Solitary pulmonary nodules: accuracy and cost-effectiveness of sodium iodide FDG-PET using Australian data

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Abstract. This study uses Australian data to confirm the accuracy of dedicated sodium iodide (NaI) fluorine-18 fluorodeoxyglucose positron emission tomography (FDG-PET) in evaluating indeterminate solitary pulmonary nodules (SPNs) and to determine the conditions under which PET could play a cost-effective role in this evaluation. Ninety-two patients from two Australian hospitals in different states underwent FDG-PET for evaluation of an SPN. Observed values for prior probability of malignancy and diagnostic accuracy of PET were applied to previously published decision tree models using published Australian health care costs. The accuracy of FDG-PET was 93% with a sensitivity of 92% and a specificity of 95%. The prior probability of malignancy (0.54), PET sensitivity and PET specificity indicated cost savings per patient of up to EUR 455 (A$ 774) based on a PET cost of EUR 706 (A$ 1,200). PET would remain cost-effective for levels of prior probability up to 0.8–0.9 and a PET cost of EUR 736–1,161 (A$ 1,252–A$ 1,974). It is concluded that NaI PET is accurate, cost saving and cost-effective for the characterisation of indeterminate pulmonary nodules in Australia. Comparison with previous reports from the United States confirms that FDG-PET can remain cost-effective despite population differences in medical costs, disease prevalence and PET diagnostic performance.

Keywords: Positron emission tomography – Cost-effectiveness – Decision tree analysis

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Introduction

Limitations of current radiographic techniques for the characterisation of solitary pulmonary nodules (SPNs) [1, 2, 3] have resulted in substantial interest in metabolic imaging using positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose (FDG), in the hope that PET will allow a significant reduction in the use of more costly and invasive methods of differentiating benign from malignant lesions [4, 5, 6, 7, 8, 9].

However, prior to introduction into routine medical practice, a new imaging modality such as FDG-PET must undergo rigorous assessment. Diagnostic performance may be assessed by comparison with an existing gold standard, but there is also a need to evaluate new technologies in terms of cost-effectiveness [10]. Considerable work evaluating the accuracy and cost-effectiveness of FDG-PET in characterising solitary pulmonary nodules has already been performed, primarily in centres in the United States with bismuth germanate (BGO) detector technology [7, 11, 12, 13]. The development of dedicated PET scanners based on less expensive sodium iodide (NaI) detectors and of models of clinical PET practice optimised for clinical service provision offers the opportunity to reduce the traditionally high cost of PET [14]. A previous European series suggests that the accuracy of NaI PET in characterising SPNs is comparable to that of BGO systems [19].

The use of cost-effectiveness data from existing US-based studies to justify funding of PET in other countries or with alternative technologies is problematic. Not only will cost structures be different but also the diagnostic performance of PET in the other country will need to be confirmed. Thus, the goals of this study were twofold: (1) to confirm the accuracy of FDG-PET in Australia using NaI-based PET scanners in characterising indeterminate lung nodules and to document the value of additional extrapulmonary findings made by PET in this clinical scenario, and (2) to use Australian data to quantitatively model under which conditions PET could play a cost-ef-

