presentation pattern and surgical strategies in bronchopulmonary carcinoid tumors: a multicenter experience in a low-income country

Research submitted to Cardiothoracic and Vascular Unit, Surgery Department in partial fulfillment of the requirement for a subspecialty certificate in cardiothoracic surgery

By; Workneh Tesfaye (MD, cardiothoracic surgery fellow)

Advisor: Seyoum Kassa (MD, Associate professor of cardiothoracic surgery)

March, 2024

Addis Ababa, Ethiopia

Addis Ababa University, College of Health Sciences
Department of Surgery

presentation pattern and surgical strategies in bronchopulmonary carcinoid tumors: a multicenter experience in a low-income country

By; Workneh Tesfaye (MD, cardiothoracic surgery fellow)

Advisor: Seyoum Kassa (MD, Associate professor of cardiothoracic surgery)

March, 2024

Addis Ababa, Ethiopia

DECLARATION

I, Workneh Tesfaye, do hereby declare that this research paper is a result of the works of my own making, except where credit is given in a review of the previous literature in the content and by my knowledge, has never been submitted for any academic award or qualifications in this Institution.

Workneh Tesfaye: signature: _____ Date: March 2023

Email: wtesfishg@gmail.com

Phone: +251912883746

Department of Surgery/ Institutional Review Board approval

The undersigned have examined an institution-based study on presentation patterns and surgical strategies in bronchopulmonary carcinoid tumors; a multicenter experience in a low-income country, a retrospective cross-sectional study by Dr. Workneh Tesfaye, with registration number GSR/2913/14 a candidate for sub-specialty certificate in cardiothoracic surgery and hereby certifies that it is a worthy of acceptance.

Advisor:

Dr. Seyoum Kassa, MD, Associate Professor of Cardiothoracic Surgery

Sign _____Date_____

Chairperson, Department of Surgery Research and Ethics Committee

Dr. Tsegazeab Leake (MD, Associate Professor of Neurosurgery)

Sign_____ Date_____

Head of Department of Surgery, Tikur anbessa Specialized Hospital

Dr. Seyoum Kassa, MD, Associate professor of Cardiothoracic Surgery

Signed_____Date_____

Principal Investigator

Workneh Tesfaye, MD, Cardiothoracic surgery fellow

Sign_____ Datre_____

ACKNOWLEDGEMENT

I would like to extend my heartfelt gratitude to my advisor Dr. Seyoum Kassa (MD, Associate Professor of Cardiothoracic Surgery) for his advice, comments, and guidance throughout this research. As well, all colleagues in our unit deserve great appreciation for their collaboration.

I would also like to acknowledge and thank the staff in the medical record department, pathology department, and department of oncology for their support and help.

TABLE OF CONTENTS

LISTS OF FIGURES AND TABLES

ACRONYMS

AAU; Addis Ababa University

AC; atypical carcinoid

BC; bronchial carcinoid

BPCTs; bronchopulmonary carcinoid tumors

BPNETs; bronchopulmonary neuroendocrine tumors

CHS; college of health sciences

CT; computed tomography

MH; Menelik II hospital

NETs; neuroendocrine tumors

OR; operation room

OS; overall survival

RFS; recurrence-free survival

SEER; surveillance, epidemiology, and results

SPSH; Saint Peter's Specialized Hospital

TASH; Tikur Anbessa Specialized hospital

TC; typical carcinoid

UK; United Kingdom

USA; United States of America

VATS; video-assisted thoracic surgery

WHO; World Health Organization

ABSTRACT

Background: Bronchopulmonary carcinoid tumors include typical and atypical carcinoids, where typical carcinoids represent 80% to 90%. The primary curative treatment for these tumors is surgical resection. To our knowledge, there are limited studies on presentation patterns and treatment strategies of bronchopulmonary carcinoid tumors in Africa.

Objective: To determine presentation patterns and surgical strategies in bronchopulmonary carcinoid tumors in patients treated at multi-centers in Ethiopia from January 2018 to December 2023.

Materials and methods: A 5-year retrospective cross-sectional study was conducted using medical record and pathology record review of patients operated on inTikur Anbessa Specialized Hospital, Menelik II Hospital, and Saint Peter's Specialized Hospital from January 1, 2018, to December 31, 2023. The completeness of data was checked before being entered into Epidata version 4.6.1 and analysis was done using SPSS version 29. Logistic regression was applied to depict the association of the histological pattern with its predictors. A P value of < 0.05 was considered significant for the association of variables.

Results: A total of 62 patients with bronchopulmonary carcinoid tumors were included in the study with a mean age of 35.29± 12.26 years that ranged from 14 - 67 years, where more than half of them [37(56.5%)] were females with male to female ratio of 1:1.3. Majority of the patients were non-smokers (90.3%) and symptomatic (98.4%) with the mean duration of symptoms of 29.7± 26 months that ranged from 3 -156 months. Nearly half of the patients (48.4%) were treated for pulmonary tuberculosis before a diagnosis of carcinoid tumor was made. The majority of the patients underwent surgery by open posterolateral thoracotomy approach (98.4%) and pneumonectomy was the most common (38.7%) resection performed. The typical carcinoid was observed in 85.5% of patients. Age, smoking history, duration of symptoms, location of tumors, and lymph node status were statistically associated with histologic patterns.

Recommendation: Based on our study findings; awareness creation for physicians on the clinical presentation of carcinoid tumors, training on less invasive surgical approaches for surgeons, and nationwide further study is recommended.

Keywords: Bronchopulmonary carcinoid tumor; presentation pattern; surgical strategies; low-income country; multi-center study

1. INTRODUCTION

1.1. Background Information

Neuroendocrine tumors are various groups of neoplasms that arise from specialized, peptide and amine-producing cells found in diffuse endocrine systems. They commonly occur in the gastrointestinal tracts (48%), followed by the lung which is 25%. Other possible sites of occurrence include; the pancreas, breast, prostate, thymus, and skin(1).

Bronchopulmonary neuroendocrine tumors (BPNETs) consist of groups of lung neoplasms with distinctive basic microscopic appearance and immunohistochemistry features. The World Health Organization (WHO) tumor classification of 2015 divides BPNETs into four subtypes. It ranges from a low-grade typical carcinoid tumor (TC), an intermediate-grade atypical carcinoid tumor (AC), and high-grade malignancies consisting of large-cell neuroendocrine carcinoma (LCNEC) and small-cell lung carcinoma (SCLC). Even though they have different clinical behaviors they are grouped together because of their neuroendocrine features(2,3).

All bronchopulmonary neuroendocrine tumors together account for 20% to 25% of all lung cancers. Small cell lung carcinoma is the most common BPNET, which accounts for approximately 14% of lung cancers. Large cell neuroendocrine tumors represent about 3% of lung cancers, while typical and atypical carcinoid tumors together account for 1% to 2% of all lung malignancies. Atypical carcinoids are the rarest BPNETs representing only 0.1% to 0.2% of all lung cancers(4,5).

TC and AC are grouped as bronchopulmonary carcinoid tumors (BPCTs) which are well-differentiated BPNETs. Typical carcinoid is commoner representing 80% to 90% of BPCTs, while AC accounts for up to only 20%. According to the Surveillance, Epidemiology, and End Results (SEER) database incidence of BPCTs has increased(3)

The distinction between TC and AC is based on the WHO tumor classification which is determined by cellular mitotic rate and the presence or absence of necrosis. TC has <2 mitoses/2 mm2 and no necrosis, AC has 2–10 mitoses/2 mm2 and focal necrosis. In general, BPCTs have very few genetic abnormalities compared with SCLC and LCNEC. Also, Patients with Carcinoid tumors are younger and have a better prognosis. The majority of TC patients are nonsmokers, whereas AC appears to be slightly more frequent in smokers(1,2)

1.2. Statement of The Problem

Bronchopulmonary carcinoid tumors are relatively rare cancers that originate from neuroendocrine Kulchitsky cells of the bronchial tree mucosa and submucosal glands. Compared to previous data in recent decades, the incidence of these tumors has increased rapidly which might be probably explained by the development of tumor screening and imaging. Incidence of BPCTs is higher in whites compared to black(3,6).

