Underuse of Radiotherapy in Lung Cancer Has Negative Consequences for Patients

Isabel Tovar, MD, * José Expósito, MD, PhD, * Javier Jaén, MD, PhD, † and Enrique Alonso, MD, PhD ‡

Introduction: Radiotherapy has proven to be an effective treatment when used alone or with other therapies. However, underuse of radiotherapy has been observed in various studies. The objective of this investigation was to assess the use of radiotherapy as initial treatment for lung cancer in a southern region of Europe.

Methods: A systematic review of lung cancer treatment guidelines and observational studies was performed to estimate expected radiation rates and the associated survival outcomes. We then reviewed the clinical and treatment records of all patients undergoing radiotherapy for lung cancer during 2007 in all the 12 public hospitals in Andalusia with radiotherapy facilities. Data were grouped according to type of hospital, patient, treatment characteristics, histological type, and tumor stage.

Results: In 2007, of the 3051 patients estimated to be diagnosed with lung cancer, 610 were treated with initial radiotherapy with an overall radiation rate of 20%, which significantly differed among provinces (range, 8.5%–25.6%, p < 0.001). Given the expected radiation rate of 1383 patients, 773 more patients of lung cancer (25%) should have been treated. According to the literature, the maximum increased survival attributable to the use of radiotherapy in patients diagnosed with non–small-cell lung cancer ranges from 1.8 to 14.1 months. The underuse estimated in the region would correspond to a loss of more than 3000 months in survival time.

Conclusions: The observed underuse of radiotherapy in lung cancer in our region should be a matter of concern, given its negative and measurable impact on the survival of the patients.

Key Words: Lung cancer, Variability, Underuse, Survival, Radiotherapy.

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Lung cancer remains a major health problem in our society. In Spain, 20,000 new cases are diagnosed every year and 18,000 people die of the disease; it is the first cause of death by cancer in men and the third, after breast and colorectal cancer, in women. The incidence in women (almost sixfold lower than in men) has begun to increase in Spain, as in other Western societies.

Non–small-cell lung cancer (NSCLC) represents 80% of lung cancer cases and its clinical management depends to a high degree on the tumor burden at the time of diagnosis, as measured by the stage classification system. According to clinical evidence accumulated over the past few decades, optimal outcomes are obtained if tumors are treated in early stages, when surgery is more feasible. Surgery at the time of diagnosis is possible in 15% to 25% of patients, usually in those with stages I or II and sometimes with IIIA. When surgery is not possible (e.g., in patients with stage IIIB, and sometimes with stages II and IIIA), there is a strong consensus that different combinations of chemotherapy (CT) and radiotherapy (RT) should be administered in a multidisciplinary approach. In most patients with stage IV, the recommended treatment is CT, which is associated with RT for palliative and symptom control purposes. At the time of diagnosis, 30% to 50% of NSCLC patients have stage III disease and 40% have stage IV.

The standard approach in small-cell lung cancer (SCLC) is combined CT and RT, if the disease is limited, which is generally followed by prophylactic cranial irradiation. In cases of extended disease, CT is the therapy of choice, reserving RT for palliative treatment and symptom control.

RT alone or in combination has proven to be effective in lung cancer but may be underused. Studies of the radiation rate (number of patients treated in proportion to total diagnosed cases) are used to examine whether adequate use is made of this important treatment modality and to identify patient groups that may not be obtaining this potential benefit. Two methodologies are used to estimate the RT in lung cancer: epidemiological and evidence-based estimations, and estimations based on benchmarking criteria. It has been calculated that 45% to 55% of patients can benefit from RT in their initial treatment and a further 15% during the course of the disease. By following this model, it is possible to determine the amount of benefit that RT may provide as a function of the stage and histological type (mainly NSCLC or SCLC) of lung cancer. Barbera et al. reported that the potential median survival benefit of RT ranges from 2.2 months in advanced stages of NSCLC and SCLC to 14.1 months in early stages of nonoperable NSCLC. Reports on clinical practice have revealed that the use of RT in lung cancer is less frequent than could be expected. Our group assessed the radiation rate for lung cancer in Andalusia in 2004 (Variability and...
Adequacy of the use of Radiotherapy in Andalusia [VARA I study] and 2007 (VARA II study)\(^5,16\) and found that initial RT was received by 20% of lung cancer patients, which indicated that it was not administered to 25% to 35% of eligible patients. The objective of the present study was to quantify the RT underuse in our setting, based on clinical data and a review of the most recent literature and clinical guidelines, and evaluate its impact on survival.

