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# Trends in Imaging Patterns of Bronchogenic Carcinoma: Reality or a Statistical Variation? A Single-Center Cross-Sectional Analysis of Outcomes

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**Highlights of the Study**

- Bronchogenic carcinoma is the leading cause of cancer death among both men and women, making up almost 25% of all cancer deaths.
- Squamous cell carcinoma followed by adenocarcinoma is the most common histologic subtype.
- Squamous cell carcinoma was noted predominantly in the peripheral location, and adenocarcinoma was noted predominantly in the central location.

**Keywords**
Bronchogenic carcinoma · Changing imaging patterns · Computed tomography · Radiomics · Artificial intelligence

**Abstract**
***Introduction:*** Bronchogenic carcinoma accounts for more cancer-related deaths than any other malignancy and is the most frequently diagnosed cancer in the world. Bronchogenic carcinoma is by far the leading cause of cancer death among both men and women, making up almost 25% of all cancer deaths. The objective of this study was to identify the changing trends, if any, in radiological patterns of bronchogenic carcinoma to document the various computed tomography (CT) appearances of bronchogenic carcinoma with histopathologic correlation. ***Methods:*** This was a single-center cross-sectional study on 162 patients with clinical or radiological suspicion of bronchogenic carcinoma with histopathological confirmation of diagnosis. ***Results:*** There was a male preponderance with bronchogenic carcinoma and smoking being the most common risk factor. Squamous cell carcinoma followed by adenocarcinoma and small cell carcinoma is the most common histologic subtype. Squamous cell carcinoma was noted to be present predominantly in the peripheral location (55.5%), and adenocarcinoma was noted to be present predominantly in the central location (68.4%). ***Conclusion:*** CT is the imaging modality of choice for evaluating bronchogenic carcinoma and provides for precise characterization of the size, extent, and staging of the carcinoma. Among 162 bronchogenic carcinoma cases evaluated in the current study, a definite changing trend in the radiological pattern of squamous cell carcinoma and adenocarcinoma was observed. Squamous cell carcinoma was predominantly noted to be a peripheral tumor, and adenocarcinoma is predominantly noted to be a central tumor. Surveillance or restaging scans are recommended, considering the high mortality rate in patients with bronchogenic carcinoma.



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## Introduction

Bronchogenic carcinoma accounts for more cancer-related deaths than any other malignancy and is the most frequently diagnosed cancer in the world [1]. Bronchogenic carcinoma is by far the leading cause of cancer death among both men and women, making up almost 25% of all cancer deaths [2]. The incidence in males has risen rapidly with each decade since the 1930s through the 1960s [3]. In women, the recent overall increase in incidence of bronchogenic carcinoma was mainly due to an increase in adenocarcinoma, which has been the predominant cell type in women [4]. Overall, the chance that a male will develop bronchogenic carcinoma in his lifetime is about 1 in 15; for a female, the risk is about 1 in 17 [5]. These numbers include both smokers and nonsmokers. For smokers, the risk is much higher, while for nonsmokers, the risk is lower [6]. Most people diagnosed with bronchogenic carcinoma are aged 65 or older; a very small number of people diagnosed are younger than 45 years of age [7]. The average age of patients when diagnosed with bronchogenic carcinoma is about 57 years [8]. Each year, more people die of bronchogenic carcinoma than of colon, breast, and prostate cancers combined [9]. Statistics on survival in people with bronchogenic carcinoma vary depending on the stage (extent of spread) of the cancer when it is diagnosed. Early diagnosis and prevention of bronchogenic carcinoma thus assumes a major public health issue in the current times.

Radiomics is an emerging method based on algorithms for data characterization, which allows the extraction of many features from medical images. By exploiting the information provided by such features, radiomic approaches aim to uncover and quantitatively describe tumor patterns and characteristics otherwise not observable through traditional algorithms for image analysis. Radiomics has shown a good ability to be considered as a potential new biomarker at different steps of patient care in the management of bronchogenic carcinoma from screening to treatment and follow-up [10]. Artificial intelligence (AI) refers to the use of a computer to simulate intelligent behavior with or without minor human intervention. In the case of bronchogenic carcinoma screening, machine learning, which is a branch of AI, provides algorithms as an aid for radiologists. Such techniques could serve as a computer-aided diagnosis for identifying candidate nodules and retrieving as much diagnostically relevant information as possible [11].

