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Distribution of Solid Solitary Pulmonary Nodules within the Lungs on Computed Tomography: A Review of 208 Consecutive Lesions of Biopsy-Proven Nature

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Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Background: The solitary pulmonary nodule (SPN) is a common radiologic abnormality on chest x-rays or computed tomography (CT) scans of the lungs. The differential diagnosis of SPNs is particularly wide as it includes a multitude of benign as well as malignant entities. Nodule location within the lungs has been proposed as a predictive feature in the literature.This study aims at illustrating the distribution within the lungs of a large current series of consecutive SPNs according to their histological subtype, which was definitely proved at core biopsy.

Material/Methods: Two hundred-eight SPNs referred to our center for characterization were reviewed in this single-centre retrospective study. Histological subtypes were defined following the IASLC/ATS/ERS and WHO (2004) histological classification.

Results: This study provides evidence with respect to the prevalence of adenocarcinomas and other non-neuroendocrine primary lung cancer types in the right upper lobe. It also provides new evidence with respect to the prevalence of carcinoid tumors in the middle and right lower lobe, with a tendency to occur in the central lung parenchyma.

Conclusions: This work updates existing knowledge of solid SPNs location within the lungs by providing a current picture of SPN distribution according to their nature.

MeSH Keywords: Carcinoid Tumor • Multidetector Computed Tomography • Solitary Pulmonary Nodule

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Background

The solitary pulmonary nodule (SPN) is a common radiological abnormality on chest x-rays or computed tomography (CT) scans of the lungs. Pulmonary nodules are defined by the Fleischner Society as rounded opacities measuring up to 3 cm in diameter on chest radiographs and CT scans [1] and as a single, isolated, relatively spherical opacity less than 3 cm in size, completely surrounded by normal lung parenchyma [2]. The reported incidence of lung cancer in patients with SPN varies widely, from 2–13% in screening studies, to 46–82% in positron emission tomography (PET) studies [3], probably reflecting the different criteria that were used to select the study population. The differential diagnosis of SPNs is particularly wide as it includes a multitude of benign as well as malignant entities. Primary cancer, metastases, infection, fibrotic changes, parasitosis and benign lesions can all present as a single focal pulmonary opacity, making accurate discrimination a challenging task. In this regard there has been intense investigation to find out which radiological, clinical and anamnestic features could be predictive for malignancy, and to which extent they could be used in the clinical practice. Smoking, nodule size, nodule enhancement on contrast enhanced CT, nodule size, nodule morphology, adipose tissue density, calcification and growth rate have been found to be major predictive factors [4].

Nodule location has been proposed as a predictive feature in models based on Bayesian inference [5] or logistic regression [6].

Table 1. Contingency table displaying lobe location for the histological subtypes considered and statistical significance of the findings.

Histological subtype	Lower right	Middle	Upper right	Lower left	Upper left	Total	Chi-Square P
Hamartomas	8	4	8	2	9	31	0.204
Other benign SPNs	9	2	3	4	3	21	0.1193
Adenocarcinomas	16	6	24	10	19	75	0.0087
Carcinoids	7	7	4	0	3	21	0.4883
Metastases	8	4	7	4	1	24	0.1701
Other malignant SPNs	3	2	19	4	8	36	<0.0001
Total	51	25	65	24	43	208	<0.0001

SPNs – solid pulmonary nodules.

This study aims at illustrating the particular distribution within the lungs of a large current series of consecutive SPNs according to their nature, which was definitely proved at core biopsy.

Material and Methods

All CT thoracic scans of Patients referred to our center for SPN characterization between September 2003 and September 2013 were reviewed in this single-centre retrospective study.

Inclusion criteria were:
- The presence of one or up to 6 solid (defined as a nodule with at least a solid component >80% of the total volume) SPNs, as stated in the Fleischner Society glossary [1], as long as each SPN had been proven of a different histological subtype;
- An available thin-section CT scan encompassing the lungs;
- A definitive diagnosis by means of a diagnostic bronchoscopic, surgical or percutaneous core biopsy.

