Mediastinal staging with Positron-Emission Tomography and Contrast-Enhanced Spiral Computer Tomography in the clinical management of potentially operable lung cancer patients: an economic evaluation.

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NOTA. Para completar el texto se necesitan tablas y apéndices. El lector puede acceder a ellos haciendo click en AMPLIACÓN.

1.- Introduction.- Within the TNM system, mediastinal staging is performed using invasive and non-invasive staging procedures: mediastinoscopy (Ms-t) and chest Computed Tomography (CT). Both techniques are somewhat inaccurate. Inaccurate N staging triggers the undesired effect of indicating surgery in patients that have undetected locally advanced disease (N2 or N3 disease). Conversely, the staging of resectable patients (N0 or N1 disease) as patients with mediastinal lymph node metastasis (N2 or N3) will deny them the possibility of surgical cure. Thus, the main goal of mediastinal staging procedure is to minimize the number of false positive and false negative patients.

Including PET in any staging strategy for staging NSCLC requires the availability of sophisticated equipment and facilities that substantially increase healthcare costs. However, these costs may be offset by a better selection of patients for beneficial resective surgery, increased life expectancy and better quality of life. Thus, assessing the cost-effectiveness of PET in the staging and treatment of NSCLC patients is of primary importance. Several attempts have been made to evaluate the cost-effectiveness of PET in lung cancer staging but to our knowledge there have been no attempts at evaluating both the actual costs (rather than charges) to the healthcare system and the consequences, quality of life, of adding PET to the standard staging strategy of NSCLC patients.

This report brings together high quality clinical data from a sample of NSCLC patients in the Hospital 12 de Octubre (Madrid, Spain), physician estimates of quality-adjusted life expectancy for those patients, and detailed hospital cost estimation to perform a cost-utility analysis, from the viewpoint of hospital of 3 strategies for the clinical management of NSCLC.

2.- The economic evaluation.

Evidence on the cost-effectiveness of PET from the medical literature: a literature review (AMPLIACIÓN, Tables 1-4). Even though results have to be handled with much care, there seems to be some evidence from the literature that including PET in the staging and treatment of NSCLC patients is cost-effective relative to alternative strategies at acceptable Willingness to Pay (WTP) per Quality Adjusted Life Year (QALY). Particularly, in relation to some alternative interventions. For example, when PET is used after CT only in CT-ve patients. Also, when Ms-t is used in those patients where PET and CT results contradict each other (i.e. in patients that have both CT+ve and PET-ve results, and in patients that have CT-ve and PET+ve results).

The "Hospital 12 de Octubre Study".

1.- **Aim**: to perform a cost-utility analysis of 3 clinical management strategies for NSCLC patients. 2.- Specific

2.-**Objectives**. 2.1.- To measure the quality-adjusted life expectancy (QALE), and to measure the costs of NSCLC patients under 3 alternative clinical management strategies. 2.2.-To calculate the incremental cost-effectiveness ratios (ICERs) for the different strategies, 2.3.- To undertake a sensitivity analysis of key uncertain parameters, and 2.4.- To discuss the implications for resource allocation