The distribution of BPCTs is mostly comparable between males and females but in other studies, female predominance is noticed. The median age of patients diagnosed with these tumors is about 48 years. Anatomically most BPCTs occur in the central bronchial tree with TC being the dominant histologic type(5–8).

The majority of patients having TC are nonsmokers, whereas AC tends to be slightly more frequent in smokers. In most of the studies, patients were symptomatic at presentation. The commonest presentation symptom varied between studies where it is a non-resolving respiratory infection in some while it is hemoptysis according to others. In general, the centrally located tumor tends to cause infection, hemoptysis, or cough. Compared with typical carcinoids, atypical carcinoid tends to be associated with larger tumor size, higher incidence of lymph node involvement, and distant metastasis. When laterality is considered BPCTs are more common in the right lung(9,10).

On the other hand, other studies have found that more than half of patients treated for BPCTs are asymptomatic at the time of presentation. According to these studies, most of these tumors are found incidentally on chest X-rays often appearing as an isolated, well-defined hilar or perihilar mass. The use of low-dose CT for lung cancer screening might even increase the proportion of these patients further(3,5).

In most patients, there is no lymph node involvement, but the percentage of nodal involvement differs between studies. When distribution of lymph node positivity is considered in all studies AC is likely to involve lymph nodes. The proportion of patients with distant metastasis also differs significantly between studies. In most cases, AC results in a higher rate of metastasis but others found no significant difference(3,4,6).

The clinical diagnosis of these patients usually involves a chest CT scan and bronchoscopy. The commonest pattern in chest CT findings varies between studies. Hilar or perihilar masses and pulmonary nodules were more frequent findings, whereas in other studies atelectasis and pulmonary infiltration were the dominant findings. Preoperative confirmation of carcinoid tumor with bronchoscopic biopsy was possible in most of the cases (11,12).

There is controversy on the optimum treatment of these tumors. In general, the primary and only curative treatment of BPCTs remains surgical resection. The principle of surgical technique in these patients is a complete negative margin resection with preservation of as much normal lung tissue as possible. Previously more radical pulmonary resection was considered necessary for atypical carcinoids, but it is found that the extent of resection does not impact overall survival(3,5).

The commonest surgical approach is open thoracotomy in most cases of studies. However, VATS was performed in the majority of cases in other studies with no conversion to open thoracotomy. According to this study, thoracotomy was done for those who undergo sleeve lobectomies or bronchial sleeve resections without lung resection (7,8).

In most of the studies, anatomic lobectomy was the most commonly performed surgical treatment, but the proportion is different between studies. Other commonly performed resections were sleeve lobectomy, wedge resections, and pneumonectomies. Pneumonectomy was performed for a tumor located in the main bronchus with obstructive pneumonia or atelectasis as well when the tumor invaded the pulmonary vessels. In some cases, bronchoplastic procedures were also performed as a primary treatment(8,10–13)

Adjuvant therapies have minimal benefit in the treatment of carcinoid tumors. BPCTs are generally resistant to radiation therapy and it is reserved for patients in whom surgical resection is not possible or as an adjunct when a resection is incomplete. The use of various chemotherapeutic agents in the treatment of BPCTs has minimal, short-lasting results(3).

Post-operative recurrence of BPCTs was found to be relatively commoner in AC than in TC. The overall survival of 5 and 10 years is comparable between studies. The overall survival is significantly lower in AC than in TC. Other factors that are found to affect survival are the presence of nodal involvement, anatomic location of the tumor, presence of distant metastasis, development of recurrence, age of the patient, and tumor size(9,13).

Up to date, there are limited studies conducted on the presentation patterns and surgical strategies used for the treatment of BPCTs in the African context (with scarce evidence from Egypt (14)and Tunisia(15)) where there is no study conducted in Ethiopia. Therefore, the purpose of this study is to explore the demographic, clinical presentation, anatomic distribution, and histological types of BPCTs in Ethiopia. It also determines the proportion of patients with carcinoid tumors treated for another presumptive diagnosis. Ultimately, we have assessed surgical strategies used in these patients, as well as factors influencing histological distributions of carcinoid tumors

1.3. Significance of The Study

Bronchopulmonary carcinoid tumors are relatively rare lung cancers with indolent growth where they can be mistaken for other benign conditions. Therefore, this study helps to establish patterns of presentation, surgical strategies, and factors associated with histologic distributions of BPCTs in our country. It also serves as a baseline information for studies to be done in the future on the same or related topics. The information gained from this study can be used to compare the differences in the institutional experience in the management of these tumors.

2. LITERATURE REVIEW

2.1. Clinical Presentation of BPCTs

According to the Surveillance, Epidemiology, and End Results SEER database BPCTs account for about 1.2% of a total of 463,338 primary lung malignancies. Particularly in the USA, the incidence of these tumors has seen a significant increment(3). Another population-based retrospective cohort study which was conducted in adult patients with a NET diagnosis from 1994 to 2009 in Ontario, Canada, has concluded a marked increment in the incidence of NETs over 15 years. They found a progressive increment in incidence in almost all primary NET site groups with bronchopulmonary being the most frequent site. The overall rise in incidence was from 2.48 in 1994 to 5.86 cases in 2004 per 100,000 per year; which means a 2.36-fold increase(16).

In both population and institution-based studies there is a female predominance in cases treated for BPCTs, with some showing a significant disparity in the proportion of cases(4,6,7). The median age at diagnosis is significantly higher in AC than in patients diagnosed with TC. However, there is no significant difference in age distribution between males and females(4,8).

A significant proportion of patients were asymptomatic at the time of diagnosis. In most of the studies, a non-resolving respiratory infection was the most frequent presenting symptom. Other frequent symptoms were hemoptysis, dyspnea, and chest pain. Carcinoid syndrome was either not there or only seen in a few proportions of patients(11,17,18). According to an institution-based study at Beijing Chest Hospital about one-third of patients have a smoking history. When a comparison of smoking habits between the groups determined it showed significant differences, with a smoking habit more commonly observed in the AC group(10). In contrary to this according to the study which was done in Denmark University Hospital the frequency of current or former smokers was not significantly different(4).

When the anatomical distribution of BPCT is considered, there are conflicting results, in studies that were done in Italy which is institution-based, and in Norway which is population-based the frequent site of occurrence of these tumors was central. However, a single-center cohort study in Denmark found a peripheral location as a more frequent site of occurrence. In all cases dominant histologic type is TC. A centrally located tumor was defined when it was visible by bronchoscopy. In general, the right lung is more affected than the left lung. Among the central locations, an intermediate bronchus is more frequently affected. In both locations, the typical carcinoid is the dominant histologic type(7–9,11).

2.2. Diagnosis of BPCTs

In most studies, the preoperative workup involved a chest X-ray followed by a CT scan. According to the study in Belgium which is a relatively old-time study, the most frequent presentations on

X-ray was a solitary pulmonary nodule. Other findings were pulmonary infiltrate, atelectasis, or an isolated hilar mass. Another finding on chest CT is an enlargement of mediastinal lymph nodes with a possibility for both false positive and false negative results(10,18).

Almost all patients were evaluated with fiber optic bronchoscopy preoperatively. According to a study in Beijing Chest Hospital China, all patients underwent endoscopic biopsy and brushing for histological diagnosis, and preoperative pathologic confirmation was made in close to half of the patients. According to a study in Italy bronchoscopic biopsy was done for all visible tumors with bronchoscopy and trans bronchial biopsy was performed for tumors that are not visible. They reported no massive hemorrhage or other complications following bronchoscopic biopsy(10,11).