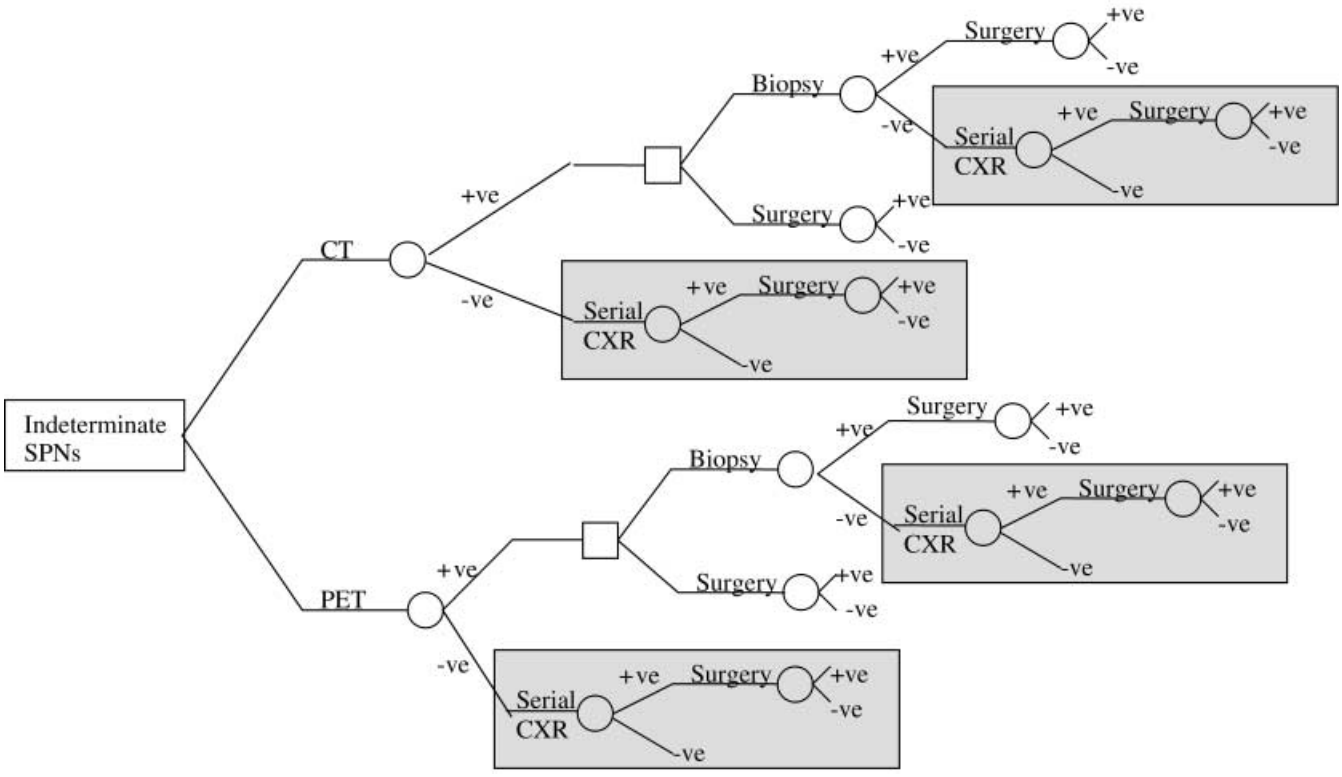

Fig. 1. Institute of Clinical PET (ICP) model. The follow-up branches of the decision tree are displayed within *grey boxes*

fective role in the evaluation of the SPN. Demonstration of cost-effectiveness of PET in a non-US population would support the contention that PET is cost-effective across a range of health-care systems, particularly in view of the large disparity in medical costs and potential differences in prevalence of malignancy between the United States and Australia.

Materials and methods

Patient studies. This study involves a retrospective review of a combined series of 92 patients (56 males, 36 females) with a mean age of 66.7 years (range 45–84 years) who underwent an FDG-PET scan as part of their clinical work-up for characterisation of an indeterminate SPN. In this paper an indeterminate pulmonary "nodule" is defined as a non-calcified, soft tissue, parenchymal lung mass with no pathognomonic imaging signs or ancillary imaging evidence strongly indicative of malignancy, such as distant metastases or unequivocal local invasion. Patients had no history of malignancy for the previous 5 years. The PET examinations were performed between July 1997 and December 2000; 56 at the Wesley Hospital, Brisbane and 36 at the Peter MacCallum Cancer Institute, Melbourne.

PET imaging and diagnostic criteria. PET studies were performed using a GE QUEST dedicated NaI PET scanner (GE Medical Systems, Milwaukee, Wis.). Following a 6-h fast, patients were imaged 45–60 min after intravenous administration of 74–200 MBq FDG. Transmission scanning was performed and attenuation-corrected images (128×128 pixels, slice thickness of 4 mm) were produced by iterative reconstruction using the ordered subset expectation maximisation (OSEM) algorithm [15].

To reproduce typical clinical conditions, the study design utilised the PET findings as reported by the on-duty imaging specialist at each institution, rather than adopting second readings by multiple observers. The diagnosis of malignancy was made using visual diagnostic criteria, with the suspected primary lesion considered to be malignant if its uptake was greater than that of normal mediastinum, in accordance with previous data showing no difference in diagnostic accuracy when using quantitative analysis rather than visual analysis [5]. All the available conventional pre-PET imaging was reviewed at the time of the PET scan. Any additional findings made at PET were recorded and verified.

The final diagnosis. The final diagnosis was established by histopathology in 52 patients (surgery n=39, biopsy n=13). Only positive histological diagnoses (whether for malignancy or for specific benign conditions, e.g. hamartoma) were accepted as final. Non-specific or inconclusive diagnoses were not considered sufficient to exclude malignancy.

