Cost-effectiveness analysis of strategies introducing FDG-PET into the mediastinal staging of non-small-cell lung cancer from the French healthcare system perspective

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AIM: To determine the most cost-effective strategy using PET for mediastinal staging of potentially operable non-small-cell lung cancer (NSCLC).

METHODS: Four decision strategies based on French NSCLC work-up practices for the selection of potential surgical candidates were compared, comprising CT only, PET for negative CT, PET for all with anatomical CT, and CT and PET for all cases. The medical literature was surveyed to obtain values for all variables of interest. Costs were assessed with reimbursements from the French healthcare insurance for the year 1999. Expected cost and life expectancy were calculated for all possible outcomes of each strategy. Sensitivity analysis was performed to determine the effects of changing variables on the expected cost and life expectancy.

RESULTS: Compared with the CT only strategy, CT and PET for all resulted in a relative reduction of 70% of surgery for persons with mediastinal lymph node metastasis. PET for all with anatomical CT was shown to be a cost-effective alternative to the CT only, with life expectancy increased by 0.10 years and expected cost savings of 61 euros. This strategy was more favourable than PET for negative CT. Overall, sensitivity analyses showed the robustness of the results.

CONCLUSION: The introduction of thoracic PET for NSCLC staging is potentially cost-effective in France. Further clinical investigation might help to validate this result.

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textbf{Introduction}

Prognosis of lung cancer remains poor and has not improved appreciably over the last two decades. In 2000, lung cancers led to 27,164 deaths in France with a mortality rate standardized to Europe of 36.6 per 100,000.\textsuperscript{1} There were 27,743 cases of newly diagnosed lung cancers in France in 2000.\textsuperscript{2} Non-Small-Cell Lung Cancer (NSCLC) represents 80% of all lung cancers. Its survival rate appears to be better if patient is medically operable and the tumor is resectable. Staging work-up of NSCLC aims to identify patients who will potentially benefit from surgical treatment from those with...
mediastinal lymph nodes metastasis (stages N2 or N3). N2 status refers to metastasis to ipsilateral mediastinal and subcarinal lymph nodes. N3 status refers to metastasis to contralateral mediastinal, contralateral hilar, ipsilateral or contralateral scalene, or to supraclavicular lymph nodes. N1 refers to metastasis to lymph nodes in the peribronchial or the ipsilateral hilar region.3,4 Currently, Computed Tomography (CT) of the chest is an accepted tool for staging mediastinal lymph nodes. Because of its low specificity, surgical biopsy by cervical mediastinoscopy or thoracoscopy, or both, is necessary to achieve an accurate mediastinal stage. However these surgical procedures present inherent risks and significant costs.5

2-[Fluorine-18] Flouro-2-Deoxy-D-Glocose (FDG) Positron Emission Tomography (PET) appears to be particularly promising. PET can identify biopsy-proven metastasis that are not identified by other tests in 10% to 20% of potentially operable patients with NSCLC.6 Recently, the PLUS study group (PET in LUng cancer Staging) conducted a randomised clinical trial and concluded that addition of FDG-PET to conventional work-up staging of NSCLC prevented unnecessary surgery in one out of five patients with suspected NSCLC, therefore FDG-PET may be included in the routine NSCLC staging protocol.7

Recent studies using decision-tree analysis have suggested the potential cost-effectiveness of using FDG-PET for the management of NSCLC.8–13 This findings could not be valid in every health care system without taking into account specificity of costing of medical care and alternative clinical practices in health care system.14,15 Published decision tree models should consider the specificity of medical costs data or insurance reimbursement systems and should reflect the practice of physician in different health care system.16 Consultation of leader’s opinion in our academic university hospital showed that the discrepancy between published decision tree analysis and reported experience in France health care system is particularly high for staging NSCLC. Since costs structures may differ in France from those in other countries and discrepancy exists between published models and actual practices, it was felt important that an incorporation of local costs and practices should be made to adjust the published models.

The objective of this work was to develop a decision analysis model to compare the cost-effectiveness of various strategies of mediastinal staging of potentially operable NSCLC combining CT, PET and biopsy from the French health care system perspective.

Material and method

Base-case

The base-case was a 65-year-old patient, in whom NSCLC has been histologically established and assessed as operable. Distant metastases had not been detected and the tumour was assessed as locally resectable by conventional staging. Estimates of the proportion of patients with a mediastinal metastasis disease at presentation varied with criteria for resectability ranging from 28% to 38%.17 So up to three-quarter of the patients with NSCLC were excluded from the base-case of our analysis.