2.3. Treatment Strategies of BPCTs

Even though there are debates on the optimum treatment of these tumors, the primary and possibly curative treatment of BPCTs is surgical resection. The principle of surgery in all surgical techniques used in these patients is a complete negative margin resection with preservation of as much normal lung tissue as possible. Previously more radical pulmonary resection was considered necessary for atypical carcinoids, but it is found that the extent of resection does not impact overall survival(3,5).

Surgical access for resection of these tumors can either be by open thoracotomy or VATS. According to an experience from Norway, all surgeries were performed by open thoracotomies. However, in Denmark, most of the surgeries were performed by VATS. They used open thoracotomies for patients with larger size tumors and in most central tumors with a high probability of sleeve lobectomy or bronchial sleeve resection. They preferred VATS for its fewer postoperative complications, less pain, shorter hospital stay, earlier return to normal activities, better tolerance of adjuvant chemotherapy, and overall reduced cost (7,8).

In most of the patients, standard lobectomy was the most frequently performed procedure. However, sleeve resection or bronchoplastic procedures in centrally located carcinoids are increasingly being used. Wedge bronchoplastic resection with large margins can cause kinking in the bronchial system, which is one of the major reasons for complications such as atelectasis, stenosis, and dehiscence. According to a study in China, Pneumonectomy was performed when the tumor is located in the main bronchus resulting in obstructive pneumonia or atelectasis and a tumor invading the pulmonary arterial trunk. Sleeve lobectomy has a better outcome as an alternative to pneumonectomy when considering both short-term complications and long-term survival and recurrence(8,10,17)

In general, BCPCTs arising within the bronchus with or without extension through the wall of the bronchial tree wall are suitable for resection with bronchoplasty, which can be either bronchial sleeve resection or wedge. This can be performed with or without parenchymal resection. Wedge lung resection and lobectomy are indicated when the tumor is located within the parenchyma. The fact that Carcinoid tumors tend to be indolent makes Broncoplasty procedures appropriate treatment as long as complete resection with disease-free margins is possible. Bronchial sleeve resections are preferred when a tumor infiltrates the origin of a lobar bronchus.

The distal lung parenchymal status is another important factor in treatment decisions. If complete occlusion of the bronchial lumen is there, laser recanalization to drain and clean the distal airway should be done. In addition to these, a cycle of antibiotics and pulmonary rehabilitation to improve the clinical status before surgery has a big impact on the outcome of these patients(19).

Adjuvant therapies have minimal benefit in the treatment of carcinoid tumors. BPCTs are generally resistant to radiation therapy and it is reserved for patients in whom surgical resection is not possible or as an adjunct when a resection is incomplete. The use of various chemotherapeutic agents in the treatment of BPCTs has minimal, short-lasting results. chemotherapeutic agents like; doxorubicin, 5-fluorouracil (5FU), dacarbazine, cisplatin, etoposide, streptozotocin, and carboplatin have resulted in about 20%–30% response rate. This is just a short-lasting response and an effective chemotherapeutic regimen for unresectable tumors is lacking (3).

2.4. Treatment Outcome and Determining Factors of BPCTs

The overall survival rate after surgical treatment of BPCTs is comparable in most of the studies but slightly variable figures. According to Aydin E, et al the 5- and 10-year overall survival rates were 89% and 72%, respectively. When histologic survival is considered; for typical carcinoid tumors, the 5- and 10-year survival rates were 92% and 83%, while for atypical carcinoids 73% and 46%, respectively. Lim E, et al, found an overall survival at 5 and 10 years of 86% and 81% respectively, whereas 5-year survival is 91% and the 10-year survival is 83%according to Bini A, et al. In all cases, TC has significantly better 5- and 10-year survival(11,12,20).

An institutional-based study in Italy and a population-based study in Norway both found a recurrence rate of about 8% during follow-up after surgical resection was done. The common sites of recurrences were; the liver, followed by lung, bone, adrenal gland, pericardium, and mediastinal lymph nodes. No bronchial recurrences as mentioned in an Italian study. In both studies, AC tends to recur more than TC (7,17)

A Danish single-center long-term cohort study has described factors affecting outcomes following the treatment of BC. They found that there was no significant difference in overall survival and recurrence-free survival between TNM stages of BPCTs. But, histologic types of BC significantly affected both OS and RFS with TC having longer overall survival while AC had shorter RFS. Another outcome-determining factor they described is the location of the tumor with central BC having better OS and RFS than BC located peripherally(8)

A retrospective cohort study which was done in western Denmark also determined factors predicting risk of death from BPCTs. A median follow-up of their study is 5.6 years and they concluded male gender, current/previous smoker, and metastatic disease at the time of diagnosis are predictors of death(4). A similar study in the UK also analyzed factors predicting outcomes in patients with pulmonary NETs. They found tumor histology, patient's age, tumor size, and nodal status are the determinants of patient survival and recurrence(20).

2.5. Conceptual Framework

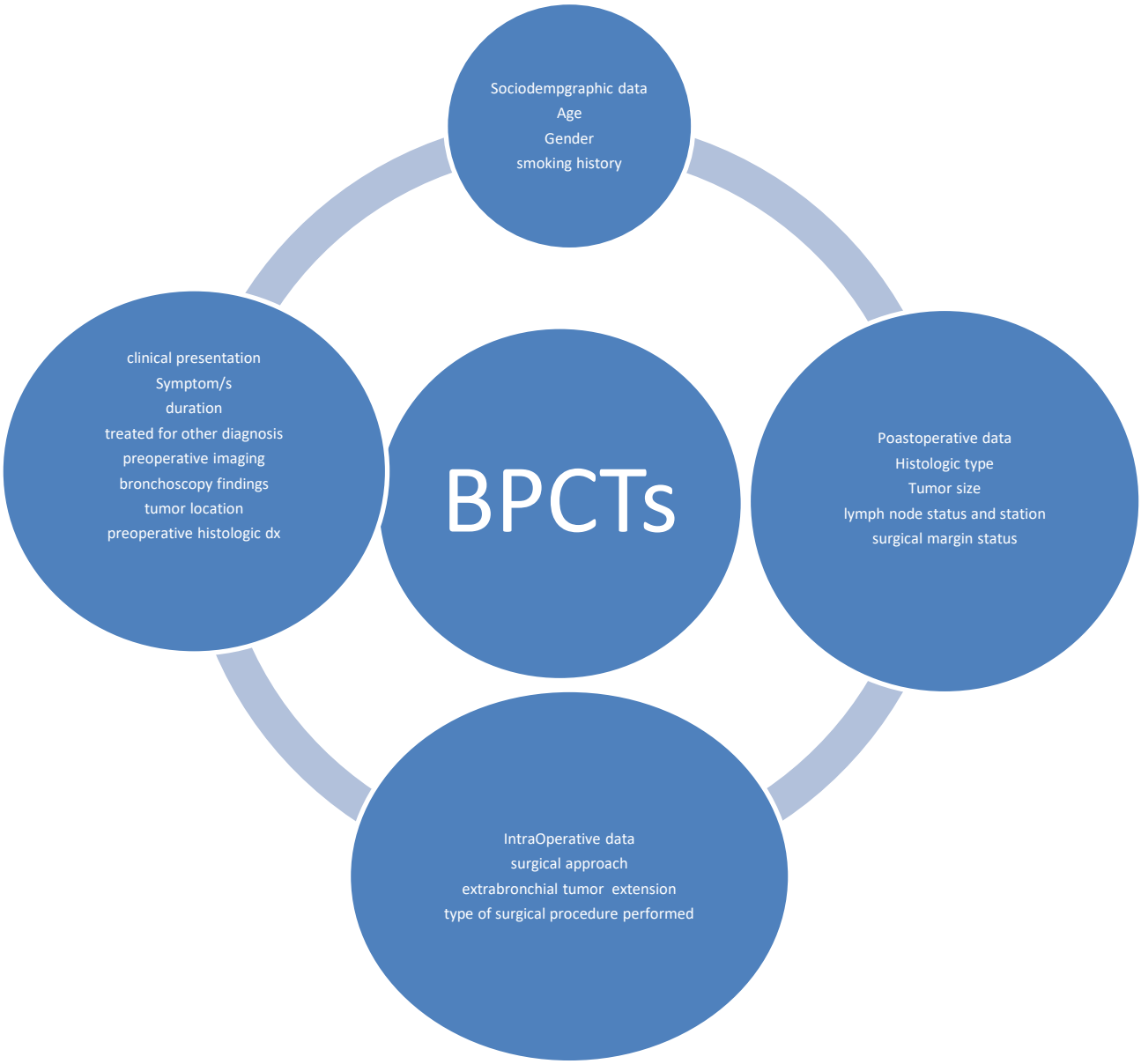

Figure 1: Conceptual framework for presentation pattern and surgical strategies of patients with BPCTs from literature review developed by investigator after literature

