Lung Cancer in Spain

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Lung Cancer Epidemiology and Tobacco Use in Spain

Lung cancer is the fourth most common cancer diagnosed in Spain in both sexes, after colorectal, prostate, and breast cancers (Table 1), with a 5-year survival of 12.7% in men and 17.6% in women reported for the period 2008 to 2013. In 2019, the incidence of lung cancer in Spain was 29,053 cases (22,083 in men and 7420 in women).1 Whereas the incidence continues to increase (29,638 estimated new cases of lung cancer), this is seen mainly among women, with an estimated 5.0% increase in 2020; in contrast, a downward trend is seen in men (−1.1%). Of particular concern is that in the age group of 45 to 64 years, a higher proportion of lung cancer cases are reported in women than men (45% versus 32%, respectively).2

In 2017, lung cancer was the leading cause of cancer-related deaths in Spain for both sexes (19.5% of cancer mortality).1 Although lung cancer mortality in Spanish women has not yet overtaken that of breast cancer (Table 1), mortality rates in women continue to rise (+2.2%), whereas, in men, there is a downward trend (−0.4%) (Fig. 1).3 This reflects the fact that the peak in smoking among men in Spain was reached in the 1950 to 1959 birth cohort, whereas smoking among women was rare until 1960. Sex remains a strong prognostic factor, and Spanish women with lung cancer have a significantly better prognosis than their male counterparts.3

Traditionally, Spain has been a country with a deeply rooted tobacco use, with a smoking rate of over 32% of the population at the beginning of the century. This has decreased over the past two decades, such that in 2017, 22.1% of the Spanish population were considered current smokers (25.6% of men, 18.8% of women), and 24.9% were former smokers. Although the tobacco control policies have been adopted in Spain after 2006, the smoking prevalence in women has remained stable in recent years (Fig. 2).4 Notwithstanding these policies, smoking continues to be a significant health problem in Spain, with a 3.3% increase in new smokers between 2017 and 2019. This increase is particularly significant given that 25% of smokers are between the ages of 20 to 29 years, and 22% are younger than 20 years, with a median age of smoking onset of 17 years. Of particular concern is the fact that in 2018, daily smoking prevalence among Spanish adolescents aged 15 to 18 years was 8.7%.5 Radon exposure is the second most common risk factor in Spain for lung cancer after tobacco consumption. Galicia, an autonomous community (AACC) in the northwest of Spain, has the highest indoor radon concentrations in all of Spain because of the granitic nature of the subsoil.6

In a recent thoracic tumor registry study by the Spanish Lung Cancer Group (SLCG), the clinical and pathologic characteristics of Spanish patients with NSCLC treated between 2016 and 2018 were reported for 6600 patients recruited in 56 centers nationwide. This study reported that the mean age at diagnosis was 64 years, 86% were current or former smokers, 80%
presented with advanced disease, and adenocarcinoma was the most frequent histologic subtype.7

Spanish Health Care System

The Spanish health care system is complex. Both private medical care (contracted by 13.5% of the population) and the public health system are available, with the public system covering 99.7% of the Spanish population. The Spanish National Health System (SNS) is funded by taxes and operates through a public network of providers. As a result, health care in Spain is free of charge for residents paying social security. The management of public hospitals in Spain was transferred to the Departments of Health of each of the 17 AACCs. The AACCs have the freedom to regulate hospital activities (including the disapproval of new drugs even when they have been approved by the National Health System) and to decide on the management of hospital finance, which can induce disparities and inequity in oncological care.

Screening

There is no national lung cancer screening program in Spain. In light of the results of recent trials reporting the favorable prognostic implications of screening, it is imperative that further efforts should be undertaken to establish a national lung cancer screening program.

Diagnosis

In Spain, computed tomography (CT) scan is the imaging technique of choice for lung cancer diagnosis, which is widely available nationwide. Staging is routinely performed using positron emission tomography –CT, which, ideally, should be done in all patients—though

### Table 1. Most Common Cancer Types in Spain by Incidence and Cancer-Related Mortality

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<th>Both Sexes (%)</th>
<th>Men (%)</th>
<th>Women (%)</th>
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| **Incidence**
| Colorectal (16) | Prostate (21) | Breast (28) |
| Prostate (12) | Colorectal (17) | Colorectal (16) |
| Breast (12) | Lung (14) | Lung (6) |
| Lung (11) | Bladder (12) | Uterus (6) |
| **Mortality**
| Lung (19.5) | Lung (25) | Breast (14) |
| Colorectal (14) | Colorectal (13) | Colorectal (14) |
| Breast (6) | Prostate (9) | Lung (11) |
| Prostate (5) | Bladder (5) | Pancreas (7) |

**Note:** Table created from Reference 1.

Bold is highlighting lung cancer in the table.


