Radiotherapy cost-effectiveness in patients with lung cancer invading the chest wall

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Short title: Adjuvant radiotherapy in clinical T3N0M0 lung cancer

1. Background

Accounting for one-fifth of all cancer deaths, lung cancer is the leading cause of cancer death in Europe [1]. The treatment of lung cancer depends upon its histologic type and its stage. Surgical resection is recommended for patients with non-small cell lung cancer (NSCLC) with clinical stages I (T1 or T2 NSCLC without any node involvement or metastasis) or II (T2N1M0 or T3N0M0). Post-operative radiotherapy is frequently used to prevent local recurrence in operated patients. However, there is no clear consensus concerning the use of adjuvant radiotherapy in NSCLC patients with a complete resection [2]. Moreover, there are few data available on chest wall involvement NSCLC without any node involvement or metastasis (T3N0M0). Indeed, no randomized trial has ever compared postoperative radiotherapy in the management of NSCLC with...
chest wall involvement [3] and the use of postoperative radiotherapy remains thus controversial. Consequently, the management of clinical T3N0M0 NSCLC with chest wall involvement varies according to hospitals. In some centres, adjuvant radiotherapy is systematic in these patients, whereas in some others, adjuvant radiotherapy is restricted only to patients for whom pathological staging revealed node involvement.

Our decision analysis aimed at comparing the effectiveness and the cost for these patients to undergo: systematic postoperative radiotherapy versus radiotherapy restricted only to patients for whom pathological staging revealed node involvement (selective radiotherapy).

2. Material and methods

Description of the model
A cost-effectiveness analysis was conducted using a decision tree model. A decision tree model is a quantitative method for synthesizing data from various sources in order to compare two strategies in a context of uncertainty [4].

Considering a 60-year old patient having a suspected T3N0M0 chest wall tumour after clinical staging (T3N0M0c), two strategies can be applied: 1) systematic postoperative radiotherapy, 2) selective postoperative radiotherapy. At the start of both strategies, all patients suspected to have a T3N0M0 chest wall tumour underwent complete surgical resection followed by the pathological assessment of the tumour. Pathological staging revealed either nodal involvement (T3N+M0p) or the absence of nodal involvement (T3N0M0p) according to the TNM Classification of malignant tumours [5]. In the first strategy (systematic postoperative radiotherapy), radiotherapy is undertaken whatever the results of the pathological staging, i.e. absence or presence of nodal involvement. The second strategy (selective postoperative radiotherapy) corresponds to radiotherapy only in case of the presence of nodal involvement (figure 1). Then the different consequences of each strategy were included at a one year horizon. It was assumed that post-surgical mortality (defined as in-hospital mortality or deaths within 30 days of surgery) may occur. For patients alive after resection, post-surgical complications (defined as any in-hospital complications) were also taken into account. For
patients undergoing radiotherapy, it was assumed that radiotherapy could lead to death after the end of all radiotherapy sessions. Non fatal toxicities related to radiotherapy were considered as occurring the same year as surgery. They included bacterial pneumonia, acute respiratory failure, radiation pneumonia or esophagitis.

**Transition probabilities**

The probabilities of these clinical events (post-surgical mortality, post surgical complications, radiotherapy death or radiotherapy complications) were estimated from the most appropriate available data [6] identified through a critical review of literature. Inclusion criteria for this review were as follows: 1) original studies on T3N0M0 tumours with chest wall involvement reporting 5-year survival or post-operative mortality, 2) articles dealing with radiotherapy toxicity or mortality in patients having first undergone surgery, or 3) sample size over 20 patients.

Articles were not selected if they dealt with non resectable cancers or non-operable patients, supportive care, relapses, multiple cancers, induction...
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chemotherapy exclusively, or with superior sulcus tumours exclusively.

Studies were selected in three steps. First, in order to identify articles, we searched Medline and Science Direct for all English or French original publications dating from 1990, and falling under the medical subject headings (MeSH) “carcinoma, non-small-cell lung/surgery”, “carcinoma, non-small-cell lung/radiotherapy”, in combination with the terms: “T3N0M0”, “stage IIIA”, “stage IIB”, “chest wall involvement”, “chest wall infiltration” or “chest wall invasion”. According to the TNM classification revision in 1997, T3N0M0 tumours, initially assigned in stage III A category, are now classified as stage II B [7]. Thus, the search was performed both on stage IIIA and IIB. We conducted a second search to identify data about radiotherapy complications using the following terms: “Radiotherapy” taken into account as MeSH and “Complications” and “Lung neoplasms” (taken into account as free text).

In the second step based on titles and abstracts, we selected papers in which relevant clinical parameters were available. Additional articles were identified from references in the retrieved articles.