3. Objectives

3.1. General Objective

To determine the presentation pattern and surgical strategies used in BPCTs among patients who were operated at TASH, MH, and SPSH from January 2018 to December 2023.

3.2 Specific Objectives

To describe the presentation pattern of BPCTs among patients who were operated at TASH, MH, and SPSH from January 2018 to December 2023.

To assess the surgical strategies used in BPCTs among patients who were operated at TASH, MH, and SPSH from January 2018 to December 2023.

To identify the association of histologic patterns of BPCTs with other covariates among patients who were operated at TASH, MH, and SPSH from January 2018 to December 2023.

3.2. Research Questions

This study aims to find answers to the following questions:

1. what are the frequent symptoms in BPCTs
2. for what other presumptive diagnoses do patients receive treatment, before surgery
3. what is the histologic and anatomic distribution of BPCTs
4. what are the surgical strategies used in patients with BPCTs
5. what factors influence the histologic pattern of BC

4. METHODS AND MATERIALS

4.1. Study Area and Period

The study was conducted at three tertiary care hospitals in Addis Ababa, Ethiopia. Ethiopia, officially the Federal Democratic Republic of Ethiopia, is a landlocked country located in the Horn of Africa region of East Africa. It shares borders with Eritrea to the north, Djibouti to the northeast, Somalia to the east and southeast, Kenya to the south, South Sudan to the west, and Sudan to the northwest. Ethiopia covers a land area of 1,112,000 square kilometers (472,000 sq. miles). As of 2022, its projected population is estimated to be 105.17 million(21) making it the 2nd most populous country in Africa after Nigeria. Addis Ababa is the national capital and largest city.

TASH, established in 1972, is a public teaching hospital of the AAU, CHS. It is the largest referral hospital in the country with 700 in-patient beds. MH is also a public hospital, established in 1909, it is the first hospital in Ethiopia. SPSH is another public hospital with a tertiary care service. All hospitals have thoracic surgery services.

The study was conducted on patients operated on from January 1, 2018, to December 31, 2023.

4.2. Study Design

A 5 years retrospective cross-sectional study was conducted using medical record and pathologic record reviews of patients operated during the study period.

4.3. Population

4.3.1. Source Population

The source population was all patients who have undergone operations at the cardiothoracic operating room of TASH, MH, and SPSH.

4.3.2. Study Population

The study population was all patients who had been operated on for a diagnosis of bronchopulmonary carcinoid tumors during the study period.

4.4. Inclusion and Exclusion Criteria

4.4.1. Inclusion Criteria

All patients who have undergone surgical treatment for a diagnosis of bronchopulmonary carcinoid tumors during the study period were included.

4.4.2. Exclusion Criteria

Patients with incomplete medical records, patients who were operated for recurrence of BPCTs, and those with post-resection biopsy result non-carcinoid were excluded.

4.5. Sample Size and its determination

All patients who were operated on for a diagnosis of BPCTs during the study period and who fulfilled inclusion criteria were included in this study.

4.6. Study Variables

Socio-demographic Characteristics; Age, Sex

Preoperative variables; presentation (symptoms, bronchoscopic findings, radiologic findings), duration of symptoms, treatment for another presumptive diagnosis, smoking history, primary tumor site, status of the associated lung parenchyma (bronchiectatic lobe, destroyed lung), associated empyema

Intraoperative variables; surgical approach (open thoracotomy, VATS), resection type (wedge lung resection, bronchoplasty, standard lobectomy, sleeve lobectomy, sleeve pneumonectomy, pneumonectomy), enlarged lymph nodes (hilar, mediastinal), extra bronchial invasion

Post-operative variables; tumor size, American Joint Committee on Cancer (AJCC) N stage, histological type, and margin status.

4.7. Operational Definition

Wedge lung resection; is a non-anatomic resection of lung parenchyma without the identification of bronchovascular structures

Standard lobectomy; is an anatomic removal of a lobe of a lung including the corresponding lobar bronchus and appropriate lobar vein and arteries

Bi-lobectomy; is standard lobectomy of either the right upper and middle lobes (upper bi-lobectomy) or the right lower and middle lobes (lower bi-lobectomy)

Sleeve lobectomy; is the removal of a lobe in addition to the first bronchial carina with anastomosis between the remaining lobe and the main bronchus

Sleeve pneumonectomy; is the removal of an entire lung in addition to the carina with anastomosis between the remaining main stem bronchus and the distal trachea

Pneumonectomy; is the removal of an entire lung with parts of the main bronchus

Bronchoplasty; resection of a bronchus and anastomosis without parenchymal resection

Recurrence; a repeated occurrence of BC either at the primary site or distant site following initial surgical resection

Post-operative survival; the duration the patient is alive following the initial surgical treatment for BC

Destroyed lung; total and irreversible destruction of one lung due to chronic bronchopulmonary infections, it is used for disease of an entire lung, not for damage of one or two lobes.

4.8. Data Collection Tool and Procedures

Data was collected using a structured questionnaire which was prepared in English. Data was extracted from the OR logbook, preoperative patient medical records, operation notes, pathologic records, and post-operative follow-up records. Three resident physicians were selected and

trained on the purpose of the study and data collection procedures. Data was filled by the principal investigator and trained physicians. A total of 97 patients were operated with pre-operative diagnosis of BC at all hospitals (74 at TASH, 17 at MH, and 6 at SPSH) during the study period. Among those who were operated at TASH only 51 were included in the study; five patients had pathologic diagnoses other than carcinoid, 2 were operations for recurrence and 16 cases had incomplete data for different reasons. From MH 8 cases were included while 2 had other diagnoses and 7 were with incomplete data. Three cases were included from SPSH and 3 were excluded because they had incomplete data.

4.9. Ethical Consideration

Data collection was commenced only after ethical approval is obtained from the Research Ethical Committee of the Surgery Department/IRB of AAU, CHS.

Medical record number was for the data collection and the personal identifier of the patient was not used in the research report. Access to the collected information was limited to the principal investigator and trained data collectors, so confidentiality was maintained throughout the project.

4.10. Data Quality Control

The completeness of the questionnaire was checked before data collection. Advisors commented on the questionnaire. Orientation was given on the objectives and relevance of the study, confidentiality of information, and how to extract data from logbooks and medical records. Daily supervision of the data collection process and checking the completeness and consistency of the collected data was carried out by the principal investigator.

4.11. Data Processing and Analysis

The collected data was first checked for completeness and consistency before being entered into the computer. The data of 62 patients was complete and then, data was coded and entered into a statistical package for social science version 29 for its management and analysis. The chi-square test was used as a measure of the strength of association, and the variables with p-value <0.05 were considered to have statistically significant association.