*Mortality estimation for 2017; excludes nonmelanoma skin cancer.

Figure 1. Mortality rates for lung cancer in Spain (per 100,000 inhabitants), standardized by age (1951-2011) in men (left), women (right). Adapted from Sociedad Española de Oncología Médica, 2020.1 SEOM, Spanish Society of Medical Oncology.
access to this technique is limited in some parts of the country and is restricted to patients with suspected lymph node involvement or metastatic disease from a CT scan. For the past 15 years, a number of public multi-disciplinary units have been created within the context of rapid diagnostic programs at a regional or local level. These units provide immediate communication between primary care and the specialized units in referral hospitals composed of pneumologists, pathologists, oncologists, and radiologists to assess patients suspected of having lung cancer and speed up diagnosis and staging. However, neither the formal fast-track referral processes nor recommended time frames in which these patients should be tested in these programs exist at a national level.

The Spanish Society of Pneumology and Thoracic Surgery (SEPAR) recommends that the diagnostic approach for lung cancer include bronchoscopic techniques performed by interventional pulmonologists. Over the past few years, the new endobronchial ultrasound (EBUS) systems (linear and radial EBUS) and ultrathin bronchoscopes for diagnosis of lesions adjacent to airways and peripheral pulmonary lesions have been increasingly introduced in clinical practice. However, not all centers have in-house access to these techniques, which may negatively affect the adequate assessment of newly diagnosed patients. The diagnosis of centrally located tumors is usually performed with flexible bronchoscopy or EBUS-transbronchial needle aspiration, collecting additional samples for molecular analyses. Rapid on-site evaluation allows operators to ensure adequate samples are collected to establish the diagnosis. However, the availability of rapid on-site evaluation is still limited in certain geographic areas and institutions.

Currently, the evaluation, implementation, and reimbursement of biomarker testing by the SNS are very fragmented; however, a strategy for personalized medicine was released in July 2020. According to a national consensus of the Spanish Society of Medical Oncology (SEOM) and the Spanish Society of Pathology (SEAP), the mandatory biomarker tests for all patients with advanced NSCLC include \textit{EGFR} and \textit{BRAF} mutations, \textit{ALK} and \textit{ROS1} rearrangements, and programmed death-ligand 1 (PD-L1) expression (Fig. 3), with nationally approved testing methodologies for \textit{EGFR} and \textit{ALK} testing.

Several national registries have reported that the percentage of patients undergoing NSCLC biomarker characterization has increased, with reports of a 58% rate before 2013, increasing to 74% in 2018. In 2019, the status of \textit{EGFR}, \textit{ALK}, \textit{ROS1}, and PD-L1 in lung adenocarcinoma samples were assessed in 91%, 80%, 56%, and 58% of patients, respectively. Furthermore, the rates vary per biomarker, by region, and institution. The implementation of next-generation sequencing is likewise increasing, but its routine application in clinical practice is still limited throughout the country and is neither covered by the SNS nor private insurance.

\textbf{Surgery}

Thoracic surgery has been a differentiated surgery specialty since 1978. In Spain, there are 250 board-certified thoracic surgeons (0.55 per 100,000 inhabitants) performing lung cancer surgery across 77 hospitals. This population of physicians is relatively young (65% are $\leq$ 50 years of age), with one-third being women.

Almost one-third of all new lung cancer cases diagnosed annually in Spain undergo resection, and
induction therapy is usually indicated for locally advanced lung cancer. With the increasing use of video-assisted thoracoscopic surgery in Spain, the impact of the surgical procedure on the chest wall is minimal, and more borderline patients can undergo lung resection, challenging the concept of patient operability. However, the rate of video-assisted thoracoscopic surgery lobectomies needs to be optimized to allow most patients with lung cancer to benefit from it. Robotic thoracic surgery is likewise being introduced progressively in many Spanish hospitals, but its use remains rare. This surgical modality requires different skills from open surgery, which makes specific training challenging for residents and certified thoracic surgeons in this surgical procedure.

Induction and adjuvant immunotherapy agents are being tested in clinical trials, redefining the concept of tumor resectability in the context of an induction strategy with either immunotherapy or targeted therapies. Surgeons worldwide should keep an open mind when reassessing patients for potential resection of residual disease after treatment of unresectable disease. This is an aspect of multidisciplinary assessment that will have to be considered seriously as more evidence becomes available from clinical trials.