Andalusia has a surface area of 87,597 km\(^2\) and 7.8 million inhabitants; approximately half (45.6%) of the population lives within a 20-km radius around the eight cities in the region. The regional public health system provides universal free coverage, whereas 10% of the total care is delivered in private health care facilities. Most of the health care is provided in the 34 public hospitals, of which 12 possess RT departments. Each province has at least one public RT facility. Data were collected from public and private centers.

**MATERIALS AND METHODS**

In 2007, a retrospective longitudinal study was conducted in Andalusian in all the 12 public hospitals that offered RT treatments.

Data on all patients with a diagnosis of lung cancer (any histological type and stage) who received initial treatment with lung RT were gathered from the hospital cancer registries, hospital discharge information systems (minimum basic data set), and clinical management computer systems linked to the RT equipment (e.g., Varis, Lantis, and Impac networks). Population data were obtained from the Spanish National Statistics Institute (http://www.ine.es).\(^17\) Cases included in the study were checked against extrapolations from the population-based cancer registry in one province of the region (Granada) and against national estimates. Distributions by histological type and stage were extrapolated from data from the Population Cancer Registry of Granada.\(^18\) Trained researchers, supervised by the staff at each center, obtained patient data from the clinical records and individual treatment records of patients who received RT as initial treatment.

Study variables included characteristics of the hospital (province, megavoltage units, and professionals), patient (age, sex, histological type, performance status with Eastern Cooperative Oncology Group scale or Karnofsky scale, weight loss, and comorbidity), and treatment (medical indication, therapeutic intent, total doses, fractions, nodal irradiation, delay, days of treatment, planning with two-dimensional or three-dimensional, electron linear accelerator or cobalt 60 treatment, and adverse effects). The radiation rate was calculated for each hospital and for the population that it covered. The number of patients on whom RT could be performed was expressed as the percentage of cases by stage (for NSCLC) or by their limited or extended nature (for SCLC).

We reviewed the literature to date on the role of RT in lung cancer and estimated its benefit in each clinical situation based on the studies by Tyldesley et al., Barbera et al.,\(^1\) and Delaney et al.\(^19\) We studied the most recent clinical practice guidelines on lung cancer and reviewed the literature over the past 10 years to ensure that the evidence-based estimate models were up to date. We used the following search algorithm in MEDLINE:

(Health Planning[Mesh]; radiotherapy[all fields]; radiotherapy[MeSH terms]; lung[MeSH terms]; lung[all fields]). The focus of our investigation was the influence of RT as an initial postdiagnosis treatment on lung cancer survival outcomes.

**Statistical Analysis**

A descriptive analysis was performed. The \(\chi^2\) test was used to study the independence of qualitative variables, applying Fisher’s exact test for binary variables. Pearson’s correlation coefficient (or the nonparametric Kendall’s tau-b or Spearman’s rho) and linear regression analysis were used to study relationships among quantitative variables. Two-sided \(p\) values less than 0.05 were considered significant. SPSS version 12.0 (SPSS, Chicago, IL) was used for statistical analyses.

**Ethical Considerations**

This was a prospective study with no diagnostic or therapeutic implications. It was approved by the Andalusian Ethics Committee for Clinical Trials.

**RESULTS**

According to estimates based on data from the Population Cancer Registry of Granada, there were 3051 incident cases of lung cancer, during the study period, in the population of Andalusia. Of these, we obtained data on 610 patients who received RT as initial treatment. Data from clinical records on the histological type, clinical stage, and radiotherapy treatment could be collected in the majority of patients (88%, 76%, and 100%, respectively). Missing data were related to performance status (47%), comorbidity (26%), weight loss (44%), and toxicity (77%).

Of the 610 irradiated patients, 58% underwent RT with radical intent (RT adjuvant to surgery in 8% of these) and 42% with palliative intent. The radiation rate was 20% (Table 1). Significant differences in radiation rates were observed among the eight provinces of Andalusia, ranging from 8.5% to 25.6% (\(p < 0.001\)).