Thirdly, the eligible articles were assessed by two independent reviewers for final selection using a check-list of methodological criteria (Table 1). Discrepancies in eligibility criteria as well as quality assessment were arbitrated between the two reviewers.

The resulting data were analysed to estimate a baseline value based on the median of all the values found in the studies with the best quality. The ranges corresponded to the lowest and highest value found in the studies for all relevant variables (Table 2).

**Payoffs**

At the end of each arm of the tree, two payoffs were assigned. They corresponded to 1) an efficacy criterion: the life expectancy in years and 2) to the total cost of care (cost of resection with possible associated complications, cost of radiotherapy and cost of possible associated complications).

Life expectancies associated with each arm of the decision analysis model were calculated using

<table>
<thead>
<tr>
<th>Variables</th>
<th>Baseline value</th>
<th>Ranges</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiotherapy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radiotherapy related acute toxicities</td>
<td>21.2%</td>
<td>6.7%-28.4%</td>
<td>28-30</td>
</tr>
<tr>
<td>Radiotherapy related deaths</td>
<td>2.2%</td>
<td>0%-4.2%</td>
<td>29-34</td>
</tr>
<tr>
<td><strong>Resection</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-surgical complications</td>
<td>26.6%</td>
<td>16.0%-44.7%</td>
<td>11-19,27</td>
</tr>
<tr>
<td>Post-surgical death</td>
<td>4.2%</td>
<td>0%-19.5%</td>
<td>11-26</td>
</tr>
<tr>
<td><strong>Life expectancy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3N0M0 associated with post-operative radiotherapy</td>
<td>6.63 years</td>
<td>5.78-7.63 years</td>
<td>21,27</td>
</tr>
<tr>
<td>T3N0M0 without post-operative radiotherapy</td>
<td>5.13 years</td>
<td>3.73-6.81 years</td>
<td>21,27,35</td>
</tr>
<tr>
<td>T3N+M0 associated with post-operative radiotherapy</td>
<td>2.80 years</td>
<td>2.68-2.92 years</td>
<td>21,27</td>
</tr>
<tr>
<td>Proportion of T3N0M0p among T3N0M0c</td>
<td>77.3%</td>
<td></td>
<td>10</td>
</tr>
</tbody>
</table>

\(p\): pathological  
\(c\): clinical
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the DEALE method (Declining Exponential Approximation of Life Expectancy) using a five-year global survival rate [8]. Five-year global survival rates after surgery and radiotherapy were extracted from selected published studies. The life expectancy for a 60 year old individual was estimated from the French National Institute of Statistics and Economic Studies. Table 2 summarizes effectiveness data used in the decision analysis.

The economic analysis was performed from the French National Health Insurance perspective. Costs were expressed in Euros (€) for the year 2006. Only direct medical costs were taken into account in the analysis. Treatment costs included the cost of resection with and without complications, the cost of radiotherapy and the cost associated with the management of patients presenting radiotherapy complications. In France, in-hospital patients are grouped in diagnosis-related-groups (DRGs) according to their diagnoses and management. Each DRG is associated to a mean national cost corresponding to national reimbursement data of the French National Insurance. In order to select the appropriate DRGs, we retrieved the whole patients with a T3N0M0 lung cancer and a surgical treatment admitted to the Dijon University Hospital in 2006 and we extracted the corresponding DRGs. The same strategy was used to identify patients with radiotherapy complications. The cost of radiotherapy was estimated by multiplying the total number of radiotherapy sessions, estimated to be 29 according to experts’ advice and the cost of the DRG associated with radiotherapy corresponding to the cost of ambulatory hospitalisation in a drug-specialised department.

Cost-effectiveness analysis
The expected mean life expectancy and the mean expected cost of care associated with each strategy were then estimated by weighting them by the probabilities that a patient experienced clinical events. A strategy could be strongly recommended if it was less costly and at least as effective as the other one. If a strategy was both more effective and costly or if it was both less effective and costly, an incremental analysis was conducted by calculating the incremental cost-effectiveness ratio (ICER). The incremental cost-effectiveness ratio (ICER) was expressed in terms of cost per life-year gained, according to the following formula:

\[
\text{ICER} = \frac{\text{Cost}_{\text{systematic postoperative radiotherapy}} - \text{Cost}_{\text{selective postoperative radiotherapy}}}{\text{Life expectancy}_{\text{systematic postoperative radiotherapy}} - \text{Life expectancy}_{\text{selective postoperative radiotherapy}}}
\]

TreeAge Pro 2006 Healthcare software (Software Inc., Williamstown, MA) was used to build and analyze the decision tree.

Sensitivity analysis
The robustness of the cost-effectiveness results obtained was assessed through sensitivity analyses [9] first on median transition probabilities, then on life expectancy and finally on cost data.

A one-way sensitivity analysis was performed for each variable in the decision tree by varying it over its entire plausible range while holding all other probabilities constant. Threshold values were determined and defined as cutoff points beyond which the hierarchy between strategies could be modified.