Imaging has a crucial role to play in the management of patients with bronchogenic carcinoma which ranges from staging in advanced disease to screening in high-risk individuals. Computed tomography (CT), in particular, is the imaging modality of choice for staging of bronchogenic carcinoma by evaluating the extent of mediastinal invasion and lymph nodal involvement [12]. The present study is aimed at evaluating the CT imaging characteristics of bronchogenic carcinoma with histopathological correlation (Table 1). The purpose of this study was to identify the changing trends, if any, in radiographic patterns of bronchogenic carcinoma to document the various CT appearances of bronchogenic carcinoma with histopathologic correlation.

**Table 1.** Comparison of location among different histopathological subtypes of bronchogenic carcinoma

| Histological subtype | Central (90), *n* (%) | Peripheral (72), *n* (%) |
|---|---|---|
| Squamous | 34 (37.7) | 40 (55.5) |
| Adenocarcinoma | 26 (28.8) | 12 (16.6) |
| Small cell carcinoma | 24 (26.6) | 5 (6.94) |
| Large cell carcinoma | 6 (6.67) | 5 (6.94) |
| Others | – | 10 (13.8) |

## Materials and Methods

*Setting*

This was a single-center, cross-sectional study on 162 patients with clinical or radiological suspicion of bronchogenic carcinoma referred to a tertiary care hospital in South India between December 26, 2019, and January 25, 2021. The current cross-sectional study is reported in line with the Standards for Reporting of Diagnostic Accuracy Studies guidelines for diagnostic accuracy studies.

*Patient Selection*

Patients with clinical or radiological suspicion of bronchogenic carcinoma were evaluated on CT. 162 patients with a confirmed histopathological diagnosis of bronchogenic carcinoma were included in the study. Mean age of the study population composed of 12 females and 150 males was noted to be 62.5 years, with age selection criteria ranging between 45 and 90 years.

*Imaging Technique of Chest CT*

The chest CT was obtained on a GE (General Electric Medical Systems, Milwaukee, WI, USA) 16-slice MDCT machine. CT scans were performed in caudocranial scanning direction from the level of lung apices to the diaphragm and routinely included the adrenals, at 120 kVp and 50–210 mAs, depending on their weight, using 16 × 1.25 collimation, 0.5 s rotation time reconstructed at 1.25-mm slices with 1.25 mm increment. Patients were instructed to hold their breath if clinically possible. Images were reconstructed using a moderately soft reconstruction filter ("DETAIL") at the mediastinal window and a sharp reconstruction filter ("LUNG") at the lung window settings. If a mass or nodule was identified, ad-

**Table 2.** Frequency correlation based on imaging features in patients with bronchogenic carcinoma

| CT imaging features | Total number of patients, *N* (%) |
|---|---|
| Smooth margins | 3 (1.8) |
| Lobulation | 55 (33.9) |
| Spiculation | 104 (64.1) |
| Calcification | 32 (19.7) |
| Mucous bronchogram sign | 16 (9.8) |
| Cavitation | 21 (12.9) |
| Pleural effusion | 83 (50.6) |
| Direct mediastinal invasion | 55 (33.9) |
| Chest wall involvement | 27 (16.6) |
| Cardia | 7 (4.3) |
| Trachea | 5 (3.0) |
| Esophagus | 19 (11.7) |
| Superior vena cava | 24 (14.8) |
| Bone metastases | 44 (27.3) |
| Liver metastases | 32 (19.7) |
| Adrenal metastases | 15 (9.1) |
| Brain metastases | 9 (5.5) |

ditional 5-mm collimation sections were obtained through the lesion. 60–70 mL of nonionic, water-soluble contrast media (Omnipaque) of strength 300 mgI/mL IV contrast were used in all the patients, except in patients with renal failure and with a past history of contrast-related allergic reaction. Five-millimeter sections at the level of hila were included on post-contrast CT images. The CT images were viewed in the lung window for evaluating the primary mediastinal window for local staging and lymphadenopathy and the bone window for ruling out distant metastases.

