Review Article on Lung Cancer Screening

Ongoing challenges in implementation of lung cancer screening

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Abstract: Lung cancer is the leading cause of cancer deaths in Europe and around the world. Although available therapies have undergone considerable development in the past decades, the five-year survival rate for lung cancer remains low. This sobering outlook results mainly from the advanced stages of cancer most patients are diagnosed with. As the population at risk is relatively well defined and early stage disease is potentially curable, lung cancer outcomes may be improved by screening. Several studies already show that lung cancer screening (LCS) with low-dose computed tomography (LDCT) reduces lung cancer mortality. However, for a successful implementation of LCS programmes, several challenges have to be overcome: selection of high-risk individuals, standardization of nodule classification and measurement, specific training of radiologists, optimization of screening intervals and screening duration, handling of ancillary findings are some of the major points which should be addressed. Last but not least, the psychological impact of screening on screened individuals and the impact of potential false positive findings should not be neglected. The aim of this review is to discuss the different challenges of implementing LCS programmes and to give some hints on how to overcome them. Finally, we will also discuss the psychological impact of screening on quality of life and the importance of smoking cessation.

Keywords: Lung cancer; screening; lung cancer screening (LCS)

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Introduction

Lung cancer is the first cause of cancer-related mortality worldwide (1). In Europe, the incidence of lung cancer is alarmingly increasing in women, with now more deaths due to lung cancer than to breast cancer. Although it is beginning to decrease, the number of lung cancer deaths is still very high among men (2). In contrast to the increase in survival for most cancer types, advances have been slow for lung cancer, because the majority of cases are diagnosed at an advanced stage (3). There is a potential for earlier lung cancer diagnosis through screening with low-dose computed tomography (LDCT). In 2011, the National Lung Screening Trial (NLST), a large randomized US trial, reported a 20% relative reduction in lung cancer–specific mortality after 7 years of follow-up in the LDCT arm (4). This was at the cost of a high false positive rate, with 24% of screenings classified as positive of which 96% were proven to be falsely positive (4). Indeed, all CT scans showing at least one non calcified 4 mm nodule were considered as positive screens (4). More recently, three European trials have confirmed the benefit of screening by also demonstrating a reduction of lung cancer mortality through screening (5-7). The Multicentric Italian Lung Detection (MILD) trial showed a 39% reduced risk of lung cancer mortality at 10 years and demonstrated that prolonged screening beyond 5 years achieves a higher lung cancer mortality reduction compared to the NLST trial (5).

The German LUSI (Lung cancer Screening Intervention) trial revealed significant reductions in lung cancer mortality among women who underwent LDCT (6). Lastly, the Dutch and Belgian NELSON trial reported a mortality reduction of 24% in men and 33% in women (7). The adopted volumetry-based nodule management strategy allowed reducing the false positive rate to only 1.2%. The reinforced evidence combined to an optimized screening strategy make the implementation of LDCT screening quite likely. However, there are many challenges to be met: It is crucial to ensure that screening is done with the same level of quality as in the studies that have demonstrated its value, and to obtain adherence of the high-risk population. Optimization of the screening intervals is also of major importance. Nodule management should aim to reduce the risk of overdiagnosis, optimize the effectiveness of screening and minimize the participants' anxiety. This article will review the prerequisites necessary for a successful implementation of screening and will reassess the influence of screening on smoking cessation.