General description of the model

We performed cost-effectiveness analysis from the French national public health system insurance perspective using a decision tree model.18 Strategies comprised of sequences of particular clinical events with associated estimated transitional probabilities. At the end of each alternative arm of the tree (represented by a terminal node), payoffs were assigned corresponding to the total cost of care and life expectancy in years. Data 4.0 software (Tree-Age, Inc Williamston, MA) was used to construct the decision tree and rolled back for analysis.

Structure of decision trees

Four strategies labelled CT only, PET for negative CT, PET for all with anatomical CT, and CT and PET for all were established (Fig. 1(a)–(d)).

The baseline strategy uses only thoracic CT for non-invasive preoperative staging, whereas other strategies include the use of thoracic PET in different approaches. For all these strategies, we assumed that biopsy of mediastinal lymph nodes is performed by cervical mediastinoscopy (CM), which was assumed to be equally sensitive to identify ipsilateral and contralateral mediastinal enlarged lymph node.

Reports that focused on the indications for CM in patients with NSCLC are controversial. Some authors recommend CM for all patients who are being considered for thoracotomies,5,19 whereas others insist that CM is indicated only when mediastinal involvement is suspected.20,21 Unfortunately, some lymph node levels are not accessible
Figure 1. (a) The strategy CT only. A square represents a decision node; circles are chance nodes; and diamonds denote terminal nodes (Biop., biopsy; CT, computed tomography; PET, positron emission tomography). (b) The strategy PET for negative CT. (Biop., biopsy; CT, computed tomography; PET, positron emission tomography). (c) The strategy PET for all with anatomical CT. (Biop., biopsy; CT, computed tomography; PET, positron emission tomography). (d) The strategy CT and PET for all. (Biop., biopsy; CT, computed tomography; PET, positron emission tomography).
Figure 1 (continued)
by the standard CM, such as para-oesophageal (level eight) nodes, pulmonary ligament (level nine) nodes, and in general hilar (level ten) nodes and all other intrapulmonary nodes. In addition, not accessible to standard CM are the subaortic (aortopulmonary window, level five) and para-aortic (level six) nodes. French respiratory physicians and thoracic surgeons do not indicate a CM in all patients with CT positive for mediastinal lymph node involvement (N1 or N2 lymph nodes with more than 1 cm in the short-axis diameter). However, we have no evidence data about the proportion of patients with CT positive to whom CM would be actually recommended. Based on the consensus of multidisiplinary experts, about half of such patients would undergo surgical staging by CM. We integrated this parameter in staging work-up of NSCLC for all strategies.

On the basis of the final diagnostic result of each staging strategy, patients are treated with chemo-radiation or surgical resection according to mediastinal lymph nodes involvement or not.

**CT only**
According to heterogeneity in practice, we assumed that 50% of patients who are CT-positive for mediastinal lymph node involvement (N2/N3) proceed directly to chemo-radiation treatment and that 50% of those patients have a biopsy to confirm that the patient is not a surgical candidate. This 50% assumption reflects frequency of the practice of mediastinoscopy for patients with CT positive as suggested by experts (see frequency of CM). If the biopsy result is negative, patients proceed to lung resection. Patients who are CT negative for mediastinal lymph node involvement (N0/N1) proceed directly to thoracotomy.

**PET for negative CT**
50% of patients who are CT positive proceed directly to chemo-radiation and the other 50% of patients undergo a confirming biopsy. If the biopsy result is negative, they proceed to the necessary operation. The CT-negative patients undergo thoracic PET. If the PET results are negative, patients proceed to the necessary operation. Of patients with positive PET, 50% had confirming biopsy and the remaining patients proceed directly to chemo-radiation therapy.

**PET for all with anatomical CT**
All patients undergo thoracic CT and PET. Of patients with positive PET, 50% proceed to biopsy and the other 50% proceeded directly to chemo-radiation therapy. The PET-negative patients proceed to thoracotomy. This strategy uses PET functional information for the staging decision and CT information for anatomic location of mediastinal nodes whereas size is ignored. It simulates practical scenario in which biopsy of mediastinal lymph node could be avoided in case of conflicting results of CT positive and PET negative scanning.

