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Use of a decision analysis model to assess the medicoeconomic implications of FDG PET imaging in diagnosing a solitary pulmonary nodule

Lung cancer is a major public health problem. It is one of the most frequent cancers in both sexes in France, with 28,000 new cases and 27,200 deaths in the year 2000 [1]. A patient's likelihood of surviving lung cancer depends on the stage of the disease at the time of diagnosis. A solitary pulmonary nodule (SPN) is indicative of early, and therefore potentially curable, bronchogenic carcinoma, but diagnosis and management are often problematic. In practice, SPNs are usually identified by chance on standard chest radiography and assessed for malignancy using computed tomography (CT). However, full radiological characterization of nodules is not always possible, and the status of many of them remains indeterminate [2].

Four strategies have been reported to provide further information: (a) wait and watch with periodic CT (WW); (b) transthoracic needle biopsy (TNB); (c) exploratory thoracotomy (ET); and (d) video-assisted thoracic surgery (VATS) [3, 4]. All have drawbacks, however; for example, patients undergoing WW may suffer recurrent anxiety about the possi-

bility of CT revealing a neoplastic nodule, and ET and VATS can result in morbidity and mortality due to anesthesia or resection.

Promising newer technologies in the initial diagnosis of SPN include [¹⁸F]2-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET), a scintigraphic imaging technique that relies on increased rates of glucose metabolism in malignant cells. Diagnosis by PET is superior to that achieved using CT, with sensitivity and specificity varying between 85% and 100% in different studies [5, 6, 7, 8, 9].

About ten PETs are currently implemented in France. To be deemed a priority from a public health policy perspective any new technique must prove itself to be effective and cost-effective. Ideally, cost-effectiveness should be analyzed using data collected in controlled studies designed to evaluate the efficacy of diagnostic strategies, but the size of the populations required and the length of the latent period between the start of a study and the availability of initial results make many options difficult to assess. A number of

cost-effectiveness analyses in this area have been published [4, 10, 11]. Overall these demonstrate that WW is the most appropriate strategy when the risk of malignancy is low, CT+PET is optimal in cases of moderate risk, and surgery is the most suitable strategy in cases of high risk. However, these findings cannot necessarily be extrapolated from one country to another because of variations in health care provision, approaches to pricing and reimbursement, and (potentially at least) clinical practice.

The present study developed a decision analysis model to compare the cost-effectiveness of PET with that of standard imaging techniques in SPN management from the French health care system perspective.

Material and methods

Base case

Published series report that SPNs vary in size between 1 and 4 cm [5, 12, 13, 14]. The present study considered only those less than 3 cm in diameter because above this

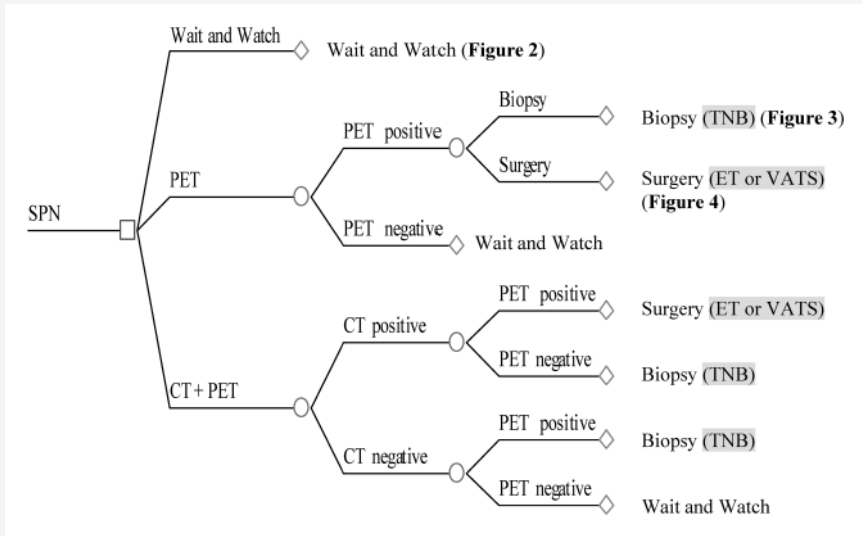


Fig. 1 ◀ Outline of decision tree showing the three modeled strategies. Squares Decision nodes; circles chance nodes; diamonds continuation to the designated strategy

