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ORIGINAL ARTICLE

Preoperative staging of lung cancer with PET/CT: cost-effectiveness evaluation alongside a randomized controlled trial

Rikke Søgaard · Barbara Malene B. Fischer · Jann Mortensen · Liselotte Højgaard · Ulrik Lassen

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Abstract
Purpose Positron emission tomography (PET)/CT has become a widely used technology for preoperative staging of non-small cell lung cancer (NSCLC). Two recent randomized controlled trials (RCT) have established its efficacy over conventional staging, but no studies have assessed its cost-effectiveness. The objective of this study was to assess the cost-effectiveness of PET/CT as an adjunct to conventional workup for preoperative staging of NSCLC.

Methods The study was conducted alongside an RCT in which 189 patients were allocated to conventional staging (n=91) or conventional staging + PET/CT (n=98) and followed for 1 year after which the numbers of futile thoracotomies in each group were monitored. A full health care sector perspective was adapted for costing resource use. The outcome parameter was defined as the number needed to treat (NNT)—here number of PET/CT scans needed—to avoid one futile thoracotomy. All monetary estimates were inflated to 2010 €.
Results The incremental cost of the PET/CT-based regimen was estimated at 3,927 € [95% confidence interval (CI) −3,331; 10,586] and the NNT at 4.92 (95% CI 3.00; 13.62). These resulted in an average incremental cost-effectiveness ratio of 19,314 €, which would be cost-effective at a probability of 0.90 given a willingness to pay of 50,000 € per avoided futile thoracotomy. When costs of comorbidity-related hospital services were excluded, the PET/CT regimen appeared dominant.
Conclusion Applying a full health care sector perspective, the cost-effectiveness of PET/CT for staging NSCLC seems to depend on the willingness to pay in order to avoid a futile thoracotomy. However, given that four outliers in terms of extreme comorbidity were all randomized to the PET/CT arm, there is uncertainty about the conclusion. When hospital costs of comorbidity were excluded, the PET/CT regimen was found to be both more accurate and cost saving.

Keywords PET/CT · Cost-effectiveness · Lung cancer staging · Randomized controlled trial

R. Søgaard
Centre for Health Service Research and Technology Assessment, University of Southern Denmark,
Copenhagen, Denmark
e-mail: ris@cast.sdu.dk

B. M. B. Fischer · J. Mortensen · L. Højgaard
Department for Clinical Physiology, Nuclear Medicine and PET, Rigshospitalet, Copenhagen University Hospital,
Copenhagen, Denmark

J. Mortensen
e-mail: jann.mortensen@rh.regionh.dk

J. Mortensen · L. Højgaard
Faculty of Health Sciences, University of Copenhagen,
Copenhagen, Denmark

U. Lassen
Department of Oncology, Rigshospitalet,
Copenhagen University Hospital,
Copenhagen, Denmark
e-mail: ulrik.lassen@rh.regionh.dk

B. M. B. Fischer (✉)
Department of Clinical Physiology and Nuclear Medicine,
Hvidovre Hospital,
Kettegård Allé 30,
2650 Hvidovre, Denmark
e-mail: bjerregaard.fischer@gmail.com

Introduction

New health care technologies continue to emerge and require most health care managements to prioritize scarce

resources. Reimbursement bodies thus increasingly require evidence not only for the clinical efficacy but also for economic efficiency in order to make rational decisions.

Combined positron emission tomography (PET)/CT is the second generation of PET technology and has rapidly gained terrain since the introduction in the early 2000s. It is a widely used technology for preoperative staging of non-small cell lung cancer (NSCLC).

The rationale for accurate preoperative staging is to choose the optimal treatment. The efficacy of adding PET/CT to conventional workup has recently been examined in two randomized controlled trials (RCT). Fischer et al. reported a relative risk reduction of 51% [95% confidence interval (CI) 32; 80] for having a futile thoracotomy when PET/CT was administered [1]. Maziak et al. reported a corresponding relative risk reduction of 51% (95% CI 33; 78) for being incorrectly understaged [2]. The cost-effectiveness of PET/CT however remains to be established.

