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Review article

CT appearance of solitary pulmonary nodules; differentiating benign and malignant: a review

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Abstract
A solitary pulmonary nodule is defined as a single nodule (abnormality) seen on an x-ray or CT scan, that is less than or equal to 3 cm (1 ½ inches) in diameter and surrounded by normal tissue, and no other signs that might suggest cancer (such as enlarged lymph nodes or a pleural effusion) are present. If a "spot" on the lung is larger than 3 cm it is considered a lung mass. The imaging evaluation of a solitary pulmonary nodule is complex. Management decisions are based on clinical history, size and appearance of the nodule and feasibility of obtaining a tissue diagnosis. The most reliable imaging features are those that are indicative of benignancy, such as a benign pattern of calcification and periodic follow-up with computed tomography for 2 years showing no growth. Fine-needle aspiration biopsy and core biopsy are important procedures that may obviate surgery (if there is specific benign diagnosis) from the procedure. While using Computed tomography(CT) as diagnostic modality as described in this review, one should strive to not only identify small malignant tumors where resection results in high survival rates but also spare patients with benign disease from undergoing unnecessary surgery. The aim of writing this paper is to review about the CT appearances of solitary pulmonary nodules so that radiologists can master their skills in differentiating benign and malignant nodules.Early detection of small nodules may potentially reduce lung cancer–specific mortality, in time. While one may not be able to establish a diagnosis based solely on the imaging features, the radiologist often plays a major role in the care of patients with Solitary pulmonary nodules (SPNs).
Keywords: Solitary pulmonary nodules; computed tomography, benign, malignant.

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Introduction

Solitary pulmonary nodule (SPN) is defined as a rounded opacity ≤3 cm in diameter surrounded by lung parenchyma [1], without concomitant pneumonia and atelectasis of involved lung segments and lobes. Diagnoses of benign and malignant SPN has been concerned and become a challenge for radiological studies. Some SPNs are indicated pathologically in the early stages of lung cancers. Therefore, it is utmost important to utilize preoperative radiography in the characterization of SPN [2]. The differential diagnosis of the solitary pulmonary nodule is extensive and includes various granulomas, hamartomas, malignancies (most of which are bronchogenic carcinomas), and a variety of miscellaneous lesions including vascular abnormalities (e.g., arteriovenous fistulas, vascular aneurysms) and congenital abnormalities of the lung (including Broncho pulmonary sequestrations and bronchial cysts) [3]. Although most solitary pulmonary nodules have benign causes, 30%–40% of these nodules are malignant [4-10, 18]. Computed tomography (CT) is the preferred radiological approach to examine SPNs. CT scans can clearly show the size, internal features, edge changes, changes of adjacent structures, and enhancement of pulmonary nodules and could provide comprehensive radiological evidences for the differential diagnosis between benign and malignant diseases. However, since most radiological signs were present in both benign and malignant lesions, it is necessary to balance the weight of various radiological signs in the identification of pulmonary nodules, in order to further understand the role of CT in the diagnosis and differential diagnosis of pulmonary nodules [2]. Lesions that may simulate solitary pulmonary nodules should also be considered, such as pulmonary pseudotumors (collections of fluid loculated within the fissures of the lung) and rounded atelectasis (commonly believed to be an involution of the lung as surrounding pleural fluid is resorbed) [3].On CT, nodules can be solid, semisolid (mixed attenuation), or ground-glass attenuation [11].

This article aims at summarizing the appearances of solitary pulmonary nodules at CT scans and thus making differentiation between benign and malignant nodules much easier. In this article, some of the radiographic features that are important to consider when determining the likelihood of malignancy of SPN will be reviewed.

Clinical history affecting risk of malignancy

One must first recognize the clinical factors that makes lung cancer a more likely cause of SPN. The likelihood of lung cancer increases if a patient has a

smoking history, and it is directly proportional to the number of pack-years as a smoker [12]. The incidence of lung cancer does not increase after smoking cessation, but it never equals that for individuals who have never smoked. Consequently, one commonly sees patients with newly diagnosed lung cancer who stopped smoking years or even decades earlier [13].