Exclusion criteria were:
- The presence of visible nodule calcifications if promptly recognizable at usual resolution (1.5:1 magnification) on medical grade monitors;
- The presence of more than one nodule in the same lobe;
- A non-diagnostic core biopsy.

A total of 208 SPNs from 200 patients matched the above-mentioned criteria.

Eight patients had two synchronous SPNs of different nature. Nodules were divided into 6 classes on the basis of their nature: chondroid hamarthomas, carcinoids, adenocarcinomas, metastases, other malignant SPNs and other benign SPNs.

Histological subtypes were defined following the International Association for the Study of Lung Cancer (IASLC)/American Thoracic Society (ATS)/European Respiratory Society (ERS) histological classification [7] and the 2004 World Health Organization Classification of Tumours [8].

Clinical data were collected from the hospital electronic records.

Patients were imaged with a 256-row MDCT system (Brilliance iCT: Philips Healthcare, Best, The Netherlands) or a 64-row MDCT system (LightSpeed: GE Healthcare, Waukesha, Wisconsin, USA).

CT scans were performed with a High Resolution Computed Tomography (HRCT) protocol, including at least one image series with millimetric (slice thickness 1.0 mm) or submillimetric (mostly 0.6 or 0.9 mm) contiguous slices.

Images were jointly reviewed by two radiologists with significant experience in thoracic imaging, respectively with 8 and more than 20 years. Differences in evaluation were resolved by consensus.

Nodule location within the lungs was manually assessed by reviewing the scans on Multi-Planar Reconstruction (MPR) images on a professional workstation (Carestream PACS, Carestream Health, 2008).

Nodules were defined as peripheral if located in the outer third of the lung parenchyma on axial CT images as suggested in literature [9].

Nodule distribution maps were plotted by reviewing the original images on the axial and coronal plane and drawing the approximate nodule position on a schematic map.

Lobe location was recorded for each nodule and a contingency table was built with the data obtained.

Statistical significance for lobe location was assessed by the Chi-square test. A p value of <0.05 was considered significant to reject the null hypothesis (i.e. the hypothesis that nodules are distributed evenly among the lobes).

Statistical analysis was conducted with a commercial statistical software (MedCalc Software bvba, Ostend, Belgium; *http://www.medcalc.org*; 2013).

Results

The study population consisted of 128 males and 72 females. Mean age was 64, ranging from 27 to 83. Median age was 66.

Table 2. Peripherally located nodules, centrally located nodules, percentage of peripherally located nodules, nodules abutting the pleural surface and percentage of nodules abutting the pleural surface for the histological subtypes considered.

Histological subtype	Peripheral	Central	Peripheral%	Pleural contact	Pleural contact%
Hamartomas	13	18	41.94%	3	9.68%
Other benign SPNs	12	9	57.14%	9	42.86%
Adenocarcinomas	41	34	54.67%	20	26.67%
Carcinoids	3	18	14.29%	1	4.76%
Metastases	11	13	45.83%	4	16.67%
Other malignant SPNs	21	15	58.33%	16	44.44%
Total	101	107	48.56%	53	25.48%

SPNs – solid pulmonary nodules.

Histological subtypes and lobe location are displayed in Table 1.

Lesions included in the "Other benign SPNs" category were respectively 5 non-tuberculoid granulomas, 3 nodules of organizing pneumonia, 10 nodules of fibrosis, 1 polypoid lesion, 1 anthracotic lymph node and 1 solitary fibrous tumor of the pleura.

Lesions included in the "Other malignant SPNs" category were respectively 20 squamocellular carcinomas, 2 small-cell carcinomas, 5 large-cell carcinomas, 6 neuroendocrine tumors, 1 undifferentiated NSCLC with mixed aspects of squamous and glandular differentiation, 1 myxoid chondrosarcoma and 1 spindle cell carcinoma of the lung.

Statistical significance for lobe location was found to reject the null hypothesis (i.e. to prove meaningful differences of distribution among the affected lobes) for adenocarcinomas (P=0.0087), other malignant SPNs (P<0.0001) and for the overall distribution (P<0.0001).