Serial imaging (n=30) was taken to represent the final diagnosis where no conclusive histology was available. The mean follow-up of lesions considered to be benign based on lack of growth during the surveillance period was 371 days, with a range of 189–757 days.

Clinical follow-up was used as the final diagnostic criterion in those patients for whom no serial imaging was available (n=7). The minimum duration of follow-up of these patients was 373 days, with a range of 373–628 days.

Three patients from the Wesley Hospital were lost to follow up.

Cost-saving and cost-effectiveness evaluations. A decision tree sensitivity analysis was performed using four different decision tree models derived from previous publications by the Institute of Clinical PET (ICP) [12] and Gambhir et al. [13] (Figs. 1, 2). The

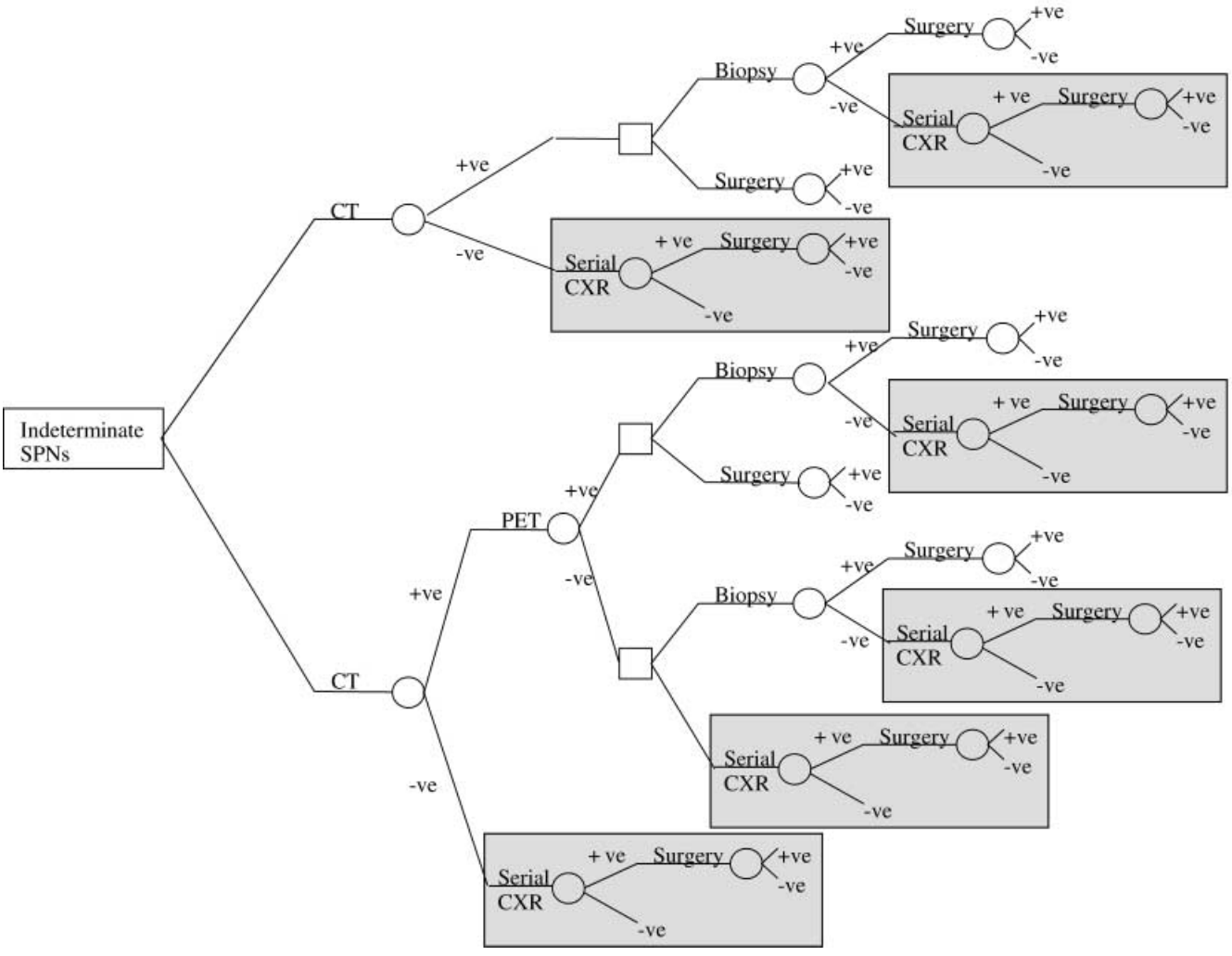

Fig. 2. Gambhir model. Follow-up branches of the decision tree are displayed within *grey boxes*