Adherence of high-risk individuals

One of the big challenges in lung cancer screening (LCS), and screening programs in general, is to reach the target group since the effectiveness of screening strongly depends on the engagement of an at-risk population (8). This can be done either by public information campaigns on LCS or by targeted patient information through the general practitioner. It is mandatory to explain to the participant the importance of LCS, the different examination steps involved and how long the examinations will take. Further, it is important to explain to the participant the difference between a "screening" CT and a "standard" CT with regard to radiation exposure and diagnostic quality. The perception of lung cancer is different from that of other cancers. Smokers feel stigmatized or even guilty about smoking. In a prospective nationwide survey conducted in France and published in 2015, lung cancer was characterized by a greater feeling of guilt compared with breast cancer, being more frequently considered as a punishment (9). It is important to present screening not with negative terms but in a positive way that can be accepted by the participants. Rather than using the term LCS, the Manchester implementation study chose to name their screening programme 'lung health checks' which is more positive and less frightening. Indeed, participants might be afraid to be diagnosed with a lung cancer. According to the authors, this term has been one of the keys to their success. They managed to screen 1,384 of the 1,423 identified high-risk individuals (10). Conversely, a report by Jemal *et al.* indicated that in 2015, only 4% of the 6.8 million eligible Americans reported being screened for lung cancer with low-dose computed tomography (11). Another study found that more individuals who did not meet guideline-recommended criteria for LCS had received a recent test than those who did meet criteria (12). Efficient implementation will require acquainting physicians with eligibility criteria for LCS. This information should also be delivered through large public information campaigns, using positive terms, and avoiding smokers' stigmatization.

Optimization of the population to be screened

Selection of the population to be screened on a priority basis is important, for cost effectiveness. Participants should at least meet the eligibility criteria of the LCS studies which have proven the benefits of screening. These criteria, based on age and smoking history, show small differences according to the different screening studies. Participants of NLST were 55 to 74 years old with 30 or more pack-years of cigarette smoking history (13). Those included in the NELSON study were 50 to 75 years old and smoked 15 cigarettes or more per day for at least 25 years or at least 10 cigarettes per day for at least 30 years (14). Other studies used risk prediction models considered more accurate in identification of high-risk individuals for screening than eligibility criteria based on age and smoking (15). Selection of participants in the UKLS study (16) was based on the Liverpool Lung Project $(LLP)_{v2}$ model (17), whereas the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial $(PLCO)_{2012}$ (18) model was used in the Manchester pilot study (10) and the PanCan model in the PanCan study (19). Higher lung cancer prevalence was reported at baseline in these studies, as compared to the NLST and NELSON studies, with 2%, 3% and 5% prevalence and 85%, 80% and 77% early stages, respectively (17-19). However, selection of individuals at higher risk might not increase cost-effectiveness. An analysis performed in the NLST population reported that participants at greater risk for lung cancer mortality were older and had more comorbid conditions and higher screening-related costs (20). Regarding the role of serum and blood-based biomarkers for LCS, such as micro RNAs or tumor-associated autoantibodies, a 2018 systematic review concluded that there is currently no evidence to support

their implementation in clinical practice (21). There are ongoing phase 4 studies, to evaluate the clinical and cost effectiveness of auto-antibodies (EarlyCDT®-Lung Test) for early lung cancer detection (22), or combining miRNA signature and LDCT, such as in the bioMILD study (ClinicalTrials.gov ID: NCT02247453) evaluating miRNA signature classifiers (MSC) in conjunction with LDCT.

Screening interval and duration of screening

Unlike NLST, where the screening interval was annual, the NELSON study used increasing intervals, first one year, then two years and finally two and a half years. More interval cancers were observed between the last two rounds of screening, 2.5 years apart (23). Furthermore, the MILD study compared in a randomized approach an interval of 1 or 2 years between CT screenings and reported the same reduction in mortality with biennial screening (24). It can be deduced from these data that a 2-year interval should not be exceeded between two controls. Adjusting the screening interval based on findings at previous CT screening could be an option (6). Participants with negative screen results and neither emphysema nor consolidation could benefit from longer screening intervals (6). Another approach for defining the screening interval between follow-up studies after baseline is the use of biomarkers (25). Genetic predisposition together with the detection of lung cancer metabolites excreted in the urine, blood, sputum or even exhaled breath are promising factors for identifying high-risk candidates for whom screening intervals could be reduced (26-30). Despite the potential of the molecular approach, no molecular biomarkers for lung cancer are currently used in routine clinical practice (25). Further studies are needed for the validation and standardisation of molecular biomarkers before they can be integrated in LCS protocols.

