Lung cancer screening: are we ready now?

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Summary

Lung cancer is main oncologic cause of death worldwide, because diagnosis is usually reached with symptomatic advanced stage disease. Reduction of lung cancer mortality could be reached especially by primary prevention because cigarette smoke is exceptionally associated with increased risk of lung cancer. Primary prevention would also grant reduction of other pulmonary (chronic obstructive pulmonary disease) and extra-pulmonary diseases (cardiovascular events, colonic cancer). Secondary prevention by early diagnosis of lung cancer is another option, apparently easier to propose to high-risk subjects, but much more expensive than primary prevention. Screening by annual low-dose computed tomography (LDCT) is currently implemented in the United States, following evidence of significant reduction in mortality from lung cancer and overall mortality. European countries have not reported efficacy of annual LDCT, currently there are results from an Italian pooled analysis that reports indeed a trend for mortality reduction, yet not significant. Pre-test selection of high-risk population, interval length of LDCT rounds, and definition of positive finding are the main topics of discussion to achieve better harm/benefit ratio from LDCT screening. Comprehensive and simple risk model for selection of subjects with relatively high risk of lung cancer is paramount for optimization of LDCT screening, furthermore subjective risk prediction by biological sampling is under investigation. Biennial and annual screening rounds might have equal performance in lung cancer detection, notably with reduction of LDCT performed. Volumetric quantification of nodules at baseline and volume doubling time for assessment of progression increase the accuracy of the test, thus reducing the number of false positive and the risk of surgery for benign disease. Nevertheless, smoking cessation is the most effective strategy for reduction of mortality, hence smoking cessation program must be integrated in case of implementation of national lung cancer screening program.

KEY WORDS: lung cancer, screening, detection, biomarker, low-dose computed-tomography.

Introduction

Lung cancer is one of the leading causes of mortality worldwide (1), in particular it is usually associated with a relatively advanced stage at diagnosis (i.e., in presence of lymph node involvement or metastasis). Early stage disease is almost always associated with poor symptoms, and mostly completely asymptomatic. The early detection of pulmonary neoplasms in asymptomatic individuals at risk for pulmonary tumors (current or former smoker, exposed to environmental inhalants…) would be ideal to improve the outcome of this disease, which is currently about 10% 5 yrs survival rate in Europe (2).

The detection of pulmonary nodules (rounded or irregular opacity of homogenous soft tissue attenuation, well or poorly defined, measuring up to 3 cm in diameter) and tumors is primarily performed through radiological examinations such as chest X-rays (CXR) or computed tomography (CT).

The past and the present of the lung cancer screening

Since the 70’s, a growing interest in the early detection of lung cancer was focused on screening by chest X-rays; the introduction of the first computed tomography scanner and the outstanding technical advances represented by both low-dose computed tomography (LDCT) performed. Volumetric quantification of nodules at baseline and volume doubling time for assessment of progression increase the accuracy of the test, thus reducing the number of false positive and the risk of surgery for benign disease. Nevertheless, smoking cessation is the most effective strategy for reduction of mortality, hence smoking cessation program must be integrated in case of implementation of national lung cancer screening program.

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CT) and the development of software for computer-aided detection (CAD) fostered the planning of various screening approaches. Lung cancer can be directly detected through the screening test or may be identified during the screening interval (i.e. “interval cancer”); the latter could have been misdiagnosed at the screening round or could have developed between the test and the detection. The Mayo Lung Project (MLP) was a 6-year cancer screening trial that evaluated chest X-ray (CXR) and sputum cytology – performed 3 times per year in the intervention arm and annually in the usual-care arm – for the detection of lung tumor in male smokers, in a period ranging from 1971 and 1983 (3). The results were controversial about the efficacy of CXR in reducing lung cancer mortality; indeed, such intense 6-year screening program did not reduce lung cancer mortality, although a case-survival difference was observed.