PET strategy from the ICP model substitutes PET for computed tomography (CT) whereas the PET strategy described by Gambhir et al. [13] uses PET only for those nodules that cannot be diagnosed as benign on CT. Each of these approaches was modelled with and without follow-up of nodules considered benign on CT scan or PET scan. Follow-up comprised four chest X-rays over 2 years and assumed that all malignancies and also 10% of benign nodules would grow within the follow-up period (sensitivity of 100% and specificity of 90%). These assumptions are the same as those used by Gambhir et al. [13] and are based on previous studies on the growth rates of nodules on serial chest radiography. Although serial CT is probably the most common follow-up methodology to be adopted in practice, there are insufficient data on the growth rates of nodules on serial CT to allow this regime to be modelled.

Values for the prior probability of malignancy, PET sensitivity and PET specificity used in all models were determined from our final diagnosis follow-up data as described above. The diagnostic performance of tests other than PET was as used in the previously published decision tree models [12, 13] (Table 1). Values for the cost of diagnostic procedures were obtained from the Medicare benefits schedule [16] with the costs of surgical and other hospital-based procedures obtained from published hospital cost-weights [17]. A cost of EUR 706 (A$ 1,200) was used for FDG-PET imaging. This cost included two separate components. First, a capital equipment component based on examining 1,000 patients per annum on a single NaI PET scanner amortised over 8 years (EUR 147 or A$ 250/patient). Second, an operational cost which was taken to be that approved by the Australian Minister of Health for interim funding of PET during acquisition of more data regarding the clinical and cost-effectiveness of this modality (EUR 559 or A$ 950/patient). The average cost per patient for each strategy (including all diagnostic tests and surgery when undertaken) was calculated and compared to determine whether adding PET was cost saving.

The effectiveness of each strategy was determined by assigning a utility value to each possible outcome as follows: a utility value of 1 was assigned to malignant nodules resected and to benign lesions treated conservatively, whereas benign lesions resected and malignant lesions treated conservatively were each assigned a utility of 0. Thus the average utility for each strategy determined the proportion of patients appropriately managed, equivalent to the accuracy of each strategy (as distinct from the accuracy of individual diagnostic tests). This effectiveness value is an intermediate outcome measure that is appropriate for the evaluation of diagnostic tests since ultimate outcome measures, such as life expectancy, are more dependent upon the treatment effectiveness rather than the effectiveness of the diagnostic test [10, 18].

Table 1. Costs and performance parameters

	Cost [EUR (A$)]		Sensitivity (%)		Specificity (%)	
	ICP	Gambhir	ICP	Gambhir	ICP	Gambhir
CT	235 (400)	235 (400)	97	99	53	61
PET	706 (1,200)	706 (1,200)	93	93	96	96
Serial chest X-ray (4)	105 (178)	105 (178)	100	100	90	90
Biopsy	707 (1,202)	708 (1,204)	95	90	88	96
Thoracotomy	4,460 (7,585)	4,460 (7,585)	100	100	100	100

The cost of biopsy includes a day case fee and chest X-ray and assumes a pneumothorax rate of 20% for the ICP models and 25% for the Gambhir models with a need for a chest tube in 5% (DRG: E68Z). The thoracotomy cost is based on the DRG E01A and E01B and assumes a complication rate of 1%

Cost-effectiveness was expressed as the incremental cost-accuracy ratio (ICAR) where:

$$\mathrm{ICAR} = \frac{(\mathrm{Cost}_{\mathrm{strat}} - \mathrm{Cost}_{\mathrm{bl}})}{(\mathrm{Accuracy}_{\mathrm{strat}} - \mathrm{Accuracy}_{\mathrm{bl}})} \quad (1)$$

