

Resectability in bronchogenic carcinoma: A single-center experience

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Abstract. Bronchogenic carcinoma comprises >90% of primary lung tumors. The present study aimed to estimate the profile of patients with bronchogenic carcinoma and assess the cancer resectability in newly diagnosed patients. This is a single-center retrospective review conducted over a period of 5 years. A total of 800 patients with bronchogenic carcinoma were included. The diagnoses were mostly proven with either cytological examination or histopathological diagnosis. Sputum analysis, cytological examination of pleural effusion and bronchoscopic examination were performed. Lymph node biopsy, minimally invasive procedures (mediastinoscopy and video-assisted thoracoscopic surgery), tru-cut biopsy or fine-needle aspiration was used to obtain the samples for diagnosis. The masses were removed by lobectomy and pneumonectomy. The age range was between 22 and 87 years, with a mean age of 62.95 years. Males represented the predominant sex. Most of the patients were smokers or ex-smokers. The most common symptom was a cough, followed by dyspnea. Chest radiography revealed abnormal findings in 699 patients. A bronchoscopic evaluation was performed for the majority of patients (n=633). Endobronchial masses and other suggestive malignancy findings were present in 473 patients (83.1%) of the 569 who underwent fiberoptic bronchoscopy. Cytological and/or histopathological samples of 581 patients (91.8%) were

positive. Small cell lung cancer (SCLC) occurred in 38 patients (4.75%) and non-SCLC was detected in 762 patients (95.25%). Lobectomy was the main surgical procedure, followed by pneumonectomy. A total of 5 patients developed postoperative complications without any mortality. In conclusion, bronchogenic carcinoma is rapidly increasing without a predilection for sex in the Iraqi population. Advanced preoperative staging and investigation tools are required to determine the rate of resectability.

Introduction

Bronchogenic carcinoma is the development of malignant tumors from the respiratory epithelium; it involves >90% of primary lung tumors (1). Pathologically, it is categorized into two types: Small cell lung cancer (SCLC) and non-SCLC (NSCLC). SCLC is known as oat cell cancer owing to the packed nature of the small dense cells. SCLCs represent ~20% of all lung cancer cases; they tend to metastasize to the lymph nodes, but are very responsive to chemotherapy (2). NSCLC consists of several types of cancer, including adenocarcinoma (the most common type), squamous carcinoma, large cell undifferentiated carcinoma, bronchioalveolar carcinoma and neuroendocrine tumors (2).

Smoking is the most common risk factor, accounting for ~85% of lung cancer cases (3). Radon gas is regarded as the second most common cause of lung cancer, which is generated by the breakdown of radioactive radium (3). Other factors, like asbestos exposure, air pollution, genetic abnormalities and pre-existing lung diseases, also play an important role in the occurrence of lung cancer (4,5). Cough, the most common symptom, is associated with almost 90% of lung cancer cases and is followed by dyspnea. Pleuritic pain, local chest wall pain, swelling of the head and arms, weakness, seizures and confusion are all among the abundant symptoms that can be associated with lung cancer (6). Despite the significant

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increase in lung cancer incidence in recent decades in Iraq, there are only a few small sample-sized studies focused on the profile of bronchogenic carcinoma (1,7).

The present study on a single-center experience aimed to estimate the profile of Iraqi patients with bronchogenic carcinoma and assess the cancer resectability in newly diagnosed patients.

Patients and methods

Study design. This is a single-center retrospective review with longitudinal follow-up conducted over 5 years (January 1, 2015, to October 1, 2019). The present study was approved by the Ethical Committee of the University of Sulaimani (Sulaimani, Iraq).

Participants. The records of 800 patients with bronchogenic carcinoma were collected from the Department of Thoracic and Vascular Surgery, Ghazzi Al-Hariri Hospital for Surgical Specialties (Baghdad, Iraq). Patients with bronchogenic carcinoma were mostly differentiated using either cytological examination or histopathological diagnosis.

Inclusion and exclusion criteria. All the patients with proven bronchogenic carcinoma were included. Patients with a carcinoid tumor, metastatic nodules regardless of size, and suspicion of bronchogenic carcinoma with negative cytological and histopathological samples were all excluded from the study.

Preoperative preparation. A detailed clinical assessment was conducted for the patients by taking the patients' history, performing physical examinations, and observing radiological imaging such as chest radiography (CXR), computed tomography (CT) and magnetic resonance imaging. Sputum analysis, cytological examination of pleural effusion and bronchoscopic examination using either flexible or rigid bronchoscopy were performed.

