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Economic Evaluation of Positron Emission Tomography (PET) in Non Small Cell Lung Cancer (NSCLC).

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Abstract

Background: There are several perceived benefits from introducing positron emission tomography (PET) scanning into the staging of non small lung cancer (NSCLC). However, its greatest primary benefit is the role it can potential perform in reducing the number of unnecessary diagnostic examinations and futile surgeries.

Objectives: To evaluate the economic impact and cost effectiveness of PET scanning in the management of potentially operable NSCLC patients using a cost-utility model.

Methods: A literature review was conducted to find relevant studies and appropriate parameters to construct a decision model. Two strategies were compared. The first strategy was a conventional work up (CWU) consisting of an x-ray, a chest computer tomography (CT) scan and brochoscopy; the second strategy consisted of a CWU plus a whole body PET scan. These two strategies were applied to two sub-groups of NSCLC patients; those that had received a positive result on their CT scan and those that got a negative result on their CT scan. The cost-effectiveness of each strategy was dependent on a number of variables that were taken from a literature review. Costs were based on the Australian diagnostic related groups, a cost calculation for a chemotherapy course and values obtained from the literature. The life expectancy and utility scores were also taken from the literature and combined to create an incremental quality adjusted life year (QALY) value for PET for each of the patient groups.

Results: The mean costs in CT negative and CT positive patients were lower in the CWU strategy, costing $A 20,427 and $A 23,578 per patient respectively compared to the PET strategy ($A 20,826 and $A 24,083 per patient respectively). The mean QALYs for both the CT positive and CT negative patients were higher in PET with 2.91 and 2.11 respectively compared to the CWU of 2.88 and 2.09. The incremental cost effectiveness ratio (ICER) for the CT negative strategy was $A 14,581 and $A 52,039 for the CT positive strategy.

Conclusion: The PET strategy in CT negative and CT positive patients appears to be cost effective, however, there is much uncertainty surrounding this base result, particularly in CT positive patients.

Introduction

Lung cancer is the leading cause of cancer related deaths in the western world with non small lung cancer (NSCLC) accounting for around 75-80% of cases and small cell lung cancer (SCLC) accounting for the rest.[1] In Australia there are approximately 8,200 cases of lung cancer diagnosed every year.[2] Lung cancer was the fifth most common cancer reported in cancer registries in 1998, but it was the leading cause of death from cancer accounting for 20.1% of cancer deaths. In the year 2000, lung cancer was responsible for 22.8% of male cancer deaths and 14.9% of female cancer deaths and 5.3% of total Australian deaths.[3] The correct and efficient diagnosis, staging and treatment of lung cancer is therefore essential and any small improvement in the handling on NSCLC could have significant effects in both decreasing costs to the Australian healthcare system and improving the length and quality of life of patients.

Lung cancer usually arises in the bronchi in response to repetitive carcinogenic stimuli, inflammation and irritation. Disruption of the cell development occurs in the mucosal lining and progresses to elevate and erode the basel membrane. The tumour then spreads throughout the lung and will eventually metastasise to the lymph nodes and to other parts of the body.[4] There are four main histological classifications of lung cancer. There are three that are closely related in their behaviour and management, these are squamous cell carcinomas, adenocarcinomas and large cell carcinomas and these are usually grouped as NSCLC: these will be the focus of this evaluation. In contrast SCLC has a distinct natural history and management and will not be assessed here.[5]

The accurate staging of NSCLC

The management of NSCLC is directed by staging based on tumour size and location, nodal involvement, and the presence or absence of distant metastasis. The aim of staging NSCLC is to accurately identify the group of patients who will have the greatest survival benefit from either surgical resection or radical radiotherapy and chemotherapy. [6] Currently, up to 50% of operations in early stage lung cancer are futile due to the presence of locally advanced tumours or distant metastasis.[7] Therefore there is a real need to improve the number of correctly staged NSCLC patients and in so doing reducing the number of futile operations that occur.

Staging NSCLC at the time of diagnosis is done by the TNM classification system which then both guides management and predicts outcome. The various T, N and M factors are grouped in different stages (from 0 to IV) in which patients are ranked to produce a system

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[1] Devaraj, A., G. J. Cook, et al. (2007). "PET/CT in non-small cell lung cancer staging-promises and problems." Clinical Radiology **62**(2), p. 97.

[2] http://www.cancer.org.au//aboutcancer/cancertypes/lungcancernonsmallcell.htm Lung Cancer Council. 3rd September 2007.

[3] Clinical Practice Guidelines for the Prevention, Diagnosis of Lung Cancer. National Health and Medical Research Council (2004), p. 3.

[4] Clinical practice guidelines, p. 3.

[5] Clinical Practice Guidelines for the Prevention, Diagnosis of Lung Cancer. National Health and Medical Research Council (2004) , p. 3

[6] Clinical Practice Guidelines for the Prevention, Diagnosis of Lung Cancer. National Health and Medical Research Council (2004), p. 53.

[7] National Institute of Health and Clinical Effectiveness, "The Diagnosis and treatment of Lung Cancer; Methods, Evidence and Guidance. *National Collaboration Centre of Acute Care.* 2005.

with a 'high prognostic value.'[8] Although practice varies from centre to centre patients with stage IIIB and above are usually considered inappropriate for surgery. Some patients with IIIA may be treated with chemotherapy with a view of down staging the tumour before radiotherapy or surgery. Meanwhile, stage I and II patients are treated with either a lobectomy or pneumonectomy with some receiving adjuvant chemotherapy.[9] In this study, all surgery will be classed under the more general heading of a thoractomy.

Figure 1: The Stage grouping (TNM subsets).

Tumour

Nodes	T1	T2	T3	T4
N0	IA	IIB	IIIB	IIIB
N1	IIA	IIB	IIIA	IIIB
N2	IIIA	IIIA	IIIA	IIIB
N3	IIIB	IIIB	IIIB	IIIB

IV=M1

Key	
	Patients should be officered surgery as long as there are no other medical complications
	Surgery may be suitable for some patients, maybe, after undergoing radio- and chemo-therapy
	Not suitable for surgery

Currently, the investigation of patients suspected of having lung cancer is based on a set of 'conventional' diagnostic techniques. A chest x-ray is usually the initial first step for detecting the presence of a pulmonary lesion, which always warrants further examination as it raises the suspicion of lung cancer. Then a brochoscopy or a transthoracic needle biopsy are usually used to determine the exact nature of the pulmonary lesion as these procedures produce a sample of the lesion that can be analysed. [10] Once lung cancer is detected it is then staged to ascertain the spread of the disease and to see if the cancer is treatable or palliative care is needed.

Traditionally, computer tomography (CT) has been the mainstay of non-invasive staging. There is, however, undoubtedly a variation in the performance of CT in its ability to accurately evaluate the individual TNM components. CT has a role in the basic T staging of NSCLC with respect to the size and the location of the tumour and the extent of invasion of chest wall because of its excellent anatomical description. However, given CT relies on morphological detail rather than histological characteristics its use in the N staging of NSCLC

[8] Chiti, A., F. A. Schreiner, et al. (1999). "Nuclear medicine procedures in lung cancer." Eur J Nucl Med **26**(5), p. 536.
[9] Devaraj, A., G. J. Cook, et al. (2007). "PET/CT in non-small cell lung cancer staging-promises and problems." Clinical Radiology **62**(2), p.99.
[10] Nguyen, V. H., S. Peloquin, et al. (2005). "Cost-effectiveness of positron emission tomography for the management of potentially operable non-small cell lung cancer in Quebec" Canadian Respiratory Journal **12**(1), pp.19-20.

has been questioned.[11] Therefore CT assessment has been estimated to incorrectly over stage or under stage T and N status in 40% of cases. Therefore some form of surgical verification is needed to confirm the CT scan. The value of the mediastinoscopy as a further staging procedure is widely accepted mainly due to its high specificity in detecting nodal involvement. However, it does have limitations as it can not access all lymph nodes (reducing its sensitivity). Furthermore, it also carries a small mortality risk.[12] In the last 15 years positron emission tomography (PET) has promised to improve the staging in NSCLC. There is a large literature supporting PET as a useful tool in detecting distant metastasis and it is generally considered that PET is more accurate than CT alone in identifying mediastinal lymph node (N2/N3) invasion.[13]

What is FDG-PET?

PET is an imaging method that allows the metabolic rate of normal and disease tissue to be compared using radiotracers, which other medical imaging techniques are unable to do. Malignant tumours have a markedly accelerated metabolism, which can be visualised by 18F-fluoro-2-dexy-D-glucose (FDG) due to a higher uptake of glucose in the tumour. Elevated uptake of FDG has been demonstrated in all lung cancer cell types and this radiotracer is used in most studies of lung cancer. The patient is administrated 350-500 megabecquerels (MBq) of FDG with the data being acquired after an uptake interval of between 30 to 60 minutes. Whole body imaging is used for screening and staging outside the limited primary field of view. False positive results are reported and account for the lower specificity of FDG-PET relative to its sensitivity. Reasons for false positives are mostly of an inflammatory nature. The high negative predictive value of PET in mediastinal staging allows patients with a negative scan to procedure to thoractomy without invasive mediastinal staging by mediastinoscopy. However it will only be through the correct combination of CT, mediastinoscopy and PET procedures that the most cost effective outcome to correctly stage NSCLC will be found.[14]

Some of the potential benefits of PET identified by the Bradbury et al study[15] were to:

a) Increase the number of correct operations for N0/1 M0 patients and also to reduce the number of missed operations within this group.
b) Avoid the resource cost of futile operations for which it does not offer a potential cure. i.e N2/N3, M1 patients.
c) Avoid the mortality and morbidity of futile operations, especially the number of ‘open and shut” cases where the patients are opened up but they are inoperable and are then referred to palliation.
d) Allow palliative care to be offered at an earlier stage for symptom control and more appropriate care to be given.
e) Reduce the number of other diagnostic tests to be given.

