CASE REPORT

Carcinoid Tumor of the Lung: Hospital-Based Descriptive Study

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ABSTRACT

Introduction: Bronchial carcinoids are slow-growing tumors that are usually asymptomatic until the later stages and mimic most benign conditions clinically. This study presented pulmonary carcinoids (PCs) in terms of diagnosis and management in a tertiary care center.

Case: The mean age of presentation was 42.5 years old. Right lung involvement was more common, and the frequency was higher in men. In all patients, second to fourth generations of airways were the site of involvement. The most common symptom was a dry cough. Bronchoscopic biopsy complemented by immune histochemistry was the main diagnostic modality. The majority of patients (60%) had a typical PC. Stage I or III of the disease was the most common presentation. Nine lobectomies and two pneumonectomies were performed on 11 of 15 patients. These patients are performing well to date. Four patients were given only chemotherapy, of which one has survived. The longest follow-up period was 26 months.

Conclusion: A high degree of clinical suspicion and familiarity with carcinoids is essential for early identification and a positive clinical outcome, especially in typical carcinoids (TC), as there are no obvious risk factors and various clinico-radiological presentations. In this study of 15 cases, most of the PCs were right-sided and more common in males. The use of a biopsy, either by a guided bronchoscopy or by computed tomography (CT), was confirmatory, and surgical removal was the treatment of choice. Medical therapy may be considered for select patients with carcinoid syndrome or terminal disease.

INTRODUCTION

Pulmonary carcinoids (PCs) are slow-growing tumors that are usually asymptomatic until the later stages and mimic most benign pulmonary conditions clinically. PC makes for 1-2% of all invasive lung cancers or around one-third of all well-differentiated neuroendocrine tumors (NETs) in the body.[1] The most frequent primary malignant lung tumors in children are PC tumors, which account for 63-80% of all cases.[2]

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The age-adjusted incidence rate in adults in the Western Hemisphere is 0.22/100,000 population/year.[3] These tumors develop from neuroendocrine (NE) bronchial mucosal cells, which can release amines and peptides. These well-differentiated NETs are referred to as carcinoids in contrast to their less differentiated cousins, which include large-cell NETs and small-cell lung cancer. There is not much data available on carcinoids, especially in South India. In this study, we presented 15 PC tumors we encountered in our tertiary institute over 2 years. To our knowledge, this is the largest case series in South India on the profile of PCs. This study aimed to report the characteristics, diagnoses, clinical and treatment outcomes of NE (PC) tumors of the lung in a tertiary care center.

This study was a single-center, prospective, and observational study consisting of 15 cases of PC tumors in a tertiary care hospital in South India, sampled between 2019 and 2021. Subjects attending the Department of Pulmonary Medicine were scrutinized and patients with a carcinoid tissue diagnosis were included in this study. All study participant's clinical features and radiological patterns, along with the diagnostic methods, treatment, and follow-up survival details, were noted.

CASE

A total of 15 PC tumor cases were diagnosed and enrolled in this study. The age of presentation varied between 23 and 71 years old, with the mean age of the study population being 42.5 years old. The incidence was higher in males than females (9 men and 6 women). Nine out of 15 patients had involvement of the right lung. Three out of 15 individuals had lower lobe involvement. Table 1 summarizes the baseline characteristics and provides a synopsis of all study participants.

In all patients, second to fourth generations of airways were the site of involvement. A dry cough was most frequently seen, followed by hemoptysis and shortness of breath (SOB). The primary method used to diagnose in the vast majority of cases was a fiber optic bronchoscopy (FOB) guided biopsy with additional histology and immunohistochemistry. Specifically, 12 out of 15 by FOB, one by endoscopic ultrasound (EUS), one by transthoracic ultrasonogram (TUS), and one by computed tomography (CT) guided biopsy.

A large majority of patients had typical carcinoids (TC), totaling 9 patients (60%), while 6 patients (40%) had an atypical carcinoid (AC) tumor. None of the participants displayed symptoms of carcinoid syndrome, and the majority of them had stage I or stage III of the disease. Following diagnosis, two participants were lost to follow-up and two died. Due to inoperability and poor performance, only chemotherapy (four cycles of Cisplatin and Etoposide) was administered to 4 patients. One of these patients is still alive today. The remaining patients (11 of 15 patients, nine lobectomies and two pneumonectomies) had surgical resection and are performing well to date. The longest follow-up duration was 26 months.