Lymph node biopsy, minimally invasive procedures [mediastinoscopy and video-assisted thoracoscopic surgery (VATS)], Tru-cut biopsy or fine-needle aspiration (FNA) were used to obtain the samples for diagnosis. Patients with a resectable mass should have undergone a positron emission tomography (PET) scan to exclude lymph node metastasis. If the PET scan was clear, the patients were scheduled for surgery. The surgeries (lobectomy and pneumonectomy) included the removal of the masses in addition to lymph node dissection.

Sputum analysis. After collecting the samples (sputum in the early morning), the samples were preserved and fixed for 30 min at 25°C using a saccomano fixative solution (BioGnost, Ltd.). A mucolytic agent such as methyl cysteine HCl (Cytoclair) (MilliporeSigma) 2% solution in normal saline was used to obtain cell suspensions in samples at a temperature of 37°C for up to 18 h. The samples were centrifuged at 7,168 x g for ~10 min at 25°C and the precipitates were then immersed in absolute alcohol (99%) for 15 min at 37°C for further fixation and dehydration. The precipitations were put in clearing agents such as xylene or acetone for 30 min before preparing cell blocks using the Leukhardt paraffin box. For each sample, a 4- μ m thick section was taken using a conventional microtome

and stained with hematoxylin and eosin for 2 min at 37°C. A light microscope was used for the valuation and examination of the section with or without using the immunocytochemical staining method for confirmation of the histogenesis of the cells.

Cytological examination. After taking FNA samples, the samples were preserved and fixed for 30 min at 25°C using a saccomano fixative solution (BioGnost, Ltd.). The samples were centrifuged at 7,168 x g for ~10 min at 25°C and the precipitates were then immersed in absolute alcohol (99%) for 15 min at 37°C for further fixation and dehydration. The precipitations were put in clearing agents such as xylene or acetone for 30 min before preparing cell blocks using the Leukhardt paraffin box. For each sample, a 4- μ m thick section was taken using a conventional microtome and stained with hematoxylin and eosin for 2 min at 37°C. A light microscope was used for the valuation and examination of the section with or without using the immunocytochemical staining method for confirmation of the histogenesis of the cells.

Data collection and analysis. A data form was designed to collect and organize the information of the patients. The form included introductory information (age, sex and smoking history), symptoms, investigations, imaging findings, bronchoscopic data, surgical operation data and the final histological or cytological diagnosis.

The patients' information was taken either prospectively during their visit to the outpatient clinic or at admission when they were prepared for the procedures. In some other cases, the data was obtained retrospectively from the patients' medical files or surgeon's notes. Final histopathological information was obtained from the pathology laboratory.

Microsoft Excel (Microsoft Corporation) was used to collect and organize the data. SPSS version 25 (IBM Corp.) was used for encoding and descriptive analysis of the data.

Surgical procedures

Lobectomy. The surgeries were conducted under general anesthesia with a double endotracheal lumen and lateral position (right or left) according to the mass location. An anterior thoracotomy was performed through the 5th or 6th intercostal space according to the mass location. After accessing the pleural space, adhesions were released (if present). A hemoclip was used to ligate the vein of the affected lobe, followed by the dissection of the fissure between the lobes to identify the arterial supply of the affected lobe. The bronchi were isolated and a bronchial clamp was applied. The lung was inflated to ensure the clamping of the affected bronchus alone, and a linear stapler was used to ligate the bronchus and separate it. A single layer of non-absorbable sutures, such as polypropylene sutures, secured the bronchus, vein and artery. The stump of the vein, artery, and bronchus were checked for hemostasis and air leakage. A single chest drain was inserted, with the wound closed in multiple layers.

Pneumonectomy. The surgeries were conducted under general anesthesia with a double endotracheal lumen and lateral position (right or left) according to the mass location. A classical posterolateral thoracotomy was performed through the 5th or 6th intercostal space according to the mass location.

After accessing the pleural space, adhesions were released (if present). The inferior pulmonary ligament was released. The pulmonary vein was identified by swab dissection between the lung and pericardium, and then ligated using a hemoclip. An apical dissection was performed to identify the main pulmonary artery, which was ligated using a hemoclip. No inflation of the lung following the clamping of the bronchus indicated a perfect closure. A linear stapler was applied and divided the main bronchus. A single layer of non-absorbable sutures, such as polypropylene sutures, secured the bronchus, vein and artery. The stump of the vein, artery and bronchus were checked for hemostasis and air leakage. A single chest drain was inserted and removed after 48 h, with the wound closed in multiple layers.

