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## Reflections on the Implementation of Low-dose Computed Tomography Screening in Individuals at High Risk of Lung Cancer in Spain<sup>☆</sup>



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### ABSTRACT

Lung cancer (LC) is a major public health issue. Despite recent advances in treatment, primary prevention and early diagnosis are key to reducing the incidence and mortality of this disease. A recent clinical trial demonstrated the efficacy of selective screening by low-dose computed tomography (LDCT) in reducing the risk of both lung cancer mortality and all-cause mortality in high-risk individuals.

This article contains the reflections of an expert group on the use of LDCT for early diagnosis of LC in high-risk individuals, and how to evaluate its implementation in Spain. The expert group was set up by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), the Spanish Society of Thoracic Surgery (SECT), the Spanish Society of Radiology (SERAM) and the Spanish Society of Medical Oncology (SEOM).

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## Reflexiones sobre la implementación del cribado mediante tomografía computarizada de baja dosis en personas con riesgo elevado de padecer cáncer de pulmón en España

### RESUMEN

El cáncer de pulmón (CP) constituye un problema de salud pública de primer orden. A pesar de los recientes avances en su tratamiento, la prevención primaria y el diagnóstico precoz son las claves para reducir su incidencia y mortalidad. Un ensayo clínico reciente demostró la eficacia del cribado selectivo con tomografía computarizada de baja dosis (TCBD) en la reducción del riesgo de muerte en personas de alto riesgo, tanto por CP como global.

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Este artículo recoge las reflexiones de un grupo de expertos designados por la Sociedad Española de Neumología y Cirugía Torácica (SEPAR), la Sociedad Española de Cirugía Torácica (SECT), la Sociedad Española de Radiología Médica (SERAM) y la Sociedad Española de Oncología Médica (SEOM) sobre el uso de la TCBD para el diagnóstico precoz del CP en personas con riesgo elevado de padecerlo y los pasos necesarios para evaluar su implementación en nuestro país.

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## Introduction

Lung cancer (LC) has gone from being a rare disease at the beginning of the 20th century to being the major cause of cancer mortality in industrialized countries.<sup>1,2</sup> In 2012, over 1.8 million cases were diagnosed worldwide and 1.5 million patients died of this disease. In Spain in 2013, 21 664 patients died of LC (17 559 men and 4105 women),<sup>3</sup> accounting for 19.5% of all cancer deaths. The incidence of this disease is no longer rising so fast, having fallen from 29.4% in the 5-year period from 1980 to 1985 to 5.1% from 1995 to 2000, but the number of new cases continues to grow: in 2013, LC increased by 0.8% in men and 7.3% in women compared to the previous year.<sup>4</sup>

Despite advances in the diagnosis and treatment of LC,<sup>5</sup> 5-year survival for all stages in Europe ranges from 9.6% in the United Kingdom to 17.9% in Austria, while in Spain, 5-year survival, at 12.6%, is lower than in the United States (18.7%), and particularly in Japan (30.1%). In Spain, incidence and mortality due to lung cancer in men are close to the European average, with a trend toward stabilization. However, although the incidence of LC in women is among the lowest in Europe, it is clearly on the rise.<sup>6,7</sup> The current men to women ratio of LC incidence is 4.2:1.0.<sup>3</sup> Median age at diagnosis of LC in Spain is 69 years for women and 70 years for men.<sup>8</sup>

LC survival is associated with disease stage at time of diagnosis. Unfortunately, most LCs are still diagnosed at advanced stages, explaining why the 5-year survival rate for all patients is less than 15%.<sup>9,10</sup>

Strategies aimed at reducing tobacco consumption have had the greatest impact on LC mortality.<sup>11</sup> During the last few decades, the value of different radiological techniques and biological markers (e.g., sputum cytology or serum biomarkers) has been investigated, but positive results were only achieved following the publication of studies on the usefulness of screening with low-dose computed tomography (LDCT). Following in the footsteps of various medical societies that have made their positions public,<sup>12</sup> this article contains the reflections of a group of experts designated by the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), the Spanish Society of Thoracic Surgery (SECT), the Spanish Society of Medical Radiology (SERAM) and the Spanish Society of Medical Oncology (SEOM) on the use of the LDCT for the early diagnosis of CP in high-risk individuals, as well as the steps needed to evaluate the implementation of this procedure in our country.

