

## ORIGINAL ARTICLE

# Estimated direct costs of non-small cell lung cancer by stage at diagnosis and disease management phase: A whole-disease model

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## Keywords

Cost of illness; economic models; lung cancer burden; practice guidelines.

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## Abstract

**Background:** Non-small cell lung cancer (NSCLC) is the first cause of cancer-related death among men and the second among women worldwide. It also poses an economic threat to the sustainability of healthcare services. This study estimated the direct costs of care for patients with NSCLC by stage at diagnosis, and management phase of pathway recommended in local and international guidelines.

**Methods:** Based on the most up-to-date guidelines, we developed a very detailed "whole-disease" model listing the probabilities of all potentially necessary diagnostic and therapeutic actions involved in the management of each stage of NSCLC. We assigned a cost to each procedure, and obtained an estimate of the total and average per-patient costs of each stage of the disease and phase of its management.

**Results:** The mean expected cost of a patient with NSCLC is 21,328 € (95% C.I. –20 897–22 322). This cost is 16 291 € in stage I, 19530 € in stage II, 21938 € in stage III, 22175 € in stage IV, and 28 711 € for a Pancoast tumor. In the early stages of the disease, the main cost is incurred by surgery, whereas in the more advanced stages radiotherapy, medical therapy, treatment for progressions, and supportive care become variously more important.

**Conclusions:** An estimation of the direct costs of care for NSCLC is fundamental in order to predict the burden of new oncological therapies and treatments on healthcare services, and thus orient the decisions of policy-makers regarding the allocation of resources.

## Key points

**Significant findings of the study:** The high costs of surgery make the early stages of the disease no less expensive than the advanced stages.

**What this study adds:** An estimation of the direct costs of care is fundamental in order to orient the decisions of policy-makers regarding the allocation of resources.

## Introduction

Lung cancer is now the first cause of cancer-related death in men and the second (after breast cancer) in women worldwide.<sup>1</sup> In this scenario, non-small cell lung cancer (NSCLC), which accounts for approximately 87% of lung cancers,<sup>2</sup> clearly emerges as a “big killer” of our times. It has become a huge public health issue, not only in terms of the related morbidity and mortality, but also from an economic standpoint. Many new oncological drugs for NSCLC have arrived on the market in recent years, improving patients’ progression-free survival (PFS) and overall survival (OS);<sup>3–10</sup> however, they are extremely costly and are seriously threatening the sustainability of healthcare systems.<sup>11</sup>

Standardized guidelines have been developed locally and internationally to help specialists make decisions regarding their patients’ management, but also in an endeavor to ensure a more rational allocation of resources.<sup>12</sup> Furthermore clinical pathways derived by guidelines provide more details about organizational aspects and timing schedule of the care for the management of chronic pathology within an integrated network of hospital and primary care.<sup>13, 14</sup>

The cost components of lung cancer care are being analyzed more and more around the world nowadays to assess the effective economic impact of this disease on healthcare systems. Such studies have been conducted in Germany (Schwarzkopf *et al.*<sup>15</sup>), in the Netherlands (Van der Linden *et al.*<sup>16</sup>), in the Czech Republic (Šimrová *et al.*<sup>17</sup>), and in Catalonia (Corral *et al.*<sup>18</sup>). Comparisons were drawn between Western European countries by McGuire *et al.*<sup>19</sup> and between different parts of the U.S. by Sheehan *et al.*<sup>20</sup> and Cipriano *et al.*<sup>21</sup> A review on the situation in Latin America has been published by Ruez *et al.*<sup>22</sup> However, all these studies were conducted before the approval for use of new costly therapies. The new therapies have been considered only referring to the USA,<sup>23</sup> which has a very different health care system, so it is not easy to apply these findings to Europe.

The purpose of the present study was therefore to develop a “whole-disease model”<sup>24</sup> of the pathways of care for NSCLC, including all the steps of a patient’s experience, from when the disease is suspected to the end of the first year of treatment, through the whole diagnostic and staging process, and all the possible interventions. Our aim was to predict with accuracy the direct costs of care for NSCLC by stage at diagnosis, and phase of its management, on the basis of the currently-adopted clinical pathway.

## Methods

We developed a model that estimated the costs, stratified by stage of diagnosis, of the clinical pathway of care for

NSCLC patients over a one-year time horizon, using a payer perspective, and only considering direct costs.