Results

The present study included a total of 800 patients with bronchogenic carcinoma. The age range was between 22 and 87 years, with a mean age of 62.95 years. With a ratio of 3.8:1, the dominant sex was male (636 patients, 79.5%). Almost half of the patients were in their sixth to seventh decades of life (373 patients, 46.6%) (Table I). Most of the patients were smokers or ex-smokers (84.3%); 87.6% of the males and 71.3% of the females were active or ex-smokers. The most common symptom was a cough (544 patients, 68.0%), followed by dyspnea (380 patients, 47.5%) (Table I). The CXR presented a suspicious mass in 699 patients (87.4%), which in most of the cases was located in the right lung. Other findings were pleural effusion (14.4%) and atelectasis (9.8%) (Fig. 1). A high-resolution CT of the chest and upper abdomen was performed for all of the patients. The most common findings were a mass (99.0%), lymphadenopathy (64.6%) and pleural effusion (19.8%) (Fig. 2). Cytological examination of the pleural effusions showed cancer cells in 90 patients (57.0%) (Fig. 3). Bronchoscopic evaluations were performed for the majority of the patients (633 patients, 79.1%). Fiberoptic bronchoscopy (FOB) was performed under local anesthesia for 569 patients (71.1%). Endobronchial masses and other suggestive malignancy findings were present in 473 of these patients (83.1%), while normal findings were observed in 96 patients (16.9%). Rigid bronchoscopy was used only for 64 non-cooperative patients under general anesthesia, and 59 of these patients (92.2%) had abnormal findings. Cytological and/or histopathological samples of 581 (91.8%) of the patients who underwent bronchoscopic evaluation were positive (Figs. 4 and 5). VATS and open lung biopsy were performed for 23 and 8 patients, respectively, with cancer detected in all of them. The findings of diagnostic modalities are all summarized in Fig. 6.

SCLC was present in 38 patients (4.75%) and NSCLC was detected in 762 patients (95.25%) (Table I).

Tumor-Node-Metastasis (TNM) staging (8) was conducted for most of the cases (95.3%) depending on their workup results, and most were in stages III (55.4%) and IV (31.8%). All stage I and 24% of stage II tumors were resectable (Table II). Regarding surgical resectability, only 28 patients (3.5%) were candidates for surgery with radical lymph node dissection (Table III). Most of the cases were investigated by PET scan and mediastinoscopy before making a surgical decision. The ratio of using PET scan and mediastinoscopy to aid in surgical resectability is presented

Table I. Characteristics of the included participants.

Characteristic	No. of cases	Percentage
Sex		
Male	636	79.50
Female	164	20.50
Age, years		
20-30	4	0.50
30-40	7	0.88
40-50	62	7.75
50-60	219	27.38
60-70	373	46.62
70-80	101	12.62
>80	34	4.25
Smoker/ex-smoker	674	84.25
Male	557	87.58 ^a
Female	117	71.34 ^a
Symptoms		
Cough	544	68.00
Dyspnoea	380	47.50
Hemoptysis	289	36.13
Weight loss	169	21.13
Chest pain	137	17.13
Hoarseness of voice	38	4.75
SVC obstruction	31	3.88
Neurological symptoms	24	3.00
Type of operation		
Non-operable	772	96.50
Lobectomy	23	2.88
Pneumonectomy	5	0.62
Histopathology		
SCLC	38	4.75
NSCLC	762	95.25
NSCLC subtypes		
Squamous cell carcinoma	402	50.25
Adenocarcinoma	345	43.12
Large cell carcinoma	15	1.88
Post-operative complications		
Wound infection	2	7.14 ^b
Air leakage	2	7.14 ^b
Arrhythmia	1	3.57 ^b

^aPercentage of total smokers/ex-smokers; ^bpercentage of total surgical candidates. SVC, superior vena cava; NSCLC, non-small cell lung cancer.

in Fig. 7. Regarding sex, 20 of the surgical candidates were male and the other 8 were female (Table IV). Lobectomy was the main surgical procedure performed for 23 of the patients (82.1%), and pneumonectomy was performed for 5 of the patients (17.9%) (Table III). Regarding morbidity, 5 of the patients (17.9%) developed postoperative complications (Table I). There were no mortalities.