[11] Devaraj, A., G. J. Cook, et al. (2007). "PET/CT in non-small cell lung cancer staging-promises and problems." Clinical Radiology **62**(2), p. 99.
[12] Clinical Practice Guidelines for the Prevention, Diagnosis of Lung Cancer. National Health and Medical Research Council (2004) p.54.
[13] Nguyen, V. H., S. Peloquin, et al. (2005). "Cost-effectiveness of positron emission tomography for the management of potentially operable non-small cell lung cancer in Quebec" Canadian Respiratory Journal **12**(1): p.20.

[14] Chiti, A., F. A. Schreiner, et al. (1999). "Nuclear medicine procedures in lung cancer." Eur J Nucl Med 26(5), pp. 544-545.
[15] Bradbury et al. Heakth Technology Board Scotland, Positron Emission Tomography (PET) Imaging in Cancer Management” October 2002.

They identified a set of potential costs of PET as:

a) The cost of setting up and running a PET scanner.
b) A change in the number of correct operations in N0/N1 M0 patients due to the specificity of PET and false positive results.
c) Additional costs of palliative care treatment to patients if given at an earlier stage.
d) Additional side effects of longer palliative care

Literature review

The literature was searched to identify any relevant cost effectiveness studies, reviews and randomised control trials (RCT's) concerning the use of FDG-PET in the staging of lung cancer. The peer-reviewed databases that were searched were PubMed and Cochrane. The relevant studies which were identified in the literature had their references hand searched and assessed to ascertain if any relevant studies had been overlooked. The inclusion/exclusion criteria were as follows:

Inclusion criteria

- Studies in English
- Studies published between 1990 and June 2007
- Studies using FDG as the radio-labelled tracer
- Cost effectiveness studies, cost utility studies or random control trials (RCTs) selected.

Exclusion Criteria

- Studies not focused on NSCLC
- Studies not relevant to the topic

There were 6 cost effectiveness studies and 3 cost utility studies identified, in addition to 3 RCT's.. A summary of the studies are given in the Appendix.

There were three cost utility studies that looked at the staging of PET with two of these being from the UK and one from Japan. The first UK Study was conducted by Bradbury et al for the Health Technology Board Scotland (HTBS)[16] and the other UK study was undertaken by the National Institute of Health and Clinical Effectiveness (NICE) in England and Wales.[17] These studies are both very recent and they have built and improved upon previous studies to give two comprehensive models using the available NSCLC literature. Furthermore, their use of QALYs to take account of the differences in the patient morbidities found in the different stages and treatments of NSCLC sets them apart from the cost effectiveness studies. Therefore, the majority of the literature review will be based on these two studies. The third cost utility study by Hayashi et al was less explicit on the sources of their data especially those concerning the utilities used and so will only be briefly looked at below.

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[16] Bradbury et al. Health Technology Board Scotland, "Positron emission tomography (PET) imaging in cancer management" October 2002.

[17] National Institute of Health and Clinical Effectiveness, "The Diagnosis and treatment of Lung Cancer; Methods, Evidence and Guidance. *National Collaboration Centre of Acute Care.* 2005.

HTBS Study

The HTBS study is based on a decision analysis with seven possible strategies analysed. They conducted their own meta-analysis to estimate the sensitivity and specificity of PET. The majority of parameters used in the model were taken from the Dietlein study.[18] The costs were estimated from a detailed costing of a Scottish PET facility. All patients had a definite diagnosis of NSCLC, were fit for surgery and had a conventional work up (CWU), which usually consists of a chest x–ray, brochoscopy and a CT scan. If the CT scan was positive then the patients had enlarge nodes and therefore a greater risk of mediastinal metastasis or distant metastasis, whereas these risk was reduced if the results were CT negative, in other words the nodes were normal. It was assumed that the rate of metastasis was 10% and could only be detected by PET.

The results for the CT positive patients found that two strategies which noticeably outperformed the other strategies. These were Strategy 3 (mediastinoscopy all and no PET), which had the second best outcome. Strategy 7 (mediastinoscopy after positive PET) had the best outcome and had a higher number of QALYs compared to just giving a PET scan with no further staging procedures to everyone mainly because of the relatively poor detection of enlarged N2/3 patients compared to the 100% specificity of mediastinoscopy. The incremental cost effectiveness ratio (ICER) was extremely high with a value of £59,000 per QALY relative to the threshold implicitly used by NICE in the UK and therefore does not seem to be cost effective at any current acceptable national healthcare threshold.

The results for CT negative patients found that strategies 1, 3 and 7 dominated the other strategies. Strategy 1 (send all to surgery) was the third best outcome with Strategy 3 the second best and Strategy 7 having the best incremental cost per QALY of £10,500. This suggests that using PET for CT negative patients is a cost effective strategy in this model.

NICE Study

The NICE study was also based and built upon the HTBS and Dietlein studies. They looked at two groups of patients who were expected to benefit most from PET. The first was those patients with normal sized lymph nodes (i.e. negative) on CT being considered for PET, they excluded positive patients because they felt that these patients would not benefit due to the high ICER recorded in the HTBS study. The second group were patients that were being considered for radical radiotherapy this consisted mainly of those patients with enlarged nodes (i.e positive) on CT.

In the surgery model they considered three strategies. Under the first strategy patients went straight to thoractomy. In the second, the patients have a mediastinoscopy and then either receive radical radiotherapy (N2/3) or thoractomy (N0/1). In the third strategy patients have a PET scan and then receive either active supportive care (M1), thoractomy (N0/1, M0) or mediastinoscopy (N2/3, M0).They found that the mediastinoscopy strategy was dominated by the PET strategy. The PET strategy compared to the thoractomy strategy resulted in 22% fewer futile thoractomies, 1% fewer surgical deaths and a more appropriate selection of patients for radical radiotherapy. This resulted in an increase in life expectancy of 0.04 per patient and an

[18] Dietlein, M., K. Weber, et al. (2000). "Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results." Eur J Nucl Med **27**(11): 1598-609

increase of 0.04 QALYs per patient. The estimated ICER of the PET strategy compared to the thoractomy strategy was £7,200 per QALY gained.

In the radiotherapy model only two strategies were compared. The first was that all patients go straight to radiotherapy and the second was that all patients have a PET scan and then receive active supportive care (M1), thoractomy (N0/1) or radical radiotherapy (N2/3). Compared to the radiotherapy strategy the PET strategy had less futile radiotherapies and some patients benefiting from curative surgery. However, some patients missed radical radiotherapies and some had unnecessary surgery. Overall, the estimated incremental cost was £9,489 per QALY gained showing PET to be a cost effective strategy rather than sending patients straight to radiotherapy.

Other International Studies

There are three further cost effectiveness studies that show similar results to the HTBS and NICE studies that a mediastinoscopy after positive PET is the most cost effective strategy. All were based on decision analyses. Dietlein found that this strategy in CT negative patients had a cost per life years (LYs) gained of €143, and in CT positive patients a cost per LYG of €36,667.[19] Scott et al found like the HTBS report that this strategy was only cost effective in negative patients.[20] While Gambhir et al did not evaluate PET separately but found overall that using this strategy for both positive and negative patients resulted in savings of $1,154 per patient without a loss of life expectancy.[21] The Hayashi et al cost utility study also confirmed the mediastinoscopy after positive PET strategy more cost effective than just conventional imaging with an ICER of $US7,555 per QALY for patients with 20% mediastinal metastasis ranging up to $44,000 per QALY for patients with 80% mediasstinal metaststasis, they did not differentiate between CT positive and CT negative patients.

The cost effectiveness study by Verboom[22] based on Dutch randomised control trial undertaken by Van Tinternern et al[23] compared a CWU with a CWU + PET strategy. The study showed that the additional use of PET in the staging of patients with NSCLC reduced unnecessary thoractomies by 20% when compared to CWU and saved costs. On the other hand, the economic evaluation conducted alongside Viney's Australian randomised control trial suggested that only 0.22 thoractomies were avoided between the no PET and PET arms. However, this trial only recruited stage I and II candidates who have a low probability of mediastinal lymph node involvement or distant metastasis reducing the likelihood of a futile thoractomy and so in this case PET was found not to be cost effective.[24]

Therefore, the literature suggests that PET is a cost effective study when used in conjunction with a mediastinoscopy after a positive result in CT negative patients compared to

[19] Dietlein, M., K. Weber, et al. (2000). "Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results." Eur J Nucl Med **27**(11): 1598-609

[20] Scott, W. J., J. Shepherd, et al. (1998). "Cost-effectiveness of FDG-PET for staging non-small cell lung cancer: a decision analysis." Ann Thorac Surg **66**(6): 1876-83; discussion 1883-5.

[21] Gambhir, S. S., C. K. Hoh, et al. (1996). "Decision tree sensitivity analysis for cost-effectiveness of FDG-PET in the staging and management of non-small-cell lung carcinoma." J Nucl Med **37**(9): 1428-36

[22] Verboom, P., H. van Tinteren, et al. (2003). "Cost-effectiveness of FDG-PET in staging non-small cell lung cancer: the PLUS study." Eur J Nucl Med Mol Imaging **30**(11): 1444-9.

[23] van Tinteren, H., O. S. Hoekstra, et al. (2002). "Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial." Lancet **359**(9315): 1388-93.

[24] Viney, R. C., M. J. Boyer, et al. (2004). "Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer.[see comment]." Journal of Clinical Oncology **22**(12)

all other possible potential strategies to stage lung cancer. However, PET scanning after CT positive results is a less clear cut strategy with some studies reporting PET to be cost effective and others reporting the opposite to be true. Whilst, studies not taking into account the difference between CT negative and CT positive patients may not be picking up this effect.

Despite the international evidence that PET is likely to be cost effective, especially in CT negative patients the results are not entirely transferable to the Australian context, that is, excluding the Viney et al trial, which only looked at stage I and II candidates. This is mainly because of the different costs structures and reimbursement rates in overseas healthcare systems, which makes the translation of them to the Australian context inappropriate.

