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Original Research Article

Clinical, radiological, laboratory and bronchoscopic features characterizing each type of bronchogenic carcinoma

Manal R. Hafez[1]*, Omaima I. Abo-Elkheir[2]

[1]Department of Chest diseases, [2]Department of Community and Occupational Medicine, Alzahraa University Hospital, Faculty of Medicine, Al-Azhar University, Cairo, Egypt

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***Correspondence:**
Dr. Manal R. Hafez,
E-mail: dr.manalrefaat@gmail.com

ABSTRACT

Background: To analyse the clinical, radiological, laboratory, and bronchoscopic findings characterizing each type of bronchogenic carcinoma.
Methods: A cross-sectional study was conducted on 123 bronchogenic carcinoma patients. They were subjected to history taking, laboratory investigations, computed tomographic scan and fiberoptic bronchoscopy.
Results: The mean age of the patients was 56.9±6.7 years, 76.4% were males and 78.9% were smokers. Most of them were symptomatic, adenocarcinoma (ADC) being the highest symptomatic one. Expectoration, fingers clubbing, and fever were common in ADC and small cell lung cancer (SCLC). Dyspnea, haemoptysis, dysphonia, dysphagia, vocal cord paralysis, anorexia and weight loss were common in SCLC and squamous cell carcinoma (SCC). Deep venous thrombosis was common in ADC and SCC. Mass lesion, atelectasis, chest wall invasion and elevated hemidiaphragm were common in SCLC and SCC. Ipsilateral mediastinal lymph nodes enlargement, cavitary lesion, and apical lesion were common in SCC and ADC. Contralateral mediastinal lymph nodes enlargement was common in SCLC. Nodular lesion, consolidation and pleural effusion were common in ADC. Hypercalcemia and hyponatremia were common in SCC. Malignant pleural effusion was common in ADC. Most of the patients had bronchoscopically-visible lesions; SCLC and SCC being the highest visible types. Most of the SCC and SCLC were centrally located, while LCC and ADC were mainly peripherally located. Most of cases were diagnosed via bronchoscopy. More than half of the studied cases were inoperable at presentation, especially SCLC and SCC.
Conclusions: The 4 pathological types are distinguished from each other's by certain clinical, radiological, laboratory and bronchoscopic features.

Keywords: Bronchogenic carcinoma, Fiberoptic bronchoscopy, Thoracic ultrasound, Radiography in lung cancer

INTRODUCTION

Lung cancer is currently the most common malignant disease and the leading cause of cancer related-deaths in all age groups and in both sexes.[1] Cigarette smoking is the major cause of lung cancer; 95% of patients are smokers.[2] At presentation, 85% of the patients are symptomatic.[3] They may present with non-specific symptoms (e.g. weight loss or fatigue) or with direct signs and symptoms caused by the primary tumour or intrathoracic and\or extrathoracic spread.[1] Hypercoagulability disorders are associated with a variety of malignancies including lung cancer.[4]

Several factors may contribute to deep venous thrombosis (DVT) in cancer patients, e.g. immobilization, procoagulant factors produced by the tumor cells, and endothelial damage caused by stimulation of endothelial cells to produce procoagulant material.[5] The occurrence of thrombosis in cancer patients reduce life expectancy,

worsen quality of life and may delay, interrupt, or completely halt treatment.[4,6]

Anemia and thrombocytosis have been reported in patients with solid tumours, mainly lung cancer and colorectal cancer.[7] It is the most common hematologic abnormality in cancer patients, and around 50% of patients will develop anemia at some point.[8] Thrombocytosis or even upper normal platelet counts have been shown to be associated with advanced stages of cancer and to be a negative prognostic marker.[9]

Although paraneoplastic syndromes can be associated with many types of malignancies, they are most frequently associated with lung cancer.[10] It is a rare disorder that caused by an altered immune system response to a neoplasm or ectopic production of a hormones or cytokines.[11] The pathological types of lung cancer influence the type of paraneoplastic syndrome. The two most common of which are humoral hypercalcemia of malignancy and the syndrome of inappropriate antidiuretic hormone.[10]

Computed tomographic (CT) scan is the principal radiological examination in diagnosis and management of lung cancer. Flexible fiberoptic bronchoscopy (FOB) is the most useful investigation as it is not only visualizing but also provide tissue for cytopathological diagnosis. Bronchial brushings, washings and fine needle aspiration have become more easy, accessible and cost-effective FOB biopsy techniques.[12] Transthoracic fine needle aspiration cytology (FNAC) is regarded as the most effective cytological methods for diagnosis of lung cancer, particularly peripherally located ones.[2]

To our knowledge there are few studies that identify characteristics of each type of bronchogenic carcinoma. Therefore, the aim of this study is to analyse the clinical, radiological, laboratory and bronchoscopic findings characterizing each type.