## Evidence on the Use of Low-dose Computed Tomography

One of the first studies to analyze the utility of LDCT to improve LC diagnosis was the National Lung Screening Trial (NLST),<sup>13</sup> which included 53 454 smokers and ex-smokers aged 55–74 years with a minimum consumption of 30 pack-years, or former smokers with less than 15 years of abstinence. Screening was performed annually over a 3-year period, and the usefulness of LDCT was compared with that of standard chest radiography. Results showed a relative reduction of 20% in death due to LC in the LDCT group compared to the chest radiography group (95% confidence interval [CI]: 6.8%–26.7%;  $P=.004$ ), and a 6.7% reduction in overall mortality (CI 95%: 1.2%–13.6%;  $P=.02$ ). The rate of major complications associated with LDCT was 0.06% in positive cases that finally did not have LC,

and 11.2% in those who did, and the surgical mortality rate was 1%. The study was stopped before completing the planned follow-up, after the minimum established endpoint of reduction in mortality was reached.

The NLST study was preceded by 3 randomized trials which found no reduction in mortality compared to the control group.<sup>14–16</sup> The investigators of another comparative European study with a larger sample size (Nederlands Leuvens Longkanker Screenings Onderzoek [NELSON]) have published data on the characteristics of the tumors observed in their study, but the mortality results are still pending.<sup>17</sup>

The International Early Lung Cancer Action Program (I-ELCAP) prospectively recorded survival in patients with stage I LC diagnosed by LDCT.<sup>18</sup> It enrolled 31 567 non-randomized asymptomatic volunteers at risk of developing LC; 484 developed LC and 85% were diagnosed in stage I, with an estimated 10-year survival of 88%. The survival rate of the 302 patients with stage I LC who underwent surgical resection within 1 month of diagnosis was 92%.

## Limitations of the NLST Study

Despite the NLST outcomes, generalized use of LDCT has been limited by some concerns, such as low specificity, overdiagnosis, and fear of radiation. In the NLST follow-up, 112 more cancers were diagnosed in the LDCT group than in the chest X-ray group. These data suggest a rate of overdiagnosis of between 11% and 18%.<sup>13</sup> The Danish Lung Cancer Screening Trial (DLCST) also found more tumors in the LDCT screening group than in the control group.<sup>14</sup> However, a pathology study of the I-ELCAP cohort confirmed that 95% of the tumors diagnosed by LDCT showed signs of invasion, so the rate of overdiagnosis may be lower.<sup>18</sup>

Specificity of the LDCT findings is limited by the finding of benign nodules. In the NLST study, if a cut-off point of a diameter of 4 mm was selected, 96% were false positives (FP). Although most positive results in the NLST study led to follow-up with LDCT alone, 1.8%, 3.8% and 4% of subjects with a positive result in any of the three rounds of screening were subjected to percutaneous aspiration, bronchoscopy or surgery, producing at least 1 complication in 1.4% of the LDCT screening group, and 1.6% in the X-ray screening group. The complication was deemed relevant in 0.06% of cases. Moreover, 0.9% of all positive subjects were subjected to surgery in which no LC was detected.<sup>13</sup> The NELSON study showed that FPs are reduced by analysis of volume-doubling time in nodules detected on LDCT (2.6% in the baseline study and 1.8% in the subsequent annual control), with no increase in false negatives (FN).<sup>19</sup> The NLST study included an analysis of stress associated with screening results in a subgroup of patients with a positive result, which found that neither quality of life nor the degree of anxiety were affected by such a result.<sup>20</sup> In contrast, in the NELSON study, an analysis of the short-term effects on quality of life showed that in a subgroup of individuals with an indeterminate result in the baseline screening round, the STAI anxiety test score was significantly higher compared to the baseline score. This outcome occurred even when the significance of a result of this type was clearly explained, with emphasis on the low risk of the individual having cancer.<sup>21</sup>

An update of the NELSON study data was presented at the 16th WCLC held in Denver (USA) in September 2015.<sup>22</sup> Sensitivity,

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