Prediction of pulmonary nodule growth: Current status and perspectives

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Abstract

With the widespread use of low-dose computed tomography for screening of lung cancer in high-risk groups, the detection rate of Pulmonary Nodules (PNs) continues to increase, which raises much concern. The key to accurate treatment is to assess the malignant potential of PNs, although most are small and lack typical imaging signs, thus often requiring follow-up examinations to observe dynamic changes. Prediction of PN growth is essential for the design of personalized treatment plans. Therefore, the aim of this review is to summarize the current criteria to assess PN growth, recent evidence of influencing factors, advancements in assessment methods, and development of prediction models.

Introduction

Lung Cancer (LC) is the leading cause of cancer-related morbidity and mortality worldwide, and the incidence in China continues to increase annually [1]. Early diagnosis and treatment can significantly reduce the mortality rate of LC [2]. Solitary Pulmonary Nodules (PNs) are round or oval lesions with diameters of ≤30 mm that occur in the lungs without pulmonary atelectasis, peripheral satellite lesions, or lymph node enlargement [3]. Based on the extent of coverage of the lung parenchyma on Computed Tomography (CT) images, PNs are classified as Solid Nodules (SNs) or Subsolid Nodules (SSNs), the latter can be further classified as Glass Ground Nodules (GGNs) or Part-Solid Nodules (PSNs) [4]. Due to the lack of typical imaging signs and the small size, most PNs require regular follow-up examinations to monitor dynamic changes and chose an appropriate manage-

ment strategy. During follow-up examinations, the growth and malignant potential of PNs should be evaluated. In addition, continued research is warranted to identify factors that influence the growth of PNs as potential therapeutic targets.

The aim of this review is to summarize current criteria to assess growth of PNs, recent evidence of factors that influence growth, advancements in assessment methods, and development of prediction models to provide references and directions for future studies.

Definition of PN growth

PN growth is defined as an increase in the diameter or volume of PNs on multi-point CT images [5]. In the Early Lung Cancer Action Project study, PN growth was defined as a change in diameter of ≥50%, ≥30%, and ≥20% for PNs with initial diam-

eters of <5, 5–9, and ≥10 mm, respectively [6], although these criteria were based on a single scan. The British Thoracic Society guidelines [7] for the management of PNs and the Neder lands Leuvens Long kanker Screenings Onder zoek protocol for PN management define PN growth as an increase in volume of ≥25% on two CT images [8]. As compared to two-dimensional (2D) measurements of diameter, three-dimensional (3D) measurements of volume can more accurately monitor changes to the sizes of small PNs. Recent studies have found that for some SSNs, growth often occurs with increased density, but no change in volume. Therefore, the Fleischner Society 2017 guidelines define an increase in diameter of ≥2 mm on two CT images as true PN growth [9]. Similarly, the Lung Imaging Reporting and Data System (version 1.1) defines PN growth as an increase in diameter of ≥1.5 mm or an increase in volume of ≥2 mm^3 on two CT images [10]. Notably, these criteria apply not only to change in the size of the total PN, but also the solid component of PSNs. Overall, the criteria to determine the growth of PNs are mostly based on change in diameter, volume, or mass. Shi et al. [11] defined PN growth as an increase in volume or mass of ≥30% on two CT images, while Qi et al. [12]. Used an increase in PN volume of ≥20% on two CT images. Although current criteria to assess change in size of PNs are mainly based on diameter (2D) or volume (3D), the accuracy of the measurements is influenced by image acquisition parameters as well as large inter- and intra-observer variances. Hence, current criteria may be insufficient to assess PN growth.

Methods to assess PN growth diameter and volume

Current methods to assess PN growth include measurement of the diameter (2D) and volume (3D). However, the diameter is measured as the maximum or average diameter of the largest section of the PN [9]. In addition, due to the small size of PNs and asymmetry of longitudinal growth, there could be considerable variance in measurements of the diameter to assess growth. Revel et al [13]. Reported that there is inter- and intra-observer measurement variability in measuring PNs of 3-18 mm, which is unreliable to evaluate small non-calcified PNs. The PN volume is calculated by multiplying the number of voxels by the volume of a single voxel. As compared to 2D measurements of the diameter, 3D measurements of the volume offer more information about the PN and greater sensitivity to more accurately assess growth [14]. However, measurements of both the diameter and volume require consistency with the scanning system, image acquisition parameters, and software [15], which can be difficult to ensure.

Mass

With the increasing detection and awareness of GGNs, 3D volume assessment is still inadequate. Since GGNs are more significantly affected by respiration than SNs, and the growth of some PNs occurs as an increase in the solid component of the PN with little change in the volume, some studies have proposed using mass to assess the growth of GGNs. The mass of a PN can increase by an increase in the volume or inner solid component. The formula to calculate mass (M) is V × (A + 1,000)/1,000 [16], where A is the average CT attenuation value (HU) and V is the volume of the PN. Liao et al [14] reported that mass is more sensitive to reflect the growth of SSNs than the diameter or volume. Similarly, Li [17]. Found that mass better

reflects the growth of PNs with less variability and improved repeatability.

Doubling Time (DT) of the volume and mass of a PN

The DT of the volume and mass is a parametric indicator of PN growth and is calculated with the modified Schwartz formula of the exponential growth model [18] as [ln2 × ΔT]/[ln(X2/X1)], where X2 and X1 are the final and initial volumes (or mass), respectively, and ΔT (days) is the interval between the two CT scans. Previous studies have validated the accuracy and reproducibility of the DT to reflect PN growth [19,20]. However, the application of DT to quantify the growth of a PN assumes that growth is exponential.

