Lung cancer kills more Canadians than breast, colon and prostate cancers combined. By the time lung cancer is symptomatic, it is often advanced, and the overall 5-year survival rate is a dismal 16\%. Chest X-ray (CXR) and sputum analysis are not effective screening tools. Yet large studies of screening computed tomography (CT), including the International Early Lung Cancer Action Program (IELCAP), with over 30,000 participants, show that screening CT detects early treatable lung cancer. The 10-year survival rate among IELCAP participants diagnosed with lung cancer was 80%.

Despite their successes, single-arm CT screening studies could not definitively prove that CT actually reduces mortality. Do the promising results simply reflect lead time bias and overdiagnosis of lung cancer in smokers who are more likely to die of another cause? In order to answer these questions, the US National Lung Screening Trial (NLST) randomized over 50,000 patients to screening CXR or screening low-dose CT and followed the patients for an average of 6.5 years. In November 2010, the NLST closed early with headlines of a statistically significant reduction in lung cancer mortality in the CT arm. The results were reported in major newspapers around the world and commanded the attention of the oncology community.

Based on the results of the NLST and other smaller studies, the National Comprehensive Cancer Network, the American College of Chest Physicians, the American Thoracic Society, the American Society of Clinical Oncology and other groups have endorsed CT screening for lung cancer in high-risk patients. The endorsements have been matched by voices of caution and CT screening remains a source of debate, particularly among policy-makers. Concerns have been raised regarding excessive radiation, high numbers of false positive results, other adverse effects and generalizability of the results outside the research setting.

**RADIATION DOSE**

The improvements in CT technology in the last 15 years have markedly improved image detail and have decreased the radiation required to obtain these images. Because the lung is composed predominantly of air (appears black on CT) and cancer is not (appears white on CT), abnormalities as small as 2 mm can be detected using a very low amount of radiation and without intravenous contrast administration. This is not possible in any other part of the body.

The CT scans used in the NLST resulted in an average radiation dose of 1.5mSv. This is less than one quarter the radiation of a standard enhanced CT of the chest, and about one tenth the radiation of a standard CT of the abdomen and pelvis. CT technology is constantly improving and today, the NLST technology is already outdated. Current low-dose CT can be performed at about half the dose used in the NLST.

A second source of radiation exposure is the additional workup of abnormalities detected on screening CT. With older technology, abnormal screens would be followed by a full-dose diagnostic CT. Today the improved quality of low-dose unenhanced screening CT renders this step obsolete. In the NLST, 5.5% of the CT arm went on to positron emission tomography (PET)-CT (at an average dose 10 times that of the screening CT). Newer evidence calls for more rational use of PET-CT with serial low-dose CT often replacing routine PET-CT. In a systematic review published in JAMA 2012, Peter Bach et al estimated that NLST participants would have received an average of 8mSv total dose throughout the course of the trial. Current CT screening programs are on track to lower this dose drastically.

Overall, the carcinogenic risk relating to radiation incurred through low-dose CT of the chest is very small but not zero. Screening CT must not be used indiscriminately and should be limited to patients at high risk of developing lung cancer.

**FALSE POSITIVES**

Up to 75% of patients will have at least one noncalcified nodule on CT, and most of these nodules are the result of a remote infectious or inflammatory process. To label as positives all scans with any noncalcified nodule — or even any noncalcified nodule greater than 4 mm — is overly simplistic. Consider that a high-risk smoker may walk into a CT scanner with a 3% likelihood of lung cancer diagnosis in the next 2 years. If the CT demonstrates a 5mm lung nodule, his risk actually decreases. Most “positive” scans do not require resection, biopsy, bronchoscopy, PET-CT or even a full-dose contrast-enhanced CT. While up to 40% of patients will have a noncalcified nodule >4mm on screening CT (the NLST criteria for a positive scan), the vast majority of these patients will require nothing more than one additional followup low-dose CT.

Subsequent to the design of the NLST, further attention has been paid to serial low-dose CT as a means to reduce the number of false positive exams. The Dutch-Belgian NELSON trial, with a greater reliance on serial CT for intermediate-sized nodules reported a false positive rate much lower than that of the NLST. Increased reliance on serial low-dose CT,
read by experienced radiologists, can further improve CT accuracy. We know that a significant portion of large lung nodules even in asymptomatic patients will be inflammatory, especially in regions where granulomatous disease is endemic. Granulomatous disease and other active inflammatory processes are a known cause of false positive PET and screening CT.9,10 Short-interval followup low-dose CT, by evaluating for malignant rates of growth, can reduce workup for benign nodules without causing a significant delay in treatment for those nodules likely to be malignant.