## Context

Italy’s health care system is a regionally-managed national health service (NHS) that provides universal coverage at the point of delivery, and free of charge for patients who are exempt for reasons such as a cancer diagnosis. The system is grounded on fundamental values of universality, free access, freedom of choice, pluralism in provision, and equity.<sup>25</sup> Regional authorities plan and organize healthcare facilities and activities in accordance with a national health plan designed to assure an equitable provision of comprehensive care throughout the country.

Consistently with other international guidelines,<sup>26</sup> the AIOM (Italian Association of Medical Oncology) developed clinical guideline for the management of lung cancer, from diagnosis to all subsequent staging, treatment and follow-up actions.<sup>27</sup> Veneto Region established a diagnostic and therapeutic patient care pathway according this national guideline to its regional context<sup>28</sup> to guarantee all of the region’s residents an equitable and effective cancer care. In particular, the Veneto Oncological Institute drafted its “Place in Therapy” (PIT) document to help its specialists allocate stage IIIB and IV patients to the most suitable chemotherapy protocol currently available.<sup>29</sup>

Based on the above-mentioned clinical pathway for NSCLC, we developed our model.

## Probabilities

The probabilities were divided into two categories, described as clinical and process probabilities.

- Clinical probabilities were estimated mostly from the literature. In particular, the probability of a given stage distribution at diagnosis was assumed from a previous study by Benitez-Majano *et al.*<sup>30</sup> Cases of superior sulcus tumor (also known as Pancoast tumors) were modeled as a separate group.<sup>31, 32</sup> OS and PFS rates, by disease stage at diagnosis, were obtained from the literature (Table 1). Mortality rates due to natural causes were drawn from the data available from the Italian Statistics Institute (ISTAT), taking into account the average age of incidence for NSCLC cohort cases.<sup>33</sup> At all disease stages, patients could be classified as “surgical” or “non-surgical” according literature probabilities: 81% of patients with stage I disease had surgery,<sup>43</sup> as did 63% of those with stage II,<sup>44</sup> 11.6% of those with stage III,<sup>45</sup> 4.5% of those with stage IV,<sup>46</sup> and 54% of those with a Pancoast tumor.<sup>40</sup>
- Process probabilities related to the diagnostic and therapeutic actions taken on patients. Most procedures were

**Table 1** Probabilities (and beta distribution parameters) of death and recurrence rate one year after diagnosis by stage at diagnosis

	Post-surgery mortality rate (only for surgical patients)	Natural mortality rate	Tumor-related mortality rate	Recurrence rate	Source
I	1.5% beta (1.5, 98.5)	3.1% beta (3.1, 96.9)	0.7% beta (0.7, 99.3)	5.0% beta (5.0, 95.0)	33–36
II	1.4% beta (1.4, 98.6)	3.1% beta (3.1, 96.9)	6.1% beta (6.1, 93.9)	10.0% beta (10.0, 90.0)	33–36
III	7.1% beta (7.1, 92.8)	3.1% beta (3.1, 96.9)	23.0% beta (23.0, 77.0)	18.0% beta (18.0, 82.0)	33, 34, 37
IV	1.9% beta (1.9, 98.1)	3.1% beta (3.1, 96.9)	53.2% beta (53.2, 46.8)	-	3–9, 33, 38
Pancoast	3.2% beta (3.2, 96.8)	3.1% beta (3.1, 96.9)	33.2% beta (33.2, 66.8)	22.0% beta (22.0, 78.0)	33, 39–42

the same for all patients since their specific condition was deterministically associated with a specific clinical pathway (eg, all patients diagnosed with a stage IV NSCLC undergo a multidisciplinary clinical examination). However, clinical and diagnostic pathway leaves some decisions regarding certain procedures to the physician's discretion. Since the other national and international guidelines consulted<sup>26, 27</sup> have the same discretionary elements, a number of NSCLC experts were asked to indicate the proportions of patients involved in such procedures, based on their professional experience, in order to estimate the probability of these procedures as accurately as possible. A survey was designed using the Delphi technique<sup>47</sup> to obtain a consensus among the experts consulted by means of a two-round questionnaire that contained both aggregate information and any open suggestions made by the experts. The questionnaire was divided into three sections: oncological, surgical, and radiotherapy. The survey was conducted using a CAWI (Computer-Assisted Web-based Interviewing) method, and the questionnaire was sent by email to 21 experts (seven surgeons, six oncologists and eight radiotherapists). The process probabilities adopted in the model were estimated from the means of the proportions indicated by the experts. In all, 11 (response rate 52.4%) experts completed two successive questionnaires and contributed to our achievement of good results in terms of convergence. The respondents included three surgeons, five oncologists and three radiotherapists (and two oncologists and one radiotherapist were female). All the process probabilities estimated with the Delphi survey and their interquartile ranges are reported in the **Supplementary Tables A, B and C**.

