Current Recommendations for Screening and Managing Lung Cancer

Written by Nicola Parry

Michael L. LeFevre, MD, MSPH, Department of Family and Community Medicine at the University of Missouri School of Medicine, Columbia, Missouri, USA, and Chairman, US Preventive Services Task Force (USPSTF), launched a series of sessions wherein participants discussed updated recommendations for lung cancer screening, as well as the use of biomarkers in screening and guidelines for the management of nodules detected at screening.

THE DATA BEHIND THE CURRENT SCREENING GUIDELINES FOR LUNG CANCER

Lung cancer is the leading cause of cancer-related death, resulting in approximately 160,000 deaths per year in the United States—more than prostate cancer, breast cancer, and colon cancer combined. Smoking is the greatest risk factor, accounting for up to 90% of cases, and the risk increases with both smoking duration and amount. Lung cancer carries a very poor prognosis, with mortality rates of ~90% secondary to late diagnosis precluding curative treatment, explained Dr. LeFevre.

Until recently, adequate methods for early detection of lung cancer have been lacking. With this in mind, Dr. LeFevre shared data from some important screening trials. The Prostate, Lung, Colon, Ovarian Screening Trial [PLCO] (1993 to 2001) was one of the largest cancer screening trials ever conducted in the United States, with the objective of determining screening efficacy for 4 types of cancer, including lung cancer [Zhu CS et al. *J Natl Cancer Inst* 2013]. The trial showed that, compared with usual care, annual screening chest radiographs (CXRs) did not reduce lung cancer mortality, even in smokers (risk ratio [RR], 0.94; 95% CI, 0.81 to 1.10).

Later, following the emergence of low-dose spiral computed tomography (LDCT)—a technology with the ability to improve early detection of lung cancer—the National Lung Screening Trial [NLST] was conducted to determine if this technology could reduce lung cancer mortality [NLST. *N Engl J Med* 2011]. Participants were randomly assigned to either LDCT or CXR at 3 annual screenings (baseline, Year 1, and Year 2), with follow-up over 6 years. Patients who underwent LDCT had a higher incidence of lung cancer compared with those who underwent CXR (1060 vs 941; RR, 1.13; 95% CI, 1.03 to 1.23) and a reduced mortality risk (247 vs 309 per 100,000 person-years), showing that patients screened with LDCT had a 20% lower risk of dying from lung cancer than did those in the CXR screening group (95% CI, 6.8 to 26.7; p=0.004).

Despite the potential of chest LDCT to reduce mortality in lung cancer, Dr. LeFevre stressed that the potential harms of this technique must also be considered. These include adverse events resulting from radiation exposure, further invasive diagnostic testing, the effects of overdiagnosis, costs associated with screening and additional diagnostic testing, and the potential negative effects of screening on smoking cessation.

Nevertheless, he noted that after weighing benefits against harms, the USPSTF updated its 2004 position and now recommends annual screening for lung cancer with LDCT in adults aged 55 to 80 years with a 30-pack-year smoking history who currently smoke or have quit within 15 years. If used correctly, these newly recommended screening guidelines could prevent as many as 20,000 deaths a year, concluded Dr. LeFevre.

BIOMARKERS FOR LUNG CANCER SCREENING

According to Gabriella Sozzi, MD, National Cancer Research Center, Milan, Italy, in the past 4 decades, the overall 5-year survival rate for non–small cell lung cancer (NSCLC)—which

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accounts for more than 85% of total lung cancer cases—has risen from only 12% to about 16% for all stages. That about only 30% of NSCLC cases are diagnosed before an advanced stage contributes to the gap between the prevailing survival rate and the best-case survival rate. Nevertheless, with appropriate treatment, early-stage NSCLC has a 5-year survival rate of up to 80%, she said, so early diagnosis and proper treatment are essential for this form of cancer.

While early detection is crucial, the NLST study revealed a notable 23% false-positive rate for LDCT screenings. This high false-positive rate leads to many additional screening rounds, all of which are associated with additional radiation exposure, as well as use of unnecessary and sometimes invasive surgical techniques. Reducing this rate of false positives and overdiagnosis through more efficient prediction of aggressive disease therefore remains an unmet clinical need in this patient population.

Prof. Sozzi stressed that although there are currently no validated biomarkers for early lung cancer detection, development of complementary and noninvasive plasma and serum biomarkers has the potential to reduce the false-positive rate with LDCT. Ideally, these should represent the gold standard for noninvasive cancer diagnosis, and extensive efforts remain underway to develop useful biomarkers.

The randomized Multicenter Italian Lung Detection [MILD] trial produced promising results, indicating that a noninvasive plasma microRNA signature classifier (MSC) has predictive, diagnostic, and prognostic value for lung cancer detection, compared with observation [Sozzi G et al. *J Clin Oncol* 2014]. The use of MSC and LDCT reduced the LDCT false-positive rate 5-fold to 3.7%, and MSC risk groups were significantly associated with survival (χ^2=49.53; p<0.001).

Despite the lack of serum biomarkers to detect lung cancer, Michael K. Gould, MS, MD, Kaiser Permanente Southern California, California, USA, highlighted that other valuable biomarkers do exist to assist clinical decision making. He presented the results of an analysis of data from 2 cohorts of participants undergoing LDCT screening that provided a simple, accurate, and practical model to predict the probability of a lung nodule being malignant [McWilliams A et al. *N Engl J Med* 2013]. The study identified useful predictors of cancer, including sex, nodule size, nodule location, and the presence of nodule spiculation. Predictive accuracy of the model was excellent, with an area under the receiver operating characteristic curve of >0.90, even for nodules that were 10 mm or smaller and typically associated with the most challenging clinical management decisions. For a threshold of a 5% risk of cancer, the sensitivity, specificity, positive predictive value, and negative predictive value based on this model are 71.4%, 95.5%, 18.5%, and 99.6%, respectively.

MANAGEMENT OF THE SCREEN-DETECTED NODULE

Dr. Gould highlighted some of the current recommendations according to the American College of Chest Physicians lung cancer guidelines [Gould MK et al. *Chest* 2013]. Small nodules (≤8 mm) are infrequently malignant, and the default option for patients with small nodules is computed tomography surveillance, although its optimal frequency and duration remain uncertain. For patients with large, solid nodules (>8 mm), however, clinical decision making should be individualized—based on review of old thoracic imaging studies and the risks of cancer, active infection, inflammation, and procedure-related complications, as well as patient preferences, anticipated adherence, and center-specific expertise.

Although new recommendations for evaluation of screening-detected nodules are forthcoming from the American College of Radiology, additional rigorously controlled studies of nodule evaluation are necessary to improve the evidence base, including patient-specific models to determine risk of invasive procedures and surgery and thereby enhance the clinical decision-making process, Dr. Gould concluded.