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The Optimality of Different Strategies for Supplemental Staging of Non–Small-Cell Lung Cancer: A Health Economic Decision Analysis

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ABSTRACT

Objectives: To assess the expected costs and outcomes of alternative strategies for staging of lung cancer to inform a Danish National Health Service perspective about the most cost-effective strategy. **Methods:** A decision tree was specified for patients with a confirmed diagnosis of non–small-cell lung cancer. Six strategies were defined from relevant combinations of mediastinoscopy, endoscopic or endobronchial ultrasound with needle aspiration, and combined positron emission tomography-computed tomography with F18-fluorodeoxyglucose. Patients without distant metastases and central or contralateral nodal involvement (N2/N3) were considered to be candidates for surgical resection. Diagnostic accuracies were informed from literature reviews, prevalence and survival from the Danish Lung Cancer Registry, and procedure costs from national average tariffs. All parameters were specified probabilistically to determine the joint decision uncertainty. The cost-effectiveness analysis was based on the net present value of expected costs and life years accrued over a time horizon of 5 years. **Results:** At threshold values of around €30,000 for cost-effectiveness, it was found to be cost-effective to send all patients to positron emission tomography-computed tomography with confirmation of positive findings on nodal involvement by endobronchial ultrasound. This result appeared robust in deterministic sensitivity analysis. The expected value of perfect information was estimated at €52 per patient, indicating that further research might be worthwhile. **Conclusions:** The policy recommendation is to make combined positron emission tomography-computed tomography and endobronchial ultrasound available for supplemental staging of patients with non–small-cell lung cancer. The effects of alternative strategies on patients' quality of life, however, should be examined in future studies.

Keywords: cost-effectiveness evaluation, decision analysis, diagnostic radiology, health economic modeling, lung cancer, probabilistic sensitivity analysis.

Introduction

Thoracotomy is the major potentially curative treatment in non–small-cell lung cancer, although it is associated with a mortality risk per se. Accurate staging of the disease to select candidates with a reasonable chance of being cured is imperative to increase the overall survival of this patient population.

The disease stage assessment is usually based on the Mountain classification, which categorizes patients into seven stages according to tumor size and location (T), nodal involvement (N), and the presence of distant metastases (M), for which reason the resulting categorization is also referred to as the TNM status [1]. The conventional modalities for staging include mediastinoscopy, computed tomography (CT), and positron emission tomography (PET) with F18-fluorodeoxyglucose. Each technology demonstrates superior diagnostic accuracy in one or more of the dimensions in the Mountain classification.

In recent years, alternatives or supplements to the conventional staging technologies have emerged and become part of clinical practice in some centers due to their superior accuracy, less disutility for the patient, and/or lower average costs. These alternatives include endoscopic ultrasound with fine needle aspiration (EUS-FNA), endobronchial ultrasound with transbronchial needle aspiration (EBUS-TBNA), and combined PET-CT with F18-fluorodeoxyglucose. These modalities are described and implemented in the European clinical guidelines, although a certain degree of flexibility is expressed in terms of the exact type of test that is appropriate, such as whether mediastinoscopy, EUS-FNA, or EBUS-TBNA should be used to confirm PET findings [2].

The cost-effectiveness of the more recent modalities has not been analyzed in a decision model. Sporadic evidence has begun to emerge in the form of trial-based cost-effectiveness evaluations based on intermediate outcomes, such as the number of futile thoracotomies [3,4]. In a decision analytic context, this

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literature, however, suffers from important limitations, many of which are related to the fast pace of technology advancements and methodological issues. First, there appear to be no studies that include all relevant comparators. Second, the diagnostic accuracies observed in a single trial may be problematic to generalize as technologies mature and disseminate to settings different from the early adaptors'. Third, the use of intermediate outcome measures and/or the analysis of survival in small samples by using only a limited time horizon render results inconclusive. These controversies essentially disqualify the early trial-based cost-effectiveness studies in a health policy decision-making context.

The objective of this study was to model expected costs and outcomes of alternative strategies for the staging and treatment of lung cancer to inform a Danish National Health Service perspective about the most cost-effective strategy.

Methods

A probabilistic decision tree model was developed [5]. Full details of the proposed model and the associated assumptions are given in a technical report [6], but a summary is provided here.

