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EBUS-TBNA versus mediastinoscopy for mediastinal staging of lung cancer: a cost-minimization analysis

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ABSTRACT

Objective: To assess cost differences between EBUS-TBNA and mediastinoscopy for mediastinal staging of non-small cell lung cancer (NSCLC). **Methods:** This was an economic evaluation study with a cost-minimization analysis. We used a decision analysis software program to construct a decision tree model to compare the downstream costs of mediastinoscopy, EBUS-TBNA without surgical confirmation of negative results, and EBUS-TBNA with surgical confirmation of negative results for the mediastinal staging of NSCLC. The study was conducted from the perspective of the Brazilian public health care system. Only direct medical costs were considered. Results are shown in Brazilian currency (Real; R$) and in International Dollars (I$). **Results:** For the base-case analysis, initial evaluation with EBUS-TBNA without surgical confirmation of negative results was found to be the least costly strategy (R$1,254/I$2,961) in comparison with mediastinoscopy (R$3,255/I$7,688) and EBUS-TBNA with surgical confirmation of negative results (R$3,688/I$8,711). The sensitivity analyses also showed that EBUS-TBNA without surgical confirmation of negative results was the least costly strategy. Mediastinoscopy would become the least costly strategy if the costs for hospital supplies for EBUS-TBNA increased by more than 300%. EBUS-TBNA with surgical confirmation of negative results, in comparison with mediastinoscopy, will be less costly if the prevalence of mediastinal lymph node metastasis is ≥ 38%. **Conclusions:** This study has demonstrated that EBUS-TBNA is the least costly strategy for invasive mediastinal staging of NSCLC in the Brazilian public health care system.

Keywords: Lung Neoplasms; Neoplasm Staging; Costs and cost analysis; Bronchoscopy; Mediastinoscopy.

INTRODUCTION

Lung cancer is a major health problem, being the second most frequent cause of cancer in the world population and the leading cause of cancer mortality, accounting for about 1,800,000 (or 18% of) annual deaths from malignant neoplasms worldwide.[1] Mediastinal staging has a major role in the definition of the therapeutic strategy in early-stage, locally-advanced non-small cell lung cancer (NSCLC), since upfront surgery is the mainstay of treatment in stages I and II, and induction or definitive chemotherapy and radiochemotherapy are indicated in the treatment of stage III tumors.[2] Although chest CT and PET-CT are the most commonly used noninvasive mediastinal staging modalities of the mediastinum, they cannot always reliably differentiate between benign and malignant mediastinal nodes, because enlarged or PET-CT-positive lymph nodes may also be inflammatory, whereas normal-sized or PET-CT-negative lymph nodes may be malignant. Current guidelines recommend invasive staging in patients with clinical N1 to N3 disease, centrally located tumors, or those larger than 3 cm.[3,4] Mediastinoscopy and video-assisted mediastinoscopy have been considered the gold standard technique for invasive mediastinal staging of lung cancer for a long time. However, the emergence of EBUS-TBNA,[1] a minimally invasive procedure capable of providing valuable information for primary tumor diagnosis and mediastinal staging,[2-4] significantly changed the approach to staging lung cancer, becoming the method of choice for invasive mediastinal evaluation of lung cancer in developed countries.[5-10] In fact, two recent systematic reviews and meta-analyses of randomized controlled trials and observational studies comparing EBUS with mediastinoscopy/video-assisted mediastinoscopy suggested that the two procedures for mediastinal staging of lung cancer are equivalent, with a lower complication rate favoring the endosonographic approach.[11,12]

As a new method being incorporated by different health care systems, the use of EBUS may lead to

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a shift in clinical outcomes and costs. Our group, in a recent systematic review,[13] compared the economic evaluation regarding the use of EBUS vs. mediastinoscopy for mediastinal staging of lung cancer and found that the costs of strategies using EBUS-TBNA were lower than those using mediastinoscopy. Two of the best quality scored studies demonstrated that the mediastinoscopy strategy is less cost-effective than the EBUS-TBNA strategy.[14,15] We found no studies from Latin America or Africa that fulfilled the inclusion criteria in that systematic review,[13] reinforcing the importance of conducting economic evaluation studies in these settings, especially because of the unfavorable economic conditions and the differentiated prevalence of infectious diseases, such as tuberculosis, which can alter mediastinal findings in patients with suspected lung cancer.[7,16] In Brazil, the most populous country in Latin America, lung cancer is also the main cause of cancer mortality.[17] The EBUS-TBNA technique, although used in referral centers for the diagnosis of lung cancer, has not been incorporated in the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System), hindering access to the procedure. This economic evaluation aims to assess cost differences between EBUS-TBNA and mediastinoscopy for mediastinal staging of lung cancer from the perspective of the Brazilian public health care system, that is, the SUS.