## Costs

The study was conducted from the perspective of the Veneto Regional Healthcare Service, considering only the direct costs sustained by the public health authorities, and

using cost data drawn from official reimbursement tariffs in effect in 2019.<sup>48, 49</sup>

We estimated the mean per-patient cost at first after diagnosis, by disease stage.

The unit costs used in the model are given in **Supplementary Tables D-E-F**.

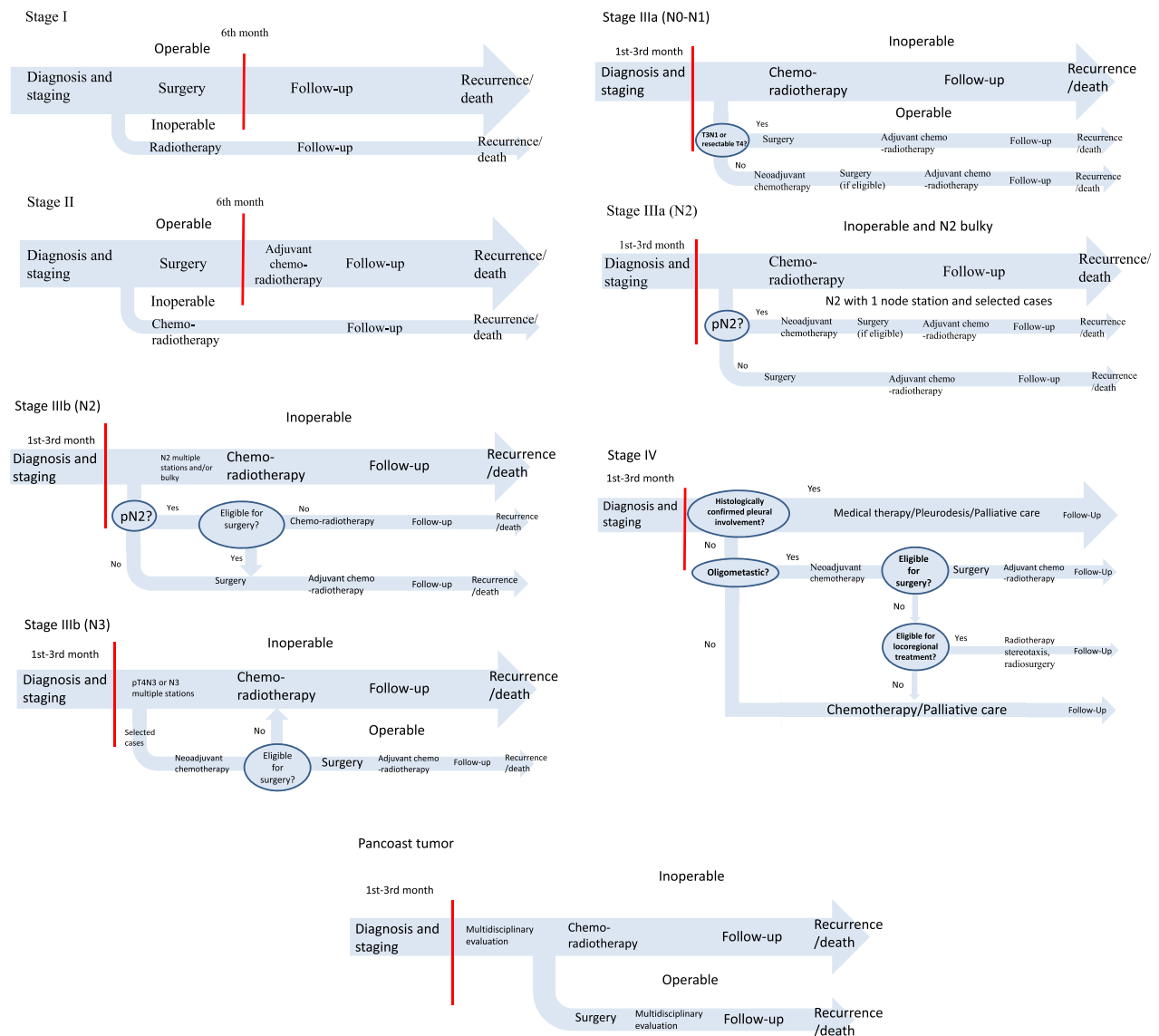
To assess the costs of adjuvant medical therapy, we estimated a monthly cost for each treatment package that included the cost of the drug, the cost of drug delivery, and the cost of routine laboratory tests. These costs were multiplied to complete the whole cycle of therapy (the standard duration of cycle of traditional chemotherapies was drawn from international protocols, whereas the duration of new targeted therapies treatment was assumed as the median progression-free survival for each drug, derived from the registration trials) and up to a maximum of six months, in the first year, because the first six months of the first year after diagnosis was occupied by the diagnostic and staging phase, a surgery phase (if any), and neoadjuvant therapies (Fig 1 and Table 2). For patients interrupting their chemo- or radiotherapy in advance due to treatment toxicities, disease progression or death, the cost was assumed at 50% of the cost of the full treatment. Costs of treatment toxicities were considered, according to the literature, for traditional chemotherapy,<sup>50</sup> for radiotherapy<sup>51–54</sup> and for the modern target-therapies.<sup>55</sup>