After CT scanners became commonly available, they gained a remarkable importance because chest CT allows the evaluation of lesions that are undetectable on CXR, namely ground-glass opacities (GGO) and small nodules located in anatomic zones of difficult radiographic analysis (the lower-zones of the lungs, the apexes or the retro cardiac parenchyma). Therefore, CT was tested against CXR for the early detection of lung cancer and it showed striking results at the baseline screening for a population of 1000 smokers (45 pack-years); Henschke (4) reported that the Early Lung Cancer Action Project (ELCAP) program showed a 4 times higher lung cancer detection through CT compared with CXR; moreover, an early diagnosis of cancer was possible, as it was observed a six fold increase in stage I lung cancer diagnosis (4). The stage I of lung cancer comprises tumors that do not present mediastinal lymph node involvement or metastases, therefore representing neoplasms that can be surgically treated with an exceptionally favorable outcome; in a high-risk population (31,567 participants) undergoing annual CT screening, such examination led to biopsy-proven lung cancer detected in the stage I and successively resected with a substantial reduction in mortality from pulmonary malignancy (5). Currently, various lung cancer-screening trials are ongoing worldwide; the European ones reported that the highest rate of lung cancer diagnosis is seen at baseline, and the majority is represented by stage I neoplasm (6). Nevertheless, it was stated that screening programs are associated with a risk of overtreatment, as one out of five resection specimen was proven to be benign condition.

The American NLST (National Lung Screening Trial) enrolled 53,454 high-risk patients in its two-arms screening program (7); during a three-year period, participants were divided into annual screenings through low-dose CT or posteroanterior CXR. The NLST reported a 20% decrease in mortality from lung cancer and a 6.7% decrease in all cause mortality in the LDCT group as compared with the CXR group; during the screening, positive findings were detected in the 39.1% of the participants in the LDCT group, while positive findings were detected in 16% of the CXR group; nevertheless, LDCT screening – as well as CXR screening – was associated with a high rate of false positive results, indeed the 96.4% of the positive results were false positive; it was stated that there was the need to screen 320 subjects to prevent one lung cancer death. The over diagnosis reflects the detection of tumors that could be clinically insignificant and leads to an increase of the economic burden of the screening, secondary to overtreatment. In a critical review of screening results, Patz et al. estimated a rate of over diagnosis of 18.5%, this meaning that such individuals, without being enrolled in the NSLT, would not have received a lung cancer diagnosis or treatment, at least for the following 5 years (8). Early-stage tumors detected in asymptomatic patients are invariably progressing into symptomatic or long-term life-threatening neoplasms; moreover, after the detection of a pulmonary lesion, the patients were to be treated, independently of the clinical behavior of the lesion, therefore post-operative sequelae may affect patients with both indolent and aggressive neoplasm. Thus, the reduction of both false positive rate and over-diagnosis is of paramount relevance when screening program is meant to exit the experimental field and start clinical practice; an Italian randomized clinical trial – the DANTE (Detection and Screening of Early Lung Cancer by Novel Imaging Technology and Molecular Essays) – reported an higher frequency of lung cancer diagnosis in the LDCT arm compared to the arm of baseline CXR and clinical review (9). The LDCT arm included 1276 subjects and among them the 4.7% was diagnosed with a lung cancer; more stage I tumors were detected in the LDCT arm, although the number of advanced lung cancer cases was the same as in the control arm. The Authors stated that there was no significant difference in the absolute numbers of late stage cancers in LDCT and control arms, reflecting the absence of an absolute stage shift and an over-diagnosis in case of early tumors. The same Authors reported that lung cancer screening should be tested in population with high-risk profiling, which is defined by criteria that are quite different from the selection applied by trials.

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compared to radiography (2.4% for LDCT arm). Authors reported a lower positive predictive value (PPV) for patients suffering from small cell lung cancer (SCLC) (15); such aggressive tumor represents frequently an interval cancer and may affect even asymptomatic individuals participating.

Efficacy of LDCT screening depends on the sensitivity and specificity of the test, namely the risk of not identifying a lung cancer through the screening test (16). Further analysis performed on patients enrolled in the NLST demonstrated the high sensitivity of LDCT in the detection of early-stage lung cancer, however the Authors did not find evidence of a protective effect of annual against biennial screening, notably without shift to higher stages in the biennial arm, but with a reduction of LDCT by about one third in the biennial screening arm (14).

A retrospective evaluation of histology-specific efficacy of screening reported the assessment of the poor results offered by LDCT screening in terms of survival for patients surviving from small cell lung cancer (4). Such aggressive tumor represents frequently an interval cancer and may affect even asymptomatic individuals participating.