METHODS

A cost-minimization analysis model was built. We chose this model since the effectiveness of EBUS-TBNA and mediastinoscopy for mediastinal staging of lung cancer, based on the results of systematic reviews and meta-analyses comparing both techniques, is similar.[11,12] Additionally, the long-term outcomes (measures of effectiveness) of all patients with stage III disease are similar regardless of how invasive the mediastinal staging technique is. Decision analysis software (TreeAge Pro 2020; TreeAge Software, Williamstown, MA, USA) was used in order to construct a decision tree model to compare the downstream costs of mediastinoscopy, EBUS-TBNA without surgical confirmation of negative results, and EBUS-TBNA with surgical confirmation of negative results for the mediastinal staging of NSCLC (Figure 1).

Patient model

The model comprised of a hypothetical population with a diagnosis or diagnostic suspicion of NSCLC after chest CT and/or PET-CT and indication for invasive mediastinal lymph node investigation according to the American College of Chest Physicians guidelines for staging NSCLC.[3]

Assumptions

The model is based on the following assumptions:

1. Patients referred for EBUS or mediastinoscopy are clinically similar.
2. All patients have clinical conditions to undergo surgical resection.
3. Patients with N2/N3 mediastinal disease identified by EBUS or mediastinoscopy will undergo multimodal treatment.
4. Patients without N2/N3 mediastinal disease will undergo surgical resection (consider lobectomy and lymphadenectomy as optimal procedures).
5. The specificity of invasive methods (EBUS and mediastinoscopy) is 100%.

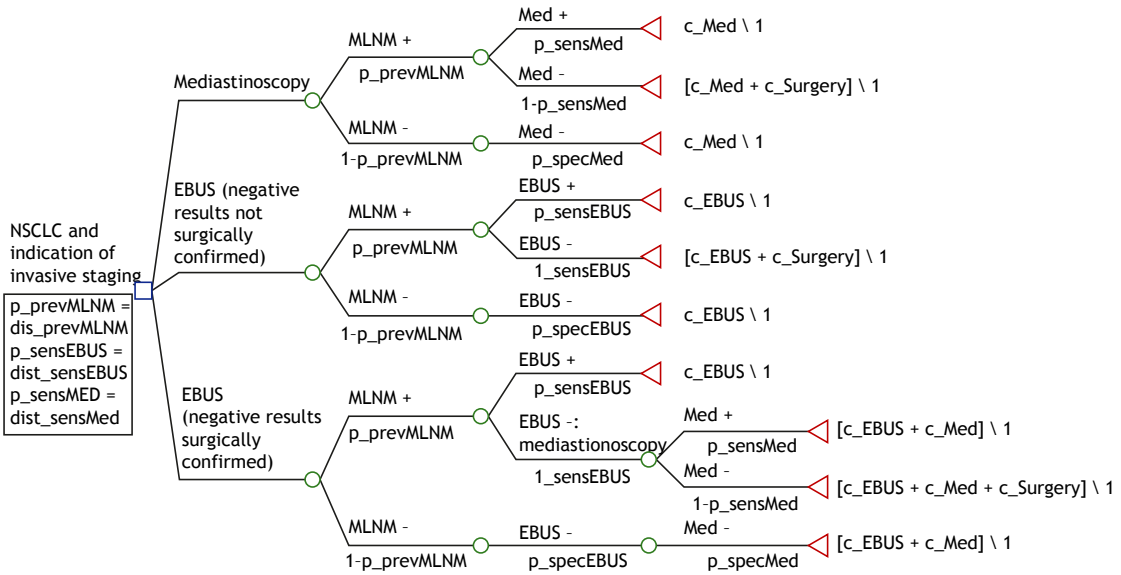

Figure 1. Decision tree model: EBUS-TBNA vs. mediastinoscopy (Med) for mediastinal staging of non-small cell lung cancer (NSCLC). p_prev: prevalence of; MLNM: mediastinal lymph node metastasis; dist_prev: distribution of prevalence (probabilistic sensitivity analysis);+: positive result; −: negative result, p_prev: prevalence of; p_sens: sensitivity; dist_sens: distribution of sensitivity; +: positive result; −: negative result; p_spec: specificity; and c_: total costs; and dist_prev: distribution of prevalence (probabilistic sensitivity analysis).