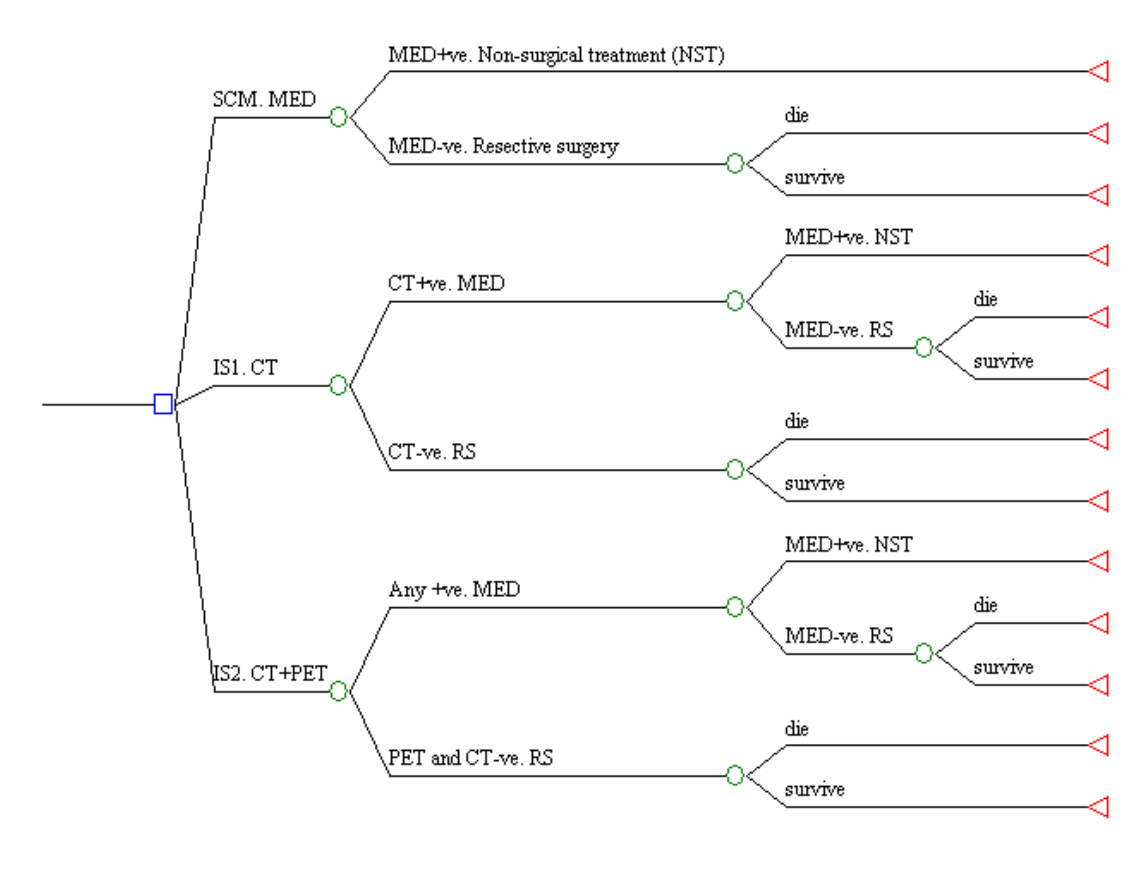
3.- **Methods**.

3.1.- Study design. Described elsewhere (F Pozo-Rodríguez et al).

3.2.- Alternative Clinical Strategies. *Standard clinical management (SCM):* Mediastinal staging using Ms-t alone followed by non-surgical treatment (chemotherapy and/or radiotherapy) in Ms-t+ve patients and resective surgery (with or without concurrent chemotherapy/radiotherapy) in MS-T-ve patients. *Intervention strategy 1 (IS1) :* Mediastinal staging using spiral CT followed by straightforward resective surgery (with or without concurrent chemotherapy/ radiotherapy) in CT-ve patients and Ms-t in CT+ve patients (MS-T+ve patients go to non-surgical treatment, Ms-t-ve patients go to resective surgery with or without concurrent chemotherapy/radiotherapy). *Intervention strategy 2(IS2):* Mediastinal staging using spiral CT followed by PET in all patients. Ms-t is performed if either PET or CT (or both) are +ve. When results of both CT and PET are –ve, the patient is referred for straightforward resective surgery with or without concurrent chemotherapy/radiotherapy.