Onset of lung cancer before the age of 40 years is rare; however, its incidence increases steadily between 40 and 80 years of age [14]. Patients with the human immunodeficiency virus have an increased risk for lung cancer and may develop cancer at a younger age [15]. Lung cancer was once far more common in men than women, but increased smoking rates among women during the 1960s and 1970s have led to an increased incidence of lung cancer in women [16].

Differentiation between benign and malignant

Since most radiological signs were present in both benign and malignant lesions, it is necessary to balance the weight of various radiological signs in the identification of pulmonary nodules, in order to further understand the role of CT in the diagnosis and differential diagnosis of pulmonary nodules. Shi et al.[2] concluded that, according to CT-based diagnosis of SPNs, the relevant factors of age, size, glitches, lobulation, vascular aggregation, air cavity density, calcification and satellite lesions should be considered; meanwhile, during the course of development from small to large nodules, air cavity density could be firstly detected in early stages, followed by glitches and vascular aggregation. Lobulation is associated with relatively large lesions. These findings deepened the understandings and knowledge of radiological signs of pulmonary nodules in different sizes.

Size of SPN

Prior chest radiographs are needed because a nodule that is unchanged on chest radiographs for 2 years is almost certainly benign and requires no further imaging. The size of the SPN is not a reliable predictor of benignity [17]; however, the larger the nodule (approaching 3 cm in diameter), the more likely it is to be malignant. More than 90% of nodules that are smaller than 2 cm in diameter are benign [18, 19]. The prevalence of cancer in SPNs smaller than 1 cm in diameter is unknown. Of non-calcified nodules smaller than 1 cm, 42%–92% have been found to be benign [17, 20, 21]. The large variability reflects selection bias, and reports from surgical series tend to show higher prevalence of malignant lesions than do reports [22]. In comparison, the Early Lung Cancer Action Project screening study showed that only 8% of lesions smaller than 1 cm in diameter were malignant [21].

SPN location

According to Gurney JW [18], both primary bronchogenic carcinomas and tuberculomas are mostly located in upper lobes than in lower lobes, whereas metastases are located in lung bases. Ray et al.[23] reported that, to map the location of both benign and malignant nodules is a surgical series. Lung cancer is 1.5 times more likely to occur in the right lung than in the left lung [24]. Studies have shown that 70% of lung cancers are located in the upper lobes and occur most frequently in the right lung [25, 26]. As benign nodules are equally distributed throughout the upper and lower lobes, location alone cannot be used as an independent predictor of malignancy [27]. Approximately half of primary pulmonary adenocarcinomas manifest as isolated peripheral SPNs, while squamous cell carcinomas that manifest as SPNs are more likely to be centrally located [28]. Clustering of multiple nodules in a single location in the lung tend to favor an infectious process, although a dominant nodule with adjacent small satellite nodules can be seen in primary lung cancer [29, 30].

Internal attenuation of SPN

Calcification

The most important imaging feature that can be used to distinguish benignSPNs from malignant SPNs is calcification. Thus, it is recommended that unenhanced CT be performed with thin sections (1–3 mm); a low-frequency, soft-tissue, or smooth reconstruction algorithm at the level of the nodule; and an attenuation value greater than 200 HU to determine whether calcifications are present within the nodule [61]. Benign nodules can be diagnosed confidently if the lesion is smaller than 3 cm in diameter and exhibits one of the following patterns of calcification: central nidus, laminated, popcorn, or diffuse. When one of these patterns is seen, the likelihood of benignity approaches 100% [17, 20]. A laminated or central pattern is typical of a granuloma, whereas a classic “popcorn” pattern is most often seen in hamartomas [31].Calcification patterns that are stippled or eccentric have been associated with cancer [1].The importance of calcification in a nodule as predictor of benignity was recognized by O’Keefe et al. [32]. Calcification in malignant tumors is