Efficacy of LDCT screening depends on the sensitivity and specificity of the test, namely the risk of not identifying a lung tumor through the screening test (16). Further analysis performed on patients enrolled in the NLST demonstrated the high sensitivity of LDCT in the detection of early-stage lung cancer, however the Authors reported a lower positive predictive value (PPV) for the detection of a nodule of any size for CT as compared to radiography (2.4% for LDCT arm versus 4.4% for CXR group); PPV increased as the nodule size increased from 4 to 30 mm (17). The Authors suggested to increase the minimum size threshold for positive findings as nodules with a diameter ranging from 4 to 6 mm were the most frequently detected, although they were associated with a diagnosis of lung cancer in less than 1% of cases. With the aim of increasing CT accuracy, Authors from the International ELCAP retrospectively analyzed the size of lung nodules detected in the 21,136 participants and built models with thresholds comprised between 5 and 9 mm; they suggest that changing the threshold for a parenchymal nodule – either solid or part-solid non-calcified – to 8.0 mm may be reasonable in the baseline round of LDCT screening; such threshold increases the LDCT efficiency, at the cost of a delay in the diagnosis of at most 9 months in 6% of the patients diagnosed with stage I lung cancer within 1 year of the baseline screening (18). Such threshold would not hamper treatable cancers, as compared to the 5-mm threshold used in the prospective study, mainly because the majority of the cases of cancer were adenocarcinomas showing a less aggressive biological behavior compared to squamous cell carcinoma.

The pulmonary nodule: a target with various peculiar features

The Dutch-Belgian NELSON trial – underlining the high prevalence of pulmonary non-calcified nodules and the relatively low incidence of lung cancer – evaluated the importance of diameter and volume of pulmonary nodules for the development of lung cancer within two years of a LDCT scan (19). 15,822 patients were enrolled and randomized to LDCT screening (7.915) or to no screening (7.907). The Authors calculated volume, volume doubling time (VDT – the number of days in which the nodule doubles its volume) and volumetry-based diameter of 9.681 non-calcified nodules; the implementation of volume assessment increased specificity and PPV, without reducing sensitivity and negative predictive value (NPV), compared to the American College of Chest Physicians (ACCP) guideline for nodules. The VDT was calculated to assess the accuracy of longitudinal behavior of solid nodules: while small nodules (diameter <5 mm or volume <100 mm³) are not predictive of lung cancer, nodules with a VDT of 400 days or shorter could be considered at high risk of developing lung cancer. Out of the 8,623 non-calcified nodules that were detected in the baseline round of the NELSON trial, 68 were fast-growing (VDT <400 days) and were subsequently evaluated by a pulmonologist; 27 of these were malignant and all malignant fast-growing lung nodules had VDT <232 days (20). Lowering the VDT cutoff from 400 to 232 days may reduce false-positive referrals.

The size of lung nodule identified in LDCT examination maintains the role of the strongest predictor of malignancy and the positive predictive value of LDCT can potentially be improved by volumetric assessment. Manual measurements are prone to errors and to a known intra- and inter-reader variability, and a growing nodule could be considered stable in case of erroneous measurements through electronic calipers (21); volume measurements can be manual or semi-automatic, the latter providing a more reproducible evaluation of the nodules. Nevertheless, the importance of a control performed by an expert chest radiologist is paramount, as it may reduce the need of a strict follow-up and the evaluation of nodules can identify features that could postpone the successive control or even avoid follow-up LDCT (e.g. in presence of a fibrotic appearance) (22). Moreover, the adherence to standardized protocols for the management of nodules has been identified as growing along with the experience of the radiologist (23). After the detection of a pulmonary lesion, specific features should be carefully evaluated, as there are several signs that have prognostic value and can be used to calculate likelihood that a nodule be benign or malignant; CT features to be evaluated size, attenuation, location, morphology, edge characteristics. Other distinctive signs can be highly suggestive of a specific diagnosis and used to determine the probability that a specific nodule is benign or malignant (24); a diffuse or central calcification,
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a popcorn or lamellar pattern usually suggests the benign nature of the nodule, whereas the presence of eccentric or randomly distributed calcifications may be identified in primary adenocarcinomas and in metastases, particularly in case of dissemination of sarcomas. Information obtained from large screening trial underline the importance of the attenuation of the nodule in the prognosis of the patient; indeed, solid, sub-solid, partially solid and non-solid nodules showed a malign behavior in 7, 35, 63% and 18%, respectively (25).