Model Structure

There is great variability in the various national clinical guidelines for treating NSCLC and therefore there is some difference in how NSCLC is treated both nationally and even locally.[25,26] The model presented here is, therefore, based on a simplification of the potential outcomes and pathways that on average most likely to used to treat NSCLC in a cost effective manner. The model uses a societal perspective.

As with the HTBS and NICE economic evaluation, the model has been based upon the decision pathway used in the Dietlein study. This is considered to be one of the best studies conducted on PET. However, there are three main problems with this study and its transferability to other decision making contexts has been highlighted.

First, it does not contain all the plausible alternatives for PET (see the HTBS study for other potential strategies).[27] However, this is unlikely to matter greatly as the other strategies suggested are unlikely to ever be used in a clinical situation because they deny patients histological confirmation of their lung cancer.

The second problem is that they take a simple approach to combing data from the literature on the sensitivity and specificity of tests independently, which is inappropriate. Therefore, the sensitivity and specificity for detecting mediastinal metastasis in this study are taken from the meta-analysis conducted by the HTBS study and sensitivity for detecting distant metastasis is taken from the meta-analysis used in the NICE guidelines.

The third problem is that the costs are based upon the German reimbursement rates and charges and are therefore are inappropriate for translation to other healthcare systems. This has bee rectified by inserting comparative costs for tests, surgery and palliative care from Australia. Nevertheless, the Dietlein model is still useful for giving the outline of the decision problem and some of the parameters are the best estimates available to the model for evaluating the cost and benefits of PET in NSCLC. The model inputs can be found in table 4.

Strategies

The model takes the two most cost effective strategies that have been identified from the literature above. These strategies also offer a histological confirmation of NSCLC and they have been applied to both CT positive and CT negative patients. The first strategy is a normal CWU without the use of PET. After the NSCLC has been diagnosed patients either proceed to

[25] Clinical Practice Guidelines for the Prevention, Diagnosis and Management of Lung Cancer. *Australian Government; National Health and Research Council*. 2004.
[26] National Institute of Health and Clinical Effectiveness, "The Diagnosis and treatment of Lung Cancer; Methods, Evidence and Guidance. *National Collaboration Centre of Acute Care.* 2005.
[27] Bradbury et al. Health Technology Board Scotland, "Positron Emission Tomography (PET) Imaging in Cancer Management" October 2002.

have a mediastinoscopy or surgery in CT negative patients depending on the results of the diagnosis this is based on evidenced cited by Dietlein on a survey of 529 thoracic surgeons. The surgeons in the survey believed that in 58% of patients with CT negative results did not require any further surgical staging and so went straight to surgery. [28] This distribution of patients going to surgery or mediastinoscopy has therefore been adopted into the model here.

In CT positive patients, because the likelihood of mediastinal metastasis is high the patients proceed to mediastinoscopy for further staging. Following mediastinoscopy patients in both CT positive and CT negative will if negative proceed to surgery or if positive they will proceed to a course of chemotherapy and radiotherapy in an effort to down stage the cancer. It is assumed that patients with distant metastasis are not detected and patients may undergo futile surgery or radiotherapy.

In the second strategy, the patients undergo a CWU but then receive a PET scan to improve staging. Therefore, if patients' results are positive on the FDG-PET then a mediastinoscopy will be performed regardless of the lymph node size on CT results. If the patients have a negative PET result then they would proceed straight to thoractomy. If PET detects distant metastasis then a patients proceed to a course of palliative care.

Underlying Distribution of disease

The baseline population consisted of 62 year old man with whom NSCLC had been confirmed and who was fit for surgery or non surgical treatment. Distant metastasis had not been detected by conventional staging. The underlying distribution of the disease has been taken from the literature.[29]

It is assumed that:

- 30% of patients have N2/3 disease.
- 10% have occult metastasis
- For N0/N1 disease, 23% have enlarged nodes
- For N2/3diseas, 60% have enlarged nodes

The underlying distribution of disease for PET candidates in the model given these parameters is in table 2 below:

Table 2: HTBS distribution for NSCLC

	N0/1, M0	N0/1, M1	N2/3, M0	N2/3, M1
Normal lymph nodes	48.4	5.4	10.7	1.2
Enlarged lymph nodes	14.6	1.6	16.3	1.8

This underlying distribution was questioned in the NICE study, suggesting that the rate of distant metastasis was too low at 10% and that the constant rate for both N0/1 and N2/3 candidates was highly unrealistic. However, given the results of random clinical trials the rate of metastasis does not seem too high, especially for N0/N1 patients where both models may be

[28] Dietlein, M., K. Weber, et al. (2000). "Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results." Eur J Nucl Med **27**(11): p.1600.

[29] Dietlein, M., K. Weber, et al. (2000). & Bradbury et al. Health Technology Board Scotland, "Positron emission tomography (PET) imaging in cancer management" October 2002.

overestimating the rate of metastasis.[30 31 32] Nevertheless, it is correct to assume based on the random clinical trial evidence that the rate of metastasis will not be the same in both N0/1 and N2/3 patients. Therefore, I will also test the NICE underlying distribution for lung cancer to see if this has any effect on the model this is giveen table 3 below.

Table 3: NICE distribution for NSCLC

	N0/1, M0	N0/1, M1	N2/3, M0	N2/3, M1
Normal lymph nodes	56.98	1.794	3.4	5.82
Enlarged lymph nodes	17.02	6.006	5.1	3.88

Life expectancy and QALYs

The quality adjusted life year (QALY) is constructed by attaching utility weights to life expectancy data with 1 being equivalent to full health and 0 being dead. The possible values between full health and death are then ranked on the unpleasantness to be in that health state providing the QALY weights.[33] However, it was not possible to find any Australian utility values associated with NSCLC.

Furthermore, there is a lack of data on the utilities of patients with NSCLC overall and the data that is used here is not of the highest quality. There is no data on the utilities of patients who receive futile operations or radiotherapy, chemotherapy or other supportive care for N0/1, N2/3 or M1 diseases. The model here is based upon the values used in the HTBS model; this is because no newer or better estimation of QALYs were found.

It has been suggested that patients experience reduced quality of life when they undergo surgery in terms of discomfort and anxiety, Therefore it was assumed that undergoing surgery results in a lost of quality of life and in this model it has taken the literature value of 0.15 undergoing surgery. But this is based on estimation and therefore major uncertainty surrounds this value.[34] Furthermore, the NICE study suggests that undergoing radical radiotherapy should also result in a reduction in quality of life, but to avoid putting any more uncertain assumptions into the model it was assumed that undergoing radiotherapy here did not result in any loss of quality of life. [34]

Table 4. Model Inputs for the model

[30] Herder, G. J., H. Kramer, et al. (2006). "Traditional versus up-front [18F] fluorodeoxyglucose-positron emission tomography staging of non-small-cell lung cancer: a Dutch cooperative randomized study." J Clin Oncol **24**(12):

[31] Viney, R. C., M. J. Boyer, et al. (2004). "Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer.[see comment]." Journal of Clinical Oncology **22**(12):

[32] van Tinteren, H., O. S. Hoekstra, et al. (2002). "Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial." Lancet **359**(9315):

[33] Hunink, M et al, Decision making in Health and Medicine: Integrating evidence and values, Cambrdige, C.U.P, 2001. p.97.

[34] National Institute of Health and Clinical Effectiveness, "The Diagnosis and treatment of Lung Cancer; Methods, Evidence and Guidance. *National Collaboration Centre of Acute Care.* 2005. Appendices p.272.

Variable	*Input/ Assumption*
Base Case Patient	62 year old man, NSCLC confirmed and fit for surgery or non surgical treatment. (Dietlein)
Diagnostic accuracy	
Sensitivity of FDG PET if CT negative	**86%** with 95% CI (0.79, 0.91) - (HTBS)
Specificity of FDG PET if CT negative	**90%** with 95% CI (0.87, 0.93) - (HTBS)
Sensitivity of FDG PET if CT positive	**92%** with 95% CI (0.87, 0.95) - (HTBS)
Specificity of FDG PET if CT positive	**76%** with 95% CI (0.69, 0.82) - (HTBS)
Sensitivity of FDG PET detecting distant Metastasis	**93%** - (NICE)
Sensitivity of Mediastinoscopy	**72%** - (Dietlein)
Specificity of Mediastinoscopy	**100%** - (Dietlein)
Mortality	
CT and PET mortality	**0%** - (Dietlein)
Surgery mortality	**3.7%** - (Dietlein)
Mediastinoscopy mortality	**0.5%** - (Dietlein)
Life Expectancy	
Life expectancy after surgery	N0/1; M0: 4.5 years N2/3; M0: 1.8 years M1: 0.5 years (Dietlein)
Life expectancy after palliation	N0/1; M0: 2.6 years N2/3; M0: 1.8 years M1: 0.5 years (Dietlein)
Other Assumptions	
Percentage of patients straight to surgery	**58%** (Dietlein)
Complication rate of surgery	**37.5%** (Own estimate based on Viney)
Probability patients upstage during thoractomy from N0/1 to N2/3	**10%** (HTBS**)**

Costs

All costs were adjusted for inflation and are in 2006 prices and can be seen in the table below. It is not currently possible to differentiate FDG-PET scan costs from the National Benefit Schedule or the National Hospital Data Collection and so a value was taken from the Viney et al article with a value of AUD$2546.6.[35]

Table 5: Unit Costs

Diagnostic techniques and treatments	***Unit costs***
Full body FDG-PET scan	**$A 2546.6** – (Viney et al)
EO1A Surgery	**$A 21,726.9 –** National Hospital data collection)
EO1B Surgery	**$A 18,176.4** - (National Hospital Data collection)
Mediastinoscopy	**$A 2,466** – (Miles)
Course of Radiotherapy	**$A 13,922** –(Rosenthal**)**
Course of Chemotherapy	**$A 9,784** – (See Appendix 2)

The surgery costs were taken from the Australian National Hospital Cost Data Collection with there being two relevant Diagnostic Related Groups (DRGs). The first is E01A which is a major chest procedure with catastrophic clinical complexity (cc) and E01B a major chest procedure without catastrophic cc. The distribution of the patients between the two procedures was taken from the Viney et al article with approximately 62.5% of patients having no catastrophic clinical complexity. The reimbursement rate for E01A was $AUD 21,727 and for E01B was $AUD 18,176. This included a comprehensive cost 'bucket' for all relevant associated costs for these procedures. It was assumed that the mediastinoscopy costs would have been factored into the estimation of the DRGs for the chest surgery. Therefore, where a mediastinoscopy was not performed the estimated cost of mediastinoscopy which was AUD$ 2,466 was taken away from the surgery costs.[36]

There were no estimates for Australian radiotherapy costs available for treating N2/3 disease. As a consequence an estimate for the radiotherapy cost of treating SCLC from the literature was used. There is evidence that the radiotherapy costs for NSCLC and SCLC overall are adequately close.[37] A value of $AUD 13,922 was used for the base case based on Rosenthal study of the cost of SCLC for radiotherapy minus diagnosis costs and chemotherapy costs.[38]

[35] Viney, R. C., M. J. Boyer, et al. (2004). "Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer.[see comment]." Journal of Clinical Oncology **22**(12).