The costs of monitoring the courses of therapy were included in the follow-up costs.

We also considered the costs associated in the case of NSCLC-related deaths, we assumed that patients' medical therapy would be stopped in the last three months of life, and the costs of supportive care (derived from a previous study) were assumed for three months.<sup>56</sup>

## Sensitivity analysis

We simulated the probabilistic uncertainty analysis using Monte Carlo simulations and assuming a beta distribution for clinical outcomes' variability, as shown in Table 2. Repeated samples were then drawn from these distributions to establish



**Figure 1** Essential diagnostic and therapeutic pathway for the different stages at diagnosis of NSCLC.

an empirical distribution of the cost estimates. These analyses were done with the TreeAge Pro 2011 software.

## Results

The mean per-patient costs of care during the first year for NSCLC by disease stage and patient management phase are shown in Table 3: 21328 € (95% CI: -20 897–22 322) was the average cost for the first year after a patient was suspected of having lung cancer. The costs were 16 291 € (95% CI: 15 284–17 505) for a patient with stage I disease (95% CI: 18 263–21 091) then dropped slightly for stages II (19 530 €), III (21 938 €) and IV (22 175 €).

A Pancoast tumor is associated with higher costs 28 711 (95% CI: 27 711–29 890). The treatment of choice in this case is surgery preceded by neoadjuvant chemo-radiotherapy, entailing high costs of staging and restaging procedures.

## Discussion

This study enabled a prediction of the direct costs and outcomes for patients diagnosed with NSCLC on a one-year timeline after disease is first clinically suspected.

Our results indicated higher costs than those estimated in previous studies, conducted before the introduction of the latest medical treatment options. For instance, the study published in 2015 by McGuire *et al.*<sup>19</sup> compared NSCLC

**Table 2** Average monthly costs of medical therapy<sup>†</sup> (€)

	Drug	Administration (i.v.)	Biochemical tests	Follow-up visits	Total
Gefitinib	2.190	0	20	14	2.224
Afatinib	1.796	0	20	14	1.830
Erlotinib	1.864	0	20	14	1.898
Crizotinib	4.154	0	20	14	4.188
Pemetrexed + cisplatin	2.914	480	0	0	3.394
Bevacizumab	4604	480	0	0	5.007
Pembrolizumab	5.938	480	0	0	6.418
Nivolumab	4.215	755	0	0	4.970
Nintedanib + docetaxel	643	480	0	0	1.123
Osimertinib	5.437	0	20	14	5.471
Alectinib (I line)	5.208	0	20	14	5.240
Alectinib (II line)	3.958	0	20	14	3.990
Atezolizumab	4.395	480	0	0	4.875
Ceritinib	2.035	0	12	9	2.055

<sup>†</sup>The table refers to the monthly cost of each drug, disregarding the duration of the therapy.

