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Original Article

Differential Diagnosis of Benign and Malignant Pulmonary Nodules Using High-resolution Computed Tomography

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ABSTRACT

Objective: To differentiate between benign pulmonary nodules and malignant pulmonary nodules by using the key radiological imaging features on high-resolution computed tomography [HRCT) taking histopathology as Gold-standard.

Methodology: This comparative cross-sectional study was conducted by using 16 slices CT scanner in a radiology department of a tertiary care hospital, Allied Hospital II Faisalabad. A total of 70 patients were included, diagnosed with benign and malignant pulmonary nodule. HRCT scans of the chest were assessed for pulmonary nodule shape, size, location, density type [solid or sub-solid) and margins. Data was analyzed using SPSS version 25, applying Chi-square and Fisher's Exact Test [where applicable). A p-value of <0.05 was considered statistically significant.

Conclusion: This current study revealed that HRCT effectively differentiate between benign and pulmonary nodules and support timely clinical decision-making. From the HRCT findings, it can be seen that malignant pulmonary nodules mostly occur in the right upper lobe and have irregular shapes, spiculated margins, solid density, necrosis, ill-defined borders, and lack of calcifications.

INTRODUCTION

Pulmonary nodules are small, focal, rounded, or irregular opacities of diameter up to 30 mm within lung parenchyma (1), that is alveolar epithelium, pulmonary capillary endothelium, basement membrane, perivascular and perilymphatic tissues (2). In the US, per year approximately 1.6 million patients are detected with pulmonary nodules (3). Approximately 50% of lung cancer patients are detected with pulmonary nodule during screening on CT(4). CT scans performed for some other conditions such as trauma, pulmonary diseases, cardiac and mediastinal pathologies, pulmonary nodules are located incidentally (5). lung cancer prevalence remains undetected and low chance of recovery, therefore over the world it is the most frequent reason for cancer-related fatality (6),(7). In Pakistan, Age-Standardized incidence rate of lung cancer in 2020 is 5.3% and Age-Standardized mortality rate is 3.6% per 100K (8). In Pakistan the incidence of lung cancer is seems to rise steadily and expected to increase in 2040 to 19,140 new cases per year (9).

Lung nodules could be benign entities such as inflammatory, infectious lesions, healed granulomas and focal fibrosis or early neoplastic processes and metastatic disease (10, 11). Benign pulmonary nodules usually do not invade to other body parts but, if their growth remains unchecked they can develop into cancer causing, malignant nodules (12). Gene mapping for disease prediction (13) and AI-based models for disease detection and classification (14) are methods used for other diseases. Similarly genes driving method based on AI-model can be used to diagnose pulmonary nodules (15). In early stages pulmonary nodules are prime sign of lung cancer and on computed tomography images manifest as pellucid or shadowy globoid-like tissue. In initial stages, if lung nodules can be diagnosed instantly and suspected patients can be followed up and treated, the lung cancer incidence can be reduced effectively (16).

For early diagnosis and treatment, it is essential to early distinguish between benign and primary malignant pulmonary nodules. For this purpose, it is necessary to assess clinical results of patient and laboratory outcomes, morphological features of nodule like size, location, composition, margins, density and growth rate as well as other pulmonary and extra pulmonary findings (17, 18). Reconstructing CT scans utilizing adjacent thin sections of less than or equal to 1.5mm and off-axis reconstructions [coronal and sagittal) is necessary to appropriately identify pulmonary nodules. Since nodules may be largely invisible when examined using the mediastinal window setting, it is preferable to assess and measure them using a lung window setting with a sharp filter. For follow-up tests, it is advised to use comparable CT parameters and reconstruction techniques, such as dose reduction techniques, slice thickness, and the reconstruction algorithm, to minimize interscan variability. (19).

Pulmonary nodules are commonly detected on HRCT, but distinguishing benign from malignant lesions remains challenging, leading to unnecessary investigations and delayed diagnosis. The aim of this study is to evaluate HRCT features of pulmonary nodules to improve diagnostic accuracy and to aid in appropriate clinical management.