$\mathrm{Cost}_{\mathrm{strat}}$ and $\mathrm{Accuracy}_{\mathrm{strat}}$ are the average cost per patient and accuracy of the strategy (either conventional or PET) and $\mathrm{Cost}_{\mathrm{bl}}$ and $\mathrm{Accuracy}_{\mathrm{bl}}$ are the cost per patient and accuracy of a baseline strategy comprising the cheapest treatment option adopted with no imaging, in this case no investigation or treatment. Incremental cost/benefit parameters, such as the ICAR, are favoured in economic analysis over absolute cost/benefit measures because incremental values report the additional cost per additional benefit of adopting one strategy in preference to another. By adopting no investigation or treatment as our baseline strategy, we avoided any pre-judgements about the value of investigating pulmonary nodules. Nevertheless, while the no investigation or treatment paradigm would be quite appropriate for patients with benign lesions, it is unlikely to lead to good outcomes for patients with malignant nodules and its use poses medicolegal issues for treating clinicians. Accordingly, in Australia, most SPNs are expected to be further evaluated. Once a decision to investigate SPNs has been made, there will inevitably be costs associated with investigating patients with benign lesions in order to identify and treat patients with malignant SPNs. On the other hand, there will also be additional costs resulting from patients inappropriately managed, e.g. resection of benign nodules. These costs are more fully reflected in the ICAR than in the average cost per patient for each strategy. Hence ICAR values are much higher than average costs per patient but may be a truer representation of the societal costs associated with the investigation and treatment of pulmonary nodules.

To determine the range of conditions under which PET imaging would remain cost-saving and/or cost-effective, sensitivity analyses were performed. Sensitivity analysis entails varying one or more parameters used in the model to evaluate the effect on the overall results in terms of cost and effectiveness. A one-way sensitivity analysis varies one parameter only whereas a two-way analysis entails simultaneous variation of two parameters. In this study, a one-way sensitivity analysis was performed to evaluate the effect of prior probability of malignancy on cost-effectiveness as described by the ICAR and a two-way analysis was used to study the effects of variable PET cost and prior probability of malignancy upon cost savings.

Table 2. Performance of NaI PET in respect of indeterminate lung nodules

	Sensitivity	Specificity	PPV	NPV	Accuracy
WH	93%	96%	96%	93%	94%
PMCI	90%	93%	95%	88%	92%
TOTAL	92%	95%	96%	91%	93%

WH, Wesley Hospital; PMCI, Peter MacCallum Cancer Institute; PPV, positive predictive value; NPV, negative predictive value

Results

Forty-eight of the 89 solitary pulmonary nodules were found to be malignant, providing a baseline prior probability of malignancy of 0.54 for use in the subsequent cost-effectiveness analyses. FDG PET correctly diagnosed 44/48 malignancies and 39/41 benign lesions, giving an accuracy of 93%, a sensitivity of 92% and a specificity of 95%. The positive predictive value was 96% and the negative predictive value, 91%. There was no appreciable difference in the results from the Wesley Hospital and the Peter MacCallum Cancer Institute (Table 2).

Additional PET findings of nodal or distant FDG uptake were made in 24 patients (27%). The majority of additional findings were made in patients with PET-positive SPNs (n=21). In 19 the findings were true positive (i.e. in 21% of all SPNs). Thus 43% (19/44) of malignant FDG-avid SPNs also had other tumour sites undetected by conventional imaging. The causes for false positive and false negative findings in the SPN and at distant sites are shown in Table 3.

The cost per patient of each strategy and cost-effectiveness as determined by incremental cost accuracy ratios for the various models are outlined in Table 4. The costs of complications are contained within the models. All four models indicate cost savings and improved cost-effectiveness are achieved by using the PET strategy over the corresponding CT strategy.

Table 3. Causes for false positive and false negative findings

	SPN	Distant
False positives	Non-necrotising granuloma (WH) Primary tuberculosis (PMCI)	Diaphragmatic crus (PMCI) Hilar node (PMCI)
False negatives	Adenocarcinoma, 2 cases (WH) Bronchoalveolar carcinoma (PMCI) 1 cm carcinoma not specified (PMCI)	

SPN, Solitary pulmonary nodule; WH, Wesley Hospital; PCMI, Peter MacCallum Cancer Institute

Table 4. Summary of cost savings per patient and cost saving per additional accurate diagnosis associated with each of the four models

		Accuracy (%)	Cost [EUR (A$)]	Cost saving [EUR (A$)]	ICAR [EUR (A$)]	ICAR saving [EUR (A$)]
ICP, no follow-up	CT	80	3,479 (5,916)	455 (774)	10,231 (17,400)	3,798 (6,460)
	PET	93	3,024 (5,143)		6,433 (10,940)	
ICP with follow-up	CT	79	3,373 (6,349)	250 (462)	11,313 (19,239)	3,630 (6,174)
	PET	93	3,462 (5,887)		7,365 (12,526)	
Gambhir, no follow-up	CT	84	3,339 (5,679)	326 (554)	8,788 (14,945)	2,509 (4,267)
	PET	94	3,014 (5,125)		6,277 (10,676)	
Gambhir with follow-up	CT	82	3,567 (6,066)	22 (38)	9,908 (16,850)	2,674 (4,547)
	PET	95	3,544 (6,028)		7,234 (12,302)	

