Type of resection and prognosis in lung cancer. 
Experience of a multicentre study

Ramón Rami-Porta\textsuperscript{a,}\*, Miquel Mateu-Navarro\textsuperscript{a,}\textsuperscript{de}, Jordi Freixinet\textsuperscript{b}, Mercedes de la Torre\textsuperscript{c}, Antonio José Torres-García\textsuperscript{d}, Yat-Wah Pun\textsuperscript{e}, Antonio Cantó Armengod\textsuperscript{f}, on behalf of the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S)\textsuperscript{1,2}

\textsuperscript{a}Thoracic Surgery Service, Hospital Mutua de Terrassa, University of Barcelona, Plaza Dr. Robert, 5. 08221 Terrassa (Barcelona), Spain
\textsuperscript{b}Thoracic Surgery Service, Hospital de Gran Canaria Dr. Negrín, Las Palmas, Gran Canaria, Spain
\textsuperscript{c}Thoracic Surgery Service, Hospital Juan Canalejo, La Coruña, Spain
\textsuperscript{d}Thoracic Surgery Service, Hospital Universitario San Carlos, Madrid, Spain
\textsuperscript{e}Thoracic Surgery Service, Hospital de la Princesa, Madrid, Spain
\textsuperscript{f}Thoracic Surgery Service, Hospital General Universitario, Valencia, Spain

Received 7 February 2005; received in revised form 18 June 2005; accepted 21 June 2005; Available online 26 August 2005

Abstract

Objective: Analysis of prognosis of the different types of resections for lung cancer defined by the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S). Methods: From October 1993 to September 1997, 2994 patients with bronchogenic carcinoma who underwent thoracotomy were prospectively recruited by the GCCB-S. Prior to recruitment, the GCCB-S had defined two types of non-resectional operations (diagnostic and exploratory thoracotomies) and three types of resections (complete-CR-: free resection margins, mediastinal nodal dissection, no extracapsular nodal involvement, no involvement of most distant removed nodes; relatively incomplete-RIR-: free resection margins, no mediastinal nodal dissection, unremoved nodes, involvement of most distant removed nodes, positive pleural effusion with no pleural implants; and incomplete-IR-: positive resection margins, extracapsular nodal involvement, unremoved positive nodes, positive pleural effusion with pleural implants). For survival analyses, patients with small cell carcinoma, induction therapy, postoperative mortality, unclassified operation, or lost to follow-up were excluded. The total number of evaluable patients was 2543. Results: In 1047 (97\%) patients, RIR was defined because they had undergone a lesser nodal evaluation than mediastinal nodal dissection. Five-year survival and 95\% confidence interval were: diagnostic thoracotomy 11\% (0–30\%), exploratory thoracotomy 5\% (1–9\%), IR 20\% (14–26\%), RIR 43\% (39–47\%), and CR 45\% (41–49\%). Differences between IR and CR or RIR were statistically significant (\(\text{P} < 0.0001\)), but those between CR and RIR were not (\(\text{P} = 0.18\)). Conclusions: CR and RIR should be combined in a single category as complete resection, because they do not discriminate prognostic differences.

© 2005 Elsevier B.V. All rights reserved.

Keywords: Lung cancer surgery; Resection for lung cancer; Complete resection in lung cancer

1. Introduction

The objective of the surgical treatment of bronchogenic carcinoma is to perform a complete resection of all known disease. This is achieved by removing the portion of the lung involved, either by lobectomy or pneumonectomy, en bloc with the peripheral structures affected by the tumour, and by adding an intraoperative nodal evaluation [1]. Although there are several definitions of complete resection [2–4], based on the R0 (no residual tumour) category of the residual tumour classification of the International Union Against Cancer (UICC) [5], there lacks one that is internationally accepted.