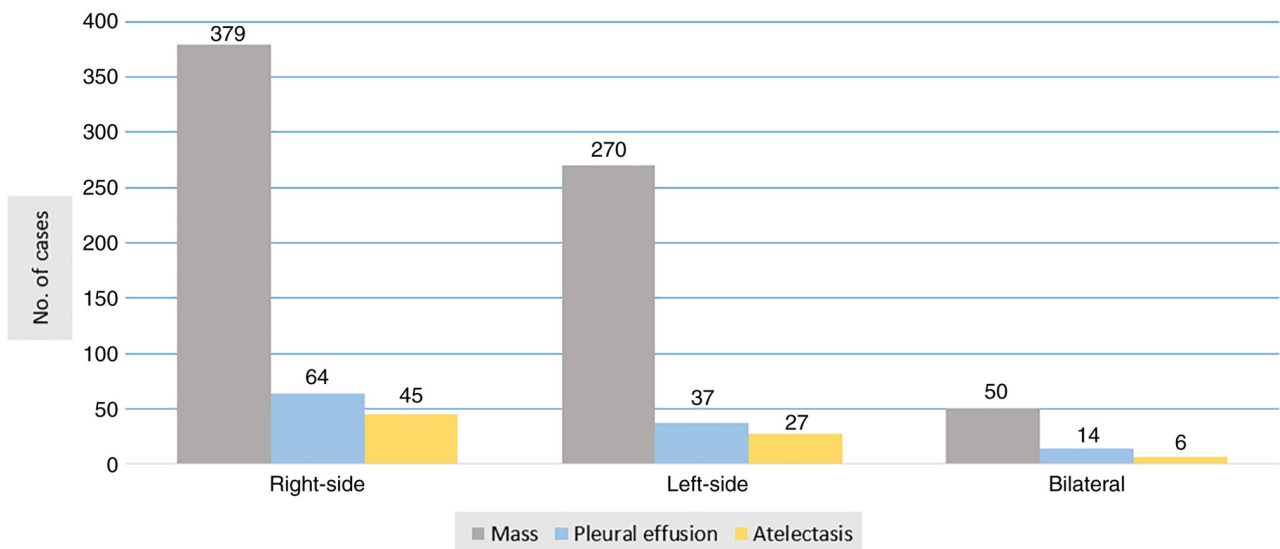


Figure 1. Chest radiography findings.

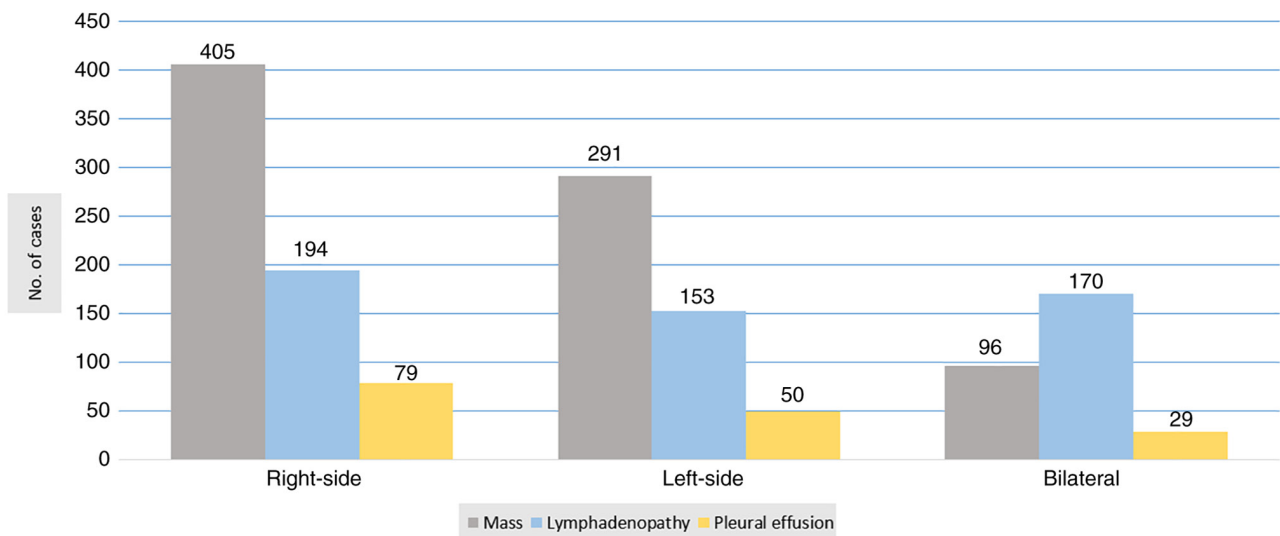


Figure 2. Chest computed tomography scan findings.

Discussion

Alongside breast cancer, lung cancer is known as a major cause of cancer-related deaths worldwide (9). Despite the advancements in diagnostic modalities and management techniques, lung cancer still has a high incidence with a poor prognosis. The overall 5-year survival rates are <20% (10). In the UK, ~40,000 new cases are recorded annually. From the time of diagnosis, a large proportion of the patients die within 1 year, and only 5% of the patients have a chance of 5-year survival. This high mortality rate makes lung cancer one of the most common causes of cancer-related death (5). In Iraq, lung cancer is regarded as the most common cancer in men and one of the five most common cancer types in women (7).