Table 2 shows the distribution by stage and histology of the 3051 expected cases, with indication of initial RT for lung cancer. Among the NSCLC cases, 62% were with stage III

<table>
<thead>
<tr>
<th>Province</th>
<th>LC Cases</th>
<th>RT for LC</th>
<th>LC RT Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>244</td>
<td>21</td>
<td>9</td>
</tr>
<tr>
<td>2</td>
<td>458</td>
<td>54</td>
<td>12</td>
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<tr>
<td>3</td>
<td>305</td>
<td>70</td>
<td>23</td>
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<td>4</td>
<td>336</td>
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<td>26</td>
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<td>5</td>
<td>183</td>
<td>48</td>
<td>26</td>
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<tr>
<td>6</td>
<td>244</td>
<td>48</td>
<td>20</td>
</tr>
<tr>
<td>7</td>
<td>580</td>
<td>132</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>701</td>
<td>150</td>
<td>21</td>
</tr>
<tr>
<td>Total</td>
<td>3051</td>
<td>610</td>
<td>20</td>
</tr>
</tbody>
</table>

\(p < 0.001\)

RT, radiotherapy; LC, lung cancer.

\(^{15,16}\) Barbera et al. \(^{17}\) Cases included in the study were checked against extrapolations from the population-based cancer registry in one province of the region (Granada) and against national estimates. Distributions by histological type and stage were extrapolated from data from the Population Cancer Registry of Granada.\(^18\) Trained researchers, supervised by the staff at each center, obtained patient data from the clinical records and individual treatment records of patients who received RT as initial treatment.

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and 26% with stage IV. According to recommended radiation rates, 9,11 1383 of these patients were expected to receive RT (1132 [82%] with NSCLC and 251 [18%] with SCLC), that is, 37% of NSCLC patients in stage II, 77% of those in stage III, and 35% of those in stage IV, and 34% of SCLC patients with limited disease. Table 2 also gives the distribution of the 610 patients who actually received initial RT (excluding prophylactic cranial irradiation) by therapeutic intent (radical or palliative). According to these results, there was a statistically significant difference between the theoretical number of lung cancer cases for whom initial RT was indicated and the actual number who received this treatment. Specifically, an additional 638 NSCLC patients should have received RT during the study period, predominantly patients with stages III and IV of NSCLC.

Of the 33 clinical practice guidelines consulted, seven were initially selected as being sufficiently comprehensive, and information from three of these6,7,21 was finally used in our update of recommendations based on their high Appraisal of Guidelines Research and Evaluation (AGREE) scores.20 Of the 46 studies yielded by our search of the literature, 18 were selected for full-length reading mostly related to differences in radiation rates and patterns of care in radiotherapy for lung cancer patients. Table 3 lists the indications for initial RT by stage and reports the clinical benefit (months of survival because of RT) described in the reviewed studies. Survival gains attributed to exclusive RT range from 1.8 months in patients with advanced disease and poor general health status to 14 to 18 months in NSCLC patients who are inoperable because of medical problems.

According to the difference between recommended and observed radiation rates in our population, the failure to administer RT to the 773 lung cancer patients who may have benefited represents a total survival loss of 3038 to 3553 months (253–296 years).

**DISCUSSION**

The radiation rate obtained in our study was 20%, which can be considered very low. The role of RT in the treatment of lung cancer is adequately established in clinical practice guidelines.5,7,21 Using a benchmark approach, Barbera et al.20 reported that initial RT was indicated in 41.3% of lung cancer cases, and similar conclusions were reached by other authors using different study methods.14,19 The Queen’s Cancer Research Institute estimated the appropriate radiotherapy rate for lung cancer patients to be as high as 61%,9 as noted by the European Estro Quarts project.22 The percentage of lung cancer patients eligible for RT includes those with resectable but nonoperable NSCLC in stages I and II, among whom RT has achieved 5-year survival rates of 22% to 37%.23,25 It also includes the much more numerous group of patients with advanced disease (stages IIIa–b) but preserved general health status (performance status 0–1), who receive RT alone or with CT.26–32 Finally, RT with palliative intent has proven beneficial in comparison to support measures alone.33–35 Small-cell tumors can also benefit from treatment with local RT and with whole-brain radiation, which has not been considered here.36

According to the literature,9,11 an additional 773 lung cancer patients (25%) should have been treated. Authors