The objective of this paper is to present the prognosis of surgically resected bronchogenic carcinoma depending on the type of surgical resection performed as defined by the Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery (GCCB-S).
2. Material and methods

2.1. General

2.1.1. Population

All patients with bronchogenic carcinoma who underwent thoracotomy from October 1993 to September 1997 in hospitals participating in the GCCB-S were registered prospectively in a homogeneous way [6]. The annual cumulative number of cases was close to 50% of the surgical cases occurring in Spain. The participating GCCB-S centres had a wide variety of activities, including a representative range of number of beds, teaching or research activities (university and non-university hospitals), public and private ownership, and number of patients registered in the study period (median: 158; range: 8-398). The fact that one hospital submitted 8 patients only is an exception; this hospital series was included because the patients had complete demographic, clinical, surgical, pathologic and follow-up data. Operative mortality was understood to include all deaths directly related with the surgical act, regardless of time of occurrence. The final number of patients included in the registry was 2994, of whom 2771 (92.6%) were male. Median age was 66 years (range: 30-91 years). Histological types were distributed as follows: squamous cell carcinoma 1774 (59%), adenocarcinoma 759 (25%), large cell carcinoma 190 (6%), unspecified non-small cell carcinoma 138 (5%), bronchoalveolar carcinoma 84 (3%), and small cell carcinoma 49 (2%). All long-term survivors have been followed up for more than 5 years.

2.1.2. Methods

Similar criteria for the functional operability of patients and oncological operability of the tumour were used in all the GCCB-S hospitals [7]. In the GCCB-S registry, each component defining the cT-category was considered separately, and the procedure used to define it was recorded for each patient.

The degree of certainty of the TNM classification depends on the diagnostic methods used [5]. By consensus among the members of the GCCB-S coordinating group (two thoracic surgeons and a chest physician), we established the methods for maximum classificatory certainty for each component of the TNM classification [8,9]. To confirm a cN1 classification, cytohistological study was required. The absence of lymph node enlargement or lymph node enlargement of less than 1 cm in diameter had to be confirmed by computed tomography in lymph node areas 4, 7 and 10, on both sides, and 5 and 6 for tumours of the left upper lobe or left main bronchus [10]. If these criteria were not met, negative mediastinoscopy–mediastinotomy or negative fine-needle aspiration biopsy (transbronchial, transthoracic, or transoesophageal) of these areas was required. The conditions for a complete resection are: free resection margins, proved microscopically, that is, an R0 resection [5]; and all of the following: mediastinal nodal dissection, no extracapsular mediastinal nodal involvement, and no involvement of nodal resection margins (nodal stations 2 and 9). Relatively incomplete resection. It requires free resection margins, proved microscopically—it also is, therefore, an R0 resection [5]—; and any of the following: no mediastinal nodal dissection, unresected lymph nodes with negative biopsy, involvement of removed nodal station 2 or 9 when a mediastinal nodal dissection had been performed, positive pleural effusion with no apparent pleural involvement, that is, with no macroscopic pleural implants. Although there is no data to suggest that these resections could be incomplete, they do not fullfill the criteria of complete resection.

Incomplete resection. It requires: positive resection margins—that is, an R1 (microscopic residual tumour) or R2 (macroscopic residual tumour) resection [5]—, or extracapsular involvement of positive mediastinal nodes, or unresected lymph nodes with positive biopsy, or positive...
pleural effusion with apparent pleural involvement, that is, there are macroscopic pleural implants.

2.2.3. Definitions of intraoperative lymph node assessment

In a similar way, the different forms of mediastinal nodal staging had been predefined:

No assessment. Biopsies or removal of lymph nodes is not performed.

Excision of lymph nodes. Removal of one or several nodes from one or several lymph node stations. Nodal sampling, defined as the removal of at least one node from every nodal station of the ipsilateral mediastinum, is included under this heading.

Mediastinal nodal dissection. Removal of all lymph nodes from all nodal stations in the ipsilateral mediastinum, en bloc with the surrounding fatty tissue, if possible, so that there is no visual or palpation evidence of remaining nodes on that side of the mediastinum.

Extended dissection. Removal of contralateral mediastinal nodes by median sternotomy as a complement to the regular mediastinal nodal dissection. It was never performed in this series.

During the period of patient registration, the American Thoracic Society (ATS) lymph node map [10], accepted by the Spanish Society of Pneumology and Thoracic Surgery in 1986 [13], was used.

2.2.4. Resection margins

Four marginal locations were defined for descriptive purposes: bronchial stump, with specification of type of involvement, i.e. carcinoma in situ or invasive carcinoma; vascular stump, either arterial or venous; and peripheral margin of the resected specimen.