It has been estimated that smoking is the major cause of lung cancer in 85-90% of all cases. In total, over 40 carcinogenic agents have been identified in cigarette smoke. Even non-smokers are susceptible to being affected by lung cancer

when there is a high rate of exposure to tobacco smoke (11). In reviewing the results of the present study, smoking was the major risk factor for bronchogenic carcinoma. This is comparable with the result of the study by Al-Kadhimi *et al* (7).

The majority of patients in the present study were between 60 and 70 years old, with a mean age of 62.95 years. This is consistent with the studies by Westermann *et al* (12), De Perrot *et al* (13) and Boffa *et al* (14). The long-term carcinogenic effect of smoking may be the reason for these findings. In the current study, most of the patients were male, with a ratio of 3.8:1, which is not consistent with the previous studies. Boffa *et al* (14) reported a ratio of 1.5:1 and the results of Al-Kadhimi *et al* (7) were significantly different, with a reported male-to-female ratio of 5.4:1.

The development of smoking habits in the female sex may be responsible for this increase in incidence of bronchogenic carcinoma in Iraq. A cough was the most common presenting symptom in the present study. This is consistent with the

Table II. Stages of bronchogenic carcinoma in non-small cell lung cancer cases.

Tumor-Node-Metastasis staging	No. of cases	Percentage	Operability, %
I	6	0.8	100.0
II	92	12.1	24.0
III	422	55.4	0.0
IV	242	31.8	0.0

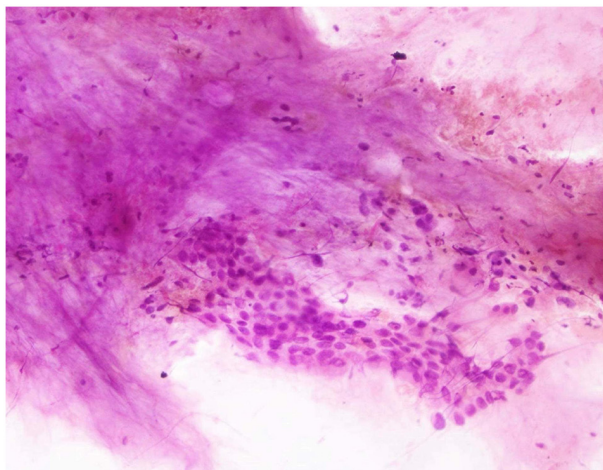


Figure 3. Fine-needle aspiration cytology sample from a peripherally located lung mass obtained under computed tomography guidance showing a mucinous background with admixed clusters of atypical cells (x400 magnification; hematoxylin and eosin).

local studies by Al-Rahim (1) and Al-Kadhimi *et al* (7). This commonality could be due to the strong association between bronchogenic carcinoma and smoking habits.

TNM staging based on clinical examination, mediastinoscopic examination, bronchoscopic examination and radiography has a vital role in deciding the resectability in most cases (15). In the present study, TNM staging was conducted for most of the cases depending on their work-up results. The CXR in a posterolateral view was taken for the patients in this study. The vast majority of abnormal radiological findings consisted of the presence of a mass, with a sensitivity of 87.3%, followed by the presence of effusion and atelectasis. This result agreed with that in the study by Gupta *et al* (16). Contrast CT of the chest and abdomen was performed for all the patients who had abnormal radiological findings on CXR, for confirmation of the diagnosis and staging of the tumor, and the disease was found in 792 patients. The lesions were distributed as follows: 405 on the right side, 291 on the left side and 96 bilateral masses. The second finding was of mediastinal lymphadenopathy (LAP) in 517 patients. Pleural effusion was found in 158 patients. These findings were consistent with the data obtained in the study by Gupta *et al* (16), in which a bronchogenic mass was reported in 96.7% of patients and LAP in 79.1%.

PET/CT imaging has been increasingly used in the last decade in the assessment of patients with lung cancer (17). In the present study, the high sensitivity of PET scans was similar

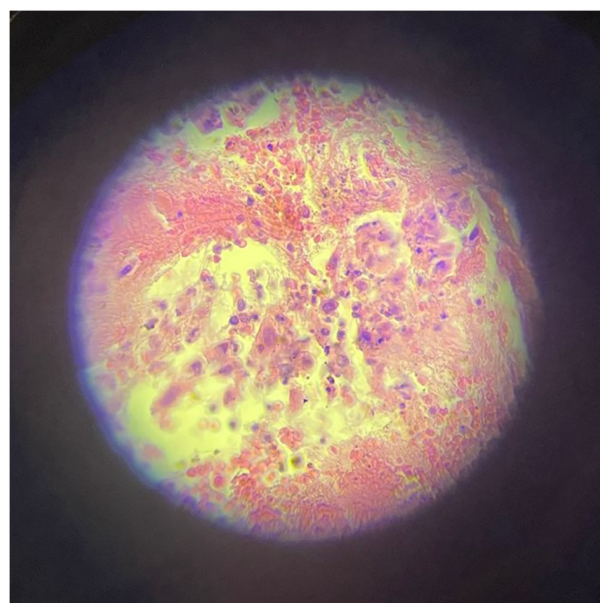


Figure 4. Section showing squamous cell carcinoma in a sample taken by bronchoalveolar lavage (x400 magnification; hematoxylin and eosin).