6. The sensitivity and specificity of thoracotomy and lymph node dissection for the detection of N2/3 metastases are 100%.
7. Pathology costs are identical regardless of the method of acquisition of tissue.
8. The sensitivity and specificity of EBUS are the same whether performed under moderate sedation or general anesthesia.
9. The sensitivity and specificity of EBUS are the same whether performed in the bronchoscopy suite or in the operating room.

Baseline costs

The study was conducted from the perspective of the SUS. Only direct medical costs were considered. The results are shown in Brazilian currency, that is, Real (R$), and in International Dollars (I$). The conversion to I$ was made using the purchasing power parity (PPP) conversion factor of the World Bank (https://data.worldbank.org/). PPP is a spatial price deflator and currency converter that controls for price level differences between countries, thereby allowing volume comparisons of gross domestic product and its expenditure components. The PPP calculated for Brazil in 2020 was 2.362. Since there are no costing estimates for the EBUS-TBNA procedure in the SUS, a micro-costing analysis was conducted, taking as an example four SUS-affiliated referral hospitals associated with the Brazilian public health care network where EBUS-TBNA and/or mediastinoscopy were available (*Hospital Universitário Clementino Fraga Filho*, *Hospital Universitário Pedro Ernesto*, *Hospital Universitário Antonio Pedro*, and *Instituto Nacional do Câncer*, all located in the state of Rio de Janeiro). The first step of the micro-costing analysis was to create an Excel spreadsheet to collect information related to EBUS-TBNA and mediastinoscopy procedures on hospital admission regime, procedure location (bronchoscopy suite or operating room), participating health professionals, type of anesthesia, permanent equipment used, hospital supplies, and medications. This spreadsheet was submitted to and completed by pulmonologists (bronchoscopists) and thoracic surgeons from the four hospitals listed above. Based on the information obtained from the professionals of the four hospitals, a cost survey was carried out in the SUS online systems for values related to daily hospital stays and hospital supplies. Brazilian federal government staff costs were used to calculate the hour value for each health professional, such as physicians (bronchoscopists, surgeons, and pathologists), nurses, and nursing technicians. Surgery costs were based on the SUS reimbursement table for pulmonary lobectomy adjusted by the costs defined by the micro-costing analysis. The costs related to complications were estimated considering 5.47 days of hospital stay in the ward (mean length of hospital stay for surgical patients according to the SUS). We used the following formula proposed by Harewood et al.[18] for the total cost of each procedure:

$$[(\text{CP without complications}) \times (1 - \text{CR})] + [(\text{CP with complications}) \times (\text{CR})]$$

where CP is the cost of the procedure and CR is the complication rate.

Considering complication costs in the cost analysis provides a more precise estimation of costs involved. Tables 1 and 2 summarize cost parameters.

Other input parameters

Other input parameters applied to the decision tree analysis are described in Table 3. The sensitivities of EBUS-TBNA and mediastinoscopy for detecting mediastinal lymph node metastasis (MLNM) and complication rates of both procedures were based on two systematic reviews and meta-analyses that compared the use of both techniques in the mediastinal staging of NSCLC.[11,12] The prevalence of MLNM was calculated on the basis of the *Fundação Oncocentro de São Paulo* database, which maintains a hospital cancer registry from the state of São Paulo, Brazil. The data provided by the database covers the period between 2017 and 2019, and patients classified as stage II and III were included to estimate prevalence.

Sensitivity analysis

One-way and two-way deterministic sensitivity analyses were performed for the parameters with the greatest influence on the decision tree model, such as prevalence of MLNM, sensitivity of EBUS-TBNA, sensitivity of mediastinoscopy, and costs of hospital supplies for EBUS. We chose to adopt a wide range (0.25-0.98) for sensitivity of EBUS-TBNA and of mediastinoscopy to account for different scenarios. To account for parameter uncertainty, we also performed a probabilistic sensitivity analysis, in which uncertainties in all values are considered simultaneously. For the probabilistic analysis, the Monte Carlo method was used, with 100,000 event simulations. The uncertainty in clinical probabilities and accuracies and in costs was assumed to have a beta distribution and a gamma distribution, respectively.