common up to 14% prevalence in the studies of Keefe et al. [32] and Zerhouni et al [17], this is true of only 2% of lung cancers smaller than3 cm in diameter [34]. If a benign pattern of calcification involving more than 10% of the cross-sectional area of the nodule is present, malignancy is unlikely and observation is appropriate [33].Eccentric calcification should not be considered a benign finding. It may represent a benign lesion that has calcified in an eccentric fashion or a malignant lesion that has dystrophic calcification or has engulfed a benign calcified lesion [17]. Furthermore, central calcification in a spiculated SPN should prompt concern for malignancy, as most benign SPNs have smooth or minimally lobulated margins [35]. Some lung cancers can have dense foci of calcification or be entirely calcified, with a pattern resembling that of benign disease. Both of these patterns can be seen in carcinoids, metastatic osteosarcomas, and chondrosarcomas. A stippled appearance or psammomatous calcification can be seen in SPNs that are metastases from mucin-secreting tumors, such as colon or ovarian cancers. In patients with a history of these tumors and abenign-appearing SPN, CT cannot be used to reliably determine benignity and biopsy may be necessary. Unfortunately, calcification is often not useful, as about 45% of benign nodules are not calcified; thus, other imaging features associated with benignity must be sought [17].

Fat

If one can determine that fat is present, hamartoma or lipoma (albeit less likely) become the most likely causes. Some malignancies, such as a metastasis from liposarcoma or renal cell carcinoma, may occasionally contain fat [36]. In patients without prior malignancy, focal fat attenuation (-40 to -120 HU) is a reliable indicator of a hamartoma and is seen in over 50% of hamartomas at thin-section CT. In a series of 47 patients with hamartomas, both fat and calcium were seen in10 and fat alone was seen in 18 [37].

Attenuation

The advent of CT has led to improved recognition of the frequency with which nodules are nonsolid, partly solid, and solid. Aerated lung parenchyma is visible through a nonsolid (ground-glass) nodule, while a partly solid nodule contains solid regions that mask an aerated lung. Approximately 34% of nonsolid nodules are due to malignancy [38].The risk of malignancy increases if the diameter of the SPN exceeds 1.5 cm or the nodule is round [38, 39]. Malignancies such as bronchioloalveolar carcinomas or invasive adenocarcinomas with bronchioloalveolar cell features may appear to be nonsolid nodules. Nonsolid nodules are often caused by benign conditions, such as inflammatory disease, and may contain premalignant lesions, such as atypical adenomatous hyperplasia or Broncho alveolar hyperplasia [40]. Precursors of adenocarcinoma are believed to begin in regions of Broncho alveolar hyperplasia [41]. Partly solid nodules are more likely to be malignant than nonsolid nodules. Between 40% and 50% of partly solid nodules smaller than 1.5 cm in diameter are cancerous, and the risk of cancer increases with increasing nodule size, particularly if the solid component is in the center of the nodule. This solid component often contains invasive adenocarcinoma [38, 39]. Although solid nodules are the most common type of nodule, they are less likely to be malignant than are partly solid or nonsolid nodules. Inflammatory diseases of the lung, particularly tuberculosis and mycoses, usually produce solid nodules that may eventually calcify and permit the designation of benign disease. Only 15% of solid nodules smaller than 1 cm in diameter contain malignant foci, but the proportion of nodules that contain such foci increases with increasing diameter. While solid nodules are usually noncancerous (granulomas), most lung cancers are found in solid nodules. Histologic types of cancerous solid nodules include adenocarcinomas and squamous cell, large-cell anaplastic, neuroendocrine, carcinoid, and (rarely) small-cell carcinomas. In addition, most metastatic nodules are solid in appearance, with a partly solid appearance occurring less frequently [42].