**CT and PET for all**
All patients undergo systematically chest CT firstly, then thoracic PET. When both CT and PET demonstrate concordant results (negatives or positives mediastinal lymph nodes), biopsy is not performed. In others cases, 50% of patients undergo lymph nodes biopsy, the others proceed directly to chemo-radiation therapy.

**Data**
The medical literature was surveyed to obtain a base-case value and range for all variables of interest, and we used short-term charges rather than cost. Since the precise values of probability, test parameters and cost varied in different studies, sensitivity analyses were performed. Values used in the model, the ranges over which they were tested, and their sources are shown in Tables 1 and 2.

**Stage of disease at presentation**
The prevalence of contralateral and mediastinal nodal involvement, in patients with NSCLC being considered for surgery was estimated at 30% on the basis of review of a retrospective cohort of 217 patients in our university hospital (unpublished data).

**Sensitivity and specificity of tests**
Estimates base-case values of the sensitivity and specificity of thoracic CT to detect enlarged lymph nodes (N2/N3 disease) were provided by published studies. We adopted sensitivity 0.57 (95% Confidence Interval CI, 0.49 to 0.66) and specificity 0.82 (95% CI, 0.77 to 0.86) for thoracic CT obtained from two meta-analyses of studies that used modern-generation scanner, CT criterion of >1 cm in the short-axis diameter to represent mediastinal lymph nodes involvement, and pathologic confirmation by mediastinal lymph nodes sampling. The sensitivity and specificity for thoracic PET has been reported in various subgroups according to CT results. We used these values for PET according to two meta-analyses recently published. The sensitivity and the specificity of CM were obtained from meta-analysis of Toloza et al. The overall sensitivity was 0.81 (95% CI, 0.76 0.85). This
value was varied from 0.65 to 0.95 to account for the fact that the sensitivity may be decreased or increased according to experience in using this procedure. We assumed that the specificity of CM was 100% (false-positive rate of CM is negligible).29,30

**Frequency of CM**

Mediastinoscopy is the gold standard to obtain histologic confirmation of mediastinal lymph node status, and its value is widely accepted. However, the precise indications for performing mediastinoscopy remain controversial. Factors taken into account in deciding whether or not to perform mediastinoscopy include size of tumor, location of tumor (peripheral vs. central), histology of tumor, size of mediastinal lymph nodes on chest CT, positivity of lymph nodes on PET, and surgeon’s preference.31 In addition, some lymph node levels are not accessible by the standard CM. So, CM is not systematically performed in all patients with abnormal mediastinal findings on chest imaging. Staffs of multidisplinary experts in our university hospital estimated that about 50% of patients with abnormal mediastinal findings would proceed to CM for histologic confirmation of mediastinal lymph node status. The frequency of CM was varied from 0 to 100% in order to take into account the uncertainty attached to this parameter.

**Life-expectancy**

The life expectancy was based on previously published data.13 Life expectancy was estimated at 4.5 years for patients with resected lung cancer, at 1.8 year for patients treated surgically with mediastinal involvement, at 1.8 years for patients with unresectable disease treated with chemo-radiation therapy and at 2.6 years for patients who were potentially eligible to surgical treatment but treated with chemo-radiation therapy solely.

**Mortality and morbidity**

Estimates for the mortality of surgical resection for lung cancer vary in different studies.32–35 We chose a baseline surgical mortality of 3% for pneumonectomy based on a recent postoperative mortality

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**Table 1** Base-case value, range and reference of parameters used in the decision tree