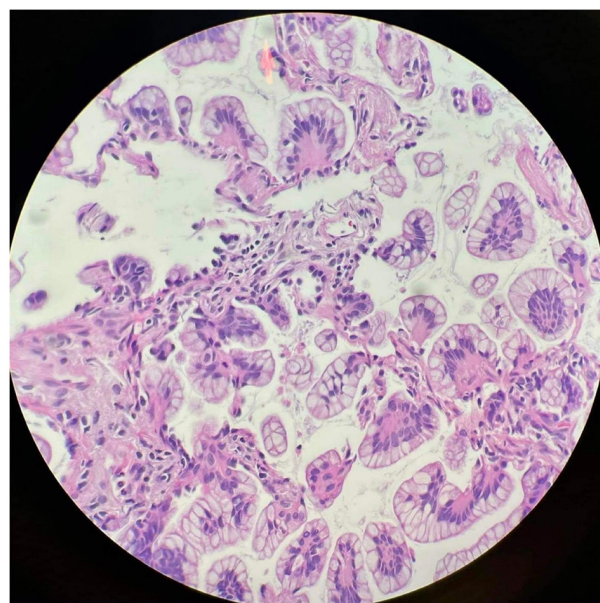


Figure 5. Well-differentiated mucinous cells with abundant intracellular mucin and bland-looking basally located nuclei, lining the alveolar septa in a lepidic fashion (x400 magnification; hematoxylin and eosin).

to that found in the study by Hussein *et al* (18). A PET/CT scan was used in the last 2 years for 13 patients. Out of those 13 patients, only 6 patients were operated on due to clear mediastinal LAP. The other 7 patients had N2 disease at the time of examination, so surgical intervention was canceled. Sputum cytology is a rapid test used for the diagnosis and screening of bronchogenic carcinoma (19). This was performed for only 113 (14.1%) patients in the present study, while another local study performed sputum cytology in almost 79.5% of the cases (1). The reduction in the use of sputum cytology in the present study is due to the availability of more accurate tests for cytological examinations, such as bronchoscopy and FNA.

Table III. Type of resections and resectability rate.

Year	No. of patients	Resectability rate, %	No. of operations	Type of resection	No. of resections
2015	167	4.70	8	Lobectomy	5
				Pneumonectomy	3
2016	163	3.60	6	Lobectomy	4
				Pneumonectomy	2
2017	169	3.50	6	Lobectomy	6
2018	161	3.10	5	Lobectomy	5
2019	140	2.10	3	Lobectomy	3

Table IV. Resectable patients according to sex, age and histopathology.

Characteristics	No. of cases	Percentage
Sex		
Male	20	71.4
Female	8	28.6
Age, years		
20-40	0	0.0
40-50	4	14.3
50-60	11	39.3
60-70	12	42.9
>70	1	3.6
Histopathology		
SCLC	0	0.0
NSCLC	28	100.0
NSCLC type		
Squamous carcinoma	14	50.0
Adenocarcinoma	14	50.0

Despite the progress in cancer treatment, the management of malignant pleural effusion (MPE) remains palliative, with median survival ranging from 3 to 12 months (20). In the present study, 158 patients (19.8%) had pleural effusion. Cytological examination revealed positive results in 90 patients (57.0%), and this may be due to the advancement of cytological techniques and the more common use of CT scans that can detect even a small amount of MPE. In addition, the present results corresponded with those of the study by Asciak and Rahman (21), which reported positive results in 60% of the patients.

The rapid evolution in imaging technology makes bronchoscopes more flexible with a smaller diameter, a finer resolution of view and a wider working channel. This provides a facility for endobronchial ultrasound (EBUS), biopsy sampling and therapeutic intervention (22,23). In the present series, rigid and flexible bronchoscopies were performed for 633 patients (79.1%). Abnormal findings were found in 59 patients (92.2%) out of 64 cases that had undergone rigid bronchoscopy. FOB was performed for the other 569 patients, with abnormal bronchoscopic findings in 473 patients (83.1%) and non-specific

findings in 96 patients (16.9%). However, in the study by Al-Rahim (1), bronchoscopy was performed in ~84% of the cases, with an abnormal finding in 64% of them.