<table>
<thead>
<tr>
<th>Table 2: Distribution and Comparison of Expected and Observed Cases of Radiotherapy-Related Lung Cancer by Histology and Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NSCLC</strong></td>
</tr>
<tr>
<td><strong>Expected Cases</strong></td>
</tr>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>I</td>
</tr>
<tr>
<td>II</td>
</tr>
<tr>
<td>III</td>
</tr>
<tr>
<td>IV</td>
</tr>
<tr>
<td><strong>SCLC</strong></td>
</tr>
<tr>
<td><strong>Expected Cases</strong></td>
</tr>
<tr>
<td>Stage</td>
</tr>
<tr>
<td>Limited</td>
</tr>
<tr>
<td>Extended</td>
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<tr>
<td>—</td>
</tr>
</tbody>
</table>

**VARA II.**
| aStage distribution following.18 |
| bPercentage of initial radiotherapy following a and 18. |
| cNSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer; RT, radiotherapy; LC, lung cancer. |
investigating the true rate of RT use in lung cancer have expressed concern about the differences in the theoretical rate.\(^{13}\)

An important discrepancy between these rates was also found in the present study, although the radiation rate (20%) was 5% higher than was recorded in a similar study of our region 3 years earlier (relative increase of 17%). Major variations among the eight provinces were observed, as in the previous report, which is consistent with geographic variations described within other countries.\(^{37,38}\) Although global outcomes remain poor in lung cancer, with a 5-year survival of approximately 15%,\(^{39}\) the 20% radiation rate found in our study represents an underuse of RT, which needs to be addressed.

Analysis of RT underuse by NSCLC stage and by the local or disseminated status of SCLC revealed significant differences between clinical practice guidelines and the different lung cancer treatment protocols in our setting. According to our data, the highest underuse rate is among patients with stages III and IV, who could obtain an important benefit from RT,\(^{26-35}\) suggesting that the main underuse lies in its application with palliative intent. It is well documented that radiotherapy significantly improves the quality of life of patients.\(^{40,41}\) According to the published data,\(^{42,43}\) a palliative effect (improvement in outcome and symptom relief) can be achieved in 60% to 80% of patients with clinical superior vena cava syndrome, and other symptoms (e.g., hemoptysis, chest pain, and anorexia) disappeared in more than 50% of cases. Endobronchial radiation has been reported to offer an 82% improvement in dyspnea, 89% improvement in hemoptysis, and 92% improvement in postobstructive pneumonia. Barbera et al.\(^{11}\) showed that the average duration of symptom control gained per case, when treated with palliative intent, is 3.9 months in SCLC and 2.9 months in NSCLC. Hence, palliative RT has an important role in lung cancer and offers benefits to the patients.

Given the population-based retrospective design of our study, the difficulty of achieving a full coverage of cancer-incidence cases, and the uncertain reliability of data sources based on clinical records, we may have underestimated the total number of patients receiving RT for lung cancer, although it is consistent with data gathered in the VARA-I study 3 years earlier. A further study limitation is the lack of an evaluation of the contribution of different components of multidisciplinary treatment to the outcome. This issue is especially critical in analyses of the clinical stages of the disease, given the variability in the effectiveness of different treatments at distinct stages. The net survival benefit of RT assumed in our study is based on our update of the relevant literature.\(^{44-46}\) In addition, as is often the case with large databases on public health, there is little detailed clinical information on individual patients in the study or on their comorbidities. This means that we are unable to determine whether the low RT rate in stage III NSCLC is because of a large number of patients with IIIb disease, a high rate of neoadjuvant chemotherapy plus surgery, or high frequency of severe chronic obstructive pulmonary or heart disease that precludes radiotherapy. However, it is unlikely that these factors could explain the large difference found between expected and observed cases. The low RT rate may also be attributable to a failure to refer the patients to radiation oncology. Stevens et al.\(^{13}\) found that some of the patients in their study were not referred to radiation oncology, although the reasons for this were not clearly understood. The lack of a multidisciplinary team that includes a radiation oncologist may in part explain this underuse. In addition, the majority of studies on trends in lung cancer management have detected an increased use of chemotherapy.\(^{47,48}\) Finally, the Andalusian public health system provides universal free coverage, therefore, economic differences in populations can be ruled out as a possible cause of reduced accessibility.