*Image Analysis*

Analysis of CT findings was made based on the site of the mass lesion – left/right, size >3 cm, 2–3 cm, 1–2 cm, or <1 cm; peripheral/central location; segmental/lobar distribution; contour of the mass lesion – smooth, lobulated, or spiculated; the presence of air bronchogram, calcification, or cavitation within the mass lesion; enhancement pattern; and the presence of satellite lesions in close proximity to the mass lesion.

CT evaluation of central tumors was based on findings such as bronchial abnormality – peribronchial thickening, luminal narrowing, extrinsic compression, or endobronchial lesion; obstructive pneumonitis; and the presence of collapse. Criteria to interpret chest wall invasion included soft tissue mass, bone destruction, obliteration of extrapleural fat plane, pleural thickening, degree of contact with the pleura exceeding 3 cm. Criteria to interpret direct mediastinal invasion include circumferential contact with the aorta exceeding 90°, a visible mediastinal fat plane between the mass and vascular structures of the mediastinum, and broad base of the mass lesion making greater than 3 cm contact with the mediastinum. TNM staging was done based on CT findings such as nodal status and mediastinal nodal involvement, distant metastases to the adrenals, bone, brain, liver, and the presence of satellite nodules. Comparison was made between CT findings and histopathological reports based on samples obtained on FNACs and bronchoscopy-based lung biopsies.

*Data Analysis and Statistics*

This is a descriptive analysis using numbers and percentages for categorical variables in patients with bronchogenic carcinoma. Statistical analyses were conducted using SPSS Statistical Package (version 20.0), IBM SPSS Statistics for Windows, V.20.0, IBM Corp., Armonk, NY, USA.

*Ethical Considerations*

All examinations performed in studies involving human participants were in accordance with the ethical standards of the Institutional Ethics Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Informed consent was obtained from all patients prior to their enrollment in this study.

## Results

The mean age of the study population comprising 12 females and 150 males was 62.5 years with age selection criteria ranging between 45 and 90 years. All nonsmoker individuals in this study were females, and all male individuals were smokers.

Based on laterality, the right lung was commonly involved, followed by the left lung. Based on the location, the upper lobe of the lung was most commonly involved.

Among 162 patients with bronchogenic carcinoma, a majority of the lesions were greater than 3 cm which demonstrated predominantly heterogenous contrast enhancement. Nodules with spiculated margins were encountered in 104 cases (64.1%), lobulated margins in 55 cases (33.9%), and smooth margins in 3 cases (1.8%). Calcifications were noted in 32 (19.7%) patients with punctate calcifications observed in 22 patients. Calcifications were frequently reported in central tumors (56.1%) as compared to peripheral tumors and also in squamous cell carcinoma subtype of bronchogenic carcinoma (42.3%). Among 28 centrally obstructing tumors causing segmental lung collapse, 16 cases demonstrated dilated fluid-filled bronchi, suggestive of positive “mucous bronchogram” sign.

On staging CT, mediastinal nodal involvement was observed in 133 (82%) patients, mediastinal invasion was observed in 55 (33.9%) patients, and vascular invasion was observed in 102 (62.9%) patients; extrathoracic metastases were observed in 99 patients (61.1%) with the most common sites of involvement being the bone (27.3%), followed by the liver (19.7%) and adrenals (9.1%) (Table 2). Most patients included in the current study were already having advanced stage of bronchogenic carcinoma at the time of presentation, with small cell carci-

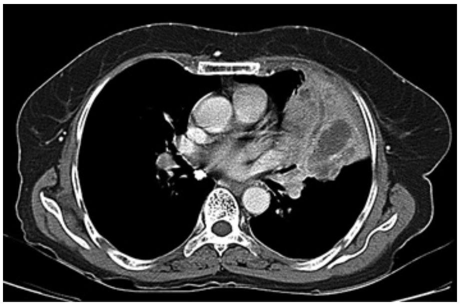

**Fig. 1.** Axial contrast-enhanced CT image of chest demonstrating extensive peripheral consolidation with numerous air bronchograms in a case of bronchoalveolar carcinoma of left lung.

noma as the predominant histopathological subtype (extensive stage 82.3%) as compared to non-small cell carcinoma (stage IIIb 42.7% and stage IV 47.1%) (Fig. 1).