A one-way analysis was performed then on life

Table 3: Baseline values of costs of treatment used in the model

<table>
<thead>
<tr>
<th></th>
<th>Cost (€)</th>
<th>Ranges (€)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery :</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient dead after resection</td>
<td>9 683</td>
<td>6 505-13 847</td>
</tr>
<tr>
<td>Patient alive after resection without complications</td>
<td>8 346</td>
<td>6 505-13 847</td>
</tr>
<tr>
<td>Patient alive after resection with complications</td>
<td>10 797</td>
<td>6 505-13 847</td>
</tr>
<tr>
<td>Radiotherapy:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>radiotherapy out-patient attendances</td>
<td>5 406</td>
<td></td>
</tr>
<tr>
<td>hospitalization due to radiotherapy complications</td>
<td>4 315</td>
<td>1 615-6 404</td>
</tr>
</tbody>
</table>
expectancy first for T3N0M0 patients with postoperative radiotherapy, and then for T3N0M0 patients without postoperative radiotherapy, according to the different values obtained from the literature. The one-way analysis was performed afterwards on the radiotherapy complications cost. Indeed, the DRG associated with a lung cancer patient varied according to the radiotherapy complications, which resulted in different costs. The costs of surgery complications or deaths were not tested in the sensitivity analysis as it was the same between the two arms of the decision tree.

3. Results

**Bibliographic search**
The electronic search and bibliographical references yielded 159 articles. Only 37 were eligible, and 26 of them that met the defined criteria were used for data extraction. The reasons for exclusion are detailed in Figure 2. Table 2 summarizes the probabilities and life expectancy used in the decision analysis.

The proportion of T3N0M0p among T3N0M0c was estimated to be 77.3% [10]. Median post-operative mortality rate was estimated to be 4.20% [11-26] whereas median post-surgical complications was estimated to be 26.6% [11-19,27]. Median toxicities or deaths both related to radiotherapy were estimated to be 21.2% [28-30] and 2.22% [29-34].

**Cost data results**
Cost data identified from DRGs are detailed in Table 3. The mean cost of in-patient stay for surgery amounted to 9,683 € when he died, 10,797 € if complications occurred and 8,346 € when surviving without complications. The cost of all scheduled radiotherapy sessions was 5,406 € and the mean additional cost of complications due to radiotherapy 4,315 €.

**Baseline cost-effectiveness results**
Results of the baseline cost-effectiveness analysis showed that systematic postoperative radiotherapy among patients with a clinical T3N0M0 chest wall tumour increased mean life expectancy by 1.01 years when compared with selective chest wall radiotherapy (5.40 years with systematic radiotherapy versus 4.39 with selective radiotherapy).

The mean cost was estimated to be 15,072 € for systematic postoperative radiotherapy versus 10,406 € for selective chest wall radiotherapy.

Systematic post operative radiotherapy was associated with an increase in life expectancy but also with a higher cost. Thus, the incremental cost-effectiveness ratio was 4,620 € per life year gained for systematic postoperative radiotherapy. It has been suggested that an ICER below the 33,000 € per quality-adjusted life-year gained in United Kingdom [36] and 50,000 € per life-year gained in France [37] could be considered as the rational threshold for allocating resources. So, the baseline cost-effectiveness analysis showed that systematic radiotherapy was a strategy that could be considered as acceptable for the National Health Insurance System.

**Sensitivity analyses**
One-way sensitivity analyses on clinical parameters (proportion of surgical and radiotherapy complications, surgical and radiotherapy deaths) and on the cost of radiotherapy complications led to consistent results. The model was shown to be robust with an incremental cost-effectiveness ratio associated with systematic radiotherapy varying only from 4,201 € to 5,142 € per life year gained.

Variations of estimations in life expectancy were then tested. The results were consistent with baseline cost-effectiveness results for T3N0M0 patients with postoperative radiotherapy (baseline value 6.63 years [5.78-6.65]). For these patients, incremental cost-effectiveness ratio varied from 2,679 to 12,051 € per life year gained, but always remained under the threshold of 37,800 € per quality-adjusted life-year gained. Then, the sensitivity analysis was applied to life-expectancy of T3N0M0 patients without postoperative radiotherapy (table 2). The base case value for this datum was 5.13 years [3.73-6.81]. Only above 6.48 years, selective radiotherapy became more effective than systematic radiotherapy (5.64 years and 5.40 years respectively instead of 4.39 years and 5.40 years in the baseline results) (figure 3).

4. Discussion
This study aimed at comparing the benefit of systematic post operative radiotherapy versus...
radiotherapy only in patients for whom pathological staging revealed node involvement for patients with clinical T3N0M0 tumour invading the chest wall and complete resection.