Ethics statement

Because the present study did not involve human participants, study approval by a research ethics committee and written consent were waived.

RESULTS

Base-case analysis

For the base-case analysis, initial evaluation with EBUS-TBNA without surgical confirmation of negative results was found to be the least costly strategy ($1,254/I$2,961) in comparison with mediastinoscopy (R$3,255/I$7,688) and EBUS-TBNA with surgical confirmation of negative results (R$3,688/I$8,711).

Sensitivity analysis

One-way sensitivity analysis showed that the EBUS-TBNA strategy without surgical confirmation of negative

Table 1. Parameter values used for costs.

Cost item	Value (R$/I$)	Reference
Post-operative location per day		
Hospital ward	242.41/572.57	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
ICU	741.90/1752.36	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Manpower per hour (average)		
Physician	107.29/253.41	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Nurse	53.64/126.69	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Nursing technician	31.39/74.14	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Hospital supplies and medication (average)		
EBUS	830.22/1,960.97	https://paineldeprecos.planejamento.gov.br/analise-materiais
Mediastinoscopy	805.97/1,903.70	https://paineldeprecos.planejamento.gov.br/analise-materiais
Complication costs[a]		
EBUS or mediastinoscopy	1,325.98/3,131.96	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Total costs for baseline costs[b]		
EBUS	1,155.52/2,729.33	All of the above and Harewood et al.[18]
Mediastinoscopy	3,149.04/7,438.03	All of the above and Harewood et al.[18]

R$: Real (Brazilian currency); and I$: International Dollars. [a]Mean number of days in the hospital ward = 5.47. Complication costs = 5.47 × cost of hospital ward per day (RS242.41/I$498.96). [b]Total costs = (costs without complication costs × 1 − complication rate) + (complication costs × complication rate).

Table 2. Baseline costs and range used for sensitivity analysis.

Cost item	Baseline costs (R$/I$)	Range used for sensitivity analysis (R$ vs. I$)	Reference
EBUS			
Total costs[a]	1,155.52/2,729.33	577.76-1,733.28 vs. 1,364.66-4,094.00	All below and Harewood et al.[18]
Hospitalization	0/0	0-242.41 vs. 0-572.57	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Manpower	320/755.84	160-480 vs. 377.92-1,133.76	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Hospital supplies	830.22/1,960.97	415.11-1,245.33 vs. 980.48-2,941.46	https://paineldeprecos.planejamento.gov.br/analise-materiais
Mediastinoscopy			
Total costs[a]	3,149.04/7,438.03	1,574.52-4,723.56 vs. 3,719.01-11,157.04	all below and Harewood et al.[18]
Hospitalization	1,226.72/2,897.51	613.36-1,840.08 vs. 1,448.75-4,342.58	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Manpower	1,091.16/2,577.31	545.58-1,636.74 vs. 1,288.65-3,865.97	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Hospital supplies	805.97/1,903.70	402.98-1,208.95 vs. 951.83-2,855.53	https://paineldeprecos.planejamento.gov.br/analise-materiais
Surgery (lobectomy)			
Total costs[a]	3,302.08/7,799.51	1,651.04-4,953.12 vs. 3,899.75-11,699.26	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/

R$: Real (Brazilian currency); and I$: International Dollars. [a]Total costs = (costs without complication costs × 1 − complication rate) + (complication costs × complication rate).

results was less costly regardless of EBUS-TBNA sensitivity values between 0.25-0.98 and prevalence of MLNM between 0.05-0.88. Mediastinoscopy would become the least costly strategy if the costs for hospital supplies for EBUS-TBNA increased by more than 300% (i.e. R$2,800–I$6,613). Comparing the EBUS-TBNA strategy with surgical confirmation of negative results and the mediastinoscopy strategy, the endosonographic procedure becomes less costly with a prevalence of MLNM of 38% (Figure 2). In the two-way sensitivity analysis, we compared the EBUS-TBNA strategy with surgical confirmation of negative results and the mediastinoscopy strategy, varying the prevalence of MLNM and the sensitivity of

Table 3. Input parameters applied to the decision tree analysis.

