threshold) values beyond which the CT + PET strategy is the strategy of choice when trying to

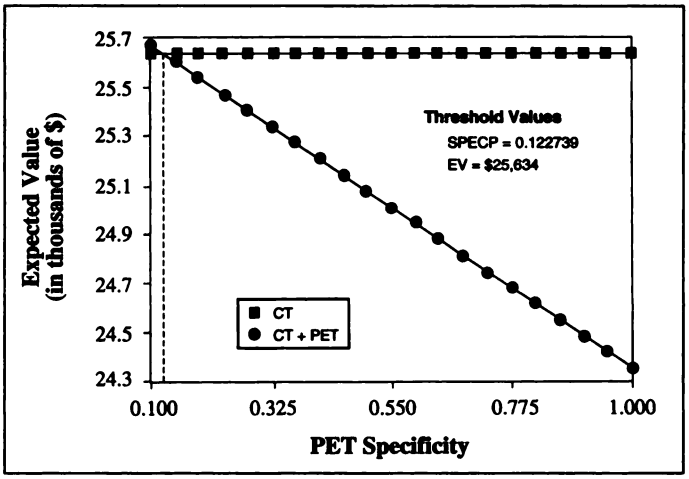

FIGURE 4. Results of the sensitivity analysis for PET specificity on the mean cost (expected value (EV)) for the CT strategy versus the CT + PET strategy of the decision tree in Figure 1. The threshold or break-even value requires a PET specificity of only 12.3% in order for the CT + PET strategy to have the same cost as the CT strategy. For a PET specificity greater than 12.3%, the CT + PET strategy saves increasing amounts of health care dollars. These calculations assume that the baseline values of all variables are as listed in Table 1.

TABLE 5
Threshold Values for Life Expectancy and Cost for the Decision Tree of Figure 1

Variable	Life expectancy	Cost
Prevalence (%)	≥5.6	≥16.9
CT sensitivity (%)	≤95.7	≤82.3
CT specificity (%)	—	—
PET sensitivity (%)	≥11.9	≥48.2
PET specificity (%)	≥31.7	≥12.3
Mortality (%)		
CT	—	—
PET	≤.16	—
Biopsy	≤2.3	—
Morbidity (yr)		
Biopsy	≤0.066	—
Surgery	—	—
Cost ($)		
CT	—	—
PET	—	≤2,354
Biopsy	—	≤11,398
Surgery	—	≥17,485

The inequality sign lists the range for which the CT + PET strategy is more cost-effective than the CT alone strategy.

minimize costs or maximize life expectancy. Of note the prevalence is a key variable in understanding the cost-effectiveness of each strategy. For a prevalence less than 16.9%, the CT + PET strategy will not save money over the CT alone strategy. Similarly, for a prevalence less than 5.6%, the CT + PET strategy cannot increase life expectancy over the CT alone strategy. These threshold values for prevalence are clearly outside the known range for this variable (see Table 1). Figure 5 shows a two-way sensitivity analysis of prevalence versus sensitivity of PET. This figure clearly illustrates that as the prevalence decreases, the sensitivity of PET has to increase in order for the CT + PET strategy to have less cost. Also seen in this figure is the fact that if the prevalence drops below 16.9%, then the CT alone strategy will have less cost. Figure 6 shows a two-way sensitivity analysis of prevalence versus specificity

TABLE 6
Threshold Values for Life Expectancy and Cost for the Decision Tree of Figure 2

Variable	Life Expectancy	Cost
Prevalence (%)	≥76.3	≥6.4
CT sensitivity (%)	—	—
CT specificity (%)	≥96.7	—
PET sensitivity (%)	—	≥23.0
PET specificity (%)	≥98.7	—
Mortality (%)		
CT	—	—
PET	—	—
Biopsy	—	—
Morbidity (yr)		
Biopsy	—	—
Surgery	—	—
Cost ($)		
CT	—	—
PET	—	≤3,466
Biopsy	—	—
Surgery	—	≥9,191

The inequality sign lists the range for which the CT + PET strategy is more cost-effective than the CT alone strategy.