Air Bronchograms

Air bronchograms and bronchiolograms are seen more commonly inpulmonary carcinomas than in benign nodules [37]. In one study, airbronchograms were seen inapproximately30% of malignant nodules but in only 6% of benign nodules [43]. Airbornchiolograms, also referred to as bubble-like lucencies or pseudocavitation, maysimulate cavities and are seen in up to 55% of bronchioloalveolar cell carcinomas [37]. This appearance is caused by a desmoplastic reaction to the tumor that distorts the airways [44, 45].

Edge and contour

Edge characteristics indicative of malignancy include irregularity, spiculation, and lobulation [11]. Edge irregularity and spiculation are associated with the radial extension of malignant cells along interlobular septa, lymphatics, small airways, or blood vessels and have been likened to the spokes of a wheel. Spiculation is attributed to growth of malignant cells

along the pulmonary interstitium, whereas lobulation is attributed to differential growth rates within nodules [46] .Two patterns of the margins of a noduleare relatively specific for cancer. One is the corona radiata sign, consisting of very fine linear strands extending 4 to 5 mm outward from the nodule. A scalloped border is associated with an intermediate probability of cancer. Although, most SPNs with smooth, well-defined margins are benign; which are sere present intrapulmonary lymph nodes [47]. In general, purely linear or sheet-like lung opacities are unlikely to represent neoplasms and do not require follow-up [48].In a study with thin-section CT, all nodules with a halo margin-97% with densely speculated margins, 93% with ragged margins, and 82% with lobulated margins-were malignant [49]. Nodule halos (peripheralnonsolid component) should not be confused with the corona radiata, which is a radiolucent halo associated with para cicatricial emphysema [46, 50].At CT, the halo sign-a poorly defined rim of ground-glass attenuation around the nodule- may represent hemorrhage, tumor infiltration, or perinodular inflammation[62].The presence of spiculation has a predictive value for malignancy of approximately 90% and should prompt an aggressive work-up [17, 18,20,37,51].While an irregular margin is indicative of malignancy, it can occasionally be seen in granulomatous disease, lipoid pneumonia, organizing pneumonia, and progressive massive fibrosis [17, 52]. A smooth margin does not indicate benignity, as up to one-third of malignant lesions have smooth margins and many of these tumors are metastatic [50,53,54].A lobulated margin indicates that the nodule has uneven rates of growth. In a series by Siegelman et al.[20], approximately 40% of smooth-edged lobulated nodules were malignant. Adjacent tiny nodules, called satellite nodules, may mimic the appearance of a lobulated margin, and the presence of these nodules is strongly associated with benignity. Even so, the presence of satellite nodules does not allow confident diagnosis of benignity, as 10% of dominant nodules with satellite nodules will be 17,46]. When cancerous, satellite nodules are usually the result of peripheralfoci of tumor or skip metastatic lesions.

Cavitation

Cavitation may develop in benign or malignant nodules. In general, benign lesions have a smooth, thin wall, while malignant lesions have a thick, irregular wall [55]. Again, the overlap between benign and malignant lesions has led most authors to downplay the value of this observation. Woodring et al. [56] and Woodring and Fried [57] reexamined the concept of wall thickness and found that measurement of the thickest part of the cavity wall was of more value than measurement of the thinnest part. Of lesions whose thickest wall measurement was 4 mm or less, 93% were benign; of lesions whose wall thickness was more than 16 mm, 97% were malignant. For cavities that were 5–15 mm in their thickest part, 51% were benign, and 49% were malignant. Thus, a cavity wall thickness of 5–15 mm may not be used to reliably differentiate benign and malignant nodules [56].