In particular adenocarcinomas occurred more frequently in the right upper (24; 35%), left upper (19; 25.33%) and right lower (16; 21.33%) lobes.

The SPNs in the group labeled "other malignant SPNs" occurred significantly more often in the right upper lobe (19; 52.77%).

A significant (P<0.0001) asymmetry in overall lesion distribution was observed between the right and left lung, which were respectively affected in 141 (67.78%) and 67 (32.21%) of cases.

Lesions were distributed unevenly also between the lower (75; 36.05%), and upper lobes (108; 51.92%), whereas they were significantly (P<0.0001) less common in the middle lobe (25; 12.01%).

Malignant SPNs were found to be significantly more common in the right upper lobe (54; P<0.0001) while benign SPNs were more frequent in the right lower lobe, however not significantly (17; P=0.0848).

A nearly even distribution of malignant and benign lesions between the peripheral and the central parenchyma was found. Malignant SPNs were located peripherally in 48.72% of the cases, while benign SPNs in 48.08% of the cases.

With regard to histological subtypes and location within the lung parenchyma we did not observe a significant disproportion between overall peripheral and central location. A significant asymmetry was found for carcinoid tumors only, which were located centrally in 18 out of 21 cases (85.71%; P=0.0023).

On the contrary a clear majority of lesions was not in contact with the pleura or fissural spaces (155; 74.51% *vs.* 53; 25.48%, P<0.0001).

Nodule location within the pulmonary parenchyma as collected on axial CT images and pleural contact for the groups considered is summarized in Table 2.

Distribution of nodules within the lungs is illustrated on schematic maps representing an ideal coronal plane in Figures 1–8.

Discussion

Main findings of this study are the prevalence of adenocarcinomas (P=0.0087) and other non-carcinoid primary lung cancer types (P<0.0001) in the right upper lobe, as well as the prevalence of carcinoid tumors in the middle and right lower lobe (66%), with a tendency to occur in the central lung parenchyma (85.71%; P=0.0023).

SPN location has been widely collected and considered as a peculiar feature of different pulmonary entities in literature.

In particular some reports found malignancies to favor an upper lobe location. On a review of 24,798 cases of primary neoplasms of the lung registered by the Surveillance, Epidemiology, and End Results Program between 1973 and 1977 Byers et al. [10] found that lung cancer including squamous cell cancer, small cell cancer and adenocarcinoma occurred predominantly in the upper lobes.

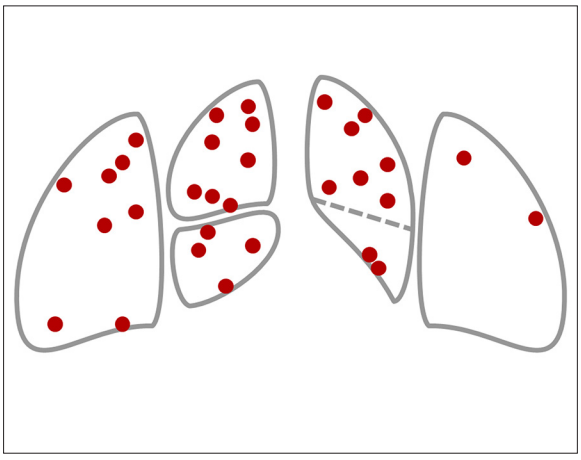

Figure 1. Schematic coronal representation of distribution within the lungs for chondroid hamartomas. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

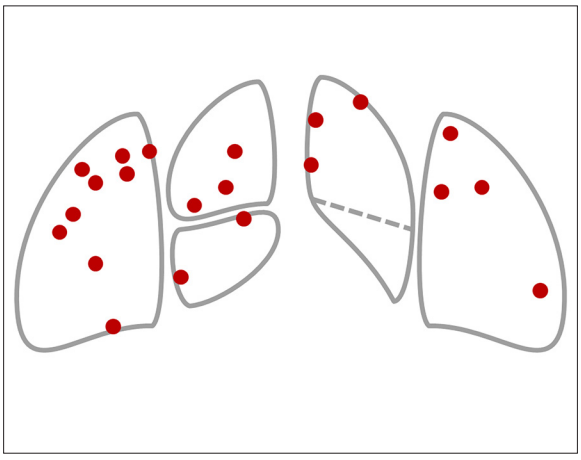

Figure 2. Schematic coronal representation of distribution within the lungs for other benign SPNs. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