4.12. Data Presentation and Dissemination of The Results

Mean and standard deviation (SD) were used to summarize continuous variables. Categorical variables were expressed in percentage and frequency. Descriptive analysis was used for displaying, describing, and summarization of data using texts, tables, and figures.

The result of the study is submitted and presented to the Department of Surgery for the partial Fulfillment of the Requirement for a Fellowship Certificate in cardiothoracic surgery. Further attempts will be made to present at professional conferences and publish in peer-reviewed and reputable journals

5. RESULTS

From the total of 2419 cases that were operated for cardiothoracic surgery cases, 97(4%) patients were operated with pre-operative diagnosis of BC at all hospitals (74 at TASH, 17 at MH, and 6 at SPSH) during the study period. Among those who were operated at TASH only 51 were included in the study; five patients had pathologic diagnoses other than carcinoid, 2 were operations for recurrence and 16 cases had incomplete data for different reasons. From MH 8 cases were included while 2 had other diagnoses and 7 were with incomplete data. Three cases were included from SPSH and 3 were excluded because they had incomplete data as displayed in Figure *2*.

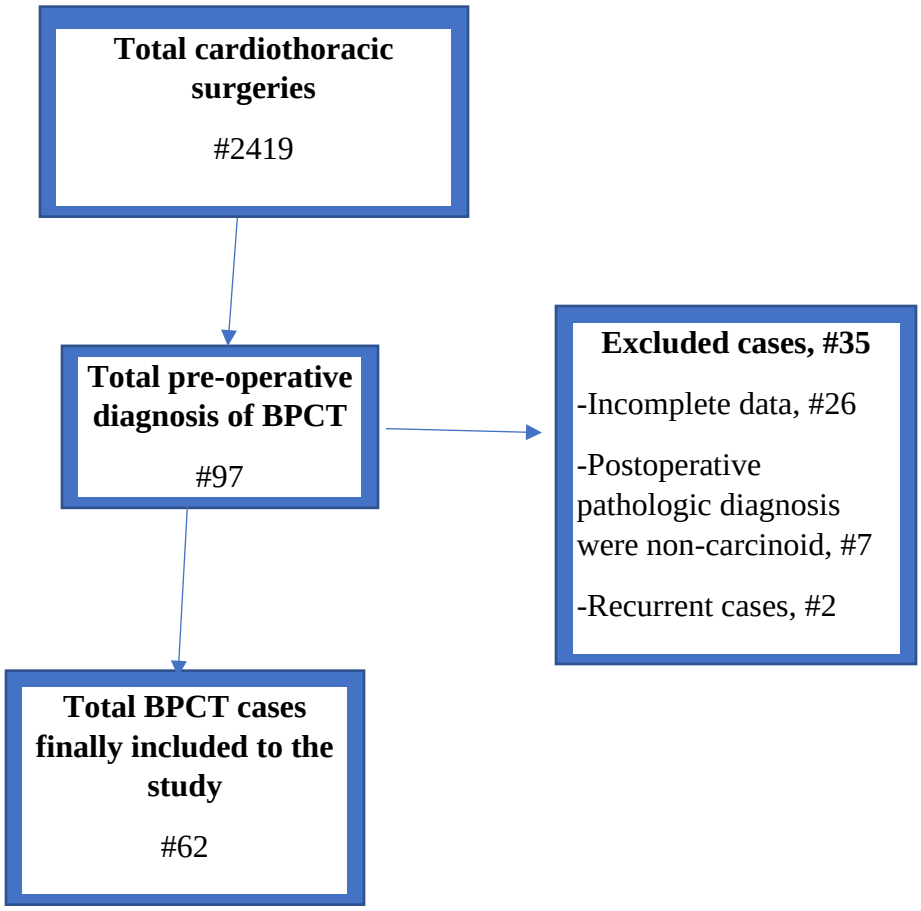

Figure 2; Flow chart for characterization of study respondents

5.1. Baseline information

A total of 62 patients with bronchopulmonary carcinoid tumors were included in the study. There was a slight female predominance in the distribution of bronchopulmonary carcinoid tumors in this study, with female patients accounting for 56.5% and giving a male-to-female ratio of 27:35(1:1.3). The age distribution in this study had a minimum age 14 years and maximum 67 years, with the mean age of 35.29 ± 12.26 years having a range of 53. Figure *3*

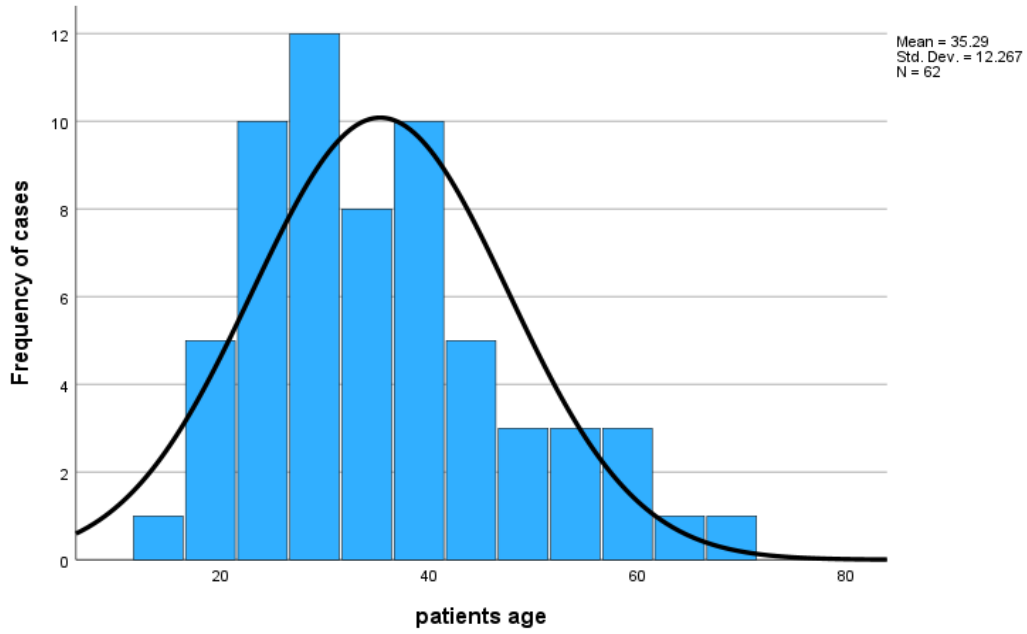

Figure 3: Distribution of BPCTs by age of the patients.

5.2. Presentation Pattern

The majority of the patients with BPCT had no history of smoking [56(90.3%)] and almost all patients were symptomatic (98.4%) during presentation. The most commonly observed symptoms were non-resolving pneumonia 47(77 %) and hemoptysis 41(67.2%). Patients having cough accounted for 62.3%, chest pain (32.8%) and dyspnea was present in 26.2% of patients. There was no patient with carcinoid syndrome during the presentation. The mean duration of symptoms was 29.7± 26.13 months, with the shortest duration being 3 months while the longest one was 156 months Table *1*.

Table 1; Pattern of bronchopulmonary carcinoid tumors in study respondents.