The cost-effectiveness of stand-alone PET, on the other hand, has been examined in several decision models. These models provide an overall indication for the average costs per life year being below conventional threshold values, although most authors comment that much uncertainty is associated [3–12]. To the best of our knowledge, only one economic evaluation has been conducted alongside an RCT. Verboom et al. reported that from a Dutch restricted hospital perspective, the addition of PET to conventional staging was associated with a cost saving of 1,289 € (1999 price level) due to the cost of the scan being more than outweighed by the more precise selection of candidates for thoracotomy, which led to fewer procedures being performed in the PET group [13]. The risk reduction for a futile thoracotomy was estimated at 51% (95% CI 32; 80).

The objective of the present study was to assess the cost-effectiveness of PET/CT as an adjunct to conventional workup for preoperative staging of NSCLC from a health care sector perspective.

Materials and methods

Study design

The study was conducted alongside a multicentre RCT of 189 patients with newly diagnosed or highly suspected NSCLC who were allocated to conventional staging or conventional staging with the addition of PET/CT. Patients were followed until death or for at least 1 year to record the number of futile thoracotomies. The study methodology has been reported in detail elsewhere, but a summary is given here [1].

Patients were eligible if they were 18–80 years of age and considered to have operable disease after conventional staging based on medical history, physical examination, blood test, contrast-enhanced CT and/or bronchoscopy. Exclusion criteria were type 1 diabetes, another malignant condition, confirmed distant metastases, known claustrophobia and a lung function with an estimated forced expiratory volume in 1 s of less than 30% of that predicted after surgery.

The intervention encompassed further invasive procedures such as mediastinoscopy and endoscopic or endobronchial ultrasonography with (PET/CT group) or without (conventional staging group) the addition of PET/CT. Validation of all positive findings on PET/CT with possible implications for the patient's possibility to receive primary surgery was sought either by biopsy or alternative imaging method, e.g. magnetic resonance imaging (MRI) or ultrasound. Positive fluorodeoxyglucose (FDG) uptake in the mediastinum was validated by mediastinoscopy and/or endoscopic ultrasound with fine-needle aspiration (EUS-FNA).

Patients in stages I–IIIA (without mediastinal lymph node involvement) were considered to be operable in accordance with the TNM system [14]. The first patient was included in January 2002 and the last in February 2007.

Outcome parameter

The primary outcome was defined as the number needed to treat (NNT) in terms of PET/CT scans to avoid a futile thoracotomy, i.e. the reciprocal of the absolute risk reduction (ARR) for a futile thoracotomy obtained by using PET/CT. The ARR and the NNT were defined as:

$$\mathrm{ARR} = \pi_{\mathrm{C}} - \pi_{\mathrm{P}} \tag{1}$$

$$\mathrm{NNT} = 1/\mathrm{ARR} \tag{2}$$

where π_{P} denotes the risk for a futile thoracotomy in the PET/CT group and π_{C} denotes the risk in the conventional staging group. The CI for the ARR was calculated using Pearson's chi-square method. The CI for the NNT was accordingly defined as reciprocals of the values defining the CI for the ARR, only in reversed order [15].

A thoracotomy was defined as futile for any one of the following reasons: benign lung lesion, pathologically proven mediastinal lymph node involvement [stage IIIA (N2)], stage IIIB or IV disease, inoperable T3 or T4 disease, or recurrent disease or death from any cause within 1 year after randomization.

Cost parameter

A health care sector perspective including all types of primary care, prescription medication and hospital services was adapted. No attempts were made to exclude resource

use not related to NSCLC (comorbidity-related resource use) due to the fact that it is extremely difficult to distinguish in a reliable manner. The primary cost parameter thus included all health care service utilization occurring from the point in time of randomization to 1-year follow-up. For descriptive purposes only a crude distinction was made between cancer-related and comorbidity-related service utilization based on the International Classification of Diseases (ICD, version 10). This was possible because the Danish National Patient Registry, which includes an ICD code for every contact with the hospital sector, was used to obtain information on health care service utilization. Diagnosis codes C00 to D48 were used to define cancer-related contacts versus all other contacts.

