

## THE WONDERFUL WORLD OF PULMONARY NODULES: AN UPDATE

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### Lung cancer screening update

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#### Abstract

Low-dose computed tomography (ld-CT) for lung cancer screening in high-risk subjects is performed within clinical trials and has started to be used in routine clinical practice. The technique is well defined, even if some methodological problems are still debated, such as the measurements of pulmonary nodules, the size to define them as clinically significant, the management of small or non-solid nodules and the best diagnostic work-up to optimize diagnostic accuracy. The data derived from an IEO observational study, started in 2000, shows a high prevalence and incidence of early stage lung cancer detected at ld-CT, demonstrating the need to prolong observation for a long period of time. The high survival rate of patients with screening-detected cancer has recently been debated in a number of papers using statistical models, but the advantage of the yearly ld-CT for the individuals is unquestionable; its benefit on the population base has still to be demonstrated by ongoing randomized trials.

**Keywords:** *Lung cancer; screening; tomography; X-ray computed; Mass screening.*

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#### Introduction

Lung cancer is very common and prevention strategies to reduce cigarette smoking have had unsatisfactory results<sup>[1]</sup>. In spite of great clinical and research efforts, mortality still remains very high, even if in early stages 70% of cases can be cured by surgery<sup>[2]</sup>. These facts justify the need to introduce lung cancer screening programs with stronger motivation than those used for assessing and spreading the standard protocols for breast, prostate and colonic cancer screening<sup>[3]</sup>. Opportunity and methods for lung cancer screening have been debated for years since the value of low-dose spiral computed tomography (ld-CT) in detecting small parenchymal lesions was demonstrated by some reports<sup>[4,5]</sup>. The diagnostic imaging technique to be applied has been stated in the first report of the Early Lung Cancer Action Program (ELCAP)<sup>[4]</sup>, which describes that the tumor detection rate by CT is four times higher than chest X-ray, and by studies demonstrating similar accuracy of ld-CT and conventional CT in the detection of pulmonary nodules<sup>[6]</sup>. Multislice spiral CT is universally recognized as the most up-to-date and accurate method for the detection of small lung cancer since 2001<sup>[7]</sup>; it

can detect and characterize a lesion at the first diagnostic step in a high percentage of cases.

Data on the impact of CT screening on mortality are few and controversial. The encouraging results of I-ELCAP, in which patients with screening-detected lung cancer had estimated lung cancer-specific survival of 80% at 10 years<sup>[8]</sup>, contrast with the absence of evidence for reduction in lung cancer deaths when screening outcomes in pilot studies were compared with those predicted by models<sup>[9]</sup>. Nevertheless, a model predicting outcomes using data from participants in the Mayo CT screening study<sup>[10]</sup> indicated a 28% reduction in lung cancer mortality at 6 years due to screening, although the reduction in all-cause mortality was only 2% at 15 years due to increased mortality from non-lung cancer causes associated with smoking<sup>[11]</sup>.

#### Controversy on reading and interpretation of ld-CT for lung cancer screening

##### *Size of nodules*

A problem with lung cancer screening by ld-CT is the frequent finding of undetermined non-calcified lung

nodules for which the best clinical management is uncertain<sup>[5,12]</sup>. The use of multi-detector CT and of thin sections have led to an increase in the number of small nodules detected, which requires the development of diagnostic algorithms for their management. Various protocols<sup>[13,14]</sup> have been proposed for the diagnostic work-up of small nodules, but the diagnostic approach to nodules  $\leq 5$  or 4 mm mainly rely on continued observation, with a view to detecting nodule growth as a sign of malignancy. Nevertheless deciding the frequency of follow-up examination is not trivial, as the risk of progression, exposure to X-rays, costs, and patient anxiety must be considered. We demonstrated<sup>[15]</sup> that 90% of nodules  $\leq 5$  mm detected at first CT scan disappear or remain unchanged over the following 4 years. Only 1.2% of these nodules became malignant (all pT1N0), supporting the concept that a prevalent pulmonary micronodule  $\leq 5$  mm can be safely monitored at 1-year intervals. This attitude is supported by data published by Swensen<sup>[16]</sup>, where none of the tumors diagnosed had a diameter  $< 5$  mm, and by Henschke<sup>[17]</sup> who reported no malignancies among 378 nodules  $< 5$  mm detected in 2000 subjects and recommended annual repeated CT screening to define interim growth in this population.

### *Diagnostic work-up*

The size of pulmonary nodules is the main (and may be the only) determinant of their management, but the accuracy of manual diameter measurements is questionable, mainly due to intra- and inter-observer variability<sup>[18]</sup>. The software that can automatically identify and isolate pulmonary nodules and calculate their volume and doubling time on subsequent CTs is commonly used in clinical practice. Generally, the diagnostic work-up of nodules detected in a screening project setting is designed according to similar guidelines<sup>[19]</sup>: solid non-calcified nodules  $> 10$  mm should be examined by positron emission tomography (PET) or biopsy and nodules  $< 5$  mm can be monitored at 1-year intervals without major risk; the diagnosis of 5–10 mm nodules is performed by follow-up repeated CTs. Since volume variations are used as the principal tool in the diagnosis of the nature of nodules  $< 10$  mm detected by screening programs, and since important clinical decisions are taken (i.e. operating on the patient or not) according to these data, the accuracy of this measurement is a critical factor. We have demonstrated that the variability of automated volume calculations for nodules between 5 mm and 10 mm could be significantly different<sup>[20]</sup> and recommend that a volume variation beyond 30% for nodules between 5 and 10 mm should be confirmed by a further follow-up CT to be sure that a nodule is actually growing.