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Range</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence of N2/N3</td>
<td>0.30</td>
<td>0.25-0.70</td>
<td>Unpublished data</td>
</tr>
<tr>
<td>CT sensitivity</td>
<td>0.57</td>
<td>0.49-0.66</td>
<td>[25,26]</td>
</tr>
<tr>
<td>CT specificity</td>
<td>0.82</td>
<td>0.77-0.86</td>
<td>[25,26]</td>
</tr>
<tr>
<td>PET sensitivity, enlarged lymph nodes on CT</td>
<td>0.95</td>
<td>0.80-1</td>
<td>[13,27]</td>
</tr>
<tr>
<td>PET sensitivity, normal lymph nodes on CT</td>
<td>0.74</td>
<td>0.59-0.79</td>
<td>[13,27]</td>
</tr>
<tr>
<td>PET specificity, normal lymph nodes on CT</td>
<td>0.96</td>
<td>0.70-1</td>
<td>[13,27]</td>
</tr>
<tr>
<td>PET specificity, enlarged lymph nodes on CT</td>
<td>0.76</td>
<td>0.61-0.81</td>
<td>[13,27]</td>
</tr>
<tr>
<td>Mediastinoscopy sensitivity</td>
<td>0.81</td>
<td>0.65-0.95</td>
<td>[28,30]</td>
</tr>
<tr>
<td>Mediastinoscopy specificity</td>
<td>1</td>
<td>-</td>
<td>[29,30]</td>
</tr>
<tr>
<td>Mediastinoscopy mortality</td>
<td>0.003</td>
<td>0-0.05</td>
<td>[39-41]</td>
</tr>
<tr>
<td>Mediastinoscopy morbidity (year)</td>
<td>0.028</td>
<td>0-1</td>
<td>[9]</td>
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<tr>
<td>Use of CM</td>
<td>0.50</td>
<td>0-1</td>
<td>Expert opinion</td>
</tr>
<tr>
<td>Lung resection mortality</td>
<td>0.03</td>
<td>0.001-0.1</td>
<td>[32-35]</td>
</tr>
<tr>
<td>Lung resection morbidity (year)</td>
<td>0.083</td>
<td>0-1</td>
<td>[9]</td>
</tr>
<tr>
<td>Life expectancy (year)</td>
<td>4.6</td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td>Surgery for N0/N1</td>
<td>1.8</td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td>Surgery for N2/N3</td>
<td>2.6</td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td>Chemo-radiation therapy for N0/N1</td>
<td>1.8</td>
<td></td>
<td>[13]</td>
</tr>
<tr>
<td>Chemo-radiation therapy for N2/N3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CT, computed tomography; PET, positron emission tomography; CM, cervical mediastinoscopy; NGAP, Nomenclature Générale des Actes Professionnels; ENC, Echelle Nationale des Coûts (see cost sections in text).
reported by Wada et al.\textsuperscript{35} In addition, we subtracted 1 month (0.083 year, range from 0 to 1 year) for the morbidity associated with the recovery from thoracotomy in decision analyses involving surgical intervention for lung cancer.\textsuperscript{9,36–38} CM is usually associated with minimal mortality (0\% to 0.3\%).\textsuperscript{39–41} We used the higher reported value of mortality as our base-case estimate (range from 0 to 5\%). We estimated the average morbidity for CM to be about one third of that for curative surgical resection (0.028 year) (10 days).\textsuperscript{9} The risk associated with chest CT is primarily attributable to administration of intravenous contrast material. We assumed that chest CT has neither morbidity nor mortality for patients with NSCLC. The risk associated with PET is assumed to be negligible since there has been no report to date of reaction or complications from the injection of FDG.

\textbf{Costs}

The economic analysis was governed from the national public health system insurance perspective. Only medical direct costs were included in our model. Because the sequence of events (diagnosis and hospital treatment) lasts maximum some weeks, costs were not discounted.

Cost of chest CT and CM were obtained from “Nomenclature Générale des Actes Professionnels” (NGAP) which is a fixed price scale of medical interventions. In France, available data concerning the cost of a PET were reported by two French simulations including the cost of FDG, transport operating costs, equipment operating, building, equipment, furniture and other miscellaneous items.\textsuperscript{42,43} According to those findings, the cost of PET was fixed at 1044 €. To estimate the costs of surgery treatment, a case-mix was derived from a regional database including various Diagnosis Related Groups (DRGs) for the year 1999 in the public health care sector. Cost was then measured using “Echelle Nationale des Coûts” (ENC), a national public cost scale compiled by the Ministry of Health using data from a representative sample of French public hospitals for the year 1999. The ENC includes several budget headings, such as costs for labour, technical procedure, consumable products, maintenance, provision for depreciation, laundering, and catering. Cost of chemo-radiation treatment for unresectable NSCLC was estimated from Schraub et al. study.\textsuperscript{44} Economic parameters are summarized in Table 2.

\textbf{Incremental cost-effectiveness ratio}

The subsequent cost effectiveness analysis was performed according to the recommendations for reference-case analysis on the Panel by Cost-Effectiveness in Health and Medicine\textsuperscript{45} and those of Drummond et al.\textsuperscript{46} Calculations of expected cost and life expectancy of competing strategies were performed by summing the products of probabilities and values of each outcome.

