The evolution of lung cancer screening with low dose computed tomography

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Background and introduction

Following promising initial data from Japan, low-dose computed tomography (LDCT) was introduced into North American research studies in the early 1990s (1). These studies assessed the ability of LDCT to detect early stage lung cancer in asymptomatic individuals, i.e. lung cancer screening. Almost a quarter of a century later, health care is finally very close in utilizing LDCT as a clinical tool for lung cancer detection. In December 2013, the United States Preventive Services Task Force (USPSTF) published a statement recommending annual screening for lung cancer with low-dose computed tomography in adults ages 55 to 80 years who have a 30 pack-year smoking history and currently smoke or have quit within the past 15 years (2). The USPSTF statement also recommends that screening should be discontinued once a person has not smoked for 15 years or develops a health problem that substantially limits life expectancy or the ability or willingness to have curative lung surgery. The USPSTF is now giving lung cancer screening a "B" recommendation. This is especially significant in the United States since under the Affordable Care Act, new private health insurance plans must cover screenings that receive an “A” or “B” rating with no deductibles or co-pays.

Although the last 25 years has brought much progress around the care of lung cancer, the cure rate has not been affected. Treatment has advanced in all areas, surgical, radiation and chemotherapy, with minimal change in the overall mortality rate. In 1990, the Canadian Cancer Statistics predicted 17,300 new lung cancer cases and 14,200 deaths from lung cancer (3). The respective numbers for 2013 were 25,000 and 20,200 (4), the ratio of deaths to new cases almost constant. Lung cancer remains the most common cause of cancer death in Canada and in Ontario.

This dismal mortality rate is expected to change once more programs offering LDCT lung cancer screening are opened up. In this article, we outline the evolution of LDCT for lung cancer screening, the benefits and harms of lung cancer screening, and emphasize the caveats of LDCT screening.

The research: single-arm trials to randomized trials - survival vs. mortality

LDCT was the subject of multiple single arm studies where an at-risk population was defined, and everybody with a reasonable risk received the same intervention, the LDCT. Since the risk of developing and dying from lung cancer increases with smoking and age, different thresholds of smoking and age were used, varying from 10 to 30 pack-years, and any age from 40 up to 65 years. Much has been gained
from these single-arm studies, including an increased understanding of the morphology of nodules and early stage lung cancers. A landmark paper was published by the I-ELCAP, the largest single arm multicenter study, in 2006: they reported 10-year survival rates of screen detected lung cancers of up to 92% (5). However, survival is not disease-specific mortality as it is subject to lead time bias, length time bias and overdiagnosis, and survival alone does not give sufficient justification for the effectiveness of a screening tool.

To address the disease-specific mortality, the NIH funded one of the largest randomized trials in the US, the National Lung Screening Trial (NLST). More than 50,000 individuals were enrolled between 2002 and 2004, randomized to either chest radiographs or LDCT. The initial results were published in November 2010 and described a 20% reduction in lung cancer mortality in the LDCT group at 6 years following a baseline scan and two annual rounds of screening (6). These results were widely regarded as the missing piece for the final acceptance of LDCT as a lung cancer screening tool.

Nevertheless, it took another 3 years until the USPSTF changed their recommendations. While it is largely accepted that a properly designed LDCT screening program can save lives, a poorly run program may be harmful and negate the benefits of early lung cancer detection. It has taken these past three years to identity and start to address these potential harms.

Minimize harm of LDCT screening

All screening causes harm, since healthy individuals undergo a procedure with different invasiveness and side effects that yields an either positive or negative result. The harms stem from the procedure as such, as well as from sequelae from positive results.

While low-dose CT techniques are used for lung cancer screening, the healthy individual is still exposed to some radiation. For a baseline CT and the annual repeat CT scans, the parameters that are generally recommended on a multi-detector scanner are 120 to 140 peak kilovoltage (kVp), 20 to 60 milliampere seconds (mAs), and an average effective dose that should be lower than 1.5 millisieverts (mSv).

Collimation should be 2.5 mm or less (7). Recommendations, however, should be defined beyond the baseline CT. According to the I-ELCAP protocol, the radiation exposure from a follow up CT that is performed only to assess the growth of a nodule, can be decreased considerably by limiting the data acquisition to a slab covering only the nodule, rather than repeating a CT of the entire chest (7). Furthermore, accumulated radiation exposure needs to be considered when recommending the intervals and overall duration of lung cancer screening. Annual repeat screening in an individual entering a screening program at the age of 50 until the age of 80 would result in 30 scans, not accounting for the occasional interim follow up for an incidental lung nodule. There is insufficient evidence on the length of long-term screening intervals, all current evidence stems from research studies with baseline and a defined end occurring after \( n \) rounds of screening; in the case of the NSLT, screening ended after three rounds. Recent guidelines suggest an annual to biennial approach depending on the findings on the baseline and first annual scans (7). The MILD trial did not see any harm in the biennial approach as there was no shift to higher-stage diseases in the biennial arm (8). The
recommendation of annual screening for three years is subject to change when longer term trial evidence (e.g. from the Pan Canadian Early Lung Cancer study (9)) or from further stratification methods (e.g. from the NELSON trial (10)) become available.