Both the SEPAR and the Spanish Society of Thoracic Surgeons have their own official journals and issue recommendations on the management of lung cancer. Spanish thoracic surgeons, in collaboration with pulmonologists and medical oncologists, have been participating in the International Association for the Study of Lung Cancer Staging Project since the first phase of this project. The Bronchogenic Carcinoma Cooperative Group of the SEPAR contributed 2362 surgical and nonsurgical patients for the eighth edition,13 and is currently registering cases to assess the ninth edition of the TNM classification, due to be published in 2024.

Radiotherapy
The volume and availability of technical equipment in Spanish radiotherapy oncology departments have increased over the past decade, mainly because of private investment. In 2011 there were 109 Radiotherapy Oncology Departments with 236 machines (5.1 machines...
Stage IV NSCLC with druggable genomic alterations

- **ALK translocation**
  - Crizotinib (I, A)
  - Ceritinib (I, A)
  - Alectinib (I, A)

- **ROS1 translocation**
  - Crizotinib (I, A)

- **Sensitizing common EGFR mutation**
  - Gefitinib (I, A)
  - Erlotinib (I, A)
  - Aftatinib (I, A)
  - Dacomitinib (I, A)
  - Osimertinib (I, A)

- **BRCA mutation**
  - Dabrafenib plus Trametinib (Not yet approved in Spain, IB)

- **ROS1 translocation**
  - Crizotinib (II, A)

- **At PD**
  - Alectinib (I, A)
  - Brigatinib (I, I, A)
  - Lorlatinib (I, A)

- **At PD**
  - Lorlatinib (II, A), if not received previously
  - Platinum-based chemotherapy ± ICI

- **For T790M-negative in liquid biopsy, a tissue biopsy is strongly recommended and if positive, osimertinib should be given**

Stage IV NSCLC without druggable genomic alterations

- **PD-L1 < 50%**
  - SCC
    - Platinum + Pemetrexed (I, A)
    - Paclitaxel + Carboplatin (I, A)

  - non-SCC
    - Platinum + Pemetrexed (I, A)
    - Paclitaxel + Carboplatin (I, A)

- **If no prior immunotherapy:**
  - Nivolumab (I, A)
  - Atezolizumab (I, A)
  - Pembrolizumab (PD-L1 > 1%) (I, A)
  - Docetaxel (I, B)

- **PD-L1 ≥ 50% SCC and non-SCC**
  - Pembrolizumab (I, A)

- **If no prior immunotherapy:**
  - Nivolumab (I, A)
  - Atezolizumab (I, A)
  - Pembrolizumab (PD-L1 > 1%) (I, A)
  - Docetaxel ± Nintedanib (II, B), Pemetrexed (I, A)

- **PD-L1 < 50% SCC and non-SCC**
  - Platinum-based chemotherapy according to histologic subtype

- **PD-L1 ≥ 50% SCC and non-SCC**
  - Platinum-based chemotherapy according to histologic subtype

- **Best supportive care (II, B)**

Figure 4. Current treatment guidelines in advanced lung cancer in Spain (A) in oncogene-addicted tumors and (B) in tumors without oncogenic drivers. BVZ, bevacizumab; CT, computed tomography; ICI, immune checkpoint inhibitor; PD, progression disease; PD-L1, programmed death-ligand 1; PS, performance status; SCC, squamous cell carcinoma.

per million inhabitants). This increased to 122 departments in 2017 (76 in the public health system and 46 in the private system) after a private initiative by the Amancio Ortega Foundation (the owner of the company Zara), which invested 320 million euros in machines for the public health care system. As a result, new
equipment and advanced techniques and treatment protocols have been standardized across different territories in Spain. Today, Spain has 721 radiation oncology specialists (78% in the public health system). However, according to the recommendations of the Spanish Society of Radiation Oncology, the optimal ratio is 17 specialists per million people, which means that with a population of 47,329,981 in 2020, there is still a shortage of up to 78 radiation oncologists in Spain. Finally, the Spanish Society of Radiation Oncology, along with other entities, regularly provide updated treatment recommendations on radiotherapy for lung cancer.