Conventional staging with CT only is the most widely used strategy and was chosen as baseline strategy to which each PET-based strategy was compared by calculating the Incremental Cost-Effectiveness Ratio (ICER).

\[
\text{ICER} = \frac{(COST_{\text{strategy}} - COST_{\text{baseline}})}{(LE_{\text{strategy}} - LE_{\text{baseline}})}
\]

where COST\text{baseline} and LE\text{baseline} represented the cost and the life expectancy for CT only strategy and COST\text{strategy} and LE\text{strategy} represented the cost and life expectancy for each PET-based strategy. The results of ICER were presented in term of Euros per Life Year Saved (€/LYS).

A negative numerator and positive denominator mean that the strategy under evaluation has lower cost and higher life expectancy being beneficial in all means. A positive numerator and negative denominator also yield a negative ICER. In that case the new strategy is dominated, because it has higher cost and lower life expectancy and should be rejected.

Positive numerator and denominator mean that the new strategy saves life years at an increased cost. In this case, cost per life year saved might be calculated and the acceptability of this value threshold of ICER could be discussed. Negative numerator and denominator (cost savings and a reduction in life expectancy) yield a positive ICER but a conflicting ethical consideration of cost savings per life year lost.

\textbf{Sensitivity analyses}

Sensitivity analyses were performed to evaluate the robustness of our results when we varied the probabilities and assumptions used in the model. The range of values over which probability and costs were tested was obtained from the medical literature and expert opinion.

\textbf{Results}

\textbf{Base-case values}

Table 3 showed the proportion of therapeutic management of patients according to the strategies
modelled. At base-case values, the strategy PET for all with anatomical CT resulted in the higher proportion of surgery for patients with N0/1 stage. If the strategy CT and PET for all is performed for mediastinal staging, the proportion of patients with N2/3 treated by surgery would be 4.2%. Compared to the baseline strategy, the strategy CT and PET for all resulted in relative reduction of 70% of surgery for patients with mediastinal lymph nodes metastasis.

The details of the ICER calculations for the base-case analysis are given in Table 4. The strategy CT only presented a mean life expectancy of 3.47 year at mean cost of 4542 €. The introduction of PET after CT resulted in various ICERS according to its place in the decision tree and the chain of modelled diagnostic and therapeutic events. Compared to baseline, ICER of PET for negative CT strategy was 33,165 €/LYS. CT and PET for all strategy was dominated with a decreased of 0.03 year in life-expectancy and a cost increased by 1008 € compared to CT only strategy. PET for all with anatomical CT strategy appeared as the most cost-effective strategy, presenting a gain of 0.10 year, a mean cost saving of 61 € and a negative ICER of −576 €/LYS compared to CT only strategy.

Sensitivity analyses

The details of the ICER calculation when changing several of the variable values though sensitivity analyses are given in Tables 5 and 6.

Probability of N2/N3

The probability of N2/3 was 0.30 at base-case. Over the whole range of variation, PET for all with anatomical CT strategy remained the most cost effective, presenting the lowest ICER compared to the baseline strategy between 0.25 and 0.40 and dominating the baseline strategy and all other alternatives over the threshold of 0.40.

Frequency use of biopsy

The frequency of biopsy after positive imaging was 0.50 at base-case and was varied between 0 and 1. When the frequency of biopsy was varied between 0 and 0.5 the strategy PET for all with anatomical CT dominated all other strategies. The strategy PET for negative CT became cost effective compared to the baseline strategy as the frequency use of biopsy exceeded 0.5. The strategy PET for all with anatomical CT remained to be the most cost effective strategy. Frequency of biopsy of 100% simulates a routine CM for assessment of all patients with positive lymph nodes on thoracic CT. For this value, ICER of the strategy PET for all with anatomical CT was 12,893 €/LYS and the ICER of the strategy PET for negative CT was 9250 €/LYS. The strategy PET

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Therapeutic management of patients according to the strategies modelled (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>CT only</td>
</tr>
<tr>
<td>Surgery for N0-1</td>
<td>61.8</td>
</tr>
<tr>
<td>Surgery for N2-3</td>
<td>14.1</td>
</tr>
<tr>
<td>Chemo-radiation for N0-1</td>
<td>6.3</td>
</tr>
<tr>
<td>Chemo-radiation for N2-3</td>
<td>15.5</td>
</tr>
<tr>
<td>Surgical mortality</td>
<td>2.3</td>
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CT, computed tomography; PET, positron emission tomography.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Cost, life expectancy of each four strategies and incremental cost-effectiveness ratio (ICERs) (all options referenced to the common baseline strategy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td>Cost (€)</td>
</tr>
<tr>
<td>CT only</td>
<td>4542</td>
</tr>
<tr>
<td>PET for negative CT</td>
<td>5206</td>
</tr>
<tr>
<td>PET for all with anatomical CT</td>
<td>4481</td>
</tr>
<tr>
<td>CT and PET for all</td>
<td>5550</td>
</tr>
</tbody>
</table>

