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# Radiomics-based Management of Indeterminate Lung Nodules? Are We There Yet?

With an estimated 229,000 new cases and 136,000 deaths in the United States alone, lung cancer remains the deadliest malignancy worldwide (1). Recently, however, the NLST (National Lung Screening Trial) and the NELSON (Dutch-Belgian Randomized Lung Cancer Screening Trial) studies have demonstrated improved lung cancer mortality for low-dose computed tomographic (CT) screening of the chest in high-risk individuals, and, consequently, lung cancer screening programs are being implemented globally (2, 3). Although this is very exciting, numerous challenges remain, including the detection of large numbers of benign pulmonary nodules, diagnosis of indolent lung cancers, and many others.

The implementation of lung cancer screening and the increased use of diagnostic chest CT, together with advances in CT technology, will undoubtedly lead to an ever-increasing number of detected lung nodules. An estimated 20 million chest CT scans are being performed annually in the United States alone (4, 5).

Despite the reliance on predictive models and nodule-management practice guidelines, considerable variability in nodule classification and uncertainty in management remain (6, 7). Continued research exploring new biological and imaging-based biomarkers is crucial to meeting these challenges.

In this issue of the *Journal*, Massion and colleagues (pp. 241–249) report the development and external validation of a novel, computer-aided, deep learning–based radiomic model, the Lung Cancer Prediction Convolutional Neural Network (LCP-CNN), to distinguish benign nodules from malignant screen-detected and incidentally detected indeterminate pulmonary nodules (8).

Radiomics refers to the identification, extraction, quantification, and analysis of imaging features from radiologic images, with the goal of better or more consistently characterizing radiologic findings. For lung nodules, quantitative and qualitative density and morphologic features provide objective characterization not available by standard visual image interpretation. The analysis of already-available imaging data renders this approach to development and validation of nodule radiomics safe and cost effective. In contrast to conventional radiomic methods in which imaging features are selected by experienced clinicians, deep learning–based radiomics relies on machine learning–extracted features that are frequently abstract and commonly difficult to link back to the underlying biology.

Several other recent studies have explored the potential role of radiomics in the classification of indeterminate pulmonary nodules with promising results (9–11). Enthusiasm has, however, been tempered by the lack of consistency in radiomics features included in these models, the need for homogeneous image acquisition, a lack of stability of the imaging features, the small numbers of scans in relationship to the extracted imaging features (type I error), and a lack of external validation. Models derived from large, heterogeneous real-life data sets, such as the NLST, that are further validated in external data sets, as in the current study, are needed.

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Data on validated radiomic models for lung nodules remain limited. We recently published our results using a conventional eight-feature radiomic model (Mayo Radiomics Model) to distinguish between benign and malignant lung nodules. Our model was trained and internally validated on all available lung cancers and matched benign controls (≥7 mm) from the NLST, generating an area under the curve (AUC) of 0.94 (12). The first successful external validation data for our model were recently presented (13). Similarly, a Google research group (Ardila and colleagues [14]) recently developed a deep-learning algorithm using patients' current and prior CT images to detect lung nodules and assess the probability of malignancy. This model, which included both nodule detection and classification, was also developed using the NLST data set, yielding a similarly impressive AUC of 0.94 (14). The authors were able to validate their results in an external validation set of 1,139 cases including 27 cancers (AUC, 0.95) (14). In the absence of prior imaging, the proposed Lung Malignancy Score outperformed expert radiologists and reduced the false-positive and false-negative risk to 11% and 5%, respectively (14).

Massion and colleagues' (8) LCP-CNN model represents another promising radiomic model for the classification of both screen-discovered and incidentally discovered pulmonary nodules. The reported AUCs are excellent at 0.92, 0.84, and 0.92 in the NLST (training set, screen-detected), Vanderbilt University, and Oxford University (validation sets, incidental) sets, respectively (8). The LCP-CNN model outperformed the clinical Mayo Clinic lung-nodule-malignancy probability model for both external validation sets (8). Compared with the clinical Mayo model, the LCP-CNN model yielded net-reclassification indexes of 0.34 and 0.30 as a rule-in test and 0.33 and 0.58 as a rule-out test for the Vanderbilt and Oxford University data sets, respectively (8). The strengths of the current study include successful validation in two independent data sets using nonprescribed, real-life CT acquisition protocols and the potential applicability of the LCP-CNN to both screen-detected and incidentally detected pulmonary nodules. Although the model still awaits external validation for screen-detected nodules, performance of the LCP-CNN model was also reported for two additional retrospective data sets (Leeds and Nottingham data) in comparison with the Oxford University data set (15).