METHODS

This cross-sectional study was conducted on 123 confirmed bronchogenic carcinoma patients. They were admitted to the Chest Diseases Department, Al-Zahraa University Hospital, Cairo, Egypt during the last 4 years. Patients with masses other than bronchogenic carcinoma and those with secondary lung tumour were excluded from the study. All participants were subjected to the following:

History taking

Age, sex, smoking status, smoking index (number of packs smoked per day X number of years) and history of any chronic respiratory diseases were recorded. The presenting symptoms and signs (table1) and its duration were also recorded.

Contrast enhanced CT-chest

It was done using multidetectors scanner (160 detectors) (Toshiba, Prime Aquilion Japan). The following abnormalities were recorded; mass [classified according to its size into nodule (≤3cm) or mass (>3cm)], cavitation's, atelectasis, consolidations, apical lesion, pleural effusion, chest wall invasion, diaphragm copula position, intrathoracic lymph nodes (LN) and/or supraclavicular LN enlargement.[13]

Laboratory investigations

Measurements of serum calcium (hypercalcemia was defined as total calcium >10.5mg\dl), serum sodium (hyponatremia was defined as sodium <135mmol/L), haemoglobin (anemia was defined as haemoglobin <11g/dl), platelets count (thrombocytosis was defined as platelets count >400.000), and erythrocytic sedimentation rate (ESR).

Cytological examination was done for patients presented with pleural effusion. This fluid was classified into

- Paramalignant (no malignant cells),
- Malignant (malignant cells).

Video-assisted fiberoptic bronchoscopy

This was done using (FB 1T 160, Olympus; Tokyo, Japan). The following findings were recorded;

- Bronchoscopic visibility; either visible or non-visible lesions. The visible lesions were classified into (endobronchial, submucosal and peribronchial),
- Location of the lesions.
- -Centrally locating (within the main or lobar bronchi),
- -Peripherally locating (beyond main or lobar bronchi).[14]

Obtaining tissue samples were done through bronchoscopy

- Forceps biopsy using (FB-15C, Olympus; Tokyo, Japan), 3-5 biopsies was obtained in patients with endobronchial lesions,
- Transbronchial needle aspiration using (NA-411D-152, Olympus; Tokyo, Japan), 3-7 needle aspiration was performed in patients without endobronchial involvement,
- Bronchial brushings using (BC-5C, Olympus; Tokyo, Japan), 4-7 brushings were obtained from the area surrounding the endobronchial lesion and suspected abnormal segments in case of patients without endobronchial involvement,
- Bronchoalveolar lavage.

Thoracic ultrasound guided biopsy

Using (Sonoscape SSI-6000 Medical Systems, Shenzhen, China) or CT-guided biopsy; three-to-five biopsies were obtained. The diagnosis of bronchogenic carcinoma was based on positive histopathological examination. The patients were classified according to the major pathological types: SCC, SCLC, adenocarcinoma (ADC), and large cell carcinoma (LCC).

Statistical analysis

Data were statistically analyzed by the Statistical Package for Social Science (SPSS) program version 17.0 (SPSS Inc.; Chicago, USA). Descriptive analysis was done for each item and the results were expressed as mean ±SD for quantitative continuous variables, and as percentages for qualitative (categorical and nominal) variables. Chi-square (X2) test and ANOVA (F) test were used to compare between groups. Values of $p<0.05$ (with a confidence limit at 95%) were considered significant. Results were presented by tables and figures.

RESULTS

Table (1) shows that the mean age of the studied patients was 56.9±6.7, 76.4% were males and 78.9% were smokers (31.6±14.9 pack⁄ year). Also, 54.5% had COPD and 8.1% had DPLD.

Table 1: General characteristics of the studied patients.

Items		Total (n=123)
Age/ years	Mean ±SD	56.9±6.7
	Range	38-75
Sex	Male	94 (76.4%)
	Female	29 (23.6%)
Smoking status	Non-smokers	26 (21.1%)
	Smokers	97 (78.9%)
Smoking index (pack/year)	Mean ±SD	31.6±14.9
	Range	5.0-60.0
Underlying chronic lung disease	Negative	46(37.4%)
	COPD	67 (54.5%)
	DPLD	10 (8.1%)
Types of bronchogenic carcinoma	SCC	39 (31.7%)
	SCLC	14 (11.4%)
	ADC	38 (30.9%)
	LCC	32 (26.0%)
Operability at time of diagnosis	Operable	54 (43.9%)
	Inoperable	69(56.1%)

Abbreviation: COPD: chronic obstructive pulmonary disease, DPLD: Diffuse parenchymal lung diseases

Table 2 shows that most of cases were symptomatic (95.9%), ADC cases had higher mean symptoms duration (4.8±1.8 months). Cough was the main presenting symptoms irrespective to pathological types. Expectoration, fingers clubbing, and fever were significantly common in patients with SCLC and ADC. Chest pain was non-significantly common in patients with LCC and ADC.