The results of ICER are presented in term of Euros per Life Year Saved €/LYS. CT, computed tomography; PET, positron emission tomography.
Increase cost and life expectancy with ICER of 9312 V/LYS compared with the strategy PET for negative CT (data not shown).

Sensitivity and specificity of PET

The one-way sensitivity analysis of parameters of PET showed that only the specificity of PET after negative CT (PET Sp/CT−), had threshold values beyond which PET for all with anatomical CT strategy was the strategy of choice. Base-case value for this parameter was 0.96 and it was varied between 0.70 and 1. For a (PET Sp/CT−) lower than 0.73, the CT only strategy dominated all other strategies. Above this value the strategy PET for all with anatomical CT was the most cost-effective strategy. Through the ranges of other parameters of PET (sensitivity of PET after negative CT, sensitivity of PET after positive CT and specificity of PET after positive CT) the sensitivity analysis showed that the strategy PET for all with anatomical CT remained the cost-effective strategy (Table 5).

Cost of FDG-PET

The cost of PET was 1044 € for base-case. Varying the costs of PET (including cost of FDG) for value above 1044 € the results remain the same. When it was raised at 1121 €, the strategy PET for all with anatomical CT increased cost and life expectancy with ICER of 170 €/LYS compared with the strategy CT only.

Cost of surgery

The cost of surgery was 2009 € for base-case. When the cost of surgery was raised above 10,000 € the strategy PET for negative CT produced negative ratios of −9200 €/LYS in comparison with the strategy CT only. The strategy PET for all with anatomical CT also saved cost and increased life expectancy with ICER of −4083 €/LYS. If saving cost was the sole consideration, the strategy PET for negative CT would be the best strategy. The ICER of PET for all with anatomical CT strategy was −2897 €/LYS in comparison with the PET for negative CT strategy which means that the strategy

### Table 5

<table>
<thead>
<tr>
<th>CT only</th>
<th>PET for negative CT</th>
<th>PET for all with anatomical CT</th>
<th>CT and PET for all</th>
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<tbody>
<tr>
<td>Cost</td>
<td>LE</td>
<td>Cost</td>
<td>LE</td>
</tr>
<tr>
<td>4542</td>
<td>3.47</td>
<td>5206</td>
<td>3.49</td>
</tr>
</tbody>
</table>

The results of ICER are presented in term of Euros by Life Year Saved €/LYS. LE, life expectancy; ICER, incremental cost-effectiveness ratio; CM, cervical mediastinoscopy; CT, computed tomography; PET, positron emission tomography; (PET Sn/CT−). PET sensitivity for normal lymph nodes on CT PET; (PET Sp/CT−). PET specificity for enlarged lymph nodes on CT.