Due to a coding error of two patients' central person number used to extract register data, the service utilizations of one patient from each of the randomization groups were missing. The economic analysis was therefore limited to 187 patients.

Resource use was considered to reflect true opportunity costs using the tariffs of collective agreements between practitioners' associations and the public health insurance for primary care, the market prices of prescription medication and the diagnosis-related grouping (DRG) case mix system for hospital services. Since DRG tariffs were available from 2005 and onwards, only the resource use of earlier years was valued using average unit costs from 2005 to 2010. Separate averages were calculated for each of the two randomization groups.

All costs were inflated to price year 2010 using the consumer price index and reported in euros (1 €=7.5 Danish krone).

Cost-effectiveness analysis

Cost-effectiveness analysis is defined by comparing both costs and consequences of two or more alternatives to provide information on whether a new (or existing) technology compares with alternative choices in terms of the associated cost per health output. The resulting parameter is a so-called incremental cost-effectiveness ratio (ICER), which usually expresses the additional cost per health gain that is associated with accepting the new technology. In the present context, the ICER was defined as the cost per avoided futile thoracotomy, which was calculated as the difference between the costs of conventional staging (C_c) and PET/CT (C_P) multiplied by the NNT from Eq. 2 to express avoided futile thoracotomies in a meaningful unit:

$$\mathrm{ICER} = (C_P - C_C)^{*}\mathrm{NNT} \quad (3)$$

Given that intervention costs and their differences were not normally distributed either on the original scale or when transformed into for example the logarithmic scale, a non-parametric technique was applied to describe the precision of means. Non-parametric bootstrapping is a standard technique, which generates a large number of replicates of sample estimates, which are then used to define a CI with the usual interpretation. In consensus with general recommendations for the present type of data, accelerated bootstrapping with bias correction was specified to estimate CI for cost differences and to generate 1,000 bootstrap estimates of C_P, C_C, π_P and π_C for the estimation of the precision of the ICER [16, 17].

For the ICER to be useful, a decision rule on when to accept a new technology is required. This is often expressed as decision-makers' willingness to pay (WTP) for an extra effect unit, for example, per avoided thoracotomy. There is no true value for WTP and it will vary from setting to setting depending on the preferences of the population and/or decision-makers [18]. For that reason, results of cost-effectiveness analysis are often summarized in a cost-effectiveness acceptability curve, illustrating the probability for the new technology being cost-effective as a function of hypothetical values of WTP (Fig. 1). In the present context, the cost-effectiveness acceptability curve illustrates the probability for PET/CT being cost-effective over conventional staging as a function of WTP per avoided futile thoracotomy [19, 20].

Sensitivity analysis, examining the impact of alternative specifications of key parameters on the ICER, was conducted by repeating the bootstrap procedure and summarizing the results in cost-effectiveness acceptability curves.

Results

Baseline and compliance

Patients were randomly assigned to conventional staging (n=91) or conventional staging plus PET/CT (n=98). The

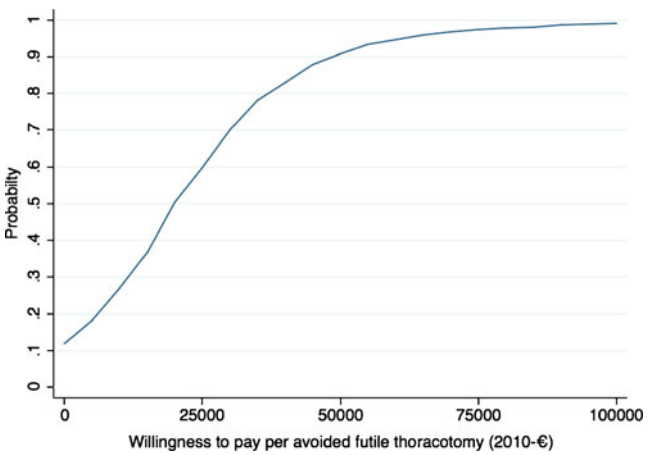

Fig. 1 Cost-effectiveness acceptability curve for PET/CT over conventional staging (n=187)

baseline characteristics of the sample are shown in Table 1. Fourteen patients in the PET/CT group did not undergo PET/CT because of an unacceptably long waiting time for a scan or technical problems requiring a new appointment.