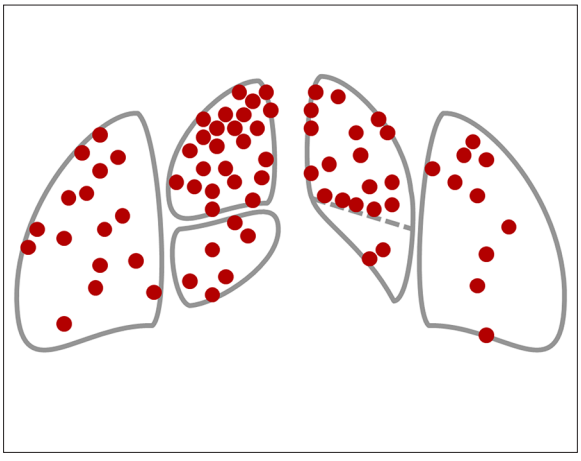

Figure 3. Schematic coronal representation of distribution within the lungs for adenocarcinomas. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

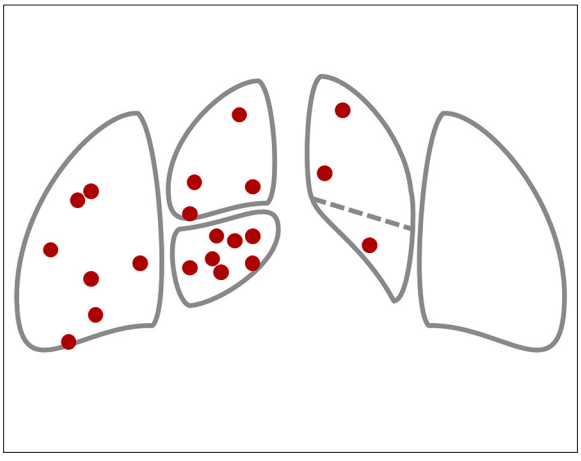

Figure 4. Schematic coronal representation of distribution within the lungs for carcinoids. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

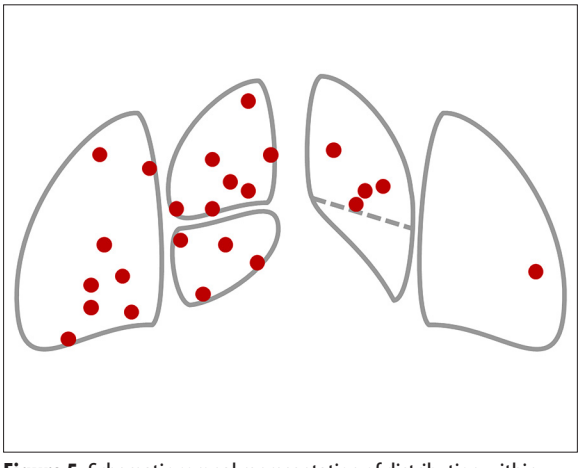

Figure 5. Schematic coronal representation of distribution within the lungs for metastases. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

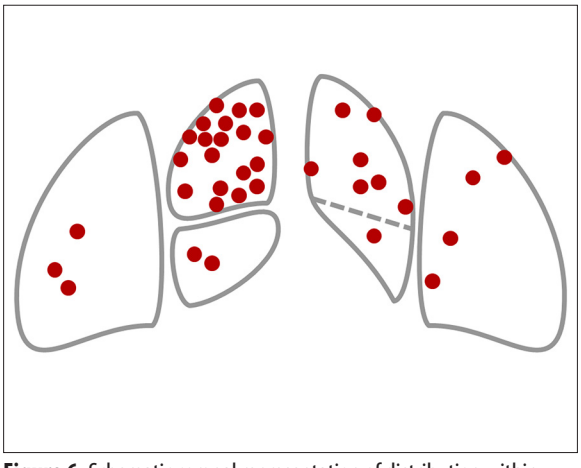

Figure 6. Schematic coronal representation of distribution within the lungs for other malignant SPNs. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