Dyspnea, haemoptysis, dysphonia, dysphagia, vocal cord paralysis, anorexia and weight loss were common in patients with SCLC and SCC ($p<0.05$). Gynaecomastia was common in patients with LCC (6.5%) ($p=0.05$). DVT was common among patients with ADC and SCC.

Table 3 shows that the highest numbers of SCC and SCLC lesions were located in right the lung (64.1% and 64.3%), while LCC and ADC lesions were mainly located in left lung (78.1% and 52.6%) ($p= 0.003$). More than fifth (22.8%) of lesions were located in RUL, with the highest percentage for SCC (30.8%) followed by SCLC (28.6%). Another one fifth of lesions were located in LUL (21.1%) with the highest percentage for LCC (43.8%). Ligula location was common in ADC (31.6%). A mass lesion was common in SCLC and SCC (50.0% and 46.2%), while nodular lesions were common in ADC and LCC (47.4% and 31.3%). Ipsilateral mediastinal LN enlargement was common in SCC and ADC, while contralateral mediastinal LN enlargement was common in SCLC (71.4%) ($p=0.001$). Apical lesions were significantly higher in SCC and ADC, while atelectasis was highest in SCLC and SCC. Consolidations was significantly highest in ADC (47.4%), while cavitary lesion was prevalent in ADC and SCC (36.8% and 30.8%). Pleural effusion was significantly common in ADC and LCC. Chest wall invasion and elevated hemidiaphragm were common in SCC and SCLC.

Table 4 shows that ESR/1st hour was elevated irrespective to pathological types. SCC showed the highest prevalence of anemia, while thrombocytosis was equally distributed in ADC and SCC. Hypercalcemia and hyponatremia were common in SCC (30.8% each), followed by SCLC (14.3% and 21.4% (p=0.001). Para-malignant effusion was common in ADC and LCC, while malignant effusion was common in ADC (36.8%) (p=0.001).

Table 2: Presenting clinical picture of the studied patients by types of bronchogenic carcinoma.

Items	Total No. = [a]118/123 (95.9)	[a] Symptomatic cases				Sign. Test and p-value
		SCC No.=38/39 (97.4)	SCLC No.=14/14 (100.0)	ADC No.=35/38 (92.1)	LCC No.=31/32 (96.9)	
Duration of symptoms\months Mean ±SD	3.6±1.6	2.8±1.0	2.6±0.84	4.8±1.8	3.7±1.4	F= 14.3
Range	1-9	1-5	2-5	2-9	1-6	P=0.001
Dyspnea %	82 (69.5)	34 (89.5)	14 (100.0)	18 (51.4)	16 (51.6)	X^2= 23.3* P< 0.001
Cough %	106 (89.8)	34 (89.5)	13 (92.9)	31 (88.6)	28 (90.3)	X^2 = 2.5 P=0.86
Expectoration %	71 (60.2)	16 (42.1)	11 (78.6)	31 (88.6)	13 (41.9)	X^2= 23.2* P <0.001
Chest pain %	64 (55.2)	18 (50.0)	5 (35.7)	20 (57.1)	21 (67.7)	X^2= 4.5 P=0.2
Haemoptysis %	38 (32.2)	18 (47.4)	8 (57.1)	8 (22.9)	4 (12.9)	X^2=14.6* P=0.002
Dysphonia %	43 (36.4)	22 (57.9)	11 (78.6)	8 (22.9)	2 (6.5)	X^2=33.0* P<0.001
Dysphagia %	39 (33.1)	16 (42.1)	10 (71.4)	9 (25.7)	4 (12.9)	X^2=17.2* P=0.001
Fever %	39 (33.1)	6 (15.8)	11 (78.6)	18 (51.4)	4 (12.9)	X^2=29.3* P=0.001
Anorexia %	39 (33.1)	18 (47.4)	9 (64.3)	6 (17.1)	6 (19.4)	X^2=16.1* P=0.001
Weight loss %	38 (32.2)	18 (47.4)	9 (64.3)	3 (8.6)	8 (25.5)	X^2=20.4* P=0.001
Clubbing of fingers%	40 (33.9)	10 (26.3)	4 (28.6)	22 (62.9)	4 (12.9)	X^2=22.3* P=0.001
Gynaecomastia %	6 (3.4)	1 (2.6)	0 (0.0)	1 (2.8)	2 (6.5)	X^2=7.8* P=0.050
DVT %	14 (11.9)	6 (15.8)	0 (0.0)	8 (22.9)	0 (0.0)	X^2=10.6* P=0.014
Vocal cord paralysis %	10 (8.5)	8 (21.1)	2 (14.3)	0 (0.0)	0 (0.0)	X^2=14.9* P=0.002