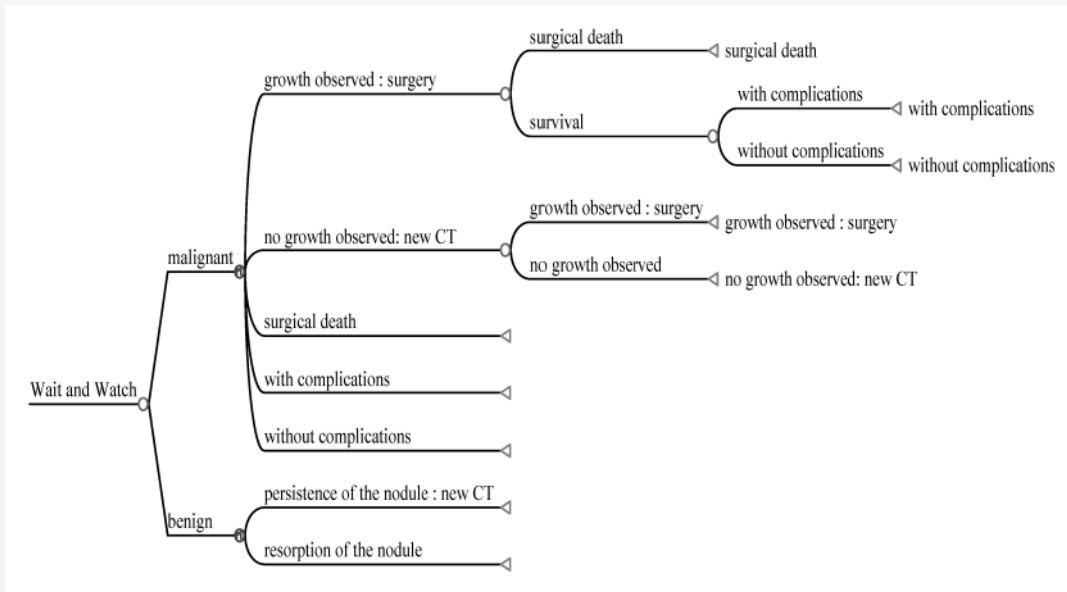


Fig. 2 ▲ Wait and watch strategy. Circles chance nodes; circles with M Markov nodes; triangles termination nodes; CT computed tomography. The Markov model presented here was created with the software Data Tree Age 3.5. Branches emanating from the Markov node enumerate all Markov health states through which the patient can progress according to transition probabilities. These health states emanating from the Markov node are then used as references when transitions between states are created. If a growth in SPN size was observed, the patient was oriented toward surgery with possible associated risks of complications and death. In the absence of growth, a new CT was performed

threshold the probability of malignancy is greater than 0.90 [15]. Other exclusion criteria were confirmed metastases or diagnosed primary lung cancer, and previous thoracic radiographic evidence establishing the stability or growth of the nodule. Based on recent clinical articles [16], the base case was a 65-year-old male-current smoker (1.5 packs per day) with a 2-cm SPN without calcification, specula and

enlargements of mediastinal lymph nodes, and a malignancy risk of 43%.

General description of the model

The decision analysis model was based on a decision tree (Figs. 1, 2, 3, 4), with each competing diagnostic strategy originating from a decision node. Strategies comprised sequences of diagnostic tests and

treatments arranged according to the estimated probability of particular clinical events occurring. At the extreme end of each arm of the tree (represented by a terminal node), payoffs were assigned corresponding to the total cost of care (diagnosis cost plus treatment cost) and life expectancy in years (LE). The sequences of medical procedures were first constructed from data obtained from published litera-

ture. A committee of multidisciplinary experts was then created and consulted to validate the model and the choice of the parameters. Data 3.5 software (TreeAge, Williamston, Mass., USA) was used to construct decision trees.

Strategies

Three strategies were compared: wait and watch (WW), PET and anatomical computed tomography (PET), and CT plus PET (CT+PET). Before any strategy was initiated, SPN was assumed to be identified by chance using standard chest radiography.

Wait and watch

Abdominal-pelvic-thoracic CT was initially performed to confirm the presence of the nodule, the size of which was then monitored every 3 months, as recommended, using thoracic CT (■ Fig. 1) [17]. The growth rate of an SPN was defined by the time that it took to double in volume, a useful indicator of malignancy. Most malignant nodules have a doubling time between 1 month and 1 year [18, 19, 20], whereas the majority of benign nodules either stabilize or decrease in size. It was assumed for present purposes that most nodules, whether benign or malignant, are likely to change in size within a year of being identified [3]. A Markov process, the aim of which is to represent repetitive events over time [21], was used to simulate follow-up with periodic thoracic CT (■ Fig. 2). The time horizon of the follow-up was divided into four 3-month increments (Markov cycles) over the course of 1 year. In other words, CT was performed every 3 months. As benign and malignant nodules progress at different rates, both were considered (■ Table 1). On the basis of a clinical study [20] we used the following probability calculations: a 50% that a malignant nodule will grow during the first 3 months, a 75% cumulatively at 6 months, 90% cumulatively at 9 months, and 100% cumulatively at 1 year. For a benign SPN the probability that the nodule would decrease in size was based on experts' opinion and considered constant at 50% every 3 months. Patients in whom growth was observed underwent exploratory thoracotomy and were treated surgically by lobectomy.

Abstract

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Use of a decision analysis model to assess the medicoeconomic implications of FDG PET imaging in diagnosing a solitary pulmonary nodule

Abstract

This study assessed the use of positron emission tomography (PET) in identifying and diagnosing solitary pulmonary nodules (SPNs). For this a decision analysis model was constructed, and three alternatives were compared: wait and watch (WW), PET and anatomical computed tomography (PET), and CT plus PET (CT+PET). Transition probabilities were estimated from published data and consultations with experts. Costs of diagnosis were derived from the French reimbursement scale, and treatment costs from a national hospital database of diagnosis-related groups. The base case was defined as a 65-year-old male smoker with a 2-cm SPN and an associated high risk of malignancy of 43%. Evaluation criteria included incremental cost-effectiveness ratios and the proportion of unnecessary operations avoided in patients without malignant SPN. For the base case WW was the least effective and cheapest strategy. CT+PET was more effective and presented lower incre-

mental cost-effectiveness ratio (€3,022 per life-year gained). It also was superior to PET in cost-effectiveness terms and resulted in 4.3% fewer unnecessary resections of benign SPN than did PET. Risk profile analyses performed on SPN malignancy risk showed that CT + PET remains the most cost-effective strategy in the range of 5.7–87%, and that WW is more cost-effective in the range of 0.3–5.0%. CT+PET is thus cost-effective in detecting malignant SPN in patients with a risk of malignancy of at least 5.7% and may avoid inappropriate resections of benign SPN. These findings support the attempts to introduce a larger number of PETs in France for SPN diagnosis.