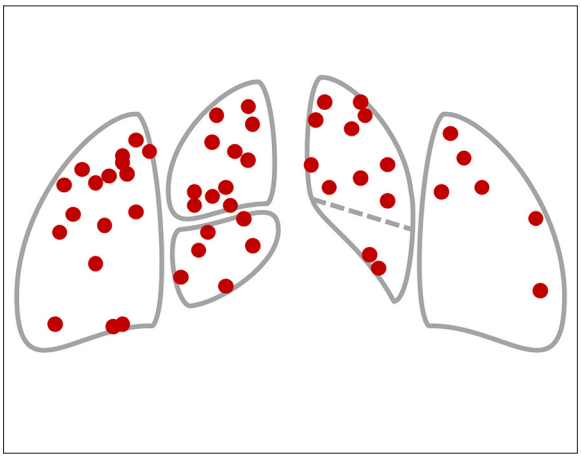

Figure 7. Schematic coronal representation of distribution within the lungs for all benign SPNs. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

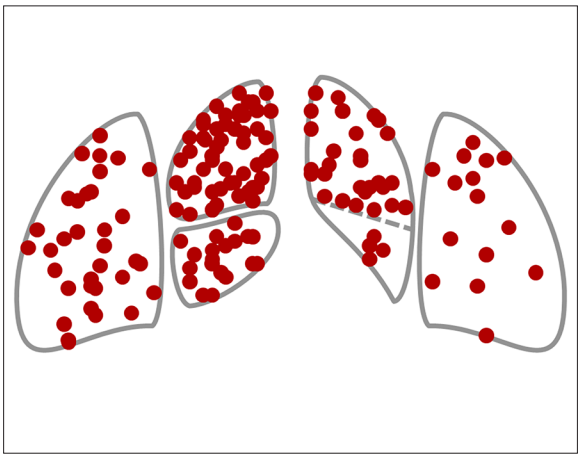

Figure 8. Schematic coronal representation of distribution within the lungs for all malignant SPNs. Dots indicate the approximate location of the lesions. Dots that are superimposed to lobe edges are in contact with the corresponding pleural surface.

A more recent report by Horeweg et al. [11] from the NELSON trial showed how there was a large proportion of cancers localized in the right lung (65.6%) and especially in the right upper lobe (45%).

Location has also been suggested as a peculiar feature of specific types of lesions. For instance in the paper of Celikoğlu et al. [12] histological subtypes other than adenocarcinoma were found to show different locations following their cell type. Squamocellular carcinoma was found more frequently in the upper lobes, while small cell carcinomas showed predilection for the main bronchus on the right side, and the upper lobe on the left. On the other hand no difference could be found between the upper and lower lobes for adenocarcinoma. Lesions other than adenocarcinoma were preferentially located in the upper lobes. More recently Lindell et al. [13] reported 61 cases of lung tumors found during a lung cancer screening program which were unevenly distributed within the lungs. In particular lesions were found to occur more frequently in the right (59%) than in the left (41%) lung, while the majority of lesions were located in the upper lobes (56%), and especially in the right upper lobe (31%). No significant lobar predominance for different tumor histologic types was observed. In the same study researchers classified the tumors as peripheral or central on the basis of their distance from the chest wall on axial images, namely as peripheral if the center of the lesion was within 2 cm from the chest wall, as central otherwise. Lesions were almost evenly distributed between the central (52%) and peripheral (48%) regions, however non-BAC adenocarcinomas proved to be mostly located peripherally (64%) while squamous cell and small cell carcinomas were mostly located centrally (71% and 88%, respectively).

Lobe location has also been suggested as a predictor of malignancy in mathematical prediction models developed by Swensen [6] and Gurney [5]. In both models an upper lobe location will substantially increase the predicted risk of malignancy. In Swensen's model this particular location is considered among the risk factors, while in Gurney's calculator the malignancy likelihood ratio for an upper lobe location is 1.22.