Study Population

The model was defined for a patient with a histologically- or cytologically verified diagnosis of non–small-cell lung cancer. This specification applies when patients are not referred to a specialized diagnostic center before they have a confirmed diagnosis of lung cancer, typically based on clinical anamnesis, chest X-ray, bronchoscopy and/or transthoracic biopsy, and CT, and was considered fit for surgery. The typical patient is 65 years old (man or woman).

Criteria for Operability

Patients who during staging workup were found without distant metastases and without involvement of the central or contralateral lymph nodes (N2/N3) were considered to be candidates for treatment with curative intent, which mainly entails surgical resection.

Choice of Comparators

Specialized staging may use one or more of the following modalities: mediastinoscopy, EUS-FNA, EBUS-TBNA, and combined PET-CT with F18-fluorodeoxyglucose. The three former modalities are relatively accurate in assessing nodal involvement (N status) but cannot assess the presence/absence of distant metastases (M status). The latter modality is able to assess both dimensions, but suffers from poorer accuracy in the assessment of N status, for which reason positive findings should be confirmed [2]. Altogether, these comparators create four relevant strategies. Two additional strategies were defined to address more speculative hypotheses: 1) the initial CT might become redundant when PET-CT is applied and 2) confirming all nodal findings (not just the positive findings) after PET-CT might be worthwhile for the prevention of futile thoracotomies. The strategies were defined as follows:

A. Patients with distant metastases at the initial CT are referred directly to nonsurgical treatment. All others are referred to mediastinoscopy. Patients without nodal involvement are referred to thoracotomy, and patients with nodal involvement are referred to nonsurgical management.
B. Identical to strategy A except that mediastinoscopy is replaced by EUS-FNA.
C. Identical to strategy A except that mediastinoscopy is replaced by EBUS-TBNA.
D. Patients with distant metastases at the initial CT are referred directly to nonsurgical treatment. All others are referred to PET-CT. In the case of upstaging due to distant metastases, the patient is referred to nonsurgical management. If not, the PET-CT results on nodal involvement determine the pathway; patients without nodal involvement are referred directly to thoracotomy, and patients with nodal involvement are referred to a conclusive EBUS-TBNA.
E. Identical to strategy D except that the initial CT is excluded.
F. Identical to strategy D except that all patients (not just those testing positive) have their PET-CT results on nodal status confirmed.

As strategies A to C all include a primary CT scan and no PET-CT scan, they are intended to contrast the performance of different modalities for mediastinal staging. Based on the comparative outcomes of these strategies (which will appear from the following analysis) plus the fact that it is widely used in clinical practice, the EBUS-TBNA was chosen as the modality for mediastinal staging in the three latter strategies. Holding this constant, strategies D to F thus contrast different ways of implementing PET-CT.

Model Structure and Assumptions

The proposed model is illustrated in Figure 1 and imposes a number of structural assumptions. First, it assumes that the N-status results of radiology-based tests are disregarded once an invasive test has been performed. This assumption has the largest impact on PET-based strategies, where diagnostic accuracy might be marginally underestimated. Second, it assumes that there is no morbidity or mortality risk associated with the tests, which could favor invasive modalities. Third, it assumes that relapse does not occur after successful thoracotomy, which could lead to an underestimation of costs for the thoracotomy arms (whereas survival is inclusive of relapse). Fourth, the model structure does not include the costs of any ad hoc tests. Most centers will confirm, for example, M1 findings on the initial CT or PET-CT by using magnetic resonance or ultrasonography before excluding the patient from potentially curative treatment. This assumption could bias the results against strategies A, B, and C, where fewer tests are included in the strategies and more supplemental tests are therefore likely to be appended. Finally, and perhaps most importantly, the choice of a decision tree model implies that the passing of time is not explicit, which may affect results in an uncertain direction depending on differences, apart from survival and costs of understaging, between strategies over the course of the defined time period.

Model Population

Tables 1 and 2 present the parameter estimates used to inform the decision model, the sources of the parameter estimates, and how they were specified for the probabilistic sensitivity analysis. These are commented on in the following sections.

True disease distribution

It was assumed that the prevalence of N- and M-positives in the Danish Lung Cancer Registry would represent true disease distributions. All patients with a valid TNM status who were diagnosed between 2003 and 2009 were included in the estimates ($n = 16{,}874$) [17]. As prevalence follows a continuous distribution bounded by 0 and 1, it was specified according to the beta distribution for the probabilistic analysis.