Keywords

Positron-emission tomography · Solitary pulmonary nodule · Decision modeling · Cost-effectiveness · Program evaluation

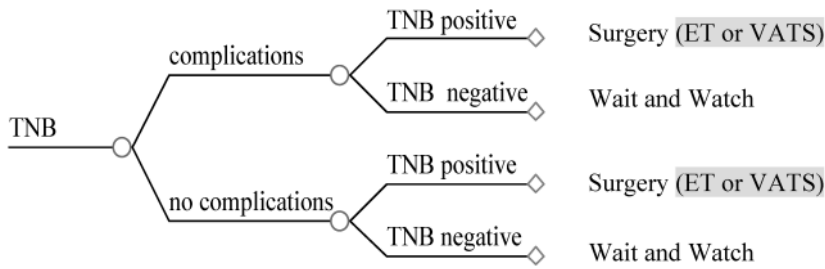


Fig. 3 ◀ Biopsy (TNB) strategy. Circles Chance nodes; diamonds continuation to the designated strategy

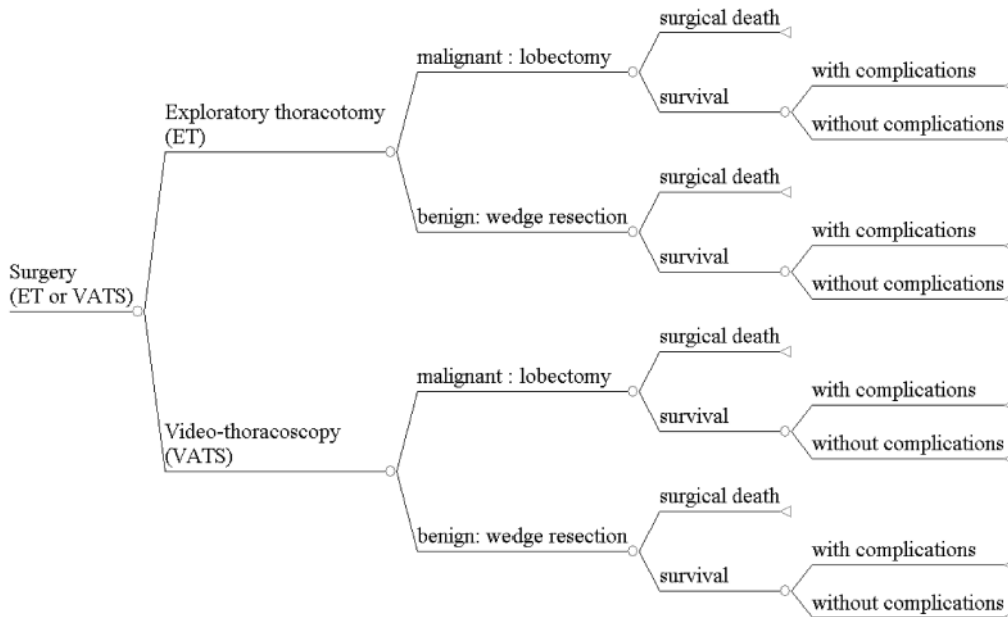


Fig. 4 ◀ Surgery strategy (ET or VATS). Circles Chance nodes; triangles termination nodes; ET eploratory thoracotomy; VATS video-assisted thoracic surgery

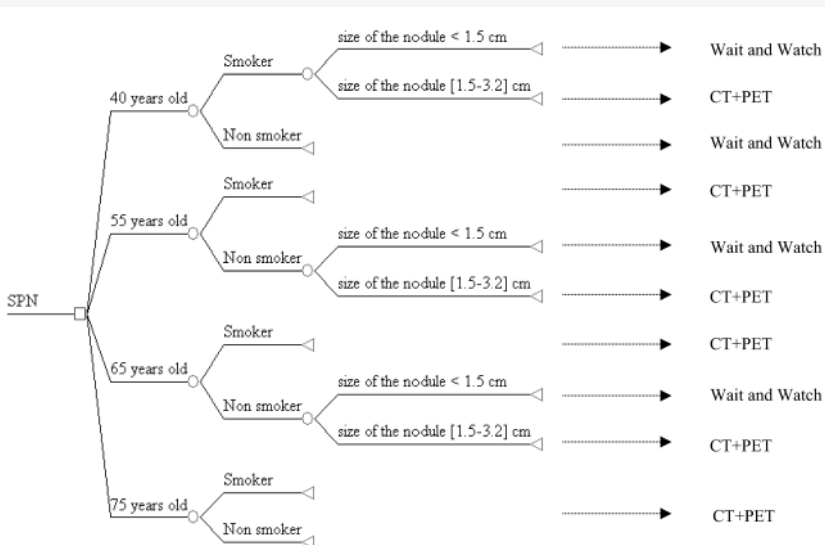


Fig. 5 ◀ Diagnostic strategies to be recommended from a medicoeconomic point of view according to the risk profiles of patients (age, smoking history, and size of the nodule)