3.3.- Decision analysis was used to assess which of the 3 strategies (*SCM, IS1, IS2*) is optimal, given 1) the number of patients diagnosed with N2/N3 disease and the number of patients diagnosed with N0/N1 disease under each strategy, 2) the consequences in terms of QALE accruing to all patients

under each strategy, 3) the actual costs borne by the hospital under each strategy, and 4) a given willingness to pay (WTP) of 50,000 EUR per QALY gained. The decision tree model is shown below



3.4.- Data were collected for the following variables before transforming them into the appropriate variables for decision tree analysis:

3.4.1.- Number of N2/N3+ve and N2/N3-ve patients with each staging procedure, and 2) number of patients that die in surgery for each clinical management strategy. This data came from the follow-up study (February 1999-February 2001) of 132 patients perforMs-t in hospital H. The study database was analysed to extract clinical information on 1) and 2).

3.4.2.- Quality-adjusted life expectancy (QALE) accruing to all patients. Expected QALYs were calculated for all 132 patients on the basis of assigning each patient 1) an initial health state, 2) an individual survival / life expectancy according to its pathological or post Ms-t stage, and 3) individualized changes in quality of life derived from the treatment and complications that each patient underwent. QALY calculations were divided into four steps:

3.4.2.1.- Step1. Patient sample QALY calculations. Four initial health state values, associated with 4 types of NSCLC patients, were elicited by a lung specialist, using the EuroQol EQ-5D descriptive instrument **(AMPLIACIÓN, Table 5).** Each of all 132 patients was assigned to one of the four types in order to obtain their quality of life status at the beginning of their treatment. This five-dimensional quality of life description was translated into a number between 0 and 1 (where 0 is the worst possible health state and 1 is perfect health) using the Spanish EuroQol tariff.

3.4.2.2.- Step 2. Patient sample QALY calculations. Duration of life was evaluated for every patient, based on either 1) actual survival if the patient had already died, or 2) survival data adjusted for stage, estimated from the Spanish Lung Cancer Cooperative Group if the patient was not dead at the end of December 2002.
3.4.2.3.- Step 3. Patient sample QALY calculations. Beginning with the initial health state, the expected change in quality of life along life expectancy (health profile) was modelled for 5 types of patient. These 5 health profiles were developed taking into account 1) the treatment each patient underwent, and 2) the complications experienced by each patient. Profiles and changes in quality of life for each profile were based in previous results from the literature and in the judgement of an expert oncologist. The different profiles modelled are displayed in **AMPLIACIÓN, Table 6.** A simple algebraic formula was used to calculate the area under each health profile, given in **AMPLIACIÓN, Table 7**. The resulting value is the number of expected QALYs accruing to each health profile.
3.4.2.4.- Step 4. Patient sample QALY calculations. QALYs accruing to each patient at the end of each branch of the decision tree were calculated on an EXCEL spreadsheet by assigning each patient the profile corresponding to his treatment/complications after surgery (profile 1, 2, 3, 4, or 5), and entering into the algebraic formula corresponding to his profile his survival time/LE and the initial health state belonging to his type (type 1, 2, 3, 4). See appendix 3 for an exhaustive list of the values accruing to each patient at each branch of the tree.