* The probability of performing cervical mediastinoscopy after abnormal mediastinal findings on chest imaging.
<table>
<thead>
<tr>
<th></th>
<th>CT only</th>
<th></th>
<th>PET for negative CT</th>
<th></th>
<th>PET for all with anatomical CT</th>
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<th>CT and PET for all</th>
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<tbody>
<tr>
<td></td>
<td>Cost</td>
<td>LE</td>
<td>Cost</td>
<td>LE</td>
<td>ICER</td>
<td>Cost</td>
<td>LE</td>
</tr>
<tr>
<td>Base-case</td>
<td>4542 3.47</td>
<td>5206 3.49</td>
<td>33,165</td>
<td>4481 3.57</td>
<td>5550 3.44</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>Cost of PET</td>
<td>938 3.47</td>
<td>5131 3.49</td>
<td>29,450</td>
<td>4376 3.57</td>
<td>5481 3.44</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>975</td>
<td>4542 3.47</td>
<td>5157 3.49</td>
<td>30,750</td>
<td>4412 3.57</td>
<td>5536 3.44</td>
<td>Dominated</td>
<td></td>
</tr>
<tr>
<td>1030</td>
<td>4542 3.47</td>
<td>5196 3.49</td>
<td>32,700</td>
<td>4467 3.57</td>
<td>5628 3.44</td>
<td>Dominated</td>
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<tr>
<td>1084</td>
<td>4542 3.47</td>
<td>5234 3.49</td>
<td>34,550</td>
<td>4522 3.57</td>
<td>5481 3.44</td>
<td>Dominated</td>
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<tr>
<td>1121</td>
<td>4542 3.47</td>
<td>5260 3.49</td>
<td>35,900</td>
<td>4559 3.57</td>
<td>5591 3.44</td>
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<td></td>
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<tr>
<td>Cost of surgery</td>
<td>3954 3.47</td>
<td>6064 3.47</td>
<td>23,650</td>
<td>5919 3.58</td>
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<td>Cost of chemo-radiation</td>
<td>7391 3.47</td>
<td>4389 3.47</td>
<td>32,850</td>
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<td>13,495</td>
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<td>37,100</td>
<td>5775 3.58</td>
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The results of ICER are presented in term of Euros by Life Year Saved €/LYS. CT, computed tomography; PET, positron emission tomography; ICER, incremental cost-effectiveness ratio.
PET for all with anatomical CT increased life expectancy and saved cost when it was compared with strategy PET for negative CT. When the cost of surgery was raised above 17,000 €, the strategy PET for all with anatomical CT increased cost and life expectancy with ICER of 1367 €/LYS compared with the strategy PET for negative CT (Table 6).

**Cost of chemoradiation**

Doubling or even tripling estimated cost of chemoradiation therapy did not change the order of ICER among four strategies tested.

**Discussion**

The results of this decision analysis clearly support the use of thoracic PET as preoperative mediastinal staging procedure for patients with NSCLC. The strategy PET for all with anatomical CT has shown to be the most cost-effective alternative compared with the CT only management strategy. It saved cost and increased life expectancy resulting in — 576 €/LYS. Even under a wide range of assumptions, the results of sensitivity analyses showed the robustness of this conclusion. Varying model parameters simulates the possibility of seeing indication for this new test to be transferred from specialized centres to the routine practice in non-specialized centres. It provides a degree of confidence on results of this cost-effectiveness analyses in France even if variations in practice exist.

Assuming a widespread diffusion of PET FDG, the discrepancies between the results of PET and CT about the involvement of mediastinal lymph nodes would be the cornerstone to avoid invasive mediastinum staging. The strategy PET for all with anatomical CT simulates this practical scenario. However, we believe that when FDG-PET results are negative, decision to perform CM or surgery with curative intent should be guided by the pre-test probability of mediastinal metastasis, the risk for surgical complications, and the patient preferences. While our results can help to inform clinical decision making, more investigations are needed to determine when surgery without previous mediastinal biopsy can be performed.

Uncertainty exists in regards to the results of cost effectiveness analysis because the level of uncertainty in each calculated ICER is unknown. In the absence of data at the patient level we used sensitivity analyses. Recently, a number of alternative complex methods based on simulation have appeared in the literature for computing confidence intervals around calculated ICER. However, a number of practical problems are associated with such methods for quantifying uncertainty of ICER.

The optimal overall strategy for staging patients with NSCLC remains controversial. Although chest CT can be used to assess patients’ T and M status, the ability of CT to accurately assess mediastinal involvement is suboptimal. CM provides a more accurate way to stage the mediastinum, but it is associated with additional risks and costs. In the present study strategy CT and PET for all resulted in relative reduction of 70% of surgery for patients with mediastinal lymph nodes metastasis. This differs from results of a recent randomized clinical trial concluding that PET does not lead to a major reduction of surgery for in patients with NSCLC. Since there is a difference in selection of patients entering the workup processes, our results do not contradict this, in so far as less than 8% of patients recruited into the Viney study had mediastinal metastasis to N2 or N3 lymph nodes, while our model was based on observational practices with a proportion of patients with a mediastinal metastasis disease of 30% as base-case.

Several studies have attempted to identify the best strategy for staging the mediastinum of patients with NSCLC. Scott et al. used decision analysis to compare various staging strategies combining PET, CT, and biopsy. In their model, patients without mediastinal disease underwent resection, whereas patients with evidence of mediastinal involvement (metastases to N2/N3 lymph nodes) were candidate for thoracotomy and lung resection as only therapy. The analysis was performed from the United States health care system perspective and Medicare reimbursements costs were used. The authors concluded that strategy that used CT PET after negative CT to stage the mediastinum generates an ICER of $ 25,286 per life-year saved.