PET and anatomical CT

This strategy involved PET immediately after chest radiography. When the findings were positive, malignant SPN was suspected, and the diagnosis was confirmed using one of three invasive techniques: TNB (■ Fig. 3), ET, or VATS (■ Fig. 4). On the basis of experts' opinion it was assumed that TNB would be used in 15% of cases, ET in 80%, and VATS in 5%. The situation in which patients experience complications during TNB was introduced in the construction of the decision tree. Histological examination of uncomplicated or complicated TNB samples might confirm that the nodule is malignant, corroborating the initial PET diagnosis and providing a rationale for surgery (thoracotomy and lobectomy). The situation in which TNB is negative although PET correctly reveals suspected malignant SPN was also modeled. These false-negative patients were followed for 1 year with a thoracic CT every 3 months. When VATS or ET was performed, histological examination was carried out at the same time. VATS and ET were assumed to have a 100% sensitivity and specificity [14, 22]. Patients underwent lobectomy if the SPN was shown histologically to be malignant, or wedge resection if it was benign. A risk of complication and mortality associated with these surgical procedures was taken into account in the decision tree. As CT was required to define the location of the SPN before operating, it was considered in the model as a cost element when exploratory surgery was indicated [23]. When PET findings were negative (i.e., when benign SPN was suspected) WW with thoracic CT every 3 months was initiated.

CT plus PET

Positive CT results (likely high probability that SPN be malignant) and negative (likely high probability that SPN be benign) were confirmed by PET. When both CT and PET were positive, an ET was carried out. Patients in whom both were negative were followed for 1 year with CT every 3 months. When CT and PET were inconsistent, TNB was performed. Because TNB does not have perfect specificity [24, 25, 26], the model included cases in which there was a positive histological diagnosis of a nodule despite a true negative PET. These false-positive patients would under-

Table 1

Baseline values and ranges of clinical parameters used in the decision tree (CT computed tomography, PET positron emission tomography, TNB transthoracic needle biopsy, VATS video-assisted thoracic surgery, ET exploratory thoracotomy, SPN solitary pulmonary nodule)			
	Baseline	Range	Sources
Diagnostic test performance (%)			
• CT sensitivity	98	95–100	[32, 33]
• CT specificity	65	60–70	[32, 33]
• PET sensitivity	95	80–100	[5, 7, 34, 35, 36]
• PET specificity	81	75–90	[5, 7, 34, 35, 36]
• TNB sensitivity	85	80–98	[24, 25, 26]
• TNB specificity	95	90–98	[24, 25, 26]
• VATS and ET sensitivity	1	–	[22]
• VATS and ET specificity	1	–	[22]
Probabilities (%)			
• If malignant SPN			
– Cumulative growth rate at 3 months	50	–	[38]
– Cumulative growth rate at 6 months	75	–	[38]
– Cumulative growth rate at 9 months	90	–	[38]
– Cumulative growth rate at 12 months	100	–	[38]
• If benign SPN			
– Probability that the SPN size decreases (every 3 months)	50	–	Experts
Morbidity rate (%)			
• TNB	20	10–30	[27, 28, 29, 30]
• Lobectomy/wedge resection	20	10–30	[23, 31]
Mortality (%)			
• Wedge resection by ET	1	0–5	[23, 31]
• Wedge resection by VATS	0.5	0.2–3	[23, 31]
• Lobectomy	3	1–5	[23, 31]
Life expectancy (years)			
• If benign SPN			
– 40 years old	40.19	–	[42]
– 55 years old	27.32	–	[42]
– 65 years old	19.2	–	[42]
– 75 years old	10.83	–	[42]
• If malignant SPN ^a			
– 40 years old: pT1/pT2	8.55/5.16	–	[18, 20, 43, 44, 45, 46]
– 55 years old: pT1/pT2	7.75/4.85	–	[18, 20, 43, 44, 45, 46]
– 65 years old: pT1/pT2	6.94/4.53	–	[18, 20, 43, 44, 45, 46]
– 75 years old: pT1/pT2	5.44/3.83	–	[18, 20, 43, 44, 45, 46]
Duration of hospital stay (years)			
• TNB	0.004	–	[20, 23, 47]
• VATS	0.014	–	[20, 23, 47]
• Lobectomy	0.03	–	[20, 23, 47]
• Wedge resection	0.02	–	[20, 23, 47]

^a pT1 SPNs are malignant, but not increased size nodules and immediately resected.
pT2 SPNs are nodules diagnosed as malignant during WW due to the increase in their size

go thoracotomy, with all the morbidity and mortality risk that this carries. Cases in which TNB was negative but PET was positive were also modeled. False-negative patients were followed for 1 year.