[a]Five cases were asymptomatic, *Significant test.
Abbreviations: SCC: Squamous cell carcinoma, SCLC: Small cell lung cancer, ADC: Adenocarcinoma, LCC: Large cell carcinoma, DVT: deep venous thrombosis

Table 5 demonstrated that SCLC and SC were the most bronchoscopically-visible lesions (92. 9% and 87.2%). SCC was mainly visible as endobronchial lesions (41.2%), followed by submucosal and peribronchial lesions (29.4% each). SCLC was visible mainly as submucosal lesions (38.5%), followed by peribronchial lesions (30.8%), ADC was visible as either submucosal or endobronchial lesions (38.5%), while LCC was mainly visible as endobronchial lesions (56.0%). Regarding bronchial site nearly three quarters of lesions were centrally located; mostly SCC and SCLC (84.6% and 78.6%). On the other hand, most cases of LCC and ADC were peripherally locating (81.3% and 55.3%).

FOB was the diagnostic methods in 61.8% of the patients; especially SCLC and ADC (71.4% and 65.8%). TUS-guided biopsy was the diagnostic method in 31.7% of the patients; especially SCC and LCC (35.9% and 34.4%).

More than half (56.1%) of the studied cases were inoperable at time of diagnosis (Table 1); especially SCLC and SCC (100.0% and 79.5%) (Figure 1). Causes of inoperability were supraclavicular LN (30.9%) mainly in SCLC (64.3%), followed by elevated hemidiaphragm (17.9%) mainly in SCLC (50.0%), chest wall invasion (15.4%) mainly in SCC (25.6%), renal and hepatic metastasis were common in patients with SCLC (50.0% and 35.7%) (p<0.05) (table 2), and malignant pleural effusion (17.0%) mainly in ADC (36.8%) (Table 3).

DISCUSSION

Bronchogenic carcinoma remains the leading cause of cancer related-mortality in the developed world and its incidence is rising in developing countries.[1]

The result of current study demonstrated that the pathological types of bronchogenic carcinoma have changed as ADC (30.9%) has nearly equal prevalence to SCC (31.7%), followed by LCC (26.0%), while SCLC was the least prevalent type (11.4%). Similarly, several studies reported higher prevalence of SCC and ADC.[6,15-21] Moreover, in some Asian and western countries, ADC has surpassed SCC as the most common subtype.[1,23,24] This shift in incidence of SCC and ADC may be due to switch from non-filtered to filtered cigarettes. Smoke from unfiltered strong cigarettes may be shallowly inhaled, resulting in carcinogen deposition in the central bronchi giving rise to SCC. While smoke from filtered

milder cigarettes with reduced nicotine content may be deeply inhaled, resulting in carcinogen deposition more peripherally giving rise to ADC.[24]

The mean age of the studied patients was 56.9±6.7 years, there was male predominance (76.4%), with male to female ratio (3.2:1), 78.9% were smokers with smokers to non-smokers ratio (3.1:1). These results were similar to that reported worldwide.[3,19-21] Additionally, 95.9% of studied patients were symptomatic, while 4.1% were asymptomatic and detected as incidental radiological finding. ADC had the highest symptoms duration (p=0.001).

The longer ADC symptoms duration could be attributed to that most of ADC cases presented with clinical and\or radiographic features suggestive of pneumonia and treated for it first before seeking tissue biopsies.

Table 3: Radiological findings of the studied patients by type of bronchogenic carcinoma.