Variables		**Categories**	**Frequency (%)**
History of smoking		Yes	6(9.7)
		No	56(90.3)
Asymptomatic		Yes	1(1.6)
		No	61(98.4)
Symptoms	Hemoptysis	Yes	41(67.2)
		No	20(32.8)
	Non-resolving pneumonia	Yes	47(77)
		No	14(23)
	Cough	Yes	38(62.3)
		No	23(37.7)
	Chest pain	Yes	20(32.8)
		No	41(67.2)
	Dyspnea	Yes	16(26.2)
		No	45(73.8)
	Carcinoid syndrome	Yes	0(0)
		No	62(100)
Treated for another presumptive diagnosis?		Yes	30(48.4)
		No	32(51.6)

Preoperative bronchoscopy done?	Yes		45(72.6)
	No		17(27.4)
Bronchoscopic biopsy done?	Yes		2(4.4)
	No		43(95.6)
Location of tumor	Central 55(88.7)	Right main bronchus	11(17.7)
		Left main bronchus	14(22.6)
		Right upper lobe bronchus	5(8.1)
		Bronchus intermedius	12(19.4)
		Right lower lobe bronchus	1(1.6)
		Right middle lobe	3(4.8)
		Left upper lobe bronchus	4(6.5)
		Left lower lobe bronchus	5(8.1)
	Peripheral 7(11.3)	Right upper lobe	1(1.6)
		Right middle lobe	1(1.6)
		Right lower lobe	0(0.0)
		Left upper lobe	1(1.6)
		Left lower lobe	4(6.5)
The finding of CT scan	Isolated mass		4(6.5)
	Atelectatic lung		21(33.9)
	Bronchiectatic lobe/s		21(33.9)
	Destroyed lung		10(16.1)
	Destroyed lung with empyema		6(9.7)
Tumor laterality	Right side		34(54.8)
	Left side		28(45.2)

Histologic types	TC	53(85.5)
	AC	9(14.5)
Extra-bronchial invasion	Yes	2(3.2)
	No	60(96.8)
Tumor size	T1	6(9.7)
	T2	30(48.4)
	T3	25(40.3)
	T4	1(1.6)
Lymph node involvement	NO	36(58.1)
	N1	12(19.4)
	N2	1(1.6)
	NX	13(21.0)

Nearly, half of the patients 30(48.4%) were treated for presumptive clinical diagnosis of pulmonary tuberculosis before the diagnosis of carcinoid tumor was made. Some of these patients were even treated for PTB repeatedly Table *2*.

Table 2; shows treatment for clinical diagnosis of PTB.

TB treatment history		Frequency	Percent (%)
Not treated		32	51.6
Treated	Once	23	37.1
	Twice	7	11.3
Total		62	100

Pre-operative bronchoscopy was performed in 45(72.6%) patients. But bronchoscopy guided biopsy diagnosis before surgery was done only for two patients (4.4 %), mainly because of concern for uncontrollable hemorrhage from the tumor manipulation. A chest CT scan was performed for all patients. The frequently observed CT scan findings were endobronchial mass with atelectasis of underlying lung 21(33.9%) and Bronchiectasis of associated lobe/s in 21 patients (33.9%). Patients with the whole ipsilateral destroyed lung were 10(16.1%) and 6(9.7%) those with and without associated empyema thoracic respectively Table *1*

Tumors were more frequently observed on the right side which was 34(54.8%) while on the left side28 (45.2%). Tumors were considered "central" if visible on bronchoscopy or the epicenter of the mass was within the main or lobar bronchus based on CT scan and "peripheral" if not visible on bronchoscopy or if the mass was located distal to the lobar bronchus on CT scan. Accordingly, in our study, 55 tumors (88.7%) were considered to be central and seven (18.2%) peripheral.

Among the central tumors, the commonest site of occurrence was the left main bronchus 14 (22.6%), followed by bronchus intermedius which was observed in 12 patients (19.4%). The right main bronchus tumor was seen in 11 patients (17.7%). Among the peripherally located carcinoid tumors, the left lower lobe was the commonest site 4(6.5%) while no case was observed in the right lower lobe. In the other three lobes, a single case of peripheral carcinoid tumor occurred in each Table *1*.

Based on the intra-operative descriptions, only two cases (3.2%) had extra-bronchial invasion. One of the two cases was a centrally located tumor from the right main bronchus with typical histology which extended to the mediastinal pleura. The other case was a peripherally located atypical carcinoid tumor with invasion to the diaphragm from the left lower lobe.

The tumor staging was performed based on the American Joint Committee on Cancer Staging Manual 8th edition. Accordingly, most of the cases [30(48.4%)] were categorized as T2whiel T1 was observed in 6(9.7%). Only one case had T4, the one with diaphragmatic invasion (table 2). Thirty-six (58.1%) patients didn't have lymph node involvement by the tumor, while 13 patients (21%) had confirmed lymph node involvement either N1 or N2. For a significant proportion of cases (21%) lymph node status was not determined either because lymph node dissection was not performed and marked appropriately or it was not assessed during pathologic specimen examination. Group staging was not performed because in several patients' lymph node status was not assessed (Nx) Table *1*.

5.3: Surgical treatment strategies for bronchopulmonary carcinoid tumors

The majority of the patients with BPCT underwent surgery by open posterolateral thoracotomy approach [61(98.4%)] and pneumonectomy was the commonest (38.7%) resection performed. In this series, no sleeve lobectomy or sleeve pneumonectomy was performed. In three cases (4.8%) the resection margin was involved, in two of these cases bronchoplastic procedure was performed Table *3*.

Table 3; Surgical treatment strategies for bronchopulmonary carcinoid tumors

Variables	**Categories**	**Frequency (%)**
Surgical approach	VATS	1(1.6)
	Open posterolateral thoracotomy	61(98.4)
Type of resection performed	Wedge resection	1(1.6)
	Bronchoplastic procedure	5(8.1)
	Standard lobectomy	22(35.5)
	Sleeve lobectomy	0(0)
	Bi-lobectomy	10(16.1)
	Pneumonectomy	24(38.7)
	Sleeve pneumonectomy	0(0)
Status of resection margin	Free	59(95.2)
	Involved	3(4.8)

5.4: The association of histologic patterns with other covariates

The commonest histologic pattern was TC that accounted for 85.5% Figure *4*

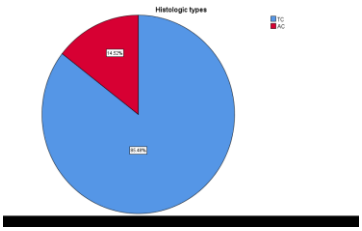

Figure 4; Histologic pattern of bronchopulmonary carcinoid tumors

The association of histologic patterns with other covariates was evaluated by employing cross-tabulation and logistic regression. Accordingly, five variables (age, smoking history, duration of symptoms, location of tumors, and lymph node status) were statistically associated with histologic patterns. Being older age had 1.17 times more likely to be AC type histologic pattern (OR 1.17(1.07-1,29), P-v = 0.001). As the duration of symptoms increased by one unit, the probability of being AC type histologic pattern was decreased by 0.75 times (OR 0.75(0.6-0.9, P-v = 0.009). Smokers had 65 times chances of being AC histologic pattern (OR 65(6-699), P-v = 0.001) as showed in Table *4*.

Table 4; association of histologic pattern with other covariates

Variable	**Category**	**Histologic pattern, Number (%)**			
		TC	AC	OR(CI)	P-value
Age in years continous variable		32.32±10	52.78± 8.9	1.17(1.07-1.29)	<0.001*
Sex	Male	22(35.5)	5(8.1)	1	
	Female	31(50.0)	4(6.5)	0.57(0.14-2.35)	0.436
Smoking status	Yes	1(1.6)	5(8.1)	65(6-699)	0.001*
	No	52(83.9)	4(6.5)	1	
Duration of symptoms in months		33..12±26.8	10± 4.6	0.75(0.6-0.9)	0.009*
Treatment for other presumptive diagnosis	Yes	28(45.2)	2(3.2)	1	
	No	25(40.3)	7(11.3)	3.9(0.7-20)	0.107*
Location of tumor	Central	50(80.6)	5(8.1)	0.07(0.01-0.4)	0.004*
	Peripheral	3(4.8)	4(6.5)	1	
Tumor laterality	Right side	30(48.4)	4(6.5)	0.6(0.15-2.5)	0.501
	Left side	23(37.1)	5(8.1)	1	
Tumor size	T1 and T2	33(53.2)	3(4.8)	1	
	T3 and T4	20(32.3)	6(9.7)	3.3(0.74-14.6)	0.117*
Lymph node status	N0	35(71.4)	1(2.0)	1	
	N1 and N2	7(14.3)	6(12.2)	30(3.1-289)	0.003*