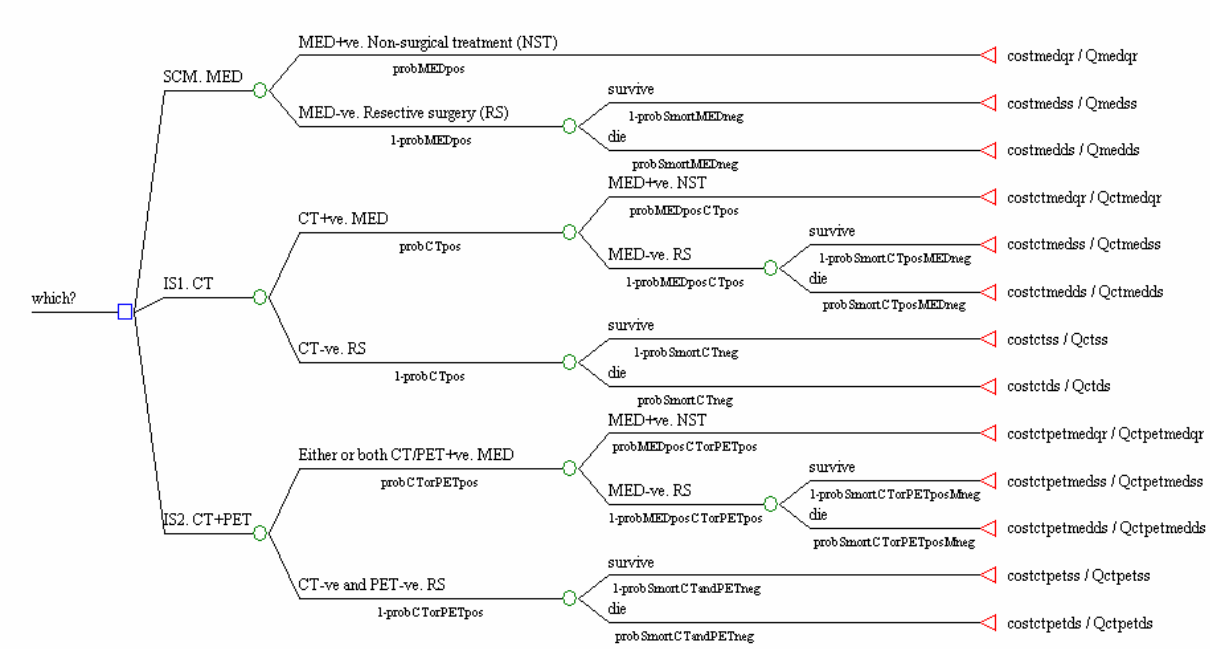
3.4.3.- Total costs for each staging procedure (PET, CT, Ms-t) and for each treatment (resective surgery, chemotherapy, radiotherapy). In order to calculate total costs for each procedure and each treatment, detailed resource use for an average (i.e. standard) procedure and treatment, as well as unit costs, were obtained directly from the Hospital 12 de Octubre. The cost of each PET scan used in the baseline cost-effectiveness analysis was not calculated in detail because Hospital 12 de Octubre purchases each PET procedure from the Centro PET Complutense, which is a private company. Since this study was conducted from the perspective of the hospital (provider organization), the baseline cost of each PET that was taken into account in this study is the price at which it was bought from PET Center. **AMPLIACIÓN, Table 8** shows the information obtained on resource use and the sources from which that information was obtained**. AMPLIACIÓN, Table 9** shows the sources of information for unit costs. Total costs of each procedure were calculated on an EXCEL spreadsheet by multiplying each unit of average resource consumption by its unitary cost. Overhead costs and capital costs were allocated across treatments and procedures (**AMPLIACIÓN, Table 10**). The price of PET and the detailed breakdown of average costs for each of the other 2 staging proceduresprocedure (MS-T/CT), as well as for each treatment (resective surgery, chemotherapy, radiotherapy) are shown in **AMPLIACIÓN Appendix.**

3.5.- Patient sample. The patient sample on which this study is based in a prospective series of 132 consecutive cases attended at Hospital 12 de Octubre between February 1999 and February 2001. Inclusion criteria: histologically diagnosed NSCLC, no distant metastases (M1 category of the TNM classification), informed consent. Non-inclusion criteria: any anatomic alteration that precludes Mediastinoscopy, pregnancy, and diabetes.

4.- Data analysis.
4.1.- Variable transformations for input in the decision tree. Data collected from the patient sample was transformed into 3 types of variables for input in the decision tree model: probabilities at each chance node, QALYs at each terminal node, and costs at each terminal node. See **AMPLIACIÓN, Tables 11-13.**

4.2.- Cost-effectiveness analysis. DATA 4.0 software was used to build the decision tree model (see Diagram 3 on the next page for its full display), and to calculate incremental cost-effectiveness ratios (ICERs) in order to evaluate the most cost-effective strategy. One-way sensitivity analysis to evaluate the impact on ICERs of changes in uncertain parameters was conducted for each probability, each

outcome and each cost. Also, an additional model was run using mean LE instead of mean QALE as health outcome. The decision tree model is shown below



5.- Results.