Epidemiological data

Transition probabilities

Epidemiological data are summarized in ■ Table 1. The probability that a patient

Table 2

Baseline values of the cost of diagnostic tests used in the decision tree (SPN solitary pulmonary nodule, FDG [¹⁸F]2-fluoro-2-deoxy-D-glucose, PET positron emission tomography, CT computed tomography, TNB transthoracic needle biopsy)

Resource used	Cost (€)	Total cost (€)	
		If malignant SPN ^a	If benign SPN ^b
Radiography		41	32
• Medical procedure	41		
CT		137	131
• Equipment	107		
• Medical procedure	30		
TNB		560	439
• Pre-anesthesia consultation	23		
• Medical Procedure (anesthesia)	48		
• Medical procedure (TNB)	77		
• Histopathology	31		
• In-patient stay	381		
PET		1,021	1,000
• FDG cost	389		
• FDG transport cost	106		
• Equipment	457		
• Medical procedure	69		

^a In the case of malignant SPN, all care is covered by the French health insurance

^b If SPN is benign, 80% of the cost for medical procedure and hospitalization stay, 70% of the cost for consultation, and 60% of the cost for biological analyses are covered by the French health insurance. The remaining 20%, 30%, and 40% are charged to the patient

experiences a complicated TNB as well as a complicated and lethal resection was estimated using morbidity and mortality rates associated with diagnostic tests and surgical procedures. Information on morbidity related to TNB [27, 28, 29, 30] as well as morbidity and mortality related to surgery [23, 31] was drawn from the internationally published literature. Complications associated with biopsy consisted essentially of pneumothorax. Complications due to surgery included hemorrhage and respiratory and cardiovascular complications. Sensitivity and specificity of CT [32, 33], PET [5, 7, 34, 35, 36], TNB [24, 25, 26], VATS, and ET [22] were also obtained from scientific reports. The probability of having a benign or a malignant SPN as well as the probability that CT, PET, TNB, VATS, and ET present false-/true-positive and false-/true-negative results was estimated using a Bayesian analysis [37] from a contingency table based on the reported sensitivity and specificity of imaging techniques and malignancy prevalence figures. The probability that SPN is malignant was calculated

from the literature [38] and depended on three main independent factors: the patient's age, the patient's smoking history, and the diameter of the nodule. Due to the absence of published data values attributed to parameters such as growth rate in the size of malignant SPN and the probability that the size of a benign SPN decreases were based on the opinions of a multidisciplinary group of experts in northeastern France created for the purpose of the study.

Life expectancies

LE values were calculated from 5-year survival rates using the "declining exponential approximation of life expectancy" method developed by Beck et al. [39, 40] and as previously used in decision analysis modeling. This method estimates LE in quantitative decision making and assumes that population survival can be approximated by a simple declining exponential function [39, 41]. The LE of an individual with a specific illness can be defined as the reciprocal of the sum of the general pop-

ulation mortality taken from tables of vital statistics (μ Pop) and the disease-specific mortality (μ Dis). The following example is that of a 64-year-old man: His life expectancy according to French census data is 15 years, i.e., a mortality calculated as μ Pop=1/15=0.067. Assuming that this patient has a 2.3-cm nodule with an associated mortality of μ Dis=0.075, the patient-specific LE is: $1/(0.075+0.067)=7.04$ years

For a benign nodule the model used the normal LE of the general population as recorded in the 1999 French census [42], varying between 40.19 years (if the patient is 40 years old) and 10.83 years (if the patient is 75 years old). Survival rates of patients with a malignant nodule were derived from published literature on resected bronchial cancer [18, 20, 43, 44, 45, 46]. A patient presenting a malignant SPN (classified pT1) was assumed to have a LE ranging from 8.55 years (if the patient is 40 years old) to 5.44 years (if the patient is 75 years old). If the same malignant SPN was discovered during the WW strategy due to the increase in its size (and classified pT2), LE ranged from 5.16 years (if the patient is 40 years old) to 3.83 years (if the patient is 75 years old). Life expectancies assigned to each arm of the decision tree were weighted by the probability that a clinical event occurs, i.e., that a patient experiences a complicated TNB and/or surgical procedure. All estimated life expectancies were also reduced for the duration of the hospital stays induced by the realization of biopsy and surgical treatments [20, 23, 47] (■ Table 1).

Economic parameters

The economic analysis was performed from the national health insurance. Costs are expressed in euros.

Cost of diagnostic tests

All imaging examinations (radiography, CT, and PET) were assumed to be performed on ambulatory patients. Costs of radiography and CT were obtained from The "Nomenclature Générale des Actes Professionnels" (NGAP), a fixed costs scale of medical procedures based on practitioners' fees, fixed costs for the medical procedures themselves, and in some cases (here for CT) fixed costs for operating the

equipment. At the time of the study PET was not included in the NGAP. The cost was therefore issued from two French studies [48, 49]. In these studies the estimated cost of PET included the cost of FDG, the FDG transport cost, the cost of operating the equipment, and the cost of medical procedure. The main part of the TNB cost was calculated on the basis of the NGAP and included the cost of the preanesthesia consultation and the anesthesia procedure, the medical procedure of TNB and the histopathological examination. Because TNB requires that the patient be followed after the procedure during a 12- to 24-h period, the cost of the patient stay was also taken into account and obtained using “Tarifs de Prestations Journalières” corresponding to the cost for short hospitalization reimbursed by the French health insurance.

All costs of diagnostic tests are summarized in **Table 2**. A distinction was made between the cost of diagnostic test for malignant SPN and for benign SPN. If the SPN is malignant, all care is covered by the French health insurance. Conversely, if SPN is benign, only part of the costs for medical procedures, consultations, hospitalization stays and biological analyses, varying between 60% to 80%, are covered by the French health insurance, the remaining costs being charged to the patient.