[36] Miles, K. A. (2001). "An approach to demonstrating cost-effectiveness of diagnostic imaging modalities in Australia illustrated by positron emission tomography." Australas Radiol **45**(1): 9-18.

[37] Fleming, I. Factors influencing hospital cost of lung cancer patients in Northern Ireland.

[38] Rosenthal, M. A., P. J. Webster, et al. (1992). "The cost of treating small cell lung cancer." Med J Aust **156**(9): 605-10.

The chemotherapy costs were based on the estimation of the costs used by the HTBS for the use of chemotherapy in advanced disease (stage III and IV) NSCLC. The chemotherapy cost was estimated for Cisplatin plus Vinorelbine but using Australian data. The cost estimation can be seen in Appendix 1. This took data from the Pharmaceutical Benefit Schedule for Cisplatin and Vinorelbine. The inpatient and outpatient costs were taken from the literature. A number of assumptions had to be made in calculating the cost with the costs of drug preparation and administration, side effects and counselling costs all having to be taken from the UK costs estimates and transferred into Australian dollars.[39] To take into account the high uncertainty over the chemotherapy and radiotherapy costs a two way sensitivity analysis will be undertaken with the values for both costs being doubled and halved.

If N0/1 M0 patients correctly underwent surgery and survived then they were assumed to be free from disease and did not undergo anymore direct costs. Patients will undergo a course of radiotherapy if they are correctly identified as N2/3 M0 patients, and then followed up with a course of chemotherapy. It is also assumed that 10% of patients with N2/3 undergoing a futile thoractomy will be identified as such and progress to radical radiotherapy and chemotherapy. All other patients that undergo a futile thoractomy are assumed to just undergo chemotherapy because when the disease reappears it is too late to treat it any other way. Those identified as having M1 disease will undergo palliative care in the form of chemotherapy.

Discounting Costs and Benefits

The majority of cost occurs immediately after or soon after diagnosis. The only patients that are likely to be affected are the N0/1 M0 patients whose life expectancy are 4.5 years if successfully operated upon and will receive post operative follow up costs and terminal care costs. However, there is no firm data on these costs and any speculation on the make up of these costs would be speculative, therefore a decision was made not to discount costs and benefits in this model this is consistent with the HTBS and NICE studies.

[39] HTBS, "Comment on NICE Technology Appraisal Guidance on the use of Docetaxel and Paclitaxel , Gemcitabine and Vinorelbine for the treatment of non small cell lung cancer" 2001B.

Results
Baseline

The model was built and run in an EXCEL spreadsheet with 100 patients progressing through the model. In the base case result there were 34.3% of patients who were CT positive and 65.6% patients who were CT negative. The CT negatives patients comprised of around 48 patients who were potentially surgically operative and close to 17 who were eligible for non surgical treatment. The results of the CT negative patients are given in table 6.

Table 6: CT negative patients

	Correct operations	Missed operations	Futile Surgery	Futile Radiotherapy	Mean QALYS	Mean Costs
CWU	48.408	0.1019	13.44	0.361	2.88	20427
PET	48.486	0.0243	0.239	0.142	2.91	20826

There is a minute difference between the PET and CWU strategies in the number of patients that undergo correct operations this includes patients who were correctly staged but died as a result of surgery. The small difference is accounted for by the CWU patients having to undergo 82% more mediastinoscopies than the PET arm and therefore having a higher risk of dying before having a correct operation. This also accounts for the negligible increase in number of missed operations with more patients dying in mediastinoscopy in the CWU strategy.

However, the main difference between the two strategies occurs with there being around a total of 13.44 more futile surgical operations in the CWU strategy compared to only 0.24 in the PET strategy. This result can be mostly explained by 58% of the CWU patients progressing straight to surgery without undergoing a mediastinoscopy thus accounting for around 9.7 of the futile operations. The other futile thoractomies can be explained by a more accurate staging by PET with its high sensitivity and specificity of 0.86 and 0.9 and then following positive patients up with a mediastinoscopy this allows better results than just conducting a pure mediastinoscopy due to its low sensitivity of 0.72. Despite the futile operations the CWU is still on average cheaper than the PET strategy by around $A400 due to the extra cost of PET scanning. The average QALYs between the two strategies are quite close with a difference of only 0.026 per patient. The relatively small difference in QALYs and costs suggests that the two strategies will be very sensitive to changes in model inputs.

There were 34.3% of patients who were CT positive with around 14.6 patients who were suitable for surgery and 21.6 suitable for non surgical treatment. The baseline results of the CT positive patients can be seen in table 7.

Table 7: CT positive patients

	Correct operations	Missed operations	Futile Surgery	Futile radiotherapy	Mean QALYS	Mean Costs
CWU	14.41755	0.072	5.93	1.28952	2.09	23578.4
PET	14.472612	0.017	4.23	0.228	2.11	24083.27

The results for the CT positive patients also show that PET marginally identifies more patients correctly for surgery and has a lower number of missed operations; this is again, because of CWU patients undergoing more mediastinoscopy with its risk of death than PET patients. There are substantial numbers of futile thoractomies occurring in both CWU and PET patients with 5.93 and 4.23 respectively. The reason the number of thoractomies is so high is because of the low sensitivity of mediastinoscopy at only 72% due to it being unable to reach some lymph nodes and with more mediastinal lymph metastasis patients in the section of the model this causes an increase in numbers of futile thoractomies proportionally when compared to the CT negative patients. The small difference in the number of futile thoractomies between the CWU and PET strategies is because of better PET staging. Furthermore, the PET strategy also reduces the number of futile radiotherapies that that would occur in the CWU cases due PET correctly identifying more of the N2/3 M1 patients. However, there are only small gains for improving the correctly staging more radiotherapy patients because N2/3 M0 patients only gain around 0.15 QALYs per patient. The difference in costs and QALYS are even closer between the two strategies and suggest that the results will be even more sensitive to changes in model inputs and variables.

An ICER examines the additional cost of one strategy compared to another against the additional benefits the strategy offers. The ICER is calculated by dividing the differences in costs by the difference in patient's benefit, to give an incremental cost per QALY.[40] The incremental costs and QALYs and the resulting ICERS were calculated and presented in table 8.

Table 8: Totals costs, QALYs and incremental cost effectiveness ratios.

	Cost	Incremental Cost	QALYS	Incremental QALYs	ICER
CT negative CWU	1346155.1		189.80		
CT negative PET	1372431.3	26276.2	191.61	1.80	14580.95
CT positive CWU	804023.6		71.49		
CT positive PET	821239.3	17215.7	71.82	0.33	52038.52
CWU Arm	2150178.7		261.29		
PET Arm	2193670.6	43491.9	263.43	2.13	20390.81

The results show that PET strategy is cost effective compared to just using the CWU strategy for both CT negative and CT positive patients with an ICER of $A 14,581 and $A 52,039 per QALY respectively. The ICER for CT positive patient is expensive and it would be down to a decision maker to decide whether this would be an acceptable cost worth paying for an additional QALY.

The difference in results between the CT negative and CT positive results in terms of their ICERs is due mostly to PET reducing the number of futile operations in non N0/1 M0

[40] Drummond et al Economic evaluation in Health care: Merging theory and practice. (Oxford, O.U.P, 2001) pp. 11-12.

patients. Therefore despite the favourable overall ICER of $A 20,291 between the CWU and PET strategy this hides large potential differences between the CT negative and CT positive patients.

Testing the Viney et al RCT Trial

The accuracy of the model was tested by comparing it to the Viney et al randomised control trial with the control group (no PET scan) containing 92 patients and a PET group of 91 patients. In the control arm, 90 of the patients underwent surgery compared with 87 in the PET arm. The two arms closely resembled the two strategies that are presented here, although some patients did undergo further tests. There were 7 patients who had mediastinoscopy in the PET arm and 4 patients that had mediastinoscopy in the control arm. The trial consisted of mainly stage I patients who therefore had limited mediastinal lymph node involvement and low rate of distant metastasis, thus the majority of the patients in both arms proceeded straight to thoractomy explaining the low number of mediastinoscopies carried out in the trial.[41]

The distribution of N0/1 and N2/3 candidates in the trial was inputted into the model and the percentage of patients going to mediastinoscopy was changed to represent the movements of the actual population in the trial. The model predicted that for the no PET arm there would be 82.77 patients having surgery compared to the trial where 90 patients underwent a thoractomy. The main reason for the difference was because the rate of metastasis in model presented here seems to be too high or at least for those patients with stage I disease. The rate of metastasis was then changed to 5% in the model the rate used in other economic models such as Dietlein and this gave a result of 87.35 patients proceeding to thoractomy.[42] The model predicted for the PET arm that there would be 81.86 patients that would receive surgery again an underestimation of the 87 patients that did receive surgery in the trial. Once again changing the rate of metastasis to 5% provided a result closer to the trial result with 87.1 patients receiving a surgery. Therefore, it would seem, at least, for stage I NSCLC patients the rate of metastasis is too high in the model presented here.