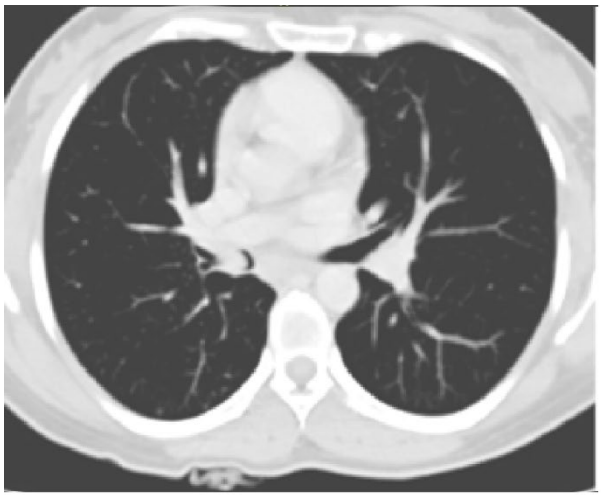

Figure- 1a

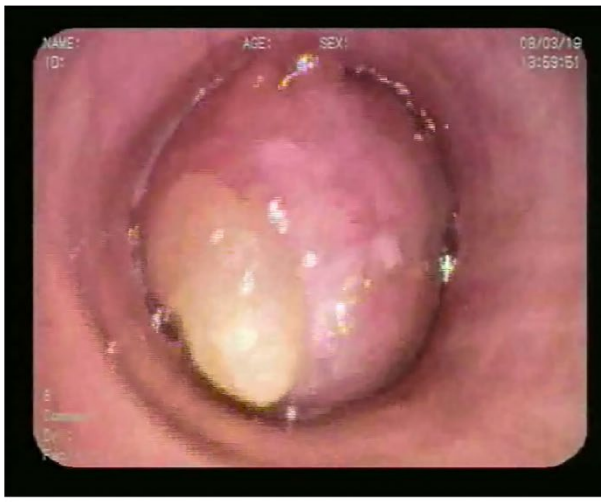

Figure- 1b

Figure 1. 1a. CT thorax of patient no. 13 (Table 1) showed an intraluminal soft tissue density mass in the right intermediate bronchus.
1b. Bronchoscopy showed right intermediate bronchus, endobronchial polypoidal, pinkish vascular mass.