At what age should the screening stop? The US preventive service task force (USPSTF) recommends annual screening in adults aged 55 to 80 years (31). The upper age limit is therefore higher than in the NELSON and NLST studies.

Quality of screening, radiologists' expertise

If screening were to become widespread, there would be a shortage of expert thoracic radiologists to read the LDCT scans, and a double reading by experts, as carried out in European studies, does not seem realistic for large-scale screening. This is the reason why the European Society of Thoracic Imaging (ESTI) prepared a dedicated training programme named Lung cancer screening (LCS) certification project (32), endorsed by the European Society of Radiology (ESR), to train general radiologists in screening. Indeed, LCS should be practiced at a similar quality level to the trials that have proven its value, in order to ensure that there is maximal benefit from its introduction. In addition to webinars, e-learning and workshops on lung nodule management and use of computer-assisted tools, technical requirements have been elaborated together with a structured report template. The implementation of screening should be accompanied by quality control assurance to ensure that the radiation dose is optimized and that the number of positive screenings does not exceed what is expected. Indeed, the high sensitivity of CT and the high prevalence of lung nodules lead to a high risk of false positives. Regarding the false negative risk, it has been demonstrated that computer aided diagnosis (CAD) has higher sensitivity than double reading by radiologists, at the cost of an increased false positive rate (33). The development of deep learning offers new perspectives. A recent report compared the performance of a deep learning-based algorithm, trained on NLST dataset to human readers and reported on-par performance with radiologists, or even higher performance when there was no previous available CT exam for comparison (34). Even though prospective validation is still lacking, this offers new perspectives, with the possibility to optimize the screening process via computer assistance and automation.

Management of screen-detected nodules, limitation of the overdiagnosis risk

Two different approaches to nodule management have been used in LCS studies, a diameter-based approach as in the NLST study, or a volume-based approach for solid nodules, as for example in the NELSON trial (4,23). The diameter-based approach used in the NLST where every non-calcified nodule of at least 4 mm was considered as a positive screen, resulted in a high proportion of false positives and a low positive predictive value (4). In order to reduce the false positive rate, the 4 mm threshold value has been raised to 6 mm in lungRADS, which retains a diameter-based approach. European trials, especially the NELSON trial, have opted for a volumetric approach where intermediate volume nodules are re-evaluated in the short term, with calculation of their volume doubling time (23).

Solid nodules with volume doubling time of more than 600 days were considered as a negative screen result in the NELSON, LUSI and MILD trials (5,23,35). This resulted in a much lower false positive rate, being only 1.2% in the NELSON study (23). Post hoc analysis of the NELSON results led to reconsider the initial volume thresholds defining negative and positive screen results (36). The initial values of 50 and 500 mm^3 should be replaced by 100 and 300 mm^3, and these values are the recommended thresholds of the EUPS guidelines (37). The volume doubling time strategy is not only a way to limit false positives, it also limits the overdiagnosis risk (38), defined as the risk of diagnosing a disease that would never be clinically relevant within the participants expected lifetime. It is now well admitted that some lung cancers are indolent in nature, particularly those presenting as ground glass nodules, whose doubling times exceed 800 days (39). Diagnosis and treatment of these indolent lung cancers should be avoided and represents the major burden of overdiagnosis. Long-term active surveillance of screen-detected subsolid nodules has been demonstrated to be a safe strategy to limit the risk of over treatment, as demonstrated by Silva *et al.* (40). These authors analyzed the risk of lung cancer and lung cancer-related death in subjects included in the MILD trial who had unresected subsolid nodules over a period of almost 10 years. They found that participants with subsolid nodules had higher risk of developing lung cancer, than individuals without lung nodules or those having solid nodules (40). However, in 73% of cases, lung cancer did not develop from the subsolid nodules but from different lung areas, and those arising from the subsolid nodules were never the cause of death during the almost 10-year follow-up period (40). Therefore, subsolid nodules should rather be considered as markers of carcinogenic exposure, and resection of future more aggressive cancers should not be compromised, which means that if resection of a subsolid nodule is decided, it should be economical for the lung parenchyma and consist of limited resection.