treatment costs between Germany, France and England: the overall cost in the first year for a patient with metastatic versus nonmetastatic disease was estimated at 19227 € versus 17 242 € in France, 10 144 € versus 8059 € in England, and 27 392 € versus 18 338 € in Germany. These last figures were essentially in line with another German study by Schwarzkopf *et al.*<sup>15</sup> published in the same year, which estimated overall spending for lung cancer at 20425 € per patient. A Spanish study<sup>18</sup> also reported per-patient costs ranging from 13 218 € for stage III to 16 120 € for stage II disease. On the other hand, a Dutch study<sup>16</sup> that considered data for the year 2012 found an average cost for stage IV patients similar to ours: after 12.6 months of observation it was 26 109 € (i.e. 22 175 € a year). The high incidence and high costs of NSCLC confirm the huge effort required of our healthcare services, now and in the future, to cope with the distribution of new oncological drugs to all candidate patients. For the time being, new oncological drugs are only approved for patients with metastatic disease,<sup>6–12</sup> However a new monoclonal antibody, durvalumab, is currently being released for stage III patients with positive PDL1 as a consolidation treatment after chemotherapy.<sup>10, 57</sup> It is therefore reasonable to expect costs to increase for locally-advanced

disease in the near future, making some economic concerns even more urgent.

Overall, the high costs of surgery make the early stages of the disease no less expensive than the advanced stages. In fact the differences between the costs of the various stages are quite limited because, as the use of surgery begins to decline for more advanced disease, medical therapies, radiotherapy, treatment for progressions and supportive care take up an increasing share of the total costs (Pancoast tumors tend to carry the highest costs due to the associated diagnostic and staging/restaging techniques, neoadjuvant chemotherapy and surgery involved in the elective treatment of this particular subtype). Actually our cost data showed quite a low stage I to stage IV cost ratio (1/1.4), as seen in previous studies: in Spain it was also 1/1.1, for instance. The cost ratio between metastatic and nonmetastatic disease was 1/1.1 in France, 1/1.3 in England, and 1/1.5 in Germany.<sup>15</sup> These data support the conviction that prevention is still the best weapon for the purpose of controlling the rising costs of lung cancer. Screening for lung cancer has been proposed only recently, and there is no consensus as yet on its efficacy.<sup>58, 59</sup> In short, stressing public health policies and campaigns against tobacco smoking is probably the main solution on which policy-makers should focus to contain the costs of lung cancer. Primary prevention oriented towards containing environmental pollution should also be considered at national political level.

The strength of this study lies in the very detailed model developed by following the main guidelines currently available. This reinforces the reliability of the economic considerations drawn from the model, and made it possible to thoroughly analyze the single stages of NSCLC, and the different phases of the diagnosis, treatment and follow-up of each stage of the disease.

**Table 3** Estimates of average (and confidence interval) per-patient costs of care for NSCLC by disease stage (€) during the first year after diagnosis

	Average total costs	Cost ratio vs. stage I
Stage I	16 291 (95% CI: 15 284–17 505)	1
Stage II	19 530 (95% CI: 18 263–21 091)	1.19
Stage III	21 938 (95% CI: 20 271–25 252)	1.34
Stage IV	22 175 (95% CI: 22 127–22 190)	1.36
Pancoast	28 711 (95% CI: 27 711–29 890)	1.79
TOTAL	21 328 (95% CI: -20 897–22 322)	

Unfortunately, the present work also suffers from some pitfalls that should be mentioned here. First, the model was constructed referring to best practices, but real-world everyday practice may sometimes differ. It is reasonable to assume that physicians do not always follow the guidelines, and that patients are not always wholly compliant. It would therefore be interesting to compare our findings on the expected costs with real-world cost data.

Second, this study only considered the direct costs of NSCLC, disregarding the burden of indirect costs. The latter were investigated in another publication and are known to be considerable, both for the individual and for the health service.<sup>60</sup> In fact, although national social policies help NSCLC patients' families financially to sustain disease-related costs, there is still a non-negligible economic burden for patients and their informal caregivers (usually family members). These indirect costs also appear to be greater the higher the stage of disease at diagnosis.

Third, with regard to the cost of new cancer drugs, we did not consider that some patients may have been enrolled in clinical trials, and that the costs of their therapies would be covered by the pharmaceutical industries, not by the health services. Last but not least, trial data was used to estimate OS and PFS, although real-world evidence has shown that patients receiving treatment may actually derive shorter survival compared to trial patients receiving the same treatment.<sup>61, 62</sup>

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## Disclosure

The authors declare that there are no conflicts of interest.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

**Table S1** Supporting information