Refining Strategies to Identify Populations to Be Screened for Lung Cancer

Ugo Pastorino, MD[a,*], Mario Silva, MD[a,b]

KEYWORDS

• Lung cancer • Screening • Biological sampling • Imaging

KEY POINTS

- The selection of populations to be screened for lung cancer must be further optimized before translation to large population.
- A 3-step refinement should be integrated into forthcoming lung cancer trials, namely, calculation of risk based on (1) demographics, (2) biological factors, and (3) radiologic inputs.
- Biological sampling should be implemented up-front to reduce the use of low-dose computed tomography scanning in patients with lower risk of aggressive disease and, notably, to detect aggressive disease that is overlooked by current screening strategies.

In the past 20 years, lung cancer screening trials have been performed with a high detection rate, notably for early-stage disease.[1] Imaging has always played a pivotal role in such screening programs, under the axiom of correlation between pulmonary nodule and lung cancer.[2] The introduction of low-dose computed tomography (LDCT) allowed for sensitive detection of extremely small pulmonary nodules.[3–23] Therefore, LDCT has been advocated as a sensitive tool for diagnosing early lung cancer and, therefore, improvement of survival. The National Lung Screening Trial (NLST) reported a 20% reduction of deaths from lung cancer in smokers, compared with the chest radiography control group.[24] This striking result is in contrast with data reported by smaller European trials, which have not shown a clear-cut advantage of LDCT screening over observational strategies.[25–27]

Since the beginning of computed tomography–based lung cancer screening trials, the detection of a solid nodule measuring 5 mm or greater has been deemed a predictive factor of lung cancer and, therefore, worthy of further investigation. This approach led to a significant increase of LDCT and invasive procedures, and, therefore, radiation exposure, risks, and health care costs. An open debate exists about the overwhelming predominance of false-positive LDCT findings[28,29] and their implications in large-population lung cancer screening (ie, anxiety, radiation exposure, diagnostic workups and the related complications).[29] In the past 2 years, data have been published about possible strategies to reduce the workup resulting from LDCT false-positive findings, while keeping the high sensitivity of LDCT.

The International Early Lung Cancer Action Project (I-ELCAP) and NLST tested the effects of using a progressively higher nodule size threshold and demonstrated a potential decrease of 34% to 75% in LDCT examinations with minimal delay in diagnosis and treatment of lung cancer.[30,31] The new guidelines issued by the American College

The authors have nothing to disclose.

[a] Division of Thoracic Surgery, Istituto Nazionale Tumori, Via Venezian 1, Milan 20133, Italy; [b] Section of Radiology, Department of Surgical Sciences, University of Parma, Via Gramsci 14, Parma 43126, Italy
* Corresponding author.
E-mail address: ugo.pastorino@istitutotumori.mi.it

Thorac Surg Clin 25 (2015) 217–221
http://dx.doi.org/10.1016/j.thorsurg.2014.11.005
1547-4127/15/$ – see front matter

of Radiology reflect the awareness that a larger size threshold (ie, 6 mm) may be appropriate for nodule management within lung cancer screening programs.[32] Further optimization of screening programs could be gained through volumetric measurement of nodules. A recent report from the NELSON (Nederlands Leuvens Screening Onderzoek) trial showed that lung nodules smaller than 100 mm^3 were not predictive of lung cancer in the following 2 years (ie, 2-year lung cancer risk of 0.6% vs 0.4% in subjects without nodules). Moreover, they calculated a 2-year lung cancer risk of 2.4% for subjects with nodules measuring 100 to 300 mm^3 (intermediate risk) and 16.9% for those with nodules greater than 300 mm^3 (high risk).[33] Accordingly, they proposed volume-doubling time (VDT) assessment of nodules measuring 100 to 300 mm^3 or immediate diagnostic investigation of nodules greater than 300 mm^3. In particular, the 2-year risk of lung cancer was shown to be 4% for VDTs of 400 to 600 days and 9.9% for VDTs of 400 days or less.[33] These results are a huge step toward higher positive predictive values of lung cancer screening.

Furthermore, not only positive predictive value (malignant vs benign) but also overdiagnosis (indolent vs aggressive tumor) was brought to the attention of lung cancer screening panelists.[34,35] In the era of LDCT lung cancer screening trials, a significant increase in detection of early-stage indolent tumors has been reported without an apportioned decrease in detection of aggressive tumors.[36] This shift to slow-growing cancers is the most likely explanation for the almost equal mortality seen in the LDCT and chest radiography arms, despite a significant increase in prevalence of resectable early-stage cancers in the former.[34] Therefore, further characterization should be sought to increase lung cancer screening accuracy.

Biomarkers have been proposed for the early detection of lung cancer.[37,38] In particular, microRNA (miRNA) has been shown to have abnormal expression in most types of cancer.[39] Specific patterns of miRNAs expression have been demonstrated in the primary tumor and the blood, thus suggesting that circulating miRNAs provide disease fingerprints.[40,41] The implementation of these markers in LDCT screening programs has been proposed to inform the optimization of protocols according to risk profiles based on miRNA patterns.[28,42] Specific serologic miRNA patterns have been tested in the selection of high-risk subjects within lung cancer screening trials.[43,44] The authors' group showed a significant association between a miRNA signature classifier (MSC) and lung cancer in retrospective analyses of circulating miRNAs, which were prospectively collected within the randomized Multicenter Italian Lung Detection (MILD) trial.[45] The high sensitivity and negative predictive value of MSC fostered a newly designed protocol for a second trial, the so-called bioMILD trial. (MSCs used in bioMILD consist of reciprocal quantification of 24 circulating miRNAs). In bioMILD, the LDCT protocol was designed to reduce the number of scans while providing dedicated surveillance to subjects with a higher risk of lung cancer. In particular, participants of bioMILD undergo blood sampling and LDC at baseline and each designated round. The evaluation of MSC provides comprehensive risk stratification and, therefore, selection of a dedicated LDCT follow-up strategy, either in 1 or 3 years. The number of LDCT scans is by default reduced to one-third in subjects with low risk, resulting in a substantial reduction in radiographic exposure for subjects who would not benefit from yearly LDCT. On the other hand, subjects at higher risk are maintained on yearly LDCT follow-up.

Furthermore, this trial integrates a risk stratification system, and therefore follow-up strategy, based on nodule features. The implementation of serologic miRNA sampling allowed for an increasing volumetric threshold for nodules, thus providing even lower recall rate based on nodule size. This strategy derives from the simulation performed on the MILD population, wherein the assessment of lung cancer risk using an MSC would have allowed for a 5-fold reduction of false-positive findings for nodules measuring 5 mm or greater (from 19.4% to 3.7%). Furthermore, a correlation was observed between interval cancers and MSC risk category. In the MILD trial, 8 of 9 (89%) subjects with interval cancer were categorized as MSC intermediate-high risk.[45] Because interval cancer remains an issue in lung cancer screening, the results of the bioMILD trial are anticipated to determine whether MSC could increase the early detection of cancers that are overlooked by current screening strategies.

MSC and LDCT together were retrospectively tested in MILD and showed a 98% cumulative sensitivity (57 of 58 cancers), whereas the sensitivity of each test alone was 87% and 84%, respectively. Furthermore, MSC risk category predicted a shorter 3-year survival; therefore, subjects with a confirmed high risk by MSC are selected for additional workup to exclude extrapulmonary causes of mortality. Another lung cancer screening program in Milan is using the miRNA test, namely the Cosmos-II trial. In this study, the 1-year risk of lung cancer is rated according to demographic risk models, with the selection of 2 main populations. In particular, participants with