Variations in medical practice constitute a well-consolidated research approach. Possible explanations of variations were compiled and classified by Wennberg and Gittelsohn.\(^{99,50}\) The underuse observed in the present study may be partly explained by a deficit in resources, compromising accessibility to the therapy. In the region as a whole, there was a mean of 4.2 megavoltage units per million inhabitants, which is low in comparison to the European Union average,\(^{22}\) and the median indication-to-treatment interval was approximately 41 days, which seems a reasonable delay, although this interval significantly differed among hospitals.

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### TABLE 3. Indication for Initial Radiotherapy Treatment in Lung Cancer, Number of Cases, Potential Survival Benefit and Radiotherapy Benefit not Received

<table>
<thead>
<tr>
<th>NSCLC/Stage</th>
<th>RT Type</th>
<th>Indication(^{a})</th>
<th>Percentage of Cases in Stage</th>
<th>Benefit (mo)</th>
<th>Source</th>
<th>Difference R/T(^{a})</th>
<th>Months of Benefit not Received</th>
</tr>
</thead>
<tbody>
<tr>
<td>I/II inoperable</td>
<td>RTr</td>
<td>1b</td>
<td>20 ± 1.8</td>
<td>14/18</td>
<td>23, 24, 25</td>
<td>−80</td>
<td>1120/1440</td>
</tr>
<tr>
<td>I/II/IIIa postsurgery</td>
<td>RTr</td>
<td>2c</td>
<td>8</td>
<td>4.8</td>
<td>26, 27</td>
<td>−41</td>
<td>196.8</td>
</tr>
<tr>
<td>IIIa potentially resectable</td>
<td>RTr+CT</td>
<td>1b</td>
<td>75 ± 10</td>
<td>5–8</td>
<td>28, 29, 30</td>
<td>−66.5</td>
<td>332/352</td>
</tr>
<tr>
<td>IIIb PS 0–1</td>
<td>RTr+CT</td>
<td>1a</td>
<td>5–8</td>
<td>30, 31, 32</td>
<td>−98.25</td>
<td>491/786</td>
<td></td>
</tr>
<tr>
<td>IIIb PS &gt;2, weight loss</td>
<td>RTp</td>
<td>1a</td>
<td>1.8</td>
<td>33, 34, 35</td>
<td>−98.25</td>
<td>176.8</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>RTp</td>
<td>1a</td>
<td>35 ± 7</td>
<td>1.8</td>
<td>21</td>
<td>−230</td>
<td>419.4</td>
</tr>
<tr>
<td>SCLC limited</td>
<td>RTrc</td>
<td>1a</td>
<td>34 ± 3</td>
<td>2.4</td>
<td>36</td>
<td>−126</td>
<td>302.4</td>
</tr>
<tr>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>Total</td>
<td>−740</td>
</tr>
</tbody>
</table>

\(^{a}\)Level of evidence and grade of recommendation (Evidence-based medicine according to reference 7)

\(^{b}\)Difference between real and theoretical cases by stage, performance status, and indication for surgery.

RT, radiotherapy; RTr, radical radiotherapy; RTp, palliative radiotherapy; RTrc, radiotherapy for consolidation; CT, chemotherapy; PS, performance status; NSCLC, non–small-cell lung cancer; SCLC, small-cell lung cancer.
The potential influence of socioeconomic factors\textsuperscript{51} was not addressed in this study. Variations in the application of RT in lung cancer may also be because of differences in clinical decision making, as reported by other authors.\textsuperscript{52,53} Interestingly, our review of clinical trials over the past decade showed that the standard treatment control arm in most of them does not include RT.\textsuperscript{50,54} A parallel investigation in our region carried out by the Health Technology Agency over the same period reached the unexpected conclusion that the higher number of patients receiving initial CT than RT for lung cancer was related to easier access to cytostatic treatments and greater discretion in their use by the attending physician,\textsuperscript{55} supporting the hypothesis that the clinical pattern of care makes a partial contribution to RT underuse.

In summary, there seems to be a suboptimal use of RT in lung cancer patients in our region. The underuse during the year under study may have been responsible for an overall loss of more than 700 patients in our region, who did not receive the clinical benefits of RT treatment with either radical or palliative intent. It is difficult to explain why a treatment of proven effectiveness is withheld from patients with a disease that has a very poor prognosis, but it clearly indicates the need for action to improve accessibility to RT resources. Furthermore, reasonable options to increase the proper use of RT in our region would include a greater involvement of radiation oncologists in multidisciplinary tumor boards to enhance appropriate evidence-based decision making.

ACKNOWLEDGMENTS

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