ICAR, Incremental cost accuracy ratio; ICP, Institute of Clinical PET

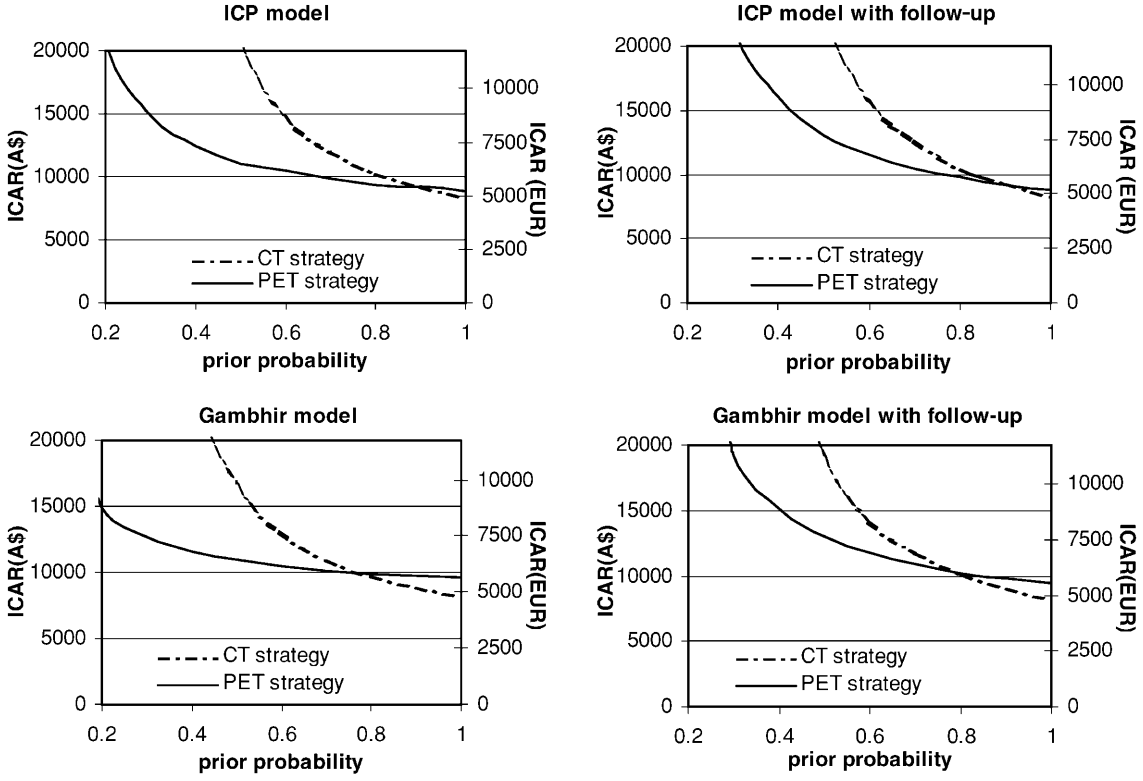

Fig. 3. One-way sensitivity analyses. Prior probability of malignancy versus incremental cost-accuracy ratios for CT and PET strategies. Costs are in Australian dollars with Euros displayed on the secondary Y-axis