## Discussion

Most studies undertaken in the Indian subcontinent have reported the commonest cell type to be squamous cell carcinoma, accounting for 34–73% of total cases of lung cancer [13]. The most common subtype of bronchogenic carcinoma noted in the current study was squamous cell carcinoma, accounting for 45.6%, followed by adenocarcinoma, accounting for 38 cases (23.4%). However, adenocarcinoma was the predominant histopathological subtype in females, especially in young women, and squamous cell carcinoma in males according to most of the published literature [14]. Chronic inflammation of the lung parenchyma causing gradual progression from epithelial dysplasia to metaplasia to carcinoma in situ relates to pathophysiology of adenocarcinoma. As much of the respiratory epithelium is located at the periphery of the lung parenchyma, statistically, adenocarcinoma has more propensity for peripheral location of the lung than for the central location [15]. However, in the current study, adenocarcinoma was more frequently encountered in a central location than in a peripheral location which reflects a changing trend in the pattern of bronchogenic carcinoma. The occurrence of adenocarcinoma predominantly in the central location was compared with a study by Sharma et al. [16] using the $\chi^2$ test and proved to be statistically significant ($p$ value <0.05). Moreover, the occurrence of squamous cell carcinoma predominantly in the peripheral location was compared with a study by Sharma et al. [16] using the $\chi^2$ test and proved to be statistically significant ($p$ value <0.05). Quinn et al. [17] found a relative increase in the frequency of adenocarcinoma among lung cancers. Conclusions drawn from their study showed a relative decrease in peripheral tumors and an increase in central tumors. A study performed in India concluded that adenocarcinoma is the most common central tumor and also the most common histological subtype [18]; they attributed the findings to an increasing trend of bronchogenic carcinoma in females and nonsmokers and an additional reason being the inclusion of large cell carcinoma under the subtype of adenocarcinoma.

The recent relative increase in the central location of adenocarcinoma and change in histopathological subtypes of bronchogenic carcinoma may be attributed to changes in lifestyle patterns with cigarette smoking showing high association with central location of adenocarcinoma [19]. Also, lowering of nicotine content in cigarette leads users to inhale deeper puffs containing larger volumes to maintain similar blood nicotine levels [20]. Additionally, the increased use of immunohistochemistry techniques for antibodies to carcinoembryonic antigen and mucin staining has led to enhanced recognition of adenocarcinoma. Finally, the inclusion of the large cell carcinoma with mucus production under the poorly differentiated adenocarcinoma subtype of bronchogenic carcinoma has accounted for the relative increase in central location of adenocarcinoma. Although the net effect of these reasons may be modest, in reality, there might be an actual statistical variation that has led to a proportional increase in centrally located adenocarcinomas, reflecting the changing trend.

The high incidence of liver metastases encountered in the current study is related partly to the high incidence of adenocarcinoma that tends to metastasize to the liver as compared to small cell carcinoma. Our findings correlate with those of Chhajed et al. [18] who reported a 23.3% incidence of liver metastases with adenocarcinoma constituting the commonest histopathological subtype (35.5%). Extrathoracic metastases were reported at the time of presentation in advanced stages of small cell carcinoma and adenocarcinoma, correlating with the findings reported in the literature [21].

In the current study, pleural effusions were commonly reported in patients with adenocarcinoma, followed by bronchoalveolar carcinoma, correlating with the findings from the literature [22]. Cavitations were frequently reported in squamous cell carcinoma, and pseudo-cavitations were commonly reported in adenocarcinomas and bronchioloalveolar carcinoma, correlating with the findings from the literature [23].