2.2.5. Statistical analysis

For the prognostic analysis, survival was calculated for each type of operation with the Kaplan-Meier method. The Log-rank test was used to compare survival of each type of operation.

3. Results

Most resections were either complete or relatively incomplete. The rate of non-resectional interventions was less than 10%, and so was the rate of incomplete resections (Table 1). Table 2 shows the type of lung resections performed, their operative mortality, and 5-year survival rates. Operative mortality for pneumonectomy was significantly higher than the rates for other resections (P=0.001). Survival of patients who underwent lobectomy was significantly better than that for patients undergoing other resections (P=0.0001).

Table 3 shows the distribution of the different interventions according to pathological tumour stage. Most diagnostic and exploratory thoracotomies were performed in patients with tumours in pathological stage IIIB, and most incomplete resections occurred in patients with pathological stages IIIA and IIIB tumours. Complete and relatively incomplete resections were distributed quite evenly among the different stages.

A lesser intraoperative nodal assessment than mediastinal nodal dissection, as defined by the GCCB-S, was performed in 1042 (97%) patients with relatively incomplete resection. Table 4 shows survival data of the different stages. The survival of patients with positive lymph nodes on stations 2 and 9, and of those with positive pleural effusion is very poor, and significantly differs from all the others.

Residual tumour at the bronchial stump, peripheral tumour margin involvement and extracapsular nodal spread were the most common causes of incomplete resections (Table 5).

For a total of 2754 evaluable patients, operative mortality was: 1 (6%) in 18 diagnostic thoracotomies; 19 (7%) in 255 exploratory thoracotomies; 30 (12%) in 257 incomplete resections; 80 (8%) in 988 relatively incomplete resections; and 106 (9%) in 1236 complete resections. Although operative mortality was slightly higher in exploratory thoracotomies, differences were not statistically significant.

Diagnostic and exploratory thoracotomies were associated with poor prognosis, with 5-year survival rates of 11 and 5%, respectively. One hundred and eighty-seven patients...
who underwent thoracotomy without lung resection received adjuvant therapy and 65 did not. Median survival (11.5 and 9.6 months, respectively) and 5-year survival rates (6 and 7%, respectively) were not statistically significant (\( P \leq 0.27 \)).

Long-term survival for patients who underwent incomplete resections was considerably reduced compared with that of patients with complete and relatively incomplete resections. Their 5-year survival rates were 20, 45, and 43%, respectively. Survival after complete and relatively incomplete resections did not differ (\( P \leq 0.18 \) (Table 6 and Fig. 1).

In order to further analyse the prognostic significance of complete and relatively incomplete resections, a specific survival analysis was carried out among patients with early-stage tumours (pIA to pIIB with classification certainty [8,9]). Five-year survival was the same for both types of resection (Table 7).

Three hundred and eighty patients with pathological stage IIIA tumours received adjuvant treatment and 97 did not. The differences between their median survival (20.7 and 25.1 months, respectively) and 5-year survival rates (6 and 7%, respectively) were not statistically significant (\( P \leq 0.27 \)).

Long-term survival for patients who underwent incomplete resections was considerably reduced compared with that of patients with complete and relatively incomplete resections. Their 5-year survival rates were 20, 45, and 43%, respectively. Survival after complete and relatively incomplete resections did not differ (\( P \leq 0.18 \) (Table 6 and Fig. 1).

In order to further analyse the prognostic significance of complete and relatively incomplete resections, a specific survival analysis was carried out among patients with early-stage tumours (pIA to pIIB with classification certainty [8,9]). Five-year survival was the same for both types of resection (Table 7).

Three hundred and eighty patients with pathological stage IIIA tumours received adjuvant treatment and 97 did not. The differences between their median survival (20.7 and 25.1 months, respectively) and 5-year survival rates (6 and 7%, respectively) were not statistically significant (\( P \leq 0.27 \)).

Long-term survival for patients who underwent incomplete resections was considerably reduced compared with that of patients with complete and relatively incomplete resections. Their 5-year survival rates were 20, 45, and 43%, respectively. Survival after complete and relatively incomplete resections did not differ (\( P \leq 0.18 \) (Table 6 and Fig. 1).

In order to further analyse the prognostic significance of complete and relatively incomplete resections, a specific survival analysis was carried out among patients with early-stage tumours (pIA to pIIB with classification certainty [8,9]). Five-year survival was the same for both types of resection (Table 7).

