Special Review

Volumes Learned: It Takes More Than Size to "Size Up" Pulmonary Lesions

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Abbreviations and Acronyms

AAH atypical adenomatous hyperplasia
AIS adenocarcinoma in situ
CT computed tomography
GGO ground-glass opacity
MIA minimally invasive adenocarcinoma
NLST National Lung Cancer Screening Trial

Rationale and Objectives: This study aimed to review the current understanding and capabilities regarding use of imaging for noninvasive lesion characterization and its relationship to lung cancer screening and treatment.

Materials and Methods: Our review of the state of the art was broken down into questions about the different lung cancer image phenotypes being characterized, the role of imaging and requirements for increasing its value with respect to increasing diagnostic confidence and quantitative assessment, and a review of the current capabilities with respect to those needs.

Results: The preponderance of the literature has so far been focused on the measurement of lesion size, with increasing contributions being made to determine the formal performance of scanners, measurement tools, and human operators in terms of bias and variability. Concurrently, an increasing number of investigators are reporting utility and predictive value of measures other than size, and sensitivity and specificity is being reported. Relatively little has been documented on quantitative measurement of non-size features with corresponding estimation of measurement performance and reproducibility.

Conclusions: The weight of the evidence suggests characterization of pulmonary lesions built on quantitative measures adds value to the screening for, and treatment of, lung cancer. Advanced image analysis techniques may identify patterns or biomarkers not readily assessed by eye and may also facilitate management of multidimensional imaging data in such a way as to efficiently integrate it into the clinical workflow.

Key Words: Computed tomography; lung-cancer; screening.

INTRODUCTION

Classic methods of image interpretation for early detection of lung cancer are based on lesion measurement and growth (1). More recently, investigators have published much on the utility and methods of lesion volumetry in multiple settings (2–18). In parallel, various measures other than size have long been proposed (13,19–39). This review explores the perspective that advanced image analysis techniques can identify and quantify imaging biomarkers, including but not limited to size, will likely offer great assistance to clinicians in assessing lesions. Taking the view that a systematic rather than ad hoc approach to quantitative analysis of imaging features grounded in an understanding of tumor biology will yield the most useful tools and approaches, we organize our review by first considering the biology to define the assessment or measurement task, identify the requirements for the settings in which this task is undertaken, and summarize the current state of the art with respect to these settings.

Lung cancer begins with neoplastic tissue arising within the cells of the airway of the lung. Primary lung cancer can be divided into two main groups: small cell lung cancers (SCLC) and non–small cell lung cancers. This grouping is done for therapeutic purposes, and the difference is also reflected by the standard "Tumor-Node-Metastasis" staging paradigm (40). The names are derived from histopathologic presentation:

- **SCLC:** This is thought to develop from neuroendocrine cells along the bronchial epithelium, and its name is based on histopathologic appearance of small cells with scant

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cytoplasm; these cells have ill-defined cell borders, finely granular nuclear chromatin, and absent or inconspicuous nucleoli. SCLC often starts in the bronchi.

- **Non-small cell lung cancer:** Three common types of lung cancer can be found in this category. They have been historically grouped together because they generally share a natural history and also respond to treatment in a different way compared to SCLC. Tumor-node-metastasis staging is useful as it is generally predictive of prognosis and treatment outcomes.
  - **Squamous cell cancer** develops from squamous cells that line the airways, and it is often found in the main airways (bronchus).
  - **Adenocarcinoma** develops from mucus producing cells that line the airways. Certain subtypes may grow slower than other types of lung cancer, and often found before metastatic spread outside the lung.
  - **Large cell carcinoma** develops from epithelial cells and is named from its microscopic appearance of large and rounded cells. The cells are undifferentiated and lack the cytologic and architectural features of small cell carcinoma and glandular or squamous differentiation. This cancer tends to grow quickly.