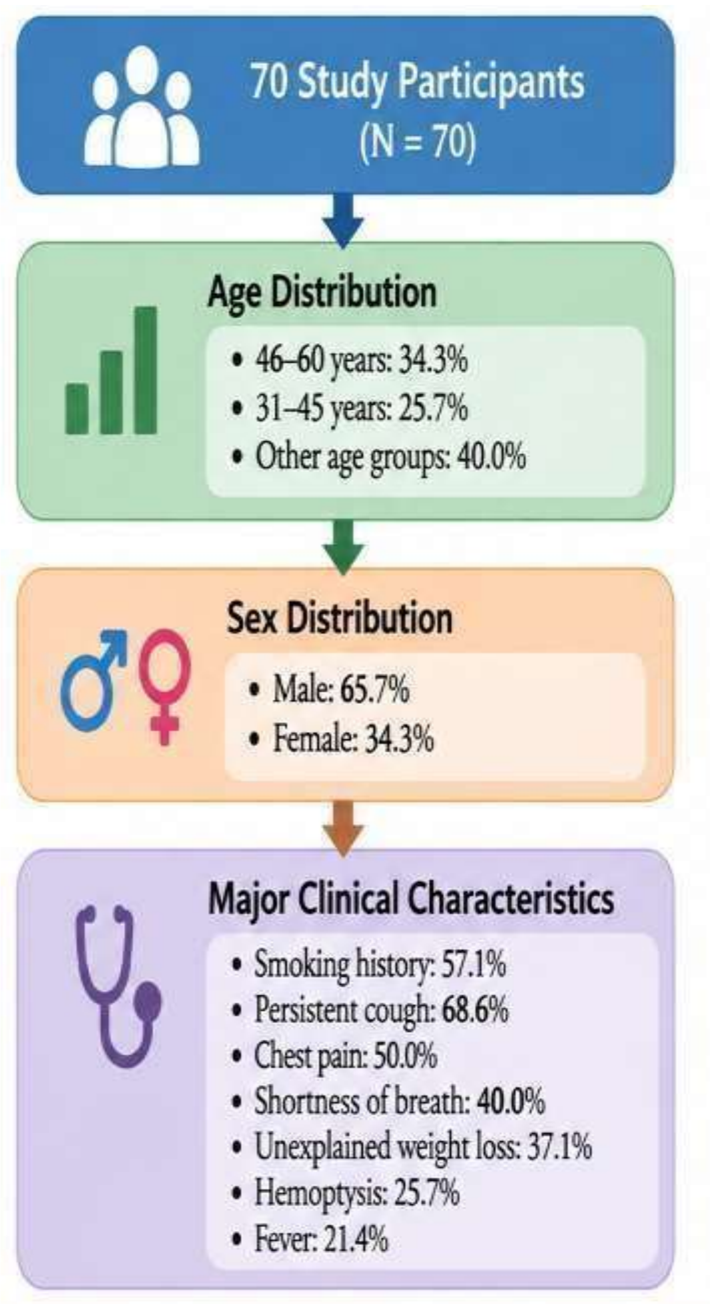
Material and Methods

This Comparative Cross-Sectional study was performed by using 16 slices CT scanner [TOSHIBA) in a radiology department of a tertiary care hospital, Allied Hospital II Faisalabad for the period of four months. Non-probability purposive sampling was used to select patients of age ≥18 years and diagnosed clinically or radiologically with benign or malignant pulmonary nodules of diameter measuring 3-30 mm on HRCT chest. Informed written consent was obtained from each participant after clearly explaining the objective of the study and procedures involved. Patients with nodules > 30 mm, known malignancy, pregnant patients, poor quality HRCT scans due to respiratory motion artifact, incomplete clinical or imaging data and patients who refused for informed consent were excluded. Demographic and clinical data, including age, gender, smoking history, and if any presenting symptom such as [persistent cough, chest pain, shortness of breath, hemoptysis, unexplained weight loss and fever) were recorded using a structured data collection form. HRCT images of 1.5mm slice thickness were interpreted by experienced radiologists to document nodule characteristics such as shape, size, location, density, margins, multiplicity, internal characteristics, calcification, pleural relation and vascular convergence. Histopathology was performed by an experienced pathologist. Final diagnosis was obtained from the histopathology reports. The data was then entered into Statistical Package for the Social Sciences SPSS version 25 for further statistical analysis.