Baseline analysis suggested that post operative radiotherapy should be systematic after complete resection in patients with clinical T3N0M0 tumour invading the chest wall, with an incremental cost-effectiveness ratio of 4 620 € per life year gained for systematic postoperative radiotherapy. The results were not modified by the sensitivity analysis results on clinical parameters and cost data. However, the model was clearly more sensitive to the life expectancy. When varying life expectancy data on T3N0M0 patients with radiotherapy, the ICER was found to be three times higher than the baseline ICER, but it remained under the accepted threshold of 50 000 € per life-year gained [37]. However, when considering life expectancy for a T3N0M0 patient without radiotherapy, selective radiotherapy became dominant over systematic treatment for a value over 6.48 years. This threshold however corresponds to the higher boundary of the variation interval. This 5-year survival was reported by Downey [21], but there might be a selection bias as women represented more than a third of patients included in his monocentric study, against only 8% [35] and 13% [27] in the other studies included. Moreover, Alexiou et al [38] reported that survival after lung carcinoma resection was better in women than in men and thus the resulting 5-year survival probability survival could be overestimated. So, the 6.48 years threshold may not reflect most of the situations, and systematic radiotherapy seems to be the best strategy.

In the present study, we wanted to identify the best radiotherapy strategy for T3N0M0 patients with chest wall involvement tumours relying on a decision analysis. In such analysis, results are very dependent of the quality of literature data, particularly for transition probabilities and life expectancy. There were few available data for these patients, and the decision analysis took into account the whole ranges reported in selected studies. All the studies identified dealing with 5-year survival were retrospective, and relied on hospital series, but only those with more than 20 patients by group were included.
Moreover, there was a great heterogeneity in the cancer characteristics within T3 patients included in the studies and retained for probabilities estimation. Indeed, T3 stage corresponded to a tumour of any size that directly invades one of the following: chest wall (including superior sulcus tumours), diaphragm, mediastinal pleura, parietal pericardium; or tumour in the main bronchus < 2 cm distal to the carina, but without involvement of the carina; or associated atelectasis or obstructive pneumonitis of the entire lung [5]. Superior sulcus tumours are included in chest wall involvement tumours, but their prognosis is quite different. Among the 3 studies used for 5-year survival data, one included patients with superior sulcus tumours [27], one excluded patients with a Pancoast syndrome [35], and another did not mention it [21]. Moreover, heterogeneity also regarded surgical treatments in the selected studies. In some studies [14,16,17,21,23,24,27,35], either extrapleural resection or “en bloc” resection was performed without always a clear distinction between corresponding prognosis. In other studies, only en bloc resection was performed [12,19,22,25,26]. It would have been interesting to compare results obtained between en bloc resection patients and results for patients having undergone another type of surgery. However, it was not possible to carry out a subgroup analysis due to the lack of data precision.

Besides in most studies, surgical and radiotherapy complications were not given according to each cancer stage (N0 or N+) but for all patients of the studies; this may well have under- or overestimated complications. On the whole, despite important variation between included studies, our sensitivity analysis led to consistent results and was in favour of systematic radiotherapy.

Concerning the cost estimation, data from the Dijon University Hospital was first used to identify DRGs related to hospital stays of patients with a T3N0M0 lung cancer, and a specific-DRG mean national cost was then applied. This national mean cost scale is obtained from a representative sampling of hospitals in order to have a cost estimation of hospital stays. So our cost data should reflect the direct medical costs induced by the management of French patients.

A discounting rate is often applied to cost and effectiveness, particularly for long time periods. Indeed, as the outcomes and costs of health care intervention protocols may sometimes spread over various time periods, discounting enables to compare such outcomes and effects more easily [39]. However, in this study, as the life expectancy of T3N0M0 patients is short, we decided not to consider that the value of the years following the first year of surgery was inferior to that of the first year post surgery. Thus, we opted for the choice of non discounting.

On the whole, systematic radiotherapy was associated with an increase of 1.01 years in life expectancy compared to selective radiotherapy. Even if such an increase may appear modest, it implies an immediate benefit in the probability of survival in some treated patients [40] corresponding to the fifth of estimated overall life expectancy.

Thus, our results are in favour of systematic radiotherapy after complete resection in T3N0M0 patients with lung cancer invading the chest wall in baseline analysis.

However, a controlled randomized trial with well defined inclusion and exclusion criteria, is required in order to get an unbiased comparison of both strategies, according to the type of surgery performed and to confirm our decision analysis.

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Potential conflicts of interest. All authors report no conflicts of interest relevant to this article.

5. References


32. Lad T. The comparison of CAP chemotherapy and radiotherapy to radiotherapy alone for resected lung cancer with positive margin or involved highest sampled paratracheal node (stage IIIA). LCSG791. Chest 1994; 106: 302S-306S.