More recently, Dietlein et al. performed a cost-effectiveness analysis comparing CT and PET to stage mediastinal lymph nodes. Patients with proven NSCLC were enrolled into the model. Patients without evidence of mediastinal disease underwent resection, whereas patients with mediastinal involvement were considered to have unresectable disease and were not considered for multimodal therapy. The economic analysis was limited to hospital costs and professional fees. The authors demonstrated that use CT and PET to staging patients with NSCLC is cost-effective for the German health system. The authors concluded that the implantation of PET in Germany would result in an additional cost of only 32,000 €.
In Japan, Kosuda et al. have proposed another decision tree that might be adapted for practices in Japan health care system.\textsuperscript{11} The results of the models showed that whole body PET in the place of CT for staging NSCLC patients avoided unnecessary bronchoscopies and thoracotomies for incurable and benign diseases. The authors concluded that the strategy that uses whole-body PET for managing NSCLC would be potentially cost-effective in Japan.

Critical appraisal of theses literatures showed that several assumptions were made to facilitate procedural modelling in terms of the architecture of the decision tree model. These assumptions were related to different approaches for the management of NSCLC given the results of FDG-PET scanning. In addition not all possible costs were included in these studies. Neither the cost of palliative care nor the cost of chemotherapy was included in the decision tree of Scott et al. The costs of palliative care and chemotherapy would be incurred in the specific population with non-resectable cancer, and so it influences the comparison between strategies. Moreover, at the time our analysis was designed, evidence suggests that practice and costs may differ in France from those in other countries. CM is not routinely used in current management of patients with CT positive to confirm that they are not surgical candidates. An important cause for such a discrepancy in France medical practice from other countries might be due to the fact that France health care system is public system and financed by national budget.\textsuperscript{51–54}

Our study has some limitations. Firstly, it does not consider all plausible options for the use of PET. Recently, the ability of PET-CT fusion imaging to improve on the sensitivity and specificity of PET alone has been reported.\textsuperscript{53} Moreover, studies have shown an additional value of PET in determining extra-thoracic spread of disease for patients with NSCLC.\textsuperscript{56,57} At this time, adequate data are available for evaluating the role of the PET in the assessment of mediastinal lymph nodes including these from two rigorous meta-analyses. There are much fewer data available regarding the sensitivity and specificity of PET for the detection of liver or bone metastases. However, several small series have suggested that the high accuracy of PET may obviate the need for a bone scan.\textsuperscript{58,59} Assessment of the role of these new approaches awaits further studies. Secondly, the simple approach taken by combining expert opinion based on their practices and original data from the literature on the sensitivity and specificity of tests independently might be inappropriate. It is likely that discrepancy might arise between the published data and the test performance as a routine procedure. The usefulness of PET in the mediastinal staging of lung cancer is evolving. So, the initial enthusiasm for PET as the staging tool for mediastinal disease might be tempered by the results of recent studies.\textsuperscript{60,61} But sensitivity analyses showed that even with lower sensitivity of PET, the strategy PET for all patients with anatomical CT is still cost-effective. On the other hand, we have no evidence data about the proportion of patients with mediastinal abnormality for whom CM would be performed. Therefore, we adapted expert opinion established in multidisciplinary staffs in our university hospital to set up the base-case for this study. Nevertheless, the frequency of use of biopsy was varied between 0 and 100% to consider the variability in practice of biopsy after positives results of thoracic imaging. Thirdly, the costs in this study are taken from France’s national perspective, and hence cannot be extended to other countries. Although, an optimal approach would have estimated the true costs of each subgroup of patient, we lacked data about adjustment cost of surgery and chimoradiotherapy for target subgroup patient. Finally, our work did not account for costs associated with bronchoscopy, bone scan, abdominal CT or others procedures that could be performed to identify underlying diseases such as Chronic Obstructive Pulmonary Diseases (COPD) or other co-morbidity. Since all the strategies assumed that patients were potential candidates for surgery and they could be operated, such co-morbidity cost consideration in the analysis is beyond the scope of the present study.

Our study showed that the additional PET cost is more than compensated for by the savings realized from avoided surgeries. It allowed drawing attention on consequences of sequence of NSCLC staging procedures. This theoretical decision model might be backed up by experience after implementation of this new technology for NSCLC work-up in France health care system.

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References