More sophisticated reporting conventions can allow us to move beyond positive and negative results. The Breast Imaging Reporting and Data System (BI-RADS®) method of reporting mammographic screening, for example, allows lesions to be categorized in one of 6 categories based on imaging features. Similar systems allow recognition that not all “positive” scans require the same workup. Many lung nodules will require nothing more than a recheck at the time of the next annual CT. Frankly invasive lesions require urgent specialist referral. New large nodules are likely inflammatory even in the absence of symptoms, and short-interval followup CT can prevent biopsy, resection or PET. Persistent ground glass nodules likely represent adenocarcinoma in situ and PET-CT should be performed with caution or not at all due to the high likelihood of false positive results for this adenocarcinoma subtype.

ADVERSE EVENTS
The rate of adverse events in the NLST was very low. Of the 26,722 patients in the low-dose CT arm, a total of 21 patients (0.08%) died within 60 days of a diagnostic procedure. The cause of death was not specified and it is not clear if the death could be attributed to the diagnostic procedure. In the 5 patients who died within 60 days of an imaging procedure, at least, the deaths were presumably unrelated. Of the remaining 16 patients, 10 were diagnosed with lung cancer and may have died secondary to the malignancy rather than the workup itself.

The numbers of patients who had a surgical procedure (thoracotomy, thoracoscopy or mediastinoscopy) for disease that was eventually determined to be benign was also very low (0.6% of patients in the CT arm). Provided screening CT continues to be performed in a controlled setting with well-defined workup protocols, this number can be further reduced as we improve our ability to use imaging to distinguish malignant from benign nodules. Advances in minimally invasive lung surgery since the time of the NLST will also lessen the impact of postoperative morbidity.

GENERALIZABILITY OF RESULTS
The NLST was performed largely in academic centres and CT scans were interpreted by thoracic subspecialist radiologists with specific training. It is probable that screening CT performed outside this setting would lead to higher numbers of false negatives and important false positives (i.e. false positives that are inappropriately referred on to full-dose CT, PET-CT, biopsy or surgery). If we wish to preserve the benefits of screening CT and limit adverse events, unnecessary radiation and cost to the healthcare system, screening must be performed in a controlled setting with ongoing quality assurance measures. The Mammography Accreditation Program provides a realistic Canadian example.

COST EFFECTIVENESS
The NLST results demonstrate that 320 patients need to be screened to prevent one death from lung cancer (vs CXR screening). This compares with the Canadian Task Force

Figure 1. 2 cm pulmonary nodule in a 63-year-old man is clearly visible on axial low-dose unenhanced CT (A) but more difficult to identify on the chest radiograph (B) obtained 2 weeks earlier. Right Lower lobectomy was performed by video-assisted thoracic surgery. Pathology revealed a T1aN0 adenocarcinoma.
on Preventive Health Care report stating that 721 women between the ages of 50 and 69 need to be screened with mammography to prevent a death from breast cancer.11 Mammography results in more biopsy and much higher rates of biopsy for benign disease.

Estimating the cost-effectiveness of screening CT is complex. The economic analysis impact data from NLST has not been released. It is likely that the costs to find and treat one early stage lung cancer is less than the cost to treat and palliate one late-stage lung cancer.12,13 Cost-effectiveness is improved when screening is limited to very high-risk patients. The Pan-Canadian Early Detection of Lung Cancer Study has prospectively collected resource utilization data to estimate the cost of screening CT within the Canadian setting, and these results are currently pending.

While smoking cessation strategies are a key factor in limiting the number of Canadians dying of lung cancer, half of screening trial participants are ex-smokers.4 For the 50% who continue to smoke, involvement in a CT screening program can provide an opportunity for smoking cessation assistance.

CONCLUSION
The NLST has shown that CT screening for lung cancer is a safe and effective means to detect early lung cancer and reduces lung cancer mortality in high-risk patients. When performed in experienced centres with evidence-based interpretation guidelines and management protocols, the risk of over-investigation and unnecessary treatment for benign disease is well controlled and cost-effectiveness maximized. One in every four cancer deaths in Canada is due to lung cancer. Even a modest improvement in lung cancer mortality has the ability to make an impact on overall Canadian cancer survival statistics.

Author’s note: After submission of this article, the American Cancer Society released guidelines supportive of lung cancer screening.14

References