Procedure	Baseline sensitivity for detection of MLNM	Range used for sensitivity analysis	Reference
EBUS-TBNA	0.87	0.25-0.98	Ge et al.[12]
Mediastinoscopy	0.86	0.25-0.98	Ge et al.[12]
Procedure	**Baseline complication rate**	**Range used for sensitivity analysis**	**Reference**
EBUS-TBNA	0.004	0.002-0.009	Ge et al.[12] & Sehgal et al.[11]
Mediastinoscopy	0.019	0.0095-0.078	Ge et al.[12] & Sehgal et al.[11]
Patient	**Baseline prevalence of MLNM**	**Range used for sensitivity analysis**	**Reference**
Stage II-III NSCLC	0.23	0.05-0.88	FOSP / O'Connell et al.[20]

MLNM: mediastinal lymph node metastasis; NSCLC: non-small cell lung cancer; and FOSP: *Fundação Oncocentro de São Paulo*.

EBUS-TBNA. In this scenario, considering a prevalence of MLNM of 63%, EBUS-TBNA becomes the preferred strategy if sensitivity is 54% or higher (Figure 3). The probabilistic sensitivity analysis also showed that EBUS-TBNA without surgical confirmation of negative results was the least costly strategy, with a median of R$1,253/I$2,959 (95% uncertainty range [UR]: R$840/I$1,984—R$1,756/I$4,147), followed by mediastinoscopy, with a median of R$3,254/I$7,685 (95% UR: R$2,411/I$5,694—R$4,219/I$9,965), and EBUS-TBNA with surgical confirmation of negative results, with a median of R$3,686/I$8,706 (95% UR: R$2,882/I$6,807—R$4,594/I$10,851).

DISCUSSION

The aim of the present study was to verify whether the use of EBUS-TBNA for the mediastinal staging of NSCLC would be able to reduce costs in comparison with that of mediastinoscopy in the SUS. Our cost-minimization study based on a micro-costing analysis showed that invasive mediastinal staging by EBUS-TBNA without surgical confirmation of negative results is the least costly strategy for mediastinal evaluation in this setting, followed by mediastinoscopy and EBUS-TBNA with surgical confirmation of negative results. Our findings are in agreement with the results of a systematic review of economic evaluation studies comparing both techniques for the mediastinal staging of lung cancer,[13] as well as with the findings of two previous cost-minimization studies.[18,19]

In this model we have considered a prevalence of MLNM of 23% and a sensitivity of EBUS-TBNA and mediastinoscopy of 87% and 86%, respectively. One-way sensitivity analysis showed that, assuming a prevalence of MLNM ≥ 38%, the EBUS-TBNA strategy with surgical confirmation of negative results surgically confirmed becomes less costly than does mediastinoscopy. O'Connell et al.[20] developed a model to predict the probability of MLNM in patients with NSCLC based on findings from chest CT, PET-CT, tumor histopathology, and tumor location. Taking into account this prediction model, a prevalence of MLNM ≥ 38% would be associated with positive findings on chest CT and/or PET-CT, which allows us to infer that a radiological suspicion of MLNM would already indicate the use of EBUS-TBNA, even if a surgical confirmation of negative results is necessary, as a more economical strategy when compared with mediastinoscopy. Two-way sensitivity analysis has demonstrated that, even when we consider a sensitivity of EBUS-TBNA as low as 54%, which is quite unlikely according to results in the literature,[11,12] the EBUS-TBNA strategy would still be the least costly option if the prevalence of MLNM was ≥ 63%. Additionally, according to the prediction model developed by O'Connell et al.,[20] such a scenario would represent a patient with a histopathological diagnosis of adenocarcinoma with enlarged mediastinal lymph nodes on chest CT and/or with hypermetabolic lymph nodes on PET-CT.[20] Considering only the costs of both strategies, the use of mediastinoscopy would become less costly than that of EBUS-TBNA only if we raised the costs of hospital supplies for EBUS-TBNA by 300%. This seems to be a reasonable margin, but it must be highlighted that EBUS costs can significantly increase if the procedure is performed in the operating room with a large number of staff and if hospitalization is necessary.