5.1.- Results of the model with baseline values. Table 11 shows the baseline values (range for sensitivity analysis) for all the variables in the decision tree model (units of measurement are QALYs for Q-variables and EUR for cost-variables). Table 12 displays the results of cost-effectiveness analysis.

Standard clinical management (strategy SCM) is the cheapest strategy (cost = 7843 EUR per patient) and it accrues a little over 2 QALYs per patient.

The next cheapest alternative, Intervention Strategy 1 (IS1, i.e. staging using spiral CT+MS-T instead of MS-T alone) has an incremental cost of 796 EUR per patient. QALE gain using IS1 is 0.028 QALYs. ICER is 28,904 EUR per QALY gained. For a willingness-to-pay threshold of 50,000 EUR/QALY, this strategy is cost-effective.

The most expensive clinical management strategy is IS2, which uses CT, PET and MS-T as staging procedures. Compared to IS1, it costs 544 extra EUR per patient, and it brings about a loss in QALE of 0.084 QALYs. It is a dominated strategy (i.e. both more expensive and less effective), both in relation to SCM and IS1.

5.2.- Results of the sensitivity analysis. One-way sensitivity analysis was perforMs-t on all probabilities, QALYs and costs using the ranges outlined in Section 4.4. Results are shown in Table 13. In a second analysis,a new model was run using LE instead of QALE as final outcome measure.

The results of the baseline model are robust to changes of up to 50% in the cost of each staging and treatment procedures. Strategy IS2 is always dominated by both IS1 and SCM. The minimum/maximum ICERs of IS1 versus SCM (18,336 EUR/QALY and 39,471 EUR/QALY) are in a range determined by changes in the cost of CT. In all cases, for a WTP of 50,000 EUR per QALY gain, IS1 is cost-effective.

Results of the baseline model are also robust to changes in the QALE of the patients in the sample. With the exception of 3 scenarios, IS2 is systematically dominated and IS1 is cost-effective (WTP threshold = 50,000 EUR/QALY) compared to SCM. ICERs of IS1 versus SCM move in a range between 1,442 EUR/QALY (for the maximum QALE accruing to patients found N2/N3+ve by CT and N2/N3-ve by MS-T, under strategy IS1) and 28,904 EUR/QALY (for the minimum QALYs accruing under any of the 3 scenarios under strategy IS2). However, IS2, the PET-including strategy, becomes cost-effective for the maximum QALE accruing to all patients under this strategy. Maximum QALE is 1.6 QALYs for patients referred straight to NST (but only 1 individual reaches 1 QALY before dying), 4.33 QALYs for patients who are CT/PET+ve and MS-T-ve and survive surgery (40% of individuals reach more than 3.5 QALYs), and 6.2 QALYs for patients CT/PET-ve that survive surgery (around 10% of all patients reach more than 5 QALYs).

Results are least robust to changes in the tree probabilities. Again, IS2 is systematically dominated, except in one case. IS2 is cost-effective compared to SCM when the probability that PET and/or CT find N2/N3 disease is at its lowest. That is, when PET and CT refer the least patients to non-surgical treatment, by far the most expensive treatment. Across scenarios, IS1 changes from being cost-effective to being dominated by SCM. The small incremental costs and incremental effectiveness at baseline change substantially when the tree probabilities are changed.

When QALE is changed in favour of LE as the outcome of the decision tree model, effectiveness results change enough to suggest that, at baseline, IS1 is no longer cost-effective compared to SCM. Incremental cost of IS1 is still 796 EUR, but QALE gain is now negative (-0.012 LYs). In fact, both IS1 and IS2 become dominated by SCM under this scenario.

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