PET with [<sup>18</sup>F]fluorodeoxyglucose (FDG) is a non-invasive technique used for identifying malignant lung lesions with reported sensitivity in the range 80–100%<sup>[21,22]</sup>, but PET suffers from poor sensitivity for small lesions and non-solid nodules (often

bronchioloalveolar carcinoma). Furthermore the high sensitivity of this method for the characterization of prevalent nodules was not confirmed for incident nodules; in particular we had a sensitivity of 88% at the first year of screening and 67% at annual screening<sup>[23]</sup>; this is mainly due to the smaller size of nodules and the slow growing rate.

Based on 10 years experience in lung cancer screening, we recommend adopting a simple diagnostic protocol:

- nodules  $\leq 5$  mm are scheduled for repeat Id-CT a year later
- nodules between 5.1 and 8 mm undergo a repeat Id-CT 3 months later
- nodules  $> 8$  mm (or growing lesions  $< 8$  mm following repeat scan) are scheduled for [<sup>18</sup>F]FDG PET/CT, unless they appear clearly benign (see below)
- lesions suspicious for malignancy (growing or PET-positive) undergo surgical biopsy
- growth of lesions is defined as a doubling time between 30 and 400 days calculated on the larger diameter of the lesion or by automatic volumetry
- lesions of any size considered to be due to infection (multifocal, ill-defined non-solid lesions with multilobar infiltration due to alveolar opacity, generally peripheral) are treated with oral antibiotics for 10 days and repeat Id-CT after 1 or 3 months
- some nodular lesions are considered benign based on CT morphology (axial longest diameter more than twice minimum diameter, thickening of fissures, liquid density) and undergo repeat Id-CT 3 months later when  $> 8$  mm

### *Non-solid nodules*

Pulmonary nodules not completely solid are defined ‘sub-solid nodules’, depicted as nodular areas of homogeneous or heterogeneous attenuation that are hypoattenuating with respect to surrounding soft-tissue structures such as vessels<sup>[24]</sup>. Sub-solid nodules can be further classified as either part-solid (in the case of nodules with patches of parenchyma that are completely obscured) or non-solid (for nodules without such areas). Non-solid nodules, when unchanged or increasing in size at follow-up CTs, can be due to atypical adenomatous hyperplasia (AAH), bronchioloalveolar cell carcinoma (BAC), pulmonary lymphoproliferative disorder, or organizing pneumonia/fibrosis<sup>[25]</sup>. About 75% of pure persistent pulmonary non-solid nodules turn out to be BAC or adenocarcinoma with a predominant BAC component, and these do not manifest distinguishing morphologic features on thin-section CT images or PET positivity that allow their differentiation from other sub-solid nodules with different histopathologic diagnoses. These tumors are generally slow growing and a careful evaluation of their growth rate together with the general condition of the patient should drive the therapeutic choice.

## IEO experience

Our data are based on two observational studies which enrolled 6214 volunteers (1035 in 2000 and 5179 in 2005) who are still undergoing annual ld-CT. We detected 212 cancers, 72% in stage I and demonstrated a relatively high incidence (mean 0.4%) throughout the 10 years of observation. The 5-year survival rate of patients with lung cancer detected at screening CT is 63%.

## Conclusion

Mass screening for lung cancer is actually not recommended, and scientific and political communities are awaiting the results of the main randomized trials ongoing in north Europe and the United States<sup>[26,27]</sup>, which will determine the efficacy of low-dose CT screening; but definitive results will not be available for several years.

Important information derived from our observational studies is that the incidence of lung cancer in high-risk subjects is relatively high, is not decreasing with time of observation and the high percentage of early stage cancers is maintained, emphasizing the importance of continuing annual screening for longer than 5 years. These data contrast with the hypothesis that over-diagnosis affects the results of ld-CT for lung cancer screening<sup>[28]</sup>; if it were a major phenomenon, the proportion of early stage cancers would decrease after the first years, due to depletion of supposed non-evolving and non-fatal cases. Furthermore, pathological and molecular analyses performed on our series demonstrated that the morphology and genetic characteristics of screening-detected cancers are closely similar to those of symptoms-detected cancers<sup>[29]</sup>.

One of the main criticisms of lung cancer screening is the lack of demonstration of a reduction in mortality<sup>[9]</sup>. In our experience 72% of screening-detected cancers were stage I, confirming the potential increased of chance of cure, compared to the rate of 16% of stage I and II symptoms-detected cancers in clinical practice. Furthermore, our results show a high 5-year survival rate for all patients with screening-detected lung cancer (63%) and those with stage I tumors (89%), confirming the results of the I-ELCAP report<sup>[8]</sup>, but in contrast with the analysis of Bach *et al.*<sup>[9]</sup> The latter found that CT screening increased the rate of detection of lung cancers but did not reduce the risk of death; their analysis is limited by a too short follow-up time and by exclusion of the data from the first year of screening when comparing deaths. McMahon<sup>[11]</sup> used a different simulation model and estimated a reduction in lung cancer-specific mortality of 28% at 6 years in subjects who received five annual CT scans, compared with observation. Chien and Chen<sup>[30]</sup> reported, in a meta-analysis on six studies, that CT can advance the diagnosis of asymptomatic lung

cancers by 2 years compared with observation and reduce lung cancer mortality by 23% at 5 years.

We conclude that the population-based benefits from ld-CT screening for lung cancer must be demonstrated by randomized trials, but there is evidence of individual advantage for a heavy smoker older than 50 years to undergo yearly ld-CT of the chest to anticipate diagnosis of lung cancer and have a benefit from intervention at early stage.

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