**Systemic Therapy**

Recommendations for systemic therapy in lung cancer are developed and published periodically by the Spanish SEOM. Standard cytotoxic immunotherapy and targeted therapies are widely available in all centers throughout the country. In the advanced disease setting, the choice of systemic therapy today is dictated according to the tumoral molecular profile and PD-L1 expression. For EGFR-mutant tumors, the third-generation EGFR tyrosine kinase inhibitor (TKI) osimertinib has been approved for clinical use in Spain since June 2019 and is now the treatment of choice for this subset of lung tumors. Another reimbursed EGFR TKIs include the first- and second-generation TKIs erlotinib, gefitinib, afatinib, and most recently, dacomitinib. However, some centers continue to adopt a sequential strategy characterized by an upfront use of first- or second-generation EGFR TKIs followed by osimertinib at the time of progression and acquired, resistant T790M mutation detected by cell-free DNA or tumor tissue genotyping. For ALK-positive advanced NSCLC, crizotinib, ceritinib, and alectinib are approved and reimbursed by the SNS as first-line treatment options, with alectinib being the most widely used upfront treatment. At progression, sequential strategies with brigatinib or lorlatinib are currently only available in the context of compassionate-use programs or clinical trials. Crizotinib has also been approved for ROSI-positive NSCLC since September 2016. Although genomic guidelines recommend testing for BRAF status and dabrafenib and trametinib is the standard treatment in BRAF V600E–mutant lung tumors, this treatment strategy is not yet approved in Spain (Fig. 4A).

For patients with advanced NSCLC without actionable mutations (EGFR/ALK/ROS-1 negative), immune checkpoint inhibitors (ICIs) are widely used. For advanced NSCLC with high PD-L1 expression (tumor proportion score higher than 50%), pembrolizumab has been considered the standard of care as first-line treatment in Spain since August 2017, regardless of the histologic subtype. However, the combination of ICIs plus platinum-based chemotherapy is not yet approved in this patient subpopulation. For advanced nonsquamous tumors with PD-L1 expression less than 50%, the ICI options include either pembrolizumab combined with platinum-based chemotherapy (approved since September 2019) or atezolizumab combined with bevacizumab and platinum-based chemotherapy, which was approved in March 2020. For advanced squamous tumors, no ICI combination strategy has yet been approved in Spain, although this is eagerly expected before the end of 2020. In the second-line setting and in immune-naive patients with NSCLC, ICIs are the standard of care regardless of the histologic subtype. The docetaxel–nimoterdanib combination is an alternative second-line option, but only in pretreated patients with adenocarcinoma, whereas docetaxel monotherapy is an option regardless of the histology subtype. Current treatment guidelines in Spain in patients without druggable targets are presented in Figure 4B.

Beyond approved molecules, drug access inequalities are one of the main challenges in the European Union (Fig. 5). In Spain, after European Union authorization, the Spanish Agency of Medicines and Medical Products must approve new oncology therapies, after which the Therapeutic Positioning Report (Informe de Posicionamiento Terapéutico) is issued. The Interministerial Commission for the Pricing of Medicines is then responsible for establishing the Pricing and Reimbursement within the SNS. Subsequently, the AACCs cover the expense of these drugs as a part of their regional budgets. In this context, a recent SEOM survey highlighted that major differences currently exist in access to oncology drugs and predictive biomarker analyses between different AACC in Spain (reflecting regional differences) and between different hospitals within the same AACC. Of note, 43% of the oncologists in the survey identified barriers to the access to specified drugs, mainly as consequence of delayed and slow approval process, as well as by the requirement of a supporting report for each patient, and the use of more restrictive criteria than those established for drug commercialization in Spain. In addition, the time taken from the designation of Pricing and Reimbursement until approval for prescription varies substantially between hospitals, with intervals ranging from 0 to 36 months. This situation directly affects our patients whose access to certain drugs and predictive biomarkers depend on the region and the center where they are being treated, raising the important challenges to the Spanish authorities to reduce this intra- and interinequalities within our country.

**Features**

In the past few years, thoracic multidisciplinary tumor boards have been established almost throughout
the entire country. Indeed, different academic groups dedicated to lung cancer diagnosis, treatment, and research, such as the Club Patología Pulmonar from SEAP (www.seap.es), SLCG (www.gecp.es), ICAPEM which focuses on lung cancer in women, and the Grupo Gallego Cancer de Pulmón (www.grupogallegocancerdepulmon.org), have contributed to improving our local knowledge and therapeutic opportunities for this disease. A pertinent example is seen with the SLCG, which amalgamates more than 400 specialists from 150 institutions, and to date, this group has completed more than 80 studies and has included more than 18,000 patients with lung cancer in its many trials. Reducing smoking prevalence (especially in teenagers and women), improving access to genomic profiling, and reducing treatment inequalities are major and pressing future challenges to overcome.

References