Futile thoracotomies avoided

After staging, 37 patients in the PET/CT group and 18 patients in the conventional staging group were considered inoperable and thus not referred for thoracotomy. In addition, one patient in the PET/CT group declined to have surgery. The remaining 60 and 73 patients, respectively, underwent thoracotomy after which 21 in the PET/CT group and 38 in the conventional staging group were found to be futile.

It was estimated that five patients should be provided PET/CT on top of conventional staging to avoid one futile thoracotomy. Table 2 shows the results of staging.

Cost-effectiveness

No significant differences were observed in resource utilization between groups. Nor were any cost differences observed for primary care, prescription medication or cancer-related hospital service utilization. In spite of this an unexpected difference of the PET/CT regimen being significantly more costly in comorbidity-related expenditures was observed. This difference carried over to the overall incremental cost of the PET/CT regimen, which was estimated at 3,927 € (Table 3).

The more costly comorbidity in the PET/CT group was found to be due to a few extreme observations as illustrated in Fig. 2. Four patients in the PET/CT group had a resource use of more than 50,000 € with the most extreme case leading to a cost of 131,542 € (one patient was admitted 42 days in total due to NSCLC and heart surgery for *aortic stenosis*; one patient was admitted 74 days in total due to NSCLC, *epilepsy* and *thryroid cancer*; one patient was admitted 56 days due to NSCLC, *thyroid cancer*, *peripheral vertigo* and *cystitis*; and one patient was admitted 125 days due to NSCLC and nonspecific *respiratory insufficiency*).

Given the extreme observations, the ICER could be estimated at an average of 19,314 € per avoided futile thoracotomy. Figure 1 illustrates the probability of PET/CT being cost-effective for a range of WTP threshold values. For a hypothetical WTP of 50,000 € the probability for PET/CT being cost-effective over conventional staging would be 0.90. If comorbidity-related hospital costs are disregarded, the incremental cost of PET/CT would transform into an average cost saving of 899 € per patient or 4,495 € per avoided futile thoracotomy. The strategy would then dominate conventional staging, meaning that for every futile thoracotomy avoided the health care sector saves money. This is true for any value of WTP.

Table 1 Baseline characteristics [1]

Parameter	Conventional staging (n=91)	PET/CT (n=98)	p value
Age (mean years)	64	63	0.22
Female sex (n)	42	45	0.97
Pre-randomization TNM stage (n)			
IA	9	13	
IB	13	17	
IIA	0	0	
IIB	7	5	
IIIA	28	26	
IIIB	32	32	
IV	2	5	0.77

TNM stage refers to the international classification by Mountain et al. [14]

Table 2 Results of staging and the NNT to avoid one futile thoracotomy [1]

Outcome	Conventional staging (n=91)	PET/CT (n=98)
Thoracotomy not indicated (n)	18	37
Declining to have thoracotomy (n)	0	1
Thoracotomies performed (n)	73	60
Futile	38	21
Non-futile	35	39
Risk of futile thoracotomy (95% CI)	0.42 (0.32; 0.53)	0.21 (0.14; 0.31)
Risk reduction futile thoracotomy (95% CI)	0.20 (0.07; 0.33)	
NNT to avoid one futile thoracotomy (95% CI)	4.92 (3.00; 13.62)	

Sensitivity analysis

The sensitivity of results to the tariff of PET/CT was examined by estimating the ICER for an added/reduced cost in the PET/CT group of 1,000 €. The resulting probabilities for cost-effectiveness fell to 0.88 or increased to 0.94 for a hypothetical WTP of 50,000 €. The impact of per protocol analysis was similarly examined and resulted in a probability for cost-effectiveness of 0.99.