Our study has some limitations. Initially, since there are no cost estimates related to EBUS-TBNA in the SUS, it was necessary to develop a micro-costing analysis of both strategies to get closer to the costs involved. Although we were careful to collect data from four different hospitals and information from bronchoscopists and thoracic surgeons, it is still uncertain whether this is an accurate reflection of health care system costs in all regions in Brazil. The EBUS procedures were performed under sedation in two hospitals (*Hospital Universitário Clementino Fraga Filho* and *Hospital Universitário Pedro Ernesto*) and under general anesthesia in another (*Instituto Nacional do Câncer*), which makes the evaluation somewhat heterogeneous. We chose to use the average of the costs between the three hospitals in the calculation of the total costs of EBUS-TBNA. Approximately 20-30% of health care services in Brazil are provided by the private network. We adopted the perspective of the public health care system in this model, and the results in the private health care network would not necessarily be the same. Finally, we did not take into account the costs for the acquisition of EBUS equipment

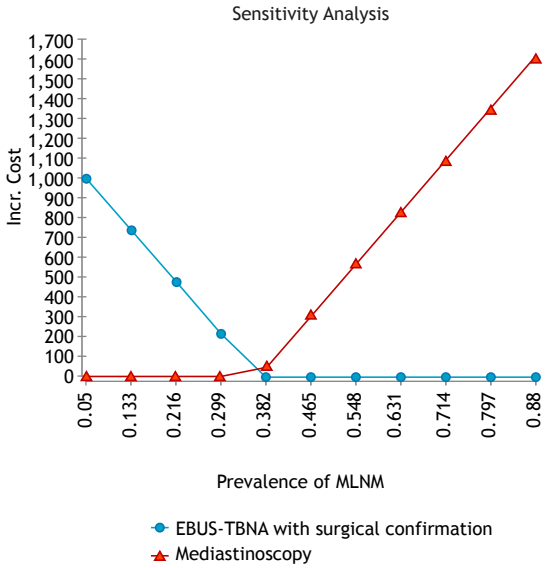

Figure 2. One-way sensitivity analysis: EBUS-TBNA with surgical confirmation of negative results vs. mediastinoscopy. Incr. Cost: incremental cost in Brazilian currency (R$); and MLNM: mediastinal lymph node metastasis.

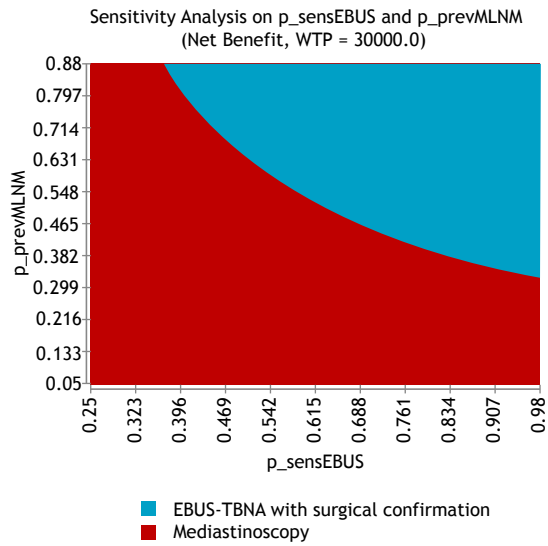

Figure 3. Two-way sensitivity analysis: EBUS-TBNA with surgical confirmation of negative results vs. mediastinoscopy. MLNM: mediastinal lymph node metastasis; p_prevMLNM: prevalence of MLNM; p_sensEBUS: sensitivity of EBUS-TBNA; and WTP: willing to pay (in Brazilian currency).

(dedicated ultrasound processor and endobronchial tube) or mediastinoscopy equipment. It is evident that the costs for purchasing an EBUS system are higher than those for a mediastinoscopy system, even if we consider video-assisted mediastinoscopy. Previous studies published by Sharples et al.[21] and Callister et al.[22] took into account capital (equipment acquisition) and maintenance costs in the cost-effectiveness calculation and, even so, they showed a reduction in costs related to the use of EBUS-TBNA. Using the equipment in referral centers with a high number of procedures can more quickly pay for capital costs.

In conclusion, our economic evaluation study with cost-minimization analyses has demonstrated that the use of EBUS-TBNA is the least costly strategy for the invasive mediastinal assessment of NSCLC in the SUS. Depending on the expected prevalence of MLNM, even the use of EBUS-TBNA with surgical confirmation of negative results is less costly than is the strategy based only on mediastinoscopy. Given the equivalence of EBUS-TBNA and mediastinoscopy in diagnostic performance, and the fact that the endosonographic method is safer, our results regarding the cost advantages of EBUS-TBNA for the diagnosis of mediastinal metastases in patients with NSCLC provide additional evidence for its clinical use and implementation in the SUS.

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AUTHOR CONTRIBUTIONS

JPSM: study design and writing the manuscript. JRLS: study planning and project supervision. AS: interpretation of results and project supervision. RES: model and computational framework design and data analysis. All authors read and approved the final version of the manuscript.

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