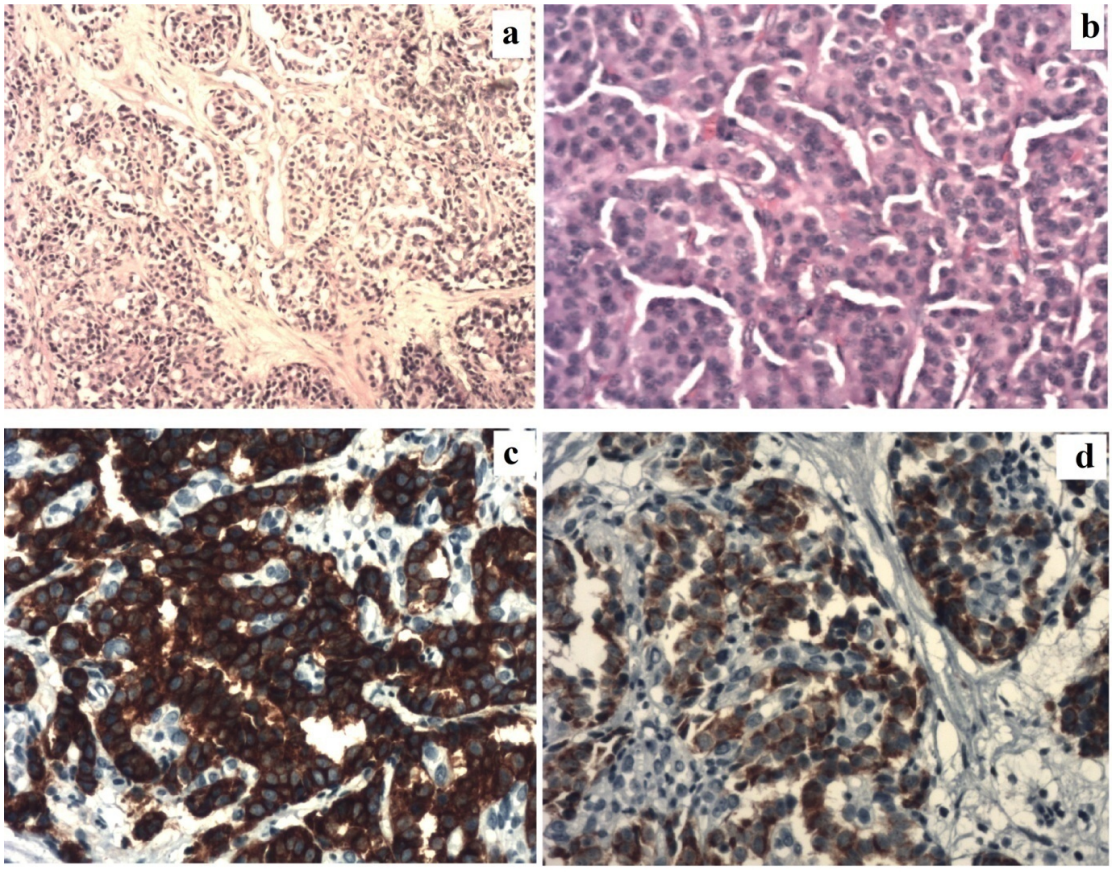

Figure- 2

Figure 2. Histopathology of bronchoscopy guided endobronchial mass biopsy (patient no. 13 (Table 1))
2a. Respiratory epithelium with sub epithelium showed an organoid pattern of arrangement of small round cells with scant cytoplasm (10X H&E staining).
2b. H&E staining showed the tumor cells which were in a polygonal shape with abundant eosinophilic cytoplasm, round to oval nuclei with chromatin showed salt and pepper appearance and inconspicuous nucleoli (20X H&E staining).
2c. The tumor cells exhibited significant synaptophysin positivity (20x immunohistochemistry).
2d. The tumor cells exhibited a significant chromogranin positivity (20x immunohistochemistry).

Table 1. Summary of the baseline characteristics and synopsis of the complete data

No.	Age/ Sex	Site	Symptoms	Tumor size	TNM & Staging	Diagnostic Technique	Pathology	Therapy	Survival
1	32/m	Rt LL	Cough & SOB	8x6 cm	T4N0M0 (IIIA)	FOB biopsy	Typical	Surgery (Rt LL lobectomy) & Adj. chemo	Till date
2	46/m	Rt LL	Dry cough	8.5 X 10.5cm	T4N2M1b# (IVA)	FOB biopsy	Atypical	Chemo	Till date
3	68/m	Rt main	Hemoptysis	2x1.5 cm	T1bN0M0 (IA2)	FOB EBNA	Typical	Surgery (Rt Pneumonectomy)	Lost follow up
4	71/m	Rt UL	Hemoptysis	4.8x3.1	T2bN2M1b** (IVA)	FOB biopsy	Atypical	Chemo	Died
5	28/f	Lt main	SOB	4x3 cm	T2b N2M0 (IIIA)	FOB biopsy	Typical	Surgery (Lt UL lobectomy) & Adj. chemo	Till date
6	56/m	Lt UL	Dry cough	11x7cm	T4N1M0 (IIIA)	TUS core biopsy	Atypical	Surgery (Lt UL lobectomy) & Adj. chemo	Till date
7	37/f	Rtint	Dry cough	1.5X1.2 cm	T1bN0M0 (IA2)	FOB biopsy	Typical	Surgery (Rt ML LL lobectomy)	Till date
8	23/f	Lt Main	Dry cough	1.7x 1.5 cm	T1bN0M0 (IA2)	FOB biopsy	Typical	Surgery (Rt Pneumonectomy)	Till date
9	40/f	Rt ML, LL	hemoptysis	7x8 cm	T4N1M0 (IIIA)	CT-guided core biopsy	Typical	Surgery (Rt ML, LL lobectomy) & Adj. chemo	Till date
10	50/m	Rt hilar and Rt UL	SOB	10x9 cm	T4N2Mx (IIIB)	FOB biopsy	Typical	chemo	Died
11	31/m	Lt UL	SOB	1x1.5cm	T1bN0M0 (IA2)	FOB-FNAC	Typical	Surgery (Lt UL lobectomy)	Till date
12	63/m	Lt hilar (APW mass)	Hoarseness	4.1x3.8 cm	T4N2M0 (IIIB)	EUS FNAC	Atypical	Palliative chemo	Expired
13	29/f	Rtint	Cough	4x2 cm	T2a N0M0 (IB)	FOB biopsy	Typical	Surgery (Rt ML, LL lobectomy)	Till date
14	33/m	Lt main	Dry cough	2x1.5 cm	T1bN0M0 (IA2)	FOB biopsy	Atypical	Surgery (Lt UL lobectomy)	Till date
15	30/f	Rt int	Hemoptysis	2x2cm	T3N1Mo (IIIA)	FOB biopsy	Atypical	Surgery (Rt ML, LL lobectomy)	Lost follow up