Impact on quality of life

Opponents of screening programmes criticize the high socio-economical costs of screening, the radiation burden the screened population is exposed to, and last but not least the potentially negative psychological effects for the participating individual (41).

The psychological impact of screening on quality of life is already a well-known problem of other screening programmes, such as for example breast cancer screening (42,43). The psychological burden a screening participant can go through, consists not only of anxiety related to positive or indeterminate results, but includes the psychological distress the patient goes through in the different phases of screening: (I) before screening, (II) during the examination, and (III) after screening while waiting for screening results. Altogether, the baseline anxiousness a screening patient goes through, paired with the psychological burden of the high rate of false positive exams, suggests that many patients are at risk for unnecessary screening-related distress. This perceived psychological distress might affect overall health-related quality of life (HRQOL) (42). Symptoms are variable between individuals, and can vary by severity from mild to severe (42). To date several studies evaluated the psychological burden LCS can have on a single individuum (44-47). Some studies evaluating the effect of screening results on the screened individual showed that a negative result led to decreased distress and anxiety while a true positive result led to increased anxiety and worse HRQOL (44,45). Additional negative factors associated with anxiety and increased lung cancer specific distress were (I) indeterminate or suspicious results who endorsed high perceived risk of lung cancer or (II) patients discomfort while waiting for CT screening results (14,46,47). Contrary to this, other studies did not report differences in HRQOL among participants with false positive and true negative results. The NLST analysis of HRQOL and state anxiety revealed no differences between participants with different screening results (i.e., false-positive, true-positive, significant incidental findings) (45). The authors partially attributed this result to the extensive counselling that study participants received while enrolled in the screening programme (45). Altogether, the current scientific evidence suggests that LCS has the potential to cause short-term psychological burden in individuals with an indeterminate scan result, although the adverse effects do not appear to persist long-term (1). This is in contrast to the current evidence in mammography screening for breast cancer, where indeterminate results requiring further investigation resulted in short-term increased anxiety which persisted long-term for up to three years (43,45,48). In order to reduce psychological burden for the participating individual, it is important that the participant is accompanied by a physician through the screening process: potential candidates for screening need to be fully informed about the risk of the possible psychological burden and individuals

who have been screened should receive clear and detailed information on screening results interpretation (46). With this approach, the participant will not feel lost in the screening process.

Management of ancillary findings

An ancillary finding can be defined through three conditions: (I) it occurs in subjects within a medical study, (II) potentially affects the health of the subjects and (III) the finding is beyond of the intended scope of the study objective (49). In the last years, the number of incidental findings has steadily increased (50), due to the widespread use of modern imaging modalities such as magnetic resonance imaging and computed tomography in clinical routine. The detection of an unexpected radiological finding can give rise to further diagnostics and therapy. While some findings need further work-up, others such as a pulmonary hamartoma or a vertebral haemangioma, are clearly benign (51). An evaluation of the different screening trials, shows that the number of reported screening-related ancillary findings is quite variable. The prevalence of significant ancillary findings varies from 1% in the Dutch-Belgian lung cancer screening trial (NELSON) to up to 19% at a Canadian centre participating in the International Early Lung Cancer Action Program (I-ELCAP) (14,52-54).The most commonly reported incidental findings are emphysema and coronary artery calcifications, which can be associated to smoking-related disease (55). The list of ancillary findings is long, and consists of incidental pulmonary findings (chronic obstructive pulmonary disease, interstitial lung abnormalities, pulmonary infection), incidental pleural findings (pleural thickening, pleural plaques), incidental mediastinal findings (thyroid nodules, lymphadenopathy, mediastinal masses and pathologies of the oesophagus), findings in the upper abdomen (malignancy, infections) and conditions of the soft tissues and skeletal apparatus (56). The American College of Radiology (ACR) included in the CT Screening Reporting and Data System (Lung-RADS) a category «S» modifier for clinically significant non-lung cancer findings (57). It is to the discretion of the radiologist to distinguish which findings have little or no clinical consequence and which are significant enough to require further evaluation. Additionally, this distinction is not only important for patient care, but also implicates the appropriate use of health care resources (56). Beside, triggering follow-up exams and increasing health-care related costs, the detection of ancillary findings can also have a positive impact: in the NLST beside a 20% reduction in lung-cancer specific mortality also a 6.7% reduction in all-cause mortality has been reported (52). The reduction of all-cause mortality might be explained because imaging from the lower neck to the upper abdomen may detect actionable or potentially significant ancillary findings in a population at risk for age- and smoking-related comorbidities (56). Lastly, ancillary findings are not specific to screening, but a known problem in radiology and should be handled as such (51). Each radiologist or physician should try to balance the diagnosis of a condition that might cause morbidity and mortality and thereby possibly alter its course against the potential to cause harm in the patient by prompting a round of unnecessary and dangerous diagnostic tests (51).