A radiological finding that may represent a precursor lesion of adenocarcinoma of the lung is an entity called the ground-glass opacity (GGO) pulmonary nodule. Some of these pulmonary nodules evolve to have greater density and thus are called semisolid or sub-solid opacities or nodules (41). Efforts have been made to accurately subdivide this cancer into separate clinical entities to determine patient prognosis and therapy options (42,43). In 2011, a new classification system for lung adenocarcinoma was proposed by the International Association for the Study of Lung Cancer, the American Thoracic Society, and the European Respiratory Society (44). This system replaces the use of the historical name bronchoalveolar carcinoma (BAC) and mixed subtype adenocarcinoma. The proposed classification system is as follows.

- **Pre-invasive histologic lesions**
  - **Atypical adenomatous hyperplasia (AAH)** is detected on computed tomography (CT) examination as localized, small (usually 5 mm or less) GGO. AAH appears microscopically as a lepidic (leaf-like) histology, composed of mildly to moderately atypical cells called type II pneumocytes or Clara cells. These cells grow in existing alveolar walls, replacing the normal lining of the terminal respiratory unit, the bronchioloalveolar epithelium, and sometimes extending into the adjacent respiratory bronchioles.
  - **Adenocarcinoma in situ (AIS)** is detected on CT examination as small to moderately sized (<3 cm) solitary neoplastic nodules. Typical cytologic features of AIS include bland, small, monomorphous nuclei which do not exhibit atypical cellular changes. No evidence of invasive behavior such as stromal, vascular, or pleural infiltration can be found by definition, and these tumors must not show papillae, micro-papillae, and intra-alveolar tumor cells.
- **Minimally invasive lesions**
  - **Minimally invasive adenocarcinoma (MIA)** is detected on CT examination as a small to moderately sized solitary lesion (≤3 cm) with lepidic pattern and also includes circumscribed invasive foci with a diameter of ≤5 mm. The invasive component to be measured in MIA is defined as being of any histologic pattern other than lepidic (ie, acinar, papillary, micropapillary or solid) or comprising single nests of tumor cells infiltrating myofibroblastic stroma. MIA should not show vascular or pleural infiltration and tumor necrosis.
- **Invasive adenocarcinoma**
  - **Lepidic predominant adenocarcinoma (LPA)** is detected on CT examination as a small to moderately sized solitary lesion (≤3 cm) but with at least one invasive focus measuring more than 5 mm in greatest dimension. The histologic appearance typically consists of atypical neoplastic cells growing along the surface of alveolar walls. Architecture and cytomorphology are also comparable with the criteria described for AIS and MIA.
  - **Non-lepidic invasive adenocarcinoma** includes subtypes such as acinar predominant, papillary predominant, and micropapillary predominant. Although these subtypes can be differentiated with histology, there is a lack of a published definition for CT examination.

Carcinoid tumors, adenoid cystic carcinomas, lymphomas, sarcomas, and hamartomas are less common examples of other lung neoplasms which can result from pulmonary nodules. Imaging phenotypes and treatments are unique for each of these lesion types.

THE ROLE OF IMAGING FOR LUNG CANCER

Imaging of the lung using CT is very informative for several reasons. The air-filled lungs which are displayed as nearly black on CT result allow for clear contrast with fluid-density and solid nodules displayed in shades of gray to white. This favorable signal-to-noise ratio (SNR) facilitates lung nodule and cancer detection as contrast between aerated lung parenchyma and solid tissue allows clear visualization of even very small volume nodules. The speed at which a CT may be performed which now only takes a few seconds can allow for near-motionless images. The resulting volumetric imaging is acquired and presented as isotropic voxels and allows for full inspection of the entire lung in multiple planes, in contrast to chest X-ray examination where normal anatomic structures routinely obscure a significant fraction of lung parenchyma and are presented as a single planar image.

Whereas CT is by far the most common modality for imaging the lung, various other modalities are used in advanced disease settings, including positron emission tomography