The principle of radiomics lies in the extraction of radiomic features which is a process to convert convention-



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al images to minable data by extracting high-dimensional quantitative semantic and/or agnostic features [24]. Semantic features are defined as those which are commonly used for the region of interest description by human observers [25]. Agnostic features are those extracted by a computational process for assessment of region of interest heterogeneity [26]. In general, there are three types of such features. The first-order features describe the distribution of all the voxel (3-dimensional pixel) values in the CT images. These are histogram-based properties detailing the mean, median, maximum, and minimum values of the voxel intensities on the images. The second-order features are textural features, which are obtained by calculating the spatial relationship between voxels. Finally, the higher order features are derived using mathematical-based formula features or deep convolutional neural network. The standard radiomic process includes data acquisition, image reconstruction, image segmentation, image preprocessing, feature extraction, feature selection, machine learning, and model evaluation. Radiomics and AI have been shown to have utility across the bronchogenic carcinoma care continuum including risk prediction, early detection, diagnosis, prognosis, and treatment response.

Since 2002, the National Lung Screening Trial (NLST) has included participants with a high risk of bronchogenic carcinoma [27]. Low-dose helical CT compared with traditional chest radiography was applied for bronchogenic carcinoma screening. Accordingly, improving the present methods to detect nodules and discriminate bronchogenic carcinoma from benign nodules is now urgent. In 2014, Lung CT Screening Reporting and Data System was first proposed as a tool for standardizing bronchogenic carcinoma screening [28]. CT reporting and management were based on the traditional radiologist's lexicon such as size, calcification, and tumor density. However, when implemented in clinical work, controversies such as decreased sensitivity and increased interobserver variability arose. As a result of interdisciplinary efforts, radiomics and AI were chosen for compensation.

Although pathologic staging remains the most important prognostic factor for lung cancer survival, there is marked variability in patient outcomes and survival among patients with the same stage of disease, suggesting that other factors contribute to lung cancer survival, progression, and recurrence. Radiomic studies have shown that image-based classifiers have the potential to complement staging and improve prognostication of lung cancer. Aerts et al. [29] analyzed NSCLC and validated a CT radiomic signature that had better prognostic performance than TNM staging and volume with a high concordance index.

Early assessment of a therapeutic efficacy and predicting treatment outcomes would aid in decision support for which treatment has the potential to have optimal benefit for the individual patient. This could eliminate unnecessary treatments, reduce costs and side effects, and increase patient survival. Studies have also investigated the utility of radiomics for treatment responses to chemotherapy or radiation therapy [30].

This study has a few limitations. External validity may be limited in the current study due to its single-center setup. The second limitation is the relatively small number of cases. A third limitation is that many patients with advanced stage of disease were included in the study.

## Conclusions

CT is the imaging modality of choice for evaluating bronchogenic carcinoma as it provides precise characterization of the size, extent, and staging. In the current study, squamous cell carcinoma was predominantly found to be a peripheral tumor, and adenocarcinoma was predominantly noted to be a central tumor. This study demonstrates that the changes in imaging patterns will have a significant impact on the management of bronchogenic carcinoma and suggests the need to prioritize strategies based on multidisciplinary teams, while the rising prominence of adenocarcinomas also has treatment implications. Furthermore, evidence from computer-derived features from CT through radiomics, AI, and deep learning technologies can identify extensive characteristics of bronchogenic carcinoma, such as nodule detection and malignant lesion discrimination. Larger prospective studies are needed to ascertain whether the relative increase in the number of cases of centrally located adenocarcinoma is merely a statistical variation or a reality reflecting the changing trend. Extended intervals between surveillance or restaging scans are also recommended, given the high risk of mortality in patients with bronchogenic carcinoma.

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## Statement of Ethics

The authors certify that they obtained all appropriate patient consent forms. Patients gave their consent for their images and other clinical information to be published. The patients understand that their names and initials will not be published, and due efforts will be made to conceal their identity, but that anonymity cannot be guaranteed.

## Conflict of Interest Statement

The authors have no conflicts of interest to disclose.


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None.


## Author Contributions

Ravikanth Reddy contributed to conception, design of the study, and drafted and critically revised the manuscript. Sandeep Reddy contributed to image acquisition and analysis and revised the manuscript. All authors gave final approval.

## Data Availability Statement

The data that support the findings of this study are not publicly available as they may contain information that could compromise the privacy of the participants but are available from the corresponding author Ravikanth Reddy upon reasonable request.

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