Cost of treatment procedures

In order to evaluate treatment costs a case-mix was derived from the national hospital database on diagnosis-related groups (DRGs, “Groupe Homogène de Malades” in French) for 2003 in the public health care sector. This database allowed us to determine which of the 580 existing DRGs covered each of the specific medical procedures modeled in the study. Once the DRG was defined, it was possible to determine the cost of the patient hospital stay using “Echelle Nationale des Coûts” (ENC), a French national public cost scale compiled by the Ministry of Health from data collected from a representative sample of public hospitals. The ENC includes budget headings such as costs for labor, technical procedure, consumable products, maintenance, provision for depreciation, laundering, catering, and general logistics. Economic parameters are summarized in **Table 3**.

Table 3

Baseline values of the cost of surgical procedures used in the decision tree (VATS video-assisted thoracic surgery)

Resource used	Cost of resource use (€)	Total cost (€)
VATS and Wedge-resection^a		8,109
• Labor cost	2,878	
• Technical procedures	2,862	
• Consumable products	499	
• Provision for depreciation + maintenance	177	
• Laundering	87	
• Catering	222	
• General logistics	1,385	
Lobectomy		13,947
• Labor cost	5,722	
• Technical procedures	3,698	
• Consumable products	1,383	
• Provision for depreciation + maintenance	517	
• Laundering	132	
• Catering	357	
• General logistics	2,139	

^a VATS and wedge-resection present a similar cost because they belong to the same DRG

Table 4

Malignancy probabilities in solitary pulmonary nodule according to the patient's age, smoking history, and the diameter of the nodule (percentages) [38]

	<1.5 cm	1.5–2.2 cm	2.3–3.2 cm
40 years			
• Smoker ^a	2.1	10.0	26.0
• Nonsmoker	0.3	2.0	5.0
55 years			
• Smoker	9.5	35.0	64.0
• Nonsmoker	1.6	7.0	21.0
65 years			
• Smoker	12.8	43.0	71.0
• Nonsmoker	2.2	10.0	27.0
75 years			
• Smoker	28.5	67.0	87.0
• Nonsmoker	5.7	23.0	50.0

^a Smoker=1.5 packs per day

Outcomes

Effectiveness, costs, and cost-effectiveness

A cost-effectiveness analysis was performed using WW as the reference strategy. Incremental effectiveness was measured in terms of the difference in expected average LE between a strategy X and the reference strategy. Incremental costs were evaluated in a similar fashion. The cost-effectiveness analysis was based on ICER. ICER was calculated by dividing the incremental costs by the incremental effects of two alternatives according to the following formula: $ICER = (\text{cost}_{\text{strategy X}} - \text{cost}_{\text{reference strategy}}) / (\text{LE}_{\text{strategy X}} - \text{LE}_{\text{reference strategy}})$. The most cost-effective strategy was defined as that with the lowest ICER compared to the reference. Incremental costs were not discounted given the time horizon of the modeling (1 year). Incremental gains in effectiveness ($\text{LE}_{\text{strategy X}} - \text{LE}_{\text{reference strategy}}$) were discounted back at the annual discount rate of 5% [50].

Table 5

Life expectancies, costs and cost-effectiveness ratios for the base case and malignancy risks. Incremental cost-effectiveness ratio (ICER, compared to WW, € per life-year gained) are calculated using incremental costs divided by incremental gains in life expectancy discounted at an annual 5% rate WW wait and watch, PET [¹⁸F]2-fluoro-2-deoxy-D-glucose positron emission tomography, CT computed tomography, LE life expectancy, ΔLE discounted incremental gains in life expectancy)

	Base case (43%) ^a	Malignancy risk					
		0.3%	5.0%	5.7%	12.8%	21.0%	87.0%
WW							
• LE	12.81	40.08	38.43	10.42	17.30	22.56	4.59
• Cost	6,327	451	1,097	1,194	2,171	3,299	12,383
PET							
• LE	13.73	40.02	38.52	10.48	17.55	23.07	5.87
• Cost	8,770	3,895	4,431	4,511	5,322	6,258	13,794
• ΔLE	0.51	–	0.01	0.04	0.11	0.17	1.04
• ICER	4,790	Dominated	333,400	82,925	28,645	17,406	1,357
CT+PET							
• LE	13.78	39.95	38.46	10.48	17.54	23.08	5.95
• Cost	7,959	2,428	3,037	3,128	4,047	5,109	13,658
• ΔLE	0.54	–	0.00	0.04	0.10	0.18	1.10
• ICER	3,022	Dominated	∞	48,350	18,760	10,056	1,159

^a 65-year-old male current smoker (1.5 packs per day) with a 2-cm SPN without calcification, specula and enlargements of mediastinal lymph nodes

Table 6

Proportion of therapeutic management of patients according to the strategies modeled and three representative malignancy risks (percentages) (CT computed tomography, PET [¹⁸F]2-fluoro-2-deoxy-D-glucose positron emission tomography)

	Appropriate resection	Wait and watch	Unnecessary resection ^a	Inappropriate wait and watch ^b
Malignancy risk 0.3%				
• PET	0.3	83.5	16.2	0.0
• CT+PET	0.3	91.0	8.7	0.0
Malignancy risk 7.0%				
• PET	6.5	77.8	15.1	0.5
• CT+PET	6.9	84.7	8.1	0.3
Malignancy risk 43% (base case)				
• PET	39.9	47.7	9.3	3.1
• CT+PET	42.5	50.8	5.0	1.8
Malignancy risk 87%				
• PET	80.7	10.9	2.1	6.2
• CT+PET	86.0	9.9	1.1	2.9

^a Resections performed when the nodule was benign

^b Wait and watch strategy adopted when the nodule was malignant

Results were also analyzed and expressed in terms of the number of unnecessary operations avoided among patients without malignant nodules.