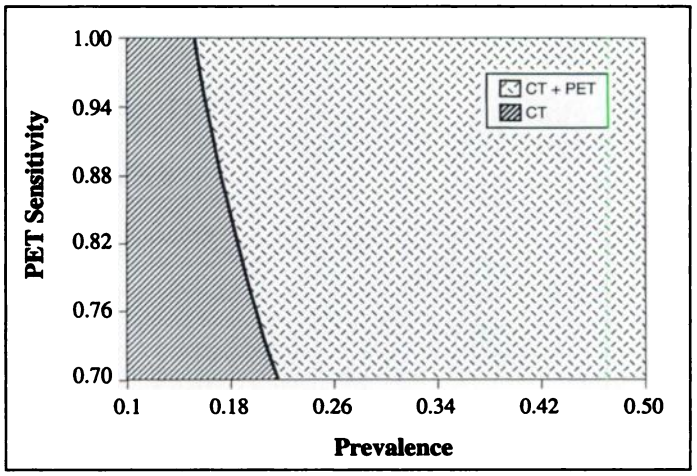

FIGURE 5. Results of the two-way sensitivity analysis for prevalence of contralateral disease and sensitivity of PET for the CT strategy versus the CT + PET strategy of the decision tree in Figure 1 (for cost as the outcome variable). As the prevalence decreases, greater PET sensitivity is required for the PET strategy to be more economical.

of PET. This figure clearly illustrates that as the prevalence decreases, the specificity of PET has to increase in order for the CT + PET strategy to have less cost.

Figure 7 depicts the two-way sensitivity analysis of surgical cost versus sensitivity of PET (for cost as the outcome variable). As expected, when the cost of surgery decreases the PET sensitivity has to increase in order for the CT + PET strategy to be more economical. If the baseline cost of thoracotomy is taken to be only $21,000 the threshold for PET sensitivity and specificity increase dramatically to 72.4% and 69.1%, respectively. If surgical costs drop below $17,485, then the CT alone strategy is always less costly than the CT + PET strategy of Figure 1.

The one-way sensitivity analysis of the morbidity of surgery on the mean life-expectancy for the CT alone strategy versus the CT + PET strategy of the decision tree in Figure 1 is shown in Figure 8. The threshold value requires a surgical morbidity of 0.008 for the CT + PET strategy to have the same life-expectancy as the CT strategy. For a surgical morbidity greater than 0.008 yr, the CT + PET strategy has greater mean patient life expectancy. These calculations assume a lower mean life expectancy for unresectable disease (0.47 yr). This is the life

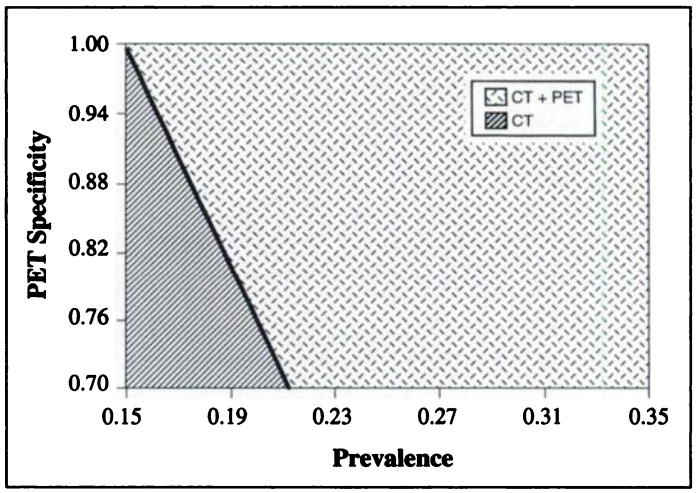

FIGURE 6. Results of the two-way sensitivity analysis for prevalence of contralateral disease and specificity of PET for the CT strategy versus the CT + PET strategy of the decision tree in Figure 1 (for cost as the outcome variable). As the prevalence decreases, a greater PET specificity is required for the PET strategy to be more economical.