Some reports have stated on the contrary the absence of a statistical difference in nodule distribution on selected study populations. For instance there was no consistent difference in the lobar distribution of the various histological types in the work of Huhti et al. [14].

With regard to pleural contact XU et al. [15] by analyzing 891 non-calcified SPNs from the NELSON study between 5 and 10 mm in diameter concluded that small nodules attached to fissures or pleura had a negligible malignancy rate. In particular all reported cancers were completely intraparenchymal, without attachment to pleura or fissures. However, in this paper an SPN "was considered attached" to the pleura "if the length of the contact surface (...) was more than 50% of the diameter of the nodule at volume-rendered reconstruction or on transverse images" and only 16 cases of malignancy were reported.

From the same screening trial Horeweg [11] again defined the lung periphery as the outer one-third of the costal – hilar diameter on axial CT images, and reported how lung cancers were largely localized in this region. In particular 62.2% of all cancers and up to 82.2% of all adenocarcinomas were peripheral.

In our case series of 208 consecutive SPNs of biopsy-proven nature, a significant difference in distribution was found between the right and the left lung and between the upper and lower lobes, findings in line with previously cited literature.

With regard to peripheral versus central location it must be preliminarily stated how the classic definition of lesions arising centrally or peripherally was based mainly on the extension or the proximity to hilar structures, while no standard definition of central and peripheral locations of lung tumors has been consistently used across different studies with regard to their CT appearance. This suboptimal overlapping of definitions to some extent explains how there could be relevant differences in lesion location among studies.

In particular this study showed a significant difference in distribution only for carcinoids, which were strikingly (85%) more likely to occur centrally in the lung parenchyma.

On the other hand, adenocarcinomas were not significantly associated with peripheral distribution in our case series, a finding that is in contrast with the abovementioned reports of Horeweg and Lindell, who found a clear majority of adenocarcinomas in the lung periphery. We think this could possibly be influenced in the first place by different inclusion criteria adopted as these are both reports from cancer screening programs, in which a smoking habit plays a pivotal role. In the second place the paucity of lesions can have played a major role. In the study by Horeweg et al., 75 out of the 107 adenocarcinomas were classified as IA cancer stage, accidentally the same amount of SPNs proved to be adenocarcinomas in our study, while the remaining 32 lesions were larger, so that the two case series are not completely comparable with regard to size. In the study of Lindell et al. only 25 non-BAC adenocarcinomas were reported, thus limiting the generalizability of the conclusions.

One limitation of the research is the relatively low accuracy of the criterion used to define peripheral and central nodules, that was nonetheless adopted to compare findings with those already available in literature.

The present study was primarily designed to illustrate the distribution within the lungs of a current case series of SPNs. In this regard this study represents to our knowledge one of the largest series of biopsy-proven SPNs in literature.

The first result is that a significant asymmetry in overall lesion distribution between the right and left lung (67.78% *vs.* 32.21%) was found, a finding in line with other reports from the literature.

A significant finding was the distribution of carcinoids presenting as SPNs. These particular lesions were much more common in the central lung parenchyma, with a tendency to occur in the middle and right lower lobe. This finding was unexpected, and has never been reported in the literature to our knowledge. An implication of this is a possibility that embryologic factors play a key role in carcinoid tumor distribution. If confirmed by further investigation, this finding can provide aid in characterizing indeterminate nodules within the middle lobe.

The present study also provides additional evidence with respect to the prevalence of adenocarcinomas and other non-carcinoid primary lung cancer types in the right upper lobe.

In contrast to earlier findings, however, no significant predilection for the outer third of lung parenchyma was demonstrated for adenocarcinomas. This finding probably reflects the lack of a common and precise definition for "peripheral" across studies.

Conclusions

In conclusion, our study updates existing knowledge of solid SPN location within the lungs by providing a picture of a large current case series of lesions which were all characterized by pathology.

Conflicts of interest and source of funding

No conflicts of interests to disclose. We have not received any funding for research.

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