The performance of PET/CT may vary across settings or even over time. While methodological uncertainties are the conventional focus of sensitivity analysis, the present analysis included an assessment of the impact of reduced/improved accuracy of PET/CT relative to the accuracy of conventional staging. The data were manipulated to simulate that five extra/less patients underwent a futile

Table 3 Resource use and costs (2010 €)

	Conventional staging (n=90)		PET/CT (n=97)		Cost difference (95% CI)
	Resource use	Total cost	Resource use	Total cost	
Primary care services					
General practitioner	21	223	19	202	−21 (−93; 26)
Other medical specialists	3	77	2	59	−18 (−62; 22)
Physiotherapy	3	33	2	17	−15 (−45; 4)
Dentistry	3	37	3	39	2 (−10; 18)
Other	6	13	7	21	7 (−3; 19)
Total	36	384	33	339	−45 (−126; 30)
Prescription medication	NA	515	NA	484	−31 (−179; 142)
Cancer-related hospital services[a]					
Outpatient visits	19	8,958	22	10,431	1,473 (−1,563; 4,366)
Inpatient admissions	3	19,034	2	16,738	−2,296 (−7,840; 1,616)
Bed days	18	NA	14	NA	NA
Total	22	27,992	25	27,168	−824 (−8,567; 4,182)
Comorbidity-related hospital services[a]					
Outpatient visits	6	2,774	6	4,874	2,101 (976; 3,313)
Inpatient admissions	2	10,077	2	12,803	2,725 (291; 7,255)
Bed days	9	NA	9	NA	NA
Total	9	12,851	8	17,677	4,826 (1,701; 9,562)
Grand total	NA	41,742	NA	45,668	3,927 (−3,331; 10,586)
Grand total ex comorbidity-related hospital costs[a]	NA	28,891	NA	27,992	−899 (−7,625; 4,682)

CI were estimated using accelerated bias-corrected non-parametric bootstrapping

NA not applicable

[a] Contacts with a primary diagnosis between C00 and D48 according to the ICD (version 10) were classified as cancer-related and the remainder as comorbidity

thoracotomy in the PET/CT group. These scenarios resulted in probabilities for cost-effectiveness of 0.78 and 0.97, again for a threshold value of WTP at 50,000 €. Figure 3 summarizes the results of the sensitivity analysis.

Discussion

This study investigated the cost-effectiveness of adding PET/CT to conventional staging. As expected, PET/CT as

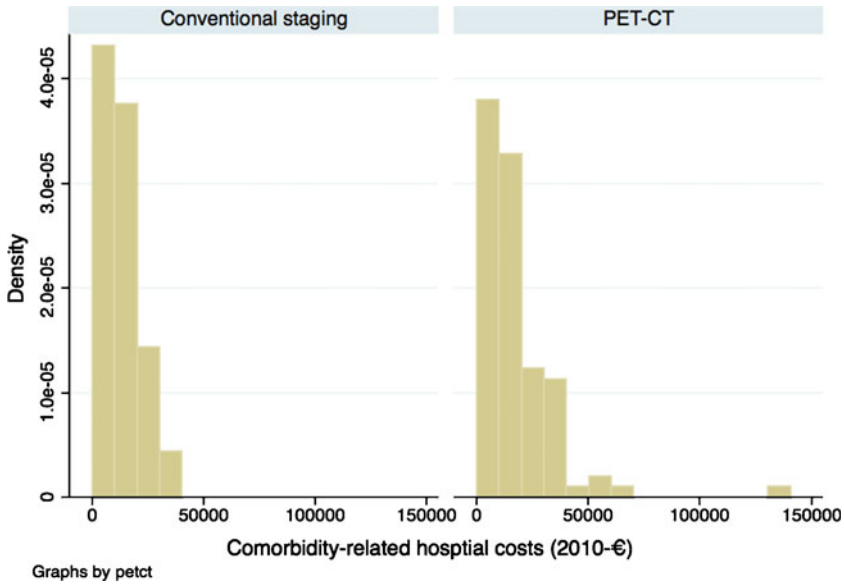

Fig. 2 Distribution of comorbidity-related hospital costs (n=187)