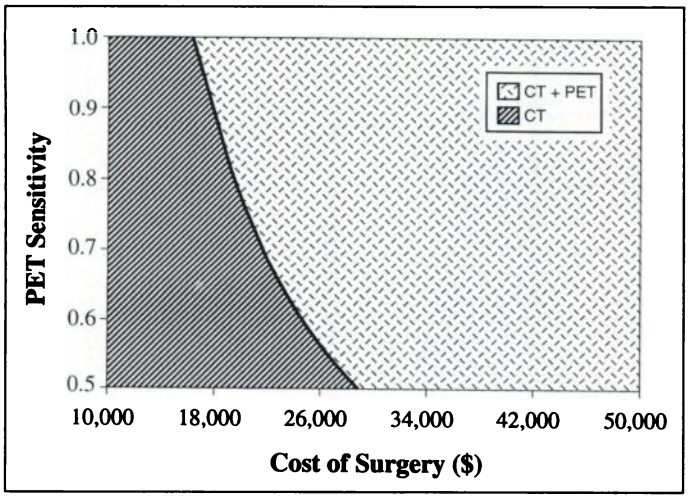

FIGURE 7. Results of the two-way sensitivity analysis for surgical costs versus sensitivity of PET for the CT strategy versus the CT + PET strategy of the decision tree in Figure 1 (for cost as the outcome variable). For surgical costs below $17,485, the CT + PET strategy is not more economical.

expectancy for highly advanced disease. If the mean life expectancy for unresectable disease is set to 1 yr, then the CT + PET strategy is always favored in terms of a higher patient mean life expectancy (graph not shown).

Figure 9 shows the two-way sensitivity analysis of surgical costs versus PET costs (for cost as the outcome variable). As expected, when the cost of surgery decreases the PET costs also have to decrease in order for the CT + PET strategy to be more economical.

Decision Tree of Figure 2

Results of analyzing the tree shown in Figure 2 (for the same baseline estimates as in Table 1 reveal a cost savings of $2,267 per patient by choosing the CT + PET strategy. This approach however does not operate on 1.7% of all patients being worked up by the CT + PET strategy who had potentially curable disease (false-positive yield from both studies). The cost savings gain of this approach is significantly more per patient ($25,634–$23,367) as compared to the more conservative approach ($1154) in the CT + PET strategy of Figure 1. The threshold values for all other variables for the tree in Figure 2

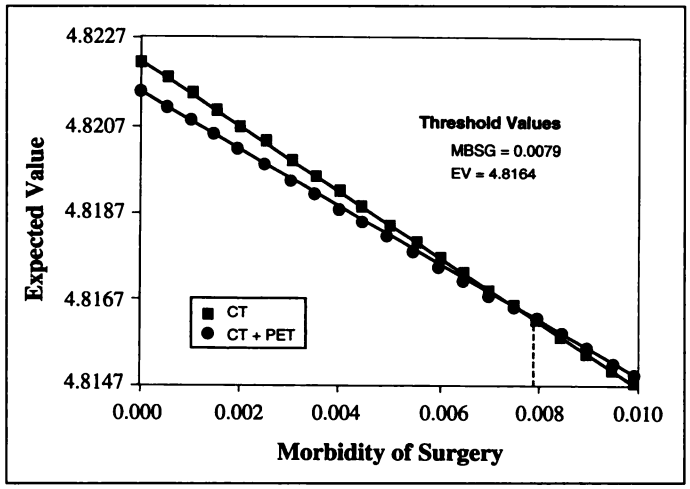

FIGURE 8. Results of the sensitivity analysis for morbidity of surgery on the mean life-expectancy [expected value (EV)] for the CT strategy versus the CT + PET strategy of the decision tree in Figure 1. Threshold or break-even value requires a surgical morbidity of 0.008 yr for the CT + PET strategy to have the same life-expectancy as the CT strategy. These calculations assume that the baseline values of all variables are as listed in Table 1, other than the mean life expectancy for unresectable disease which was set equal to 0.47 yr.

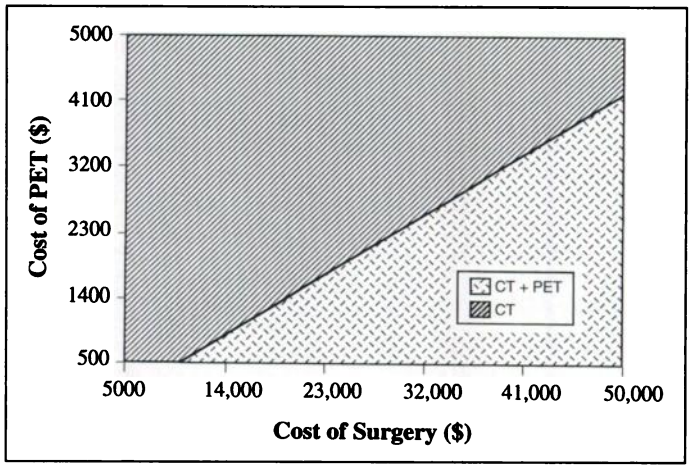

FIGURE 9. Results of the two-way sensitivity analysis for PET costs versus surgical costs for the CT strategy versus the CT + PET strategy of the decision tree in Figure 1 (for cost as the outcome variable).

are listed in Table 2. These values represent the cut-off values beyond which the CT + PET strategy is the strategy of choice when trying to minimize costs or maximize life expectancy.