Nodule growth

A doubling in volume manifests as a 26% increase in diameter. Malignant solid SPNs usually have a volume doubling time of less than 100 days, with a range of 20–400 days [63]. Typically, nodules with a volume doubling time of less than 20 days have an infectious or inflammatory cause, whereas those with a volume doubling time of more than 400 days are usually benign [64]. This growth characteristic does not apply to sub solid adenocarcinomas, which may take up to 1346 days to double in volume [65]. For solid nodules, it is generally accepted that a stable size over a 2-year period (which indicates a doubling time greater than 730 days) is a reliable determinant of benignity [66]. However, for small nodules that double in volume, a change in diameter is difficult to perceive. Thus, concern has been raised about the accuracy of conferring benignity to small nodules on the basis of an absence of growth over 2 years [67].

Contrast enhancement

The increase in tissue attenuation after contrast material enhancement depends on blood supply and the volume of the extravascular fluid in the tissue [58, 59]. Early changes in the time-attenuation curve correlate with blood flow per unit of tissue, and the latter changes mainly correlate with interstitial extravascular space [60]. In general, malignant nodules tend to enhance substantially more than benign nodules [25, 70-74].Yamashita et al.[75]reported that a maximum attenuation of20–60 HU appears to be a good predictor of malignancy. A report by Swensen et al.[25] in 2000 is also noteworthy, in that the authors reported a threshold value of 15HU produced a sensitivity of 98%, a specificity of 58%, and an accuracy of 77% for malignant nodules. Cutoff values for the differentiation between benign and malignant nodules have since been set at 15or 20 HU. However, in a dynamic study with multi–detector row CT [72], higher peak enhancement was obtained in comparison with that in previous studies performed

with conventional or single– detector row helical CT, and thus higher attenuation cutoff values could be used for differentiation. Actually, with a cutoff value of 30 HU of net enhancement, overall diagnostic accuracy (sensitivity of 99%, specificity of 54%, positive predictive value of 71%, negative predictive value of 97%, and an accuracy of 78%) was similar to that in previous studies performed by using single–detector row spiral CT. In 2005, Jeong et al. [76] concluded, malignant nodules can be characterized by means of a net enhancement of 25 HU or more and a washout of 5–31 HU. Benign nodules can be characterized by means of a net enhancement of less than 25 HU, a net enhancement of 25 HU or more in combination with a washout enhancement of 31 HU or more, or a net enhancement of 25 HU or more and persistent enhancement without washout. Cronin et al. [68] reported dynamic CT and MR, FDG PET, and 99mTc-depreotide SPECT are noninvasive and accurate in distinguishing malignant from benign SPNs; differences among these tests are non-significant. Ohnoet al. [69] described dynamic perfusion area-detector CT is more specific and accurate than dynamic MR imaging and FDG PET/CT in the diagnosis of solitary pulmonary nodules in routine clinical practice.

Conclusions

Nodule features such as shape, edge characteristics, cavitation, and location have not yet been found to be accurate for distinguishing benign from malignant nodules. Nodule that is unchanged on chest radiographs for 2 years is almost certainly benign and requires no further imaging. We should always compare current radiographs with previous radiographs (if available). Nodules approaching 3 cm in diameter are more likely to be malignant, while nodules smaller than 1 cm in diameter are more likely to be benign. The right upper lobe is the most common location of lung cancer. With the exception of SPNs in patients with a history of bone malignancy, SPNs with a benign pattern of calcification are indeed benign. Demonstration of fat in an SPN in patients without a history of liposarcoma or renal cell carcinoma suggests that the SPN is benign. While most cancerous nodules aresolid, partly solid nodules are most likely to be malignant. Several imaging features (nodule attenuation, presence of air bronchograms, edge characteristics, and cavity wall thickness) must be considered when assessing the likelihood of malignancy; however, there is considerable overlap in the appearance of benign and malignant lesions. When performing contrast-enhanced CT, enhancement of less than 15 HU indicates benignity. In general, SPNs can be considered benign if they exhibit a pattern of benign calcification and/or show no growth for2 years. When the imaging features indicate that the probability of malignancy is high, tissue samples should be obtained for diagnosis. No single CT feature can diagnose solitary pulmonary nodules with certainty, but the combinations of all these features have helped radiologists with the diagnosis.

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