Items		Total (n=123)	Type of bronchogenic carcinoma				Sig. Test and P-value
			SCC (n=39)	SCLC (n=14)	ADC (n=38)	LCC (n=32)	
Lung	Right	59 (48.0)	25 (64.1)	9 (64.3)	18 (47.4)	7 (21.9)	X^2=14.3* P= 0.003
	Left	64 (52.0)	14 (35.9)	5 (35.7)	20 (52.)	25 (78.1)	
Affected lobe (%)	RUL	28 (22.8)	12 (30.8)	4 (28.6)	9 (23.7)	3 (9.4)	X^2=33.2* P= 0.004
	ML	11 (8.9)	3 (7.7)	2 (14.3)	4 (10.5)	2 (6.3)	
	RLL	20 (16.3)	10 (25.6)	3 (21.4)	5 (13.2)	2 (6.3)	
	LUL	26 (21.1)	6 (15.4)	0 (0.0)	6 (15.)	14 (43.8)	
	Lingula	21 (17.1)	2 (5.1)	3 (21.4)	12 (31.6)	4 (12.5)	
	LLL	17 (13.8)	6 (15.4)	2 (14.3)	2 (5.3)	7 (21.9)	
Mass lesion (%)	No	40 (32.5)	12 (30.8)	5 (35.7)	14 (36.8)	9 (28.1)	X^2=12.1 P= 0.06
	Mass	44 (35.8)	18 (46.2)	7 (50.0)	6 (15.8)	10 (40.6)	
	Nodule	39 (31.7)	9 (23.1)	2 (14.3)	18 (47.4)	13 (31.3)	
Mediastinal lymph node enlargement (%)	No	68 (55.3)	19 (48.7)	4 (28.6)	22 (57.9)	23 (71.9)	X^2=45.9* P= 0.001
	Ipsilateral	37 (30.1)	16 (41.0)	0 (0.0)	14 (36.8)	7 (21.9)	
	Contralateral	18 (14.6)	4 (10.3)	10 (71.4)	2 (5.3)	2 (6.3)	
Apical lesion (%)		27 (22.0)	16 (41.0)	0 (0.0)	7 (18.4)	4 (12.5)	X^2=14.2* P= 0.003
Atelectasis (%)		24 (19.5)	16 (41.0)	6 (42.9)	0 (0.0)	2 (6.3)	X^2=29.1* P= 0.001
Consolidation (%)		25 (20.3)	7 (17.9)	0 (0.0)	18 (47.4)	0 (0.0)	X^2=29.0* P= 0.001
Cavitary lesion (%)		26 (21.1)	12 (30.8)	0 (0.0)	14 (36.8)	0 (0.0)	X^2=20.1* P= 0.001
Pleural effusion (%)		48 (39.0)	10 (25.6)	2 (14.3)	26 (68.4)	10 (31.3)	X^2=21.1* P= 0.001
Chest wall invasion (%)		19 (15.4)	10 (25.6)	3 (21.4)	2 (5.3)	4 (12.5)	X^2=6.7 P= 0.08
Elevated hemidiaphragm (%)		22 (17.9)	12 (30.8)	7 (50.0)	1 (2.6)	2 (6.3)	X^2=23.2* P= 0.001
Supraclavicular LN enlargement (%)		3 (30.9)	14 (35.9)	9 (64.3)	9 (23.7)	6 (18.8)	X^2=10.9* P=0.012
Hepatic metastasis (%)		11 (9.8)	2 (5.1)	5 (35.7)	2 (5.3)	2 (6.3)	X^2=24.5* P=0.001
Renal metastasis (%)		14 (11.4)	4 (10.3)	7 (50.0)	1 (2.6)	2 (6.3)	X^2=20.3* P= 0.001

RUL: right upper lobe, RML: right middle lobe, RLL: right lower lobe, LUL: left upper lobe, LLL: left lower lobe, LN: lymph nodes. *Significant test

Similar delay in presentation up to 3-4 months was reported in other studies with only 2.5 % of patients were asymptomatic.[1,3,16,21] Cough and chest were the main presenting symptoms among our patients irrespective to pathological types (p=0.8). The mechanism of cough is multifactorial as it may be due to either local growth in a centrally locating tumours (e.g. SCC, SCLC), or a feature of airway obstruction causing postobstructive pneumonia

(e.g. ADC). Similarly, other studies reported that cough was the most common presenting symptoms.[1,23] The mediastinal compression symptoms (dyspnea, dysphonia, dysphagia) and vocal cord paralysis were significantly highest in SCLC and SCC ($p<0.05$).

This is due to which both SCLC and SCC are mainly centrally locating tumours (table 5) that cause compression of a major airways, trachea, esophagus and recurrent laryngeal nerve. Similar results were reported in other studies.[17,20]

Hassan et al reported that dysphagia was diagnosed in 12.1% of patients regardless the stage of malignancy.[25] Haemoptysis, anorexia and weight loss were common among (32.2%, 33.1% and 32.2%) of our patients with the highest prevalence among SCLC and SCC ($p<0.05$), while, fever was significantly linked to SCLC and ADC. Fever could be paraneoplastic manifestation, or it may be due to postobstructive pneumonia. Similar frequency of haemoptysis was reported in previous studies.[16,23] Hathila and Goswami reported that weight loss and anorexia were prevalent among their patients.[20]

Table 4: Laboratory data of the studied patients by type of bronchogenic carcinoma.

Items		Total (n=123)	Type of bronchogenic carcinoma				Sig. Test and P-value
			SCC (n=39)	SCLC (n=14)	ADC (n=38)	LCC (n=32)	
ESR\1st hour Mean ±SD		79.9±34.9	74.3±33.6	82.9±28.2	77.4±41.3	88.4±30.3	F=1.0
Range		15.0-150.0	25.0-150.0	15.0-125.0	15.0-150.0	35.0-150.0	P=0.36
Anemia (%)		57 (46.3)	25 (64.1)	5 (35.7)	9 (39.5)	12 (37.5)	X^2=7.3 P=0.6
Thrombocytosis (%)		14 (11.4)	6 (15.4)	0 (0.0)	6 (15.8)	2 (6.3)	X^2= 4.0 P=0.26
Hypercalcemia (%)		15 (12.2)	12 (30.8)	2 (14.3)	1 (2.6)	0 (0.0)	X^2=20.3* P= 0.001
Hyponatremia (%)		23 (18.7)	12 (30.8)	3 (21.4)	5 (13.2)	3 (9.4)	X^2= 52.2* P=0.001
Type of effusion (%)	Para-malignant	27 (22.0)	7 (17.9)	1 (7.1)	12 (31.6)	7 (21.9)	X^2=24.2* P= 0.001
	Malignant	21 (17.0)	3 (7.7)	1 (7.1)	14 (36.8)	3 (9.4)	