*- statistically significant

6. Discussion

Bronchopulmonary carcinoid tumors are relatively rare cancers that originate from neuroendocrine “Kulchitsky” cells of the bronchial tree mucosa and submucosal glands. According to the Surveillance, Epidemiology, and End Results (SEER) database BPCTs accounted for about 1.2% of a total of 463,338 primary lung malignancies with rapid increment over the last three decades in the USA. A population-based retrospective cohort study which was conducted in adult patients with a NET diagnosis from 1994 to 2009 in Ontario, Canada, has also concluded a marked increment in the incidence of NETs over 15 years (3,16). In our case which is an institution-based study, we found that operations for bronchopulmonary carcinoid tumors accounted for 4% of total cardiothoracic surgeries performed during the study period. However, Z. Yang et.al. found that carcinoid tumors accounted for only 1 % of operations done for lung cancers(10). The reason we got a higher proportion of surgeries BPCTs when even counted from total cardiothoracic surgeries is probably malignancies like lung cancer commonly present at stage IV according to a previous study in the same institution (22).

In our study, we found that a higher proportion of female patients were operated for bronchopulmonary carcinoid tumors accounting for 56.5%. In other studies, also, performed by Z. Yang et al., L. Kornerup et.al., and A. Naalsund et.al. they found a significant female predominance(4,7,10). The mean age of the respondents in our study was 35.29 + 12.26 years which ranged from 14 - 67 years which is supported by other literatures as well.

In the current study majority of the patients were non-smokers 90.3%. this finding is in harmony with other studies (11,12,18). However, studies conducted in Denmark revealed a higher proportion of smokers in patients having BPCTs (4,8). This disparity could be due to population differences in smoking habits.

Almost all of our patients were clinically symptomatic during the presentation (98.4%), which is also supported by other literature. The frequent symptoms were non-resolving pneumonia and hemoptysis which goes with the findings of other studies (9–12,17,18). In addition to these, in our series unlike other literatures, we found dyspnea in a greater proportion of patients (26.2%) which could be explained by the fact that a significant percentage of patients (25.8%) were presented with destroyed lung (9,17,23).

The mean duration of symptoms before patients received treatment was 29.7 months with a range of 3-156 months in our current study. This finding is nearly similar to a study that was done in Sweden by T. Blondal et al. from 1971 to 1976, where they found patients delayed with symptoms an average of 7 months and doctor's delay before treatment was on an average, 1.1 years (24).

In contrast to most studies, we found that almost half of the patients (48.4) were treated for pulmonary tuberculosis empirically. This is mainly because of the lack of appropriate imaging facilities in hospitals out of the city where most patients are referred.

In our case, the pre-operative bronchoscopic examination was done for 72.6% of patients, from which bronchoscopy-guided biopsy was done only for two patients. This finding is very low when compared to other studies. In our setting, the main reason for deferring bronchoscopy-guided biopsy is concerns for uncontrollable hemorrhage, but other literature reported a low chance of having major hemorrhage following biopsy concluding it as a safe procedure(9,17,23) .

The most frequent radiologic findings were atelectasis (33.9%) and bronchiectasis of lobe/s (33.9%), where these patterns are in harmony with other literature (12,18). In addition to these patterns, destroyed lung with or without empyema (25.8%) were also the CT scan findings in the current study which is not reported in other studies. These could be explained by a delayed presentation and empirical treatment for PTB in a significant proportion of our patients.

Similar to other studies, the incidence of BPCTs was found to be more common on the right side. We found also the central location is dominant (88.7) which is similar to studies done in other areas (3,7,9,11,13,17) .

The most common histologic finding in the current study was typical carcinoid which accounted for 85.5%. This finding goes with the findings of other literature (3,11,17,20).

According to AJCC 8th edition(25) in our study, we found T2 and T3 accounted for 48.4% and 40.3% respectively. This finding is in contradiction to most literature where they found T1 as the commonest presentation (1,4,10,11,20). The reason for the higher T stage in our study might be related to the late presentation of our patients after developing symptoms. In most of our cases, lymph nodes were negative for tumors in 58.1% on post-operative pathologic assessment which is also supported by other studies. In addition, our study finding is unique in that we found NX in 21% of cases. This is probably because lymph node dissection is not done routinely for carcinoid tumors or lymph node is not assessed thoroughly on pathologic tissue examination.

For almost all patients surgical approach was through open posterolateral thoracotomy in our study. This finding has a significant disparity with studies done in other countries. The reason we had a low number of VATS approaches is the lack of expertise and late presentation of patients with significant inflammatory adhesions which makes the VATS approach difficult. the commonest type of resection performed for BPCTs in this study was pneumonectomy, which contradicts other literature (7,11,13,17,20). The reasons we had a higher rate of pneumonectomy include; a higher proportion of patients who presented with destroyed lung (25.8%) and lack of experience in performing parenchymal sparing procedures. The same with other literature, in this study also negative surgical margin was achieved in most of the operated cases.

Finally, five variables (age, smoking history, duration of symptoms, location of tumors, and lymph node status) were statistically associated with histologic patterns of the disease.

In the current study, patients who had a history of smoking have a 65 times chance of developing AC histologic patterns compared to non-smokers. This study finding is also supported by findings of other literature performed in other countries earlier (5,10,12,13,23).

In our current series being an older age had 1.17 times more association with AC histologic pattern. This finding is similar to a study that was done in Turkey by E. Aydin et al.where they found a significant association between older age and atypical histologic pattern (12). Others as well found a higher mean age in the atypical carcinoid group even though the figures differ. E. Lim et al. found the mean age of 48 and 58 for typical and atypical carcinoids respectively, while P. Soldath et al. found the mean age of 60 and 68 years for TC and AC respectively(8,20) .

Our study revealed that patients with shorter duration of symptoms were more likely to have atypical histologic patterns. This can be explained by the fact that atypical histology has a higher mitotic rate and rapid growth compared to the typical carcinoid (5).

We found also carcinoid tumors that were located centrally were more likely to be typical histologic patterns. This finding is in line with other study findings by other authors (10–13,17).

Atypical carcinoids were more associated with lymph node involvement by the tumor. This finding is similar to other studies performed in different settings(4,8,9,17,18,20) . The limitation of our study in lymph node staging was the fact that a significant percentage of patients had undetermined lymph node status.

7. Conclusion and Recommendation

There was slight female predominance (56.5%) with the mean age of patients being 35.29 years. The majority of the patients had no history of smoking (90.3%) and most of them were symptomatic at presentation (98.4%). The majority of the patients underwent surgery by open posterolateral thoracotomy approach (98.4%) and pneumonectomy was the most frequent (38.7%) resection performed. The commonest histologic pattern was TC which accounted for 85.5%. Age, smoking history, duration of symptoms, location of tumors, and lymph node status were statistically associated with histologic patterns.

We found nearly half of the patients were treated for PTB before surgical treatment for carcinoid tumors. This empirical treatment causes delays in patient presentation, unnecessary costs, and exposes patients to adverse reactions to anti-Tb drugs. Probably this is a factor for a significantly higher proportion of pneumonectomy, which causes more morbidity than resections which are less than pneumonectomy. Therefore, all physicians should think of alternate diagnoses and investigate patients appropriately if a patient is negative for routine TB workup or has inadequate response to appropriate antibiotics.

The most common surgical approach was open posterolateral thoracotomy which is invasive for early tumors without extensive intrathoracic adhesion. Thus, we recommend institutions provide facilities to undergo VATS and prepare surgeons to perform this relatively less invasive procedure for appropriate cases. During surgical treatment for carcinoid tumors, the lymph nodes should be dissected routinely and stations marked for the pathologists to complete the staging. Thus, the pathologist also should assess all lymph nodes to stage the disease of the patient well. In conclusion, we recommend researchers to further study on this topic.