The HTBS study with its similar model to the one presented here assessed the Van Tintertern et al trial, which differed from the Viney trial in that any patients with NSCLC were recruited into the model instead of just stage I and II patients. It was found that the HTBS model predicted the trial well with their model predicting the difference in futile operations between the CWU and PET arms being that PET saved 17 operations per 100 in the model; whereas the Dutch trial showed there were actually 16 operations per 100 saved.[43][44]

The results of testing the models against the random clinical trails suggest that the overall level of metastasis for all patients with NSCLC maybe correct. However, as the NICE study suggests, the rate of metastasis may change depending on which stage of NSCLC the patients have and with the results here actually suggesting that for stage I candidates the rate of distant metastasis maybe too high.[45]

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[41] Viney, R. C., M. J. Boyer, et al. (2004). "Randomized controlled trial of the role of positron emission tomography in the management of stage I and II non-small-cell lung cancer.[see comment]." Journal of Clinical Oncology **22**(12).

[42] Dietlein, M., K. Weber, et al. (2000). "Cost-effectiveness of FDG-PET for the management of potentially operable non-small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results." Eur J Nucl Med **27**(11): 1598-609.

[43] Bradbury et al. Health Technology Board Scotland, "Positron emission tomography (PET) imaging in cancer management" October 2002. "Economic Evaluation", pp.23-24.

[44] van Tinteren, H., O. S. Hoekstra, et al. (2002). "Effectiveness of positron emission tomography in the preoperative assessment of patients with suspected non-small-cell lung cancer: the PLUS multicentre randomised trial." Lancet **359**(9315).

[45] National Institute of Health and Clinical Effectiveness, "The Diagnosis and treatment of Lung Cancer; Methods, Evidence and Guidance. *National Collaboration Centre of Acute Care.* 2005. Appendices p.271.

Sensitivity Analysis

There were several assumptions that have had to be made in this model to fill in the gaps in our knowledge about the resource use and how the staging of NSCLC is conducted, which are based on weak evidence. Therefore sensitivity analyses are used to evaluate how changes in assumptions used in economic evaluations change the conclusions of studies.[46] Therefore to test the robustness of the model and the cost effectiveness of PET several one way sensitivity analyses, a two way sensitivity analysis and a probabilistic sensitivity analysis were carried out on a number of parameters.

PET accuracy

The first sensitivity analysis that was undertaken was to look at the accuracy of PET scanning for staging N2/N3 patients using the confidence intervals from the HTBS meta-analysis as the upper and lower limits of PET sensitivity and specificity. In the NICE meta-analysis for the sensitivity and specificity of detecting distant metastasis there were no confidence intervals given. Therefore, a value of 6% lower and 4% higher than the point estimate was allocated to the PET sensitivity giving a lower limit of 87.4% and upper limit of 96.7% this is roughly consistent with the confidence intervals around the sensitivity and specificity of PET found in the HTBS meta-analysis. See table 10 below.

Table 10 Sensitivity analysis of PET sensitivity and specificity for CT Negative and CT positive patients

	Cost	Incremental Change	QALYS	Incremental Change	ICER
PET Accuracy: lower bound CI for Sensitivity and specificity					
CT negative CWU	1346155.1		189.80		
CT negative PET	1376356.6	30201.5	191.48	1.68	18002.896
PET Accuracy: Upper bound CI for Sensitivity and specificity					
CT negative CWU	1346155.1		189.80		
CT negative PET	1368637.6	22482.5	191.70	1.90	11841.310

PET Accuracy: lower bound CI for Sensitivity and specificity					
CT positive CWU	804023.6		71.49		
CT positive PET	827303.5	23279.9	71.67	0.18	131065.397
PET Accuracy: Upper bound CI for Sensitivity and specificity					
CT positive CWU	804023.6		71.49		
CT positive PET	816788.2	12764.6	71.92	0.43	29730.504

The main direct impact of lowering the sensitivity and specificity is that the number of futile operations and missed operations increases in both CT negative patients and CT positive patients in the PET strategy. This causes more false negatives in both to be incorrectly sent

[46] Drummond et al, Methods for the Economic Evaluation of Health Care Programmes; Third edition. (Oxford, O.U.P, 2005), p. 42.

straight to surgery and virtually doubled the number of futile surgeries. While the increase in the number of false positive patients causes more of the patients to undergo a mediastinoscopy with its accompanied risk of death causing some patients to miss out on potentially curable surgery. This, therefore, reduces the number of QALYs gained and at the same time increases the costs in the PET strategy due to more futile surgeries. The effect of moving from CWU to the PET strategy in both CT negative and CT positive patients is a increase in the ICER from $A 14,581 to $A18,003 and $A 52,038 to $A 131,065 per QALY.

On the other hand, increasing the sensitivity and specificity of PET has the opposite outcome of correctly staging more patients reducing the number of futile operations and reducing the number of missed operations. This increases the number of QALYs and reduces the cost of the treatments with the predictable result of the ICER falling to $A 11,841 in CT negative patients and $A 29,730 and CT positive patients.

The overall effects in the movement of the ICER are smaller when using the higher confidence interval because the confidence intervals around the point estimates are not symmetrical. The large changes in the CT positive patients ICER can be attributed to the small incremental change in the QALYs between the two strategies making the results more sensitive. This gives much more uncertainty around the PET strategy in the CT positive patients, because it is unlikely from a decision maker's perspective they will accept an ICER of $A 131,065 per QALY if the sensitivity and specificity of PET were found to be lower in reality

Surgical morbidity rate

The base case assumed that the surgical morbidity rate caused a reduction in utility of 0.15 for every operation undergone. This parameter was only an estimation given in the HTBS study and so no firm value was attached to it other than what seemed reasonable. The loss of utility was therefore decreased to 0.1 and increased to 0.2 to take account of this uncertainty.

Table 11: Sensitivity analysis of the surgical morbidity rate

	Cost	Incremental Change	QALYS	Incremental Change	ICER
Surgical morbidity decreased to 0.1					
CT negative CWU	1346155.1		192.80		
CT negative PET	1372431.3	26276.2	194.16	1.36	19268.02
Surgical mortality increased to 0.2					
CT negative CWU	1346155.1		186.81		
CT negative PET	1372431.3	26276.2	189.05	2.24	11728.03
Surgical morbidity decreased to 0.1					
CT positive CWU	804023.6		72.50		
CT positive PET	821239.3	17215.7	72.79	0.29	59630.20
Surgical mortality increased to 0.2					
CT positive CWU	804023.6		70.48		
CT positive PET	821239.3	17215.7	70.85	0.37	46161.57

The results for decreasing the surgical morbidity to 0.1 shows that for CT negative patients the QALYs for both the CWU and PET patients increase. Nevertheless, there are more patients who are undergoing surgery whether they are correct operations or futile operations in

the CWU patients, therefore there are more patients that benefit from a reduction in surgical morbidity than in the PET strategy. Therefore, the ICER of PET over the CWU for CT negative patients actually becomes less cost effective with it rising to $A19,268 per QALY.

This is also the case for the CT positive patients with the number of QALYs increasing in both CWU and PET with more surgeries taking place in the CWU patients again and so the ICER becomes less cost effective rising to 59,630 per QALY. While the opposite is true when the rate of surgical morbidity increases with the ICERs improving to $A11,728 and $A 46,161 per QALY in both the CT positive and CT negative patients. The sizes of effects are relatively tight around the baseline results showing that this is a relatively robust result.

Rate of upstaging during Surgery

The rate of upstaging to radical radiotherapy and chemotherapy in N2/3 M0 patients undergoing thoractomy was 10%. This was increased and decreased by 50% to take into the consideration the uncertainty of this parameter.

Table 12: Rate of upstaging during surgery for CT negative and CT positive patients

	Cost $A	Incremental Change	QALYS	Incremental Change	ICER
Increasing upstaging in N2/3 patients during surgery by 50%					
CT negative CWU	1357735.0		189.80		
CT negative PET	1377927.6	20192.6	191.61	1.80	11205.12
Decreasing upstaging in N2/3 patients during surgery by 50%					
CT negative CWU	1340365.2		189.80		
CT negative PET	1369683.1	29318.0	191.61	1.80	16268.86

Increasing upstaging in N2/3 patients during surgery by 50%					
CT positive CWU	810074.6		71.49		
CT positive PET	828543.7	18469.2	71.82	0.33	55827.38
Decreasing upstaging in N2/3 patients during surgery by 50%					
CT positive CWU	800998.1		71.49		
CT positive PET	817587.1	16589.0	71.82	0.33	50144.09

The QALYS were not affected by this change because it is assumed there is no difference in terms of quality of life or life expectancy for N2/3 M0 patients undergoing chemotherapy or a combination of chemotherapy and radiotherapy in an attempt to downstage the cancer. This maybe an incorrect assumption, but there is no evidence to suggest that there is indeed a difference and so it was felt rather than add in a further baseless assumption to the model the quality of life and life expectancy would be left unchanged.

However, the costs do increase for both CT negative and CT positive patients as the rate of upstaging increase with more N2/3 M0 patients being correctly moved to more expensive chemotherapy and radiotherapy. The ICER in CT negative patients becomes more cost effective decreasing to $11,205 per QALY and as the rate of upstaging increases due to more CWU patients undergo surgery, whether this is correct or futile, relative to the PET patients and this incurs greater cost but without any improvement in benefits. When the rate of upstaging is decreased this has the opposite effect as fewer patients in the CWU arm undergo expensive radiotherapy and chemotherapy with no change to the benefits and so the ICER increase to $A 16,269 per QALY.