Three hundred and eighty patients with pathological stage IIIA tumours received adjuvant treatment and 97 did not. The differences between their median survival (20.7 and 25.1 months, respectively) and 5-year survival rates (6 and 7%, respectively) were not statistically significant (\( P \leq 0.27 \)).

Long-term survival for patients who underwent incomplete resections was considerably reduced compared with that of patients with complete and relatively incomplete resections. Their 5-year survival rates were 20, 45, and 43%, respectively. Survival after complete and relatively incomplete resections did not differ (\( P \leq 0.18 \) (Table 6 and Fig. 1).

In order to further analyse the prognostic significance of complete and relatively incomplete resections, a specific survival analysis was carried out among patients with early-stage tumours (pIA to pIIB with classification certainty [8,9]). Five-year survival was the same for both types of resection (Table 7).

Three hundred and eighty patients with pathological stage IIIA tumours received adjuvant treatment and 97 did not. The differences between their median survival (20.7 and 25.1 months, respectively) and 5-year survival rates (6 and 7%, respectively) were not statistically significant (\( P \leq 0.27 \)).

Long-term survival for patients who underwent incomplete resections was considerably reduced compared with that of patients with complete and relatively incomplete resections. Their 5-year survival rates were 20, 45, and 43%, respectively. Survival after complete and relatively incomplete resections did not differ (\( P \leq 0.18 \) (Table 6 and Fig. 1).

In order to further analyse the prognostic significance of complete and relatively incomplete resections, a specific survival analysis was carried out among patients with early-stage tumours (pIA to pIIB with classification certainty [8,9]). Five-year survival was the same for both types of resection (Table 7).

Three hundred and eighty patients with pathological stage IIIA tumours received adjuvant treatment and 97 did not. The differences between their median survival (20.7 and 25.1 months, respectively) and 5-year survival rates (6 and 7%, respectively) were not statistically significant (\( P \leq 0.27 \)).
of the extent of resection needed in order to perform a resection with no residual tumour left [5].

Different authors and working groups have established their own criteria for complete resection. In one of these definitions, a complete resection requires that the tumour does not extend beyond the visceral pleura or invade the suture line; that there is no mediastinal nodal involvement; and that a complete nodal dissection has been performed [2]. Others, in addition to free tumour margins, include the concept of the most distant node, which must be free of tumour, proved microscopically, as well as the integrity of the nodal capsule, as requirements for complete resection [3]. A multicentre study group accepts a nodal sampling of paratracheal, subcarinal, hilar and bronchopulmonary nodes as a defining factor of complete resection, if the highest node is not involved [4,14].

The GCCB-S established its own definitions of surgical interventions for lung cancer after consideration of all

Table 6

<table>
<thead>
<tr>
<th>Intervention</th>
<th>n</th>
<th>5-year survival</th>
<th>95%CI</th>
<th>Median survival (months)</th>
<th>Log rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnostic</td>
<td>12</td>
<td>11%</td>
<td>0.30</td>
<td>7.67</td>
<td>0.21</td>
</tr>
<tr>
<td>Exploratory</td>
<td>223</td>
<td>5%</td>
<td>1.9</td>
<td>10.82</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Incomplete</td>
<td>223</td>
<td>20%</td>
<td>14.26</td>
<td>19.10</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Relatively incomplete</td>
<td>936</td>
<td>43%</td>
<td>39.47</td>
<td>45.00</td>
<td>0.18</td>
</tr>
<tr>
<td>Complete</td>
<td>1145</td>
<td>45%</td>
<td>41.49</td>
<td>48.20</td>
<td></td>
</tr>
</tbody>
</table>

Notes. 95%CI: 95% confidence interval; other differences are statistically significant: diagnostic versus incomplete resection (P=0.0023), diagnostic versus relatively incomplete (P=0.0001), diagnostic versus complete (P=0.0001), exploratory versus relatively incomplete (P=0.0001), and exploratory versus complete (P=0.0001).