LL: lower lobe; UL: upper lobe; Rt: right; Lt: left; Int: intermediate bronchus; APW: aortopulmonary window; Bx: biopsy; Chemo: chemotherapy (cisplatin and etoposide); Adj. Chemo: adjuvant chemotherapy; FNAC: fine needle aspiration cytology; EUS: endoscopic ultrasound; EBNA: endobronchial needle aspiration; FOB: fiber optic bronchoscopy; CT: computed tomography; TUS: transthoracic ultrasonogram

#: Single extrathoracic metastasis to liver

**: Single extrathoracic metastasis to liver

DISCUSSION

Lung NETs are a rare class of lung neoplasm that exhibit NE activity and clinical behavior that is generally indolent. Lung NETs are divided into four histologic variations according to the 2015 World Health Organization (WHO) categorization of lung tumors, 1) TC which are low-grade, well-differentiated tumors with a low mitotic rate (<2 mitoses/10 HPFs); 2) AC which are intermediate-grade, well-differentiated tumors with a higher mitotic rate (2–10 mitoses/10 HPFs) and/or necrosis; 3) large cell neuroendocrine carcinoma (LCNEC) which are high-grade, poorly differentiated tumors; and 4) small cell lung carcinoma (SCLC) which are high grade and poorly differentiated.[4] Extensive geographic necrosis and more than 10 mitoses per millimeter square (often more than 50/mm^2) are present in SCLC and LCNEC.[5] Poorly differentiated neuroendocrine carcinoma/NECs (SCLC and LCNEC) are better classified using diagnostic criteria based on the evaluation of cell characteristics (tumor cell dimensions, nucleolar prominence, and chromatin pattern), whereas TC and AC are not distinguished by these criteria. TC and AC are indistinguishable from one another where there is the use of microscopic biopsies and cytology samples. Separating TC from AC requires an adequate surgical specimen. Surgical biopsy pathological reports should include documentation of tumor necrosis, mitotic count, as well as the Ki-67 index, which is a measure of cellular proliferation, specifically the percentage of cells that have Ki-67-nuclear protein positive on nuclear immunostaining.

All of these factors are included in the categorization criteria and have an effect on survival. Tumor grading, which consists of a combination of tumor necrosis, mitotic count, and Ki-67 index, can be important clinically if it is able to be validated.[6]

NE cells can develop neoplasms in different organs out of which the most common site is the gastrointestinal tract (GIT), followed by the lungs.[7] More than two-thirds of all NE tumors, including TC, are thought to originate in the digestive system. A quarter is thought to originate in the airways or pulmonary parenchyma, according to a recent review of 13,715 carcinoid tumors.[8] Carcinoid tumor incidence in the United States is 1-2 cases per 100,000 individuals.[9] In India, population-based incidence studies are lacking. Studies on carcinoids suggest that because of advanced medical techniques, more asymptomatic tumors are being diagnosed and the incidence is on the rise.[6] The incidence of carcinoids is more in women and whites compared to men and blacks. Additionally, 40-50 years old is the typical age range for carcinoid tumors.[10] Bronchopulmonary carcinoid tumors account for 1–2% of all lung cancers and one-quarter of all carcinoid tumors. PC is the most common primary lung neoplasm in children and late adolescents, with TC far outnumbering AC.[11] Furthermore, 70% of PCs arise centrally in terms of the proximal bronchial generations, while 10–20% arise in the periphery.[12]

The etiology of carcinoid tumors is unknown. There are no known environmental or dietary carcinogens that have been linked to carcinogenesis. Up to two-thirds of carcinoid patients are reported as being smokers. The association between smoking and carcinoid tumors is higher in patients with AC.[13] Almost all PCs are sporadic. Rarely they are inherited as autosomal dominant in multiple endocrine neoplasia type 1 (MEN1). According to Ospina, *et al.* (2015), approximately up to 4.9% of carcinoids are associated with MEN1.[14] In some instances, familial carcinoids are also reported without any MEN1 syndrome association.[15]