The paramount relevance of the radiologist evaluating the findings has been described by Scholten et al.; they reported the most difficult conditions that can lead to a misinterpretation of a nodular lesion identified in the population of the NELSON trial (26). Briefly, missed carcinomas can be a consequence of detection errors (i.e. the lesion was not described but can be retrospectively identified) or interpretation errors (i.e. the lesion was considered benign); the Authors reported that missed carcinomas were mostly due to detection error, because of an intrabronchial localization (22% of missed carcinomas) or the presentation as a lymphadenopathy or as pleural fluid of the tumor. Moreover, missed carcinomas are frequently represented by focal wall thickening of a bulla (22% of interval cancers); the detection of such finding should be reported, as the underreporting of focal wall thickening represents an important cause of interpretation error. Interestingly, in the NELSON trial sub-solid nodules were not a source of missed carcinomas; furthermore, the 76 sub-solid nodules detected at baseline in the MILD trial variably evolved with a complete resolution (31.3% of cases), a reduction in size (8.3% of cases), stability (43.8% of cases) and an increase in size (16.7% of cases) (27), and only 1 case underwent surgery.

Smoking cessation and small cell lung cancer

Lung cancer accounts for less than 30% of overall mortality in heavy smokers (28); the effect of smoking cessation was represented by a reduction of the overall mortality (namely a reduction of 3 to 5% per year), hence smoking cessation should be suggested and fostered even after the diagnosis of lung cancer, as there are evidences that it can increase the overall survival of patients (29); indeed, compared with those who continue smoking, the ones who stopped smoking at 30, 40, 50 years of age gain about 10, 9, and 6 years of life expectancy, respectively.

Blood sampling and microRNA

Individuals participating in a lung cancer screening should be investigated to define their biologic profile evaluating various elements, namely the individual susceptibility, the presence of risk factors (smoking and COPD) as well as blood analysis. The assessment of the biologic profile should help the stratification of the patient into the appropriate risk category for a malignant lesion; indeed, not all the lesions detected during a screening are malignant, therefore the reduction of unnecessary treatment – either medical or surgical – should be pursued.

In the MILD trial both tissue samples and blood were prospectively collected, with the purpose to compare potential biomarkers of aggressive disease (31). MicroRNAs (miRNAs) were hypothesized to bear a role as a marker for cancer detection with prognostic value; indeed, they are small molecules of RNA that are frequently deregulated and aberrantly expressed in cancer and are detectable in plasma and serum samples through quantitative real-time PCR (qRT-PCR). MiRNAs profiles were developed for both tumor and healthy parenchyma and it was shown that microRNA signatures in lung cancer were substantially different from normal lung tissue. Moreover, the presence of specific miRNAs in plasma samples obtained before disease onset were predictors of tumor with worse prognosis; hence, the identification of miRNAs has been described as a reproducible and easy tool that can be potentially useful in the selection of patients in the pre-disease stage that could benefit from a strict surveillance and from smoking cessation. The complementary diagnostic performance of miRNA signature classifier (MSC) and LDCT was evaluated by using a MSC showing high sensitivity and a negative-predictive value of 99%; it allowed to obtain four categories of risk (risk of disease, risk of aggressive disease, presence of disease, presence of aggressive disease) based on different expression ratio signatures of 24 miRNAs; the patients were consequently inserted into group of low, intermediate or high risk of developing disease. Briefly, the integration of MSC and LDCT (at least one positive test) was able to raise the sensitivity from 87% for MSC and 84% for LDCT alone, to 98%, with a false-positive rate of 35%; the presence of both positive findings (MSC and LDCT) determined the reduction of the false-positive rate to 3.7% (versus 19.7% of LDCT alone). Such an important reduction in terms of rate of false-positive findings can deeply affect the cost of the screening, as it reduces the number of unnecessary procedures and examinations during the follow-up (32).

Accounting for all subjects with circulating microRNA sampling along a 3-year follow up, the Authors determined the prognostic performance of the three pre-defined MSC risk groups to predict overall survival; two-year survival was 100, 98, 87% for low, intermediate and high-risk MSC, respectively and the three-year survival was 100, 97 and 77% for low, intermediate and high-risk MSC, respectively. The integrated approach is being prospectively tested within the bio-
MILD, with the aim of increase the efficiency of the screening program (i.e. predetermined LDCT interval of 3 years).

Conclusions

The purpose of the screening of lung cancer is to detect pulmonary nodules especially in high-risk patient that can benefit from the early diagnosis of malignant lesions. LDCT screening currently has good prospects; nevertheless, the final results of European randomized clinical trials will be crucial for the future planning and management of projects for early lung cancer detection. One of the most important features of the screening programs is represented by the possibility of tailoring the diagnostic algorithm based on the patient’s model. For this purpose, validation of biomarkers will be helpful for both selection of high-risk population and reduction of false positive rate.

Conflict of interest

No conflict of interest is known from the Authors.

References

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