Association to smoking cessation

Smoking plays a causal role in at least over 15 types of cancer and is the most important risk factor for developing lung cancer (58-60). Additionally, there has been shown a causal relationship between continued tobacco consumption and all-cause and cancer-specific mortality, higher risk of progression, and increased risk for smoking-related second primary cancers in oncological patients (61). The cancerogenic effect of smoking is well accepted in the scientific community and it is self-evident, that patients participating in screening programmes should also get smoking cessation counselling. Interestingly, participating LCS programmes showed different effects on participating individuals. A study which evaluated attitudes and perceptions about smoking cessation in a group of LCS participants (62), observed that patients may substantially overestimate the benefit of cancer screening and may have misperceptions about the harm reduction itself. Although, most screening patients reported an increased perception on the harms and long-term consequences of tobacco use, half of the evaluated patients reported decreased motivation to quit smoking following screening. Reasons for this were misperceptions such as “undergoing screening yields the same benefits as smoking cessation” and “everyone who undergoes screening will benefit” (62). Another study evaluating risk perceptions associated with LCS reported that most patients understood the link between tobacco-use and development of lung cancer and other smoking related diseases. However, study participants did not translate them into quitting behaviours (15). This phenomenon is not exclusive to LCS but has also been described in

other screening programmes (63). Contrary to this, a recently published observational cohort study investigating smoking behaviour and LCS in socio-economically deprived populations, found that community-based LCS programmes positively impacts smoking behavior, with no evidence of misperceptions such 'screening is a license to smoke' in the participating individuals (64). A study evaluating screening participants in the Danish lung cancer screening trial (DLCST) found that participants after one year of screening showed a significant increase in cessation attempts and decrease in relapse to smoking among patients with a positive scan versus those with a negative scan (65). This effect however, was not observed when all five years of screening were analysed (66). Another study reported no statistical significant differences in smoking cessation attempts and quit rates between smokers who participated in a screening programme and a control group that was not screened (67). However, also in this trial smokers with a positive screening result showed a significantly higher number of quit attempts (67) compared to those with negative screening results. Similarly, other studies suggest (19-22) that any positive, and also false-positive, screening result was associated with greater motivation to quit smoking and a higher likelihood of quitting and sustained abstinence. Although, there is evidence that individuals undergoing screening programmes may quit at slightly higher rates than the general population of smokers (68), this might not necessarily being attributed to the screening programme itself, but may also be partly due to demographic or motivational differences in populations willing to undergo screening (69). Overall, smoking cessation remains the most harmless and cost effective manner to reduce lung cancer related mortality and therefore smokers participating in screening programmes should be carefully counselled to ensure that screening itself is not perceived as an adequate replacement for smoking cessation (42,70).

Conclusions

LCS will inevitably be implemented in Europe. It is essential to train general radiologists and define the reading modalities which would be efficient and realistic for large scale screening. The role of artificial intelligence remains to be prospectively validated. Screening individuals at higher risk of lung cancer, based on the use of risk models, will increase screening effectiveness but not necessarily cost-effectiveness. Implementation research programmes could help to improve the screening process (71). Quality assurance needs to be implemented and a European registry for collection of lung cancer CT screening data should ideally be developed.

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