Many PCs are asymptomatic or exhibit nonspecific symptoms which causes problems and delays in diagnosis. Symptomatology usually depends on the location of the tumor and whether the tumor is situated centrally or peripherally. In this study, most of the tumors were central and in the right lung. They presented with hemoptysis, SOB, and recurrent bronchial obstructions leading to post-obstructive pneumonitis features. In one case, the patient presented with hoarseness of voice because of recurrent laryngeal nerve (RLN) compression by the lymph nodes in the aortopulmonary window. Chest pain, wheezing, and SOB may be noted in some individuals depending on the amount of endobronchial obstruction or compression.[16] Foreign body aspiration, hamartomas, chronic obstructive pulmonary disease (COPD), acute asthma, and endobronchial metastasis are eliminated in patients presenting with similar clinical features. PC may be accompanied by paraneoplastic syndrome. As carcinoid tumors involve NE activity, they are capable of secreting different biologically active hormones and peptides like antidiuretic hormones (ADH), causing a syndrome where there is the inappropriate secretion of antidiuretic hormone (SIADH), cortisol causing Cushing syndrome, insulin resulting in hypoglycemia, and serotonin resulting in carcinoid syndrome.

Carcinoid syndrome is characterized by tachycardia, hemodynamic instability, flushing, diarrhea, bronchoconstriction, and acidosis. The incidence of carcinoid syndrome in association with PC tumors is about 2%. These endocrinopathies can be produced by a carcinoid tumor even in an otherwise asymptomatic patient.[17] Clinical features should be taken into account when performing biochemical tests which should include the necessary 24-hour urine 5-hydroxy-indole-acetic acid, growth hormone-releasing hormone (GHRH), and adrenocorticotropic hormone (ACTH) level examinations. In this study, none of the participants displayed symptoms of carcinoid syndrome/NE activity.

The tumor, node, and metastasis (TNM) staging of lung NETs was performed by using the combined American Joint Committee on Cancer (AJCC) (8th edition, 2017)/Union for International Cancer Control (UICC) classification which is also used for bronchogenic lung carcinomas. Low-grade (typical) lung NETs most commonly present as stage I tumors and more than half of intermediate-grade (atypical) tumors present as stage II (bronchopulmonary nodal involvement) or III (mediastinal nodal involvement).[18] In this study, 83% (5 out of 6) of AC presented in stage III/ IV, and all variants presented in stage I were TC. Regional nodal involvement was low (3-20%) in TC compared to AC (48-75%). Likewise, malignant potential and distant metastases are less common in the typical group compared to the atypical group.[1] None of the patients presented with N3 nodes. Two of AC showed distant metastasis.

Nearly 40% of carcinoid tumors are diagnosed incidentally on a chest X-ray during the preliminary evaluation of chest symptoms.[19] Initial diagnosis is usually performed by CT imaging of the thorax which is non-invasive and easily available. Contrast CT is the gold standard investigation of choice for diagnosing PCs. High-resolution CT may be utilized to examine patients for whom contrast is not recommended. CT gives an excellent morphological characterization of the location (central/peripheral) and relation with the bronchus (purely intraluminal/extraluminal or a mixture

of intra-bronchial and extra bronchial components, called an iceberg lesion) (Figure 1a). CT also gives information about the tumor extension and associated adenopathy. CT may also help differentiate between complications due to the tumor, such as post-obstructive atelectasis/pneumonitis, and bronchial obstruction secondary to mucoid impaction or any number of infections. In all of the patients, contrast CT of the chest was used in the evaluation stage of the diagnosis and to eliminate other co-existing diseases.

In preoperative staging and for the evaluation of tumors situated in the major airways, bronchoscopy may be necessary. Rigid bronchoscopy is preferred for collecting biopsy specimens in the majority of the patients. However, in individuals with a high risk of bleeding, flexible bronchoscopy is generally chosen. Typically, a PC appears as a pink to reddish mass that is polypoidal in shape and attached to the bronchus by a broad base (Figure 1b). Up to three-fourths of PCs are situated centrally and easily accessible for biopsy through bronchoscopy. The added utility of new bronchoscopic procedures to improve the sensitivity of tumor diagnosis or recurrence was currently only weakly supported by the available data.