However, unlike the CT negative results we see the ICER for CT positive patients increase as the rate of upstaging is increased. This is because slightly more upstaging occurs in the PET strategy than the CWU strategy with 0.525 patients being upstaged compared to 0.43 due to false negatives in PET proceeding straight to surgery without a mediastinoscopy. Therefore, we see the PET versus the CWU strategy becoming less cost effective with the ICER increasing to $A 55,827 when the rate of upstaging is increased and falling to $A 50,144 when the rate of upstaging is decreased. These results may radically change if QALY assumptions are introduced.

Radiotherapy and chemotherapy costs

There was much uncertainty about the chemotherapy and radiotherapy costs in the model as there is no certain Australia data on costs of these treatments in NSCLC. Therefore, a two way sensitivity analyses was carried out to take account of this uncertainty and can be seen in table 13 for CT negative patients and

Table 13: Two way sensitivity analysis of the cost of chemotherapy and radiotherapy in CT negative patients

	Chemotherapy Costs							
Radiotherapy Costs		**4000**	**6000**	**8000**	**9,784**	**10000**	**12000**	**14000**
	6000	696.1	1373.1	2050.1	2653.9	2727.0	3404.0	4081.0
	8000	3707.2	4384.2	5061.2	5665.0	5738.1	6415.1	7092.1
	10000	6718.3	7395.3	8072.3	8676.1	8749.2	9426.2	10103.2
	12000	9729.4	10406.4	11083.4	11687.2	11760.3	12437.3	13114.3
	13922	12623.14	13300.1	13977.0	14580.95	14654.0	15331.0	16008.0
	14000	12740.5	13417.5	14094.5	14698.3	14771.4	15448.4	16125.4
	16000	15751.6	16428.6	17105.6	17709.4	17782.6	18459.5	19136.5
	18000	18762.7	19439.7	20116.7	20720.5	20793.7	21470.6	22147.6
	20000	21773.8	22450.8	23127.8	23731.6	23804.8	24481.7	25158.7

The results show that in the CT negative patients that as the costs of radiotherapy and chemotherapy increase the ICERs is also increases. This reflects that PET correctly stages more patients with N2/3 for joint chemotherapy and radiotherapy and identifies more patients with M1 disease than the CWU strategy. However, the ICERs for the CT negative patients do not change greatly considering the large movements in the costs and never become excessively high.

Table 14: Two way sensitivity analysis of chemotherapy and radiotherapy in CT positive patients

	Chemotherapy Costs							
Radiotherapy costs		**4000**	**6000**	**8000**	**9784**	**10000**	**12000**	**14000**
	6000	79436.1	87582.1	95728.1	102994.3	103874.0	112020.0	120166.0
	8000	66571.8	74717.7	82863.7	90129.9	91009.7	99155.6	107301.6
	10000	53707.4	61853.3	69999.3	77265.5	78145.3	86291.3	94437.2
	12000	40843.0	48989.0	57134.9	64401.1	65280.9	73426.9	81572.8
	13922	28480.3	36626.3	44772.3	52038.5	52918.2	61064.2	69210.2
	14000	27978.6	36124.6	44270.6	51536.8	52416.5	60562.5	68708.5
	16000	15114.2	23260.2	31406.2	38672.4	39552.1	47698.1	55844.1
	18000	2249.90	10395.8	18541.8	25808.0	26687.8	34833.7	42979.7
	20000	-10614.4	-2468.5	5677.4	12943.6	13823.4	21969.4	30115.3

In the CT positive results we see that as the chemotherapy cost increase the ICER starts to increase, however when the radiotherapy cost increase the ICER start to fall and eventually PET comes to dominates the CWU strategy. A possible explanation of the difference between the results of the CT positive and CT negative patients is the different distribution of the underlying disease. The chemotherapy costs raise in both N2/3 and M1 and so the ICER increases as chemotherapy costs increase. But, because there are nearly 1.3 more futile radiotherapies in the CWU strategy compared to only 0.075 in the PET strategy; we see that at low prices for radiotherapy this means that PET is the far more expensive strategy, but as radiotherapy costs start to increase then so do the total costs for the CWU strategy reducing the difference in costs between the two strategies making PET strategy more cost effective.

Testing the NICE distribution

The NICE paper used a different underlying distribution of lung cancer and, although, their distribution improved on some of the assumptions made in previous model it was felt that it may have had a rate of metastasis that was too high for N0/1 patients and that overall the number of N2/3 patients was too low. Therefore, their distribution was not used as the base case. Although it did have the added benefit in suggesting that the rate of metastasis would not be the same for both N0/1 and N2/3 patients so it was decided to test the distribution.

Table 15: The NICE distribution

	Cost $A	**Incremental Change**	**QALYS**	**Incremental Change**	**ICER**
NICE distribution of lung cancer patients					
CT negative PET	1361521.06		215.64808		
CT negative CWU	1391567.23	30,046	215.42801	-0.22	DOMINATED

NICE distribution of lung cancer patients					
CT positive PET	598912.2		70.25457		
CT positive CWU	671965.1	73053	73.24	2.98	24484.222

It was found that for CT negative patients the PET strategy dominated the CWU strategy this was also what was found in the NICE model with sending all patients to

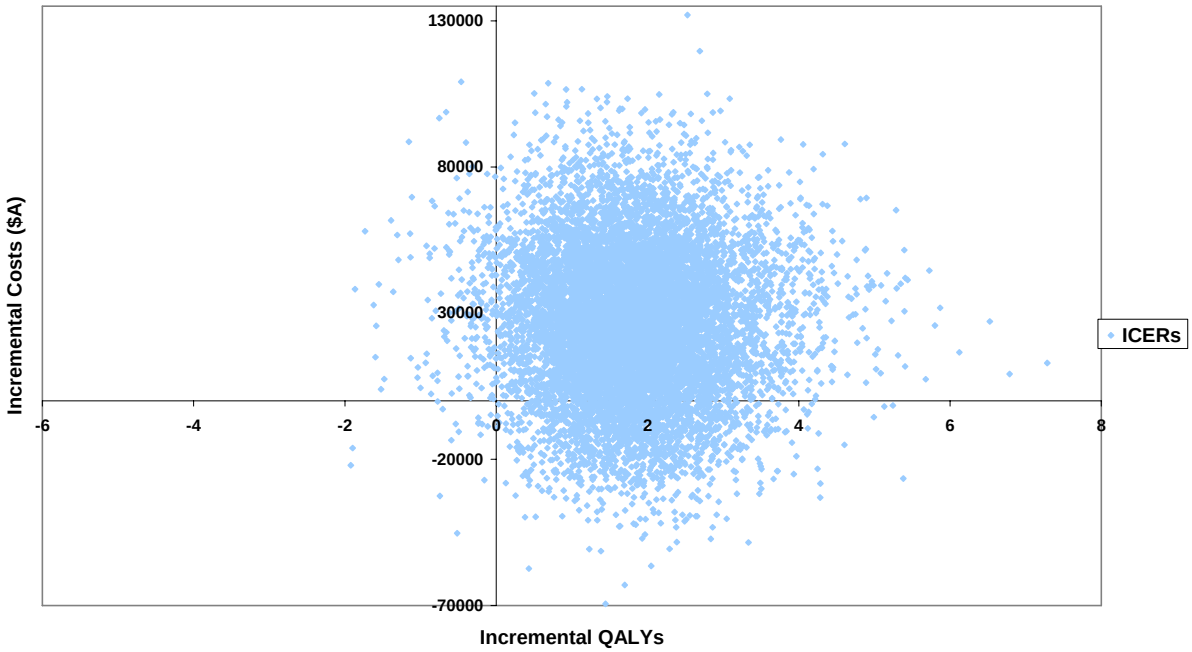
thoractomy being the second best outcome. Turning to look at the CT positive patients, we see that the CWU strategy was actually more cost effective than the PET strategy with an ICER of $A 24,484 per QALY. It is not possible to compare this with the NICE results because they did not look at the CT positive patients as they believed this would not be a cost effective outcome for PET as the model here shows.

Probabilistic sensitivity analysis

The role of probabilistic modelling is to further reflect the uncertainty in the parameters used in the decision model and to see what effect this has, in this case, over the incremental net benefit.[47] The parameters in the model were given distributions with probabilities and utilities given a beta distribution and all other costs and life expectancy given a gamma distribution. A simulation was then run 10,000 times using the macro given in appendix 4.

The graph below shows the following distribution of QALYS and costs and their subsequent ICERs from the 10,000 simulation runs for the CT negative patients. It is clear that the distribution is primary located in the more costly and more effective section of the graph with a tight distribution of point with few extreme values. The current willingness to pay for one QALY is not known and so the existing threshold ratio has not been added, but it clearly shows that the threshold ratio would not have to be that high for the PET strategy to be implemented.