Thoracoscopy is considered a standard diagnostic modality, but less invasive techniques have emerged as potential alternatives, including transthoracic needle aspiration and EBUS with needle aspiration (24). In the present study, in the 106 cases (13.3%) that were unable to undergo surgical intervention due to medical contraindications or advanced disease, FNA and Tru-cut biopsy were conducted to obtain tissue for histological diagnosis.

The use of an open cervical and scalene lymph node biopsy to confirm bronchogenic carcinoma has decreased with the advancement of other modalities. Recently, it has only been preserved for patients with palpable lymph nodes and those who have experienced the failure of less invasive techniques to confirm the diagnosis. In the present study experience, the results of the lymph node biopsy were almost the same as those of the study by Al-Rahim (1). Cervical mediastinoscopy was conducted for only 1.5% of the patients in the present study, with a positive histopathological finding in 83.3% of them. However, in the study by Bousema *et al* (25), it was performed for 29.5% of the patients. The cause of this low application in the present study is the late introduction of video-assisted mediastinoscopy in the Department of Thoracic and Vascular Surgery, Ghazzi Al-Hariri Hospital for Surgical Specialties. Furthermore, the data were obtained from a single center while the data collected in the study by Bousema *et al* (25) were from six Dutch thoracic surgery centers.

VATS represents a new developing technique for diagnosing patients with bronchogenic carcinoma; it greatly improves a patient's prognosis and significantly reduces morbidity and mortality rates (26). In the present series, VATS was performed for 23 patients, and open lung biopsy for 8 patients. In a previous study, a biopsy was required for 22 patients, and all of these were performed by open thoracic surgery (1).

Regarding the histological types of lung cancer, the most common type was squamous cell carcinoma, followed by adenocarcinoma in the present study. This result agreed with that found in the study by Al-Rahim (1) and differed from that found in the study by Strand *et al* (27), where the results showed that adenocarcinoma was the most common type compared with squamous cell carcinoma.

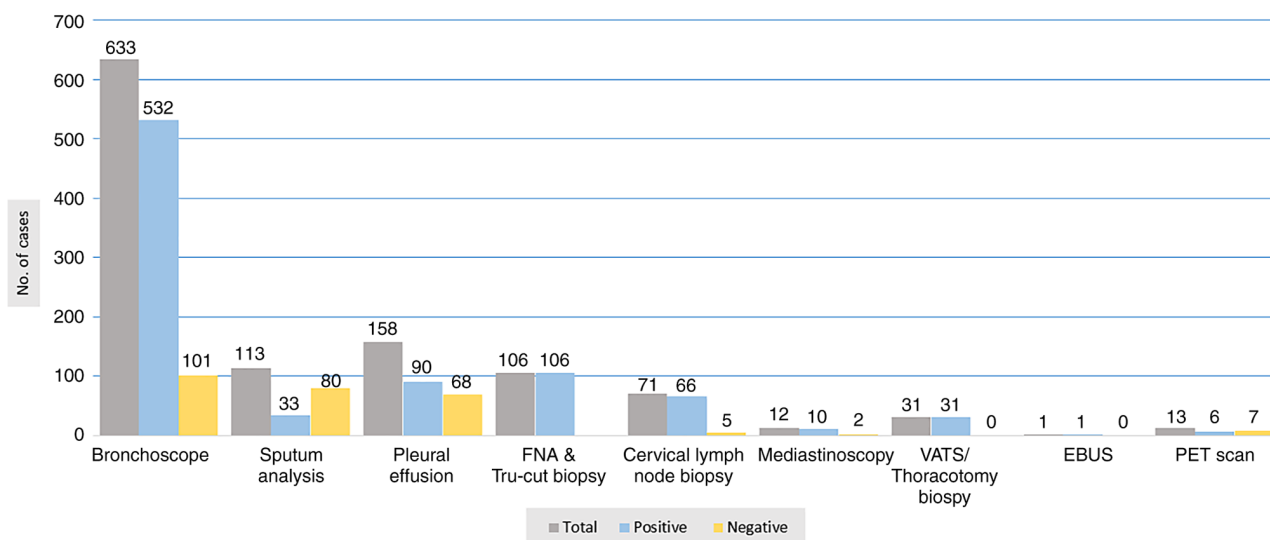


Figure 6. Diagnostic approaches for bronchogenic carcinoma. FNA, fine-needle aspiration; VATS, video-assisted thoracoscopic surgery; EBUS, endobronchial ultrasound; PET, positron emission tomography.