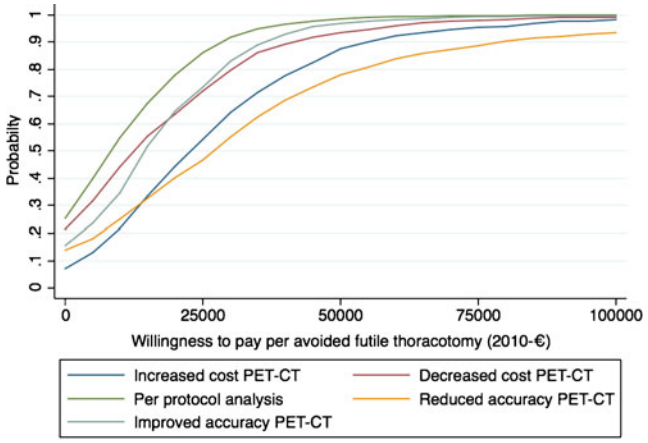

Fig. 3 Cost-effectiveness acceptability curves for alternative scenarios (n=187)

an adjunct was associated with fewer futile thoracotomies and, on average, cost savings on primary care, prescription medication and cancer-related hospital costs. Unexpectedly however four extreme cases in terms of comorbidity-related hospital costs were observed in the PET/CT group and that led the total cost to accumulate to 3,927 € rather than a cost saving. Excluding comorbidity-related hospital costs from the analysis would lead the PET/CT strategy to dominate the conventional staging with average cost savings of 899 € per patient.

The unexpected finding of PET/CT leading to more costly comorbidity in the secondary health care sector seems implausible. For that reason we took advantage of detailed register data to validate the observations and to identify exactly what caused the high costs. It appeared that repeated and long-lasting hospital admissions for common comorbidities explained the high costs and it was accordingly concluded that the extreme observations in the PET/CT arm were due to random rather than systematic variation (i.e. the randomization had failed to distribute these evenly between randomization groups). We could have chosen to exclude comorbidity-related costs from the analysis, which would have led to less variation in the cost parameter and a significant and clear-cut conclusion. But, given that it is very difficult to disentangle completely what is cancer-related activity and what is comorbidity-related activity, we chose the conservative approach of including it all after which the randomized design would normally lead to irrelevant activity cancelling out (if extreme observations are equally distributed between randomization groups). Although this did not happen, we chose to maintain the broad perspective and leave it for the reader to judge our results. Not least because in health economics all activity that deviates between comparators are by definition relevant to the decision-maker [21]. Finally it should be mentioned that the validity of the National Patient Registry used for obtaining information on resource use might not be perfect; as the system is continuously revised, studies of its validity are generally outdated before they are reported and no studies exist for the specific entity of lung cancer.

To the best of our knowledge this is the first study to have conducted an economic evaluation of PET/CT alongside an RCT. There is one study though, which has been reported for stand-alone PET. Verboom et al. conducted a cost-effectiveness evaluation alongside the Dutch PLUS trial, which was designed almost identical to the present study [13]. The authors reported an NNT of 5 and a cost saving of 1,289 €, leading to a conclusion that the PET-based strategy is dominant. Our results for the PET/CT-based regimen, when restricting the analysis to a comparable costing perspective, are almost identical to the results of Verboom et al.

Basing cost-effectiveness evaluation on the NNT to prevent a bad outcome has been demonstrated to be inappropriate in a number of circumstances. These relate to the nature of the bad event because unless the prevention effect manifests immediately the NNT may vary over time. It seems reasonable to consider (an avoided) thoracotomy to be an almost immediate effect of staging, although the definition of whether it is futile or not involves an argument of no recurrence within 1 year postoperatively. This argument however has to do with retrospective classification only and does not alter the fact that the thoracotomy was an immediate one-off effect. In such special cases, as in the present study and the PLUS study, the NNT may serve as a simple measure, which can be shown to produce an unbiased estimate of the ratio of costs to effects [22].