In the series reported in this paper, 2410 (80.5%) patients underwent complete or relatively incomplete resection and their 5-year survival did not differ: 45 and 43%, respectively. This similar survival was also found in patients with tumours in pathological stages IA to IIB (Table 7). In 1042 (97%) patients of the 1068 who underwent relatively incomplete resection, the defining criterion for this type of resection was that mediastinal nodal dissection, as defined by the Group, had not been performed; excision of lymph nodes or nodal sampling had been performed, instead. The main difference between both types of resection was, therefore, the intraoperative nodal assessment. This is a very controversial issue in lung cancer surgery. While some authors consider that a complete nodal dissection is necessary for complete resections [2], others accept a relatively large nodal sampling as an adequate intraoperative nodal assessment that qualifies for complete resection [4,14]. In fact, a prospective, randomised, study comparing complete mediastinal nodal dissection with nodal sampling has shown that both procedures identify a similar number of involved N1 and N2 nodes [11] and that complete mediastinal nodal dissection had a discrete survival benefit over nodal sampling in patients with pH1 and pN2 with one positive nodal station, only [15]. Another study showed that complete mediastinal nodal dissection had some survival benefit over nodal sampling in patients with right-sided others already reported. These definitions were used by all members participating in the Group’s project and were applied to 2994 patients prospectively recruited and registered in the 4-year period from October 1993 to September 1997. Once the definition of complete resection was established, the requirements for incomplete resection were also defined. Any residual tumour, either at the resection margins, or in the form of extracapsular nodal involvement, unexcised positve nodes, or positive pleural effusion with apparent pleural involvement, qualified for incomplete resection. In complete resections, there is no evidence of residual tumour, while in incomplete resections, there is evident residual tumour left in the chest. However, there are certain resections in which there is no evidence of residual tumour, but do not fulfil all the established criteria for complete resection. For these cases, the GCCB-S defined the relatively incomplete resections.

Table 7

<table>
<thead>
<tr>
<th>Intervention</th>
<th>n</th>
<th>5-year survival</th>
<th>95%CI</th>
<th>Median survival (months)</th>
<th>Log rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete</td>
<td>877</td>
<td>51%</td>
<td>47.55</td>
<td>+60</td>
<td>0.0002</td>
</tr>
<tr>
<td>Incomplete</td>
<td>60</td>
<td>29%</td>
<td>17.41</td>
<td>24</td>
<td>0.0004</td>
</tr>
<tr>
<td>Relatively incomplete</td>
<td>582</td>
<td>50%</td>
<td>46.54</td>
<td>59.5</td>
<td></td>
</tr>
</tbody>
</table>

Notes. 95%CI: 95% confidence interval; survival differences between complete and relatively incomplete resections did not reach statistical significance: P=0.67.

Fig. 1. Survival curves of complete resection (red), relatively incomplete resection (blue), incomplete resection (magenta), and non-resectional operations (exploratory and diagnostic thoracotomies) (grey).
carcinoma and pN2 [16]. A specific analysis of survival considering the circumstances that define relatively incomplete resections shows that three of them have a similar prognosis, but the other two (positive nodal stations 2 and 9, and positive pleural effusion) have a very poor prognosis (Table 4). These findings suggest that these two categories should be removed from the definition of relatively incomplete resection and transferred to the definition of incomplete resection.

In 1996, the term systematic nodal dissection was agreed upon in an international workshop on intrathoracic staging [17]. For the excision of mediastinal nodes, two standards were accepted: while it would be desirable that a complete dissection of all mediastinal tissue were performed, the excision of three mediastinal nodal stations, one of which should be the subcarinal station, could be accepted to fulfil the definition. That is, the removal of nodes of three mediastinal nodal stations can also be called systematic nodal dissection. Our results seem to justify the two standards of this definition and the requirements for complete resection of other groups [4,14]: the survival of patients with mediastinal nodal dissection and with mediastinal nodal sampling was the same.

Interventions in which no therapeutic lung resection is performed represent less than 10% of all the thoracotomies of the GCCB-S. Their prognosis is poor, with 5-year survival rates of 11 and 5% for diagnostic and exploratory thoracotomies, respectively. The difference between both procedures is subtle, but has practical and academic meaning. While a diagnostic thoracotomy is a failure of thoracotomy usually is a failure of clinical staging. Although their mortality rates do not differ from those of thoracotomies with lung resection, they should be avoided because they have no therapeutic benefit. In these non-resectional interventions and in advanced tumours (pIIA, pIIIB and pIV), adjuvant treatment does not seem to affect long-term survival.