Sensitivity analysis

One-way sensitivity analyses were performed on diagnostic test findings and on

the rate of use of TNB, ET, and VATS and the value of economic parameters. Moreover ICERs were recalculated without adjusting LE for the time spent in the hospital. Threshold values were determined and defined as cutoff points beyond which the hierarchy between strategies could be modified, therefore affecting the conclusion of the study.

Analysis of the risk profiles of patients

Separate analyses were performed according to different SPN malignancy risks. The risk of malignancy was considered low (0.3–5.0%) in young nonsmokers with nodules less than 1.5 cm in diameter, moderate (5.7–12.8%) in most nonsmokers with an

average age of 60 years and nodules of intermediate size, and high (21–87%) among 70-year-old (on average) smokers with large nodules (■ **Table 4**).

Results

Cost-effectiveness modeling baseline value

■ **Table 5** illustrates LEs, costs, and ICERs for each alternative compared with WW. WW was the least effective strategy and CT+PET the most effective. Compared to WW, all alternatives presented positive ICERs, with higher costs and higher LEs. CT+PET had the lowest cost-effectiveness ratio, €3,022 per life-year gained (LYG). When alternatives were compared, PET was inferior to CT+PET.

Sensitivity analysis

Parameters of diagnostic tests

The diagnostic performance ranges of CT, PET, and TNB were successively tested in one-way sensitivity analyses, but no threshold values were found. CT+PET remained the most cost-effective strategy.

Frequency of Use of ET and VATS

In the base case TNB was assumed to be used in 15% of patients, ET in 80%, and VATS in 5%. With respective frequencies of 80%, 5% and 15%, and then 5%, 15% and 80% to test the robustness of the model, no changes were observed in the hierarchy of alternatives.

Economic parameters

The cost of PET was tested over the interval (€250–1500). No threshold was found when these data were subjected to sensitivity analyses.

Adjustment of life expectancy for the length of stay at hospital

Calculations were performed without any adjustment for the time spent in the hospital due to the completion of biopsy and surgical treatments. The conclusion of the analysis was unchanged.

Analyses of risk profiles of patients with an SPN

Discontinuous malignancy rates, estimated according to the average patient's age,

SPN diameter, and smoking history were introduced into the model. They varied between 0.3% and 87% [38]. ■ **Table 5** presents LEs, costs, and ICERs for a number of representative probabilities of SPN malignancy in low-, moderate- and high-risk cases. WW was the most effective strategy in the risk range of 0.3–2.1%, PET in that of 2.2–12.8%, and CT+PET in that of 21–87%. WW was the most cost-effective strategy in the risk range of 0.3–5%. CT+PET was the most attractive approach between 5.7% and 87% with ICERs varying from €1,159 to €48,350 per LYG.

Therapeutic outcomes and SPN management

■ **Table 6** shows the changes observed in three representative levels of malignancy risk around the baseline risk of 43%: low risk of 0.3%, moderate risk of 7%, and high risk of 87%. The results indicate that the proportion of resection increases with the degree of malignancy, regardless of the alternative modeled. The proportion of appropriate resections in cases of malignant nodule varied from 0.3% (with a 0.3% malignancy risk) to 80.7% (with a 87.0% malignancy risk) when using PET. These proportions were 0.3% and 86.0%, respectively, when using CT+PET. Depending on the level of malignancy, the rate of unwarranted surgery was lowest with CT+PET, resulting in 1.0–7.5% fewer unnecessary resections of benign SPN than with PET alone. With the baseline risk of 43%, 4.3% inappropriate resection compared to PET may be avoided due to the association CT+PET.

Discussion

The objective of the present investigation was to determine the medicoeconomic consequences of introducing PET into the process of diagnosing SPN and to estimate the modification in the management of patients due to the introduction of PET. The results show that WW can be recommended for use among individuals at very low risk of malignancy ($\leq 5\%$), for example, a 40-year-old nonsmoker with an SPN of less than 1.5 cm. Results also clearly indicate that CT+PET is appropriate for moderate risk individuals (5.7–12.8%), such as

nonsmokers aged about 65 years with an SPN of 1.5–2.2 cm, and individuals at high risk of malignancy (21–87%), illustrated by a 75-year-old smoker with an SPN of more than 2.3 cm (■ **Fig. 5**).

These recommendations have been based on the comparison between the estimated ICERs obtained in this study and the lowest commonly accepted threshold of \$50,000 per quality-adjusted life-year (QALY) [51, 52, 53]. Indeed, in the 0.3–2.1% risk range WW was superior to all other alternatives. At 5% PET presented lower ICER than WW (€333,400 per LYG), but this ratio was well above the threshold of \$50,000 per QALY. Finally, CT+PET was the most attractive approach in the risk range of 5.7–87% with ICERs varying from €1,159 to €48,350 per LYG. Another usual alternative is to compare the cost-effectiveness ratio estimated by the model to the cost-effectiveness ratio of programs for other pathologies. However, the comparison with published tables is difficult and would be biased because these tables rarely include results by subgroups of patients.