Graph 1: The distribution of costs and QALYs and the resulting ICERs for CT negative patients

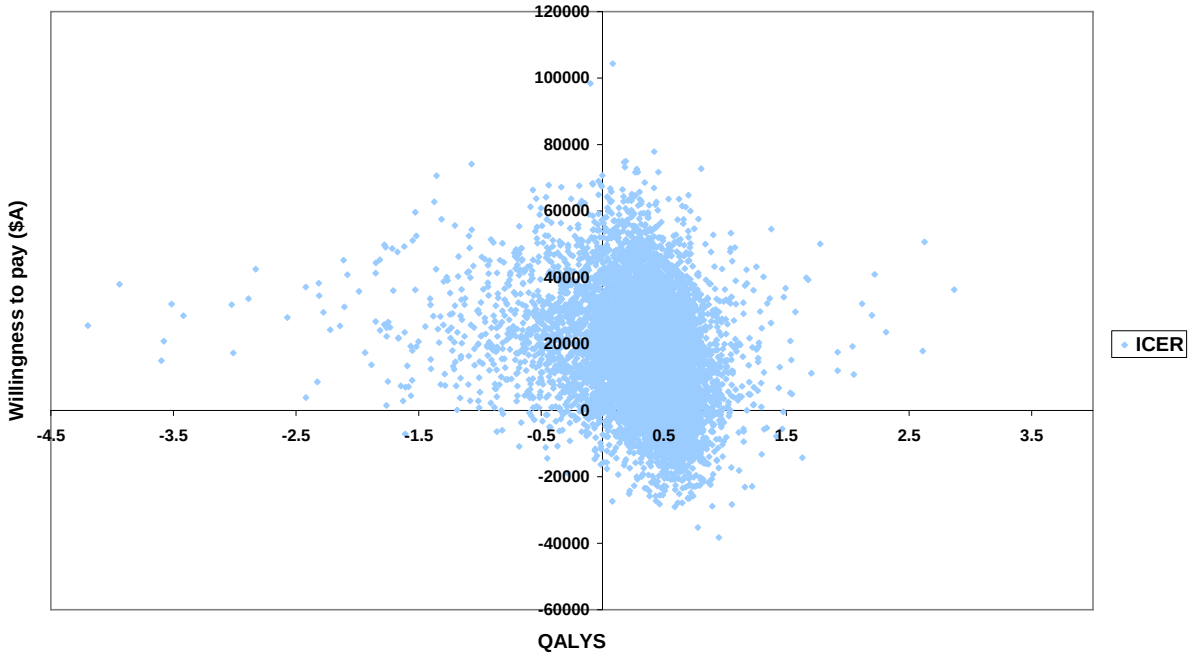


The next graph shows the distribution of ICERs in the 10,000 simulation runs for CT positive patients. The distribution is also mostly located in the more effective and more costly quadrant of the cost effectiveness plane. However the majority QALYs are located in a narrow

[47] Briggs A., Claxton K. and Sculpher MJ. Decision analytic modelling for the evaluation of health technologies. O.U.P., Oxford, 2006. p77

band of QALY scores mostly ranging from 0 to 0.9 QALYS compared to the CT negative range of around 0.5 to 3 QALYs, whilst there is similar variability in the costs to the CT negative results. This results in the clear implication that higher threshold ratio will be needed for the PET strategy to be implemented by a decision maker than compared to the CT negative results. There are also a larger number of negative QALYs in the CT positive with a significantly dense spread to the left of the graph suggesting much more uncertainty in the CT positive results.

Graph 2: The distribution of costs and Benefits and the resulting QALYs for CT positive patients



The mean, median and inter quartile range were taken from the simulation of 10,000 runs. In the CT negative patients the mean ICER for the PSA is very close to the mean in the baseline result with only a difference of about $A 37 per QALY and therefore shows that the baseline model is robust in the results with little variability in the parameters. The median is also close to the mean and shows that the distribution does not appear to be heavily skewed.

Table16: The mean, median and inter quartile range for Ct negative patients in the simulation

CT negative patients		Incremental Costs	Incremental QALYS	ICER
Mean		26197.16	1.80	14543.1
Median		25628.17	1.76	13596.0
Inter-Quartiles	25	10692.55	1.23	5047.8
	75	43202.51	2.38	25236.8

The CT positive patients show that the mean is also very close to the mean in the original baseline result but not as close as the CT negative results with the a difference of around $A 816 per QALY cheaper than the PSA result. But the most interesting result is that the median is so low compared to the median suggesting that there is a substantial amount of skewness in the results and this could be potentially suggesting that the is a lot of variability in outcomes and is further evidence to question PET as a cost effective strategy in CT positive patients.

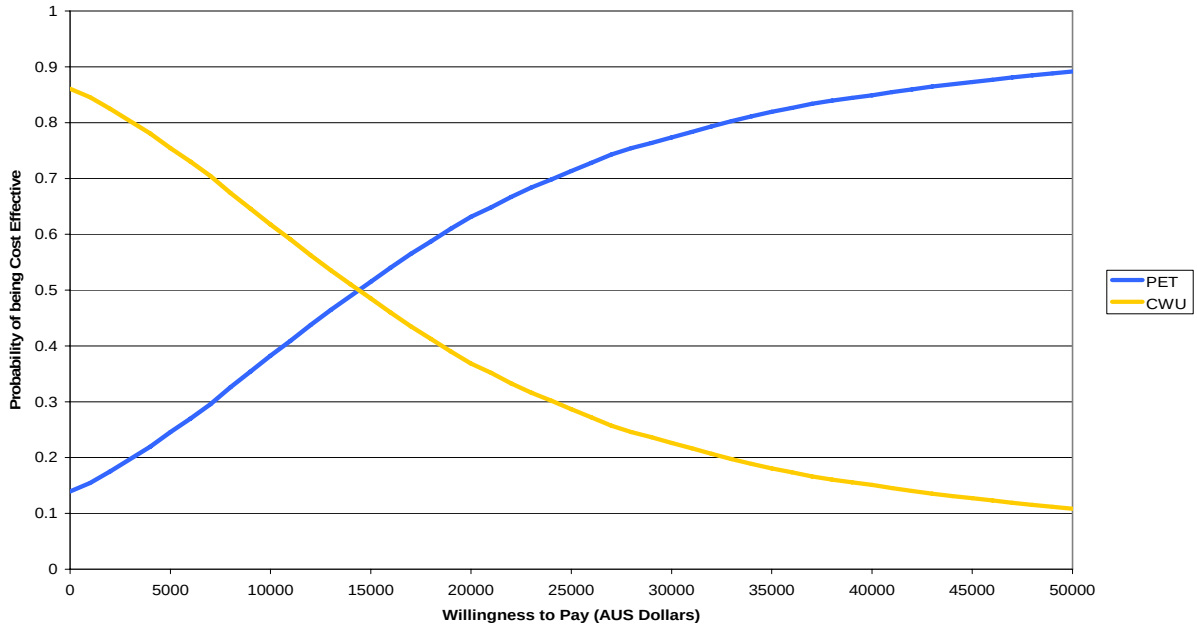
Table 17: The mean, median and inter quartile range for Ct positive patients in the simulation

CT positive patients		Incremental Costs	Incremental QALYs	ICER
Mean		16742.87	0.33	50854.9
Median		15499.46	0.40	27256.2
Inter-Quartiles	25	5813.80	0.20	64.8
	75	26654.65	0.56	62985.8

We now turn to look at the cost effectiveness acceptability curve (CEAC) for PET and CWU in NSCLC for CT negative patients. A CEAC shows the probability that an intervention is more cost effective than it comparator. The results for CT negative patients show that as the threshold willingness-to-pay increases the probability that PET is cost effective rises while the probability that CWU is cost effective decreases. [48] The CEAC shows the decision maker the probability that they have made the right on wrong decision and, in this case, the decision maker will make the right decision more than 50% of the time if the willingness to pay is just over $A 15,000, while if the decision maker is willing to pay $A 50,000 the probability that they have made the right decision increases to 90%.[49]

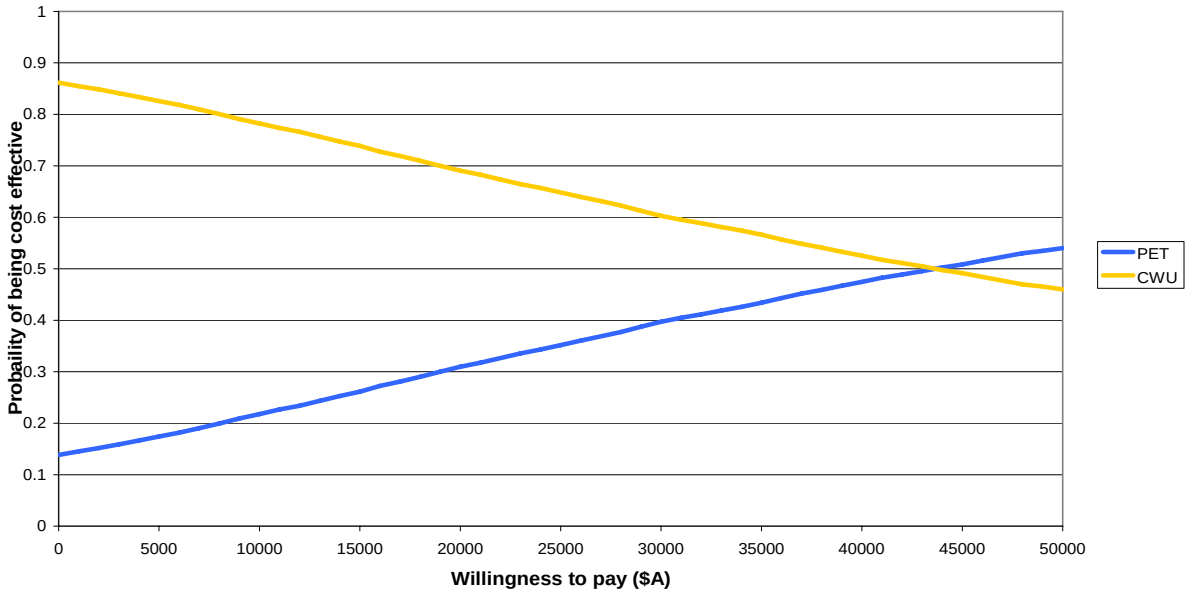
[48] Drummond et al, Methods for the Economic Evaluation of Health Care Programmes; Third edition. (Oxford, O.U.P, 2005), p. 265.
[49] Drummond et al, Methods for the Economic Evaluation of Health Care Programmes; Third edition. (Oxford, O.U.P, 2005), p. 267

Graph 3: The cost effectiveness acceptability curve for CT negative patients



The results for the CEAC in CT positive are shown in graph 4 below. The threshold needed for the probability that PET is 50% more of the time cost effective compared to the CWU strategy would be $A 43,000. However, given the sensitivity of the CT positive strategy results to changes in individual parameters much more certainty would be needed before it would be acceptable to recommend PET in CT positive patients as robustly cost effective result.