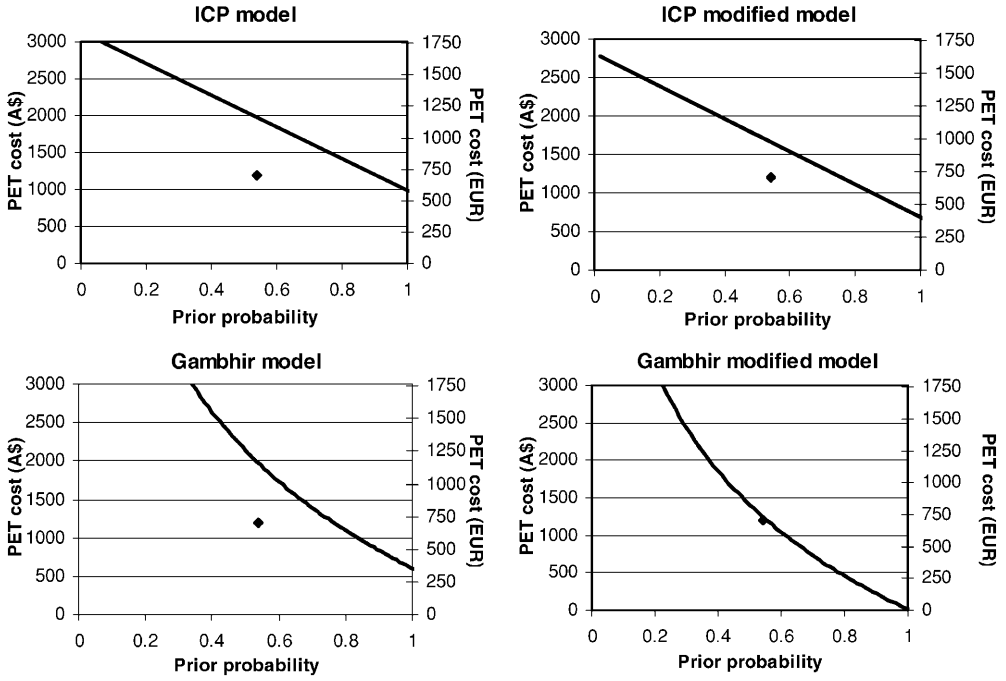

Fig. 4. Two-way sensitivity analyses. Prior probability of malignancy versus PET costs. The single point on each graph represents the values used in this paper. Costs are in Australian dollars with Euros on the secondary Y-axis

Figure 3 demonstrates the one-way sensitivity analyses of the effect of prior probability of malignancy on the ICAR. It is seen that the PET strategy remains more cost-effective than the CT strategy until the prior probability of disease reaches approximately 0.9 for the ICP models and 0.8 for the Gambhir models. Figure 4 displays the results of the two-way sensitivity analyses. The line on each graph indicates the values of prior probability of malignancy and PET cost for which the average cost per patient of the PET and no-PET strategies are equal. Values below the line indicate that the PET strategy has the lower cost per patient whereas the no-PET strategy has a lower average cost for values above the line. The single point marked indicates the baseline values for prior probability of malignancy and PET costs. The baseline prior probability of malignancy of 0.54 would result in cost savings with PET costs as high as EUR 736 (A$ 1,252) for the Gambhir model with follow-up and up to EUR 1,161 (A$ 1,974) for the ICP model without follow-up. Alternatively, with a PET cost of EUR 706 (A$ 1,200), the use of PET would remain cost saving with values for prior probability of malignancy of up to 56% for the Gambhir model with follow-up, and with a prevalence value as high as 90% for the ICP model without follow-up.

Discussion

This study shows that, in Australia, NaI PET as performed by the participating institutions is an accurate and cost-effective technique for characterising indeterminate pulmonary lesions as benign or malignant. The sensitivity and specificity values of 92% and 95% respectively are comparable to those in other series, including a smaller European study of 50 patients examined with dedicated NaI PET [19].

The current strategy used in most centres relies on CT alone, whereas from the various analyses performed here, PET, either in addition or in place of CT, is advantageous in terms of both absolute cost savings and cost-effectiveness. With the prior probability of malignancy observed in this study, PET-based strategies can produce cost savings of between approximately EUR 22 and EUR 455 (A$ 38 and A$ 774) per patient evaluated. When the greater accuracy of PET strategies is also taken into account by using the ICAR, the benefits of the PET strategies are even more pronounced. CT-based strategies result in a cost of EUR 8,788–11,313 (A$ 14,945–A$ 19,239) per correctly managed SPN (ICAR). With PET this could be reduced to EUR 6,277–7,365 (A$ 10,676–A$ 12,526). In all four models the PET strategy remains the optimal choice in characterising indeterminate SPNs up to a prior probability of malignancy of at least 0.80. The CT strategy becomes more cost-effective once the proportion of patients with malignancy exceeds approximately 80% as the low specificity of CT then affects fewer patients, and the additional cost of PET scanning is not offset by avoiding unnecessary biopsy and/or surgery. However, in such cases PET may also provide useful information regarding the stage of disease that has been shown to directly influence management decisions [20]. The value of this incremental staging information was not modelled in this study.