DISCUSSION

The CT + PET based strategy of Figure 1 appears to be clinically useful in the staging of NSCLC patients because it reduces the probability that a patient with unresectable disease will undergo an unnecessary attempt at curative surgery. Although the marginal effectiveness of using PET for staging is small (about three days of life expectancy), it is positive over a wide range of conditions.

A CT + PET strategy also has been shown to be economical. With the use of baseline values for all variables, the CT + PET strategy of Figure 1 saves about $1154 per patient. This number is significantly less ($324) when a lower surgical cost ($21,000) is used, but it is still a net savings per patient. This lower figure would still translate to $27,540,000 in cost savings nationwide, assuming 85,000 patients undergo the diagnostic algorithm yearly. The real cost savings nationwide will depend on the exact reimbursement for surgery (and PET) on an individual basis. In general, the exact surgical reimbursement will be between the DRG value of $17,000 and an upper bound near our institution cost of $30,000. However, over a wide range of baseline values for the variables, the cost savings for the CT + PET strategy is shown to be positive. These costs include technical costs, professional costs and cost of any tracers, but they do not account for equipment depreciation costs. The true costs are difficult to precisely ascertain, but the sensitivity analysis allows for assessment of a strategy in the context of this uncertainty.

Although a PET alone strategy is a possible strategy to consider, it is a strategy that is unlikely to gain clinical acceptance. This is due to the fact that most surgeons would prefer to have a CT scan prior to surgery for anatomical considerations. Furthermore, it would be unlikely that anyone would consider biopsy in patients without first having a CT scan of the thorax. It could be argued that a potential decision tree is one in which a PET study is performed first, followed by CT only in those patients in which the PET is negative prior to going to surgery. However, then patients with positive PET scans might have false-positive results and may miss potential curative surgical resection. In the decision tree of Figure 1, these patients go on to have final confirmation with biopsy, but this would require a CT scan. If all PET-positive patients are not considered as further candidates for surgery, then some patients

who had potential for surgical cure would be missed. The conservative strategy of Figure 1 has the advantage of minimizing the number of patients who have a chance for surgical cure (only false-positive biopsy patients would be missed, which in the present analysis is assumed to be negligible). This strategy is therefore optimal both from a point of view of giving all patients the maximum potential diagnostic tools available, and from the point of view of giving clinicians the most possible information prior to the decision for surgery.

The CT + PET strategy of Figure 2 saves significantly more by not pursuing biopsy in those patients with positive CT and PET results. However, this approach will still miss a small percentage of patients with false-positive results. If one wishes to expend greater dollars of medical care to catch potential false-positives, then the CT + PET strategy of Figure 1 seems more appropriate.

PET has significant potential to be used for detecting extrathoracic metastases in addition to looking for contralateral and mediastinal involvement. Significant additional savings would result if PET was used to rule out surgical candidates based on the detection of distant metastases. The sensitivity and specificity of PET for the detection of distant metastases will probably vary on a region-by-region basis and is currently not known. The current study was based on using PET in a role similar to that played by thoracic CT. Decision trees which can be used to address the role of PET in detecting distant metastases in NSCLC are currently being studied.

Some of the limitations of this decision analysis imposed by our assumptions and tree structure deserve mention. These analyses assume that PET is readily available, and that extra days in the hospital are not required while waiting for this study. Although PET availability is currently limited, this study shows the significant savings when using a PET-based strategy, thus warranting the more widespread dissemination of the technology. Furthermore, this analysis supports the fact that technologies such as PET, which may be more expensive, can be more cost-effective due to their improved accuracy and negligible to no risk. The current analysis could easily be extended to an alternate imaging modality other than PET (e.g., SPECT-FDG imaging), with the appropriate sensitivity, specificity and costs. This may be useful in the future when more data are available on alternate newly emerging modalities. The current study has also used life expectancy as an outcome measure to model effectiveness. Future studies which use quality-adjusted life years may prove to be an additional outcome measure to model effectiveness.