Results

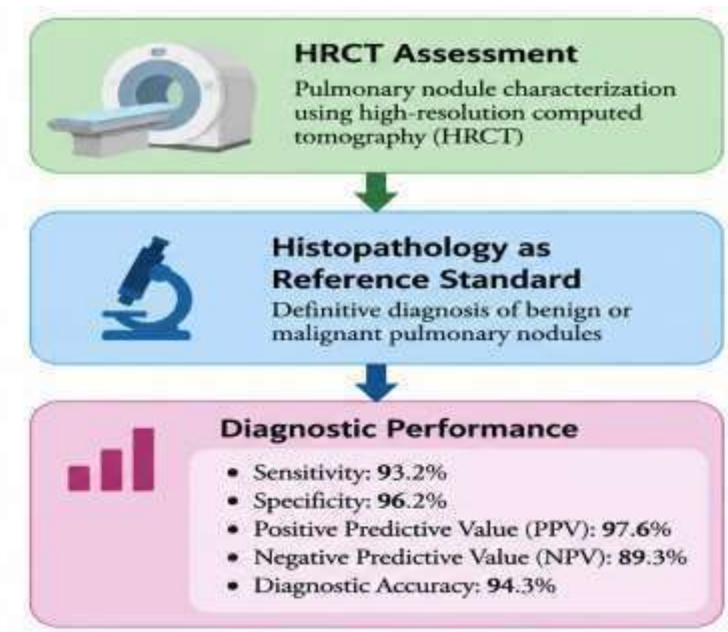
A total of 70 patients with pulmonary nodules were included in the study. The largest proportion of participants belonged to the 46–60 years age group [34.3%), followed by those aged 31–45 years [25.7%), indicating that pulmonary nodules were more frequently observed among middle-aged and older adults [Figure 1). Male participants accounted for 46 [65.7%), while females accounted for 24 [34.3%) [Table 1). Smoking history was reported in 40 [57.1%) participants and was the most frequently documented associated risk factor. Persistent cough was the most common presenting symptom, reported by 48 [68.6%) participants, followed by chest pain [50.0%), shortness of breath [40.0%), unexplained weight loss [37.1%), hemoptysis [25.7%), and fever [21.4%) [Table 1).

Figure 1. Demographic and Clinical Characteristics of Study Participants



Percentages represent the proportion of the 70 study participants. Clinical symptoms were reported among the study participants.

Figure 2. Diagnostic Performance of HRCT for Differentiating Benign and Malignant Pulmonary Nodules



HRCT = high-resolution computed tomography; PPV = positive predictive value; NPV = negative predictive value. Histopathology wa used as the reference standard for diagnostic evaluation.

Table 1. Demographic Characteristics, Smoking History and Clinical Symptoms of Study Participants

Variable	Category	Frequency	Percentage [%)
Gender	**Male**	**46**	**65.7**
	Female	**24**	**34.3**
Smoking history	**Present**	**40**	**57.1**
Clinical symptoms	**Persistent cough**	**48**	**68.6**
	Chest pain	**35**	**50.0**
	Shortness of breath	**28**	**40.0**
	Unexplained weight loss	**26**	**37.1**
	Hemoptysis	**18**	**25.7**
	Fever	**15**	**21.4**

Percentages are based on the total sample [N=70). Symptom frequencies should be checked against the original dataset before publication because the manuscript provides these symptoms primarily as percentages