Factors associated with PN growth

Factors associated with the growth of PNs include the morphology of the PN and surrounding structures, in addition to clinical history. Several studies [21-26] have shown that the larger the diameter, volume, and mass of the PN, the faster the growth. Chang [27] and Xia [28] suggested that PN growth is related to the size of inner solid component and the appearance of new solid components, whereas Yoon et al [29]. Suggested that the appearance of new solid components was not a risk factor for growth of SSNs. Previous studies have demonstrated that the structural characteristics of PNs, such as lobulation, cavitation [24,30], and bronchographic parameters [26], are also predictive of PN growth, together with peri-nodular pleural traction and vascular convergence [28]. In addition to imaging data, Sun et al [31]. Found that advanced age is also a risk factor for the growth of GGNs. Kobayashi [25] and Xia [28]. Emonstrated that a history of smoking is strongly associated with the growth of GGNs. Some studies have found that PN growth is associated with a history of LC [22,23,26], while others have also found that PN growth is associated with a history of cancer besides LC [30]. Therefore, prediction of PN growth requires adequate mining of PNs as well as clinical data.

Models to predict PN growth

Traditional models

Traditionally, mathematical models (i.e., linear, quadratic, power-law, and exponential) are used to predict PN growth. Heuvelmans [32] demonstrated the exponential growth of nodules by evaluating and quantifying the nodules identified in the Neder lands Leuvens Long kanker Screenings Onderzoek screening. However, due to the lack of follow-up images for the majority of PNs with high malignancy, the growth of included PNs was relatively slow. De Margerie-Mellon et al [33] found that the exponential model was best for quantification of growth of SSNs of lung adenocarcinoma with the use of manually aligned images and also applied volume DT to assess PN growth. However, the sample size of this study was relatively small and pathologically confirmed benign PNs were not included. Similarly, a retrospective study by Qi, et al [12]. Found that the growth patterns of 110 pure GGNs were consistent with the exponential growth model, but this study included some enhanced images, which likely impacted both density and mass measurements, and the pathological results were not available for 71.8% of the PNs. Notably, each of these studies included relatively small sample sizes and specific patient populations, thus the results cannot

be generalized to different populations.

Predictive model of PN growth based on radiomics

Radiomics can extract and transform a large number of features from images into comprehensive quantitative data through high-throughput computing [34,35]. Xue [36] developed a radiomics nomogram that integrated sex and PN type to noninvasively predict the 2-year growth of indeterminate small PNs. However, although the PNs included clinicopathological findings, most were malignant. Sun [37] combined age, sex, PN location, and radiomics to construct a nomogram to predict the potential of GGNs for growth or long-term stability. Although thearea under the receiver operating characteristic curve (AUC) was 0.843 and 0.824 for the training and validation set, respectively, this was a single-center retrospective study and lacked external validation. Yang et al [38] developed several machine learning models to predict PN growth within 1 year and found that a logistic regression model that included age and radiomics achieved the best performance (AUC of 0.87 and 0.82 for the training and validation set, respectively). However, the sample size of this study was small and there were no follow-up data for one-third of the patients, thus demonstrating selection bias. Besides radiomics of PNs, Yoon [39]. Demonstrated the usefulness of the marginal features of PNs to predict the DT of lung adenocarcinoma. Since radiomics analysis is tedious and most of the above studies were conducted in single centers, included small sample sizes, and lacked external validation, future studies with larger sample sizes are needed. With the continued development of artificial intelligence, radiomics is expected to become more convenient and reliable.

Deep learning model to predict PN growth

Deep learning is a branch of artificial intelligence with the ability to learn complex representations in order to improve pattern recognition from raw data, rather than requiring human engineering and domain expertise to interpret structural data and design feature extractors [40]. Zhang [41] developed a deep convolutional neural network to assess the likelihood of cell invasion and the effect of mass to predict the subsequent involvement regions of tumor, and found that the method was superior to mathematical model-based methods. Subsequently, Zhang [42] used Convolutional Long Short-Term Memory (Conv LSTM) with the ability to simultaneously extract static images of a tumor and temporal dynamic changes to predict tumor growth, then extended the Conv LSTM with a spatio-temporal domain by learning multiple patient inter-slice 3D contexts and longitudinal or temporal dynamics. The authors reported that the model significantly outperformed the traditional linear model, Conv LSTM, and generative adversarial network for prediction of tumor volume. Liao [14] built a deep learning model (Siam Model) and a radiomics model based on CT images of 3120 SSNs with at least 2 years of follow-up data retrieved from the National Lung Screening Trial dataset and reported that the AUC of the Siam Model using baseline CT to predict SSN growth was 0.855 for the validation set and 0.821 for the external validation set. However, the ratio of growing to non-growing PNs was 1:14, demonstrating an imbalance in the distribution of data. Rafael-Palou [43] proposed a novel method based on a 3D Siamese neural network for re-identification of PNs from two CT scans of the same patient. Although the accuracy of the model to predict PN growth in the independent validation set was 88.4%, the sample size was small and follow-up data were lacking for the malignant potential of the PNs, as the surgeons chose to operate immediately, which likely skewed the number of benign PNs. Notably, there have been relatively few studies of deep learning methods to predict PN growth and most were single-center retrospective studies with small sample sizes and inconsistent acquisition protocols. Hence, future prospective multicenter studies with larger sample sizes are warranted.

Conclusion

Prediction of PN growth is important for disease management and risk stratification, in addition to differentiation of benign vs. malignant PNs, and standardization of the frequency and time interval of follow-up examinations, which can be appropriately extended for slow-growing PNs and shortened for fast-growing PNs. However, most recent studies of the prediction of PN growth were limited by inconsistent image acquisition methods, insufficient data, and imbalanced data distribution. In addition, most studies lacked mining of clinical and pathological data. Given the limitations of current prediction models, many challenges must be addressed in future research prior to clinical application of models to predict PN growth.

Declarations

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