The decision tree analysis assumes independence of the CT sensitivity and specificity from the PET values. This is approximately valid when both scans are read without the knowledge of the other scan results. In practice, the PET scan may be read with the use of the CT results, which would presumably improve the overall accuracy of a strategy using both studies and even greater cost savings may be realized.

The number of PET studies on NSCLC patients on which our baseline estimates of PET sensitivity and specificity are based are relatively small. It could be argued that as more patients are studied, the true PET sensitivity and specificity will be found to be less than the baseline values of 90% and 91% used in the present analysis. This may prove to be the case, but even with significantly lower sensitivity and specificity of PET, the CT + PET strategy is still more cost-effective as shown by the sensitivity analysis.

This study assumes that biopsy has 100% accuracy. Although biopsy is very accurate, it will produce some false-negative cases. These patients would be sent for surgery when in fact they are not surgical candidates. This error will increase costs for both the CT and CT + PET strategies. Therefore, the results are not expected to be sensitive to small deviations in accuracy of 100% for biopsy. Future studies to explore the effects of inaccuracies of biopsy are currently underway.

This work has also not directly accounted for costs associated with bone scans, whole-body screening, plain films, etc. These studies will vary significantly on an individual-by-individual basis. This is not expected to alter the outcome of the present study because most patients would not require this work-up, and both the CT strategy and CT + PET strategy would be affected equally. Some patients will be operable even though they have a distant metastasis (e.g., single brain metastasis). This category of patients is not explicitly accounted for in the current analysis. These patients are very small in number and are therefore not expected to alter the results of this study significantly. Also, the current analysis assumes all patients are operable. There will be a few patients who will not be surgical candidates for various medical reasons. Alternate decision trees which only perform PET imaging on patients who are operable by CT criterion are being currently explored.

The decision analysis strategies used in this work have significant wide-application potential. This is the case not only for other issues in which PET can play a role, but in nuclear medicine and medicine as well. This study illustrates the power of sensitivity analysis in proving hypotheses when there is uncertainty in numerous variables. Even with this uncertainty, the cost effectiveness can be proven over a wide range for all variables. It is important to note that it is critical to prove not only less costs but no loss in life expectancy, as was done in the current analysis. The tools and mathematics available for analysis are currently not user-friendly, but their application is critical to rigorously showing the cost-effectiveness for a particular application. We are currently also developing tools that are easier to utilize. These tools do not require the explicit definition of path probabilities by the user.

CONCLUSION

The present study has quantitatively shown the cost-effectiveness of using a PET-based strategy in the management of NSCLC. It has been shown that a CT + PET strategy is more economical and has a marginal increase in patient life expectancy as compared to the conventional strategy of staging patients with CT alone. Furthermore, even with the uncertainty in various variables, the effectiveness of the CT + PET strategy has been shown over a large range. The present study supports the wider use of PET in managing NSCLC as a significant cost-effective tool that can save millions of dollars nationwide. Furthermore, our data illustrate the power of decision analysis in quantitatively proving the utility of a particular strategy. Through extension of this work, it should be possible to study numerous other areas relevant to the use of PET in oncology as well as the role of many nuclear medicine procedures in the cost-effective clinical management of patients.

ACKNOWLEDGMENT

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EDITORIAL

Sense and Sensitivity: Issues in Technology Assessment

Evaluation of a new imaging technology in oncology is usually based on determination of sensitivity and specificity by correlation of imaging results with histologic diagnosis. Meaningful estimation of sensitivity and specificity is possible when the study population is appropriate and when full histologic evaluation of the target lesion or tissue is feasible. Examples of such studies include assessments of imaging in axillary staging of breast cancer and mediastinal staging of lung cancer. In both instances, surgical sampling can be performed, and the accuracy of positive and negative imaging findings can be determined with acceptable precision.

In many diagnostic situations, such precision cannot be achieved. Validation of imaging for detection of hepatic metastasis is one example. Even if all study subjects undergo surgical evaluation after imaging, undetected lesions will be diagnosed only if they are sufficiently large and superficial to be apparent on inspection and palpation of the accessible portions of the liver. Smaller and deeper lesions, which have not been detected by imaging and are not found at surgery, will remain undiagnosed and will not be recog-

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