Table 2. HRCT Imaging Characteristics of Pulmonary Nodules

Variable	Category	n [%)
Number of nodules	Single	44 [62.9)
	Multiple	26 [37.1)
Location	Right lung	32 [45.7)
	Left lung	24 [34.3)
	Bilateral	14 [20.0)
Lobar distribution	RUL	18 [25.7)
	RML	8 [11.4)
	RLL	16 [22.9)
	LUL	12 [17.1)
	LLL	16 [22.9)
Size	≤15 mm	38 [54.3)
	>15 mm	32 [45.7)
Shape	Round	20 [28.6)
	Oval	16 [22.9)
	Irregular	26 [37.1)
	Polygonal	8 [11.4)
Margins	Smooth	18 [25.7)
	Lobulated	20 [28.6)
	Spiculated	24 [34.3)
	Ill-defined	8 [11.4)
Density	Solid	40 [57.1)
	Ground-glass	18 [25.7)
	Part-solid	12 [17.1)
Internal characteristics	Air bronchogram	10 [14.3)
	Fat	4 [5.7)
	Cavitation	18 [25.7)
	Necrosis	38 [54.3)
Calcification	None	40 [57.1)
	Central	10 [14.3)
	Eccentric	8 [11.4)
	Popcorn	5 [7.1)
	Diffuse	7 [10.0)
Vascular convergence	Present	30 [42.9)
	Absent	40 [57.1)
Border definition	Well-defined	26 [37.1)
	Poorly-defined	44 [62.9)
Associated findings	Lymphadenopathy	22 [31.4)
	Pleural effusion	16 [22.9)
	Emphysema	18 [25.7)
	Fibrosis	14 [20.0)

N=70. HRCT = high-resolution computed tomography. The original manuscript's "15 mm" category has been standardized to ">15 mm" to match the stated Results.

Table 3. HRCT Diagnosis and Histopathological Findings

Diagnostic assessment	Category	Frequency	Percentage [%)
HRCT diagnosis	Benign	28	40.0
	Malignant	42	60.0
Histopathological diagnosis	Benign	26	37.1
	Malignant	44	62.9

Histopathology was used as the reference standard. HRCT high-resolution computed tomography

Discussion

In the current study, the most common localization of pulmonary nodules was found to be the right lung [45.7%), with the right upper lobe [25.7%) being the most common lobe for such nodules. The results obtained in the current study are in agreement with the observations made by Lai et al. (20), who found that malignant pulmonary nodules are more often localized in the upper lobes, and especially in the right lung. Similarly, Chen et al. (21) have found that upper lobe nodules had a statistically significant risk of developing lung cancer as compared to nodules situated in other parts of lungs. It might be due to the fact that right upper lobes of the lungs receive comparatively more exposure to tobacco smoke and environmental carcinogens and hence more prone to malignant changes as the repeated episodes of epithelial injury increase the chances of malignant changes.According to our findings, 54.3% of the pulmonary nodules had a diameter of ≤15 mm while 45.7% had a diameter >15mm. Even though small nodules were somewhat common, large nodules have a higher chance of being malignant since larger size is correlated with higher chances of growth of tumor. Likewise, Catelli et al. (22) have observed that nodules which are larger than 15mm have greater probability to be cancerous as compared to smaller nodules. The reason why larger nodules in lung are more probable to be malignant is that growing tumor causes growth in the size of the nodule and thus makes it easily visible through HRCT.In terms of nodule shape, irregularly shaped nodules

[37.1%) accounted for the most number of patients while round [28.6%) and oval [22.9%) nodules made up for the least. Irregular nodule shape is one of the HRCT characteristics that is associated with malignancy since it indicates uncontrolled and infiltrative tumor growth. This observation supports previous research findings by Deng et al. (23) , where it was found out that irregular nodule shape was the strongest HRCT predictor of malignancy that had more diagnostic power compared to regularly shaped nodules. Also, Hendrix et al. (24) reported that irregular nodules had a significantly higher chance to be malignant than round and oval nodules. The presence of mostly irregularly shaped nodules may be attributed to the development of tumors that grew unevenly and infiltrated the lung parenchyma.