Including comorbidity-related costs, we found that the cost-effectiveness of PET/CT for staging NSCLC depends on the WTP in order to avoid a futile thoracotomy for which there is no true threshold value. A futile thoracotomy can be futile either because it is performed in patients with a benign lung lesion or because it is performed in patients with non-resectable, end-stage cancer. In any case it poses an immense physical and psychological hazard, sometimes with a fatal outcome, to a vulnerable patient group. There are examples of other cost-effectiveness analyses generating an incremental cost for an avoided bad event but few relate to a comparable population and few concern events with as severe consequences as futile thoracotomies.

In 2002, Wallace et al. compared different staging strategies for patients with carcinoma of the oesophagus, finding that a combination of PET and EUS-FNA resulted in fewer oesophageal resections in patients with distant metastases than the cheaper strategy of CT and EUS-FNA [23]. The PET-based strategy was considered to be cost-effective based on an incremental cost-effectiveness ratio of US $60,544 per quality-adjusted life year (QALY). More recently, Hövels et al. compared the cost-effectiveness of

MR lymphography to pelvic lymph node dissection (PLND) in staging patients with prostate cancer [24]. MR was found to dominate PLND (a cost saving of US $126 per QALY). The latter study did not include cost associated with comorbidity. We have not been able to identify other studies basing ICER on NNT with regard to cancer staging; however, the method is well known from other medical fields. In a study assessing the cost-effectiveness of using perioperative beta-blockers to prevent postoperative cardiovascular complications, the authors estimated the incremental cost to be £1,254 (based on the NHS reference costs for 2004) per complication prevented [25]. A North American study assessed the cost-effectiveness of recombinant human erythropoietin to avoid one transfusion-related adverse event in critically ill patients. The authors estimated the incremental cost at US $4.7 million (expressed in 2004 dollars) to avoid one transfusion-related adverse event and US $71.8 million (expressed in 2004 dollars) to avoid a likely fatal transfusion-related adverse event. It was concluded that routine use of erythropoietin was not likely to be cost-effective [26].

A cost-effectiveness analysis compares alternative interventions using costs and a common effectiveness measure (here numbers of futile thoracotomies). It does not, as in a cost-utility analysis, adjust for disutility or quality of life [27]. Data regarding patient preferences and quality of life were not collected in the present study, making a cost-effectiveness analysis the most rational choice. Thus, the usual disclaimer for conducting a cost-effectiveness rather than a cost-utility evaluation applies: Unless the effect difference between interventions is truly unidimensional results are not appropriate for decision-making [21]. In the present study intervention was unidimensional, as the PET/CT procedure was the only difference between the comparators. Further, given that PET/CT is a noninvasive test perceived to support diagnostic accuracy, it seems sensible to assume that no disutility was associated with undergoing it. There was however some additional waiting time associated with the PET/CT, which could have affected patient preferences.

Another issue that would make the cost-effectiveness evaluation fail in providing a rational foundation for decision-making is if the two comparators do not represent all relevant or, at least, a first- and a second-best alternative. The decision for some decision-makers might be whether to upgrade from PET to combined PET/CT rather than whether to introduce a PET technology. It has also been proposed that the introduction of the PET/CT makes the initial CT redundant, which would lead the PET/CT regimen to be even more cost saving [28]. On the other hand, technologies such as endoscopic and endobronchial ultrasound are gaining terrain as more precise and less invasive substitutes for mediastinoscopy, which would make the effectiveness of the control arm more appealing [29].

Conclusion

The present study provides a trial-based estimate for the incremental cost per avoided futile thoracotomy of using PET/CT as an adjunct to conventional staging in NSCLC: an average incremental cost-effectiveness ratio of 19,314 €, which would be cost-effective at a probability of 0.90 given a WTP of 50,000 € per avoided futile thoracotomy. However, extreme costs of comorbidity-related hospital resource use were found to be unevenly distributed in the randomization groups. When hospital costs of comorbidity were excluded from analysis, the PET/CT regimen appeared dominant, i.e. less costly and more effective, saving an estimated 899 € per patient and resulting in fewer futile thoracotomies. These results provide a step on the road towards informing rational decision-making, but future research using a generic outcome measure and possibly a wider range of comparators is recommended.

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Conflicts of interest None.

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