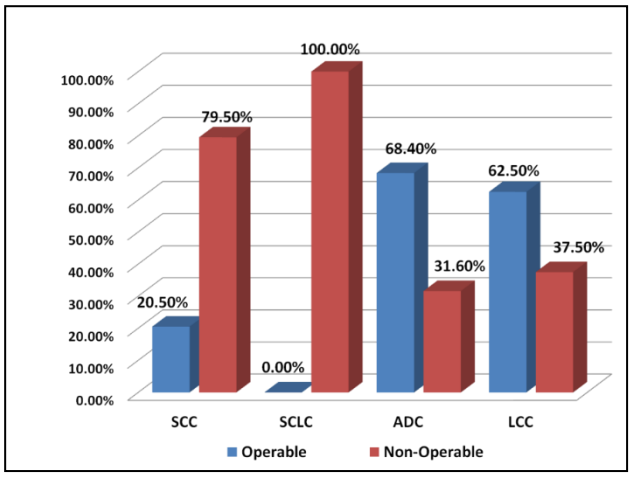
* Significant test. Abbreviations: SCC: Squamous cell carcinoma, SCLC: Small cell lung cancer, ADC: Adenocarcinoma, LCC: Large cell carcinoma, ESR: erythrocyte sedimentation rate

Table 5: Bronchoscopic findings and diagnostic methods by types of bronchogenic carcinoma.

Items		Total (n=123)	Type of bronchogenic carcinoma				Sig. Test and P-value
			SCC (n=39)	SCLC (n=14)	ADC (n=38)	LCC (n=32)	
Visibility	Non-visible (%)	25 (20.3)	5 (12.8)	1 (7.1)	12 (31.6)	7 (21.9)	X^2=5.6 P=0.11
	Visible (%)	98 (79.7)	34 (87.2)	13 (92.9)	26 (68.4)	25 (78.1)	
Types of visible bronchial lesions	Submucosal (%)	29 (29.6)	10 (29.4)	5 (38.5)	10 (38.5)	4 (16.0)	X^2=3.6 P=0.31
	Endobronchial (%)	40 (40.8)	14 (41.2)	2 (15.4)	10 (38.5)	14 (56.0)	X^2=4.8 P=0.18
	Peribronchial (%)	29 (29.6)	10 (29.4)	4 (30.8)	8 (30.8)	7 (28.0)	X^2=0.5 P=0.92
Bronchial site	Central (%)	87 (70.7)	33 (84.6)	11 (78.6)	17 (44.7)	6 (18.8)	X^2=18.2* P=0.001
	Peripheral (%)	36 (29.3)	6 (15.4)	3 (21.4)	21 (55.3)	26 (81.3)	
Diagnostic methods	FOB-biopsy (%)	76 (61.8)	22 (56.4)	10 (71.4)	25 (65.8)	19 (59.4)	X^2=2.3 P= 0.88
	TUS-guided biopsy (%)	39 (31.7)	14 (35.9)	4 (28.6)	10 (26.3)	11 (34.4)	X^2=1.1 P=0.7
	CT-guided biopsy (%)	8 (6.5)	3 (7.7)	0 (0.0)	3 (7.9)	2 (6.3)	X^2=1.2 P= 0.7

*Significant test. Abbreviations: SCC: Squamous cell carcinoma, SCLC: Small cell lung cancer, ADC: Adenocarcinoma, LCC: Large cell carcinoma, TUS: thoracic ultrasound, CT: computed tomography scan, FOB: fiberoptic bronchoscopy

In present study DVT was prevalent among 11.9% of the studied patients with highest prevalence in ADC (21.9%), followed by SCC (15.8%) (p=0.014). It is assumed that the presence of mucus in ADC may lead to increased secretion of procoagulant factors and activation of platelets with subsequent microthrombi formation.[5] Other studies reported similar frequency of DVT in patients with bronchogenic carcinoma.[6,26,27] Other investigators have reported stronger association of DVT with ADC than with SCC.[5,6,27,28] However, Mitra et al reported that DVT was common in SCLC than ADC and SCC.[29] Gynaecomastia was prevalent among 6.5% of our patients with LCC. Gynaecomastia in lung cancer is usually caused by an increased oestrogen/ androgen ratio as raised β-human chorionic gonadotropin concentrations stimulate Leydig cell-mediated oestrogen synthesis.[30] In our study fingers clubbing was linked to ADC (65.8%), followed by SCLC and SCC. Similarly, Beckles et al stated that fingers clubbing was more prevalent in SCC and ADC than SCLC.[31]



Abbreviations: SCC: Squamous cell carcinoma, SCLC: Small cell lung cancer, ADC: Adenocarcinoma, LCC: Large cell carcinoma.