The objective of surgical treatment of lung cancer is to completely resect all known disease. However, this is not always possible for varied reasons (Table 4). Incomplete resections occurred in 287 (9.6%) patients of this series and the most common causes were extracapsular nodal involvement, residual tumour at the bronchial stump, and residual tumour at the peripheral tumour margin. Although in some cases, a complete resection might be possible with extracapsular tumour spread, especially when this occurs in a cluster of nodes, the fact is that when the tumour goes beyond the nodal capsule and involves the perinodal fat, a complete resection cannot be guaranteed. When there is extracapsular nodal spread, prognosis is worse and 5-year survival generally is under 20% [18,19], similar to the survival of patients with incomplete resection of this series.

Some series have shown that the presence of carcinoma in situ at the bronchial stump does not seem to affect survival, but when there is mucosal or peribronchial involvement, prognosis is adversely affected [20-22]. Regardless of its prognosis, the presence of any type of residual disease at the bronchial stump should be considered an incomplete resection. At present, residual in situ carcinoma is indicated as R1 (is), in order to differentiate this type of residual disease from residual invasive carcinoma [23].

From the experience of this multicentre study we can conclude that lung resections with no residual tumour associated with mediastinal nodal dissection or a wide sampling, with negative nodal stations 2 and 9 and no positive pleural effusion, qualify for complete resections. Although this may not apply to individual institutions or surgeons, combining these two types of resections into one may be of practical importance to plan larger international multicentre studies in which it might be easier to reach an agreement on a certain nodal sampling than in the technique and extent of mediastinal nodal dissection.

References

[14] Mountain CF, Lukeman JM, Hammar SP, Chamberlain DW, Coulson WF, Page DL, the Lung Cancer Study Group Pathology
Appendix. Bronchogenic Carcinoma Cooperative Group of the Spanish Society of Pneumology and Thoracic Surgery

Coordinators:
José Luis Duque, MD (Hospital Universitario, Valladolid); Ángel López Encuentra, MD (Hospital Universitario 12 de Octubre, Madrid); Ramón Rami-Porta, MD (Hospital Mutua de Terrassa, Barcelona).

Local representatives:
Julio Astudillo, MD (Hospital Germans Trias i Pujol, Barcelona); Emilio Canalis, MD (Hospital Clinic, Barcelona); Antonio Cantó Armengod, MD (Hospital Clínico, Valencia); Juan Casanova, MD and Manuel Maríñan, MD (Hospital de Cruces, Bilbao); Jorge Cerezal, MD (Hospital Universitario, Valladolid); Antonio Fernández de Rota, MD and Ricardo Arrabal, MD (Hospital Carlos Haya, Málaga); Federico González Aragoneses, MD and Nicolás Moreno Mata, MD (Hospital Gregorio Marañón, Madrid); Jorge Freixinet, MD and Pedro Rodríguez-Suárez, MD (Hospital de Gran Canaria Dr. Negrín, Las Palmas); Nicolás Llobregat Poyán, MD (Hospital Central de la Defensa, Madrid); Nuria Maíles, MD (Fundación Jiménez Díaz, Madrid); Miguel Mateu-Navarro, MD and Mireia Serra-Mitjans, MD (Hospital Mutua de Terrassa, Barcelona); José Luis Martín de Nicolás, MD (Hospital Universitario 12 de Octubre, Madrid); Nuria Novoa Valentín, MD (Complejo Hospitalario, Salamanca); Jesús Rodriguez, MD (Complejo Hospitalario, Oviedo); Antonio José Torres García, MD and Ana Gómez, MD (Hospital Universitario San Carlos, Madrid); Mercedes de la Torre (Hospital Juan Canalejo, La Coruña); Abel Sánchez-Palencia Ramos, MD and Javier Ruiz Zafra, MD (Hospital Virgen de las Nieves, Granada); Andrés Varela Ugarte, MD (Clínica Puerta de Hierro, Madrid); Yat Wah Pun, MD (Hospital de la Princesa, Madrid).

Data analysis:
Agustín Gómez de la Cámara, MD and Francisco Pozo Rodríguez, MD (Hospital Universitario 12 de Octubre, Madrid).