In terms of nodule shape, irregularly shaped nodules [37.1%) accounted for the most number of patients while round [28.6%) and oval [22.9%) nodules made up for the least. Irregular nodule shape is one of the HRCT characteristics that are associated with malignancy since it indicates uncontrolled and infiltrative tumor growth. This observation supports previous research findings by Deng et al. (23) , where it was found out that irregular nodule shape was the strongest HRCT predictor of malignancy that had more diagnostic power compared to regularly shaped nodules. Also, Hendrix et al. (24) reported that irregular nodules had a significantly higher chance to be malignant than round and oval nodules. The presence of mostly irregularly shaped nodules may be attributed to the development of tumors that grew unevenly and infiltrated the lung parenchyma.

In the current study, it was found that there was a lack of calcification in 57.1% of pulmonary nodules, whereas various types of calcifications were found in the rest. Lack of calcification has been described frequently in case of malignant pulmonary nodules, while benign pulmonary nodules usually show various patterns of benign calcifications. Such results are consistent with the observations made by He B et al. (25), where it was observed that calcification was found in case of benign pulmonary nodules, while lack of calcification was usually associated with malignancy. Likewise Yang et al. (26) discovered that non-calcified lung nodules were more likely to be malignant than not. Calcification, however, cannot be viewed alone as a sure sign of malignancy, but it has to be correlated with other findings on HRCT Hou X et al. (27). Malignant lung nodules show evidence of cellular proliferation and not calcification; hence calcification is less common while benign granulomas and hamartomas show characteristic calcification patterns.

This current research study discovered that poorly demarcated margins [62.9%) were more frequent as compared to well-defined margins. Furthermore, it was noted that the most common finding in HRCT scan associated with pulmonary nodules was lymphadenopathy [31.4%). Poorly demarcated margins and enlarged lymph nodes are known radiological features that are suggestive of malignant pulmonary nodules. These results were in accordance with Xie X et al. (28). Poorly demarcated tumors will be due to penetration of adjacent lung tissue with the malignant cells, whereas lymphadenopathy is usually due to regional metastasis of the cancer.

Conclusion

This current study revealed that HRCT is an ideal imaging modality in the assessment and diagnosis of pulmonary nodules because of its ability to identify significant morphological characteristics indicative of malignancy. Most of the patients were middle-aged men, and smoking was the leading risk factor while persistent cough was the presenting complaint. From the results of HRCT, it can be seen that pulmonary nodules mostly occur in the right upper lobe and have irregular shapes, spiculated margins, solid density, necrosis, ill-defined borders, and lack of calcifications. This study indicates that HRCT delivers full morphological data that helps distinguish between benign and malignant nodules in the lung and support timely clinical decision-making.

Limitations

There were various limitations associated with the current study. To begin with, the study was done in one hospital. This may reduce the generalizability of the study's results to the general public. Secondly, the number of participants involved in the study was relatively low [n=70). Furthermore, this did not include all types of pulmonary nodules. Thirdly, the study only looked into the findings from HRCT scanning and did not involve PET/CT, MRI, and image analysis through artificial intelligence as diagnostic tools. Moreover, long-term follow up of the patients and the interobserver variability among the radiologists were not part of the study.

Recommendations

As per the results of the present study, HRCT can be utilized regularly as the main method for assessing patients with potential lung nodules due to its high capability in characterization of lesion morphology. The assessment of HRCT findings, including nodule size, site, shape, margins, density, internal structure, calcification pattern, and other associated features, will help enhance the ability to distinguish benign and malignant nodules. HRCT-positive patients need to have histopathological verification to make an accurate diagnosis. Future studies with large multicenter samples, new imaging methods, including artificial intelligence and radiomics, and long follow-ups are suggested.

Conflict of Interest

The authors declare that they have no conflict of interest related to this study, its publication, or the findings reported in this manuscript.

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Authors' Contributions

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Data analysis and interpretation: **Tahira Batool, Ahmad Hassan**
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Critical review of the manuscript for important intellectual content: **Tahira Batool, Mahnoor Fatima, Ahmad Hassan**
Final approval of the version to be published: **All authors**
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