Figure 1: Operability among the studied cases by bronchogenic carcinoma types.

Regarding radiological features this study revealed that 52.0% of lesions were located in the left lung, and 48.0% were located in the right lung, mainly both upper lobes. SCC and SCLC were common in right lung (64.1% and 64.3%), while LCC and ADC were common in left lung (78.1% and 52.6%) (p=0.003). Right lung predilection was reported in previous studies especially upper lobes.[2,3,15,17] The upper lobes susceptibility to lung cancer might be attributed to that the upper lobes are less vascular and more aerated than the lower ones, therefore it is more affected by smoking.[17] Lung masses was commonly detected in (50.0%, 46.2% and 40.6%) of our patients with SCLC, SCC and LCC respectively, while lung nodule was commonly detected in ADC (47.4 %) (p=0.06). Previous studies reported similar results as mass was the commonest radiological abnormalities in all pathological types.[19] However, it is more common in SCLC and SCC.[19,3] Other studies reported different results as more than half of ADC cases presented with lung mass.[16,3] The contralateral mediastinal LN enlargement was common in 71.4% of our SCLC patients, while ipsilateral mediastinal LN enlargement was common in SCC (41.0%, p=0.001); moreover, atelectasis was common in SCLC and SCC (p=0.001). These findings could be attributed to the finding that both SCLC and SCC are mainly centrally locating tumors which may easily invade mediastinal LN and compress large bronchi leading to distal atelectasis. Chaudhary reported that mediastinal LN invasion was common in SCLC while, others reported that SCC was the commonest ones.[19,20]

In this study apical lesion was common in SCC (41.0%, p=0.003). Similar result was reported by Akl et al who stated that SCC was commonly associated with apical lesion.[19] Meanwhile, consolidations was common in ADC (47.4%) (p=0.001), that may be due to excessive mucin production from tumour cells with development of pneumonic form of bronchoalveolar carcinoma. Similarly, other studies reported that consolidation was common in ADC while consolidations /collapse was prevalent in SCC.[3,20]

In the current study cavitary lesion was exclusively linked to ADC and SCC (36.8% and 30.8%) (p= 0.001). The mechanism of this cavitary lesion in SCC is due to excessive tumor growth that superpass its blood supply leading to cell death, necrosis and cavity formation. While in ADC this may be pseudocavitations, as some nodules have focal lucent areas. Same results were reported in previous studies as cavitations were common in SCC3 and ADC.[15,20]

In the current study chest wall invasion was more prevalent in SCC followed SCLC (p=0.08). While involvement of diaphragm was prevalent among patients with either SCLC or SCC (p=0.001). Similar result was reported in previous study as chest wall infiltration was common in SCC, while Hathila and Goswami stated that chest wall invasion was seen in 20% of ADC cases.[3,20] Moreover, Rawat et al reported that involvement of diaphragm was common in SCLC.[16] Additionally, paramalignant pleural effusion was common in our ADC and LCC patients, while malignant effusion was prevalent in ADC (36.8%) (p=0.001). These association could be explained by that ADC and LCC are peripherally located tumors (table 5) that either irritate or invade pleural membrane with formation of paramalignant or malignant pleural effusion respectively. Other investigators reported lower frequencies of pleural effusion in ADC however, in these studies ADC was the commonest type associated with effusion.[3,15,19,20]

Regarding laboratory investigations our study the revealed that the ESR was elevated irrespective to

pathological types; which signifies that ESR is an acute phase reactant elevated in many inflammatory and neoplastic conditions. Meanwhile, anaemia was reported in 46.3% of studied patients with the highest prevalence in SCC. The cancer associated anemia is due to either activation of the immune system leading to diminution of erythropoiesis, chronic blood loss at tumor sites or bone marrow invasion by tumor cells.[8,32,33] Similarly previous studies reported that anemia was prevalent in 38%-56% of newly diagnosed lung cancer patients especially SCC.[34-36] Additionally, thrombocytosis was found in 11.4% of our patients with highest prevalence in ADC and SCC (15.8%, 15.4%) (p=0.26). Thrombocytosis in lung cancer may be due to either humoral factors secreted by tumour cells or it is a part of systemic inflammatory reaction.[7,37] A similar prevalence of thrombocytosis (13-32%) had been reported in previous studies.[34,38] While, other reported a higher prevalence of thrombocytosis (50-60%) without showing any significant differences between pathological types.[37-39] Moreover, survival in patients with thrombocytosis has been significantly shorter than in those without thrombocytosis.[38]