Strengths and Limitations of the Study

The study describes the demographic, clinical presentation, anatomic distribution, histological types, and surgical strategies used for BPCTs in Ethiopia. It also determines the proportion of patients with carcinoid tumors who were treated for another presumptive diagnosis and also describes factors influencing the histological distributions of these tumors. This study is multi-institutional which increases the chances of including a diverse population, so having better representativeness of the general population.

This is a retrospective study extracted from chart review, which negatively affect data quality and resulted in the exclusion of some cases because of incomplete charts. Our study also included a relatively small sample size which affects its generalizability. The inconsistency in appropriate lymph node dissection with pulmonary resection for BPCTs has resulted in difficulty in putting group staging and knowing the true extent of the disease. The post-operative outcome was not included in this study which needs to be studied with a larger sample size from different centers in the country.

REFERENCES

1. Soldath P, Petersen RH. The Surgical Management of Lung Neuroendocrine Neoplasms. Vol. 15, Cancers. MDPI AG; 2023. p. 1695.

2. Travis WD, Brambilla E, Nicholson AG, Yatabe Y, Austin JHM, Beasley MB, et al. The 2015 World Health Organization Classification of Lung Tumors: Impact of Genetic, Clinical and Radiologic Advances since the 2004 Classification. Vol. 10, Journal of Thoracic Oncology. Elsevier Inc; 2015. 1243–1260 p.

3. Gustafsson BI, Kidd M, Chan A, Malfertheiner M V., Modlin IM. Bronchopulmonary neuroendocrine tumors. Cancer. 2008 Jul 1;113(1):5–21.

4. Kornerup LS, Dam G, Gronbek H. Survival and predictors of death for patients with bronchopulmonary carcinoid at a danish tertiary NET centre. In Vivo (Brooklyn). 2017 May 1;31(3):397–402.

5. LoCicero (III) J, Feins RH, Colson YL, Rocco G. Shields' General Thoracic Surgery: volume one & volume two. Shields' General Thoracic Surgery. 2019. 1–2384 p.

6. Wang T, Zhou J, Zheng Q, Wu D, Lu T, Lin M, et al. A Competing Risk Model Nomogram to Predict the Long-Term Prognosis of Lung Carcinoid. Ann Surg Oncol. 2023;

7. Naalsund A, Rostad H, Strøm EH, Lund MB, Strand TE. Carcinoid lung tumors - incidence, treatment and outcomes: A population-based study. European Journal of Cardio-thoracic Surgery [Internet]. 2011;39(4):565–9. Available from: http://dx.doi.org/10.1016/j.ejcts.2010.08.036

8. Soldath P, Binderup T, Kjær A, Federspiel B, Langer SW, Knigge U, et al. Long-term survival and recurrence after resection of bronchopulmonary carcinoids: A single-center cohort study of 236 patients. Lung Cancer. 2021 Jun 1;156:109–16.

9. Filosso PL, Rena O, Donati G, Casadio C, Ruffini E, Papalia E, et al. Bronchial carcinoid tumors: Surgical management and long-term outcome. Journal of Thoracic and Cardiovascular Surgery. 2002;123(2):303–9.

10. Yang Z, Wang Z, Duan Y, Xu S. Clinicopathological characteristics and prognosis of resected cases of carcinoid tumors of the lung. Thorac Cancer. 2016 Nov 1;7(6):633–8.

11. Bini A, Brandolini J, Cassanelli N, Davoli F, Dolci G, Sellitri F, et al. Typical and atypical pulmonary carcinoids: Our institutional experience. Interact Cardiovasc Thorac Surg. 2008;7(3):415–8.

12. Aydin E, Yazici U, Gulgosteren M, Agackiran Y, Kaya S, Gulhan E, et al. Long-term outcomes and prognostic factors of patients with surgically treated pulmonary carcinoid: Our institutional experience with 104 patients. European Journal of Cardio-thoracic Surgery [Internet]. 2011;39(4):549–54. Available from: http://dx.doi.org/10.1016/j.ejcts.2010.08.010

13. García-Yuste M, Matilla JM, Cueto A, Paniagua JMR, Ramos G, Cañizares MA, et al. Typical and atypical carcinoid tumours: analysis of the experience of the Spanish Multi-centric Study of Neuroendocrine Tumours of the Lung. European Journal of Cardio-thoracic Surgery. 2007 Feb;31(2):192–7.

14. Saber M, Ismail Y, Alieldin N, Loay I, El Zawahry M. Neuroendocrine tumors of the lung: A five-year retrospective experience of Egyptian NCI (2010–2014). J Egypt Natl Canc Inst. 2018;30(4):151–8.

15. Ayadi-Kaddour A, Marghli A, Zairi S, Zribi H, Ismail O, Braham E, et al. Bronchopulmonary carcinoid tumors: Tunisian experience with 115 surgically treated cases. Rev Pneumol Clin [Internet]. 2015;71(6):319–26. Available from: http://dx.doi.org/10.1016/j.pneumo.2015.04.003

16. Hallet J, Law CHL, Cukier M, Saskin R, Liu N, Singh S. Exploring the rising incidence of neuroendocrine tumors: A population-based analysis of epidemiology, metastatic presentation, and outcomes. Cancer. 2015 Feb 1;121(4):589–97.

17. Rea F, Rizzardi G, Zuin A, Marulli G, Nicotra S, Bulf R, et al. Outcome and surgical strategy in bronchial carcinoid tumors: single institution experience with 252 patients. European Journal of Cardio-thoracic Surgery. 2007 Feb;31(2):186–91.

18. Schrevens L, Vansteenkiste J, Deneffe G, De Leyn P, Verbeken E, Vandenberghe T, et al. Clinical-radiological presentation and outcome of surgically treated pulmonary carcinoid tumours: A long-term single institution experience. Lung Cancer. 2004;43(1):39–45.

19. Anile M, Diso D, Rendina EA, Venuta F. Bronchoplastic Procedures for Carcinoid Tumors. Thorac Surg Clin [Internet]. 2014;24(3):299–303. Available from: http://dx.doi.org/10.1016/j.thorsurg.2014.04.003

20. Lim E, Yap YK, De Stavola BL, Nicholson AG, Goldstraw P. The impact of stage and cell type on the prognosis of pulmonary neuroendocrine tumors. Journal of Thoracic and Cardiovascular Surgery. 2005 Oct;130(4):969–72.

21. CSA. Population Projections for Ethiopia 2007-2037. Central Statistical Agency Population, Ethiopia. 2013;(July):188.

22. Gebremariam TH, Huluka DK, Binegdie AB, Ashagre AW, Woldegeorgis MA, Ergetie W, et al. Lung Cancer in Addis Ababa, Ethiopia: Clinical, Radiological, Pathological Features, and Socio-Demographic Correlates: Update. 2020;A2458–A2458.

23. Fink G, Krelbaum T, Yellin A, Bendayan D, Saute M, Glazer M, et al. Pulmonary carcinoid: Presentation, diagnosis, and outcome in 142 cases in Israel and review of 640 cases from the literature. Chest [Internet]. 2001;119(6):1647–51. Available from: http://dx.doi.org/10.1378/chest.119.6.1647

24. Blondal T, Grimelius L, Nou E, Wilander E, Aberg T. Argyrophil carcinoid tumors of the lung. Incidence, clinical study, and follow-up of 46 patients. Chest [Internet]. 1980;78(6):840–4. Available from: http://dx.doi.org/10.1378/chest.78.6.840

25. Detterbeck FC. The eighth edition TNM stage classification for lung cancer: What does it mean on main street? Journal of Thoracic and Cardiovascular Surgery [Internet]. 2018;155(1):356–9. Available from: https://doi.org/10.1016/j.jtcvs.2017.08.138