There are a few study-design decisions and potential sources of bias in the LPC-CNN training and validation. In particular, these consist of the inclusion of images from multiple time points of the same nodule as independent data points, the limited information about the actual imaging variables selected by machine learning, and the influence of nodule size on the radiomic model. Specifically, it would have been helpful if the radiologic features driving the LCP-CNN model had been reported. However, these concerns are lessened by the successful external validation of the model.

What could the implementation of the LCP-CNN model or other automated decision-support tools within our current clinical workflow mean? Radiomics models such as the LCP-CNN model could either replace or supplement clinical models to classify nodules on the basis of the probability of malignancy. The data for the LCP-CNN model suggests that, compared with the clinical Mayo Clinic model, there would be no significant increase in cancers classified as low-risk lesions. Application of the LCP-CNN model would result in a desirable decrease in intermediate-risk pulmonary nodules. However, the rates of potential benign resection (benign lesions classified as high risk), which ranged from 20% (Vanderbilt) to 30% (Oxford) in the data sets, would potentially be suboptimal (8). The resection of benign nodules should be kept to a minimum (10–20%); in fact, application of the British Thoracic Society guidelines kept it to <5% (16). However, as pointed out by the authors, we are currently lacking data on how this information would impact the clinical decision-making process because of the retrospective nature of this data. The impact of the nodule classification used prospectively for management remains unknown.

This work represents a major step toward demonstrating the potential utility of radiomic classification in optimizing the management of screen-detected and incidentally detected pulmonary nodules. However, validation in larger, prospective randomized studies investigating the actual clinical impact on patient outcomes is needed. Any decision-support tool must eventually prove to offer clinically important improvements, and for lung cancer, we should expect real-world use of these tools to result in a reduced time to the identification and treatment of lung cancers, improved survival, decreased morbidity and cost incurred from futile procedures performed on benign lesions, and optimized use of invasive diagnostic procedures. Certainly, confidence in the decision-support tool based on real-world data, widespread availability, and the cost of any new clinically useful biomarker will play a critical role in its clinical adoption. ■

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# Protective Mechanical Ventilation in Organ Donors: A Lifesaving Maneuver

Lung transplantation has become an effective lifesaving intervention for patients with end-stage lung disease. However, the number of available organs does not meet the current demand, with only around 15–25% of lungs being procured from potential donors (1), leading to persistently high mortality rates on the waiting list. Thus, strategies to enhance lung procurement have been suggested as means to reduce the mismatch between organ demand and supply (2) and include extended lung-donor selection criteria (1), *ex vivo* lung perfusion (EVLP) (3), and optimization of donor management (4).

Use of extended lung-donor selection criteria may easily increase the availability of organs within the donor pool. Nonetheless, it may increase the risk of post–lung transplantation primary graft dysfunction, which occurs in about 20% of recipients and is associated with increased morbidity and mortality (5). EVLP has shown excellent reliability for donor lung assessment. Organs that would be declined for transplantation according to standard criteria can be maintained viable for up to 6 hours in clinical settings but up to 24 hours in experimental conditions. This allows a rigorous anatomical, mechanical, functional, and biological evaluation of the donor lung properties, which can more accurately inform the risk–benefit profile of transplantation. This approach has resulted in an impressive increase in the number of lung transplantations worldwide with encouraging long-term outcome (6). However, EVLP is a complex strategy and requires specific skills and advanced resources.

Optimizing management of the lung in the donor may be the strategy that can provide the greatest expansion in organs suitable for transplant without significant increase in resource utilization. Potential lung donors are prone to develop acute lung injury from the exposure to a series of potential mechanical and inflammatory insults, including brain death, atelectasis, lung trauma, aspiration pneumonitis, and ventilator-associated pneumonia (7, 8). These conditions make donor lungs particularly vulnerable and susceptible to the so-called ventilator-induced lung injury (VILI) (9). Mechanical ventilation, although necessary in donors to ensure adequate oxygenation to protect organs potentially suitable for transplant, can itself cause lung injury from excessive regional alveolar stress and strain and tidal recruitment, with the consequent exacerbation of pulmonary and systemic inflammation (9). Lung-protective mechanical ventilation strategies aiming to avoid VILI can hence potentially determine a great impact on lung availability for transplantation.

A prior landmark randomized clinical trial (10) implementing low $V_T$ (6–8 ml/kg of predicted body weight [PBW]), higher positive end-expiratory pressure (PEEP; 8–10 cm $H_2O$), and derecruitment preventive strategies (inline suctioning and continuous positive airway pressure during the apnea test) showed increased rates of organ procurement with similar survival rates. However, the trial was stopped earlier than planned, thereby introducing an important bias in the analysis of its findings.

In this issue of the *Journal*, Mal and colleagues (pp. 250–258) assessed in organ donors the impact of lung-protective ventilation, defined as PEEP $\geq$8 cm $H_2O$ and $V_T$ $\leq$8 ml/kg PBW, on the rate of lung procurement and recipient survival (11). The authors

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