Ultrasound sonography (USG) or CT-guided transthoracic needle aspiration is frequently used to diagnose peripheral carcinoids that present as solitary pulmonary nodules (SPN) or as a mass. Somatostatin receptors are expressed by approximately 80% of TC and 60% of AC. This can be used in immunohistochemistry and may be imaged using somatostatin receptor scintigraphy (SRS) for staging and to assess treatment response. Fluoro-deoxy-glucose positron emission tomography (FDG-PET) scans and some tumor markers like neuroamines and neuropeptides that can be measured in blood or urine are some of the other modalities that can be used for diagnosing carcinoid tumors. SRS and somatostatin receptor PET/CT (SSTR-PET/CT) imaging may detect bone metastases with a better degree of sensitivity. Gallium-68-DOTA (somatostatin analog/SSAs), if available, is more sensitive and superior to SRS. When it comes to the use of FDG-PET, the majority of TCs show little to no uptake but ACs can. FDG-PET is especially beneficial for forms with poor differentiation (SCLC and large-cell lung carcinomas/LCLC).

Compared to other types of lung cancer, carcinoid tumors of the lung typically have a better prognosis. Among PCs, AC is aggressive, usually presents at a more advanced stage, and has a poorer prognosis than typical ones. TC has an overall 5-year survival rate of 78-95% and a 10-year survival rate of 77-90%.[20] An accurate histopathological diagnosis differentiating TC and AC is crucial for further management as the two entities respond differently to treatment. Of the many histopathologic techniques available, immunohistochemistry is considered to be the most sensitive and accurate at distinguishing between TC and AC (Figure 2). With limited diagnostic material, immunohistochemical markers like synaptophysin and/or CD56, thyroid transcription factor-1 (TTF1), chromogranin A, and cytokeratins can be used to confirm epithelial and NE differentiation.[21] In this study, synaptophysin, chromogranin A, and TTF1 were used for the differentiation of cells. These immunohistochemical markers cannot differentiate AC from TC, despite the latter being more irregular in terms of the distribution of NE markers. Markers like Islet1, CDX-2, TTF1, specific hormones, and a few other amines can be used to differentiate between metastasis due to well-differentiated NETs of other organs like gastropancreatic and pulmonary NET. Other prognostic factors, aside from histology, include the involvement of the lymph nodes and metastasis at the time of presentation.[22]

Preoperative staging should involve an abdominal and chest CT. To evaluate the surgical risk and if there is a relationship with COPD, and to screen for bronchostenosis, functional respiratory tests should always be performed. Additionally, the relationship between AC syndrome and bronchospasm may affect cardiac function.[23] To assess the existence and progression of carcinoid cardiac disease, as a part of the preoperative evaluation, echocardiography should be performed initially at the time of diagnosis and throughout the follow-up period. Both the left and right-side valves should be examined. Carcinoid heart disease may exist in these patients, especially on the left side.

The multidisciplinary team, which includes oncologists, radiologists, nuclear medicine specialists, thoracic surgeons, pulmonologists, and endocrinologists, should discuss the pathology report on the pulmonary NETs. Therefore, the pathologists can participate in the clinical decision-making process. In a subgroup of asymptomatic patients, particularly those with a low proliferative index, a wait-and-watch approach may be taken. Acromegaly and carcinoid syndrome are first-line conditions that are treated with SSAs, either octreotate, octreotide, or Nal(3)-octreotide. Cortisol secretion must be under control in Cushing syndrome patients. Adrenalectomy can be considered for Cushing syndrome which is refractory. If the somatostatin receptor imaging (SRI) is positive, SSA may be used as the first-line antiproliferative choice of treatment in cases where the tumor is unresectable and who have a favorable outcome, especially carcinoids with low proliferative indices and slow progression.[24]

The treatment of choice for both TC and AC tumors is bronchial sleeve resection and the anastomosis of the involved segments if the tumor presents in a

respectable stage and the performance score of the patient is good. Surgery that preserves the lung's parenchyma should be chosen over pneumonectomy. Lobectomy and pneumonectomy are the preferred options for AC as they are more aggressive than TC.[25] The location of the tumor, which is intraluminal or extraluminal, and the tumor diameter on the CT of the thorax are the independent parameters for successful endoluminal management in patients with an endobronchial carcinoid. Patients who are presenting with pure intrabronchial carcinoids with a tumor diameter of <2cm on CT are ideal candidates for endobronchial treatment. Patients with a tumor diameter of ≥2cm are ideal for surgical intervention, regardless of histological grade.[26] Patients deemed to be at very high risk for bronchopulmonary surgery should only have a local resection.