Two studies have compared WW with invasive techniques such as ET, VATS, and TNB [3, 4]. Kunstaeffer et al. [4] developed a simplified model with which to compare the LE implications of ET, TNB, and management by a single chest radiography. The study by Bernard et al. [3] compared four strategies: ET, VATS, TNB, and WW. Despite differences in the construction of the decision analysis trees between the studies, WW was recommended when the risk of cancer is low, TNB when it is moderate, and surgery when it is high. The aim of the present study was to integrate PET with other imaging techniques as reported by Gambhir et al. [11], Dietlein et al. [10], and Gould et al. [54]. Gambhir et al. [11] compared WW to CT alone, CT+PET, and surgery. They demonstrated that WW was the most cost-effective strategy in the 0–12% risk range, as were CT+PET in 12% to 69%, CT alone from 69% to 90%, and surgery above 90%. Dietlein et al. [10] compared the use of WW to TNB, surgery and PET after work-up including CT. WW was the preferred strategy at 5%, CT+PET was optimal from 10% to 70%, and surgery was the most appropriate strategy above 75%. Gould et al. [54] de-

veloped a more complex model with alternatives that we did not consider, with 40 clinical combinations of five diagnostic interventions (including CT, PET, TNB, surgery, and WW). PET was recommended to be used among patients presenting a 55% pretest probability and at high risk for surgical complications. In all these studies results were obtained from decision analysis models. Other alternative techniques could have been used such as discrete event simulation [55, 56]. This type of model is particularly useful to avoid the representation of an excessive number of states and branches in the tree but can be greatly time-consuming. In the present study the only parameter changing over time was the probability that the size of a malignant SPN would increase. Only two health states were modeled (growth observed, no growth observed) and the time period was limited to 1 year. The use of a simple Markov model was also considered as sufficiently relevant given the natural history of the disease.

There are a number of differences between the present study and the previous cost-effectiveness analyses. The outcomes of the present study were not expressed in QALY, in contrast to the Gould et al. [54] study. No French data are available to adjust LE for quality of life. Another difference concerns the timeframe of the analysis. In the Gould et al. study the model followed a hypothetical cohort over their remaining life span, and average long-term health care costs for patients with surgically treated local lung cancer were estimated. In the present study the national hospital database of DRGs (the ENC) did not allow the costs of follow-up to be estimated. Despite these differences the present study reached several similar conclusions. WW was the optimal approach when the risk of malignancy was low ($\leq 5.0\%$), but CT+PET was preferable at a level of risk between 5.7% and 87%. These results suggest that technologically highly developed strategies present a particular interest when patients are at greater risk of disease. At a lower risk these strategies lose in effectiveness compared to conventional methods because they are often associated with more aggressive techniques such as TNB, ET, and VATS.

Limitations to the present analysis include the omission of a single CT-based approach. Experts consulted to validate the decision analysis tree considered that radiological criteria on the basis of a single CT only were not sufficiently precise to manage the patient with an SPN smaller than 3 cm, and that WW based on the reiteration of CT would be more relevant. Similarly, the combination of PET and CT was not modeled due to a lack of relevant data in published literature. Second, it was assumed that TNB was used in 15% of patients, ET in 80%, and VATS in 5% after positive PET results. A sensitivity analysis was performed here demonstrating the robustness of the cost-effectiveness results. In a similar fashion there is an argument for modeling a 1-year period of observation. A number of other published studies [10, 11] have monitored SPN growth over a 2-year observation period with periodic CT supervision. However, the 1-year period is supported by published literature and was validated by experts [3], as were concerning growth rates of benign/malignant nodule.

The analytic perspective used here is open to question. The cost-effectiveness analysis was performed from the point of view of the national health insurance. Only reimbursed costs were considered. Therefore the choice of different sources of costs used in the analysis can be disputed. Indeed, the cost of diagnostic tests was estimated using the NGAP, a fixed cost scale used by the French insurance for reimbursements, whereas treatment costs were issued from the ENC, a national hospital costs database of DRGs. This database is not used for reimbursing hospital costs but is used to evaluate hospital activity, and to help with the budget allocation between hospitals. The ENC was chosen for this study because it is not possible at present to determine the cost of hospital stays for a specific procedure and pathology using the published reimbursement database of the French health insurance. Another limitation is the absence of distinction in the costs, especially treatment costs, with and without complications. The DRGs selected for this study did not allow this distinction to be made. Adopting another point of view in this study, such as the societal viewpoint, would have been prob-

lematical also because of the difficulty involved in estimating indirect costs, and intangible costs. Finally, the baseline values of the performances of diagnostic tests introduced into the model could be a potential source of error. Ideally, as a sequence of two tests was modeled, the sensitivity and specificity of PET to be introduced into the contingency table should have been determined in various subgroups according to CT results. However, such data were not available at the time of this work. Therefore sensitivity and specificity for PET were issued from studies analyzing independently the diagnostic performances for PET and CT.

At the moment very few PETs exist in France, and the medicoeconomic consequences of its use are still poorly understood. This work, performed from the French health care insurance perspective, demonstrated the importance of the association between CT and PET both in cost-effectiveness and in clinical terms. The model was also able to define a place for PET in future practice according to the risk of malignancy of SPN. These results support the attempts to generalize the introduction of PET for SPN diagnosis. However, a long-term clinical trial with a representative sample remains the only way to properly assess all these outcomes. It would be interesting to confirm the results of the model especially in subgroups with a moderate risk of malignancy (5.7–18%) and to determine whether they differ using cost per QALY instead of cost per LYG.

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