The second, and quite likely much larger harm, comes from a false positive test result. In lung cancer screening studies, 18-27% (6,11-16) of participants have a positive test, i.e. a nodule larger than a predefined threshold. Follow up of these nodules is usually conservative, consisting of repeat CT scanning to confirm a lack of growth, resulting in an incrementally increasing confidence of benignity with the number of CT scans and the time lapsed. Even though the outcome is eventually good, i.e. a benign nodule, the follow up process is not without harms. Obviously there is radiation exposure from the follow up scans (which can be limited as described above). The mere awareness of a "nodule" in the lungs causes anxiety; the documentation in medical record has implication for employment, insurability, etc. It may take months, even years, of observation to be sure that nodule is benign. Almost all positive tests are "false positives" since most nodules in question are benign. Therefore, the target should be to decrease the number of positive screening results and, as a result, the number of false positives. The rate of positive screening CT scans is influenced by the chosen threshold above which a nodule is regarded as positive. In general, the smaller the nodule that defines a positive scan, the larger the number of positive scans. Unfortunately there is no evidence on the correct nodule threshold in the literature, and a positive screening scan is arbitrarily defined. E.g. the NLST called the presence of any nodule 4 mm or larger a positive scan, which resulted in a high number of positive scans, i.e. 27%. A 5 mm threshold will decrease the rate of (false) positive scans, without significant impact on the detection and cure rate of early stage lung cancers (17,18). Recently it was suggested to further increase the threshold for a positive scan to 7mm or even 8 mm, which would decrease further work-up without delaying diagnosis (19).

Identifying a high-risk population for lung cancer screening

Given that the harms from screening can be minimized but not entirely eliminated, and the benefit of lung cancer screening has been documented for people at a certain risk to develop and die from lung cancer, an LDCT scan should not be offered to the general population. A population at-risk for lung cancer, in which screening can be effective, needs to be defined, but again there is no agreement on this in the literature. The easiest way to determine risk includes age and smoking, since the risk of dying from lung cancer increases with age and tobacco smoking. Currently, there is no evidence to support specific ages when screening should be initiated or ceased. In the published screening studies the age for screening initiation ranges from 40 years to 60 years (20), the upper age ranges from 69 years to 85 years (20), the minimum smoking history ranges from 10 pack-years to 30 pack-years. Most of the recent recommendations follow the NLST, i.e. require a smoking history of 30 pack-years or more, between 55 and 75 years of age, and smoking cessation of no longer than 15 years. Noticeably, the USPSTF recommendations already deviate from one parameter, having increased the maximum age to 80 years.
Defining risk by age and smoking is a first step in the right direction, but excludes a lot of individuals who are not quite fulfilling the criteria and yet are at risk, and also other risk populations such as passive smokers. The Pan Canadian Lung Cancer Detection study uses a multifactorial risk assessment model that incorporates age and smoking in addition to family history, BMI, education level, COPD and prior chest radiographs, and they have yielded higher detection rates (9).

There is need for an independent biomarker to identify the non- or light smokers at risk, since more and more lung cancers are found in this apparent low risk population.

**Need for accreditation and quality control**

If lung cancer screening becomes widely available, quality control becomes an important feature. Starting with the risk assessment, followed by the data acquisition, the detection and follow up of nodules and the connection to the immediate treatment, an entire program has to be in place. Minimum requirements on the CT scanners are simple and should be met, including helical scanning and low dose technique.

Accredited screening centers need to ensure they have the appropriate equipment and skills to provide screening, through regular phantom dose measurements, training and testing of reading radiologists, and training of other medical specialties on the conservative management of small lung nodules. Referral processes between the disciplines need to be streamlined. The evidence on the benefit of lung cancer screening comes from centers with tight interdisciplinary collaboration between radiology, respirology, thoracic surgery, and medical and radiation oncology, and future data collection will need to show how lung cancer screening performs in other clinical environments. Most importantly, data needs to be collected to address the cost-effectiveness of lung cancer screening in the different health care environments.

**Outlook**

Today, in January of 2014, we are at the onset of a new era in lung cancer screening. We have guidelines and recommendations from various organizations such as the American College of Chest Physicians, the American Society of Clinical Oncology, the American Thoracic Society, the American Association for Thoracic Surgery, the National Comprehensive Cancer Network and the American Cancer Society, and also Ontario recommendations from Cancer Care Ontario (7). If the harms described above are addressed and limited, and appropriate and continued education is taking place, lung cancer screening is going to save a lot of lives. As the next step, initiatives are needed to reach out and get compliance from those at-risk individuals that are generally less interested in being screened, including minorities and immigrant groups.