In the current study hypercalcemia and hyponatremia were highest in SCC (30.8%, and 14.3%) and SCLC (30.8% and 21.4%) (p=0.001). The major mechanisms of hypercalcemia in cancer patients are; humoral hypercalcemia of malignancy and osteolytic activity at sites of skeletal metastasis. Spiro et al reported that hypercalcemia in lung cancer patients ranges from 2- 6% at the initial diagnosis raising to 8-12% throughout the course of the disease.[40] SCC is the most common pathological type associated with hypercalcemia.[17] Hyponatremia in lung cancer may be due to either increase production of antidiuretic hormone, syndrome of inappropriate antidiuretic hormone secretion, or atrial natriuretic hormone secretion.[41] Previous studies reported that hyponatremia is common in patients with SCLC while it was less common in NSCLC.[11,31,42] Additionally, lung cancer patients with either hypercalcemia or hyponatremia had shorter survival times.[43,44]

In our study SCLC and SCC were the highest bronchoscopically-visible types (92.9% and 87.2%). SCLC was visualized mainly as submucosal lesions (38.5%), ADC was visualized mainly as submucosal or endobronchial lesions (38.5% each), while LCC and SCC were predominantly seen as endobronchial lesions (56.0% and 41.2%); peribronchial lesions was nearly equally seen in all pathological types. Additionally, SCC and SCLC were mainly centrally locating (84.6%, and 78.6%), while LCC and ADC were commonly peripherally located (81.3% and 55.3%) (p=0.001). Rabahi et al reported that SCC and SCLC were the most bronchoscopically-visible tumours. SCC was visualized as an endobronchial mass (74%).[18]

In SCLC submucosal lesions is the most common finding, while in ADC luminal narrowing and external compression prevail. Shetty et al found that ADC is presenting as central tumor in 70.5%, while SCC is presenting as peripheral tumor in 52.7%.[15]

The majority (61.8%) of our cases were diagnosed through FOB, with higher percentages in SCLC and ADC (71.4% and 65.8%) (p=0.8). While 38.2% were diagnosed through transthoracic guided biopsy (31.7% via TUS and 6.5% via CT), mainly SCC and LCC. The higher diagnostic yield of FOB could be due to that the majority of studied patients had centrally locating tumors, which are better accessed by FOB. In accordance of these results, previous studies reported that FOB-biopsy had the most diagnostic yield especially in SCLC and SCC.[1,17,19] Moreover, FOB provided diagnostic specimen in 36-88% by a meta-analysis study of peripheral lung cancers.[16,45] However, Dhandapani et al reported that image guided percutaneous biopsy (both CT and US) was shown to be slightly more efficient than FOB, with ADC being the highest ones.[23]

Unfortunately, more than half (56.1%) of the studied patients presented at advanced inoperable stages with distant metastasis. All patients with SCLC and 79.5% of those with SCC were inoperable at time of diagnosis. This high percentage of inoperability among our patients might be attributed to several factors;

1. The majority of the patients had either underlying COPD (54.5%) or DPLD (8.1%) thereby their symptoms were interpreted as acute exacerbation of underlying diseases,
2. The smokers often attribute any cough as smoker's cough, and
3. Lack of diagnostic facilities at primary health-care centres. Similarly, previous studies reported distant metastasis in 49.1- 67% while others reported a lower frequency of metastasis (2%).[1,2,17] Additionally, Santos-Martínez et al reported that metastasis was more common in SCLC (55%) than those with NSCLC (42%).[46]

CONCLUSION

We can have concluded that expectoration, fingers clubbing and fever where was common in ADC and SCLC. Dyspnea, haemoptysis, dysphonia, dysphagia, vocal cord paralysis, anorexia and weight loss were common in SCLC and SCC, while DVT was common in ADC and SCC. ADC had the highest symptoms duration. Mass lesion, atelectasis, chest wall invasion and elevated hemidiaphragm were common in SCLC and SCC. Ipsilateral mediastinal LN metastasis, cavitary lesion, and apical lesion were common in SCC and ADC, while contralateral mediastinal LN metastasis was common in SCLC. Nodular lesion, consolidation and pleural effusion were common in ADC.

Therefore, there is a need to create awareness about lung cancer; it's clinical, radiological, laboratory and radiological features of each pathological types among

the general practitioners for an early diagnosis and treatment to improve its outcome.

Hypercalcemia and hyponatremia were common in SCC and SCLC, while malignant effusion was common in ADC. SCLC and SCC are mainly centrally locating, therefore they are the highest bronchoscopically-visible types; SCC was seen mainly as endobronchial lesions, while SCLC was seen mainly as either submucosal or peribronchial lesions. LCC and ADC were mainly peripherally locating, ADC was seen mainly as submucosal or endobronchial lesions, while LCC was seen mainly as endobronchial lesions. More than half of our patients presented at far advanced stages, especially SCLC and SCC.

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