To treat TC more effectively, endoluminal bronchoscopic therapy should only be used on individuals deemed to be at high risk for surgery or on occasion as a viable interim measure before surgery. All patients with carcinoids should be closely monitored for a long time after the main surgery. Surgery as a component of the multimodality care of patients with extensive metastasis is not well supported by evidence. If pulmonary surgery is thought about, it is generally agreed that it should only be performed on individuals who have a small number of diseased sites. This type of surgery is typically performed on TC and maybe AC with low mitotic numbers. For highly select patients with central, polypoid, and low-grade carcinoids, trans-bronchoscopic resection by using a Neodymium-doped Yttrium Aluminium Garnet (Nd: YAG) laser can be sufficient to provide recurrence-free survival. In a carcinoid series consisting of 112 patients (83 TC, 29 AC), the FOB-guided resection of tumors avoided surgery in 47 cases (42% of TC and 17% of AC), even after the five-year follow-up.[27] Brain magnetic resonance imaging (MRI) or CTs in poorly differentiated NETs are where cerebral metastases are a frequent occurrence. They are reported in PC more frequently with a higher-grade AC. Although it is not generally advised, staging and follow-up procedures involving a cerebral CT or MRI should be performed if there are any features or signs suggestive of disease. Prophylactic cranial irradiation, which is commonly used in SCLC, is not warranted in these tumors for the same reasons.

Since the 5 to 10-year survival rate of carcinoids is more than 90%, the use of adjuvant chemo or radiation therapies is usually not recommended for TCs as they are less likely to present with regional lymph node involvement.[1] In some cases, although TCs are known as low-grade tumors, 5-20% can metastasize to the liver or bones.[28]

Chemotherapy can be considered for use as adjuvant or neoadjuvant therapy along with surgery in operable cases and cases with metastatic disease. The rationale of using adjuvant chemotherapy in PCs is not approved as there was no clear consensus or trials performed on chemotherapy or chemotherapy in combination with radiotherapy in patients with early-stage tumors. Although the currently available chemotherapy regimens show a modest impact, cytotoxic therapy has long been considered the gold standard treatment for metastatic aggressive PCs. The limited data suggests that chemotherapy regimens validated in the SCLC, including platinum compounds along with etoposides, can be used to treat large-cell NE carcinoma.[29] There are no local or systemic chemotherapeutic drugs available for the treatment of carcinoid tumors.

The role of antiangiogenic substances in PC is still unclear. The kinase inhibitor sunitinib, which is taken orally, has efficacy against several tyrosine kinase inhibitors, including vascular endothelial growth factor receptor (VEGFR)-1, -2, -3, and platelet-derived growth factor receptors (PDGFR)-a and -b.[30] A partial response has been seen in patients with PCs after taking the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab.[31] Based on the RADIANT-4 trial, the United States Food and Drug Administration (FDA) in 2016 approved everolimus for non-functional, well-differentiated, progressive, pulmonary NE tumors of the lung which are locally advanced and not amenable for resection or associated with distant metastasis.[32] Apart from surgery and chemotherapy, lanreotide and octreotide, which are SSAs, can be used in patients presenting with carcinoid syndrome.[24]

CONCLUSION

PCs are uncommon lung tumors and are encountered less in our day-to-day practice. A high degree of clinical suspicion and familiarity with carcinoids is essential for their early identification and a positive clinical outcome. We encountered 15 cases of PC tumors. Right lung involvement was more common and the frequency was higher in men. All lesions were central and involved second to fourth airway generations. A dry cough was most frequently seen, followed by hemoptysis. The majority of the patients had their diagnosis established by bronchoscopic guided biopsy. Surgical removal was the treatment of choice and the aim was to remove the tumor and to preserve as much lung tissue as possible. Endoluminal bronchoscopic therapy should be reserved for patients who are considered at a high risk for surgery. Medical therapy may be considered in a few select patients like

those with carcinoid syndrome or patients with a terminal disease.

Consent

Written informed consent was obtained from the patients.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Designed the study: RM, GRA, SL. Data collection: RM, SL, PU. Performed the analysis: RM, GRA, SL, PU. Prepared the manuscript: RM, GRA, PCT. Reviewed the manuscript: RM, GRA, SL, PU, PCT. All authors contributed and approved the final version of the manuscript.

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