Interestingly, follow-up of patients with negative investigations reduced the cost-effectiveness of CT and

PET strategies owing to a low diagnostic yield and occasional growth of benign lesions. The reduction in cost-effectiveness would have been even greater had a CT-based follow-up regime been modelled. Despite this finding, the authors would recommend follow-up of PET-negative SPNs, either with chest X-rays or with CT, in view of the comparatively low incremental cost per additional patient correctly managed (EUR 530 or A$ 903 for the Gambhir model).

This study shows that FDG-PET would generate cost savings with a prior probability of malignancy of 0.54 and a PET cost of EUR 706 (A$ 1,200). PET would remain cost saving at this level of prior probability up to a cost of EUR 736–1,161 (A$ 1,252–1,974) depending on the model used. A fee for PET at these levels in Australia, while more in line with that used in the United States, would be in danger of removing the cost-effectiveness of PET for other indications [10]. The use of FDG-PET achieves the greatest cost savings when the results enable cancellation of surgery that is shown by PET to be unhelpful. The ratio of surgical costs to PET costs (6.3:1 in this study) is thus the major determinant of the extent of cost savings produced. Therefore, where surgical costs are low (as in Australia) there will be a corresponding need to minimise the costs associated with PET scanning, which in turn will depend on the volume of patients being scanned, as well as tracer and running costs. Future government decisions regarding the level and extent of PET funding need to recognise the importance of economies of scale in providing efficient and therefore cost-effective use of this relatively expensive imaging technique.

In the United States in November 1997, Medicare coverage for PET imaging of lung tumours was approved (applying to both full ring PET scanners and gamma cameras) [21]. A recent Australian federal government review [22] has recommended a restricted Medicare rebate for PET imaging of SPNs in Australia, pending further data. The review also identified dedicated NaI PET (but not gamma camera-based systems) as a suitable technology for delivering clinical PET services, a conclusion that is supported by the high accuracy of SPN characterisation found in this study. Indeed, the high count rate capability that is the major advantage of BGO systems would not be of value with the low-dose technique used in this study, and the superior energy resolution of NaI, resulting in enhanced scatter rejection, is advantageous for whole-body PET applications in oncology.

The PET costs used for our cost-effectiveness evaluations are based on the interim funding level for SPN characterisation that was approved by the Australian Minister of Health after consideration of the review findings. These costs may have reflected the lower radiopharmaceutical costs associated with the low-dose technique appropriate for dedicated NaI PET systems, and the capital component adopted in this study also takes into account the lower cost of NaI systems as compared with BGO technologies. The results of this study suggest that the recent decision to expand patient access to PET for investigation of SPNs in Australia was appropriate.

Cost-effectiveness studies performed in one country are not readily transferable to another nation. This is due not only to differences in the cost of procedures but also to potential differences in disease prevalence and diagnostic performance. Whereas the diagnostic performance of PET is unlikely to differ in terms of ability to detect disease (sensitivity), the specificity may differ between countries owing to the presence of a second condition that may produce false positive results on PET. The regional variations in the accuracy of FDG-PET in the United States due to differences in the incidence of granulomatous disease are such an example [11]. This study confirms that false positive PET results due to granulomatous disease occur infrequently in Australia. There was no discernible difference in the results between the Wesley Hospital in Queensland and the Peter MacCallum Cancer Institute in Victoria, with high specificity found for both centres (Table 2). A similarly low rate of granulomatous disease has been observed in a series of lung nodules examined with NaI PET in Western Europe [19].

Medical costs in Australia are also much lower than in the United States and Europe. Previous studies using costs and disease prevalence data from the United States have demonstrated the cost-effectiveness of PET for characterisation of lung nodules [12, 13]. Our study has shown that use of FDG-PET for SPN characterisation can remain cost-effective despite population differences in medical costs, disease prevalence and PET specificity. These population characteristics in European countries are likely to be intermediate between those in Australia and the United States, suggesting that use of FDG-PET for characterisation of lung nodules would also probably be cost-effective in Europe. Indeed, the prior probability of malignancy of 0.66 that can be inferred from a previous European study of NaI PET in pulmonary nodules falls within the cost-effective range indicated by our results. However, this conclusion needs to be confirmed by similar studies undertaken in Europe, for which our study could provide a convenient template.

In conclusion, FDG-PET with dedicated NaI systems is accurate in the characterisation of SPNs. This high accuracy of diagnosis translates into cost savings and improved cost-effectiveness in Australia for a range of management strategies. The demonstration of PET cost-effectiveness in Australia, in addition to previous reports of cost-effectiveness in the United States, confirms that FDG-PET can remain cost-effective despite population differences in medical costs, disease prevalence and PET diagnostic performance.

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