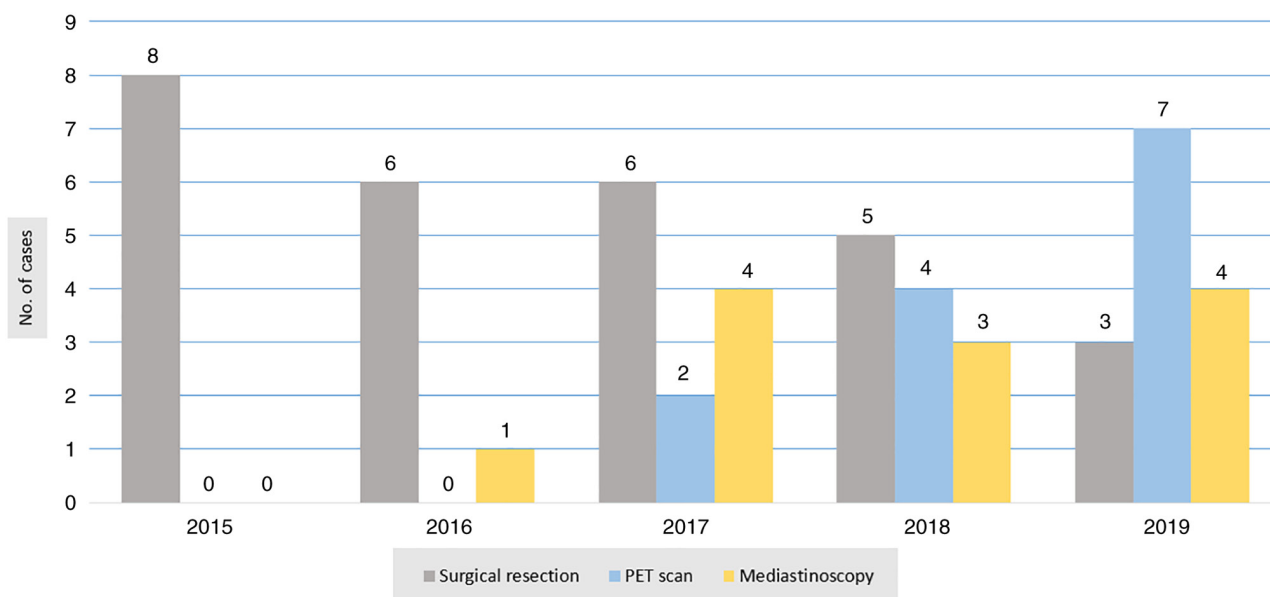


Figure 7. Yearly usage of PET scans, mediastinoscopy and surgical resectability. PET, positron emission tomography.

The first lobectomy for lung cancer was conducted by Hugh Davies in 1912 (28). The patient died with empyema 8 days after the resection. Surgical resection for lung cancer has become prevalent with the advancement of the water-sealed drainage system and anesthetic techniques. In 1933, Graham and Singer reported the first successful one-stage pneumonectomy (29). Since then, the standard operation for lung cancer has become pneumonectomy. Around the same time, Barney and Churchill (30) described an experience of lobectomies with hilar dissections. The vast majority of surgical procedures in the present study were lobectomies in 23 patients. Pneumonectomy was performed in only 5 cases.

Other studies used the segmentectomy technique alongside lobectomy and pneumectomy in a specific portion of the cases (14,27). The absence of segmentectomy in the present

study can be explained by the lack of an intraoperative frozen section facility, which is necessary to confirm a cancer-free margin. The morbidity rate in the present study was 17.9%, without any mortality. In a study by Boffa *et al* (14), the morbidity rate was 32%, with a mortality rate of 2.5%. As most of the patients at the time of diagnosis were non-operable, the rate of surgical resectability in the present study was 3.5%. This result was lower than the percentage of resectability in the global studies by Strand *et al* (27) and Boffa *et al* (14).

In conclusion, bronchogenic carcinoma is an aggressive tumor with various presentations. The incidence of bronchogenic carcinoma is rapidly increasing without a predilection for either sex in the Iraqi population. Advanced preoperative staging and investigation tools are required to determine the rate of resectability.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

MMM provided major contributions to the study concept and final approval of the manuscript. SNJ and OFA performed the operations. FHK was involved in the conception of the study, literature review and drafting the manuscript. BJHA, SHT, AMS, SHA, RKA, RJR, SHM, SMM, RAA and HMR were involved in critically revising the manuscript, data analysis and revision of the tables and figures. All authors read and approved the final manuscript. MMM, FHK and OFA confirm the authenticity of all the raw data. All authors agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of Sulaimani University (Sulaimani, Iraq). Written informed consent was obtained from all patients.

Patient consent for publication

The patients provided written consent for the publication of their data.

Competing interests

The authors declare that they have no competing interests.

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