Graph 4: Cost effectiveness acceptability curve for CT positive patients



Discussion

The two most cost effective strategies, which also allowed histological confirmation of the NSCLC, were identified from the literature. The study here suggests that PET is the more cost effective than the CWU for both the CT negative and CT positive patients with ICERs of $A 14,580 per QALY and $A 52,039 per QALY respectively. The CT positive ICER is high, but there is no explicit threshold used in the Australian health care system for an acceptable ICER, although, it is generally implicitly assumed to be around $A 50,000 dollars per QALY. So whether this strategy would be used by a societal decision maker is questionable. However, due to the large amount of variability in the strategy's ICERs shown by the sensitivity analyses this throws the strategy's cost effectiveness seriously into doubt.

However, the sensitivity analyses show that for CT negative patients the results seem to be extremely robust. The only sensitivity analysis that saw the ICER decrease noticeably was when the rate of metastasis was decreased to 0.05 and then the ICER increased to $A 54,453 per QALY, otherwise it stayed within a range of $A 11,728 to $A 19,268 or it dominated the CWU strategy.

This study largely confirms the results of the previous studies but in an Australian context which has not been looked at before and it is thought that this is the first time that a probabilistic sensitivity analysis has been carried out on PET looking at CT positive and CT negative patients separately. Compared to the other studies there was more movement in the results when the individual parameters were changed especially for the CT positive patients. This no doubt reflects the substantial uncertainty over some of parameters in the model especially concerning the underlying distribution of disease. This study has provided more evidence suggesting that rate of metastasis is not the same for patients with different stages of NSCLC. Further work on the quality of life estimates and the cost of radiotherapy and chemotherapy in an Australian context would yield extra certainty in the reliability of these results.

Despite the overwhelming international evidence and the now this study showing that PET in CT negative patients is a cost effective and with greater uncertainty for CT positive patients these results should still be interpreted cautiously due to many of the assumptions used in the modelling. However, the recent introduction of a new generation of PET scanners and the new combination CT-PET scanners that not only ensure better T staging, but improvements in N and M staging. We should, therefore, start to see the cost effectiveness of PET improve even further as scanning times are reduced and the accuracy improves .[50]

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[50] Devaraj, A., G. J. Cook, et al. (2007). "PET/CT in non-small cell lung cancer staging-promises and problems." Clinical Radiology **62**(2): p.106

Appendices

Appendix 1 Estimating the cost of Chemotherapy

Estimation of the Cost of Chemotherapy for a course of Cisplatin - Vinobrine to treat NSCLC	
Cost per cycle	
Cisplatin	3 x $A 61.05 (PBS)
In patient attendances	1 x $A 650 (Rosenthal)
Out Patient attendances	3x A$ 303.8 Rosenthal
Cost Per Course	
Number of Cycles	3
Vinolbrine	$A 3601.44 (PBS)
Drug preparation	$A 24.2 (Estimation based on HTBS)
Side Effects	$A 1,100 (Estimation based on HTBS)
Cost per cycle	$A 1,744.6
Cost per course	$A 9,784.0

Appendix 2: Macro for the 10,000 patient simulations.

```
Sub simulation_trial()

' simulation_trial Macro

    Index = 0
    Do While Index < 10000
    Range("B5:I5").Select
    Selection.Copy
    Range("B6:I6").Select
    ActiveCell.Offset(Index, 0).Range("A1").Select
    Selection.PasteSpecial Paste:=xlPasteValues, Operation:=xlNone, SkipBlanks _
        :=False, Transpose:=False
        Index = Index + 1
        Loop
End Sub
```

Appendix 3: Summary of the studies found in the literature review

Study	Comparison	Patient group	Incremental analysis	Measure of effectiveness	Method	Effectiveness (per patient)	Cost (per patient)	Incremental cost effectiveness
NICE guidelines Surgery model (2005) UK	a) Patients go straight to thoracotomy b) Patients have a mediastinoscopy and then receive either radical radiotherapy (N2/N3) or Thoractomy (N0/1) c) Patients have a PET scan and then receive either active supportive care (M1+) OR Thoractomy (M0,N0/N1) OR Radical radiotherapy (M0, N2/N3)	Potential operable patients with normal sized lymph nodes on CT considered for surgery	Cost Utility	Quality adjusted life year (QALYs)	Decision Analysis	a) 2.846 QALYS b) 2.864 QALYS c) 2.883 QALYS	a) 6317.39 b) 7519.71 c) 6581.87	c) vs a) £7,199/QALY gained b) dominated by c)
NICE guidelines Radiotherapy model (2005) UK	a) Patients go straight to radical radiotherapy b) Patients have a PET scan and then receive either ASC (M1) or thoractomy (N0/1) or radical radiotherapy (n2/3)	Patients being considered for radical radiology (mainly enlarged nodes)	Cost Utility	Quality adjusted life year (QALYs)	Decision Analysis	b) vs a) 4.3 QALYs	b) vs a) 40,936	b) vs a) £9,489/QALY gained

HTBS Bradbury et al, (2002), Scotland	a) All to surgery b) Palliatation c) Mediastinoscopy d) Mediastinoscopy with PET after a negative mediastinoscopy. e) PET f) PET with mediastinoscopy	Potential Operable NSCLC	Cost Utility	Quality adjusted life year (QALYs)	Decision Analysis	a) 2.88 QALYS b) 1.46 QALYS c) 2.89 QALYS d) 2.76 QALYS e) 2.77 QALYS f) 2.76 QALYS g) 2.91 QALYS	a) 4,467 b) 6,105 c) 4,642 d) 5,137 e) 4,899 f) 5,124 g) 4, 854	c) vs a) £18,589/QALY gained g) vs c) £10,475/QALY gained b, d, e and f were all dominated by g.
Dietlein et al 2000. Germany	a) Conventional staging – CT and Mediastinoscopy b) Whole body FDG-PET in patients with negative CT c) Whole body FDG-PET in all patients – if positive PET then Mediastinoscopy d) Whole body FDG-PET in all patients – excluded form surgery if positive PET and Positive CT Whole body FDG-PET in all patients – excluded from surgery if positive PET	Potentially operable NSCLC	Cost effectiveness	Unnecessary Thoractomies	Decision Analysis	a) 3.30 LYs b) 3.32 LYs c) 3.33 LYs d) 3.39 LYs e) 3.36 LYs	a) 16, 890 b) 16,892 c) 17,712 d) 16, 279 e) 15, 839	b) vs a) €143/LY gained c) vs b) €36,6670/ LY gained.

Hayashi et al (2005) Japan	a) CT only (If negative surgery, If positive chemotheraphy) b) PET +CT (If negative thoractomy, if positive chemotheraphy) c) PET + CT (If PET positive then mediastinoscopy, if negative then surgery)	Potentially operable NSCLC free of M1	Cost utility	Quality adjusted Life Year (QALY)	Decision Analysis	a) 4.79 LYs/ 4.35 QALYs b) 5.33 LYs/ 4.93 QALYs c) 5.68 LYs/ 5.33 QALYS	n/a	c) vs a) $4,775/QALY c) vs b) $7,555/QALY
Nguyen et al (2005) Canada	a) CT (If positive then mediastinoscopy, if negative then surgery) b) CT + PET (Biopsy or mediastinoscopy to confirm PET results)	Potentially operable NSCLC	Cost effectiveness	LY gained	Decision Analysis	b) vs a) 0.27 LY	b) vs a) $1,268	b) vs a) $4,689/LY gained
Gambhir 1996, USA	a) CT – if positive then Mediastinoscopy b) CT and PET – if positive PET or positive CT then mediastinoscopy c) CT and PET – Mediastinoscopy if discordant	Potentially operable NSCLC	Cost-effectiveness	LY gained	Decision analysis	b) vs a) +3 days	b) vs a) - $1,154 c) vs a) - $2267	b) Dominate a) c) Saves additional costs $1,524

Scott 1998, USA	a) CT – if positive then mediastinoscopy b) PET after negative CT (mediastinoscopy after +ve PET or +ve CT) c) PET and CT (mediastinoscopy after +ve PET) d) PET and CT (mediastinoscopy after +ve CT or +ve PET or –ve CT)	Potentially operable NSCLC	Cost effectiveness	LY gained	Decision Analysis	b) vs a) 0.007 LY c) vs a) 0.009 LY d) vs a) 0.007 LY	b) vs a) $177 c) vs a) $638 d) vs a) $965	b) vs a) $25,286/ LY gained c) vs a) $70,889/ LY gained d) vs a) $37,857/ LY gained
Verboom et al (2003) The Netherlands	a) Conventional work up (CWU) Including CT, MRI, ultrasound, bone scan, invasive test brochoscopym mediastinoscopy and invasive surgery. b) CWU + 18 FDG- PET (whole body)	Medically operable NSCLC (n188)	Cost effectiveness	Number of futile thoractomies	Randomised Control trial	a) 39 futile thoractomies b) 19 futile thoractomies	a) € 9,573 b) € 8284	CWU + PET dominates
Viney et al (2002) Australia	a) CT scan (Thorax, upper abdomen and brain + X ray) b) CT scan + PET	Patients with stage I and II lung cancer potentially opeperable (n184)	Cost effectiveness	Number of futile thoractomies	Randomised control trial	b) vs a) 0.22 thoractomies avoided	b vs a) $A 2,655	b) vs a) $120,681/ thoractomy avoided
Kosuda et al (2002)	a) Whole body (WB) PET b) Conventional imaging + WB-PET	Potentially operable NSCLC	Cost effectiveness	Life expectancy	Decision analysis	b) vs a) gain in LE of minus 0.0246 years to 0.0136 years.	b) vs a) cost saving of $951 to $1,493 per patient	n/a

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